Studies on the Zinc-Mediated Phenyl and Alkynyl Addition to Carbon-Heteroatom Double Bonds

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Parts of this work have already been published:

1) C. Bolm, L. Zani, J. Rudolph, I. Schiffers
"New chiral ligands derived from mandelic acid: synthesis and application in the asymmetric phenyl transfer reaction to an aromatic aldehyde"
Synthesis **2004**, 2173-2180.

2) C. Bolm, F. Schmidt, L. Zani
"New chiral hydroxy oxazolines as useful ligands for the asymmetric phenylation of aromatic aldehydes"
Tetrahedron: Asymmetry **2005**, *16*, 1367-1376.

3) L. Zani, S. Alesi, P. G. Cozzi, C. Bolm
"Dimethylzinc-mediated alkynylation of imines"
J. Org. Chem. **2006**, *71*, 1558-1562.

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As you can see, this list is already very long, but still I fear I forgot someone. If this is the case, please forgive me, you know that was not done on purpose.

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"…the inadequacy of our preparation, and the need to make up for it with luck, intuition, stratagems and a river of patience. […] I wanted to put on display […] the strong and bitter flavour of our trade, which is only a more strenuous version of the business of living"

Primo Levi, *The Periodic Table*

"Provando e riprovando
[Trying and trying again]"

Motto of the "Accademia del Cimento", the first
european scientific society, founded in Florence in 1657

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1. Introduction

1.1. Organometallic Compounds in Organic Synthesis

Organometallic chemistry is an interdisciplinary science which lies at the interface between the classical disciplines of organic and inorganic chemistry. *Organometallic compounds*, can be defined as species in which organic groups or functionalities are attached to metal atoms by metal-carbon bonds.[1] On the contrary, compounds in which the organic fragment is bonded to a metal through a heteroatom (as in many *metal complexes*) are often referred to as *metallorganic* or *elementorganic compounds*.[2] As can be expected, many compounds cannot be easily classified into one or the other category, and often exceptions have to be made in single cases.

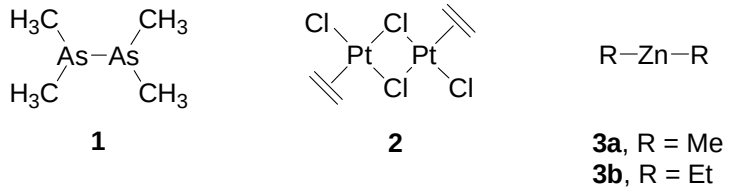
Since organic groups can be bound to almost all the elements of the periodic table (except probably the noble gases), the number of organometallic compounds that can be prepared is potentially almost unlimited. Moreover, the suffix 'metallic' in the term 'organometallic' is often loosely interpreted to include compounds possessing carbon bonded to such elements as boron, silicon, phosphorous, arsenic, selenium and tellurium. It is therefore not surprising that an enormous, and ever increasing, volume of information about organometallic compounds, their structure and reactivity, is currently available in the literature.[3]

Organometallic compounds have a long history. The first organometallic derivative ever synthesized was probably tetramethyldiarsine (**1**), isolated as early as 1760 by a Prussian military apothecary, CADET DE GLAUSSICOURT. As is often the case in science, this was a chance discovery: upon pyrolization of arsenious oxide with potassium acetate, a reddish brown fuming liquid was formed which was called 'cacodyl' due to its awful smell.

After some work by other researchers, 'cacodyl' was finally characterized in 1842 by ROBERT BUNSEN. Meanwhile, the danish chemist WILLIAM C. ZEISE had already prepared, in 1831, the first transition metal-organic complex, $[PtCl_2(C_2H_4)]_2$ (**2**), since then known as "Zeise's salt". Shortly

[1] M. E. O'Neill, K. Wade in *Comprehensive Organometallic Chemistry*, Vol. 1, p. 2, (Eds: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, New York, **1982**.
[2] R. H. Crabtree *The Organometallic Chemistry of the Transition Metals*, 4th Ed., John Wiley & Sons, Hoboken, **2005**
[3] For a general survey: (a) *Comprehensive Organometallic Chemistry* (Ed: J. R. Wardell), Elsevier, Oxford; **1995**. (b) R.C. Mahrotra, A. Singh *Organometallic Chemistry (a Unified Approach)*, John Wiley & Sons, New York, **1991**.

after these discoveries, in 1849 EDWARD FRANKLAND, an english student of BUNSEN, succedeed in preparing of simple alkylzinc compounds (**3**).[4]



1 **2** **3a**, R = Me
3b, R = Et

FIGURE 1. Some early organometallic compounds.

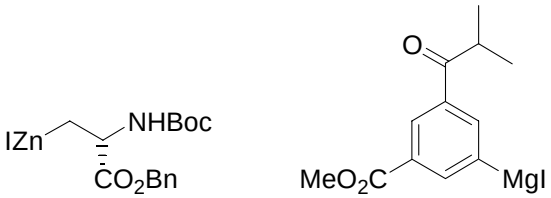
Although the first organometallic compounds were synthesized and characterized prior to 1850, it was not until the turn of the century that their potential as reagents in organic synthesis began to be recognized and exploited. A milestone in this process was the discovery of organomagnesium halides ("Grignard reagents"), in 1899-1901 by BARBIER and GRIGNARD, who received the Nobel Prize in recognition of his studies in 1912.[5] Since their first preparation, these compounds have found ever increasing applications as reactive and versatile intermediates for a wide range of organic transformations, such as cross-coupling reactions, additions to carbonyl groups, conjugate additions, and others.[6,7]

Another episode that is worth mentioning in this short introduction is surely the discovery by PAUSON and KEALY of dicyclopentadienyliron, today universally known as ferrocene,[8,9] which displayed an extraordinary stability and an unconventional "sandwich" structure. Similar compounds have been discribed for a large number of metals, and η^5-bonded C_5H_5 is now a common ligand. One recent application of substituted metallocenes in the field of asymmetric synthesis has been as axially chiral ligands and their use in various metal-catalyzed enantioselective reactions.[10]

In the last few decades, organometallic chemistry has grown at a formidable pace; a better understanding of the structural properties and the reactivity of organometallic compounds has

[4] E. Frankland *Liebigs Ann.* **1849**, *71*, 171.
[5] See, for example: V. Grignard *Ann. Chim. Phys.* **1901**, *24*, 433.
[6] (a) B. J. Wakefield *Organomagnesium Methods in Organic Synthesis*, Academic Press, San Diego, **1995**. (b) *Handbook of Grignard Reagents*, (Eds: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1996**.
[7] The application of Grignard compounds in the synthesis of novel chiral hydroxy oxazolines will be described in section *4.2.1.*
[8] (a) T. J. Kealy, P. L. Pauson *Nature* **1951**, *168*, 1039. For a personal account on the discovery of ferrocene and the determination of its structure, see: (b) P. L. Pauson *J. Organomet. Chem.* **2001**, *637-639*, 3.
[9] For a comprehensive survey, see: *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Materials Science* (Eds: A. Togni, T. Hayashi), Wiley-VCH, Weinheim, **1995**.
[10] The use of metallocene-derived ligands in the enantioselective arylation of aldehydes will be discussed in detail in section *2.2.2.* and following.

opened a range of new possibilities to synthetic chemists. For example, the preparation and use of functionalized organometallics, such as those depicted in Figure 2, is today possible through careful choice of solvent and reaction conditions.[11]



4a **4b**

FIGURE 2. Functionalized organometallics for synthetic applications.

The central role that metal-mediated organic synthesis[12] plays nowadays in the broader field of chemical sciences, from both an academic and industrial perspective, has once again been acknowledged by the awarding of the Nobel Prize in chemistry to WILLIAM S. KNOWLES, RYOJI NOYORI and K. BARRY SHARPLESS in 2001, for their work on asymmetric reductions and oxidations of organic compounds,[13] and to YVES CHAUVIN, ROBERT H. GRUBBS and RICHARD R. SCHROCK in 2005, for their studies in the field of olefin metathesis.[14]

Common features in the work of all these researchers are complexes formed from a metal with organic compounds that function as ligands which are able to catalyze specific transformations with high efficiency and selectivity.

In the case of the 2001 prize, these transformations involved the formation of bonds between a carbon atom and atoms of other elements (hydrogen for reduction, oxygen or nitrogen for oxidation), accompanied by the formation of one or more stereogenic centers in an enantioselective manner. As an example, the famous *Monsanto* process for the synthesis of the rare amino acid L-DOPA (**7**), which had proved useful in the treatment of Parkinson's desease, can be considered (Scheme 1).

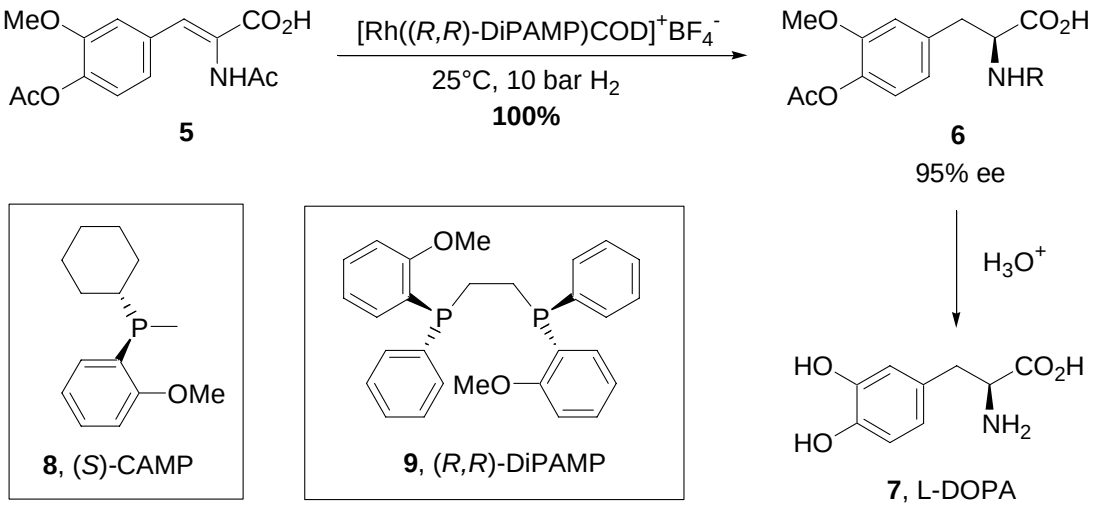
---

[11] (a) R. F. W. Jackson, K. James, M. J. Wythes, A. Wood *J. Chem. Soc., Chem. Commun.* **1989**, 644. (b) P. Knochel, F. F. Kneisel *Synlett* **2002**, 1799. For a general reference, see: (c) *Handbook of Functionalized Organometallics* (Ed: P. Knochel), Wiley-VCH, Weinheim, **2005**.

[12] (a) *Transition Metals for Organic Synthesis*, 2nd Ed. (Eds: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**. For many useful synthetic procedures, see: (b) *Organometallics in Synthesis*, 2nd Ed. (Ed: M. Schlosser), John Wiley & Sons, Chichester, **2002**.

[13] (a) P. Ahlberg *Advanced Information on the Nobel Prize in Chemistry 2001*, Kungl. Vetenskapakademien, (The Royal Swedish Academy of Science), **2001**. For the Nobel lectures, see: (b) W. S. Knowles *Angew. Chem.* **2002**, *114*, 2097; *Angew. Chem. Int. Ed.* **2002**, *41*, 1998. (c) R. Noyori *Angew. Chem.* **2002**, *114*, 2109; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008. (d) K. B. Sharpless *Angew. Chem.* **2002**, *114*, 2126; *Angew. Chem. Int. Ed.* **2002**, *41*, 2024.

[14] (a) P. Ahlberg *Advanced Information on the Nobel Prize in Chemistry 2005*, Kungl. Vetenskapakademien, (The Royal Swedish Academy of Science), **2005**. For the Nobel lectures, see: (b) http://www.nobelprize.org/chemistry/laureates/2005 and related links.

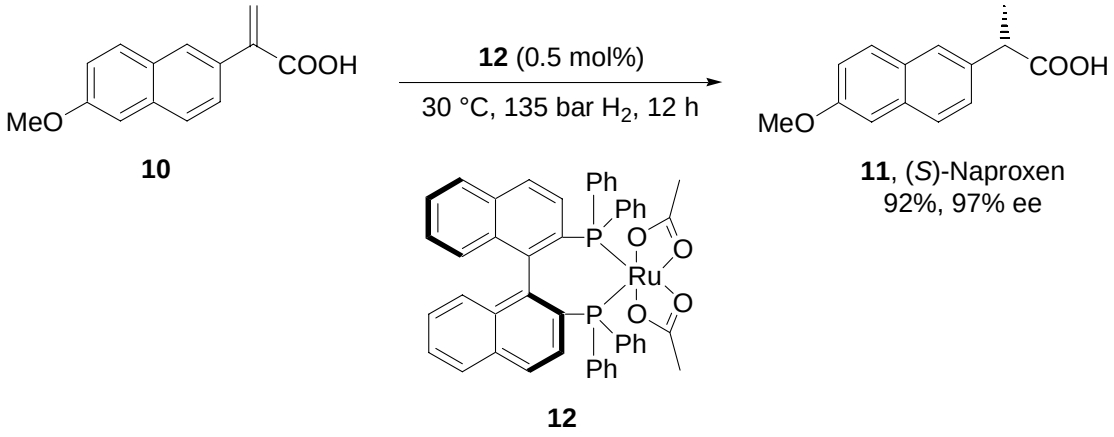


SCHEME 1. The *Monsanto* synthesis of L-DOPA.

First, KNOWLES' monodentate ligand (*S*)-CAMP (**8**)[15] was used in the process, which constitutes the first commercialized catalytic enantioselective synthesis employing a chiral transition metal complex.[16] The conversion of **5** into **6** was later further improved by the use of the bidentate species (*R,R*)-DiPAMP (**9**).[17] Notably, both ligands **8** and **9** possess stereogenic centers on the ligating phosphorous atoms; the proximity of the chiral environment to the metal center can thus be considered as the basis for the effectiveness of these species in inducing an enantioselective transformation.

Equally important was the introduction by NOYORI of the ruthenium / BINAP (an axially chiral ligand) catalytic system, which is able to efficiently promote a wide range of enantioselective reductions, which often require only small adjustments to achieve high enantioselectivities.[18] As an example, the reduction of the α,β-unsaturated carboxylic acid **10**, which constitutes the key step for the synthesis of the anti-inflammatory drug Naproxen® (**11**), is shown in Scheme 2.[19]

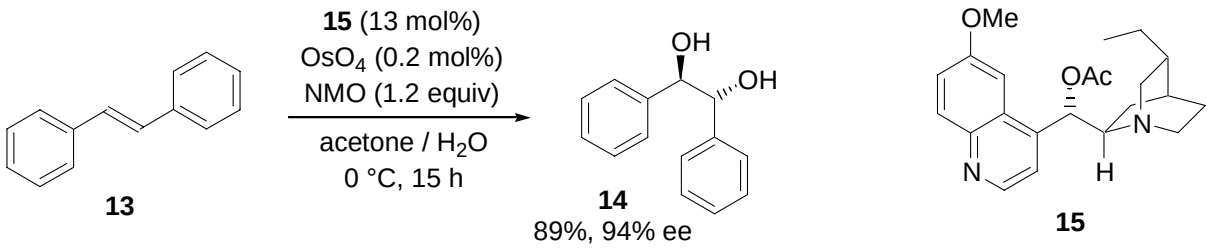
[15] (a) W. S. Knowles, M. J. Sabacky *J. Chem. Soc., Chem. Commun.* **1968**, 1445. Review: (b) W. S. Knowles *Acc. Chem. Res.* **1983**, *16*, 106.
[16] W. S. Knowles, M. J. Sabacky, B. D. Vineyard *J. Chem. Soc. Chem. Commun.* **1972**, 10.
[17] B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachmann, O. J. Weinkauff *J. Am. Chem. Soc.* **1977**, *99*, 5946.
[18] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori *J. Am. Chem. Soc.* **1980**, *102*, 7932.
[19] T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori *J. Org. Chem.* **1987**, *52*, 3174.



SCHEME 2. Catalytic enantioselective synthesis of (*S*)-Naproxen®.

This reaction, unlike the Rh(I) catalyzed olefin hydrogenation, proceeds *via* a metal monohydride mechanism. Processes relying on the use of the Ru / BINAP catalytic systems are also used for the industrial production of compounds such as (*R*)-1,2-propanediol and a chiral azetidinone for carbapenem synthesis.

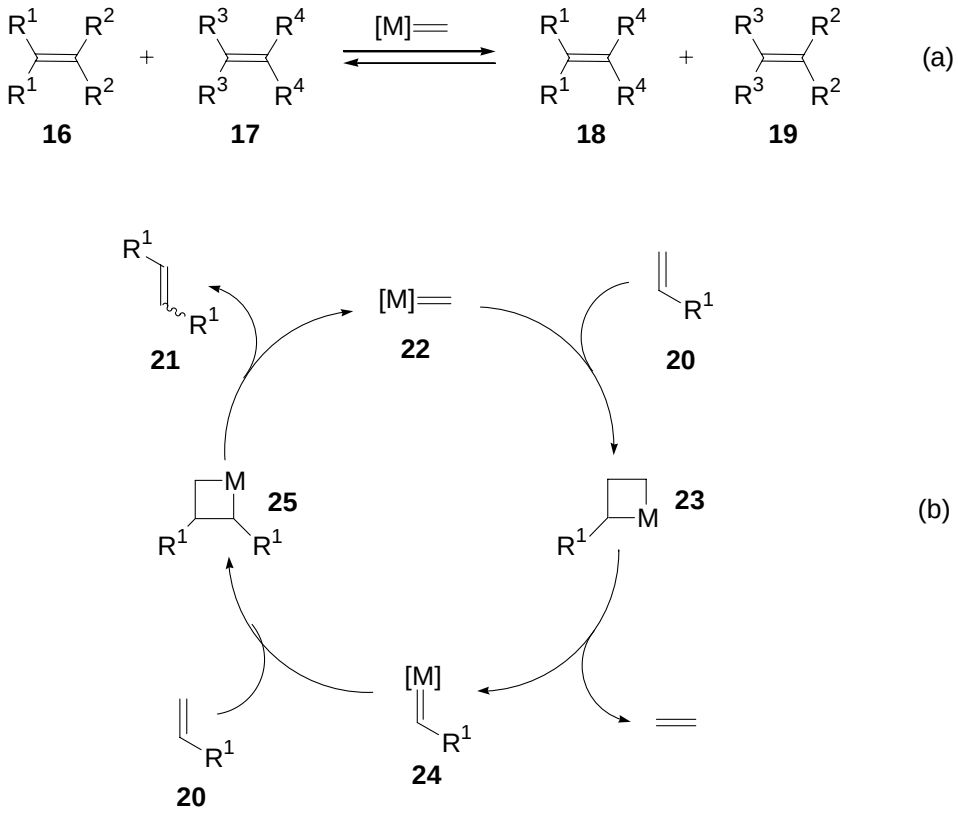
Concurrent with the progress in catalytic asymmetric hydrogenations, SHARPLESS developed chiral catalysts for very important oxidation reactions. The epoxidation reaction discovered in 1980 by SHARPLESS and KATSUKI employs titanium(IV) tetraisopropoxide, *tert*-butyl hydroperoxide and enantiomerically pure dialkyl tartrate to promote the epoxidation of allylic alcohols with excellent enantioselectivity.[20] A set of specific rules allows prediction of which enantiomer of the product will be formed preferentially. Some years later, SHARPLESS introduced another important oxidative transformation, the OsO_4-catalyzed asymmetric dihydroxylation of olefins, in which the chiral ligand is a naturally occurring *Cinchona* alkaloid (and after further optimization, a derivative thereof).[21] An example is shown in Scheme 3.



SCHEME 3. SHARPLESS' asymmetric dihydroxylation.

[20] (a) T. Katsuki, K. B. Sharpless *J. Am. Chem. Soc.* **1980**, *102*, 5976. For an interesting personal account, see: (b) M. Rouhi *Chem. Eng. News* **2003**, *81(43)*, 42.
[21] (a) E. N. Jacobsen, I. Markó, W. S. Mungall, G. Schröder, K. B. Sharpless *J. Am. Chem. Soc.* **1988**, *110*, 1968. For a review, see: (b) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless *Chem. Rev.* **1994**, *94*, 2483.

In the case of the 2005 Nobel prize the recombination of carbon-carbon double bonds was instead at the heart of the process awarded. In this olefin methatesis process, carbon-carbon bonds are broken and formed under the influence of a metal catalyst. When the two alkenes **16** and **17** are subjected to the reaction conditions in the presence of a metal carbene, two new compounds **18** and **19** are formed (Scheme 4a).[22]



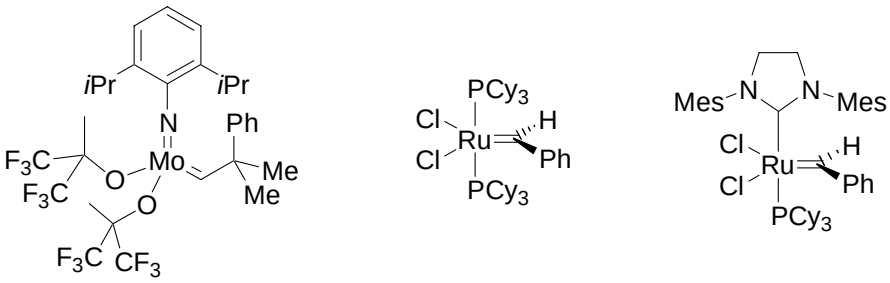
SCHEME 4. Generic olefin metathesis reaction (a) and its mechanism according to CHAUVIN (b).

In Scheme 4b the CHAUVIN catalytic cycle is shown, in the case of the dimerization of a terminal alkene. The metal alkylidene **22** (the active catalyst) forms with olefin **20** a metallacyclobutane intermediate **23**. Cleavage of the intermediate causes the elimination of ethylene (in this simplified picture, the formation of a gas constitutes the driving force of the reaction) and the formation of a new metal alkylidene **24**. Repetition of the same two steps leads to the formation of **21** (the product of the reaction) and to the regeneration of **22**, which is able to enter a new catalytic cycle.[23]

An understanding of the mechanism helped in the design of new and more effective well-defined catalysts for this reaction, mostly thanks to the efforts of the groups led by SCHROCK and GRUBBS.

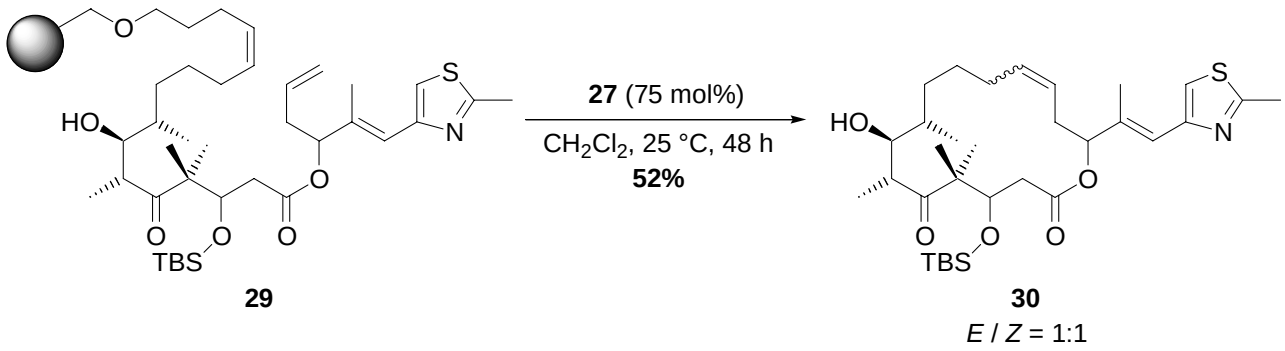
[22] (a) *Handbook of Metathesis* (Ed: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**. For an excellent overview, see: (b) K. C. Nicolaou, S. A. Snyder *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, **2003**, p. 163.
[23] (a) J.-L. Hérisson, Y. Chauvin *Makromol. Chem.* **1971**, *141*, 161. (b) J.-P. Soufflet, D. Commereuc, Y. Chauvin *C. R. Acad. Sci. Sér. C* **1972**, *276*, 169.

The structures of these, now commercially available, compounds are shown in Figure 3. In Scheme 5 the application of catalyst **27** in NICOLAOU's solid-phase total synthesis of epothilone A, a compound possessing anticancer activity, is depicted.[24]



26, SCHROCK | **27**, GRUBBS (1st generation) | **28**, GRUBBS (2nd generation)

FIGURE 3. Catalysts for olefin metathesis.



SCHEME 5. Use of a "cyclorelease *via* olefin metathesis" approach in NICOLAOU's solid-phase total synthesis of epothilone A.

It should be noted that in the reaction in Scheme 5, the formation of a macrocycle *via* olefin metathesis (*ring closing metathesis* or RCM) is accompanied by cleavage from the solid support, thus combining two fundamental steps in a single synthetic operation.

Finally, it is worth mentioning that an enantioselective version of the metathesis reaction has been developed, in which the chiral catalyst consists of a modified version of **26**, where the hexafluoroisopropanolate ligands have been replaced by an axially chiral binaphtholato unit. Ee's

[24] K. C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel *Nature* **1997**, *387*, 268.

superior to 98% have been obtained in the desymmetrization of prochiral norbornene derivatives by ring-opening with styrene.[25]

In the previous pages, the discussion of some outstanding examples taken from the work of the 2001 and 2005 Nobel laureates provided the opportunity to show the enormous potential of organometallic compounds and transition metal complexes as tools for synthetic chemistry.

It is surely true that organometallics are able to effect transformations, such as olefin metathesis, that would otherwise be impossible in their absence, i.e. are not carried out in nature. In many other cases, processes that are sluggish under "classic" or purely "organic" conditions can be dramatically accelerated by the use of metal promoters or catalysts.

According to TROST, a key factor in synthesis is *efficiency*.[26] Synthetic efficiency can be divided in two sub-categories, *atom economy*[27] and *selectivity*.[28]

An atom-economic reaction is a process in which as many as possible of the atoms of the reactants should end up in the product with the ideal being the product as simply the sum of the reactants. On the other hand, selectivity can be defined as the ability of a reaction to discriminate between different possible pathways. Among the different kinds of selectivity, *chemo-, regio-, diastereo-*, and *enantioselectivity*, the latter, i.e. the ability to control the absolute stereochemistry of a reaction, has proven to be the most challenging to achieve in most cases. An enantioselective reaction in which the chiral inducing agent is needed only catalytically, and that fulfills the requirement of atom economy, can be considered the ideal goal of every synthetic endeavour.

Clearly, thanks to developments in organometallic chemistry, much has been done towards that objective and many enantioselective metal catalysts[29] have been found that can match, or even surpass, the efficiency of enzymes, nature's catalysts.[30]

Nevertheless, the ideal yet remains beyond reach and, using TROST's words, "*Opportunities to invent new reactions catalyzed by transition metals to solve problems of selectivity and to do so with as much atom economy as possible appear infinite.*".[26]

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[25] (a) S. L. Aeilts, D. R. Cefalo, P. J. Bonetatebus Jr., J. H. Houser, A. H. Hoveyda, R. R. Schrock *Angew. Chem* **2001**, *113*, 1500; *Angew. Chem. Int. Ed.* **2001**, *40*, 1452. (b) X. Teng, D. R. Cefalo, R. R. Schrock, A. H. Hoveyda *J. Am. Chem. Soc.* **2002**, *124*, 10779. For a review on enantioselective olefin-metathesis reactions, see: (c) R. R. Schrock, A. H. Hoveyda *Angew. Chem.* **2003**, *115*, 4741; *Angew. Chem. Int. Ed.* **2003**, *42*, 4592.
[26] B. M. Trost in ref.12a, Chap. 1.1, p. 3.
[27] B. M. Trost *Science* **1991**, *254*, 1471.
[28] B. M. Trost *Science* **1983**, *219*, 245.
[29] For extenstive overviews, see (a) R. Noyori *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**. (b) *Comprehensive Asymmetric Catalysis* (Eds: E. N. Jacobsen, A. Pfalz, H. Yamamoto), Springer, Berlin, **1999**. (c) *Catalytic Asymmetric Synthesis*, 2nd Ed. (Ed: I. Ojima), Wiley-VCH, New York, **2000**. (d) Ref. 12a.
[30] For general references, see: (a) *Enzyme Catalyst in Organic Synthesis* (Eds: K. Drauz, H. Waldmann), Wiley-VCH, Weinheim, **1995**. (b) K. Faber *Biotransformations in Organic Chemistry*, 2nd Ed., Springer, Heidelberg, **1995**.

1.2. Zinc-Mediated Organic Reactions

Applications of organozinc chemistry in organic synthesis has increased in importance over the years. As already mentioned, organozinc compounds were discovered by FRANKLAND more than 150 years ago,[4,31] but despite this, their advantageous exploitation for selective carbon-carbon bond forming reactions with high generality and wide scope has only been shown in recent years.

Organozinc species are versatile nucleophiles and, thanks to their lower reactivity in comparison to organolithium and organomagnesium compounds, are easier to prepare and display a superior functional group tolerance.[32] Moreover, the presence of low-lying orbitals facilitates transmetallation to other metals (Cu, Ni, Pd etc.), which provides the basis for a rich synthetic chemistry with organozinc compounds. These favourable characteristics account for the numerous applications that organozinc compounds have found in modern organic synthesis.[33]

Among the various examples reported in the literature, transition metal-catalyzed cross-coupling reactions (*Negishi couplings*),[34] also with C(sp^3) electrophiles,[35] enantioselective copper-[36] and nickel-catalyzed[37] conjugate additions to enones, cyclopropanations (*Simmons-Smith reactions*),[38] epoxidations[39] and reactions of zinc-enolates with various electrophiles (*Reformatsky-type reactions*)[40] should be mentioned.

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[31] For a contribution on the history of early organozinc chemistry, see: D. Seyferth *Organometallics* **2001**, *20*, 2940.

[32] Organozinc compounds react nevertheless violently with water and should be manipulated under an inert atmosphere of Ar or N_2. FRANKLAND himself described that when he first prepared dimethylzinc in July 1849 in BUNSEN's laboratories, he was testing the action of water on the residue in the tube used for the synthesis and suddenly a greenish-blue flame several feet long shot out of the tube. BUNSEN thought that was due to cacodyl and warned FRANKLAND that he was "already irrevocably poisoned". Fortunately, things did not turn out to be as bad, and FRANKLAND lived, and researched, for many years.

[33] For leading references: (a) P. O'Brien in ref. 3a, p.175. (b) E. Erdik *Organozinc Reagents in Organic Synthesis*, CRC Press, Boca Raton, **1996**. (c) *Organozinc Reagents: a Practical Approach* (Eds: P. Knochel, P. Jones), Oxford University Press, New York, **1999**. (d) A. Jacobi von Wangelin, M. U. Frederiksen in ref. 12a, Chap. 3.7, p. 519.

[34] (a) E. Negishi *Acc. Chem. Res.* **1982**, *15*, 340. (b) E. Negishi, X. Zeng, Z. Tan, M. Qian, Q. Hu, Z. Huang in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed. (Eds: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **2004** (c) For a review on Negishi coupling reactions with aryl chlorides, see: (b) G. C. Fu, A. F. Littke *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

[35] (a) R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel *Angew. Chem.***1998**, *110*, 2512; *Angew. Chem. Int. Ed.* **1998**, *37*, 2387. (b) R. Giovannini, T. Stüdemann , A. Devasagayaraj, G. Dussin, P. Knochel *J. Org. Chem.* **1999**, *64*, 3544. (c) D. J. Cárdenas *Angew. Chem.* **2003**, *115*, 398; *Angew. Chem. Int. Ed.* **2003**, *42*, 384.

[36] First example: (a) A. Alexakis, S. Mutti, J.-F. Normant *J. Am. Chem. Soc.* **1991**, *113*, 6332. Review: (b) B. L. Feringa *Acc. Chem. Res.* **2000**, *33*, 346.

[37] C. Bolm, M. Ewald, M. Felder *Chem. Ber.* **1992**, *125*, 1205.

[38] First report: (a) H. E. Simmons, R. D. Smith *J. Am. Chem. Soc.* **1958**, *80*, 5323. For a comprehensive review, see: (b) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette *Chem. Rev.* **2003**, *103*, 977.

[39] (a) D. Enders, J. Zhu, G. Raabe *Angew. Chem.* **1996**, *108*, 1827; *Angew. Chem. Int. Ed.* **1996**, *35*, 1725. (b) D. Enders, L. Kramps, J. Zhu *Tetrahedron Lett.* **1998**, *9*, 3959.

[40] (a) A. Fürstner in ref. 33c, p. 287. For recent examples, see: (b) A. Ojida, T. Yamano, N. Taya, A. Tasaka *Org. Lett.* **2002**, *4*, 3051. (c) E.-k. Shin, H. J. Kim, Y. Kim, Y. Kim, Y. S. Park *Tetrahedron Lett.* **2006**, *47*, 1933. (d) R. J.

The most widely studied and applied transformation involving organozinc species is their enantioselective addition to carbon-heteroatom (typically oxygen or nitrogen) double bonds in the presence of a suitable ligand.[41] In the next chapter some of the most important aspects of this process will be discussed, including reactions of $C(sp^3)$- and $C(sp^2)$-Zn nucleophiles. Moreover, the addition of organometallic C(sp) nucleophiles to C=X (X = O, N) electrophiles will also be described.

Kloetzing, T. Thaler, P. Knochel *Org. Lett.* **2006**, *8*, 1125. For a recent three-component, asymmetric aza-Reformatsky reaction, see: (e) P. G. Cozzi, E. Rivalta *Angew. Chem.* **2005**, *117*, 3666; *Angew. Chem. Int. Ed.* **2005**, *44*, 3600.

[41] For comprehensive reviews, see: (a) D. A. Evans *Science* **1988**, *240*, 420. (b) R. Noyori, M. Kitamura *Angew. Chem.* **1991**, *103*, 34; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49. (c) K. Soai, S. Niwa *Chem. Rev.* **1992**, *92*, 833. (d) Ref. 29a, Chap. 5. (e) K. Soai, T. Shibata in ref. 29b, Chap. 26.1, p. 911. (f) L. Pu, H.-B. Yu *Chem. Rev.* **2001**, *101*, 757. For a recent review about titanium-catalyzed additions to aldehydes, see: (g) P. J. Walsh *Acc. Chem. Res.* **2003**, *36*, 739.

2. Addition of Organometallic Reagents to Carbon-Heteroatom Double Bonds

2.1. Addition of Alkylzinc Reagents to Carbonyl Compounds and Imines

As already mentioned, organozinc compounds are, in general, far less reactive towards electrophiles than their lithium or magnesium counterparts. The direct addition of organozinc reagents alone to aldehydes is extremely sluggish and often affected by side-reactions, such as reduction.[42]

On the other hand, a clear reaction of diethylzinc with benzaldehyde was observed by MUKAIYAMA and co-workers when the reaction was performed in the presence of chiral amino alcohol **31** derived from (*S*)-proline, although the addition proceeded with no asymmetric induction.[43] The reason of the observed change in reactivity may be explained as follows. Dimethylzinc (structure **32**), for example, has a linear geometry with a 1.95 Å bond length between carbon and zinc. When a ligand, such as *N*,*N'*,*N''*-trimethyl-1,3,5-hexahydrotriazine (**33**), is added to the zinc compound an X-ray analysis of the corresponding 1:2 complex **34** reveals that the compound has a tetrahedral geometry about the zinc atom with a 145° carbon-zinc-carbon bond angle (Figure 4).[44] Moreover, the bonds between zinc and carbon become longer (1.98 Å). This means that the energy of these bonds decreases and, as a consequence, the nucleophilicity of the methyl group increases. Accordingly, 5 mol% of *N*,*N*,*N'*,*N'*-tetramethylethylendiamine (TMEDA), which is also able to form complexes with dialkylzinc compounds, catalyzes the reaction between diethylzinc and aldehydes to afford the corresponding alcohols quantitatively.[45]

Obviously, if a chiral ligand is used instead of TMEDA to coordinate the dialkylzinc compound, an asymmetric induction in the transition state of the reaction leading to optically-active products can be expected as a consequence of coordination. Moreover, the absence of a non-catalyzed background reaction should help to obtain high enantiomeric excesses.

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[42] B. Marx, E. Henry-Basch, P. Freon *C. R. Acad. Sci., Sér. C* **1967**, *264*, 527.
[43] (a) T. Sato, K. Soai, K. Suzuki, T. Mukaiyama *Chem. Lett.* **1978**, 601. (b) T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, K. Suzuki *J. Am. Chem. Soc.* **1979**, *101*, 1455.
[44] M. B. Hursthouse, M. Montevaili, P. O'Brien, J. R. Walsh, A. C. Jones *J. Mater. Chem.* **1991**, *1*, 139.
[45] K. Soai, M. Watanabe, M. Koyano *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2124.

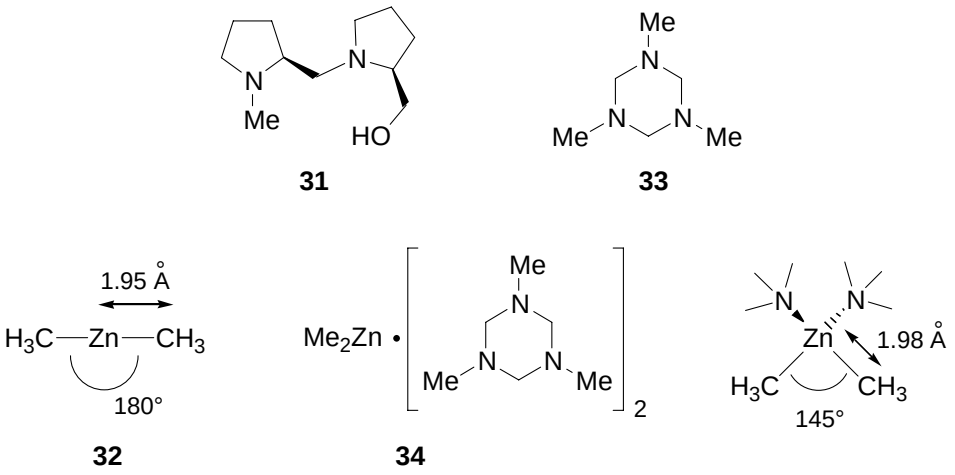
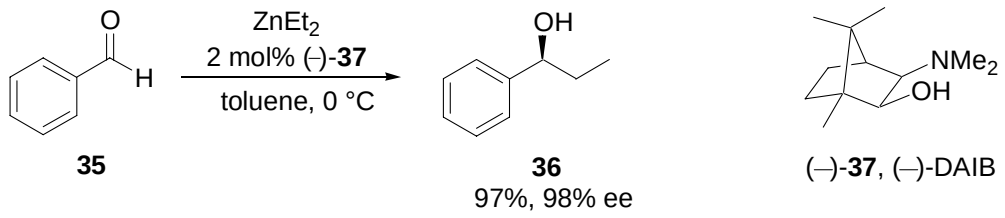


FIGURE 4. Effect of ligands on the coordination chemistry of Me_2Zn.

The first enantioselective addition of diethylzinc to benzaldehyde was reported in 1984 by OGUNI and ONI, who prepared 1-phenylpropanol (**36**) with 49% ee in the presence of the chiral amino alcohol (*S*)-leucinol.[46] The first ligand that exhibited high enantioselectivity in this process was NOYORI's (−)-3-*exo*-dimethylaminoisoborneol [(−)-DAIB, **37**]. As depicted in Scheme 6, 2 mol% of this amino alcohol proved sufficient to obtain alcohol **36** in 97% yield with 98% ee.[47]

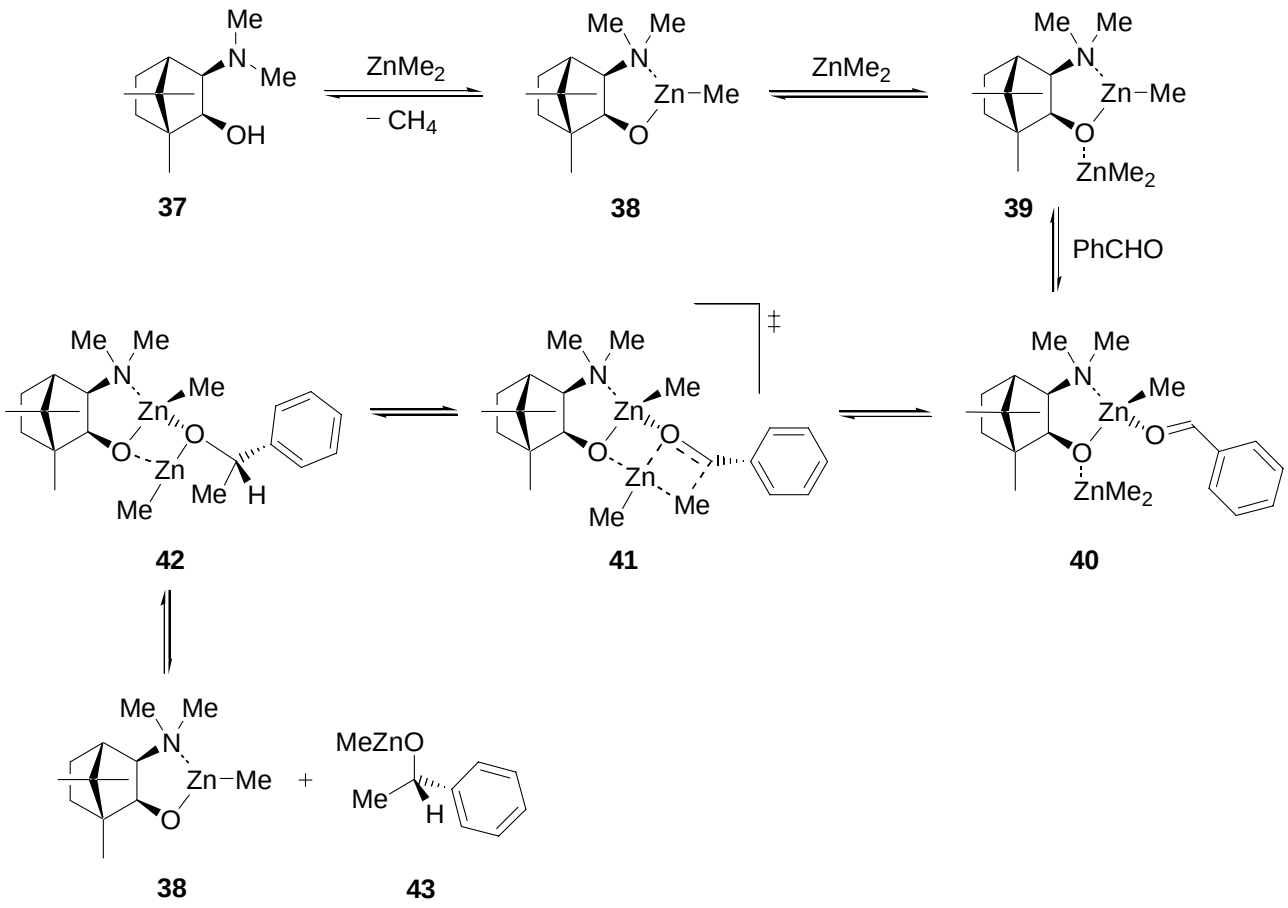


SCHEME 6. (−)-DAIB-catalyzed diethylzinc addition to benzaldehyde by NOYORI.

In the years following its discovery, the mechanism of the reaction was extensively studied by NOYORI[48] as well as by other researchers,[49] and the following picture is now commonly accepted as the means by which the process occurs (Scheme 7). In the first step the amino alcohol reacts with dimethylzinc to form complex **38**, which is unable to react directly with the aldehyde, and constitutes the actual catalyst of the reaction. Indeed, for the methylation to occur, another molecule

[46] N. Oguni, T. Oni *Tetrahedron Lett.* **1984**, *25*, 2823.
[47] M. Kitamura, S. Suga, K. Kawai, R. Noyori *J. Am. Chem. Soc.* **1986**, *108*, 6071.
[48] (a) M. Kitamura, S. Okada, S. Suga, R. Noyori *J. Am. Chem .Soc.* **1989**, *111*, 4028. (b) M. Yamakawa, R. Noyori *J. Am. Chem. Soc.* **1995**, *117*, 6327. (c) M. Kitamura, H. Oka, R. Noyori *Tetrahedron* **1999**, *55*, 3605. (d) M. Yamakawa, R. Noyori *Organometallics* **1999**, *18*, 128.
[49] (a) B. Goldfuss, K. N. Houk *J. Org. Chem.* **1998**, *63*, 8998. (b) B. Goldfuss, M. Steigelmann, S. I. Khan, K. N. Houk *J. Org. Chem.* **2000**, *65*, 77. (c) T. Rasmussen, P.-O. Norrby *J. Am. Chem. Soc.* **2001**, *123*, 2464.

of dimethylzinc is required, which will initially coordinate to the alkoxyzinc group (**39**). Through the coordination the second dimethylzinc molecule is activated for the addition, just as described above. Coordination of a molecule of substrate leads to complex **40** and the activated methyl group is transferred *via* transition state **41** to form complex **42**. Liberation of the product as zinc alkoxide (**43**) regenerates complex **38**, which may undergo another catalytic cycle.



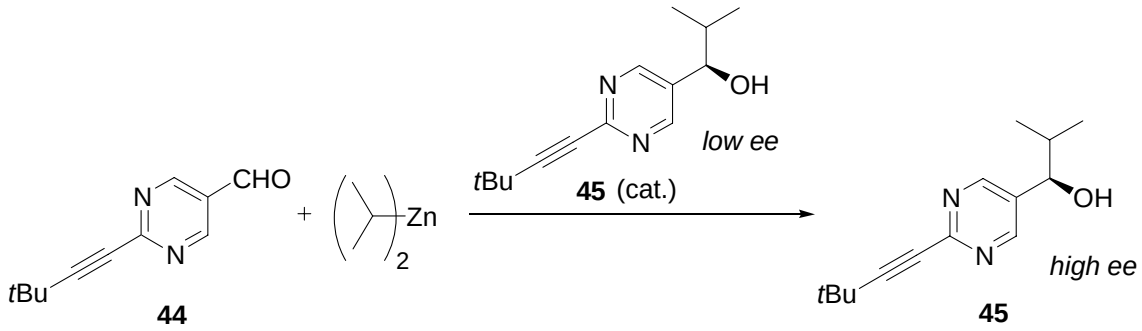
SCHEME 7. Mechanism of the (−)-DAIB-catalyzed diethylzinc addition to benzaldehyde.

After these first reports, an impressive number of publications concerning this reaction have appeared in the literature, so that today the diethylzinc addition to aldheydes is among the standard test reactions used to evaluate the potential of a new organic molecule to serve as ligand for asymmetric catalysis.[50]

[50] For recent examples, see: (a) A. L. Braga, D. S. Lüdtke, L. A. Wessjohann, M. W. Paixão, P. H. Schneider *J. Mol. Cat. A* **2005**, *229*, 47. (b) G. Blay, I. Fernandez, A. Marco-Alexandre, J. R. Pedro *Tetrahedron: Asymmetry* **2005**, *16*, 1207. (c) M.-J. Jin, Y.-M. Kim, K.-S. Lee *Tetrahedron Lett.* **2005**, *46*, 2695. (d) P. Västilä, I. M. Pastor, H. Adolfsson *J. Org. Chem.* **2005**, *70*, 2921. (e) Y. Hari, T.Aoyama *Synthesis* **2005**, 583. (f) A. L. Braga, E. F. Alves, C. C. Silveira, G. Zeni, H. R. Appelt, L. A. Wessjohann *Synthesis* **2005**, 588. (g) M.-J. Jin, Y.-M. Kim *Bull. Kor. Chem. Soc.* **2005**, *26*, 215. (h) G. Ricci, R. Ruzziconi *Tetrahedron: Asymmetry* **2005**, *16*, 1817. (i) H. S. Eriksen, S. C. Oyaga, D. C. Sherrington, C. L. Gibson *Synlett* **2005**, 1235. (j) Y.-F. Kang, L. Liu, R. Wang, M. Ni, Z. Han *Synth. Commun.* **2005**, *35*, 1819. (k) B. T. Cho, S. K. Kang *Bull. Kor. Chem. Soc.* **2005**, *26*, 1101. (l) A. Johansson, E. Wingstrand, M.

In some cases, the amino-alcohol-catalyzed diethylzinc addition to aldehydes can exhibit very strong, positive *non-linear effects* (+-NLE): in other words, a catalyst with a modest enantiomeric excess is able to afford products possessing a much higher ee.[51] This is the case, for example, when (−)-DAIB is used as a ligand.[52] Although the origin of this phenomenon is not completely clear, a possible explanation is provided by the formation, in solution, of catalytically-inactive dimers of the amino alcohol. In solution both the (*R*)- and the (*S*)-enantiomers of the amino alcohol are present, such that their interactions can lead to the formation of *homodimers* (*R*)-(*R*) and (*S*)-(*S*) or of *heterodimers* (*R*)-(*S*). If the latter species are thermodynamically favoured, the net effect will be an increase in the enantiomeric excess of the (catalytically-active) monomer in solution and, therefore, of the product.

Some alkylzinc additions to aldehydes have been reported to display an even more fascinating behaviour: they have been described as *autocatalytic reactions*. An impressive example was reported by SOAI and coworkers in 1995 (Scheme 8).[53] The "Soai reaction" is an example of an enantioselective, autocatalytic process which employs a catalyst of very low enantiomeric excess to ultimately yield the catalyst itself (which is also the product of the reaction) with a very high level of enantioselectivity.



SCHEME 8. Autocatalytic dialkylzinc addition by SOAI.

Hakansson *J. Organomet. Chem.* **2005**, *690*, 3846. (m) Y. Kasashima, N. Hanyu, T. Aoki, T. Mino, M. Sakamoto, T. Fujita *J. Oleo Sci.* **2005**, *54*, 495. (n) L. Xu, X. Shen, C. Zhang, K. Mikami *Chirality* **2005,** *17*, 476. (o) Q.-S. Guo, B. Liu, Y.-N. Lu, F.-Y. Jiang, H.-B. Song, J.-S. Li *Tetrahedron: Asymmetry* **2005**, *16*, 3667. (p) M.-C. Wang, X.-H. Hou, C.-L. Xu, L.-T. Liu, G.-L. Li, D.-K. Wang *Synthesis* **2005**, 3620. (q) X.-P. Hui, C.-A. Chen, H.-M. Gau *Chirality* **2005**, *17*, 51.

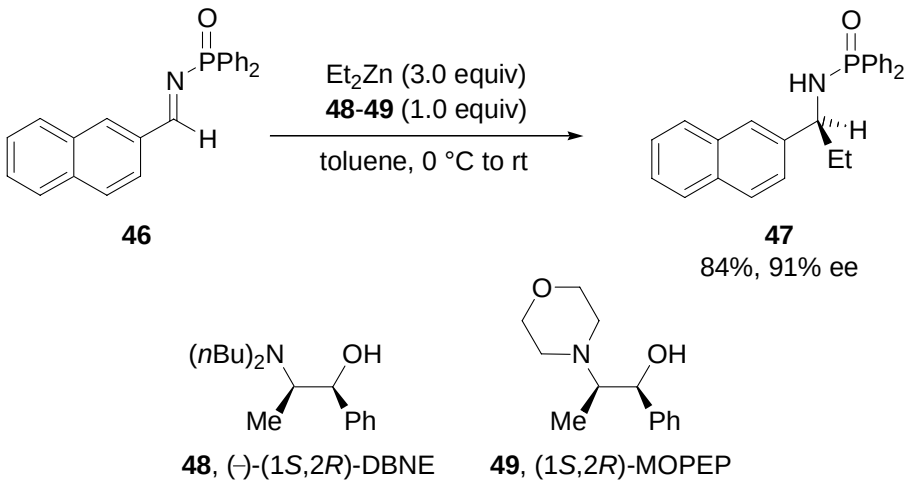
[51] For reviews, see: (a) H. B. Kagan, T. O. Luukas in ref. 29b, p. 101. (b) H. B. Kagan *Adv. Synth. Catal.* **2001**, *343*, 227.

[52] M. Kitamura, S. Suga, H. Oka, R. Noyori *J. Am. Chem. Soc.* **1998**, *120*, 9800.

[53] First publication: (a) K. Soai, T. Shibata, H. Morioka, K. Choji *Nature* **1995**, *378*, 767. For a recent review, see: (b) K. Soai, I. Sato *Chirality* **2002**, *14*, 548. (c) For an excellent overview of the Soai reaction, providing also a possible explanation of the phenomenon see: D. G. Blackmond *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5732, and references therein.

The asymmetric addition of organometallic reagents to the C=N double bond has, for a long time been quite under-developed in comparison with the corresponding addition to aldehydes.[54] This has been primarily due to the poor electrophilicity of the azomethine moiety relative to the carbonyl functionality, because of the tendency of imines to undergo deprotonation instead of alkylation under basic (nucleophilic) conditions.

While strong organolithium reagents were initially used as nucleophiles in the reaction, the first report on the use of milder nucleophilic dialkylzinc compounds was published by KATRITZKY in 1992.[55] In this study, *N*-(amidobenzyl)benzotriazoles, which acted as masked *N*-acylimines, were alkylated with diethylzinc in the presence of chiral (−)-*N*,*N*-dibutylnorephedrine [(−)-(1*R*,2*S*)-DBNE, **48**] to give the corresponding products with up to 76% ee. In the same year, SOAI reported the first highly enantioselective (up to 91% ee) zinc-mediated alkylation of *N*-diphenylphosphinoylimines (Scheme 9) using a stoichiometric amount of the chiral amino alcohol (1*S*,2*R*)-MOPEP (**49**).[56]



SCHEME 9. Asymmetric alkylation of *N*-diphenylphosphinoylimines by SOAI.

Since these first reports, this transformation has been extensively studied and excellent results have been described in the literature. Most of the reported protocols employ a transition metal

[54] For excellent reviews, see: (a) D. Enders, U. Reinhold *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (b) S. E. Denmark, O. J.-C. Nicaise in ref. 29b, Chap. 26.2, p. 923. (c) R. Bloch *Chem. Rev.* **1998**, *98*, 1407. (d) S. Kobayashi, H. Ishitani *Chem. Rev.* **1999**, *99*, 1069.
[55] A. R. Katritzky, P. A. Harris *Tetrahedron: Asymmetry* **1992**, *3*, 437.
[56] (a) K. Soai, T. Hatanaka, T. Miyazawa *J. Chem. Soc., Chem. Commun.* **1992**, 1097. For successive studies, see (b) T. Hayase, Y. Inoue, T. Shibata, K. Soai *Tetrahedron: Asymmetry* **1996**, *7*, 2509. (c) T. Suzuki, N. Narisada, T. Shibata, K. Soai *Tetrahedron: Asymmetry* **1996**, *7*, 2519.

complex as the catalyst in the presence of an excess of a dialkylzinc reagent,[57,58,59,60] but very high ee's have also been obtained with the organozinc reagent alone, in the presence of chiral *N,O*-ligands.[61]

When prochiral ketones are used as electrophiles in the place of aldehydes or aldimines and reacted with organozinc nucleophiles, the products stemming from the reaction are tertiary alcohols possessing a quaternary stereogenic center. The enantioselective construction of such units represents one of the most challenging areas of research in the field of organic synthesis.[62]

While there are literally hundreds of catalysts able to promote the asymmetric alkylation of aldehydes,[41,50] only a handful of systems are able to promote additions to ketones. This discrepancy is mostly due to the lower reactivity of ketones in comparison to their aldehyde counterparts, and to the reduced ability of chiral catalysts to discriminate between the two enantiotopic faces of a prochiral ketone, which bears substituents of similar steric hindrance attached to the carbonyl group.

The first catalytic asymmetric alkylation of ketones by means of organozinc reagents was reported by YUS and co-workers in 1998.[63] In 2002, this research group and that of WALSH independently described the use of camphorsulfonamide-derived diol **52** in combination with Ti(*i*PrO)$_4$ as a catalyst for the addition of alkylzinc reagents to aryl-alkyl ketones and α,β-unsaturated ketones.[64,65] Excellent enantiomeric excesses (up to 99%) could be obtained with a catalyst loading of 2-10 mol%, although the titanium alkoxide had to be used in stoichiometric amounts (Scheme 10).

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[57] Zr: (a) J. R. Porter, J. F. Traverse, A. H. Hoveyda, M. L. Snapper *J. Am. Chem. Soc.* **2001**, *123*, 10409. (b) L. C. Akullian, M. L. Snapper, A. H. Hoveyda *Angew. Chem.* **2003**, *115*, 4376; *Angew. Chem. Int. Ed.* **2003**, *42*, 4244.

[58] Cu: (a) T. Soeta, K. Nagai, H. Fujihara, M. Kuriyama, K. Tomioka *J. Org. Chem.* **2003**, *68*, 10864. (b) A. A. Boezio, A. B. Charette *J. Am. Chem. Soc.* **2003**, *125*, 1692. (c) A. A. Boezio, J. Pytkowicz, A. Côté, A. B. Charette *J. Am. Chem. Soc.* **2003**, *125*, 14260. (d) A. A. Boezio, A. Côté, A. B. Charette *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405. (e) J.-N. Desrosiers, A. Côté, A. B. Charette *Tetrahedron* **2005**, *61*, 6186. (f) A. Côté, A. B. Charette *J. Org. Chem.* **2005**, *70*, 10864. (g) C. Wang, M. Shi *J. Org. Chem.* **2003**, *68*, 6229.

[59] Zn: H. Zhang, H. Liu, X. Cui, A. Mi, Y. Jiang, L. Z. Gong *Synlett* **2005**, 615.

[60] Rh: T. Nishimura, Y. Yasuhara, T. Hayashi *Org. Lett.* **2006**, *8*, 979.

[61] (a) C. Jimeno, K. S. Reddy, L. Solà, A. Moyano. M. A. Pericàs, A. Riera *Org. Lett.* **2000**, *2*, 3157. Use of 1-sulfinylamines as masked *N*-formylimines: (b) S. Dahmen, S. Bräse *J. Am. Chem. Soc.* **2002**, *124*, 5940. (c) H.-L. Zhang, F. Jiang, X.-M. Zhang, X. Cui, L. Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu *Chem. Eur. J.* **2004**, *10*, 1481.

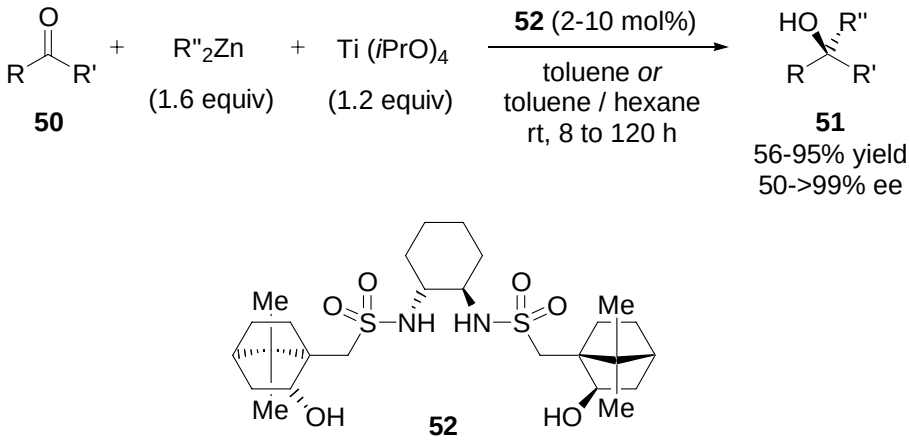
[62] Reviews: (a) E. J. Corey, A. Guzman-Perez *Angew. Chem.* **1998**, *110*, 402; *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (b) J. Christoffers, A. Mann *Angew. Chem.* **2001**, *113*, 4725; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591. (c) D. J. Ramón, M. Yus *Angew. Chem.* **2004**, *116*, 286; *Angew. Chem. Int. Ed.* **2004**, *43*, 284. (d) J. Christoffers, A. Baro *Adv. Synth. Catal.* **2005**, *347*, 1473.

[63] (a) D. J. Ramón, M. Yus *Tetrahedron Lett.* **1998**, *39*, 1239. (b) D. J. Ramón, M. Yus *Tetrahedron* **1998**, 54, 5651.

[64] (a) C. Garcia, L. K. LaRochelle, P. J. Walsh *J. Am. Chem. Soc.* **2002**, *124*, 10970. (b) M. Yus, D. J. Ramón, O. Prieto *Tetrahedron: Asymmetry* **2002**, *13*, 2291. Variation of the ligand structure: (c) P. J. Walsh, C. Anaya de Parrodi *Synlett* **2004**, 2417. Use of functionalized organozinc reagents: (d) S.-J. Jeon, C. Garcia, L. K. LaRochelle, P. J. Walsh *J. Org. Chem.* **2005**, *70*, 448. Review: (e) J. M. Betancort, C. García, P. J. Walsh *Synlett* **2004**, 749.

[65] For a catalytic, enantioselective alkylation of α-ketoesters employing a chiral salen / Ti complex as a catalyst, see: E. F. DiMauro, M. C. Kozlowski *J. Am. Chem. Soc.* **2002**, *124*, 12668.

Interestingly, other diastereoisomers of **52** furnished much worse results. Application of **52** to the reaction of diethylzinc with 4-phenylbutan-2-one afforded the corresponding tertiary alcohol with 70% ee. Although this enantiomeric excess is not in the synthetically-useful range, it is impressive that catalyst **52** is able to differentiate reasonably well between the methyl and methylene groups of the substrate.



SCHEME 10. Catalytic asymmetric alkylation of ketones by WALSH and, independently, YUS.

A year after these initial reports, a tandem, enantioselective alkylzinc addition / diastereoselective epoxidation was described, in which cyclic α,β-unsaturated ketones were employed as substrates.[66] The valuable cyclic epoxyalcohols obtained from this protocol could be isolated in synthetically-useful yields with very high enantiomeric excesses (96-99% ee). It is noteworthy that in the addition step titanium catalysis chemoselectively afforded the products of 1,2-addition; under similar conditions, a "softer" copper catalyst would have selectively promoted the corresponding conjugate addition.

A last and very interesting development in this field was recently reported by WALSH, who introduced the use of highly concentrated, or even solvent-free, conditions for the titanium catalyzed alkylation of aryl-alkyl ketones.[67] The use of these conditions greatly improved the efficiency and selectivity of the reaction, and a 4- to 40-fold reduction in the catalyst loading was possible while maintaining similar yields and levels of enantioselectivity compared to those reactions conducted in solvents. The authors also highlighted the positive implications of minimizing solvent use and catalyst loading in terms of scalability, environmental compatibility and cost reduction of the process.

[66] S.-J. Jeon, P. J. Walsh *J. Am. Chem. Soc.* **2003**, *125*, 9544.
[67] S.-J. Jeon, H. Li, P. J. Walsh *J. Am. Chem. Soc.* **2005**, *127*, 16416.

2.2. Zinc-Mediated Arylation of Carbon-Heteroatom Double Bonds

2.2.1. Diarylmethanols and Diarylmethylamines: Important Targets for Stereoselective Synthesis

Among the various carbon-carbon bond-forming processes, arylation reactions have been the subject of a large number of investigations, such that in the last decades many successful examples of catalytic enantioselective arylation processes have been reported.[68]

One of the arylation reactions in which organozinc compounds have been extensively employed is in their addition to carbonyl compounds and, to a lesser extent, imines. However, the development of such reactions has proved to be a much more challenging pursuit in comparison to the very well-established alkylation process.

When the addition of arylzinc nucleophiles is performed on aromatic aldehydes or aldimines, its products are, respectively, diarylmethanols and diarylmethylamines (Figure 5).[69] These compounds have found important applications as synthetic precursors to several biologically-active agents, some of which are depicted in Figure 5.

For example, the diphenhydramine derivatives (*R*)-orphenadrine [(*R*)-**53**] and (*R*)-neobenodine [(*R*)-**54**][70] show antihistaminic, as well as anticholinergic, activity. (*R*,*R*)-Clemastine [(*R*,*R*)-**55**][71] was used as a first-generation histamine H_1 antagonist for the treatment of allergic diseases. Subsequently, other histamine H_1 antagonists with related structures have been discovered, such as (*S*)-carbinoxamine [(*S*)-**56**][72] and the second-generation antagonist (*S*)-cetirizine hydrochloride [(*S*)-**57**, *Zyrtec*®].[73] Interestingly, only the (*S*)-enantiomer of this compound is biologically-active[74] and it has, therefore, marketed in enantiopure form since the beginning of 2002 as levocetirizine (*Xyzall*®). The phosphodiesterase IV inhibitor (*R*)-CDP-840 [(*R*)-**58**] can be prepared, starting from

[68] For a review, see: C. Bolm, J. P. Hildebrand, K. Muñiz, N. Hermanns *Angew. Chem.* **2001**, *113*, 3382; *Angew. Chem. Int. Ed.* **2001**, *40*, 3284.
[69] For a comprehensive review on the synthesis of such compounds, see: F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm *Chem. Soc. Rev.* **2006**, *35*, 454.
[70] (a) R. F. Rekker, H. Timmerman, A. F. Harms, W. T. Nauta *Arzneim. Forsch.* **1971**, *21*, 688. For the enantioselective synthesis of (*S*)-**53** and (*R*)-**54** by means of hydrogenation of the corresponding diarylketones, see: (b) T. Ohkuma, M. Koizumi, H. Ikehira, T. Yokozawa, R. Noyori *Org. Lett.* **2000**, *2*, 659.
[71] A. Ebnöther, H. P. Weber *Helv. Chim. Acta* **1976**, *59*, 2462.
[72] V. Barouh, H. Dall, G. Hite *J. Med. Chem.* **1971**, *14*, 834.
[73] For the enantioselective synthesis of this compound by means of CBS-reduction, see: E. J. Corey, C. J. Helal *Tetrahedron Lett.* **1996**, *37*, 4837.
[74] J. L. Devalia, C. De Vos, F. Hanotte, E. Baltes *Allergy* **2001**, *56*, 50.

a diarylmethanol, by displacement of a suitable leaving group with a *C*-nucleophile, effecting selective inversion of configuration at the stereogenic center.[75]

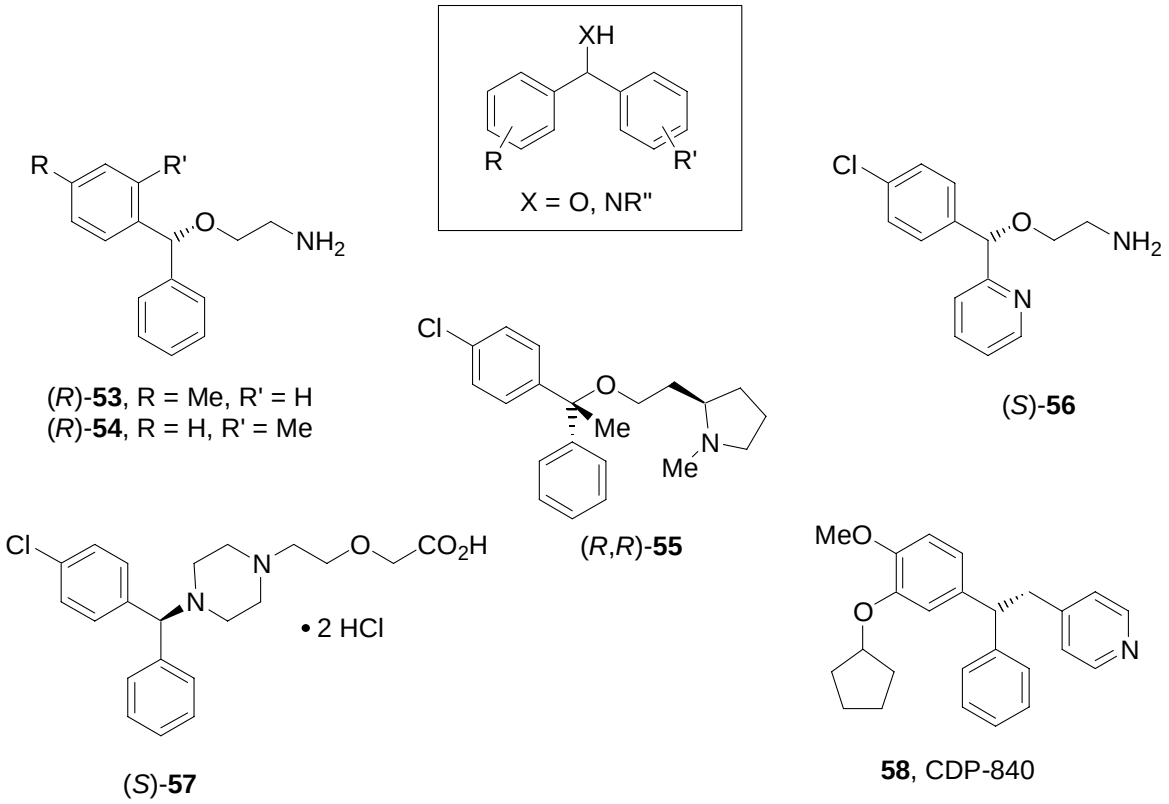


FIGURE 5. Biologically active diarylmethanols and diarylmethylamines and a related compound.

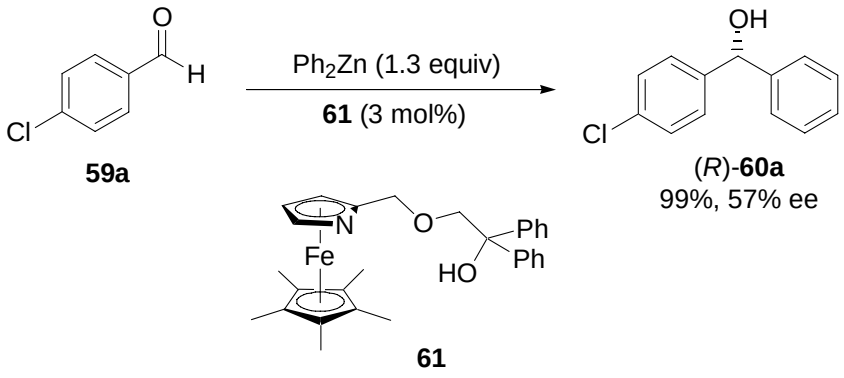
The first stoichiometric phenylation of aldehydes, mediated by an organotitanium reagent, was reported by SEEBACH and co-workers in 1985.[76a] Approximately ten years later, the same research group was able to describe an enantioselective, catalytic version of this protocol, in which a Ti-TADDOLate complex was used as a catalyst to promote the addition of $PhTi(iPrO)_3$ [generated in situ from the reaction of PhLi with $ClTi(iPrO)_3$] to aromatic aldehydes with up to 96% ee.[76b] Other transition metal-catalyzed processes that do not involve organozinc species have, similarly, been reported in the course of the years, which make use of Rh- or Cu-based chiral catalysts.[77,78]

[75] Y. Bolshan, C. Y. Chen, J. R. Chilenski, F. Gosselin, D. J. Mathre, P. D. O'Shea, A. Roy, D. Tillyer *Org. Lett.* **2004**, *6*, 111.
[76] (a) D. Seebach, A. K. Beck, S. Roggo, A. Wonnacott *Chem. Ber.* **1985**, *118*, 3673. (b) B. Weber, D. Seebach *Tetrahedron* **1994**, *50*, 7473.
[77] Rh: (a) M. Sakai, M. Ueda, N. Miyaura *Angew. Chem.* **1998**, *110*, 3475; *Angew. Chem. Int. Ed.* **1998**, *37*, 3279. (b) A. Fürstner, H. Krause *Adv. Synth. Catal.* **2001**, *343*, 343. (c) C. Moreau, C. Hague, A. Weller, C. Frost *Tetrahedron Lett.* **2001**, *42*, 6957. (d) T. Focken, J. Rudolph, C. Bolm *Synthesis* **2005**, 429. (e) K. Suzuki, S. Ishii, K. Kondo, T. Aoyama *Synlett* **2006**, 648. (f) R. B. C. Jagt, P. Y. Toullec, J. G. de Vries, B. L. Feringa, A. J. Minnaard *Org. Biomol. Chem.* **2006**, *4*, 773.
[78] Cu: D. Tomita, R. Wada, M. Kanai, M. Shibasaki *J. Am. Chem. Soc.* **2005**, *127*, 4138.

2.2.2. Phenyl Transfer Reactions Employing Diphenylzinc as a Phenyl Source

In 1991 SOAI described the first enantioselective phenylation of aromatic aldehydes by means of an organozinc species generated in situ from $ZnCl_2$ and phenylmagnesium bromide.[79] Since this reagent, differently from dialkylzinc species, could react directly with the carbonyl group at room temperature, this reaction proved much more challenging than the related alkylations, and the chiral promoter (DBNE, **48**) had to be used in stoichiometric amounts to obtain acceptable enantiomeric excesses (up to 82% ee).

It was not until 1997 that the first *catalytic*, enantioselective addition of diphenylzinc to aldehydes appeared in the literature, courtesy of FU.[80,81] Diphenylzinc, 4-chlorobenzaldehyde (**59a**) and a catalytic amount of planar-chiral azaferrocene **61** generated the desired diarylmethanol (*R*)-**60a** in almost quantitative yield and with 57% ee (Scheme 11). Since the absolute configuration of the major enantiomer was the same as that of the ethylation product, the same mechanistic picture (see Scheme 7) could be inferred for this reaction as well.



SCHEME 11. Catalytic asymmetric phenylation by FU.

Although at this stage the enantiomeric excesses of this kind of reactions were still only moderate, this work clearly set the stage for future developments and served as source of inspiration for many subsequent studies that were to appear thereafter.

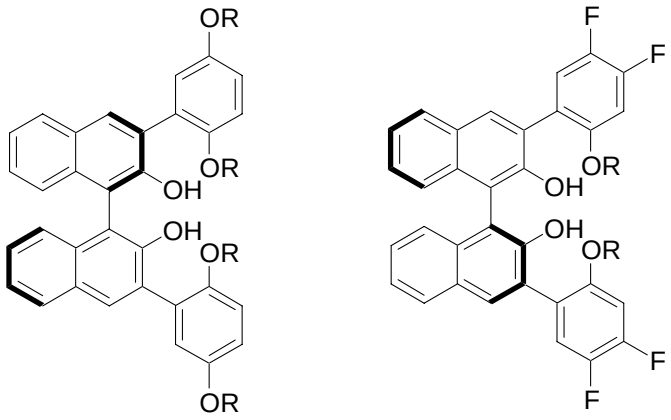
The first highly enantioselective phenylation reaction was described by PU in 1999.[82] In that study, 20 mol% of enantiopure 3,3'-diarylbinaphthol (*R*)-**62** (Figure 6) was required to obtain

[79] K. Soai, Y. Kawase, A. Oshio *J. Chem. Soc., Perkin Trans. 1* **1991**, 1613.
[80] The first catalytic *diastereoselective* phenylation using diphenylzinc was reported by HÜBSCHER and BARNER in 1990: J. Hübscher, R. Barner *Helv. Chim. Acta* **1990**, *73*, 1068.
[81] P. I. Dosa, J. C. Ruble, G. C. Fu *J. Org. Chem.* **1997**, *62*, 444.
[82] W.-S. Huang, L. Pu *J. Org. Chem.***1999**, *64*, 4222.

product **60a** in 86% yield and with 94% ee at rt in the presence of one equivalent of pure diethylzinc. As the authors pointed out, pre-treatment of the ligand with 40 mol% Et_2Zn (2.0 equiv relative to the binaphthol) was required, in many cases, to obtain high asymmetric induction. For some substrates, good results were obtained only at low concentration (5 mM) of the reactants and at low temperature (−30 °C).

This, and the observed requirement for high catalyst loading, can be explained considering the presence of the already-mentioned, uncatalyzed *background* reaction: the authors observed the reaction of diphenylzinc and 4-methoxybenzaldehyde (**59b**) to proceed cleanly and afford the corresponding racemic diarylmethanol **60b** in good yield, even in the absence of (*R*)-**62**.

The use of binaphthol (*S*)-**63**, a fluorinated analogue of **62**, was reported by PU a year later (Figure 6). In the presence of 20 mol% of (*S*)-**63** various aromatic aldehydes could be reacted with phenylzinc to give the products in high yields (86-92%) and with good to high enantioselectivities (70-95% ee).[83]



(*R*)-**62**
R = *n*-C_6H_{13}

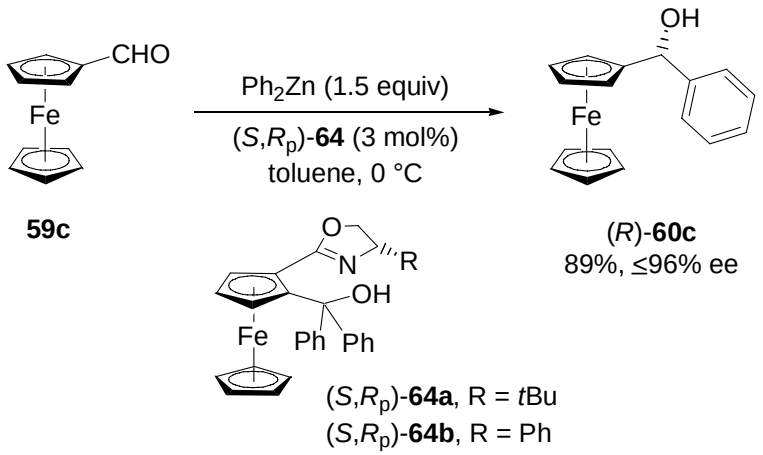
(*S*)-**63**
R = *n*-C_6H_{13}

FIGURE 6. Chiral binaphthols described by PU.

Contemporaneous to the studies of PU, BOLM and MUÑIZ described in 1999 the use of planar chiral ferrocene-based hydroxy oxazolines (*S*,R_p)-**64**.[84,85] Both these ligands proved to be equally efficient, and a catalyst loading of 10 mol% in toluene at 0 °C was sufficient to obtain (*R*)-**60a** in

[83] W.-S. Huang, L. Pu *Tetrahedron Lett.* **2000**, *41*, 145.
[84] For the synthesis of (*S*,R_p)-**64a-b** and their application in the enantioselective alkylation of aldehydes, see: (a) C. Bolm, K. Muñiz-Fernández, A. Seger, G. Raabe *Synlett* **1997**, 1051. (b) C. Bolm, K. Muñiz-Fernández, A. Seger, G. Raabe, K. Günther *J. Org. Chem.* **1998**, *63*, 7860.
[85] C. Bolm, K. Muñiz *Chem. Commun.* **1999**, 1295.

nearly quantitative yield with 88% ee. The best result was obtained using ferrocenylcarbaldehyde (**59c**) as a substrate with a catalyst loading of only 5 mol% (Scheme 12).



SCHEME 12. Asymmetric phenyl transfer reaction by BOLM and MUÑIZ.

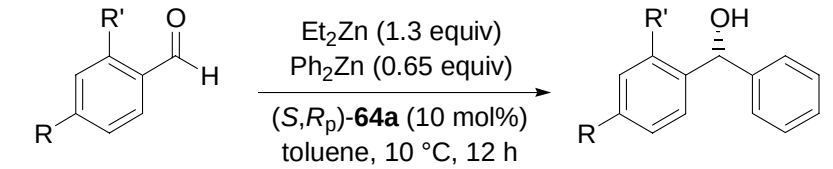
The presence of substituents in the *ortho* position of the aromatic aldehyde resulted in reduced enantioselectivities, as exhibited by the use of 2-bromobenzaldehyde (**59d**) and 1-naphthaldehyde (**59e**) as substrates, which afforded products in excellent yields but with only 31 and 28% ee, respectively. Additionally, aryl transfer on the heteroaromatic 2-formylpyridine (**59f**) furnished a disappointing result, with the product possessing an extremely low ee (3%).[86]

Clearly, the major drawback of all the phenylation protocols described so far lies in the necessity to use stoichiometric amounts or even an excess of the expensive and air- and moisture-sensitive diphenylzinc. Moreover, the loss of one phenyl as nontransferable aryl group on zinc has to be accepted.

