Synthesis of New Sulfoximines for Asymmetric Synthesis and Pseudopeptides

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften
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vorgelegt von

Gae Young Cho
(MASTER IN SCIENCE)

aus Seoul, Korea

Berichter: Universitätsprofessor Dr. C. Bolm
Universitätsprofessor Dr. D. Enders

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Cho, G. Y.; Bolm, C. *Org. Lett.* **2005**, *7*, 1351.

Cho, G. Y.; Okamura, H.; Bolm, C. *J. Org. Chem.* **2005**, *20*, 2346.

Cho, G. Y.; Remy, P.; Jansson, J.; Moessner, C.; Bolm, C. *Org. Lett.* **2004**, *6*, 3293.

Index

3. Part I. Synthesis and Palladium-catalyzed cross coupling of *p*-bromophenyl methyl sulfoximine

4. Part II. Palladium-catalyzed α-arylation of *N*-benzoyl sulfoximine ethyl ester

5. Part III. Copper-mediated N-arylation of sulfoximines

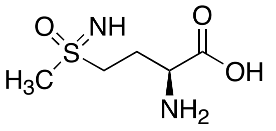
6. Part IV. Silver-catalyzed and metal-free imination of sulfoxides and sulfides

7. Miscellaneous

9. Appendix

1. General introduction to sulfoximines

Since the discovery of sulfoximine **1** (Figure 1) as a toxic factor of the disease *canine hysteria* at the end of 1940s,[1] sulfoximines have been widely used as versatile building blocks in organic chemistry. Sulfoximines, the monoaza analogues of sulfones, have several interesting features including a stereogenic sulfur atom, nucleophilic nitrogen and acidic α-hydrogens.



1
(2*S*,5*S*)-methionine sulfoximine

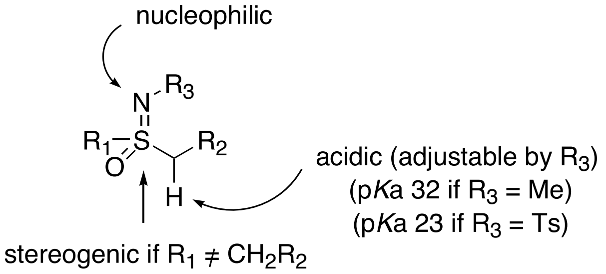


Figure 1.

In general, sulfoximines are synthesized from sulfides in two steps involving oxidation[2] and imination.[3,4] Enantiomerically pure sulfoximines are accessible by the stereospecific imination[5] of optically active sulfoxides or resolution of racemic sulfoximines[6] (Scheme 1). In the case of NH-methylphenyl sulfoximine, the resolution method reported by Gais is most commonly used.[7]

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[1] (a) Whitehead, J. K.; Bentley, H. R. *J. Chem. Soc.* **1952**, 1572. For reviews on sulfoximine, see: (b) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482. (c) Harmata, M. *Chemtracts* **2003**, *16*, 660. (d) Reggelin, M.; Zur, C. *Synthesis* **2002** 1.

[2] (a) Rynbrandt, R. H.; Balgoyen, D. P. *J. Org. Chem.* **1978**, *43*, 1824. (b) Stoss, P.; Satzinger, G. *Angew. Chem.* **1971**, *83*, 83. (c) Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594. (d) Bentley, H. R.; Whitehead, J. K. *J. Chem. Soc.* **1952**, 1572. Asymmetric sulfoxidation, see section 3-1.

[3] NaN_3/H^+: (a) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418. (b) Fusco, R.; Tericoni, F. *Chim. Ind. (Milan)* **1965**, *47*, 61.

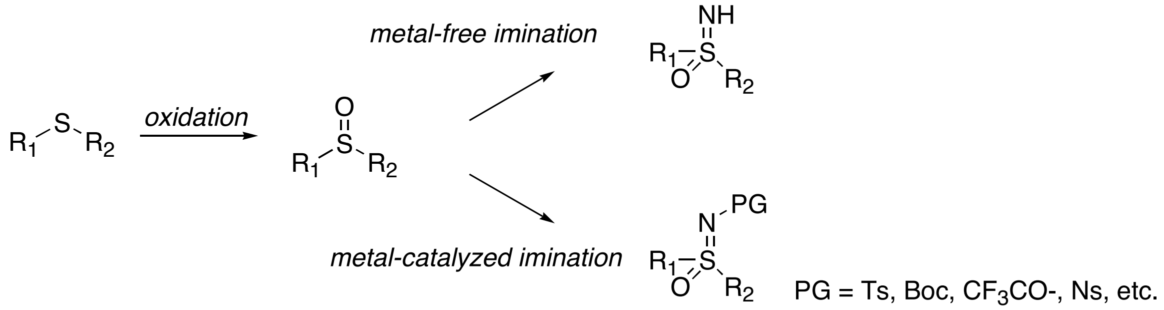
[4] MSH: (a) Tamura, Y.; Matushima, H.; Minamikawa, J.; Ikeda, M.; Sumoto, K. *Tetrahedron* **1975**, *31*, 3035. (b) Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; John-Wiley & Sons: New York, 1975, Vol. 5; p 430. (c) Johnson, C. R.; Kirchhoff, R. A.; Corkins, H. G. *J. Org. Chem.* **1974**, *39*, 2458. (d) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239.

[5] See section 3-1.

[6] (a) Shiner, C. S.; Berks, A. H. *J. Org. Chem.* **1988**, *53*, 5542. (b) Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424.

[7] Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *6*, 909.

Scheme 1. Synthesis of sulfoximines



Sulfoximines have been applied as chiral auxiliaries[8] in asymmetric synthesis by including Johnson, Gais, Harmata, Pyne, Craig, Reggelin and others. Their use in pseudopeptides[9] has been investigated by Mock, Tsujihara, Bolm and Weinhold.

Furthermore, Bolm and coworkers initiated the application of sulfoximines as chiral ligands for enantioselective C-C bond formation reactions in 1992.[10] Since then, a number of successful applications of sulfoximines have been reported in asymmetric catalyses such as Diels-Alder,[11] hetero Diels-Alder,[12] Mukaiyama aldol,[13] ene-reaction,[14] asymmetric hydrogenantion,[15] and vinylogous aldol reaction.[16]

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[8] (a) Craig, D.; Grellepois, F.; White, A. J. P. *J. Org. Chem.* **2005**, *70*, 6827. (b) Harmata, M.; Hong, X. *Org. Lett.* **2005**, *7*, 3581. (c) Gais, H.-J.; Babu, G. S.; Günter, M.; Das, P. *Eur. J. Org. Chem.* **2004**, 1464. (d) Harmata, M.; Hong, X. *J. Am. Chem Soc.* **2003**, *125*, 5754. (e) Hamata, M.; Hong, X.; Barnes, C. L. *Tetrahedron Lett.* **2003**, *44*, 7261. (f) Koep, S.; Gais, H.-J.; Raabe, G. *J. Am. Chem. Soc.* **2003**, *125*, 13243. (g) Reddy, R. R.; Gais, H.-J.; Woo, W. -W.; Raabe, G. *J. Am. Chem. Soc.* **2002**, *124*, 10427. (h) Harmata, M.; Pavri, N. *Angew. Chem.* **1999**, *111*, 2577. (i) Harmata, M.; Kahraman, M.; Jones, D. E.; Pavri, N.; Weatherwax, S. E. *Tetrahedron* **1998**, *54*, 9995. (j) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543. (k) Bosshammer, S.; Gais, H.-J. *Synthesis* **1998**, 919. (l) Reggelin, M.; Heinrich, T. *Angew. Chem.* **1998**, *110*, 3005. (m) Pyne, S. G.; Dong, Z.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **1997**, *62*, 2337. (n) Trost, B. M.; Matuoka, R. T. *Synlett* **1992**, 27. (o) Haiza, M.; Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 5008.

[9] (a) Kumar, P.; Bharatam, P. V. *Tetrahedron* **2005**, *61*, 5633. (b) Hackenberger, C. P. R.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2004**, *10*, 2942. (c) Bolm, C.; Müller, C.; Dalhoff, C.; Hackenberger, C. P. R.; Weinhold, E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3207. (d) Tye, H.; Skinner, C. L. *Helv. Chim. Acta* **2002**, *85*, 3272. (e) Bolm, C.; Müller, D.; Hackenberger, C. P. R. *Org. Lett.* **2002**, *4*, 893. (f) Bolm, C.; Moll, G.; Kahmann, J. D. *Chem. Eur. J.* **2001**, *7*, 1118. (g) Kawanishi, H.; Morimoto, H.; Nakano, T.; Watanabe, T.; Oda, K.; Tsujihara, K. *Heterocycles* **1998**, *49*, 181. (h) Bolm, C.; Kahnmann, J. D.; Moll, G. *Tetrahedron Lett.* **1997**, *38*, 1169. (i) Mock, W. L.; Zhang, J. Z. *J. Biol. Chem.* **1991**, *266*, 6393. (j) Mock, W. L.; Tsay, J.-T. *J. Am. Chem. Soc.* **1989**, *111*, 4467.

[10] Bolm, C.; Felder, M.; Müller, J. *Synlett* **1992**, 439.

[11] Bolm, C.; Martin, M.; Simic, O.; Verrucci, M. *Org. Lett.* **2003**, *5*, 427.

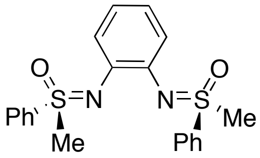
[12] (a) Bolm, C.; Verrucci, M.; Simic, O.; Cozzi, P. G.; Raabe, G.; Okamura, H. *Chem. Commun.* **2003**, 2826. (b) Bolm, C.; Simic, O. *J. Am. Chem. Soc.* **2001**, *123*, 3830.

[13] Langner, M.; Bolm, C. *Angew. Chem.* **2004**, *116*, 6110.

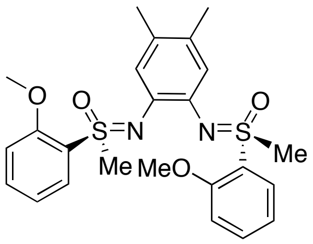
[14] (a) Langner, M.; Remy, P.; Bolm, C. *Chem. Eur. J.* **2005**, *11*, 6254. (b) Langner, M.; Remy, P.; Bolm, C. *Synlett* **2005**, 781.

[15] Moessner, C.; Bolm, C. *Angew. Chem.* **2005**, *117*, 7736.

[16] Remy, P.; Langner, M.; Bolm, C. submitted for publication.



2
Hetero Diels-Alder
up to 98% ee



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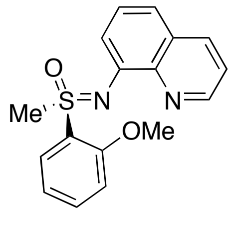
Diels-Alder
up to 93% ee



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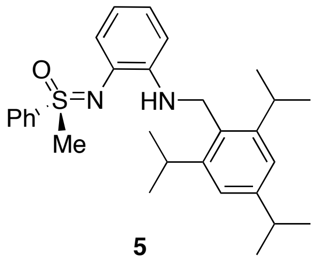
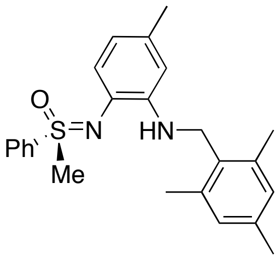
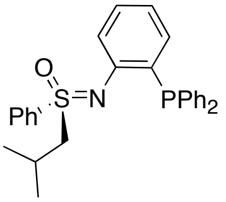
Hetero Diels-Alder
up to 96% ee



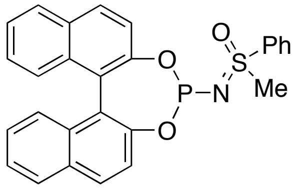
5
Mukayama Aldol
Vinylogous Aldol
up to 99% ee



6
Ene reaction
up to 91% ee



7
Asymmetric hydrogenation
up to 98% ee



8
Asymmetric hydrogenation
up to 99% ee

Figure 2. Sulfoximine Ligands

Together with the application of sulfoximines to asymmetric catalysis, a variety of efficient synthetic methods to prepare sulfoximine derivatives have also been investigated by Bolm.[17]

2. Research objectives

Sulfoximines are attractive compounds for biomedical and pharmaceutical chemistry, and their application as chiral ligands and building blocks for pseudopeptides is increasing. Hence, the synthesis of sulfoximines with any scaffold needs to be possible. This thesis is mainly focused on the development of new synthetic methodologies and the improvement of ones in order to prepare various sulfoximine compounds conveniently. The strategies for these purposes involve: (i) aryl substitution on sulfoximines by metal-catalyzed cross coupling, (ii) α-functionalization of sulfoximines by metal-catalyzed C-arylation, (iii) N-arylation of sulfoximines and (iv) metal-catalyzed or metal-free iminations of sulfoxides to afford sulfoximines (Figure 3).

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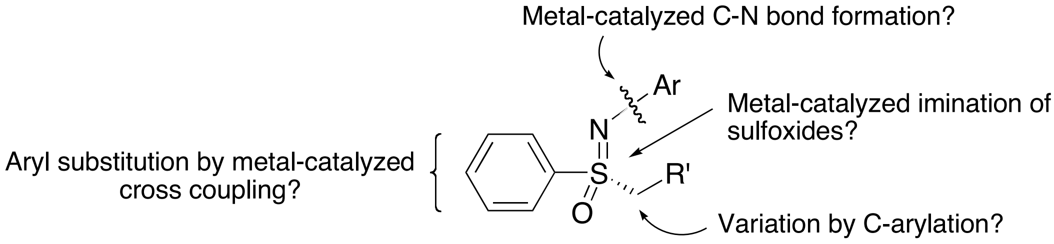
[17] (a) Sedelmeier, J.; Bolm, C. *J. Org. Chem.* **2005**, *70*, 6904. (b) Moessner, C.; Bolm, C. *Org. Lett.* **2005**, *7*, 2667. (c) Dehli, J. R.; Bolm, C. *Synthesis* **2005**, 105. (d) Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 239. (e) Bolm, C.; Villar, H. *Synthesis* **2005**, 1421. (f) Moessner, C.; Bolm, C. *Org. Lett.* **2005**, *7*, 2667. (g) Dehli, J. R.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 8518. (h) Bolm, C.; Okamura, H.; Verrucci, M. *J. Organomet. Chem.* **2003**, *687*, 444.

A substituent on the aryl group of a sulfoximine is expected to vary the electronic properties of the sulfur fragment as well as having an impact on the conformation of the molecule. This led us to devise a convenient synthetic tool to prepare diverse *para*-substituted phenylmethylsulfoximines in enantiomerically pure form. Since preparative routes to optically active sulfoximines are rather limited by existing methods, research was concentrated on the development of a stereospecific transformation starting from enantiomerically pure sulfoximines which can be readily prepared.



Metal-catalyzed C-N bond formation?

Metal-catalyzed imination of sulfoxides?

Aryl substitution by metal-catalyzed cross coupling?

Variation by C-arylation?

Figure 3. Research objectives

Another methodology which we aimed for was the α-functionalization of sulfoximines to give various optically active benzylphenylsulfoximine derivatives which, with existing methods, are either difficult to prepare in enantiomerically pure form or required a number of synthetic steps.

The sulfoximines most successfully applied as ligands contain N-aryl substituents (Figure 2) and are usually prepared by palladium-catalyzed N-arylation as reported by Bolm.[18] Although palladium complexes are efficient catalysts for this transformation, an alternative approach for the C-N bond formation of NH-sulfoximines was required in order to extend the substrate scope and improve the applicability to large scale. We, therefore, focused on the development of a new method to introduce diverse aryl groups on the nitrogen atom of sulfoximines.

In order to avoid using toxic and explosive iminating reagents or expensive catalysts, we also planned to modify the imination reaction of sulfoxides. There is no doubt that the development of safe and efficient imination reactions to prepare sulfoximines is very important for the practical application of sulfoximines on a large scale.

Along with the investigation of these methodologies, novel sulfoximine compounds were designed and attempted to be applied as chiral ligands for various asymmetric catalysis.

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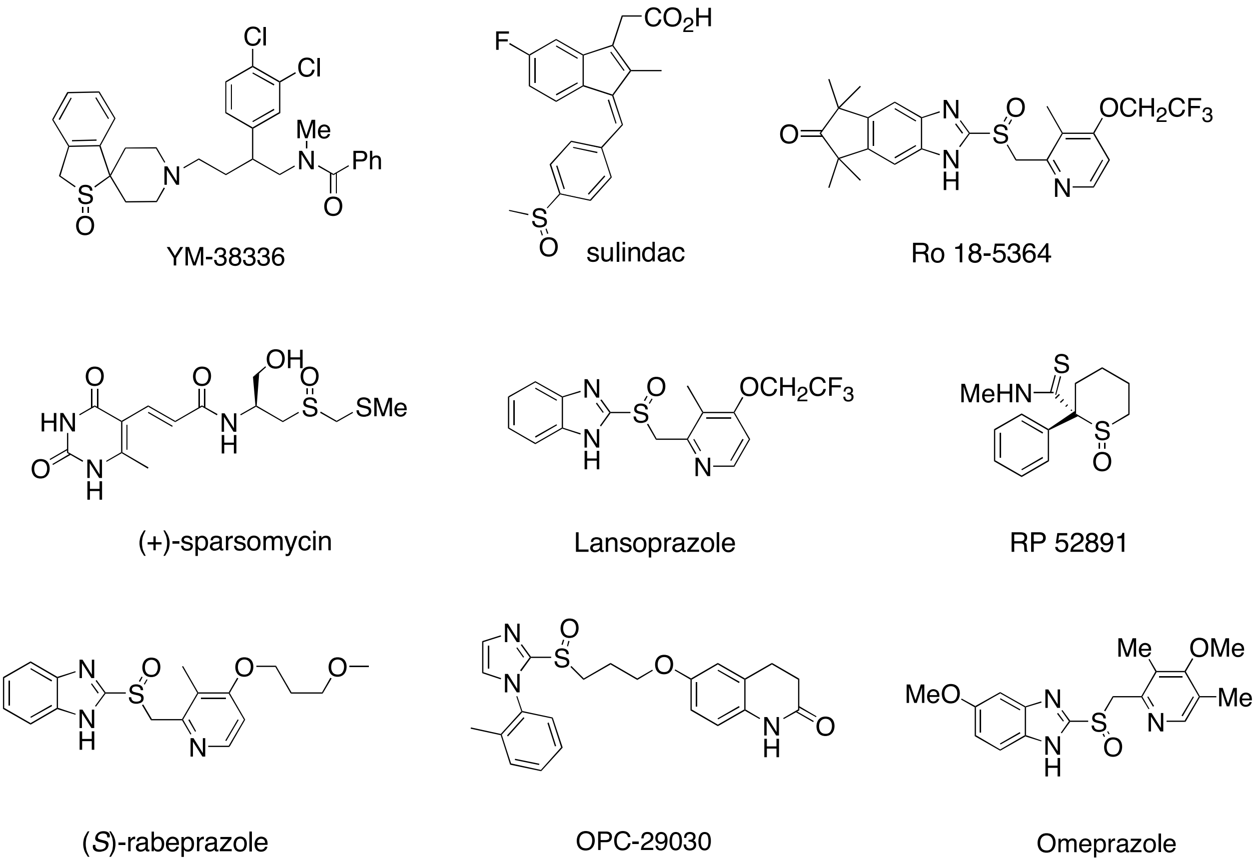
[18] (a) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169. (b) Bolm, C.; Hildebrand, J. P. *Synthesis* **2000**, 911. (c) Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *39*, 5731.

3. Part I. Palladium-catalyzed cross coupling of *p*-bromophenylmethyl sulfoximines

3-1. The preparation of chiral sulfoxides: Introduction

Enantiomerically pure sulfoxides are important moieties for medicinal and pharmaceutical chemistry and a large number of bioactive compounds contain optically active sulfoxides (Figure 4).[19]


YM-38336 sulindac Ro 18-5364

(+)-sparsomycin Lansoprazole RP 52891

(*S*)-rabeprazole OPC-29030 Omeprazole

Figure 4. Bioactive sulfoxides

In general, the synthetic methods available for their preparation in enantiomerically pure form can be divided into two categories: (i) metal-catalyzed asymmetric oxidation of sulfides and (ii) nucleophilic substitution on diastereomerically or enantiomerically pure chiral sulfur derivatives.[20] This chapter describes asymmetric sulfoxidation by these two methods.

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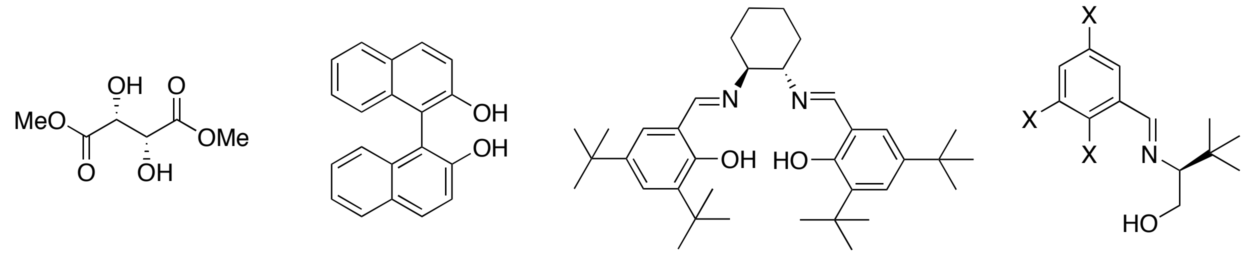
[19] For recent review, see: Legros, J.; Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 19 and references therein.

[20] For recent review of asymmetric sulfoxidation, see: Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651.

3-1-1. Metal-catalyzed asymmetric oxidation of sulfides

One of the most powerful and straightforward methods of obtaining enantiomerically pure sulfoxides from pure sulfides involves the use of an oxidant with a chiral metal complex as catalyst. As a pioneering research, Kagan and Modena utilized a chiral titanium reagent prepared by the mixture of Ti(O*i*Pr)$_4$ and tartrate. Uemura extended this procedure by using BINOL as a ligand. Mn^{III}(salen) was introduced as a catalyst for the asymmetric sulfoxidation by Jacobsen and Katsuki. In addition, Bolm developed vanadium- and iron-catalyzed asymmetric oxidations using chiral Schiff-based ligands **IV** (Figure 5).



I
DET

II
BINOL

III
salen

IV
Schiff base ligand

Figure 5. Chiral ligands for asymmetric sulfoxidation

3-1-1-1. Metal-catalyzed asymmetric oxidation of sulfides by using chiral titanium reagents

The chiral titanium complex formed in situ from Ti(O*i*Pr)$_4$ and diethyl tartrate (DET) has been successfully applied to the asymmetric epoxidation of allylic alcohols by Sharpless.[21] This outstanding system was extended to the enantioselective sulfoxidation by Kagan and Modena, independently.

In the initial study, Kagan and coworkers discovered that adding 1.0 equiv of water to the mixture of Ti(O*i*Pr)$_4$/DET catalyst enhanced the enantioselectivity of the asymmetric oxidation of sulfides (condition A in Scheme 2).[22] Under optimal conditions with *tert*-butyl hydroperoxide (TBHP) as oxidant and Ti(O*i*Pr)$_4$/DET/H_2O (1:2:1) as catalyst in dichloromethane at –20 °C, a variety of optically active alkylaryl or dialkyl sulfoxides were synthesized in good yields and enantioselectivities. Modena and coworkers also applied

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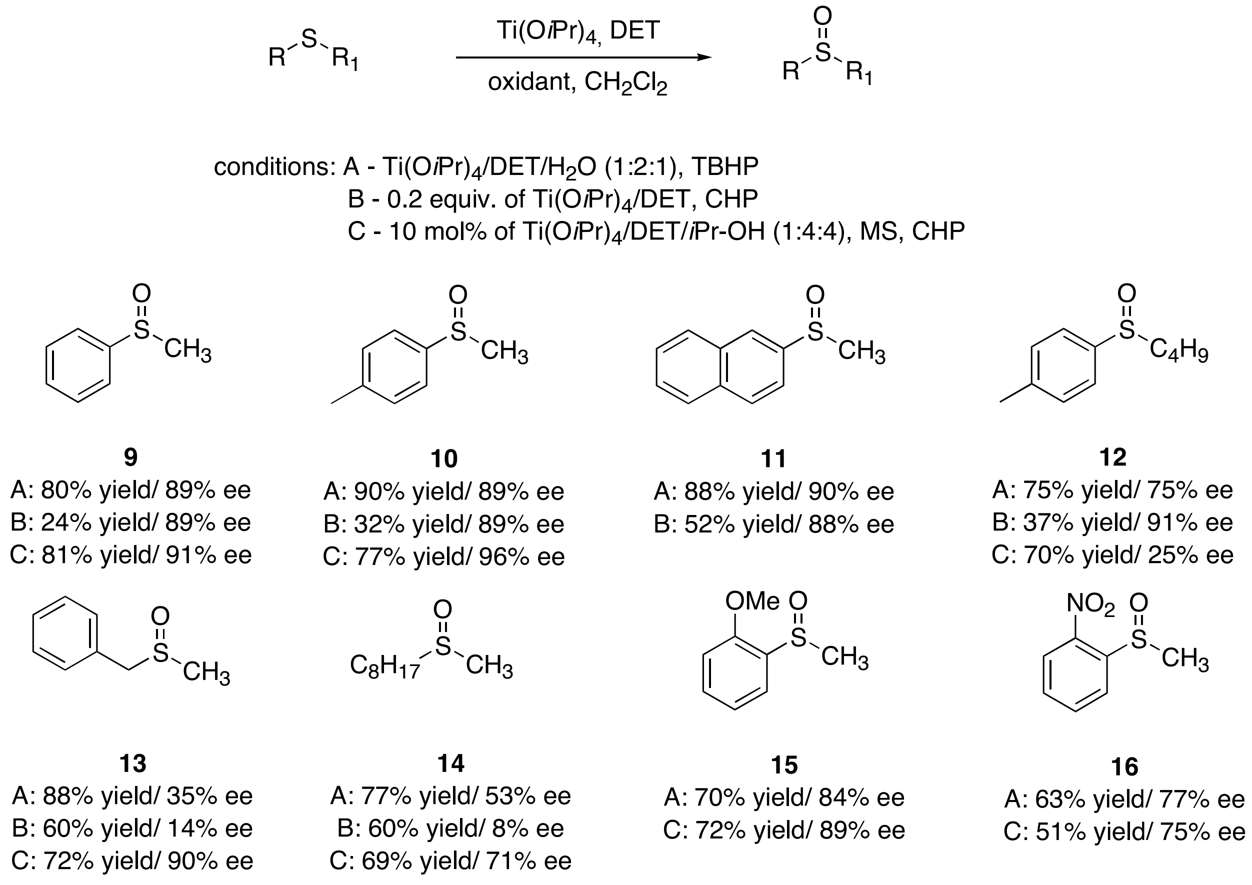
[21] Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993: p 227.

[22] Pitchen, P.; Deshmukh, M. N.; Dunach, E.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188.

this chiral titanium catalyst in the same transformation, utilizing a 1:1:4 mixture of TBHP, Ti(O*i*Pr)$_4$ and DET in toluene or 1,2-dichloroethane at –20 °C.[23] The results of Modena's system were similar to those obtained with Kagan´s except in the oxidation of 1,3-dithiolane which gave better results under Modena's conditions.

Kagan and coworkers then achieved a dramatic improvement of this transformation by the substitution of TBHP for cumene hydroperoxide (CHP) as oxidant (condition B in Scheme 2).[24] With CHP the use of only 0.2 equiv of chiral titanium complexes was possible without loss of enantioselectivity although low reaction yields were still problematic.

Scheme 2. Asymmetric sulfoxidation



conditions: A - Ti(O*i*Pr)$_4$/DET/H$_2$O (1:2:1), TBHP
B - 0.2 equiv. of Ti(O*i*Pr)$_4$/DET, CHP
C - 10 mol% of Ti(O*i*Pr)$_4$/DET/*i*Pr-OH (1:4:4), MS, CHP

9
A: 80% yield/ 89% ee
B: 24% yield/ 89% ee
C: 81% yield/ 91% ee

10
A: 90% yield/ 89% ee
B: 32% yield/ 89% ee
C: 77% yield/ 96% ee

11
A: 88% yield/ 90% ee
B: 52% yield/ 88% ee

12
A: 75% yield/ 75% ee
B: 37% yield/ 91% ee
C: 70% yield/ 25% ee

13
A: 88% yield/ 35% ee
B: 60% yield/ 14% ee
C: 72% yield/ 90% ee

14
A: 77% yield/ 53% ee
B: 60% yield/ 8% ee
C: 69% yield/ 71% ee

15
A: 70% yield/ 84% ee
C: 72% yield/ 89% ee

16
A: 63% yield/ 77% ee
C: 51% yield/ 75% ee

However, further advancement of the catalytic process was accomplished later (method C in Scheme 2).[25,26] The use of isopropanol with Ti(O*i*Pr)$_4$/DET (4:1:4, respectively) and molecular sieves as a moisture scavanger led to increased reaction yields and allowed the

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[23] Furia, F. D.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325.

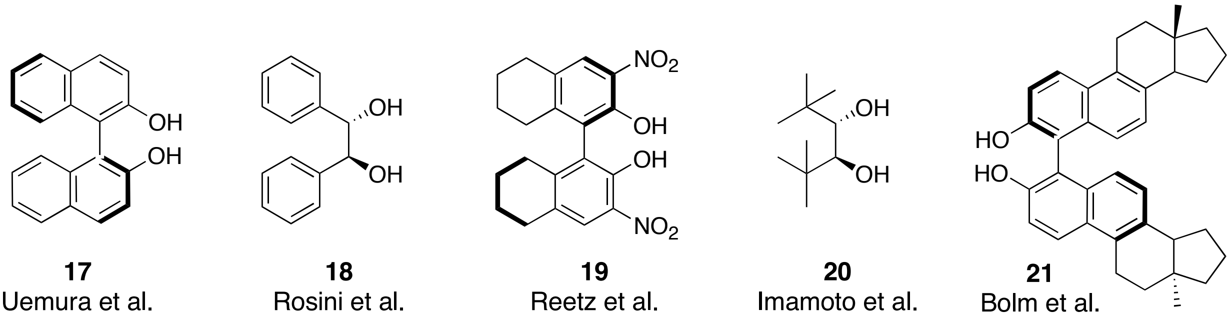
[24] (a) Zhao, S. H.; Saumel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135. (b) Zhao, S. H.; Saumel, O.; Kagan, H. B. *Org. Synth.* **1998**, *68*, 49.

[25] Brunel, J. M.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1996**, *133*. 1109.

[26] Brunel, J. M.; Kagan, H. B. *Synlett* **1996**, 404.

catalyst loading to be decreased to 10 mol%. Almost similar or slightly improved enantioselectivities were obtained compared to the procedure without isopropanol (method B).

After the pioneering work of Kagan and Modena, many groups began to exploit C_2-symmetric diols as ligands (Figure 6). The most successful application was carried out by Uemura and coworkers.[27,28] They found that Ti(O*i*Pr)$_4$/(*R*)-binaphthol (5 mol%) efficiently catalyzed the asymmetric oxidation of arylmethyl sulfides in the presence of TBHP as an oxidant and H_2O at room temperature. Using this catalytic system, the corresponding sulfoxides were synthesized in high enantioselectivities (up to 96% ee) and in moderate to good yields (32-88%).



17 Uemura et al. **18** Rosini et al. **19** Reetz et al. **20** Imamoto et al. **21** Bolm et al.

Figure 6.

Besides BINOL, several other chiral diols were investigated, including 1,2-diphenylethane-1,2-diol (**18**),[29] 3,3'-dinitrooctahydrobinaphthol (**19**),[30] 2,2,5,5-tetramethyl-3,4-hexanediol (**20**),[31] and steroid-derived BINOL **21** (Figure 6).[32]

3-1-1-2. Metal-catalyzed asymmetric oxidation of sulfides by using chiral manganese reagents

Jacobsen, followed by Katsuki, reported the use of Mn^{III}(salen) as a catalyst for the asymmetric oxidation of alkylaryl sulfides. Jacobsen employed 2 mol% of the chiral manganese reagent **22a** (Figure 7) which led to outstanding enantioselectivities in the

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[27] Kamatsu, N.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *Tetrahedron Lett.* **1992**, *33*, 5391.

[28] Kamatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529.

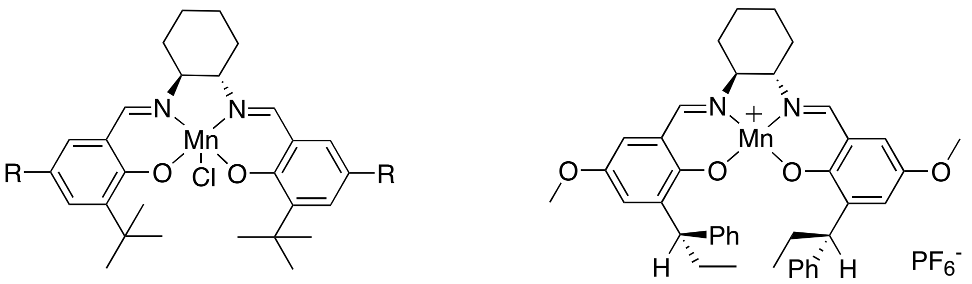
[29] (a) Superchi, M. I.; Donnoli, M. I.; Rosini, C. *Tetrahedron Lett.* **1998**, *39*, 8541. (b) Donnoli, M. I.; Superchi, M. I. M.; Rosini, C. *J. Org. Chem.* **1998**, *63*, 9392. (c) Superchi, M. I.; Rosini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 349.

[30] Reetz, M. T.; Merck, C.; Nberfeld, G.; Rudolph, J.; Griebenow, N.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 5273.

[31] Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1997**, *62*, 8560.

[32] Bolm, C.; Dabard, O. A. G. *Synlett* **1999**, 360.

epoxidation of conjugated olefines, with H_2O_2 as an oxidant.[33] However, in the asymmetric sulfoxidation, only maximum 24% ee was observed with the complex **22a**. Use of the more electron rich chiral manganese complex **22b** (Figure 7) increased the enantioselectivities up to 47% ee.



22a: R = *t*Bu
22b: R = OMe

23

Figure 7.

Katsuki and coworkers devised new salen-type catalysts such as **23** (Figure 7) for the use in this transformation. The combination of the new manganese catalyst **23** and PhIO as oxidant provided the corresponding sulfoxides in high enantioselectivities (up to 90% ee).[34]

3-1-1-3. Metal-catalyzed asymmetric oxidation of sulfides using chiral vanadium catalysts

Asymmetric vanadium catalysts have been used for many transformations in organic chemistry.[35] Among them, asymmetric sulfoxidation was performed for the first time by Nakajima and coworkers in 1986.[36] They utilized an oxovanadium(IV) complex (5 mol%) bearing a chiral salen-type ligand as a catalyst and cumene hydroperoxide (CHP) as an oxidant in the oxidation of methylphenylsulfide to the corresponding sulfoxide.[37] As a result, an enantioselectivity of 42% ee was achieved. In 1995, Bolm and Bienewald applied the chiral Schiff-base ligand **24** (Scheme 3), which can be readily prepared from

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[33] Palucki, M.; Hanson, P.; Jacobsen, E. N. *Tetrahedron Lett.* **1992**, 33, 7111.

[34] (a) Kokubo, C.; Katsuki, T. *Tetrahedron* **1997**, *52*, 13895. (b) Kokubo, C.; Katsuki, T. *Tetrahedron* **1996**, *52*, 13895. (c) Noda, K.; Hosoya, N.; Irie, R.; Yamashita, Y.; Katsuki, T. *Tetrahedron* **1994**, *50*, 9609. (d) Sasaki, H.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1994**, 356. (e) Noda, K.; Hosoya, N.; Yanai, K.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **1994**, *35*, 1887.

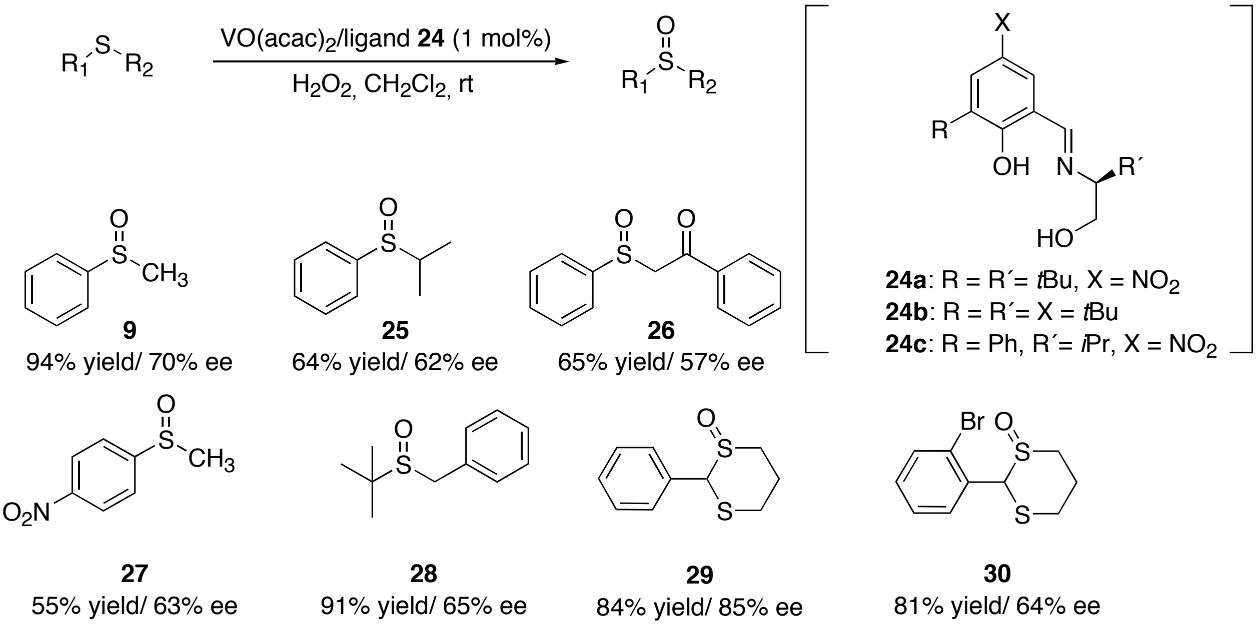
[35] Bolm, C. *Coord. Chem. Rev.* **2003**, *237*, 245.

[36] Nakajima, K.; Kojima, K.; Aoyama, T.; Fujita, J. *Chem. Lett.* **1986**, 1483.

[37] (a) Sasaki, C.; Nakajima, K.; Kojima, K.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1318. (b) Nakajima, K.; Kojima, K.; Aoyama, T.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2620.

salicylaldehyde and amino alcohols, in the same transformation.[38] The combination of vanadyl acetylacetonate with compound **24** as ligand produced a remarkable catalyst for the oxidation of sulfide. With this, extremely low catalyst loadings (down to 0.01 mol%) were still effective. Moreover, hydrogen peroxide, a safe and inexpensive oxidant, could be used in open vessels. The Schiff-base ligands derived from *tert*-leucinol (**24a** and **24b**) gave the best results. A number of optically pure sulfoxides could be prepared by this method in moderate to good yields and enantioselectivities (Scheme 3).[39]

Scheme 3. Vanadium-catalyzed oxidation of sulfoxides



After its intial discovery by Bolm and Bienewald, this vanadium-catalyzed asymmetric oxidation, with a ligand type **24** was further utilized and modified by several other groups including Skarzewski,[40] Berkessel,[41] Ellman,[42] Katsuki and Ahn.[43]

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[38] Bolm, C.; Bienewald, F. *Angew. Chem.* **1995**, *107*, 2883.

[39] (a) Bolm, C.; Bienewald, F. *Synlett* **1998**, 1327. (b) Bolm, C.; Schlingloff, G.; Bienewald, F. *J. Mol. Catal. A* **1997**, *117*, 347.

[40] Skarzewski, J.; Ostrycharz, E.; Siedlecka, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3457.

[41] Vetter, A. H.; Berkessel, A. *Tetrahedron Lett.* **1998**, *39*, 1741.

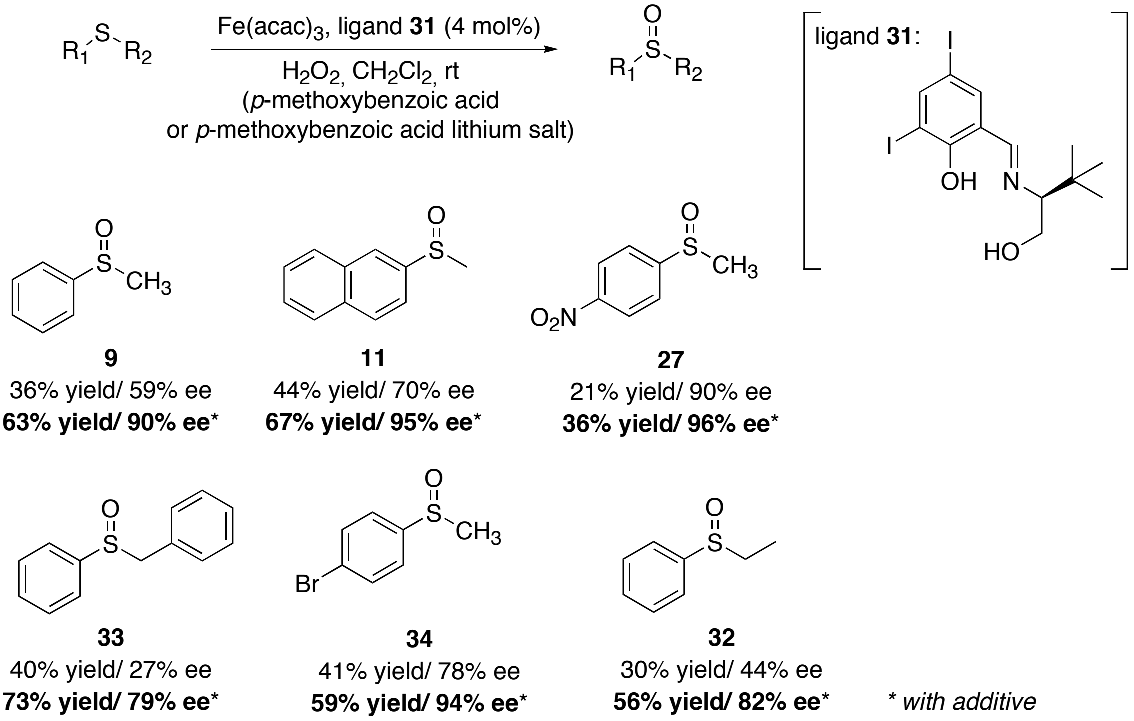
[42] (a) Weix, D. J.; Ellman, J. A. *Org. Synth.* **2005**, *82*, 157. (b) Cogan, D. A.; Liu, G.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011. (c) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.

[43] (a) Ohta, C.; Shimizu, H.; Kondo, A.; Katsuki, T. *Synlett* **2002**, 161. (b) Jeong, Y. C.; Huang, Y. D.; Choi, S.; Ahn, K. H. *Tetrahedron: Asymmetry* **2005**, *16*, 3497.

3-1-1-4. Metal-catalyzed asymmetric oxidation of sulfides using a chiral iron complex

Significant progress has been made in metal-catalyzed asymmetric sulfoxidations with titanium, manganese and vanadium, but iron has been much less exploited in this field. A few iron complexes such as iron phorphyrin and $[Fe_2O(pb)_4(H_2O)_2(ClO_4)_4]$ [pb = (–)-4,5-pinene-2,2'-bipyridine][44] have been reported as catalysts with oxidants such as iodosylbenzene or H_2O_2 in asymmetric oxidation, but their enantioselectivities were only moderate or low (up to 73% ee). This was the case until Bolm and Legros found that the combination of the iron complex formed in situ from $Fe(acac)_3$/chiral Schiff-base ligand **31** and hydrogen peroxide, as oxidant, was remarkable for asymmetric sulfoxidation (Scheme 4).[45]

Scheme 4. Iron-catalyzed oxidation of sulfoxides



It was revealed that the relatively non-toxic and inexpensive $Fe(acac)_3$ was superior to other iron sources and aqueous hydrogen peroxide was the most efficient oxidizing reagent. Using this chiral iron complex/H_2O_2 system described in Scheme 4, a number of

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[44] (a) Mekmouche, Y.; Hummel, H.; Ho, R. Y. N.; Que, L.; Schünemann, V.; Thomas, F.; Trautwein, A. X.; Lebrun, C.; Gorgy, K.; Lepretre, J. C.; Collomb, M. N.; Deronzien, A.; Fontecave, M.; Menage, S. *Chem. Eur. J.* **2002**, *8*, 1196. (b) Duboc-Toia, C.; Menage, S.; Lambeaux, C.; Fontecave, M. *Tetrahedron Lett.* **1997**, *38*, 3727.

[45] Legros, J.; Bolm, C. *Angew. Chem.* **2003**, *115*, 5645.

optically active sulfoxides could be prepared. Arylmethyl sulfides were particularly good substrates for these conditions giving moderate to good enantioselectivites (59-90% ee). Only small qunantities of sulfones formed during the oxidation, which indicated that the asymmetric oxidation of the sulfides resulted directly in the enantioselectivities.