An excellent solution to this problem was found in 2000 by BOLM and co-workers, who first reported the use of a modified phenylzinc reagent prepared in situ by mixing diphenyl- and diethylzinc in a 1:2 ratio (Scheme 13). Two positive effects were observed: firstly, Ph_2Zn could be used in sub-stoichiometric amounts (0.65 equiv), since both its phenyl groups were now available for the reaction and, secondly, the undesired background reaction could be suppressed, leading to a

[86] In this case it was hypothesized that, due to the favorable position of the N and O atoms in the substrate, **59f** was able to initiate the reaction itself, leading to a product able to catalyze its own formation in a non-stereoselective manner. The presence of this background reaction would account for the observed lack of selectivity. 2-Pyridylalcohols have already been used as ligands in enantioselective Et_2Zn additions, see: (a) C. Bolm, M. Zehnder, D. Bur *Angew. Chem.* **1990**, *102*, 206; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205. (b) C. Bolm, G. Schlingloff, K. Harms *Chem. Ber.* **1992**, *125*, 1191.

significative increase in the enantiomeric excesses of the products.[87,88] For example, diarylmethanol **60a** could now be obtained with 97% ee compared to 88% ee under the original conditions. It is noteworthy that, using this improved procedure, 2-bromobenzaldehyde (**59d**) furnished a product with 91% ee, and even some aliphatic aldehydes could be phenylated with up to 94% ee.

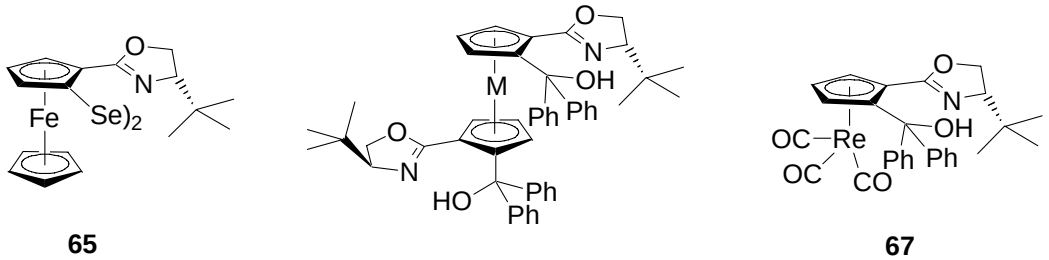


59a, R = Cl, R' = H
59d, R = H, R' = Br
59g, R = Me, R' = H

60a, 86%, 97% ee
60d, 64%, 91% ee
60g, 85%, 98% ee

SCHEME 13. Enantioselective phenylation by means of a mixed organozinc reagent by BOLM.

In seeking further improvements to this reaction, various ligands structurally-related to **64** were prepared and tested by BOLM and co-workers. These included the ferrocenyl diselenide **65**,[89] 1,1'-*bis*(oxazolinyl)metallocenes **66**[90] and the cyrhetrenyl complex **67** (Figure 7).[91]



65

66a, M = Fe
66b, M = Ru

67

FIGURE 7. Further metallocenyl-based ligands by BOLM.

[87] C. Bolm, N. Hermanns, J. P. Hildebrand, K. Muñiz *Angew. Chem.* **2000**, *112*, 3607; *Angew. Chem. Int. Ed.* **2000**, *39*, 3465.
[88] In this study, EtPhZn, formed in an equilibrium with Ph_2Zn and Et_2Zn, is supposed to be the actual phenylating agent. Apparently the ethyl group behaves as a nontransferable moiety on zinc, while phenyl is transferred to aldehyde with complete selectivity. For NMR and in situ-IR studies, see: (a) N. Hermanns *Dissertation*, RWTH Aachen, **2002**. For computational studies, see: (b) J. Rudolph, T. Rasmussen, C. Bolm, P.-O. Norrby *Angew. Chem.* **2003**, *115*, 3110; *Angew. Chem. Int. Ed.* **2003**, *42*, 3002. (c) J. Rudolph, C. Bolm, P.-O. Norrby *J. Am. Chem. Soc.* **2005**, *127*, 1548.
[89] C. Bolm, M. Kesselgruber, A. Grenz, N. Hermanns, J. P. Hildebrand *New J. Chem.* **2001**, *25*, 13.
[90] C. Bolm, N. Hermanns, M. Kesselgruber, J. P. Hildebrand *J. Organomet. Chem.* **2001**, *624*, 157.
[91] C. Bolm, M. Kesselgruber, N. Hermanns, J. P. Hildebrand, G. Raabe *Angew. Chem.* **2001**, *113*, 1536; *Angew. Chem. Int. Ed.* **2001**, *40*, 1488.

Although the use of compound **65** as a ligand furnished the products of phenylation in useful yields, the enantiomeric excesses unfortunately did not exceed 85%. Interestingly the results obtained in the phenyl transfer reaction were superior in terms of yield and enantiomeric excess to those obtained in the related ethylation reaction. In contrast, reactions involving metallocenes **66a-b** procedeed with high selectivity, and the products were obtained with up to 96% ee. However, if it is considered that metallocenes **66a-b** have two catalytic sites instead of one, based on the number of oxazoline diphenylhydroxymethyl units, these results were slightly inferior to those obtained with compounds **64**. A possible explanation was seen in the mutual interference of the two catalytic sites during the catalysis.[92] Finally, the cyrhetrene (S,R_p)-**67** proved to be an excellent ligand for the diphenylzinc addition and, for most examples, higher enantiomeric excesses of the products were obtained (up to 99% ee) than with the use of ferrocene (S,R_p)-**64a**. Even the *ortho*-disubstituted aldehyde, 2,4,6-trimethylbenzaldehyde (**59h**), was tolerated as a substrate, furnishing the corresponding diarylmethanol **60h** in >80% yield with 98% ee. Notably, that was the first example of the use of a chiral η^5-cyclopentadienylrhenium(I)tricarbonyl complex in asymmetric catalysis.

Subsequent to these seminal contributions by FU, PU and BOLM, the enantioselective phenyl transfer reaction to aldehydes attracted the interest of many research groups, which directed efforts towards further optimizing the efficiency of this process.

At this stage, although high yields and enantiomeric excesses had already been attained, three main problems remained to be solved. Firstly, the ligands that effectively catalyzed the phenyl transfer reaction required multistep syntheses and were generally only available in a single enantiomeric / diastereomeric form. Secondly, diphenylzinc as a phenylating agent displayed a considerable background reaction with aldehydes, making it necessary to use the ligands in substantial amounts (10-20 mol%). Thirdly, diphenylzinc is expensive and very air- and moisture-sensitive, and its use limits the reaction solely to the transfer of *phenyl* groups, making a more general option for the transfer of *aryl* groups highly desirable.

Considering these issues, efforts were primarily directed at broadening the family of compounds able to promote the reaction, and to find alternatives to diphenylzinc as the nucleophilic reagent. The effect of additives was also taken into consideration in order to solve the issue of catalyst loading.

[92] In agreement with this hypothesis, superior results, especially at low catalyst loading, were obtained with ruthenocene **66b**, where the distance between the two Cp rings is larger than in ferrocene **66a**.

2.2.3. Variation of the Ligand Structure

As a consequence of the considerable attention raised by the catalytic enantioselective phenyl transfer reaction to aldehydes, many research groups reported the synthesis and application of a large number of chiral, enantiopure compounds as ligands, all bearing one oxygen (in one case sulfur) and one nitrogen, or two oxygens, as the ligating atoms (Figure 8).

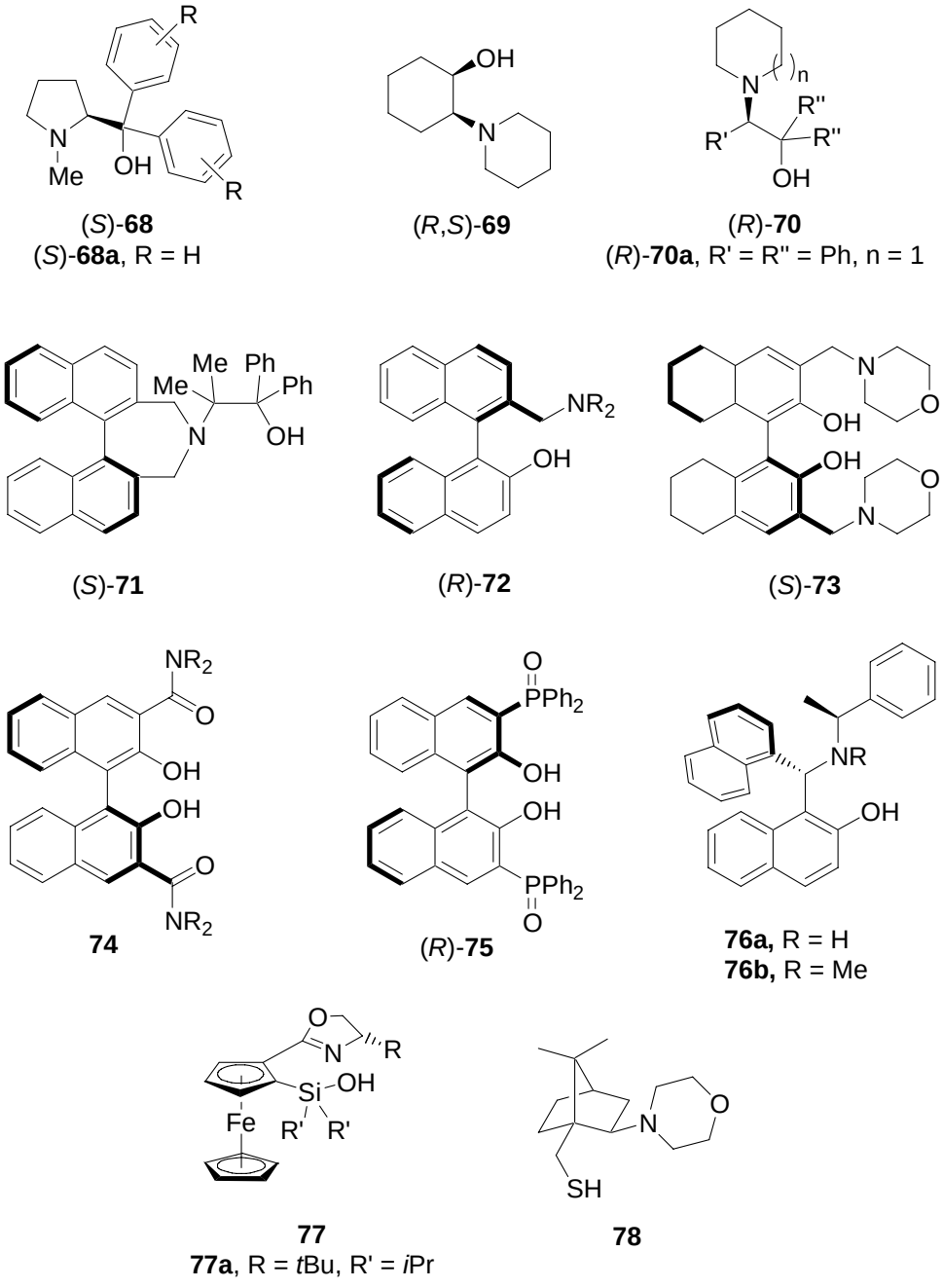


FIGURE 8. Chiral ligands for the enantioselective aryl transfer to aldehydes

In this section some of the most significative contributions will be briefly highlighted: for a more comprehensive discussion, consultation of ref. 69 is recommended. In some of the following examples, phenyl or aryl sources other than diphenylzinc have been used, and the effect of additives has been investigated; these two topics will be discussed further in sections *2.2.4.* and *2.2.5.*, respectively.

Proline derived β-aminoalcohols **68** were reported in 2001 by ZHAO.[93] The best result (89% ee) was obtained with the already known compound **68a** (R = H in the figure).[94]

cis-Amino alcohol (*R*,*S*)-**69** and related aminocyclohexanol derivatives were first prepared by BOLM and co-workers through an efficient resolution of racemic *N*-benzyl-*trans*-2-aminocyclohexanol and subsequent stereospecific functional group interconversions.[95] Their use in the phenyl transfer reaction afforded products with up to 87% ee.

Structurally-related β-amino alcohols (*R*)-**70** reported by PERICÀS in 2004 proved to be very effective ligands for the reaction promoted by a 1:2 mixture of Ph_2Zn / Et_2Zn.[96] Due to its high activity, ligand (*R*)-**70a** could be used at a catalyst loading of only 1.5 mol%, and still was able to furnish products with excellent enantioselectivity (up to 99% ee). A study of the temperature / ee relationship revealed that 10 °C was the ideal temperature to perform the reaction with high selectivity. The intermediacy of a mixed zinc species (EtPhZn) was suggested by DFT calculations.

The complex binaphthylazepine-based amino alcohol (*S*)-**71** reported in 2005 by SUPERCHI was able to catalyze the phenyl transfer reaction to **59a** to furnish diarylmethanol **60a** with 54% ee.[97]

Another class of binaphtyl-based amino alcohols (*R*)-**72** was described by HA in 2002.[98] 10 mol% of the ligand bearing a morpholine ring on the nitrogen was able to catalyze the phenylation of various aromatic aldehydes with high yield (95-98%) and selectivity (92-98%). Worse results were obtained for α,β-unsaturated and aliphatic aldehydes (up to 85% and 68% ee, respectively).

Some compounds based on the binaphthol backbone, which use two oxygens as ligating atoms have also been introduced.

H_8-BINOL derivative (*S*)-**73** was recently reported by PU, who employed it in the enantioselective phenyl transfer reaction.[99] Compound (*S*)-**73** was particularly effective in promoting the conversion

[93] (a) G. Zhao, X.-G. Li, X.-R. Wang *Tetrahedron: Asymmetry* **2001**, *12*, 399. For the use of the same ligands in a related process, see: (b) A. L. Braga, D. S. Lüdtke, P. H. Schneider, F. Vargas, A. Schneider, L. A. Wessjohann, M. W. Paixão *Tetrahedron Lett.* **2005**, *46*, 7827.
[94] First synthesis: K. Soai, A. Ookawa, T. Kaba, K. Ogawa *J. Am. Chem. Soc.* **1987**, *109*, 7111.
[95] I. Schiffers, T. Rantanen, F. Schmidt, W. Bergmans, L. Zani, C. Bolm *J. Org. Chem.* **2006**, *71*, 2320.
[96] (a) M. Fontes, X. Verdaguer, L. Solà, M. A. Pericàs, A. Riera *J. Org. Chem.* **2004**, *69*, 2532. For a related study, see: (b) A. L. Braga, D. S. Lüdtke, F. Vargas, M. W. Paixão *Chem. Commun.* **2005**, 2512.
[97] M. G. Pizzuti, S. Superchi *Tetrahedron: Asymmetry* **2005**, *16*, 2263.
[98] D.-H. Ko, K. H. Kim, D.-C. Ha *Org. Lett.* **2002**, *4*, 3759.
[99] Y.-C. Qin, L. Pu *Angew. Chem.* **2006**, *118*, 279; *Angew. Chem. Int. Ed.* **2006**, *45*, 273.

of aliphatic aldehydes, with enantiomeric excesses up to 98%. Aromatic aldehydes were also tolerated as substrates, generating the products with up to 96% ee.

Enantiopure binaphthol dicarboxamides **74** were introduced in 2005 as bifunctional catalysts by KATSUKI.[100] They were able to furnish diarylmethanols of high enantiomeric purity (up to 96% ee) in a very short reaction time (typically 2.5 h). Interestingly, the use of a mixture of toluene and MTBE as the solvent was crucial to achieve high enantioselectivities. Use of DiMPEG as an additive had no impact on the selectivity (see paragraph *2.2.5.*).

ISHIHARA described 3,3'-*bis*(diphenylphosphinoyl)-BINOL (*R*)-**75** in 2005.[101] It furnished products **60** with 81-88% ee at rt using a catalyst loading of 10 mol%.

In the same year, axial chiral aminonaphthol **76b** was introduced by CHAN for the catalytic asymmetric phenyl transfer to aldehydes.[102] Excellent selectivity (up to 98% ee) was observed using phenylboronic acid as a phenyl source in the presence of 10 mol% of DiMPEG (see paragraph *2.2.4.* and *2.2.5.*), with a catalyst loading of 8 mol%.

The first application of a chiral silanol as a ligand for asymmetric catalysis was reported by BOLM and co-workers in 2005.[103] When used as a promoter for the enantioselective phenyl transfer reaction, compound **77a** (10 mol%) afforded diarylmethanols **60** in up to 82% yield and with up to 91% ee. Other silanols **77** led to inferior results, presumably due to insufficient steric impact of their substituents on the silicon atom and the oxazoline ring.

Camphor-derived γ-aminothiol **78** was reported by UANG in 2006.[104] Its application in catalysis furnished alcohols **60** with outstanding enantiomeric excesses (95%-99.5% ee), although a temperature of −35 °C and a relatively long reaction time of 48 h were required to obtain these results.

In concluding this paragraph, it should be mentioned that some protocols have been published which make use of polymeric or polymer-supported species as ligands for the enantioselective phenyl- and aryl transfer reactions. The use of such polymer-bound systems allows, in many cases, the recovery of the catalyst and greatly simplifies the purification of the products. The protocols published to date include the use of enantiopure binaphthyl-based polymers,[105] employment of ferrocenyl hydroxyoxazolines bound to a linear polyether chain,[106] appendage of tertiary amino alcohols to a polystyrene resin,[107] or use of proline-derived dendritic aminoalcohols.[108] An

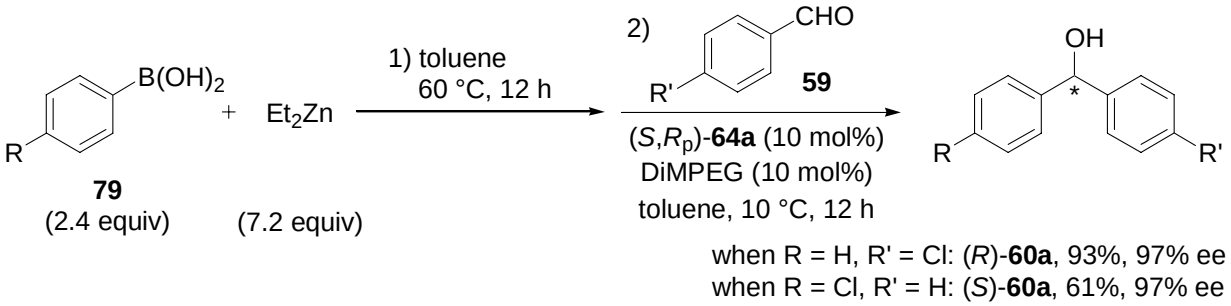
[100] K. Ito, Y. Tomita, T. Katsuki *Tetrahedron Lett.* **2005**, *46*, 6083.
[101] M. Hatano, T. Miyamoto, K. Ishihara *Adv. Synth. Catal.* **2005** *347*, 1561.
[102] J.-X. Ji, J. Wu, T. T.-L. Au-Yeung, C.-W. Yip, R. K. Haynes, A. S. C. Chan *J. Org. Chem.* **2005**, *70*, 1093.
[103] S. Özçubukçu, F. Schmidt, C. Bolm *Org. Lett.* **2005**, *7*, 1407.
[104] P.-Y. Wu, H.-L. Wu, B.-J. Uang *J. Org. Chem.* **2006**, *71*, 833.
[105] W.-S. Huang, Q.-S. Hu, L. Pu *J. Org. Chem.* **1999**, *64*, 7940.
[106] C. Bolm, N. Hermanns, A. Claßen, K. Muñiz *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1795.
[107] D. Casetellnou, M. Fontes, C. Jimeno, D. Font, L. Solà, X. Verdaguer, M. A. Pericàs *Tetrahedron* **2005**, *61*, 12111.

alternative approach was recently described by BOLM and KIM,[109] in which proline derivatives (structurally reminiscent of **68**) bearing "perfluoro ponytails" were used in a fluorous organic biphasic system, leading to isolation of products with up to 88% ee. The catalysts could be recycled by simple phase separation and reused up to six times with no appreciable loss in enantioselectivity.

2.2.4. Use of Alternative Aryl Sources

In 2002, BOLM and RUDOLPH reported the first general, catalytic enantioselective *aryl* transfer reaction to aldehydes using ferrocene (S,R_p)-**64a** as a ligand along with arylzinc species formed in situ from commercially available arylboronic acids and diethylzinc.[110] In this protocol, a transmetallation step[111] is supposed to take place between the latter two species, to generate the active arylating agent, which is, in analogy to what discussed above, assumed to be EtArZn.

The main advantage of this protocol is that it provides access to both enantiomers of the product using the same catalyst by simply choosing the appropriate combination of arylboronic acid **79** and aldehyde **59** (Scheme 14).



SCHEME 14. Catalytic, enantioselective aryl transfer reaction by BOLM and RUDOLPH.

For example, reaction of phenylboronic acid (R = H in Scheme 13) and 4-chlorobenzaldehyde (**59a**) gave the (*R*)-enantiomer of the corresponding product **60a** with excellent enantioselectivity (97% ee). Conversely, when 4-chlorophenylboronic acid (R = Cl) and benzaldehyde were used as reaction partners, the opposite enantiomer of the product was obtained. Although the yield was, in

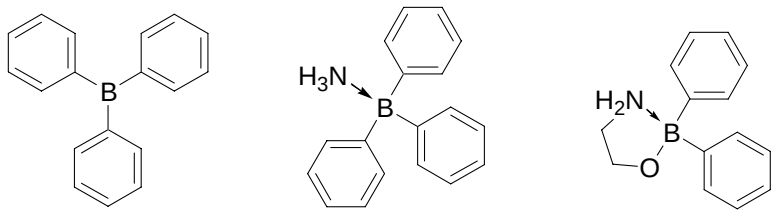
[108] X. Y. Liu, X. Y. Wu, Z. Chai, Y. Y. Wu, G. Zhao, S. Z. Zhu *J. Org. Chem.* **2005**, *70*, 7432.
[109] J. K. Park, K. G. Lee, C. Bolm, B. M. Kim *Chem. Eur. J.* **2005**, *11*, 945.
[110] (a) C. Bolm, J. Rudolph *J. Am. Chem. Soc.* **2002**, *124*, 14850. For a multigram scale application, see (b) J. Rudolph, F. Schmidt, C. Bolm *Synthesis* **2004**, 840.
[111] For pioneering studies concerning B/Zn transmetallation in the enantioselective alkenylation of aldehydes, see: (a) W. Oppolzer, R. N. Radinov *Helv. Chim. Acta* **1992**, *75*, 170. Total synthesis of (*R*)-(−)-muscone: (b) W. Oppolzer, R. N. Radinov *J. Am. Chem. Soc.* **1993**, *115*, 1593. For a more detailed discussion, see section *2.2.8.*

this case, only moderate, the enantiomeric excess was again excellent (97% ee). It should be noted that the addition of 10 mol% dimethylpolyethylene glycol (DiMPEG, MW = 2000 g mol^{-1}) as an additive proved beneficial for the enantioselectivity without greatly affecting the yield.[112]

A drawback of this methodology is that it requires an excess of arylboronic acid to generate the mixed organozinc reagent (compared to the 0.65 equivalents of the protocol employing diphenylzinc). In this regard, the process is not especially economic when compared to the already-reported protocol. Moreover, a three-fold excess of diethylzinc must be used in order to provide useful results.

Triphenylborane (**80**) was recently found to be an interesting alternative to diphenylzinc as a phenyl source, since it is commercially available in large quantities and is rather inexpensive[113] compared to diphenylzinc. By analogy with the protocol employing arylboronic acids, the phenylating agent (once again assumed to be EtPhZn) was generated in situ by mixing 1 equiv of **80** with 3 equiv of Et_2Zn.[114] For many substrates, this new protocol gave almost identical results to those described using the Ph_2Zn/Et_2Zn mixture. In the case of 2-bromobenzaldehyde (**59d**) the enantiomeric excess dropped from 98% to 87%, probably because of unfavourable steric interactions or due to chelation by the substituent in *ortho*-position. Nevertheless, linear and branched aliphatic aldehydes reacted smoothly to give the corresponding secondary alcohols in almost quantitative yield and 80-97% ee.

A further extension of this protocol, in connection with some interesting kinetic investigations, was reported by DAHMEN in 2005.[115] In this study, the ability of compound **80** to act as a phenyl source was compared with that of the corresponding ammonia complex (**81a**) and of diphenylborinate (**82**) (Figure 9).



80 **81a** **82**

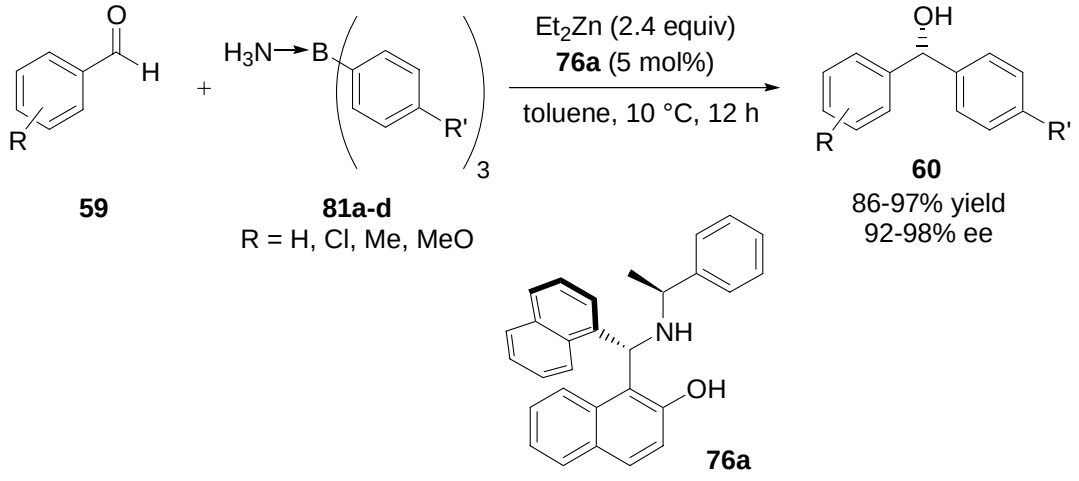
FIGURE 9. Some alternative phenyl sources.

[112] For a more detailed discussion on the effect of DiMPEG and other additives, see section *2.2.5*.
[113] Current prices taken from the *Sigma-Aldrich* 2005-2006 catalogue (Germany / Austria) are: Ph_2Zn, 346 € for 5 g; Ph_3B, 152 € for 10 g.
[114] J. Rudolph, F. Schmidt, C. Bolm *Adv. Synth. Catal.* **2004**, *346*, 867.
[115] S. Dahmen, M. Lormann *Org. Lett.* **2005**, *7*, 4597.

It was first determined that transmetallation with Et_2Zn at rt is much faster for compound **80** (50% exchange is reached after only 1 min) than for compound **81a** or **82** (50% exchange is reached after approximately one hour). The dissimilar transmetallation patterns were expected to influence the behaviour of these three compounds in catalysis. Indeed, when compounds **80**-**82** were used in the phenylation of aldehyde **59a** in the presence of 5 mol% of the chiral ligand **76a**,[116] they gave rise to very different results.

Rapid transmetallation with triphenylborane (**80**) produced **60a** in 95% yield but with only 36% ee. The low enantiomeric excess is assumed to arise from the large amount of EtPhZn immediately generated in the reaction mixture, allowing the non-enantioselective background reaction to predominate. In contrast, compounds **81a** and **82** gave better results (97 and 87% ee, respectively). For ammonia complex **81a**, in particular, a kinetic investigation of the reaction profile showed that a very small amount of phenylating reagent relative to the aldehyde is present throughout the reaction, which leads to an overall slower process. As a consequence, the background reaction is efficiently minimized and the catalytic enantioselective pathway predominates, affording the product in high enantiomeric excess.

A small adjustment in the stoichiometry allowed a broad range of diarylmethanols to be obtained in high yields with 92-98% ee (Scheme 15). Other triarylborane-ammonia complexes **81b-d** could be used without major changes in yield and selectivity. Unfortunately, application of this procedure to aliphatic aldehydes proved much less successful, generating products with 70-71% ee.

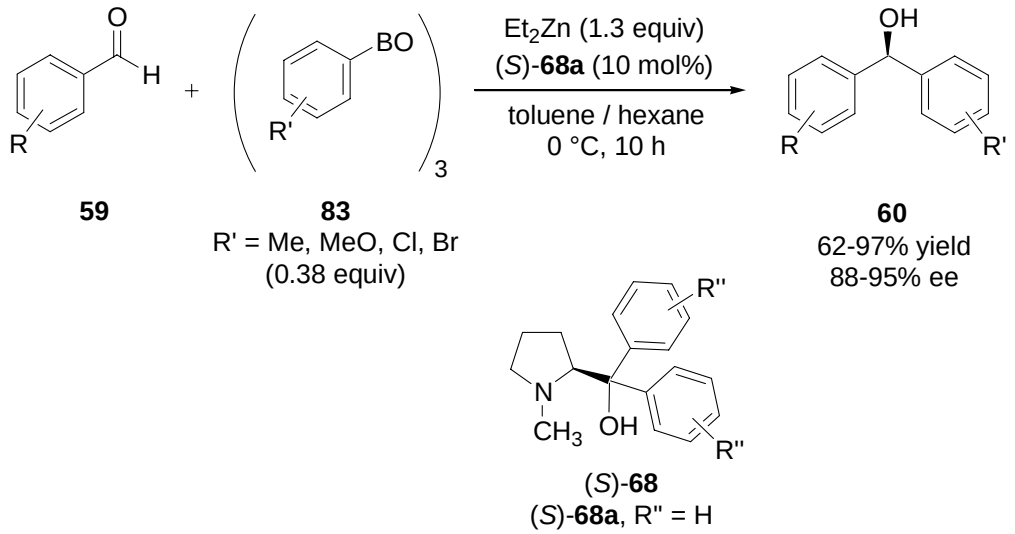


SCHEME 15. Catalytic, enantioselective aryl transfer reaction by DAHMEN.

[116] For the synthesis of this compound, see: C. Cimarelli, A. Mazzanti, G. Palmieri, E, Volpini *J. Org. Chem.* **2001**, *66*, 4759.

A final addition to the range of compounds able to function as aryl sources was recently published by ZHAO and co-workers, who employed arylboroxines **83** in conjunction with Et_2Zn.[117] The ligands were in this case β-amino alcohols **68** derived from (*S*)-proline. The authors considered that the use of arylboroxines **83** lacking acidic O-H moieties would help to minimize the large excess of diethylzinc needed for the reaction to occur when arylboronic acids **79** were employed, according to BOLM's protocol.[110a]

Phenylboroxine (**83a**) and 4-chlorobenzaldehyde (**59a**) were chosen as test substrates for optimizing the reaction conditions. Almost all the ligands furnished comparable results, affording alcohol **60a** with 81-89% ee. the highest enantioselectivity was obtained with compound (*S*)-**68a**. Addition of 10 mol% DiMPEG proved beneficial for the selectivity (up to 96% ee) but caused a significant decrease in yield. Finally, it was discovered that pre-treatment of compound (*S*)-**68a** with Et_2Zn could greatly improve the enantioselectivity of the reaction, as already established by PU in 1999.[82] Thus, the stoichiometry of the reaction could be optimized and 0.38 equiv of $(PhBO)_3$ (**83a**) in the presence of 1.3 equiv Et_2Zn and of 10 mol% of ligand (*S*)-**68a** proved sufficient to prepare various diarylmethanols **60** with 88-95% ee. The scope of the reaction could also be extended to other arylboroxines which furnished results comparable with those obtained using compound **83a** (Scheme 16).



SCHEME 16. Catalytic, enantioselective aryl transfer reaction by ZHAO.

Considering that arylboroxines **83** were used in substoichiometric amounts, the fact that, in many cases, yields superior to 80% were obtained, indicates a very high efficiency in the aryl transfer

[117] X. Wu, X. Liu, G. Zhao *Tetrahedron: Asymmetry* **2005**, *16*, 2299.

process. In the best example, the boroxine-based yield of compound **60** was ca. 255%, which corresponds to approximately 85% of the aryl groups initially present in compound **83** being activated and transferred to the substrate.

2.2.5. Additive Effects

As briefly mentioned above, a positive effect on the enantioselectivity of some catalytic enantioselective aryl transfer reactions was observed when a catalytic quantity of DiMPEG (MW = 2000 $g \cdot mol^{-1}$) was added to the reaction mixture.[110,117]

Prompted by this observation, BOLM and co-workers studied the effect of this and other additives on the reaction of aldehydes **59** with Ph_2Zn / Et_2Zn catalyzed by (1*R*,2*S*)-DBNE [(1*R*,2*S*)-**48**] or ferrocene (S,R_p)-**64a**.[118] Products prepared in the presence of small quantities of PEG ethers had, in almost all cases, a higher enantiomeric excess than those synthesized in the absence of the additive. This "MPEG effect" may be explained as follows: the presence of compounds such as PEG ethers would suppress unwanted, non-enantioselective pathways by deactivating achiral Lewis acidic species (such as zinc alkoxides and diphenylzinc, which, as already noted, also adds to aldehydes in the absence of the catalyst) thereby preventing their contribution to the overall process.[119,120]

As a consequence of the "MPEG effect" it was possible to maintain the selectivity of the reaction, even with a ten-fold reduction of the catalyst loading.

Later, thanks to automated, high-throughput screening technology, an extended study on the reaction promoted by Ph_3B / Et_2Zn with (1*R*,2*S*)-DBNE [(1*R*,2*S*)-**48**] as a catalyst was conducted.[121] Besides the polyethyleneglycols, other additives, namely 2-propanol, TMEDA and *N*-methylimidazole were also found to increase the enantioselectivity of the reaction leading to the formation of compound **60d**. Surprisingly, addition of 1 equiv of imidazole led to a reversal of the absolute configuration of the product.

[118] J. Rudolph, N. Hermanns, C. Bolm *J. Org. Chem.* **2004**, *69*, 3997.
[119] In this case the price to pay seems to be a decrease in the reaction rate, since reactions conducted in the presence of polyethers invariably show a drop in the yield in comparison to those conducted in their absence.
[120] It should be mentioned that other research groups observed no improvement in the enantioselectivity of the reaction upon addition of a catalytic quantity of DiMPEG or other PEG ethers. The generality of the "MPEG effect" is, therefore, still a subject of research. See for example: (a) Ref. 100. (b) Ref. 104.
[121] J. Rudolph, M. Lormann, C. Bolm, S. Dahmen *Adv. Synth. Catal.* **2005**, *347*, 1361.

2.2.6. Zinc-Mediated Phenyl Transfer Reaction to Imines

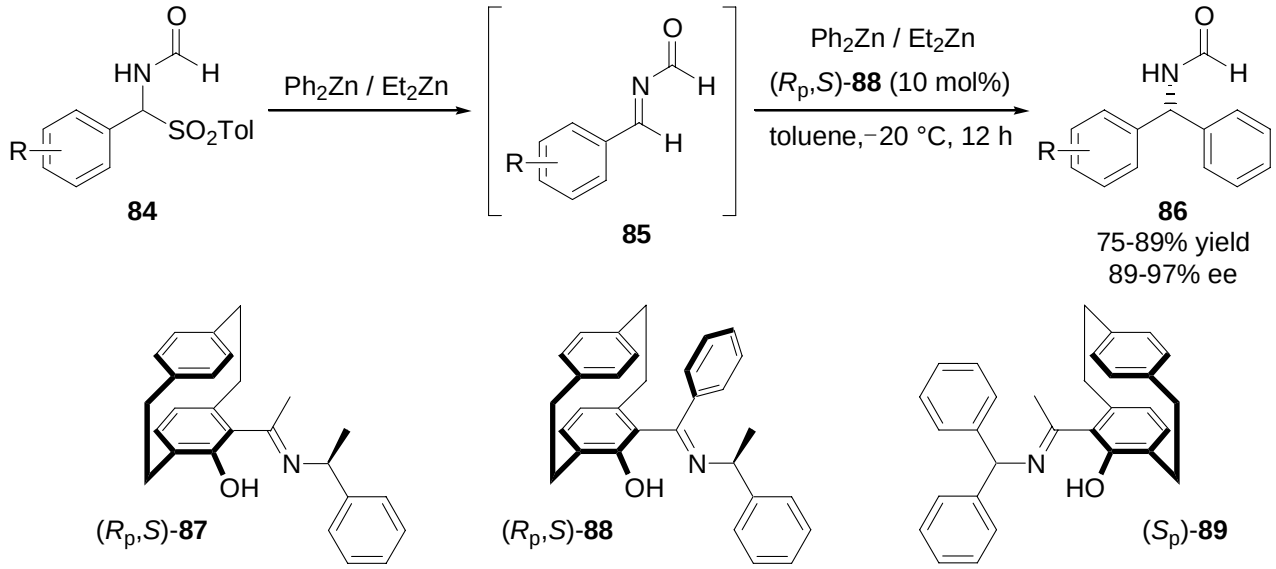
The first enantioselective arylation of imines was described by TOMIOKA in 1990,[122] but it required ten years before the first *catalytic* approach to this reaction was published by HAYASHI.[123] The reported methodology made use of a complex of Rh(I) with a monodentate, chiral phosphine as the catalyst, while trimethylarylstannanes ($ArSnMe_3$) were employed as nucleophiles.

Since then, some other protocols for this reaction have appeared in the literature, most of them relying on the use of rhodium(I) complexes, prepared in situ, to promote the addition. Chiral phosphines were often employed as ligands,[124] but the application of chiral dienes has also been documented.[125] In addition, the arylation of imines using aryllithium reagents in the presence of chiral diamines (sometimes used in stoichiometric amounts) as ligands has recently been reported by ALEXAKIS.[126]

To date, the sole example of a catalytic enantioselective phenyl transfer reaction to imines employing organozinc reagents is that reported by BOLM and BRÄSE.[127] In their approach, a combination of Ph_2Zn / Et_2Zn (this time in a 1:1 ratio, 1.5 equiv), in the presence of a catalytic amount of chiral N,O-ligands, was used to prepare *N*-formyldiarylmethylamines **86** from masked imines **84.**[128] The actual substrates, imines **85**, are generated using diethylzinc to mediate a base-induced elimination of *p*-toluenesulfinic acid from the corresponding masked imine **84**.

The ligands tested in the reaction included the two diastereoisomers of ferrocene **64a**, the cyrhetrene **67** and paracyclophane-based hydroxyimines **87-89** (Scheme 17).

[122] K. Tomioka, I. Inoue, M. Shindo, K. Koga *Tetrahedron Lett.* **1990**, *31*, 6681.
[123] T. Hayashi, M. Ishigedani *J. Am. Chem. Soc.* **2000**, *122*, 976.
[124] (a) M. Kuriyama, T. Soeta, X. Hao, Q. Chen, K. Tomioka *J. Am. Chem. Soc.* **2004,** *126*, 8128. (b) T. Hayashi, M. Kawai, N. Tokunaga *Angew. Chem.* **2004**, *116*, 6251; *Angew. Chem. It. Ed.* **2004**, *43*, 6125 (c) D. J. Weix, Y. Shi, J. A. Ellman *J. Am .Chem. Soc.* **2005**, *127*, 1092.
[125] (a) N. Tokunaga, Y. Otumaru, K. Okamoto, K. Ueyama, R. Shintani, T. Hayashi *J. Am. Chem. Soc.* **2004**, *126*, 13584. (b) Y. Otomaru, N. Tokunaga, R. Shintani, T. Hayashi *Org. Lett.* **2005**, *7*, 307. (c) Y. Otumaru, A. Kina, R. Shintani, T. Hayashi *Tetrahedron: Asymmetry* **2005**, *16*, 1673.
[126] (a) N. Cabello, J.-C. Kizirian, A. Alexakis *Tetrahedron Lett.* **2004**, *45*, 4639. (b) N. Cabello, J.-C. Kizirian, S. Gille, A. Alexakis, G. Bernardinelli, L. Pinchard, J.-C. Caille *Eur. J. Org. Chem.* **2005**, 4835
[127] N. Hermanns, S. Dahmen, C. Bolm, S. Bräse *Angew. Chem.* **2002**, *114*, 3844; *Angew. Chem. Int. Ed.* **2002** *114*, 3692.
[128] For a comprehensive account on the preparation and the application of such compounds, see: M. Petrini *Chem. Rev.* **2005**, *105*, 3949.



SCHEME 17. Catalytic, enantioselective phenyl transfer reaction to imine derivatives by BOLM and BRÄSE.

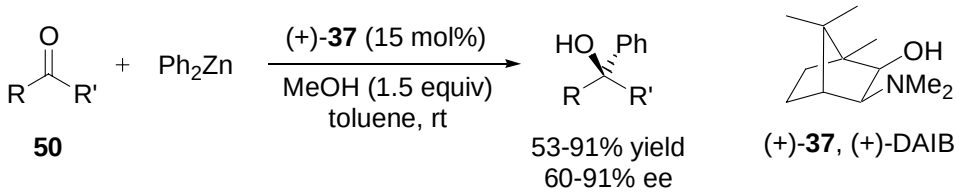
The best results were obtained using 10 mol% of compound (R_p,*S*)-**88**, which gave products with up to 97% ee in good yields. Working at –20 °C was crucial to obtain high enantioselectivities, but a further lowering of the temperature provided no further benefit. Various electronic and steric modifications of the aryl acceptors were tolerated, with only *meta*-substituted substrates giving rise to somewhat lower enantioselectivities. Interestingly, compound (S_p)-**89**, possessing only the element of planar chirality, still afforded the product of the test reaction (R = *p*-Me in Scheme 17) with 91% ee. While attempts to extend this reaction to an aryl-transfer process by the use of arylboronic acids were largely unsuccessful, the first results obtained utilizing triarylboranes and the corresponding ammonia complexes as aryl sources were more encouraging.[129]

2.2.7. Phenyl and Aryl Transfer to Ketones: Synthesis of Quaternary Stereogenic Centers

The importance of the enantioselective construction of quaternary stereogenic centers in modern organic synthesis has already been underlined.[62] As for the corresponding alkylation process, few catalytic systems are known that are able to efficiently promote the formation of quaternary stereogenic centers *via* the arylation of ketones, compared to the wealth of reports concerning the use of aldehydes as substrates.

[129] J. Rudolph *Dissertation*, RWTH Aachen, **2004**.

A pioneering contribution to this area of research was published in 1998 by DOSA and FU.[130] In this work, the authors employed NOYORI's (+)-DAIB ligand [(+)-**37**][47] and an excess of diphenylzinc (Scheme 18).



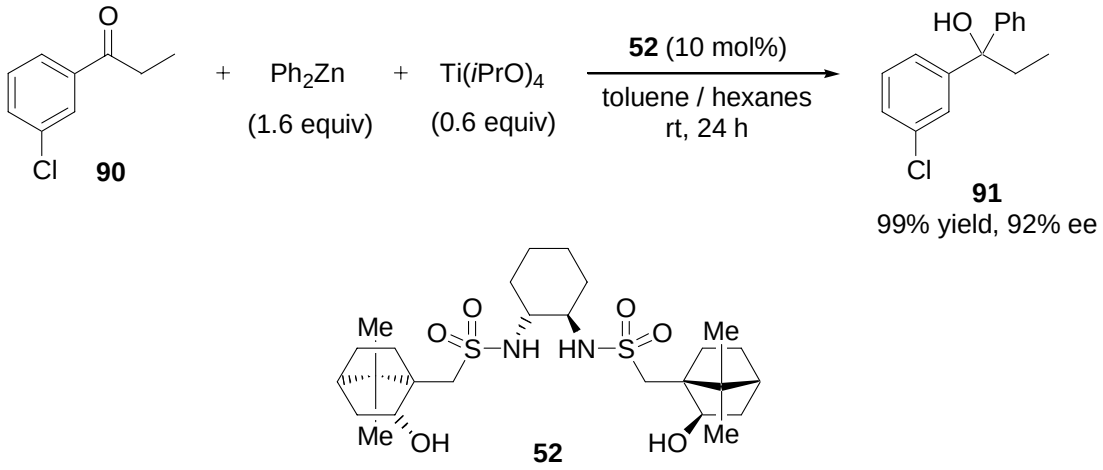
SCHEME 18. Catalytic, enantioselective phenyl transfer reaction to ketones by DOSA and FU.

Interestingly, while the use of diphenylzinc alone furnished poor results, addition of 1.5 equiv of methanol as an additive greatly improved both yield and enantiomeric excess. The formation of a mixed alkoxy phenyl zinc species that is less reactive than Ph_2Zn, was invoked to explain this behavior.

No further improvements were registered in this field until 2003 when, once again, the groups of YUS and WALSH independently reported the use of camphorsulfonamide-based ligand **52** in the titanium-catalyzed phenyl addition to alkyl-aryl ketones.[131] While in the former protocol[131a] 5 mol% of the ligand was used in the presence of a slight excess of Ti(*i*PrO)$_4$ (1.1 equiv), in the latter[131b] the catalyst loading was 10 mol% and a substoichiometric quantity of the titanium alkoxide was employed (0.6 equiv). In both cases an excess amount of diphenylzinc had to be used.[132]

In general, the latter set of conditions furnished the better results and various aceto- and propiophenones could be converted to the corresponding tertiary alcohols with up to 96% ee (Scheme 19). In comparison, phenylation of 4-bromopropiophenone under the conditions reported by YUS furnished the product with only 80% ee.

[130] P. I. Dosa, G. C. Fu *J. Am. Chem. Soc.* **1998**, *120*, 445.
[131] (a) O. Prieto, D. J. Ramón, M. Yus *Tetrahedron: Asymmetry* **2003**, *14*, 1955. (b) C. Garcia, P. J. Walsh *Org. Lett.* **2003**, *5*, 3641.
[132] Although YUS does not indicate the amount of zinc reagent used, it can be assumed that the same quantity was employed as in the related protocol for the alkyl addition to ketones (*i. e.* 2.0 equiv). See ref. 64b.



SCHEME 19. Catalytic, enantioselective phenylation of ketones by WALSH.

In his study, YUS also described the possibility to use arylzinc reagents generated in situ from boronic acids and diethylzinc, according to the procedure published by BOLM.[110] Although an enantiomeric excess of 93% was obtained in the best case, this procedure proved difficult to generalize and yields and / or enantiomeric excesses were often unsatisfactory.[131a]

A slight modification in the reaction conditions allowed WALSH to extend his methodology to the phenyl addition to cyclic α,β-unsaturated ketones, as already reported for the alkylation reaction.[133] Substrates bearing one substituent in the 2-position gave excellent results,[134] and the tertiary allylic alcohols produced were isolated in synthetically useful yields with up to 97% ee. Interestingly, cyclic enones with a halogen in 2-position were also tolerated as substrates: the resulting enantioenriched vinyl halides constitute useful building blocks for the synthesis of more complex structures by means of, for example, cross-coupling reactions. Finally, it is noteworthy that also in this case, as in the alkyl addition reaction, 1,2-addition products were chemoselectively obtained under titanium catalysis, with no trace of the compounds resulting from the related conjugate addition.

2.2.8. Enantioselective Addition of Other C(sp^2)-Zn Nucleophiles

The addition of an organometallic C(sp^2) nucleophile to a carbon-heteroatom double bond allows access to allylic alcohols and allylic amines. These compounds are among the most useful building

[133] H. Li, C. Garcia, P. J. Walsh *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5425.
[134] On the contrary, the allylic alcohol stemming from 2-cyclohexenone was produced in high yield, but in nearly racemic form.

blocks in organic synthesis, capable of being converted into any of a wide range of products *via* such transformations as epoxidations, aziridinations, cyclopropanations, dihydroxylations, halogenations, allylic substitutions and more.

It is therefore quite surprising that, until now, not many contributions have appeared in the literature concerning the enantioselective generation of such compounds by means of $C(sp^2)$-Zn nucleophiles, especially when the abundance of informations available on the related alkylation and arylation processes is considered.

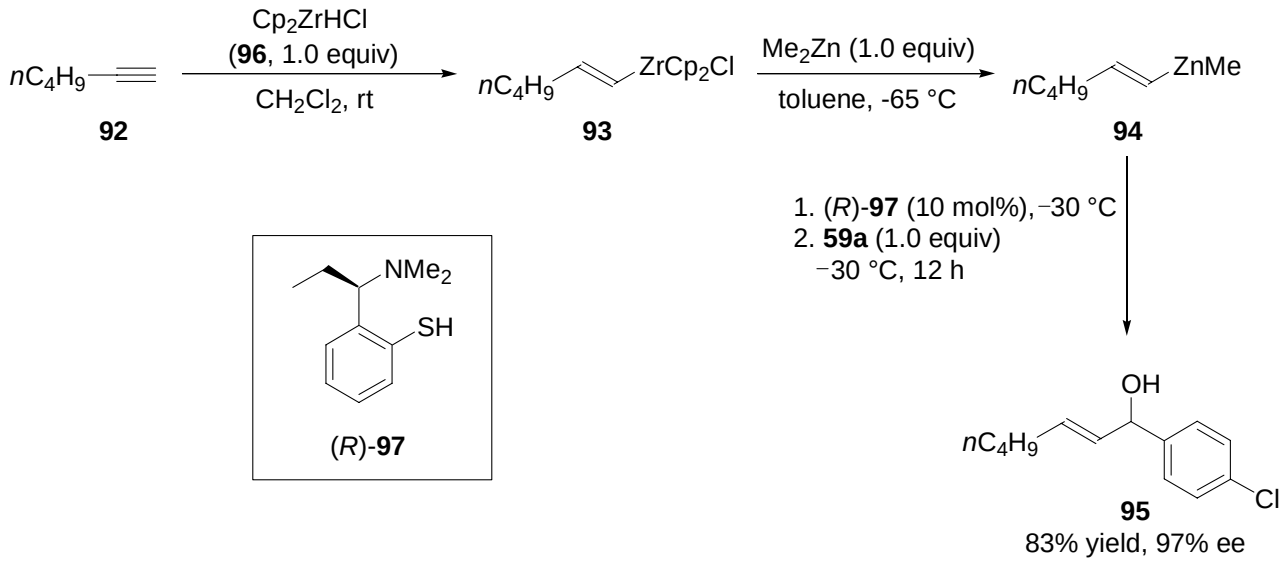
In part, this situation derives from the thermal instability of alkenylzinc species, which makes their preparation and storage difficult. This problem has been circumvented by the employment of alkenylzinc species prepared in situ from various precursors.

In some pioneering studies, OPPOLZER formed dialkenylzinc compounds or alkenylzinc halides by transmetallation of the corresponding Grignard reagents with $ZnCl_2$ or $ZnBr_2$.[135]

A second original approach was developed by WIPF and relies on the generation of alkenylzirconium species by hydrozirconation of alkynes with the commercially available Schwartz reagent (**96**).[136] A subsequent transmetallation reaction with Me_2Zn affords the mixed alkenyl-alkylzinc compounds that can be reacted in situ with aldehydes to generate the corresponding allylic alcohols as products.[137] When the addition is conducted in the presence of a chiral amino alcohol or thiol as a ligand, enantioenriched allylic alcohols are obtained (Scheme 20, enantiomeric excesses up to 99%).[138]

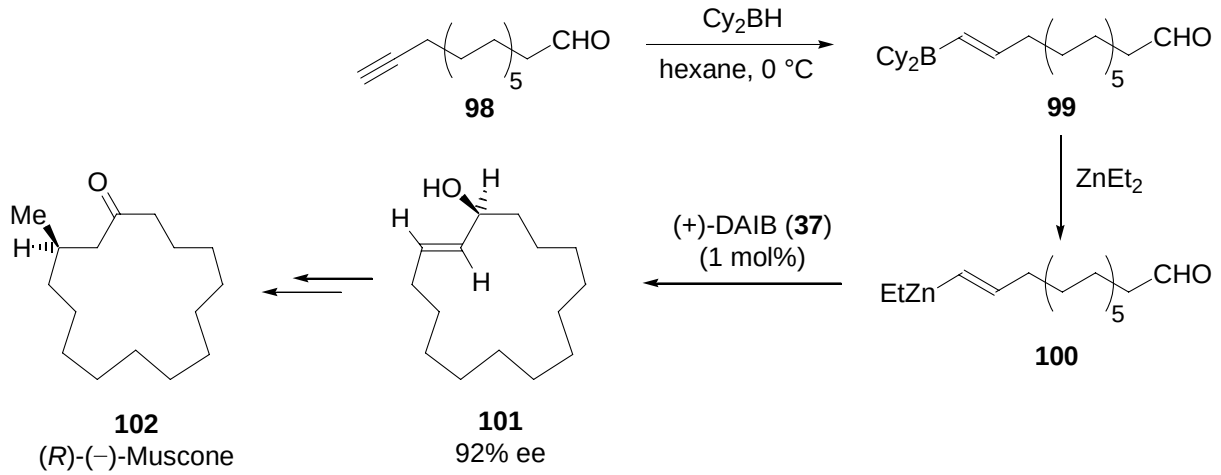
Interestingly, the use of amino thiol (*R*)-**97** furnished much better enantioselectivities than did the well-established ligands (+)-**37**, (1*R*,2*S*)-**48** and (*S*)-**68a**. The presence of the ethyl substituent in the benzylic position was necessary, since the parent compound bearing a methyl group gave a lower enantioselectivity in the test reaction.

[135] (a) W. Oppolzer, R. N. Radinov *Tetrahedron Lett.* **1988**, *29*, 5645. (b) W. Oppolzer, R. N. Radinov *Tetrahedron Lett.* **1991**, *32*, 5777.
[136] For the preparation of this compound, see: S. L. Buchwald, S. J. LaMaire, R. B. Nielsen, B. T. Watson, S. M. King *Tetrahedron Lett.* **1987**, *28*, 3895.
[137] (a) P. Wipf, W. Xu *Tetrahedron Lett.* **1994**, *35*, 5197. (b) P. Wipf, W. Xu *Org. Synth.* **1996**, *74*, 205. For a review on the use of alkenylzirconocenes in organic synthesis, see: (c) P. Wipf, C. Kendall *Chem. Eur. J.* **2002**, *8*, 1778. For an addition to *N*-diphenylphosphinoylimines and subsequent cyclopropanation reaction, see: (d) P. Wipf, C. Kendall, C. R. J. Stephenson *J. Am. Chem. Soc.* **2001**, *123*, 5122. (e) P. Wipf, C. Kendall, C. R. J. Stephenson *J. Am. Chem. Soc.* **2003**, *125*, 761. For an application of this transmetallation procedure in a Rh(I)-catalyzed 1,4-addition, see: (f) S. Oi, T. Sato, Y. Inoue *Tetrahedron Lett.* **2004,** *45*, 5051.
[138] P. Wipf, S. Ribe *J. Org. Chem.* **1998**, *63*, 6454.



SCHEME 20. Catalytic, enantioselective addition of alkenylzinc reagents to aldehydes by WIPF.

The most popular approach to produce alkenylzinc reagents in situ is, however, based on the hydroboration / transmetallation approach developed by OPPOLZER.[111] Here, an alkyne is treated with a dialkylborane (typically dicyclohexylborane) and the resulting alkenylborane is transmetallated with diethyl- or dimethylzinc to give a vinylzinc intermediate, that can undergo reaction with an electrophile, as already seen in the case of the previous methodology. In this case, a chiral amino alcohol is also responsible for the chiral induction. A beautiful application of OPPOLZER's methodology is constituted by his total synthesis of (*R*)-(−)-muscone (**102**, Scheme 21).[111b]



SCHEME 21. OPPOLZER's total synthesis of (*R*)-(−)-muscone.

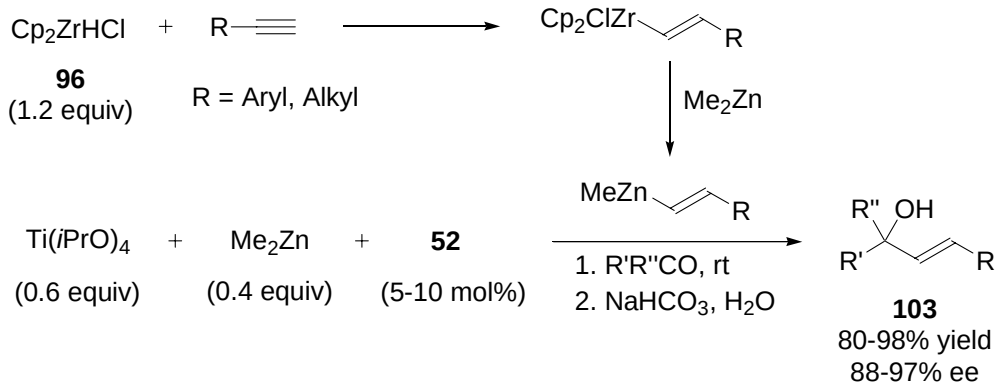
The same protocol was later employed by DAHMEN and BRÄSE, who used paracyclophane-based iminoalcohols **87**-**88** as ligands.[139] Under optimized conditions, 2 mol% of ligand (R_p,*S*)-**87** were sufficient to furnish products with up to 98% ee.

Subsequently, this transmetallation procedure has been applied to various systems by other research groups.[140] In particular, the contributions of WALSH in this area deserve mention: his group developed procedures for the enantioselective syntheses of D- and L-α-amino acids and allylic amines,[141] γ-unsaturated β-amino acid derivatives,[142] acyclic and allylic epoxy alcohols,[143] and hydroxy enol ethers (precursors to β-hydroxy aldehydes),[144] starting from the asymmetric alkenylzinc addition to aldehydes.

It must be pointed out that also in the case of the alkenyl addition reaction not only aldehydes, but also ketones, can be used as substrates. Whilst a zinc-mediated diastereoselective addition of alkenylzirconocenes to α-keto (but also α-imino) esters was described by WIPF in 2003,[145] the first catalytic, asymmetric vinylation of ketones was published a year later, once again by WALSH.[146]

First, it was determined that the hydroboration / transmetallation protocol was in this case unable to furnish the desired tertiary allylic alcohols.[147] Fortunately, application of WIPF's methodology was more fruitful, and in the presence of 5-10 mol% of the powerful ligand **52**, aryl-alkyl ketones and enones could be vinylated in high yields and enantioselectivities (Scheme 22).

[139] S. Dahmen, S. Bräse *Org. Lett.* **2001**, *3*, 4119.
[140] (a) J.-X. Ji, L.-Q. Qiu, C. W. Yip, A. S. C. Chan *J. Org. Chem.* **2003**, *68*, 1589. (b) C. M. Sprout, M. L. Richmond, C. T. Seto *J. Org. Chem.* **2004**, *69*, 6666. (c) S.-L. Tseng, T.-K. Yang *Tetrahedron: Asymmetry* **2005**, *16*, 773. (d) M. L. Richmond, C. M. Sprout, C. T. Seto *J. Org. Chem.* **2005**, *70*, 8835.
[141] Y. K. Chen, A. E. Lurain, P. J. Walsh *J. Am. Chem. Soc.* **2002**, *124*, 12225.
[142] A. E. Lurain, P. J. Walsh *J. Am. Chem. Soc.* **2003**, *125*, 10677.
[143] (a) A. E. Lurain, A. Maestri, A. R. Kelly, P. J. Carroll, P. J. Walsh *J. Am. Chem. Soc.* **2004**, *126*, 13608. (b) A. R. Kelly, A. E. Lurain, P. J. Walsh *J. Am. Chem. Soc.* **2005**, *127*, 14668.
[144] S.-J. Jeon, Y. K. Chen, P. J. Walsh *Org. Lett.* **2005**, *7*, 1729.
[145] P. Wipf, C. R. J. Stephenson *Org. Lett.* **2003**, *5*, 2449.
[146] (a) H. Li, P. J. Walsh *J. Am. Chem. Soc.* **2004**, *126*, 6539. (b) H. Li, P. J. Walsh *J. Am. Chem. Soc.* **2005**, *127*, 8355.
[147] Since dimeric products were formed in the reaction, it was hypothesized by the authors that a borane-promoted dimerization of the intermediate alkenyl-alkylzinc species occurred.



SCHEME 22. Catalytic enantioselective vinylation of ketones by WALSH.

As can be seen from Scheme 22, the transmetallation step and the subsequent titanium-catalyzed addition to the electrophile were performed in two separate reaction vessels, in order to minimize the quantity of alkyne and Schwartz reagent needed for the reaction to occur.

When aryl-alkyl ketones and cyclic enones were used as substrates, the enantioselectivities were consistently high: lower values were obtained only when dialkylketones were employed as substrates. The method exhibited broad functional group compatibility and tolerated moieties such as alkyl chlorides, sulfides, esters and silylethers.

The use of 1-ene-3-ynes as starting materials, in particular, allowed the development of an unprecedented catalytic enantioselective dienylation of ketones. Moreover, application of preformed divinylzinc reagents gave access to the synthesis of tertiary allylic alcohols with trisubstituted double bonds.[146b]

2.3. Addition of Alkynes to Carbon-Heteroatom Double Bonds

2.3.1. Propargylic Alcohols and Amines in Organic Synthesis

In the previous sections *2.1.* and *2.2.*, the addition of C(sp^3)- and C(sp^2)-Zn nucleophiles to carbonyl compounds and imines has been discussed, with particular emphasis placed upon catalytic enantioselective processes. The products of the reaction of such electrophiles with a metal acetylide as the nucleophilic partner are propargylic alcohols and propargylamines, respectively.

Propargylic alcohols have long been recognized as useful intermediates in organic synthesis, due to the ability of easily modify their functional groups: for example, the hydroxy group can be

displaced by nucleophilic substitution after transformation in a good leaving group,[148] or the triple bond can be completely or partially reduced, in this last case giving rise to allylic alcohols (the alkynylation of carbonyl compounds can therefore become an alternative to the direct vinylation, in cases where the latter reaction cannot be applied). Propargylic alcohols have been used in many total syntheses as precursors of natural products or pharmaceutical compounds.[149]

Propargylamines have also found broad application in the synthesis of nitrogen containing compounds such as allylamines, pyrroles, and pyrrolidines.[150] As their oxygenated counterparts, they have been often used in synthesis of natural products[151] or pharmaceuticals,[152] and moreover some simple derivatives of propargylamines were found to possess interesting biological properties.[153,154]

Classical methodologies for the preparation of propargylic alcohols and amines starting from terminal alkynes usually exploited the relatively high acidity of the acetylenic C-H bond to form alkynyl-metal reagents by reaction with bases. The so-formed organometallic compounds can easily undergo nucleophilic addition to suitable electrophiles to form the desired products.

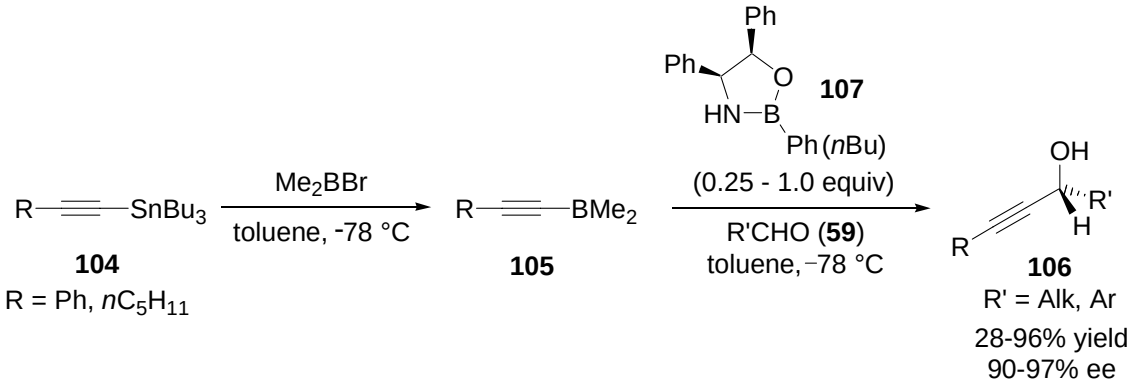
Typically, strong bases such as butyllithium,[155] organomagnesium compounds,[156] sodium amide and other metalated amines,[157] potassium *tert*-butoxide,[158] or cesium hydroxide hydrate[159] were

[148] J. A. Marshall, M. A. Wolf *J. Org. Chem.* **1996**, *61*, 3238.
[149] Vitamins E and K: (a) N. Cohen, R. J. Lopresti, C. Neukom, G. Saucy *J. Org. Chem.* **1980**, *45*, 582. Alkaloids: (b) L. E. Overman, K. L. Bell *J. Am. Chem. Soc.* **1981**, *103*, 1851. Palytoxin: (c) J. Leder, H. Fujioka, Y. Kishi *Tetrahedron Lett.* **1983**, *24*, 1463. Cystochalasin: (d) G. Stork, E. J. Nakamura *J. Am. Chem. Soc.* **1983**, *105*, 5510. (d) S. H. Cheon, W. J. Christ, L. D. Hawkins, H. Jin, Y. Kishi *Tetrahedron Lett.* **1986**, *27*, 4759. Sterepolide: (f) B. M. Trost, P. A. Hipskind, J. Y. L. Chung, C. Chan *Angew. Chem.* **1989**, *101*, 1559; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1502. Chlorotricholide: (g) W. R. Roush, R. J. Sciotti *J. Am. Chem. Soc.* **1994**, *116*, 6457. Methylenolactocin: (f) G. Zhu, X. Lu *J. Org. Chem.* **1995**, *60*, 1087. For a recent application towards the synthesis of polyketide members of the cytostatine family, see: (g) J. A. Marshall, M. P. Borbeau *Org. Lett.* **2003**, *5*, 3197.
[150] (a) B. M. Nilsson, U. J. Hacksell *J. Heterocycl. Chem.* **1989**, *26*, 269. (b) D. F. Havey, D. M. Sigano *J. Org. Chem.* **1996**, *61*, 2268. (c) A. Arcadi, S. Cacchi, L. Cascia, G. Fabrizi, F. Marinelli *Org. Lett.* **2001**, *3*, 2501. For an excellent example of the use of *N*-allyl propargylamines in the synthesis of polycyclic pyrrole-2-carboxylates, see: (d) Y. Yamamoto, H. Hayashi, T. Saigoku, H. Nishiyama *J. Am. Chem. Soc.* **2005**, *127*, 10804.
[151] Synthesis of Dynemicines: (a) J. A. Porco, Jr., F. J. Schoenen, T. J. Stout, J. Clardy, S. L. Schreiber *J. Am. Chem. Soc.* **1990**, *112*, 7410. (b) K. C. Nicolaou, C.-K. Hwang, A. L. Smith, S. V. Wendeborn *J. Am. Chem. Soc.* **1990**, *112*, 7416. (c) T. Yoon, M. D. Shair, S. J. Danishefsky, G. K. Shulte *J. Org. Chem.* **1994**, *59*, 3752. Formal total synthesis of (+)-Conessine: (d) B. Jiang, M. Xu *Angew. Chem.* **2004**, *116*, 2597; *Angew. Chem. Int. Ed.* **2004**, *43*, 2543. Synthesis of (+)-Saxitoxin: (e) J. J. Fleming, J. Du Bois *J. Am. Chem. Soc.*, **2006**, *128*, 3926.
[152] Synthesis of β-lactams: (a) M. Shibasaki, Y. Ishida, G. Iwasaki, T. Iimori *J. Org. Chem.* **1987**, *52*, 3488. (b) N. Miyachi, F. Kanda, M. Shibasaki *J. Org. Chem.* **1989**, *54*, 3511. Synthesis of inhibitors of the serotonine and norepinephrine transporter: (c) A. Hoepping, K. M. Johnson, C. George, J. Flippen-Anderson, A. P. Kozikowski *J. Med. Chem.* **2000**, *43*, 2064.
[153] Inhibitors of the enzyme monoamide oxidase B (MAO B): P. H. Yu, B. Davis, A. A. Boulton *J. Med. Chem.* **1992**, *35*, 3705 and references cited therein.
[154] J. L. Wright, T. F. Gregory, S. R. Kesten, P. A. Boxer, K. A. Serpa, L. T. Meltzer, L. D. Wise, S. A. Espitia, C. S. Konkoy, E. R. Whittemore, R. M. Woodward *J. Med. Chem.* **2000**, *43*, 3408.
[155] (a) H. G. Viehe, M. Reinstein *Chem. Ber.* **1962**, *95*, 2557. (b) B. J. Wakefield *Organolithium Methods in Organic Synthesis*, Chap. 3, p. 32, Academic Press, London, **1988**.
[156] (a) P. E. Eaton, A. Srikrishna, F. Uggeri *J. Org. Chem.* **1984**, *49*, 1728. (b) Ref. 6a, Chap. 3, p. 46.
[157] J. H. Saunders *Org. Synth.* **1955**, *33*, 416.
[158] J. H. Babler, V. P. Liptak, N. Phan *J. Org. Chem.* **1996**, *61*, 416.
[159] D. Tzalis, P. Knochel *Angew. Chem.* **1999**, *111*, 1547; *Angew. Chem. Int. Ed.* **1999**, *38*, 1463.

used in the process.[160] Clearly, such strong basic reagents are incompatible with carbonyl compounds or imines, and therefore alkyne deprotonation had to be carried out in a separate step.

Moreover, even in the presence of a stoichiometric amount of a chiral promoter, the reactivity of the resulting polar lithium-, sodium- or magnesium-alkynylides is in general too high to allow the reaction to proceed in a stereocontrolled manner under mild conditions. For example, MUKAIYAMA succedeed in preparing propargylic alcohols with up to 92% ee from lithium acetylides and benzaldehyde, but this result could be obtained only using 4.0 equiv of a chiral diamino alcohol as a promoter at a temperature of –123 °C.[161] Another report describes the addition of lithium trimethylsilylacetylide to substituted cyclohexanones in the presence of ligand **31**. Enantiomeric excesses up to 82% were obtained in presence of a stoichiometric quantity of the aminoalcohol.[162]

The first highly enantioselective addition of an alkynyl nucleophile to aldehydes was described by COREY and CIMPRICH in 1994.[163] They showed that use of alkynylboranes as nucleophiles in the presence of a stoichiometric or substoichiometric (0.25 equiv) amount of a chiral oxazaborolidine gave access to propargylic alcohols in useful yields with up to 96% ee. Also in this case, a low temperature (−78 °C) was necessary to obtain high enantioselectivity (Scheme 23).



SCHEME 23. Enantioselective alkynylborane addition to aldehydes by COREY.

In the last decade, exceptional progress has been made in the field of the direct alkynyl addition to carbon-heteroatom double bonds. This transformation has often been carried out with transition

[160] In particular for the preparation of propargylic amines, see: (a) L. M. Harwood, K. J. Vines, M. G. B. Drew *Synlett* **1996**, 1051. (b) D. Brasseur, I. Marek, J.-F. Normant, *Tetrahedron* **1996**, *52*, 7235. (c) G. Curtois, V. Desre, L. Miginiac *J. Organomet. Chem.* **1998**, *570*, 279. (d) J. Cossy, C. Poitevin, D. G. Pardo, J.-L. Peglion, A. Dessinges *Synlett* **1998**, 251. (e) S. Florio, L. Troisi, V. Capriati, G. Suppa *Eur. J. Org. Chem.* **2000**, 3793. Review: (f) J. Blanchet, M. Bonin, L. Micouin *Org. Prep. Proced. Int.* **2002**, *34*, 457.

[161] (a) T. Mukaiyama, K. Suzuki, K. Soai, T. Sato *Chem. Lett.* **1979**, 447. (b) T. Mukaiyama, K. Suzuki *Chem. Lett.* **1980**, 255.

[162] K. Scharpwinkel, S. Matull, H. J. Schäfer *Tetrahedron: Asymmetry* **1996**, *7*, 2497.

[163] E. J. Corey, K. A. Cimprich *J. Am. Chem. Soc.* **1994**, *116*, 3151.

metals as catalysts or promoters, and unquestionably organozinc compounds have now a prominent role in this chemistry.

The following paragraphs will provide an overview of the most significant developments recently appeared in the literature.[164]

2.3.2. Direct Addition of Alkynes to Aldehydes

2.3.2.1. Metal Salt-Promoted Addition and Double Activation Strategy

In the last decade of the twentieth century, some reports were published about the use of *stoichiometric* quantities of metal salts to promote the alkynylation of aldehydes. These activators included $Sn(OTf)_2$, $SnCl_2$[165] and GaI_3.[166]

On the basis of these reports, a new strategy for the in situ generation of metal acetylides and their addition to carbon-heteroatoms double bonds was elaborated by CARREIRA and co-workers, which relied on the use of a zinc salt in combination with a weak base, typically a tertiary amine.[167]

Initial investigations focused on the use of Cu(I) or Ag(I) salts for this reaction; it is in fact known that these metals are able to form π-complexes with alkynes by coordination of the triple bond. As a consequence of coordination, the terminal C(sp)-H bond is labilized, so that even weakly basic amines can effect its deprotonation with concomitant generation of the corresponding metal alkynylide.[168] Unfortunately, however, the latter were found to be ineffective in the reaction with nitrones or aldehydes as substrates, probably as a result of the excessive strenght of the C(sp)-metal bond.

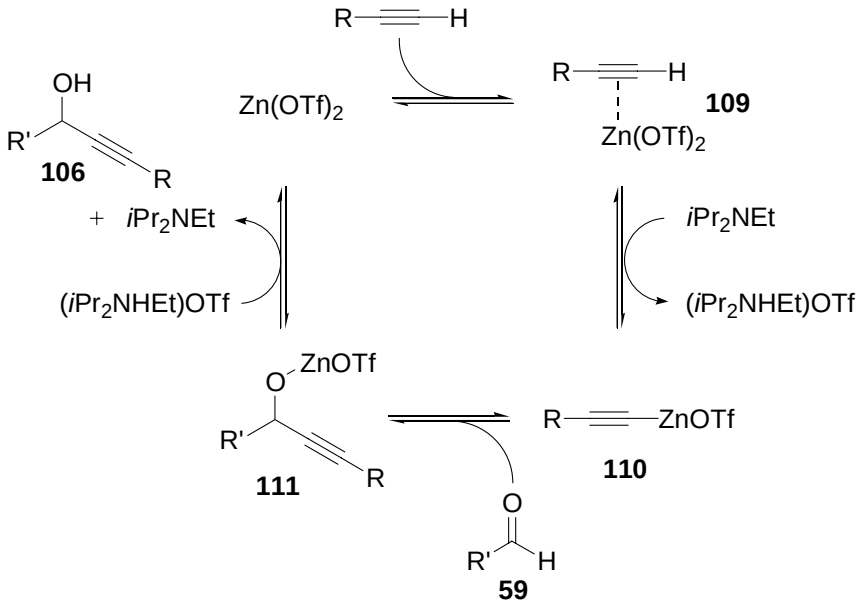
After an extensive screening of metal precursors and organic bases, it was found that a combination of 10 mol% $Zn(OTf)_2$ and 25 mol% $i Pr_2NEt$ led to product formation.[169,170] Although the initial report was primarily focused on the use of nitrones as substrates, to give propargylic

[164] For leading reviews, see: (a) L. Pu *Tetrahedron* **2003**, *59*, 9873. (b) P. G. Cozzi, R. Hilgraf, N. Zimmermann *Eur. J. Org. Chem.* **2004**, 4095.
[165] (a) M. Yamaguchi, A. Hayashi, T. Minami *J. Org. Chem.* **1991**, *56,* 4091. (b) M. Yamaguchi, A. Hayashi, M. Dirama *Chem. Lett.* **1992**, 2479.
[166] Y. Han, Y.-Z. Huang *Tetrahedron Lett.* **1995**, *36*, 7277.
[167] For an account on the early stages of the development of this methodology, see: D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira *Acc. Chem. Res.* **2000**, *33*, 373.
[168] F. A. Cotton, G. Wilkinson, C. A. Murillo, M. Bochmann *Advanced Inorganic Chemistry*, 6th Ed., Wiley, New York, **1999**.
[169] D. E. Frantz, R. Fässler, E. M. Carreira *J. Am. Chem. Soc.* **1999**, *121*, 11245.
[170] The authors state here that zinc halides such as $ZnCl_2$ and ZnI_2 were ineffective in this reaction. Later, however, a $ZnCl_2$-mediated alkynylation of aldehydes employing TMSCl as a Lewis acid has been reported, see: B. Jiang, Y.-G. Si *Tetrahedron Lett.* **2002**, *43*, 8323.

hydroxylamines as products, the possibility to convert aldehydes, ketones and a *N*-tosylimine was also demonstrated.[171] The authors pointed out that all the reagents, including the solvent (CH_2Cl_2), could be used as received from commercial sources, without the need for prior purification.

The formation of the zinc acetylenides was confirmed by ^{13}C-NMR[169] and, later, in situ-IR studies.[172] In the NMR experiment, the resonances of the sp-hybridized carbons of 4-phenyl-1-butyne showed a large downfield shift after treatment with *i*Pr_2NEt and $Zn(OTf)_2$. Analogously, the addition of those two reactants to an acetonitrile solution of phenylacetylene (**108**) induced the disappearance of the C(sp)-H stretching resonance in the IR spectrum of the alkyne, while addition of the amine alone had almost no effect. The reversible character of the process was demonstrated by the subsequent addition of an excess of a strong acid, which led to reappearance of the C(sp)-H stretching signal.

The commonly-accepted mechanistic picture (in the case of an aldehyde as substrate) is depicted in Scheme 24.



SCHEME 24. Mechanism of the $Zn(OTf)_2$-catalyzed alkynylation of aldehydes by CARREIRA.

Shortly after, an enantioselective version of this reaction was reported, in which enantioenriched propargylic alcohols could be obtained in the presence of (+)-*N*-methylephedrine [(+)-NME, **114**] as a chiral promoter.[173] Very high enantiomeric excesses (94-99% ee) were observed for both

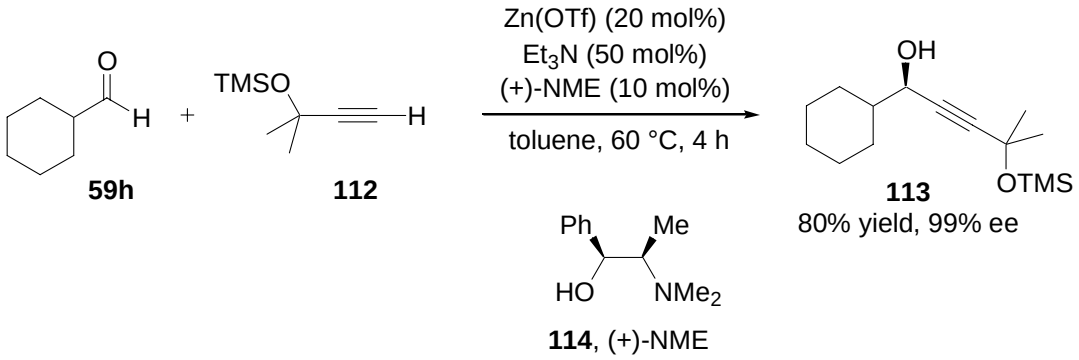
[171] With the last substrate, however, only a modest 43% yield was obtained, in contrast to the often high yields afforded by the other starting materials.
[172] R. Fässler, C. S. Tomooka, D. E. Frantz, E. M. Carreira *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843.
[173] D. E. Frantz, R. Fässler, E. M. Carreira *J. Am. Chem. Soc.* **2000**, *122*, 1806.

aliphatic and aromatic substrates, but the latter generally furnished diminished yields due to side reactions, such as the Cannizzaro disproportionation. In this initial report, however, the zinc salt, the base and the chiral ligand had to be used in stoichiometric amounts to obtain good results.[174]

Interestingly, the authors demonstrated that also in the case of the enantioselective process, use of distilled solvent and inert atmosphere was not required: the reaction performed in ACS reagent-grade toluene (containing ~ 300 ppm H_2O) under air afforded the product in slightly lower yield (92 vs. 99%) but with essentially the same ee as the reaction run in distilled toluene under a nitrogen atmosphere.

A further improvement of the process, reported by the same research group, was represented by the possibility of using the metal salt, the amine and the chiral ligand in catalytic amount. To overcome the problem of low turnover in the catalytic cycle, it was sufficient to perform the reaction at 60 °C using Et_3N instead of iPr$_2$NEt (Scheme 25).[175] The ideal substrates were found to be aliphatic α-branched aldehydes (up to 94% yield, 99% ee), with linear aliphatic aldehydes affording only slightly inferior results. The use of aromatic aldehydes, on the contrary, was not reported.

The authors described also a solvent-free version of the same reaction, which proceeded with equally high selectivity. Furthermore, this latter procedure simplified the work-up and purification of the products.



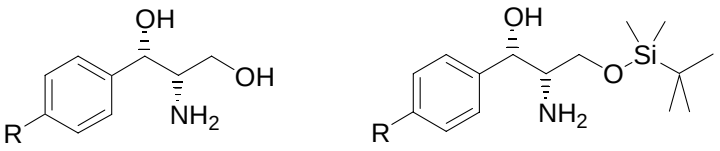
SCHEME 25. Catalytic enantioselctive additon of alkynes to aliphatic aldehydes by CARREIRA.

[174] For further applications of the same methodology, see: (a) H. Sasaki, D. Boyall, E. N. Carreira *Helv. Chim. Acta* **2001**, *84*, 964 (direct addition of acetylene). (b) D. Boyall, F. López, H. Sasaki, D. E. Frantz, E. M. Carreira *Org. Lett.* **2000**, *2*, 4223. (c) E. El-Sayed, N. K. Anand, E. M. Carreira *Org. Lett.* **2001**, *3*, 3017. (d) R. S. Diez, B. Adger, E. M. Carreira *Tetrahedron* **2002**, *58*, 8341.

[175] N. K. Anand, E. M. Carreira *J. Am. Chem. Soc.* **2001**, *123*, 9687.

In the following years, this reaction was applied in the total synthesis of several natural products. The enantioselective syntheses of (*R*)-strongylodiols A and B,[176] musclide B,[177] epothilones A and B,[178] and leucascandrolide A[179] were all accomplished with the stereoselective addition of acetylenes to aldehydes mediated by ephedrine derivatives as the key step.[180]

After the reports of CARREIRA, a variation of the same reaction based on the use of ligands (1*S*,2*S*)-**115a-b** and (1*S*,2*S*)-**116a-b** has been published by JIANG (Figure 10).[181] Although that seems to be the only point in which this procedure differs from the original one, the authors reported that good yields were obtained also for benzaldehyde, which nevertheless needed a longer reaction time. Moreover, the formation of products arising from a Cannizzaro reaction was not mentioned.



(1*S*,2*S*)-**115a**, R = H
(1*S*,2*S*)-**115b**, R = NO_2

(1*S*,2*S*)-**116a**, R = H
(1*S*,2*S*)-**116b**, R = NO_2

FIGURE 10. Ligands for the enantioselective alkynylation of aldehydes by JIANG.

While amino alcohols (1*S*,2*S*)-**115a-b** furnished poor yields of the products under various conditions (albeit with high ee), the more lipophile structures (1*S*,2*S*)-**116a-b** proved superior, allowing isolation of propargylic alcohols in 73-99% yields with 93-99% ee. The reactions were usually stoichiometric, but catalytic conditions similar to those reported by CARREIRA[173] could also be applied, furnishing only slightly inferior results.

[176] S. Reber, T. F. Knöpfel, E. M. Carreira *Tetrahedron* **2003**, *59*, 6813.
[177] M. Amador, X. Ariza, J. Garcia, J. Ortiz *Tetrahedron Lett.* **2002**, *43*, 2691.
[178] J. W. Bode, E. M. Carreira *J. Am. Chem. Soc.* **2001**, *123*, 3611.
[179] (a) A. Fettes, E. M. Carriera *Angew. Chem.* **2002**, *114*, 4272; *Angew Chem. Int. Ed.* **2002**, *41*, 4098. (b) A. Fettes, E. M. Carriera *J. Org. Chem.* **2003,** *68*, 9774.
[180] It must be mentioned at this point that the generality of the Carreira reaction has been questioned by part of the scientific community. Although many groups have applied successfully this methodology, the number of failed Carreira reactions reported in the literature is in fact considerable. For a detailed discussion of this topic, in the context of the second total synthesis of strongylodiols A and B, see: J. E. D. Kirkham, T. D. L. Courtney, V. Lee, J. E. Baldwin *Tetrahedron* **2005**, *61*, 7219, and references cited therein. The authors suggest that problems in reproducibility could depend from the commercial source of $Zn(OTf)_2$. Since the reaction is essentially an heterogeneous mixture, it is possible that it actually takes place on the surface of the salt, rather than in solution. Since the morphology of the surface can depend from the commercial source, as well as from other factors, this would account for the differences observed in its outcome.
[181] B. Jiang, Z. Chen, W. Xiong *Chem. Commun.* **2002**, 1524.

The same research group shortly after introduced zinc diflate, $Zn(ODf)_2$, obtained from difluoromethanesulfonic acid, as an alternative to the corresponding triflate for the same reaction.[182] This new metal salt performed equally well, and propargylic alcohols could be once again obtained in high yield and enantioselectivity.

A further modification of the ligand structure was recently introduced by DAVIS, who employed carbohydrate-derived chiral ligands.[183] The large availability of the starting materials and the possibility to introduce structural modifications with well-established methodologies allowed the rapid preparation of a small initial library of ten amino alcohols, which were tested in the reaction of aldehyde **59h** with phenylacetylene (**108**). Some of the compounds proved to be excellent ligands [even better than (+)-**114**] and, after optimization, the enantioselective addition of various alkynes to aliphatic aldehydes could be conducted with satisfying yields and enantioselectivities. Unfortunately, challenging substrates for this reaction such as aromatic aldehydes and unbranched aliphatic aldehydes were often converted with good enantioselectivity, but in rather low yield: isolation of by-products suggested the intervention in these cases of aldol / Tischenko or Cannizzaro reactions.

In recent years, other metal salts have found application in the same kind of reactions. For example, $InBr_3$ was used for this purpose in combination with an equimolar quantity of a weak organic base like Et_3N.[184] In this last case, the authors also reported the use of *N*,*O*-acetals as surrogates of imines for the preparation of propargylimines.

No clear explanation of the reaction mechanism was provided, although also here the formation of metal-acetylides seemed feasible. On the other hand, the electrophiles were certainly activated by the metal salt acting as a Lewis acid.

Prompted by these observations, OHSHIMA and SHIBASAKI developed an efficient *catalytic* alkynylation of carbonyl compounds by means of In(III)-salts based on the principle of the double activation.[185] Taking inspiration from their previous work on heterobimetallic and Lewis acid / Lewis base bifunctional catalysts,[186] the authors supposed that an indium salt should have been able both to activate the alkyne for deprotonation via π-coordination, and to increase the electrophilicity of the carbonyl compound by coordination of one of the oxygen lone pairs.[187]

[182] Z. Chen, W. Xiong, B. Jiang *Chem. Commun.* **2002**, 2098.
[183] D. P. G. Emmerson, W. P. Hems, B. G. Davis *Org. Lett.* **2006**, *8*, 207.
[184] N. Sakai, M. Hirasawa, T. Konokahara *Tetrahedron Lett.* **2003**, *44*, 4171.
[185] R. Takita, Y. Fukuta, R. Tsuji, T. Ohshima, M. Shibasaki *Org. Lett.* **2005**, *7*, 1363.
[186] (a) M. Shibasaki, N. Yoshikawa *Chem. Rev.* **2002**, *102*, 2187. (b) *Multimetallic Catalysts in Organic Synthesis* (Eds: M. Shibasaki, Y. Yamamoto), Wiley-VCH, Weinheim, **2004**.
[187] A system based on the same principle, but using two different metal sources [$In(OAc)_3$ and $RuCl_3$], has also been reported: C. Wei, C.-J. Li *Green Chem.* **2002**, *4*, 39. In this case water was used as the solvent.

Indeed, this hypothesis proved right and in the presence of 10 mol% of $InBr_3$ and 20 mol% of di(*iso*-propyl)ethylamine many aromatic and aliphatic aldehydes as well as ketones could be smoothly converted into the corresponding propargylic alcohols with 58 to 99% yield. In situ-IR and NMR studies confirmed the supposed mechanism.

Subsequently, an enantioselective version of this protocol was developed, by the use of (*R*)-BINOL as the chiral ligand. After some minor adjustments in the stoichiometry and in the reaction conditions, secondary propargylic alcohols could be obtained from aliphatic and aromatic aldehydes in good yields and constantly high enantiomeric excesses (89->99% ee).[188] Interestingly, the reaction showed a very strong positive non-linear effect. This seems to indicate that two atoms of indium are actually involved in the bifunctional activation.

A similar process, using a phosphine-silver (I) complex as the catalyst in water, has also been reported.[189] As already mentioned, the C-Ag bond in a silver-acetylide compound is considered too strong to undergo addition to carbonyl compounds. Use of a phosphine as the ligand for silver increases the electron density on the metal, thus weakening the C-Ag bond. As a consequence, the silver acetylide is now reactive enough to add to the aldehyde. Additionally, the authors propose that silver coordinates the substrate and activates it for the reaction. Interestingly, the reaction takes place only in water,[190] while no product is formed in toluene. This suggests that coordination by the solvent can also play a role in this process.

2.3.2.2. Dialkylzinc-Promoted Enantioselective Additions of Acetylenes to Aldehydes

Among the various approaches to the synthesis of enantioenriched propargylic alcohols, the dialkylzinc-mediated enantioselective addition of acetylenes to aldehydes[164a] is the most investigated one, probably due to similarities with the already well-known alkyl addition.

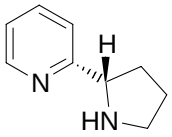
This reaction has usually been conducted in the presence of chiral amino alcohols as ligands, either in stoichiometric or in catalytic amount, but the use of pyridine-based compounds and 1,1'-binaphthols in combination with $Ti(iPrO)_4$ have also been described.

The first example of a catalytic asymmetric addition of an alkynylzinc reagent to an aldehyde was reported by SOAI and co-workers, who generated this species by heating an alkyne with Et_2Zn in an

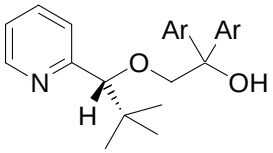
[188] R. Takita, K. Yakura, T. Ohshima, M. Shibasaki *J. Am. Chem. Soc.* **2005**, *127*, 13760.
[189] X. Yao, C.-J. Li *Org. Lett.* **2005**, *7*, 4395.
[190] More precisely, since neither the catalyst nor the substrate are water-soluble, the reaction takes place "on water". For more detailed informations regarding reactions "on water", see: S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless *Angew. Chem.* **2005**, *116*, 2; *Angew. Chem. Int. Ed.* **2005**, *44*, 2.

organic solvent.[191] Use of chiral aminoalcohols including (1*R*,2*S*)-DBNE [(1*R*,2*S*)-**48**], (*S*)-DPMPM [(*S*)-**68a**] and derivatives thereof furnished the products in high yields but with low enantiomeric excesses (≤43%).

Shortly after, use of pyridyl ligands (*S*)-**117** and (*R*)-**118a-c** was described by FALORNI and co-workers,[192] and by ISHZAKI and OSHINO,[193] respectively (Figure 11).



(*S*)-**117**

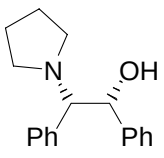


(*R*)-**118a**, Ar = Ph
(*R*)-**118b**, Ar = 1-Naph
(*R*)-**118c**, Ar = 2-Naph

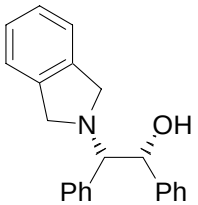
FIGURE 11. Pyridine-based ligands for the enantioselective alkynylation of aldehydes.

While compound (*S*)-**117**, used in combination with pre-formed (*n*BuCCH)$_2$Zn, gave products with very low enantiomeric excess, up to 95% ee could be obtained with ligand (*R*)-**118b**, although some substrates, like unbranched aliphatic aldehydes, gave much worse results. The authors generated the alkynylzinc species by refluxing acetylenes with Et_2Zn in THF; with aliphatic alkynes considerable amounts of the products of the alkylzinc addition were found in some cases.

In 1999, the application of amino alcohols (1*R*,2*S*)-**119** and (1*R*,2*S*)-**120** (Figure 12) was described by LI.[194] Aromatic aldehydes were reacted with phenylacetylene or 1-butyne to furnish products with up to 85% ee.



(1*R*,2*S*)-**119**



(1*R*,2*S*)-**120**

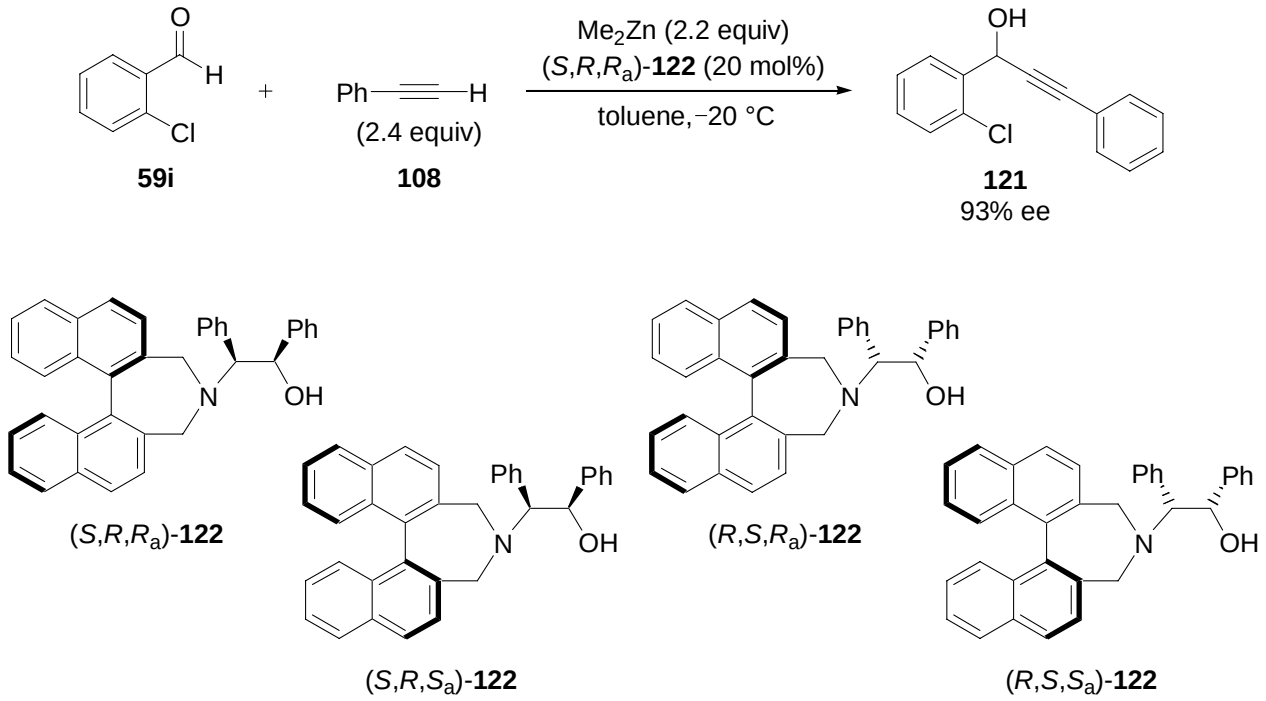
FIGURE 12. Amino alcohols as ligands for the enantioselective alkynyl addition to aldehydes.

[191] S. Niwa, K. Soai *J. Chem. Soc., Perkin Trans. I* **1990**, 937.
[192] G. Chelucci, S. Conti, M. Falorni, G. Giacomelli *Tetrahedron* **1991**, *47*, 8251.
[193] M. Ishizaki, O. Oshino *Tetrahedron: Asymmetry* **1994**, *5*, 1901.
[194] Z. Li, V. Upadhyay, A. E. DeCamp, L. DiMichele, P. J. Reider *Synthesis* **1999**, 1453.

Notably, in this case the alkynylzinc reagent was formed simply by mixing Me_2Zn with the alkyne in toluene in the presence of the ligand at –20 °C. As demonstrated by in situ-NMR studies, mixing of those two compounds in the absence of ligand (1*R*,2*S*)-**119** or (1*R*,2*S*)-**120** did not lead to any reaction. The change in the geometry of Me_2Zn in the presence of a complexating agent is probably responsible for this behavior (see paragraph *2.1.*, Figure 4).

After these first reports, research in this field has been primarily directed toward the development of new and more efficient ligands for this reaction, whereas standardized conditions, mostly based on the use of mixtures of toluene and other solvents and on application of low temperatures (typically between –30 and 0 °C) have usually been employed.

An interesting family of ligands was introduced in 2001 by CHAN, who prepared 1,1'-binaphthyl derived amino alcohols **122**, which can be synthesized in few steps starting from commercially available BINOL.[195] This method allowed a good enantiocontrol for aromatic aldehydes (up to 93% ee), albeit at a temperature of –20 °C, while employment of aliphatic aldehydes resulted in products with decreased enantiomeric excesses (Scheme 26).



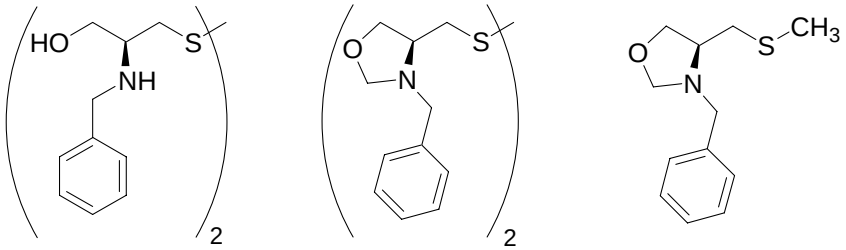
SCHEME 26. Enantioselective alkynyl addition to aldehydes by CHAN.

It is noteworthy that the choice of Me_2Zn as the promoting agent in the place of the more common Et_2Zn was crucial for the success of the reaction. Since Me_2Zn is less reactive than its homologue,

[195] G. Lu, X.-S. Li, Z.-Y. Zhou, W. L. Chan, A. S. C. Chan *Tetrahedron: Asymmetry* **2001**, *12*, 2147.

even in the presence of amino alcohols **122** it is unable to furnish the product of the alkyl addition to aldehydes, but simply forms the active zinc complex and deprotonates phenylacetylene. This is in agreement with the already-mentioned observation of LI, who reports that the direct methyl addition to aldehydes was negligible under optimized conditions.[194]

In 2002, a novel class of cysteine-derived di- and monosulfide-alcohols and oxazolidines **123-125** has been introduced by BRAGA (Figure 13), who screened them as ligands in the diethylzinc-mediated addition of phenylacetylene (**108**) to benzaldehyde (**35**) in a mixture of THF and toluene at –20 °C.[196]



(*R*,*R*)-**123** (*R*,*R*)-**124** (*R*)-**125**

FIGURE 13. Cysteine-derived N,S-ligands by BRAGA.

While the product obtained from a reaction in which 10 mol% of disulfide (*R*,*R*)-**123** were used was racemic, the other two compounds proved able to furnish enantioenriched propargylic alcohols; interestingly, dimeric ligand (*R*,*R*)-**124** was superior to its monomeric analogue (*R*)-**125** in the test reaction (56% ee vs. 18% ee). After optimization, products were obtained in good yields with 36-60% ee. Although the enantiomeric excesses in this reaction were low compared to those observed with other systems, it must be pointed out that aliphatic aldehydes furnished results very close to those obtained for benzaldehydes.

As already discussed, metallocene-based hydroxy oxazolines have been found to be very useful ligands for the catalytic enantioselective addition of arylzinc compounds to aldehydes.[81,85,89-91,103] Inspired by these studies, in 2004 HOU reported the synthesis and the application to the diethylzinc-mediated alkynylation of aldehydes of new ferrocenyl hydroxy oxazolines **126** (Figure 14, where BOLM's ferrocenes (S,R_p)-**64** are also shown for comparison).[197]

[196] A. L. Braga, H. R. Appelt, C. C. Silveira, L. A. Wessjohann, P. H. Schneider *Tetrahedron* **2002**, *58*, 10413.
[197] M. Li, X.-Z. Zhu, K. Yuan, B.-X. Cao, X.-L. Hou *Tetrahedron: Asymmetry* **2004**, *15*, 219.

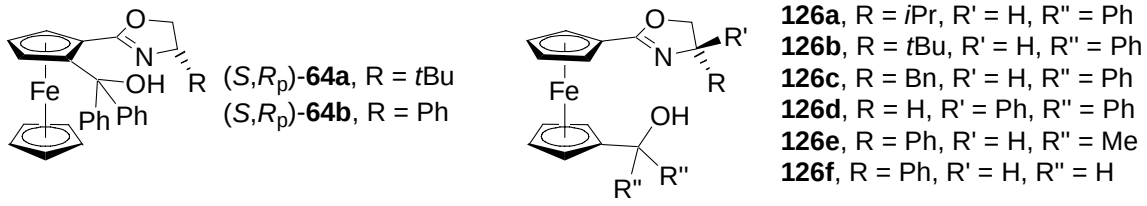
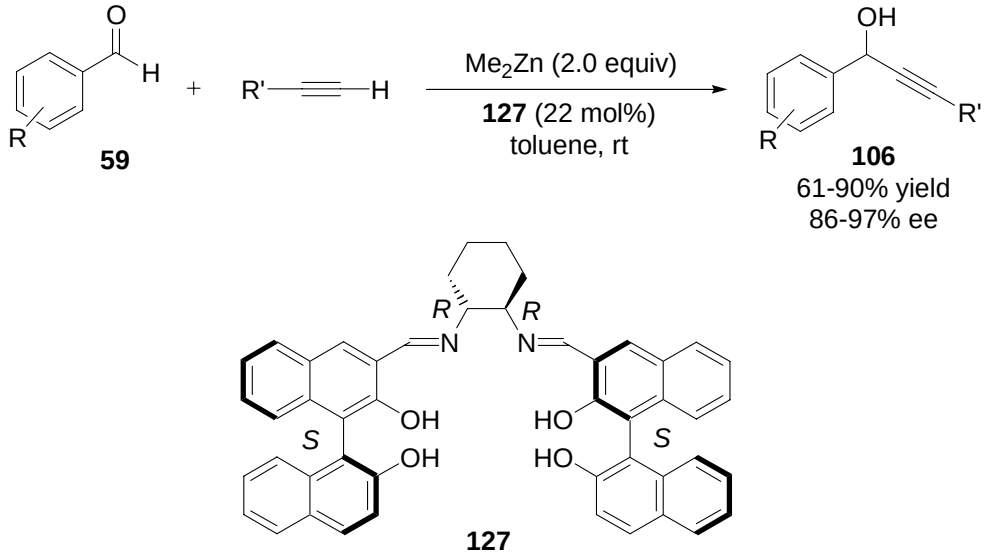


FIGURE 14. New ferrocenyl-based ligands for the enantioselective alkynylation of aldehydes by HOU.

Under the conditions chosen by the authors, compounds **126** performed better than ferrocene (S,R_p)-**64a**, wich gave the product with only 23% ee. The best ligand was **126d** which, after optimization, was able to catalyze (10-20 mol%) the reaction to give secondary propargylic alcohols with up to 88% yield and 93% ee. Also in this case, aliphatic aldehydes were converted with an enantioselectivity comparable to that of aromatic aldehydes, while α,β-unsaturated substrates furnished worse results (54-59% ee).

In the same year an efficient BINOL-Salen ligand system[198] was applied to the alkynlation reaction by PU and LI.[199] They found that this system was superior to the other BINOL-based catalysts in that it did not require the addition of Ti(*i*PrO)$_4$ as a promoter.[200] Indeed, although many structurally-related compounds were prepared, the only one that showed a considerable selectivity in the reaction was BINOL-Salen **127** (Scheme 27). Use of JACOBSEN's salen furnished also a poor result, indicating that the BINOL moiety was necessary to achieve high selectivity.



SCHEME 27. Enantioselective alkynylation of aldehydes with BINOL-Salen ligands by PU.

[198] This catalytic system had already been reported : E. F. DiMauro, M. C. Kozlowski *Org. Lett.* **2001**, *3*, 1641.
[199] Z.-B. Li, L. Pu *Org. Lett.* **2004**, *6*, 1065.
[200] For Ti-mediated alkynylations using organozinc nucleophiles, see paragraph *2.3.2.3.*

The alkynylation of various aromatic aldehydes proceeded at room temperature with remarkably high enantioselectivity (86-97% ee), although the catalyst loading was rather high (22 mol%). Interestingly, the addition to a vinyl aldehyde gave excellent stereocontrol as well (94% ee).

Later on, a bifunctional catalyst system was described by WANG and co-workers, which relied on the use of 2-pyridyl secondary amino alcohols (*S*)-**128a-c** as ligands, obtained by reductive amination of the corresponding primary amino alcohols with 2-formylpyridine (Figure 15).[201] The authors took inspiration from the work of KOZLOWSKI, who reported bifunctional Salen-derived ligands (*R*,*R*)-**129** for the alkylation of aldehydes and α-ketoesters, and demonstrated their higher capacity to promote the reaction in comparison, for example with (−)-DAIB [(−)**37**].[65] They also propose, according to the "bifunctional" character of the ligands, that while the amino alcohol moiety should form a chelate complex with zinc, which would then act as a Lewis acid to activate the electrophile, the second nitrogen on the pyridine ring should coordinate the alkyl-alkynylzinc species, thus activating the nucleophile.

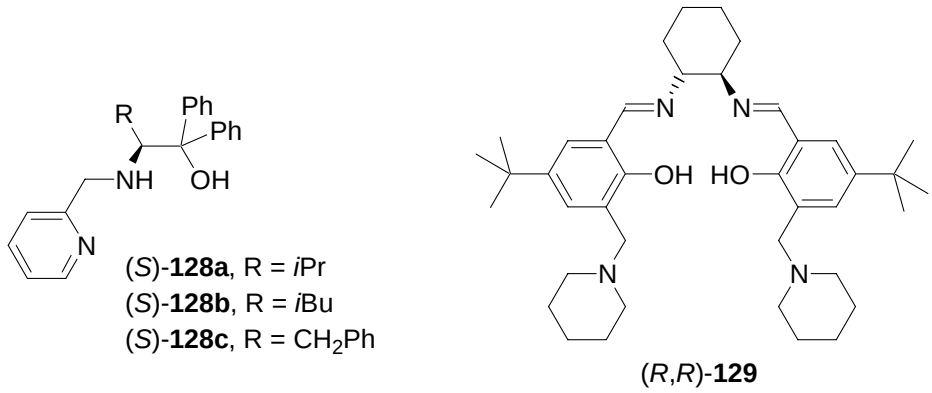


FIGURE 15. Bifunctional N,O-ligands by WANG [(*S*)-**128**] and KOZLOWSKI [(*R*,*R*)-**129**].

WANG's ligands demonstrated a remarkable activity in the addition of phenylacetylene to benzaldehyde [up to 95% yield and 94% ee, with 10 mol% catalyst loading, (*S*)-**128a**]. The need for the second nitrogen atom on the pyridine ring was demonstrated by the synthesis and application in catalysis of the phenyl-analogue of (*S*)-**128a**, which displayed a diminished selectivity (only 57% ee).

After optimization, amino alcohol (*S*)-**128a** could be efficiently used to promote the addition of phenylacetylene to various aromatic aldehydes with 85-98% ee. Isobutyraldehyde and cyclohexane carboxaldehyde were also very well tolerated, the corresponding secondary alcohols being isolated

[201] Y.-F. Kang, L. Liu, R. Wang, W.-J. Wan, Y.-F. Zhu *Tetrahedron: Asymmetry* **2004**, *15*, 3155.

in 91 and 88% yield and 91 and 90% ee, respectively. Slightly inferior enantioselectivity displayed the addition on cinnamaldehyde (81% ee).

In 2004 DAHMEN demonstrated the applicability of paracyclophane ligands **87-88**, introduced by him and BRÄSE in 2001 and since them applied in the catalytic asymmetric vinylation of aldehydes[139] and in the alkylation and phenylation of masked imines [61b,127] also to the Zn-mediated enantioselective alkynylation of aldehydes.[202] Use of ligand (R_p,*S*)-**87** allowed to drastically reduce the amount of catalyst in comparison with the other systems discussed above, and 2-5 mol% catalyst loading was enough to afford high enantioselectivities. Furthermore, additive effects on the stereoselectivity were observed in this reaction as already happened for the enantioselective aryl addition to aldehydes, and DiMPEG (MW = 2000 g·mol^{-1}) proved superior to MeOPEG. No remarkable effects on the yield was detected in the reactions run with additives. Once again, use of dimethylzinc was required to avoid the formation of the products of alkyl addition. Moreover, reactions conducted with Me_2Zn usually exhibited better yield and selectivity than those conducted with Et_2Zn.

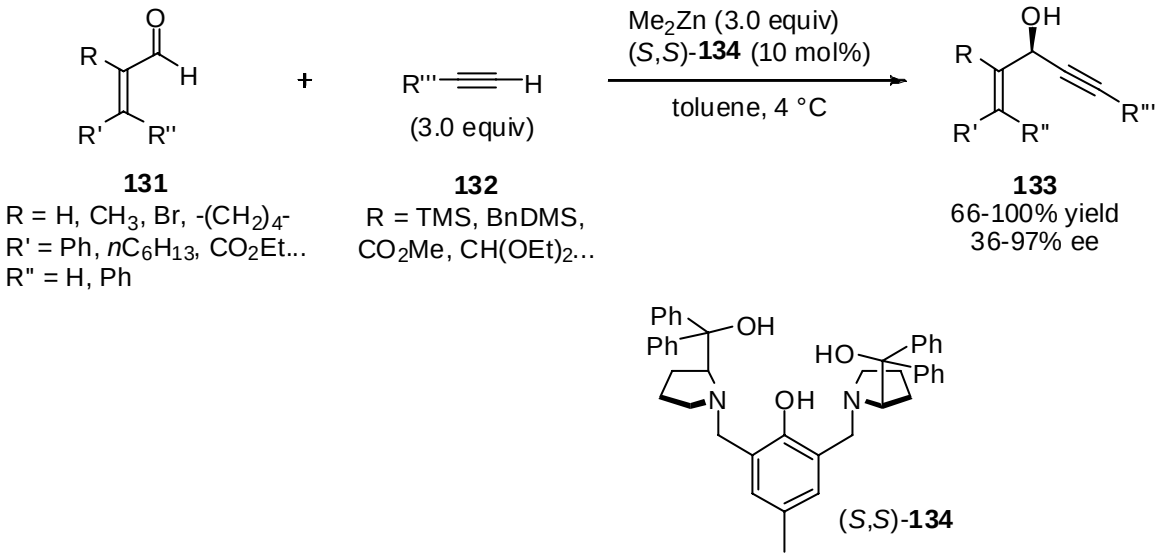
After optimization, various aromatic aldehydes could efficiently undergo alkynyl addition with phenylacetylene (**108**), giving products with high enantiomeric excess (up to >98% ee). Other alkynes were tolerated, but use of TMS-acetylene (**130**) instead of phenylacetylene caused a decrease in the enantioselectivity, as well as the employment of aliphatic aldehydes as substrates (up to 77% ee).

The application of limonene- and carene-derived amino alcohols in the asymmetric alkynylation of aldehydes was reported in 2005 by SINGARAM, who obtained them by diastereoselective ring-opening of the corresponding epoxide (in the case of limonene) or by diastereoselective epoxidaton and subsequent ring-opening reaction (in the case of carene).[203] Use in catalysis with a typical loading of 10 mol% afforded products in useful yields but only with up to 69% ee. Aromatic aldehydes as substrates performed much better than aliphatic ones, whose products were isolated in nearly racemic form. Even if these results cannot compete with the best ones reported in the literature, the possibiliy to prepare active ligands from inexpensive terpenes whose structure can be easily modified and optimized should allow to obtain significant improvements in the future.

Amino alcohols **71** (see Figure 8, p. 25) which proved to be active catalysts for the enantioselective addition of diphenylzinc to aromatic aldehydes,[97] were applied in the same study also to the enantioselective addition of phenylacetylene to the same substrates. Although also in this case propargylic alcohols were generally formed in good yields, enantiomeric excesses did not exceed 70%.

[202] S. Dahmen *Org. Lett.* **2004**, *6*, 2113.
[203] C. C. Watts, P. Thoniyot, L. C. Hirayama, T. Romano, B. Singaram *Tetrahedron: Asymmetry* **2005**, *16*, 1829.

Finally, an important contribution was recently published by TROST and co-workers, who employed the well-established proline-derived bimetallic catalyst system based on ligand (*S*,*S*)-**134**[204] to the dimethylzinc-mediated enantioselective alkynylation of aldehydes.[205] Feeling that previous researches focused almost exclusively on the addition of phenylacetylene to aromatic aldehydes, the authors concentrated on broadening the scope of the reaction relative to the alkyne. Moreover, α,β-unsaturated aldehydes were chosen as substrates, in consideration of the little success achieved to date with these substrates, at least in comparison with their aromatic counterparts (Scheme 28).



SCHEME 28. Catalytic, enantioselective alkynylation of α,β-unsaturated aldehydes by TROST.

Although, as can be seen in Scheme 28, very high enantiomeric excesses have been obtained in many cases, probably the most important aspect of this approach is represented by the generalization of the alkyne moiety (silicon-containing groups, esters and acetals are tolerated), as well as the extension of the methodology to variously-substituted vinyl aldehydes. The resulting propargyl-allylic alcohols can be very useful intermediates in organic synthesis, as demonstrated by the preparation of an 1,2-dialkylidenecyclopentane, a compound difficult to form through traditional methods. The authors propose a transition state in wich three zinc atoms are involved, acting both as Lewis acid to activate the aldehyde and as alkynyl transfer units.

[204] First synthesis: (a) B. M. Trost, H. Ito *J. Am. Chem. Soc.* **2000**, *122*, 12003. Further applications: (b) B. M. Trost, H. Ito, E. M. Silcoff *J. Am. Chem. Soc.* **2001**, *123*, 3367. (c) B. M. Trost, L. R. Terrell *J. Am. Chem. Soc.* **2003**, *125*, 338. (d) B. M. Trost, D. Mino *J. Am. Chem. Soc.* **2003**, *125*, 2410. (e) B. M. Trost, A. Fettes, B. T. Shireman *J. Am. Chem. Soc.* **2004**, *126*, 2660. (f) B. M. Trost, M. Shin, J. A. Sclafani *J. Am. Chem. Soc.* **2005**, *127*, 8602.
[205] B. M. Trost, A. H. Weiss, A. Jacobi von Wangelin *J. Am. Chem. Soc.* **2006**, *128*, 9.

2.3.2.3. Titanium-Promoted Enantioselective Additions of Acetylenes to Aldehydes Employing Dialkylzinc Reagents.

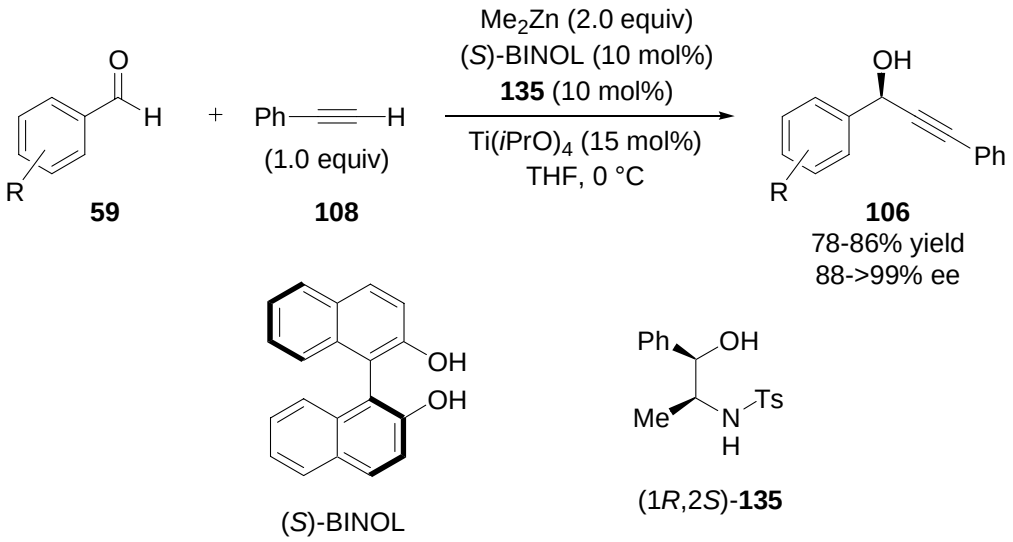
As already described in the previous paragraphs, alkylzinc reagents can be used in combination with titanium alkoxides to promote the addition reaction of carbon nucleophiles to carbonyl compounds.[64,65,131,146] In this case the reaction is more properly described as titanium-promoted (or catalyzed, if the titanium salt is used in substoichiometric amount), while the role of the alkylzinc compound is just to form the active nucleophilic species. Recent studies on the mechanism of the dialkylzinc addition to aldehydes in the presence of Ti(*i*PrO)$_4$ seem to indicate that the alkyl moiety is transferred from zinc to titanium by transmetallation and then delivered from the latter to the aldehyde.[206]

In 2002, CHAN and PU were indipendently working on the use of BINOL as a ligand for the enantioselective alkynyl additions to aldehydes. They found that BINOL in combination with Ti(*i*PrO)$_4$ could effect such reactions with high efficiency. The two groups used a different alkylzinc precursor and developed different experimental procedures to perform the catalysis.

CHAN and co-workers studied both enantiopure BINOL and its partially hydrogenated analogue H_8-BINOL for the reaction of phenylacetylene (**108**) with aldehydes.[207] In their experiments, a slight excess of Me_2Zn, phenylacetylene and Ti(*i*PrO)$_4$ was required, while the ligand was used in a 20 mol% amount. For the reaction in THF at 0 °C, the hydrogenated binaphthol gave somewhat higher enantioselectivities than the completely aromatic ligand, in particular for *para*- and *meta*-substituted aromatic aldehydes (up to 96% ee). *Ortho*-substituted aromatic aldehydes as well as aliphatic substrates showed reduced enantiomeric excesses.

An improvement of this protocol was obtained when a catalytic quantity of a co-catalyst was added to the reaction mixture, according to the principle of "asymmetric activation" originally introduced by MIKAMI.[208] Thus, use of 10 mol% of *N*-toluenesulfonyl norephedrine (1*R*,2*S*)-**135**, in combination with 10 mol% BINOL and only 15 mol% Ti(*i*PrO)$_4$ allowed the conversion of several aromatic aldehydes with remarkably high enantiomeric excesses (up to >99% ee, Scheme 29).[209]

[206] K.-H. Wu, H.-M. Gau *Organometallics* **2004**, *23*, 580.
[207] G. Lu, X.-S. Li, W. L. Chan, A. S. C. Chan *Chem. Commun.* **2002**, 172.
[208] K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, M. Ueki, R. Angelaud *Angew. Chem.* **2000**, *112*, 3676; *Angew. Chem. Int. Ed.* **2000**, *39*, 3352.
[209] X.-S. Li, G. Lu, W. H. Kwok, A. S. C. Chan *J. Am .Chem. Soc.* **2002**, *124*, 12636.



SCHEME 29. Titanium-catalyzed enantioselective addition of phenylacetylene to aldehydes by CHAN.

By using this methodology, a complex mixture of several titanium catalysts is formed in solution, and the introduction of an additive modifies the equilibrium among the different species to form a selective and highly active catalyst. Surprisingly, the employment of an achiral additive such as phenol had also a positive effect on the enantioselectivity, and even aliphatic propargylic alcohols could be obtained with up to 90% ee.[210]

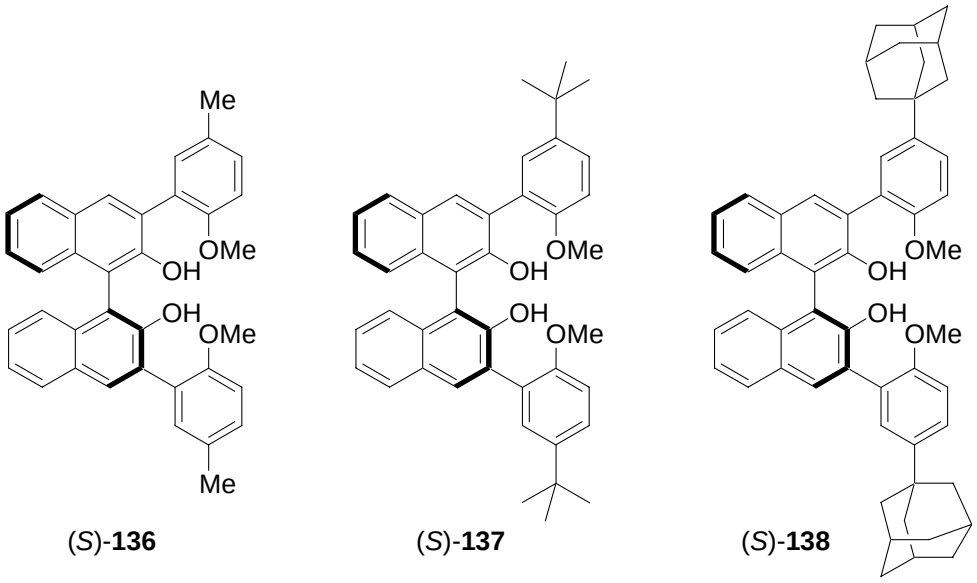
The procedure reported by PU employed in general the same components as the first report of CHAN, but Et_2Zn instead of Me_2Zn was used as the zinc source, and a different protocol was developed to generate the alkynyl-alkylzinc nucleophile, which required heating of a toluene solution of diethylzinc and phenylacetylene at reflux for 5 hours under a nitrogen atmosphere. Use of 20 mol% of enantiopure (*R*)-BINOL and 50 mol% of Ti(*i*PrO)$_4$ allowed the preparation of propargylic alcohols derived from aromatic aldehydes in good yields and 92-98% ee, also with alkynes different than phenylacetylene (**108**).[211]

Slight variations in the practical procedure as well as in the stoichiometry of the reaction, and use of a relatively high catalyst loading [40 mol% of (*S*)-BINOL and 1.0 equiv of titanium alkoxide] allowed the conversion of aliphatic (also unbranched) and α,β-unsaturated aldehydes with high enantioselectivities (91-99% ee).[212] Interestingly, use of freshly destilled substrates afforded the products with higher yields (91% vs. 66% for nonyl aldehyde), but unchanged enantiomeric excesses (always 91% ee in this example), than those obtained starting from undestilled aldehydes.

[210] G. Lu, X. Li, G. Chen, W. L. Chan, A. S. C. Chan *Tetrahedron: Asymmetry* **2003,** *14*, 449.
[211] D. Moore, L. Pu *Org. Lett.* **2002**, *4*, 1855.
[212] G. Gao, D. Moore, R.-G. Xie, L. Pu *Org. Lett.* **2002**, *4*, 4143.

More recently, it was found that the deprotonation of terminal alkynes with diethylzinc was greatly accelerated by the addition of hexamethylphosphoramide (HMPA).[213] Use of HMPA made possible to perform the deprotonation at room temperature, thus enhancing the functional group tolerance of the methodology. For example, alkyl propiolates could now be added to aromatic aldehydes in presence of 40 mol% of (*R*)-BINOL and 1.0 equiv of Ti(*i*PrO)$_4$ with high yields and enantioselectivities (85-95% ee).[214] This reaction was not possible following the original protocol because, as reported by the authors, heating a solution of diethylzinc and methyl propiolate to reflux leads to complete decomposition of the latter.

PU and co-workers also investigated the effect of variations of the ligand structure on the enantioselectivity. Thus, 3,3'-substituted binaphthols including **62-63**[82] (Figure 6, page 21) plus many other derivatives were tested in the addition of phenylacetylene to benzaldehydes (20 mol% ligand), in presence of 50 mol% of Ti(*i*PrO)$_4$.[215] Ligand (*S*)-**136** and (*S*)-**137** (Figure 16) were found to be the best ones giving enantiomeric excesses up to 89%; therefore, no improvement was observed in comparison with the Ti / BINOL-catalyzed reaction. Interestingly, however, compound (*S*)-**138**, bearing adamantyl substituents, was found to catalyze the reaction (10 mol%) even in the absence of Ti(*i*PrO)$_4$, giving products in 42-75% yield and 80-94% ee (only aromatic aldehydes were used as substrates).



(*S*)-**136** (*S*)-**137** (*S*)-**138**

FIGURE 16. 3,3'-disubstituted BINOLs by PU.

[213] G. Gao, R.-G. Xie, L. Pu *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5417.
[214] (a) G. Gao, Q. Wang, X.-Q. Yu, R.-G. Xie, L. Pu *Angew. Chem.* **2006**, *118*, 128; *Angew. Chem. Int. Ed.* **2006**, *45*, 122. (b) A. R. Rajaram, L. Pu *Org. Lett.* **2006**, *8*, 2019.
[215] D. Moore, W.-S. Huang, M.-H. Xu, L. Pu *Tetrahedron Lett.***2002,** *43*, 8831.

Another modification of the 1,1'-binaphthol backbone was described by GONG and JIANG, who introduced optically pure 7,7'-disubstituted BINOLs as ligands for the titanium-catalyzed addition.[216] These compounds were prepared by an asymmetric oxidative homocoupling of 7-substituted-2-naphthols, catalyzed by a chiral oxovanadium catalyst.[217] Although the enantioselectivities observed in the addition of phenylacetylene to aliphatic and aromatic aldehydes were comparable with those displayed by unmodified BINOL, the yields of propargylic alcohols were generally higher. Moreover, the enantioselectivity was not significantly dependent on the substrate structure, and all the aldehydes examined furnished products with 91-95% ee.

Chiral compounds having a different backbone than a 1,1'-binaphthol unit were also examined in the titanium-catalyzed phenylacetylene addition to aryl and alkyl aldehydes. For example, the alkaloids cinchonidine and quinidine were tested by KAMBLE and SINGH, giving rise to products with 62-85% ee, although with a high catalyst loading of 40 mol%.[218]

Very efficient hydroxy sulfonamide ligands (*S*)-**139** and (1*S*,2*R*)-**140** were introduced by WANG for the addition of phenylacetylene to aromatic aldehydes (Figure 17). Compound (*S*)-**139**[219] was derived in few steps from L-phenylalanine, while (1*S*,2*R*)-**140**[220] was prepared from (+)-camphor in four steps, which resembled closely the synthesis of NOYORI's (−)-DAIB [(−)-**37**]. 10-20 mol% of (*S*)-**139** or (1*S*,2*R*)-**140** in combination with 40-60 mol% of Ti(*i*PrO)$_4$ and 3.0 equiv of diethylzinc were able to give propargylic alcohols resulting from aromatic aldehydes with up to 99% and 98% ee, respectively, in useful yields. Unfortunately, lower enantiomeric excesses (in the 70 to 80% range) were observed for the products stemming from aliphatic substrates. An interesting detail is that the experimental procedure is here simpler than in PU's protocol: no reflux is required and the different components can just be mixed toghether at room temperature to yield the mixed alkynylzinc reagent and the active catalyst.[221]

Finally, an original structural variation was proposed by DU and XU, who reported C_3-symmetric tris(β-hydroxy)amides **141** as ligands for the alkynyl transfer to aldehydes.[222] In the presence of a strong excess of the alkyne and diethylzinc (4.0 equiv) and a stoichiometric amount of titanium alkoxide, 20 mol% of **141** catalyzed the addition with 64-86% yield and 82-92% ee, for the

[216] Q. Liu, N. Xie, Z. Luo, X. Cui, L. Cun, L. Gong, A. Mi, Y. Jiang *J. Org. Chem.* **2003**, *68*, 7921.
[217] Z. Luo, Q. Liu, L. Gong, A. Mi, X. Cui, Y. Jiang *Angew. Chem.* **2002**, *114*, 4714; *Angew. Chem. Int. Ed.* **2002**, *41*, 4532.
[218] R. M. Kamble, V. K. Singh *Tetrahedron Lett.* **2003**, *44*, 5347.
[219] Preliminary communication: (a) Z. Xu, R. Wang, J. Xu, C.-S. Da, W.-J. Yan, C. Chen *Angew. Chem.* **2003**, *115*, 5925; *Angew. Chem. Int. Ed.* **2003**, *42*, 5747. Full paper, featuring further variations of the ligand structure: (b) Z. Xu, L. Lin, J. Xu, W. Yan, R. Wang *Adv. Synth. Catal.* **2006**, *348*, 506.
[220] Z. Xu, C. Chen, J. Xu, M. Miao, W. Yan, R. Wang *Org. Lett.* **2004**, *6*, 1193.
[221] For the use in the same reaction of amino acid derivatives as ligands, furnishing products with up to 90% ee, see: Z. Han, R. Wang, Y. Zhou, L. Liu *Eur. J. Org. Chem.* **2005**, 934.
[222] T. Fang, D.-M. Du, S.-F Lu, J. Xu *Org. Lett.* **2005**, *7*, 2081.

products arising from aromatic and α,β-unsaturated substrates. Once again, aliphatic aldehydes were not well tolerated and furnished products with 47-72% ee.

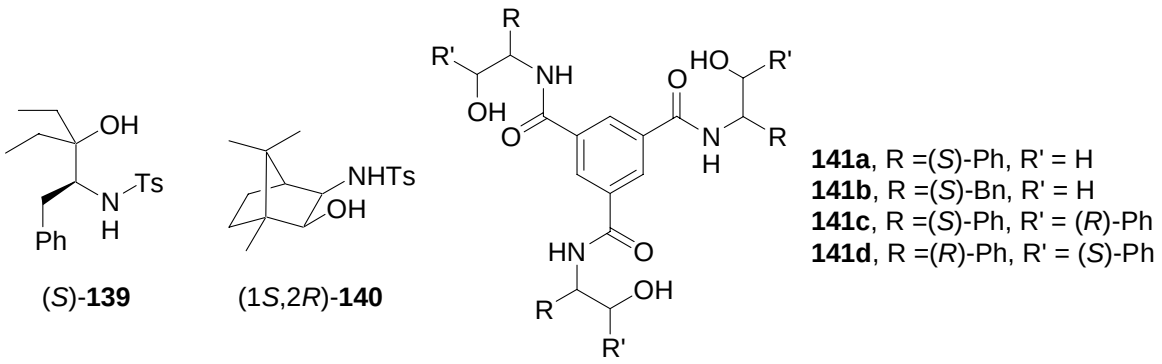


FIGURE 17. Chiral ligands for the asymmetric alkynyl addition to aldehydes by WANG (**139-140**) and DU and XU (**141**).

Surprisingly, the starting amino alcohols of ligands **141c** and **141d** are enantiomers, but the result obtained in catalysis with these ligands were quite different, with only **141c** furnishing high enantioselectivity. To justify this counterintuitive result, a cooperative effect of the ligand and the Lewis acid is proposed by the authors. To demonstrate the efficiency of C_3-symmetric ligands the authors also synthesized and applied the C_1- and C_2-symmetric analogues, which indeed afforded the products with reduced yield and selectivity.

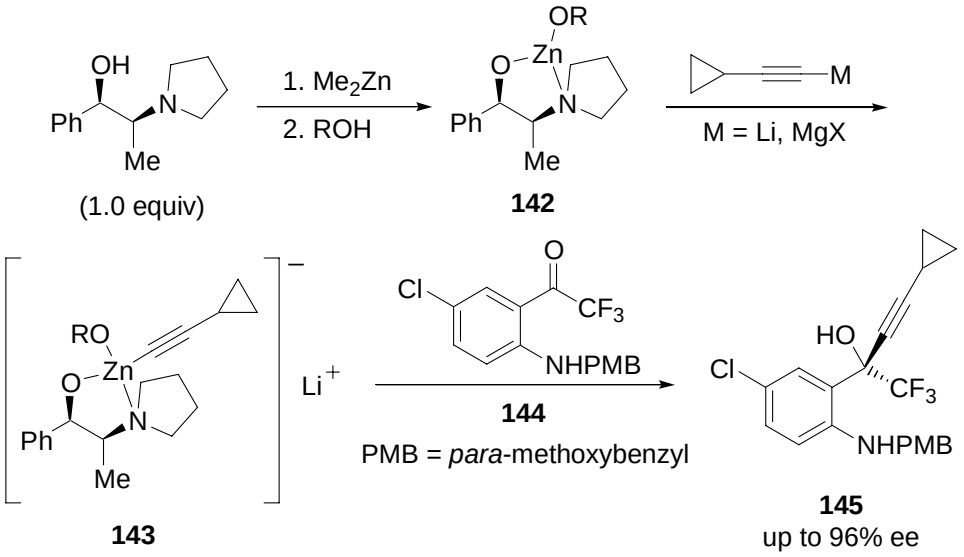
2.3.3. Direct Addition of Alkynes to Ketones

In the paragraphs dedicated to alkyl (cf. § *2.1.*), aryl and vinyl (cf. § *2.2.*) additions to carbonyl compounds, it has already been mentioned that the use of ketones as substrates for those reactions is largely underdeveloped in comparison with that of aldehydes; among the explanations provided for this state of things the lower reactivity of ketones compared to aldehydes is often cited.

The addition of C(sp) nucleophiles constitutes no exception, so that it is safe to say that to date only a little number of accounts on the direct additions of alkynes to ketones has appeared in the literature. While some reliable methods exist for the preparation of racemic tertiary propargylic

alcohols,[158,159,185,223] this is particularly true for enantioselective reactions (problems in the discrimination of prochiral faces are here an additional issue).

An early example of enantioselective addition of an alkynylmetal nucleophile to a ketone was reported by TAN and co-workers at *Merck*,[224] in the context of a synthesis of the well known anti-AIDS drug *Efavirenz*.[225] In this case, a zinc-alkynylide was generated by transmetallation from an alkynyllithium or alkynylmagnesium reagent with a chiral zinc complex. Addition of the chiral zinc nucleophile to a ketone activated with a strong electron-withdrawing trifluoromethyl group afforded the product in up to 96% ee (Scheme 30).



SCHEME 30. Asymmetric alkynylation of a ketone towards the synthesis of *Efavirenz*.

Interestingly, use of an alkynylmagnesium halide provided a better result than employment of the corresponding alkynyllithium. Furthermore, addition of an alcohol was necessary to generate complex **142**: when *neo*-pentyl alcohol or hexafluoropropanol where used instead of methanol the enantiomeric excess of the product rose from 87% to 95-96% ee.

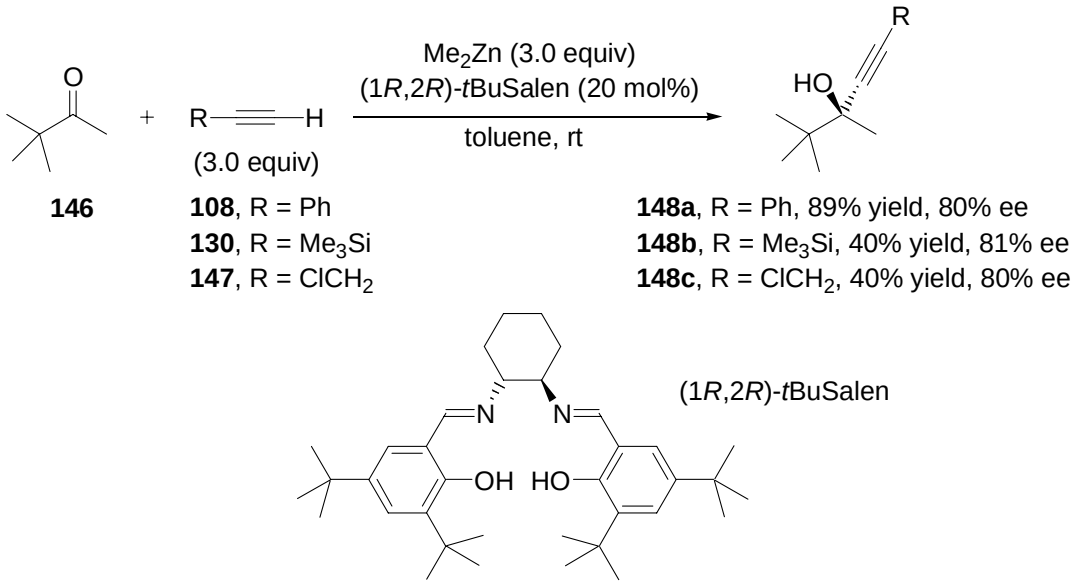
The first catalytic enantioselective alkynylation of ketones was reported by JIANG, who described a modification of CARREIRA's protocol to prepare tertiary propargylic alcohols from activated α-ketoesters.[226] Therefore, the classic combination of $Zn(OTf)_2$ and Et_3N in the presence of ligand

[223] (a) For an interesting organocatalytic approach based on phase-transfer catalysis (also on aldehydes), see: T. Weil, P. R. Schreiner *Eur. J. Org. Chem.* **2005**, 2213. For a Lewis base-catalyzed reaction using trialkoxysilylalkynes (also on aldehydes and an imine), see: (b) R. B. Lettan II, K. A. Scheidt *Org. Lett.* **2005**, *7*, 3227.
[224] L. Tan, C. Chen, R. D. Tillyer, E. J. J. Grabowski, P. J. Reider *Angew. Chem.* **1999**, *111*, 724; *Angew. Chem. Int. Ed.* **1999**, *38*, 711.
[225] More precisely, *Efavirenz* is a non-nucleosidic inhibitor of the reverse transcriptase enzyme of the Human Immunodeficiency Virus (HIV).
[226] B. Jiang, Z. Chen, X. Tang *Org. Lett.* **2002**, *4*, 3451.

(1*S*,2*S*)-**116b** was used to promote the addition of three different alkynes to aromatic, aliphatic and cyclic substrates. While initially the reaction in toluene required stoichiometric amounts of zinc triflate, triethylamine and compound (1*S*,2*S*)-**116b**, the authors discovered that operating in "solvent-free" conditions and increasing the temperature to 70 °C allowed to use substoichiometric quantities of the three reagents (under optimized conditions, respectively 0.2, 0.5 and 0.22 equiv).

The products were generally formed in good to high yields, but use of an enolizable α-ketoester as ethyl glyoxylate furnished a very low yield, due to formation of the corresponding zinc enolate that inhibited the reaction. In any case, the enantiomeric excesses were satisfying, ranging from 73 to 94%.

Shortly after, the first general catalytic enantioselective addition of terminal alkynes to ketones was described by COZZI, who used commercially available JACOBSEN's Salen as ligand.[227] By the addition of Me_2Zn, a Zn(Salen) complex was formed, which, as inferred by the author, could act as a bifunctional catalyst to enhance the reactivity of ketones toward the attack of zinc alkynylides.[228] Indeed, treatment of acetophenone with phenylacetylene (3.0 equiv), dimethylzinc (3.0 equiv.) and (1R,2R)-*t*BuSalen (20 mol%) in toluene at room temperature afforded the product tertiary alcohol in 72% yield and 61% ee. After optimization, several ketones, including dialkyl- and cyclic substrates, could undergo addition of acetylenes in moderate to high yield. 3,3'-Dimethylbutan-2-one furnished the best ee values (Scheme 31).



SCHEME 31. Enantioselective addition of alkynes to ketones by COZZI.

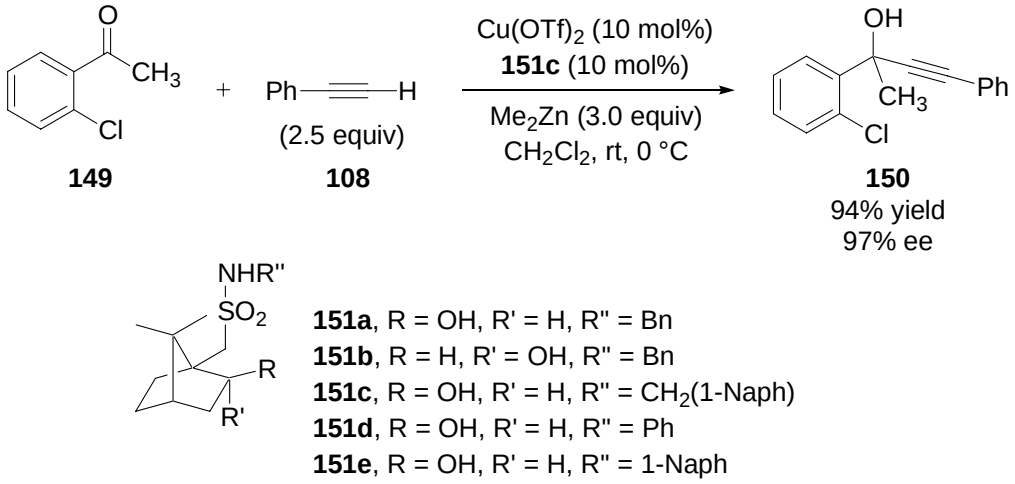
[227] P. G. Cozzi *Angew. Chem.* **2003**, *115*, 3001; *Angew. Chem. Int. Ed.* **2003**, *42*, 2895.
[228] This hypothesis was confirmed when the author prepared separately a Zn(Salen) complex and used it in the reaction, obtaining the same result.

The absence of non-linear effects indicated the involvement of only one molecule of ligand in the transition state. The author hypothesizes a transition state resembling that of the alkylzinc addition to carbonyl compounds, where a zinc atom functions as Lewis acid to activate the substrate and the oxygens of the Salen work as Lewis bases to coordinate the mixed alkynyl-alkylzinc species.

Later, COZZI developed another original protocol for the asymmetric alkynylation of ketones, based on the use of an alkynyltitanium nucleophile in the presence of a substoichiometric quantity of (*R*)-BINOL as ligand.[229] The nucleophile was in this case generated by transmetallation of lithium phenylacetylenide with $ClTi(iPrO)_3$, as already reported in a pioneering study by KRAUSE and SEEBACH.[230] Mixing a toluene solution of the alkynyltitanium reagent with (*R*)-BINOL at –50 °C afforded the active catalysts, that was then able to convert various acetophenones into the corresponding products. The high reactivity of the nucleophile allowed to use only a slight excess (1.3-1.8 equiv) of it, but made also necessary to raise the catalyst loading to 22 mol% to overcome the quick background reaction. Tertiary propargylic acohols were thus obtained in up to 84% yield and 90% ee.

The first highly enantioselective addition of alkynes to ketones by means of organozinc reagents was reported by CHAN and co-workers in 2003.[231] Since all the attempts to use titanium complexes to catalyze the reaction were unsuccessful, the authors devised to use a stronger Lewis acid such as $Cu(OTf)_2$ as catalyst in combination with a chiral ligand and dimethylzinc as a zinc source. After an extensive ligand screening, that included BINOL, amino alcohols **122**, sulfonamide **135** and Ph-Pybox, it was found that chiral camphorsulfonamides **151**[63] were able to promote the reaction, the best being **151c**. After optimization, various acetophenones could be reacted with phenylacetylene affording tertiary propargylic alcohols in 49-94% yield and 85-97% ee (Scheme 32).

[229] P. G. Cozzi, S. Alesi *Chem. Commun.* **2004**, 2448.
[230] N. Krause, D. Seebach *Chem. Ber.* **1987,** *120*, 1845.
[231] G. Lu, X. Li, X. Jia, W. L. Chan, A. S. C. Chan *Angew. Chem.* **2003**, *115*, 5211; *Angew. Chem. Int. Ed.* **2003**, *42*, 5057.



SCHEME 32. Catalytic, enantioselective addition of phenylacetylene to ketones by CHAN.

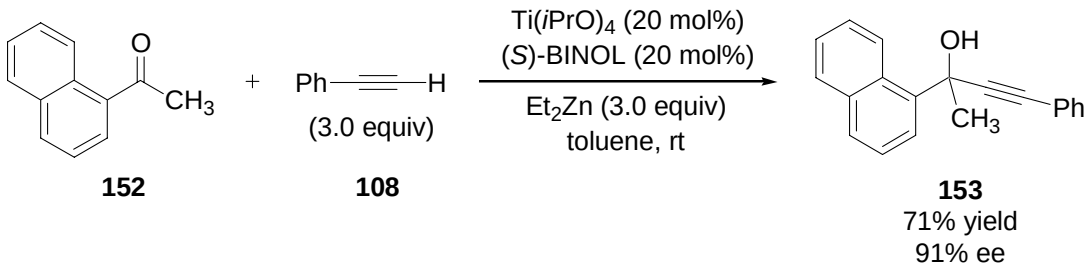
Despite these good results, the method was limited to the addition of phenylacetylene, since aliphatic alkynes as **130** gave products with much lower enantiomeric excess. Moreover, an alkyl rest larger than methyl was not well tolerated, so that the product of the addition of phenylacetylene to propiophenone had only 75% ee.

As briefly mentioned above, CHAN reported that the application of the Ti(*i*PrO)$_4$/BINOL catalytic system, which proved to be very effective for the alkynylzinc addition to aldehydes, was not possible with ketones as substrates, due to their inferior reactivity.[231] As a consequence, the stronger Lewis acid Cu(OTf)$_2$ was chosen as a catalyst.

WANG and co-workers recognized that the Lewis acidity of the complexes formed when Ti(*i*PrO)$_4$ and BINOL are mixed in solution is depending on the ratio between these two compounds. While usually in the addition to aldehydes the titanium alkoxide is used in excess, the strongest Lewis acidic combination, (BINOLate)Ti(*i*PrO)$_2$, should be obtained with a 1:1 ratio of the components.[232]

Several experiments were conducted performing the reaction of phenylacetylene and acetophenone with diethylzinc in the presence of mixtures of Ti(*i*PrO)$_4$ and BINOL of different stoichiometry.[233] In agreement with the initial hypothesis, the best result was obtained with a 1:1 ratio between those two reagents. When the ratio exceeded 1.5, the yield of product decreased quickly. Several other parameters were optimized, such as temperature, catalyst loading and solvent. Finally, various ketones could be reacted with phenylacetylene in the presence of diethylzinc and 20 mol% each of Ti(*i*PrO)$_4$ and (*S*)-BINOL to afford propargylic alcohols with up to 92% ee. A representative example is depicted in Scheme 33.

[232] J. Balsells, T. J. Davis, P. Carrol, P. J. Walsh *J. Am. Chem. Soc.* **2002**, *124*, 10336.
[233] Y. Zhou, R. Wang, Z. Xu, W. Yan, L. Liu, Y. Kang, Z. Han *Org. Lett.* **2004**, *6*, 4147.



152 **108** **153**
71% yield
91% ee

SCHEME 33. Catalytic, enantioselective alkynylation of ketones by WANG.

It should be pointed out that also in this case aliphatic and α,β-unsaturated substrates could not be selectively converted by the catalytic system, and the resulting tertiary alcohols were isolated with lower enantiomeric excesses (66-73%).

In 2005, the research group of WANG published two more contributions in the field of the enantioselective alkynylation of ketones. First, the use of Et_3Al as Lewis acid was introduced in combination with *Cinchona* alkaloids as ligands, and diethylzinc as the zinc source. The ratio between the two compounds was, after optimization, 1:2, and a rather large amount of ligand was needed (0.8 equiv).[234] It is not yet clear if the intermediate is in this case an alkynylzinc or an alkynylaluminum species, but the authors report that an almost racemic product was obtained when the reaction was run in the absence of Et_2Zn. Various acetophenones could undergo addition by phenylacetylene under these conditions to give products with 61-83% yield and 70-89% ee.

Finally, new chiral oxazolidines were introduced, which could serve as ligand for the direct reaction of phenylacetylene with alkyl-aryl ketones in presence of Et_2Zn, without the need for Ti, Cu or Al Lewis acids.[235] The ligands were prepared in three steps from the corresponding amino acids through esterification, addition of 2.0 equiv of a Grignard reagent, and subsequent cyclization *via* condensation with acetone. After optimization, 20 mol% of these ligands were sufficient to perform the addition of phenylacetylene to several acetophenones with 57-85% yield and 68-88% ee.

[234] L. Liu, R. Wang, Y.-F. Kang, C. Chen, Z.-Q. Xu, Y.-F. Zhou, M. Ni, H.-Q. Cai, M.-Z. Gong *J. Org. Chem.* **2005**, *70*, 1084.
[235] (a) Y.-F. Kang, L. Liu, R. Wang, Y.-F. Zhou, W.-J. Yan *Adv. Synth. Catal.* **2005**, *347*, 243. An improvement of this methodology, based on the use of Schiff bases-imino alcohols as ligands, was recently published: (b) C. Chen, L. Hong, Z.-Q. Xu, L. Liu, R. Wang *Org. Lett.* **2006**, *8*, 2277.

2.3.4. Direct Addition of Alkynes to Imines and Related C=N Electrophiles

As mentioned earlier, propargylamines can serve as very useful building blocks in organic synthesis, and the propargylic amine functional motif is present in various natural products and compounds of pharmaceutical interest.

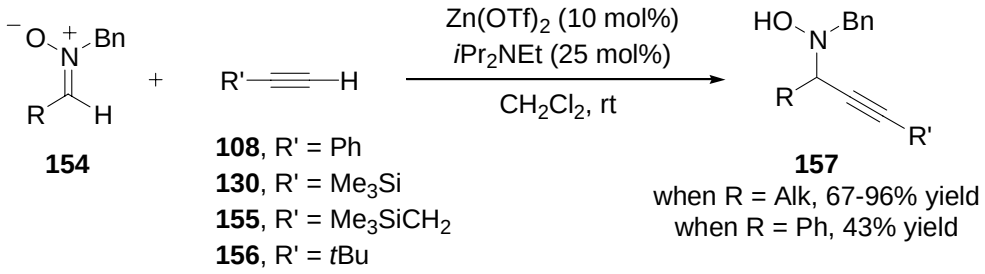
However, while propargylic alcohols can be prepared by a variety of transformations, the number of reliable methods that provide access to propargylic amines has remained limited for a long time. This is primarily due to the relative inertness of the azomethine carbon towards nucleophiles. To overcome this problem of reactivity, often activated substrates like nitrones or in situ-generated iminium ions have been employed.

Although in the last years considerable progresses have been made in expanding the scope of the direct addition of alkynes to C=N double bonds,[164b] this area still remains underdeveloped in comparison with the related field of the direct alkynylation of aldehydes. This is particularly true for the enantioselective version of this reaction, which has been only recently discovered and whose potential has yet to be completely exploited.

2.3.4.1. Racemic and Diastereoselective Metal-Mediated and Metal-Catalyzed Direct Alkynylation of C=N Electrophiles

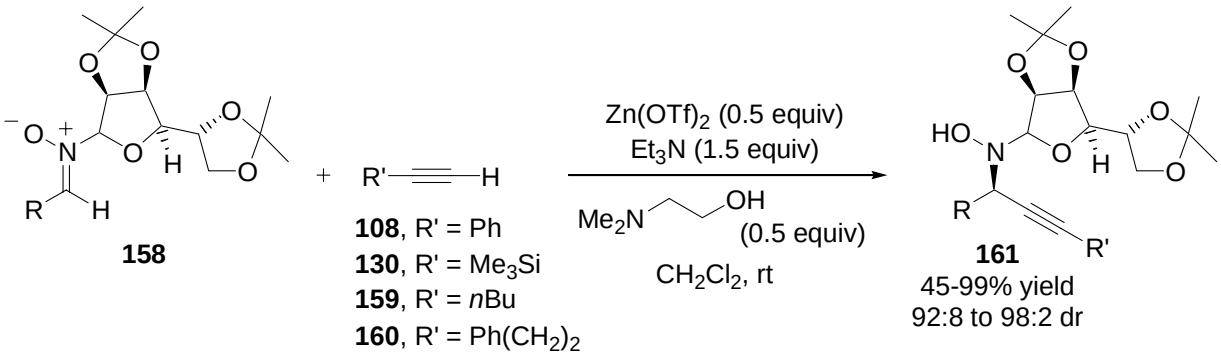
As already seen in paragraph *2.3.2.1.*, the first metal-catalyzed addition of alkynes to C=N electrophiles was reported in 1999 by CARREIRA and co-workers,[169,236] who employed nitrones as substrates due to the easy preparation and superior reactivity of these compounds in comparison to imines. Use of 10 mol% of $Zn(OTf)_2$ and 25 mol% of *i*Pr_2NEt at rt afforded the products propargyl *N*-hydroxylamines in moderate to high yields. Interestingly, the nitrone derived from benzaldehyde was much less reactive than those resulting from aliphatic aldehydes, and also phenyl *N*-tosylimine (**165a**, see Scheme 37) furnished a lower yield of the product (43%) when it was subjected to the reaction (Scheme 34).

[236] A synthesis of propargylic imines from terminal alkynes and nitrones has been reported, which occurs in the presence of CuI and dppe as ligand under harsh conditions, probably proceeding through the initial formation of 1,3-polar cycloaddition products: M. Miura, M. Enna, K. Okuro, M. Nomura *J. Org. Chem.* **1995**, *60*, 4999.



SCHEME 34. Direct alkynylation of nitrones by CARREIRA.

The potential of this transformation for the preparation of optically active propargyl-*N*-hydroxylamines was quickly recognized, and in 2002 the same research group published a highly diastereoselective version of the reaction, in which chiral enantiopure nitrones were used as the substrates (Scheme 35).[237] A mannose-derived chiral auxiliary was employed, which after the reaction could be easily recovered in one step in quantitative yield.



SCHEME 35. Diastereoselective alkynylation of nitrones by CARREIRA.

A large number of combinations between various alkynes and nitrones were screened, and the diastereomeric ratios were found to be very high in each case. Interestingly, during the course of the optimization studies, the authors found that the addition of 0.5 equiv of *N*,*N*-dimethyl-2-aminoethanol was beneficial, because it led to enhanced reaction rates (fivefold), and furnished an homogeneous solution throughout the course of the reaction. Once again, aromatic derivatives proved to be less reactive than aliphatic ones, and stoichiometric conditions had to be applied to achieve their full conversion.

An extension of this work has been recently published by the same group. In search of new zinc sources it was found that rigorously dried $ZnCl_2$ was able to promote the reaction of terminal

[237] R. Fässler, D. E. Frantz, J. Oetiker, E. M. Carreira *Angew. Chem.* **2002**, *114*, 3180; *Angew. Chem. Int. Ed.* **2002**, *41*, 3054.

alkynes with the chiral mannofuranosylnitrone **158** affording products with high diastereoselectivities (up to 98:2 dr).[238] The conditions were this time stoichiometric and 1.5 equiv each of the zinc salt, triethylamine and the alkyne [mostly trimethylsilylacetylene (**130**)] had to be used. Since now the reaction mixture was homogeneous an additional ligand like *N*,*N*-dimethyl-2-aminoethanol was unnecessary. A further improvement was represented by the possibility to use toluene as a solvent instead of the environmentally less friendly dichloromethane.

A further protocol for the addition of in situ-generated zinc alkynylides to nitrones was reported in 2002 by VALLEE and co-workers, who prepared the reactive nucleophile by mixing an alkyne with diethylzinc in the presence of the substrate.[239] While initial experiments were conducted using a stoichiometric amount of the alkylzinc species, working in toluene accelerated the reaction and made it possible to use only 20 mol% of Et_2Zn. It should be noted that in this case no additional base is required. After optimization various alkynes could be added to four different nitrones affording products in good to high yields under mild conditions, even if sometimes 2,3-dihydroisooxazoles, resulting from the cyclization of the *N*-hydroxy propargylamines, were detected as side products. The authors conducted also detailed NMR studies with the aim to elucidate the mechanism of the transformation. The results suggest that zinc hydroxylamides can be involved as metallating agents, which would explain why only a substoichiometric amount of the initial dialkylzinc species is needed to induce the transformation.

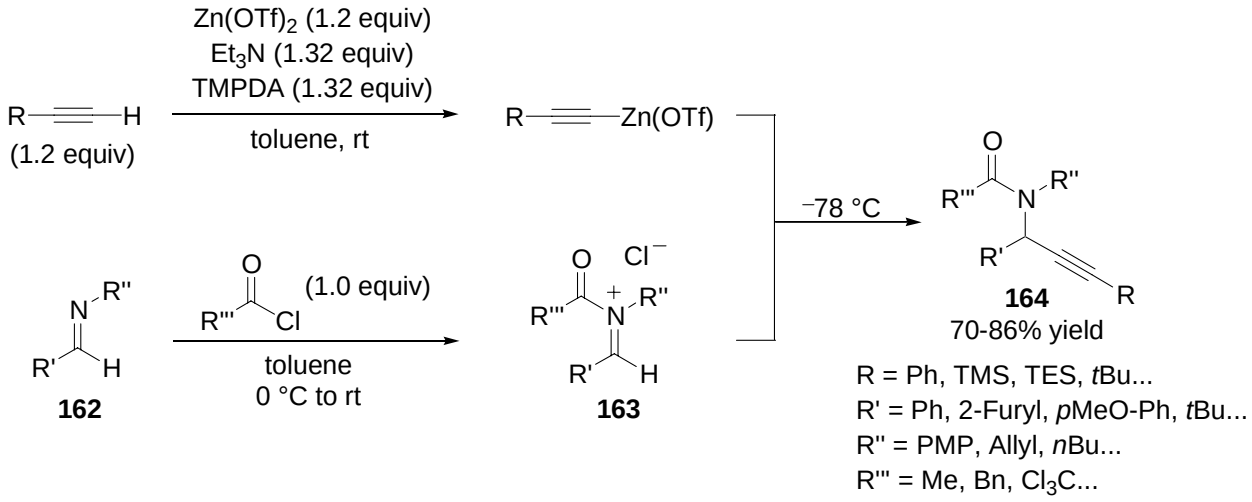
In 2003, a diastereoselective addition of acetylenes to chiral *N*-alkylimines was reported by JIANG and SI.[240] Inspired by the methodology published by CARREIRA, the authors employed $ZnCl_2$ as the promoter in presence of triethylamine as the base (1.2 equiv each); the inferior reactivity of imines in comparison to nitrones made it necessary to use a Lewis acid additive such as TMSCl to activate the substrate and obtain a satisfactory conversion into the product propargylamines. The enantiopure substrates were obtained by condensation of benzaldehyde with (*R*)-1-phenylethylamine and with three optically pure aminoalcohols derived from the corresponding α-amino acids. The best dr value (90.5 : 9.5) was obtained from the reaction of the imine derived from benzaldehyde and (*S*)-*tert*-leucinol with phenylacetylene (**108**). Some other *N*-benzylimines stemming from different aldehydes could also be converted using this method, giving products in 62-93% yield.

Another strategy for the Zn-mediated addition of terminal alkynes to activated C=N electrophiles was described once again by CARREIRA. He devised that treatment of an *N*-aryl- or *N*-alkylimine with an acyl chloride would lead to the generation of a very reactive acyliminium species, that

[238] D. Topić, P. Aschwanden, R. Fässler, E. M. Carreira *Org. Lett.* **2005**, *7*, 5329.
[239] S. Pinet, S. U. Pandya, P. Y. Chavant, A. Ayling, Y. Vallee *Org. Lett.* **2002**, *4*, 1463.
[240] B. Jiang, Y.-G. Si *Tetrahedron Lett.* **2003**, *44*, 6767.

should rapidly react with a zinc acetylenide to furnish a propargylic *N*-aryl- or *N*-alkylamide as product.[241]

Indeed, this proved to be the case, and several alkynes could be added to acyliminiums obtained with different acyl chlorides in 70-86% yields (Scheme 36). Furthermore, it was demonstrated that diphenylphosphinoyl chloride could also be used to generate the iminium ion: the corresponding *N*-diphenylphosphinoylamines are compounds easy to elaborate because the protecting group is simply removed by treatment with Brønsted acids.