Despite the remarkable application of the chiral iron complex with H_2O_2, the rather low reaction yields and the moderate enantioselectivites remained problematic. These limitations, however, could be overcome by the use of additives such as benzoic acid derivatives or their lithium salts.[46] After a comprehensive screening of carboxylic acids, *p*-methoxybenzoic acid or the corresponding lithium carboxylate was found to be the most efficient additive in this transformation. The use of this additive dramatically improved the reaction yields as well as the enantioselectivities (Scheme 4).

3-1-2. Nucleophilic substitution on chiral sulfur derivatives

The use of Andersen's reagent[47] is the classical method for the preparation of enantiomerically pure sulfoxides. Menthyl *p*-toluenesulfinate (**35**) has been utilized in the transfer of a chiral sulfinyl moiety to a variety of nucleophiles with excellent enantioselection (Scheme 5).

Scheme 5. Nucleophilic substitution reaction of menthyl sulfinate **35**

35 **36**

The drawbacks of this procedure are the strictly limited substrate scope only allowing the synthesis of aryl or alkyl *p*-tolylsulfoxides, and the difficult preparation of compound **35**. After the introduction of the Andersen procedure, many groups modified the method in order to expand the substrate scope and obtain diverse chiral sulfoxides. Among them, procedures reported by Kagan, Evans and Naso will be covered in the following section.

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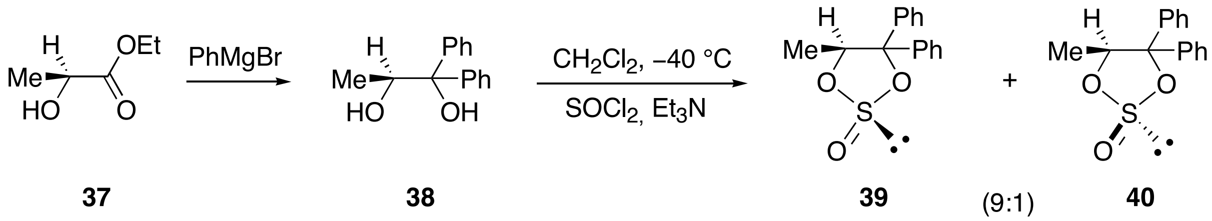
[46] (a) Legros, J.; Bolm, C. *Chem. Eur. J.* **2005**, *11*, 1086. (b) Legros, J.; Bolm, C. *Angew. Chem.* **2004**, *116*, 4321.

[47] (a) Andersen, K. K. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S.; Rappoport, Z.; Stirling, C., Eds.; John Wiley & Sons: New York, 1988; p 55. (b) Andersen, K. K. *Tetrahedron Lett.* **1962**, *3*, 93. (c) Andersen, K. K. *Int. J. Sulfur. Chem.* **1971**, *6*, 69. (d) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637.

3-1-2-1. Nucleophilic substitution on chiral sulfur derivatives: Kagan procedure

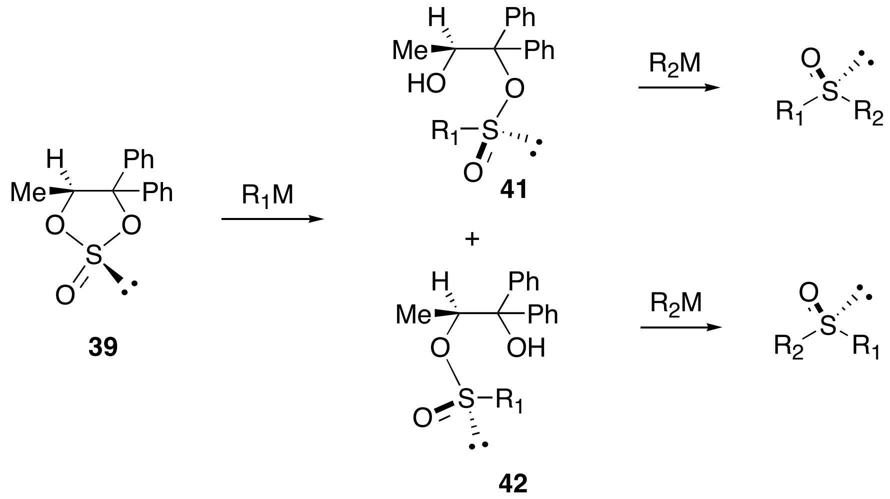
The classic Andersen method was extended by Kagan and coworkers. Instead of menthyl sulfinate, they used chiral cyclic sulfites such as **39** and **40** (Scheme 6) as precursors to synthesize optically active dialkyl sulfoxides.[48] Enantiomerically pure sulfite **39** could be readily obtained in two steps from (*S*)-ethyl lactate.[49] Although a 9:1 mixture of *trans*- and *cis*-sulfite was obtained from the reaction with thionyl chloride, *trans*-cyclic sulfite **39** (major product) could be prepared in pure form and in high yield (70%) by crystallization.

Scheme 6. Synthesis of cyclic sulfites **39** and **40**



The *trans*-cyclic sulfite **39** was revealed to react cleanly with diverse organometallic reagents such as Grignard reagents and organolithium compounds to give a mixture of regioisomers **41** and **42** (Scheme 7) in good yields (50-80%).

Scheme 7. Nucleophilic substitution of cyclic sulfites



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[48] Rebiere, F.; Samuel, O.; Ricard, N.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991.

[49] (a) Rebiere, F.; Riant, O.; Kagan, H. B. *Tetrahedron: Asymmetry* **1990**, *1*, 199. (b) Devant, R.; Malher, U.; Braon, M. *Chem. Ber.* **1988**, *121*, 397.

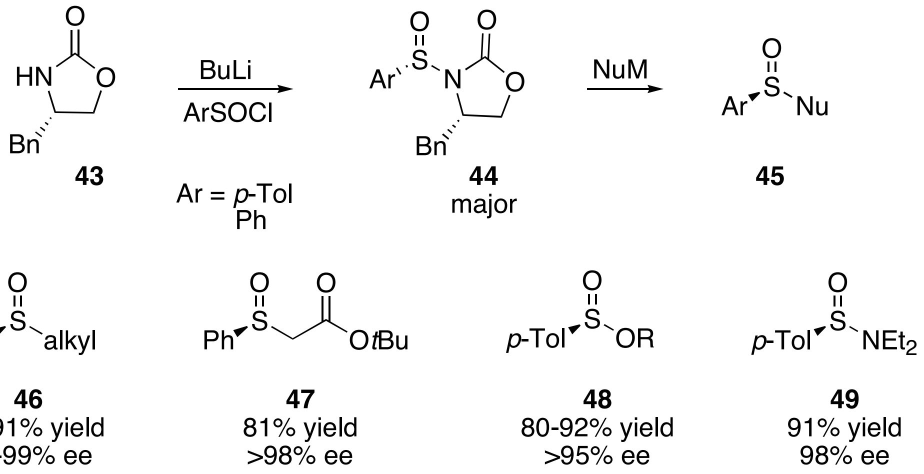
The regioselectivity between sulfinate **41** and **42** was depended on the nature of organometallic compound. For example, when (*n*Oct)MgBr or (vinyl)MgCl were used as nucleophiles, the corresponding sulfinate **41** was obtained as a major product in a ratio of 95/5 ratio of compounds **41**/**42**. On the other hand, the opposite regioselectivity was observed when (*t*Bu)MgBr was used as a nucleophile.

The two regioisomers **41** and **42** could be separated by chromatography. Transformation of sulfinate **41** or **42** with a second organometallic nucleophile was almost quantitive, affording the corresponding enantiomerically pure sulfoxides with a predictable absolute configuration (Scheme 7).

3-1-2-2. Nucleophilic substitution on chiral sulfur derivatives: Evans procedure

In 1992, Evans and coworkers utilized *N*-sulfinyloxazolidinones as chiral sulfinyl transfer reagents to acquire enantiomerically pure arylalkyl or dialkyl sulfoxides.[50] The *N*-(arylsulfinyl)oxazolidinone **44** was synthesized by sulfinylation of the metalated oxazolidinone **43** in good yields as a mixture of diastereomers (Scheme 8). The major diastereomer **44** could be readily purified by chromatography. The *N*-(arylsulfinyl)oxazolidinone **44** reacted rapidly with alkyl Grignard reagents in a stereospecific manner to give chiral arylalkyl sulfoxides **46** in high yields and enantioselectivities (up to 91% yield and 99% ee).

Scheme 8. Nucleophilic substitution of *N*-sulfinyloxazolidinones



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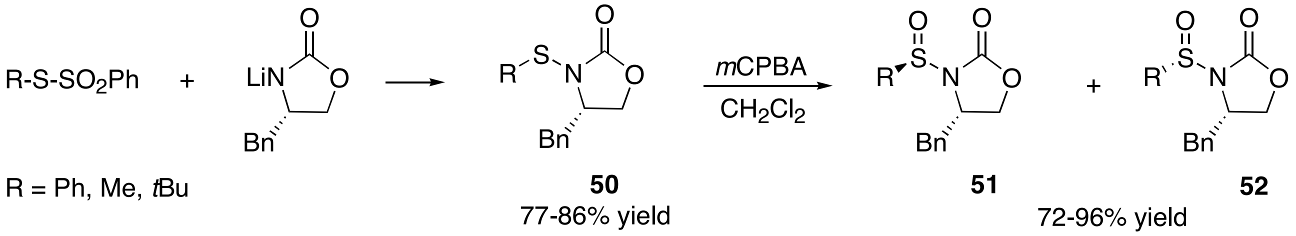
[50] (a) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977. (b) Evans, D. A.; Kandor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

In addition, *tert*-butyl α-(phenylsulfinyl)acetate (**47**), *p*-toluenesulfinates **48** and sulfinamide **49** could be prepared in enantiomerically enriched form by reaction with a Reformatsky reagent, lithium alkoxides and Et_2NMgBr, respectively, as nucleophiles.

On the other hand, *N*-(alkylsulfinyl)oxazolidinone **51** and **52** were obtained by oxidation of the *N*-(arylthio)- and *N*-(alkylthio)oxazolidinone derivatives **50** followed by column chromatography (Scheme 9). Nucleophilic substitution by alkyl Grignard reagents, as depicted in Scheme 8, afforded optically active dialkyl sulfoxides in high yields and enantioselectivities.

Scheme 9. Synthesis of *N*-sulfinyloxazolidinone **51** and **52**

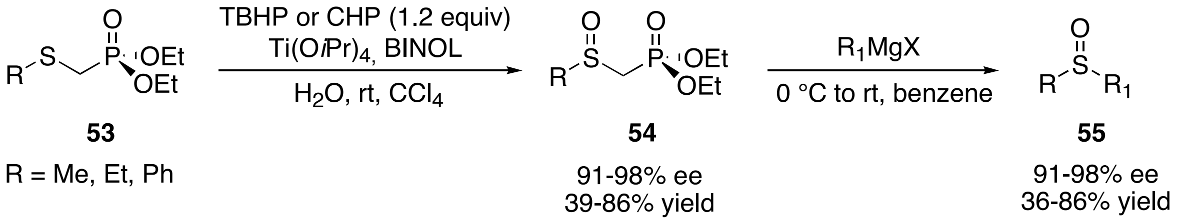


Although the diastereoselectivity in the *N*-sulfinyloxazolidinone formation still remained a problem, it is noteworthy that *N*-sulfinyloxazolidinones were much more reactive towards Grignard reagents than the corresponding menthyl sulfinate ester.

3-1-2-3. Nucleophilic substitution on chiral sulfur derivatives: Naso procedure

In 1999 Naso and coworkers reported the enantioselective catalytic oxidation of (arylthio)- or (alkylthio)methylphosphonates as a route to enantiopure arylalkyl or dialkyl sulfoxides (Scheme 10).[51]

Scheme 10. Synthesis of sulfoxides **55** from thiophosphonates **53**



* $Ti(OiPr)_4$: BINOL : water : substrate (1 : 2 : 20 : 40)

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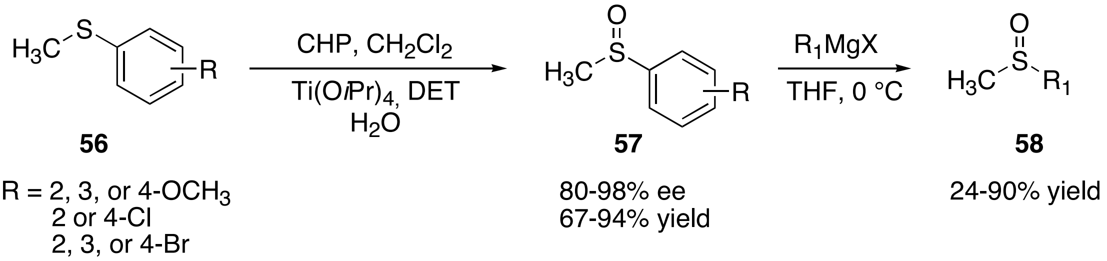
[51] (a) Capozzi, M. A. M.; Cardellicchio, C.; Fracchiolla, G.; Naso, F.; Tortorella, P. *J. Am. Chem. Soc.* **1999**, *121*, 4708. (b) Cardellicchio, C.; Fracchiolla, G.; Naso, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 525.

This method involved two steps; (i) the enantioselective oxidation of commerically available thiomethylphosphonates **53** and (ii) the replacement of the carbanionic leaving group by organometallic reagents. *tert*-Butylhydroperoxide (TBHP) or cumene hydroperoxide (CHP) were used as oxidizing reagents in the asymmetric oxidation of compound **53**. The application of an excess of oxidant reduced the reaction yield due to the formation of sulfones as side products. A high enantioselectivity (up to 98% ee) was observed when BINOL and water were used in the presence of Ti(O*i*Pr)$_4$. The resulting sulfinylmethylphosphonates **54** were stereospecifically converted into sulfoxides **55** with alkyl Grignard reagents.[52] Using this procedure, diverse alkylaryl or dialkyl sulfoxides could be prepared in moderate to good yields and high enantioselectivities.

As another route to prepare dialkyl sulfoxides in enantiomerically pure form, Naso and coworkers also investigated the displacement of an aryl carbanion by organometallic reagents as described in Scheme 11.[53]

Scheme 11. Synthesis of optically active sulfoxides



R = 2, 3, or 4-OCH$_3$
2 or 4-Cl
2, 3, or 4-Br

80-98% ee
67-94% yield

24-90% yield

As aryl carbanions for displacement by Grignard reagents, *o-, m-*, or *p*-halophenyl groups were far superior to other substituted aryl groups. For example, methyl phenyl sulfoxide and *p*-nitrophenyl methyl sulfoxide were not converted into the corresponding alkylmethyl sulfoxides at all. The reaction of *o-, m-, p*-anisylmethylsulfoxides with Grignard reagents gave only moderate reaction yields (up to 48%). On the other hand, *o-, m-, p*-halophenyl methyl sulfoxides afforded the desired products in good yields (64-90%). As a route to prepare these enantiomerically pure sulfoxides **57**, the asymmetric sulfoxidation method using Ti(O*i*Pr)$_4$ and DET as a catalyst was used in the presence of H_2O. When BINOL was applied with Ti(O*i*Pr)$_4$, much poorer enantioselectivities (1-18% ee) were observed. As shown in their previous study, the use of water and 1.2 equiv of oxidant was important for

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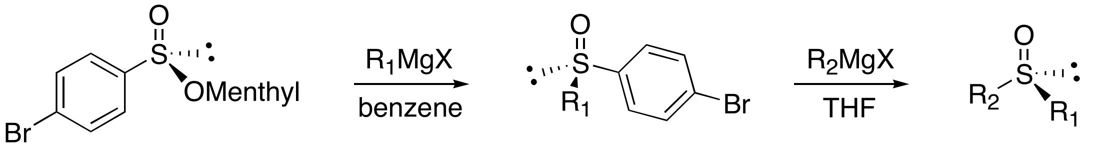
[52] (a) Cardellicchio, C.; Fiandanese, V.; Naso, F.; Pacifico, S.; Koprowski, M.; Pietrusiewicz, K. M. *Tetrahedron Lett.* **1994**, *35*, 6343. (b) Cardellicchio, C.; Fiandanese, V.; Naso, F.; Pietrusiewicz, K. M.; Wisniewski, W. *Tetrahedron Lett.* **1993**, *34*, 3135.

[53] Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Tortorella, P. *J. Org. Chem.* **2000**, *65*, 2843.

high enantioselectivities. The limitation of this procedure was that the satisfactory enantioselectivities were only obtained when a methyl or ethyl group was present in the substrate. This limitation, however, could be circumvented by combining this method with the classical displacement of a menthoxide anion from a suitable menthylsulfinate.[54] Hence, the menthyl *p*-bromobenzenesulfinate (**59** in Scheme 12) proved an appropriate precursor for a two-step synthesis of chiral sulfoxides.

Scheme 12. Nucleophilic substitution of menthyl *p*-bromobenzenesulfinate (**59**)



59 **60** **61**

R_1, R_2 = alkyl
> 98% ee
76-97% yield

Menthyl *p*-bromosulfinate **59** with the (*S*)-configuration at sulfur was synthesized by reaction of *p*-bromophenylsulfonyl chloride with (–)-menthol in the presence of trimethylphosphite as a reducing reagent. Crystallization allowed seperation of the diastereomers. It is worthy of note that this procedure is also suitable for scales of several grams. The reaction with 1.1 equiv of alkyl Grignard reagent led to substitution of the menthoxy group to give alkyl *p*-bromophenyl sulfoxides **60** in stereospecific manner and high reaction yields.

Reaction of **60** with various alkyl Grignard reagents afforded the corresponding dialkyl sulfoxides **61** in high yields (76-97%). Using this method, enantiomerically pure dialky sulfoxides, which are difficult to prepare by metal-catalyzed asymmetric oxidation of sulfides, could be synthesized even in large scale.

As an alternative synthetic route to enantiomerically pure dialkyl sulfoxides, Naso and coworkers utilized benzyl *p*-bromophenyl sulfoxide (**63**) for two carbon-for-carbon displacements (Scheme 13).[55] Benzyl *p*-bromophenyl sulfoxide (**63**) was prepared by enantioselective oxidation using *tert*-butylhydroperoxide and (*S,S*)-stilbene diol in 98% ee and 85% yield. The stereospecific substitution of the benzyl group of sulfoxide **63** took place first during the reaction with a alkyl Grignard reagents in good yields (53-87%). The second displacement of the *p*-bromobenzene anion by an alkyl Grignard reagent, as

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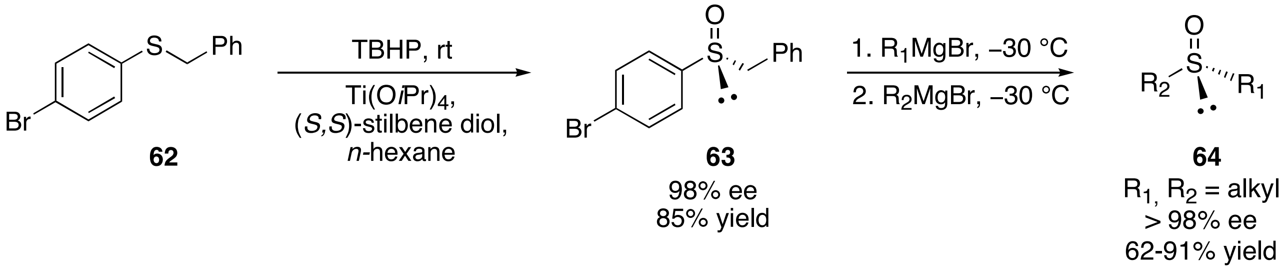
[54] Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Tortorella, P. *J. Org. Chem.* **2001**, *66*, 5933.
[55] Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Rosito, V. *J. Org. Chem.* **2002**, *67*, 7289.

already described in their previous study (Scheme 3), gave the dialkyl sulfoxides **64** in high yields and enantioselectivities.

Scheme 13. Synthesis of optically active sulfoxides



It is noteworthy that this method provides the high enantioselectivities without presenting any problems related to the separation of stereoisomers.

3-2. Synthesis and Palladium-catalyzed cross coupling reaction of *p*-bromophenylmethyl sulfoximine: Results and discussion

In order to use sulfoximines as building blocks in chiral ligands and structural units in pseudopeptides, enantiopure sulfoximines are required.[1b,1d,56] By asymmetric sulfoxidation followed by stereospecific imination, a variety of enantiopure sulfoximines can be synthesized. However, the limitation of this route lies in the fact that each sulfoximine requires the intermediacy of the corresponding sulfoxide and these compounds are often difficult to prepare in enantiopure form. In the context of our previous studies on pseudopeptides containing sulfoximines such as **67** (Figure 8), we became particularly interested in modifying the aryl group of sulfoximines. By variation of the electronic and steric properties of the aryl group, we expected to be able to examine the chemical stabililty of the pseudopeptides towards peptidases[9c] and eventually develop interesting candidates as prodrugs. Furthermore, sulfoximine derivatives with modified aryl groups would be of interest for the synthesis of novel ligands, since in several cases sulfoximines with substituted aryl groups showed improved activity in asymmetric catalysis compared to their phenyl analogues.[12a]

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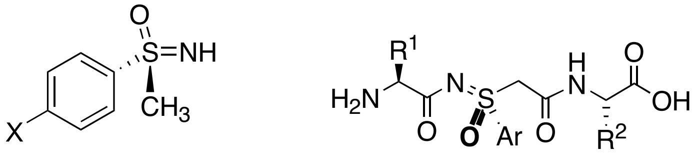
[56] (a) Mikolajczk, M.; Drabowicz, J.; Kielbasinski, P. *Chiral Sulfur Reagents*; CRC press: Boca Raton, 1997. (b) Pyne, S. *Sulfur Reports* **1992**, *12*, 57. (c) Haake, M. In *Houben-Weyl*; Klamann, D., Ed.; VCH Thieme: Stuttgart, 1985; Vol. E11, p 1299. (d) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341. (e) Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 3.



(*S*)-**65**: X = H
(*S*)-**66**: X = Br

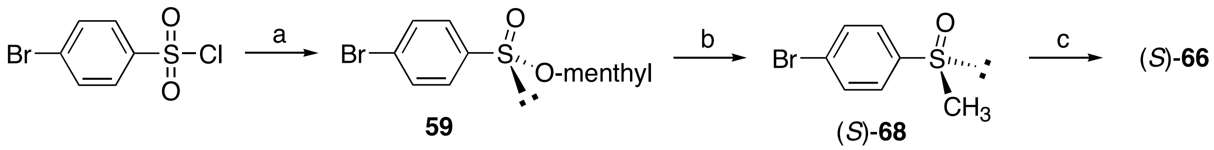
67

Figure 8.

In order to develop a more flexible synthetic strategy, which would allow the production of sulfoximines of high structual diversity, we focused our attention on the search for a single key intermediate, which should be readily available on a large scale and easily modified. For this purpose, *p*-bromophenyl methyl sulfoximine (**66**) was identified as the target compound. The bromo substituent at the para position was expected to be replaced by a variety of other groups by palladium-catalyzed cross coupling reactions. Enantiomerically pure sulfoximine (*S*)-**66** was synthesized by a short reaction sequence and subsequent palladium-catalyzed coupling reactions such as Buchwald/Hartwig,[57] Suzuki,[58] and Stille couplings[59] led to diverse *para*-substituted sulfoximines.

Following Naso´s procedure, *p*-bromophenyl menthyl sulfinate ester (**59**) was prepared from readily available *p*-bromonbenzenesulfonyl chloride and (–)-menthol in the presence of trimethyl phosphite as a reducing agent (Scheme 1).[60]

Scheme 14. The preparation of sulfoximine (*S*)-**66**



(a) (–)-menthol, $P(OMe)_3$, Et_3N, CH_2Cl_2; (b) MeMgBr, toluene; (c) MSH, CH_2Cl_2.

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[57] (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000; p 195. (c) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051.

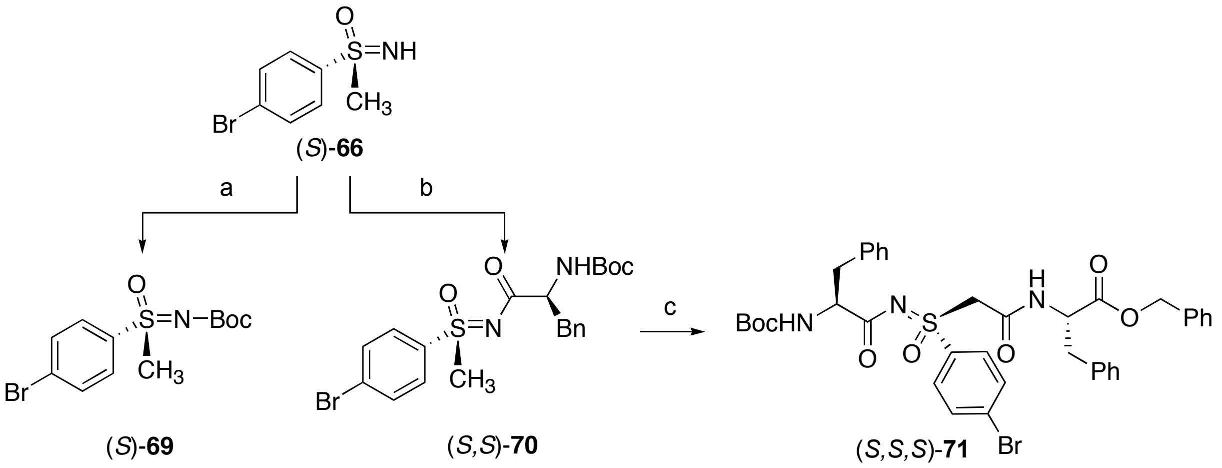
[58] (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419. (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (e) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (f) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (g) Miura, M. *Angew. Chem.* **2004**, *116*, 2251 and references therein.

[59] (a) Handy, S. T.; Zhang, X. *Org. Lett.* **2001**, *3*, 233. (b) Mitchel, T. N. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; p 167 and references therein. (c) Farina, V.; Krishnamurthy, V.; Scott, W. *Org. React.* **1997**, *50*, 1. (d) Stille, J. K. *Angew. Chem.* **1986**, *98*, 504.

[60] Klunder, J. M.; Sharpless, K. B. *J. Org. Chem.* **1987**, *52*, 2598.

The diastereomer with (*S*)-configuration at the stereogenic center of sulfur was isolated by crystallization and subsequently treated with methylmagnesium bromide to afford (*S*)-*p*-bromophenyl methyl sulfoxide [(*S*)-**68**, >99% ee] as described in literature.[54] Finally, imination of (*S*)-**68** with mesitylenesulfonylhydroxylamine (MSH)[4] gave sulfoximine (*S*)-**66** in 86% yield and >99% ee (after recrystallization).[*]

Scheme 15. Synthesis of compounds (*S*)-**69**, (*S,S*)-**70** and (*S,S,S*)-**71**



(a) $(Boc)_2O$, NaH, THF, rt, 74% yield; (b) (*S*)-Boc-PheOH, DCC, HOBt, CH_2Cl_2, rt, 96% yield; (c) (i) *n*BuLi, cyclohexylisopropylamine, 0 °C, THF. (ii) CO_2 bubbling, −78 °C. (iii) HCl-HPheOBn, DCC, DMAP, CH_2Cl_2, ca. 20% yield in two steps.

Taking into account the next step of palladium catalysis and the synthetic applications of the corresponding products, (*S*)-**66** was treated with $(Boc)_2O$ to give *N*-Boc-protected sulfoximine (*S*)-**69** in 74% yield. In addition to this, with the intention of examining the substrate scope of the following palladium-catalyzed coupling reactions, pseudopeptides containing sulfoximine unit, such as compound (*S,S*)-**70** and (*S,S,S*)-**71**, were also prepared (Scheme 15). DCC/HOBt-coupling of sulfoximine (*S*)-**66** with (*S*)-*N*-Boc-phenylalanine[9f,h] led to the corresponding product (*S,S*)-**70** in excellent yield (96%) and no racemization was detected by ^{1}H NMR spectroscopy throughout this sequence.[61] Metallation of (*S,S*)-**70** with lithium cyclohexyl isopropyl amide (LCHIPA) followed by reaction of the resulting anion with dried gaseous CO_2 and subsequent DCC coupling with (*S*)-H-PheOBn afforded pseudotripeptide (*S,S,S*)-**71** in ca. 20% yield over two steps. No

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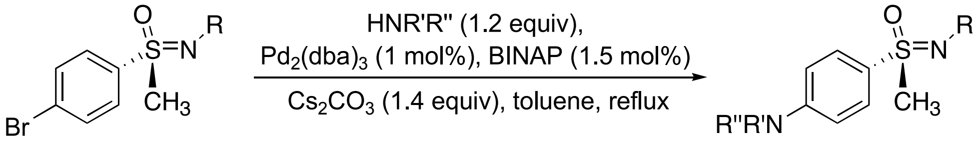
[*] This work was performed in collaboration with Professor Dr. Hiroaki Okamura at University of Kagoshima in Japan.

[61] The ^{1}H NMR spectra of sulfoximines coupled to *N*-Boc-phenylalanine indicated the presence of rotamers in a ratio of ca. 6:1. For example, compound (*S,S*)-**70** showed two separate sets of signals at 5.14/4.97 ppm and 4.60-4.55/4.41 ppm for the N*H* and C*H*N protons, respectively. Only one set of signals was found in a spectrum taken at 55 °C (in $CDCl_3$).

epimerization occurred during the coupling. The low coupling yield of (*S,S*)-**70** could be slightly improved when (*S*)-H-ValOBn was used (40% yield over two steps) as a coupling partner instead of (*S*)-H-PheOBn.

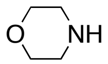
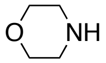
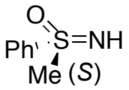
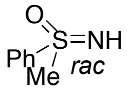
With the intention of increasing the electron-donating ability of the sulfoximine aryl group, we first investigated the palladium-catalyzed Buchwald/Hartwig amination reaction using compounds **69** and (*S,S*)-**70** as substrates (Table 1).

Table 1. Palladium-catalyzed Buchwald/Hartwig amination of *rac*-**69** and (*S,S*)-**70** with amines and related compounds



rac-**69** or (*S,S*)-**70**

72a-k

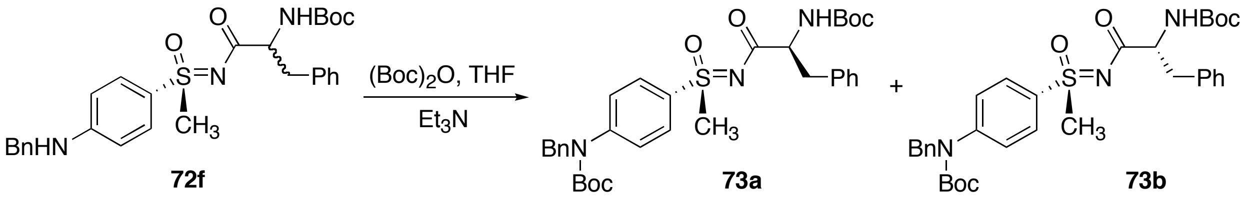
entry	educt	HNR´R´´	product	yield (%)	entry	educt	HNR´R´´	product[c]	yield (%)[d]
1	*rac*-**69**	$BnNH_2$	*rac*-**72a**	94	6	(*S,S*)-**70**	$BnNH_2$	(*S,S*)-**72f**	98 (88)
2[a]	*rac*-**69**		*rac*-**72b**	79	7[a]	(*S,S*)-**70**		(*S,S*)-**72g**	92 (18)
3	*rac*-**69**	$PhNH_2$	*rac*-**72c**	96	8	(*S,S*)-**70**	$PhNH_2$	(*S,S*)-**72h**	99 (92)
4	*rac*-**69**	$nBuNH_2$	*rac*-**72d**	81	9	(*S,S*)-**70**		(*S,S*)-**72i**	95 (99)
5[a]	*rac*-**69**		*rac*-**72e**[b]	72	10	(*S,S*)-**70**	$H_2NNHBoc$	(*S,S*)-**72j**	87 (73)[e]

[a] $Pd(OAc)_2$ (2 mol %) and BINAP (4 mol %) were used instead of Pd_2dba_3 (1 mol%) and BINAP (1.5 mol%). [b] As a mixture of diastereomers. [c] In reactions with (*S,S*)-**70** and Cs_2CO_3, diastereomers were formed (see text). [d] Values for reactions with K_2CO_3 instead of Cs_2CO_3 are given in parentheses. Single diastereomers were obtained in these reactions (see text). [e] A 1:1 mixture of diastereomers was obtained with both bases Cs_2CO_3 and K_2CO_3.

Although (*S*)-**69** could be prepared in high yield, *rac*-**69** was used as a starting material in most studies of the reactivity. To establish the optimal reaction conditions, a limited screening was carried out with *rac*-**69** and (*S,S*)-**70** as substrates. As a result, the combination of $Pd_2(dba)_3$, *rac*-BINAP, and Cs_2CO_3 was found to be the best system for the coupling reactions with primary amines. For the reactions with morpholine (Table 1, entries 2 and 7), $Pd(OAc)_2$ was superior to $Pd_2(dba)_3$. The same trend was observed in reactions of sulfoximine **65** with *rac*-**69** and (*S,S*)-**70** (Table 1, entries 5 and 9) where, by applying $Pd(OAc)_2$ as metal source, the corresponding products *rac*-**72e** and (*S,S,S*)-**72i** were obtained in 72 and 95% yield, respectively. Using $Pd_2(dba)_3$ in the coupling of (*S,S*)-**70** and sulfoximine (*S*)-**65** gave the product (*S,S*)-**72i** in only 40% yield. Most reactions proceeded to completion within less than 24 h under reflux and gave high yields (up to 99%). In fact, a proper choice of the N-protecting group was important for the successful coupling reaction. *N*-TBDMS protected sulfoximine, for example, did not afford any desired cross-coupled products and decomposition was observed under reflux in the presence of the palladium catalyst and base.

Although the reaction yields in the palladium-catalyzed amine couplings were satisfying, another aspect of this transformation was problematic. Under the reaction conditions described above in Table 1, (*S,S*)-**70** was converted into the corresponding products efficiently, but unfortunately a significant amount of epimerization (ca. 40%) occurred in most cases. This was presumably caused by the harsh reaction conditions of refluxing in the presence of base.

Scheme 16. Boc-protection of compound **72f**



The diastereomers of **72f** and **72j** (Table 1) could not be separated by silica gel column chromatography. However, the resulting *N*-Boc protected isomers **73a** and **73b** (Scheme 16), which were obtained with $(Boc)_2O$, could be partially separated and their structures were confirmed by ^1H NMR spectroscopy. On the basis of previous results in this area,[62] we assumed that the loss of stereochemical integrity occurred at the amino acid part of the products rather than the sulfoximine. In order to prove this hypothesis, sulfoximine (*S*)-**72c**, which is the coupling product of (*S*)-**69** and aniline, was converted into both diastereomers of **72h** (Scheme 17). Removal of the Boc protecting group from compound (*S*)-**72c** followed by DCC/HOBt coupling reaction with either (*S*)-*N*-Boc-PheOBn or (*R*)-*N*-Boc-PheOBn afforded the corresponding products (*S,S*)-**72h** or (*S,R*)-**72h**, respectively. A comparison of these coupled products by ^1H NMR spectroscopy showed that the assumed formation of (*S,S*)-**72h** and (*S,R*)-**72h** during the palladium-catalyzed coupling reaction of (*S,S*)-**70** was correct.

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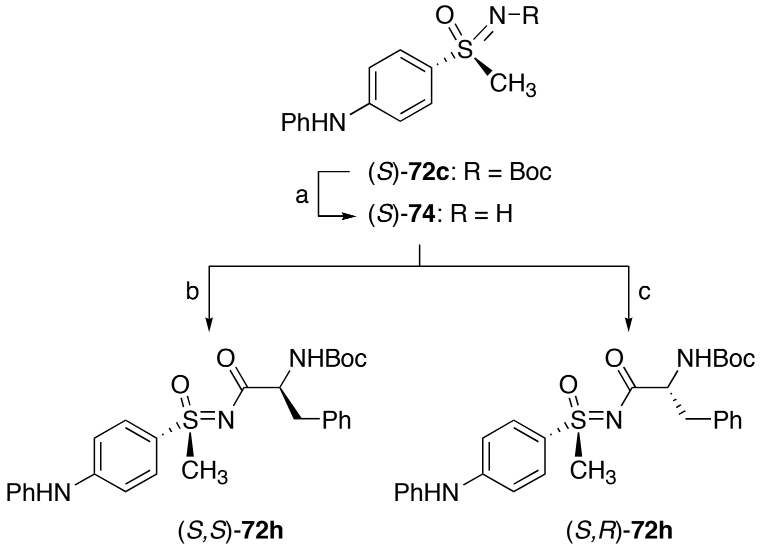
[62] Hackenberger, C. P. R.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2004**, *10*, 2942.

Scheme 17.



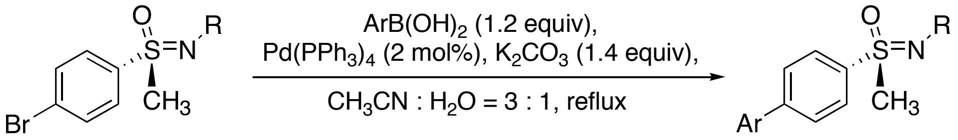
(a) TFA/CH_2Cl_2 = 1:3; (b) (*S*)-Boc-Phe-OH, DCC, HOBt, CH_2Cl_2; (c) (*R*)-Boc-Phe-OH, DCC, HOBt, CH_2Cl_2.

Suspecting that the epimerization was most likely caused by the base (Cs_2CO_3) in toluene under reflux, a brief base screening was performed. To our delight, it was revealed that K_2CO_3 could also be employed in the C-N coupling reactions. As shown by the data presented in Table 1 (entries 6-10), a slight decrease in reaction yield had to be accepted in some cases, but most significantly, with K_2CO_3 as base, the epimerization was suppressed. Only in the coupling reaction with *tert*-butyl carbazate (entry 10) two diastereomers of **72j** were still observed as almost 1:1 mixture.

Next, palladium-catalyzed Suzuki couplings of *rac*-**69** and (*S,S*)-**70** with boronic acids were investigated. In order to establish the optimal reaction conditions, several reactions using different palladium catalysts, bases and solvents were performed with *p*-biphenylboronic acid. As a result, a system consisting of $Pd(PPh_3)_4$ and K_2CO_3 in acetonitrile/water (3:1) proved to be optimal for both compound *rac*-**69** and (*S,S*)-**70** (Table 2).

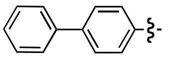
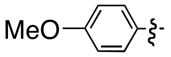
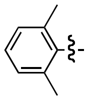
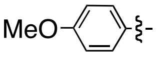
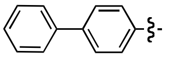
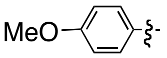
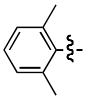
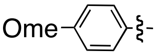
Attempts to use $Pd(OAc)_2$, P(*o*-Tol)$_3$ and K_2CO_3 in dioxane for Suzuki-type couplings of *rac*-**69** gave **75a** in lower yield (74%). In contrast, the coupling reaction between (*S,S*)-**70** and *p*-biphenylboronic acid under these reaction conditions gave the product in excellent yield (91%). In this case, however, a significant amount of epimerization occurred (dr = 1.6:1). Other reagent combinations such as $Pd(PPh_3)_4$ and Cs_2CO_3 in CH_3CN/water or $Pd(PPh_3)_4$ and K_2CO_3 in DME/water led to lower yields of **75e** (69 and 71%, respectively). Interestingly, both the yield and the degree of epimerization appeared to be influenced by the ratio of acetonitrile to water. For example, compound **75g** was obtained as an 11:1 mixture of diastereomers in 42% yield, when a 1:1 mixture of CH_3CN/water was used as solvent in the presence of $Pd(PPh_3)_4$ and K_2CO_3. In a 3:1 mixture of CH_3CN/water, however, the yield of **75g** increased to 75% although the diastereomer ratio decreased to 8:1 (Table **2**, entry **7**). Finally, the optimal reaction conditions [$Pd(PPh_3)_4$ and K_2CO_3 in acetonitrile/water=3:1] were applied successfully with various aryl boronic acids, and the corresponding *para*-substituted aryl sulfoximines were synthesized in high yields (up to 97%) as summarized in Table 2.

Table 2. Palladium-catayzed (Suzuki) coupling of *rac*-**69** and (*S,S*)-**70** with boronic acids



rac-**69** or (*S,S*)-**70**

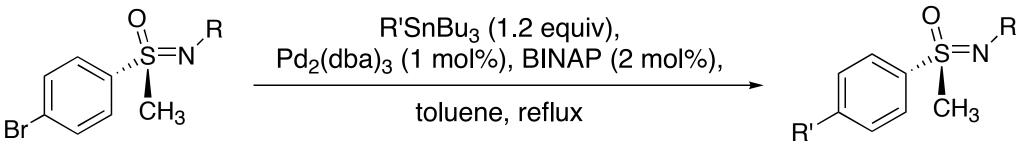
75a-h

entry	educt	$ArB(OH)_2$	product	yield (%)[a]
1	*rac*-**69**		*rac*-**75a**	95
2	*rac*-**69**		*rac*-**75b**	90
3	*rac*-**69**		*rac*-**75c**	93
4	*rac*-**69**		*rac*-**75d**	97
5	(*S,S*)-**70**		(*S,S*)-**75e**	79 (>10:1)
6	(*S,S*)-**70**		(*S,S*)-**75f**	90 (-)[b]
7	(*S,S*)-**70**		(*S,S*)-**75g**	75 (8:1)
8	(*S,S*)-**70**		(*S,S*)-**75h**	70 (>10:1)[c]

[a] The epimer ratio is given in parentheses. [b] Single stereoisomer. [c] After recrystallization dr >30:1.

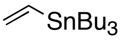
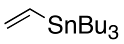
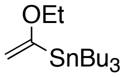
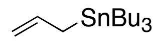
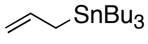
In order to introduce alternative unsaturated functional groups in the *para*-position of the sulfoximine aryl group, a study of palladium-catalyzed Stille coupling reactions with *rac*-**69** and (*S,S*)-**70** was undertaken and the results are summarized in Table 3. After limited optimization, all reactions with both *rac*-**69** and (*S,S*)-**70** proceeded well to give the corresponding products **76** in high yields (up to 98%) by using $Pd_2(dba)_3$ and *rac*-BINAP in toluene under reflux. No epimerization was observed in either substrate. As a ligand, *rac*-BINAP was more effective than $P(tBu)_3$ or $P(o\text{-Tol})_3$. In most reactions full conversion was achieved in less than 24 h. The corresponding products from the reaction with *rac*-**69** and allyltributyltin or ethynyltributytin were too unstable to keep at room temperature although high coupling yields were observed (89 and 77%, respectively, not included in Table 3).

Table 3. Palladium-catalyzed Stille coupling reaction of *rac*-**69** and (*S,S*)-**70**



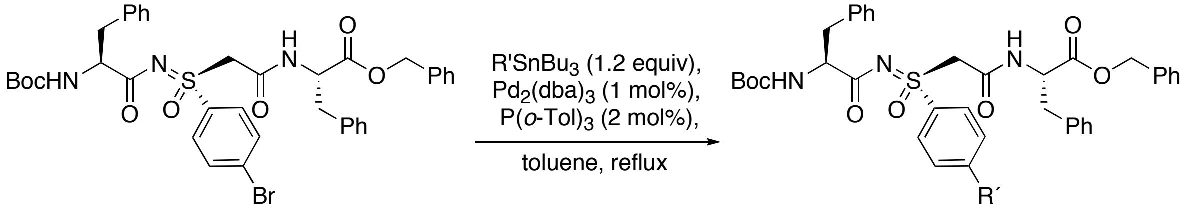
rac-**69** or (*S,S*)-**70**

76a-j

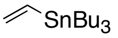
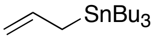
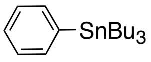
entry	educt	R´SnBu$_3$	product	yield (%)	entry	educt	R´SnBu$_3$	product	yield (%)
1	*rac*-**69**		*rac*-**76a**	98	5	(*S,S*)-**70**		(*S,S*)-**76e**	97
2	*rac*-**69**	Ph-SnBu$_3$	*rac*-**76b**	96	6	(*S,S*)-**70**	Ph-SnBu$_3$	(*S,S*)-**76f**	98
3	*rac*-**69**	Ph—≡—SnBu$_3$	*rac*-**76c**	94	7	(*S,S*)-**70**		(*S,S*)-**76g**	87
4	*rac*-**69**		*rac*-**76d**	89	8	(*S,S*)-**70**	Ph—≡—SnBu$_3$	(*S,S*)-**76h**	86
					9	(*S,S*)-**70**		(*S,S*)-**76i**	91

Since no epimerization was observed during the reaction, (*S,S,S*)-**71** was also tested as a starting material in this Stille coupling reaction. To find the optimal reaction conditions, several reactions were performed with vinyltributyltin as coupling partner. The combination of $Pd_2(dba)_3$ and $P(o\text{-Tol})_3$ (81% yield) was superior to others, such as the combination of $Pd_2(dba)_3$/*rac*-BINAP (75% yield) or $Pd(OAc)_2$/*rac*-BINAP (51% yield), and no epimerization was observed. Several unsaturated functional groups could be introduced under these conditions (Table 4) although the reaction yields were slightly lower compared to the results of compound *rac*-**69** and (*S,S*)-**77**.

Table 4. Palladium-catalyzed Stille coupling reaction of (*S,S,S*)-**71**

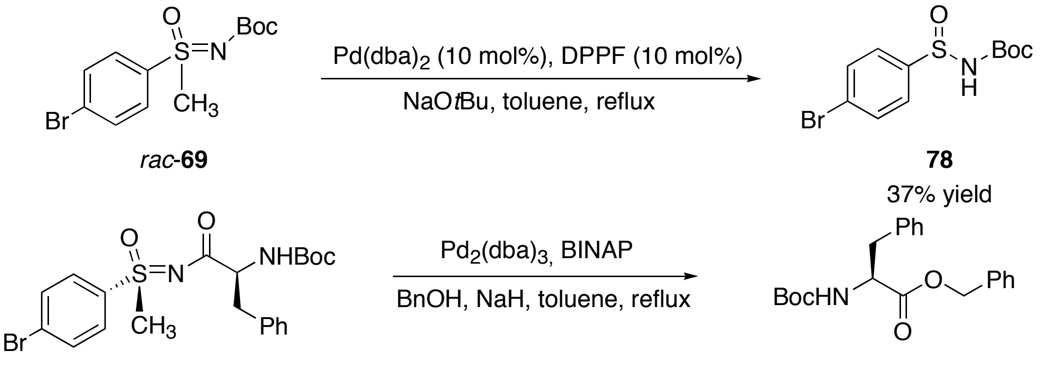


(*S,S,S*)-**71** (*S,S,S*)-**77**

entry	educt	R´SnBu$_3$	product	yield (%)
1	(*S,S,S*)-**71**		(*S,S,S*)-**77a**	81
2	(*S,S,S*)-**71**		(*S,S,S*)-**77b**	45
3	(*S,S,S*)-**71**		(*S,S,S*)-**77c**	71

As well as the Buchwald/Hartwig amination, Suzuki and Stille couplings, C-O couplings with *rac*-**69** and (*S,S*)-**70** were tested but, unfortunately, all trials failed. With *rac*-**69** or (*S,S*)-**70** as starting materials, various C-O couplings were performed with benzyl alcohol, sodium *tert*-butoxide or sodium methoxide in the presence of palladium catalysts such as $Pd_2(dba)_3$/*rac*-BINAP, $Pd(dba)_2$/DPPF etc. However, either no conversion occurred or only undesired products, such as sulfinimine **78** and amino acid ester **79** (Scheme 18), was obtained.

Scheme 18. Attempted palladium-catalyzed C-O coupling reactions of *rac*-**69** and (*S,S,S*)-**70**



rac-**69**

78
37% yield

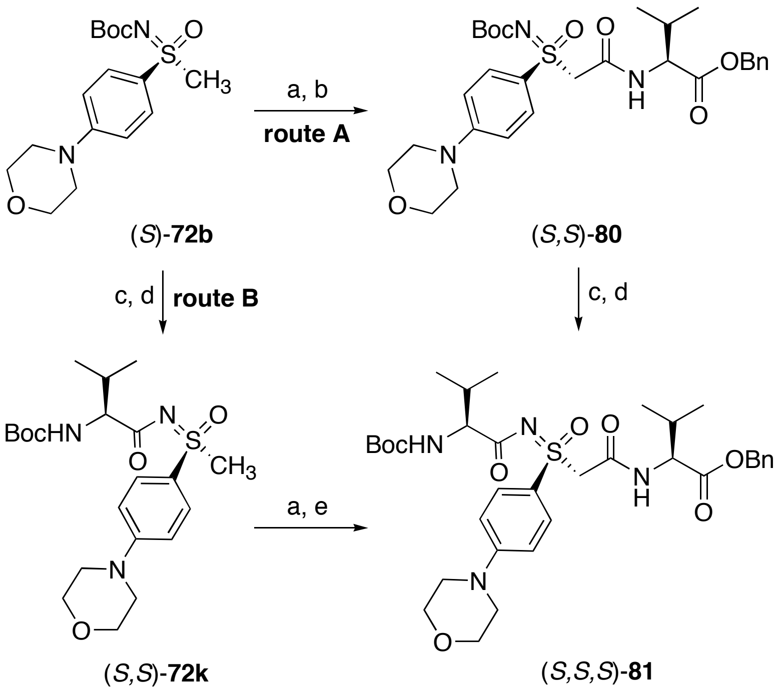
(*S,S*)-**70**

79
28% yield

After establishing that a broad range of compounds with various substituents at the *para*-position of the sulfoximine aryl group was accessible by coupling reactions, our attention was focused on incorporation of the novel building blocks into pseudopeptidic structures.

Morpholino-substituted sulfoximine (*S*)-**72b** was selected as a representative substrate for the synthesis of a pseudopeptide. This compound was considered to be particularly interesting because the amino substitutent at the *para*-position was expected to have a significant electronic effect on the sulfoximine unit. Furthermore, amine protonation could enhance the water-solubility of such modified pseudopeptides, which is one of the serious problems of pseudopeptides containing a sulfoximine. In order to make comparisons with our previous studies, both α-amino acids next to the new sulfoximine unit in target compound **81** (Scheme 19) were protected valines.

Scheme 19. Synthesis of Pseudopeptide containing sulfoximine **81**



(a) LCHIPA, THF, −78 °C, then CO_2; (b) (*S*)-H-Val-OBn, DCC, DMAP, CH_2Cl_2; (c) TFA/CH_2Cl_2 = 1:3; (d) (*S*)-Boc-Val-OH, DCC, HOBt, CH_2Cl_2; (e) (*S*)-H-Val-OBn, EEDQ, DMAP, CH_2Cl_2.

To our surprise, the standard reaction sequence for the synthesis of pseudopeptides of this type (route A)[9f,h] involving carboxylation of (*S*)-**72b** at the sulfoximine methyl group followed by DCC coupling of the resulting ammonium salt with the (*S*)-H-ValOBn proved inefficient giving (*S,S*)-**80** in only 14% yield. After cleavage of the Boc-group of (*S,S*)-**80** at the sulfoximine nitrogen, DCC coupling with (*S*)-*N*-Boc-ValOH afforded (*S,S,S*)-**81** in 67% yield, over two steps. The alternative reaction sequence for the synthesis of pseudotripeptide **81,** route B, involves first coupling the sulfoximine nitrogen with *N*-Boc-ValOH and then extending the carbon chain by carboxylation, also required significant optimization and it was the second step (carboxylation and coupling) that was most critical.

The Boc-deprotection and the subsequent DCC coupling of the resulting *NH*-sulfoximine (not shown) proceeded well and gave pseudodipeptide (*S,S*)-**72k** in good yield (88% over two steps). The following carboxylation of (*S,S*)-**72** and the subsequent DCC/HOBt coupling of the resulting ammonium salt with benzyl-protected (*S*)-valine, however, gave (*S,S,S*)-**81** in only 16% yield. Interestingly, the metallation of *N*-amino acid substituted sulfoximine with lithium cyclohexyl isopropyl amide (LCHIPA) followed by reaction of resulting anion with dried gaseous CO_2 was influenced by the para substituent on the aryl group of the sulfoximine. For example, when compounds containing *para*-NHBn or –$CHCHCO_2Me$ instead of morpholino group of compound **72k** were treated with LCHIPA, decomposition was observed and the desired products were not obtained at all after DCC/HOBt coupling. After an intensive investigation to find new conditions (involving the application of alternative bases such as *n*BuLi and KHMDS for the metallation before the introduction of CO_2, and the exchange of DCC for EDC and HBTU[63] as a coupling reagent), gratifyingly, it was found that the best yield could be obtained when the standard carboxylation protocol with LCHIPA as base was used and the following coupling reaction with benzyl protected (*S*)-valine was performed using EEDQ[64] as coupling reagent. Under these conditions pseudotripeptide (*S,S,S*)-**81** was obtained in 55% yield over two steps [starting from (*S,S*)-**72k**].

3-3. Summary and outlook

In conclusion, we have synthesized *p*-bromophenyl methyl sulfoximine (**66**) in enantiomerically pure form from *p*-bromophenyl menthyl sulfinate (**59**) in a short reaction sequence. Enantiomerically pure sulfoximine **66** was used as the key-intermediate for the preparation of diverse sulfoximines with a functionalized aryl group. Palladium-catalyzed Buchwald/Hartwig amination, Suzuki and Stille coupling reactions provided the corresponding products in high yields which are otherwise difficult to prepare in enantiopure form by existing methods. By fine-tuning of the reaction conditions, the observed epimerization during couplings of sulfoximine-pseudopeptide (*S,S*)-**70** was minimized in Buchwald/Hartwig and Suzuki coupling reaction. Finally, the potential application of these new sulfoximine (*S*)-**69** as a building block in the synthesis of pseudotripeptides was demonstrated. Further investigations should be focused on not only

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[63] HBTU: *O*-Benzotriazol-1-yl-*N,N,N',N''*-tetramethyluronium hexafluorophosphate.

[64] EEDQ: 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline ethyl 1,2-dihydro-2-ethoxy-1-quinolinecarboxylate.

incorporating these coupling products into alternative peptidic structures, but also on utilizing them as ligands for asymmetric catalysis.

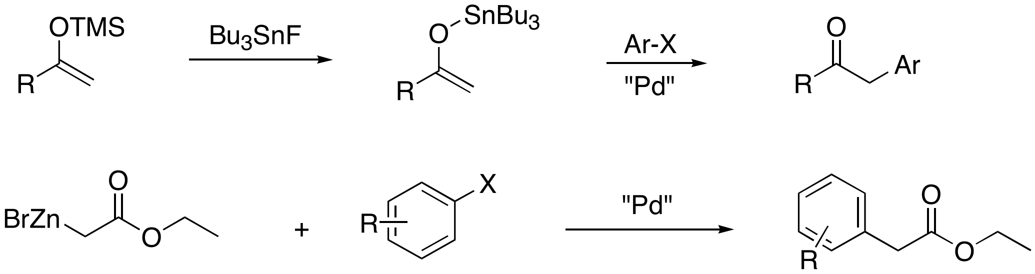
4. Part II. Palladium-catalyzed α-arylation of sulfoximines

4-1. Palladium-catalyzed α-arylation of carbonyl compounds, nitriles and sulfones: introduction

A classic method to form C-C bonds involves deprotonation of the hydrogen α to a carbonyl compound and addition of the resulting nucleophile to an electrophile such as an aldehyde, ketone, Michael acceptor and alkyl halide.[65] However, examples of the attachment of aryl group to the carbonyl compound are rare although nucleophilic aromatic substitution is a useful method to prepare α-arylated products of carbonyl compounds under the appropriate conditions.

In the 1980's palladium-catalyzed coupling reactions of reactive enolates with aryl or vinyl halides were investigated,[66] but those methods remained limited to only conversions of ethylacetate or methyl ketones (Scheme 20).

Scheme 20. Pd-catalyzed α-arylation with tin and zinc enolates



Practical palladium-catalyzed α-arylations of ketones with aryl bromides were introduced by Hartwig,[67] Buchwald[68] and Miura,[69] independently, at the same time. Since then a number of publications came out and this method became a useful and general strategy to

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[65] *March*, in *Advanced Organic Chemistry*, 4th Ed.; John Wiley & Sons: New York, 2001; Chapters 10-16.

[66] Silyl enol ether, see: (a) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181. Zinc enolate, see: (b) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273. Tin enolate, see: (c) Galarini, R.; Musco, A.; Pontellini, R.; Santi, R. *J. Mol. Catal.* **1992**, *72*, L11.

[67] Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

[68] Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

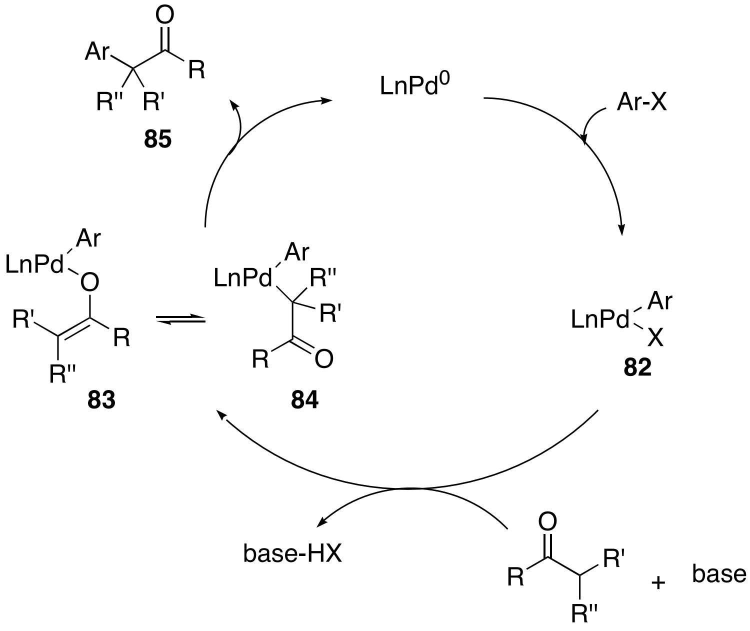
[69] Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem.* **1997**, *109*, 1820.

prepare α-arylated compounds from amides, esters, aldehydes,[70] nitriles, malonates, cyanoesters, nitroalkanes,[71] sulfones and so forth. Among them, palladium-catalyzed α-arylation of carbonyl compounds, nitriles and sulfones are going to be discussed in this section.

4-1-1. Palladium-catalyzed α-arylation of carbonyl compounds

The plausible catalytic cycle for the palladium-catalyzed α-arylation of carbonyl compounds[72] is depicted in Scheme 21. This mechanism involves in three steps: (i) the oxidative addition of an aryl halide to a Pd(0) complex, (ii) the ligand substitution of the halide by an enolate nucleophile, and (iii) the reductive elimination from the resulting palladium enolate complex **83** or **84**.

Scheme 21. Plausible mechanism of the Pd-catalyzed α-arylation of carbonyl compounds



Due to the high regioselectivity of the arylation, it is believed that the deprotonation of the carbonyl compounds occurs prior to the coordination to the palladium center.

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[70] Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101.

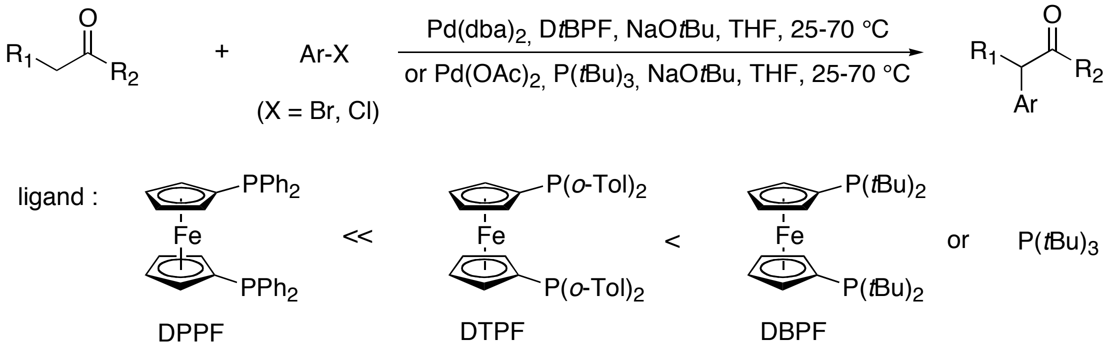
[71] (a) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355. (b) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106.

[72] For review, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

4-1-1-1. Palladium-catalyzed α-arylation of ketones

Hartwig and coworkers observed that an α-arylated product, phenylacetone, was formed as a side product from the reaction of amines with phenyl bromide in acetone as a solvent in the presence of a palladium catalyst.[73] On the basis of this initial discovery, they developed the palladium-catalyzed α-arylation of ketones as a general synthetic method to prepare α-aryl ketones. In the preliminary investigation,[67] they used DPPF or DTPF as a ligand in the presence of $Pd(dba)_2$ and KHMDS as a base for the α-arylation of ketone enolates (Scheme 22). However, introducing more bulky ligands such as DBPF or $P(tBu)_3$ in combination with NaO*t*Bu as base allowed this transformation to proceed even at room temperature. Furthermore, the reaction yields were increased. In addition, aryl chlorides could be used as a coupling partner.[74]

Scheme 22.



Buchwald and coworkers employed *rac*-BINAP as ligand in conjunction with $Pd(OAc)_2$ for their first investigation of palladium-catalyzed α-arylations of dialkyl ketones in 1997.[68] However, by using sterically hindered and electron-rich *o*-biphenyl monophosphine derivatives (**86** to **88** in Scheme 23) they could optimize these reactions with ketones and a number of α–arylated carbonyl compounds were prepared in high yields.[75] Interestingly, a higher selectivity for monoarylation over diarylation was observed when bidentate ligands such as BINAP and Xantphos were used instead of monophosphines **86** to **88** although the reaction yields were slightly diminished. In this study, ligandless α-arylations with the stoichiometric amount of $Pd(OAc)_2$ and NaO*t*Bu were also included. However, this process was only suitable for a limited number of substrate combinations.

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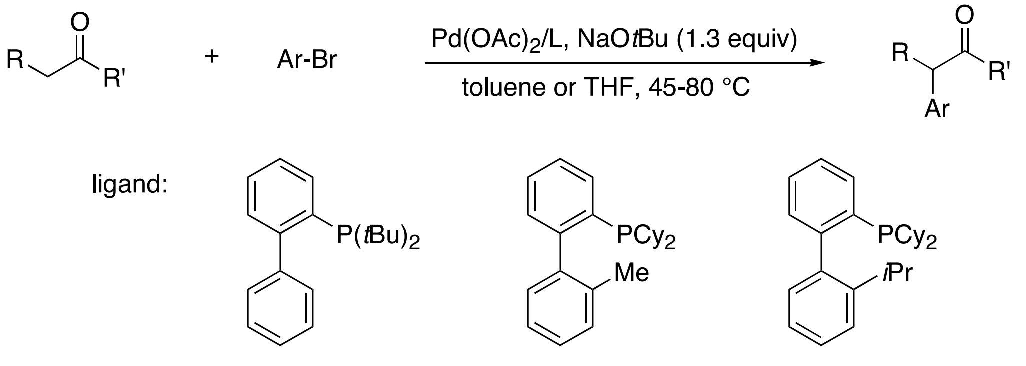
[73] Hartwig, J. F. *Angew. Chem.* **1998**, *110*, 2154.

[74] (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.

[75] Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

Scheme 23.

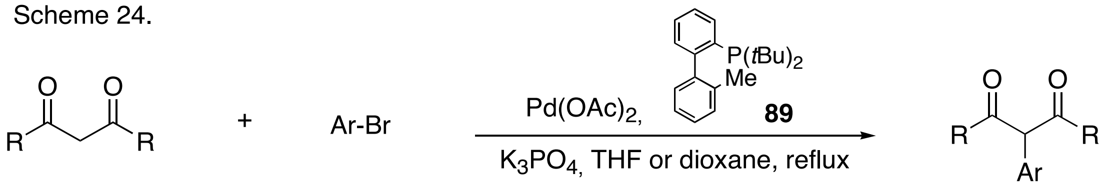


86 **87** **88**

In addition, Miura and coworkers have reported ligandless α-arylation of 1,3-diphenyl-2-propanon with phenyl iodide by using $PdCl_2$-4LiCl (5 mol%) and Cs_2CO_3 (2.0 equiv) in DMF at 100 °C.[70] Beller and coworkers utilized the palladium complexs of *n*-butyldi(1-adamantyl)phosphine for the α-arylation of acetophenone with aryl chlorides.[76]

With 1,3-diketones as substrates, the sterically more demanding phosphine **89** was much superior to the other ligands in the presence of $Pd(OAc)_2$ (Scheme 24).[75] This reaction allowed to use a mild base (K_3PO_4 instead of NaO*t*Bu) presumably due to the high p*K*a values of the 1,3-diketones.[77]

Scheme 24.



4-1-1-2. Palladium-catalyzed α-arylation of amides

The significantly higher p*K*a value of amides[77] required a modification of the palladium-catalyzed α-arylation with ketones. Hartwig and coworkers reported α-arylations of amides with aryl bromides in the presence of $Pd(dba)_2$, *rac*-BINAP and KHMDS in dioxane (Scheme 25).[78] In this study, they found that a careful selection of the base and the use of more than 2.0 equiv of it were critical to obtain the products in the high yields. Interestingly,

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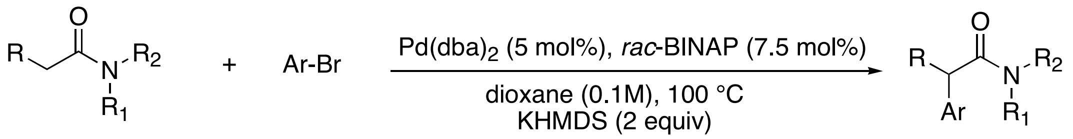
[76] Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209.
[77] Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
[78] Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546.

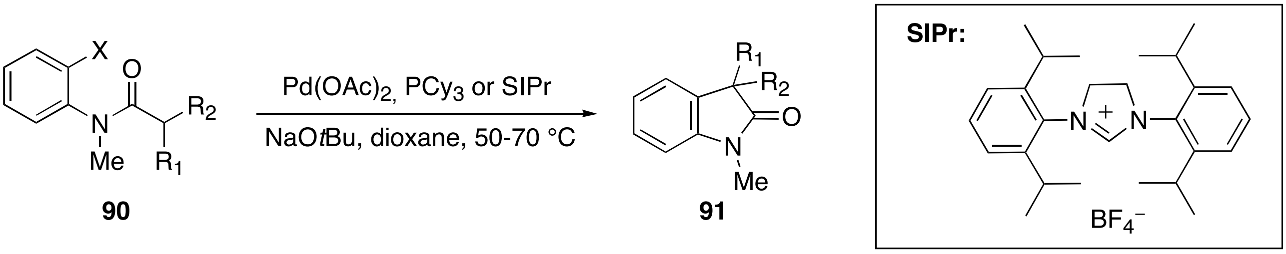
a higher selectivity for the mono-arylation and improved reaction yields were observed with decreasing the reaction concentration of the aryl bromides.

Scheme 25.



The intra-molecular α-arylation of amides was also investigated by the same group. In the initial study, they employed Pd(dba)$_2$ and *rac*-BINAP as a catalyst for the preparation of oxindoles.[78] However, the reaction rate and the yields could be improved by changing the catalyst to combination of Pd(OAc)$_2$ and PCy$_3$ or N-heterocyclic carbene ligand, SIPr, as a catalyst in conjunction with NaO*t*Bu as a base (Scheme 26).[79] Morerover, the choice of base was important. For example, using KHMDS increased the amount of deacylated products and Cs$_2$CO$_3$ did not afford the expected α-arylated products at all. The enantioselective α-arylation was attempted by using chiral phosphine and carbene ligands, but only poor enantioselectivities were achieved in this transformation.

Scheme 26.



90 **91**

4-1-1-3. Palladium-catalyzed α-arylation of esters

In 2001, Buchwald and coworker used Pd(OAc)$_2$ in combination with phosphine **87** as a catalyst for α-arylations of esters with LiHMDS as a base in toluene (Scheme 27).[80]

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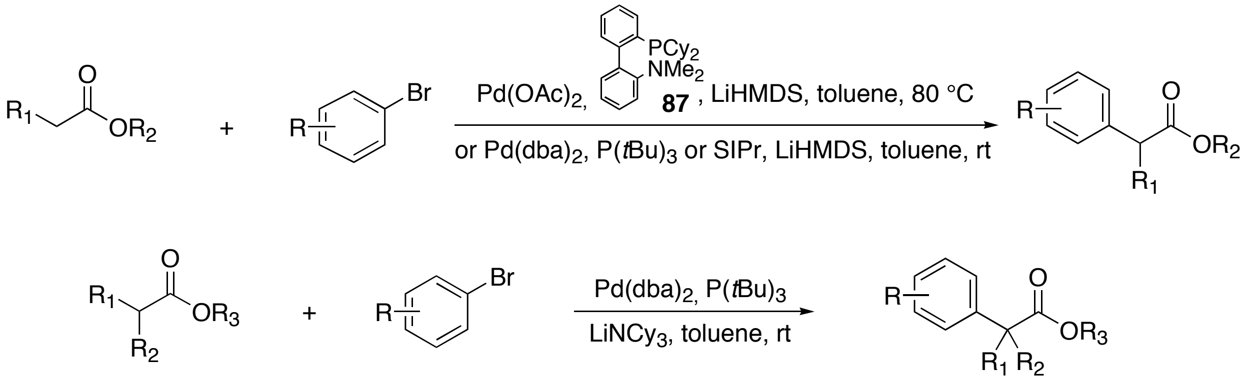
[79] Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402.

[80] Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996.

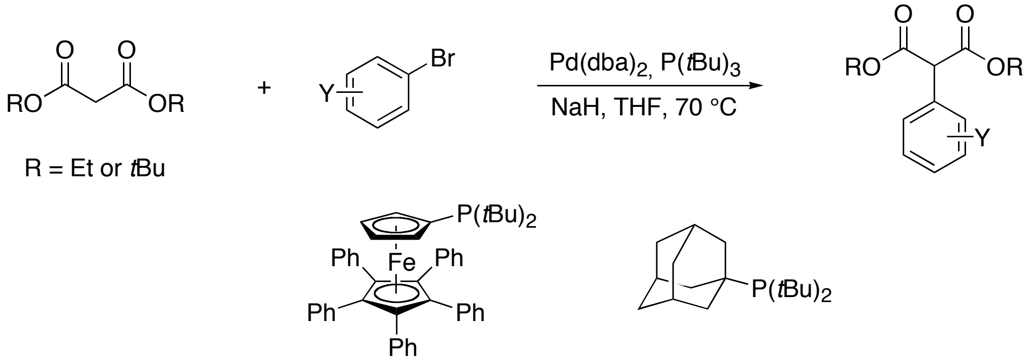
Scheme 27.



This method showed a high functional group tolerance and led to efficient mono-arylations with aryl bromides. However, a high temperature (80 °C) was required for the effective coupling reaction. In the same year, Hartwig and coworkers reported palladium-catalyzed α-arylations of *tert*-butyl acetate or *tert*-butyl propionate by using $Pd(dba)_2/P(tBu)_3$ or SIPr in the presence of LiHMDS at room temperature (Scheme 27). A high selectivity for monoarylation was observed.[81] In the case of α,α-disubstituted esters, on the other hand, the use of the stronger and sterically hindered base, $LiNCy_2$, was demanded for the efficient transformation and higher reaction yields.

The palladium-catalyzed α-arylation of malonates with aryl halides was investigated by Hartwig and his coworkers (Scheme 28).[82]

Scheme 28.



92 **93**

$Pd(dba)_2$ and $P(tBu)_3$ catalyzed this coupling reaction efficiently with aryl bromides in the presence of NaH as base. Aryl chlorides were also used as a coupling partners. In this case, use of sterically more hindered phosphines such as $Ph_5FcP(tBu)_2$ or (1-Ad)-$P(tBu)_2$

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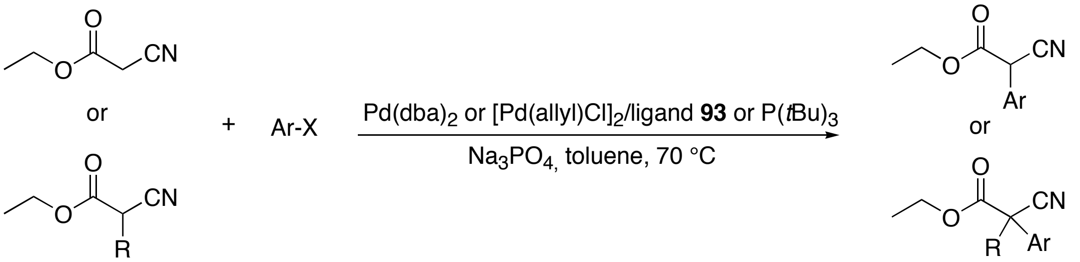
[81] Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410.
[82] Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541.

(**92** and **93**, respectively, in Scheme 28) was essential for high reaction yields and use of P(*t*Bu)$_3$ led to significant amounts of the hydrodehalogenated product as a side product. As a base, K_3PO_4 was superior to NaH, and a slightly higher temperature (100 °C) in toluene was required with aryl chlorides. Unfortunately, the coupling reactions with pyridylhalides and halobenzonitriles remained unsuccessful.

A similar reaction condition could be applied to the α-arylation of cyanoesters because of the similar p*K*a values (Scheme 29).[77,83] Pd(dba)$_2$ or [Pd(ally)Cl]$_2$ was superior to Pd(OAc)$_2$ and sterically hindered alkyl phosphines were more effective than arylphosphines. The use of Na_3PO_4 as a base was important for high yields. No corresponding arylated product was observed when NaH was used as a base, and the reaction proceeded very slow with K_3PO_4.

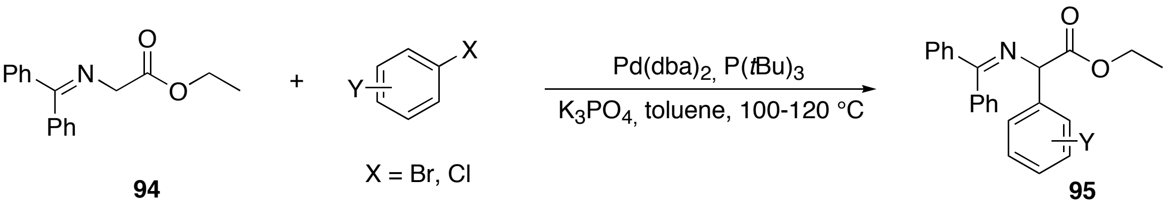
Scheme 29.



4-1-1-4. Palladium-catalyzed α-arylation of protected α-amino acids

Hartwig and coworker investigated the palladium-catalyzed α-arylation of the N-protected amino acid ester **94** (Scheme 30).[81]

Scheme 30.



94

95

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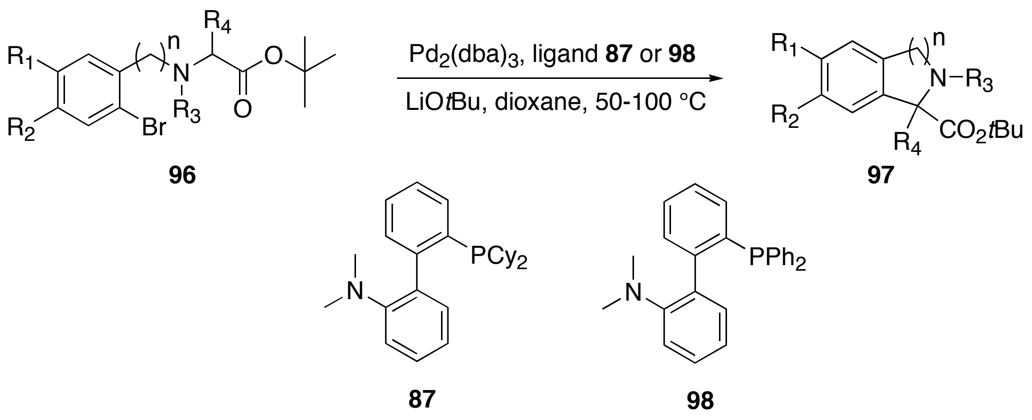
[83] Stauffer, S. R.; Beare, N. A.; Stambuli, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 4641.

The best reaction yield was obtained when a combination of $Pd(dba)_2$ and $P(tBu)_3$ were used. Due to the high p*K*a value of **94**,[84] a relatively weak base such as K_3PO_4 could be applied in this transformation. Even electron rich, *ortho*-substituted or sterically hindered aryl halides could be coupled with **94** in high yields.

Buchwald and coworker reported the intramolecular α−arylation of α-amino acid ester catalyzed by a palladium complex (Scheme 31).[85] Sterically hindered, biphenyl-type ligands **87** or **98** with $Pd_2(dba)_3$ catalyzed efficiently the cyclization to afford dihydroisoindole and tetrahydroisoquinoline carboxylic acid esters **97**. The choice of base was crucial in order to obtain the desired products. For example, NaHMDS or LiHMDS led to decomposition of starting material, presumably due to an unselective Claisen condensation reaction. No conversion was observed when weaker bases such as K_3PO_4 and Cs_2CO_3. LiO*t*Bu provided the cyclized products **97** in high yields, and KO*t*Bu was inferior to LiO*t*Bu. As a solvent, dioxane was superior to the other solvents such as toluene, THF and DME. The formation of the five-membered ring was faster than its six-membered analogue, and electron rich bromoarenes also cyclized well under the described condition although a longer reaction time was required.

Scheme 31.



4-1-2. Palladium-catalyzed α-arylation of nitriles

Hartwig and coworker have developed the α-arylation of alkyl nitriles **99** in the presence of a palladium catalyst (Scheme 32).[86] They assumed that the reductive elimination step could be very slow due to the strongly electron-withdrawing cyano group. Furthermore, the

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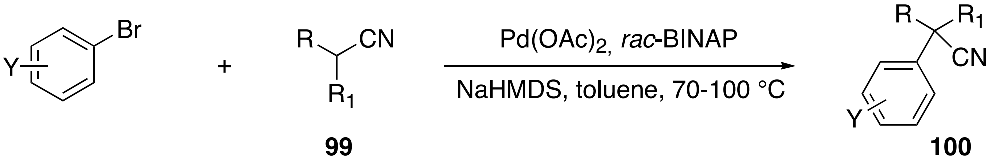
[84] O'Donell, M. J.; Bennett. W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L.; Bordwell, F. G.; Mrozack, S. R.; Cripe, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 8520.

[85] Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465.

[86] Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330.

use of strong base was expected to be unavoidable owing to the high p*K*a values of the alkyl nitriles. On the basis of the mechanistic study of arylpalladium cyanoalkyl complexes, it was proved that *rac*-BINAP-ligated palladium complexes were the most efficient catalysts in this transformation. The desired α-aryl nitriles **100** were generated in high yields and short reaction time. $Pd(OAc)_2$ and NaHMDS were superior to the other palladium sources and bases.

Scheme 32.



99

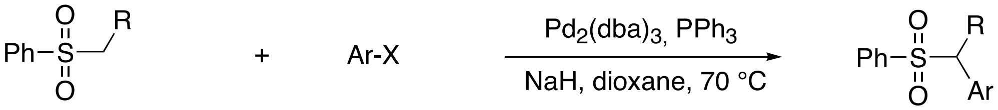
100

Interestingly, acetonitrile and sterically unhindered primary nitriles such as butyronitrile provided only diarylated nitriles as products of this process.

4-1-3. Palladium-catalyzed α-arylation of sulfones

Sulfones are one of the most important organic synthons and they have been extensively used in the total synthesis of natural products and bioactive compounds.[87] In order to establish a useful synthetic route to arylmethyl sulfones, Beletskaya and coworkers developed the palladium-catalyzed α-arylation of α-functionalized sulfones **101** (Scheme 32-1).[88] They found that sulfonyl CH-acids reacted with aryl halides in the presence of $Pd_2(dba)_3/PPh_3$ and NaH in dioxane to afford the corresponding arylated sulfones **102** in high yields.

Scheme 32-1. Pd-catalyzed α-arylation of sulfones



101

102

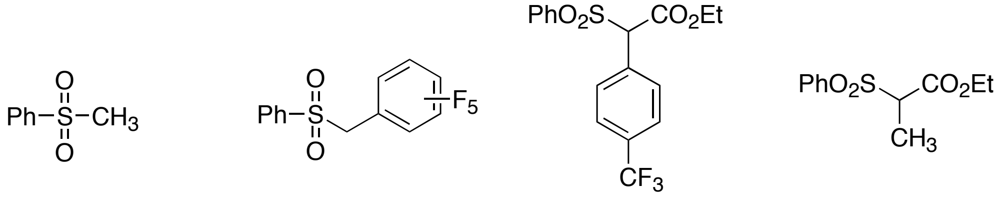
R = $-SO_2Ph$, $-CO_2Et$
$-COPh$, $-CN$, $-NO_2$

---

[87] (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993. (b) Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10546.

[88] Kashin, A. N.; Mitin, A. V.; Beletskaya, I. P.; Wife, R. *Tetrahedron Lett.* **2002**, *43*, 2539.

A broad range of ligands could be applied in this transformation. PPh_3, dppf, *rac*-BINAP and Xanphos showed similar activities, but PPh_3 was utilized due to the consideration of its low cost. In contrast to this, the choice of palladium source was critical. $Pd_2(dba)_3$ was much superior to other palladium complexes such as $PdCl_2$ or $[Pd_2(m\text{Cl})_2(o\text{-dimethylaminomethylphenyl}]_2$. Furthermore, the use of NaH as a base was critical. KO*t*Bu provided significant amounts of biaryl compounds as side products, and a weaker base such as K_3PO_4 or Cs_2CO_3 did not catalyze the transformation. Diverse aryl bromides and iodides were efficiently coupled with α-functionalized sulfones. Aryl chlorides gave only small amounts of arylated products.



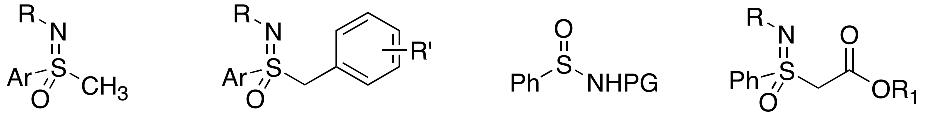
103a **103b** **103c** **103d**

Figure 9.

The coupling reaction did not proceed with α-unfunctionalized or α–substituted methylphenylsulfones (**103a** to **103d** in Figure 9). The reaction occurred successfully only in the case of relatively strong CH-acids containing sulfones, and weak CH-acids possessing the precursors of highly nucleophilic carbanions remained unreactive.

4-2. Palladium-catalyzed α-arylation of sulfoximines: results and discussion

Sulfoximine derivatives containing aryl groups in the α-position such as **105** (Figure 10) are either unavailable by existing methods or at least difficult to prepare in enantiopure form. Thus, a useful and general method to prepare them is required and utilization of palladium-catalyzed α-arylation method was attempted. If sulfoximine **104** or an appropriate protected derivative of it could efficiently be arylated at the *S*-methyl group with an appropriate aryl halide, structurally diverse arylbenzyl sulfoximines **105**, which we intended to apply as key constituents in chiral ligands, would be accessible in a highly flexible manner. Therefore, a comprehensive screening of reaction conditions was undertaken. At this stage, *rac*-sulfoximine derivatives were used for all of these reactivity studies.

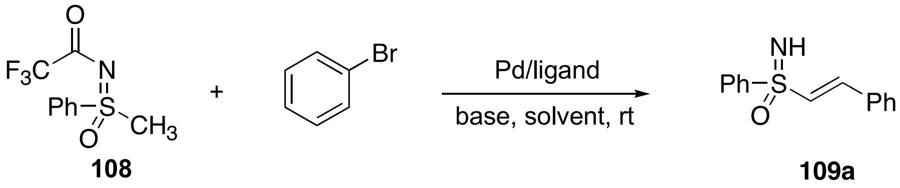


104 **105** **106** **107**
107a (R = CH_3CO, R_1 = CH_3)

Figure 10.

Initial screenings revealed that the coupling reaction required carefully selected starting materials and strictly optimized reaction conditions. First of all, we focused on developing α-arylations reaction with N-substituted phenylmethyl sulfoximines, which would directly lead to the benzyl derivatives **105**. Various N-protected methylphenyl sulfoximines having Boc, trifluoroacetyl, TBDMS, or tosyl groups at the nitrogen were examined as starting materials with phenyl bromide or phenyl iodide in the presence of diverse combinations of palladium catalysts [for example, $Pd_2(dba)_3$, $Pd(dba)_2$ and $Pd(OAc)_2$ as a palladium source and *rac*-BINAP, DPPF and $P(tBu)_3$ as a ligand] and bases (for instance, KHMDS, NaHMDS, LiHMDS, K_3PO_4, phosphazene base P_2-*t*Bu, Cs_2CO_3, KO*t*Bu, NaH, etc.). Toluene or dioxane was the solvents and furthermore, the temperature was varied. However, in most reactions either no reaction or decomposition occurred. Instead of the expected α-arylated sulfoximines, undesired side products such as sulfinamides **106** (Figure 10) or olefinic NH-sulfoximine **109a** (Table 5) were observed and their structures were confirmed by ^1H NMR and mass spectroscopy. Interestingly, compound **109a** was obtained up to 80% yield from *N*-trifluoroacetyl protected methylphenyl sulfoximine (**108**) as starting material. This product was not observed by using *N*-tosyl methylphenyl sulfoximine or NH-free sulfoximine as educts under described condition in Table 5. Although further mechanistic studies are required in order to understand the formation of compound **109a**, a few features of this reaction were observed. For example, the higher reaction yield was obtained with using polar solvent such as dioxane and DMF instead of toluene (not included in Table 5). Furthermore, the ligand had a great influence on the reaction yields. DPPF with $Pd(dba)_2$ catalyzed this reaction efficiently to afford product **109a** in high yield (entry 1), while only low yields were obtained using DPPF or $P(tBu)_3$ as a ligand.

Table 5. Pd-catalyzed coupling reaction to yield **109a**

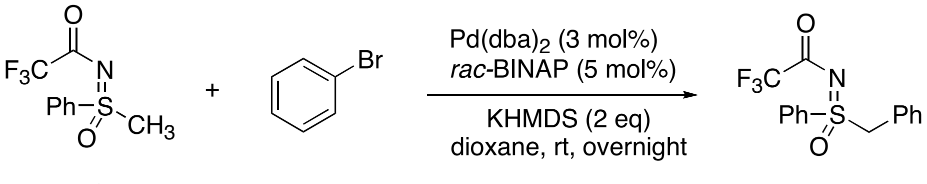


entry	Pd source	ligand	base	solvent	yield (%)*
1	Pd(dba)$_2$	DPPF	KHMDS	dioxane	80
2	Pd(dba)$_2$	BINAP	KHMDS	dioxane	42
3	Pd(dba)$_2$	BINAP	KHMDS	DMF	76
4	Pd(dba)$_2$	BINAP	NaHMDS	dioxane	46
5	Pd(dba)$_2$	P(*t*Bu)$_3$	KHMDS	dioxane	25

* based on assummed dimerization followed by elimination.

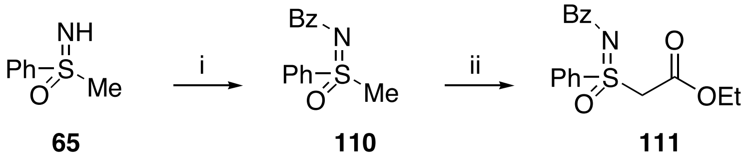
Together with compound **109a**, to our delight, the expected α-arylated product **109b** from sulfoximine **108** was also obtained in 20% yield when Pd(dba)$_2$/*rac*-BINAP as a catalyst was used in conjunction with KHMDS in dioxane at room temperature (Scheme 34). However, attempts to further optimize the reaction conditions for improving the yield was unsuccessful with *N*-trifluoroacetyl protected sulfoximine **108** as a starting material.

Scheme 34. Pd-catalyzed α-arylation of *N*-trifluoroacetyl sulfoximine **108**



Assuming that the p*K*a values of the *S*-methyl protons were relevant for the coupling and the acidity at this α-position needed being increased more, a positioning of electron-withdrawing groups on the α-position of the sulfoximine appeared essential. According to this hypothesis, *N*-methoxylcarbonyl sulfoximine methyl ester **107a** (Figure 10) was prepared as a starting material for the α-arylation. **107a** was available in a single step by reaction of methylphenyl sulfoximine (**65**) with NaHMDS and dimethylcarbonate in 63% yield. After an intensive screening of the reaction condition, the corresponding α-arylated product from this sulfoximine ester **107a** and phenyl bromide could be earned in 44% yield using $Pd_2(dba)_3/PCy_3$ as a catalyst and NaO*t*Bu as a base in dioxane at 70 °C. However, variable reaction yields were often observed under the same reaction condition (12-60% yield). With the aim to increase the efficiency of the catalysis and taking into account the stability of *N*-aroylated sulfoximines,[89] we next focused our attention on the synthesis and the use of *N*-benzoyl sulfoximine ethyl ester (**111**). The reaction sequence, which led to **111** starting from NH-sulfoximine **65** in high overall yield, is depicted in Scheme 35.

Scheme 35. The preparation of *N*-benzoyl sulfoximine ethyl ester **111**.



(i) Benzoyl chloride, NaH, CH_2Cl_2, rt, 90%; (ii) *n*BuLi, tetramethylpiperidine, THF, –78 °C; then ethyl chloroformate, –78 °C, 89%.

In fact, the procedure for the synthesis of sulfoximine a-ethyl ester **111** demanded a great optimization process. Finally, it was found that adding ethyl chloroformate at –78 °C to the corresponding sulfoximine anion generated by the mixture of *n*BuLi and tetramethylpiperidine was crucial in order to achieve a high selectivity for the formation of sulfoximine mono-ester **111** in the high yield. Gratifyingly, the *N*-benzoyl protected sulfoximine ester **111** proved to be a very suitable substrate for the α-arylation. An intensive optimization of the reaction conditions using phenyl bromide as coupling partner was carried out, and representative results are summerized in Table 6.