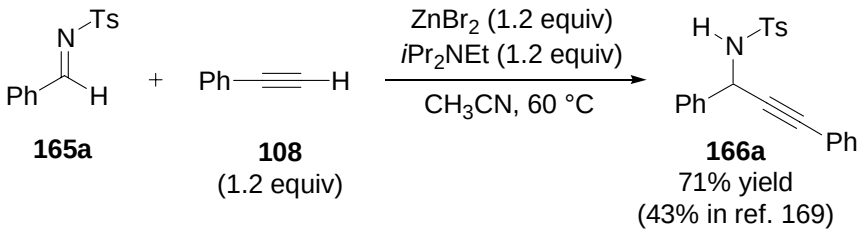


SCHEME 36. Synthesis of *N*-substituted propargylic amides by CARREIRA.

It should be noted that also in this case an additional ligand (TMPDA = *N*,*N*,*N'*,*N'*-tetramethylpropylene diamine) was required to obtain an homogeneous reaction mixture. The reaction can be applied also to cyclic substrates; thus, the combination of isoquinoline, benzoyl chloride and phenylacetylene furnished the resulting cyclic *N*-benzoyl propargylic amine in 83% yield.

The last addition to the family of the zinc salts available to generate zinc alkynylides in situ was reported by KIM and co-workers, who described the use of a stoichiometric quantity of $ZnBr_2$ in combination with *i*Pr_2NEt to promote the addition of substituted phenylacetylenes to *N*-sulfonylimines.[242] In this study only aromatic substrates were used, which could be converted into the corresponding N-protected propargylamines in 61-81% yield. In particular, *N*-benzylidene *p*-toluenesulfonamide **165a** furnished with phenylacetylene product **166a** in 71% yield, which is superior to the 43% yield reported earlier by CARREIRA (Scheme 37).[169]

[241] C. Fischer, E. M. Carreira *Org. Lett.* **2004**, *6*, 1497.
[242] K. Y. Lee, C. G. Lee, J. E. Na, J. N. Kim *Tetrahedron Lett.* **2005**, *46*, 69.



SCHEME 37. Addition of phenylacetylene to *N*-tosylimines by KIM.

Shortly after, a variation of this methodology was published by the same research group, which this time examined the addition of phenylacetylene to quinoline, isoquinoline and pyridine. Addition of an acyl chloride (or ethyl chloroformate) to an acetonitrile solution of these heterocycles generated a strongly electrophilic acyliminium species, which underwent addition by the zinc acetylenide generated in situ from phenylacetylene and $ZnBr_2$ in the presence of Hünig's base.[243] The resulting cyclic propargylic amides or carbamates were isolated in 63-79% yield.

In the field of metal-mediated addition of alkynes to imines and related C=N electrophiles, a prominent role is occupied by copper-catalyzed reactions. As already described in paragraph *2.3.2.1.*, copper salts are able to form π-complexes with alkynes, which can subsequently react with a weak base to afford metal acetylenides. Although use of copper catalysis proved ineffective in promoting the reaction of alkynes with aldehydes, in recent years it was often applied to perform the analogous reaction with C=N electrophiles, some of which were generated in situ.

Use of chiral copper complexes as catalysts for *enantioselective* alkynylations of imines and related species has been extensively studied, and will be discussed in paragraph *2.3.4.2.* In the present section, only *racemic* syntheses of propargylic amines will be presented.

A first report of a mixed Ru/Cu catalytic system for the addition of acetylenes to imines was published in 2002,[244] after a similar methodology for the addition to aldehydes, employing iridium instead of copper, had already been described.[187] In this work, $RuCl_3$ (3 mol%) and CuBr (30 mol%) were used to induce the addition of phenylacetylene (**108**) and other alkynes to imines generated in situ from aldehydes and anilines. Interestingly, the reactions took place in water or in solvent-free conditions. Use of the two metal salts proved necessary to obtain the product *N*-aryl propargylic amines in high yields (77-96%); while copper (I) alone was able to afford the products, albeit in reduced yield, employment of the sole $RuCl_3$ resulted in no conversion of the in situ-

[243] K. Y. Lee, M. J. Lee, J. N. Kim *Bull. Korean Chem. Soc.* **2005**, *26*, 665.
[244] C.-J. Li, C. Wei *Chem. Commun.* **2002**, 268.

generated imines. A mechanistic proposal involving formation of a ruthenium alkynylide was formulated by the authors, but no experimental demonstration was provided.

In 2002 KNOCHEL demonstrated that a catalytic quantity of Cu(I) or Cu(II) bromide (max. 5 mol%) could be used to induce the addition of terminal alkynes to enamines, through intermediacy of the corresponding iminium species.[245,246] Toluene was the solvent of choice, and the reactions were run at a temperature of 60-80 °C. Under these conditions, *N,N*-disubstituted propargylic amines were obtained in good to excellent yields. A limitation of this protocol consists in the necessity to use enolizable aldehydes to generate the enamines; thus no aromatic derivatives could be prepared.

Almost contemporarily to the findings of CARREIRA on the zinc-promoted alkynylation of acyliminium ions,[241] the same transformation was reported by BLACK and ARNDTSEN employing a catalytic quantity of copper (I) iodide as the catalyst.[247] While only 10 mol% of CuI were required to promote the reaction, a small excess of a weak base (iPr$_2$NEt, Et$_3$N were preferable to K$_3$PO$_4$) had to be used. After optimization, the reactions needed only 15 mins in CH$_3$CN at room temperature to reach completeness. *N*-acyl propargylamines (essentially the same products resulting from CARREIRA's reaction, see Scheme 36, p. 69) and *N*-carbamate propargylamines could be prepared in 68-99% yield.

Also the mechanistic picture proposed by the authors is essentially in agreement with the other reports in the area:[241,242,243] coordination by the copper catalyst would allow the easy deprotonation of the alkyne to generate the active nucleophile copper alkynylide. Addition of this species to the in situ-generated acyliminium ion would provide the ultimate product of the reaction.

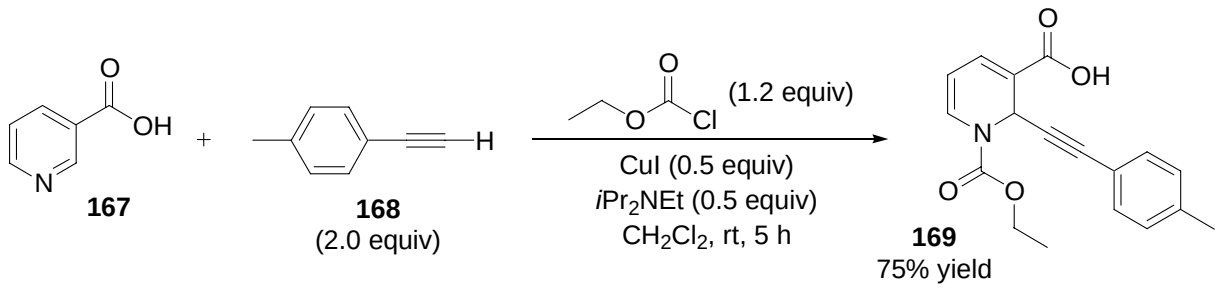
Later the same authors extended the scope of the reaction to the use of *N*-trimethylsilylimines as substrates, either under copper or zinc catalysis.[248] The *N*-trimethylsilylimines could be preformed, or even generated in situ by reaction of aldehydes with LiN(TMS)$_2$. The reaction is interesting because cleavage of the N-Si bond allows an easy access to *secondary* propargylamides, which was precluded with the pre-existing methodology. As demonstrated in the same work, secondary propargylamides can undergo cyclization, thus opening the way for a new synthesis of 2,4,5-trisubstituted oxazoles.

In the first paper of ARNDTSEN[247] a single example of copper-catalyzed alkynylation of the acyliminium ion derived from pyridine and benzoyl chloride was described. The same reaction was

[245] (a) C. Koradin, K. Polborn, P. Knochel *Angew. Chem.* **2002**, *114*, 2651; *Angew. Chem. Int. Ed.* **2002**, *41*, 2535. Full paper: (b) C. Koradin, N. Gommermann, K. Polborn, P. Knochel *Chem. Eur. J.* **2003**, *9*, 2797.
[246] The authors report that other metal species such as Ag(OAc), AuI, AuBr$_3$, Sc(OTf)$_3$, Yb(OTf)$_3$, La(OTf)$_3$, Ru(acac)$_3$, Rh(acac)$_3$, Rh(acac)(COD) and Zn(OTf)$_2$ gave no or inferior conversions to the desired propargylic amines. They also mention that other copper salts gave worse results than CuBr or CuBr$_2$ in the reaction.
[247] D. A. Black, B. A. Arndtsen *Org. Lett.* **2004**, *6*, 1107.
[248] D. A. Black, B. A. Arndtsen *Tetrahedron* **2005**, *61*, 11317.

examined in greater detail by YADAV, who reported the use of copper (I) iodide as the promoter for the addition of various alkynes to iminiums prepared from pyridines, quinolines and isoquinolines.[249] The reaction conditions were essentially the same, with the exception that a catalyst loading of 50 mol% was used and CH_2Cl_2 was chosen as the solvent instead of CH_3CN.

Several 2-alkynyl substituted heterocycles could be prepared following this protocol, generally in good yields (70-90%). The functional group tolerance was remarkable, and alkynes bearing unprotected hydroxy groups, as well as substrates carrying halogen atoms, nitro groups, esters and even free carboxylic acids could be employed without major changes in the procedure, reaction time or yield (Scheme 38).



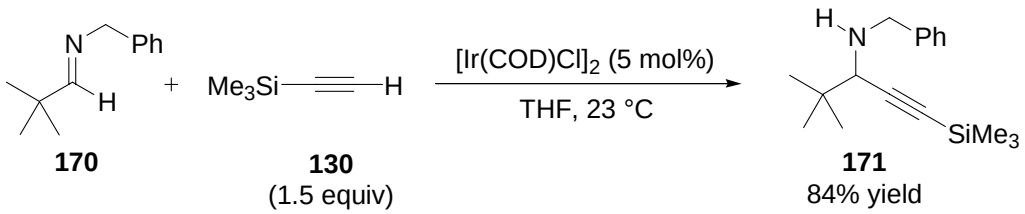
SCHEME 38. Copper-mediated alkynylation of *aza*-heterocycles by YADAV.

As for many other classes of reactions, the use of ionic liquids as solvents for the copper-catalyzed alkynylation of C=N electrophiles has also been recently documented.[250] Four different acetylenes were added to the iminium ion generated in situ from various aldehydes and secondary amines, using 1-butyl-3-methylimidazolium hexafluorophosphate (abbreviated in [bmim]PF_6) as the solvent (68-98% yield). Various copper sources were evaluated as catalysts for the reaction, and the best results were obtained with CuI and CuBr, although also the cyanide, the chloride and even elemental copper were found to be active catalysts. A very low catalyst loading could be used (2 mol%), but a temperature of 120 °C was required to obtain full conversion of the substrate within 4 h. Catalyst recycling tests were conducted, in which it was shown that CuI or CuCN could be reused up to 5 times without affecting the yield of the reaction. Moreover, as usual when ionic liquids are used as solvents, a simple extraction with an organic solvent was the only operation required to separate the products from the catalyst and therefore to obtain them in pure form.

[249] J. S. Yadav, B. V. S. Reddy, M. Sreenivas, K. Sathaiah *Tetrahedron Lett.* **2005**, *46*, 8905.
[250] S. B. Park, H. Alper *Chem. Commun.* **2005**, 1315.

The other metal salts or complexes that have been used to promote the addition of alkynes to carbon-nitrogen double bonds include compounds of iridium, gold and silver.

The iridium-catalyzed addition of trimethylsilylacetylene (**130**) to *N*-benzyl and *N*-arylimines has been reported already in 2001 by CARREIRA.[251] In this study, treatment of the substrates in THF at rt with 4-5 mol% of $[Ir(COD)Cl]_2$ led to the formation of the corresponding propargylic amines in synthetically useful yields of 65-84% (Scheme 39). Both aromatic and aliphatic imines reacted under these conditions. The authors demonstrated that the reactions could be performed with the same level of efficiency also in the absence of a solvent, which could be useful in view of possible large-scale applications, and that the addition of some ligands, like tri-*tert*-butylphosphine, helped to accelerate the reaction. This latter observation could be the starting point for the identification and development of an asymmetric process.



SCHEME 39. Iridium-catalyzed addition of TMS-acetylene (**130**) to imines by CARREIRA.

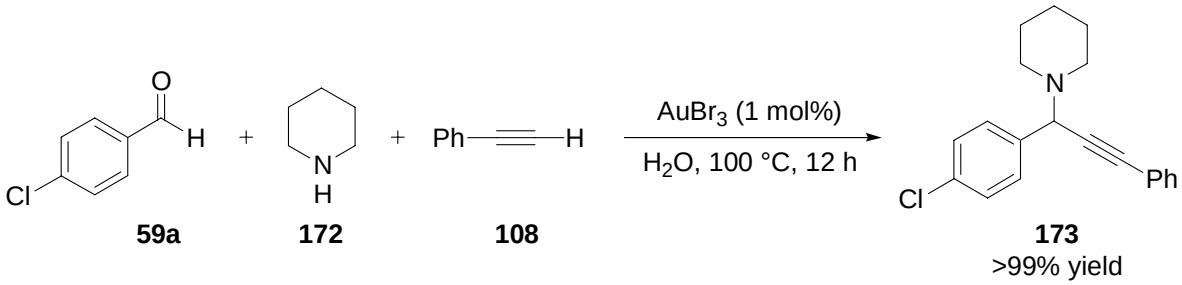
More recently, an iridium-catalyzed addition of **130** to acylisoquinolinium ions *via* C-H activation has also been described.[252]

The first gold-catalyzed three component coupling of an aldehyde, an alkyne and an amine in water as the solvent was published in 2003 by LI.[253a] In this reaction, the iminium ion generated by a secondary amine and an aldehyde undergoes addition by an alkynylgold species formed by reaction of a gold salt with an alkyne, probably *via* C-H activation.

Interestingly, both Au(I) and Au(III) salts were able to catalyze the reaction, the best one being $AuBr_3$, but not gold itself. The catalyst loading is extremely low (typically 1 mol%, but full conversion can be obtained also with 0.25 mol%), but a temperature of 100 °C is required. It is noteworthy that the reaction proceeds cleanly in water, whereas when it is conducted in organic solvents as THF, toluene or DMF it gives a lower conversion and a higher amount of by-products.

[251] (a) C. Fischer, E. M. Carreira *Org. Lett.* **2001**, *3*, 4319. (b) For an improved protocol, based on the use of MgI_2 as an additive, see: C. Fischer, E. M. Carreira *Synthesis* **2004**, 1497.
[252] Y. Yamazaki, K. I. Fujita, R. Yamaguchi *Chem. Lett.* **2004**, *33*, 1316.
[253] (a) C. Wei, C.-J. Li *J. Am. Chem. Soc.* **2003**, *125*, 9584. Recently, use of Salen-gold (III) complexes as catalysts for the same reaction has been reported: (b) V. K.-Y. Lo, Y. Liu, M.-K. Wong and C.-M. Che, *Org. Lett.*, 2006, **8**, 1529.

Under optimized conditions, the adducts resulting from the combination of three different alkynes, three different secondary amines and several aliphatic and aromatic aldehydes were obtained in yields ranging from 53% to >99% (Scheme 40). A limitation of this methodology is constituted by the impossibility to use anilines or primary amines.



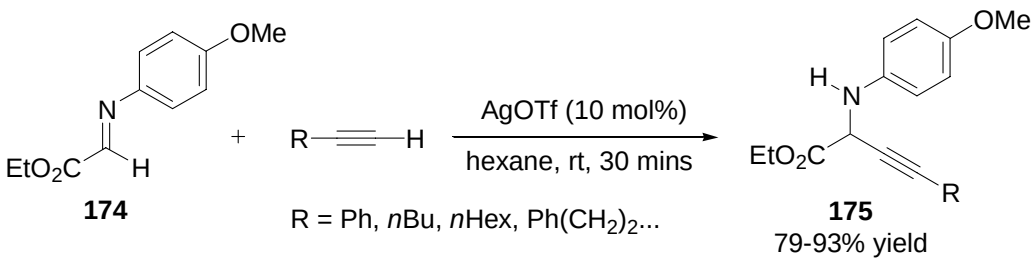
SCHEME 40. Gold-catalyzed three-component synthesis of propargylic amines by LI.

Recently, a variation of this protocol has been reported, in which a heterogeneous gold-catalyst was used to promote the reaction.[254] Layered double hydroxide-supported gold tetrachloride (LDH-$AuCl_4$) was able to catalyze the coupling between secondary amines, aromatic and aliphatic aldehydes and phenylacetylene (**108**) in refluxing THF with constantly high yields (60-93%). Only employment of alkyl monosubstituted alkynes as substrates reduced the efficiency of the reaction (31-55% yield). Due to its heterogeneous nature, the catalyst could be easily recycled and reused. Partial reduction of the gold atoms on its surface, however, led to a strong reduction of the yields after the third cycle.

In an effort to seek a more efficient catalyst for the conversion of aliphatic aldehydes, LI and co-workers found that the same three-component reaction could also be effectively promoted by silver salts.[255,256] Conducting the reaction at 100 °C in water, several silver compounds (AgI, AgCl, AgBr, AgOTf, Ag_2O and others) were screened, and all of them proved able to induce the formation of the product, the best one being silver iodide. In this case aliphatic aldehydes reacted better than aromatic ones, and a catalyst loading of 1.5-3 mol% was generally sufficient to obtain good yields of *N*,*N*-dialkyl propargylamines, especially when cyclic secondary amines were used in the coupling. As already mentioned, the same protocol could be used to produce propargylic alcohols from aldehydes and alkynes, provided that a silver-phosphine complex was used as the catalyst.[189]

[254] M. Lakshmi Kantam, B. Veda Prakash, C. R. V. Reddy, B. Sreedhar *Synlett* **2005**, 2329.
[255] C. Wei, Z. Li, C.-J. Li *Org. Lett.* **2003**, *5*, 4473.
[256] For an NMR study on the mechanism of formation of alkynylsilver species from mixtures of alkynes and silver salts, see: U. Létinois-Halbes, P. Pale, S. Berger *J. Org. Chem.* **2005**, *70*, 9185.

Finally, an Ag(I)-catalyzed alkynylation of α-iminoesters was published by CHAN in 2004. In this work, various silver salts, among which AgOTf was found to be the best one, were used to promote the addition of acetylene **108** and other alkynes to *N*-PMP-α-iminoethyl glyoxalate (**174**) at rt in hexane.[257] Usually the reactions were complete within 30 mins, affording the corresponding propargyl amino acid derivatives **175** in 79-93% yield (Scheme 41).



SCHEME 41. Ag(I)-catalyzed alkynylation of an α-iminoester by CHAN.

2.3.4.2. Enantioselective Metal-Mediated and Metal-Catalyzed Direct Alkynylation of C=N Electrophiles

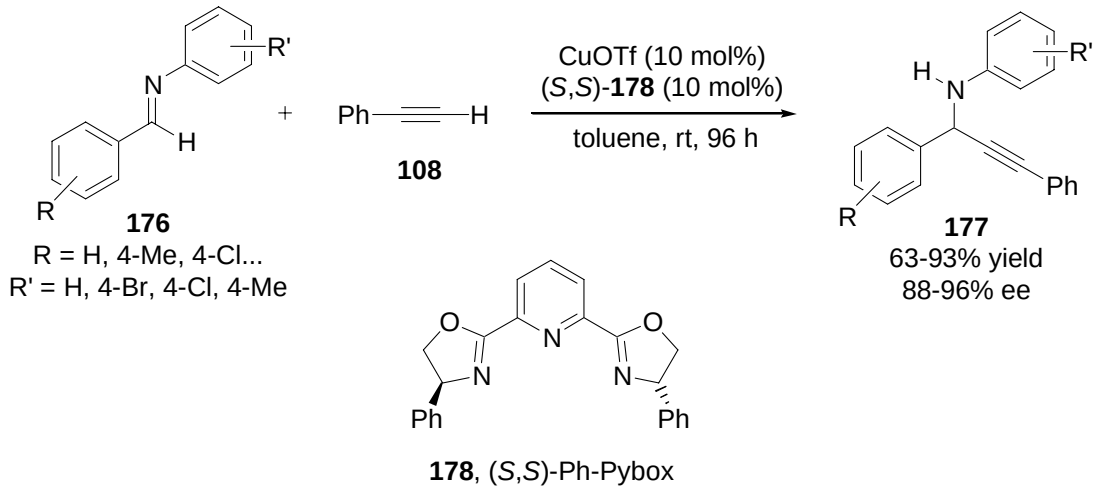
Despite the substantial amount of work dedicated to the development of enantioselective metal-mediated or catalyzed alkynylations, the application of this class of reactions to C=N electrophiles has been for long time underrepresented. Although excellent protocols have already been reported, they still lack generality, and only some of them employ catalytic quantities of metal compounds or chiral ligands, while many others rely on the use of stochiometric amounts of such promoters.

Many of the existing methods have been developed starting from the above-described non-enantioselective syntheses of propargylic amines, by addition of a suitable chiral ligand for the metal catalyst. In most of the enantioselective processes copper complexes are used as promoters, but protocols employing other metals like zinc and zirconium, or chiral boronates, have been published.

The first copper-catalyzed enantioselective addition of phenylacetylene (**108**) to imines has been described in 2002 by WEI and LI,[258] who started from the already reported racemic reaction employing a Ru/Cu catalytic system.[244] The imines were generated in situ by heating a mixture of

[257] J.-X. Ji, T. T.-L. Au Yeung, J. Wu, C. W. Yip, A. S. C. Chan *Adv. Synth. Catal.* **2004**, *346*, 42.
[258] (a) C. Wei, C.-J. Li *J. Am. Chem. Soc.* **2002**, *124*, 5638. Full paper: (b) C. Wei, J. T. Mague, C.-J. Li *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749. For a review, see: (c) C. Wei, Z. Li, C.-J. Li *Synlett* **2004**, 1472. An improvement based on the use of a different Pybox ligand has been recently described, see: (d) A. Bisai, V. K. Singh *Org. Lett.* **2006**, *8*, 2405.

an aldehyde and an aniline for 2 h, before addition of the other components. Various nitrogen-containing ligands were screened in combination with Cu(I) salts using toluene or water as solvents. After some unfruitful efforts, it was found that employment of tridentate Pybox ligands such as (*S*,*S*)-**178** could lead to products in high enantioselectivities at room temperature. Several *N*-aryl imines could then be alkynylated with phenylacetylene furnishing the corresponding propargylic amines in high yield with up to 96% ee in toluene (Scheme 42). In water the reaction was found to proceed equally well in terms of efficiency, but the enatiomeric excesses of the products were generally lower than in toluene (up to 91% ee).



SCHEME 42. Catalytic enantioselective alkynylation of *N*-arylimines by LI.

The rather long reaction time of 4 days could be shortened to 2 days by performing the reactions at 35 °C instead that at room temperature, but this led generally to a slight decrease in the enantiomeric excesses.

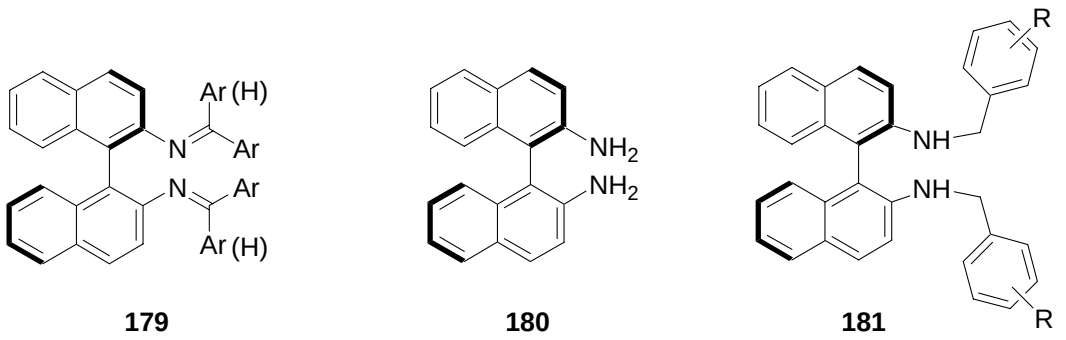
Subsequently, an extension of the method to the addition of alkynes other than phenylacetylene was also reported.[258b]

Recently, a series of polymer-bound Pybox ligands having the same structure as compound (*S*,*S*)-**178**, with different substituents on the oxazoline rings, have been synthesized on solid phase and treated with CuOTf to form the corresponding copper (I) complexes. Those complexes have been used as catalysts (10 mol%) for the enantioselective addition of phenylacetylene (**108**) to *N*-benzylidene aniline.[259] Interestingly, all of these complexes were found to be able to promote the reaction, except that bearing phenyl groups on the oxazoline rings, i. e. the solid-supported analogue of ligand (*S*,*S*)-**178.** The enantiomeric excesses of the products were lower than those of the

[259] A. Weissberg, B. Halak, M. Portnoy *J. Org. Chem.* **2005**, *70*, 4556.

propargylic amines prepared using the soluble catalyst (up to 83%). The authors demonstrated the possibility to reuse the catalyst for at least three runs.

A protocol similar to that of LI, employing chiral binaphthyl-based diimines **179**[260] or diamines **180-181**[261] (Figure 18) has been recently reported by BENAGLIA and co-workers, who worked on preformed *N*-aryl imines. Generally, compounds **179** were able to furnish the products with higher yields and enantioselectivities than diamines **180-181**.



179 **180** **181**

FIGURE 18. Chiral diimines and diamines for the Cu(I)-catalyzed enantioselective alkynylation of imines by BENAGLIA.

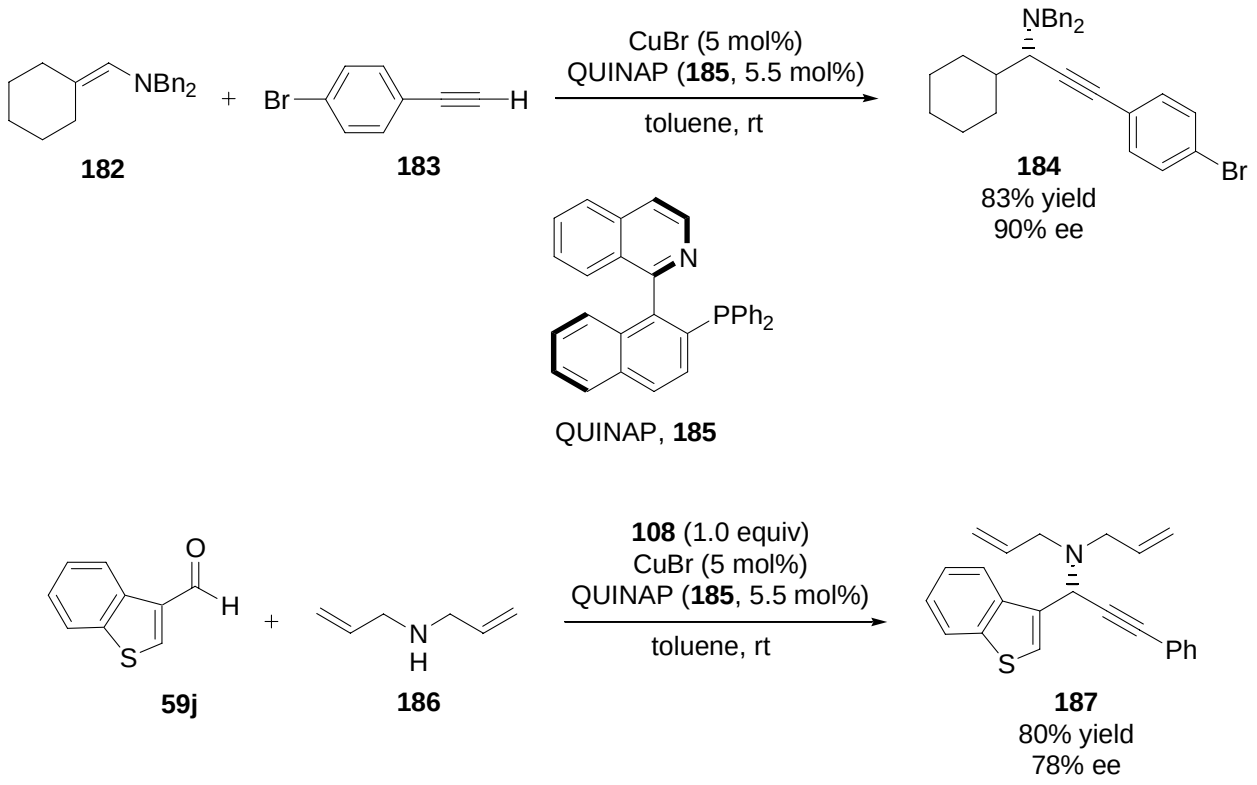
Although use of a catalytic quantity (1-10 mol%) of diimine **179** (Ar = pentafluorophenyl) in combination with CuOTf gave a good result for the additon of phenylacetylene (**108**) to *N*-benzylidene aniline (up to 85% ee), application of the same catalytic system to the reaction of other *N*-aryl imines and other acetylenes afforded generally products with much lower enantiomeric excesses, generally under 80% ee. Variation of the reaction conditions (solvent, temperature) as well as of the copper source (CuBr, CuCl, $CuPF_6$) didn't help to improve the results.

As already mentioned, an extremely efficient protocol for the addition of alkynes to enamines (derived from aliphatic aldehydes) by means of a copper (I) catalyst has been discovered by KNOCHEL[245] (see paragraph *2.3.2.1.*). Addition of a suitable chiral ligand allowed the development of an enantioselective version of this reaction; after an extensive screening it was found that QUINAP (**185**)[262] was the ligand of choice. Its use in combination with CuBr provided access to a large array of propargylamines with enantiomeric excesses up to 90% (Scheme 43).

To overcome the limitations connected to the use of enamines as starting materials, a three component procedure was subsequently introduced, in which the reactive iminium intermediate is

[260] (a) M. Benaglia, D. Negri, G. Dell'Anna *Tetrahedron Lett.* **2004**, *45*, 8705. (b) F. Colombo, M. Benaglia, S. Orlandi, F. Usuelli, G. Celentano *J. Org. Chem.* **2006**, *71*, 2064.
[261] S. Orlandi, F. Colombo, M. Benaglia *Synthesis* **2005**, 1689.
[262] N. W. Alock, J. M. Brown, D. I. Hulmes *Tetrahedron: Asymmetry* **1993**, *4*, 743.

generated by reaction of an aldehyde with a secondary amine (generally dibenzyl- or diallylamine).[263] Slightly higher enantioselectivities were generally obtained in comparison with the original methodology (up to 96% ee) and, more importantly, the new protocol allowed to use also aromatic aldehydes as starting materials (Scheme 43). Unfortunately, however, this latter class of substrates remains problematic, and to date only enantiomeric excesses in the range of 70-80% have been obtained for the corresponding propargylic derivatives (with heteroaromatic aldehydes being slightly superior to the others).



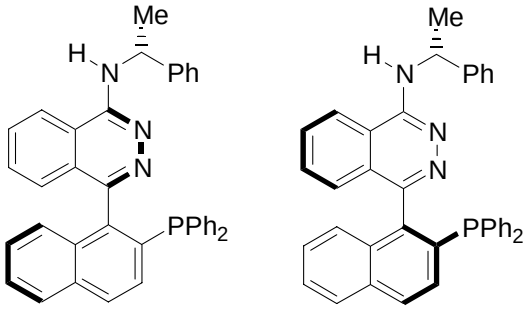
SCHEME 43. Copper-catalyzed addition of alkynes to enamines and three-component syntesis of propargylamines by KNOCHEL.

Reactions conducted with scalemic QUINAP revealed the presence of a considerable positive non-linear effect, which suggested the participation of more than one molecule of ligand to the transition state of the enantiodiscriminating step of the reaction. Subsequent applications of this methodology included the preparation of terminal propargylic amines and resulting synthesis of (*S*)-(+)-coniine,[264] the synthesis of functionalized primary chiral amines (by deprotection of the

[263] N. Gommermann, C. Koradin, K. Polborn, P. Knochel *Angew. Chem.* **2003**, *115*, 5941; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763.
[264] N. Gommermann, P. Knochel *Chem. Commun.* **2004**, 2324.

nitrogen atom and elaboration of the triple bond),[265] and the synthesis of chiral triazoles *via* 1,3-dipolar cycloaddition with azides.[266] Furthermore, it was demonstrated that an increase in the steric bulk on the amine component, by employment of (mesitylmethyl)benzylamine in place of dibenzyl- or diallylamine, led to an increase in the enantiomeric excess of the resulting propargylic amines (up to 98% ee).[267] KNOCHEL's method found also recently application in the enantioselective alkynylation of isolated isoquinoline iminium ions, which allowed the asymmetric synthesis of (*S*)-(−)-homolaudanosine, an isoquinoline-based product possessing neurologic activity.[268]

A major drawback of this methodology consists in the need to use QUINAP (**185**) as the chiral ligand. The preparation of this compound is time-expensive and includes one resolution step.[262] On the other hand, ligand **185** is today commercially available, but it is rather expensive.[269] For this reasons, various research groups focused on the synthesis of alternative P,N-ligands, strucurally related to compound **185**. In 2004, CARREIRA reported the synthesis and the application of one of these compounds, PINAP (**188**, Figure 19), to the three-component synthesis of propagylic amines.[270]



188a **188b**

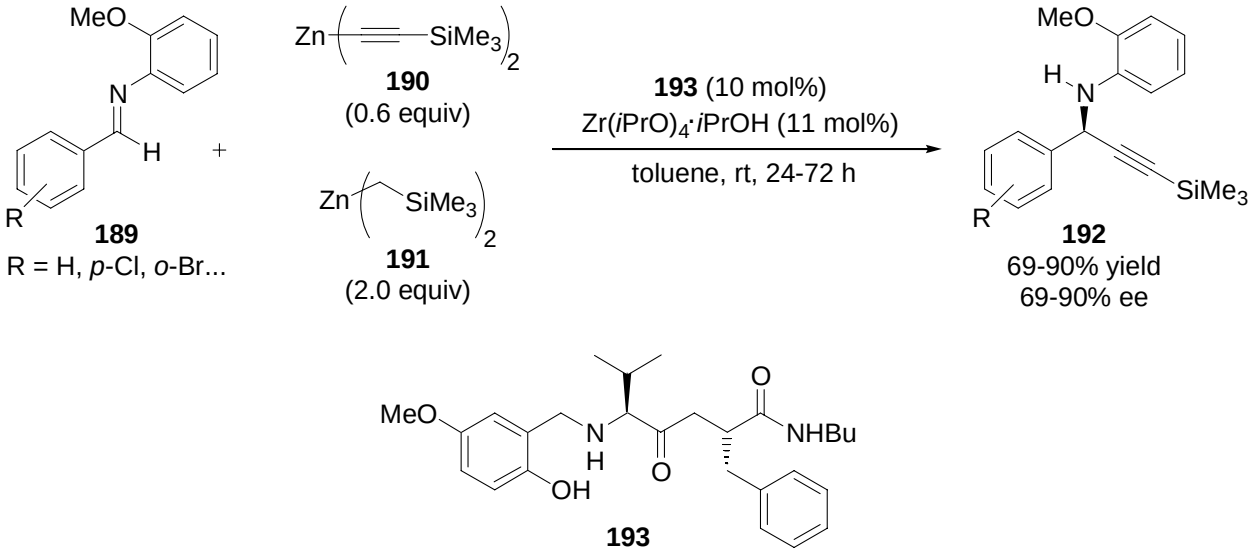
FIGURE 19. Diastereomeric PINAP ligands (**188**) by CARREIRA.

The synthesis of compounds **188** comprises of only four steps. The presence of an element of central chirality in addition to the axially chiral binaphthyl unit allows a simple separation of the diastereoisomers **188a** and **188b** on silica gel or by crystallization. The authors reported that use of compounds **188** as ligands in place of compound **185** in the three-component synthesis of

[265] N. Gommermann, P. Knochel *Tetrahedron* **2005**, *61*, 11418.
[266] N. Gommermann, A. Gherig, P. Knochel *Synlett* **2005**, 2796.
[267] N. Gommermann, P. Knochel *Synlett* **2005**, 2799.
[268] (a) A. M. Taylor, S. L. Schreiber *Org. Lett.* **2006**, *8*, 143. The same reaction has been later reported by another research group: (b) Z. Li, P. D. McLeod, C.-J. Li *Tetrahedon: Asymmetry* **2006**, *17*, 590.
[269] 50 mg of (*P*)- or (*M*)-Quinap cost 143 € (*Strem*, 2004).
[270] (a) T. F. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira *Angew. Chem.* **2004**, *116*, 6097; *Angew. Chem. Int. Ed.* **2004**, *43*, 5971. Use of 4-piperidinone as a protecting group for nitrogen: (b) P. Aschwanden, C. R. J. Stephenson, E. M. Carreira *Org. Lett.* **2006**, *8*, 2437.

propargylic amines as described by KNOCHEL[263] generally furnished products with higher enantioselectivity (90-99% ee); compound **188b** afforded slightly better results than its diastereomer **188a**.

To date, only three examples of enantioselective additions of alkynes to imines employing chiral promoters other than copper complexes have been described in the literature. First, in 2003, HOVEYDA and SNAPPER utilized a peptide-based chiral ligand (**193**) in combination with Zr(*i*PrO)$_4$·*i*PrOH to promote the addition of a mixed alkynylzinc reagent to aromatic aldimines (Scheme 44).[271]



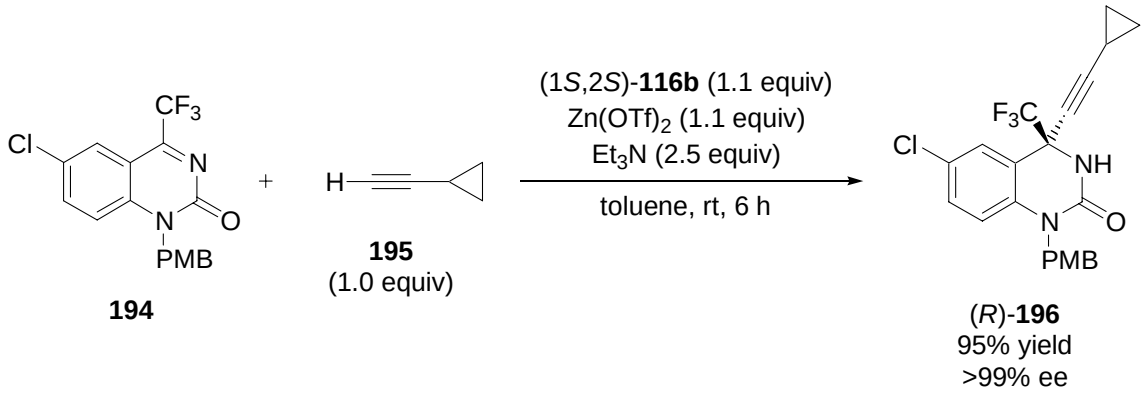
SCHEME 44. Enantioselective alkynylation of aromatic aldimines by HOVEYDA and SNAPPER.

Although good to high enantioselectivities were observed in this reaction, the necessity to use preformed organometallic compounds **190** and **191** in order to generate the mixed organozinc reagent that would add to the substrate makes the protocol less attractive. Furthermore, addition of alkynes other than **130**, like phenylacetlyene (**108**) and 1-hexyne (**159**) led to products with lower enantiomeric excesses (68-79% ee).

JIANG described in 2004 the application of his aminoalcohols (1*S*,2*S*)-**116a-b** as stoichiometric ligands for the asymmetric addition of alkynes to a cyclic α-trifluoromethyl activated imine.[272] This was the key step in the preparation of DPC 961, an aza-analogue of the already mentioned anti-

[271] J. F. Traverse, A. H. Hoveyda, M. L. Snapper *Org. Lett.* **2003**, *5*, 3273. For an alternative approach to the same class of products, based on the Zr-catalyzed *alkyl*zinc addition to *propargyl*imines see ref. 57b
[272] B. Jiang, Y.-G. Si *Angew. Chem.* **2004**, *116*, 218; *Angew. Chem. Int. Ed.* **2004**, *43*, 216.

AIDS drug *Efavirenz*.[273] Use of (1*S*,2*S*)-**116b** in combination with $Zn(OTf)_2$ and triethylamine led to isolation of the addition product in extremely high enantiomeric excess (Scheme 45).

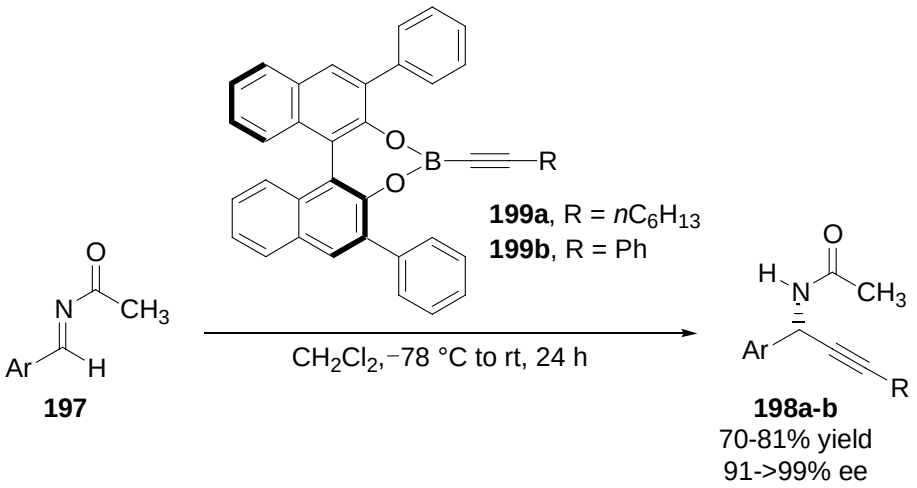


SCHEME 45. Enantioselective addition of an alkyne to a DPC 961-precursor by JIANG.

The applicability of this methodology to the industrial synthesis of DPC 961 was demonstrated by carrying out the reaction on 100 g-scale, which furnished a result comparable with that of the small-scale reaction. The authors also demonstrated the possibility to add alkynes other than **195** (the corresponding products were formed in 98->99% ee), and to recover and reuse the catalyst for at least three times with no loss in yield and selectivity (although the reaction time had to be increased to 10 h).

Finally, use of binaphthol-based alkynylboronates was recently reported by CHONG to perform the enantioselective alkynylation of *N*-acyl aldimines.[274] In this approach, the chiral alkynylboron nucleophile has to be prepared and isolated prior to the reaction, as well as the electrophile *N*-acylimine. The reaction then proceeds in a similar way to a conjugate addition, with initial coordination of the alkynylboron species by the oxygen of the substrate (which is consequently activated) and subsequent alkynyl transfer. The authors found that substitution at the 3,3'-position of the binaphthol unit is essential to achieve high enantioselectivity; after optimization, propargylamides with enantiomeric excesses ranging from 91 to >99% could be prepared (Scheme 46).

[273] For an excellent account on the development of an asymmetric synthesis of DPC 961 and DPC 963 (another analogue of *Efavirenz*) see: W. A. Nugent *Adv. Synth. Catal.* **2003**, *345*, 415.
[274] T. R. Wu, J. M. Chong *Org. Lett.* **2006**, *8*, 15.



SCHEME 46. Enantioselective synthesis of propargylamides by CHONG.

The authors demonstrated the utility of this protocol by the first total synthesis of (−)-*N*-acetylcolchinol, a compound useful in the treatment of cancer, which could previously be obtained only by degradation of natural colchicine.

3. Research Objective

As already mentioned in paragraphs *2.2.2.* and *2.2.3.*, a considerable part of the research in the field of the asymmetric aryl transfer reaction to aldehydes has been concentrated on the design and preparation of new and more powerful ligands. Despite the fact that high yields and enantioselectivities had already been achieved in the reaction, at the outset of this study the introduction of more easily accessible and efficient catalysts appeared yet desirable.

The number of ligands able to promote the reaction was still rather limited, and in many cases they had to be synthesized through multistep sequences that often involved resolution processes. Moreover, they had to be used in relatively large amount (10-20 mol%) and in general only one enantiomer / diastereomer of those compounds was made available by the synthesis. The preparation of both enantiomers of a certain diarylmethanol using the same reaction,[275] or the identification of match / mismatch effects to improve the ligand structure were therefore impossible.

In the case of the very effective metallocenes **64** and **67**, assuming that the aryl transfer reaction proceeds with a mechanism similar to that of the diethylzinc addition to aldehydes (see Scheme 7, p. 13), the ligands coordinate the first zinc atom through the nitrogen of an oxazoline ring and the oxygen of a benzylic alcohol moiety. Chelation of the metal forms a seven-membered ring.

The preparation of new compounds possessing the same coordinating functionalities on a different backbone, that could be obtained in few synthetic steps, and their application to the enantioselective aryl transfer reaction to aldehydes seemed an attractive way to meet the demand for more easily accessible ligands. Moreover, the absence of the element of planar chirality in the ligand's backbone, and the formation of a chelate ring of different dimension could help to evaluate the effective importance of those elements for the high selectivity displayed by **64** and **67**.

In addition, a flexible synthetic pathway had to be identified to allow the easy modification of the ligand structure, in order to give access to different diastereomers to evaluate match / mismatch effects, and to different substitution patterns on the oxazoline ring as well as around the alcohol moiety (Figure 20).

[275] A brilliant solution to this problem consists, as we have already seen, in the use of functionalized boronic acids for the addition to benzaldehyde; see ref.110a.

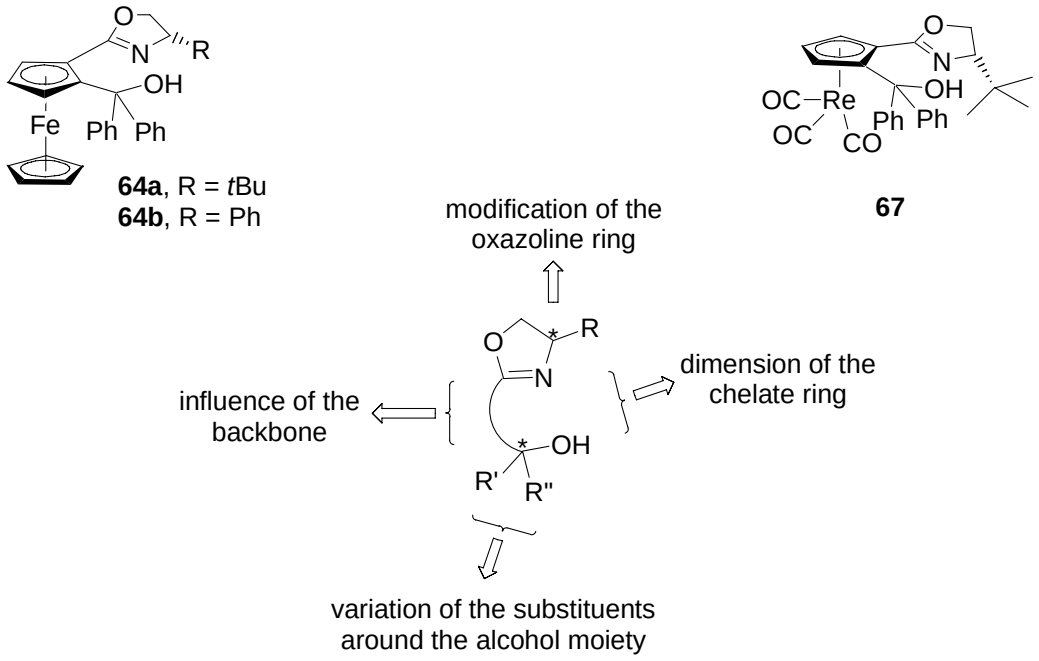


FIGURE 20. Design of new ligands for the asymmetric aryl transfer reaction to aldehydes.

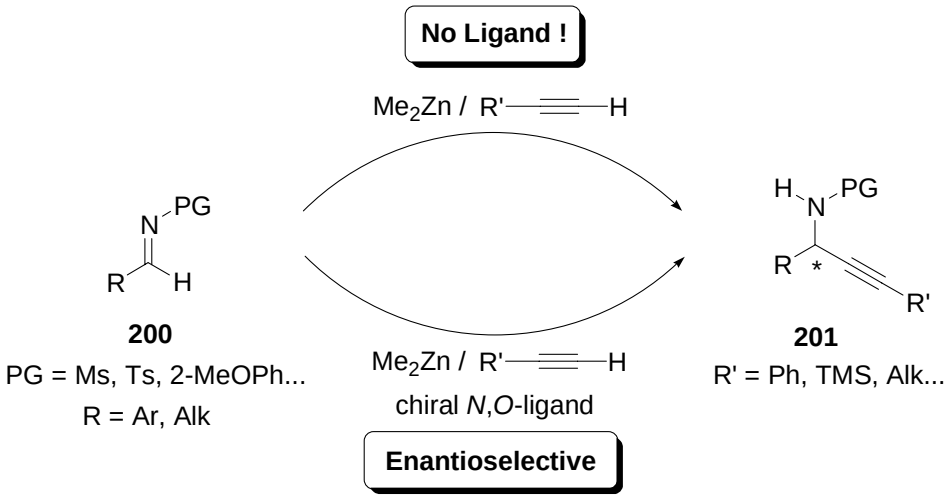
In the second part of the present work, the development of a dialkylzinc mediated alkynylation of imines was identified as the research objective. As discussed in paragraph *2.3.*, a considerable effort was made in recent years to develop the direct addition of acetylenes to carbon-heteroatom double bonds. While at the outset of this work many dialkylzinc-mediated reactions had already been reported that made use of carbonyl compounds as substrates, only a diethylzinc-catalyzed addition of alkynes to *nitrones* had been published,[239] but no addition to *imines*. Moreover, the only *enantioselective* Zn-mediated alkynylation of an imine described was the stoichiometric process reported by JIANG for the synthesis of DPC 961. No enantioselective alkynylation of imines by means of dialkylzinc reagents as promoters was known.

Considering that, on the contrary, analogous alkylation processes are very well-known reactions,[54-61] and that a highly enantioselective diethylzinc-promoted phenylation of imines has also been reported,[127] the extension of this chemistry to the use of C(sp)-nucleophiles was envisaged as an attractive research objective. Moreover, the possibility to deprotonate terminal alkynes with a dialkylzinc species was supposed to allow their direct use in the reaction, without the need for the prior preparation of an alkynylzinc species or for a transmetallation step.

On the basis of these considerations, first the dialkylzinc-promoted alkynylation of imines in the absence of a ligand was attempted, in order to provide an easy access to *N*-protected

propargylamines in racemic form. The recent finding that such a reaction is possible using carbonyl compounds as substrates[276] constituted the starting point of this study.

The development of an enantioselective version of the same reaction, by employment of chiral *N,O*-ligands was then examined. This involved not only the identification of suitable reaction conditions, but also the preparation of new ligands based on the well-established norephedrine backbone (Scheme 47).



SCHEME 47. Development of a dimethylzinc-mediated alkynylation of imines.

[276] P. G. Cozzi, J. Rudolph, C. Bolm, P.-O. Norrby, C. Tomasini *J. Org. Chem.* **2005**, *70*, 5733. For a more detailed discussion in relation with the results presented in this work, see paragraph *4.3*.

"An expert is a man who has made all the mistakes which can be made in a very narrow field."

Niels Bohr

4. Results and Discussion

4.1. Synthesis and Application of Chiral Hydroxy Oxazolines Derived from Mandelic Acid[277]

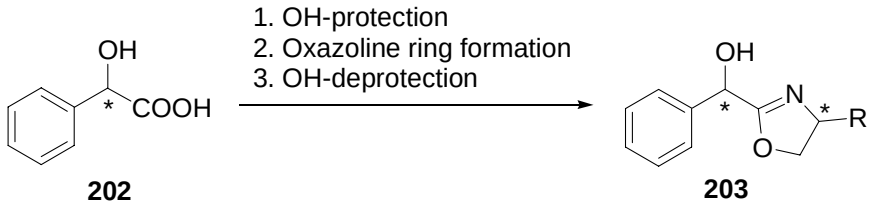
A common approach to the synthesis of new potential ligands for asymmetric catalysis is based on the exploitation of nature's structural diversity. Molecules belonging to the so-called chiral pool constitute an easily accessible and cheap source of chiral starting materials, which have often been used for the preparation of candidate ligands.[278]

Among these compounds, hydroxy and amino acids, and their derivatives, are of enormous synthetic value. In view of the preparation of novel hydroxy oxazolines according to the criteria introduced in the previous chapter, mandelic acid (**202**) appeared a particularly attractive starting material for various reasons. First, it is inexpensive and commercially available in both enantiomeric forms.[279] Moreover, it possesses easily modifiable hydroxy- and carboxyl groups.[280]

Considering that carboxylic acids and related compounds are normally used as starting materials for the preparation of oxazolines,[281,282] the transformation of mandelic acid into α-hydroxy-2-oxazolines **203** provided a very easy access to a new class of compounds potentially able to work as ligands in the asymmetric aryl transfer reaction to aldehydes (Scheme 48).

[277] C. Bolm, L. Zani, J. Rudolph, I. Schiffers *Synthesis* **2004**, 2173.
[278] H. U. Blaser *Chem. Rev.* **1992**, *92*, 935.
[279] Current prices for 5 g (33 mmol) of (*R*)- and (*S*)-mandelic acid (99% ee) taken from the *Sigma-Aldrich* 2005-2006 catalogue (Germany / Austria) are 22.30 € and 11.80 €, respectively.
[280] For a recent application of mandelic acid as resolving agent for the synthesis of enantiopure *trans*-2-aminocyclohexanol derivatives, see ref. 95
[281] Oxazolines have originally been used as protecting groups for carboxylic acids, since they are usually base-stable, but can be easily cleaved under acidic conditions: (a) A. I. Meyers, T. G. Gant *Tetrahedron* **1994**, *50*, 2297. (b) T. W. Greene, P. J. M. Wuts *Protective Groups in Organic Chemistry*, 2nd Ed., Wiley, New York, **1999**. (c) P. J. Kocienski *Protective Groups*, 3rd Ed., Thieme, Stuttgart, **2003**.
[282] For reviews on the use of oxazolines as ligands in enantioselective catalysis, see: (a) C. Bolm *Angew. Chem.* **1991**, *103*, 556: *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 542. (b) A. Pfaltz *Acc. Chem. Res.* **1993**, *26*, 339. (c) A. I. Meyers *J. Heterocycl. Chem.* **1998**, *35*, 991. (d) A. K. Ghosh, P. Mathivanan, J. Cappiello *Tetrahedron: Asymmetry* **1998**, *9*, 1. (e) J. S. Johnson, D. A. Evans *Acc. Chem. Res.* **2000**, *33*, 325. (f) P. Braunstein, F. Naud *Angew. Chem.* **2001**, *113*, 702; *Angew. Chem. Int. Ed.* **2001**, *40*, 680.

In compounds of type **203**, two natural products from the chiral pool (mandelic acid and β-amino alcohols stemming from α-amino acids) are combined to give a set of potential ligands with very interesting properties. The availability of both enantiomers of mandelic acid (**202**) allows the preparation of both diastereomers of each oxazoline **203**, giving access to matched and mismatched combinations; moreover, the steric properties of these compounds are tunable, by introducing substituens of different steric bulk on the oxazoline ring.



202 **203**

SCHEME 48. Synthetic operations required for the conversion of mandelic acid (**202**) into α-hydroxy-2-oxazolines **203**.

The synthetic route followed to prepare compounds **203** will be described in detail in the next paragraph.

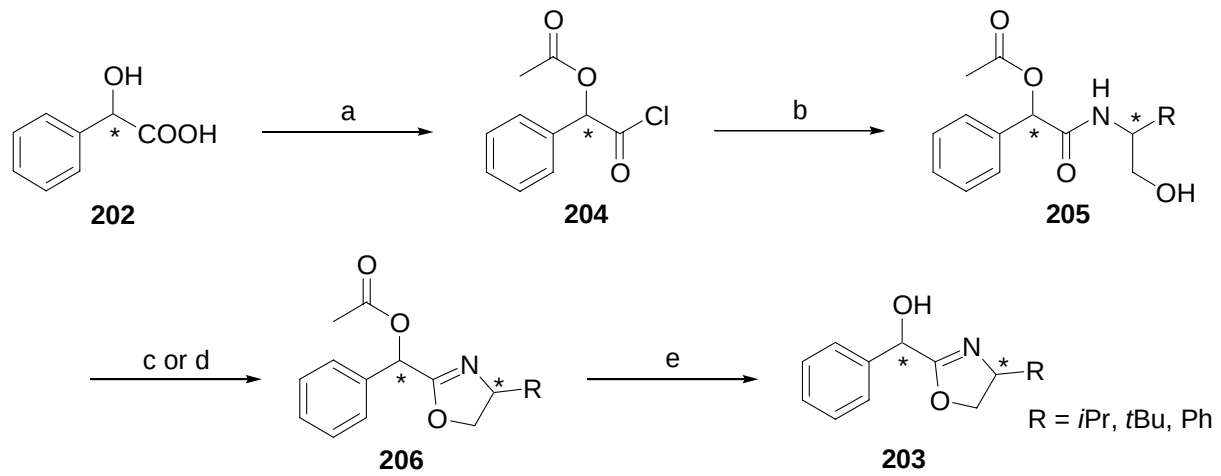
4.1.1. Synthesis of Diastereomerically Pure α-Hydroxy-2-oxazolines 203a-c

Formally, compounds **203** are simply condensation products of mandelic acid (**202**) and β-amino alcohols. The conversion of the carboxyl group of **202** into an oxazoline ring can be achieved employing standard synthetic operations; in this case the only precaution required was to protect the free alcohol moiety of the starting material to avoid its interference in the cyclization step.

The reagents and the reaction conditions that have been applied to the synthesis of **203** are reported in Scheme 49.

First, mandelic acid was converted into an acetyl-protected intermediate by reaction with acetyl chloride (here used also as the solvent) at rt. Subsequent addition of $SOCl_2$ to this intermediate generated compound **204** quantitatively. The reactions were performed with both (*R*)- and (*S*)-**202**, in order to get both the enantiomers of **204**.

In the following step, enantiopure (*R*)- or (*S*)-**204** was treated with 1.0 equiv of a chiral β-amino alcohol in the presence of triethylamine as the base to give condensation products **205** as single diastereomers in useful yields (up to 78%).



Reagents and conditions: (a) acetyl chloride, rt, 2 h, *then* $SOCl_2$, reflux, 3 h, 100%; (b) β-amino alcohol (1.0 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0 °C to rt, 17 h, 59-78%; (c) mesyl chloride (3.0 equiv), DMAP (10 mol%), Et_3N-CH_2Cl_2 (3:1), 0 °C to rt, 17 h, 62-67%; (d) DAST (1.1 equiv), CH_2Cl_2, −78 °C, 1 h, 56-71%; (e) LiOH (3.0 equiv), MeOH, 0 °C, 3 h, 62-94%.

SCHEME 49. Synthetic sequence employed for the preparation of α-hydroxy-2-oxazolines **203**.

The subsequent formation of the oxazoline ring was initially attempted by treatment of amides **205** with mesyl chloride in the presence of a large excess of triethylamine. Under these conditions, compounds (*R*,*S*)-**205b** and (*S*,*S*)-**205b**, derived from both enantiomers of **202** and the amino alcohol (*S*)-*tert*-leucinol, could be cleanly converted into the corresponding α-acetoxy-2-oxazolines (*R*,*S*)-**206b** and (*S*,*S*)-**206b** with complete diastereoselectivity in 62-67% yield.[283] Unfortunately, when other amides **205**, prepared from different amino alcohols, such as (*R*,*R*)-**205a** and (*S*,*R*)-**205a** [obtained from(*R*)-valinol] or (*R*,*R*)-**205c** and (*S*,*R*)-**205c** [prepared from (*R*)-phenylglycinol] were subjected to the reaction, the ring closure occurred with partial epimerization, probably at the benzylic stereogenic center. As a result, diastereomeric mixtures of **206a** and **206c** were obtained.

The chromatographic separation of these diastereomers proved difficult, and therefore an alternative method for the oxazoline-formation step was required. This was provided by the diethylaminosulfur trifluoride (DAST)-mediated cyclization, recently developed by WIPF and co-workers.[284] The authors reported the transformation of a large number of highly functionalized

[283] It must be mentioned that in this reaction the use of *ethanol-free* dichloromethane as the solvent is strictly necessary. Ethanol is still used by some suppliers as a stabilizer for commercially available dichloromethane. In the presence of ethanol, in the transformation of **205b** to **206b** a considerable quantity of ethyl methanesulfonate ($CH_3SO_3CH_2CH_3$) was formed as a by-product. Chromatographic separation of **206b** from ethyl methanesulfonate proved extremely difficult, and the desired product could not be obtained in pure form.

[284] (a) A. J. Phillips, Y. Uto, P. Wipf, M. J. Reno, D. R. Williams *Org. Lett.* **2000**, *2*, 1165. For pioneering studies, see: (b) G. Burrel, J. M. Evans, G. E. Jones, G. Stemp *Tetrahedron Lett.* **1990**, *31*, 3649. (c) P. Lafargue, P. Guenot, J.-P. Lellouche *Heterocycles* **1995**, *41*, 947.

hydroxy amides into the corresponding oxazolines, and pointed out that sensitive stereochemical features are usually very well tolerated under these conditions. Indeed, cyclization of both the diastereoisomers of **205a** and **205c** with 1.1 equiv of DAST in dichloromethane at low temperature proceeded without problems, and α-acetoxy-2-oxazolines (*R*,*R*)-**206a**, (*S*,*R*)-**206a**, (*R*,*R*)-**206c** and (*S*,*R*)-**206c** were now isolated after the reaction in diastereomerically pure form. In comparison with the MsCl-Et_3N methodology, a minor decrease in the yield had to be accepted in some cases.

Finally, the synthesis of compounds **203a-c** was completed by hydrolysis of the acetyl groups under basic conditions, by means of an excess of lithium hydroxide in methanol.

In Figure 21 the structures of all six α-hydroxy-2-oxazolines **203** are depicted, together with their overall yields (after four steps, referred to the initial amount of mandelic acid).

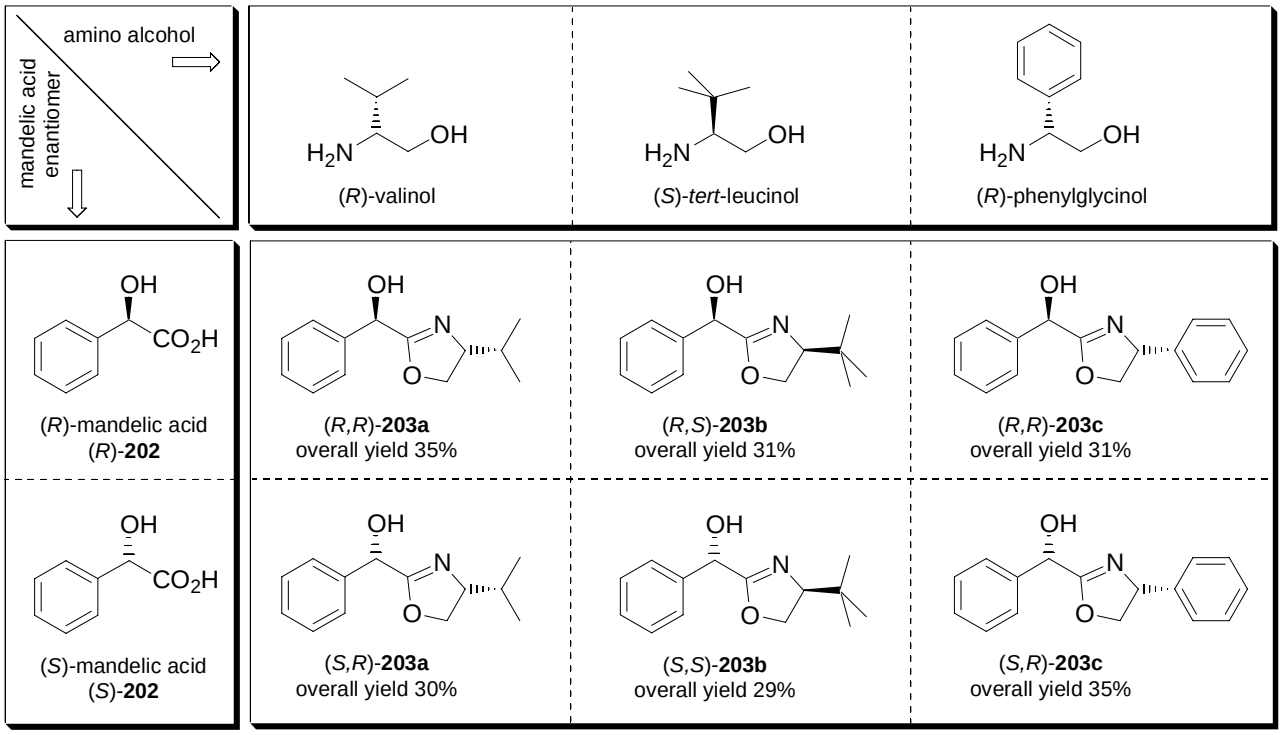


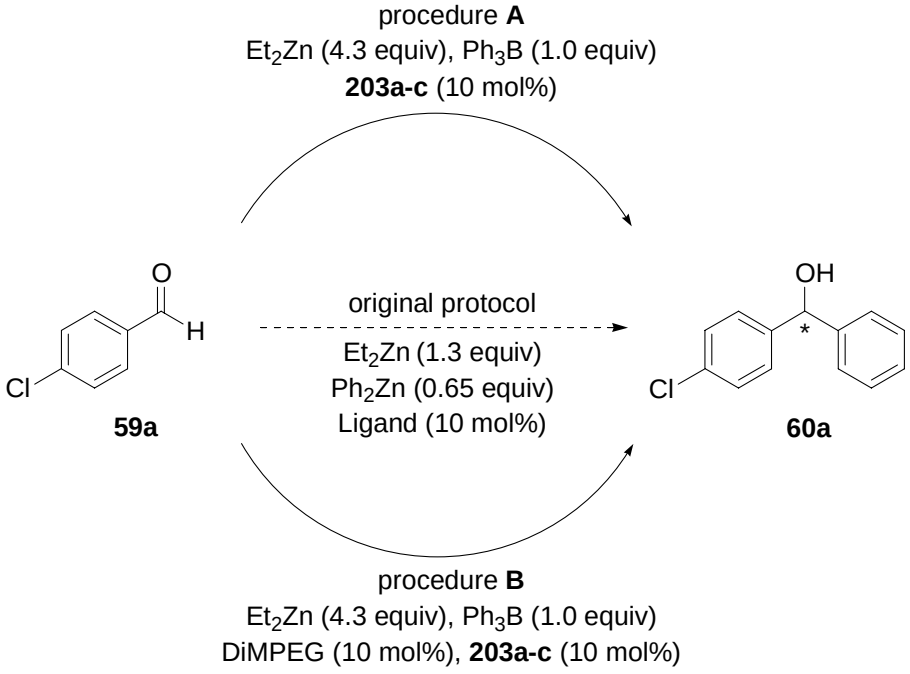
FIGURE 21. Diastereomerically pure α-hydroxy-2-oxazolines **203a-c** stemming from the combination of the two enantiomers of mandelic acid with three enantiopure amino alcohols.

As a consequence of the applied synthetic pathway it was possible to easily modify the structural features of the target compounds in a very little number of steps, just by changing the substituent on the oxazoline ring, or by adjusting the configurations of the two stereogenic centers.

Next, the capability of diastereomerically pure α-hydroxy-2-oxazolines **203** to serve as ligands for the catalytic, enantioselective phenyl transfer reaction toward 4-chlorobenzaldehyde (**59a**) was evaluated.

4.1.2. Enantioselective Phenyl Transfer Reaction

As described in paragraph *2.2.*, the original protocol developed in BOLM's research group for the catalytic, enantioselective phenylation of aldehydes involved the use of a mixture of diethyl- and diphenylzinc as the phenylating agent.[87] In the present study, two different procedures were applied for the catalysis (Scheme 50).



SCHEME 50. Catalytic, enantioselective phenyl transfer reaction to *p*-chlorobenzaldehyde (**59a**).

In procedure **A**, triphenylborane (**80**)[114] was utilized in the place of diphenylzinc (with a different stoichiometry) as a phenyl source, with the aim to demonstrate its applicability also to catalytic systems not using ferrocene (*S*,R_p)-**64a** as the chiral ligand. Moreover, since it was recently discovered that the addition of small quantities of polyethers had a beneficial effect on the enantioselectivity of the aryl transfer reaction,[118] procedure **B** employed a reagent combination consisting of Ph_3B (**80**), Et_2Zn and DiMPEG as additive.

The results obtained are summarized in Table 1.[285]

[285] The experiments described in Table 1 were performed in collaboration with JENS RUDOLPH.

TABLE 1. Enantioselective phenyl transfer reaction to **59a** catalyzed by α-hydroxy-2-oxazolines **203a-c**.

Entry	Ligand	Procedure **A**		Procedure **B**	
		Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	(*R*,*R*)-**203a**	33	16 (*R*)	26	21 (*R*)
2	(*S*,*R*)-**203a**	76	9 (*S*)	<5	n.d.[c]
3	(*R*,*S*)-**203b**	72	32 (*S*)	54	30 (*S*)
4	(*S*,*S*)-**203b**	19	32 (*S*)	20	35 (*S*)
5[d]	(*R*,*R*)-**203c**	74	*rac*	74	3 (*R*)
6[d]	(*R*,*S*)-**203c**	50	24 (*S*)	35	26 (*S*)

[a] After column chromatography. [b] The enantiomeric excess was determined by HPLC using a chiral Chiralcel OB-H column (see experimental section for details). [c] Not determined. [d] Use of the original protocol employing a mixture of Ph_2Zn and Et_2Zn led to irreproducible results.

Although the majority of α-hydroxy-2-oxazolines **203** was able to give active catalytic systems, it must be recognized that neither the activity nor the enantioselectivity in the formation of **60a** were satisfactory, since they did not reach the levels of already known systems. The best yield of the product was 76% (entry 2, without DiMPEG), while the best values for the enantiomeric excess ranged between 30 and 35%. These were obtained using compounds (*R*,*S*)-**203b** and (*S*,*S*)-**203b**, derived from *tert*-leucinol (entries 3-4).

Interestingly, those two diastereoisomers provided comparable results in terms of enantioselectivity, but (*R*,*S*)-**203b** was able to furnish the product in much better yield than (*S*,*S*)-**203b**. Moreover, in all cases the absolute configuration of the major enantiomer, as determined by comparison with literature data,[85] was (*S*), indicating that the stereogenic center on the oxazoline ring was responsible for the sense of asymmetric induction.

On the basis of these results, it can be suggested that the two diastereomeric transition states of the reaction catalyzed by (*S*,*S*)-**203b** (which lead to the formation of the two different enantiomers) are higher in energy than those of the reaction catalyzed by (*R*,*S*)-**203b**, but the relative energetic difference between them remains in both cases approximately the same, and depends probably by steric interactions between the substrate and the side chain of the oxazoline ring.

Catalytic systems based on α-hydroxy-2-oxazolines **203a** (entries 1-2) and **203c** (entries 5-6) were less enantioselective than those derived from **203b**. Probably, this was due to the reduced steric bulk on the oxazoline ring, as a consequence of the replacement of the *tert*-butyl substituent of **203b** with smaller *iso*-propyl or phenyl groups. Also in this case, one of the two diastereomers was in

general more catalytically active than the other, but differences in enantioselectivity were also observed.

The use of DiMPEG as an additive gave in the present study results similar to those already observed in the course of previous investigations.[110,114] In general, compared to procedure **A**, the ee values of the product increased slightly (except in one case, entry 3) when the catalyses were performed in presence of the additive according to procedure **B**. On the other hand, as observed later also by other research groups,[117] the beneficial effect on the enantioselectivity was often accompanied by a decrease in the yield of **60a**. This was particularly evident in the case of compound (*S*,*R*)-**203a** (entry 2).

Some more experimental details should be mentioned, which may help to better understand the reasons for the unsatisfactory selectivity displayed by compounds **203a-c**. First, while both diastereomers of **203b** showed a good solubility in toluene (usually the solvent of choice for the catalyzed aryl transfer reaction), a clear solution could not be obtained when **203a** and **203c** were used.[286] This probably reduced the amount of the active catalyst in solution, thus accounting, at least in part, for the bad results obtained. On the other hand, this observation was rather surprising, since such a difference in solubility had not been observed in the case of ferrocene derivatives **64a** and **64b**.

Moreover, due to partial or full decomposition during the catalysis, none of the α-hydroxy-2-oxazolines **203a-c** could be recovered at the end of the reaction and reused. This phenomenon is also in contrast with the behavior of ferrocenes **64a-b**, which were not destroyed during the reaction. The decomposition of the ligand, especially if much faster than the phenyl transfer reaction, probably caused a reduction in the concentration of the active catalyst too, and is therefore another factor to consider to explain the low enantioselectivity observed. Since oxazolines are normally stable against basic reagents, the reason of the lability of compounds **203a-c** under the applied reaction conditions is probably to be found in the reactivity of the benzylic alcohol moiety (in this case also *aza*-allylic), with possible oxidation or epimerization at the corresponding carbon atom. Another explanation would involve an intramolecular ring-opening of the oxazoline ring by the incipient zinc alkoxide,[287] but all these hypotheses could not be experimentally proven.

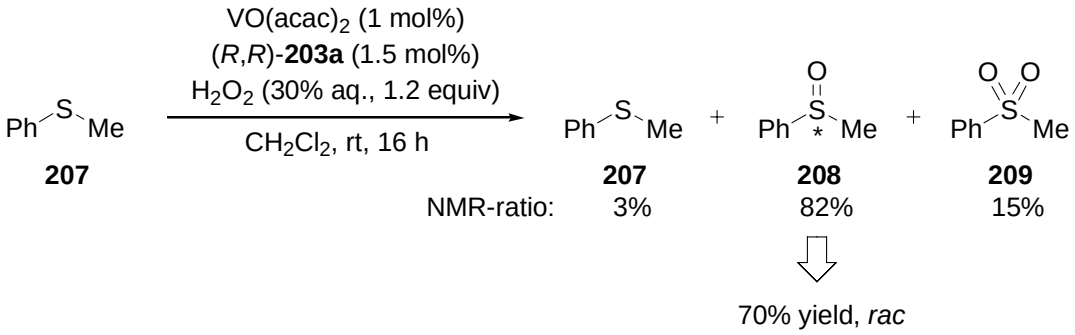
[286] Application of a prolonged time of vigorous stirring or use of an ultrasound bath could not help to solve this problem.

[287] For the description of a similar phenomenon during the preparation of paracyclophane- and benzene-derived hydroxy oxazolines, see: (a) K. Muñiz Fernandez *Dissertation*, RWTH Aachen, **1999**. (b) K. Wenz *Dissertation*, RWTH Aachen, **2002**. The compounds resulting from the intramolecular reaction, however, were in that case active catalysts for the aryl transfer reaction.

Most probably, bad solubility in toluene and decomposition during the catalysis are also the factors that caused irreproducible results to be obtained when the original protocol employing Ph_2Zn and Et_2Zn was applied with (*R*,*R*)- and (*R*,*S*)-**203c** as ligand.

Although the use of compounds **203a-c** as ligands for the asymmetric phenyl transfer reaction toward *p*-chlorobenzaldehyde (**59a**) furnished product **60a** with only moderate enantiomeric excesses, some positive aspects of this study should not be neglected. First, the optimized protocol for the synthesis of α-hydroxy-2-oxazolines **203** comprises of only four synthetic steps, during which no racemization or epimerization was observed; specific access to all different diastereoisomers of the target compounds is therefore guaranteed. Second, the reaction sequence appears to be general, and it should then be applicable to other hydroxy acid / amino alcohol combinations, thus allowing the preparation of large libraries of compounds structurally related to **203**. For these reasons, it can be expected that ligand optimization through extensive library screening will help in the future to identify more effective and selective catalytic systems based on α-hydroxy-2-oxazolines.

In concluding this paragraph, it should be mentioned that compounds **203** were tested also in other catalytic asymmetric reactions. (*R*,*R*)-**203a** was employed in the vanadium-catalyzed oxidation of thioanisole (**207**) using hydrogen peroxide as stoichiometric oxidant (Scheme 51).[288]



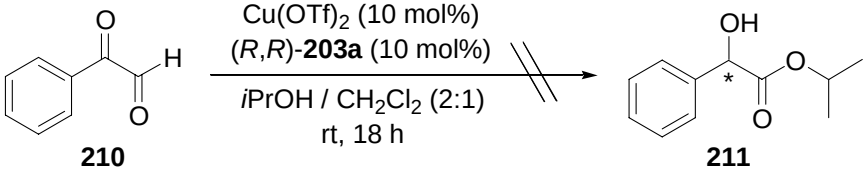
SCHEME 51. Attempted asymmetric sulfide oxidation with compound (*R*,*R*)-**203a** as ligand.

Interestingly, the catalytic system formed in situ by (*R*,*R*)-**203a** and vanadyl acetylacetonate efficiently promoted the reaction. Substrate **207** was almost completely converted, and only a small amount of sulfoxide **208** was further oxidized to sulfone **209**; the product distribution was similar to

[288] For a review on enantioselective sulfoxidation reactions, see: (a) H. B. Kagan, T. O. Luukas in ref. 12a, pp. 479. For leading references from this research group, see: (b) C. Bolm, F. Bienewald *Angew. Chem.* **1995**, *107*, 2883; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2640. (c) C. Bolm, G. Schlingloff, F. Bienewald *J. Mol. Cat. A* **1997**, *117*, 347. (d) C. Bolm, F. Bienewald *Synlett* **1998**, 1327. (e) C. Bolm *Coord. Chem. Rev.* **2003**, *237*, 245.

that observed with well-established Schiff base ligands.[288] On the other hand, no enantioselectivity was observed, as sulfoxide **208** was isolated in good yield but as a racemate.

A second reaction in which compound (*R*,*R*)-**203a** was tested as ligand was the copper-catalyzed, enantioselective, intramolecular Cannizzaro reaction (Scheme 52) first developed by MORKEN and co-workers,[289] who used a phenyl-*bis*oxazoline in combination with $Cu(OTf)_2$ as the catalyst.



210 **211**

SCHEME 52. Attempted enantioselective intramolecular Cannizzaro reaction.

Unfortunately, by combining $Cu(OTf)_2$ with (*R*,*R*)-**203a** no catalytically active species was formed, and the desired *iso*-propyl mandelate **211** could not be obtained.

4.2. Synthesis and Applications of New Chiral Hydroxy Oxazolines Possessing a Quaternary Benzylic Position[290]

As discussed in the previous paragraph, low solubility in toluene and partial or full decomposition under the reaction conditions were identified as the two major factors that probably determined the poor performance of α-hydroxy-2-oxazolines **203** as promoters for the asymmetric phenylation of *p*-chlorobenzaldehyde (**59a**).

A possible explanation for their behavior involves the destruction of the active catalyst by oxidation or epimerization at the reactive benzylic position under the strongly basic conditions employed, or the intramolecular ring-opening of the aziridine ring by the incipient zinc alkoxide.

Irrespective of the ultimate cause, a possible solution to the problem was expected to arise from the preparation of hydroxy oxazolines **212** possessing a quaternary hydroxyl-bearing carbon atom (Figure 22).

[289] A. E. Russell, S. P. Miller, J. P. Morken *J. Org. Chem.* **2000**, *65*, 8381.
[290] C. Bolm, F. Schmidt, L. Zani *Tetrahedron: Asymmetry* **2005**, *16*, 1367.

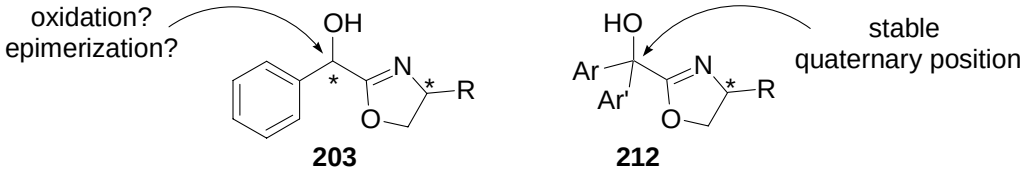


FIGURE 22. Stability of compounds **203** vs. that of compounds **212**.

Although, in the case of compounds bearing two identical substituents on the benzylic position (Ar = Ar' in Figure 22), the loss of one stereogenic center compared to **203** would have prevented the exploitation of possible match / mismatch effects, hydroxy oxazolines **212** were supposed to exhibit an improved stability, thus allowing to increase the overall enantioselectivity of the process.

Moreover, the addition of a further substituent on the benzylic position could also help to more effectively screen one of the two sides of the active catalyst, forcing the substrate to approach from only one direction, determined by the configuration of the stereogenic center on the oxazoline ring (Figure 23, where Ar = Ar' = Ph and R = *t*Bu). An improvement of the facial selectivity was also possible, as a result of the steric repulsion between the second substituent on the benzylic position and the R group of the aldehyde.

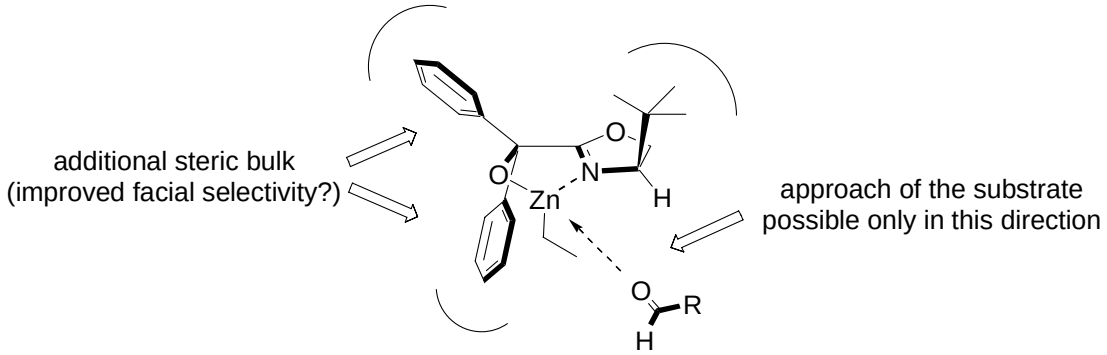


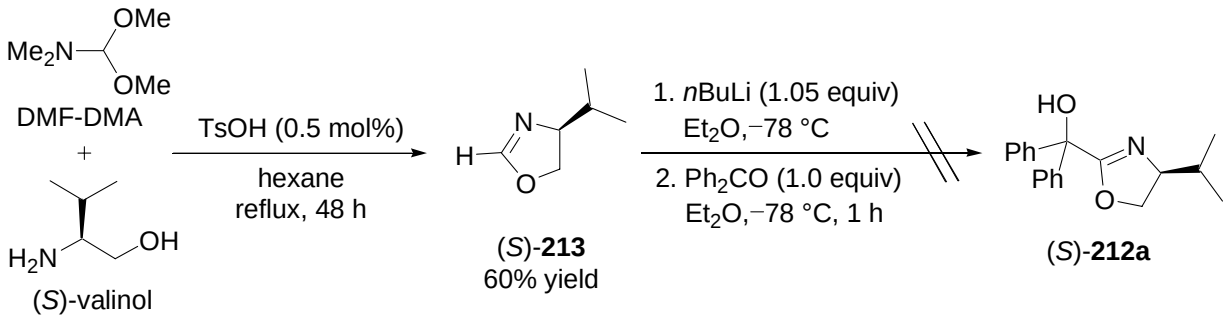
FIGURE 23. Possible factors of enhanced selectivity for α-hydroxy-2-oxazolines **212**.

4.2.1. Synthesis of New Chiral α,α-Disubstituted Hydroxy Oxazolines 212a-k

The first approach to the synthesis of compounds **212** was based on the preparation of the enantiopure 4-substituted 2-oxazoline (*S*)-**213**,[291] bearing an *iso*-propyl group, and its subsequent deprotonation with a strong base such as *n*-butyllithium. It had already been shown that structurally

[291] A. I. Meyers, W. R. Leonard, J. L. Romine *Tetrahedron Lett.* **1991**, *32*, 597.

related lithium oxazolidinides were able to react with electrophiles like silyl- or stannylchlorides to furnish the corresponding 2-substituted products.[292] Consequently, reaction of (*S*)-**213** with *n*-butyllithium followed by quench with a ketone such as benzophenone was expected to yield α-hydroxy-2-oxazoline (*S*)-**212a** (Scheme 53).



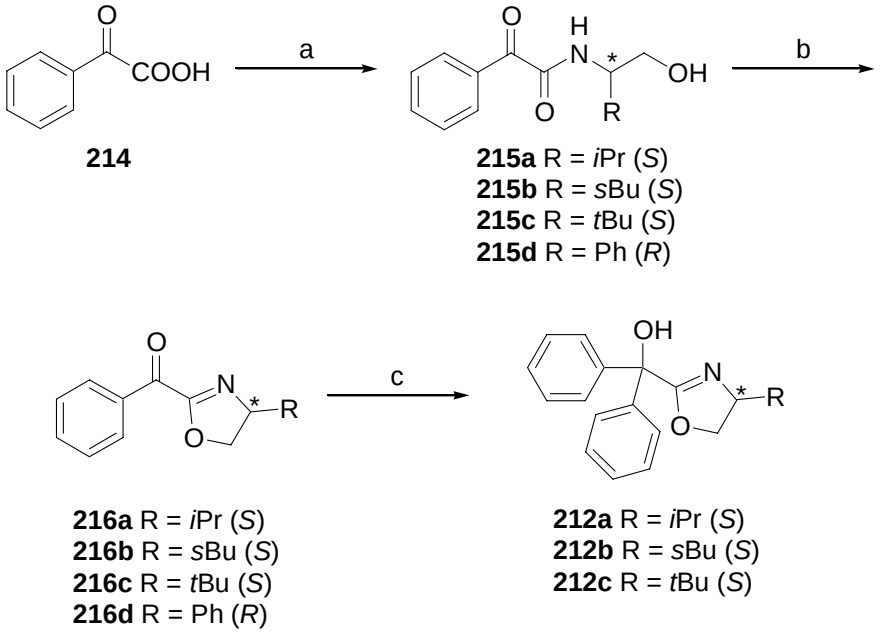
SCHEME 53. First approach to the synthesis of hydroxy oxazoline (*S*)-**212a.**

Synthesis of compound (*S*)-**213** by condensation of the dimethylacetal of dimethylformamide (DMF-DMA) with (*S*)-valinol proceeded smoothly, and the product was isolated in 60% yield after bulb-to-bulb destillation. Unfortunately, however, treatment of oxazoline (*S*)-**213** with *n*-butyllithium followed by addition of benzophenone at low temperature failed to give compound (*S*)-**212a**. Application of a higher temperature (up to rt) or a longer reaction time (up to 16 h), and use of *s*BuLi instead of *n*BuLi did not lead to improvements.

Since upon addition of *n*BuLi to (*S*)-**213** a dark yellow / brown clear solution was obtained, the deprotonation step was probably successful. This indicates that the reason for the failed conversion of (*S*)-**213** into (*S*)-**212a** should be found in the impossibility to carry out the final addition to the carbonyl compound.

A reconsideration of the synthetic approach to **212** led to identify in commercially available benzoylformic acid (**214**) another suitable precursor of the target α-hydroxy-2-oxazolines. Condensation of the acid functionality of **214** with the amino group of a chiral amino alcohol (to furnish amides **215**) followed by ring closure, would lead to α-oxo-2-oxazolines **216**, the oxidized analogues of **203**. Reaction with an excess amount of phenylmagnesium chloride would then afford compounds **212** bearing different substituents on the oxazoline ring (Scheme 54).

[292] A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini *Synthesis* **1987**, 693.



Reagents and conditions: (a) HOBt (1.0 equiv), β-amino alcohol (1.0 equiv), DMAP (0.1 equiv), DCC (1.1 equiv), CH_2Cl_2, 0 °C to rt, 16 h, 61-63%; (b) $SOCl_2$ (5.0 equiv), CH_2Cl_2, rt, 16 h *then* Na_2CO_3 (5.0 equiv), DMF, 85 °C, 24 h, for R = *i*Pr, *s*Bu, *t*Bu 62-71%, for R = Ph <20%; (c) PhMgCl (1.2 equiv), THF, rt, 2-12 h, 41-53%.

SCHEME 54. Synthesis of chiral α-hydroxy-2-oxazolines (*S*)-**212a-c**.

Indeed, treatment of **214** with four different amino alcohols under standard peptide-coupling conditions[293] cleanly afforded the corresponding hydroxy amides **215a-d** in good yields (61-63%). In this step, the combination of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) was preferred to 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) as the coupling reagent, although it furnished slightly lower yields, due to the easier purification of amides **215** after the reaction.

Surprisingly, employment of the already mentioned DAST-mediated cyclization to generate the oxazoline ring under the same conditions used to convert compounds **205a,c** to **206a,c** led this time to a complex mixture of products. Therefore, a new protocol for the ring-closing reaction had to be found. After screening of various procedures, it was found that transformation of the terminal alcohol of **215** into the corresponding chloride by reaction with an excess amount of thionyl chloride, followed by treatment with sodium carbonate in hot *N*,*N*-dimethylformamide furnished the highest yields of 2-benzoyl oxazolines (*S*)-**216a-c**, bearing alkyl side-chains (62-71%). Problems were instead encountered in the conversion of compound (*R*)-**215d** (R = Ph), which gave oxazoline (*R*)-**216d** in very low yield (<20%).

[293] (a) Y. S. Klausner, M. Bodanszky *Synthesis* **1972**, 453. (b) M. Bodanszky *Principles of Peptide Synthesis*, Springer, Berlin, **1984**.

Finally, reaction of compounds (*S*)-**216a-c** with a small excess of phenylmagnesium chloride in THF at rt provided α-hydroxy-2-oxazolines (*S*)-**212a-c**, which were purified by recrystallization.

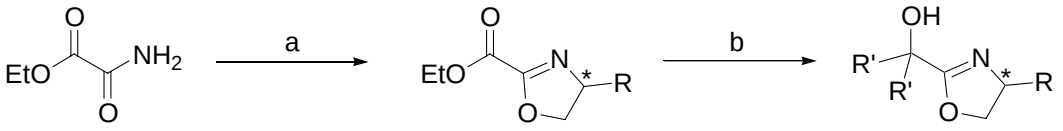
In theory, addition to **216** of a Grignard reagent different than phenylmagenesium chloride would have provided access to hydroxy oxazolines with two stereocenters, most likely as a mixture of diastereomers. A literature precedent was found for this transformation, in which various organometallic reagents were added to chiral enantiopure ketooxazolines with the aim to prepare, after hydrolysis of the oxazoline ring, enantioenriched α-hydroxy acids.[294] Since it was found that generally the diastereoselectivities in this process were only moderate (with a maximum 87% ee for the resulting quaternary hydroxy acid), a similar addition was not attempted here, albeit a chromatographic separation of the diastereomeric hydroxy oxazolines should in principle be possible.

Although the above described sequence was quite convenient, it suffered from some considerable drawbacks. Firstly, it could not give access to compound (*R*)-**216d** in acceptable yield, which raised doubts on its generality. Secondly, it was limited to the preparation of compounds with two phenyl groups at the α-position. In order to synthesize hydroxy oxazolines with different structural and electronic properties, the possibility of obtaining compounds with substituents other than simple phenyl rings at that position was desirable.

A brief survey of the literature furnished a possible solution to the problem. It was found that ethyl oxazoline-2-carboxylates **218** could be prepared in a single step starting from ethyl oxamate **217** following a procedure originally reported by PFALTZ and co-workers.[295,296] Subsequent reaction of **218** with an excess of a Grignard reagent should have then led to α-hydroxy-2-oxazolines **212** possessing different substituents at the α-position (Scheme 55).

Thus, activation of **217** with a slight excess of triethyloxonium tetrafluoroborate, followed by addition of (*R*)-phenylglicinol or (*S*)-*tert*-leucinol led, through transamidation and subsequent ring closure, to compounds (*R*)-**218a** and (*S*)-**218b**, respectively. The possibility to obtain the products in a single step from commercially available starting materials compensated for the drawback of the moderate yields (34-36%) obtained.[297]

[294] A. I. Meyers, J. Slade *J. Org. Chem.* **1980**, *45*, 2785.
[295] F. Glorius, M. Neuburger, A. Pfaltz *Helv. Chim. Acta* **2001**, *84*, 3178.
[296] An initial attempt to prepare (*S*)-**218b** starting from ethyl oxalylchloride and (*S*)-*tert*-leucinol by condensation and subsequent ring closure was not successful
[297] Such values are nevertheless comparable to those reported by PFALTZ and co-workers, see ref. 295.



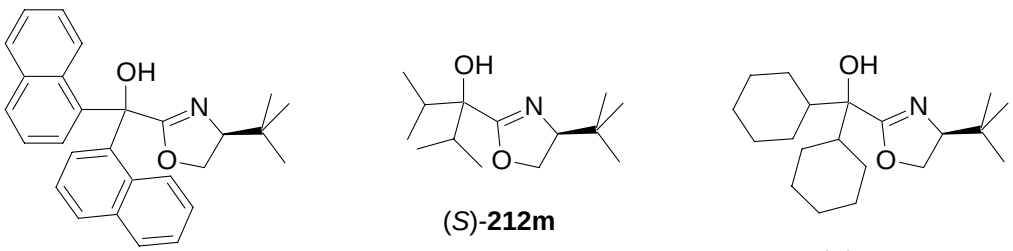
217 **218a** R = Ph; **218b** R = *t*Bu; **212d-k**

Reagents and conditions: (a) Et_3OBF_4 (1.2 equiv), 1,2-dichloroethane, rt, 24 h *then* β-amino alcohol (1.2 equiv), reflux, 24 h, 34-36%. (b) R'MgX (≥ 3.0 equiv), THF, rt, 16 h, 60-86% (for a list of all the compounds prepared, see Table 2).

SCHEME 55. Synthesis of variuosly α,α-disubstituted hydroxy oxazolines **212**.

With compounds **218a-b** in hand, the addition of various Grignard reagents usually proceeded as expected to yield differently-substituted α-hydroxy-2-oxazolines **212d-k** (for a description of all compounds prepared, see Table 2).

Some exceptions should however be mentioned (Figure 24). Firstly, when 1-naphthylmagnesium bromide was used in combination with (*S*)-**218b**, a complex mixture was obtained which contained a very large amount of naphthalene together with the expected product (*S*)-**212l**; a chromatographic purification of the latter was attempted with no success. *Iso*-propylmagnesium chloride gave an incomplete reaction, and after 16 h at room temperature a large amount of starting material (*S*)-**218b** was still present in the reaction mixture; addition of two further equivalents of Grignard reagent and stirring for further 16 h did not lead to improvements. Finally, cyclohexylmagnesium chloride reacted well with (*S*)-**218b** to afford hydroxy oxazoline (*S*)-**212n** (as deduced by the analysis of the NMR spectrum of the crude); unfortunately, also in this case problems were encountered during the purification step. Since it was not possible to obtain a full characterization of (*S*)-**212n**, this compound was not applied in catalysis.



(*S*)-**212l** (*S*)-**212m** (*S*)-**212n**

FIGURE 24. α-Hydroxy-2-oxazolines whose synthesis failed.

Table 2 summarizes the structural data of the products which could be fully characterized, together with the reaction sequence used for their preparation, where "Method A" indicates the route starting from benzoylformic acid (**214**, Scheme 54), while "Method B" refers to that using ethyl oxamate (**217**) as the starting material (Scheme 55).

TABLE 2. Hydroxy oxazolines **212a-k** prepared in this study.

Entry	Compound	Method	Config.	R	R'
1	**212a**	A	*S*	*i*Pr	Ph
2	**212b**	A	*S*	*s*Bu	Ph
3	**212c**	A	*S*	*t*Bu	Ph
4	**212d**	B	*R*	Ph	Ph
5	**212e**	B	*S*	*t*Bu	Me
6	**209f**	B	*S*	*t*Bu	4-(MeO)Ph
7	**212g**	B	*S*	*t*Bu	3,5-$(CF_3)_2$Ph
8	**212h**	B	*S*	*t*Bu	2-(Me)Ph
9	**212i**	B	*S*	*t*Bu	3,5-$(Me)_2$Ph
10	**212j**	B	*S*	*t*Bu	2,4,6-$(Me)_3$Ph
11	**212k**	B	*S*	*t*Bu	2-(MeO)Ph

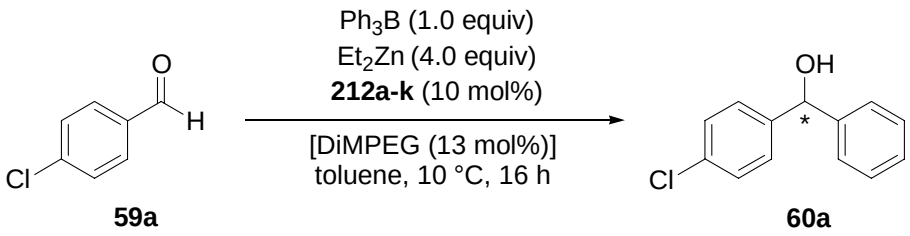
According to the criteria exposed in chapter *3.*, also in this case a high degree of structural diversity could be introduced in the products after only a few synthetic steps. The choice of the amino alcohol determined the absolute configuration of the stereogenic center as well as the structure of the oxazoline ring, and use of the appropriate Grignard reagents allowed several different substituents to be placed at the α-position.

As already done for compounds **203a-c**, also hydroxy oxazolines **212a-k** were then employed in the catalytic, enantioselective phenyl transfer reactions to aldehydes.

4.2.2. Enantioselective Phenyl Transfer Reactions

In order to compare the ability of compounds **212a-k** to serve as ligands for the title reaction with that of hydroxy oxazolines **203a-c**, the same protocol employing triphenylborane (**80**) as phenyl source was applied here, again with 4-chlorobenzaldehyde (**59a**) as the test substrate. Moreover,

since a beneficial effect of the use of DiMPEG on the enantioselectivity was found in the reactions with **203a-c**, also in this case two series of experiments were conducted. In a first series no additive was used, while in the second 13 mol% of DiMPEG (MW = 2000 g mol^{-1}) were added to the reaction mixture (Scheme 56).



59a **60a**

SCHEME 56. Catalytic, enantioselective phenyl transfer reaction catalyzed by hydroxy oxazolines **212a-k**.

The results obtained in the catalytic reactions are listed in Table 3.[298]

TABLE 3. Results of the enantioselective phenylation of **59a** catalyzed by compounds **212a-k**.

Entry	Ligand	without additive		with additive (13 mol % DiMPEG)	
		Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	(*S*)-**212a**	74	12 (*S*)	50	14 (*S*)
2	(*S*)-**212b**	74	*rac* (-)	44	*rac* (-)
3	(*S*)-**212c**	91	27 (*S*)	56	43 (*S*)
4	(*R*)-**212d**	87	*rac* (-)	48	*rac* (-)
5	(*S*)-**212e**	43	*rac* (-)	65	*rac* (-)
6	(*S*)-**212f**	83	31 (*S*)	74	35 (*S*)
7	(*S*)-**212g**	92	17 (*S*)	80	30 (*S*)
8	(*S*)-**212h**	81	68 (*S*)	**80**	**71 (*S*)**
9	(*S*)-**212i**	84	24 (*S*)	72	39 (*S*)
10	(*S*)-**212j**	76	*rac* (-)	72	*rac* (-)
11	(*S*)-**212k**	80	26 (*R*)	70	20 (*R*)

[a] After column chromatography. [b] The enantiomeric excess was determined by chiral HPLC (see experimental section for details).

[298] Some of the experiments reported in Table 3 were performed by FRANK SCHMIDT.

Two general conclusions could be immediately drawn: first, all the compounds tested led to the formation of active catalysts, furnishing products in good yields (up to 92%) with variable enantioselectivities (up to 71% ee). Second, also in this case the presence of DiMPEG proved beneficial for the enantioselectivity, leading in most cases to an increased ee of the product. Once again, however, this positive effect was often accompanied by a decrease in the yield of diarylmethanol **60a.**

In a first set of experiments (Table 3, entries 1-4) the impact of different substituents on the oxazoline ring was evaluated, keeping phenyl groups as substituents in the α-position. While (*S*)-**212b** and (*R*)-**212d**, derived from (*S*)-leucinol and (*R*)-phenylglycinol, respectively, furnished only racemic products (entries 2 and 4), a slightly better result was obtained with compound (*S*)-**212a** derived from (*S*)-valinol (14% ee in presence of the additive, entry 1). A more pronounced improvement was observed with hydroxy oxazoline (*S*)-**212c**, resulting from (*S*)-*tert*-leucinol, which was able to catalyze the phenyl addition to **59a** to provide the product in 56% yield and 43% ee in presence of DiMPEG (entry 3). Although both yield and enantiomeric excess were still just moderate, this result was already superior to those obtained in the same reaction with mandelic acid-derived ligands **203**.

These first experiments indicated that a bulky *tert*-butyl group on the oxazoline ring was required to obtain at least a moderate asymmetric induction. For this reason, several hydroxy oxazolines (*S*)-**212e-k** derived from (*S*)-*tert*-leucinol were then tested (Table 3, entries 5-11).

When the phenyl groups at the hydroxyl-bearing carbon were changed to methyl groups [compound (*S*)-**212e**], the racemic product was isolated in moderate yield (entry 5).[299] Introduction of electron-donating [compound (*S*)-**212f**, R' = *p*-methoxyphenyl in Scheme 55] or electron-withdrawing [compound (*S*)-**212g**, R' = 3,5-di(trifluoromethyl)phenyl in Scheme 55] groups on the phenyl rings at the α-position had a scarce influence on the enantioselectivity (entries 6-7).

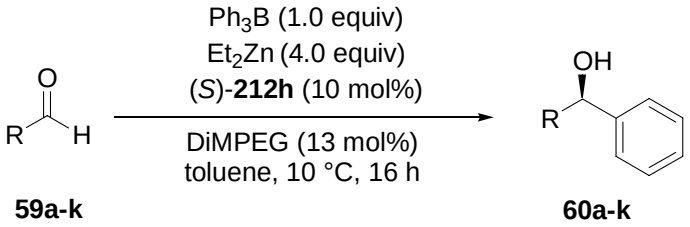
On the other hand, a variation in the steric hindrance of the aromatic rings was more effective. Thus, (*S*)-**212h**, having two *o*-methylphenyl substituents, was able to catalyze the formation of (*S*)-**60a** in 80% yield with a promising 71% ee in the presence of DiMPEG (entry 8). Unfortunately, a further increase in the steric bulk did not lead to the expected improvements. For example, compound (*S*)-**212i**, bearing two 3,5-di(methyl)phenyl groups at the α-position, gave the product diarylmethanol with almost the same enantioselectivity of the parent α,α-diphenyl hydroxy oxazoline (*S*)-**212c** (39% ee vs. 43% ee, entry 9 vs. entry 3). Application of dimesityl derivative (*S*)-

[299] Compound (*S*)-**212e** has been already prepared. However, it was only employed as an intermediate, and not directly as a ligand for asymmetric catalysis, see. (a) R. Hilgraf, A. Pfaltz *Synlett* **1999**, 1814. (b) S. P. Smidt, F. Menges, A. Pfaltz *Org. Lett.* **2004**, *6*, 2023. For the preparation and catalytic application of related compounds, see: (c) L. N. Pridgen, G. Miller *J. Heterocycl. Chem.* **1983**, *20*, 1223. (d) J. V. Allen, J. M. J. Williams *Tetrahedron: Asymmetry* **1994**, *5*, 277.

212j was even worse, since only the racemic product could be isolated after the reaction (entry 10). It can be suggested that the extreme bulk of the mesityl group forced the transition state of the reaction to assume a different conformation, which resulted in the observed lack of asymmetric induction, although no experimental proof could be found for this assumption.

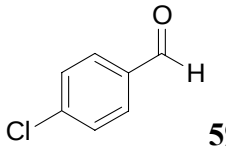
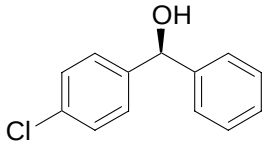
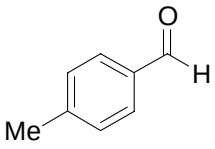
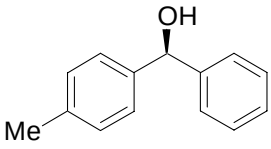
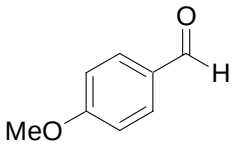
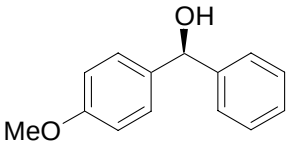
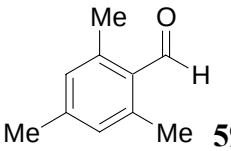
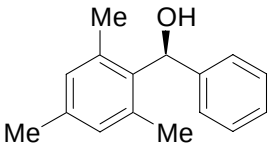
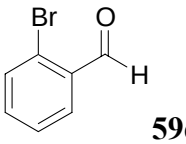
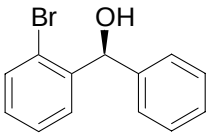
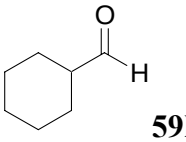
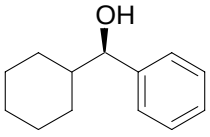
Finally, having noticed that in the absence of DiMPEG the enantiomeric excess of **60a** registered in the reaction with (*S*)-**212f** was slighltly superior to that induced by (*S*)-**212c** (entry 6 vs. entry 3), exploitation of both steric and electronic effects was attempted by utilizing hydroxy oxazoline (*S*)-**212k**, having two *o*-methoxyphenyl rings at the α-position. The results obtained were unusual (entry 11). Firstly, in this case use of DiMPEG did not increase, but lowered the enantioselectivity, and secondly, the absolute configuration of the product was opposite to that of the products of all the other reactions, even if the absolute stereochemistry of the oxazoline ring was the same. A possible explanation of the observed reversal of enantioselectivity would involve a coordination of one of the metal atoms by one of the methoxy groups on the aromatic rings, which would act as a Lewis base (cfr. Scheme 7, where the oxygen of (−)-DAIB coordinates the organozinc compound responsible for the alkyl transfer); also in this case, however, this hypotesis is missing an experimental confirmation.

Since hydroxy oxazoline (*S*)-**212h** led to the best results in the test reaction, the scope of the enantioselective phenylation of aldehydes catalyzed by (*S*)-**212h** was briefly examined (Scheme 57). The results obtained are summarized in Table 4.



SCHEME 57. Catalytic, enantioselective phenyl transfer reaction to aldehydes using (*S*)-**212h**.

TABLE 4. Scope of the enantioselective phenyl transfer reaction catalyzed by (*S*)-**212h**.

Entry	Starting Material	Product	Yield (%)[a]	ee (%)[b]
1	 **59a**	 **60a**	80	71 (*S*)
2	 **59g**	 **60g**	89	77 (*S*)
3	 **59b**	 **60b**	60	81 (*S*)
4	 **59k**	 **60k**	33	(75)[c] (*S*)
5	 **59d**	 **60d**	85	55 (*S*)
6	 **59h**	 **60h**	65	20 (*R*)

[a] After column chromatography. [b] The enantiomeric excess was determined by chiral HPLC (see experimental section for details). [c] A precise evaluation of the enantiomeric excess was not possible due to partial superimposition of the peaks.

4-Methylbenzaldehyde (**59g**) reacted smoothly under the optimized reaction conditions to give the corresponding diarylmethanol (*S*)-**60g** in 89% yield with 77% ee (entry 2). The product stemming from 4-methoxybenzaldehyde **59b** was isolated in lower yield (60%), but with an enantiomeric excess of 81% (entry 3).

The extremely bulky 2,4,6-trimethylbenzaldehyde (**59k**) proved reluctant to react, as the corresponding product was obtained in only 33% yield. Surprisingly, however, the enantiomeric excess seemed to be more or less the same as those observed with the three previous substrates. Since the two signals relative to the two enantiomers were not perfectly separated in the HPLC-

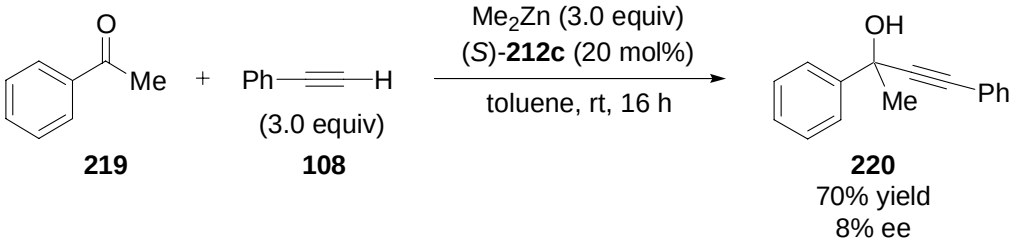
chromatogram, however, the value given in the table (75% ee, entry 4) cannot be considered an accurate measure of the enantiomeric excess, although it is certainly representative of the level of asymmetric induction obtained in the reaction.

Unfortunately, when 2-bromobenzaldehyde **59d**, which is known to be a challenging substrate for the asymmetric phenylation, was subjected to the reaction, diarylmethanol (*S*)-**60d** was isolated in satisfying yield (85%), but with only 55% ee (entry 5). Finally, as demonstrated with cyclohexane carbaldehyde **59h**, aliphatic aldehydes could also be converted, but in this case the enantioselectivity was very low (20% ee, entry 6).

Although once again the results obtained with hydroxy oxazolines **212a-k** in the catalytic asymmetric phenylation of aldehydes were inferior to the best ones reported in the literature, a comparison between Table 1 and Tables 3-4 clearly indicates that the latter compounds formed much more active and selective catalysts for that reaction than mandelic acid-derived hydroxy oxazolines **203**. This confirms the assumption made at the beginning of this paragraph, that a variation at the benzylic position of **203** would have helped to increase both yields and optical purities of diarylmethanols **60a-k**.

As a consequence of the easy and modular approach utilized in the preparation of **212a-k** (maximum of three steps from commercially available starting materials, indipendent choice of different substituents both on the oxazoline ring and at the α-position), even greater improvements can be expected to result from further optimization of the ligands structure.

In conclusion of this paragraph, it should be mentioned that the ability of oxazoline (*S*)-**212c** to serve as a ligand also for other catalytic enantioselective reactions was tested. First, a dimethylzinc-mediated enantioselective addition of phenylacetylene (**108**) to acetophenone was attempted, following the procedure reported by COZZI (Scheme 58).[227]

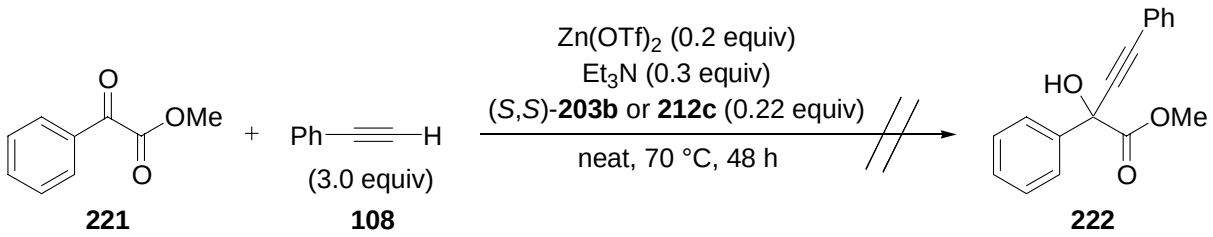


219 **108** **220**
70% yield
8% ee

SCHEME 58. Enantioselective addition of phenylacetylene (**108**) to acetophenone catalyzed by (*S*)-**212c**.

As can be seen from the scheme, (*S*)-**212c** was able to provide an active catalyst for the reaction, and the product quaternary propargylic alcohol **220** was isolated in 70% yield after column chromatography. On the other hand, the enantiomeric excess was very low (8% ee).

Subsequently, (*S*)-**212c** and also mandelic acid-derived α-hydroxy-2-oxazoline (*S*,*S*)-**203b** were used as ligands for the enantioselective addition of phenylacetylene to the activated ketone **221**, following the procedure reported by JIANG.[226] Unfortunately, however, no product was obtained as the starting material was recovered unchanged after the reaction (Scheme 59).



SCHEME 59. Attempted catalytic, enantioselective addition of phenylacetylene (**108**) to an α-ketoester.

4.3. Development of a Dimethylzinc-Mediated Alkynyl Addition to Imines[300]

As already mentioned in chapter *3.*, the second part of the present research work was dedicated to the development of a novel methodology for the preparation of variously substituted propargylic amines, by means of a dimethylzinc-mediated alkynylation of imines.

Although at the outset of this study zinc-mediated and catalyzed alkynylation reactions of C=N electrophiles had already been described,[169,237-241] the use of dimethylzinc to effect this transformation on imines was still unknown, and only one example of enantioselective addition of alkynes to imines involving a zinc compound as a promoter was present in the literature.[272]

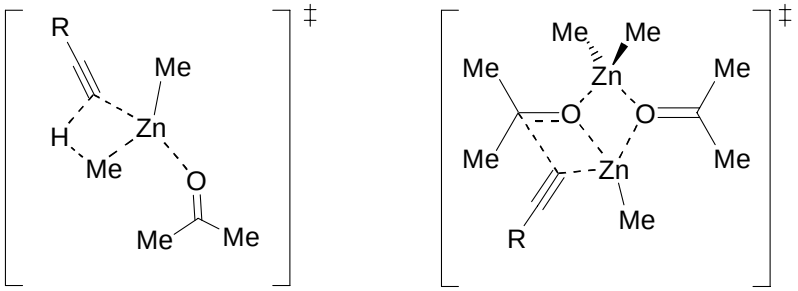
The starting point for this research was provided by the recent finding by COZZI and BOLM that a mixture of Me_2Zn and phenylacetylene was able to promote the alkynylation of aldehydes and ketones also in the absence of a ligand,[276] to furnish propargylic alcohols in good to excellent yields. This observation was in contrast with the results of previous investigations: for example, as already seen in paragraph *2.3.2.2.*, LI observed no change in the NMR spectrum of

[300] L. Zani, S. Alesi, P. G. Cozzi, C. Bolm *J. Org. Chem.* **2006**, *71*, 1558.

phenylacetylene (**108**) upon addition of dimethylzinc, and reported that a mixture of Me_2Zn and alkyne **108** was rather unreactive toward aldehydes.[301]

Since it is usually believed that dimethylzinc needs a proper activation to make it a more reactive base toward acetylenes, the results of COZZI and BOLM suggested that the oxygen of the carbonyl compound could act in a "ligand like" fashion, promoting the reaction between dimethylzinc and an alkyne by coordinating the metal with one of its lone pairs. In order to gain informations about the deprotonation and the subsequent addition step, a DFT study of a small model system consisting of acetone, acetylene and dimethylzinc was undertaken.

The study showed that the energy barrier for the deprotonation of acetylene by Me_2Zn in the presence of coordination was much lower than in the absence of the ketone ($\Delta\Delta G^{\ddagger}$ = 17 kJ/mol). Moreover, the activaton energy for the subsequent addition step was found to be very low, indicating that the alkyl-alkynylzinc species should react with the ketone as soon as it is formed (Figure 24).



223a **223b**

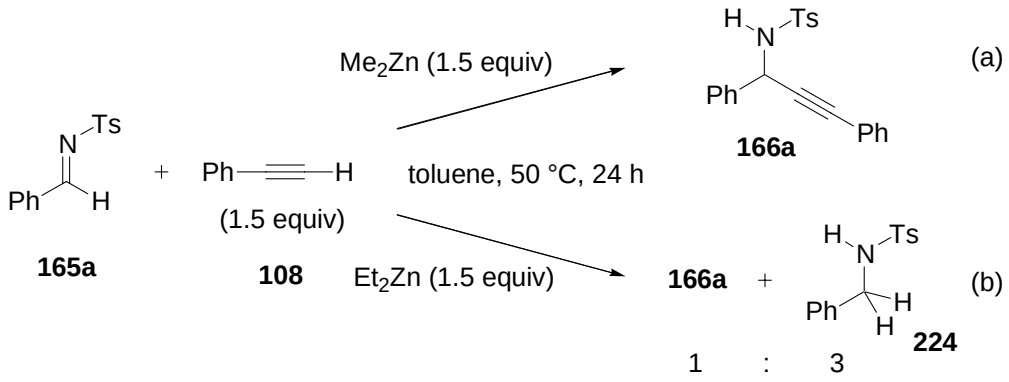
FIGURE 24. Calculated transition states for the deprotonotation of an acetylene by Me_2Zn (**223a**) and for the subsequent addition to acetone (**223b**).

On the basis of these results, it seemed natural to look at the reactivity of C=N electrophiles, like activated imines, under similar conditions, to find if they exhibit a behaviour similar to that of carbonyl compounds. Due to the lower reactivity of imines compared to aldehydes and ketones, activated compounds, bearing an electron-withdrawing group on the nitrogen atom were initially used, but, as it will be seen, later less reactive substrates could also be converted. The results of these investigations will be discussed in the following paragraphs.

[301] More recent studies revealed that the formation of the mixed organozinc species is promoted by the adventitious presence of moisture, although the reaction is incomplete, see ref. 239

4.3.1. Direct Alkyne Addition to Activated Imines Mediated by Dimethylzinc

The typical conditions for the alkynylation of aldehydes with a mixture of an alkyne and dimethylzinc involved use of 1.5 equiv each of these two reagents in anhydrous toluene at rt. Therefore, the alkynylation of *N*-tosylphenylimine (**165a**) was first attempted using 3.0 equiv each of Me_2Zn (as a commercially availabe 2.0 M solution in toluene) and phenylacetylene (**108**), with the same solvent and temperature. Under those conditions, the conversion was limited to ca. 65% after two days (as determined by NMR-analysis of the crude reaction mixture). A slight increase in the temperature helped to accelerate the reaction and, after a short optimization, it was finally found that a mixture of phenylacetylene (**108**) and dimethylzinc (1.5 equiv each) in anhydrous toluene at 50 °C was able to convert **165a** quantitatively, affording the corresponding protected propargylamine **166a** in 80% yield after column chromatography [Scheme 60, eq. (a), and Table 5, entry 1].



SCHEME 60. Alkynylation of *N*-tosylphenylimine (**165a**) with Me_2Zn [eq. (a)] and Et_2Zn [eq. (b)] as promoters.

It should be noted that the same transformation had already been reported by CARREIRA,[169] who employed zinc (II) triflate in combination with a tertiary amine, and KIM,[242] who utilized zinc (II) bromide under the same conditions. They isolated compound **166a** in 43% and 71% yield, respectively, which are both inferior to the yield obtained in this study.

Surprisingly, use of Et_2Zn instead of Me_2Zn as the zinc source did not lead to the same result. When diethylzinc was utilized, in fact, substrate **165a** was completely converted, but benzylamide **224**, resulting from the reduction of **165a**, was the major product of the reaction, in a ratio of 3:1 to the propargylic amine (Scheme 60, eq. b).

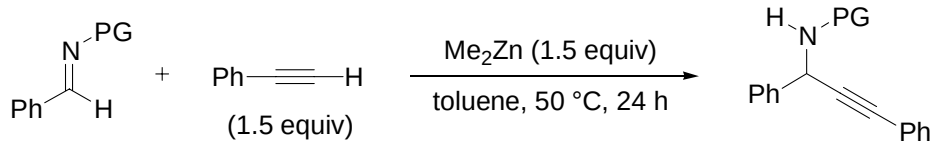
Although this result was initially puzzling, since the same behavior is not usually observed for carbonyl compounds,[276] later it was found to be in agreement with the recent findings of QUIAN and co-workers, who reported that in non-coordinating solvents such as toluene or hexane, Et_2Zn can be used to reduce *N*-sulfonylimines to the corresponding amines in good to high yields.[302] The reaction is supposed to proceed through a β-hydride transfer accompanied by elimination of ethylene, and therefore it cannot take place when Me_2Zn is used. A more detailed inspection of the literature revealed that a similar observation was made by TOMIOKA in the context of his copper-catalyzed enantioselective alkylation of imines.[58a]

As could be expected from the fact that dialkylzinc compounds are notoriously unable to react with carbon-heteroatom double bonds in the absence of a ligand, no trace of the product resulting from the direct alkyl addition to the substrate was found.

Once the optimal conditions for the conversion of **165a** had been established, the influence of the protecting group at the nitrogen atom on the reactivity of the substrate was evaluated. Thus, various *N*-sulfonyl phenylimines **165b-d**, *N*-diphenylphosphinoyl phenylimine **225**, *N*-benzyl phenylimine **227** and *N*-methoxyphenyl phenylimines **229a-b** were treated with phenylacetylene (**108**) in the presence of dimethylzinc. The results obtained are listed in Table 5.

[302] F. Gao M. Deng, C. Quian *Tetrahedron* **2005**, *61*, 12238.

TABLE 5. Alkynylation of differently *N*-substituted phenylimines with a mixture of Me_2Zn and phenylacetylene (**108**)



108

Entry	Substrate	PG	Product	Yield[a] (%)
1	**165a**	Ts	**166a**	80
2	**165b**	Ms	**166b**	78
3[b]	**165c**	SO_2Mes	**166c**	(82)[c]
4	**165d**	Ns	**166d**	91
5	**225**	$P(O)Ph_2$	**226**	69
6	**227**	Bn	**228**	0
7	**229a**	4-(MeO)Ph	**230a**	0
8	**229b**	2-(MeO)Ph	**230b**	76[d]

[a] After flash column chromatography (see experimental section for details). [b] The reaction was carried out at 70 °C. [c] The product was only ca. 90% pure (as determined by NMR). [d] The amount of 2.5 equiv each of dimethylzinc and phenylacetylene was used.

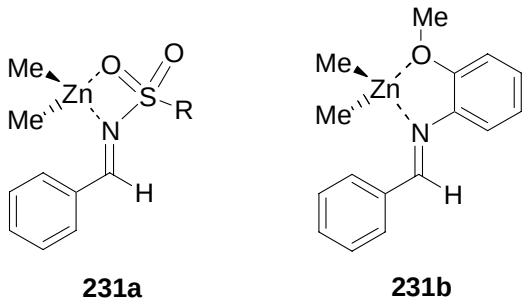
Phenylimines bearing a sulfonyl group on the nitrogen atom were found to be excellent substrates for the reaction (Table 5, entries 1-4) affording propargylamines in high yields (78-91%), the best one being *N*-benzylidene 4-nitrobenzensulfonamide (**165d**). This was probably due to the strong electron-withdrawing character of the nosyl group, which made the imine more reactive and thus helped to improve the yield of the reaction.

Only in the case of substrate **165c**, bearing a mesitylsulfonyl (mesityl = 2,4,6-trimethylphenyl) protecting group on the nitrogen, was it necessary to increase the temperature to 70 °C in order to get full conversion (entry 3). Although the NMR signals of the desired product **166c** could be clearly observed, problems were encountered during its purification, and therefore an analytically pure sample could not be obtained.

N-diphenylphosphinoyl phenylimine **225** also gave full conversion to the product, but the yield was in this case slightly lower (69%), although still synthetically useful (entry 5). Non electron-

withdrawing groups like benzyl (imine **227**) and 4-methoxyphenyl (imine **229a**) failed to sufficiently activate the substrate for the reaction with the nucleophile, and therefore no conversion was observed in those cases. Surprisingly, however, the product could be obtained in good yield when *N*-benzylidene 2-methoxyaniline (**229b**) was employed as the starting material. This is likely to be due to the possibility for **229b** to act as a ligand, which would activate dimethylzinc for the reaction with phenylacetylene and thus facilitate the reaction. In contrast to *para*-substituted **229a**, the two donor atoms, N and O, present in **229b** are in the perfect position to form a chelate complex with zinc. The strong activation provided by the chelation would then allow the reaction to proceed even if **229b** is a far less reactive substrate than, for example, **165a-d**.

Considering the presence of one or two oxygen atoms also in the N-substituents of **165a-d** and **225**, a similar activation mechanism could be operating also in the reactions in which they are used as starting materials (Figure 25).



231a **231b**

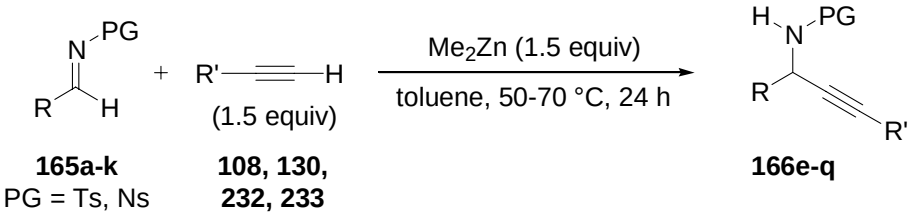
FIGURE 25. Possible coordination of dimethylzinc by *N*-sulfonyl- (**231a**) and *N*-(2-methoxyphenyl)- (**231b**) phenylimines.

Application of substrate **229b** is also interesting in view of the possibility to easily remove the *ortho*-methoxyphenyl group from the nitrogen atom under oxidative conditions.[303] Since removal of sulfonyl-based protecting groups is not always easy, depending also on the chemical properties of the substrate, the possibilty of using substrates such as **229b** represents a valuable alternative to *N*-sulfonylimines.

In the next set of experiments, the possibility to use alkynes different than phenylacetylene (**108**) and to modify the residue on the imines was examined. The results of these investigations are reported in Table 6.

[303] For a recent example, see ref. 40c.

TABLE 6. Substrate and alkyne scope of the dimethylzinc-mediated alkynylation reaction.



165a-k PG = Ts, Ns | **108, 130, 232, 233** | **166e-q**

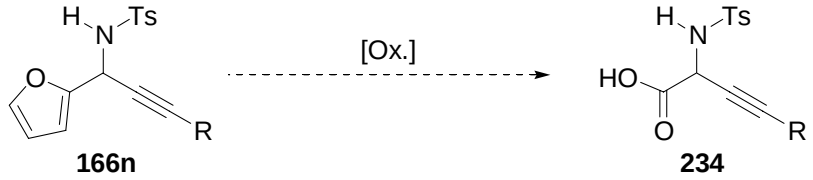
Entry	Substrate	PG	R	R' (Alkyne)	Product	Temp (°C)	Yield (%)[a]
1	**165a**	Ts	Ph	*n*-hexyl (**232**)	**166e**	70	67
2	**165a**	Ts	Ph	TMS (**130**)	**166f**	70	52[b]
3	**165a**	Ts	Ph	TMS (**130**)	**166f**	70	60[b,c]
4	**165a**	Ts	Ph	4-CF_3-Ph (**233**)	**166g**	50	87
5	**165d**	Ns	Ph	*n*-hexyl (**232**)	**166h**	70	79
6	**165e**	Ts	4-Me-Ph	Ph (**108**)	**166i**	60	77
7	**165e**	Ts	4-Me-Ph	*n*-hexyl (**232**)	**166j**	70	60
8	**165f**	Ts	4-MeO-Ph	Ph (**108**)	**166k**	60	85
9	**165g**	Ts	2-Naph	Ph (**108**)	**166l**	50	85
10	**165h**	Ts	2-Br-Ph	Ph (**108**)	**166m**	50	93
11	**165i**	Ts	2-Furyl	Ph (**108**)	**166n**	50	80
12	**165i**	Ts	2-Furyl	4-CF_3-Ph (**233**)	**166o**	50	95
13	**165j**	Ts	*c*-Hex	Ph (**108**)	**166p**	70	84
14	**165k**	Ts	2-Me-propyl	Ph (**108**)	**166q**	70	15

[a] After flash column chromatography (see experimental section for details). [b] The amount of 2.5 equiv each of dimethylzinc and trimethylsilylethyne was used. [c] The reaction was performed on a 2.0 mmol scale, instead of the usual 0.5 mmol scale

Alkynes such as 1-octyne (**232**) and trimethylsilylethyne (**130**) could also be employed (Table 6, entries 1-2), albeit they proved to be less reactive than **108**, probably as a result of their lower acidity compared to phenylacetylene. Consequently, a higher temperature was required and, in the case of **130**, 2.5 equiv of both Me_2Zn and the alkyne were needed to obtain the product in reasonable yield. In agreement with these observations, when a more acidic alkyne, such as 4-(trifluoromethyl)phenylacetylene (**233**), was used in the reaction with imine **165a**, the yield of the corresponding propargylic amine **166g** was superior to that of compound **166a**, resulting from the addition of **108** to **165a** (Table 6, entry 4 vs. Table 5, entry 1).

More electronrich imines such as **165e-g** could also be readily converted into the corresponding propargylamines **166i-l**, although sometimes the temperature had to be raised to 60-70 °C to obtain full conversion (entries 6-9). A bulky halogen atom in the *ortho*-position was also tolerated, and the resulting propargylic amine **166m** could be isolated in remarkably high yield (93%, entry 10).

The reaction was also applicable to imines possessing an heteroaryl substituent, which indeed turned out to be among the best substrates (entries 11-12). Thus, the combination of *N*-furfurylidene toluene-4-sulfonamide (**165i**) and alkyne **233** furnished amide **166o** in the highest yield observed in this study (95%, entry 12). This latter transformation is particularly interesting because the furane ring could be in principle oxidized to carboxylic acid,[304] thus giving access to alkynyl-α-amino acids (Scheme 61).



166n **234**

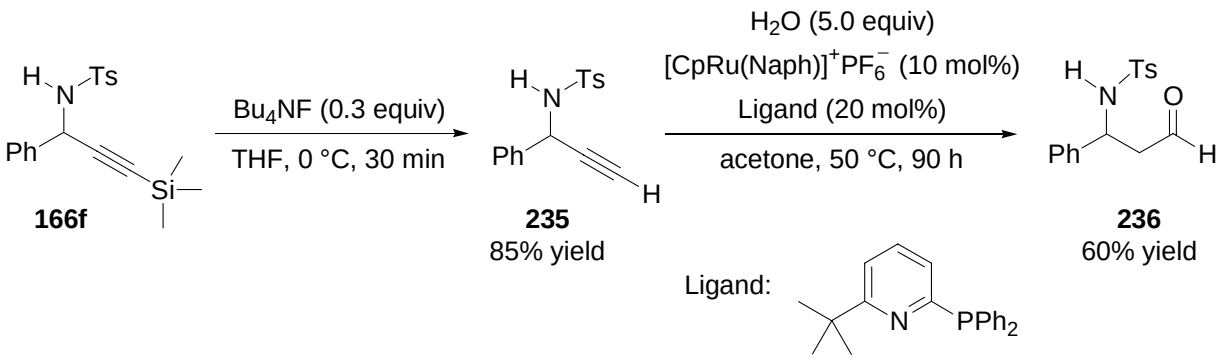
SCHEME 61. Oxidation of a furfuryl-propargylic amine to the corresponding protected amino acid.

Interestingly, when the reaction of **165a** with trimethylsilylethyne (**130**) was performed on a 2.0 mmol scale instead of the usual 0.5 mmol scale, the product yield was slightly superior (entry 3). Treatment of amine **166f** with tetrabutylammonium fluoride in THF for 30 mins at 0 °C afforded the corresponding terminal alkyne **235** in satisfying yield. This latter class of compounds is particularly interesting in view of a possible elaboration of the triple bond, for example by deprotonation and successive reaction with an electrophile, or by cross-coupling or hydrogenation.[265] In this case, the possibility to subject compound **235** to ruthenium-catalyzed hydration[305] to produce the corresponding terminal aldehyde **236** was demonstrated (Scheme 62).[306]

[304] (a) A. S. Demir *Pure Appl. Chem.* **1997**, *69*, 105. (b) G. Alvaro, G. Martelli, D. Savoia, A. Zoffoli *Synthesis* **1998**, 1773. (c) G. Borg, M. Chino, J. A. Ellman *Tetrahedron Lett.* **2001**, *42*, 1433. (d) A. S. Demir, Ö. Sesenoglu, D. Ülkü, C. Arici *Helv. Chim. Acta* **2003**, *86*, 91.

[305] First publication: (a) M. Tokunaga, Y. Wakatsuki *Angew. Chem.* **1998**, *110*, 3024; *Angew. Chem. Int. Ed.* **1998**, *37*, 2867. For the ligand used in the reaction in Scheme 62, see: (b) D. B. Grotjahn, D. A. Lev *J. Am. Chem. Soc.* **2004**, *126*, 12232.

[306] The hydration experiment was performed in collaboration with AURELIE LABONNE and LUKAS HINTERMANN. Application of the same reaction to other terminal propargylamines as well as its scope and limitations will be reported in due course.



SCHEME 62. Desilylation of **166f** and subsequent ruthenium-catalyzed hydration of terminal alkyne **235**.

The results obtained with *N*-tosylimines derived from aliphatic aldehydes were more complex. Substrate **165j**, obtained from cyclohexane carbaldehyde **59h**, reacted smoothly with **108** at 70 °C, to furnish the corresponding product **166p** in remarkable 84% yield (entry 13). No difference was observed in this reaction in comparison with those performed with aromatic aldimines.

On the other hand, substrate **165k**, stemming from the α-unbranched aldehyde isovaleraldehyde, gave a very sluggish reaction with **108**, and the presence of several by-products could be observed in the NMR spectrum of the crude reaction mixture. These by-products are likely to result from self aldolization processes, triggered by deprotonation of the imine on the more accessible α-position.

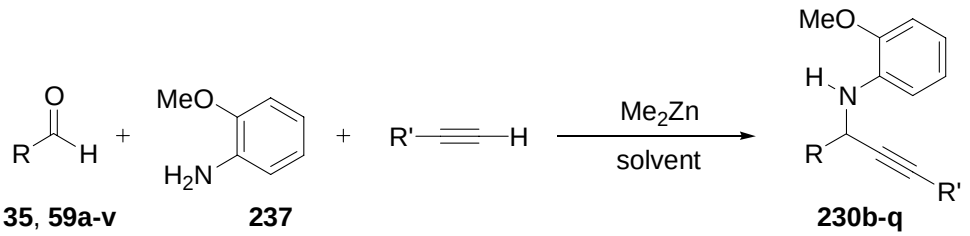
The expected propargylic amine could therefore be isolated only in very small amount (15% yield, entry 14). These findings indicate that while α-branched aliphatic imines are suitable substrates for the alkynylation reaction, more appropriate conditions should be found for the efficient conversion of α-unbranched starting materials.[307]

4.3.2. Zinc-Mediated Three-Component Synthesis of Propargylic Amines

The observation that imine **229b**, having an *ortho*-methoxyphenyl group on the nitrogen atom, was able to furnish the desired propargylic amine **230b** after reaction with a mixture of phenylacetylene and dimethylzinc, coupled with the knowledge of already published protocols for the three-component synthesis of α,α-dialkyl-[57a,58f] and propargylamines,[253,255,258b,263-267] led to start investigations on the possibility to prepare amines **230** by means of a three-component reaction of 2-methoxyaniline (**237**), an aldehyde (**35**, **59a-v**), and an acetylene in the presence of dimethylzinc. Me_2Zn was expected in this case not only to act as zinc source and base, as in the previous

[307] In the present case, performing the reaction at rt, or shortening the reaction time to 6 h or 12 h did not lead to improvements.

reactions, but also as dehydrating agent to facilitate formation of imine **229** from the starting materials (Scheme 63). Consequently, use of an additional equivalent of dimethylzinc with respect to the acetylene partner was required in the process.



SCHEME 63. Three-component reaction among an aldehyde, 2-methoxyaniline and an alkyne.

The reaction of 4-chlorobenzaldehyde (**59a**) with **237** and phenylacetylene (**108**) was investigated first. It was initially found that toluene was the best solvent for the transformation, although also CH_2Cl_2 could be used. No reaction was observed in THF, probably as a consequence of the strong coordination of the solvent around dimethylzinc, that hindered the reaction.

Subsequently, the stoichiometry was adjusted. It was established that use of 2.5 equiv of phenylacetylene and 3.5 equiv of dimethylzinc led to the highest yield of the product in toluene (76%, Table 7, entry 2). When the excess of these two reagents was reduced or increased, the yield of compound **230c** decreased. The reaction was found to reach completeness within 48 h.

Having established the optimal reaction conditions, the scope of the dimethylzinc-mediated, three-component synthesis of propargylamines was then examined. The results are reported in Table 7.[308]

While the reaction with benzaldehyde (**35**) and 4-phenylbenzaldehyde (**59o**) furnished the corresponding products **230b** and **230g**, respectively, in only moderate yields (Table 7, entries 1 and 6), benzaldehydes bearing an halogen atom on the aryl ring (**59a,l,m**) were much better substrates (entries 2-4), furnishing the resulting propargylamines in 73-76% yield. The best result of all was obtained when 2-naphthaldehyde (**59n**) was used as the starting material, with the corresponding amine being isolated in remarkable 92% yield (entry 5).

Aldehydes **59p-r**, having electron-withdrawing substituents on the ring, could also be converted (entries 7-9), although in the case of 3-nitrobenzaldehyde (**59p**) a longer reaction time was required. Interestingly, perfluorinated compound **59s** and heterocyclic aldehyde **59t**[309] were also suitable substrates for the reaction (entries 10-11).

[308] Almost all the experiments reported in Table 7 (except the last two) were performed by PIER GIORGIO COZZI and SILVIA ALESI at the Department of Chemistry "G. Ciamician", Alma Mater Studiorum, Università di Bologna.
[309] Often problems are encountered in the efficient conversion of such substrates, due to the possibility of coordination of the organometallic species by the additional nitrogen on the aromatic ring and consequent formation of aggregates.

TABLE 7. Three-component synthesis of propargylic amines

Entry	Aldehyde	Product	R'	Method[a]	Time (h)	Yield (%)[b]
1	benzaldehyde (**35**)	**230b**	Ph	A	48	48
2	4-chlorobenzaldehyde (**59a**)	**230c**	Ph	A	48	76
3	3-bromobenzaldehyde (**59l**)	**230d**	Ph	A	48	73
4	4-bromobenzaldehyde (**59m**)	**230e**	Ph	A	48	73
5	2-naphthaldehyde (**59n**)	**230f**	Ph	A	48	92
6	4-phenylbenzaldehyde (**59o**)	**230g**	Ph	A	48	30
7	3-nitrobenzaldehyde (**59p**)	**230h**	Ph	A	60	66
8	4-trifluoromethylbenzaldehyde (**59q**)	**230i**	Ph	A	48	79
9	4-COOMe-benzaldehyde (**59r**)	**230j**	Ph	A	48	65
10	pentafluorobenzaldehyde (**59s**)	**230k**	Ph	A	48	63
11	3-carboxypyridine (**59t**)	**230l**	Ph	A	48	65
12	cyclohexane carbaldehyde (**59h**)	**230m**	Ph	A	48	22
13	cyclohexane carbaldehyde (**59h**)	**230m**	Ph	B	48	85
14	2,2-dimethylpropionaldehyde (**59u**)	**230n**	Ph	B	96	67
15	octanal (**59v**)	**230o**	Ph	B	96	45
16	4-chlorobenzaldehyde (**59a**)	**230p**	*n*Hex	A	48	42
17	4-chlorobenzaldehyde (**59a**)	**230q**	TMS	A	48	0

[a] Method A: reactions were carried out in toluene (ca. 0.1 M relative to the aldehyde) at room temperature, employing $ZnMe_2$ (2.0 M solution in toluene, 3.5 equiv) and phenylacetylene (**108**, 2.5 equiv); Method B: no additional solvent was used (see discussion and experimental section for details). [b] After flash column chromatography (see experimental section for details).

Unfortunately, when an aliphatic aldehyde such as cyclohexane carbaldehyde (**59h**) was subjected to the reaction, the corresponding product **230m** could be obtained only in very low yield (entry 12).

As already discussed in paragraph *2.1.*, WALSH recently demonstrated that the efficiency and selectivity of the enantioselective addition of alkylzinc compounds to ketones could be substantially enhanced by working under "concentrated" or solvent-free reaction conditions.[67] On the basis of these observations, the addition of phenylacetylene (**108**) to cyclohexane carbaldehyde (**59h**) was performed using as the only solvent the toluene present in the commercial Me_2Zn solution employed throughout this study (method B; it corresponds to an approx. 0.6 M concentration

relative to the aldehyde). Gratifingly, it was found that propargylamine **230m** could now be isolated in a 85% yield after two days at room temperature (entry 13).

Application of the same modified reaction conditions to other aliphatic aldehydes such as 2,2-dimethylpropionaldehyde (**59u**), and octanal (**59v**), allowed to prepare the corresponding propargylamines in moderate to good yield (45-67%), although a longer reaction time was needed by the reaction to reach completeness (entries 14-15). The reason of the somehow lower yield obtained in the case of the unbranched substrate **59v** can probably be found in the intervention of side-processes (most likely once again enolization and aldol-type reactions) which led to the formation of by-products. As could be expected, no trace of such by-products was observed for the reactions with branched substrates **59h** and **59u**.

Finally, efforts were initiated to expand the scope of the present three-component transformation with regard to the alkyne moiety, since until now only phenylacetylene (**108**) had been applied. Thus, 1-octyne (**232**) was reacted with 2-methoxyaniline (**237**) and 4-chlorobenzaldehyde (**59a**) under the conditions of method A. Although after 48 h full conversion of the intermediate imine was not yet reached, the presence of propargylic amine **230p** was detected in the NMR spectrum of the crude reacion mixture. Purification by flash column chromatography (see experimental section for details) allowed to isolate **230p** in acceptable, albeit improvable, yield (entry 16). Unfortunately, application of the same reaction conditions to the addition of TMS-acetylene (**130**) to **59a** was not successful, and the intermediate *N*-*ortho*-methoxyphenylimine was the only product recovered after the reaction (entry 17). In these last two cases, improvements can be certainly expected to come from a more careful optimization of the reaction conditions; considering that the transformation is usually conducted at room temperature with a concentration of 0.1 M (relative to the aldehyde), performing the reaction at higher temperature or applying "concentrated" or solvent-free conditions could have a beneficial impact on the yield of propargylic amines.

In conclusion of this paragraph, a dimethylzinc-mediated direct alkynylation of imines has been successfully developed, which, in analogy with the already described alkynylation of carbonyl compounds,[276] does not require the use of specific ligands. The experimental procedure is straightforward, and the only precautions needed relate to the use of anhydrous solvents under an inert atmosphere. This methodology has been extended to the first zinc-mediated three-component synthesis of propargylic amines. The need for the prior preparation of the imine substrates could therefore be circumvented. Although aromatic aldehydes were found to be superior substrates for the reaction, it was demonstrated that a simple modification in the procedure allowed the conversion of aliphatic starting materials with a similar level of efficiency.

Efforts to expand the scope of the transformation with regard to the alkyne moiety have also been initiated. Improvements can be expected to arise from a further optimization of the reaction conditions.

4.4. Studies Towards the Enantioselective Dimethylzinc-Mediated Alkynylation of Imines

Having found a reliable procedure for the synthesis of protected propargylic amines by means of a mixture of dimethylzinc and an alkyne, the next step was represented by the development of a process for the preparation of such chiral compounds in enantioenriched form.

As already described in paragraph *2.3.4.2.*, not many procedures exist for the enantioselective direct addition of acetylenes to imines, and most of them employ copper complexes as promoters or catalysts. To date, the only enantioselective process reported in the literature that makes use of zinc organometallics is the synthesis of DPC 961 and analogues described by JIANG and co-workers.[272]

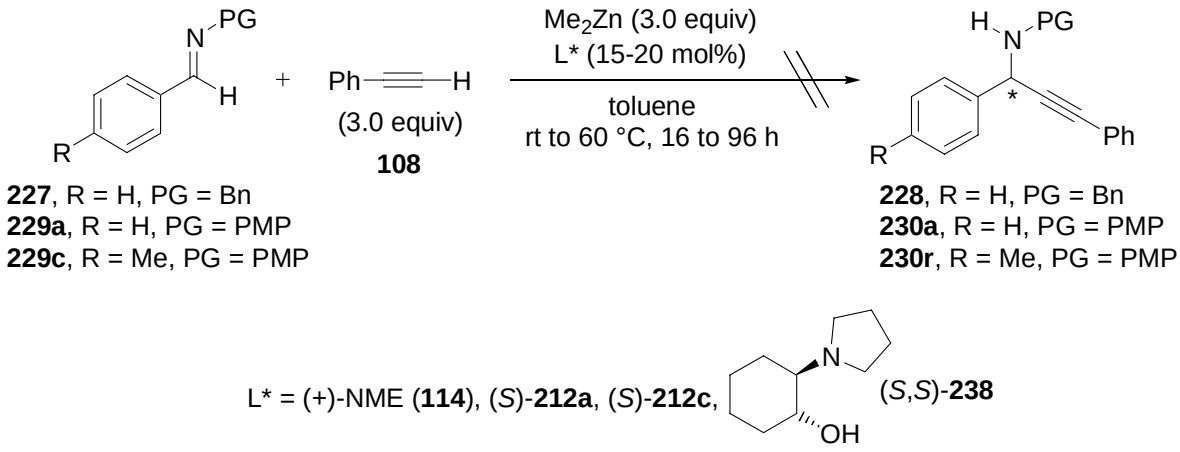
In order to achieve asymmetric induction in the alkynyl addition reaction, the most obvious modification to introduce in the already-developed protocol was the employment of a chiral ligand, either in stoichiometric or sub-stoichiometric amount. Since it is known that in most cases the presence of a ligand has a positive effect on the rate of alkyl- and arylzinc additions to C=O and C=N electrophiles,[310] such "ligand-acceleration" was expected to occur also in this case, allowing to run all the reactions at rt, or even at lower temperature, and possibly to use non-activated imines.

Since the majority of the enantioselective additions of organozinc compounds to carbonyls and imines reported in the literature make use of N,O-ligands such as amino alcohols, hydroxy oxazolines and similar compounds,[41,69] it was decided to focus the ligand screening on such species, starting with already-reported compounds and later developing new catalysts.

The reaction was therefore intended to be an extension to C(sp)-nucleophiles of the Zn-mediated asymmetric phenylation of imines already described by BRÄSE and BOLM,[127] who used a mixture of diethyl- and diphenylzinc to prepare the mixed zinc nucleophile (Scheme 17); in the present case, the acidity of the C(sp)-H bond was expected to allow the direct use of acetylenes without the need for the prior preparation of dialkynylzinc compounds.

[310] For an overview on ligand-accelerated reactions, see: D. J. Berrisford, C. Bolm, K. B. Sharpless *Angew. Chem.* **1995**, *107*, 1159; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

On the basis of these considerations, the alkynylation of imines **227**, **229a** and **229c** with a mixture of dimethylzinc and phenylacetylene (**108**) in the presence of various chiral ligands[311] was first attempted (Scheme 64).



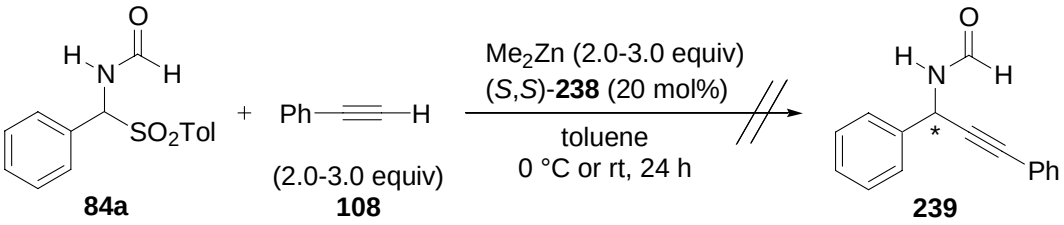
SCHEME 64. First attempted enantioselective, dimethylzinc-mediated alkynylation of imines.

Unfortunately, as can be seen in the Scheme, employment of ligands had no effect on the reactivity in comparison with what had already been observed for the ligand-free alkyne addition (cfr. Table 5, entries 6-7), and non-activated aldehydes **227** and **229a**,**c** could not be converted into the corresponding propargylamines. Raising the temperature from rt to 60 °C or increasing the reaction time from 16 to 96 h, as well as use of Lewis acids such as Ti(*i*PrO)$_4$ or Cu(OTf)$_2$ as additives did not lead to improvements.

Considering the parallelism introduced above with the enantioselective imine phenylation by BRÄSE and BOLM,[127] the second class of substrates that was considered in the transformation were masked imines **84** (Scheme 17); it was reasoned that also here an excess of dimethyl- or diethylzinc should have been able to generate imines **85**, the real substrate, from **84**. Compounds **85** should have then readily undergone addition by the mixed alkyl-alkynylzinc species also present in the solution to furnish product *N*-formylamines **239.**

When compound **84a** was treated with 2.0 equiv of a mixture of dimethylzinc and **108** in toluene at 0 °C, in presence of 20 mol% of compound **238**, however, the expected product was not formed, and a very complicated mixture was instead obtained (Scheme 65).

[311] Compound (*S*,*S*)-**238** was prepared by INGO SCHIFFERS.



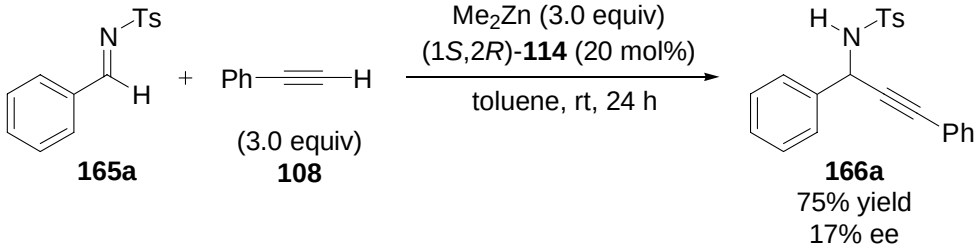
SCHEME 65. Attempted enantioselective alkynylation of masked imine **84a**.

Once again, increasing the temperature or varying the stoichiometry did not seem to have any influence on the reaction, since the product could not be obtained in any case.

At this point, it was necessary to find another class of imines to be used as starting materials, since substrates **227-229** proved to be not enough activated to undergo the addition, while **84a** or the corresponding intermediate imine were destroyed during the reaction.

The new substrates had therefore to be more reactive than simple benzyl- or arylimines, but at the same time less labile than *N*-formyl species. Considering the good results obtained in the ligand-free alkynylation with *N*-sulfonylimines **165a-d**, it seemed natural to apply those substrates also in the enantioselective transformation.[312]

When imine **165a** was treated with 3.0 equiv of an equimolecular mixture of phenylacetylene (**108**) and dimethylzinc in the presence of a substoichiometric quantity of (+)-(1*S*,2*R*)-NME (**114**) as the ligand, the corresponding *N*-tosyl propargylamine could be obtained in good yield with a enantiomeric excess of 17% (Scheme 66).

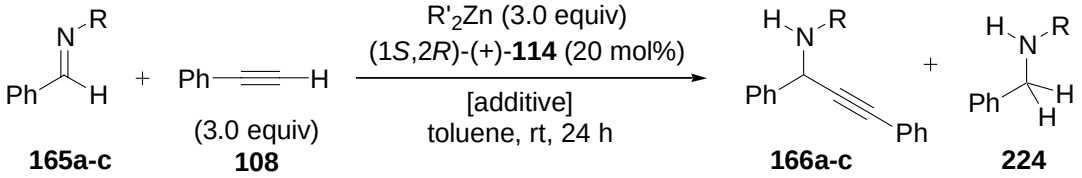


SCHEME 66. Alkynylation of imine **165a** employing (+)-*N*-methylephedrine (**114**) as a chiral ligand.

On the basis of this result, the influence of the alkylzinc reagent and of the nitrogen protecting group on the yield and enantioselectivity of the reaction was examined; in addition, the use of additives was also considered. These initial results are reported in Table 8.

[312] It must be pointed out that compounds of the type **165** were poor substrates for the enantioselective phenylzinc addition reaction, giving rise to products in low yields and enantiomeric excesses (<20% ee). See: N. Hermanns *Dissertation*, RWTH Aachen, **2002**.

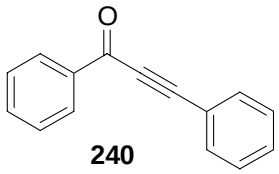
TABLE 8. Initial studies on the enantioselective alkynylation of *N*-sulfonylimines **165a-c**



Entry	R	R'	Yield of **166** (%)[a]	Yield of **224** (%)[a]	ee of **166** (%)[b]
1	Ts	Me	75	0	17
2[c]	Ts	Me	70	0	9
3	Ts	Et	25	55	6
4	Ms	Me	57[d]	0	5
5	SO_2Mes	Me	86[e]	0	*rac*
6[f]	Ts	Me	95	0	10
7[g]	Ts	Me	36	32	*rac*
8[h]	Ts	Me	55	0	10

[a] After column chromatography (see experimental section for details). [b] Determined by chiral HPLC (see experimental section for details). [c] 1.5 equiv each of phenylacetylene and Me_2Zn were used. [d] Ketone **240** was also isolated in 24% yield. [e] Starting material **166c** was recovered in 12% yield, together with approx. 2% of benzaldehyde **35**. [f] 1.1 equiv of (+)-**114** were used. [g] Me_3Al (20 mol%) was used as an additive. [h] DiMPEG (MW = 2000 $g \cdot mol^{-1}$, 20 mol%) was used as an additive.

These experiments allowed to gather some interesting informations about the reaction. First, a good yield of product **166a-c** could be obtained in most cases, but the enantiomeric excesses employing (+)-**114** as the ligand were in general extremely low. Variation of the stoichiometry with regard to the phenylacetylene / dimethylzinc mixture did not lead to improvements (Table 8, entry 2). When diethylzinc was used in place of dimethlyzinc, once again the major product of the reaction was the amine resulting from the reduction of the starting material; therefore, introduction of a ligand did not change significantly the ratio of **166a** and **224** in comparison with the ligand-free reaction (entry 3, cf. Scheme 60, eq. b). Use of differently *N*-substituted imines **165b-c** furnished the products in good yield but in essentially racemic form (entries 4-5); in the case of imine **165b** a considerable quantity of ketone **240** also resulted from the transformation, probably as a consequence of an elimination / hydrolysis pathway (Figure 26).



240

FIGURE 26. By-product of the alkynyl transfer reaction toward imine **165b**

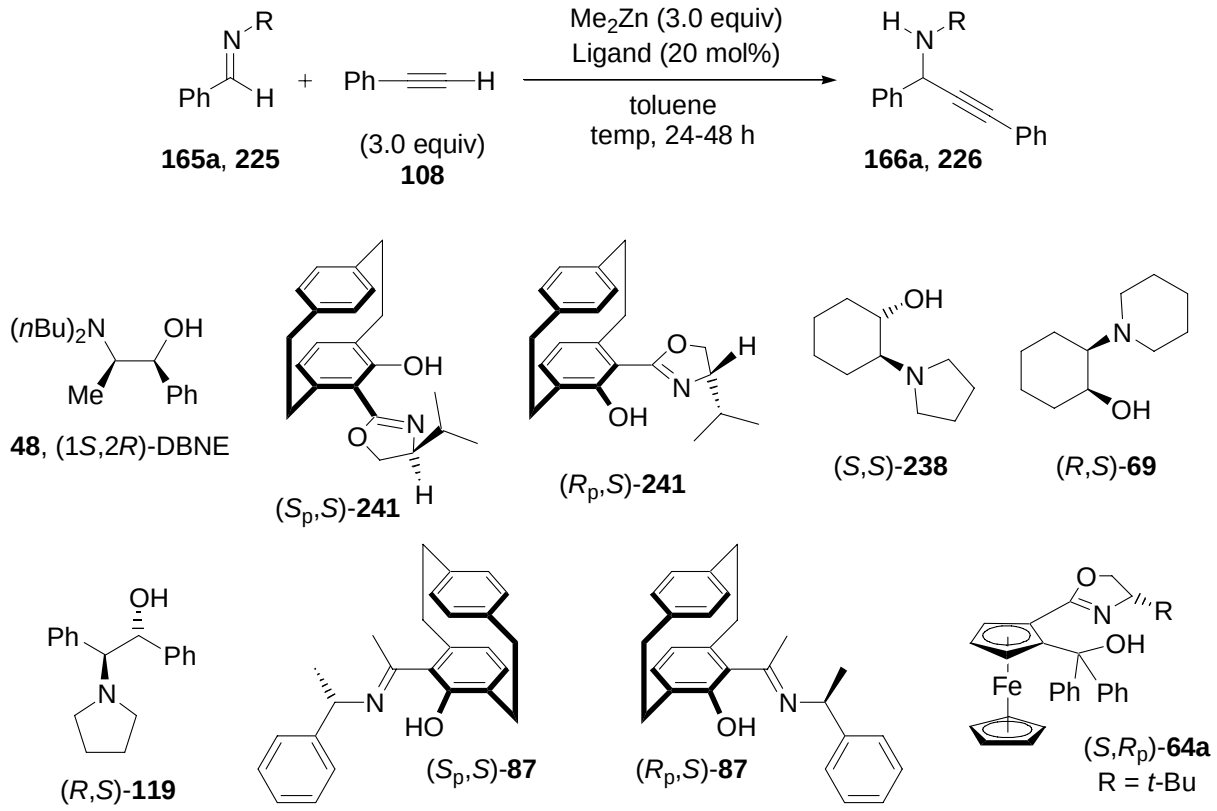
When a stoichiometric quantity of (+)-*N*-methylephedrine (**114**) was employed, the product **166a** could be isolated in almost quantitative yield. Surprisingly, however, the ee was only 10%, which is lower than the value observed with only 20 mol% of (+)-**114** (entry 6).

Finally use of additives was examined. While trimethylaluminum, which effectively promoted the reaction of phenylacetylene / Et_2Zn with ketones,[234] reduced considerably the yield and the enantiomeric excess of **166a**, furnishing a large quantity of the reduction product (entry 7), the same effect was not observed in the case of DiMPEG (entry 8), but still no improvement could be obtained.

Considering the low level of enantioselectivity shown in the experiments reported in Table 8, and the fact that in all of them (+)-*N*-methylephedrine (**114**) was used as the ligand, in the next set of experiments the possibility of using other compounds as chiral promoters was examined. The good yields already obtained indicated that structures bearing an hydroxy group in combination with a tertiary nitrogen atom in a suitable position to form a chelate complex could be utilized for this purpose. The reaction and the compounds applied as ligands in it are depicted in Scheme 67.[313] The results obtained in these reactions are reported in Table 9.

Also in this case, all the compounds tested demonstrated to be competent ligands for the reaction, affording propagylic amines **166a** and **226** in moderate to good yields at room temperature; on the other hand, the enantiomeric excesses of the isolated products were unsatisfying, ranging from 0 to 30% ee.

[313] Compounds (S_p,*S*)- and (R_p,*S*)-**241** were prepared by DANIEL K. WHELLIGHAN, compounds (*R*,*S*)-**69** and (*S*,*S*)-**238** were prepared by INGO SCHIFFERS, compound (*R*,*S*)-**119** was prepared by TONI RANTANEN, while ferrocene (*S*,R_p)-**64a** was provided by FRANK SCHMIDT.



SCHEME 67. Asymmetric alkynylation of two phenylimines using chiral *N*,*O*-ligands.

Particularly surprising was the bad result obtained with compounds (S_p,*S*)-**87** and (R_p,*S*)-**87** (Table 9, entries 8-9). These paracyclophane-derived structures, in fact, displayed a high selectivity in the asymmetric phenyl addition to imines,[127] although in that case the related structure (R_p,*S*)-**88** proved to be the ligand of choice (see Scheme 17); on the other hand, (R_p,*S*)-**87** was the most effective ligand among those tested by DAHMEN for his asymmetric alkynylation of aldehydes, in which it was able to give enantiomeric excesses up to 98% ee.[202] In this case, its diastereomer (R_p,*S*)-**87** furnished a slightly better result in terms of ee, being also more active (72% yield of isolated product vs. 52%, entry 8 vs. entry 9).