In general, combinations of $Pd(OAc)_2/PCy_3$ or $Pd_2(dba)_3$/*rac*-BINAP were the most efficient as catalysts (entry 1 and 4 in Table 6), and the reaction was complete within 1 h. The catalyst loading could be reduced to as low as 1 mol% (entry 3) although a slightly longer reaction time was required (2 h). Increasing it to 9 mol% gave an effect to the reaction rate, but had only a minor influence on the yield of **112a** (74 and 79%, respectively, entry 3 and 5). Subsequently, most α-arylations of **111** were conducted with the catalyst consisting of 3 mol% of $Pd(OAc)_2$ and 9 mol% of PCy_3 or 5 mol% of *rac*-BINAP. Several

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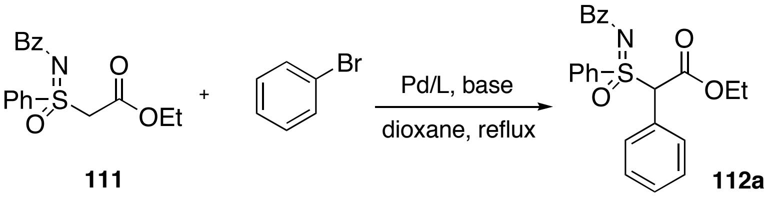
[89] *N*-Aroylated sulfoximines are rather stable compounds with a peculiar reactivity pattern (see: Bolm, C.; Hackenberger, C. P. R.; Simic, O.; Verrucci, M.; Müller, D.; Bienewald, F. *Synthesis* **2002**, 879). Their treatment with boran-based reducing agents does not lead to the expected *N*-benzyl derivatives, but results in either no conversion or the formation of free NH-sulfoximines. This particular aspect was expected to be benefical in the program described here, since it allowed a selective deprotecting of the α-arylated products under reductive conditions.

bases such as NaH, KHMDS, NaHMDS, Cs_2CO_3, KO*t*Bu, NaOMe, and Na_2CO_3 were tested, but none of them was as effective as sodium *tert*-butoxide. Using dry NaO*t*Bu and reflux condition was very important for the reproducibility of this transformation. Furthermore, in order to achieve complete conversion, use of at least 2.0 equiv of base was essential and under the optimal condition, 3.0 equiv of NaO*t*Bu were applied for all reactions. The yield from the reaction adding 1.8 equiv of phenyl bromide was almost equal to the one with 1.2 equiv (not included in Table 6). As a solvent, dioxane was superior to others such as THF, toluene or DMF.

Table 6. Optimization of Pd-catalyzed α-arylation with phenyl bromide[a]



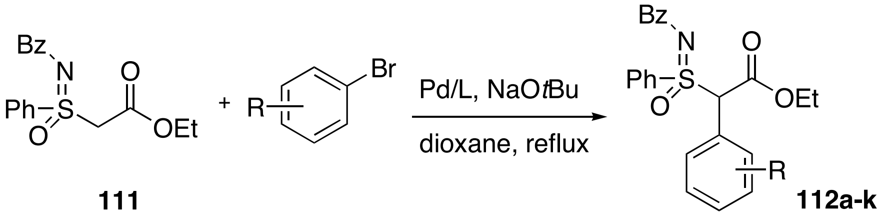
111 **112a**

entry	Pd	ligand	base	yield (%)
1	$Pd(OAc)_2$	PCy_3	NaO*t*Bu	79
2	$Pd_2(dba)_3$	PCy_3	NaO*t*Bu	68
3	$Pd_2(dba)_3$	*rac*-BINAP	NaO*t*Bu	74[b]
4	$Pd_2(dba)_3$	*rac*-BINAP	NaO*t*Bu	76
5	$Pd_2(dba)_3$	*rac*-BINAP	NaO*t*Bu	79[c]
6	$Pd_2(dba)_3$	P(*o*-Tol)$_3$	NaO*t*Bu	45
7	$Pd_2(dba)_3$	P(*t*Bu)$_3$	NaO*t*Bu	20
8	$Pd(OAc)_2$	*rac*-BINAP	NaO*t*Bu	76[d]
9	$Pd_2(dba)_3$	*rac*-BINAP	KO*t*Bu	51
10	$Pd_2(dba)_3$	*rac*-BINAP	NaOMe	NR

[a] Reagents and reaction conditions: *N*-benzoyl sulfoximine ethyl ester **111** (1 equiv), Ph-Br (1.8 equiv), Pd source (3 mol%), ligand (9 mol%) except BINAP (5 mol%), base (3 equiv), dioxane, reflux for 1 or 2 h. [b] 1 mol% of Pd and 1.7 mol% of ligand was used. [c] 9 mol% of Pd and 15 mol% of ligand was used. [d] 7 h of reaction time.

To the next, in order to investigate the scope of this reaction, other aryl bromides were applied under the conditions developed for the conversion of phenyl bromide. The results are summarized in Table 7.

Table 7. Optimized protocol for the palladium-catalyzed α-arylation of sulfoximine ethyl ester **111** with aryl bromides.[a]



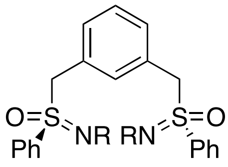
entry	R	product	yield (%)
1	H	**112a**	79
2	4-OCH_3	**112b**	87
3	4-CN	**112c**	90^b
4	4-NO_2	**112d**	73
5	4-Cl	**112e**	$71^{b, c}$
6	4-SCH_3	**112f**	85
7	4-Ph	**112g**	86
8	3-OCH_3	**112h**	79
9	3-NO_2	**112i**	50^b
10	3-Br	**112j**	82^d
11	2-CH_3	**112k**	73

[a] Reagents and reaction conditions: *N*-benzoyl sulfoximine ethyl ester **111** (1 equiv), Ar-Br (1.2 equiv), $Pd(OAc)_2$ (3 mol%), PCy_3 (9 mol%), NaO*t*Bu (3 equiv), dioxane, reflux. [b] $Pd_2(dba)_3$ (3 mol%) was used instead of $Pd(OAc)_2$. [c] Only the 4-chlorobenzene derivative was formed. [d] Combined yield of mono-(**112j-A**) and dicoupled (**112j-B**) products (in a ratio of 1:1).

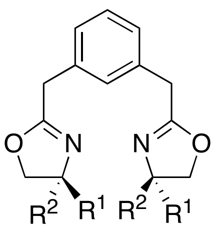
As revealed by the data presented in Table 7, diverse aryl bromides could efficiently be coupled with *N*-benzoyl sulfoximine ethyl ester **111**. The most suitable catalyst system was the combination of $Pd(OAc)_2$ and PCy_3, but depending on a substrate slight modifications were unavoidable. In contrast to the result with phenyl bromide, interestingly, the activity between catalysts with *rac*-BINAP and PCy_3 was dramatically different and the use of PCy_3 was even crucial for obtaining the desired products. For example, the coupling reaction of sulfoximine **111** with 4-bromobenzonitrile, 4- or 3-nitrophenyl bromide did not give any of the corresponding products with *rac*-BINAP, while moderate to good yields of product **112c**, **112d** and **112i** were achieved using PCy_3 as the ligand (entries 3, 4 and 9, Table 7).

In general, catalysts prepared from $Pd(OAc)_2$ gave better yields than those obtained from $Pd_2(dba)_3$. In reactions of 4-bromobenzonitrile, 4-bromochlorobenzene and 3-nitrophenyl bromide, however, the latter palladium source proved more effective (entries 3, 5, and 9, Table 7). The conversion of 4-bromochlorobenzene gave the corresponding 4-chloro derivate exclusively, which indicated a high degree of chemoselectivity of the coupling. Although the reaction with 2-bromotoluene provided α-arylated compound **112k** in good yield (entry 11), *ortho*-substituted aryl bromides were generally unsuitable substrates under the described condition in Table 7. For instance, 2-bromoanisole gave the corresponding coupled product in only 25% yield under the optimized reaction condition (not included in Table 7). *N,N*-Dimethyl-2-bromoaniline, 2-bromobenzonitrile and 2-bromobenzaldehyde did not afford the expected products at all. Use of heterocyclic aryl halides such as 2-bromopyridine, 2-bromothiophene and 3-bromopyridine as a coupling partner was also investigated, but only 17% of the corresponding product from 2-bromopyridine was observed (not included in Table 7) and the rest of reactions ended in failures. In this study mostly racemic sulfoximines were used, and generally, the α-arylated products were isolated as a ca. 1:1 mixture of diastereomers (for **112k** = 2:1 in Table 7). Based on previous results, we expect that a "chiral switch" should simply lead to idential compounds in enantiomerically pure form.

A particularly interesting coupling reaction is shown in entry 10 of Table 7, which demonstrates the α-arylation of sulfoximine **111** with 1,3-dibromobenzene. The dicoupled product **112j-B** from this process can be converted into the corresponding C_2-symmetric bissulfoximine **113** which could be applied in analogy to pincer-type ligands[90] such as **114** (Figure 11). As a product of the developed α-arylation process with 1,3-dibromobenzene, a ca. 1:1 mixture of mono- and diarylated sulfoximine ethyl esters **112j-A** and **112j-B**, respectively, was observed. In order to enhance the ratio of diarylated sulfoximine product, using 5.0 equiv of sulfoximine **111** was also tested. However, it did neither affect the ratio of mono- and diarylation nor the reaction yield.



(*S*,*S*)-**113**



114
(pincer-type bisoxazoline)

Figure 11.

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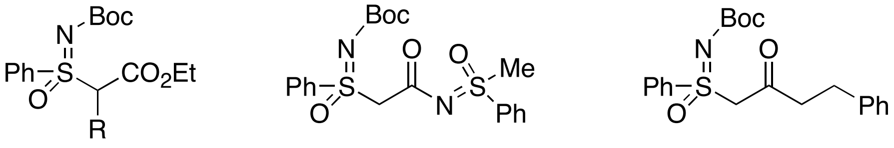
[90] Gerisch, M.; Krumper, J. R.; Bergman, R. G.; Tilley, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 5818.

Next, various sulfoximine derivatives such as **115**, **116** and **117** (Figure 12) were tested as substrates under the optimized condition described in Table 7. *N*-Boc protected sulfoximine ester **115** showed the same reactivity as *N*-benzoyl compound **111** and gave the corresponding product **115a** in the catalysis with phenyl bromide in 79% yield. Attempts to arylate sulfoximine dimer **116** and β-keto-sulfoximine **117** remained unsuccessful.



115: R = H
115a: R = Ph

116

117

Pd-cat. α-arylation: 79% yield

Figure 12.

In order to fully benefit from the developed α-arylation process in the synthesis of chiral ligands and building blocks for pseudopeptides, a selective deprotection strategy had to be established. With this objective in mind, we first ensured that arylated compound **112a** could be easily hydrolyzed by brief treatment with an aqueous methanolic solution of NaOH affording N-protected benzyl phenyl sulfoximine **118** in quantitative yield (Scheme 36).[91]

Since in most ligand and pseudopeptide syntheses the “free” NH-sulfoximines are demanded and applied, the possibility to cleave the N-protecting group also had to be ensured. Much to our surprise, *N*-benzoyl sulfoximine **118** proved rather stable under basic conditions (K_2CO_3, NaOH, NaOMe, and NH_3-ethanol),[62] and even after extended reaction time no conversion was observed. Acidic conditions such as 1.2 N HCl, reflux led to the decomposition of the substrate. Attempts to reductively cleave the *N*-benzoyl group by treatment of sulfoximine **118** with DIBAL-H remained unsuccessful as well. Finally, we used the BH_3•THF complex for the reductive *N*-benzoyl cleavage, which afforded the desired “free” NH-benzyl phenyl sulfoximine (**119**) in good yield (Scheme 36).

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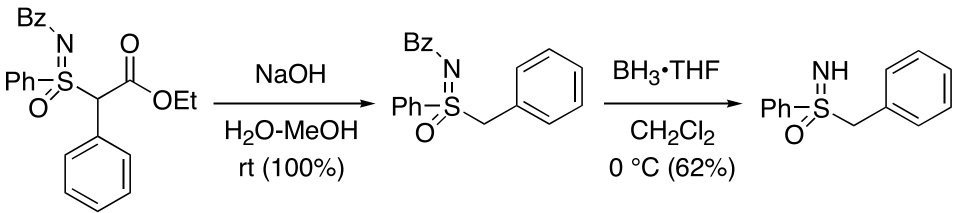
[91] Rapid decarboxylations have also been observed in reaction sequences involving other a-sulfoximidoyl carboxylates. Since some ammonium salts proved rather stable at ambient temperature, they could be applied in coupling reactions providing sulfoximine-containing pesudopeptides. For details, see ref 9f and 9g.

Scheme 36. Conversion of ester **112a** into NH-sulfoximine **119**



112a **118** **119**

4-3. Summary and outlook

Various enantiomerically pure benzylphenyl sulfoximines can be readily synthesized from *N*-benzoyl sulfoximine ester by palladium-catalyzed α-arylation with aryl bromides. In order to achieve a successful coupling reaction, the appropriate combination of palladium source, ligand and base are as well as the careful choice of starting sulfoximine derivatives very important. *N*-Benzoyl protected sulfoximine ethyl ester **111** proved to be a particularly suitable educt for the coupling. In this area, further studies should be performed to prepare and utilize enantiopure derivatives of this type in the preparation of new chiral ligands for asymmetric catalysis and building blocks for pseudopeptides. Especially, enantiopure C_2-symmetric bissulfoximine **113** or its derivatives are expected to show interesting activity as a pincer-type ligand and could be applied for several asymmetric catalyses. The relatively low reaction yield of dicoupled product **112j-B** due to the competitive formation of the mono-arylation should be also improved by modifying the reaction condition. Morerover, the further development of the α-arylation process with heterocyclic halides is worthful to be investigated since heterocyclic sulfoximines are of great interest in biomedical and pharmaceutical chemistry.

5. Part III. Copper-mediated N-arylation of sulfoximines

5-1. Copper-mediated and -catalyzed coupling reactions with aryl halides: Introduction

Carbon (aryl)-carbon (aryl or alkyl) and carbon (aryl)-heteroatom bond formations are important transformations to synthesize the cardinal structual motifs of many organic compounds, and they have been developed with various transition metal catalysts such as palladium,[57c,92] nickel,[93] and so forth. Among them, copper-mediated or –catalyzed cross-coupling reactions have been intensively investigated especially in recent years and became a general synthetic tool for aryl substitutions.[94] The classic Ullmann reaction and Ullmann condensation reaction[95] required harsh reaction conditions such as high temperature (over 200 °C), strong bases, long reaction time, stoichiometric amounts of copper metal or copper salts and displayed the limited substrate scope. However, recently significant improvements in this transformation have been accomplished by using appropriate copper salts, bases, ligands and other additives. Furthermore, the introduction of diverse coupling partners such as aryl boronic acids,[96] iodonium salts,[97] siloxanes,[98] stannanes,[99] bismuthates[100] and trifluoroboronic acids[101] as aryl donors besides aryl halides led to mild reaction conditions. The following section covers copper-mediated or -catalyzed cross coupling reactions with aryl halides as aryl donors.

5-1-1. Copper-mediated or -catalyzed coupling with aryl halides: C-N bond formation

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[97] (a) Davydov, D. V.; Beltskaya, I. P.; Semenov, B. S.; Smushkevich, Y. L. *Tetrahedron Lett.* **2002**, *43*, 6217. (b) Beletskaya, I. P.; Davydov, D. V.; Gorovoy, M. S. *Tetrahedron Lett* **2002**, *43*, 6221. (c) Zhou, T.; Chen, Z. C. *Synth. Commun.* **2002**, *32*, 903. (d) Kang, S. K.; Lee, S. H.; Lee, D. *Synlett* **2000**, 1022. (e) Beringer, F. M.; Brierley, A.; Drexler, M.; Gindler, E. M.; Lumpkin, C. C. *J. Am. Chem. Soc.* **1953**, *75*, 2708.

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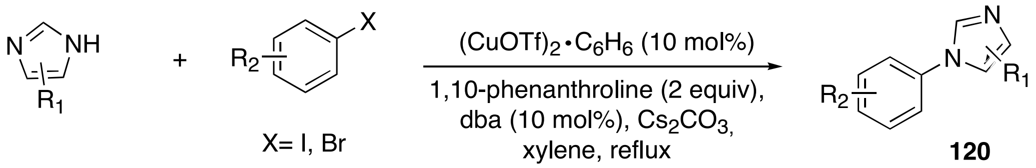
Since the Ullmann condensation reaction[102] was reported in 1903, the copper-mediated or -catalyzed cross coupling with aryl halides was renewed by many groups in recent years and the limitations of classic Ullmann condensation reaction such as harsh reaction condition and limited substrate scope could be circumvented. In 1999, Buchwald and coworkers discovered that CuOTf efficiently catalyzed the coupling reaction between aryl halides (iodide and bromide) and imidazole derivatives in the presence of 1,10-phenanthroline (2.0 equiv), *trans, trans*-dibenzylidineacetone and Cs_2CO_3 in xylene under reflux (Scheme 37).[103] Although a high temperature in xylene was still required, this method showed general substrate scope of aryl halides and the corresponding coupled imidazole **120** was obtained in high yields (79-97%).

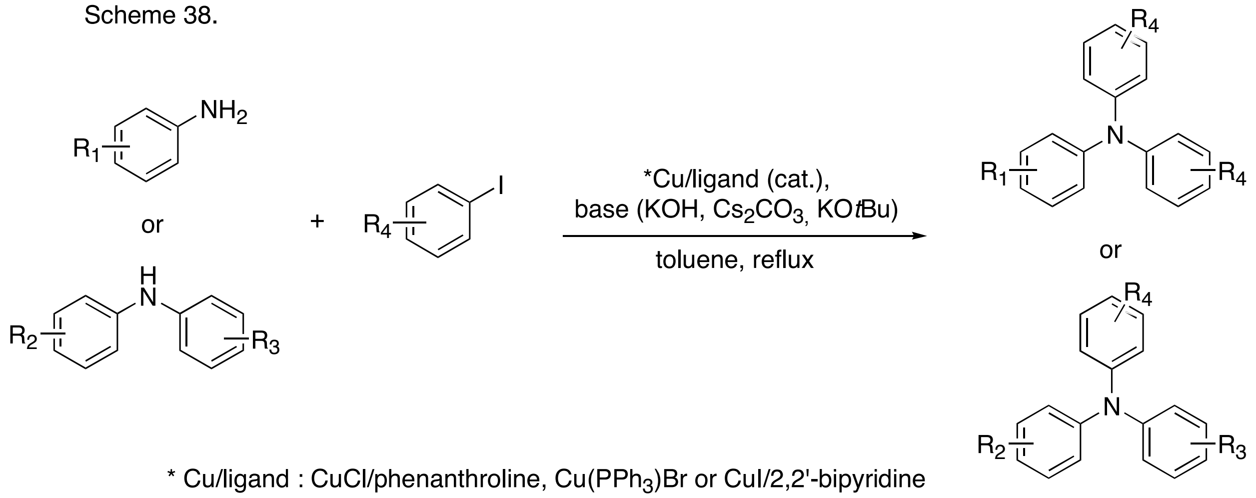
Scheme 37.



120

The copper-catalyzed coupling of aryl amines or diaryl amines with aryl halides was investigated by Goodbrand and Hu (Scheme 38).[104]

Scheme 38.



They exploited the use of a catalytic amount of CuCl and phenanthroline as a ligand in the presence of KOH in toluene and various triaryl amines could be prepared by this method.

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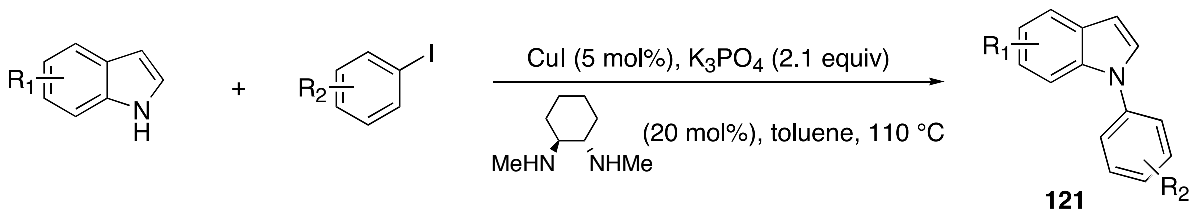
[102] For a possible mechanism of the Ullman condensation, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
[103] Kiymori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657.
[104] Goodbrand, H. B.; Hu, N. X. *J. Org. Chem.* **1999**, *64*, 670.

Venkataraman and coworkers modified this reaction condition by using Cs_2CO_3 in combination with $Cu(PPh_3)_3Br$ (20 mol%), which is air-stable, well-soluble in general organic solvents and readily prepared from CuBr and PPh_3 in methanol.[105] In addition, a ligand-free Cu-catalyzed amination reaction of aryl amines was reported by Claudhari and coworkers.[106] In this study, it was proved that KO*t*Bu was the most efficient base and diamino chelating ligands gave improved amination activity as well as selectivity for triarylamines. With this method, various triaryl amines could be synthesized in a relatively short reaction time (4 h).

A number of substituted indoles were efficiently synthesized from the reaction of indoles and aryl iodides in the presence of a CuI/*N,N*-dimethyl-1,2-cyclohexyldiamine catalyst by Buchwald and coworkers (Scheme 39).[107] In this transformation, CuI or Cu^0 was superior to the other copper salts such as $Cu(OAc)_2$, $Cu(OMe)_2$ and $CuCl_2$, and tri- or tetramethyl substituted ligands gave lower yields. Furthermore they reported that the corresponding *cis*-diamine ligands showed reduced activity and increased ligand arylation.

Scheme 39.



The same group developed the copper-catalyzed N-arylation of benzylamine (Scheme 40).[108] They concluded that the combination of CuI/ethyleneglycol catalyzed the coupling reaction most efficiently, but that CuBr, CuCl and CuOAc could be also applied for this reaction. They observed that the formation of O-arylated products with ethyleneglycol was preferred when Cs_2CO_3 was used as a base, and propylene and butylene glycol gave only trace amount of products. Except benzyl amine, primary alkyl amines were mono-arylated under similar reaction condition. In this case, commercially available *N,N*-diethylsalicylamide was revealed as the best ligand with CuI.

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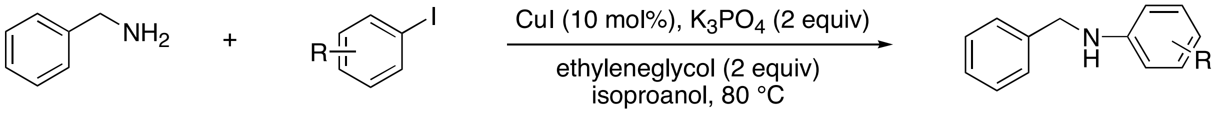
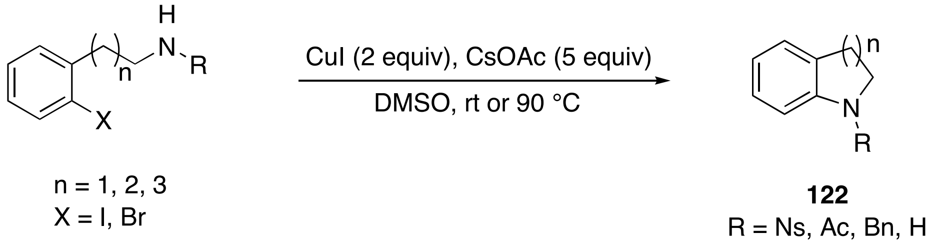
[105] Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791.
[106] Kelkar, A. A.; Pati, N. M.; Claudhari, R. V. *Tetrahedron Lett.* **2002**, *43*, 7143.
[107] Antila, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684.
[108] Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.

Scheme 40.



Fukuyama and coworkers reported a related intramolecular cyclization by using stoichiometric amount of CuI and CsOAc as a base in DMSO at rt or 90 °C (Scheme 41).[109] The use of CsOAc was crucial to obtain the corresponding products and no reaction occurred using Cs_2CO_3, Na*Ot*Bu and K*Ot*Bu. Removing air from the solvent improved the yield and reproducibility, and oxygen bubbling proved to inhibit the reaction. Furthermore, Cu(II) salts did not catalyze this transformation, and CuBr or (thienyl)Cu could be used instead of CuI.

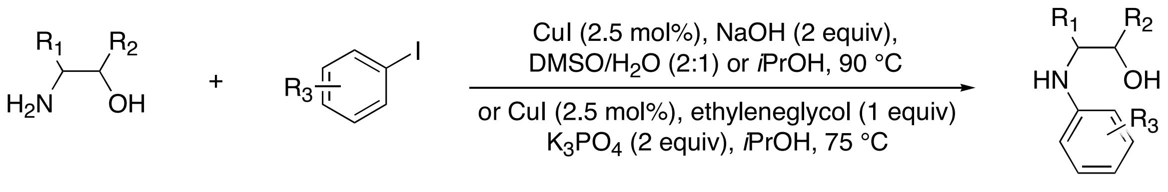
Scheme 41



122

Under similar reaction conditions as those depicted in Scheme 41, the copper-catalyzed selective arylation of β-amino alcohols was described by Buchwald and coworkers (Scheme 42).[110]

Scheme 42.



123

The N-arylated β-amino alcohols were selectively formed by using a catalytic amount of CuI in the presence of a base. NaOH or K_3PO_4 were superior to the other bases and ethyleneglycol (1.0 equiv) was required to suppress the O-arylation of β-amino alcohols

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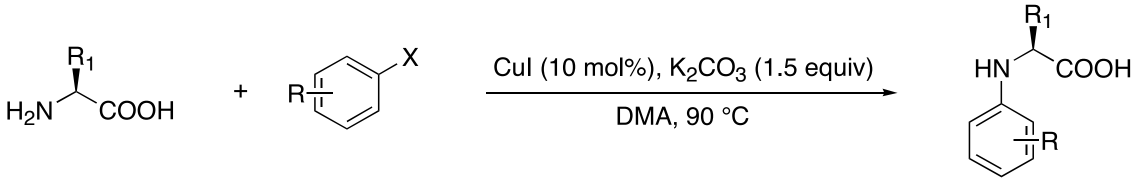
[109] Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231.
[110] Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3703.

when a mild base, K_3PO_4, was employed. On the other hand, interestingly, the selectivity of O-arylation was dramatically increased by using Cs_2CO_3 in combination with CuI (5 mol%).

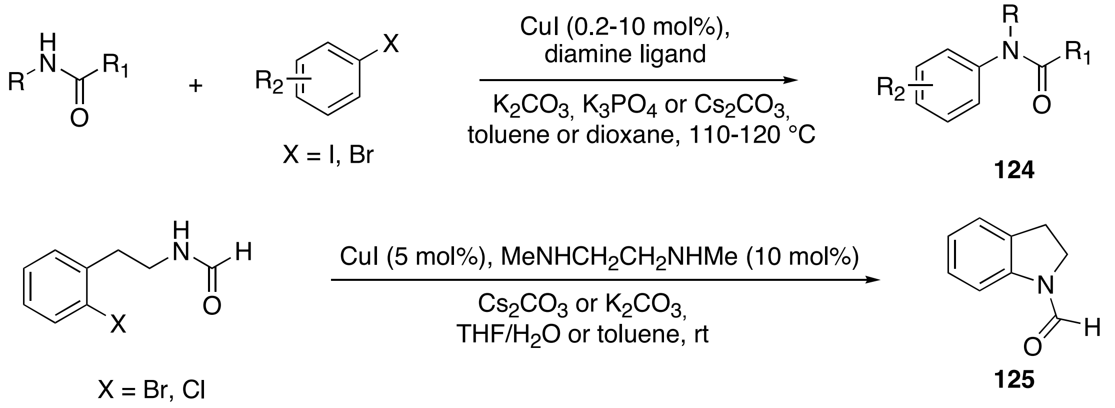
The copper-catalyzed coupling of aryl halides with α-amino acids was studied by Ma and coworkers.[111] A number of N-arylated α-amino acids were synthesized in good yields by using mild reaction conditions involving CuI (10 mol%) and K_2CO_3 in DMA at 90 °C (Scheme 43).

Scheme 43.



Buchwald and coworkers used CuI as a catalyst with a diamine ligand for the inter- and intra-amidation of aryl halides (Scheme 44).[112] They described that in the inter-amidation reaction, the combination of CuI and *trans*-1,2-cyclohexanediamine or *trans*-1,2-cyclohexanedimethyldiamine gave the most efficient catalyst in the presence of a mild base such as K_2CO_3, K_3PO_4 or Cs_2CO_3. On the other hand, ethylenedimethyldiamine proved to be the best ligand for the intra-molecular amidation.

Scheme 44.



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[111] Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

[112] (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (b) Klapars, A.; Antila, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

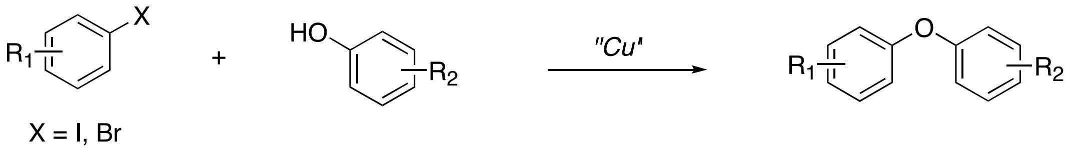
Kang and coworkers reported N-arylations of benzamide or nitrogen heterocycles by using ethylenediamine as a ligand with CuI (10 mol%) and K_3PO_4 in dioxane.[113] Their study also revealed that the appropriate combination of copper salt, ligand and base was crucial to catalyze the N-arylation efficiently.

In addition to this, Padwa and coworkers have contributed in this area by developing a ligand-free arylation of thiopheno and furano halides from various amides and carbamates.[114] In this study, CuI (10 mol%) and K_2CO_3 (4.3 equiv) in dioxane at 110 °C were used and a range of 2- and 3-amido-substituted thiophenes and furanes were synthesized in good yields.

5-1-2. Copper-mediated or catalyzed coupling with aryl halides: C-O bond formation

Buchwald and coworkers found that using Cs_2CO_3 as a base, the Ullmann condensation reaction afforded the O-arylated product as the major product.[115] Accordingly, they developed a general procedure of the copper-catalyzed synthesis of diaryl ethers with a broad range of activated and unactivated arylhalides (bromides and iodides) and phenol derivatives (Scheme 45, conditions A). CuCl, CuBr, CuI or $CuSO_4$ could replace CuOTf although a slightly accelerated reaction rate was observed by using the more soluble copper species, $(CuOTf)_2$benzene, in toluene. Furthermore, use of carboxylic acids (1-naphthoic acid with molecular sieves) and addition of a catalytic amount of ethyl acetate was necessary to improve the reaction yields.

Scheme 45. Initial investigation of the copper-catalyzed C-O bond formation with aryl halides



conditions: A. $(CuOTf)_2PhH$ (0.25-2.5 mol%), EtOAc (5 mol%), Cs_2CO_3 (1.4 or 2 equiv)
1-naphthoic acid (1 equiv), toluene, 110 °C
B. CuBr (2 equiv or 20 mol%), P_4-*t*Bu, toluene, reflux
C. $Cu(PPh_3)_3Br$ (20 mol%), Cs_2CO_3, NMP, 100 °C
D. CuCl (50 mol%), Cs_2CO_3 (2 equiv), NMP, $(CH_3)_3CC(O)CH_2C(O)C(CH_3)_3$ (10 mol%), 120 °C

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[113] Kang, S. K.; Kim, D. H.; Park, J. N. *Synlett* **2002**, 427.

[114] (a) Padwa, A.; Crawford, K. R.; Rashataskhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609. (b) Crawford, K. R.; Padwa, A. *Tetrahedron Lett.* **2002**, *43*, 7365.

[115] Marcoux, J. F.; Doyle, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539.

A phosphazene base P_4-*t*Bu was applied in the copper-catalyzed O-arylation to prepare diaryl ethers by Palomo and coworkers (Scheme 45, conditions B).[116] CuBr (catalytic or stoichiometric amount) was superior to $(CuOTf)_2$benzene in the presence of P_4-*t*Bu in toluene, and no reaction occurred with Cu(II) salts. They reasoned out that the effect of phosphazene base was its complete solubility as well as the formation of highly nucleophilic naked anions.

Venkataraman and coworkers contributed to this development by introducing $Cu(PPh_3)_3Br$ as a catalyst which is readily prepared and air-stable (Scheme 45, conditions C).[117] The coupling reaction did not proceed with K_2CO_3, KO*t*Bu or DMAP as a base.

It was reported by Song and coworkers that the reaction rate of copper-catalyzed O-arylation with aryl halides and phenols could be enhanced by adding 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) in the presence of CuCl as a catalyst (Scheme 45, condition D).[118] Interestingly, TMHD accelerated the coupling reaction only when was used Cs_2CO_3 as a base.

Besides coupling with phenols Buchwald and coworkers developed the copper-catalyzed cross coupling reaction of aryl iodides with aliphatic alcohols.[119] Using neat alcohol as the solvent (isopropanol, ethanol, *n*-butanol, methanol, heptanol, etc.) in the presence of CuI (15 mol%), and phenanthroline (20 mol%) and Cs_2CO_3 afforded a number of alkylaryl ethers with various aryl iodides.

An interesting approach to synthesize a series of 1,2,3-contiguously substituted diaryl ethers has been developed by Sineckus and coworker (Scheme 46).[120] A catalytic amount of $[CuPF_6(MeCN)_4]$ was used as a catalyst in conjuction with Cs_2CO_3 as a base in toluene or xylene, and various products from aryl iodides, aryl bromides and secondary chlorobenzamides were synthesized.

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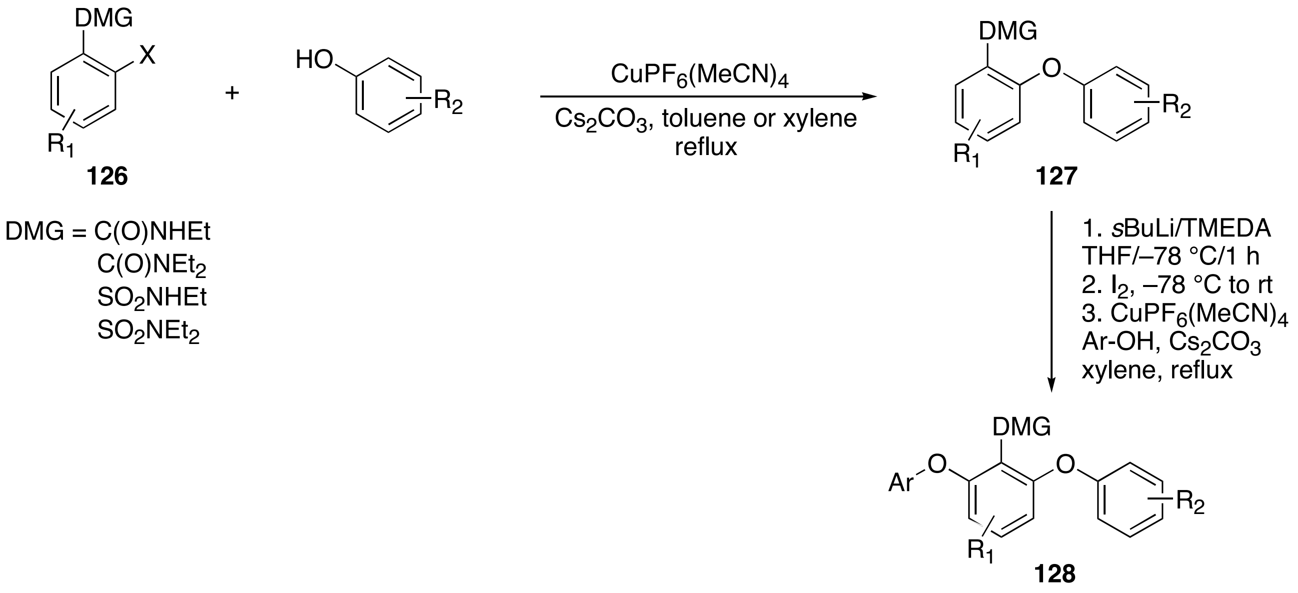
[116] Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoa, E. *Chem. Commun.* **1998**, 2091.
[117] Gujadhur, K.; Venkataraman, D. *Synth. Commun.* **2001**, *31*, 2865.
[118] Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623.
[119] Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973.
[120] Kalinin, A. V.; Bower, J. F.; Reibel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986.

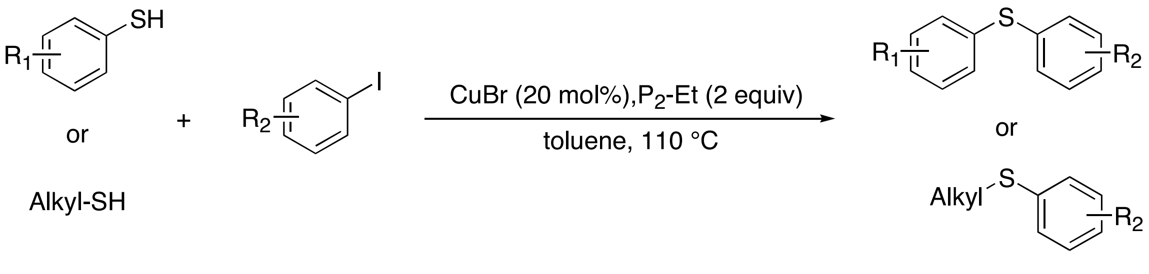
Scheme 46.



5-1-3. Copper-mediated or -catalyzed coupling with aryl halides: C-S bond formation

Compared to the C-arylation and the O-arylation, copper-catalyzed carbon (aryl)-sulfur bond forming reactions have been less investigated. Among them, Palomo and coworkers recently developed a copper-catalyzed process using phosphazene base P_2-Et for the synthesis of various diaryl sulfides (Scheme 47).[121] In this transformation, the stronger base P_4-*t*Bu was much less effective than P_2-Et and the cross coupling reaction also proceeded well with DBU although in this case a longer reaction time was required.

Scheme 47.



conditions: A. CuI (10 mol%), neocuproine (10 mol%), NaO*t*Bu (1.5 equiv), toluene, 110 °C
B. CuI (5 mol%), $HOCH_2CH_2OH$ (2 equiv), K_2CO_3, *i*PrOH, 80 °C

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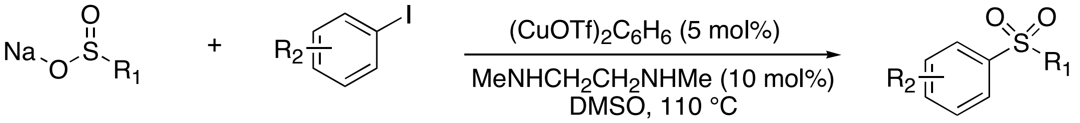
[121] Palomo, C.; Oiabide, M.; Lopez, R.; Gomez-Bengoa, E. *Tetrahedron Lett.* **2000**, *41*, 1283.

A number of diaryl sulfides and alkylaryl sulfides have also been prepared by Venkataraman and coworkers (Scheme 47, conditions A).[122] They used CuI (10 mol%) in combination with neocuproline (10 mol%) as a catalyst in the presence of NaO*t*Bu. Interestingly, using Cs_2CO_3 as a base led to the formation of the disulfides as major products, and the combination of CuI/neocuproine/NaO*t*Bu was much superior to the [Cu(neocuproine)(PPh_3)Br].

Buchwald and coworkers modified this transformation in order to make it experimentally simple and highly general (Scheme 47, conditions B).[123] The cross coupling of aromatic or aliphatic thiols with CuI (5 mol%), K_2CO_3 (2.0 equiv) and ethyleneglycol (2.0 equiv) in isopropanol at 80 °C provided a variety of the corresponding products in high yields. It is worthy to note that this method tolerates a broad range of functional groups.

Various arylmethyl and diaryl sulfones from aryl iodides and the corresponding sulfinic acids salts have been prepared with the help of a copper catalyst by Baskin and Wang (Scheme 48).[124] It was found that CuOTf was superior to Cu or $CuBr{\cdot}SMe_2$. DMSO was the most appropriate solvent and better than DMF, dioxane, toluene or acetonitrile. Although aryl bromides did not react under these conditions, the efficient access to sulfinic acid salts and the high functional group tolerance have to be featured in this method.

Scheme 48.



5-2. Copper-mediated N-arylation of sulfoximine: results and discussion

N-Aryl sulfoximines have been successfully applied as ligands in asymmetric catalysis for various transformations such as Hetero-Diels-Alder,[12] Diels-Alder,[11] Mukaiyama Aldol reaction[13] and asymmetric hydrogenation.[15] In order to prepare such compounds, stereospecific palladium-catalyzed cross-coupling reaction have been developed,[18] in which aryl bromides, nonaflates, and triflates can be used as coupling partners. Despite this success, some limitations of the palladium catalysis such as long reaction time, restricted substrate scope, and high metal/ligand (catalyst) cost motivated the search for

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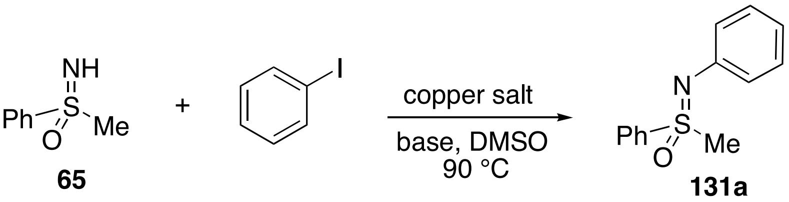
[122] Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803.
[123] Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517.
[124] Baskin, J. M.; Wang, Z. *Org. Lett.* **2002**, *4*, 4423.

an alternative cross-coupling protocol. In this context, the first copper-promoted cross-couplings to give N-arylated sulfoximines was developed. The catalysis is easy to perform and provides the arylated products in high yields.

Initially as a test reaction, the cross coupling between methylphenyl sulfoximine (**65**) and phenyl iodide was choosen. To establish the optimum reaction conditions, the effects of base, solvent and copper salt were evaluated and the results of this screening are summarized in Table 8.

Table 8. Effect of the reaction parameters on the copper-mediated cross coupling of sulfoximine **65** and phenyl iodide to give *N*-phenyl sulfoximine **131a**[a]



entry	copper salt	base	yield (%)
1	CuI	Cs_2CO_3	94
2	CuI	CsOAc	78
3	CuI	NaO*t*Bu	91
4	CuI	K_3PO_4	39
5	CuBr	Cs_2CO_3	85
6	$CuSO_4$	Cs_2CO_3	46

[a] Reaction conditions: sulfoximine (1.0 equiv), phenyl iodide (2.0 equiv), base (2.5 equiv), copper salt (1.0 equiv), in DMSO (1 M with respect to **65**) at 90 °C.

Gratifyingly, several copper salts such as CuI, CuBr and $CuSO_4$ were found to promote the N-arylation giving the *N*-phenyl sulfoximine **131a** in good to excellent yield. The best result was obtained with a combination of copper(I) iodide (1.0 equiv) and Cs_2CO_3 (2.5 equiv) in DMSO at 90 °C (94% yield, entry 1 in Table 8). Other copper salts such as copper(I) bromide or copper(II) sulfate also promoted the reaction, but the yields with them were lower than with CuI (entry 5 and 6). Cs_2CO_3 proved to be superior to other bases such as CsOAc, NaO*t*Bu and K_3PO_4. The use of other solvent such as DMF, THF, dichloroethane, and toluene instead of degassed DMSO as well as lower amounts of copper salt, base, or aryl halide than described in Table 8 decreased the reaction yield. Exposure of the reaction mixture to oxygen also led to a reduced yield of product **131a**. The stereospecificity of the copper-promoted cross coupling was illustrated by the conversion of enantiopure (*S*)-**65** into (*S*)-**131a**. HPLC analysis confirmed that it was formed as a single enantiomer.[125]

With the optimum condition identified with phenyl iodide, the reaction scope was examined by variation of the aryl halide component. The results are summarized in Table 9.[**]

For most aryl iodides, the conditions optimized for the cross coupling of **65** with phenyl iodide (method A) proved applicable and the corresponding arylated sulfoximines **131** were obtained in high yields. In some cases, the use of CsOAc instead of Cs_2CO_3 (method B) or the application of an excess of sulfoximine (method C) resulted in improved yields. For example, when 4-iodobenzaldehyde was applied in the coupling with Cs_2CO_3 as a base, a complex mixture of products was observed. In contrast, with CsOAc a very smooth and near complete conversion led to the corresponding N-arylated sulfoximine **131i** in 85% yield (entry 8, Table 9). Generally, electronic effects had a minor role and high conversions were observed no matter if the substituents were electron withdrawing or donating. *Ortho*-substituents did not hamper the coupling reactions. Both aryl bromides as well as aryl iodides (entries 1-13 and 14-17, respectively) could be used in contrast to the palladium catalyzed N-arylation in which aryl iodides were not suitable coupling partners. By comparison between aryl iodide and aryl bromide in the coupling with methylphenyl sulfoximine, it was disclosed that both aryl halides reacted almost equally well (entries 3 and 14). A difference of reactivity between iodide and bromide, however, was indicated in the conversion of 2-bromophenyl iodide, which selectively gave *N*-2-bromoaryl sulfoximine **131c** in 68% yield (Table 9, entry 2). Interestingly, the chemoselectivity (iodide preferred over bromide) was base dependent, and switching from Cs_2CO_3 to CsOAc afforded a mixture of both possible mono-coupled products.

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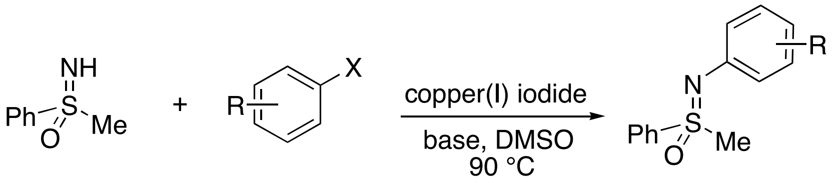
[125] HPLC analysis of **131a**: Chiralcel OD-H, 9:1 heptane:2-propanol, 0.5 mL/min; t_R = 30 min (*S*), t_R = 44 min (*R*).

[**] This work was performed in collaboration with Jenny Jansson at Uppsala University, Pauline Remy and Christian Moessner at RWTH Aachen University.

Table 9. Copper-mediated cross coupling of sulfoximine **65** and aryl iodides or aryl bromides to give N-arylated sulfoximines **131b-r**

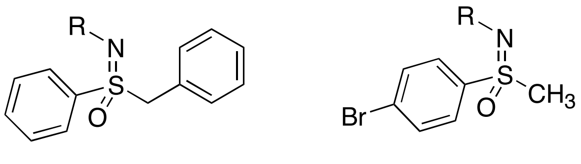


65 **131b-r**

entry	X	R	method[a]	**131**	yield (%)
1	I	2-Me	A	**b**	84
2	I	2-Br	A	**c**	68
3	I	2-NO_2	A	**d**	83
4	I	2-OMe	A	**e**	72
5[b]	I	2-P(O)Ph_2	B	**f**	71
6	I	3-CN	A	**g**	94
7	I	4-Me	A	**h**	93
8	I	4-CHO	C	**i**	85
9	I	4-CO_2Et	A	**j**	88
10	I	4-NO_2	A	**k**	82
11	I	2-NO_2,4-F	B	**l**	95
12	I	2-NO_2,4-OMe	B	**m**	80
13	I	2,4,6-Cl_3	B	**n**	60
14	Br	2-NO_2	B	**d**	78
15	Br	2-NO_2,4-CF_3	B	**p**	83
16	Br	2-NHAc,5-NO_2	C	**q**	65
17	Br	2-NHAc,3-NO_2	C	**r**	48

[a] Method A: sulfoximine (1.0 equiv), aryl halide (2.0 equiv), CuI (1.0 equiv), Cs_2CO_3 (2.5 equiv) in DMSO at 90 °C. Method B: same as A except CsOAc (2.5 equiv) instead of Cs_2CO_3. Method C: sulfoximine (2.0 equiv), aryl halide (1.0 equiv), CuI (1.0 equiv), CsOAc (2.5 equiv) in DMSO at 90 °C. [b] Enantiopure (*S*)-**65** was used.

N-Arylations of sulfoximines **119** and **66** (Figure 13) with phenyl iodide as aryl source and Cs_2CO_3 as a base to give **132** and **133** in 63 and 53% yield, respectively, confirmed that the protocol could be extended to other NH-sulfoximines.



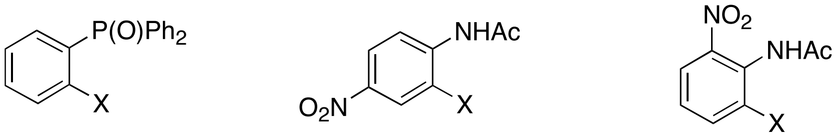
119: R = H
132: R = Ph (63% yield)

66: R = H
133: R = Ph (53% yield)

Figure 13.

Especially noteworthy are the results that highlight the differences between the copper-mediated and the palladium-catalyzed cross coupling. For example, previously it was reported that transformations of aryl iodides under palladium catalysis were sluggish, even in the presence of additives such as lithium and silver salts.[18] In the copper-mediated reactions described here, those substrates behave perfectly well giving products in high yields. Moreover, we found that in several cases even for aryl bromides the copper-based protocol was superior to the palladium-based one. For instance, attempts to cross couple multiple substituted aryl bromide **135** (Scheme 49) under palladium catalysis gave **131q** in only 10% yield after two days.[♣] In contrast, the novel copper-mediated transformation afforded the desired product in 65% yield after only 12 h (Table 9, entry 16). Furthermore, N-arylated sulfoximine **131r** could only be obtained by the copper-mediated route (entry 17), while no product was observed under palladium catalysis.[♣]

Scheme 49. Cu-mediated versus Pd-catalyzed coupling



134: X = Br
131f: X = NSOPhMe
Pd-catalyzed: low
Cu-mediated: **71%**

135: X = Br
131q: X = NSOPhMe
Pd-catalyzed: 10%
Cu-mediated: **65%**

136: X = Br
131r: X = NSOPhMe
Pd-catalyzed: --
Cu-mediated: **48%**

The synthesis of **131f** was improved by using copper for a different reason. There, the N-arylated sulfoximine was formed in the palladium-catalyzed coupling albeit in low quantities. However, isolation of the product proved cumbersome due to the presence of inseparable impurities. Fortunately, the copper methodology allowed the preparation of the desired product in a very straightforward manner giving pure **131f** in 71% yield after simple purification by column chromatography.[♠]

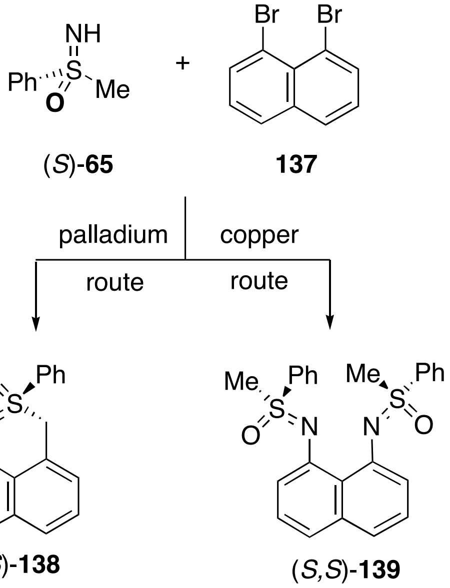
The most remarkable difference between the palladium-catalyzed and the copper-mediated routes is depicted in Scheme 50.[♣] It was reported that the palladium-catalyzed coupling of dibromoarenes and sulfoximines afforded six- to eight-membered heterocycles in excellent yields.[17g,126] For example, 1,8-dibromonaphthalene (**137**) gave compound **138**

[♣] These reactions were performed by Pauline Remy at RWTH Aachen Unversity.

[♠] This reaction was performed by Christian Moessner at RWTH Aachen University.
[♣] This reaction was performed by Pauline Remy at RWTH Aachen University.
[126] Bolm, C.; Martin, M.; Gibson, L. *Synlett* **2002**, 832.

in 90% yield by a sequence of *inter*molecular *N*-arylation followed by *intra*molecular α-arylation. Interestingly, the copper-mediated reaction of the same substrates gave an entirely different product. As a result, C_2-symmetric bissulfoximine **139** is formed in 56% yield, which was caused by a double cross coupling reaction lacking the intramolecular cyclization through C-C-bond formation. In this context it is noteworthy that related C_2-symmetric bissulfoximines (Figure 2) have been successfully applied as ligands in asymmetric catalysis leading to excellent enantioselectivities in hetero-Diels-Alder reactions, other cycloadditions, and nucleophilic allylic substitutions.

Scheme 50.[a]



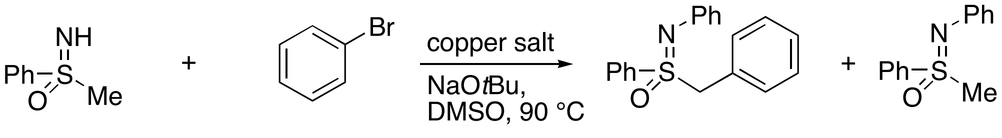
[a] Key: palladium route: $Pd(OAc)_2$, *rac*-BINAP, NaO*t*Bu, toluene, reflux, 48 h; copper route: CuI, CsOAc, DMSO, 90 °C, 12 h.

5-3. Summary and outlook

To summarize, a ligand-free copper-mediated cross coupling reactions for the synthesis of various N-arylated sulfoximines in high yields (up to 95% yield) was developed. The novel protocol proved to be a powerful complement to the previously developed palladium catalysis. Shorter reaction times, higher reactivity as well as economical practicality (owing to the low cost of copper salt compared to palladium/phosphine ligand complex) are advantages of the copper methodology. The novel N-arylated sulfoximine products, especially **131f** and (*S,S*)-**139**, from this method can be applied as ligands in asymmetric catalysis.[127]

In addition to the N-arylation, the investigation of the copper-catalyzed or -mediated C-arylation of sulfoximines should be considered. During this research, we observed α-arylated product **132** as a side product in up to 20% yield (Scheme 50).

Scheme 50.



65   **132**   **131a**

This result demonstrates that α-arylation of sulfoximine with aryl bromide can proceed in the presence of a copper salt and a strong base, to give access to various aryl benzyl sulfoximines. For successful copper-mediated α-arylations of sulfoximines, an intensive screening of reaction conditions should be done in order to gain a greater understanding of the mechanism by which this reaction proceeds.

6. Part IV. Silver-catalyzed imination of sulfoxides and sulfides

6-1. Silver-catalyzed reaction: introduction

In spite of the fact that silver is used as an efficient catalyst for olefin epoxidation in industry,[128] silver has been considered for long time to have low catalytic activity. Conventionally, silver(I) salts are employed as oxidants for the oxidation of various organic or inorganic substrates. Furthermore, silver complexes have often been utilized as Lewis acids[129] for many organic reactions. Especially, those with chiral ligands caught attention,

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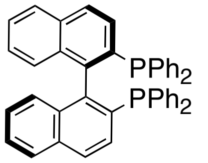
[127] For the copper-catalyzed N-arylation of sulfoximines, see reference 17a and 17b.

[128] (a) van Santen, R. A.; Kuipers, H. P. C. *Adv. Catal.* **1987**, *35*, 265 and references therein. (b) Stinson, S. *Chem. Eng. News* **1995**, *73,* 7.

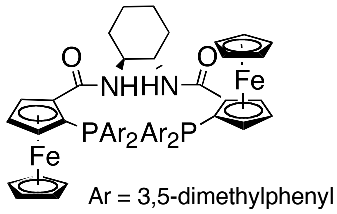
[129] For selected examples, see: (a) Yanagisawa, A.; Touge, T.; Arai, T. *Angew. Chem.* **2005**, *117*, 1570. (b) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734. (c) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360. (d) Peddibhotla, S.; Tepe, J. J. *J. Am. Chem. Soc.* **2004**, *126*, 12766. (e) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174. (f) Wang, C. J.; Shi, M. *Eur. J. Org. Chem.* **2003**, 2823. (g) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018. (h) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593. (i) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038. (j) Longmire, L. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400. (k) Yangisawa, A.; Matsumoto, Y.; Asakawa, K.;

since they led to asymmetric catalysts for various transformation including diverse cyclization reaction[130] (Scheme 52).

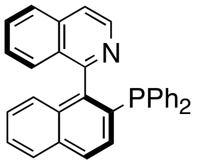
Figure 14. Representative chiral ligands for silver-catalyzed reactions



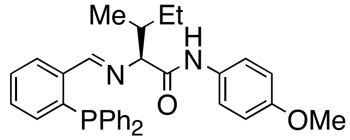
140, (*R*)-BINAP
Silver salt: AgOTf, $AgClO_4$, AgF
Applications: synthesis of chiral α-hydroxy ketones (up to 97% ee)
Asymmetric Sakurai-Hosomi allylation (up to 97% ee)
Mukaiyama aldol reaction (up to 97% ee)
Asymmetric aldol reaction of enol trichloroacetate (up to 96% ee)



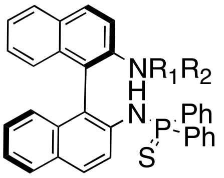
141, Bis-ferrocenyl amide
Silver salt: AgOAc
Application: [3+2] cycloaddition of azomethine ylides (up to 96% ee)



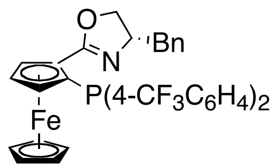
142, (*S*)-QUINAP
Silver salt: AgOAc
Application: [3+2] cycloaddition of azomethine ylides (up to 96% ee)



143
Silver salt: AgOAc
Applications: cycloaddition between arylimines and the Danishefsky diene (up to 95% ee)
asymmetric Mannich reaction (up to 98% ee)



144, (*R*)-binaphthylthiophosphoramide
Silver salt: AgOTf
Application: asymmetric allylation of arylaldehydes (up to 98% ee)



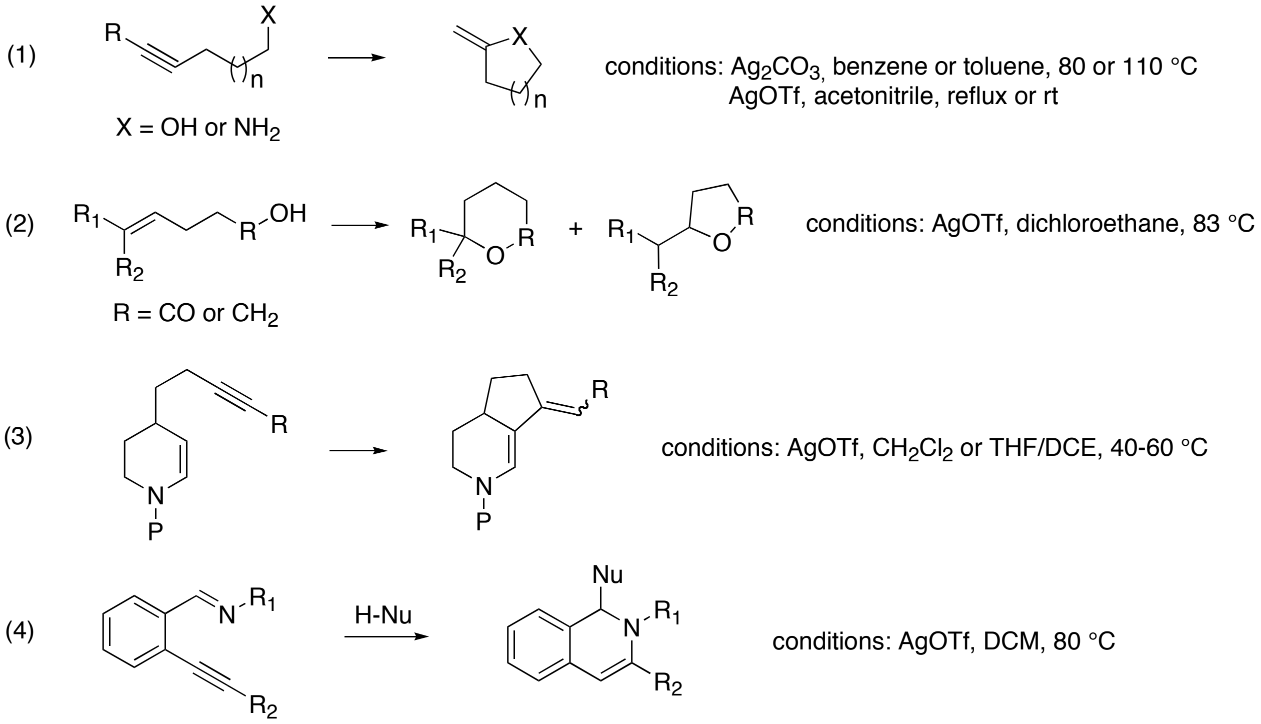
145
Silver salt: AgOAc
Application: asymmetric [3+2] cycloaddition of azomethine ylides (up to 98% ee)

Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 892. (l) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Org. Chem.* **1990**, *55*, 5935.

[130] (a) Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493. (b) van Esseveldt, B. C. J.; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791. (c) Yang, C. G.; Reich, N. W.; Shi, Y.; He, C. *Org. Lett.* **2005**, *7*, 4553. (d) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204. (e) Harrison, T. J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023. (f) Sweis, R. F.; Schramm, M. P.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 7442. (g) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1013. (h) Dalla, V.; Pale, P. *Tetrahedron Lett.* **1994**, *35*, 3525. (h) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *28*, 6447.

In addtion, a number of reports focused on the use of silver catalysts in cross coupling or group transfer reactions and significant progress has been achieved in these areas. In this section, recent progress in the latter fields will be presented.

Scheme 52. Representative cyclization catalyzed by silver salts



6-1-1. Silver-catalyzed cross coupling reactions

In 1996, Pale and coworker utilized a silver salt as a co-catalyst with a palladium complex in a sp-sp^2 coupling reaction for the synthesis of epoxyenynes (Scheme 53).[131]

The coupling reaction of terminal acetylenes containing epoxy groups with vinyl triflate also occurred in the presence of the palladium complex alone (without a co-catalysts such as silver salts). However, in the absence of the co-catalyst, evaluated temperatures and the use of an excess amount of base were required. Even so, lower reaction yields were obtained. Several silver salts such as $AgNO_3$, AgI, Ag_2CO_3 and AgOTf were evaluated as co-catalysts in the presence of $Pd(PPh_3)_4$ and diisopropylethylamine as a base in DMF. Among them, silver iodide was slightly superior to the other silver salts, while some decomposition was observed during the reaction with silver triflate as co-catalyst. Under

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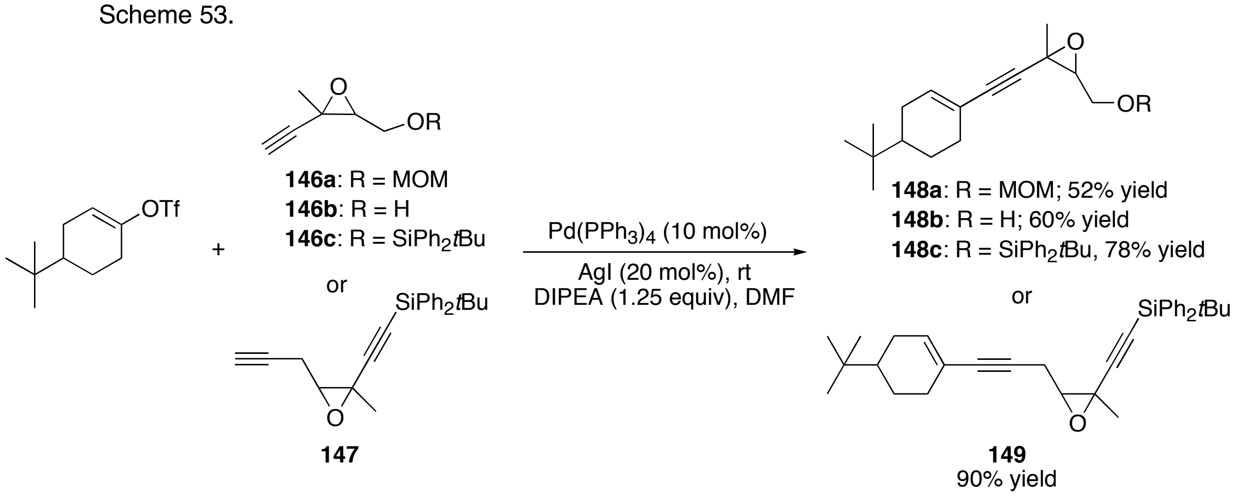
[131] Bertus, P.; Pale, P. *Tetrahedron Lett.* **1996**, *37*, 2019.

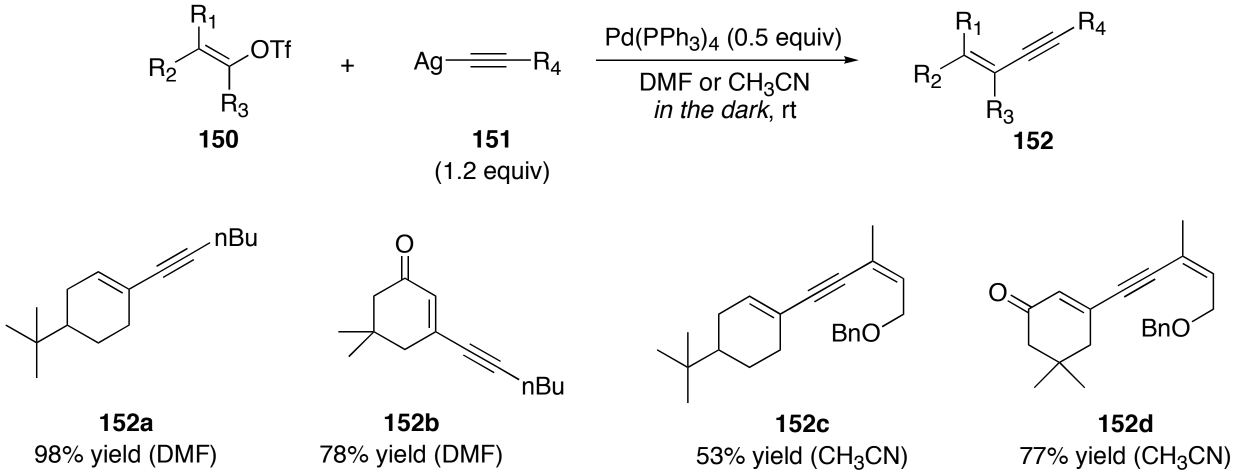
optimal condition various protected or non-protected acetylenic epoxyalcohols **148** and **149** could be prepared.

Scheme 53.



In order to clarify the function of the silver salts, silver acetylides **151** were prepared and applied directly to the palladium-catalyzed sp-sp^2 coupling reaction.[132] Silver *n*-butylacetylide and silver benzylated (*Z*)-3-methylpentylide were synthesized and employed in the coupling reactions. The reaction of silver acetylides **151** and vinyl triflates **150** in the presence of Pd(PPh$_3$)$_4$ (0.5 equiv) at room temperature provided the desired coupling product **152** in good yields (Scheme 54).

Scheme 54. Palladium-catalyzed couplings with silver acetylides **151**



Interestingly, the complex between silver acetylide and silver nitrate did not catalyze the coupling reaction at all, even with higher loading of Pd(PPh$_3$)$_4$. Furthermore, the reaction

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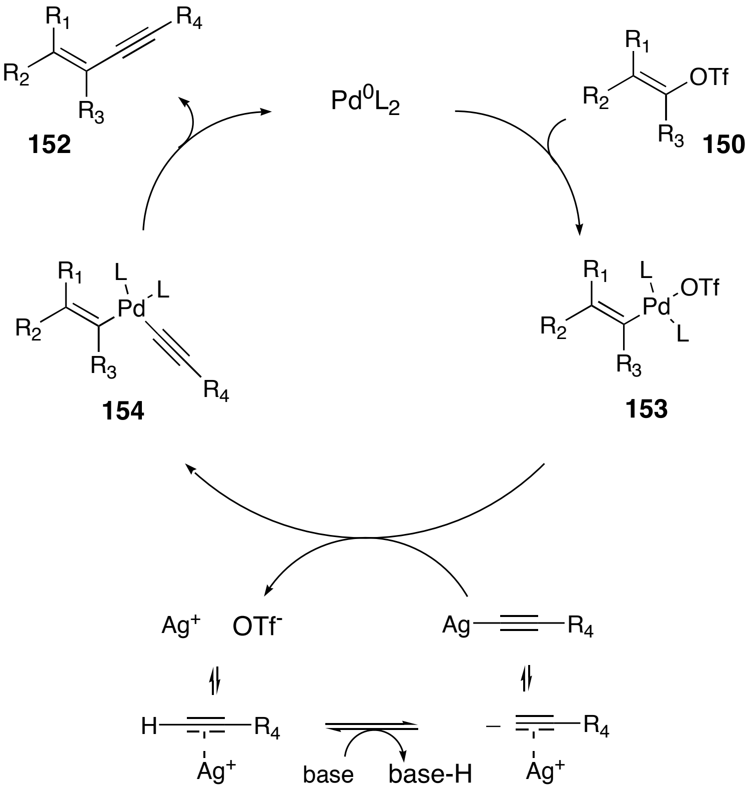
[132] Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* **2001**, *3*, 1661.

did not proceed in the absence of the palladium complex, and the use of more than 0.5 equiv of it was necessary in order to achieve complete conversion and high yields. As a solvent, DMF or acetonitrile gave the best results in terms of the yields and reaction times. On the basis of the previously investigated mechanism of the Sonogashira-Linstrumelle reaction,[133] Pale and coworkers proposed the mechanism depicted in Scheme 55. Interestingly, the role of the co-catalyst, silver, is still not clear. Well-established coordination of alkenes or alkynes to silver[134] and the results of this coupling reaction clearly support the idea that silver acetylides can be formed *in situ* from acetylides and silver salts, and that those are involved in the palladium-catalyzed reaction.

Scheme 55. Plausible mechanism of the silver-catalyzed cross coupling



Another interesting reaction, which presumably involves silver acetylenes, was reported by Li and coworkers in 2003.[135] They performed the three-component coupling of aldehydes, alkynes, and amines in the presence of silver salts in aqueous solutions to generate

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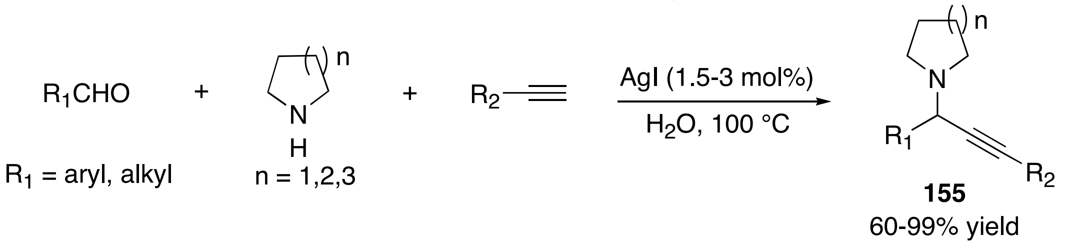
[133] (a) Sonogashira, K. In *Comphrehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds; Pergamon: Oxford; 1991, vol. 3, p 521. (b) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403.

[134] (a) Noltes, J. G.; van Koten, G. In *Comprehensive Organometallic Chemistry 1*; Willkinson, G., Abel, E. W., Stone, F. G. A., Eds; Pergamon: Oxford, 1982; vol. 2, pp 709. (b) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019. (c) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem.* **1984**, *96*, 720. (d) Lewandos, G. S.; Maki, J. W.; Ginnebaugh, J. P. *Organometallics* **1982**, *1*, 1700.

[135] Wei, C.; Li, Z.; Li, C. J. *Org. Lett.* **2003**, *5*, 4473.

propargylamines in excellent yields (Scheme 56). Most of water-soluble or partially soluble silver salts such as $AgNO_3$, AgOAc, AgOTf, Ag_2O and $AgBF_4$ were found to catalyze the coupling reaction of benzaldehyde, piperidine and phenylacetylene albeit in low conversion (25-45% yields). Among the water-insoluble silver salts, silver iodide was much superior to the others (AgBr, AgCl and Ag_2S) and afforded the desired product in high yield when performed in water or organic solvents (DMF and toluene). However, this procedure has limited to the cyclic amines. Also, aryl aldehydes gave lower reaction yields than aliphatic aldehydes.

Scheme 56. Silver-catalyzed three component coupling in water



155
60-99% yield

This silver-catalyzed three-component coupling reaction could be also conducted in ionic liquid.[136] Thus, the reaction occurred smoothly in 1-butyl-3-methyl-imidazolium hexafluorophosphate [(Bmim)PF_6] as a solvent in the presence of AgI (3 mol%) to provide the coupling products in high yields (73-92%). Worthy of note is that the reaction proceeded not only well with cyclic amines but also with acyclic amines such as diallyamine, dibenzylamine and ethylphenylamine. Furthermore, clean and high conversions were observed with both aliphatic and aromatic aldehydes.

Mori and coworkers utilized silver salts as activators for the palladium-catalyzed cross-coupling of silanols, silanediols and silanetriols with aryl iodides (Scheme 57).[137] They discovered that adding 1.0 equiv of Ag_2O remarkably activated the cross coupling reaction of silanols with aryl iodides in the presence of $Pd(PPh)_3$ (5 mol%) in THF at 60 °C to generate various coupling products **158** and **159** in moderate to high yield (30-99%). Other silver salts such as AgOTf, $AgBF_4$ and $AgNO_3$ provided much lower yields than Ag_2O and no reaction occurred in the absence of silver salts. In general, silanediols and silanetriols were more reactive than silanols and afforded higher yields.

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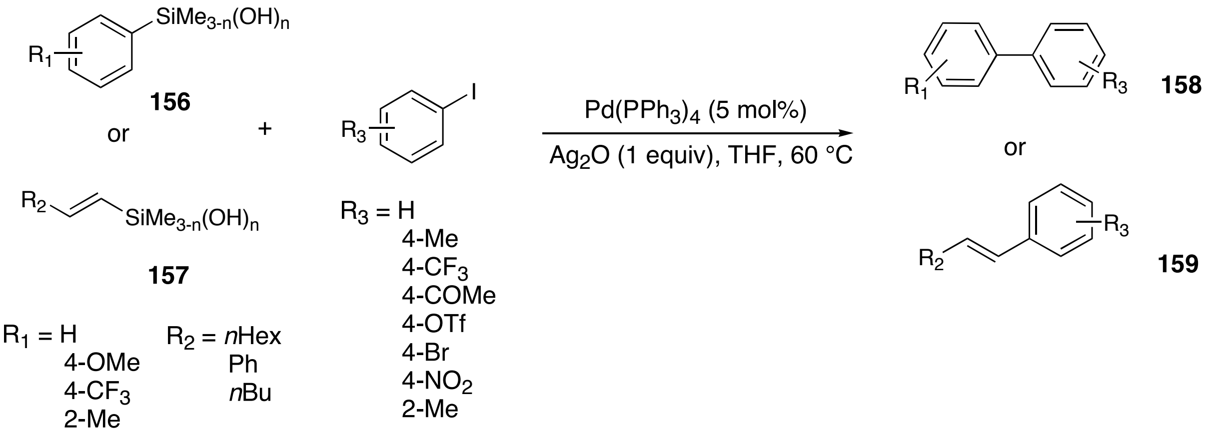
[136] Li, Z.; Wei, C.; Chen, L.; Varma, R. S.; Li, C. J. *Tetrahedron Lett.* **2004**, *45*, 2443.

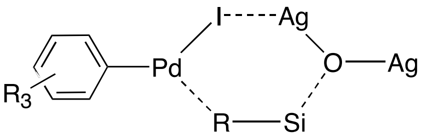
[137] Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342.

Scheme 57.



The coupling reaction did not occur with either disiloxanes or silanes under the conditions described in Scheme 57. Bromobenzene and phenyl triflate were also tested as substitutes for the aryl iodides, but no desired product was observed.

From the mechanistic study they proposed that Ag_2O might take a role of both an activator of the intermediary organopalladium(II) iodide complex[138] (Figure 15) and a nucleophilic activator of the silanol to generate a pentacoordinate silicate species. In other words, Ag_2O serves to interact with both iodide and silanol in both cases to accelerate the transfer of an organic group on silicon to palladium. The fact that the coupling reaction proceeded particularly well with aryl iodides (not with aryl bromides and triflates) and that the formation of AgI was observed during the process supported this hypothesis.



160

Figure 15.

However, a more complicated role of silver(I) oxide could also be taken into consideration. Mori and coworkers also reported that the palladium-catalyzed cross coupling of terminal alkynes with aryl iodides is assisted by Ag_2O (Scheme 58).[139]

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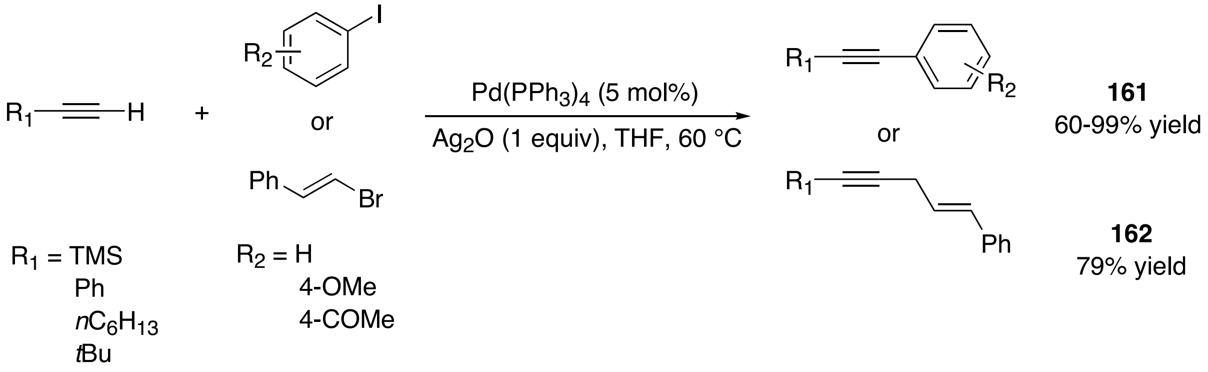
[138] Grove, D. M.; van Koten, G.; Louwen, J. N.; Noltes, J. G.; Spec, A. L. *J. Am. Chem. Soc.* **1982**, *104*, 6609.

[139] Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935.

Scheme 58



They found that a number of phenylethynes **161** could be prepared in high yields by the coupling of terminal alkynes with aryl iodides, using 5 mol% of $Pd(PPh_3)_4$ in combination with silver(I) oxides (1.0 equiv) as catalysts in THF at 60 °C. As observed in the coupling of silanols, aryl bromides and triflates did not react at all under described conditions. In contrast, alkenyl bromides coupled with terminal alkynes to afford the corresponding enynes **162** in high yield.

The silver(I) oxide involved in this reaction can be assumed to interact with the iodide in analogy to the observations made in the coupling of silanols. However, the involvment of silver acetylene (Scheme 54 and 55) as an intermediate cannot, in this case, be excluded especially for the coupling with alkenyl bromides.

Li and coworkers have also employed silver as a catalyst for other C-C bond formations.[140] In their initial study it was revealed that a variety of diketones could be efficiently added to styrene and its derivatives in the presence of gold and silver salts at room temerature (Scheme 59, method A). Among several gold and silver salts, the combination of $AuCl_3$ and AgOTf led to give the best result in dichloromethane. Only trace amounts of products were obtained using $AuCl_3$ or AgOTf alone under the described conditions. This reaction, however, was limited to styrene derivatives, and low conversion was observed with simple terminal alkenes except for norbornene (81% yield).

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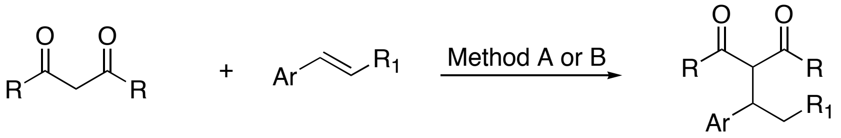
[140] Yao, X.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 6884.

Scheme 59. Silver-catalyzed C-C bond formation reaction

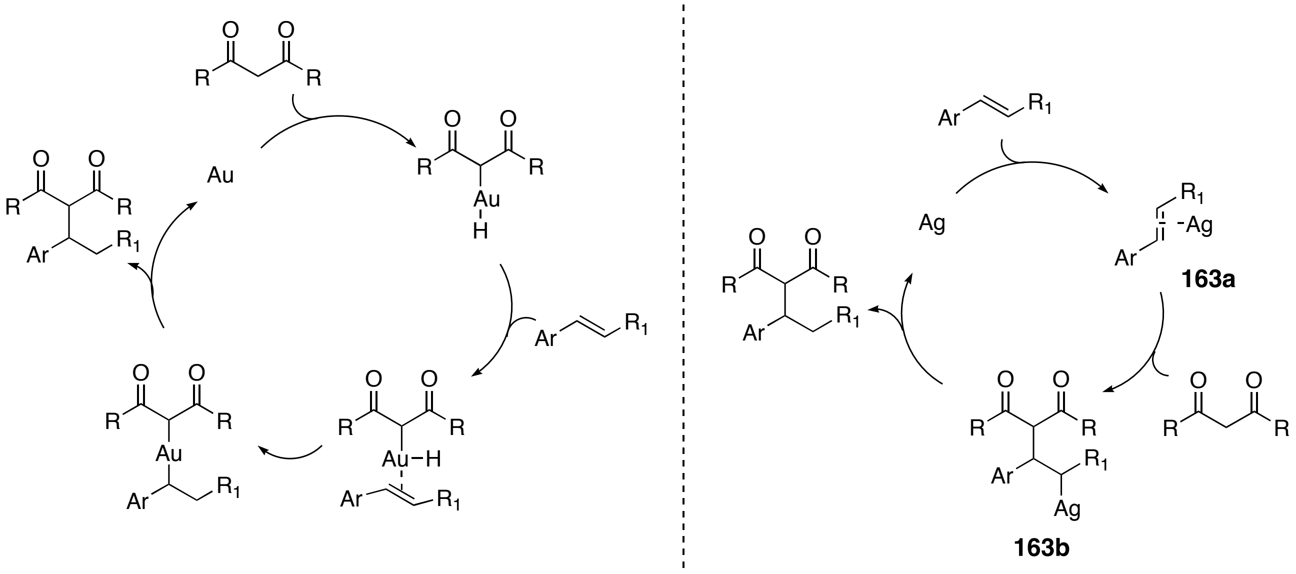


Method A. $AuCl_3$ (5 mol%), AgOTf (15 mol%), CH_2Cl_2, rt; 39-98% yield
Method B. AgOTf (10 mol%), CH_3NO_2 or dichloroethane, 100 °C; 23-92% yield

After this initial study they discovered that cyclic dienes, trienes and enol ethers could be added to 1,3-diketones under identical reaction conditions (method A in Scheme 59) to give the corresponding products in good yields (35-68%).[141] Based on these investigations they suggested a plausible mechanism for the addition reaction, in which the silver salts were involved in the exchange of their respective anions on the gold catalyst, which resulted in a catalyst activation.

Li and Yao also attempted the utilization of silver salts alone as catalysts in this transformation.[142] They found that the addition of 1,3-dicarbonyls to the styrenes successfully occurred in the presence of silver triflate (10 mol%) in nitromethane or dichloroethane at 100 °C (method B in Scheme 59). It is worthy of note that the silver-catalyzed addition reaction is reversible, which indicates that a silver-catalyzed C-C bond cleavage is also possible during this process.

Scheme 60. Proposed mechanism of gold and silver-catalyzed C-C bond formations



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[141] Nguyen, R. V.; Yao, X. Q.; Bohle, D. S.; Li, C. J. *Org. Lett.* **2005**, *7*, 673.
[142] Yao, X.; Li, C. J. *J. Org. Chem.* **2005**, *70*, 5752.

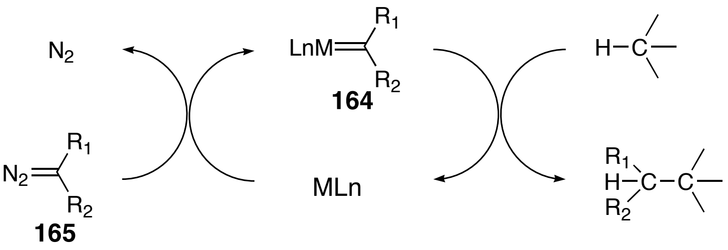
The tentative mechanism proposed by Li and Yao involves the coordination of alkene to Ag(I) (**163a**) and the formation of the 1,3-diketone-Ag(I) intermediate **163b** (Scheme 60). The reversible pathway was not mentioned.

6-1-2. Silver-catalyzed group transfer reactions

6-1-2-1. Silver-catalyzed group transfer reactions: carbene

The metal-catalyzed carbene insertion process is one of the most powerful methods used to activate unfunctionalized carbon-hydrogen bonds.[143] Diazo compounds **165**, which contain electron-withdrawing substituents, are most commonly used as a carbene source.[144] Rhodium (II) and copper (I) complexes can generate metal carbenes **164** featuring good σ-acceptor and poor π-donor metal ions, and they are well-established catalysts for C-H insertion reactions (Scheme 61).[145]

Scheme 61. Metal-mediated carbene insertion into a C-H bond



Compared to rhodium and copper,[145,146] silver complexes have barely been investigated in the carbene transfer reaction until quite recently. In 2003, Dias and Lovely reported an interesting silver-catalyzed carbene insertion into the C-X bonds of alkyl halides (Scheme 62).[147] On the basis of their previous studies, metal complexes, which contained a

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[143] (a) Shilov, A. E.; Shul'pin, G. B. *Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes*; Kluwer: Dordrecht, The Netherlands, 2000. (b) Dyker, G. *Angew. Chem.* **1999**, *111*, 1808. (c) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (d) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154.

[144] Meier, H.; Zeller, K. P. *Angew. Chem.* **1975**, *87*, 52.

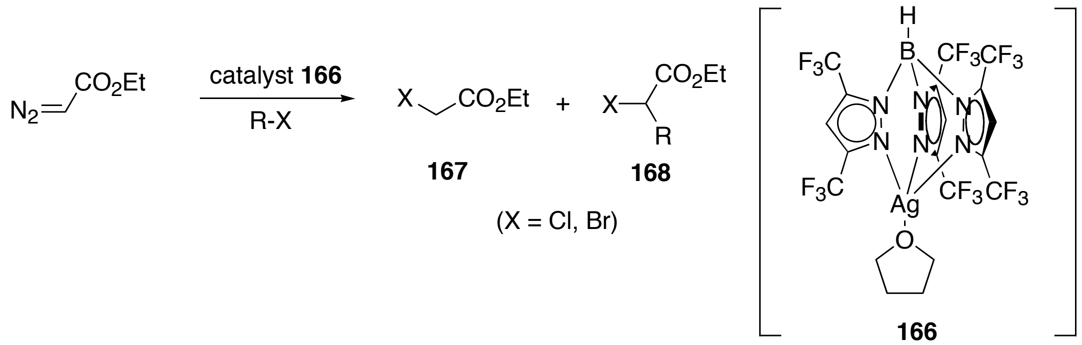
[145] (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Doyle, M. P.; Mckervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998; p 652.

[146] (a) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063. (b) Caballero, A.; Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *Organometallics* **2003**, *22*, 4145. (c) Caballero, A.; Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 1446. (d) Marchand, A. P.; Brockway, N. M. *Chem. Rev.* **1974**, *74*, 431.

[147] Dias, H. V. R.; Browning, R. G.; Polach, S. A.; Diyabalanage, H. V. K.; Lovely, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9270.

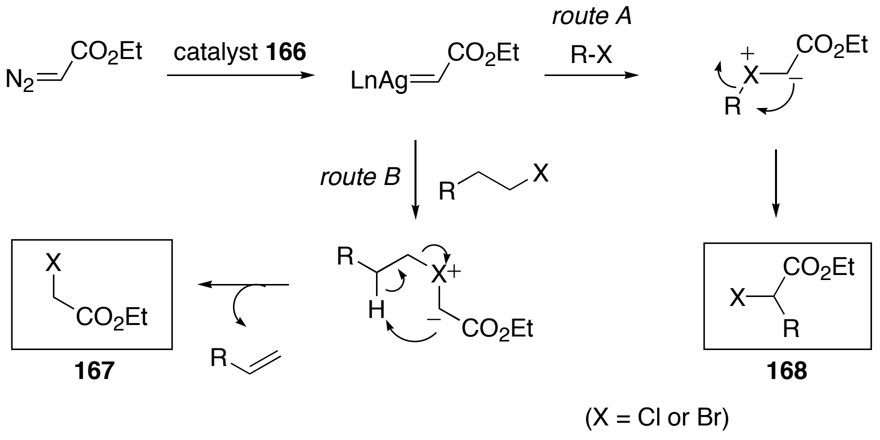
fluorinated tris(pyrazolyl)borate ligand such as $[HB(3,5-(CF_3)_2Pz)_3]^-$ (Pz = pyrazolyl) were evaluated as catalysts for this transformation.[148] This ligand provided extraordinary stability to the complexes of Cu, Ag, Au and Ga. Among them, it was revealed that the air and thermal stable silver complex-$[HB(3,5-(CF_3)_2Pz)_3]Ag(THF)$ (**166**)[149] was an efficient catalyst for carbene transfer reactions into the carbon-halide bond. Ethyl diazoacetate (EDA) reacted at room temperature with chloroalkanes or bromoalkanes in the presence of silver complex **166** to afford α-halo ethylacetates in moderate to good yields (Scheme 62).

Scheme 62. Silver-catalyzed carbene insertion reaction



In fact, two types of inserted products were observed from the reaction, indicating two pathways; (i) insertion into the C-X bond (route A) and (ii) 1,1-hydrohalogenation (route B, Scheme 63).

Scheme 63.