The only compound that was able to promote the reaction with a slightly superior level of enantioselectivity compared to all others was ferrocene (*S*,R_p)-**64a** which afforded compound **166a** with 30% ee at room temperature (entry 10). Remembering that the enantioselectivity of the zinc-mediated phenylation of formylimines[127] could be improved by working at low temperature, the same reaction was repeated at 10 °C; in this case a full conversion could not be reached after 48 h, and therefore the product could be only isolated in low yield and, most importantly, with no improvement in the enantioselectivity. At 0 °C the reaction was completely inhibited and no product was formed after two days (entries 11-12).

TABLE 9. Results of the ligand screening for the asymmetric alkynylation of compounds **165a** and **225**.

Entry	R	Ligand	Temp (°C)	Yield (%)[a]	ee (%)[b]
1	Ts	(1*S*,2*R*)-**48**	25	80	*rac*
2	Ts	(S_p,*S*)-**241**	25	69	8
3	Ts	(R_p,*S*)-**241**	25	72	18
4	Ts	(*S*,*S*)-**238**	25	68	*rac*
5	Ts	(*R*,*S*)-**69**	25	97	11
6	Ts	(*R*,*S*)-**119**	25	82	*rac*
7	Ts	(*R*,*S*)-**119**	0	25	8
8	Ts	(S_p,*S*)-**87**	25	72	15
9	Ts	(R_p,*S*)-**87**	25	52	13
10	Ts	(*S*,R_p)-**64a**	25	66	30
11	Ts	(*S*,R_p)-**64a**	10	30	27
12	Ts	(*S*,R_p)-**64a**	0	0	-
13[c]	Ts	(*S*,R_p)-**64a**	25	33	22
14[d]	Ts	(*S*,R_p)-**64a**	0	0	-
15	$P(O)Ph_2$	(*S*,R_p)-**64a**	25	67	20

[a] After column chromatography (see experimental section for details). [b] Determined by chiral HPLC (see experimental section for details). [c] Ti(*i*PrO)$_4$ (50 mol%) was used as additive. [d] Cu(OTf)$_2$ (20 mol%) was used as additive.

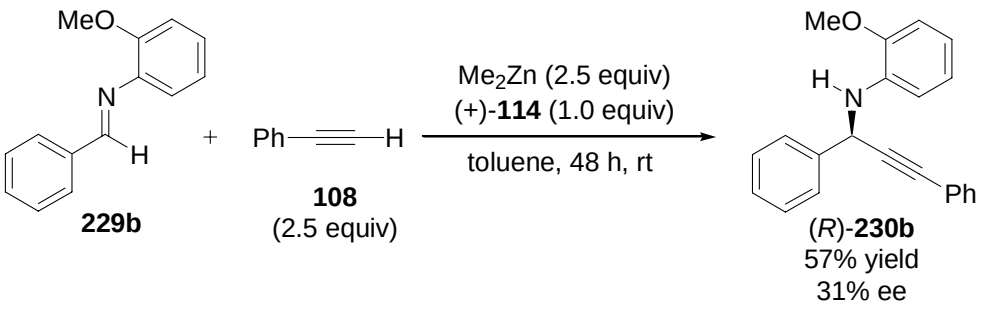
Employment of Lewis acids such as Ti(*i*PrO)$_4$ or Cu(OTf)$_2$ as additives did not lead to improvements (entries 13-14), and also changing the substrate from **165a** to **225** was not fruitful, as the corresponding product **227** could be obtained in good yield but with only 20% ee (entry 15).

A racemization of the product under the reaction conditions could be at this point hypothesized to explain the generally low level of enantioselectivity observed in the transformation, taking into account the relatively extended reaction time (24-48 h) and the basic environment in which the reaction takes place. To rule out this possibility, an experiment was conducted under the conditions of Table 8, entry 10, in which samples of the reaction mixture were taken after 3, 5, 7 and 20 hours respectively, worked-up and analyzed by chiral HPLC. No significant erosion of the enantiomeric excess of the product was observed, indicating that no racemization process took place during the reaction.

Since appropriate conditions for an highly enantioselective addition of phenylacetylene to activated imines such as **165a** and **225** could not be found, albeit some of the most succesful ligands

for related alkylation and arylation processes were used, it was once again necessary to look for another class of suitable substrates.

It has already been pointed out that imines like **229a** and **229c**, bearing a *para*-methoxyphenyl substitent on the nitrogen atom could not be converted into the corresponding propargylamines even in the presence of an activator such as (+)-*N*-methylephedrine (**114**), or related ligands (see Scheme 64). On the other hand, the ligand-free alkynylation process was successful when *ortho*-methoxyphenylimines were used (see Table 5, entry 8), which led ultimately to the development of a three-component synthesis of propargylic amines. Therefore, the next approach towards an enantioselective alkynyl addition to imines involved use of compound **229b** as the substrate. Treatment of **229b** with 2.5 equiv of a mixture of phenylacetylene and dimethylzinc in the presence of (+)-NME (**114**) at room temperature led to isolation of the resulting amine (*R*)-**230b**[271] in acceptable yield and with 31% ee (Scheme 68).



SCHEME 68. Enantioselective addition of phenylacetylene to phenylimine **229b**.

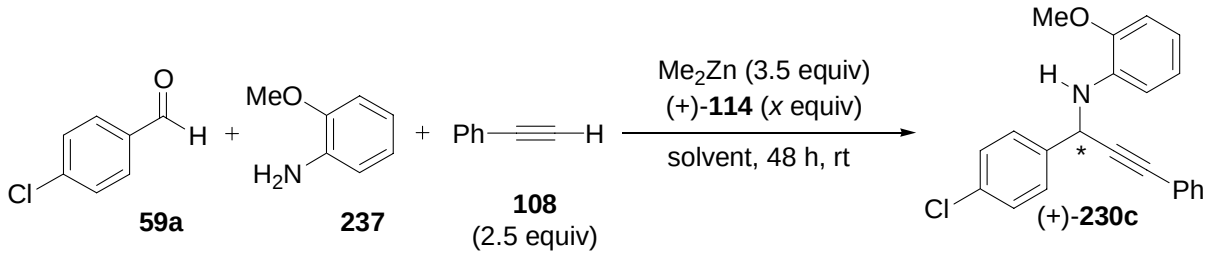
Although the level of enantioselectivity was still modest, the enantiomeric excess obtained in this reaction should be compared with the value of 10% resulting from the reaction of *N*-tosylimine **165a** under essentially the same conditions (Table 8, entry 6). From this point of view, a clear improvement had been obtained by simple changing the N-substituent of the substrate, which stimulated further investigations.

Considering that the three-component synthesis of propargylamines reported in paragraph *4.3.2.* is supposed to proceed through an imine of the type **229**, the possibility to perform such a reaction in an enantioselective fashion was then considered.

Thus, using 4-chlorobenzaldehyde (**59a**) as the starting material, synthesis of the corresponding propargylic amine **230c** in enantioenriched form was attempted by applying the same protocol used for the reactions in Table 7, the only modification being the employment of 1.0 equiv of (+)-NME (**114**) as a chiral promoter. As a result, (+)-**230c** was obtained in 30% yield with 39% ee. With the

aim to improve this result, a first set of experiments was performed changing the solvent and the amount of the ligand (Table 10).

TABLE 10. Optimization of the solvent and of the ligand amount for the enantioselective, three-component synthesis of propargylic amine **230c**.



Entry	Solvent	*x*	Additive	Yield (%)[a]	ee (%)[b,c]
1	toluene	1.0	-	30	(+) 39
2	*n*-hexane	1.0	-	0	-
3	CH_2Cl_2	1.0	-	30	(+) 53
4	toluene	0.5	-	45	(+) 17
5	toluene	1.5	-	0	-
6	toluene	1.0	MS 4Å	0	-
7[d]	toluene	1.0	-	0[e]	-
8[f]	toluene	1.0	MS 4Å	29	(+) 41

[a] After column chromatography (see experimental section for details). [b] Determined by chiral HPLC (see experimental section for details). [c] The sign in parentheses corresponds to the sign of optical rotation. [d] A different procedure was used compared to the experiment in entry 1 (see discussion for details). [e] Only the product stemming from Me-addition was detected in the NMR spectrum of the crude reaction mixture. [f] A different procedure was used compared to the experiment in entry 6 (see discussion for details).

While the reaction was found to proceed in toluene, *n*-hexane was revealed as a non compatible medium (Table 10, entry 2); this is likely to be due to the poor solubility of 2-methoxyaniline (**237**) in that solvent, that probably prevented the imine formation step to occur.[314] The result obtained using dichloromethane as a solvent was most encouraging, since (+)-**230c** could be prepared in moderate yield but with 53% ee (entry 3); a very pronounced solvent-effect could therefore be observed for this reaction, which is even more surprising considering that toluene, or mixtures of

[314] THF had already been found to be not applicable for the ligand-free reaction, cf. paragraph *4.3.2.*

toluene and hexanes, is generally the solvent of choice for the additions of organozinc compounds to C=O or C=N electrophiles.

Next, the effect of the amount of ligand on the reaction outcome was examined. When only 50 mol% of (+)-**114** were used, a higher yield of the product was obtained, but the ee was only 17% (entry 4). When the alkynylation was performed in the presence of 1.5 equiv of the chiral promoter, instead, no conversion of the intermediate imine was observed (entry 5). The results of entries 1, 4 and 5 suggest that an increase in the amount of ligand used provoked a decrease in the yield of the product. This is in agreement with the fact that the ligand-free reaction proceeded in 76% yield (Table 7, entry 2), which is higher than the values observed in the presence of (+)-**114.**

A possible explanation can be formulated as follows. In the hypothesis that the reaction proceeds through a mechanistic pathway similar to that of the alkyl- and aryl addition to aldehydes (see Scheme 7), two zinc atoms are involved in the transition state, one of which forms a chelate complex with the ligand and activates the electrophile, while the other is responsible for the alkynyl transfer. With 1.0 equiv of (+)-*N*-methylephedrine in the reaction mixture, it can be inferred that an equimolar amount of Me_2Zn is consumed to form the chelate complex. Considering that another equivalent of dimethylzinc is needed for the formation of the imine, and that the latter is in principle also capable of coordinating the metal, probably under the applied conditions the concentration of "free" Me_2Zn able to form the mixed nucleophile and to deliver the alkynyl group to the substrate was very low, and that is the likely cause of the low yield observed. Increasing the amount of ligand further reduced the amount of free dimethylzinc, and therefore no conversion was observed; on the other hand, with less ligand a higher yield was obtained.

Further optimization with regard to the stoichiometry of the reaction was then required to overcome this problem. The related investigations will be discussed later.

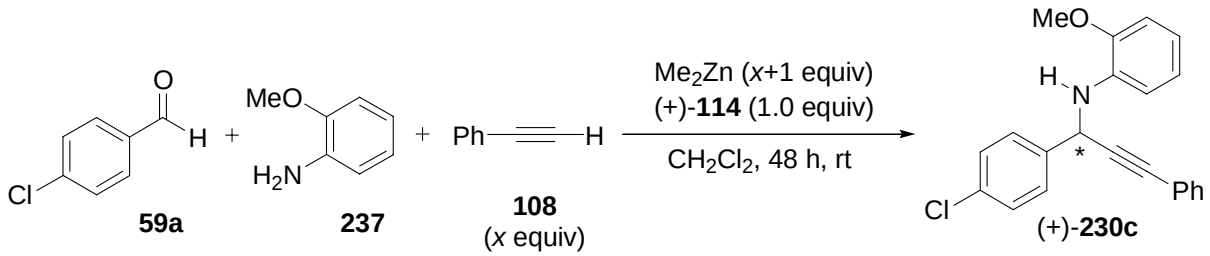
To determine if the low yield could be linked to problems in the formation of the intermediate imine, some reactions were conducted varying the experimental procedure (entries 6-8). When the reaction was run in presence of molecular sieves, surprisingly no product was observed (entry 6). In the experiment in Table 10, entry 7, aldehyde **59a** and aniline **237** were reacted in the presence of dimethylzinc for 16 h at room temperature (instead of the usual 30 mins); subsequently the other components were added and the reaction continued for further 48 h. Also in this case the expected product could not be detected. On the other hand, the NMR spectrum of the crude reaction mixture showed signals compatible with the formation of the methyl addition product. Finally, in the reaction corresponding to entry 8, aldehyde **59a** and aniline **237** were mixed in toluene and stirred for 16 h at 50 °C in the presence of molecular sieves; the resulting solution was filtered, and the other components added. After 48 h stirring at room temperature, product(+)-**230c** could be

obtained in 29% yield and 41% ee. Since these values were practically identical to those obtained with the original protocol, an influence of the rate of the imine-formation step on the outcome of the alkynylation reaction could be excluded.

As already mentioned, the two main parameters that needed to be optimized in order to obtain a high yielding and highly enantioselective process were the stoichiometry of the reaction and the ligand structure.

As far as the stoichiometry is concerned, various experiments were conducted in dichloromethane at room temperature, always using aldehyde **59a** and aniline **237** as reaction partners in the presence of 1.0 equiv of (+)-*N*-methylephedrine **114** as a ligand, systematically varying the amount of dimethylzinc and phenylacetylene (**108**) employed. The results obtained in these investigations are reported in Table 11.

TABLE 11. Studies on the stoichiometry of the enantioselective three-component synthesis of **230c**.



Entry	Ligand	*x*	Yield (%)[a]	ee (%)[b,c]
1	(+)-**114**	2.5	30	(+) 53
2	(+)-**114**	3.0	56	(+) 65
3	(+)-**114**	3.5	58	(+) 63
4	(+)-**114**	4.0	50	(+) 55
5	(+)-**114**	5.0	38	(+) 52

[a] After column chromatography (see experimental section for details). [b] Determined by chiral HPLC (see experimental section for details). [c] The sign in parentheses corresponds to the sign of optical rotation.

As can be seen from the table, an increase in the amount of the mixture of phenylacetylene and dimethylzinc of only half an equivalent in comparison with the initial conditions (Table 11, entry 1) caused an improvement in the yield of the reaction, that was almost doubled (entry 2), and therefore near to a synthetically useful value. Surprisingly, also the enantiomeric excess of the product was increased, reaching a promising value of 65% ee.

While a further increase of 0.5 equiv did not change the outcome much, with the product having essentially the same enantiomeric excess as in the previous attempt (enty 3), use of 5.0 equiv of Me_2Zn furnished a slightly inferior result both in terms of yield and enantioselectivity (entry 4). Finally, a further increase of 1.0 equiv did provide a result comparable with that obtained under the initial conditions (entry 5).

Having determined the ideal stoichiometry of the reaction, the next step in terms of optimization was represented by the variation of the ligand structure. Several candidate ligands were chosen, which were either commercially available or easily accessible by known literature methods. The majority of them had already found application in organozinc additions to carbon-heteroatom double bonds. Their structures are reported in Figure 27.[315]

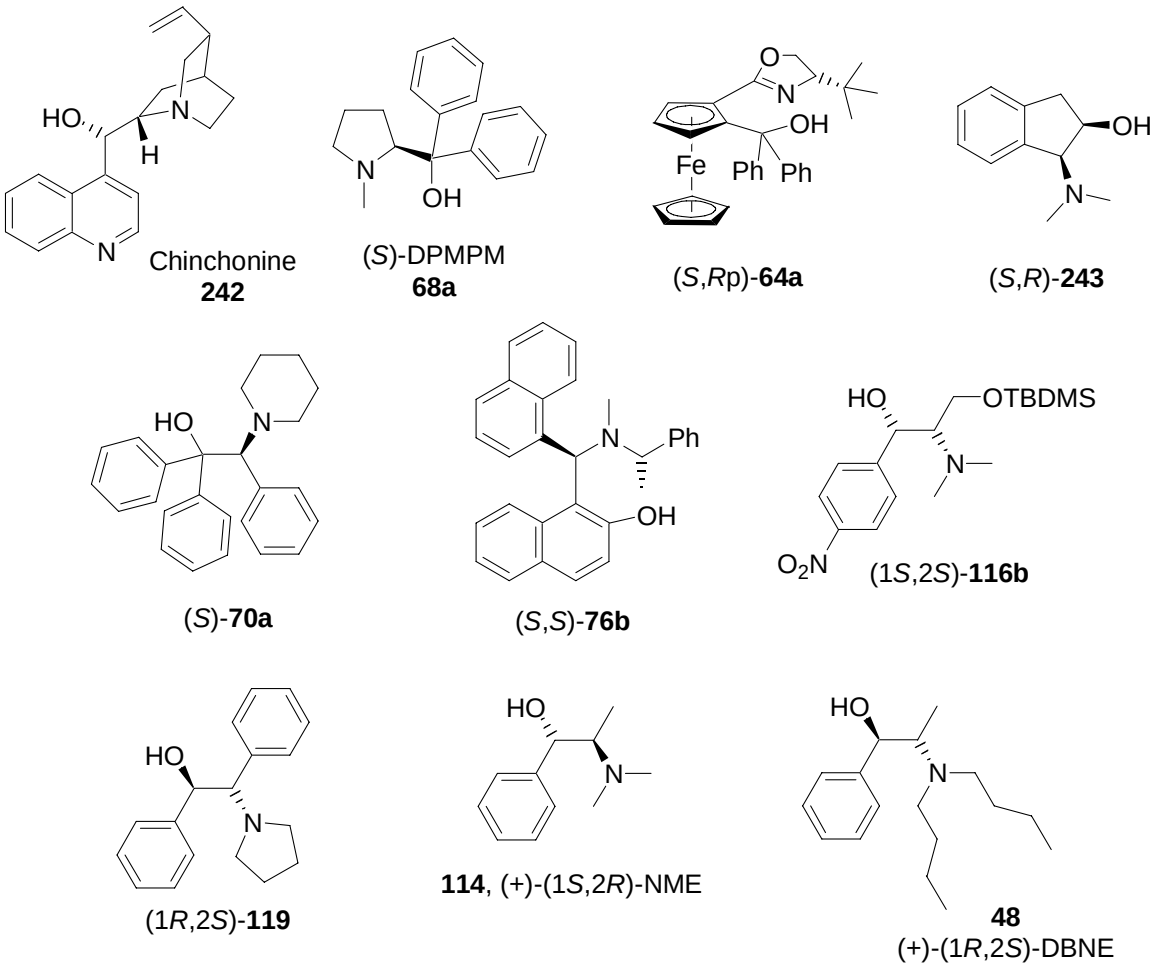


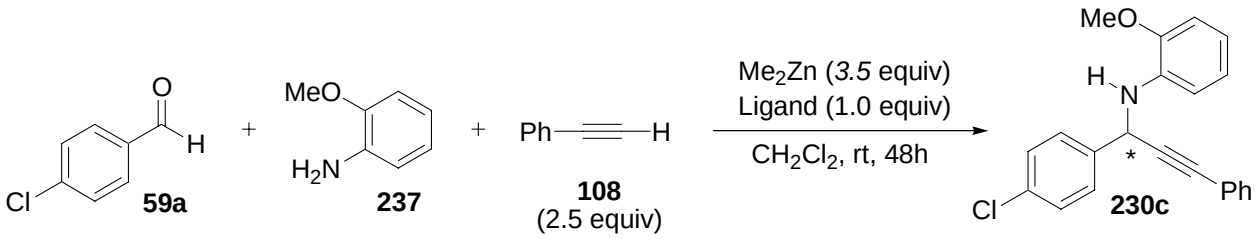
FIGURE 27. Compounds tested as ligands in the asymmetric three-component synthesis of **230c**.

[315] Compound **76b** was prepared by FRANK SCHMIDT.

The compounds depicted in Figure 27 were employed working under unoptimized reaction conditions (corresponding to Table 11, entry 1). Since by using amino alcohol (+)-**114** with the original stoichiometry of the phenylacetylene / Me_2Zn mixture both the yield and the enantiomeric excess were moderate, possible improvements connected with the variation of the ligand were expected to be easily recognizable under those particular conditions.

The results obtained in the ligand screening are reported in Table 12 [the result of Table 11, entry 1 with (+)-NME (**114**) is repeated in Table 12, entry 9, to facilitate the comparison with the others]

TABLE 12. Results of the ligand screening for the asymmetric addition of phenylacetylene to an imine.



Entry	Ligand	Yield (%)[a]	ee (%)[b,c]
1	**242**	0	-
2	(*S*)-**68a**	20	(+) 16
3	(*S*,R_p)-**64a**	20	(+) 24
4	(*S*,*R*)-**243**	32	(+) 12
5	(*S*)-**70a**	26	(+) 9
6	(*S*,*S*)-**76b**	40	(+) 7
7	(1*S*,2*S*)-**116b**	45	(−) 21
8	(1*R*,2*S*)-**119**	26	(−) 51
9	(+)-(1*S*,2*R*)-**114**	30	(+) 53
10	(+)-(1*R*,2*S*)-**48**	49	(−) 65

[a] After column chromatography (see experimental section for details). [b] Determined by chiral HPLC (see experimental section for details). [c] The sign in parentheses corresponds to the sign of optical rotation

While the *Cinchona* alkaloid cinchonine (**242**) was not able to catalyze the reaction (Table 12, entry 1), a low yield of product **230c** was obtained with (*S*)-DPMPM [(*S*)-**68a**], which also furnished the product with only 16% ee (entry 2). The result obtained with ferrocene (*S*,R_p)-**64a** was particularly disappointing, considering that (*S*,R_p)-**64a** gave the best result in the asymmetric addition of

phenylacetylene (**108**) to imine **165a** (cfr. Table 9, entry 10); in this case amine **230c** was isolated in low yield and enantiomeric excess (entry 3).

Compounds (*S*,*R*)-**243** and (*S*)-**70a** showed similar performances, with the product obtained in 26-32% yield and 9-12% ee (entries 4-5). Compound (*S*,*S*)-**76b**, successfully employed by CHAN in the asymmetric phenylation of aldehydes,[102] furnished **230c** in a yield slightly superior to that obtained with (+)-NME (40% vs. 30%, entry 6 vs. entry 9), although also in this case the enantiomeric excess was very low (7% ee).

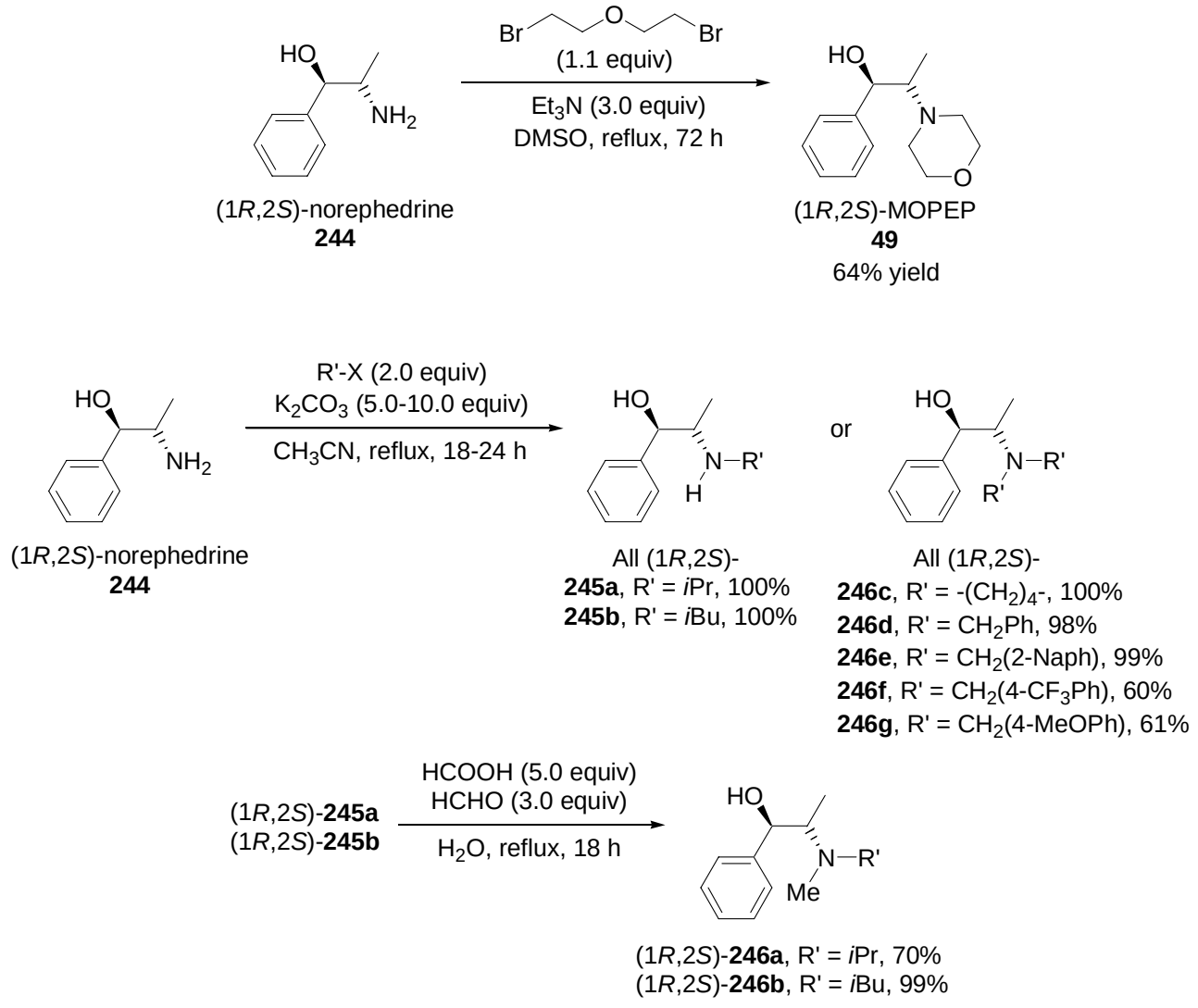
The outcome of the reaction in the presence of amino alcohol (1*S*,2*S*)-**116b** was surprising. While the yield of the product was acceptable (45%), the enantiomeric excess was only 21% (entry 7); such a low level of selectivity was unexpected, since compound (1*S*,2*S*)-**116b** had already been used by JIANG to carry out highly enantioselective alkynylation processes, using aldehydes,[181,182] ketones[226] and even an imine[272] as substrates. In the present case, however, a modest enantioselectivity was observed, probably as a result of the increased steric bulk around the nitrogen atom in comparison with the other substrates previously converted using (1*S*,2*S*)-**116b**.

Amino alcohol (1*R*,2*S*)-**119** gave a result very similar to that obtained with (+)-(1*S*,2*R*)-NME (**114**), both in terms of activity and selectivity (entry 8). Finally, use of well-established (+)-(1*R*,2*S*)-DBNE (**48**) provided **230c** in moderate yield (49%), with 65% ee, the highest value observed in this first ligand screening study (entry 10). It should be pointed out that, albeit (+)-(1*S*,2*R*)-NME (**114**) and (+)-(1*R*,2*S*)-DBNE (**48**) both induce rotation of circularly polarized light in the same sense, and therefore have the same sign of optical rotation, the absolute configuration of their stereocenters is opposite; accordingly, the sense of the asymmetric induction in the reaction promoted by (+)-**114** was opposite to that of the reaction promoted by (+)-**48**.

The data reported in Table 12 indicated that the most succesful ligands found so far for the reaction were β-amino alcohols possessing an open chain structure with two adjacent stereogenic centers. Moreover, comparing the structure of (1*S*,2*S*)-**116b** with that of (1*R*,2*S*)-**119**, (1*S*,2*R*)-**114** and (1*R*,2*S*)-**48**, it was easy to recognize that the first compound has a *threo* relative configuration of the stereogenic centers, while the other three are *erythro* diastereoisomers. From the results obtained, it seemed that an *erythro* relative stereochemistry was required in order to achieve a good enantioselectivity in the alkynylation reaction.

Compounds **114** and **48** are both derived from the norephedrine backbone, and the only difference between them is the replacement of the two methyl substituents on the nitrogen in **114** with two *n*-butyl groups in **48**. Since an increase in the enantioselectivity of 12% (from 53% to 65%, entry 9 vs. entry 10) was observed as a result of this small variation, it seemed useful to prepare other norephedrine derivatives and test them as ligands in the reaction, hoping for further improvements.

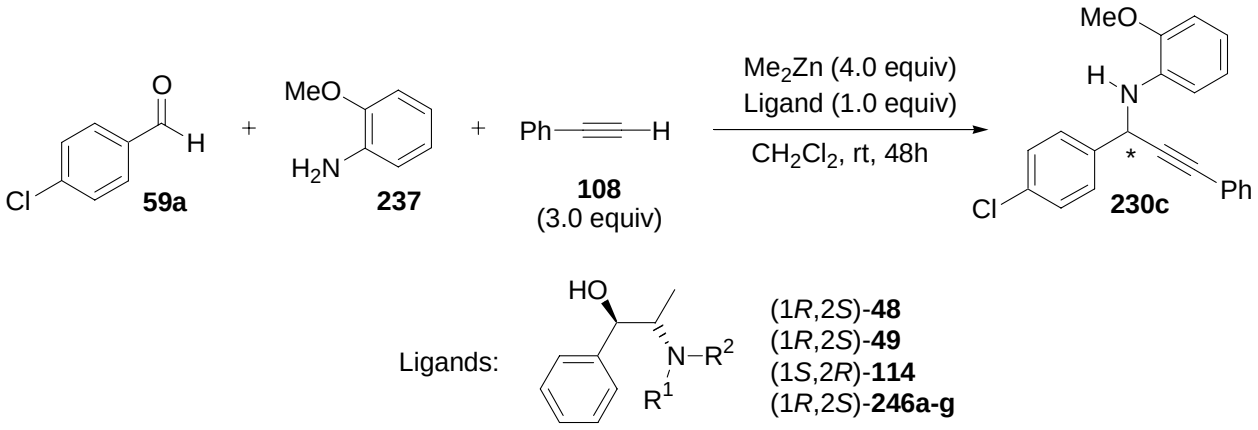
The preparation of tertiary amino alcohols (1*R*,2*S*)-**49**, (1*R*,2*S*)-**246a-g** involved a simple double alkylation of (1*R*,2*S*)-norephedrine **244** (with opposite absolute stereochemistry in comparison with (+)-**114**), with 2.0 equiv of an alkyl bromide or iodide, or 1.0 equiv of a dibromide in the case of compounds with a cyclic amine moiety (Scheme 69). When *iso*-propyliodide or 2-methylpropyliodide were used in the reaction, only the mono alkylated product could be obtained, probably as a consequence of the increased steric hindrance of these compounds. In this case, the resulting secondary amines (1*R*,2*S*)-**245a-b** were methylated to furnish compounds (1*R*,2*S*)-**246a-b** with two different substituents on the nitrogen (Scheme 69).



SCHEME 69. Synthesis of differently substituted norephedrine derivatives (1*R*,2*S*)-**49** and (1*R*,2*S*)-**246a-g**.

The results obtained with the use of the aforementioned ligands in the enantioselective synthesis of propargylamine **230c** (under optimized conditions) are reported in Table 13 (The result already reported in Table 11, entry 2 is reproduced in entry 1 to facilitate the comparison with the others).

TABLE 13. Screening of compounds (1*R*,2*S*)-**49**, (1*R*,2*S*)-**246a-g** as ligands for the enantioselective synthesis of **230c**.



Entry	Ligand	R^1	R^2	Yield (%)[a]	ee (%)[b,c,d]
1	(1*S*,2*R*)-**114**	Me	Me	56	(+) 65
2	(1*R*,2*S*)-**48**	*n*Bu	*n*Bu	76	(−) 63
3	(1*R*,2*S*)-**49**	-$(CH_2)_2O(CH_2)_2$-		71	(−) 30
4	(1*R*,2*S*)-**246a**	Me	*i*Pr	55	(−) 64
5	(1*R*,2*S*)-**246b**	Me	*i*Bu	56	(−) 52
6	(1*R*,2*S*)-**246c**	-$(CH_2)_4$-		40	(−) 43
7	(1*R*,2*S*)-**246d**	CH_2Ph	CH_2Ph	83	(−) 82 (91)
8[e]	(1*R*,2*S*)-**246d**	CH_2Ph	CH_2Ph	73	(−) 83
9[f]	(1*R*,2*S*)-**246d**	CH_2Ph	CH_2Ph	84	(−) 82
10[g]	(1*R*,2*S*)-**246d**	CH_2Ph	CH_2Ph	90	(−) 70
11	(1*R*,2*S*)-**246e**	CH_2(2-Naph)	CH_2(2-Naph)	80	(−) 80
12	(1*R*,2*S*)-**246f**	CH_2(4-CF_3Ph)	CH_2(4-CF_3Ph)	85	(−) 58
13	(1*R*,2*S*)-**246g**	CH_2(4-MeOPh)	CH_2(4-MeOPh)	83	(−) 87 (93)

[a] After column chromatography (see experimental section for details). [b] Determined by chiral HPLC (see experimental section for details). [c] The sign in parentheses corresponds to the sign of optical rotation [d] Values in parentheses indicate the ee of the product after a single recrystallization from *n*-hexane. [e] Reaction performed using recycled ligand from the reaction in entry 7. [f] The reaction was performed at 10 °C for 96 h. [g] Reaction conducted under concentrated conditions (see discussion for details).

When (+)-(1*R*,2*S*)-DBNE [(1*R*,2*S*)-**48**] was employed under optimized conditions, **230c** was for the first time isolated in synthetically useful yield (76%, Table 13, entry 2), but no improvement in the enantioselectivity was observed in comparison with (+)-(1*S*,2*R*)-NME [(1*R*,2*S*)-**114**]; this was surprising, because, as shown in Table 11, a variation of the stoichiometry of the reaction had a

positive effect on the enantioselectivity in the case of the latter ligand (Table 11, entry 1 vs. entry 2); a similar effect could not be observed here (Table 12, entry 10 vs. Table 13, entry 2).

Application of (1*R*,2*S*)-MOPEP (**49**) furnished the product propargylic amine in acceptable yield, but the ee was only 30% (entry 3). Compounds (1*R*,2*S*)-**246a-b**, with two different substituents on the nitrogen atom, furnished results very similar to that obtained with (+)-(1*S*,2*R*)-**114**, with the more bulky (1*R*,2*S*)-**246a** being slightly superior to (1*R*,2*S*)-**246b** (entries 4-5). These results suggest that only one bulky substituent on the nitrogen atom is not enough to induce a significant increase of the selectivity in comparison with the reaction performed with a ligand bearing two small alkyl groups on N.

Application of compound (1*R*,2*S*)-**246c** bearing a cyclic amine moiety was less than fruitful, since product (−)-**230c** was in this case obtained in low yield (with an incomplete conversion) and enantioselectivity. Considering that the differences in the enantioselectivity for compounds (1*R*,2*S*)-**48**, (1*R*,2*S*)-**49**, (1*S*,2*R*)-**114** and (1*R*,2*S*)-**246a-c** are probably reconducible to differences in the steric hindrance of the substituents on the nitrogen atom, it remains unclear which is the cause of the different yields and conversions obtained, since the aforementioned amino alcohols are all chemically very similar. It seems that also in this case an increase in the dimensions of the alkyl groups on nitrogen had a positive influence on the conversion of the intermediate imines to the product propargylamine.

In agreement with this suggestion, application of the dibenzyl derivative (1*R*,2*S*)-**246d** afforded product (−)-**230c** in 83% yield and 82% ee (entry 7). Once again, a simple variation of the substituents on the nitrogen atom provoked a major change in the outcome of the reaction. The fact that compound (1*R*,2*S*)-**246d** was much more effective than all the others in promoting the transformation was surprising, since a highly enantioselective addition of alkyl or arylzinc organometallics employing (1*R*,2*S*)-**246d** as ligand has never been reported, and therefore the latter is in general regarded as less effective than its more famous congeners (1*R*,2*S*)-**48** and (1*S*,2*R*)-**114**.

At this level of enantiomeric purity, it was noticed that propargylamine **230c**, usually an oil, tended to solidify after few hours at room temperature. A single recrystallization from *n*-hexane allowed to obtain the product in 91% ee.

Since 1.0 equiv of the ligand was used in the reaction, the possibility to recover and reuse it would have considerably increased the synthetic value of the method. Therefore, after chromatographic purification of **230c** using a mixture of diethylether and *n*-pentane as eluent (see experimental section), an attempt to recover (1*R*,2*S*)-**246d** from the column by simple eluting with pure diethylether was made: fortunately, the amino alcohol could be again isolated in ca. 85% yield

(compared to its initial amount).[316] After addition of the remaining 0.15 equiv to reconstitute the initial quantity, recovered (1*R*,2*S*)-**246d** was reused in the same reaction, giving rise to the product in slightly lower yield but with the same enantiomeric excess (entry 8). This finding suggest that the same process could be repeated several times; moreover, the recovery of the ligand should be more effective in case the reaction is run on a larger scale.

Considering the good result obtained with compound (1*R*,2*S*)-**246d** as the ligand, a few more experiments were conducted with it, changing again the reaction conditions. Performing the three-component reaction at 10 °C instead of rt furnished practically the same result (entry 9), although a longer reaction time was needed. The transformation conducted under concentrated conditions[67] (using only the toluene already present in the 2.0 M dimethylzinc solution, plus ca. 0.4 mL needed to dissolve the ligand) was very effective, affording the product in 90% yield, but the ee was in this case only 70% (entry 10). This is likely to be due to the use of toluene as the solvent instead of dichloromethane (albeit in a very limited quantity); as already noticed, the enantioselectivity of the reaction in CH_2Cl_2 was clearly superior to that in toluene (Table 10, entry 1 vs. entry 3).

Since compound (1*R*,2*S*)-**246d** bearing two benzyl groups on the nitrogen atom furnished a result superior to those obtained with all the other ligands, some other (1*R*,2*S*)-norephedrine (**244**) derivatives with benzylic substituents were prepared and applied in the same reaction.

Compound (1*R*,2*S*)-**246e** with two 2-naphthylmethyl groups provided a result similar to that observed with (1*R*,2*S*)-**246d** (entry 11). In the case of (1*R*,2*S*)-**246f**, which possessed two electronpoor aromatic rings, as the consequence of the presence of a trifluoromethyl substituent in *para*-position, the yield of **230c** was high, but the ee dropped to only 58% (entry 12). Perhaps, the electron-withdrawing substituents on the aromatic rings contribute to reduce the electron density on the nitrogen atom; compound (1*R*,2*S*)-**246f** would in this case form a less strong chelate complex with the metal, which would ultimately lead to a decrease in the enantioselectivity.

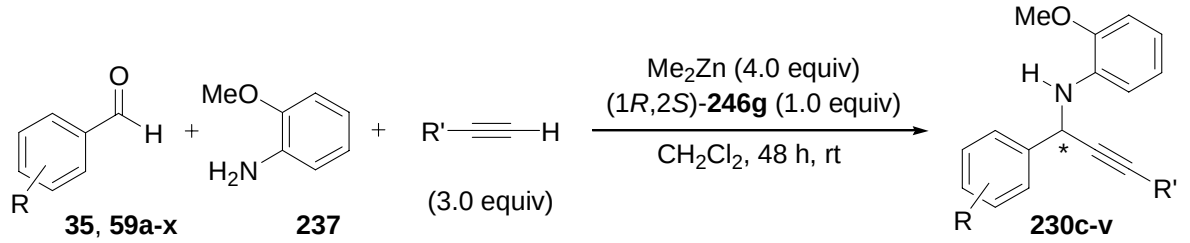
If this hypothesis was correct, a ligand possessing electronrich aromatic rings should have provided a better result. Indeed, when disubstituted norephedrine (1*R*,2*S*)-**246g** was applied to the reaction, the product was isolated in 83% yield and 87% ee (entry 13). Also in this case, a single recrystallization from *n*-hexane allowed to increase the enantiomeric excess to 93% ee. Ligand (1*R*,2*S*)-**246g** could also be recovered after the reaction using the same procedure already employed for (1*R*,2*S*)-**246d.** in this case, more than 90% of the amino alcohol was isolated after elution with pure diethyl ether.

[316] The NMR spectrum of the fraction coming from flash column chromatography was identical to that of clean **246d** resulting from the alkylation reaction depicted in Scheme 69.

Considering the ease of preparation of compounds (1*R*,2*S*)-**246a-g**, and the commercial availability of many different benzyl halides, or their precursors, a further improvement of the reported values through further ligand optimization can be expected in the future.

With compound (1*R*,2*S*)-**246g** in hand, a ligand had been finally found which was able to deliver propargylic amines with synthetically useful yields and good enantiomeric excesses. To test the applicability of (1*R*,2*S*)-**246g** also to other substrates, and the possibility to use alkynes other than phenylacetylene in the transformation, the scope of the enantioselective dimethylzinc-mediated three-component synthesis of propargylic amines was subsequently examined (Table 14).

TABLE 14. Scope of the enantioselective dimethylzinc-mediated three-component synthesis of propargylic amines **230c-v**.



35, **59a-x** **237** **230c-v**

Entry	R	R'	Product[a]	Yield (%)[b]	ee (%)[c,d]
1	H	Ph	(*S*)-(−)-**230b**	80	83
2	4-Cl	Ph	(−)-**230c**	83	87 (93)
3	4-Me	Ph	(−)-**230r**	71	85
4	4-MeO	Ph	(−)-**230s**	52	87 (92)
5	3-MeO	Ph	(−)-**230t**	81	88
6	2-MeO	Ph	(−)-**230u**	75	97
7	2-Br	Ph	(−)-**230v**	73	81
8	(2-Naph)	Ph	(−)-**230f**	82	81 (91)
9	4-Cl	*n*Hex	(−)-**230p**	48	81

[a] The sign in parentheses indicates the sign of optical rotation. [b] After column chromatography (see experimental section for details). [c] Determined by chiral HPLC (see experimental section for details). [d] The value in parentheses indicate the ee of the product after a single recrystallization from *n*-hexane.

As can be seen from Table 14, all the substrates treated gave the corresponding propargylic amines **230c-v** in moderate to good yields (up to 83%) and good to high enantiomeric excesses (up to 97% ee). In the case of solid compounds, the enantiomeric excess could be increased after a single recrystallization from *n*-hexane. Benzaldehyde **35** furnished the product with (*S*)-configuration[271] in

83% ee (Table 14, entry 1). Considering the analogies in the structures of the substrates, and assuming a similar mode of action of the catalyst in all cases, the same absolute configuration can be tentatively assigned also to the other propargylamines. The sign of optical rotation was (−) for all the compounds prepared.

The amine resulting from 4-methylbenzaldehyde was isolated in 85% ee (entry 3); therefore, the presence of a substituent in *para*-position did not seem to alter considerably the enantioselectivity of the process.

To better understand the influence of the substitution pattern of the aromatic rest on the outcome of the reaction, the three regioisomers of methoxybenzaldehyde were subjected to the transformation (entries 4-6). While the ee's obtained with 4-methoxy- and 3-methoxybenzaldehyde (entries 4-5) were comparable with that obtained with the test substrate, 2-methoxybenzaldehyde reacted surprisingly well, affording product (−)-**230u** in 75% yield and 97% ee (entry 6). A comparison with other works present in the literature revealed that this is not an unprecedented phenomenon. For example, in his alkynylation of aromatic aldehydes, TROST found that the ee of the propargylic alcohols stemming from *ortho*-substituted substrates was higher than that of the others.[205] A similar trend was observed by CHONG in its borate-mediated alkynylation of *N*-acetylimines.[274]

It is likely that this increase in enantioselectivity is due to coordination effects; when a very bulky and non-coordinating group such as a bromine atom was placed in *ortho* position, the ee dropped to 81% (entry 7). The same enantiomeric excess was observed for the product stemming from 2-naphthaldehyde. In this case a single recrystallization allowed to obtain amine (−)-**230f** in 91% ee.

Finally, to demonstrate that the reaction could be conducted also with alkynes other than phenylacetylene (**108**), 1-octyne (**232**) was also employed (entry 9). The corresponding product was obtained in moderate yield with 81% ee. Although this value can seem not very high in absolute terms, it must be pointed out that the use of alkyl-substituted alkynes in asymmetric alkynylation reactions is not very common, and that level of enantioselectivity is superior to those obtained for similar reactions by BENAGLIA[260b] and HOVEYDA,[271] and only slightly lower than those reported by LI.[258b]

In conclusion, after a careful optimization process, it was found that (1*R*,2*S*)-norephedrine derivatives bearing two benzylic substituents on the nitrogen atom are able to efficiently promote the asymmetric three-component synthesis of propargylic amine **230c**. Among those tested, compound (1*R*,2*S*)-**246g** possessing two electronrich aromatic rings proved to be the best one, being able to induce the formation of propargylamines stemming from several aromatic aldehydes in moderate to good yields (48-83%) and good to high enantiomeric excess (81-97% ee).

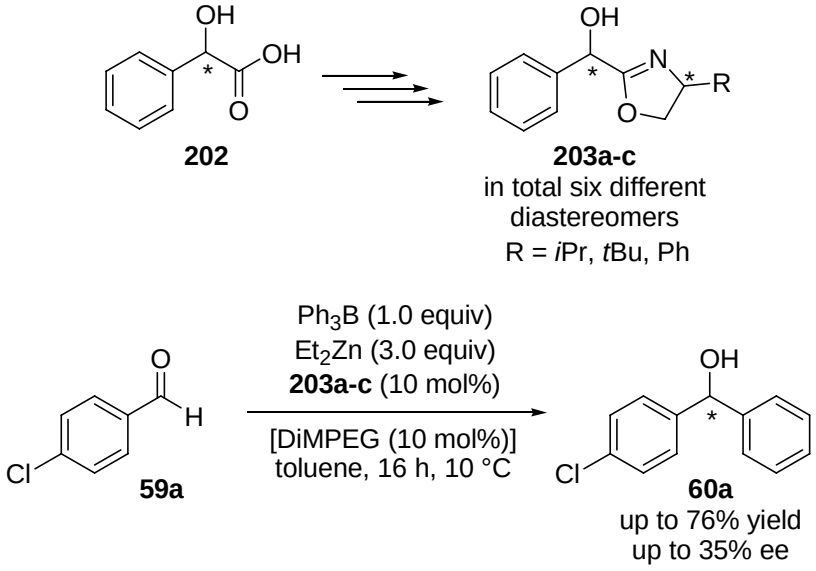
Compounds of the type **246** are easily accessible in one step from (1*R*,2*S*)-norephedrine (**244**) and a benzyl halide. As a consequence of their ease of preparation, many more of these amino alcohols bearing different groups on the aromatic rings are expected to be synthesized and tested in the asymmetric reaction, which should rapidly lead to improvements in both the efficiency and the enantioselectivity of the process.

5. Summary and Outlook

Methods for the efficient formation of carbon-carbon bonds are of paramount interest in organic chemistry, given the possibility that they offer to rapidly increase molecular complexity with only one synthetic operation. To carry out such processes in an enantioselective manner, i. e. controlling the absolute stereochemistry of the products, is one of the main goals of modern organic synthesis.

Additions of zinc organometallics to carbonyl compounds, imines and related C=N electrophiles,[41,69,164] and especially their asymmetric variants, are among the most developed reactions in this area, since they provide access to extremely useful intermediates such as chiral alcohols, amines and derivatives, in enantioenriched form.

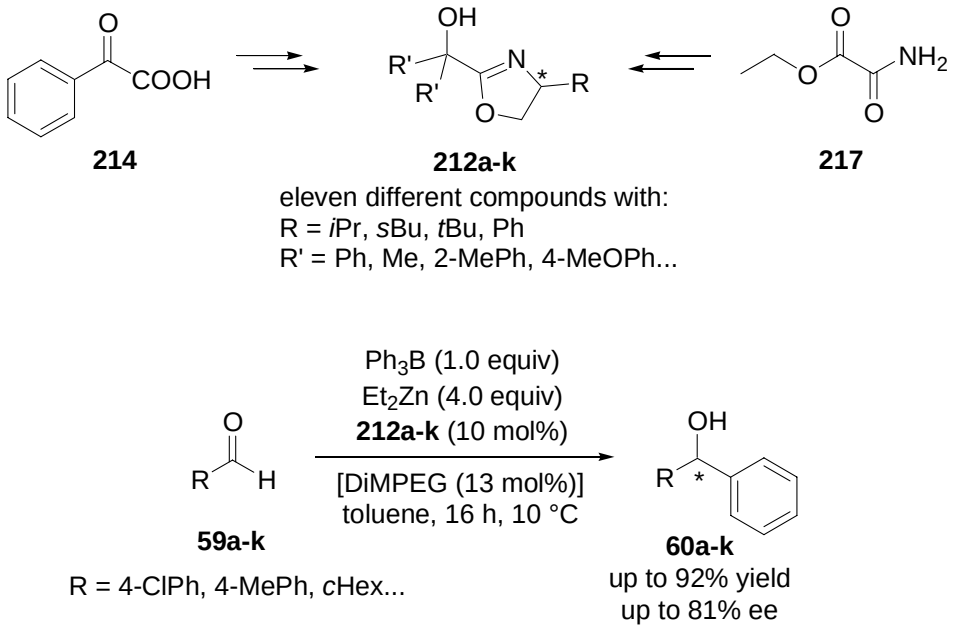
In the present work, the synthesis of novel α-hydroxy-2-oxazolines to be used as ligands in the asymmetric phenyl addition to aldehydes was first described. In an initial approach, compounds **203**, derived from the condensation of enantiopure amino alcohols with both enantiomers of mandelic acid (**202**) were prepared in diastereomerically pure form and used as ligands for the phenylation of 4-chlorobenzaldehyde (**59a**), furnishing the corresponding diarylmethanol **60a** with up to 76% yield and 35% ee (Scheme 70).



SCHEME 70. Enantioselective phenyl transfer reaction catalyzed by **203a-c**.

A possible explanation of the low enantioselectivity induced by compounds **203a-c** involved racemization or oxidation processes taking place on the reactive benzylic position, or a ring-opening reaction promoted by the incipient zinc alkoxide. On the basis of these considerations, it was reasoned that hydroxy oxazolines having a quaternary benzylic position should provide better results than those obtained with compounds **203a-c.**

Thus, novel α-hydroxy-2-oxazolines (*R*)- or (*S*)-**212a-k** were prepared following a flexible and very short route starting either from benzoylformic acid (**214**) or ethyl oxamate (**217**). Subsequently, their ability to function as ligands in the enantioselective phenyl transfer reaction to various aldehydes was assessed; products with up to 92% yield and 81% ee were obtained (Scheme 71).



SCHEME 71. Enantioselective phenyl transfer reaction to various aldehydes catalyzed by **212a-k**.

The best ligand was the one having two *o*-methylphenyl substituents in α-position; it is possible that a further increase of the steric bulk on that position will help to improve the selectivity of the transformation.

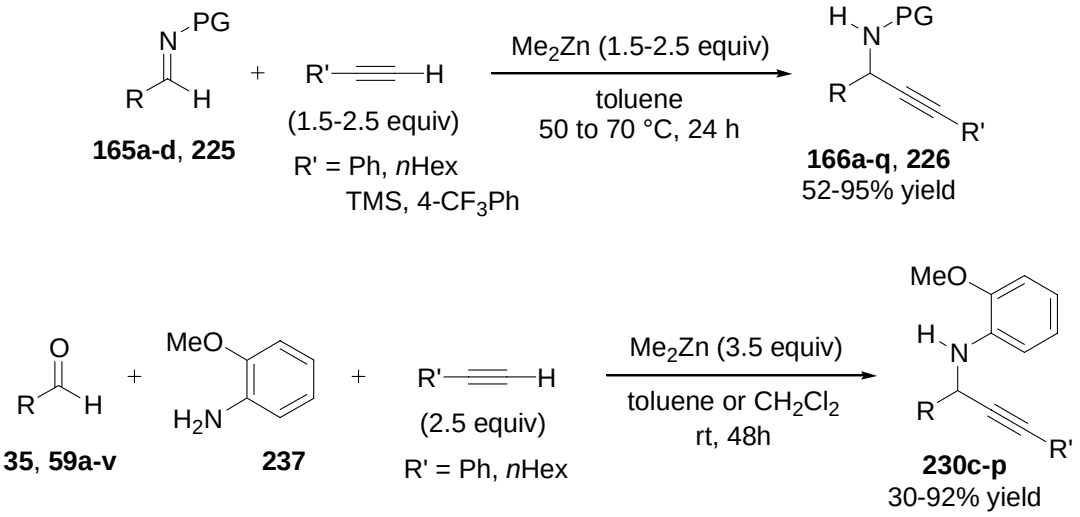
Although the enantiomeric excesses resulting from the use of ligands **212a-k** were inferior to the best ones already reported in the literature, the initial hypothesis that hydroxy oxazolines possessing a quaternary benzylic position would have provided more active and selective catalyst for the reaction was confirmed.

Moreover, two features of the two systems described here are noteworthy: first, the use of triphenylborane as the phenyl source constituted a cheaper and more practical alternative to the

employment of diphenylzinc; secondly, the use of dimethylpolyethylene glycol (DiMPEG) as an additive helped in almost all cases to improve the ee of the products, probably by slowing down the uncatalyzed background reaction.

Given the possibility to prepare compounds **203a-c** and **212a-k** in few synthetic steps starting from inexpensive and commercially available precursors, and the flexibility of the chosen synthetic pathways, improvements are expected to result from a further optimization of the ligand structure, especially as far as the substituents in α-position (R' in Scheme 71) in the compounds of type **212** are concerned.

In the second part of the present work, the possibility to develop a dimethylzinc mediated addition of monosubstituted alkynes to imines was examined. In agreement with previous findings regarding the alkynylation of carbonyl compounds,[276] it was found that an equimolar mixture of dimethylzinc and an alkyne was able to convert various activated imines into the corresponding protected propargylamines in good yields. On the basis of such observations, a one-pot protocol was developed, that allowed the preparation of *N*-arylpropargylic amines in one step starting from the corresponding aldehydes **59**, which in the first step underwent condensation with *o*-methoxyaniline (**237**). The reaction is general with regard to the aldehyde, since after some modifications in the practical procedure, not only aromatic, but also aliphatic substrates could be used (Scheme 72).

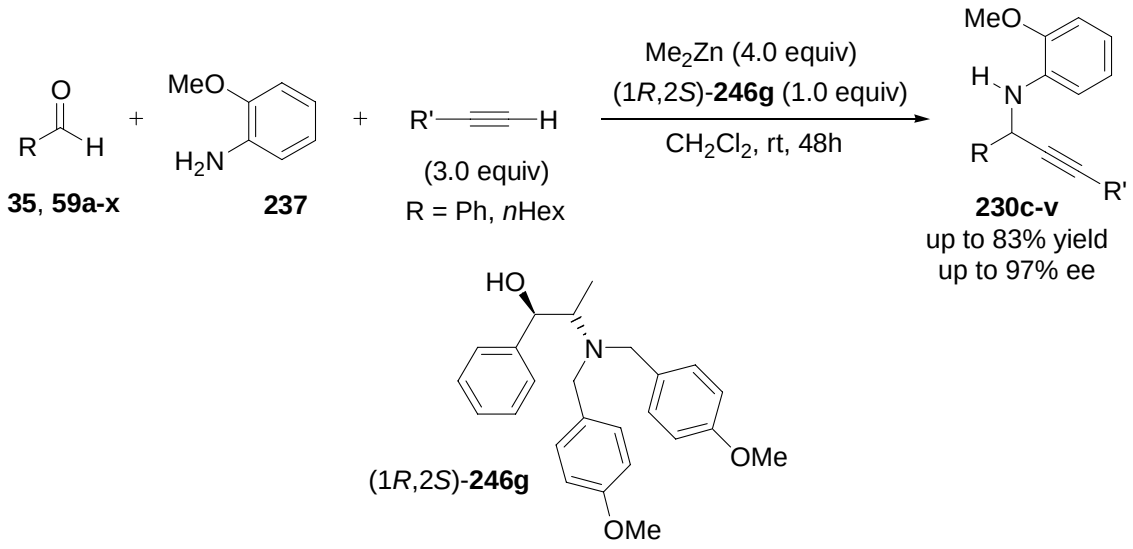


SCHEME 72. Me_2Zn-mediated addition of terminal alkynes to imines, and three-component synthesis of propargylamines.

The application of the latter reaction to TMS-acetylene (**130**) and similar compounds, which would give easy access to terminal propargylic amines after removal of the silyl substituent, would

be a synthetically very useful extension of the present method, which will be the subject of further investigations in the near future.

After a considerable optimization effort, an enantioselective version of the zinc-mediated three-component synthesis of propargylamines of the type **230** was developed, which makes use of derivatives of (1*R*,2*S*)-norephedrine as chiral ligands. Various amines stemming from aromatic aldehydes could be prepared in good yields with enantiomeric excesses ranging from 81 to 97% ee (Scheme 73), when compound (1*R*,*2S*)-**246g** was employed as the chiral promoter.



SCHEME 73. Dimethylzinc mediated asymmetric three-component synthesis of propargylamines.

Although good enantiomeric excesses could in general been obtained, the selectivity of the present method for many substrates is not yet satisfying; once again, since compounds of the type **246** are very easily prepared from commercially available starting materials, an extensive ligand screening is expected to quickly lead to improvements in this aspect of the reaction.

Another drawback of this methodology is represented by the need of a stoichiometric quantity of chiral promoter. Albeit at the beginning of the optimization process it was observed that the use of a substoichiometric amount of ligand led to a considerable decrease in the enantioselectivity, it must be noticed that the ligand, the solvent and the stoichiometry of that reaction were different from those employed after optimization. Preliminary studies conducted under optimized conditions suggest that a reduction of the quantity of the chiral auxiliary to a certain extent is possible without any decrease in the ee, and that also the reaction time can be decreased from 48 to 24 h.[317]

[317] These investigations, as well as the application of new ligands, are currently been conducted by TORSTEN EICHHORN. A comprehensive account on the outcome of these experiments will be reported in due course in: T. Eichhorn *Planed Diploma Thesis*, RWTH Aachen, **2006**.

Another critical point that needs to be addressed regards the scope of the reaction. Although it has been already demonstrated that variously substituted aromatic aldehydes can be transformed with comparable levels of selectivity, the application of aliphatic aldehydes as starting materials for the same reaction has not yet been established. It is likely that some further modifications of the reaction conditions will be required to achieve good results also with those substrates.

On the other hand, mostly phenylacetylene has been employed as the alkyne component. Although it was demonstrated that terminal alkynes with an aliphatic sustituent are also applicable, the yields of the process remain unsatisfactory, and the selectivity is lower than that observed with **108**. Moreover, it has not yet been possible to extend the reaction to the use of trimethylsilylethine (**130**) or related, easily deprotectable, acetylenes. Further studies are certainly needed in order to expand the scope of the present asymmetric three-component synthesis of propargylic imines, and therefore to sensibly increase its utility and applicability in the broader field of organic synthesis.

"A tidy laboratory means a lazy chemist."

Jöns Jacob Berzelius

6. Experimental Section

6.1. General Remarks

All the synthetic operations described in the present experimental part including reactions, work-ups and chromatographic separations were carried out in a well ventilated hood according to the current safety dispositions.

Air and moisture sensitive manipulations were carried out under an atmosphere of argon using either standard Schlenk techniques or a Glovebox.[318] The glassware employed for those manipulations was either oven- or flame-dried, and then cooled under a stream of argon. Reagents and solvents were transferred under argon using cannulae or syringes.

6.1.1. Solvents

Solvents for anhydrous reactions were dried and purified according to standard techniques.[319]

CH_2Cl_2: Simple destillation, followed by destillation from calcium hydride.

Toluene: Destillation from sodium-benzophenone ketyl radical.

THF: Pre-drying on KOH / Al_2O_3, followed by destillation from sodium-benzophenone ketyl radical.

Ethyl acetate (EtOAc), diethyl ether (Et_2O), petroleum ether (PE) and *n*-pentane for flash column chromatography were distilled before use. DMF (*Merck*) and *n*-hexane were dried over molecular sieves 4Å before use. MeOH (*Merck*), 1,2-dichloroethane (*Riedel de Haen*), DMSO (*Merck*) and acetonitrile (*Promochem*) were HPLC- or reagent grade and were used as received.

[318] D. F. Shriver, M. D. Drezdzon *The Manipulation of Air-Sensitive Compounds*, Wiley, Chichester, **1986**.
[319] W. L. F. Armarego, D. D. Perrin *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, **1996**.

6.1.2. Chemicals

All the chemicals employed were purchased from the companies *Sigma-Aldrich*, *Fluka*, *Acros*, *Lancaster*, *ABCR*, *Novabiochem* and *Merck*, and were used as received unless otherwise stated.

(*R*)-phenylglycine, (*R*)- and (*S*)-valine, (*S*)-leucine and (*S*)-*tert*-leucine were donated by *Degussa AG*, triphenylborane was donated by *Bayer AG*, and diethylzinc was donated by *Crompton Corp.* (previously *Witco*).

6.1.3. Determination of the Physical Properties of the Synthesized Compounds

^{1}H-NMR Spectroscopy

^{1}H-NMR spectra were recorded either on a *Varian* Gemini 300 spectrometer (300 MHz) or on a *Varian* Inova 400 spectrometer (400 MHz). Chemical shifts are given in ppm relative to tetramethylsilane (TMS, δ 0.00 ppm). Solvent residual peaks ($CDCl_3$, δ 7.26 ppm; CD_2Cl_2, δ 5.23 ppm) were used as internal standard. Coupling patterns are described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), se (sextet), sept (septet), m (multiplet). Coupling costants (*J*) are given in Herz.

^{13}C-NMR Spectroscopy

^{13}C-NMR spectra were recorded either on a *Varian* Gemini 300 spectrometer (75 MHz) or on a *Varian* Inova 400 spectrometer (100 MHz). Chemical shifts are given in ppm and were determined by comparison with solvent residual peaks ($CDCl_3$, δ 77.0 ppm; CD_2Cl_2, δ 53.8 ppm).

IR Spectroscopy

IR spectra were measured on a *Perkin-Elmer* PE 1760 FT spectrometer as KBr pellets or neat (in case of liquid compounds). Only characteristic absorption bands are reported. Absorptions are given in wavenumbers (cm^{-1}).

Mass Spectroscopy

Mass spectra were recorded on a *Varian* MAT 212 or on a *Finnigan* MAT 95 spectrometer with EI (electronic impact) ionization, at a 70 eV ionization potential. Peaks are listed according to their

m/z value. High resolution mass spectra (HRMS) were recorded on a *Finnigan* MAT 95 spectrometer.

GC-MS Measurements

GC-MS measurements were conducted with the following instrument: GC (HP 6890 Series), MSD 5973. Column: HP-5 MS (30 m × 0.25 mm × 0.25 μm). Carrier gas: He, constant flow 200 °C.

Elemental Analysis

Elemental analyses were performed using an *Heraeus* CHN-O-Rapid instrument.

Optical Rotation

Optical rotation measurements were conducted at room temperature with a *Perkin-Elmer* PE 241 polarimeter, using solvents of *Merck* UVASOL® quality at a wavelenght of 589 nm (D-line of a Na-vapour lamp). Concentrations are given in g / 100 mL.

Melting Point

Melting points were measured in open glass capillaries with a *Büchi* B-540 apparatus and are uncorrected.

6.1.4. Chromatographic Methods

Preparative Column Chromatograpy

Purifications by Flash Column Chromatography were carried out in glass columns (10-50 mm diameter) according to STILL,[320] using *Merck* silica gel 60, particle size 0.040-0.063 mm (230-400 mesh).

Thin Layer Chromatography (TLC)

Support: TLC aluminum sheets silica gel 60 F_{254} (*Merck*) with a fluorescent indicator.

Detection: 1) exposition to UV-light ($\lambda = 254$ nm).

2) treatment with an acidic aqueous solution of ammonium molybdate tetrahydrate $[(NH_4)_6Mo_7O_{24}]\cdot 4H_2O$ and cerium sulfate tetrahydrate $[Ce(SO_4)]\cdot 4H_2O$ (Mostain).

3) treatment with a basic aqueous solution of potassium permanganate ($KMnO_4$).

[320] W. C. Still, M. Kahn, A. Mitra *J. Org. Chem.* **1978**, *43*, 2923.

Analytical High Performance Liquid Chromatography (HPLC)

HPLC measurements were performed on a *Merck-Hitachi* HPLC apparatus (L-7400 UV-detector, L-7100 pump and D-7000 integrator) or on a *Gynkotek* HPLC system (Gina 50 autosampler, UVD 170S UV-detector, DG 503 degasser and M480G pump), using columns with a chiral stationary phase purchased from *Chiral Technologies Ltd.* (formerly *Daicel Chemical Industries Ltd.*). All the measurements were conducted at room temperature.

6.1.5. Compounds Prepared Following Literature Procedures

(*R*)-*O*-Acetylmandelic acid chloride [(*R*)-**204**] and (*S*)-*O*-acetylmandelic acid chloride [(*S*)-**204**],[321] (*R*)- and (*S*)-valinol, (*S*)-leucinol and (*R*)-phenylglycinol,[322] (*S*)-*tert*-leucinol,[323] (*S*,R_p)-2-[2'-(diphenylhydroxymethyl)ferrocenyl]-4-*tert*-butyloxazoline [(*S*,R_p)-**64a**],[84] ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate [(*S*)-**218b**],[295] 3,5-di(trifluoromethyl)phenylmagnesium bromide,[324] 3,5-dimethylphenylmagnesium bromide,[325] *N*-arylidene sulfonylimines **165a-k**,[326] *N*-alkylidene tosylimines **165l-m**,[327] *N*-benzylidene diphenylphosphinamide (**225**),[328] *N*-(1-benzenesulfonyl)benzylformamide (**84a**),[329] (R_p,*S*)- and (S_p,*S*)-paracyclophanes **87**,[330] (1*S*,2*S*)-*N*,*N*-dimethyl-2-amino-1-indanol [(1*S*,2*S*)-**243**] ,[331] CHAN's ligand (**76b**),[102] (1*S*,2*S*)-*N*,*N*-dimethyl-*O*-(*tert*-butyldimethyl)silyl-2-amino-1-(4-nitrophenyl)-1,3-propandiol [(1*S*,2*S*)-**116b**].[181]

6.2. General Synthetic Procedures

General procedure for the preparation of *O*-acetyl mandelic acid chloride (GP-1).[321] In a flame dried round-bottom flask (*R*)- or (*S*)-mandelic acid (0.15 mol, 22.82 g) was dissolved in

[321] (a) T. Schmidlin, D. Wallach, C. Tamm *Helv. Chim. Acta* **1984**, *67*, 1998. (b) F. Babudri, V. Fiandanese, G. Marchese, A. Punzi *Tetrahedron* **1999**, *55*, 2431.
[322] M.-L. Anhoury, M. Arickx, P. Crooy, R. De Neys, J. Eliaers *J. Chem. Soc., Perkin Trans. 1* **1974**, 191.
[323] M. J. Mckennon, A. I. Meyers, K. Drauz, M. Schwarm *J. Org. Chem.* **1993**, *58*, 3568.
[324] A. L. Casalnuovo, T. V. RajanBabu, T. A. Ayers, T. H. Warren *J. Am. Chem. Soc.* **1994**, *116*, 9869.
[325] T. V. RajanBabu, T. A. Ayers, G. A. Halliday, K. K. You, J. C. Calabrese *J. Org. Chem.* **1997**, *62*, 6012.
[326] A modified version of the following procedure, employing 1,2-dichloroethane as the solvent instead of CH_2Cl_2, and heating at reflux for 48 h instead of 12 h, was used: K. Y. Lee, C. G. Lee, J. N. Kim *Tetrahedron Lett.* **2003**, *44*, 1231.
[327] F. Chemla, V. Hebbe, J.-F. Normant *Synthesis* **2000**, 75.
[328] W. B. Jennings, C. J. Lovely *Tetrahedron* **1991**, *47*, 5568.
[329] J. Sisko, M. Mellinger, P. W. Sheldrake, N. H. Baine *Org. Synth.* **2000**, *77*, 198.
[330] V. Rozenberg, T. Danilova, E. Sergeeva, E. Vorontsov, Z. Starikova, K. Lysenko, Y. Belokon' *Eur. J. Org. Chem.* **2000**, 3295.
[331] L. Bernardi, B. F. Bonini, M. Comes-Franchini, M. Fochi, G. Mazzanti, A. Ricci, G. Varchi *Eur. J. Org. Chem.* **2002**, 2776.

acetyl chloride (175 mL). The solution was stirred at room temperature for 2 h after complete dissolution of the substrate. Excess acetyl chloride was removed under high vacuum to give the intermediate (*R*)- or (*S*)-*O*-acetylmandelic acid. In the same flask thionyl chloride (100 mL) was added to the oily residue. The resulting solution was heated at reflux and stirred for additional 3 h. After this time, the reaction mixture was cooled to rt and excess thionyl chloride was removed under high vacuum, to furnish pure (*R*)- or (*S*)-*O*-acetyl mandelic acid chloride (**204**) which has been successively used without further purification.

General procedure for the condensation of acid chlorides (*R*)- and (*S*)-204 with amino alcohols to give amides 205a-c (GP-2). In a flame dried round-bottom Schlenk flask under an inert atmosphere of argon, the appropriate amino alcohol (50 mmol, 1.0 equiv) and Et_3N (100 mmol, 10.12 g, 2.0 equiv) were dissolved in anhydrous CH_2Cl_2 (80 mL). The mixture was cooled to 0 °C and a solution of (*R*)- or (*S*)-*O*-acetyl mandelic acid chloride (**204**, 50 mmol, 10.63 g, 1.0 eq.) in anhydrous CH_2Cl_2 (70 mL) was added dropwise during 10 mins. The resulting reaction mixture was warmed to rt, stirred for 17 h and washed with 1.0 M aq HCl (2 × 100 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL), and the combined organic layers were washed with brine (2 × 100 mL), and dried over $MgSO_4$. Removal of the solvent in vacuo afforded crude **205a-c**, which were then purified by recrystallization.

General procedure for the synthesis of 2-acetoxyoxazolines 206. Method A (GP-3). In a flame dried round-bottom Schlenk flask under an inert atmosphere of argon, the appropriate *O*-acetyl mandelic acid amide **206** (10.0 mmol) was dissolved in a 3/1 (v/v) mixture of anhydrous CH_2Cl_2 and Et_3N (160 mL). To this solution 4-dimethylaminopyridine (DMAP, 1.0 mmol, 0.122 g, 0.1 equiv) was added, and the reaction mixture was cooled to 0 °C. Subsequently, mesyl chloride (30 mmol, 3.44 g, 3.0 equiv), dissolved in anhydrous CH_2Cl_2 (10 mL), was added dropwise, and the reaction was stirred overnight at rt. The solvent was then removed by rotary evaporation and replaced by a 4/1 (v/v) mixture of EtOAc and H_2O (150 mL). The aqueous phase was extracted with EtOAc (150 mL). The combined organic layers were washed with water (2 × 150 mL) and dried over $MgSO_4$. Removal of the solvent in vacuo afforded crude **206** as a yellow-brown oil, which was then purified by flash column chromatography.

General procedure for the synthesis of 2-acetoxyoxazolines 206. Method B (GP-4). In a flame dried round-bottom Schlenk flask under an inert atmosphere of argon, the appropriate *O*-acetyl mandelic acid amide **205** (10.0 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL). The resulting

solution was cooled to −78 °C and diethylaminosulfur trifluoride (DAST, 11.0 mmol, 1.44 mL, 1.1 equiv) was added dropwise during 5 mins. After the addition the reaction mixture was stirred at −78 °C for 1 h, then K_2CO_3 (15 mmol, 2.07 g, 1.5 equiv) was added in one portion and the reaction was allowed to warm to rt. The reaction mixture was then poured into satd aq $NaHCO_3$ (200 mL) and the organic layer was collected; the aqueous layer was extracted once more with CH_2Cl_2 (200 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude **206** as a brown or yellow oil, which was subsequently purified by flash column chromatography.

General procedure for the synthesis of α-hydroxy-2-oxazolines 203a-c (GP-5). In a round-bottom flask 2-acetoxyoxazoline **206a-c** (5.0 mmol) were dissolved in MeOH (30 mL). The solution was cooled to 0 °C and 1.0 M aq LiOH (15.0 mmol, 15 mL, 3.0 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h, and was then allowed to warm to rt. The mixture was then extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded crude hydroxy oxazolines **203a-c** typically as yellow semisolids, which were then purified by recrystallization.

General procedure for the condensation of benzoylformic acid 214 with amino alcohols to give oxo hydroxy amides 215a-d. (GP-6). In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon, benzoylformic acid **214** (20.0 mmol, 3.00 g) was dissolved in dry CH_2Cl_2 (150 mL) and 1-hydroxybenzotriazol (HOBt, 20.0 mmol, 2.70 g, 1.0 equiv) was added in one portion. The mixture was stirred at room temperature for 30 min, and then DMAP (2.0 mmol, 244 mg, 0.1 equiv) and the appropriate amino alcohol (20 mmol, 1.0 equiv) were added. The resulting mixture was cooled to 0 °C and a solution of *N*,*N*'-dicyclohexylcarbodiimide (DCC, 22.0 mmol, 4.54 g, 1.1 equiv) in dry CH_2Cl_2 (100 mL) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C, and then allowed to warm to rt and stirred overnight. The solvent was then removed under reduced pressure and replaced with EtOAc (250 mL). The precipitate thus formed was filtered off on a short pad of Celite®, and the organic layer washed in sequence with 1.0 M aq HCl (200 mL), satd aq $NaHCO_3$ (200 mL) and brine (200 mL) and finally dried over $MgSO_4$. Evaporation of the solvent afforded crude **215a-d**, which were then purified by flash column chromatography.

General procedure for the synthesis of 2-benzoyloxazolines 216a-c (GP-7). In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon, oxo hydroxy amides **215a-c** (2.0

mmol) were dissolved in dry CH_2Cl_2 (20 mL). The resulting solution was cooled to 0 °C and $SOCl_2$ (10.0 mmol, 1.19 g, 0.73 mL, 5.0 equiv) was added dropwise over 10 mins. The reaction mixture was warmed to rt and stirred overnight. The solvent and excess $SOCl_2$ were then evaporated and replaced with DMF (20 mL). Solid Na_2CO_3 (10.0 mmol, 1.06 g, 5.0 equiv) was added in one portion at room temperature and the reaction mixture heated to 85 °C and stirred for 24 h. The heterogeneous mixture was then diluted with EtOAc (20 mL) and the organic phase washed with water (5 × 20 mL). The aqueous phase was extracted with EtOAc (20 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude **216a-c**, which were then purified by flash column chromatography.

General procedure for the addition of phenylmagnesium chloride to 2-benzoyloxazolines 216a-c (GP-8). In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon, 2-benzoyloxazolines **216a-c** (1.0 mmol) were dissolved in dry THF (15 mL). The resulting solution was cooled to 0 °C and PhMgCl (2.0 M solution in THF, 1.1 mmol, 0.55 mL, 1.1 equiv) was added dropwise over 5 mins. The reaction mixture was then warmed to rt and stirred for 2 h. The reaction was quenched with satd aq NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (25 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude **212a-c**, which were subsequently purified either by recrystallization or flash column chromatography.

General procedure for the synthesis of ethyl oxazoline-2-carboxylates 218a-b from ethyl oxamate 217 (GP-9). In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon, triethyloxonium tetrafluoroborate (15.1 mmol, 2.87 g) was dissolved in 1,2-dichloroethane (DCE, 80 mL). To the resulting solution, ethyl oxamate (**217**, 15.1 mmol, 1.77 g, 1.0 equiv) was added in one portion at rt. The reaction mixture was stirred at rt for 24 h and then the appropriate amino alcohol (17.1 mmol, 1.15 equiv) was added in one portion. The reaction mixture was heated to reflux and stirred for an additional 24 h. It was then cooled to room temperature and poured into ice-cold satd aq NH_4Cl (25 mL). CH_2Cl_2 was added (80 mL) and the organic layer was washed with satd aq NH_4Cl (2 × 25 mL), and brine (25 mL), and finally dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude **218a-b**, which were then purified by flash column chromatography.

General procedure for the addition of Grignard reagents to ethyl oxazoline-2-carboxylates 218a-b (GP-10). In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon,

ethyl oxazoline-2-carboxylates **218a-b** (1.0 mmol) were dissolved in dry THF (10 mL). The resulting mixture was cooled to 0 °C and a solution of the appropriate Grignard reagent (≥3.0 mmol, ≥3.0 equiv) in THF or Et_2O was added dropwise over 5 mins. The reaction mixture was warmed to rt and stirred for 16–24 h. The reaction was quenched by the addition of satd aq NH_4Cl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude **212d-k**, which were then purified either by recrystallization or flash column chromatography.

General procedures for the phenyl transfer reaction on aldehydes catalyzed by compounds 203a-c and 212a-k.

General procedure without additive (GP-11A). In a glovebox under an inert atmosphere of argon, Ph_3B (0.25 mmol, 60 mg, 1.0 equiv) was sealed in a flame-dried reaction vessel (18 × 50 mm). Toluene (2 mL) was added and the resulting solution was treated with Et_2Zn (1.0 M solution in heptane, 1.0 mmol, 1.0 mL, 4.0 equiv). After stirring at rt for 30 mins, the appropriate hydroxy oxazoline **203a-c** or **212a-k** (0.025 mmol, 10 mol%) was added as toluene solution (1.0 mL) and stirring was continued for further 45–60 mins at rt. The resulting clear solution was cooled to 10 °C and the appropriate aldehyde **59** (0.25 mmol), dissolved in toluene (1.0 mL), was slowly added. After stirring at 10 °C for 12–18 h, the reaction mixture was quenched with water (10 mL). Aqueous AcOH (10%) was added (10 mL) and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (25 mL) and dried over $MgSO_4$. Evaporation of the solvent furnished crude alcohols **60**, which were then purified by flash column chromatography.

General procedure with additive (GP-11B). In a glovebox under an inert atmosphere of argon, Ph_3B (0.25 mmol, 60 mg, 1.0 equiv) and DiMPEG (M = 2000 g mol^{-1}, 0.032 mmol, 63 mg, 13 mol %) were sealed in a flame-dried reaction vessel (18 × 50 mm). Toluene (2 mL) was added, and the resulting solution was treated with Et_2Zn (1.0 M solution in heptane, 1.0 mmol, 1.0 mL, 4.0 equiv), to give a clear solution containing a small quantity of precipitate. After stirring at rt for 30 min, the appropriate hydroxy oxazoline **203a-c** or **212a-k** (0.025 mmol, 10 mol%) was added as a toluene solution (1.0 mL) and stirring was continued for further 45–60 min at rt. The resulting mixture was cooled to 10 °C and the appropriate aldehyde **59** (0.25 mmol) dissolved in toluene (1.0 mL), was slowly added. From hereon, the protocol followed the procedure reported above for the reactions performed without additive.

General procedure for the alkynylation of imines 165a-k, 225, 229b (GP-12). In an oven-dried Schlenk flask under an inert atmosphere of argon the desired alkyne (0.75–1.25 mmol, 1.5–2.5 equiv) was dissolved in anhydrous toluene (4.5 mL). A 2.0 M solution of dimethylzinc in toluene (0.75–1.25 mmol, 0.38–0.63 mL, 1.5–2.5 equiv) was then carefully added, and the resulting mixture was stirred at room temperature for 30 mins. The appropriate imine **165a-k**, **225**, **229b** (0.5 mmol) was then added in one portion, and the temperature was increased to the desired value (50–70 °C). The resulting solution was stirred for 24 h, after which a white precipitate appeared in some cases. The reaction was quenched with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the organic phase was washed with brine (25 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure furnished crude **166a-q**, **226**, **230b** typically as a solid, which was purified by flash column chromatography and/or by recrystallization.

General procedures for the three-component synthesis of propargylic imines 230c-p.

Method A (GP-13A). In an oven-dried Schlenk flask under an inert atmosphere of argon were placed the appropriate aldehyde **59** (0.2 mmol) and 2-methoxyaniline (**237**, 0.2 mmol, 0.025 g, 1.0 equiv), followed by anhydrous toluene (2 mL). After 30 mins stirring, a 2.0 M solution of dimethylzinc in toluene (0.7 mmol, 0.35 mL, 3.5 equiv) was added. The reaction mixture was then stirred for another 30 mins, before adding phenylacetylene (**108**, 0.5 mmol, 0.051 g, 2.5 equiv) or 1-octyne (**232**, 0.5 mmol, 0.055 mg, 2.5 equiv). The resulting solution was stirred at room temperature for 48-60 h. The reaction mixture was then diluted with Et_2O (5 mL), and quenched with water (10 mL). The resulting heterogeneous mixture was filtered over Celite®. The aqueous phase was separated and washed with Et_2O (2 × 5 mL). The combined organic layers were then dried over Na_2SO_4 and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography.

Method B (GP-13B, concentrated conditions): In an oven-dried Schlenk flask under an inert atmosphere of argon were placed the appropriate aldehyde **59** (0.4 mmol) and 2-methoxyaniline (**237**, 0.4 mmol, 0.049 g, 1.0 equiv). A 2.0 M solution of dimethylzinc in toluene (1.4 mmol, 0.7 mL, 3.5 equiv) was immediately added. The reaction mixture was then stirred for 15 mins, before adding phenylacetylene (**108**, 1.0 mmol, 0.102 g, 2.5 equiv). The resulting solution was stirred at room temperature for 48-96 h. From hereon the protocol followed the procedure reported above for Method A.

General procedure for the double alkylation of norephedrine (GP-14): To a solution of norephedrine (**244**, 5.0 mmol, 0.756 g) in CH_3CN (30 mL) were added the appropriate alkyl halide

(5.0 mmol, 1.0 equiv in the case of 1,4-dibromobutane and 10.0 mmol, 2.0 equiv in the case of the other alkyl halides) and K_2CO_3 (25.0-50.0 mmol, 3.46-6.92 g, 5.0-10.0 equiv). The mixture was refluxed for 18-24 h. After the reaction was complete according to TLC, the mixture was cooled and the solid was separated by filtration and washed with EtOAc. The combined filtrates were concentrated in vacuo. The residue was purified by flash column chromatography affording the double alkylated norephedrines (**246c-g**).

When *tert*-butyl iodide and 2-methylpropyl iodide were used, only the corresponding monoalkylated products (**245a-b**) were obtained, which were used without further purification, for the following methylation reaction (GP-15).

General procedure for the methylation of monoalkylnorephedrines 245a-b (GP-15). In a round-bottom flask was placed compound **245a** or **245b** (5.0 mmol). Formic acid (90% solution in H_2O, 25.0 mmol, 0.75 mL, 5.0 equiv) and formaldehyde (37% solution in H_2O, 15.0 mmol, 0.82 mL, 3.0 equiv) were added in sequence at rt, and the resulting mixture was heated to reflux and stirred for 18 h. The solution was allowed to cool to rt, and 1.0 M aq NaOH was added until pH > 8. The aqueous layer was then extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was washed with brine (50 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo afforded crude **246a-b**, which were then purified by flash column chromatography.

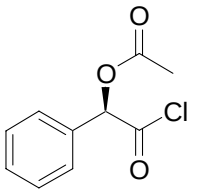
General procedure for the asymmetric alkynylation of imines 165a-c and **225 (GP-16).** In an oven-dried Schlenk flask under an inert atmosphere of argon phenylacetylene **108** (1.5 mmol, 0.153 g, 3.0 equiv) was dissolved in anhydrous toluene (4 mL). A 2.0 M solution of dimethylzinc in toluene (1.5 mmol, 0.75 mL, 3.0 equiv) was then carefully added, and the resulting mixture was stirred at room temperature for 30 mins. The appropriate ligand (0.1 mmol, 20 mol %) was subsequently added, and the reaction mixture was stirred for additional 30 mins. Imine **165a** or **225** (0.5 mmol) was then added in one portion, and the resulting solution was stirred for 24 h. The reaction was quenched with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (25 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure furnished crude **166a-c** or **226** typically as a solid, which was purified by flash column chromatography and/or by recrystallization.

General procedure for the asymmetric synthesis of propargylic amines 230c, f, p, r-v (GP-17). In an oven-dried Schlenk flask under an inert atmosphere of argon were placed the appropriate aldehyde **59** (0.4 mmol) and 2-methoxyaniline (**237**, 0.4 mmol, 0.049 g, 1.0 equiv), followed by

anhydrous toluene (3-4 mL). After 30 mins stirring, a 2.0 M solution of dimethylzinc in toluene (1.4-2.4 mmol, 0.7-1.2 mL, 3.5-6.0 equiv) was added. The reaction mixture was stirred for 30 mins, and the appropriate ligand (0.4 mmol, 1.0 equiv) was added (dissolved in 1 mL of toluene in the case of oils). The reaction mixture was then stirred for another 30 mins, before adding phenylacetylene (**108**, 1.0-2.0 mmol, 0.102-0.204 g, 2.5-5.0 equiv) or 1-octyne (**232**, 1.2 mmol, 0.132 mg, 3.0 equiv). The resulting solution was stirred at room temperature for 48 h. The reaction mixture was then diluted with Et_2O (5 mL), and quenched with water (10 mL). The resulting heterogeneous mixture was filtered over Celite®. The aqueous phase was separated and washed with Et_2O (2 × 5 mL). The combined organic layers were then dried over $MgSO_4$ and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography.

6.3. Synthesis of Hydroxy Oxazolines 203a-c

6.3.1. (*R*)-*O*-acetyl mandelic acid chloride [(*R*)-204]



$C_{10}H_9O_3Cl$; MW = 212.63 g mol^{-1}

Prepared according to GP-1. After work-up, the title compound (0.15 mol, 31.9 g, yield 100%) was obtained in pure form as a yellow oil.

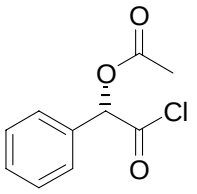
Optical rotation: $[\alpha]^{20}_D = -184.0$ (c = 1.96 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3H), 6.08 (s, 1H), 7.37-7.52 (m, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.6, 81.0, 128.4, 129.2, 130.3, 130.8, 169.9, 170.7.

All the other data are in agreement with those reported in the literature.

6.3.2. (*S*)-*O*-acetyl mandelic acid chloride [(*S*)-204]



$C_{10}H_9O_3Cl$; MW = 212.63 g mol^{-1}

Prepared according to GP-1. After work-up, the title compound (0.15 mol, 31.9 g, yield 100%) was obtained in pure form as a yellow oil.

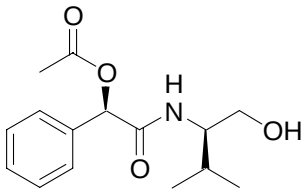
Optical rotation: $[\alpha]^{20}_D$ = +183.2 (c = 1.94 in $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3H), 6.08 (s, 1H), 7.38-7.53 (m, 5H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.4, 80.9, 128.4, 129.2, 130.3, 130.8, 169.9, 170.8.

All the other data are in agreement with those reported in the literature.

6.3.3. (*R*,*R*)-*O*-acetyl mandelic acid (1-hydroxymethyl-2-methyl)propylamide [(*R*,*R*)-205a]



$C_{15}H_{21}NO_4$; MW = 279.33 g mol^{-1}

Prepared according to GP-2, starting from (*R*)-**204** and (*R*)-valinol (50 mmol, 5.19 g, 1.0 equiv). Purification by recrystallization from Et_2O furnished pure (*R*,*R*)-**205a** (30 mmol, 8.36 g, yield 60%) as a colorless solid.

Mp: 91-92 °C.

Optical rotation: $[\alpha]^{20}_D$ = −41.4 (c = 0.82 in $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 1.90 (se, *J* = 6.8 Hz, 1H), 2.17 (s, 3H), 2.92 (br s, 1H), 3.56-3.73 (m, 3H), 6.06 (s, 1H), 6.57-6.61 (m, 1H), 7.32-7.48 (m, 5H).

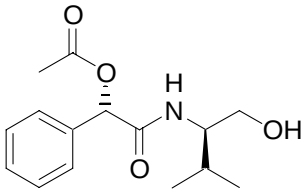
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.9, 19.6, 21.0, 29.0, 56.9, 62.9, 75.8, 127.4, 128.8, 129.0, 135.6, 169.0, 169.5.

MS (EI, 70 eV): *m/z* = 280 $[M+1]^+$, 149, 130, 108, 107, 77, 69.

IR (KBr): ν = 3284, 2962, 1747, 1663, 1563, 1238, 1052 cm^{-1}.

Elemental analysis for $C_{15}H_{21}NO_4$ Calcd: C, 64.50; H, 7.58; N, 5.01.
Found: C, 64.70; H, 7.59; N, 5.21.

6.3.4. (*S*,*R*)-*O*-acetyl mandelic acid (1-hydroxymethyl-2-methyl)propylamide [(*S*,*R*)-205a]



$C_{15}H_{21}NO_4$; MW = 279.33 g mol^{-1}

Prepared according to GP-2, starting from (*S*)-**204** and (*R*)-valinol (50 mmol, 5.19 g, 1.0 equiv). Purification by recrystallization from Et_2O furnished pure (*S*,*R*)-**205a** (31 mmol, 8.62 g, yield 62%) as a colorless solid.

Mp: 88-89 °C.

Optical rotation: $[\alpha]^{20}_D$ = +118.6 (c = 1.00 in $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 1.84 (se, *J* = 6.8 Hz, 1H), 2.17 (s, 3H), 3.59-3.78 (m, 3H), 6.05 (s, 1H), 6.44 (br s, 1H), 7.32-7.40 (m, 3H), 7.42-7.50 (m, 2H).

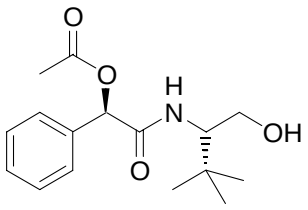
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.6, 19.6, 21.0, 29.0, 56.9, 63.2, 75.8, 127.6, 128.8, 129.1, 135.4, 169.2, 169.8.

MS (EI, 70 eV): *m/z* = 279 $[M]^+$, 149, 130, 108, 107, 91, 77, 69.

IR (KBr): ν = 3471, 3300, 1734, 1655, 1549, 1373, 1238, 1068 cm^{-1}.

Elemental analysis for $C_{15}H_{21}NO_4$ Calcd: C, 64.50; H, 7.58; N, 5.01.
Found: C, 64.15; H, 7.37; N, 4.99.

6.3.5. (*R*,*S*)-*O*-acetyl mandelic acid (1-hydroxymethyl-2,2-dimethyl)propylamide [(*R*,*S*)-205b]



$C_{16}H_{23}NO_4$; MW = 293.36 g mol^{-1}

Prepared according to GP-2, starting from (*R*)-**204** and (*S*)-*tert*-leucinol (50 mmol, 5.86 g, 1.0 equiv). Purification by recrystallization from EtOAc furnished pure (*R*,*S*)-**205b** (39 mmol, 11.44 g, yield 78%) as a colorless solid.

Mp: 151-152 °C.

Optical rotation: $[\alpha]^{20}_D = -84.1$ (c = 0.84 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.84 (s, 9H), 2.17 (s, 3H), 2.83 (br s, 1H), 3.52-3.60 (m, 1H), 3.77-3.87 (m, 2H), 6.07 (s, 1H), 6.47-6.51 (m, 1H), 7.32-7.37 (m, 3H) 7.46-7.52 (m, 2H).

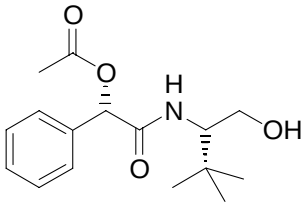
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.1, 26.9, 33.9, 59.4, 62.3, 76.0, 127.6, 128.8, 129.1, 135.4, 169.3, 170.0.

MS (EI, 70 eV): *m/z* = 294 $[M+1]^+$, 262, 177 ,174, 149, 144, 107, 91, 77, 57.

IR (KBr): ν = 3297, 3079, 2968, 1742, 1659, 1576, 1370, 1233, 1052 cm^{-1}.

Elemental analysis for $C_{16}H_{23}NO_4$ Calcd: C, 65.51; H, 7.90; N, 4.77.
Found: C, 65.41; H, 7.95; N, 4.74.

6.3.6. (*S*,*S*)-*O*-acetyl mandelic acid (1-hydroxymethyl-2,2-dimethyl)propylamide [(*S*,*S*)-205b]



$C_{16}H_{23}NO_4$; MW = 293.36 g mol^{-1}

Prepared according to GP-2, starting from (*S*)-**204** and (*S*)-*tert*-leucinol (50 mmol, 5.86 g, 1.0 equiv). Purification by recrystallization from Et_2O furnished pure (*S*,*S*)-**205b** (32 mmol, 9.33 g, yield 64%) as a colorless solid.

Mp: 93-94 °C.

Optical rotation: $[\alpha]^{20}_D = +46.4$ (c = 1.00 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.93 (s, 9H), 2.20 (s, 3H), 2.45 (br s, 1H), 3.53-3.62 (m, 1H), 3.75-3.84 (m, 2H), 6.10 (s, 1H), 6.43 (br s, 1H), 7.32-7.41 (m, 3H), 7.42-7.48 (m, 2H).

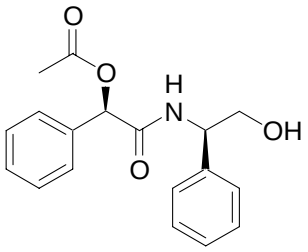
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.0, 26.7, 33.8, 59.2, 62.4, 75.8, 127.1, 128.6, 128.8, 135.4, 169.01, 169.04.

MS (EI, 70 eV): *m/z* = 278, 262, 177, 149, 144, 118, 107, 86, 77, 57.

IR (KBr): ν = 3444, 3337, 2959, 1749, 1661, 1560, 1373, 1229, 1050 cm^{-1}.

Elemental analysis for $C_{16}H_{23}NO_4$ Calcd: C, 65.51; H, 7.90; N, 4.77.
Found: C, 65.67; H, 7.92; N, 4.65.

6.3.7. (*R*,*R*)-*O*-acetyl mandelic acid (2-hydroxy-1-phenyl)ethylamide [(*R*,*R*)-205c]



$C_{18}H_{19}NO_4$; MW = 313.34 g mol^{-1}

Prepared according to GP-2, starting from (*R*)-**204** and (*R*)-phenylglycinol (50 mmol, 6.86 g, 1.0 equiv). Purification by recrystallization from Et_2O furnished pure (*R*,*R*)-**205c** (30.5 mmol, 9.49 g, yield 61%) as a colorless solid.

Mp: 126-127 °C.

Optical rotation: $[\alpha]^{20}_D = -107.0$ (c = 1.00 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3H), 2.67 (br s, 1H), 3.78-3.82 (m, 2H), 5.02 (dt, *J* = 7.3 Hz, 4.7 Hz, 1H), 6.10 (s, 1H), 7.01-7.18 (m, 1H), 7.20-7.44 (m, 10H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.9, 55.3, 65.7, 75.5, 126.4, 127.1, 127.6, 128.6, 128.6, 128.8, 135.1, 138.4, 168.5, 169.2.

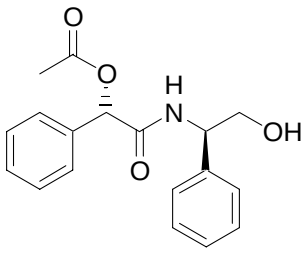
MS (EI, 70 eV): *m/z* = 314 $[M+1]^+$, 282, 223, 194, 165, 164, 149, 107, 91, 77.

IR (KBr): ν = 3469, 3325, 1705, 1557, 1375, 1294, 1249, 1030 cm^{-1}.

Elemental analysis for $C_{18}H_{19}NO_4$ Calcd: C, 68.99; H, 6.11; N, 4.47.

Found: C, 68.63; H, 6.18; N, 4.41.

6.3.8. (*S*,*R*)-*O*-acetyl mandelic acid (2-hydroxy-1-phenyl)ethylamide [(*S*,*R*)-205c]



$C_{18}H_{19}NO_4$; MW = 313.34 g mol^{-1}

Prepared according to GP-2, starting from (*S*)-**204** and (*R*)-phenylglycinol (50 mmol, 6.86 g, 1.0 equiv). Purification by recrystallization from Et_2O furnished pure (*S*,*R*)-**205c** (29.5 mmol, 9.24 g, yield 59%) as a colorless solid.

Mp: 123-124 °C.

Optical rotation: $[\alpha]^{20}_D$ = +31.5 (c = 1.00 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3H), 2.75 (br s, 1H), 3.75-3.84 (m, 2H), 5.00-5.06 (m, 1H), 6.07 (s, 1H), 6.96-7.02 (m, 1H), 7.10-7.15 (m, 2H), 7.26-7.32 (m, 3H), 7.32-7.37 (m, 3H), 7.40-7.47 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.9, 55.3, 65.7, 75.5, 126.3, 127.4, 127.6, 128.5, 128.6, 128.9, 135.0, 138.4, 168.5, 169.5.

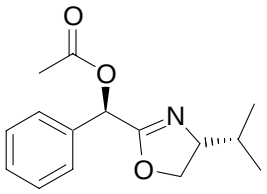
MS (EI, 70 eV): *m/z* = 314 $[M+1]^+$, 282, 255, 254, 226, 164, 91, 77.

IR (KBr): ν = 3548, 3337, 1725, 1661, 1540, 1372, 1241, 1074 cm^{-1}.

Elemental analysis for $C_{18}H_{19}NO_4$ Calcd: C, 68.99; H, 6.11; N, 4.47.

Found: C, 68.94; H, 6.24; N, 4.40.

6.3.9. (*R,R*)-2-acetoxyphenylmethyl-4-*iso*-propyl-4,5-dihydrooxazole [(*R,R*)-206a]



$C_{15}H_{19}NO_3$; MW = 261.32 g mol^{-1}

According to GP-4, the title compound was prepared starting from (*R,R*)-**205a** (10 mmol, 2.79 g). Purification by flash column chromatography (PE / EtOAc 2:1) afforded pure (*R,R*)-**206a** (7.1 mmol, 1.86 g, 71% yield) as a colorless oil.

Optical rotation: $[\alpha]^{20}_D$ = +71.7 (c = 0.47 in $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 1.77 (dse, *J* = 6.8 Hz, *J* = 1.1 Hz, 1H), 2.18 (s, 3H), 3.93-4.07 (m, 2H), 4.21 (dd, *J* = 9.4 Hz, *J* = 7.7 Hz, 1H), 6.28 (s, 1H), 7.31-7.42 (m, 3H), 7.45-7.53 (m, 2H).

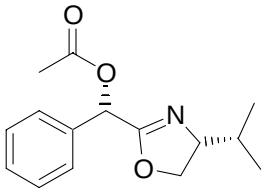
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.8, 18.5, 20.9, 32.4, 70.6, 70.9, 71.8, 127.6, 128.7, 129.0, 135.3, 163.8, 169.8.

MS (EI, 70 eV): *m/z* = 261 $[M]^+$, 218, 176, 158, 149, 107, 91, 77.

IR (neat): ν = 2962, 1747, 1673, 1372, 1230, 1044 cm^{-1}.

Elemental analysis for $C_{15}H_{19}NO_3$ Calcd: C, 68.94; H, 7.33; N, 5.36.
Found: C, 68.60; H, 7.38; N, 5.30.

6.3.10. (*S,R*)-2-acetoxyphenylmethyl-4-*iso*-propyl-4,5-dihydrooxazole [(*S,R*)-206a]



$C_{15}H_{19}NO_3$; MW = 261.32 g mol^{-1}

According to GP-4, the title compound was prepared starting from (*S,R*)-**205a** (10 mmol, 2.79 g). Purification by flash column chromatography (PE / EtOAc 2:1) afforded pure (*S,R*)-**206a** (5.6 mmol, 1.46 g, 56% yield) as a colorless oil.

Optical rotation: $[\alpha]^{20}_D$ = +89.1 (c = 2.12 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 1.84 (dse, *J* = 6.9 Hz, *J* = 1.1 Hz, 3H), 2.17 (s, 3H), 3.93-4.01 (m, 2H), 4.18-4.31 (m, 1H), 6.29 (s, 1H), 7.32-7.41 (m, 3H), 7.47-7.53 (m, 2H).

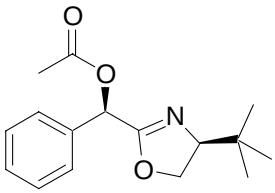
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.6, 18.8, 21.0, 32.1, 70.1, 70.9, 71.8, 127.4, 128.4, 128.8, 135.3, 163.5, 169.6.

MS (EI, 70 eV): *m/z* = 261 $[M]^+$, 246, 218, 176, 158, 105, 91, 77.

IR (neat): ν = 1043, 1231, 1372, 1677, 1747, 2962, 3340 cm^{-1}.

Elemental analysis for $C_{15}H_{19}NO_3$ Calcd: C, 68.94; H, 7.33; N, 5.36.
Found: C, 68.84; H, 7.19; N, 5.69.

6.3.11. (*R,S*)-2-acetoxyphenylmethyl-4-*tert*-butyl-4,5-dihydrooxazole [(*R,S*)-206b]



$C_{16}H_{21}NO_3$; MW = 275.34 g mol^{-1}

According to GP-3, the title compound was prepared starting from (*R,S*)-**205b** (10 mmol, 2.93 g). Purification by flash column chromatography (PE / EtOAc / Et_3N 3:2:0.25) afforded pure (*R,S*)-**206b** (6.2 mmol, 1.71 g, 62% yield) as a yellow oil.

Optical rotation: $[\alpha]^{20}_D$ = −94.0 (c = 1.01 in $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.88 (s, 9H), 2.15 (s, 3H), 3.88 (ddd, *J* = 10.1 Hz, *J* = 8.3 Hz, *J* = 1.1 Hz, 1H), 4.03 (t, *J* = 8.3 Hz, 1H), 4.20 (dd, *J* = 10.1 Hz, *J* = 8.7 Hz, 1H), 6.30 (s, 1H), 7.29-7.41 (m, 3H), 7.45-7.54 (m, 2H).

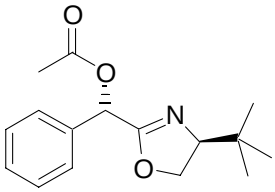
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.0 , 25.9, 33.8, 69.2, 71.1, 75.7, 127.6, 128.6, 129.0, 135.6 163.5, 169.8.

MS (EI, 70 eV): *m/z* = 275 $[M]^+$, 218, 176, 159, 105, 77.

IR (neat): ν = 2957, 1748, 1678, 1570, 1230, 1046 cm^{-1}.

HRMS (EI): *m/z* calcd for $C_{16}H_{21}NO_3$: 275.1521; found: 275.1521.

6.3.12. (*S,S*)-2-acetoxyphenylmethyl-4-*tert*-butyl-4,5-dihydrooxazole [(*S,S*)-206b]



$C_{16}H_{21}NO_3$; MW = 275.34 g mol^{-1}

According to GP-3, the title compound was prepared starting from (*S,S*)-**205b** (10 mmol, 2.93 g). Purification by flash column chromatography (PE / EtOAc 5:4) afforded pure (*S,S*)-**206b** (6.7 mmol, 1.85 g, 67% yield) as a pale yellow oil.

Optical rotation: $[\alpha]^{20}_D$ = +6.0 (c = 1.07 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.84 (s, 9H), 2.18 (s, 3H), 3.90 (dd, *J* = 9.9 Hz, *J* = 7.4 Hz, 1H), 4.11-4.18 (m, 2H), 6.29 (s, 1H), 7.32-7.42 (m, 3H), 7.46-7.52 (m, 2H).

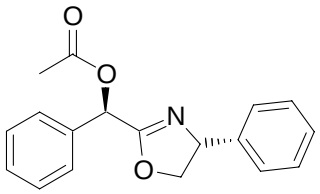
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.9, 25.6, 33.8, 69.4, 70.9, 75.4, 127.4, 128.4, 128.8, 135.0, 163.5, 169.6.

MS (EI, 70 eV): *m/z* = 275 $[M]^+$, 176, 159, 105, 77, 57.

IR (neat): ν = 2956, 1747, 1678, 1232, 1048 cm^{-1}.

HRMS (EI): *m/z* calcd for $C_{16}H_{21}NO_3$: 275.1521; found: 275.1521.

6.3.13. (*R,R*)-2-acetoxyphenylmethyl-4-phenyl-4,5-dihydrooxazole [(*R,R*)-206c]



$C_{18}H_{17}NO_3$. MW = 295.33 g mol^{-1}

According to GP-4, the title compound was prepared starting from (*R,R*)-**205c** (10 mmol, 3.13 g). Purification by flash column chromatography (PE / EtOAc 2:1) afforded pure (*R,R*)-**206c** (6.5 mmol, 1.61 g, 65% yield) as a yellow oil.

Optical rotation: $[\alpha]^{20}_D$ = −31.3 (c = 0.78 in $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3H), 4.08 (t, *J* = 8.4 Hz, 1H), 4.66 (dd, *J* = 10.1 Hz, *J* = 8.4 Hz, 1H), 5.18-5.27 (m, 1H), 6.37 (s, 1H), 7.14-7.46 (m, 8H), 7.53-7.61 (m, 2H).

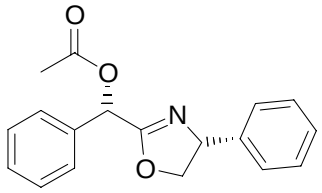
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.0, 69.6, 71.0, 75.4, 126.7, 127.6, 127.7, 128.7, 128.8, 129.2, 135.2, 141.7, 165.4, 170.0.

MS (EI, 70 eV): *m/z* = 295 $[M]^+$, 280, 252, 236, 174, 118, 91, 77.

IR (neat): ν = 3032, 2903, 1748, 1672, 1373, 1229, 1045 cm^{-1}.

Elemental analysis for $C_{18}H_{17}NO_3$ Calcd: C, 73.20; H, 5.80; N, 4.74.
Found: C, 72.94; H, 6.00; N, 4.67.

6.3.14. (*S,R*)-2-acetoxyphenylmethyl-4-phenyl-4,5-dihydrooxazole [(*S,R*)-206c]



$C_{18}H_{17}NO_3$. MW = 295.33 g mol^{-1}

According to GP-4, the title compound was prepared starting from (*S,R*)-**205c** (10 mmol, 3.13 g). Purification by flash column chromatography (PE / EtOAc 2:1) afforded pure (*S,R*)-**206c** (6.4 mmol, 1.89 g, 64% yield) as a colorless solid.

Mp: 113-114 °C.

Optical rotation: $[\alpha]^{20}_D$ = +134.3 (c = 1.03 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.19 (s, 3H), 4.07 (t, *J* = 8.4 Hz, 1H), 4.65 (dd, *J* = 10.3 Hz, 8.4 Hz, 1H), 5.17-5.25 (m, 1H), 6.35 (s, 1H), 7.15-7.21 (m, 2H), 7.23-7.47 (m, 6H), 7.53-7.60 (m, 2H).

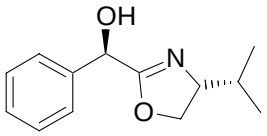
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.9, 69.5, 70.9, 75.3, 126.5, 127.4, 127.5, 128.5, 128.6, 129.0, 135.0, 141.5, 165.1, 169.7.

MS (EI, 70 eV): *m/z* = 295 $[M]^+$, 280, 252, 236, 175, 118, 105, 91, 77.

IR (KBr): ν = 3460, 2969, 1741, 1676, 1371, 1233, 1182, 1047 cm^{-1}.

Elemental analysis for $C_{18}H_{17}NO_3$ Calcd: C, 73.20; H, 5.80; N, 4.74.
Found: C, 72.86; H, 5.94; N, 4.61.

6.3.15. (*R,R*)-2-hydroxyphenylmethyl-4-*iso*-propyl-4,5-dihydrooxazole [(*R,R*)-203a]



$C_{13}H_{17}NO_2$. MW = 219.28 g mol^{-1}

Prepared according to GP-5, starting from (*R,R*)-**206a** (5.0 mmol, 1.31 g). Recrystallization from EtOAc gave pure (*R,R*)-**203a** (4.1 mmol, 0.898 g, 82% yield) as a colorless crystalline solid.

Mp: 73-74 °C.

Optical rotation: $[\alpha]^{20}_D$ = +7.4 (c = 1.00 in $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 1.74 (se, *J* = 6.7 Hz, 1H), 3.83 (m, 1H), 4.05 (t, *J* = 8.5 Hz, 1H), 4.25 (dd, *J* = 9.6 Hz, *J* = 8.5 Hz, 1H), 4.57 (br s, 1H), 5.32 (s, 1H), 7.27-7.40 (m, 3H), 7.42-7.49 (m, 2H).

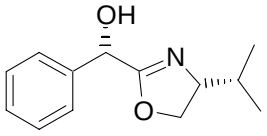
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.1, 18.7, 32.5, 69.7, 71.2, 71.8, 126.7, 128.3, 128.5, 139.3, 168.5.

MS (EI, 70 eV): *m/z* = 219 $[M]^+$, 176, 146, 107, 91, 77.

IR (KBr): ν = 3174, 2909, 1741, 1673, 1266, 1200, 1089 cm^{-1}.

Elemental analysis for $C_{13}H_{17}NO_2$ Calcd: C, 71.21; H, 7.81; N, 6.39.
Found: C, 71.03; H, 7.82; N, 6.36.

6.3.16. (*S,R*)-2-hydroxyphenylmethyl-4-*iso*-propyl-4,5-dihydrooxazole [(*S,R*)-203a]



$C_{13}H_{17}NO_2$. MW = 219.28 g mol^{-1}

Prepared according to GP-5, starting from (*S,R*)-**206a** (5.0 mmol, 1.31 g). Recrystallization from EtOAc gave pure (*S,R*)-**203a** (4.2 mmol, 0.918 g, 84% yield) as a colorless crystalline solid.

Mp: 85-86 °C.

Optical rotation: $[\alpha]^{20}_D$ = +152.5 (c = 0.97 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 1.74 (sept, *J* = 6.8 Hz, 1H), 3.90-4.01 (m, 1H), 4.24-4.36 (m, 2H), 5.26 (s, 1H), 7.28-7.38 (m, 3H), 7.41-7.47 (m, 2H).

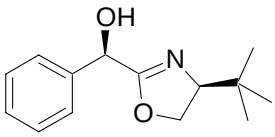
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.0, 18.7, 32.4, 69.7, 71.1, 71.6, 126.6, 128.2, 128.3, 139.1, 168.2.

MS (EI, 70 eV): *m/z* = 219 $[M]^+$, 176, 146, 107, 91, 77.

IR (KBr): ν = 3148, 2971, 2754, 1670, 1462, 1198, 1090 cm^{-1}.

Elemental analysis for $C_{13}H_{17}NO_2$ Calcd: C, 71.21; H, 7.81; N, 6.39.
Found: C, 71.25; H, 7.86; N, 6.33.

6.3.17. (*R,S*)-2-hydroxyphenylmethyl-4-*tert*-butyl-4,5-dihydrooxazole [(*R,S*)-203b]



$C_{14}H_{19}NO_2$. MW = 233.31 g mol^{-1}

Prepared according to GP-5, starting from (*R,S*)-**206b** (5.0 mmol, 1.40 g). Recrystallization from EtOAc gave pure (*R,S*)-**203b** (3.3 mmol, 0.769 g, 65% yield) as a colorless solid.

Mp: 123-124 °C.

Optical rotation: $[\alpha]^{20}_D$ = +1.5 (c = 0.84 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 9H), 3.75-3.83 (m, 1H), 4.11-4.23 (m, 2H), 4.49 (br s, 1H), 5.33 (s, 1H), 7.27-7.39 (m, 3H), 7.40-7.48 (m, 2H).

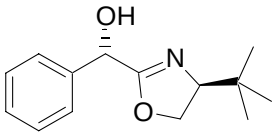
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.9, 33.8, 69.7, 70.5, 74.8, 126.6, 128.3, 128.5, 139.3, 168.4.

MS (EI, 70 eV): *m/z* = 233 $[M]^+$, 219, 177, 146, 107, 91, 77.

IR (KBr): ν = 3195, 2869, 1671, 1411, 1101, 1029 cm^{-1}.

Elemental analysis for $C_{14}H_{19}NO_2$ Calcd: C, 72.07; H, 8.21; N, 6.00.
Found: C, 71.95; H, 8.50; N, 5.99.

6.3.18. (*S,S*)-2-hydroxyphenylmethyl-4-*tert*-butyl-4,5-dihydrooxazole [(*S,S*)-203b]



$C_{14}H_{19}NO_2$. MW = 233.31 g mol^{-1}

Prepared according to GP-5, starting from (*S,S*)-**206b** (5.0 mmol, 1.31 g). Recrystallization from EtOAc gave pure (*S,S*)-**203b** (3.1 mmol, 0.718 g, 62% yield) as a colorless solid.

Mp: 104-105 °C.

Optical rotation: $[\alpha]^{20}_D = -1.7$ (c = 1.05 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 9H), 3.82 (dd, *J* = 9.9 Hz, *J* = 8.0 Hz, 1H), 4.12-4.24 (m, 3H), 5.32 (s, 1H), 7.28-7.39 (m, 3H), 7.42-7.48 (m, 2H).

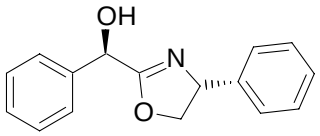
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.9, 33.8, 69.7, 70.6, 74.8, 126.6, 128.3, 128.5, 139.2, 168.3.

MS (EI, 70 eV): m/z = 234 $[M+1]^+$, 233 $[M]^+$, 177, 146, 107, 91, 77.

IR (KBr): ν = 3163, 2957, 1673, 1197, 1089 cm^{-1}.

Elemental analysis for $C_{14}H_{19}NO_2$ Calcd: C, 72.07; H, 8.21; N, 6.00.
Found: C, 71.80; H, 7.88; N, 6.00.

6.3.19. (*R,R*)-2-hydroxyphenylmethyl-4-phenyl-4,5-dihydrooxazole [(*R,R*)-203c]



$C_{16}H_{15}NO_2$. MW = 253.30 g mol^{-1}

Prepared according to GP-5, starting from (*R,R*)-**206c** (5.0 mmol, 1.48 g). Recrystallization from EtOAc gave pure (*R,R*)-**203c** (3.9 mmol, 0.997 g, 79% yield) as a colorless crystalline solid.

Mp: 108-109 °C.

Optical rotation: $[\alpha]^{20}_D = -29.1$ (c = 1.01 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.20 (t, *J* = 8.7 Hz, 1H), 4.60 (dd, *J* = 10.0 Hz, *J* = 8.7 Hz, 1H), 4.95 (br s, 1H), 5.09-5.17 (m, 1H), 5.14 (s, 1H), 7.21-7.27 (m, 2H), 7.29-7.41 (m, 6H), 7.42-7.47 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 68.6, 69.4, 75.9, 126.5, 126.6, 127.7, 128.2, 128.3, 128.6, 138.8, 141.3, 169.8.

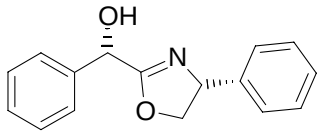
MS (EI, 70 eV): *m/z* = 255 $[M]^+$, 254, 236, 176, 120, 91, 77.

IR (KBr): ν = 3390, 3138, 2967, 2871, 1664, 1454, 1177, 1080 cm^{-1}.

Elemental analysis for $C_{16}H_{15}NO_2$ Calcd: C, 75.87; H, 5.97; N, 5.53.

Found: C, 75.67; H, 6.07; N, 5.48.

6.3.20. (*S,R*)-2-hydroxyphenylmethyl-4-phenyl-4,5-dihydrooxazole [(*S,R*)-203c]



$C_{16}H_{15}NO_2$. MW = 253.30 g mol^{-1}

Prepared according to GP-5, starting from (*S,R*)-**206c** (5.0 mmol, 1.48 g). Recrystallization from EtOAc gave pure (*S,R*)-**203c** (4.7 mmol, 1.11 g, 94 % yield) as a colorless crystalline solid.

Mp: 124-125 °C.

Optical rotation: $[\alpha]^{20}_D$ = + 175.3 (c = 0.99 in $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.09 (t, *J* = 8.4 Hz, 1H), 4.25 (br s, 1H), 4.68 (dd, *J* = 10.0 Hz, *J* = 8.4 Hz, 1H), 5.15-5.25 (m, 1H), 5.35 (s, 1H), 7.12-7.18 (m, 2H), 7.23-7.40 (m, 6H), 7.43-7.50 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 68.7, 69.9, 74.0, 126.5, 126.7, 127.8, 128.5, 128.6, 128.8, 139.2, 141.6, 169.9.

MS (EI, 70 eV): m/z = 255 $[M+1]^+$, 254 $[M]^+$, 236, 208, 176, 120, 107, 91, 77.

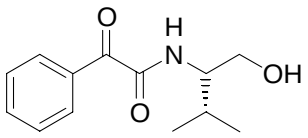
IR (KBr): ν = 3164, 2970, 2905, 1651, 1455, 1241, 1056 cm^{-1}.

Elemental analysis for $C_{16}H_{15}NO_2$ Calcd: C, 75.87; H, 5.97; N, 5.53.

Found: C, 75.70; H, 6.03; N, 5.51.

6.4. Synthesis of Hydroxy Oxazolines 212a-k

6.4.1. (*S*)-*N*-(1-*iso*-propyl-2-hydroxyethyl)benzoylformamide [(*S*)-215a]



$C_{13}H_{17}NO_3$. MW = 235.28 g mol^{-1}

Prepared according to GP-6, starting from (*S*)-valinol (20.0 mmol, 2.06 g). Purification by flash column chromatography (PE / EtOAc 1:1) afforded pure (*S*)-**215a** (12.6 mmol, 2.97 g, 63% yield) as a colorless oil.

Optical rotation: $[\alpha]^{20}_D = -13.7$ (c = 0.18, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.99 (sept, *J* = 6.8 Hz, 1H), 2.78 (br s, 1H), 3.73-3.78 (m, 2H), 3.79-3.89 (m, 1H), 7.29-7.39 (m, 1H), 7.41-7.50 (m, 2H), 7.57-7.65 (m, 1H), 8.25-8.28 (m, 2H).

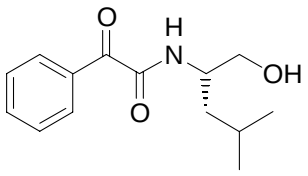
^{13}C-NMR (75 MHz, CDCl3): δ = 18.8, 19.6, 29.1, 57.2, 63.2, 128.5, 131.2, 133.3, 134.5, 162.6, 188.1.

MS (EI, 70 eV): *m/z* = 235 $[M]^+$, 204, 130, 105, 87, 77, 69.

IR (neat): ν = 3358, 2964, 2878, 1663, 1525, 1270, 1219 cm^{-1}.

HRMS (EI): *m/z* calcd for $C_{13}H_{17}NO_3$: 235.1208; found 235.1208.

6.4.2. (*S*)-*N*-(1-*sec*-butyl-2-hydroxyethyl)benzoylformamide [(*S*)-215b]



$C_{14}H_{19}NO_3$. MW = 249.31 g mol^{-1}

Prepared according to GP-6, starting from (*S*)-leucinol (20.0 mmol, 2.34 g). Purification by flash column chromatography (PE / EtOAc 1:1) afforded pure (*S*)-**215b** (12.2 mmol, 3.03 g, 61% yield) as a colorless oil.

Optical rotation: $[\alpha]^{20}_{D} = -19.1$ (c = 0.50, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.94 (s, 3H), 0.96 (s, 3H), 1.38–1.47 (m, 1H), 1.48–1.56 (m, 1H), 1.67 (dsept, *J* = 6.4 Hz, *J* = 2.1 Hz, 1H), 2.80 (br s, 1H), 3.63 (dd, *J* = 9.3 Hz, *J* = 5.5 Hz, 1H), 3.76 (dd, *J* = 9.3 Hz, *J* = 3.6 Hz, 1H), 4.11–4.21 (m, 1H), 7.22–7.27 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.4 Hz, 2H), 8.28 (d, *J* = 8.4 Hz, 2H).

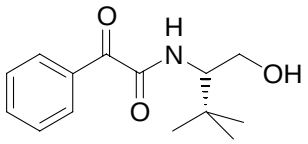
^{13}C-NMR (100 MHz, CDCl3): δ = 22.3, 23.2, 25.1, 40.1, 50.2, 65.5, 128.5, 131.1, 133.3, 134.4, 162.2, 187.9.

MS (EI, 70 eV): *m/z* = 249 $[M]^+$, 218, 144, 105, 83, 77, 55.

IR (neat): ν = 3339, 2956, 2872, 1662, 1529, 1251, 1221 cm^{-1}.

HRMS (EI): *m/z* calcd for $C_{14}H_{19}NO_3$: 249.1365; found 249.1364.

6.4.3. (*S*)-*N*-(1-*tert*-butyl-2-hydroxyethyl)benzoylformamide [(*S*)-215c]



$C_{14}H_{19}NO_3$. MW = 249.31 g mol^{-1}

Prepared according to GP-6, starting from (*S*)-*tert*-leucinol (20.0 mmol, 2.34 g). Purification by flash column chromatography (PE / EtOAc 1:1) afforded pure (*S*)-**215c** (12.0 mmol, 2.78 g, 60% yield) as a colorless oil.

Optical rotation: $[\alpha]^{20}_{D} = -60.2$ (c = 1.03, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.00 (s, 9H), 2.78 (br s, 1H), 3.60-3.70 (m, 1H), 3.86-3.97 (m, 2H), 7.28-7.38 (m, 1H), 7.40-7.48 (m, 2H), 7.55-7.64 (m, 1H), 8.24-8.28 (m, 2H).

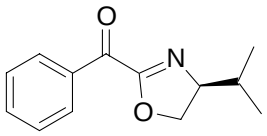
^{13}C-NMR (75 MHz, CDCl3): δ = 26.9, 33.9, 59.9, 62.3, 128.5, 131.2, 133.3, 134.5, 163.0, 188.2.

MS (EI, 70 eV): *m/z* = 249 $[M]^+$, 218, 164, 144, 105, 86, 77, 69, 57.

IR (neat): ν = 3257, 3170, 3095, 2958, 1661, 1325, 1234, 1064 cm^{-1}.

HRMS (EI): *m/z* calcd for $C_9H_{10}NO_2$ [$C_{14}H_{19}NO_3 - C_5H_9O$]: 164.0712; found: 164.0711.

6.4.4. (*S*)-2-benzoyl-4-*iso*-propyl-4,5-dihydrooxazole [(*S*)-216a]



$C_{13}H_{15}NO_2$. MW = 217.26 g mol^{-1}

Prepared according to GP-7, starting from (*S*)-**215a** (2.0 mmol, 0.471 g). Purification by flash column chromatography (PE / EtOAc 3:1) afforded pure (*S*)-**216a** (1.24 mmol, 0.270 g, 62% yield) as a colorless oil.

Optical rotation: $[\alpha]^{20}_D$ = +112.7 (c = 0.97, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.9 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 1H), 1.85–1.99 (m, 1H), 4.17 (t, *J* = 8.3 Hz, 1H), 4.21–4.30 (m, 1H), 4.46 (dd, *J* = 9.6 Hz, *J* = 8.3 Hz, 1H), 7.45–7.52 (m, 2H), 7.58–7.65 (m, 1H), 8.27–8.32 (m, 2H).

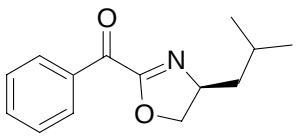
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.6, 19.1, 32.8, 70.2, 73.7, 128.5, 130.7, 134.2, 134.9, 159.1, 183.7.

MS (EI, 70 eV): *m/z* = 217 $[M]^+$, 173, 144, 104, 77, 70, 55.

IR (neat): ν = 2964, 1739, 1607, 1194, 1174 cm^{-1};

HRMS (EI): *m/z* calcd for $C_{13}H_{15}NO_2$: 217.1103; found 217.1103.

6.4.5. (*S*)-2-benzoyl-4-*sec*-butyl-4,5-dihydrooxazole [(*S*)-216b]



$C_{14}H_{17}NO_2$. MW = 231.29 g mol^{-1}

Prepared according to GP-7, starting from (*S*)-**215b** (2.0 mmol, 0.499 g). Purification by flash column chromatography (PE / EtOAc 4:1) afforded pure (*S*)-**216b** (1.42 mmol, 0.329 g, 71% yield) as a colorless oil.

Optical rotation: $[\alpha]^{20}_D$ = −31.0 (c = 1.06, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H), 1.40–1.52 (m, 1H), 1.70–1.92 (m, 2H), 4.03 (t, *J* = 7.3 Hz, 1H), 4.40–4.58 (m, 2H), 7.43–7.52 (m, 2H), 7.57–7.66 (m, 1H), 8.25–8.32 (m, 2H).

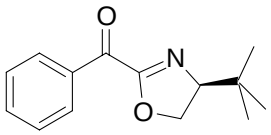
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.7, 22.8, 25.6, 45.2, 66.3, 73.0, 128.5, 130.7, 134.2, 134.9, 159.1, 183.7.

MS (EI, 70 eV): *m/z* = 231 $[M]^+$, 174, 105, 77, 51.

IR (neat): ν = 3257, 3170, 2958, 1661, 1326, 1233, 1064 cm^{-1}.

HRMS (EI): *m/z* calcd for $C_{14}H_{17}NO_2$: 231.1259; found: 231.1258.

6.4.6. (*S*)-2-benzoyl-4-*tert*-butyl-4,5-dihydrooxazole [(*S*)-216c]



$C_{14}H_{17}NO_2$. MW = 231.29 g mol^{-1}

Prepared according to GP-7, starting from (*S*)-**215c** (2.0 mmol, 0.499 g). Purification by flash column chromatography (PE / EtOAc 3:1) afforded pure (*S*)-**216c** (1.36 mmol, 0.315 g, 68% yield) as a colorless oil.

Optical rotation: $[\alpha]^{20}_D$ = +219.8 (c = 0.80, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.01 (s, 9H), 4.16–4.29 (m, 2H), 4.34–4.46 (m, 1H), 7.43–7.53 (m, 2H), 7.58–7.66 (m, 1H), 8.28–8.35 (m, 2H).

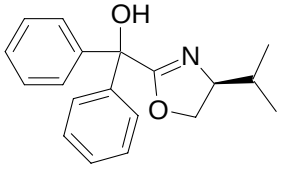
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 26.1, 34.0, 68.7, 77.4, 128.5, 130.8, 134.2, 135.0, 159.2, 183.7.

MS (EI, 70 eV): *m/z* = 231 $[M]^+$, 175, 158, 130, 104, 84, 77, 69, 57.

IR (neat): ν = 2960, 2907, 1741, 1608, 1476, 1176, 1054 cm^{-1}.

HRMS (EI): *m/z* calcd for $C_{14}H_{17}NO_2$: 231.1259; found 231.1260.

6.4.7. (*S*)-2-(diphenylhydroxy)methyl-4-*iso*-propyl-4,5-dihydrooxazole [(*S*)-212a]



$C_{19}H_{21}NO_2$. MW = 295.38 g mol^{-1}

Prepared according to GP-8, starting from (*S*)-**216a** (1.0 mmol, 0.217 g). Purification by recrystallization from *n*-hexane / CH_2Cl_2 afforded pure (*S*)-**212a** (0.41 mmol, 0.120 g, 41% yield) as colorless crystals.

Mp: 91–92 °C.

Optical rotation: $[\alpha]^{20}_D = -58.9$ (c = 0.95, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 1.68–1.81 (m, 1H), 3.80–3.90 (m, 1H), 4.13–4.20 (m, 1H), 4.38–4.47 (m, 1H), 5.00 (br s, 1H), 7.25–7.37 (m, 6H), 7.40–7.48 (m, 4H).

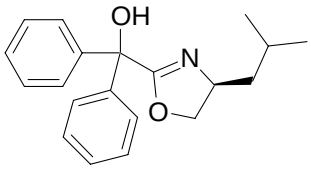
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.4, 18.9, 32.8, 71.0, 73.0, 77.4, 127.3, 127.4, 127.8, 128.0, 143.0, 143.1, 170.2.

MS (EI, 70 eV): *m/z* = 295 $[M]^+$, 222, 218, 165, 105, 77.

IR (KBr): ν = 3093, 2959, 2893, 2870, 1659, 1451, 1228, 1181 cm^{-1}.

Elemental analysis for $C_{19}H_{21}NO_2$ Calcd: C, 77.26; H, 7.17; N, 4.74.
Found: C, 77.42; H, 7.34; N, 4.52.

6.4.8. (*S*)-2-(diphenylhydroxy)methyl-4-*sec*-butyl-4,5-dihydrooxazole [(*S*)-212b]



$C_{20}H_{23}NO_2$. MW = 309.40 g mol^{-1}

Prepared according to GP-8, starting from (*S*)-**216b** (1.0 mmol, 0.231 g). Purification by flash column chromatography (PE / EtOAc 4:1) afforded pure (*S*)-**212b** (0.47 mmol, 0.144 g, 47% yield) as a colorless oil.

Optical rotation: $[\alpha]^{20}_D = -57.2$ (c = 0.67, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 1.24–1.35 (m, 1H), 1.50–1.66 (m, 1H), 1.68–1.83 (m, 1H), 4.02 (t, *J* = 7.9 Hz, 1H), 4.06–4.19 (m, 1H), 4.49 (dd, *J* = 8.9 Hz, *J* = 7.9 Hz, 1H), 4.90 (s, 1H), 7.25–7.37 (m, 6H), 7.38–7.49 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.7, 22.8, 25.4, 45.3, 63.8, 75.6, 77.3, 127.3, 127.4, 127.6, 127.9, 128.0, 128.1, 142.9, 143.1, 170.1.

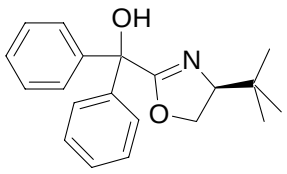
MS (EI, 70 eV): *m/z* = 309 $[M]^+$, 232, 183, 165, 105, 77.

IR (neat): ν = 3065, 2953, 2892, 2792, 1655, 1450, 1224, 1179 cm^{-1}.

Elemental analysis for $C_{20}H_{23}NO_2$ Calcd: C, 77.64; H, 7.49; N, 4.53.

Found: C, 77.60; H, 7.44; N, 4.20.

6.4.9. (*S*)-2-(diphenylhydroxy)methyl-4-*tert*-butyl-4,5-dihydrooxazole [(*S*)-212c]



$C_{20}H_{23}NO_2$. MW = 309.40 g mol^{-1}

Prepared according to GP-8, starting from (*S*)-**216c** (1.0 mmol, 0.231 g). Purification by recrystallization from *n*-hexane afforded pure (*S*)-**212c** (0.54 mmol, 0.166 g, 54%) as colorless needles.

Mp: 130–131 °C.

Optical rotation: $[\alpha]^{20}_D = -59.7$ (c = 0.87, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 9H), 3.89 (dd, *J* = 10.1 Hz, *J* = 8.4 Hz, 1H), 4.28 (t, *J* = 8.5 Hz, 1H), 4.36–4.44 (m, 1H), 4.98 (br s, 1H), 7.25–7.36 (m, 6H), 7.38–7.49 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.0, 34.0, 71.7, 74.4, 77.1, 127.3, 127.4, 127.8, 127.8, 128.0, 128.0, 142.7, 143.0, 170.6.

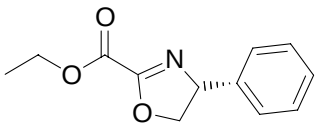
MS (EI, 70 eV): *m/z* = 309 $[M]^+$, 232, 222, 183, 105, 77.

IR (KBr): ν = 3062, 2957, 2895, 2868, 1657, 1451, 1227, 1181, 1060 cm^{-1}.

Elemental analysis for $C_{20}H_{23}NO_2$ Calcd: C, 77.64; H, 7.49; N, 4.53.

Found: C, 77.89; H, 7.71; N, 4.21.

6.4.10. ethyl (*R*)-4-phenyloxazoline-2-carboxylate [(*R*)-218a]



$C_{12}H_{13}NO_3$. MW = 219.24 g mol^{-1}

Prepared according to GP-9, starting from (*R*)-phenylglycinol (17.1 mmol, 2.35 g). Purification by flash column chromatography (PE / EtOAc 4:3) afforded pure (*R*)-**218a** (5.2 mmol, 1.141 g, 34% yield) as a yellow oil.

Optical rotation: $[\alpha]^{20}_D = -38.3$ (c = 0.48, $CHCl_3$).

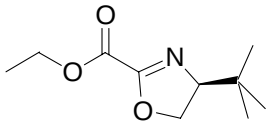
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 7.1 Hz, 3H), 4.32–4.38 (t, *J* = 8.9 Hz, 1H), 4.36–4.46 (m, 2H), 4.83 (dd, *J* = 10.6 Hz, *J* = 8.9 Hz, 1H), 5.41 (dd, *J* = 10.5 Hz, *J* = 9.0 Hz, 1H), 7.23–7.29 (m, 3H), 7.29–7.41 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.0, 63.0, 70.3, 75.4, 126.6, 127.9, 128.7, 140.1, 156.5, 157.3.

MS (EI, 70 eV): *m/z* = 219 $[M]^+$, 189, 144, 117, 90, 77.

IR (neat): ν = 3358, 1745, 1697, 1529, 1306, 1188 cm^{-1}.

6.4.11. ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate [(*S*)-218b]



$C_{10}H_{17}NO_3$. MW = 199.25 g mol^{-1}

Prepared according to GP-9, starting from (*S*)-*tert*-leucinol (17.1 mmol, 2.00 g). Purification by flash column chromatography (PE / EtOAc 3:2) afforded pure (*S*)-**218b** (5.3 mmol, 1.050 g, 36% yield) as a colorless oil.

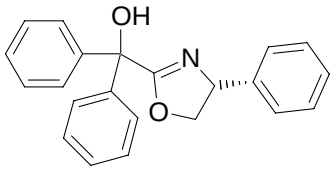
Optical rotation: $[\alpha]^{20}_D = -74.7$ (c = 1.02, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.95 (s, 9H), 1.39 (t, *J* = 7.3 Hz, 3H), 4.09 (dd, *J* = 10.6 Hz, *J* = 8.8 Hz, 1H), 4.25 (t, *J* = 8.8 Hz, 1H), 4.34–4.42 (m, 2H), 4.40 (dd, *J* = 10.6 Hz, *J* = 1.9 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.2, 26.0, 33.9, 62.9, 69.8, 76.7, 155.4, 157.6.

All the other data are in agreement with those previously reported in the literature.

6.4.12. (*R*)-2-(diphenylhydroxy)methyl-4-phenyl-4,5-dihydrooxazole [(*R*)-212d]



$C_{22}H_{19}NO_2$. MW = 329.39 g mol^{-1}

Prepared according to GP-10, starting from ethyl (*R*)-4-phenyloxazoline-2-carboxylate [(*R*)-**218a**] (1.0 mmol, 0.219 g) and PhMgCl (2.0 M solution in THF, 3.0 mmol, 1.5 mL, 3.0 equiv). Purification by flash column chromatography (PE / EtOAc 7:2) afforded pure (*R*)-**212d** (0.86 mmol, 0.284 g, 86% yield) as a colorless solid.

Mp: 84–85 °C.

Optical rotation: $[\alpha]^{20}_D$ = +113.9 (c = 0.99, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.26–4.33 (m, 1H), 4.77–4.86 (m, 1H), 4.88 (s, 1H), 5.16–5.25 (m, 1H), 7.16–7.22 (m, 2H), 7.25–7.40 (m, 9H), 7.46–7.54 (m, 4H).

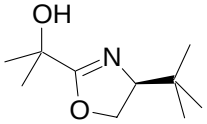
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 68.3, 77.1, 77.4, 126.3, 127.1, 127.2, 127.6, 127.81, 127.84, 127.92, 127.94, 128.6,141.2, 142.4, 142.6, 171.5.

MS (EI, 70 eV): *m/z* = 329 $[M]^+$, 252, 183, 105, 77.

IR (KBr): ν = 3062, 3027, 1736, 1655, 1494, 1450, 1220, 1172, 1057 cm^{-1}.

Elemental analysis for $C_{22}H_{19}NO_2$ Calcd: C, 80.22; H, 5.81; N, 4.25.
Found: C, 80.16; H, 5.55; N, 3.98.

6.4.13. (*S*)-2-(dimethylhydroxy)methyl-4-*tert*-butyl-4,5-dihydrooxazole [(*S*)-212e]



$C_{10}H_{19}NO_2$. MW = 185.26 g mol^{-1}

Prepared according to GP-10, starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate [(*S*)-**218b**] (1.0 mmol, 0.199 g) and MeMgCl (3.0 M solution in Et_2O, 3.0 mmol, 1.0 mL, 3.0 equiv).

Purification by recrystallization from *n*-hexane afforded pure (*S*)-**212e** (0.60 mmol, 0.110 g, 60% yield) as a colorless solid.

Mp: 86–87 °C.

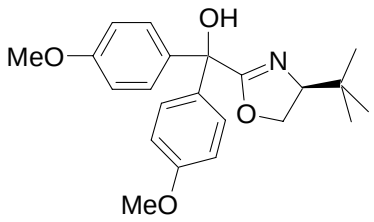
Optical rotation: $[\alpha]^{20}_{D} = -28.9$ (c = 1.02, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.90 (s, 9H), 1.44 (s, 6H), 3.40 (s, 1H), 3.86 (dd, *J* = 9.9 Hz, *J* = 7.4 Hz, 1H), 4.15–4.35 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.6, 27.7, 28.1, 33.7, 68.8, 70.6, 75.0, 172.4.

All the other data are in agreement with those previously reported in the literature.[299a,b]

6.4.14. (*S*)-2-[di-(4'-methoxyphenyl)hydroxy]methyl-4-*tert*-butyl-4,5-dihydrooxazole [(S)-212f]



$C_{22}H_{27}NO_4$. MW = 369.45 g mol^{-1}

Prepared according to GP-10, starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate [(*S*)-**218b**] (1.0 mmol, 0.199 g) and [4-(MeO)Ph]MgBr (0.5 M solution in THF, 3.0 mmol, 6.0 mL, 3.0 equiv). Purification by double recrystallization from Et_2O afforded pure (*S*)-**212f** (0.86 mmol, 0.320 g, 86% yield) as a light brown solid.

Mp: 136–137 °C.

Optical rotation: $[\alpha]^{20}_{D} = -48.3$ (c = 0.78, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 9H), 3.79 (s, 3H), 3.80 (s, 3H), 3.90 (dd, *J* = 10.0 Hz, *J* = 8.5 Hz, 1H), 4.27 (t, *J* = 8.5 Hz, 1H), 4.40 (dd, *J* = 10.0 Hz, *J* = 8.8 Hz, 1H), 4.90 (br s, 1H), 6.80–6.89 (m, 4H), 7.29–7.41 (m, 4H).

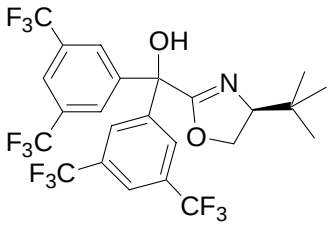
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.0, 33.9, 55.35, 55.37, 71.7, 74.4, 77.1, 113.29, 113.31, 128.5, 128.6, 135.1, 135.3, 159.0, 159.1, 171.0.

MS (EI, 70 eV): *m/z* = 369 $[M]^+$, 262, 151, 135, 107, 77.

IR (KBr): ν = 3175, 2956, 2898, 1650, 1508, 1466, 1247, 1175, 1075 cm^{-1}.

Elemental analysis for $C_{22}H_{27}NO_4$ Calcd: C, 71.52; H, 7.37; N, 3.79.
Found: C, 71.22; H, 7.09; N, 3.54.

6.4.15. (*S*)-2-[di-(3',5'-di(trifluoromethyl)phenyl)hydroxy]methyl-4-*tert*-butyl-4,5-dihydrooxazole [(*S*)-212g]



$C_{24}H_{19}F_{12}NO_2$. MW = 581.39 g mol^{-1}

Prepared according to GP-10, starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate [(*S*)-**218b**] (1.0 mmol, 0.199 g) and 3,5-$(CF_3)_2$PhMgBr (approx. 1.0 M solution in THF, 5.0 mmol, 5.0 mL, 5.0 equiv, prepared according to the literature[324]). Purification by flash column chromatography (PE / EtOAc 4:1) afforded pure (*S*)-**212g** (0.88 mmol, 0.510 g, 88% yield) as a white solid. An analytical sample was obtained by recrystallization from *n*-hexane.

Mp: 121–122 °C.

Optical rotation: $[\alpha]^{20}_D = -28.5$ (c = 1.06, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 9H), 3.92–4.02 (m, 1H), 4.36–4.44 (m, 1H), 4.46–4.54 (m, 1H), 5.27 (br s, 1H), 7.86–7.92 (m, 4H), 7.97 (s, 2H).

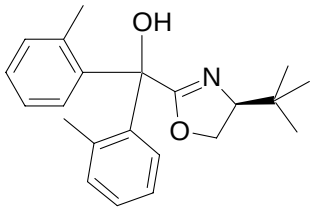
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.7, 34.0, 72.6, 74.6, 76.0, 122.6, 122.6, 123.0 (q, *J* = 70.8 Hz), 123.1 (q, *J* = 70.9 Hz), 127.2, 127.4, 131.8 (q, *J* = 33.0 Hz), 131.9 (q, *J* = 33.4 Hz), 143.6, 144.4, 167.5.

MS (EI, 70 eV): *m/z* = 581 $[M]^+$, 562, 525, 455, 241, 213, 163, 70, 57.

IR (KBr): ν = 3420, 2968, 1660, 1372, 1283, 1176, 1137 cm^{-1}.

Elemental analysis for $C_{24}H_{19}F_{12}NO_2$ Calcd: C, 49.58; H, 3.29; N, 2.41.
Found: C, 49.97; H, 3.49; N, 2.40.

6.4.16. (*S*)-2-[di-(2'-methylphenyl)hydroxy]methyl-4-*tert*-butyl-4,5-dihydrooxazole [(*S*)-212h]



$C_{22}H_{27}NO_2$. MW = 337.46 g mol^{-1}

Prepared according to GP-10, starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate [(*S*)-**218b**] (1.0 mmol, 0.199 g) and 2-MePhMgCl (1.0 M solution in THF, 3.0 mmol, 3.0 mL, 3.0 equiv). Purification by recrystallization from *n*-hexane afforded pure **212h** (0.79 mmol, 0.226 g, 79% yield) as a white solid.

Mp: 188–189 °C.

Optical rotation: $[\alpha]^{20}_D = -52.3$ (c = 0.96, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 9H), 2.13 (s, 3H), 2.15 (s, 3H), 3.87–3.99 (m, 1H), 4.21–4.32 (m, 1H), 4.38–4.49 (m, 1H), 4.94 (br s, 1H), 7.06–7.30 (m, 8H).

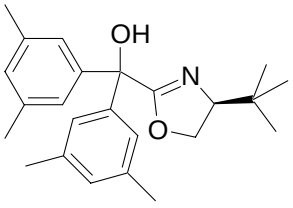
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.5, 21.7, 26.1, 33.8, 71.6, 74.5, 79.4, 125.4, 125.5, 127.4, 127.6, 127.8, 127.9, 132.3, 132.3, 137.9, 137.9, 140.7, 140.8, 171.4.

MS (EI, 70 eV): *m/z* = 337 $[M]^+$, 304, 231, 192, 128, 119, 91, 65, 57.

IR (KBr): ν = 3167, 2957, 1654, 1483, 1461, 1218, 1049 cm^{-1}.

Elemental analysis for $C_{22}H_{27}NO_2$ Calcd: C, 78.30; H, 8.06; N, 4.15.
Found: C, 77.92; H, 8.22; N, 3.91.

6.4.17. (*S*)-2-[di-(3',5'-dimethylphenyl)hydroxy]methyl-4-*tert*-butyl-4,5-dihydrooxazole [(S)-212i]



$C_{24}H_{31}NO_2$. MW = 365.51 g mol^{-1}

Prepared according to GP-10, starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate [(*S*)-**218b**] (1.0 mmol, 0.199 g) and 3,5-$(Me)_2$PhMgBr (approx. 1.0 M solution in THF, 5.0 mmol, 5.0 mL, 5.0 equiv, prepared according to the literature[325]). Purification by recrystallization from PE afforded pure (*S*)-**212i** (0.70 mmol, 0.256 g, 70% yield) as a white solid.

Mp: 115–116 °C.

Optical rotation: $[\alpha]^{20}_D = -33.8$ (c = 1.06, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 9H), 2.27 (s, 6H), 2.29 (s, 6H), 3.89 (dd, *J* = 10.0 Hz, *J* = 8.3 Hz, 1H), 4.23–4.34 (m, 1H), 4.35–4.46 (m, 1H), 4.81 (br s, 1H), 6.84–7.13 (m, 6H).

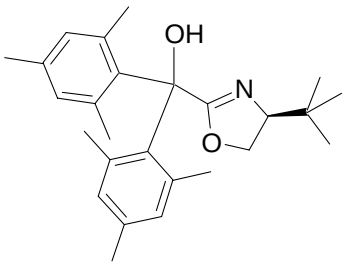
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.4, 21.5, 25.9, 33.9, 71.6, 74.4, 77.4, 125.18, 125.21, 129.5, 129.5, 137.3, 137.4, 142.5, 143.1, 170.9.

MS (EI, 70 eV): *m/z* = 365 $[M]^+$, 347, 278, 260, 133, 105, 77, 57.

IR (KBr): ν = 3152, 2957, 2867, 1660, 1602, 1467, 1218, 1151, 1100, 1037 cm^{-1}.

Elemental analysis for $C_{24}H_{31}NO_2$ Calcd: C, 78.87; H, 8.55; N, 3.83.
Found: C, 78.66; H, 8.83; N, 3.58.

6.4.18. (*S*)-2-[di-(2',4',6'-trimethylphenyl)hydroxy]methyl-4-*tert*-butyl-4,5-dihydrooxazole [(*S*)-212j]



$C_{26}H_{35}NO_2$. MW = 393.56 g mol^{-1}

Prepared according to GP-10, starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate [(*S*)-**218b**] (1.0 mmol, 0.199 g) and 2,4,6-$(Me)_3$PhMgBr (1.0 M solution in THF, 3.0 mmol, 3.0 mL, 3.0 equiv). Purification by flash column chromatography (PE / EtOAc 13:1) afforded pure (*S*)-**212j** (0.57 mmol, 0.223 g, 57% yield) as a yellow oil.

Optical rotation: $[\alpha]^{20}_D = -157.7$ (c = 1.02, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 9H), 2.10 (s, 6H), 2.12 (s, 6H), 2.20 (s, 3H), 2.21 (s, 3H), 3.84 (t, *J* = 10.0 Hz, 1H), 4.15 (t, *J* = 9.1 Hz, 1H), 4.40 (dd, *J* = 10.0 Hz, *J* = 8.9 Hz, 1H), 5.05 (br s, 1H), 6.70 (s, 2H), 6.73 (s, 2H).

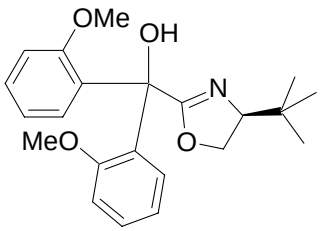
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.7, 22.0, 23.5, 26.3, 27.1 33.8, 71.6, 74.4, 79.7, 131.4, 131.5, 136.0, 136.1, 136.2, 136.9, 138.3, 139.8, 172.8.

MS (EI, 70 eV): *m/z* = 393 $[M]^+$, 360, 259, 202, 147, 119, 91, 57.

IR ($CHCl_3$): ν = 3429, 2958, 2870, 1646, 1477, 1382, 1220, 1057 cm^{-1}.

Elemental analysis for $C_{26}H_{35}NO_2$ Calcd: C, 79.35; H, 8.96; N, 3.56.
Found: C, 79.65; H, 9.24; N, 3.35.

6.4.19. (*S*)-2-[di-(2'-methoxyphenyl)hydroxy]methyl-4-*tert*-butyl-4,5-dihydrooxazole [(*S*)-212k]



$C_{22}H_{27}NO_4$. MW = 369.45 g mol^{-1}

Prepared according to GP-10, starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate [(*S*)-**218b**] (1.0 mmol, 0.199 g) and 2-MeO-PhMgBr (1.0 M solution in THF, 3.0 mmol, 3.0 mL, 3.0 equiv). Purification by flash column chromatography (PE / EtOAc 4:1, then 2:1) afforded pure (*S*)-**212k** (0.64 mmol, 0.235 g, 64% yield) as a pale yellow oil.

Optical rotation: $[\alpha]^{20}_D = -14.7$ (c = 0.96, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 9H), 3.74 (s, 3H), 3.81 (s, 3H), 3.98 (dd, *J* = 10.2 Hz, *J* = 7.8 Hz, 1H), 4.14–4.32 (m, 2H), 5.52 (br s, 1H), 6.83–7.05 (m, 6H), 7.27–7.39 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 26.0, 33.9, 55.6, 55.7, 69.8, 75.4, 84.1, 111.4, 111.6, 120.8, 120.8, 128.6, 129.1, 129.3, 129.3, 130.0, 130.2, 157.3, 157.5, 171.2.

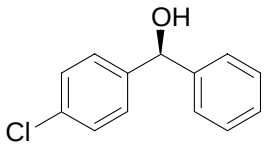
MS (EI, 70 eV): *m/z* = 369 $[M]^+$, 338, 262, 238, 135, 121, 91, 77.

IR ($CHCl_3$): ν = 3495, 2956, 1662, 1488, 1464, 1243, 1030 cm^{-1}.

Elemental analysis for $C_{22}H_{27}NO_4$ Calcd: C, 71.52; H, 7.37; N, 3.79.
Found: C, 71.60; H, 7.44; N, 3.63.

6.5. Phenyl Transfer Reaction to Aldehydes 59a-k

6.5.1. (*S*)-(4-chlorophenyl)phenylmethanol [(*S*)-60a]



$C_{13}H_{11}OCl$. MW = 218.68 g mol^{-1}

Obtained from 4-chlorobenzaldehyde **59a** (0.25 mmol, 0.035 g), according to GP-11, using ligand (*S*)-**212h**. Purification by flash column chromatography (*n*-pentane / Et_2O 85:15) furnished pure (*S*)-**60a** (0.20 mmol, 0.044 g, 80% yield) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.50 (br s, 1H), 5.78 (s, 1H), 7.23–7.45 (m, 9H).

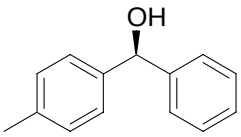
^{13}C-NMR (75MHz, $CDCl_3$): δ =75.7, 126.6, 127.9, 127.9, 128.7, 128.8, 133.3, 142.3, 143.5.

HPLC separation conditions: Chiralcel OB-H, 230 nm, heptane / *i*-PrOH 90:10, 0.5 mL/min; ret. time = 24.1 min (*R*, minor), 30.4 min (*S*, major).

Enantiomeric excess: ee = 71% (*S*).

All the other analytical data are in agreement with those reported in the literature.[114]

6.5.2. (*S*)-(4-methylphenyl)phenylmethanol [(*S*)-60g]



$C_{14}H_{14}O$. MW = 198.26 g mol^{-1}

Obtained from 4-methylbenzaldehyde **59g** (0.25 mmol, 0.030 g), according to GP-11, using ligand (*S*)-**212h**. Purification by flash column chromatography (*n*-pentane / Et_2O 8:2) furnished pure (*S*)-**60g** (0.22 mmol, 0.044 g, 89% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.30 (br s, 1H), 2.32 (s, 3H), 5.79 (s, 1H), 7.08–7.39 (m, 9H).

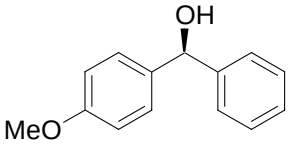
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.1, 76.0, 126.2, 126.3, 127.2, 128.2, 129.0, 137.0, 140.8, 143.8.

HPLC separation conditions: Chiralcel OD, 230 nm, heptane / *i*-PrOH 98:2, 0.9 mL/min; ret. time = 27.2 min (*S*, major), 30.8 min (*R*, minor).

Enantiomeric excess: ee = 77% (*S*).

All the other analytical data are in agreement with those reported in the literature.[114]

6.5.3. (*S*)-(4-methoxyphenyl)phenylmethanol [(*S*)-60b]



$C_{14}H_{14}O_2$. MW = 214.26 g mol^{-1}

Obtained from 4-methoxybenzaldehyde **59b** (0.25 mmol, 0.034 g), according to GP-11, using ligand (*S*)-**212h**. Purification by flash column chromatography (*n*-pentane / Et_2O 85:15) furnished pure (*S*)-**60b** (0.15 mmol, 0.032 g, 60% yield) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.35 (br s, 1H), 3.76 (s, 3H), 5.77 (s, 1H), 6.81–6.88 (m, 2H), 7.21–7.38 (m, 7H).

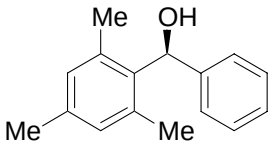
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 55.4, 75.9, 113.9, 126.4, 127.3, 127.9, 128.4, 136.2, 144.0, 159.0.

HPLC separation conditions: Chiralcel OJ, 230 nm, heptane / *i*-PrOH 90:10, 1.0 mL/min; ret. time = 30.6 min (*R*, minor), 33.7 min (*S*, major).

Enantiomeric excess: ee = 81% (*S*).

All the other analytical data are in agreement with those reported in the literature.[114]

6.5.4. (*S*)-(2,4,6-trimethylphenyl)phenylmethanol [(*S*)-60k]



$C_{16}H_{18}O$. MW = 226.32 g mol^{-1}

Obtained from 2,4,6-trimethylbenzaldehyde **59k** (0.25 mmol, 0.037 g), according to GP-11, using ligand (*S*)-**212h**. Purification by flash column chromatography (*n*-pentane / Et_2O 8:2) furnished pure (*S*)-**60k** (0.08 mmol, 0.019 g, 33% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.10 (br s, 1H), 2.23 (s, 6H), 2.27 (s, 3H), 6.33 (s, 1H), 6.85 (s, 2H), 7.20-7.35 (m, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.7, 21.0, 71.3, 125.5, 126.8, 128.4, 130.3, 136.7, 137.4, 143.2.

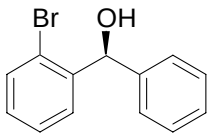
HPLC separation conditions: Chiralcel OD, 230 nm, heptane / *i*-PrOH 95:5, 0.7 mL/min; ret. time = 12.4 min (*R*, minor), 14.1 min (*S*, major).

Enantiomeric excess: ee = 75% (*S*).

Note: the retention times varied slightly in comparison with those reported in the literature,[114] *and therefore a perfect separation could not be obtained.*

All the other analytical data are in agreement with those reported in the literature.[114]

6.5.5. (*S*)-(2-bromophenyl)phenylmethanol [(*S*)-60d]



$C_{13}H_{11}OBr$. MW = 263.13 g mol^{-1}

Obtained from 2-bromobenzaldehyde **59d** (0.25 mmol, 0.046 g), according to GP-11, using ligand (*S*)-**212h**. Purification by flash column chromatography (*n*-pentane / Et_2O 8:2) furnished pure (*S*)-**60d** (0.21 mmol, 0.056 g, 85% yield) as a yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.81 (br s, 1H), 6.18 (s, 1H), 7.19–7.47 (m, 7H), 7.50–7.60 (m, 2H).

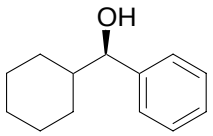
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 74.8, 122.8, 127.1, 127.8, 128.5, 128.6 129.1, 129.6, 132.8, 142.2, 142.6.

HPLC separation conditions: Chiralcel OD, 230 nm, heptane / *i*-PrOH 90:10, 0.8 mL/min; ret. time = 10.3 min (*R*, minor), 13.2 min (*S*, major).

Enantimeric excess: ee = 55% (*S*).

All the other analytical data are in agreement with those reported in the literature.[114]

6.5.6. (*R*)-cyclohexylphenylmethanol [(*R*)-60h]



$C_{13}H_{18}O$. MW = 190.28 g mol^{-1}

Obtained from cyclohexylcarbaldehyde **59h** (0.25 mmol, 0.028 g), according to GP-11, using ligand (*S*)-**212h**. Purification by flash column chromatography (*n*-pentane / Et_2O 8:2) furnished pure (*R*)-**60h** (0.16 mmol, 0.031 g, 65% ee) as a yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.85–1.42 (m, 6H), 1.53–1.80 (m, 4H), 1.93–2.04 (m, 1H), 2.85 (br s, 1H), 4.34 (d, *J* = 7.2 Hz, 1H), 7.17–7.37 (m, 5H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 26.1, 26.1, 26.5, 28.9, 29.3, 45.0, 79.5, 126.7, 127.3, 128.2, 143.6.

HPLC separation conditions: Chiralcel OD, 254 nm, heptane / *i*-PrOH 95:5, 0.5 mL/min; ret. time = 14.2 min (*R*, major), 15.6 min (*S*, minor).

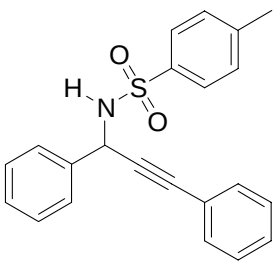
Enantiomeric excess: ee = 20% (*R*).

All the other analytical data are in agreement with those reported in the literature.[114]

6.6. Synthesis of Protected Propargylic Amines 166a-q, 226, 230b, p.

Compounds **230c-o** (see paragraph *4.3.2.*, Table 7) were synthesized following GP-13A, B by PIER GIORGIO COZZI and SILVIA ALESI. For their characterization see ref. 276.

6.6.1. *N*-(*p*-toluenesulfonyl)-3-amino 1,3-diphenylprop-1-yne (166a)



$C_{22}H_{19}NO_2S$. MW = 361.46 g mol^{-1}

Prepared according to GP-12, starting from imine **165a** (0.5 mmol, 0.130 g) and phenylacetylene (**108**, 0.75 mmol, 0.077 g, 1.5 equiv). Purification by flash column chromatography (*n*-pentane / EtOAc 4:1) afforded pure **166a** (0.4 mmol, 0.145 g, 80% yield) as a colorless solid.

Mp: 188-189 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.24 (s, 3H), 4.91 (d, *J* = 9.2 Hz, 1H), 5.48 (d, *J* = 9.2 Hz, 1H), 7.01-7.08 (m, 2H), 7.11-7.34 (m, 8H), 7.44-7.52 (m, 2H), 7.70-7.79 (m, 2H).

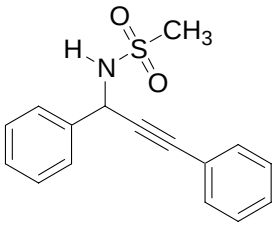
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 21.4, 49.8, 85.4, 86.7, 121.9, 127.3, 127.5, 128.1, 128.4, 128.6, 128.7, 129.5, 129.7, 131.5, 137.4, 143.5.

MS (EI, 70 eV): *m/z* = 360 $[M-1]^+$, 222, 206 $[M-Ts]^+$, 191, 105, 91, 77.

IR (KBr): ν = 3265, 2223, 1595, 1431, 1327, 1290, 1154, 1047 cm^{-1}.