For example, when methyl halides CH_2X_2, CHX_3 or CX_4 was applied as a substrate in the presence of 5 mol% of catalyst **166**, the corresponding inserted products **168** were

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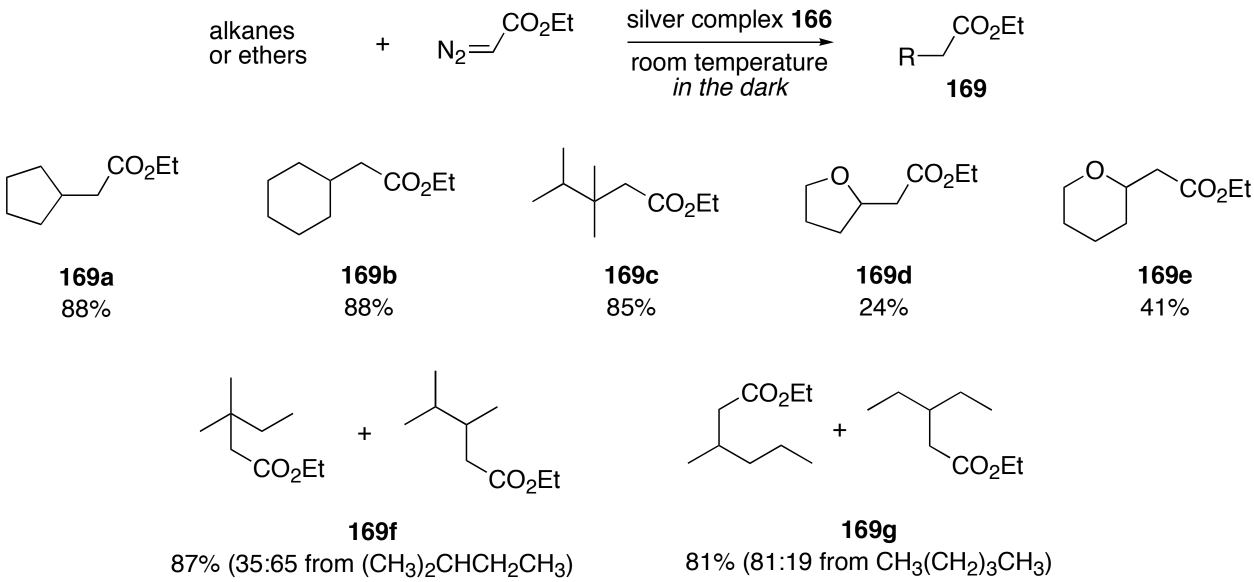
[148] Dias, H. V. R.; Polach, S. A. *Inorg. Chem.* **2000**, *39*, 4676.

[149] Dias, H. V. R.; Lu, H. L.; Goh, T. K. H. H.; Polach, S. A.; Browning, G.; Lovely, C. J. *Organometallics* **2002**, *21*, 1466.

obtained. On the other hand, reactions of secondary, or tertiary alkyl halides with ethyl diazoacetate (EDA) provided ethyl haloacetates **167** as major products. Other applicable silver(I) salts such as Ag_2O, AgOTf, Ag[HB(3,5-$Me_2Pz)_3$] and $AgSbF_6$ as well as $Rh_2(OAc)_4$ were also tested as catalysts giving either no reaction or very poor yields (2-7% yield).

Besides the insertion of carbenes into carbon halide bonds, silver complex [HB(3,5-$(CF_3)_2Pz)_3$]Ag(THF) (**166**) efficiently catalyzed carbene insertion reactions into C-H bonds of cyclic and acyclic hydrocarbons under remarkably mild conditions (Scheme 64).[150]

Scheme 64. Silver-catalyzed carbene insertion into C-H bonds



The carbene insertion products **169** were obtained in high yields (81-88%) using a mixture of alkanes and ethyl diazoacetate (EDA) with silver catalyst **166** (5 mol%) in the dark. In the case of branched hydrocarbons, mixtures of regioisomers were obtained, which showed that the selectivity of the C-H insertion into methylene or methine moieties was superior to that of the methyl groups (**169c**, **169f** and **169g** in Scheme 64). In contrast to the insertion of alkanes, the C-H bond activation of ethers by silver-complex **166** was less efficient. Yield of only 24% and 41% were observed from THF and oxane in the formation of **169d** and **169e**, respectively. No insertion products were obtained from 1,4-dioxane and 1,3-dioxalane.

In this year, the same group extended the utility of the silver scorpionate complex **166** to the Büchner reaction (Scheme 65).[151] They found that benzene and its derivatives reacted with EDA in the presence of 5 mol% of silver complex **166**. The formation of cyclopropane

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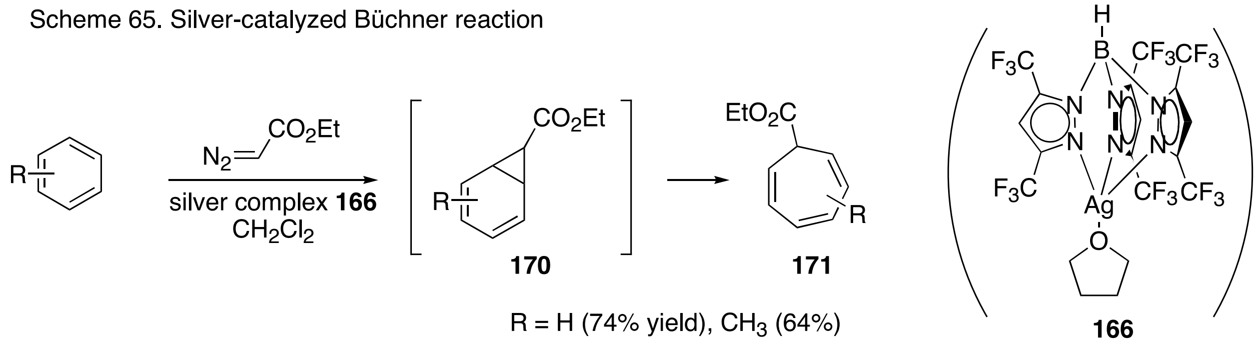
[150] Dias, H. V. R.; Browning, G.; Richey, S. A.; Lovely, C. J. *Organometallics* **2004**, *23*, 1200.
[151] Lovely, C. J.; Browning, G.; Badarinarayana, V.; Dias, H. V. R. *Tetrahedron Lett.* **2005**, *46*, 2453.

170 by the addition of the carbene to the aromatic moiety was followed by a ring expansion to afford cycloheptatrienes **171** in modest to good yields (14-74%).

Scheme 65. Silver-catalyzed Büchner reaction



R = H (74% yield), CH_3 (64%)
OCH_3 (40%), Cl (49%)
CO_2Me (14%), 1,3,5-trimethyl (35%)

Interestingly, silver-catalyst **166** showed greater selectivity for the Büchner reaction than for benzylic C-H insertion. For example, only 4% yield of benzylic C-H inserted product **172a** (Figure 16) was isolated from the reaction with toluene, whereas 64% yield of the Büchner product was obtained from the same system.

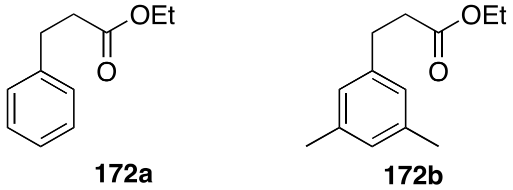


Figure 16.

Likewise the reaction of mesitylene under conditions described in Scheme 65 led to compound **172a** as the major product (35% yield) and only 28% of C-H inserted compound **172b** (Figure 16) were formed.

6-1-2-2. Silver-catalyzed group transfer reaction: nitrene

Together with the silver-catalyzed carbene insertion reaction, an interesting investigation of silver-catalyzed nitrene transfer reactions has been published by He and Cui.[152] They used the novel disilver(I) compound formed from the mixture of $AgNO_3$ and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (*t*Bu_3tpy) as a catalyst for the aziridination of diverse olefins with TsN=IPh as nitrogen source. As a result, the corresponding aziridines were obtained as

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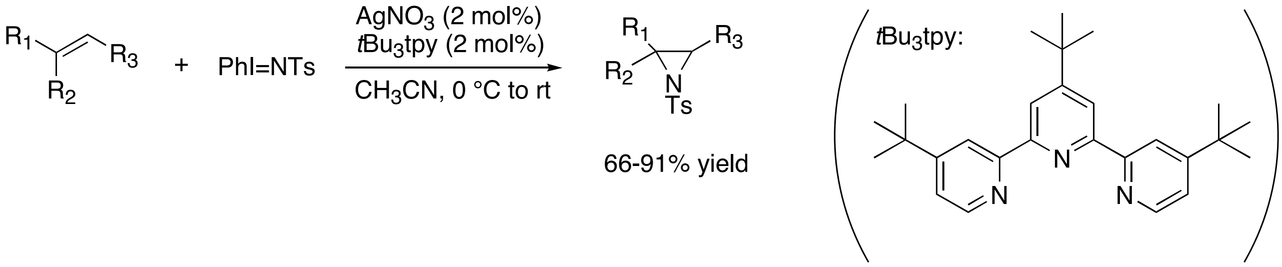
[152] Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202.

products in high yields (Scheme 66). Indeed, instead of $AgNO_3$, other silver salts such as AgOTf, $AgClO_4$ and $AgBF_4$ could also be applied to give similar results. Without the silver(I) salt the reaction did not proceed. Surprisingly, the choice of ligand was most crucial for the success of the transformation. For instance, no reaction occurred with the *t*Bu-bis(oxazoline) or Ph-bis(oxazoline)-pyridine. Only trace amounts of desired product were observed using pyridine or 4-*tert*-butyl-pyridine as a ligand with $AgNO_3$. Although bipyridine, 4,4'-di-*tert*-butyl-bipyridine, or 2,2':6',2''-terpyridine (tpy) afforded 35-50% yields of products, a number of side products were formed using these ligands.

Scheme 66. Silver-catalyzed aziridination



They assumed that a silver nitrene (Ag=NTs) was formed under the conditions described and that high-valent silver intermediates could also be involved owing to the change in color from pale yellow to brown during the reaction. Moreover, they proved that the silver did not behave as a simple Lewis acid catalyst largely due to the fact that no reaction occurred when Zn(II) was substituted for Ag(I) in the presence of *t*Bu_3tpy ligand.

He and Cui also discovered that this novel silver complex efficiently catalyzed the intramolecular amidation of saturated C-H bonds.[153] By using $AgNO_3$ (4 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (4 mol%) as a catalyst, and iodobenzenediacetate as an oxidant, five- and six-membered ring insertion products **175** and **176** were obtained in high yields from a range of carbamates **173** and sulfamates **174** (Scheme 67). As revealed in their previous study of the aziridination, the utilization of *t*Bu_3tpy as a ligand was important for an efficient catalysis. No reaction occurred using pyridines and bis(oxazoline) derivatives as ligands while catalysts with bipyridine and terpyridine gave only small amounts of the desired products (22 and 41% yield, respectively). In some cases, adding 2 mol% of 4-*tert*-butylpyridine to the reaction mixture led to improved yields and a cleaner reaction. In addition to this, the retention of configuration in product **176e** formed from a (*S*)-2-methyl-1-butanol-derived substrate indicated that the silver-catalyzed reaction was

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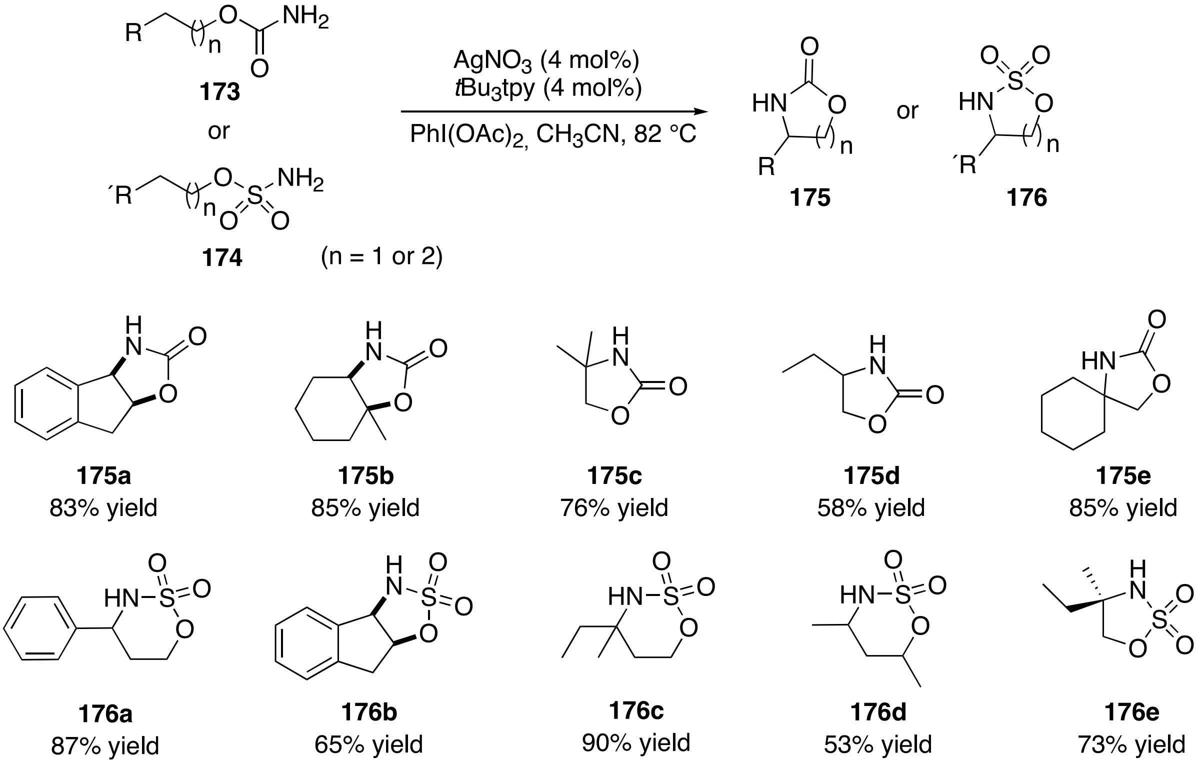
[153] Cui, Y.; He, C. *Angew. Chem.* **2004**, *116*, 4306.

stereospecific and involved a nitrene-type oxidant. It is worthy of note that the copper complex was not able to catalyze the insertion into C-H bonds, unlike silver, although both copper salts and silver complexes have been applied as catalysts to the aziridination reaction.[154]

Scheme 67. Oxidative cyclization of carbamates and sulfamates



175a 83% yield
175b 85% yield
175c 76% yield
175d 58% yield
175e 85% yield
176a 87% yield
176b 65% yield
176c 90% yield
176d 53% yield
176e 73% yield

6-1-2-3. Silver-catalyzed group transfer reaction: silylene

In another interesting application of silver catalysts, silacyclopropanations of mono- and disubstituted alkenes were reported for the first time by Woerpel and coworkers in 2002.[155] In contrast to the previous methods for the formation of silyene species, which required elevated temperature, strongly reducing conditions or photolysis, Woerpel and coworkers employed silver triflate as a catalyst to generate and transfer a silyene at –27 °C. Silacyclopropane **177** was used as silyene source. As solvent, toluene or dichloromethane afforded the best results in terms of the yields and allowed the lowest reaction temperature. Complete conversion was observed even with 1 mol% of the silver catalyst

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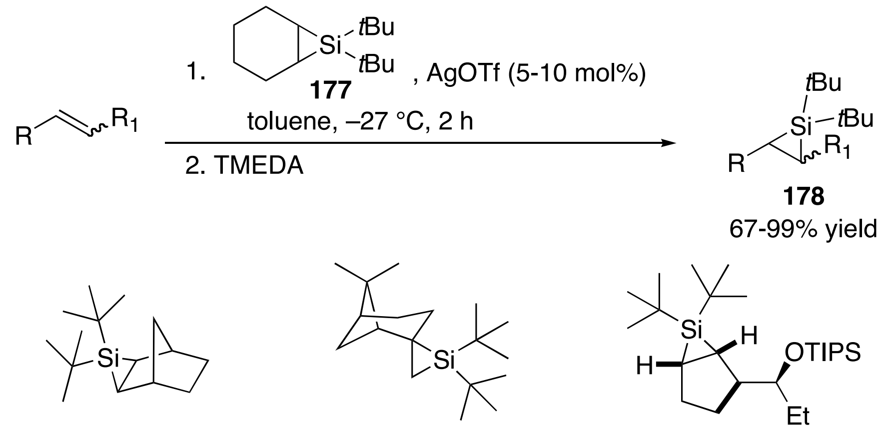
[154] Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, N. S.; Perez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 12078.
[155] Cirakovic, J.; Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 9370.

although in this case, a higher temperature (25 °C) was inevitable as well as a longer reaction time. Under the optimal condition, which is the use of silver triflate (5-10 mol%) in toluene at –27 °C, mono- and disubstituted alkenes were stereospecifically converted into the corresponding silacyclopropanes in high yields (Scheme 68).

Scheme 68. Silver-catalyzed silacyclopropanation



178a 90% yield

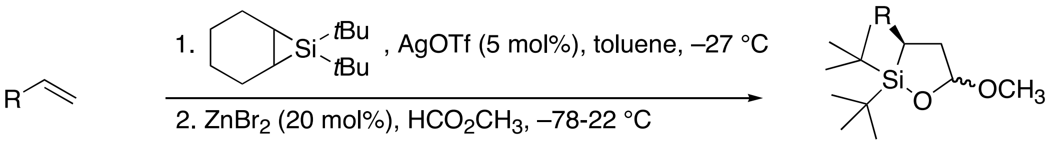
178b 72% yield

178c 85% yield

It is noteworthy that this silver-catalyzed silacyclopropanation is highly diastereoselective. Only single diastereomers of the products **178a**, **178b**, and **178c** (Scheme 68) were observed in high yields.

In addition to this, oxasilacyclopentanes **179** could be prepared from the alkenes in high yields using the silver triflate-catalyzed silacyclopropanation followed by zinc bromide-catalyzed insertion of methyl formate into the carbon-silicon bond of the silacyclopropane intermediate (Scheme 69).

Scheme 69. *One-pot* synthesis of oxasilacyclopentanes **179**



179
61-92% yield
d.r. = ca. 70:30

High regioselectivities (97:3-99:1, in favor of the formation of an Si-O bond) for the formate insertion were observed with most of mono-substituted alkenes. Exceptions were only formed in reactions with the sterically hindered *tert*-butyl-substituted alkene (74:26).

6-2. Silver-catalyzed imination of sulfoxides and sulfides: results and discussion

Various methods are known for the preparation of sulfoximines. Many of them involve methylphenyl sulfoximine due to the fact that it can be readily synthesized in both racemic and enantiomerically pure form. Sulfoximines, including forementioned one, are generally prepared in two steps from the sulfides by the oxidation and subsequent imination of the sulfoxide, thus formed. Of particular interest is the imination of sulfoxides, since classical non-metal catalyzed imination methods rely on the use of toxic and potentially explosive reagents.[3,4,156] Furthermore the metal-catalyzed iminations of sulfoxides,[157] which have more recently been developed, are either leading to products with protecting groups such as tosyl at the sulfoximine nitrogen, which are difficult to cleave to give synthetically valuable NH-sulfoximines, or using potentially dangerous reagents such as Boc-azide. Rhodium-catalyzed imination reaction[158] reported by Bolm and Okamura circumvented these problems, but the high cost of the catalyst has remained problematic especially for large scale synthesis. Therefore we intended to find alternatives which could avoid the use of toxic and explosive iminating reagents as well as expensive catalyst. In this respect, the silver catalyst which was used in aziridinations[150] and C-H bond insertions[151] attracted our attention and it was decided to evaluated it as a catalyst for the imination reaction.

For the initial screening and optimization, *rac*-methylphenyl sulfoxide (**9**) was chosen as a starting material in combination with mixtures of $NsNH_2$ and $PhI(OAc)_2$ as nitrogen source. In order to establish the optimal reaction conditions, several silver salts and ligands (8 mol% of both) were first examined, and the most relevant results are summarized in Table 10.

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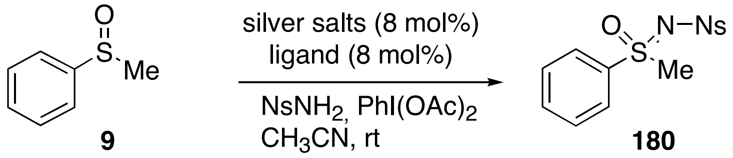
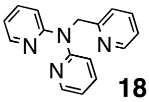
[156] Use of electrochemistry, see: (a) Siu, T.; Picard, C. J.; Yudin, A. K. *J. Org. Chem*. **2005**, *70*, 932. (b) Krasnova, L. B.; Hili, R. M.; Chernoloz, O. V.; Yudin, A. K. *Arkivoc* **2005**, *iv*, 26. (c) Siu, T.; Yudin, A. K. *Org. Lett.* **2002**, 4, 1839.

[157] Cu salts: (a) Müller, J. F. K.; Vogt, P. *Tetrahedron Lett.* **1998**, *39*, 4805. (b) Lacôte, E.; Amatore, M.; Fensterbank, L.; Malacria, M. *Synlett* **2002**, 116. (c) Cren, S.; Kinahan, T. C.; Skinner, C. L.; Tye, H. *Tetrahedron Lett.* **2002**, *43*, 2749. (d) Tomooka, C. S.; Carreira, E. M. *Helv. Chim. Acta* **2003**, *85*, 3773. (e) Takada, H.; Ohe, K.; Uemura, S. *Angew. Chem.* **1999**, *111*, 1367. Fe salts: (f) Bach, T.; Körber, C. *Tetrahedron Lett.* **1998**, *39*, 5015. (g) Bach, T.; Körber, C. *Eur. J. Org. Chem.* **1999**, *64*, 1033. Mn complexes: (h) Nishikori, H.; Ohta, C.; Oberlin, E.; Irie, R.; Katsuki, T. *Tetrahedron* **1999**, *55*, 13937. (i) Ohta, C.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 3885. Ru complexes: (j) Murakami, M.; Uchida, T.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 7071. (k) Tamura, Y.; Uchida, T.; Katsuki, T. *Tetrahedron Lett.* **2003**, *44*, 3301. (l) Murakami, M.; Uchida, T.; Saito, B.; Katsuki, T. *Chirality* **2003**, *15*, 116. (m) Uchida, T.; Tamura, Y.; Ohba, M.; Katsuki, T. *Tetrahedron Lett.* **2003**, *44*, 7965.

[158] Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305.

Table 10. Optimization of silver-catalyzed imination with NsNH$_2$[a]



entry	silver salts	ligands	yield (%)
1	AgNO$_3$	 **181**	$40^{b, c}$
2	AgNO$_3$	terpyridine	52
3	AgNO$_3$	4, 4´, 4´´-*t*-Bu$_3$tpy	83
4	AgNO$_3$	4, 4´, 4´´-*t*-Bu$_3$tpy	66^{b}
5	AgOTf	4, 4´, 4´´-*t*-Bu$_3$tpy	85
6	AgOAc	4, 4´, 4´´-*t*-Bu$_3$tpy	74
7	AgNO$_3$	4, 4´, 4´´-*t*-Bu$_3$tpy	86^{d}

[a] Reaction conditions: sulfoxide **9** (1 equiv), AgNO$_3$ (8 mol%), 4,4´,4´´-*t*Bu$_3$tpy (8 mol%), NsNH$_2$ (1,2 equiv), PhI(OAc)$_2$ (1.5 equiv) in CH$_3$CN (0.1 M) at room temperature. [b] CH$_2$Cl$_2$ was used as a solvent instead of CH$_3$CN.[c] NsN=IPh was used instead of the mixure of NsNH$_2$ and PhI(OAc)$_2$. [d] Reflux and 4 mol% of catalyst were applied instead of rt and 8 mol% of catalyst.

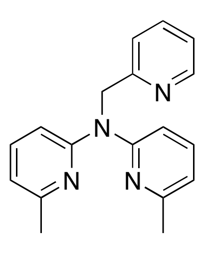
As silver salts, AgNO$_3$ and AgOTf (entries 3 and 5 in Table 10) were superior to AgOAc (entry 6), and no complete conversion was observed when Ag$_2$CO$_3$ (not included in Table 10) was used. As such, these silver salts were then tested in conjunction with diverse ligands. In contrast to the relatively broad choice of silver salts, the imination reaction of sulfoxides required carefully selected ligands as also observed in the previous studies of silver-catalyzed aziridinations and intramolecular amidations. All attempts to iminate under silver catalysis using diamines, phosphines and pyridines as ligands failed (Figure 17). Finally, dipyridylamine **181**,[#] terpyridine, and 4,4´,4´´-tri-*tert*-buty-2,2´:6´,2´´-terpyridine (*t*Bu$_3$tpy) proved to be the most suitable ligands to give catalysts from silver nitrate, which catalyzed the formation of sulfoximine **180** in 40, 52 and 83% yield, respectively (entry 1-3, Table 10).[159] The use of a ligand was essential for substrate conversion. Silver salts such as AgNO$_3$ or AgOTf did not catalyze the imination in the absence of a ligand. Moreover, no reaction occurred at room temperature without the catalyst. Adding a base such as MgO

[#] Dipyridylamines (**181**, **182**, **183**, **184** and **185**) were synthesized by Masafumi Nakanishi in RWTH Aachen University.

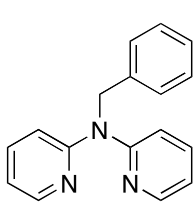
[159] Colorless single crystals were obtained from the solution of AgNO$_3$ and dipyridylamine **182** in a mixture of CH$_3$CN and CH$_2$Cl$_2$. The X-ray crystal structure data are presented in section 9-appendix.

did not improve the reaction yield. Acetonitrile gave the products in superior yield (83%) when used in conjunction with $AgNO_3$ and *t*Bu_3tpy compared to those reactions carried out in dichloromethane, DMF and THF (66, 60 and 52%, respectively). Less polar solvents such as toluene and diethyl ether did not lead to the imination at all. In general, the imination was completed within 16 h. Under reflux full conversion was obtained in 1 h and slightly improved yields were achieved (entry 7). Furthermore, microwave-assisted (200 W) imination of methyl phenyl sulfoxide led to sulfoximine **180** within 20 minutes in 85% yield.[160]

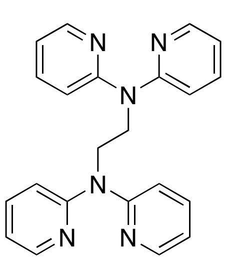
Figure 17. Compounds which in combination with silver salts ($AgNO_3$, AgOTf and AgOAc) did not affect sulfoxide imination reaction



182



183



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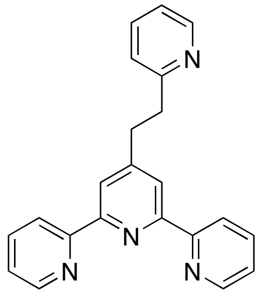
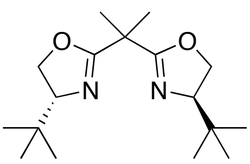
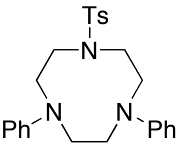


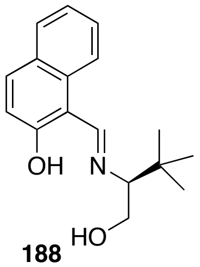
185



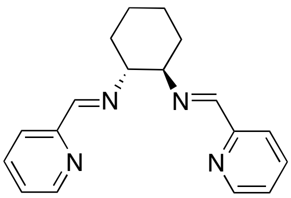
186



187



188



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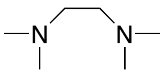

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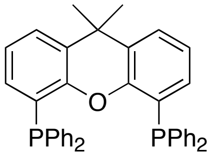

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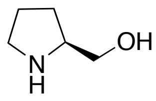
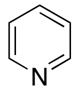


192



PPh_3
PCy_3
BINAP

The catalyst loading could be reduced to 2 mol% although under these conditions longer reaction times were demanded for the complete conversion and the yield was lower than that obtained with higher catalyst loadings (Table 11). Applying more than 4 mol% of catalyst did neither shorten the reaction time nor improve the yield (Table 11, entries 2 and 3).

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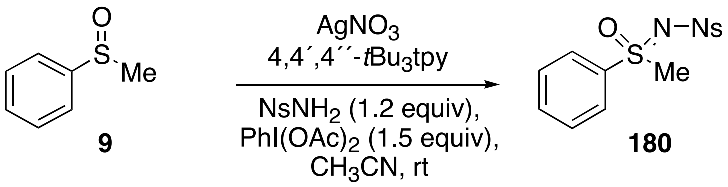
[160] Methylphenyl sulfoximine (**65**, 0.1 equiv) was obtained in 26% yield from the reaction with $FeCl_3$ (0.5 equiv) and NsN=IPh (1.2 equiv) in acetonitrile at room temperature.

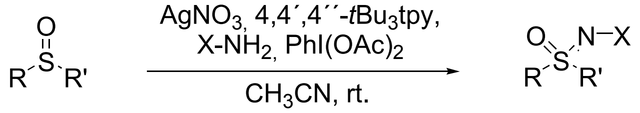
Table 11. Optimization of the catalyst loading



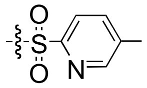
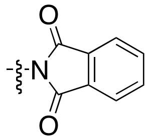
entry	catalyst loading	reaction time	yield (%)
1	2 mol%	48 h	62
2	4 mol%	16 h	83
3	8 mol%	16 h	83

In order to investigate the scope of the substrates amenable to silver-catalyzed imination, several sulfoxides and sulfonylamides were examined as starting materials and iminating reagents, respectively. As summarized in Table 12, most of sulfonylamides such as *p*-nitrobenenesulfonylamide ($NsNH_2$), *p*-toluenesulfonylamide ($TsNH_2$) and *p*-methyl-2-pyridinesulfonylamide were effective iminating reagents giving the corresponding sulfoximines **194** in good to excellent yield (up to 98%) at room temperature. The imination of **9** with trimethylsilylethyl sulfonylamide (Ses-NH_2) occurred very slowly for 7 days at room temperature albeit in good yield (83%). Under reflux condition the reaction proceeded much faster (1.5 h) and gave the corresponding product **194e** in 66% yield (entry 5). No conversion was observed from the reaction with methyl(phenylsulfinyl)acetate as a substrate and $NsNH_2$ in the presence of the silver catalyst. Although the reaction proceeded very well, the products resulting from the use of benzyl phenyl sulfoxide and *p*-bromophenylmethyl sulfoxide could not be purified by column chromatography or crystallization due to the low solubility of the crude product in organic solvents. Unfortunately, trifluoroacetamide, which would afford a product with a N-protecting group that could readily be cleaved under mild hydrolysis to provide synthetically useful NH-free sulfoximines, did not afford the corresponding sulfoximine under silver catalysts despites great efforts. In addition to trifluoroacetamide, a number of carbamates, amides and hydroxyl amines (benzyl carbamate, methyl carbamate, acetamide, benzamide, *O*-benzyl hydroxylamine, *O*-pentafluorophenyl hydroxylamine, etc.) were also tested as a nitrogen source in the presence of various silver and ligand complexes. However, none of them yielded the corresponding sulfoximines, and no conversion was observed in most cases.

Table 12. Silver-catalyzed imination of sulfoxides[a]



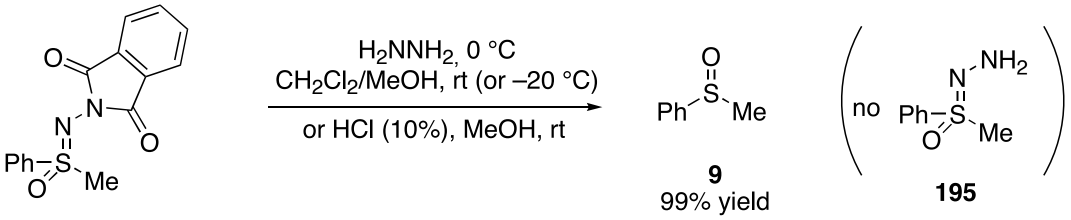
193 or 9 **194**

entry	substrate	R'	R'	X	product	yield (%)
1	**193a**	Ph	Ph	Ns	**194a**	98
2	**193b**	$-[CH_2CH_2]_2-$		Ns	**194b**	84
3	**193c**	Ph	$-CH=CH_2$	Ns	**194c**	92
4	**193d**	Ph	$-CH_2CH=CH_2$	Ns	**194d**	91
5	**9**	Ph	Me	Ts	**194e**	79
6	**9**	Ph	Me	SES	**194f**	83[b] (66[c])
7	**9**	Ph	Me		**194g**	73 (94[b])
8	**9**	Ph	Me		**194h**	85

[a] Reaction conditions: sulfoxide (1.0 equiv), $X-NH_2$ (1.2 equiv), $PhI(OAc)_2$ (1.5 equiv), $AgNO_3$ (8 mol%), 4,4´,4´´-*t*Bu_3tpy (8 mol%) in CH_3CN (0.1 M) at rt. [b] Reaction time of 7 days. [c] The use of 4 mol% of catalyst under reflux instead of 8 mol% at room temperature.

We had a particular interest in the *N*-phthalimide methylphenyl sulfoximine product **194h**,[156] as a chiral hydrazine derivative. Therefore, the reaction conditions necessary to remove the phthalimine protecting group and obtain *N*-amino sulfoximine **195** were examined. However, neither basic hydrazine nor acidic hydrolysis using HCl afforded the expected product **195**, with only methylphenyl sulfoxide being obtained in quantitive yield (Scheme 70), even at –20 °C.

Scheme 70.



194h

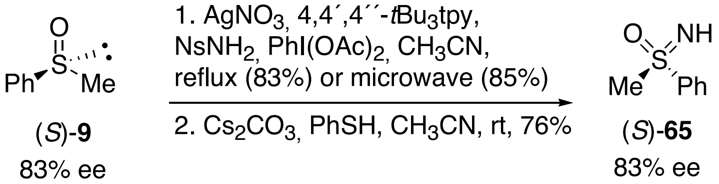
9
99% yield

195

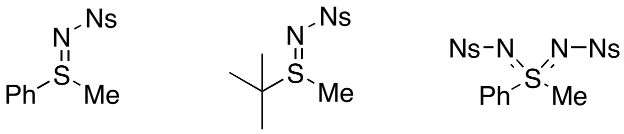
Presumably, this observation results from the stability of compound **195** which led to the decomposition to N_2 and the corresponding sulfoxide via the nitrene resonance.[161]

The stereospecificity in this transformation was investigated with sulfoxide (*S*)-**9** (83% ee, Scheme 71) as starting material under reflux and microwave (200W) conditions. The silver-catalyzed imination and subsequent removal of the nosyl group with Cs_2CO_3 and thiophenol in acetonitrile afforded the corresponding sulfoximine (*S*)-**65** with retention of configuration in good yield (80% in two steps).[162] It is noteworthy that high yields of deprotecting nosyl group of compound **180** can be obtained in more than 0.5 mmol scale of substrate.

Scheme 71.



Sulfilimines such as compounds **196** and **197** (Figure 18) could be also prepared under identical reaction conditions, as displayed in Table 12. In contrast to the rhodium-catalyzed imination,[158] nearly the same reactivities between sulfides and sulfoxides were observed for the silver-catalyzed imination. The synthesis of sulfodiimines such as compound **198** from sulfilimine **196** with $NsNH_2$ and $PhI(OAc)_2$ in the presence of silver-ligand catalyst was also attempted. However, the reaction did not proceed and no conversion was observed under described condition. Presumably, the strongly electron withdrawing *N*-nosyl group of sulfilimine **196** inhibited the second imination.



196
83% yield

197
77% yield

198

Figure 18.

---

[161] For its thermal decomposition, see: (a) Kim, M. G.; White, J. D. *J. Am Chem. Soc.* **1977**, *99*, 1172.

[162] The enantiomer ratio was determined by HPLC using a chiral column (Chiralcel OJ, 20 °C, heptane:*i*PrOH = 85:15, 0.5 mL/min); $t_R(R)$ = 36.8 min, $t_R(S)$ = 42.6 min.

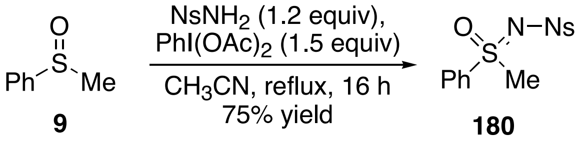
6-3. Summary and outlook

A silver-catalyzed imination was successfully applied to prepare various sulfoximines and sulfilimines from sulfoxides and sulfides, respectively. Diverse sulfonylamides combined with iodobenzene diacetate were used as nitrene precusors. The combination of $AgNO_3$ and 4,4´,4´´-*t*Bu_3tpy is the most efficient catalyst for this transformation which occurrs at both room temperature and reflux with retention of configuration at the stereogenic sulfur atom in those cases where sulfoxides were the substrate. Therefore, enantiomerically pure sulfoximines are accessible from enantiopure sulfoxides by this method. Synthetically-valuable sulfoximines bearing a free NH group are accessible by removal of the nosyl protecting group of sulfoximines with Cs_2CO_3 and thiophenol in high yields without epimerization at the stereogenic center. Besides silver, iron-catalyzed imination of sulfoxides and sulfides is also interesting and a valuable method. Although poor yields were obtained from the imination of methylphenyl sulfoxide using $FeCl_3$, $NsNH_2$ and $PhI(OAc)_2$, it is expected that this reaction can be optimized by changing reaction conditions, iron salts, solvents, nitrene sources and so forth.

6-4. Metal-free imination of sulfoxides and sulfides: results and discussion

During our study of the silver-catalyzed imination of sulfoxides and sulfides with the mixture of $NsNH_2$ and iodobenzene diacetate,[163] we discovered, to our delight, that the imination of methylphenyl sulfoxide (**9**) to afford the nosyl-protected sulfoximine **180** could also be effected in the absence of silver catalyst. After optimization of reaction conditions with methylphenyl sulfoxide, the highest yields (75%) of sulfoximine **180** were obtained by refluxing a mixure of $NsNH_2$ and $PhI(OAc)_2$ in acetonitrile for 16 h (Scheme 72).

Scheme 72. Metal-free imination of methyl phenyl sulfoxide with $NsNH_2$



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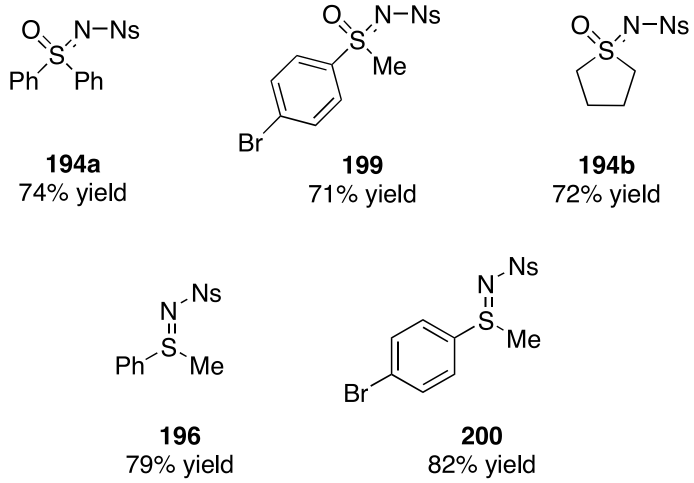
[163] Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571.

Acetonitrile gave superior yields when used as a solvent, compared to reactions performed in dichloroethane and THF (60 and 33%, respectively) and this imination reaction did not proceed at room temperature. Addition of a base such as MgO did neither influence the yield nor the reaction time. A number of sulfonylamides such as as *p*-toluenesulfonylamide ($TsNH_2$), *p*-methyl-2-pyridinesulfonylamide, trimethylsilylethyl sulfonyl amide ($SesNH_2$) as a nitrogen source were tested in combination with iodobenzene diacetate. Unfortunately, no conversion or very low yields were observed with those compounds under conditions identical to those used in the reaction with *p*-nitrobenzenesulfonylamide ($NsNH_2$).



194a
74% yield

199
71% yield

194b
72% yield

196
79% yield

200
82% yield

Figure 19.

In order to investigate the substrate scope, several sulfoxides were examined under the optimized conditions described in Scheme 72. Most of sulfoxides were converted into the corresponding *N*-nosyl protected sulfoximines in good yields (compounds **194a**, **199** and **194b** in Figure 19) although the reaction with benzyl phenyl sulfoxide and phenyl vinyl sulfoxide did not afford the desired sulfoximines. The imination of sulfides was also tested, and sulfilimines such as compound **196** and **200** (Figure 19) could be prepared from the corresponding sulfides in high yields (79 and 82% yield, respectively) without further optimization of the reaction condition.

The stereospecificity of this transformation was examined using (*S*)-methlyphenyl sulfoxide (**9**) as a starting material with 83% ee. As the result of the imination and subsequent removal of the nosyl group, partially racemized NH-sulfoximine **65** was obtained with 43% ee.

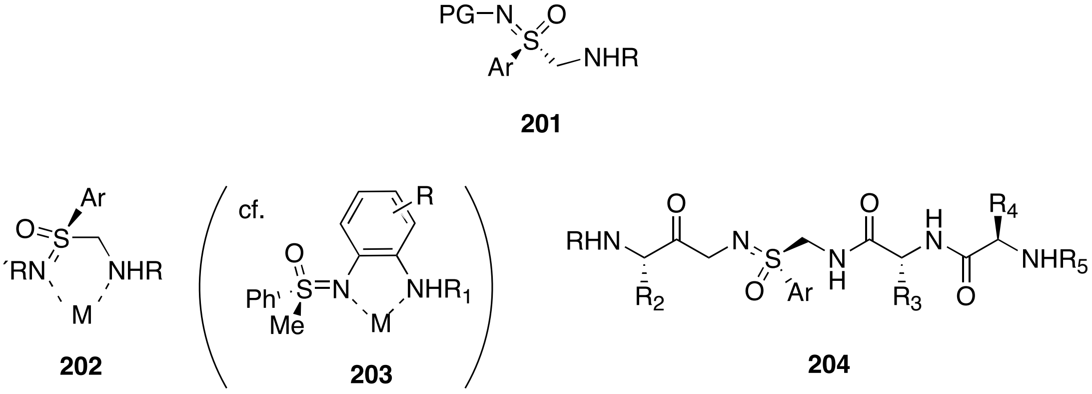
6-5. Summary and outlook

In conclusion, the imination of sulfoxides and sulfides was successfully performed with the mixture of $NsNH_2$ and $PhI(OAc)_2$ in the absence of metal catalysts. This method combining the deprotection step of nosyl group can be conveniently applied to prepare racemic NH-sulfoximines, especially such as methylphenyl sulfoximine which is the most commonly used and valuable substrate in sulfoximine chemistry. Although alternative nitrene precursors instead of the rather expensive and environment-unfriendly hypervalent iodine (III) reagent should be still considered, it is noteworthy that diverse sulfoximines can be prepared with this method under rather safer and less toxic condition than existing non-metal catalyzed imination methods.

7. Miscellaneous

7-1. Synthetic approaches towards α-amino sulfoximines

In order to apply as ligand in asymmetric catalysis as well as building block of pseudopeptides, α-amino sulfoximine **201** was designed. Compared to the established sulfoximines such as **203**, α-amino sulfoximine **201** has the stereogenic center in the chelate (Figure 20) and it therefore appeared promising as chiral N,N-ligand for asymmetric catalysis. Furthermore, as depicted in its structure, α-amino sulfoximine **201** can be regarded as an α-amino acid analogue and incorporated into pseudopeptides such as **204** having a tetrahedral component which can be considered as a transition state analogues for the inhibition of carboxypeptidase A.



201

202

203

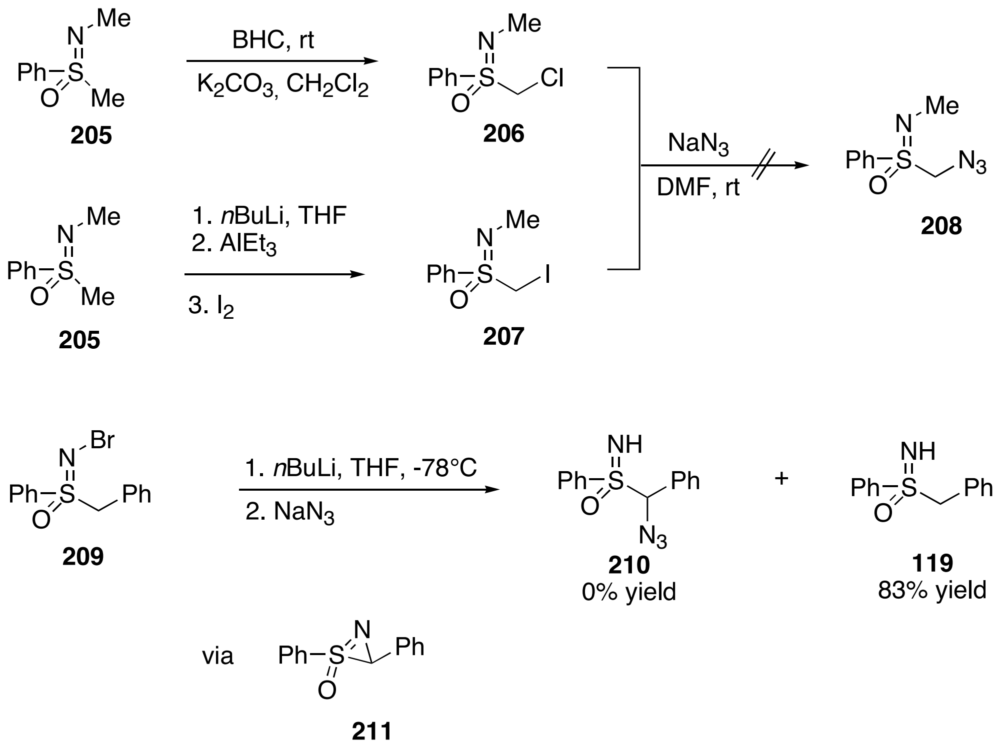
204

Figure 20.