Elemental analysis for $C_{22}H_{19}NO_2S$ Calcd: C, 73.31; H, 5.03; N, 3.88.
Found: C, 73.09; H, 5.17; N, 3.75.

6.6.2. *N*-(methanesulfonyl)-3-amino-1,3-diphenylprop-1-yne (166b)



$C_{16}H_{15}NO_2S$. MW = 285.36 g mol^{-1}

Prepared according to GP-12, starting from imine **165b** (0.5 mmol, 0.092 g) and phenylacetylene (**108**, 0.75 mmol, 0.077 g, 1.5 equiv). Purification by flash column chromatography (*n*-pentane / EtOAc 4:1) afforded pure **166b** (0.39 mmol, 0.112 g, 78% yield) as a colorless solid.

Mp: 100-101 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.00 (s, 3H), 4.92 (d, *J* = 8.2 Hz, 1H), 5.56 (d, *J* = 8.2 Hz, 1H), 7.23-7.36 (m, 6H), 7.37-7.42 (m, 2H), 7.52-7.57 (m, 2H).

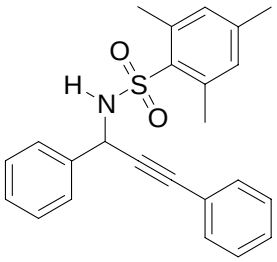
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 42.0, 49.9, 86.1, 87.1, 121.8, 127.4, 128.5, 128.8, 128.9, 129.0, 131.6, 137.2.

MS (EI, 70 eV): *m/z* = 285 $[M]^+$, 284 $[M-1]^+$, 222, 206 $[M-Ms]^+$, 191, 178, 105, 77.

IR (KBr): ν = 3198, 2199, 1596, 1490, 1445, 1320, 1146, 1054 cm^{-1}.

Elemental analysis for $C_{16}H_{15}NO_2S$ Calcd: C, 67.34; H, 5.30; N, 4.91.
Found: C, 67.02; H, 5.10; N, 4.83.

6.6.3. *N*-(2,4,6-trimethylbenzenesulfonyl)-3-amino-1,3-diphenylprop-1-yne (166c)



$C_{24}H_{23}NO_2S$. MW = 389.51 g mol^{-1}

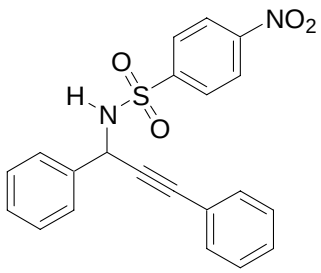
Prepared according to GP-12, starting from imine **165c** (0.5 mmol, 0.144 g) and phenylacetylene (**108**, 0.75 mmol, 0.077 g, 1.5 equiv). Purification by flash column chromatography (*n*-pentane / EtOAc 4:1) afforded **166c** (0.41 mmol, 0.160 g, 82% yield) as a yellow oil that solidified upon standing.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.11 (s, 3H), 2.60 (s, 6H), 4.94 (d, *J* = 8.5 Hz, 1H), 5.43 (d, *J* = 8.8 Hz, 1H), 6.80 (s, 2H), 7.02-7.07 (m, 2H), 7.14-7.31 (m, 8H), 7.45-7.51 (m, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 21.0, 23.2, 49.5, 84.9, 86.4, 122.0, 127.3, 128.1, 128.49, 128.53, 128.7, 131.6, 131.9, 134.4, 137.3, 139.0, 142.2.

Note: an analytically pure sample could not be obtained in this case (see discussion in paragraph 4.3.1. for details).

6.6.4. *N*-(*p*-nitrobenzenesulfonyl)-3-amino-1,3-diphenylprop-1-yne (166d)



$C_{21}H_{26}N_2O_4S$. MW = 392.43 g mol^{-1}

Prepared according to GP-12, starting from imine **165d** (0.5 mmol, 0.145 g) and phenylacetylene (**108**, 0.75 mmol, 0.077 g, 1.5 equiv). Purification by flash column chromatography (*n*-pentane / EtOAc 4:1) afforded pure **166d** (0.45 mmol, 0.175 g, 91% yield) as a colorless solid.

Mp: 167-168 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 5.20 (d, *J* = 8.7 Hz, 1H), 5.64 (d, *J* = 8.7 Hz, 1H), 7.04-7.13 (m, 2H); 7.19-7.41 (m, 6H), 7.49-7.57 (m, 2H), 8.02-8.09 (m, 2H), 8.16-8.23 (m, 2H).

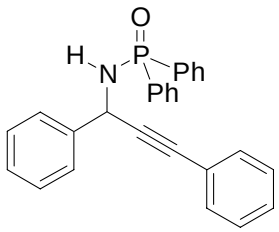
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 50.2, 84.8, 87.6, 121.3, 124.1, 127.4, 128.4, 128.8, 128.9, 128.9, 129.2, 131.3, 136.5, 146.2, 149.9.

MS (EI, 70 eV): *m/z* = 391 $[M-1]^+$, 222, 206 $[M-Ts]^+$, 191, 128, 105, 77.

IR (KBr): ν = 3269, 1693, 1605, 1528, 1343, 1310, 1162, 1040 cm^{-1}.

Elemental analysis for $C_{21}H_{16}N_2O_4S$ Calcd: C, 64.27; H, 4.11; N, 7.14.
Found: C, 64.18; H, 4.11; N, 6.95.

6.6.5. *N*-(diphenylphosphinoyl)-3-amino-1,3-diphenylprop-1-yne (226)



$C_{27}H_{22}NOP$. MW = 407.44 g mol^{-1}

Prepared according to GP-12, starting from imine **225** (0.4 mmol, 0.122 g) and phenylacetylene (**108**, 0.6 mmol, 0.061 g, 1.5 equiv). Purification by flash column chromatography (*n*-pentane / EtOAc 1:1) afforded pure **226** (0.27 mmol, 0.113 g, 69% yield) as a colorless solid.

Mp: 160-161 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.56 (t, *J* = 9.2 Hz, 1H), 5.40 (t, *J* = 9.9 Hz, 1H), 7.27-7.59 (m, 14H), 7.66-7.74 (m, 2H), 7.81-7.91 (m, 2H), 8.05-8.13 (m, 2H).

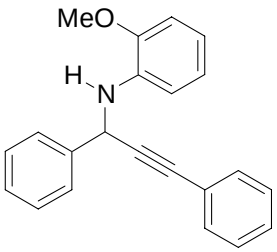
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 47.2, 85.5, 88.8, 122.6, 127.2, 127.9, 128.1, 128.3, 128.5, 128.6, 131.6, 131.7, 131.8, 131.9, 132.6, 132.7, 133.1, 140.2, 140.2.

MS (EI, 70 eV): *m/z* = 407 $[M]^+$, 330 $[M-C_6H_5]^+$, 206 $[M-P(O)Ph_2]^+$, 191, 155, 77.

IR (KBr): ν = 3162, 1961, 1901, 1435, 1188, 1114, 1056 cm^{-1}.

Elemental analysis for $C_{27}H_{22}NOP$ Calcd: C, 79.59; H, 5.44; N, 3.44.
Found: C, 79.75; H, 5.18; N, 3.35.

6.6.6. *N*-(2-methoxyphenyl)-3-amino-1,3-diphenylprop-1-yne (230b)[271]



$C_{22}H_{19}NO$. MW = 313.39 g mol^{-1}

Prepared according to GP-12, starting from imine **229b** (0.5 mmol, 0.106 g) and phenylacetylene (**108**, 1.25 mmol, 0.128 g, 2.5 equiv). Purification by flash column chromatography (PE / Et_2O 20:1) afforded pure **230b** (0.38 mmol, 0.119 g, 76% yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.83 (s, 3H), 4.78 (s, 1H), 5.50 (s, 1H), 6.71-6.91 (m, 4H), 7.23-7.44 (m, 8H), 7.64-7.70 (m, 2H).

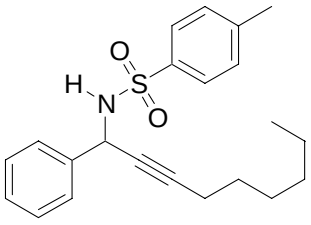
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 50.4, 55.5, 84.9, 88.7, 109.6, 111.7, 117.7, 121.1, 122.9, 127.4, 128.0, 128.16, 128.20, 128.7, 131.8, 136.4, 139.9, 147.1.

MS (EI, 70 eV): *m/z* = 313 $[M]^+$, 282 $[M-CH_3O]^+$, 236, 225, 191 $[M-C_7H_8NO]^+$.

IR (neat): ν = 3418, 3062, 2934, 2834, 1600, 1510, 1243, 1223 cm^{-1}.

Elemental analysis for $C_{22}H_{19}NO$ Calcd: C, 84.31; H, 6.11; N, 4.47.
Found: C, 84.43; H, 6.22; N, 4.20.

6.6.7. *N*-(*p*-toluenesulfonyl)-1-amino-1-phenylnon-2-yne (166e)



$C_{22}H_{27}NO_2S$. MW = 369.52 g mol^{-1}

Prepared according to GP-12, starting from imine **165a** (0.5 mmol, 0.130 g) and 1-octyne (**232**, 0.75 mmol, 0.083 g, 1.5 equiv). Purification by flash column chromatography (PE / EtOAc 3:1) afforded pure **166e** (0.35 mmol, 0.125 g, 69% yield) as a colorless solid.

Mp: 82-83 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.81 (t, *J* = 7.0 Hz, 3H), 1.11-1.28 (m, 8H), 1.89 (dt, *J* = 6.9 Hz, *J* = 2.0 Hz, 2H), 2.35 (s, 3H), 4.73 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1H), 5.23 (d, *J* = 8.8 Hz, 1H), 7.17-7.27 (m, 5H); 7.37-7.43 (m, 2H), 7.67-7.73 (m, 2H).

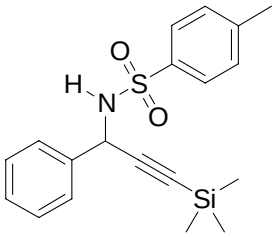
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 14.1, 18.6, 21.6, 22.6, 28.3, 28.6, 31.3, 49.5, 76.6, 87.6, 127.2, 127.4, 128.1, 128.4, 129.3, 137.5, 138.0, 143.1.

MS (EI, 70 eV): *m/z* = 299, 214 $[M-Ts]^+$, 155, 143, 91, 77.

IR (KBr): ν = 3288, 2928, 2857, 2227, 1597, 1330, 1157, 1031 cm^{-1}.

Elemental analysis for $C_{22}H_{27}NO_2S$ Calcd: C, 71.51; H, 7.36; N, 3.79.
Found: C, 71.65; H, 7.70; N, 3.66.

6.6.8. *N*-(*p*-toluenesulfonyl)-3-amino-3-phenyl-1-trimethylsilylprop-1-yne (166f)



$C_{19}H_{23}NO_2SSi$. MW = 357.54 g mol^{-1}

Prepared according to GP-12, starting from imine **165a** (0.5 mmol, 0.130 g) and trimethylsilylethyne (**130**, 1.25 mmol, 0.123 g, 2.5 equiv). Purification by flash column chromatography (PE / EtOAc 5:1) afforded pure **166f** (0.26 mmol, 0.091 g, 52% yield) as a colorless solid.

Mp: 139-140 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 9H), 2.43 (s, 3H), 4.81 (d, *J* = 8.5 Hz, 1H), 5.34 (d, *J* = 9.2 Hz, 1H), 7.25-7.36 (m, 5H), 7.46-7.52 (m, 2H), 7.76-7.82 (m, 2H).

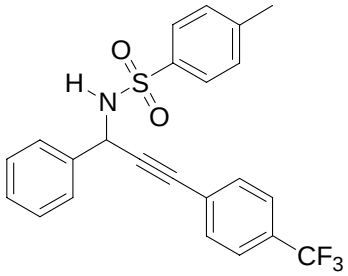
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = –0.3, 21.6, 49.7, 91.6, 101.4, 127.2, 127.4, 128.3, 128.5, 129.5, 137.2, 137.3, 143.3.

MS (EI, 70 eV): *m/z* = 356 $[M-1]^+$, 260, 234, 218, 202 $[M-Ts]^+$, 159, 91.

IR (KBr): ν = 3256, 2175, 1952, 1911, 1425, 1328, 1249, 1162, 1056 cm^{-1}.

Elemental analysis for $C_{19}H_{23}NO_2SSi$ Calcd: C, 63.83; H, 6.48; N, 3.92.
Found: C, 63.75; H, 6.35; N, 3.78.

6.6.9. *N*-(*p*-toluenesulfonyl)-3-amino-3-phenyl-1-(4-trifluoromethyl)phenylprop-1-yne (166g)



$C_{23}H_{18}NO_2F_3S$. MW = 429.46 g mol^{-1}

Prepared according to GP-12, starting from imine **165a** (0.5 mmol, 0.130 g) and 4-(trifluoromethyl)phenylacetylene (**233**, 0.75 mmol, 0.128 g, 1.5 equiv). Purification by flash column chromatography (PE / EtOAc 4:1) afforded pure **166g** (0.43 mmol, 0.183 g, 86% yield) as a colorless solid.

Mp: 140-141 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.24 (s, 3H), 4.96 (d, *J* = 8.9 Hz, 1H), 5.50 (d, *J* = 9.1 Hz, 1H), 7.12-7.34 (m, 7H), 7.40-7.49 (m, 4H), 7.70-7.77 (m, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 21.4, 49.7, 85.2, 88.1, 125.0, 125.1, 125.8, 127.3, 127.5, 128.6, 128.7, 128.8, 129.6, 131.8, 136.9, 137.4, 143.6.

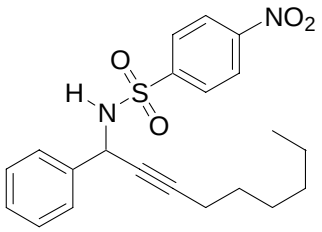
MS (EI, 70 eV): *m/z* = 410 $[M-F]^+$, 274 $[M-Ts]^+$, 259, 173, 91, 77.

IR (KBr): ν = 3278, 1924, 1807, 1736, 1606, 1328, 1163 cm^{-1}.

HRMS (EI): *m/z* calcd. for $C_{23}H_{18}NO_2F_3S$-SO_2H: 364.1313. Found: 364.1313.

Elemental analysis for $C_{23}H_{18}NO_2F_3S$ Calcd: C, 64.33; H, 4.22; N, 3.26.
Found: C, 63.99; H, 4.69; N, 3.25.

6.6.10. *N*-(*p*-nitrobenzenesulfonyl)-1-amino-1-phenylnon-2-yne (166h)



$C_{21}H_{24}N_2O_4S$. MW = 400.49 g mol^{-1}

Prepared according to GP-12, starting from imine **165d** (0.5 mmol, 0.145 g) and 1-octyne (**232**, 0.75 mmol, 0.083 g, 1.5 equiv). Purification by flash column chromatography (PE / EtOAc 4:1), followed by recrystallization from MTBE afforded pure **166h** (0.39 mmol, 0.159 g, 79% yield) as a yellow solid.

Mp: 103-104 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 0.87 (t, *J* = 6.9 Hz, 3H), 1.14-1.36 (m, 8H), 1.96 (dt, *J* = 6.9 Hz, *J* = 2.1 Hz, 2H), 5.04 (d, *J* = 7.8 Hz, 1H), 5.39 (d, *J* = 8.2 Hz, 1H), 7.27-7.36 (m, 3H), 7.39-7.48 (m, 2H), 7.97-8.07 (m, 2H), 8.25-8.34 (m, 2H).

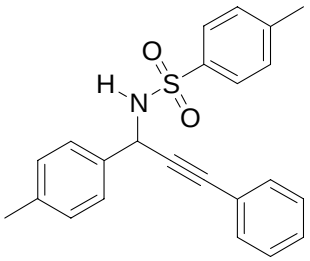
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 14.0, 18.5, 22.5, 28.2, 28.3, 28.5, 31.2, 49.9, 76.1, 88.3, 123.9, 127.3, 128.6, 128.7, 128.7, 137.3, 146.4, 149.9.

MS (EI, 70 eV): *m/z* = 330, 291 $[M-C_8H_{15}]^+$, 214 $[M-Ns]^+$, 143, 91, 77.

IR (KBr): ν = 3268, 2927, 2230, 1602, 1525, 1345, 1309, 1166, 1044 cm^{-1}.

Elemental analysis for $C_{21}H_{24}N_2O_4S$ Calcd: C, 62.98; H, 6.04; N, 6.99.
Found: C, 63.38; H, 6.06; N, 6.94.

6.6.11. *N*-(*p*-toluenesulfonyl)-3-amino-3-(4-methylphenyl)-1-phenylprop-1-yne (166i)



$C_{23}H_{21}NO_2S$. MW = 375.48 g mol^{-1}

Prepared according to GP-12, starting from imine **165e** (0.4 mmol, 0.109 g) and phenylacetylene (**108**, 0.6 mmol, 0.061 g, 1.5 equiv). Purification by flash column chromatography (PE / EtOAc 4:1) afforded pure **166i** (0.31 mmol, 0.116 g, 77% yield) as a colorless solid.

Mp: 190-191 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.32 (s, 3H), 2.34 (s, 3H), 4.89 (d, *J* = 9.1 Hz, 1H), 5.52 (d, *J* = 9.1 Hz, 1H), 7.07-7.17 (m, 4H), 7.19-7.33 (m, 5H), 7.38-7.46 (m, 2H), 7.77-7.85 (m, 2H).

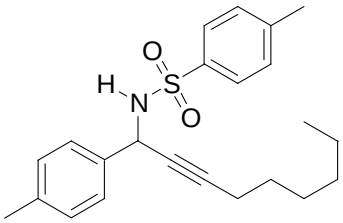
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 21.2, 21.5, 49.6, 85.7, 86.5, 122.0, 127.1, 127.4, 128.0, 128.4, 129.3, 129.4, 131.4, 134.4, 137.3, 138.2, 143.4.

MS (EI, 70 eV): *m/z* = 310, 236, 220 $[M-Ts]^+$, 205, 128, 105, 91, 77.

IR (KBr): ν = 3269, 2221, 1430, 1329, 1155, 1047 cm^{-1}.

HRMS (EI): *m/z* calcd. for $C_{23}H_{21}NO_2S$-SO_2H: 310.1596. Found: 310.1595.

6.6.12. *N*-(*p*-toluenesulfonyl)-1-amino-1-(4-methylphenyl)non-2-yne (166j)



$C_{23}H_{29}NO_2S$. MW = 383.55 g mol^{-1}

Prepared according to GP-12, starting from imine **165e** (0.4 mmol, 0.109 g) and 1-octyne (**232**, 0.6 mmol, 0.066 g, 1.5 equiv). Purification by flash column chromatography (PE / EtOAc 3:1) afforded pure **166j** (0.24 mmol, 0.092 g, 60% yield) as a colorless solid.

Mp: 107-108 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, *J* = 6.9 Hz, 3H), 1.16-1.36 (m, 8H), 1.95 (dt, *J* = 6.9 Hz, *J* = 2.1 Hz, 2H), 2.32 (s, 3H), 2.43 (s, 3H), 4.72 (d, *J* = 8.7 Hz, 1H), 5.26 (d, *J* = 8.7 Hz, 1H), 7.06-7.16 (m, 2H), 7.24-7.37 (m, 4H), 7.73-7.81 (m, 2H).

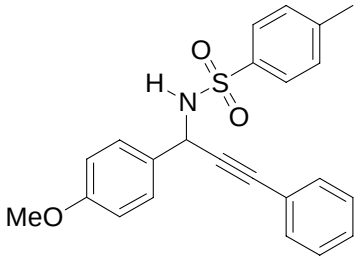
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 14.0, 18.5, 21.1, 21.5, 22.5, 28.3, 28.5, 31.3, 49.2, 76.8, 87.3, 127.2, 127.5, 129.2, 129.3, 135.2, 137.6, 138.0, 143.2.

MS (EI, 70 eV): *m/z* = 313, 274 $[M-C_8H_{15}]^+$, 228 $[M-Ts]^+$, 157, 105, 91, 77.

IR (KBr): ν = 3271, 2930, 2224, 1916, 1334, 1160, 1028 cm^{-1}.

Elemental analysis for $C_{23}H_{29}NO_2S$ Calcd: C, 72.03; H, 7.62; N, 3.65.
Found: C, 71.64; H, 7.76; N, 3.73.

6.6.13. *N*-(*p*-toluenesulfonyl)-3-amino-3-(4-methoxyphenyl)-1-phenylprop-1-yne (166k)



$C_{23}H_{21}NO_3S$. MW = 391.48 g mol^{-1}

Prepared according to GP-12, starting from imine **165f** (0.5 mmol, 0.145 g) and phenylacetylene (**108**, 0.75 mmol, 0.077 g, 1.5 equiv). Purification by flash column chromatography (PE / EtOAc 3:1) afforded pure **166k** (0.44 mmol, 0.171 g, 87% yield) as a colorless solid.

Mp: 186-187 °C.

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 2.32 (s, 3H), 3.80 (s, 3H), 4.90 (d, *J* = 8.9 Hz, 1H), 5.51 (d, *J* = 9.0 Hz, 1H), 6.84-6.90 (m, 2H), 7.08-7.15 (m, 2H), 7.20-7.33 (m, 5H), 7.43-7.50 (m, 2H), 7.78-7.84 (m, 2H).

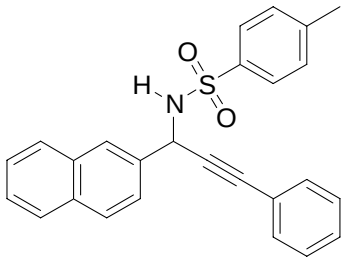
^{13}C-NMR (CDCl$_3$, 100 MHz): δ = 21.5, 49.3, 55.4, 85.7, 86.5, 114.0, 121.9, 127.4, 128.0, 128.4, 128.5, 129.4, 129.4, 131.4, 137.3, 143.4, 159.5.

MS (EI, 70 eV): *m/z* = 391 $[M]^+$, 326, 236 $[M-Ts]^+$, 235, 221, 178, 91, 77.

IR (KBr): ν = 3263, 2221, 1509, 1329, 1250, 1157, 1034 cm^{-1}.

Elemental analysis for $C_{23}H_{21}NO_3S$ Calcd: C, 70.56; H, 5.41; N, 3.58.
Found: C, 70.42; H, 5.36; N, 3.57.

6.6.14. *N*-(*p*-toluenesulfonyl)-3-amino-3-(2-naphtyl)-1-phenylprop-1-yne (166l)



$C_{26}H_{21}NO_2S$. MW = 411.52 g mol^{-1}

Prepared according to GP-12, starting from imine **165g** (0.5 mmol, 0.143 g) and phenylacetylene (**108**, 0.75 mmol, 0.077 g, 1.5 equiv). Purification by recrystallization from EtOAc afforded pure **166l** (0.43 mmol, 0.116 g, 85% yield) as a colorless solid.

Mp: 206-207 °C.

^{1}H-NMR (CD_2Cl_2, 400 MHz): δ = 2.21 (s, 3H), 5.06 (d, *J* = 9.2 Hz, 1H), 5.60 (d, *J* = 9.2 Hz, 1H), 7.07-7.30 (m, 7H), 7.39-7.47 (m, 2H), 7.51-7.57 (m, 1H), 7.68-7.81 (m, 5H), 7.90 (s, 1H).

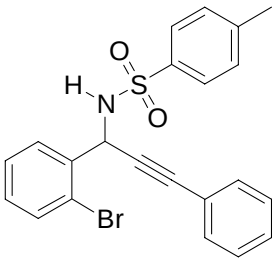
^{13}C-NMR (CD_2Cl_2, 100 MHz): δ = 21.2, 50.0, 85.4, 86.7, 125.0, 126.0, 126.1, 126.4, 126.5, 127.4, 127.5, 128.0, 128.1, 128.6, 128.6, 129.5, 131.5, 133.0, 133.1, 134.8, 137.2, 143.8.

MS (EI, 70 eV): *m/z* = 411 $[M]^+$, 346, 272, 256 $[M-Ts]^+$, 241, 228, 155, 128, 91, 77.

IR (KBr): ν = 3259, 2220, 1427, 1329, 1156, 1039 cm^{-1}.

Elemental analysis for $C_{26}H_{21}NO_2S$ Calcd: C, 75.89; H, 5.14; N, 3.40.
Found: C, 75.95; H, 5.10; N, 3.36.

6.6.15. *N*-(*p*-toluenesulfonyl)-3-amino-3-(2-bromophenyl)-1-phenylprop-1-yne (166m)



$C_{22}H_{18}NO_2BrS$. MW = 440.35 g mol^{-1}

Prepared according to GP-12, starting from imine **165h** (0.5 mmol, 0.169 g) and phenylacetylene (**108**, 0.75 mmol, 0.077 g, 1.5 equiv). Purification by flash column chromatography (PE / EtOAc 4:1) afforded pure **166m** (0.47 mmol, 0.205 g, 93% yield) as a colorless solid.

Mp: 169-170 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.24 (s, 3H), 5.10 (d, *J* = 8.3 Hz, 1H), 5.75 (d, *J* = 8.3 Hz, 1H), 7.04-7.26 (m, 9H), 7.43-7.52 (m, 2H), 7.67-7.74 (m, 2H).

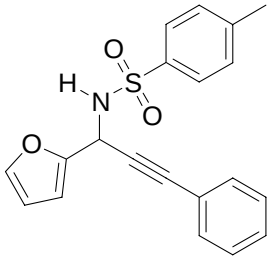
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 21.4, 50.1, 85.0, 86.5, 121.9, 123.0, 127.5, 127.8, 128.1, 128.6, 129.4, 129.6, 130.0, 131.6, 133.5, 136.7, 137.2, 143.5.

MS (EI, 70 eV): *m/z* = 441 $[M]^+$, 439, 378, 376, 302, 300, 286 $[M-Ts]^+$, 284, 204, 105, 91, 77.

IR (KBr): ν = 3268, 1923, 1594, 1329, 1156, 1054 cm^{-1}.

Elemental analysis for $C_{22}H_{18}NO_2BrS$ Calcd: C, 60.01; H, 4.12; N, 3.18.
Found: C, 60.05; H, 4.48; N, 3.05.

6.6.16. *N*-(*p*-toluenesulfonyl)-3-amino-3-(2-furyl)-1-phenylprop-1-yne (166n)



$C_{20}H_{17}NO_3S$. MW = 351.42 g mol^{-1}

Prepared according to GP-12, starting from imine **165i** (0.5 mmol, 0.125 g) and phenylacetylene (**108**, 0.75 mmol, 0.077 g, 1.5 equiv). Purification by flash column chromatography (PE / EtOAc 7:2) afforded pure **166n** (0.40 mmol, 0.140 g, 80% yield) as a pale brown solid.

Mp: 151-152 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.25 (s, 3H), 4.98 (d, *J* = 9.0 Hz, 1H), 5.53 (d, *J* = 9.0 Hz, 1H), 6.22 (dd, *J* = 3.3 Hz, *J* = 1.9 Hz, 1H), 6.31 (d, *J* = 3.3 Hz, 1H), 7.05-7.29 (m, 8H), 7.69-7.76 (m, 2H).

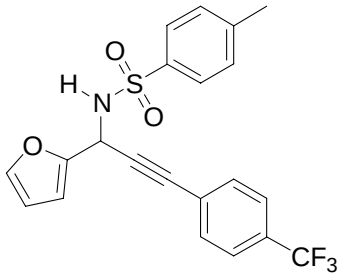
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 21.5, 44.2, 83.4, 85.3, 108.3, 110.4, 121.6, 127.3, 128.0, 128.6, 129.4, 131.5, 137.2, 143.1, 143.5, 149.4.

MS (EI, 70 eV): *m/z* = 303, 250 $[M-C_8H_5]^+$, 196 $[M-Ts]^+$, 181 $[M-C_7H_8NO_2S]^+$, 168, 152, 105, 91, 77.

IR (KBr): ν = 3263, 2225, 1433, 1333, 1157, 1039 cm^{-1}.

Elemental analysis for $C_{20}H_{17}NO_3S$ Calcd: C, 68.35; H, 4.88; N, 3.89.
Found: C, 68.00; H, 5.20; N, 3.89.

6.6.17. *N*-(*p*-toluenesulfonyl)-3-amino-3-(2-furyl)-1-(4-trifluoromethylphenyl)prop-1-yne (166o)



$C_{21}H_{16}NO_3F_3S$. MW = 419.42 g mol^{-1}

Prepared according to GP-12, starting from imine **165i** (0.5 mmol, 0.125 g) and 4-(trifluoromethyl)phenylacetylene (**233**, 0.75 mmol, 0.128 g, 1.5 equiv). Purification by recrystallization from MTBE afforded pure **166o** (0.47 mmol, 0.119 g, 95% yield) as a colorless solid.

Mp: 117-118 °C.

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 2.25 (s, 3H), 5.06 (d, *J* = 8.9 Hz, 1H), 5.55 (d, *J* = 8.9 Hz, 1H), 6.24 (dd, *J* = 3.2 Hz, *J* = 1.9 Hz, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 7.12-7.31 (m, 5H), 7.41-7.48 (m, 2H), 7.69-7.76 (m, 2H).

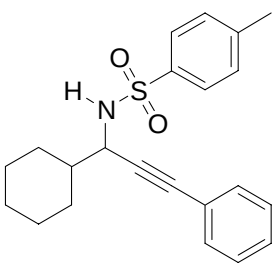
^{13}C-NMR (CDCl$_3$, 100 MHz): δ = 21.5, 44.0, 83.9, 86.0, 108.5, 110.5, 125.0, 125.0, 125.4, 127.4, 129.5, 131.8, 137.2, 143.2, 143.6, 148.8.

MS (EI, 70 eV): *m/z* = 400, 354, 280, 264 [M−Ts]$^+$, 249, 139, 91, 77.

IR (KBr): ν = 3270, 2923, 1926, 1616, 1329, 1162, 1132 cm^{-1}.

Elemental analysis for $C_{21}H_{16}NO_3SF_3$ Calcd: C, 60.14; H, 3.85; N, 3.34.
Found: C, 60.03; H, 4.15; N, 3.32.

6.6.18. *N*-(*p*-toluenesulfonyl)-3-amino-3-cyclohexyl-1-phenylprop-1-yne (166p)



$C_{22}H_{25}NO_2S$. MW = 367.51 g mol^{-1}

Prepared according to GP-12, starting from imine **165j** (0.5 mmol, 0.133 g) and phenylacetylene (**108**, 0.75 mmol, 0.077 g, 1.5 equiv). Purification by recrystallization from EtOAc afforded pure **166p** (0.42 mmol, 0.155 g, 84% yield) as a colorless solid.

Mp: 202-203 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.95-1.23 (m, 5H), 1.66-1.87 (m, 6H), 2.25 (s, 3H), 4.04 (dd, *J* = 9.9 Hz, *J* = 6.0 Hz, 1H), 4.59 (d, *J* = 9.9 Hz, 1H), 6.93-7.00 (m, 2H), 7.11-7.22 (m, 5H), 7.70-7.76 (m, 2H).

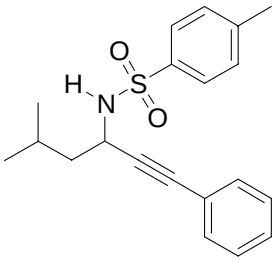
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 21.6, 25.86, 25.94, 26.3, 28.6, 29.3, 43.3, 51.6, 85.2, 86.2, 122.2, 127.5, 128.0, 128.3, 129.5, 131.5, 137.4, 143.4.

MS (EI, 70 eV): *m/z* = 367 $[M]^+$, 284 $[M-C_6H_{11}]^+$, 212 $[M-Ts]^+$, 155 $[Ts]^+$, 139, 91.

IR (KBr): ν = 3853, 3744, 3452, 3279, 2925, 2360, 2337, 1650, 1331, 1156 cm^{-1}.

Elemental analysis for $C_{22}H_{25}NO_2S$ Calcd: C, 71.90; H, 6.86; N, 3.81.
Found: C, 71.54; H, 7.14; N, 3.75.

6.6.19. *N*-(*p*-toluenesulfonyl)-3-amino-5-methyl-1-phenylhex-1-yne (166q)



$C_{20}H_{23}NO_2S$. MW = 341.47 g mol^{-1}

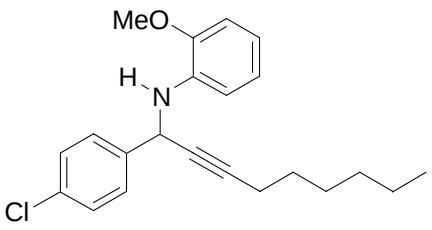
Prepared according to GP-12, starting from imine **165k** (0.5 mmol, 0.120 g) and phenylacetylene (**108**, 0.75 mmol, 0.077 g, 1.5 equiv). Purification by flash column chromatography (PE / EtOAc 7:1) afforded pure **166q** (0.08 mmol, 0.025 g, 15% yield) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.90 (t, *J* = 6.5 Hz, 6H), 1.16-1.29 (m, 1H), 1.50-1.64 (m, 2H), 2.27 (s, 3H), 4.28 (dt, *J* = 9.6 Hz, *J* = 7.7 Hz, 1H), 4.51 (d, *J* = 9.6 Hz, 1H), 6.95-7.00 (m, 2H), 7.13-7.28 (m, 5H), 7.74-7.80 (m, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 21.5, 22.3, 22.4, 24.9, 44.9, 45.8, 84.3, 87.4, 127.5, 128.0, 128.3, 129.5, 131.4, 135.8, 137.4, 143.4.

Note: an analytically pure sample could not be obtained in this case, due to the low yield of the product (see discussion in paragraph 4.3.1. for details).

6.6.20. *N*-(2-methoxyphenyl)-1-amino-1-(4-chlorophenyl)non-1-yne (230p)



$C_{22}H_{26}NOCl$. MW = 355.90 g mol^{-1}

Prepared according to GP-13A, starting from 4-chlorobenzaldehyde (**59a**, 0.4 mmol, 0.056 g), 2-methoxyaniline (**237**, 0.4 mmol, 0.049 mg, 1.0 equiv) and 1-octyne (**232**, 1.0 mmol, 0.110 g, 2.5 equiv). Purification by flash column chromatography (*n*-pentane / Et_2O 65:1) afforded pure **230p** (0.16 mmol, 0.055 g, 40% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.80 (t, *J* = 6.9 Hz, 3H), 1.11-1.31 (m, 6H), 1.36, 1.45 (m, 2H), 2.12 (dt, *J* = 7.1 Hz, *J* = 2.0 Hz, 2H), 3.75 (s, 3H), 4.57 (br s, 1H), 5.13 (s, 1H), 6.57-6.66 (m, 2H), 6.68-6.78 (m, 2H), 7.22-7.28 (m, 2H), 7.41-7.47 (m, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 13.0, 17.7, 21.5, 27.4, 27.5, 30.2, 48.2, 54.3, 77.9, 84.7, 108.3, 110.4, 116.5, 119.8, 127.4, 127.5, 132.2, 135.1, 138.0, 145.8.

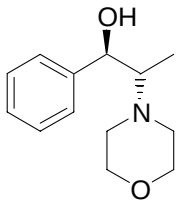
MS (EI, 70 eV): *m/z* = 357-355 $[M]^+$, 272-270 $[M-C_6H_{11}]^+$, 244 $[M-C_6H_4Cl]^+$, 235-233 $[M-C_7H_8NO]^+$, 153-151, 127-125, 95.

IR (KBr): ν = 3418, 2930, 2857, 1600, 1511, 1456, 1242, 1224, 1029 cm^{-1}.

Elemental analysis for $C_{22}H_{26}NOCl$ Calcd: C, 74.24; H, 7.36; N, 3.94.
Found: C, 73.43; H, 7.13; N, 4.26.

6.7. Synthesis of *N*,*N*-dialkylnorephedrines 49, 246a-g.

6.7.1. (1*R*,2*S*)-2-(morpholin-4-yl)-1-phenyl-1-propanol [(1*R*,2*S*)-49]



$C_{13}H_{19}NO_2$. MW = 221.30 g mol^{-1}

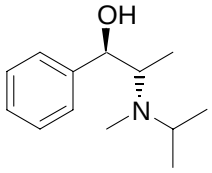
To a mixture of (1*R*,2*S*)-norephedrine (**244**, 0.907 g, 6.0 mmol) and Et_3N (17.5 mmol, 2.5 mL, 1.78 g, 2.9 equiv) in 6 mL of DMSO was added dropwise a solution of 2,2'-dibromodiethyl ether (90%, 7.0 mmol, 0.88 mL, 1.62 g, 1.2 equiv) in 5 mL of DMSO. The reaction mixture was stirred at reflux for 72 h, then poured into 60 mL aq 0.25 N NaOH and extracted three times with 25 mL of Et_2O. The combined organic phases were dried on $MgSO_4$. Evaporation of the solvent yielded the crude product. Purification by recrystallization from *n*-hexane afforded pure (1*R*,2*S*)-**49** (3.4 mmol, 0.744 g, 57% yield) as light yellow needles.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.9 Hz, 3H), 2.46-2.64 (m, 5H), 3.48 (br s, 1H), 3.66 (t, *J* = 4.7 Hz, 4H), 4.85 (d, *J* = 3.9 Hz, 1H), 7.14-7.20 (m, 1H), 7.22-7.29 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.0, 51.0, 64.9, 67.5, 71.8, 125.9, 126.9, 128.0, 141.7.

All the other analytical data are in agreement with those reported in the literature.[332]

6.7.2. (1*R*,2*S*)-*N*-*iso*-propyl-*N*-methylnorephedrine [(1*R*,2*S*)-246a]



$C_{13}H_{21}NO$. MW = 207.31 g mol^{-1}

[332] K. Soai, T. Hatanaka, T. Miyazawa *J. Chem. Soc., Chem. Commun.* **1992**, 1097.

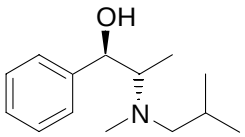
According to GP-14, (1*R*,2*S*)-norephedrine (**244**, 5.0 mmol, 0.756 g) was treated with 2-iodopropane (10.0 mmol, 1.70 g, 2.0 equiv) to furnish the monoalkylated product (1*R*,2*S*)-**245a** in quantitative yield. (1*R*,2*S*)-**245a** was subsequently methylated according to GP-15. Purification by flash column chromatography (PE / EtOAc / Et_3N 5:1:0.1) afforded pure (1*R*,2*S*)-**246a** (3.5 mmol, 0.720 g, 69% yield) as a light yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 2.18 (s, 3H), 2.92 (dq, *J* = 6.9 Hz, *J* = 4.3 Hz, 1H), 3.12 (sept, *J* = 6.5 Hz, 1H), 4.11 (br s, 1H), 4.80 (d, *J* = 4.3 Hz, 1H), 7.21-7.29 (m, 1H), 7.31-7.37 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 11.8, 18.3, 19.0, 31.6, 51.1, 60.9, 72.5, 126.1, 126.7, 127.9, 142.3.

All the other analytical data are in agreement with those reported in the literature.[333]

6.7.3. (1*R*,2*S*)-*N*-*iso*-butyl-*N*-methylnorephedrine [(1*R*,2*S*)-246b]



$C_{14}H_{23}NO$. MW = 221.34 g mol^{-1}

According to GP-14, (1*R*,2*S*)-norephedrine (**244**, 5.0 mmol, 0.756 g) was treated with 1-iodo-2-methylpropane (10.0 mmol, 1.84 g, 2.0 equiv) to furnish the monoalkylated product (1*R*,2*S*)-**245b** in quantitative yield. (1*R*,2*S*)-**245b** was subsequently methylated according to GP-15. Purification by flash column chromatography (PE / EtOAc / Et_3N 2:1:0.05) afforded pure (1*R*,2*S*)-**246b** (3.3 mmol, 0.730 g, 66% yield) as a light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 6.6 Hz, 6H), 0.82 (d, *J* = 6.6 Hz, 3H), 1.69 (sept, *J* = 6.6 Hz, 1H), 2.10 (s, 3H), 2.09-2.22 (m, 2H), 2.68 (dq, *J* = 6.8 Hz, *J* = 4.7 Hz, 1H), 3.68 (br s, 1H), 4.71 (d, *J* = 4.4 Hz, 1H), 7.12-7.19 (m, 1H), 7.22-7.28 (m, 4H).

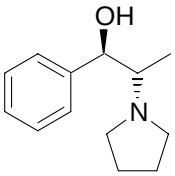
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.3, 20.7, 20.9, 26.6, 38.8, 63.9, 64.4, 73.2, 126.1, 126.7, 127.9, 142.3.

All the other analytical data are in agreement with those reported in the literature.[334]

[333] (a) P. A. Chaloner, S. A. R. Perera *Tetrahedron Lett.* **1987**, *28*, 3013. (b) P. A. Chaloner, E. Langadianou *Tetrahedron Lett.* **1990**, *31*, 5185. (c) P. A. Chaloner, E. Lanagadianou, S. A. R. Perera *J. Chem. Soc., Perkin Trans. I* **1991**, 2731.

[334] S. Terashima, N. Tanno, K. Koga *Tetrahedron Lett.* **1980**, *21*, 2753.

6.7.4. (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)-1-propanol [(1*R*,2*S*)-246c]



$C_{13}H_{19}NO$. MW = 205.30 g mol^{-1}

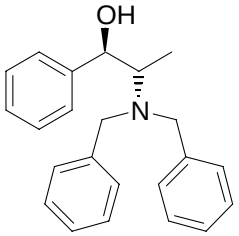
Prepared starting from (1*R*,2*S*)-norephedrine (**244**, 5.0 mmol, 0.756 g) and 1,4-dibromobutane (5.0 mmol, 1.08 g, 1.0 equiv), according to GP-14. Purification by flash column chromatography (PE / EtOAc / Et_3N 4:1:0.1) afforded pure (1*R*,2*S*)-**246c** (4.9 mmol, 1.02 g, 99% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 6.6 Hz, 3H), 1.69-1.79 (m, 2H), 2.41 (dq, *J* = 6.6 Hz, *J* = 3.3 Hz, 1H), 2.52-2.62 (m, 1H), 2.66-2.76 (m, 1H), 4.94 (d, *J* = 3.0 Hz), 7.13-7.20 (m, 1H), 7.23-7.30 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.2, 23.6, 51,9, 65.4, 72.7, 125.8, 126.7, 127.9, 141.7.

All the other analytical data are in agreement with those reported in the literature.[335]

6.7.5. (1*R*,2*S*)-*N*,*N*-dibenzylnorephedrine [(1*R*,2*S*)-246d]



$C_{23}H_{25}NO$. MW = 331.45 g mol^{-1}

Prepared starting from (1*R*,2*S*)-norephedrine (**244**, 5.0 mmol, 0.756 g) and benzylbromide (10.0 mmol, 1.71 g, 2.0 equiv), according to GP-14. Pure (1*R*,2*S*)-**246d** (4.9 mmol, 1.62 g, 98% yield) was immediately obtained as a colorless oil, and could be used without further purification.

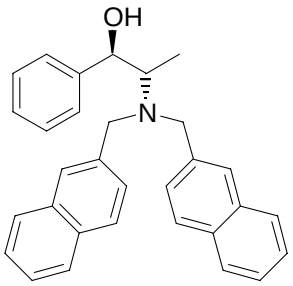
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.6 Hz, 3H), 2.56 (br s, 1H), 3.10 (qu, *J* = 6.7 Hz, 1H), 3.60 (AB system, 4H), 4.75 (d, *J* = 6.0 Hz, 1H), 7.17-7.32 (m, 15H).

[335] K. Soai, S. Yokoyama, T. Hayasaka *J. Org. Chem.* **1991**, *56*, 4264.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 9.3, 54.7, 58.5, 75.7, 126.7, 126.9, 127.3, 128.0, 128.2, 128.7, 139.8, 143.1.

All the other analytical data are in agreement with those reported in the literature.[336]

6.7.6. (1*R*,2*S*)-*N*,*N*-di(2-naphthyl)norephedrine [(1*R*,2*S*)-246e]



$C_{31}H_{29}NO$. MW = 431.57 g mol^{-1}

Prepared starting from (1*R*,2*S*)-norephedrine (**244**, 5.0 mmol, 0.756 g) and 2-bromomethylnaphthalene (10.0 mmol, 2.21 g, 2.0 equiv), according to GP-14. Pure (1*R*,2*S*)-**246e** (4.75 mmol, 2.05 g, 95% yield) was immediately obtained as a yellow solid, and could be used without further purification.

Mp: 50-51 °C

Optical rotation: $[\alpha]^{20}_D = -121.6$ (c = 1.01, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.7 Hz, 3H), 2.33 (br s, 1H), 3.09 (qu, *J* = 6.7 Hz, 1H), 3.68 (AB system, 4H), 4.68 (d, *J* = 6.7 Hz, 1H), 7.06-7.12 (m, 2H), 7.14-7.26 (m, 5H), 7.30-7.42 (m, 4H), 7.53 (s, 2H), 7.62-7.75 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 9.2, 54.7, 58.4, 76.1, 125.5, 125.9, 127.0, 127.1, 127.40, 127.44, 127.7, 127.7, 127.9, 128.1, 132.8, 133.3, 137.4, 143.2.

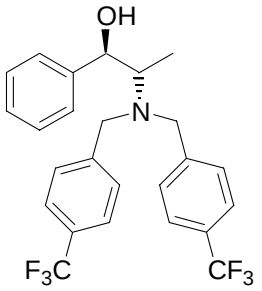
MS (EI, 70 eV): *m/z* = 324 $[M-C_7H_7O]^+$, 281, 182, 141 $[C_{11}H_9]^+$, 115, 77.

IR (KBr): ν = 3424, 3053, 2926, 2805, 1506, 1365, 1153, 1127 cm^{-1}.

HRMS (EI): *m/z* calcd for $C_{24}H_{22}N$ $[C_{31}H_{29}NO-C_7H_7O]$: 324.1752; found: 324.1753.

[336] (a) M. T. Reetz, M. W. Drewes, A. Schmitz *Angew. Chem.* **1987**, *99*, 1186; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (b) R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, V. Molteni, L. Raimondi *Tetrahedron* **1995**, *51*, 8941.

6.7.7. (1*R*,2*S*)-*N*,*N*-di[(4-trifluoromethylphenyl)methyl]norephedrine [(1*R*,2*S*)-246f]



$C_{25}H_{23}F_6NO$. MW = 467.45 g mol^{-1}

Prepared starting from (1*R*,2*S*)-norephedrine (**244**, 5.0 mmol, 0.756 g) and 1-bromomethyl-4-trifluoromethylbenzene (10.0 mmol, 2.39 g, 2.0 equiv), according to GP-14. Purification by flash column chromatography (PE / EtOAc / Et_3N 8:1:0.05) afforded pure (1*R*,2*S*)-**246f** (2.99 mmol, 1.400 g, 60% yield) as a colorless oil.

Optical rotation: $[\alpha]^{20}_D = -32.4$ (c = 0.80, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.7 Hz, 3H), 1.99 (br s, 1H), 2.89 (qu, *J* = 6.7 Hz, 1H), 3.57 (AB system, 4H), 4.68 (d, *J* = 6.7 Hz, 1H), 7.02-7.08 (m, 2H), 7.10-7.17 (m, 4H), 7.19-7.28 (m, 3H), 7.37-7.44 (m, 4H).

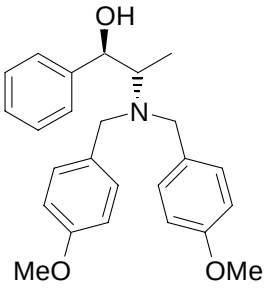
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 9.0, 54.2, 59.1, 76.3, 125.12, 125.18, 126.8, 127.8, 128.3, 128.8, 129.1, 129.5, 143.3, 143.8.

MS (EI, 70 eV): *m/z* = 448 $[M-F]^+$, 360 $[M-C_7H_7O]^+$, 200, 159 $[C_8H_6F_3]^+$, 109, 77.

IR (KBr): ν = 3402, 2968, 2930, 1920, 1727, 1619, 1326, 1125, 1067 cm^{-1}.

HRMS (EI): *m/z* calcd for $C_{18}H_{23}NOF_6$ $[C_{25}H_{23}F_6NO-C_7H_7O]$: 360.1187; found: 360.1187.

6.7.8. (1*R*,2*S*)-*N*,*N*-di[(4-methoxyphenyl)methyl]norephedrine [(1*R*,2*S*)-246g]



$C_{25}H_{29}NO_3$. MW = 391.50 g mol^{-1}

Prepared starting from (1*R*,2*S*)-norephedrine (**244**, 5.0 mmol, 0.756 g) and 1-bromomethyl-4-methoxybenzene (10.0 mmol, 2.01 g, 2.0 equiv), according to GP-14. Purification by flash column chromatography (PE / EtOAc / Et_3N 6:1:0.05) afforded pure (1*R*,2*S*)-**246g** (3.07 mmol, 1.20 g, 61% yield) as a colorless oil.

Optical rotation: $[\alpha]^{20}_D = -64.7$ (c = 1.08, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.6 Hz, 3H), 2.70 (br s, 1H), 3.10 (qu, *J* = 6.7 Hz, 1H), 3.48 (AB system, 4H), 3.79 (s, 6H), 4.70 (d, *J* = 6.3 Hz), 6.77-6.83 (m, 4H), 7.05-7.11 (m, 4H), 7.17-7.23 (m, 2H), 7.24-7.33 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 9.4, 53.8, 55.3, 58.1, 75.6, 113.6, 126.8, 127.2, 128.0, 129.7, 131.8, 143.1, 158.5.

MS (EI, 70 eV): *m/z* = 285, 284 $[M-C_7H_7O]^+$, 162, 122, 121 $[C_8H_9O]^+$, 77

IR (KBr): ν = 3447, 2933, 2833, 2248, 2060, 1883, 1610, 1510, 1457, 1246, 1173, 1034 cm^{-1}.

HRMS (EI): *m/z* calcd for $C_{18}H_{22}NO_2$ $[C_{25}H_{29}NO_3-C_7H_7O]$: 284.1650; found: 284.1650.

6.8. Asymmetric Synthesis of *N*-Substituted Propargylic Amines 166a-c, 226, 230c, f, p, r-v.

6.8.1. *N*-(*p*-toluenesulfonyl)-3-amino 1,3-diphenylprop-1-yne (166a)

Obtained from imine **165a** (0.5 mmol, 0.130 g) and phenylacetylene (**108**, 1.5 mmol, 0.153 g, 3.0 equiv) according to GP-16, using ligand (*S*,*R*$_p$)-**64a**. Purification by flash column chromatography (*n*-pentane / EtOAc 4:1) afforded pure **166a** (0.33 mmol, 0.119 g, 66% yield) as a colorless solid.

The analytical data have already been reported in paragraph *6.6.1.*

HPLC separation conditions: Chiralcel OD-H, 254 nm, heptane / *i*-PrOH 95:5, 0.7 mL/min; ret. time = 19.8 min (major), 23.5 min (minor).

Enantiomeric excess: ee = 30%

6.8.2. *N*-(methanesulfonyl)-3-amino 1,3-diphenylprop-1-yne (166b)

Obtained from imine **165b** (0.5 mmol, 0.092 g) and phenylacetylene (**108**, 1.5 mmol, 0.153 g, 3.0 equiv) according to GP-16, using ligand (+)-**114**. Purification by flash column chromatography (*n*-pentane / EtOAc 4:1) afforded pure **166b** (0.29 mmol, 0.082 g, 57% yield) as a colorless solid.

The analytical data have already been reported in paragraph *6.6.2.*

HPLC separation conditions: Chiralcel OD-H, 254 nm, heptane / *i*-PrOH 95:5, 0.6 mL/min; ret. time = 38.7 min (major), 101.1 min (minor).

Enantiomeric excess: ee = 5%

6.8.3. *N*-(2,4,6-trimethylbenzenesulfonyl)-3-amino-1,3-diphenylprop-1-yne (166c)

Obtained from imine **165c** (0.5 mmol, 0.144 g) and phenylacetylene (**108**, 1.5 mmol, 0.153 g, 3.0 equiv) according to GP-16, using ligand (+)-**114**. Purification by flash column chromatography (*n*-pentane / EtOAc 4:1) afforded pure **166c** (0.43 mmol, 0.168 g, 86% yield) as a yellow oil that solidified upon standing.

The analytical data have already been reported in paragraph *6.6.3.*

HPLC separation conditions: Chiralcel OD-H, 254 nm, heptane / *i*-PrOH 98:2, 0.6 mL/min; ret. time = 43.4 min, 50.8 min.

Enantiomeric excess: ee = 0%

6.8.4. *N*-(diphenylphosphinoyl)-3-amino-1,3-diphenylprop-1-yne (226)

Obtained from imine **225** (0.4 mmol, 0.122 g) and phenylacetylene (**108**, 1.2 mmol, 0.123 g, 3.0 equiv) according to GP-16, using ligand (S,R_p)-**64a**. Purification by flash column chromatography (*n*-pentane / EtOAc 1:1) afforded pure **226** (0.27 mmol, 0.109 g, 67% yield) as a colorless solid.

The analytical data have already been reported in paragraph *6.6.5.*

HPLC separation conditions: Chiralpak AD, 254 nm, heptane / *i*-PrOH 92:8, 0.6 mL/min; ret. time = 52.5 min (minor), 62.1 min (major).

Enatiomeric excess: ee = 20%

6.8.5. (*S*)-*N*-(2-methoxyphenyl)-3-amino-1,3-diphenylprop-1-yne [(*S*)-230b][271]

Obtained from benzaldehyde (**35**, 0.4 mmol, 0.042 g), 2-methoxyaniline (**237**, 0.4 mmol, 0.049 g, 1.0 equiv) and phenylacetylene (**108**, 1.2 mmol, 0.123 g, 3.0 equiv), according to GP-17, using ligand (1*R*,2*S*)-**246g**. Purification by flash column chromatography (*n*-pentane / Et_2O 25:1) afforded pure (*S*)-**230b** (0.32 mmol, 0.100 g, 80% yield) as a yellow oil.

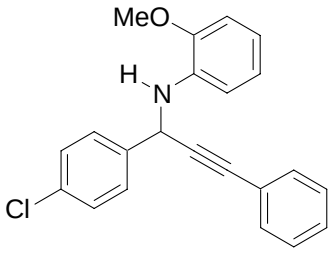
The analytical data have already been reported in paragraph *6.6.6.*

Optical rotation: $[\alpha]^{20}_D = -78.4$ (c = 1.01, $CHCl_3$).

HPLC separation conditions: Chiralcel OD-H, 254 nm, heptane / *i*-PrOH 95:5, 0.6 mL/min; ret. time = 8.4 min (*R*, minor), 12.0 min (*S*, major).

Enantiomeric excess: ee = 83% (*S*).

6.8.6. (−)-*N*-(2-methoxyphenyl)-3-amino-3-(4-chlorophenyl)-1-phenylprop-1-yne [(−)-230c]



$C_{22}H_{18}NOCl$. MW = 347.84 g mol^{-1}

Obtained from 4-chlorobenzaldehyde (**59a**, 0.4 mmol, 0.056 g), 2-methoxyaniline (**237**, 0.4 mmol, 0.049 g, 1.0 equiv) and phenylacetylene (**108**, 1.2 mmol, 0.123 g, 3.0 equiv), according to GP-17, using ligand (1*R*,2*S*)-**246g**. Purification by flash column chromatography (*n*-pentane / Et_2O 30:1) afforded pure (−)-**230c** (0.33 mmol, 0.115 g, 83% yield) as a light yellow oil that solidified upon standing. Recrystallization from *n*-hexane furnished the product as colorless needles.

Optical rotation: $[\alpha]^{20}_D = -84.9$ (c = 0.7, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.83 (s, 3H), 4.81 (brs, 1H), 5.43(s, 1H), 6.78-6.85 (m, 4H), 7.26-7.33 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.42-7.45 (m, 2H), 7.62 (d, *J* =8.1 Hz, 2H).

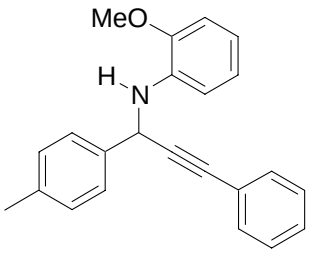
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 49.8, 55.4, 85.1, 88.1, 109.5, 111.6, 117.9, 121.0, 122.6, 128.2, 128.4, 128.6, 128.8, 131.7, 133.7, 136.1, 138.5, 147.1.

MS (EI, 70 eV): *m/z* = 350-348 $[M+1]^+$, 349-347 $[M]^+$, 236 $[M-C_6H_4Cl]^+$, 227-225, 189, 77.

HPLC separation conditions: Chiralcel OD-H, 254 nm, heptane / *i*-PrOH 95:5, 0.6 mL/min; ret. time = 9.2 min (+, minor), 11.0 min (−, major).

Enantiomeric excess: ee = 87% (−). After recrystallization the ee was 93% (−).

6.8.7. (−)-*N*-(2-methoxyphenyl)-3-amino-3-(4-methylphenyl)-1-phenylprop-1-yne [(−)-230r]



$C_{23}H_{21}NO$. MW = 327.42 g mol^{-1}

Obtained from 4-methylbenzaldehyde (**59g**, 0.4 mmol, 0.048 g), 2-methoxyaniline (**237**, 0.4 mmol, 0.049 g, 1.0 equiv) and phenylacetylene (**108**, 1.2 mmol, 0.123 g, 3.0 equiv), according to GP-17, using ligand (1*R*,2*S*)-**246g**. Purification by flash column chromatography (*n*-pentane / Et_2O 25:1) afforded pure (−)-**230r** (0.28 mmol, 0.093 g, 71% yield) as a yellow oil.

Optical rotation: $[\alpha]^{20}_D = -72.6$ (c = 1.01, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.29 (s, 3H), 3.75 (s, 3H), 4.66 (br s, 1H), 5.38 (s, 1H), 6.63-6.74 (m, 2H), 6.76-6.84 (m, 2H), 7.10-7.23 (m, 5H), 7.30-7.36 (m, 2H), 7.44-7.50 (m, 2H).

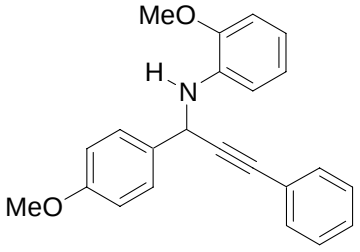
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 21.3, 50.2, 55.5, 84.7, 89.0, 109.6, 111.6, 117.6, 121.1, 123.0, 127.3, 128.2, 128.2, 129.4, 131.8, 136.5, 137.0, 137.7, 147.1.

MS (EI, 70 eV): *m/z* = 327 $[M]^+$, 295, 236 $[M-C_7H_7]^+$, 205 $[M-C_7H_8NO]^+$, 189, 178, 91, 77.

HPLC separation conditions: Chiralcel OD-H, 254 nm, heptane / *i*-PrOH 95:5, 0.6 mL/min; ret. time = 8.1 min (+, minor), 10.0 min (−, major).

Enantiomeric excess: ee = 85% (−).

6.8.8. (−)-*N*-(2-methoxyphenyl)-3-amino-3-(4-methoxyphenyl)-1-phenylprop-1-yne [(−)-230s]



$C_{23}H_{21}NO_2$. MW = 343.42 g mol^{-1}

Obtained from 4-methoxybenzaldehyde (**59b**, 0.4 mmol, 0.054 g), 2-methoxyaniline (**237**, 0.4 mmol, 0.049 g, 1.0 equiv) and phenylacetylene (**108**, 1.2 mmol, 0.123 g, 3.0 equiv), according to GP-17, using ligand (1*R*,2*S*)-**246g**. Purification by flash column chromatography (*n*-pentane / Et_2O 10:1) afforded pure (−)-**230s** (0.21 mmol, 0.071 g, 52% yield) as a yellow oil that solidified upon standing. Recrystallization from *n*-hexane afforded the product as yellow crystals.

Optical rotation: $[\alpha]^{20}_D = -89.1$ (c = 0.6, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 3.85 (s, 3H), 3.86 (s, 3H), 4.74 (d, *J* = 5.5 Hz, 1H), 5.47 (d, *J* = 5.5 Hz, 1H), 6.73-6.85 (m, 2H), 6.88-7.00 (m, 4H), 7.27-7.35 (m, 3H), 7.40-7.48 (m, 2H), 7.57-7.66 (m, 2H).

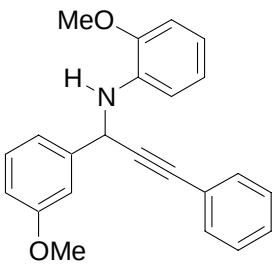
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 49.8, 55.36, 55.41, 84.6, 89.0, 109.6, 111.7, 114.1, 117.6, 121.1, 123.0, 128.2, 128.2, 128.6, 131.8, 132.1, 136.5, 147.2, 159.4.

MS (EI, 70 eV): *m/z* = 343 $[M]^+$, 236, 221 $[M-C_7H_8NO]^+$, 206, 178, 152, 92, 77.

HPLC separation conditions: Chiralcel OD-H, 254 nm, heptane / *i*-PrOH 98:2, 0.6 mL/min; ret. time = 13.6 min (+, minor), 15.5 min (−, major).

Enantiomeric excess: ee = 87% (−). After recrystallization the ee was 92% (−).

6.8.9. (−)-*N*-(2-methoxyphenyl)-3-amino-3-(3-methoxyphenyl)-1-phenylprop-1-yne [(−)-230t]



$C_{23}H_{21}NO_2$. MW = 343.42 g mol^{-1}

Obtained from 3-methoxybenzaldehyde (**59w**, 0.4 mmol, 0.054 g), 2-methoxyaniline (**237**, 0.4 mmol, 0.049 g, 1.0 equiv) and phenylacetylene (**108**, 1.2 mmol, 0.123 g, 3.0 equiv), according to GP-17, using ligand (1*R*,2*S*)-**246g**. Purification by flash column chromatography (*n*-pentane / Et_2O 15:1) afforded pure (−)-**230t** (0.32 mmol, 0.111 g, 81% yield) as a yellow oil.

Optical rotation: $[\alpha]^{20}_D = -75.2$ (c = 0.94, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.84 (s, 3H), 3.85 (s, 3H), 4.79 (br s, 1H), 5.48 (s, 1H), 6.73-6.78 (m, 1H), 6.80-6.93 (m, 5H), 7.23-7.37 (m, 6H), 7.39-7.47 (m, 2H).

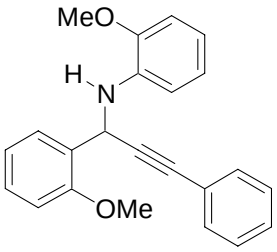
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 50.5, 55.4, 55.5, 84.8, 88.7, 109.6, 111.6, 113.0, 113.5, 117.7, 119.7, 121.1, 122.9, 128.17, 128.21, 129.7, 131.8, 136.4, 141.5, 147.1, 159.9.

MS (EI, 70 eV): *m/z* = 343 $[M]^+$, 312, 236 $[M-C_7H_7O]^+$, 221 $[M-C_7H_8NO]^+$, 178, 120, 77.

HPLC separation conditions: Chiralcel OD-H, 254 nm, heptane / *i*-PrOH 95:5, 0.6 mL/min; ret. time = 10.6 min (+, minor), 14.0 min (−, major).

Enantiomeric excess: ee = 88% (−).

6.8.10. (−)-*N*-(2-methoxyphenyl)-3-amino-3-(2-methoxyphenyl)-1-phenylprop-1-yne [(−)-230u]



$C_{23}H_{21}NO_2$. MW = 343.42 g mol^{-1}

Obtained from 2-methoxybenzaldehyde (**59x**, 0.4 mmol, 0.054 g), 2-methoxyaniline (**237**, 0.4 mmol, 0.049 g, 1.0 equiv) and phenylacetylene (**108**, 1.2 mmol, 0.123 g, 3.0 equiv), according to GP-17, using ligand (1*R*,2*S*)-**246g**. Purification by flash column chromatography (*n*-pentane / Et_2O 25:1) afforded pure (−)-**230u** (0.30 mmol, 0.103 g, 75% yield) as a yellow oil.

Optical rotation: $[\alpha]^{20}_D$ = −52.7 (c = 0.63, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.74 (s, 3H), 3.80 (s, 3H), 4.73 (br s, 1H), 5.76 (d, *J* = 4.4 Hz, 1H), 6.60-6.66 (m, 1H), 6.68-6.72 (m, 1H), 6.75-6.82 (m, 2H), 6.85 (dd, *J* = 8.2 Hz, *J* = 0.9 Hz, 1H), 6.92 (dt, *J* = 7.4 Hz, *J* = 0.9 Hz, 1H), 7.15-7.26 (m, 3H), 7.29-7.35 (m, 2H), 7.62 (dd, *J* =7.5 Hz, *J* =1.7 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 44.7, 55.5, 55.8, 83.5, 89.4, 109.5, 111.0, 111.7, 117.4, 120.9, 121.1, 123.2, 128.0, 128.1, 128.2, 128.4, 129.2, 131.8, 136.6, 147.2, 159.6.

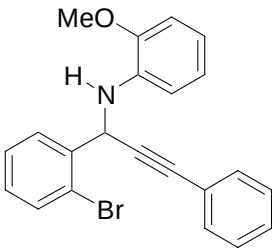
MS (EI, 70 eV): *m/z* = 343 $[M]^+$, 312, 236 $[M-C_7H_7O]^+$, 221 $[M-C_7H_8NO]^+$, 189, 178, 115, 65.

HPLC separation conditions: Chiralcel OD, 254 nm, heptane / *i*-PrOH 99.5:0.5, 0.6 mL/min; ret. time = 27.6 min (−, major), 35.0 min (+, minor).

Note: *considering the small amount of isopropanol needed, it is advised to use a pre-mixed eluent for the measurement, and to measure first a sample of racemic* ***230u****, since the retention times can slightly vary.*

Enantiomeric excess: ee = 97% (−).

6.8.11. (−)-*N*-(2-methoxyphenyl)-3-amino-3-(2-bromophenyl)-1-phenylprop-1-yne [(−)-230v]



$C_{22}H_{18}NOBr$. MW = 392.29 g mol^{-1}

Obtained from 2-bromobenzaldehyde (**59d**, 0.4 mmol, 0.074 g), 2-methoxyaniline (**237**, 0.4 mmol, 0.049 g, 1.0 equiv) and phenylacetylene (**108**, 1.2 mmol, 0.123 g, 3.0 equiv), according to GP-17, using ligand (1*R*,2*S*)-**246g**. Purification by flash column chromatography (*n*-pentane / Et_2O 20:1) afforded pure (−)-**230v** (0.29 mmol, 0.115 g, 73% yield) as a yellow oil.

Optical rotation: $[\alpha]^{20}_D = -47.2$ (c = 1.0, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.78 (s, 3H), 4.78 (br s, 1H), 5.71 (s, 1H), 6.57-6.81 (m, 4H), 7.07-7.40 (m, 5H), 7.50-7.56 (m, 2H), 7.70-7.76 (m, 2H).

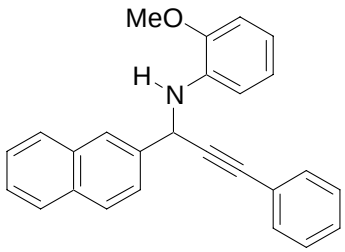
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 50.4, 55.5, 84.7, 87.8, 109.6, 111.5, 117.9, 121.2, 122.7, 123.6, 128.0, 128.2, 128.4, 128.9, 129.5, 131.8, 133.2, 136.1, 139.0, 147.1.

MS (EI, 70 eV): *m/z* = 393-391 $[M]^+$, 362-360, 271-269 $[M-C_7H_8NO]^+$, 236 $[M-C_6H_4Br]^+$, 189.

HPLC separation conditions: Chiralcel OD-H, 254 nm, heptane / *i*-PrOH 95:5, 0.6 mL/min; ret. time = 8.8 min (+, minor), 10.0 min (−, major).

Enantiomeric excess: ee = 81% (−).

6.8.12. (−)-*N*-(2-methoxyphenyl)-3-amino-3-(2-naphtyl)-1-phenylprop-1-yne [(−)-230f]



$C_{26}H_{21}NO$. MW = 363.45 g mol^{-1}

Obtained from 2-naphtaldehyde (**59n**, 0.4 mmol, 0.062 g), 2-methoxyaniline (**237**, 0.4 mmol, 0.049 g, 1.0 equiv) and phenylacetylene (**108**, 1.2 mmol, 0.123 g, 3.0 equiv), according to GP-17, using ligand (1*R*,2*S*)-**246g**. Purification by flash column chromatography (*n*-pentane / Et_2O 18:1) afforded pure (−)-**230f** (0.33 mmol, 0.119 g, 82% yield) as a colorless oil that solidified upon standing. Recrystallization from *n*-hexane afforded the product as colorless crystals.

Optical rotation: $[\alpha]^{20}_D = -69.9$ (c = 0.85, $CHCl_3$).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.76 (s, 3H), 4.80 (br s, 1H), 5.58 (s, 1H), 6.63-6.82 (m, 4H), 7.17-7.24 (m, 3H), 7.32-7.44 (m, 4H), 7.67 (dd, *J* = 8.7 Hz, *J* = 1.7 Hz, 1H), 7.74-7.83 (m, 3H), 8.05 (s, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 50.7, 55.5, 85.2, 88.7, 109.6, 111.7, 117.8, 121.1, 122.9, 125.4, 126.1, 126.2, 127.7, 128.15, 128.21, 128.3, 128.6, 131.8, 133.1, 133.4, 136.5, 137.3, 147.2.

MS (EI, 70 eV): *m/z* = 363 $[M]^+$, 241 $[M-C_7H_8NO]^+$, 226, 139, 115, 77.

HPLC separation conditions: Chiralcel OD-H, 254 nm, heptane / *i*-PrOH 95:5, 0.6 mL/min; ret. time = 11.4 min (+, minor), 16.1 min (−, major).

Enantiomeric excess: ee = 81% (−). After recrystallization the ee was 91% (−).

6.8.13. (−)-*N*-(2-methoxyphenyl)-1-amino-1-(4-chlorophenyl)non-1-yne [(−)-230p]

Obtained from 4-chlorobenzaldehyde (**59a**, 0.4 mmol, 0.056 g), 2-methoxyaniline (**237**, 0.4 mmol, 0.049 g, 1.0 equiv) and 1-octyne (**232**, 1.2 mmol, 0.132 g, 3.0 equiv), according to GP-17, using ligand (1*R*,2*S*)-**246g**. Purification by flash column chromatography (*n*-pentane / Et_2O 65:1) afforded pure (−)-**230p** (0.19 mmol, 0.068 g, 48% yield) as a colorless oil.

The analytical data have already been reported in paragraph *6.6.20.*

Optical rotation: $[\alpha]^{20}_D = -51.6$ (c = 0.86, $CHCl_3$).

HPLC separation conditions: Chiralcel OD-H, 254 nm, heptane / *i*-PrOH 95:5, 0.6 mL/min; ret. time = 7.5 min (−, major), 10.7 min (+, minor).

Enantiomeric excess: 81% (−).

7. Appendix

7.1. List of Abbreviations

Å	Ångstrom
[α]	specific optical rotation
Ac	acetyl
aq.	aqueous (solution)
Ar	aromatic substituent
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
br	broad (NMR signal)
Bu	butyl
*i*Bu	*iso*-butyl
*t*Bu	*tert*-butyl
CAMP	cyclohexyl-(*o*-methoxy)phenyl-methylphosphine
Cp	cyclopentadienyl
δ	chemical shift
DAIB	3-*exo*-dimethylaminoisoborneol
DAST	dimethylaminosulfur trifluoride
DBNE	*N*,*N*-dibutylnorephedrine
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DFT	density function theory
DiMPEG	polyethyleneglycol dimethylether
DiPAMP	1,2-ethanediyl-bis-[(*o*-methoxyphenyl)phenylphosphine]
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMF-DMA	*N*,*N*-dimethylformamide-dimethylacetal

DMSO	dimethylsulfoxide
DPMPM	diphenyl(1-methylpyrrolidin-2-yl)methanol
ee	enantiomeric excess
EEDQ	2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
EI	electronic impact (in mass spectroscopy)
Et	ethyl
eV	electronvolt
GC	gas chromatography
*c*Hex	cyclohexyl
*n*Hex	*n*-hexyl
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infrared spectroscopy
J	coupling constant (in NMR spectroscopy)
L	ligand
L*	chiral ligand
M	molar
Me	methyl
MeO-PEG	polyethyleneglycol monomethylether
Mes	2,4,6-trimethylphenyl (mesityl)
mol	mole
MOPEP	2-(morpholin-4-yl)-1-phenyl-1-propanol
Mp	melting point
Ms	methanesulfonyl (mesyl)
MS	mass spectroscopy
MTBE	methyl-*tert*-butylether
N	normal (concentration)
NLE	non-linear effect
ν	wave number
NME	*N*-methylephedrine
NMR	nuclear magnetic resonance (spectroscopy)
Ns	*p*-nitrobenzenesulfonyl (nosyl)

OMP	*o*-methoxyphenyl
PMP	*p*-methoxyphenyl
ppm	parts per million
*i*Pr	*iso*-propyl
*n*Pr	*n*-propyl
PyBOX	pyridine-bisoxazoline
rac	racemic
rt	room temperature
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol
THF	tetrahydrofuran
TMEDA	tetramethylethylendiamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl (tosyl)

7.2. List of Publications

Academic Publications:

1) Diploma thesis (in Italian): "Studies on aziridines' isomerization induced by mixed organometallic bases", University of Florence, 2002.

Publications on Journals:

1) A. Mordini, F. Russo, M. Valacchi, L. Zani, A. Degl'Innocenti and G. Reginato
"Base promoted elaboration of aziridines"
Tetrahedron **2002**, *58*, 7153-7163.

2) C. Bolm, L. Zani, J. Rudolph, I. Schiffers
"New chiral ligands derived from mandelic acid: synthesis and application in the asymmetric phenyl transfer reaction to an aromatic aldehyde"
Synthesis **2004**, 2173-2180.

3) C. Bolm, J. Legros, J. LePaih, L. Zani
"Iron-catalyzed reactions in organic synthesis"
Chem. Rev. **2004**, *104*, 6217-6254.

4) C. Bolm, F. Schmidt, L. Zani
"New chiral hydroxy oxazolines as useful ligands for the asymmetric phenylation of aromatic aldehydes"
Tetrahedron: Asymmetry **2005**, *16*, 1367-1376.

5) C. Bolm, T. Rantanen, I. Schiffers, L. Zani
"Protonated chiral catalysts: new and versatile tools for asymmetric synthesis"
Angew. Chem. **2005**, *116*, 1788-1793.
Angew. Chem. Int. Ed. **2005**, *44*, 1758-1763.

6) L. Zani, S. Alesi, P. G. Cozzi, C. Bolm
"Dimethylzinc-mediated alkynylation of imines"
J. Org. Chem. **2006**, *71*, 1558-1562.

7) I. Schiffers, T. Rantanen, F. Schmidt, W. Bergmans, L. Zani, C. Bolm
"Resolution of racemic 2-aminocyclohexanol derivatives and their application as ligands in asymmetric catalysis"
J. Org. Chem. **2006**, *71*, 2320-2331.

8) L. Zani, C. Bolm
"Direct addition of alkynes to imines and related C=N electrophiles: a convenient access to propargylamines"
Manuscript submitted for publication.

Poster and Oral Communications:

1) Riccione, Italy, October 18th-19th, 2001: 1st Sigma-Aldrich Young Chemists Symposium. Poster Communication "Studi sull'isomerizzazione di aziridine indotta da basi organometalliche miste", *Alessandro Mordini, Gianna Reginato, Francesco Russo, Michela Valacchi, Lorenzo Zani*

2) Bari, Italy, June 20th-24th, 2002: 2nd Transmediterrenean Colloquium on Heterocyclic Chemistry. Brief Communication "Useful elaborations of small ring heterocycles", *Alessandro Mordini, Gianna Reginato, Francesco Russo, Michela Valacchi, Lorenzo Zani*

3) Venice, Italy, July 1st-3rd, 2002: 5th Congress of the Interdivisional Group of Organometallic Chemistry of the Italian Chemical Society. Oral Communication "Application of mixed organometallics bases to the isomerization of N-activated aziridines", *Alessandro Mordini, Gianna Reginato, Francesco Russo, Lorenzo Zani, Michela Valacchi*

4) Ischia, Italy, September 21st-26th, 2002: Ischia Advanced School of Organic Chemistry. Poster Communication "Elaboration of Aziridines Promoted by Mixed Organometallic Bases", *Francesco Russo, Alessandro Mordini, Michela Valacchi, Lorenzo Zani, Gianna Reginato*

5) Cavtat-Dubrovnik, Croatia, September 10th-15th, 2003: 13th European Symposium on Organic Chemistry (ESOC 13). Poster Communication "Synthesis and Applications of Chiral Ligands derived from Mandelic Acid", *Carsten Bolm, Jens Rudolph, Ingo Schiffers, Lorenzo Zani*

6) Juelich, Germany, October 16th-17th, 2003: 7th Symposium of Sonderforschungsbereich (SFB) 380. Poster Communication "New Chiral Ligands Derived from Mandelic Acid – Synthesis and Application in Asymmetric Catalysis", *Carsten Bolm, Jens Rudolph, Ingo Schiffers, Lorenzo Zani*

7) Munich, Germany, July 5th-9th, 2004: 14th International Symposium on Homogeneous Catalysis (ISHC-14). Poster Communication "New Chiral Hydroxy Oxazolines as Ligands for the Asymmetric Aryl Transfer Reaction to Aldehydes", *Lorenzo Zani, Carsten Bolm, Frank Schmidt*

8) Juelich, Germany, October 7th-8th, 2004: 8th Symposium of Sonderforschungsbereich (SFB) 380. Poster Communication "New Chiral Hydroxy Oxazolines as Ligands for the Asymmetric Phenylation of Aldehydes", *Carsten Bolm, Frank Schmidt, Lorenzo Zani*

9) Spa, Belgium, December 2nd-3rd, 2004, 8th Sigma-Aldrich Organic Synthesis Meeting. Poster Communication "Novel Chiral Hydroxy Oxazolines as Ligands for the Asymmetric Phenylation of Aldehydes", *Carsten Bolm, Frank Schmidt, Lorenzo Zani*

10) Geneva, Switzerland, July 17th-22nd, 2005, 13th Symposium on Organometallic Chemistry directed towards Organic Synthesis (OMCOS-13). Poster Communication "Studies on the Zinc-mediated Alkynylation of N-Activated Aromatic Imines", *Lorenzo Zani, Carsten Bolm*

11) Aachen, Germany, October 10th-11th, 2005: 9th Symposium of Sonderforschungsbereich (SFB) 380. Poster Communication "The First Dimethylzinc-mediated Alkynylation of Aromatic Imines", *Carsten Bolm, Pier Giorgio Cozzi, Silvia Alesi, Lorenzo Zani*

7.3. Curriculum Vitae et Studiorum

Personal Informations

Name: Lorenzo Zani
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Educational Background

7/1996: Scientific High School Diploma with a 60/60 mark.

1996-2002: Course of studies in chemistry (Organic Chemistry) at the University of Florence, Faculty of Natural Sciences.

2001-2002: Experimental work in a CNR-ICCOM (Italian National Research Council – Institute for the Chemistry of Organometallic Compounds) laboratory associated to the Department of Organic Chemistry of the University of Florence as a part of the Diploma thesis, under the supervision of Dr. Alessandro Mordini.

4/2002: Graduation ("Laurea in Chimica") with a 110/110 *cum laude* (honors) mark.

2003-2006: Ph. D. work at RWTH Aachen under the supervision of Prof. Dr. Carsten Bolm, working on asymmetric C-C bond forming reactions mediated by organozinc compounds.