In order to synthesize α-amino sulfoximine **201**, various approaches (nucleophilic substitution, the reduction of α-nitro sulfoximine, Curtius and Hoffman rearrangement, electrophilic amination, etc) were screened.

First, the target compound was attempted to be accessed by nucleophilic substitution of an α-halo sulfoximine with sodium azide, which was considered as the most direct and straightforward synthetic route for its synthesis. α-Chloro and iodo sulfoximine[164] were prepared from *N*-methyl sulfoximine **205**[165] following in literature (Scheme 73). Then, compound **206** and **207** were treated with sodium azide in DMF. However, no reaction occurred and a large amount of starting material was recovered after the reaction. Presumably this was due to the steric hinderance of the sulfoximine which is in the α-position of the reaction site.

Scheme 73.



As an alternative, *N*-bromo benzylphenyl sulfoximine (**209,** Scheme 73) was prepared. Compound **209** was expected to undergo a reaction with *n*-butyllithium to give the key intermediate **211**,[166] which subsequencially reacts with sodium azide to afford the

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[164] (a) Bosshammer, S.; Gais, H. J. *Synlett* **1998**, 99. (b) Johnson, C. R.; Corkins, H. G. *J. Org. Chem.* **1978**, *43*, 4136.

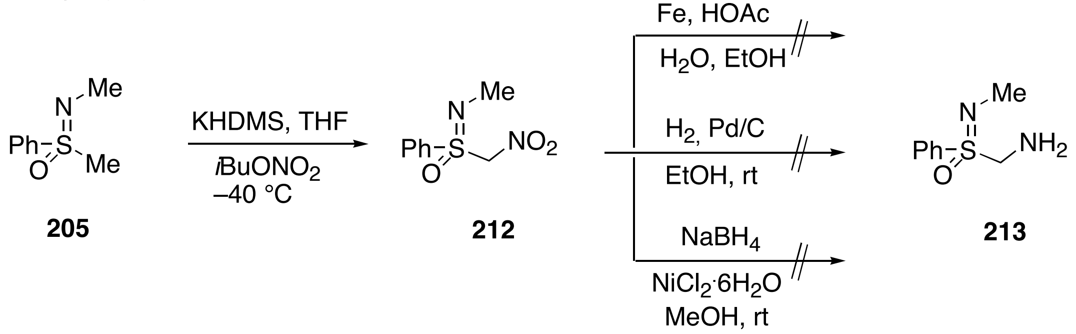
[165] Shiner, C. S.; Berks, A. H. *J. Org. Chem.* **1988**, *53*, 5542.

[166] Yoshida, T.; Naruto, S.; Uno, H.; Nishimura, H. *Chem. Pharm. Bull.* **1982**, *30*, 4346.

corresponding α-azido sulfoximine **210**. *N*-Bromo benzylphenyl sulfoximine (**209**) was readily synthesized in 99% yield from the reaction of *NH*-benzylphenyl sulfoximine and NBS in chloroform.[164] As a result of the reaction with *n*BuLi and sodium azide, however, only NH-free benzylphenyl sulfoximine (**119**) was obtained in 83% yield and no expected product **210** was detected.

To the next, it was attempted to obtain α-amino sulfoximine **213** from the reduction of α-nitro sulfoximine **212** (Scheme 74). Following the literature[167] *N*-methyl α-nitro sulfoximine **212** was prepared by the reaction with *N*-methyl sulfoximine **205** and isobutyl nitrate in the presence of KHMDS in 40% yield. Since the resulting compound **212** was rather unstable even at low temperature, the next step followed immediately after its purification.

Scheme 74.



Three different approaches, Fe-catalyzed reduction, Pd/C-catalyzed hydrogenation and NiCl$_2$-catalyzed NaBH$_4$ reduction, were followed in order to reduce the nitro group as depicted in Scheme 74. However none of them was successful to yield compound **213** and only *N*-methyl phenyl sulfinimde was observed as a side product.

The attempt to synthesize α-amino sulfoximine derivatives was extended by the attempt to utilize the Curtius rearrangement. Metallation of *N*-benzoyl sulfoximine **110** with lithium cyclohexyl(isopropyl)amide (LCHIPA) followed by the reaction of the resulting anion with dried gaseous CO$_2$ at –78 °C in anhydrous THF and subsequent aqueous workup gave the corresponding ammonium carboxylate **214** (Scheme 75).[9f,g] Without further purification, the reaction with diphenylphosphoryl azide (DPPA) in toluene was carried out directly under reflux followed by the addition of benzyl alcohol. However, the expected product **215** could not be formed and the reaction mixture seemed to decompose during the reaction as indicated by TLC monitoring. As an alternative, sulfoximine acyl azide **216** was isolated from the reaction with sodium azide and compound **214**. Taking into account

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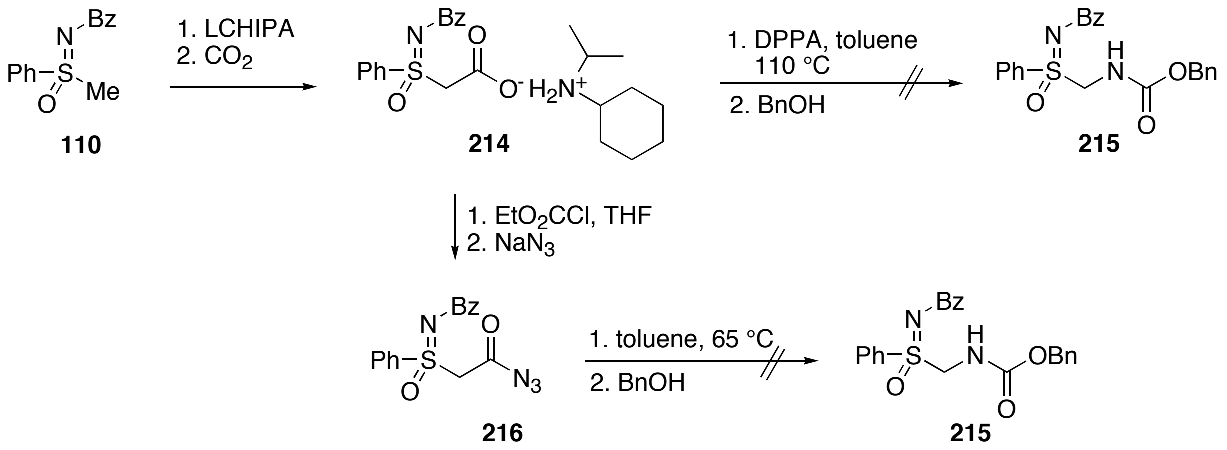
[167] Wade, P. A.; Le, H.; Amin, N, V. *J. Org. Chem.* **2002**, *67*, 2859.

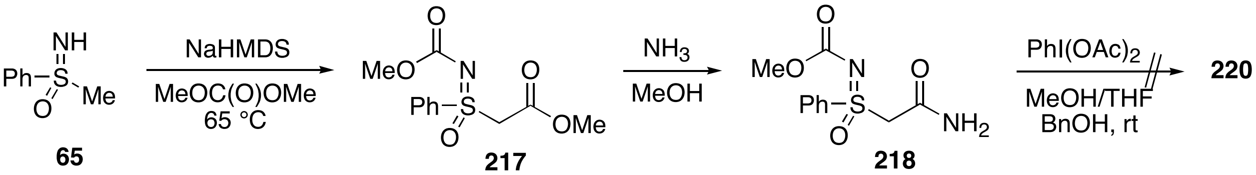
the stability of compound **216**, the Curtius rearrangement was performed directly in toluene at 65 °C and benzyl alcohol was then added in order to achieve the formation of sulfoximine benzyl carbamate **215**. To our disappointment, no desired product was detected and only decomposition occurred during the reaction.

Scheme 75. Attempted Curtius rearrangement of sulfoximine derivatives



Besides the Curtius rearrangement an attempt to utilize the Hoffmann rearrangement for the synthesis of α-amino sulfoximine **220** was undertaken (Scheme 76).

Scheme 76. Hoffman rearrangement of sulfoximine **218**.



The starting compound **218** for the Hoffmann rearrangement was prepared in a short reaction sequence. Treatment of NH-free methylphenyl sulfoximine **65** with dimethyl carbonate in the presence of NaHMDS afforded the *N*-methoxycarbonyl sulfoximine methyl ester **217** in good yield (66%). Compound **217**, then, was aminated with ammonia providing the corresponding amide **218** in high yield (over 90%).[168] The Hoffmann rearrangement of amide **218** was tested by treatment with $PhI(OAc)_2$ but, unfortunately, the corresponding product **220** was not produced under the condition described in Scheme 76.

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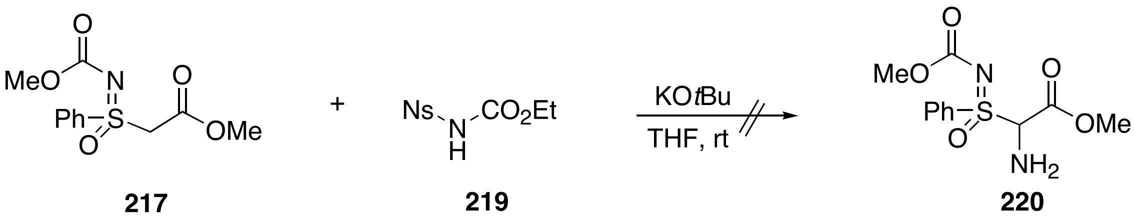
[168] Schaffner-Sabba, K.; Tomaselli, H.; Henrici, B.; Renfroe, H. B. *J. Org. Chem.* **1977**, *42*, 952.

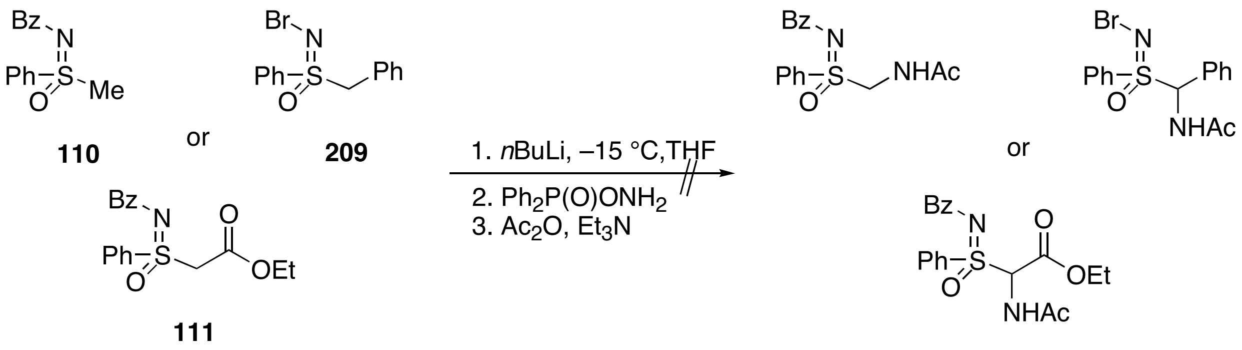
In addition, the electrophilic amination reaction[169] was considered as an alternative method to synthesize the target compound, α-amino sulfoximine **201**. Thus, various electrophilic aminating reagents were examined. First of all, $NsNHCO_2Et$[170] as a nitrogen source which is reported as a nitrene precursor in the presence of base was applied. N-Protected sulfoximine methyl ester **217** was treated with $NsNHCO_2Et$ and KO*t*Bu in THF at room temperature, but the reaction failed to afford the expected aminated product **220** (Scheme 77). Under a similar condition as described in Scheme 77 diethylazodicarboxylate (DEAD) and BocN=NBoc were tested as electrophiles but also these trials were unsuccessful and did not lead to α-amino sulfoximines.

Scheme 77. Attempted electrophilic amination of sulfoximine **217**



The reaction using diphenylphosphoryl hydroxylamine[171] was excuted with N-protected sulfoximine such as *N*-benzoyl sulfoximine **110**, *N*-bromobenzyl phenyl sulfoximine (**209**) and sulfoximine ester **111** as starting materials (Scheme 78). However, none of them provided the corresponding aminated products under the described condition and either decomposition or no conversion was observed during the reaction.

Scheme 78.



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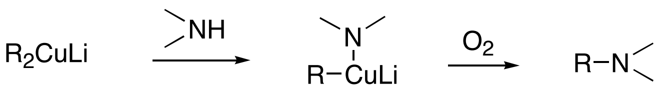
[169] For a review, see: Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947.

[170] (a) Lwowski, W.; Maricich, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 3630. (b) Major, R. T.; Dürsch, F.; Hess, H. J. *J. Org. Chem.* **1959**, *24*, 431.

[171] (a) Smulik, J. A.; Vedejs, E. *Org. Lett.* **2003**, *5*, 4187. (b) Harger, M. J. P. *J. Chem. Soc., Chem. Comm.* **1979**, 768.

To the last, the N-alkylation with organocopper reagents, which has been reported as mild and efficient method for the N-alkylation of amines, was attempted in order to accomplish our goal.[172] This method is based on the oxidative coupling of lithium alkylcopper amide **221**, which is generated from lithium dialkylcuprates and primary or secondary amines, as illustrated in Scheme 79.

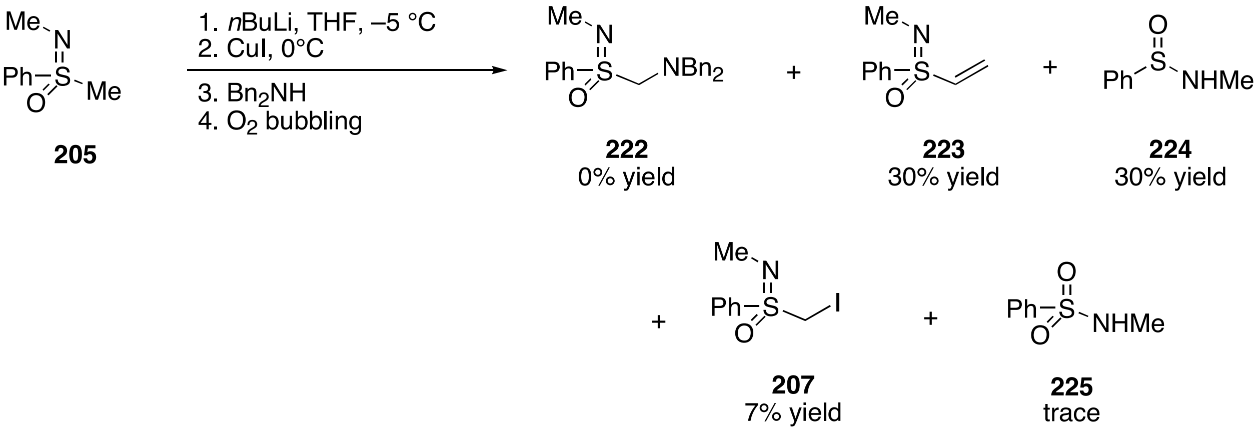
Scheme 79.



221

Since sulfoximine cuprates[164a] have been already applied in the reaction with propargyl bromides, this transformation was considered as an appropriate method for the synthesis of α-amino sulfoximines.

Scheme 80.



After forming sulfoximine cuprate from *N*-methyl sulfoximine **205** (2 equiv) using *n*BuLi and CuI, dibenzyl amine was added to the lithium disulfoximinecuprate at –20 °C. After 2 h, excess molecular oxygen was bubbled in the suspension via syringe at –20 °C for 5 min and the mixture was then quenched in concentrated ammonium hydroxide extracted with ethyl acetate. As a result of the purification by column chromatography, it was revealed that this N-alkylation with organocuprate reagent gave not the expected α-dibenzyl amino sulfoximine **222** but vinyl sulfoximine **223** and sulfinamide **224** as major products together with small amount of α-iodo sulfoximine **207** and sulfonamide **225** (Scheme 80).

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[172] Yamamoto, H.; Maruoka, K. *J. Org. Chem.* **1980**, *45*, 2739.

Although we were not able to synthesize α-amino sulfoximines with mentioned approaches, we can still prospect that further optimizing reaction condition of those methods allows to prepare α-amino sulfoximines together with the exploitation of new methods.

7-2. Synthetic approaches towards novel *N*-protected sulfoximine esters

The structures of pseudopeptides containing sulfoximines as well as their stability against enzymatic degradation have been investigated,[9] which indicated that sulfoximine-containing pseudopeptides can be potential new enzyme inhibitors. For further research in this area, efficient synthetic methods to prepare them are essentially requested. Previously the synthesis of pseudopeptides containing sulfoximines by selective carboxylation at the acidic methyl group of the sulfoximine to generate a carboxylate, which could be used in a subsequent coupling with a carboxy-protected amino acid, was suggested.[9f,h] According to this synthetic strategy the C-terminal of sulfoximine was extended with various amino acids. In spite of this method, it appeared worthful to investigate an alternative route to prepare sulfoximine containing pseudopeptides because the sulfoximine ammonium carboxylates **227** (Figure 21) obtained from metallation with LCHIPA followed by CO_2 bubbling are rather unstable and this procedure has a limited substrate scope. In this context, new sulfoximine esters such as **226a**, **226b** and **226c** (Figure 21) were designed which were supposed to be stable and ready to use in couplings with amino acids to give the corresponding products in good yields.

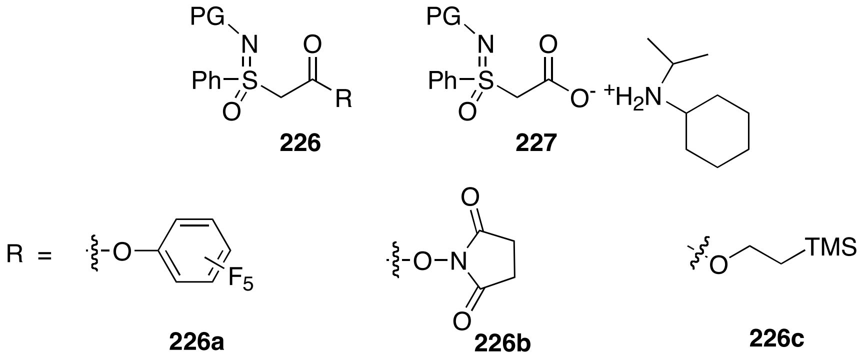
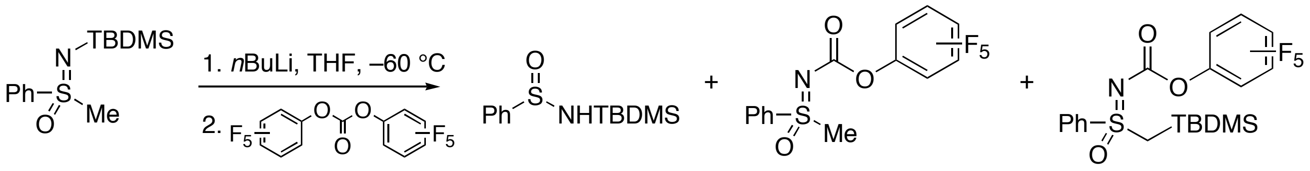


Figure 21.

First, the attention was focused on the synthesis of sulfoximine pentafluorophenylester **226a**. *N*-TBDMS methylphenyl sulfoximine was deprotonated with *n*-buthyllithium in THF and the resulting anion was treated by dipentafluorophenyl carbonate,[173] which was prepared from the reaction with phosgene and pentafluorophenol in the presence of sodium hydride in THF (Scheme 81). However, either decomposition occurred or side products such as sulfinamide **228** and pentafluorophenoxy carbonyl sulfoximine **229** were formed when *N*-TBDMS sulfoximine was used as starting material. Also the attempt to prepare compound **226b** by using disuccinimide carbonate under the similar condition as described in Scheme 81 remained unsuccessful.

Scheme 81.



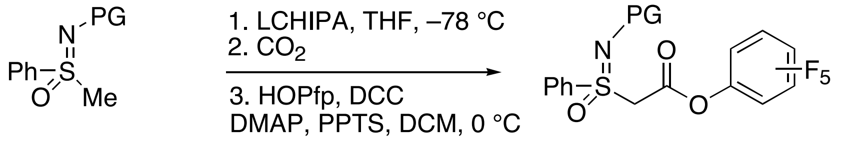
228
32%

229
15%

230
trace amount

As an alternative, carboxylation and DCC coupling with pentafluorophenol were attempted instead of the reaction with difluorophenyl carbonate (Scheme 82). After metallation of *N*-TBDMS or *N*-Boc protected sulfoximine with LCHIPA followed by CO_2 bubbling, the resulting ammonium salts were reacted with pentafluorophenol in the presence of DCC, DMAP and PPTS in dichloromethane. As a result the expected sulfoximine ester **231** and **232** were earned from *N*-TBDMS and Boc sulfoximine, respectively, albeit in very low yields (11 and 15%, respectively). However, to our disappointment, the resulting products (**231** and **232**) were rather unstable at room temperature and their decomposition was observed in 24 h at room temperature.

Scheme 82.



PG = TBDMS; **231** (11% yield)
Boc; **232** (15% yield)

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[173] Dipentafluorophenyl carbonate is commerically available in Aldrich. For its application, see: (a) Hansen, T. K. *Tetrahedron Lett.* **1999**, *40*, 9119. (b) Zain, R.; Stawinski, J. *J. Org. Chem.* **1996**, *61*, 6617. (c) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539.

We therefore turned our attention to the synthesis and application of sulfoximine TMS ethylester **226c**. This compound was expected to be more stable than **226a** or **226b** and react with amino acids in the presence of coupling reagents and TBAF.

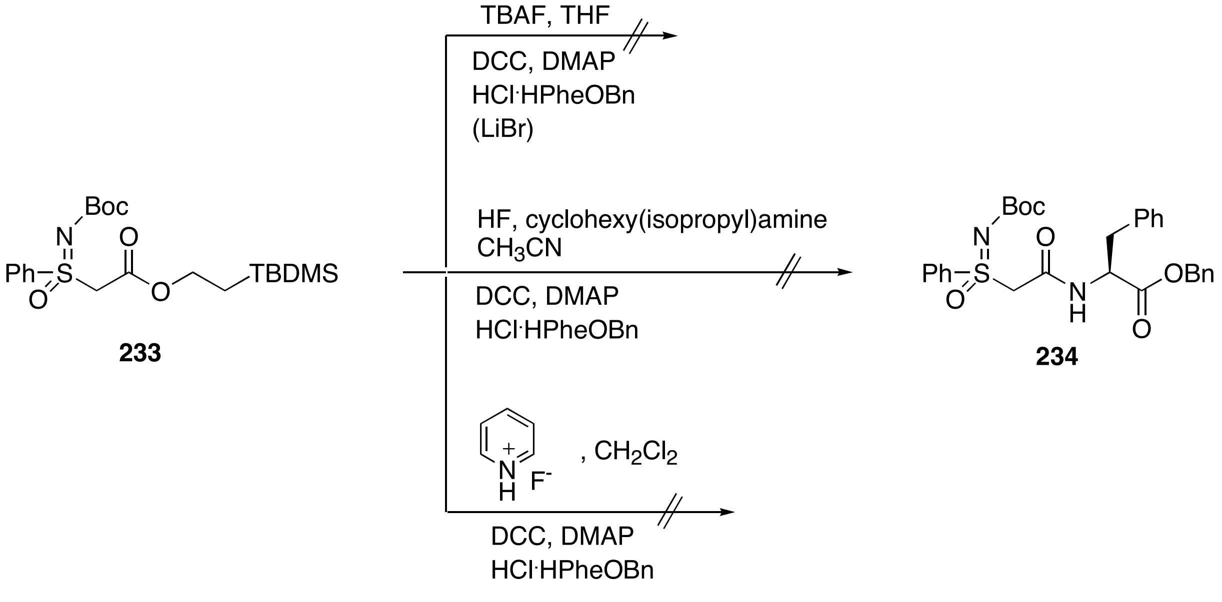
Scheme 83.

233
70% yield

By using the same method as describe in Scheme 82, which is the metallation, carboxylation and coupling with 2-(trimethylsilyl)ethanol, compound **233** was synthesized in 70% yield (Scheme 83). It was stable enough to keep for long period of time.

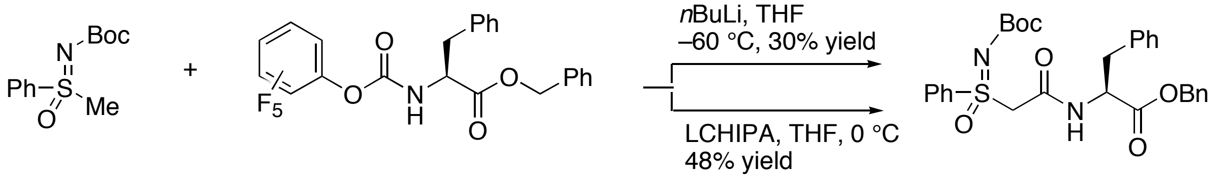
To the next, coupling reactions of compound **233** with phenyl alanine benzylester in the presence of different fluoride sources were attempted (Scheme 84). However, none of them afforded the expected coupled product **234**. When TBAF was used, only *N*-Boc methylphenylsulfoximine was obtained quantitively, which indicated that the decarboxylation of compound **233** proceeded too fast to undergo the coupling reaction appropriately. No reaction occurred by using HF/cyclohexyl(isopropyl)amine and pyridinium fluoride and most of the starting compound **233** was recovered after the reaction.

Scheme 84. Attempted coupling reaction of **233** with HPheOBn



Although the efforts to prepare and utilize active sulfoximine esters **226** for building up the pseudopeptides proved to be unsuccessful, the other approach of using N-activated α-amino acid ester **235** as a coupling partner was partially successful. The coupling reaction of *N*-Boc protected methylphenyl sulfoximine and the activated phenylalanine **235** prepared from the reaction with dipentafluorophenyl carbonate was performed in the presence of a base such as *n*BuLi or LCHIPA. As a result, the corresponding pseudopeptide **234** was obtained in moderate yields.

Scheme 85.



235 **234**

Although the reaction yields of this approach were not as high as in the preivous procedure (metallation, carboxylation and coupling), this method can be a complementary synthetic route to prepare sulfoximine pseudopeptides owing to its easy operation. Furthermore the reaction yields are expected to be improved by further optimization.

7-3. Synthesis and application of proline-sulfoximine and its applications as an organocatalyst and a chiral ligand

Organocatalysis[174] has been highlighted in particular recently, and spectacular progress has been accomplished in the development of new catalytic methods based on the use of metal-free chiral organic compounds. Among them L-proline and its derivatives (Figure 22) have been described as efficient catalysts of a variety of imine- and enamine-based reactions such as asymmetric aldol reactions,[175] Michael additions,[176] asymmetric Mannich

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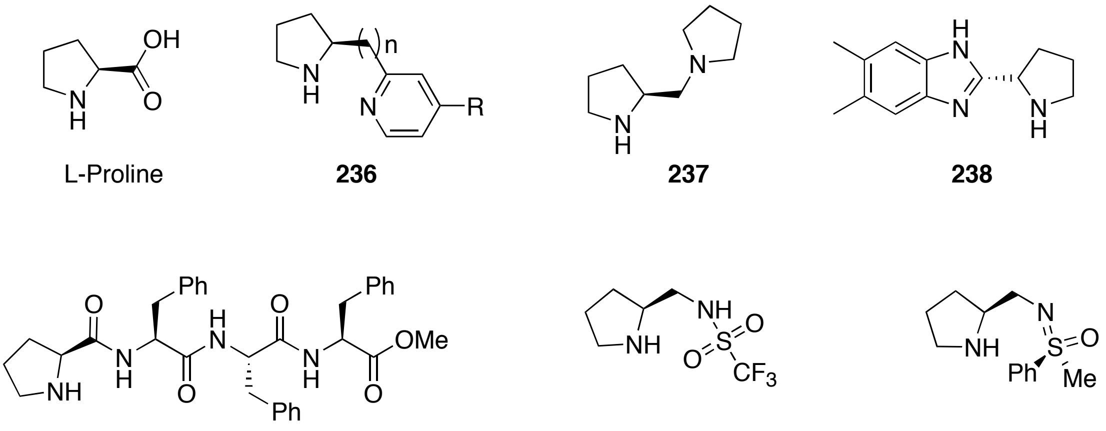
[174] (a) Houk, K. N.; List, B. *Acc. Chem. Res.* **2004**, *37*, 487. (b) Dalko, P. I.; Moisan, L. *Angew. Chem.* **2004**, *116*, 5248. (c) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580.

[175] (a) Tang, Z.; Yang, Z. H.; Chen, X. H.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285. (b) Wang, W.; Li, H.; Wang, J. *Tetrahedron Lett.* **2005**, *46*, 5077. (c) Tang, Z.; Yang, Z. H.; Cun, L. F.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z. *Org. Lett.* **2004**, *6*, 2285. (d) Mase, N.; Tanaka, F.; Barbas, C. F. *Angew. Chem.* **2004**, *116*, 2474. (e) Lacoste, E.; Landais, Y.; Schenk, K.; Verlhac, J.; Vincet, J. M. *Tetrahedron Lett.* **2004**, *45*, 8035. (f) Mase, N.; Tanaka, F.; Barbas, C. F. *Org. Lett.* **2003**, *5*, 4369. (g) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (h) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem.* **2002**, *114*, 1868. (i) Sakthivel, K.; Notz,

or Mannich-type reactions,[177] Diels-Alder reactions,[178] asymmetric halogenations,[179] epoxidations[180] and so forth. In most reactions, the formation of an enamine between L-proline derivatives and the corresponding donor substrate is considered as the key step and both a base and an acidic proton as well as hydrogen bonding between the organocatalysts and the electrophilic substrate are essentially required for effective catalysis.[181]



L-Proline **236** **237** **238**

239 **240** **241a**

Figure 22.

We designed *N*-(pyrrolidinylmethyl)sulfoximine **241a** (Firgure 22), which may be useful for both metal and metal-free catalyzed organic processes and intended to utilize it as an organocatalyst for asymmetric catalysis.

W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (j) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (k) Gijsen, H. J.; Wong, C. H. *J. Am. Chem. Soc.* **1995**, *117*, 7585.

[176] (a) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558. (b) Mase, N. M.; Thayumanavan, R.; Tanaka, F. Barbas, C. F. *Org. Lett.* **2004**, *6*, 2527. (c) Betancort, J. M.; Barbas, C. F. *Synthesis* **2004**, 1509. (d) Betancort, J. M.; Sakthivel, K.; Thayumanava, R.; Barbas, C. F. *Tetrahedron Lett.* **2001**, *42*, 4441. (e) Betancort, J. M.; Barbas, C. F. *Org. Lett.* **2001**, *3*, 3737. (f) Bui, T.; Barbas, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951.

[177] (a) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem.* **2005**, *117*, 4147. (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F. *Angew. Chem.* **2003**, *115*, 4365. (c) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F. *Synlett* **2003**, 1906. (d) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F. *J. Org. Chem.* **2003**, *68*, 9624. (e) Cordova, A.; Barbas, C. F. *Tetrahedron Lett.* **2002**, *43*, 7749. (f) Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W. Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (g) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (h) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F. *Tetrahedron Lett.* **2001**, *42*, 199.

[178] (a) Ramachary, D. B.; Chowdari, N. S.; Sakthivel, K.; Tanaka, F.; Barbas, C. F. *Tetrahedron Lett.* **2002**, *43*, 6743. (b) Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas, C. F. *Tetrahedron Lett.* **2002**, *43*, 3817. (c) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

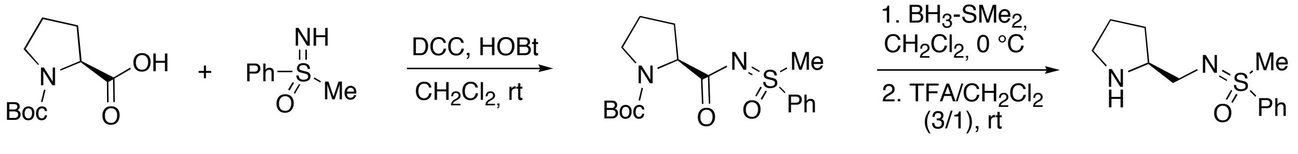
[179] (a) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem.* **2005**, *117*, 6375. (b) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826. (c) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991. (d) Halland, N.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790. (e) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.

[180] Ho, C. Y.; Chen, Y. C.; Wong, M. K.; Yang, D. *J. Org. Chem.* **2005**, *70*, 898.

[181] Bolm, C.; Schiffers, I.; Zani, L.; Rantanen, T. *Angew. Chem.* **2005**, *117*, 1788.

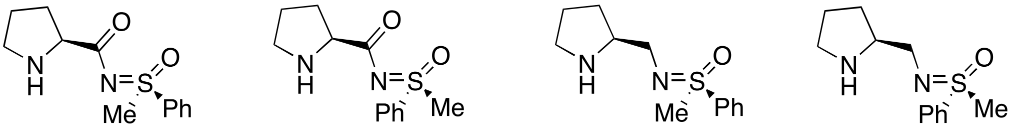
The synthesis of compound **241** was rather straightforward, and it is illustrated in Scheme 86.

Scheme 86. Synthesis of sulfoximines **242** and **241**



242 **241**

DCC/HOBt coupling with *N*-Boc protected proline and NH-free sulfoximine led to the resulting coupling product **242** in 90% yield.[9f,g] Although the DCC coupling proceeded well in terms of the reaction yield, the purification of proline-sulfoximine **242** was extremely problematic due to the presence of the DCC urea. In order to avoid the forming of this byproduct, EDC which yields a water-soluble urea as a byproduct, was used as coupling reagent. In this case, however, only 15% of product **242** was obtained. For a more efficient synthesis of compound **242**, further optimization in this coupling step is required. Finally, the pyrrolidine-sulfoximine **241** was synthesized in good yield from the reduction with BH_3-SMe_2 complex followed by the removal of Boc-group using TFA:CH_2Cl_2 (3:1). According to this reaction scheme, compounds **242** and **241** were prepared each from L-proline and (*S*) or (*R*)-sulfoximine (Figure 23).

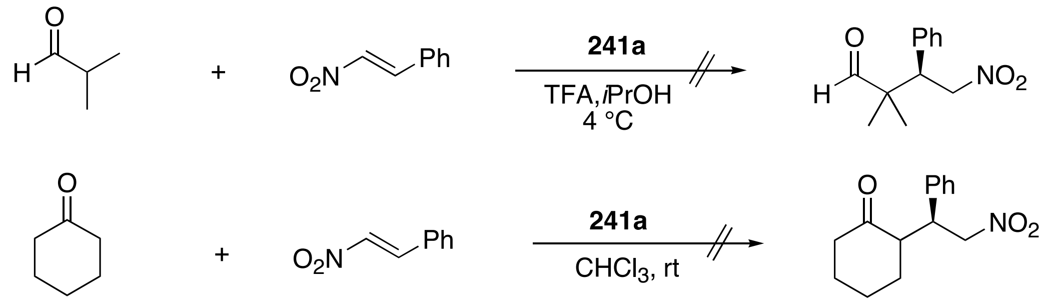


242a **242b** **241a** **241b**

Figure 23.

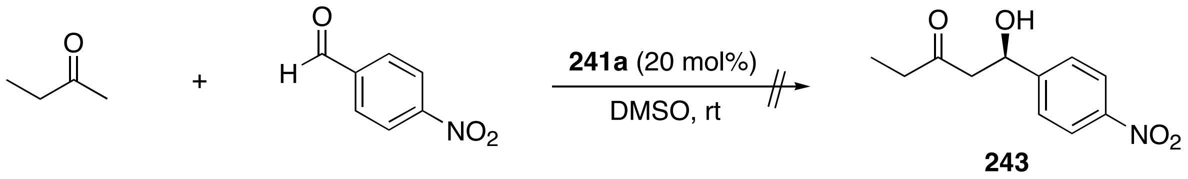
As test reaction for the use of pyrrolidine-sulfoximine **241** as an organocatalyst, the Michael addition reaction of an α,α-disubstitutied aldehyde with β-nitrostyrene[176b] was performed first, but unfortunately no conversion was observed even in the presence of TFA as an acid additive and isopropanol as a solvent (Scheme 87). Cyclohexanone instead of the aldehyde was also examined as starting material for the reaction with β-nitrostyrene. However, also in this case no reaction occurred under the described condition in Scheme 87.

Scheme 87.



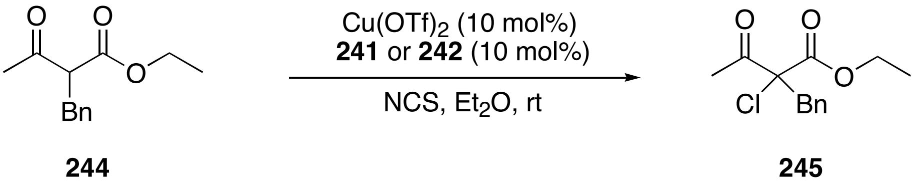
In addition to this, an asymmetric aldol reaction[175i] was attempted with compound **241a** as organocatalyst (Scheme 88). The reaction of 2-butanone and *p*-nitrobenzaldehyde in the presence of L-proline was reported to afford the corresponding product **243** in 77% ee and 65% yield in DMSO. Unfortunately, no conversion was observed when compound **241a** was applied as a catalyst instead of L-proline.

Scheme 88.



With the intention of testing the applicability of compounds **241** and **242** as chiral ligands in metal complex, asymmetric halogenations of β-ketoesters were performed (Scheme 89).

Scheme 89. Asymmetric chlorination of 2-benzyl-3-oxobutyric acid ethylester (**244**)



with **241a**: 23% ee
241b: *rac*
242c: *rac*
242d: *rac*

Under the same reaction condition as reproted by Jørgensen,[182] in which copper(II) triflate and NCS as a chloride source were employed in Et_2O at room temperature, 2-benzyl-3-

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[182] Marigo, M.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Eur. J.* **2004**, *10*, 2133.

oxobutyric acid ethylester (**244**) was converted into the corresponding α-chlorinated product **245** in the presence of compound **241** or **242**. Almost complete conversion was observed in most cases. However, only a low enantioselectiviy was achieved in the formation of **245** (23% ee) using compound **241a** as a ligand. Complexes of $Cu(OTf)_2$ and compounds **241b** to **242b** afforded only racemic product.

Although these trials showed unsatisfying results, a number of different reaction conditions should be examined in these transformation. In addition, use of compounds **241** should be tested in other several asymmetric catalyses such as Mannich and Diels-Alder reactions can be tested with compound **241**. Since pyrrolidine-sulfoximine **241** and its derivatives can be synthesized in a short reaction sequence and high yield and they have the structual similarity with exsiting organocatalysts, the investigations in this field should be continued and promising results are expected.

7-4. Asymmetric chlorination by using sulfoximines as chiral ligands[§]

Asymmetric halogenation[179,183] is a powerful tool to prepare chiral building blocks for organic synthesis, and optically active halogen containing compounds are important as synthetic intermediates in biomedical and pharmaceutical sciences. In spite of this fact highly enantioselective carbon-halogen (F, Br, and Cl) bond formation reactions were rarely reported. Over the last a few years, however, significant progress has been accomplished in asymmetric α-halogenation. Since the first catalytic and asymmetric chiral Lewis acid-catalyzed α-fluorination of β-keto esters was reported by Togni in 2000,[184] a variety of asymmetric methodologies have been explored. In the catalytic enantioselective halogenations, a chiral BINAP-palladium complex[185] and bisoxazoline-copper complexes[182,186,187] were applied as catalysts by Sodeoka, Cahard and Jørgensen. The quaternary ammonium salt from cinchonine was introduced as a chiral phase-transfer catalyst in the α-fluorination by Kim,[188] while Lectka[189] and Bartoli[190] employed

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[§] This work performed in the collaboration with Monica Carril Garcia at University of the Basque Country in Spain.

[183] For the recent review: (a) Oestreich, M. *Angew. Chem.* **2005**, *117*, 2376. (b) France, S.; Weatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* **2005**, 475. (c) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147.

[184] (a) Hintermann, L.; Togni, A. *Angew. Chem.* **2000**, *112*, 4530. Asymmetric fluorination review: (b) Ma, J. A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119.

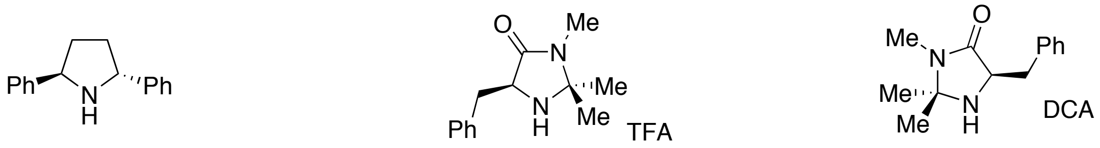
[185] Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem.* **2002**, *124*, 14530.

[186] Bernardi, L.; Jørgensen, K. A. *Chem. Commun.* **2005**, 1324.

[187] Ma, J. A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007.

[188] Kim, D. A.; Park, E. J. *Org. Lett.* **2002**, *4*, 545.

benzoylquinine (BQ) as a catalyst for the α-halogenation (Cl and Br) of acyl chloride and 1,3-dicarbonyl compounds, respectively. Furthermore, several highly efficient organocatalytic approaches[164] have been investigated in this field and usually proline-derivatives were utilized as organocatalysts (Figure 24).



246a
Jørgensen
Asymmetric α-chlorination of aldehydes
up to 97% ee

246b
MacMillan
Asymmetric α-chlorination of aldehydes
up to 95% ee

246c
MacMillan
Asymmetric α-fluorination of aldehydes
up to 99% ee

Figure 24. Organocatalysts in asymmetric halogenation

In recent years, our group proved that sulfoximines can be successfully applied as a chiral ligand in various asymmetric catalyses such as Diels-Alder, Mukaiyama aldol reactions, asymmetric hydrogenation and so forth. Since bisoxazoline-copper complexes afforded mild to good enantioselectivities and the structual similarity between bisoxazolines and sulfoximines such as **139** (Scheme 50) was considered, we wondered about the applicability of sulfoximines as ligands in asymmetric halogenations. For a test reaction the copper-catalyzed asymmetric chlorination of β-ketoesters was conducted. 2-Benzyl-3-oxobutyric acid ethylester (**244**) as a starting material was attempted to convert into the corresponding α-chloronated product **245** using *N*-chlorosuccinimide (NCS) as a chloride source in the presence of $Cu(OTf)_2$ and sulfoximines in ether.[182] Several sulfoximines were examined and the results are summarized in Scheme 90.[$] Nearly complete conversion was observed in most reactions[191] and the best enantioselectivity was obtained with compound **252** which afforded **245** with 30% ee. Compound **139**, which has a similar structure to a Box ligand afforded **245** with 25% ee, whereas pyBox analogue sulfoximine **257** gave only racemic product. In the case of the reaction with compound **257**, changing solvent from ether to dichloromethane, in order to increase the solubility of the copper-

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[189] (a) France, S.; Wack, H.; Taggi, A. E.; Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, *126*, 4245. (b) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531.

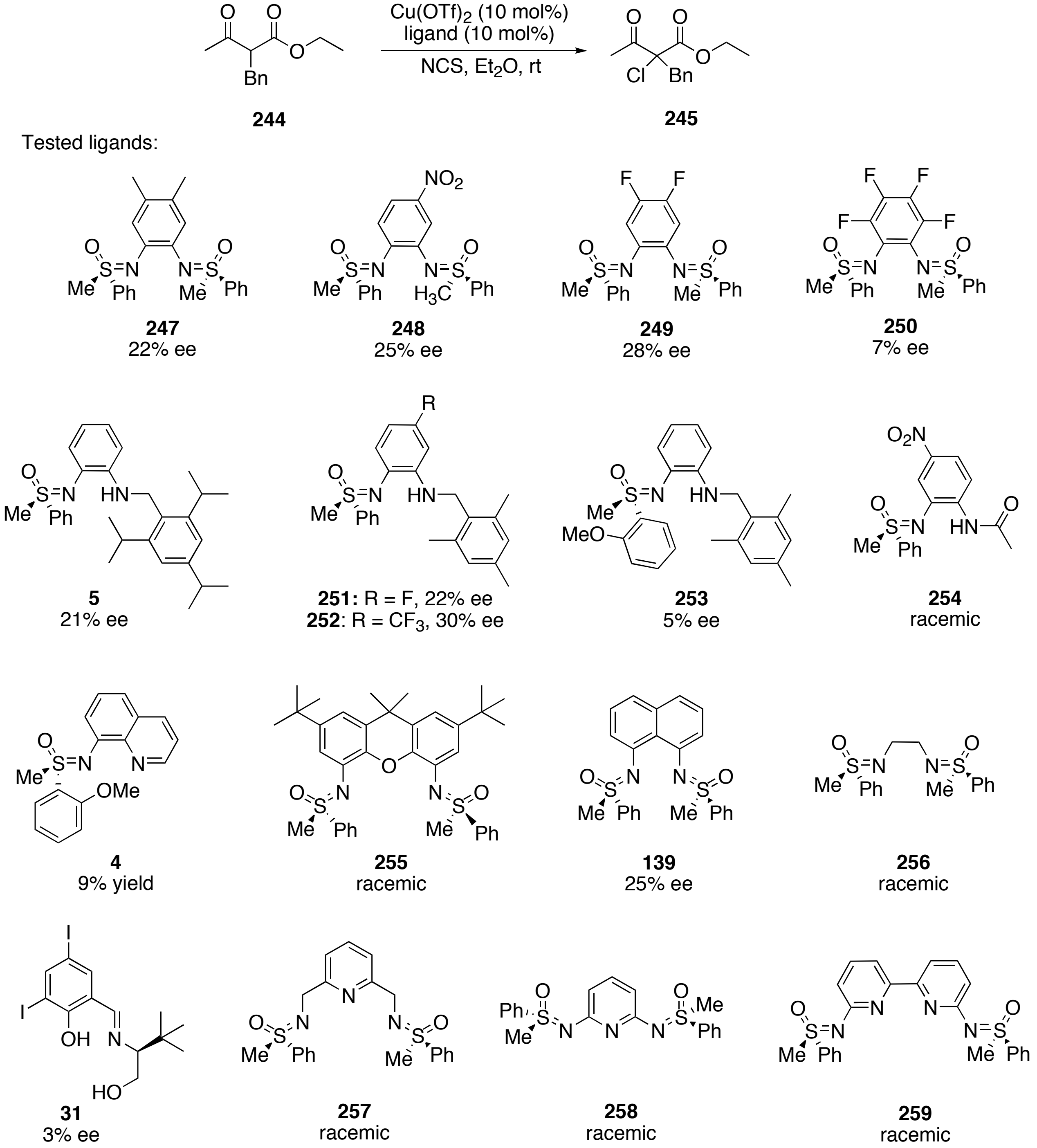
[190] Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem.* **2005**, *117*, 6375.

[$] Comounds **5, 247, 248, 249, 250, 251, 252, 253, 254, 255, 139** (Scheme 90) were synthesized by Pauline Remy at RWTH Aachen University.

[191] The complete conversion with $Cu(OTf)_2$ was observed without ligand.

sulfoximine complex, slightly improved the enantioselectivity (from 0% to 10% ee). Obviously, the compounds which are not expected to have appropriate bite angle with metal such as **255** and **258** led to poor results.

Scheme 90.



244

245

Tested ligands:

247
22% ee

248
25% ee

249
28% ee

250
7% ee

5
21% ee

251: R = F, 22% ee
252: R = CF_3, 30% ee

253
5% ee

254
racemic

4
9% yield

255
racemic

139
25% ee

256
racemic

31
3% ee

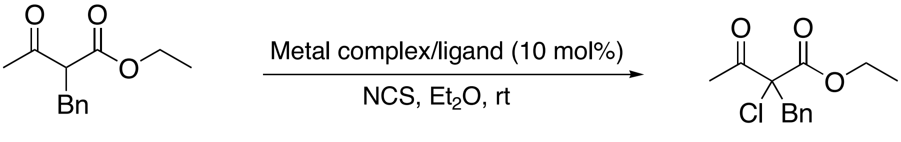
257
racemic

258
racemic

259
racemic

Futhermore, we tested other metal complexes instead of $Cu(OTf)_2$ in the presence of compound **139**, **257** or **31** as a ligand and the results are summarized in Table 13. In most cases no complete conversion was observed. Most reactions proved to be inferior to Cu-catalyzed halogenation. However, interesting result was obtained from the reaction using iron as a catalyst. The combination of Fe(acac)$_3$ and ligand **31**, which was reported as an efficient catalyst in asymmetric oxidation of sulfides by Bolm et al.,[45,46] gave the α-chlorinated product **245** in 36% ee (entry 6). Fe(OAc)$_2$ was much less efficient than Fe(acac)$_3$ with ligand **31** (entry 5 and 6).

Table 13. Metal-catalyzed asymmetric chlorination with sulfoximine ligands



244 **245**

entry	metal complex	ligand	ee
1	$Ni(ClO_4)_2 6H_2O$	**139**	7%
2	$Ni(acac)_2$	**139**	7%
3	$AgNO_3$	**257**	17%
4	$Zn(NO_3)_2 6H_2O$	**139**	7%
5	$Fe(OAc)_2$	**31**	10%
6	$Fe(acac)_3$	**31**	36%
7	$MgCl_2$	**139**	7%

In fact, the results described in Scheme 90 and Table 13 were poorer than the ones reported for catalyses with Box-copper catalysts (61% ee). Taking into accout the non-optimized results, however, a successful application of sulfoximines as new ligands in asymmetric halogenations with copper or the other metal complexes is expected after further investigation. Since the countanion of metal catalyst also influences the enantioselectivity and reactivity in this transformation, it will be essential to screen appropriate metal complexes. Even more interestingly, to our best knowledge, iron catalysts have not been reported in this field. Further optimization (changing solvent, temperature, adding additives, and screening with Schiff-base ligand **31** derivatives) is strongly expected to improve both enantioselectivities and reaction yields.

7-5. Three-component coupling reaction of aldehydes, amines and alkynes in water[§]

As mentioned in section 6-1-introduction, very recently Li and coworkers reported the first silver-catalyzed three component coupling of aldehydes, amine and alkynes in water.[135] This reaction condition caught our attention and made us wonder about the design of chiral ligands for silver. Furthermore, interesting reactivities in reactions *on water* were observed even though the effect of water is still unclear and under discussion.[192] During the study of the silver-catalyzed imination reaction of sulfides and sulfoxides (section 6), we discovered that the complex from silver nitrate and dipyridylamine **181** could catalyze the imination reaction. In order to extend the utility of this complex, we intended to test it as a catalyst in a three-component coupling reaction. Since chiral dipyridylamine derivatives such as **260, 261** and **262** (Figure 25) have been already reported,[193] those compounds were also applied as chiral ligands for silver salts.

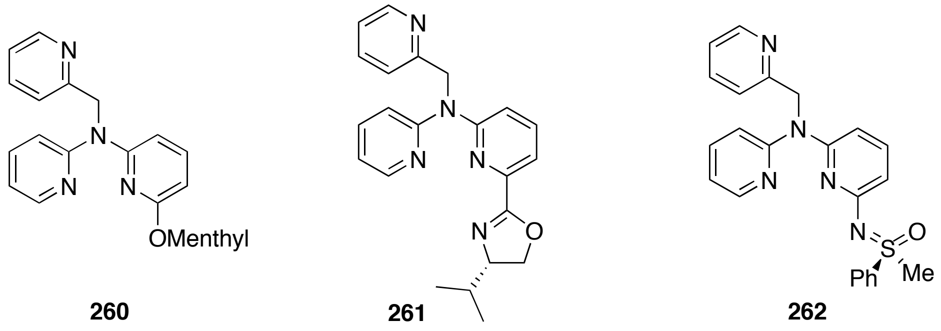


Figure 25.

First, in order to check their activities, the silver complex isolated from the mixture of $AgNO_3$ and compound **181** was employed as a catalyst in the coupling reaction of cyclohexancarboxaldehyde, pyrrolidine and phenyl acetylene in water (Scheme 90). As a result, the corresponding product **263** was obtained in 66% yield.

However, to our surprise, we found that on water this coupling reaction proceeded well even without any catalyst. Mixing cyclohexancarboxaldehyde, pyrrolidine and phenyl

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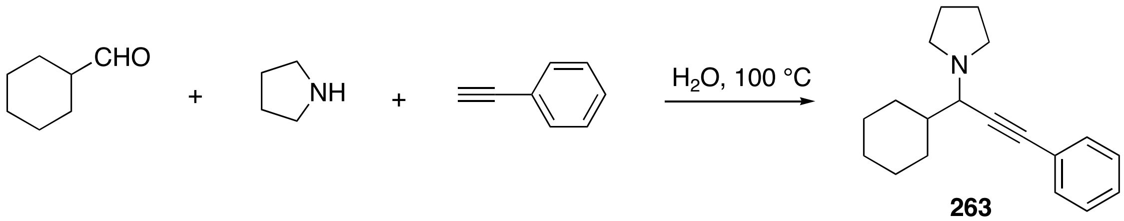
[§] This work performed in the collaboration with Monica Carril Garcia at University of the Basque Country in Spain.

[192] (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem.* **2005**, *117*, 3339. For the review, see: (b) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095.

[193] (a) Bolm, C.; Frison, J. C.; Le Paih, J.; Moessner, C. *Tetrahedron Lett.* **2004**, *45*, 5019. (b) Bolm, C.; Frison, J. C.; Le Paih, J.; Moessner, C.; Raabe, G. *J. Organomet. Chem.* **2004**, *689*, 3767.

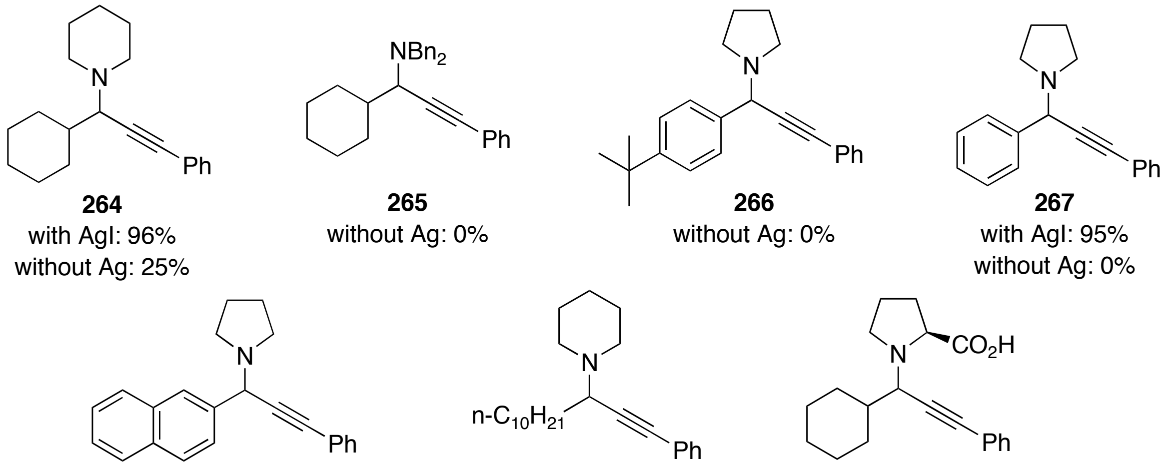
acetylene on water under air and heating the reaction mixture to reflux for 3 h afforded the corresponding product **263** in 60% yield (Scheme 90).

Scheme 90.



263
60% yield

In order to survey the substrate scope, several aldehydes and secondary amines were tested with phenyl acetylene in this transformation (Figure 26).



264
with AgI: 96%
without Ag: 25%

265
without Ag: 0%

266
without Ag: 0%

267
with AgI: 95%
without Ag: 0%

268
without Ag: 0%

269
with AgI: 79%
without Ag: 3%

270
without Ag: 0%

Figure 26.

As a result of this screening, only compound **264** could be obtained in 25% yield from the reaction of cyclohexancarboxaldehyde, piperidine and phenyl acetylene. Almost no conversion was observed from the other reactions using aromatic and aliphatic aldehydes, dibenzylamine and L-proline. Under consideration of trimerization of aldehydes which is often observed in gold- or copper-catalyzed three-component reactions, the aldehyde was added slowly, but this procedure did not give any effect on the reaction yield. In addition to this, the coupling reaction of cyclohexancarboxaldehyde, pyrrolidine and phenylacetylene on water was performed under microwave. However, only low reaction yields were achieved in reactions with microwave irradiation at 100 and 200W for 20 min (6% and 12% yield, respectively).

It is still not clear how this reaction occurred without any catalyst or base on water due to the low p*Ka* value of phenylacetylene. Since this reaction is strictly limited only to the combination of cyclohexancarboxaldehyde, pyrrolidine and phenylacetylene at the present time, further studies in order to understand the mechanism and extend the substrate scope are essentially required.

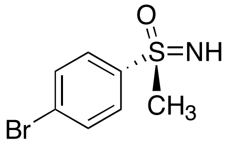
8. Experimental Section

8-1. General Information

The NMR spectra were recorded in $CDCl_3$ or in acetone-D_6 on a Varian Mercury 300 (^1H NMR at 300 MHz; ^{13}C NMR at 75 MHz) or a Varian Inova 400 (^1H NMR at 400 MHz; ^{13}C NMR at 100 MHz) spectrometer using TMS or residual solvent peaks (at 7.26 ppm for ^1H NMR or 77 ppm for ^{13}C NMR) as internal standard. Chemical shifts are given in ppm and spin-spin coupling constants, *J*, are given in Hz. Mass spectra were recorded on a Varian MAT 212 (EI and CI) and a Finnigan Mat 95 (SIMS-FAB) spectrometer. IR spectra were recorded on a Perkin-Elmer PE 1760FT PE 1760S spectrometer as KBr discs, in capillaries or in $CHCl_3$. DMSO was degassed against a positive argon flow without distillation or drying. Melting points were recorded on a Büchi B-540 melting point apparatus. Elemental analyses were recorded in the microanalytic laboratory at the Institute of Organic Chemistry, RWTH Aachen University, using a CHNO-Rapid machine from the company Heraeus. The optical rotations were determined using a Perkin-Elmer PE-241 Polarimeter. The enantioselectivities were determined by chiral HPLC, using a program from the company Gynkothek (GINA 50 Autosampler, a UVD170S UV/Vis-detector, a M480G pump and DG503 degassing apparatus). Unless otherwise noted all reactions were performed under argon using standard Schlenk and vacuum line techniques.

8-2. Palladium-catalyzed cross coupling of *p*-bromophenylmethyl sulfoximine

8-2-1. The synthesis of (*S*)-*p*-bromophenyl methyl sulfoximine (66)



(*S*)-**66**

O-(Mesitylsulfonyl)acetohydroxamate (24.00 g, 84.2 mmol)[194] was dissolved in dioxane (41 mL). The reaction mixture was cooled to 0 °C and perchloric acid (70% aq., 41 mL) was slowly added to the mixture under vigorous stirring. After 10 min ice water (200 mL)

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[194] Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239.

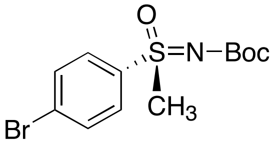
and dichloromethane were added sequentially, and the organic phase was separated. (*S*)-*p*-Bromophenyl methyl sulfoxide (**68**, 6.24 g, 28.5 mmol)[53] was added to the organic phase at room temperature. After 2 d the reaction mixture was poured into a cold aqueous solution of NaOH (10%, 200 mL), stirred for 10 min, and extracted with dichloromethane. The combined extracts were washed with HCl (10%). Sulfoximine **66** was isolated by neutralizing the acidic aqueous layer with Na_2CO_3 (solid) and extracting it with dichloromethane. After concentration in vacuo (using a rotary evaporation), (*S*)-*p*-bromophenyl methylsulfoximine [(*S*)-**66**] was obtained in 86% yield (5.73 g) as a solid with ≥99% ee. Mp. 105-106 °C; $[\alpha]_D$ –13.0 (*c* 1.07, MeOH); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83-7.79 (m, 2H), 7.63-7.60 (m, 2H), 3.04 (s, 3H), 2.74 (s, br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.5, 132.3, 129.2, 128.0, 46.0; IR (neat, cm^{-1}) 3304, 3081, 1915, 1219; MS (EI, *m/z*) 233 (M^+); Anal. Calcd for C_7H_8BrNOS: C, 35.91; H, 3.44; N, 5.98. Found: C, 35.56; H, 3.54; N, 5.90. The enantiomer ratio was determined by HPLC using a chiral column (250 x 4.6 mm Chiralcel OJ column, 0.5 mL/min, 85:15 heptane/2-propanol); t_R = 44 min (*S*) and t_R = 71 min (*R*).

8-2-2. The preparation of *racemic* *p*-bromophenyl methyl sulfoximine (*rac*-66)

To a solution of *p*-bromophenylthioanisole (16.90 g, 83.3 mmol) and acetic acid (20 mL), aqueous H_2O_2 (35%, 124.0 mmol) was slowly added at –5 °C. The reaction mixture was then warmed to room temperature and stirred overnight. An aqueous solution of NaOH (12 N, 30 mL) was added at 0 °C and the resulting mixture was extracted with dichloromethane several times. The combined organic layers were dried ($MgSO_4$) and concentrated affording pure *p*-bromophenyl methyl sulfoxide (15.90 g) as a white solid in 86% yield. In the subsequent imination reaction this product was used without further purification.

p-Bromophenyl methyl sulfoxide (10.80 g, 49.5 mmol) and sodium azide (3.50 g, 54.3 mmol) were dissolved in chloroform (55 mL). The mixture was cooled to 0 °C and concentrated sulfuric acid (23.00 g) was slowly added over 15 min. The reaction mixture was then warmed to room temperature and stirred overnight. Subsequently, ice water was added until the salts were dissolved completely. The aqueous layer was extracted with chloroform, neutralized with an aqueous solution of NaOH (16 N), and extracted with dichloromethane. Drying of the organic phase ($MgSO_4$) followed by its concentration in vacuo afforded *p*-bromophenyl methyl sulfoximine (**66**, 6.4 g) as a white solid in 56% yield.

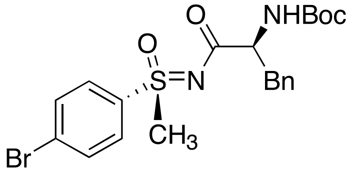
8-2-3. The synthesis of *N*-Boc-*p*-bromophenyl methyl sulfoximine [(*S*)-69]



(*S*)-**69**

To a solution of sulfoximine (*S*)-**66** (2.00 g, 8.6 mmol) in dry THF (25 mL) was added NaH (478.8 mg, 12 mmol, 60% in mineral oil) at room temperature under argon, followed by di-*tert*-butyl-dicarbonate (3.70 g, 17 mmol). The reaction mixture was then stirred at room temperature overnight and subsequently quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with dichloromethane several times, and the combined organic extracts were then dried ($MgSO_4$) and concentrated. Purification by column chromatography (SiO_2, 1:2 = hexane:ethyl acetate) gave (*S*)-**69** (2.10 g) as a white solid in 74% yield. Mp. 116-117 °C; $[\alpha]_D$ –76.8 (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86-7.81 (m, 2H), 7.76-7.72 (m, 2H), 3.23 (s, 3H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.4, 137.8, 132.9, 129.1, 128.9, 80.9, 44.6, 28.0; IR (neat, cm^{-1}) 3090, 2933, 1388, 1272; MS (CI, *m/z*) 334 (MH^+); Anal. Calcd for $C_{12}H_{16}BrNO_3S$: C, 43.12; H, 4.83; N, 4.19. Found: C, 42.96; H, 4.78; N, 4.00.

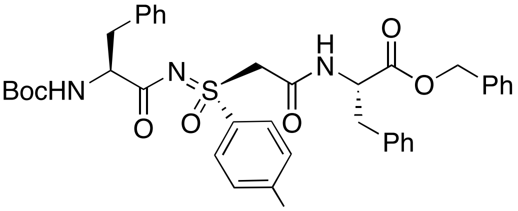
8-2-4. The synthesis of (*S*,*S*)-70



(*S,S*)-**70**

Boc-Phe-OH (1.60 g, 6 mmol) was dissolved in dichloromethane (50 mL), and after sequential addition of DCC (1.30 g, 6.3 mmol), HOBt (854.0 mg, 6.3 mmol) and (*S*)-*p*-bromophenyl methyl sulfoximine [(*S*)-**66**] at room temperature the reaction mixture was stirred overnight. After DCC urea was filtered out, the reaction mixture was concentrated and the product was purified by column chromatography (SiO_2, 3:2 = hexane: ethyl acetate) to give (*S*,*S*)-**70** (2.40 g) as a white solid in 96% yield. Mp. 163-165 °C; $[\alpha]_D$ –40.2 (*c* 1.03, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71-7.65 (m, 4H), 7.30-7.20 (m, 5H), 5.14 (d, 1H, *J* = 7.1 Hz), 4.60-4.55 (m, 1H) 3.31 (s, 3H), 3.23-3.08 (m, 2H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 155.3, 137.3, 137.1, 132.9, 129.7, 129.4, 128.7, 128.3, 126.6, 79.4, 57.4, 44.0, 38.5, 28.3; IR (neat, cm^{-1}) 2984, 1648, 1507, 1217; MS (CI, *m/z*) 481 (MH$^+$); HRMS of [M]$^+$ Calcd. 480.0719; found 480.0718.

8-2-5. The synthesis of (*S*,*S*,*S*)-71



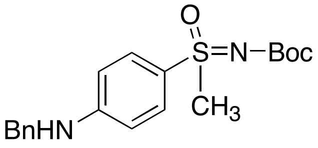
(*S,S,S*)-**71**

To a solution of cyclohexyl(isopropyl)amine (860.0 mL, 5.11 mmol) in THF (8 mL) at 0 °C under argon was added *n*-BuLi (15% in hexane, 3.16 mL, 5.11 mmol). The reaction mixture was stirred for 30 min at 0 °C and then cooled at –78 °C. A solution of (*S,S*)-**70** (811.0 mg, 1.69 mmol) and THF (4 mL) was added dropwise at this temperature. After stirring for 30 min at –78 °C, dried CO_2 was bubbled through the solution for 10 min. The cooling bath was removed and the gas flow reduced. After 10 min the gas flow stopped, and the reaction mixture was warmed to room temperature. Under vigorous stirring water was added. The organic phase was separated and the aqueous phase extracted once with diethyl ether. The organic phases were discarded and to the aqueous phase NH_4Cl (solid) was added until a precipitate formed. The suspension was extracted with dichloromethane several times, the dichloromethane phase dried ($MgSO_4$), and the solvent removed under reduced pressure at room temperature (without heating!). After drying (and without further purification) the resulting crude product was dissolved in dichloromethane (10 mL) at 0 °C, and DMAP (20.0 mg, 0.01 mmol) and H-Phe-OBn•HCl (493.0 mg, 1.69 mmol) and DCC (348.0 mg, 1.69 mmol) was added. The reaction mixture was slowly warmed to room temperature and stirred over night. After evaporating the solvent under reduced pressure, purification by column chromatography (SiO_2) gave (*S,S,S*)-**71** (258.0 mg) as colorless oil in 20% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.55 (m, 5H), 7.45-7.11 (m, 14H), 5.24-5.23 (m, 2H), 5.17-5.15 (m, 1H), 4.88-4.81 (m, 1H), 4.66-4.61 (m, 1H), 4.54 (d, *J* = 13.4 Hz, 1H), 4.30 (d, *J* = 13.6 Hz, 1H), 3.29-3.24 (m, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.8, 170.6, 159.5, 155.6, 136.8, 135.6, 134.4, 132.6, 130.1, 129.8, 129.4, 129.1, 128.6, 128.5, 128.4, 128.3, 127.1, 126.6, 79.5, 67.3, 60.5, 57.7, 54.1, 37.7, 37.3, 28.2; IR (neat, cm^{-1}) 3370, 3321, 1741, 1650, 1525, 1247.; MS (FAB, *m/z*) 764 (MH$^+$).

8-2-6. General Procedure (GP 1) for the Palladium-Catalyzed Amination of *rac*-69 and (*S,S*)-70

A solution of (*S,S*)-**70** (96.0 mg, 0.2 mmol) or *rac*-**65** (100.0 mg, 0.3 mmol), amine (1.2 equiv), potassium carbonate or cesium carbonate (1.4 equiv), tris(dibenzylideneacetone)dipalladium (0) or palladium acetate (II) (2 mol%) and *rac*-BINAP (1.5 equiv/Pd) in toluene (0.2 M) was heated to reflux under argon until the starting material completely disappeared (TLC analysis). After cooling to room temperature, aq. HCl (1 N, ca. 20 mL) and ethyl acetate (ca. 30 mL) were added, and the organic phase was separated, dried ($MgSO_4$), and concentrated. The product was purified by column chromatography (SiO_2).

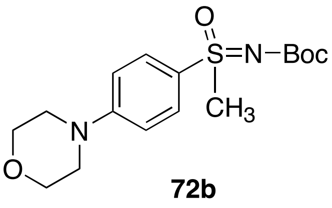
8-2-6-1. The synthesis of *rac*-72a



72a

Following GP 1 using *rac*-**69**, benzylamine, Cs_2CO_3, *rac*-BINAP and $Pd_2(dba)_3$ gave 101.0 mg (94%) of *rac*-**72a** as a white solid. Mp. 162-163 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 8.8 Hz, 2H), 7.38-7.28 (m, 5H), 6.67 (d, J = 8.8 Hz, 2H), 4.39 (s, 2H), 3.19 (s, 3H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.8, 152.0, 137.6, 129.3, 128.8, 128.6, 124.2, 112.1, 79.9, 47.4, 45.3, 28.0; IR (neat, cm^{-1}) 3303, 2963, 1669, 1261; MS (EI, *m/z*) 360 (M^+); Anal. Calcd for $C_{19}H_{24}N_2O_3S$: C, 63.31; H, 6.71; N, 7.77. Found: C, 63.23; H, 6.57; N, 7.66.

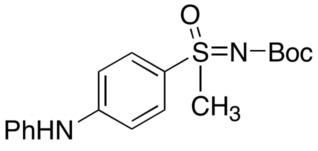
8-2-6-2. The synthesis of *rac*-72b



72b

Following GP 1 using *rac*-**69**, morpholine, Cs_2CO_3, *rac*-BINAP and $Pd(OAc)_2$ gave 80.4 mg (79%) of *rac*-**72b** as a white solid. Mp. 187 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.82-7.77 (m, 2H), 6.96-6.93 (m, 4H), 3.86-3.83 (m, 4H), 3.32-3.29 (m, 4H), 3.20 (s, 3H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.9, 154.4, 129.0, 126.3, 114.0, 80.1, 66.4, 47.3, 45.2, 28.0; IR (neat, cm^{-1}) 3447, 2966, 1656, 1287; MS (EI, *m/z*) 340 (M^+); Anal. Calcd for $C_{16}H_{24}N_2O_4S$: C, 56.45; H, 7.11; N, 8.23. Found: C, 56.83; H, 7.28; N, 8.14.

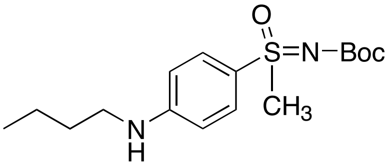
8-2-6-3. The synthesis of *rac*-72c



72c

Following GP 1 using *rac*-**69**, aniline, Cs_2CO_3, *rac*-BINAP and $Pd_2(dba)_3$ gave 99.1 mg (96%) of *rac*-**72c** as a white solid. Mp. 182 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, *J* = 9.1 Hz, 2H), 7.71-7.32 (m, 2H), 7.19-7.16 (m, 2H), 7.12-7.08 (m, 1H), 7.01 (d, *J* = 9.1 Hz, 2H), 3.20 (s, 3H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.9, 149.1, 140.0, 129.5, 129.2, 126.5, 123.8, 121.2, 114.8, 80.3, 45.4, 28.2; IR (neat, cm^{-1}) 3324, 1587, 1499, 1287; MS (EI, *m/z*) 346 (M^+); HRMS of $[M]^+$: Calcd. 346.1351; found 346.1351.

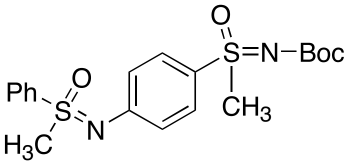
8-2-6-4. The synthesis of *rac*-72d



72d

Following GP 1 using *rac*-**69**, *n*-butylamine, Cs_2CO_3, *rac*-BINAP and $Pd_2(dba)_3$ gave 79.2 mg (81%) of *rac*-**72d** as a white solid. Mp. 99-100 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, *J* = 9.1 Hz, 2H), 6.59 (d, *J* = 8.8 Hz, 2H), 4.41 (s, br, 1H), 3.18 (s, 3H), 3.16-3.12 (m, 2H), 1.64-1.55 (m, 2H), 1.46-1.37 (m, 2H), 1.40 (s, 9H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.8, 152.4, 129.1, 123.3, 111.8, 79.9, 45.5, 43.0, 31.2, 28.1, 20.2, 13.8; IR (neat, cm^{-1}) 3333, 2955, 1676, 1281; MS (EI, *m/z*) 326 (M^+); HRMS of $[M]^+$: Calcd. 326.1664; found 326.1665.

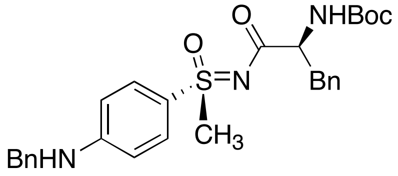
8-2-6-5. The synthesis of 72e



72e

Following GP 1 using *rac*-**69**, *rac*-*S*-methyl-*S*-phenyl sulfoximine (*rac*-**65**), Cs_2CO_3, *rac*-BINAP and $Pd(OAc)_2$ gave 87.6 mg (72%) of **72e** as a white solid and as a mixture of diastereomers. Mp. 156-158 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95-7.92 (m, 2H), 7.69-7.52 (m, 5H), 7.12-7.07 (m, 2H), 3.30/3.29 (s, 3H), 3.18/3.17 (s, 3H), 1.34/1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.6, 151.2, 138.3, 129.8, 128.6, 128.4, 123.2, 80.2, 46.5, 45.0/44.9, 28 (signal pairs of diastereomers are indicated by /; one C_{aryl} signal could not be assigned); IR (neat, cm^{-1}) 3443, 2926, 1684, 1275; MS (EI, *m/z*) 408 (M^+); HRMS of $[M]^+$: Calcd. 408.1178; found 408.117.

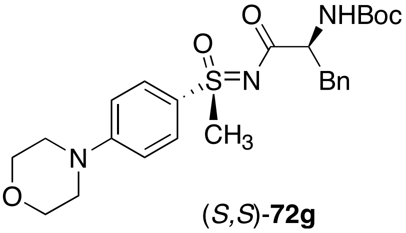
8-2-6-6. The synthesis of (*S,S*)-72f



(*S,S*)-**72f**

Following GP 1 using (*S,S*)-**70**, benzylamine, K_2CO_3, *rac*-BINAP and $Pd_2(dba)_3$ gave 89.2 mg (88%) of (*S,S*)-**72f** as a colorless oil (and as a single isomer): $[\alpha]_D$ –32.4 (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, 2H, *J* = 8.8 Hz), 7.38-7.15 (m, 10H), 6.62 (d, 2H, *J* = 8.8 Hz), 5.20 (d, 1H, *J* = 8.0 Hz), 5.02 (s, br, 1H), 4.55 (dd, *J* = 5.8, 13.2 Hz, 1H), 4.38 (s, br, 2H), 3.27 (s, 3H), 3.24-3.07 (m, 2H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.7, 155.2, 152.4, 137.6, 137.2, 129.7, 129.1, 128.8, 128.1, 127.7, 127.2, 126.4, 123.8, 112.2, 79.1, 57.4, 47.4, 44.5, 38.7, 28.3; IR (neat, cm^{-1}) 3376, 2978, 1706, 1596; MS (CI, *m/z*) 508 (MH^+); Anal. Calcd for $C_{28}H_{33}N_3O_4S$: C, 66.25; H, 6.55; N, 8.28. Found: C, 66.03; H, 6.59; N, 8.22.

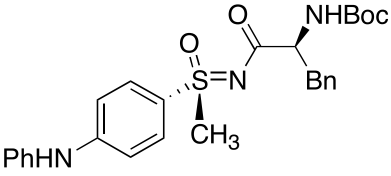
8-2-6-7. The synthesis of 72g.



(*S,S*)-**72g**

Following GP 1 using (*S,S*)-**70**, morpholine, Cs_2CO_3, *rac*-BINAP and $Pd(OAc)_2$ gave 89.3 mg (92%) of **72g** as a colorless oil and as a mixture of diastereomers: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70-7.64 (m, 2H), 7.29-7.18 (m, 5H), 6.94-6.89 (m, 2H), 5.25-5.17 (m, 1H), 4.58-4.56 (m, 1H), 3.87-3.83 (m, 4H), 3.33-3.29 (m, 4H), 3.24-3.07 (m, 5H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.8/179.7, 155.2, 154.4, 137.4/137.3, 129.7/129.6, 128.9, 128.1, 126.4, 126.1, 114.0, 79.1, 66.3, 57.5, 47.4, 44.4, 39.1/38.7 28.4 (signal pairs of diastereomers are indicated by /); IR (neat, cm^{-1}) 3424, 2974, 1707, 1363; MS (CI, *m/z*) 488 (MH^+); HRMS of $[M-C_4H_9O]^+$: Calcd. 414.1529; found 414.1529.

8-2-6-8. The synthesis of (*S,S*)-72h

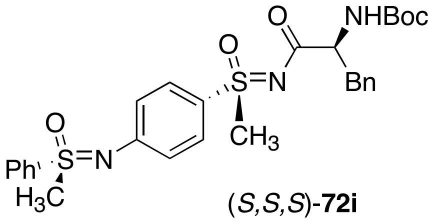


(*S,S*)-**72h**

Following GP 1 using (*S,S*)-**70**, aniline, K_2CO_3, *rac*-BINAP and $Pd_2(dba)_3$ gave 94.6 mg (92%) of (*S,S*)-**72h** as a yellow oil and as a single isomer: $[\alpha]_D$ –36.3 (*c* 0.91, MeOH); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, *J* = 8.7 Hz, 2H), 7.43-7.38 (m, 2H), 7.37-7.14 (m, 8H), 7.03 (d, *J* = 8.9 Hz, 2H), 6.54 (s, br, 1H), 5.23 (d, *J* = 7.9 Hz, 1H), 4.62-4.60 (m, 1H), 3.54 (s, 3H), 3.30-3.11(m, 2H), 1.45(s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 155.3, 149.5, 139.9, 137.2, 129.7, 129.6, 129.1, 128.2, 126.5, 126.1, 124.1, 121.5, 114.7, 79.2, 57.5, 44.6, 38.7, 28.3; IR (neat, cm^{-1}) 3335, 2928, 1882, 1584; MS (CI, *m/z*) 494 (MH^+); Anal. Calcd for $C_{27}H_{31}N_3O_4S$: C, 65.70; H, 6.33; N, 8.51. Found: C, 65.74; H,6.63; N, 8.27.

^1H and ^{13}C NMR data of compound (*S*,*R*)-**72h**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60-7.57 (m, 2H), 7.38-7.09 (m, 8H), 7.00-6.95 (m, 2H), 6.57 (s, br, 1H), 5.22 (d, *J* = 7.4 Hz, 1H), 4.61-4.54 (m, 1H), 3.23-3.17 (m, 5H), 1.40(s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 155.2, 149.5, 139.9, 137.3, 129.6, 129.6, 129.1, 128.2, 126.5, 125.9, 124.0, 121.4, 114.7, 79.2, 57.5, 44.6, 39.0, 28.3.

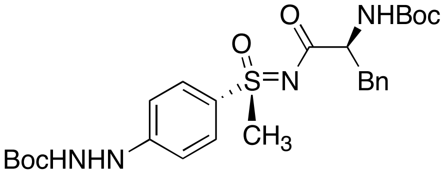
8-2-6-9. The synthesis of (*S,S,S*)-72i



(*S,S,S*)-**72i**

Following GP 1 using (*S,S*)-**70**, (*S*)-*S*-methyl-*S*-phenyl sulfoximine [(*S*)-**65**], K_2CO_3, *rac*-BINAP and $Pd(OAc)_2$ gave 113.3 mg (99%) of (*S,S,S*)-**72i** as a white solid and as a single isomer. Mp. 70-72 °C; $[\alpha]_D$ 75.43 (*c* 1.19, MeOH); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.96-7.90 (m, 2H), 7.69-7.65 (m, 1H), 7.61-7.52 (m, 4H), 7.20-7.12 (m, 5H), 7.08-7.05 (m, 2H), 5.16 (d, *J* = 7.7 Hz, 1H), 4.55-4.51 (m, 1H), 3.29 (s, 3H), 3.26 (s, 3H), 3.19-3.05 (m, 2H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.7, 155.2, 151.2, 138.4, 137.2, 134.0, 130.0, 129.7, 129.4, 128.5, 128.4, 128.1, 126.4, 123.1, 79.2, 57.4, 46.5, 44.3, 38.7, 28.4; IR (neat, cm^{-1}) 3422, 2923, 1711, 1450; MS (CI, *m/z*) 556 (MH^+); Anal. Calcd for $C_{28}H_{33}N_3O_5S_2{\bullet}H_2O$: C, 58,62; H, 6,15; N, 7,32. Found: C, 58.67; H, 6.10; N, 6.92.

8-2-6-10. The synthesis of 72j



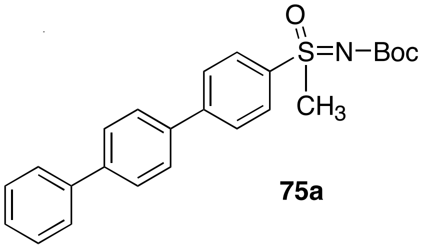
(*S,S*)-**72j**

Following GP 1 using (*S,S*)-**70**, *tert*-butyl carbazate, K_2CO_3, *rac*-BINAP and $Pd_2(dba)_3$ gave 77.5 mg (73%) of **72j** as a white solid and as a mixture of diastereomers (ca. 1:1). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86-7.82 (m, 2H), 7.75-7.70 (m, 2H), 7.30-7.21 (m, 5H), 5.22-5.16 (m, 1H), 4.58-4.57 (m, 1H), 3.33-3.10 (m, 5H), 1.57/1.56 (s, 9H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.8, 154.0, 148.1, 137.3, 137.1, 129.6, 129.5, 128.1, 127.4, 126.4, 122.0, 83.4, 79.2, 57.6/57.5, 44.2/44.2, 39.1/38.7, 28.4, 28.3 (signal pairs of diastereomers are indicated by /; in the aromatic region those pairs can not reliably be assigned); IR (neat, cm^{-1}) 3349, 2979, 1707, 1494; MS (CI, *m/z*) 533 (MH^+); HRMS of $[M]^+$: Calcd. 532.2356; found 532.2356.

8-2-7. General Procedure (GP 2) for Palladium-Catalyzed Suzuki Coupling of *rac*-69 and (*S*,*S*)-70

To a mixture of (*S*,*S*)-**70** (96.0 mg, 0.2 mmol) or *rac*-**69** (100.0 mg, 0.3 mmol) and $Pd(PPh_3)_4$ (2 mol%) in acetonitrile (3 mL) was added the aryl boronic acid (1.2 equiv), followed by K_2CO_3 (1.5 equiv) in H_2O (1 mL). The mixture was heated to reflux until the starting material was completely consumed (TLC analysis). After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and brine. The organic phase was separated, dried ($MgSO_4$) and concentrated. The product was purified by column chromatography (SiO_2).

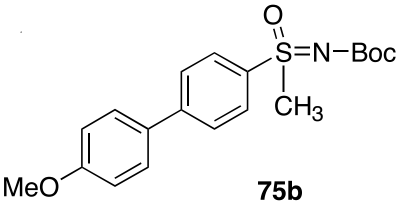
8-2-7-1. The synthesis of *rac*-75a



75a

Following GP 2 using *rac*-**69** and using 4-biphenylboronic acid gave 115.0 mg (95%) of *rac*-**75a** as a white solid. Mp. 196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07-8.03 (m, 2H), 7.86-7.82 (m, 2H), 7.74-7.62 (m, 6H), 7.51-7.45 (m, 2H), 7.44-7.36 (m, 1H), 3.29 (s, 3H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.7, 146.2, 141.6, 140.1, 137.7, 137.2, 128.9, 128.0, 127.9, 127.8, 127.7, 127.7, 127.0, 80.6, 44.8, 28.0; IR (neat, cm^{-1}) 3418, 2977, 1664, 1283; MS (EI, *m/z*) 407 (M^+); Anal. Calcd for $C_{24}H_{25}NO_3S$: C, 70.73; H, 6.18; N, 3.44. Found: C, 70.95; H, 6.29; N, 3.31.

8-2-7-2. The synthesis of *rac*-75b

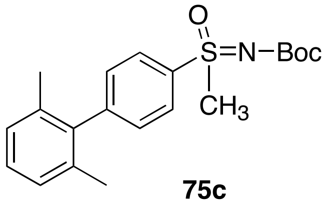


75b

Following GP 2 using *rac*-**69** and 4-methoxyphenylboronic acid gave 97.5 mg (90%) of *rac*-**75b** as a white solid. Mp. 135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01-7.98 (m, 2H), 7.76-7.73 (m, 2H), 7.58-7.54 (m, 2H), 7.02-6.99 (m, 2H), 3.87 (s, 3H), 3.26 (s, 3H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2, 157.7, 146.3, 136.3, 131.3, 128.5, 127.9, 127.6, 114.5, 80.6, 55.4, 44.9, 28.0; IR (neat, cm^{-1}) 3381, 2973, 1697, 1604; MS (CI, *m/z*) 362

(MH$^+$); Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 62.81; H, 6.53; N, 3.67.

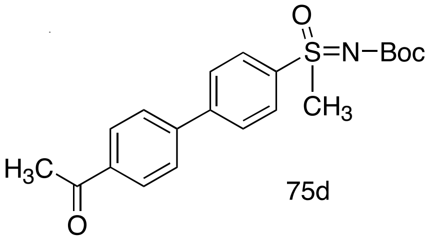
8-2-7-3. The synthesis of *rac*-75c.



75c

Following GP 2 using *rac*-**69** and 2,6-dimethylphenylboronic acid gave 99.7 mg (93%) of *rac*-**75c** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00-7.96 (m, 2H), 7.35-7.31 (m, 2H), 7.19-7.12 (m, 1H), 7.07-7.05 (m, 2H), 3.27 (s, 3H), 2.0 (s, 6H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.4, 147.3, 139.6, 137.2, 135.4, 130.4, 127.9, 127.6, 127.6, 80.6, 44.6, 28.0, 20.7; IR (neat, cm^{-1}) 3462, 2975, 1695, 1367; MS (CI, *m/z*) 360 (MH$^+$); Anal. Calcd for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.52; H, 7.15; N, 3.82.

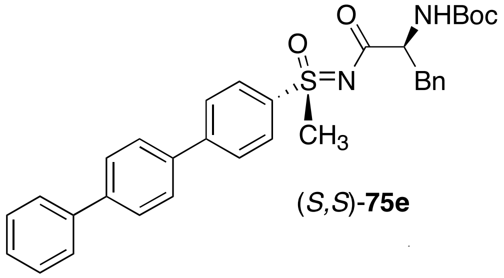
8-2-7-4. The synthesis of *rac*-75d



75d

Following GP 2 using *rac*-**69** and 4-acetylphenylboronic acid gave 107.7 mg (97%) of *rac*-**75d** as a solid. Mp. 135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09-8.06 (m, 4H), 7.84-7.81 (m, 2H), 7.72-7.70 (m, 2H), 3.28 (s, 3H), 2.66 (s, 3H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.4, 157.6, 145.2, 143.2, 138.1, 136.8, 129.0, 128.4, 128.0, 127.5, 80.6, 44.7, 27.9, 26.6; IR (neat, cm^{-1}) 3443, 2979, 1674, 1603; MS (CI, *m/z*) 374 (MH$^+$); Anal. Calcd for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.34; H, 6.33; N, 3.61.

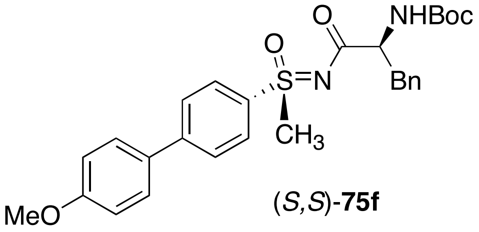
8-2-7-5. The synthesis of 75e.



(*S,S*)-**75e**

Following GP 2 using (*S*,*S*)-**70** and 4-biphenylboronic acid gave 89.5 mg (78%) of **75e** as a white solid and as a mixture of diastereomers (>10:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.73-7.71 (m, 2H), 7.67-7.56 (m, 6H), 7.42-7.38 (m, 2H), 7.34-7.29 (m, 1H), 7.23-7.13 (m, 5H), 5.12 (d, *J* = 7.7 Hz, 1H), 4.57-4.52 (m, 1H), 3.30/3.24 (s, 3H), 3.21-3.04 (m, 2H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 155.3, 146.5, 141.7, 140.1, 137.6, 137.2, 136.7, 129.7, 128.9, 128.2, 128.0, 127.8, 127.7, 127.0, 126.5, 79.3, 57.4, 44.1, 38.6, 28.3 (signal pairs of diastereomers are indicated by /; two C_{aryl} signals could not be assigned); IR (neat, cm^{-1}) 3375, 2928, 1648, 1501; MS (CI, *m/z*) 555 (MH$^+$); Anal. Calcd for $C_{33}H_{34}N_2O_4S$: C, 71.45; H, 6.18; N, 5.05. Found: C, 71.67; H, 6.18; N, 4.75.

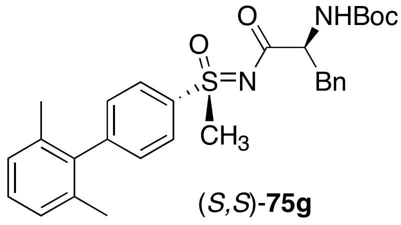
8-2-7-6. The synthesis of (*S,S*)-75f



(*S,S*)-**75f**

Following GP 2 using (*S*,*S*)-**70** and 4-methoxyphenylboronic acid gave 94.9 mg (90%) of (*S*,*S*)-**75f** as a white solid and as a single isomer. Mp. 124-125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.74-7.69 (m, 2H), 7.59-7.54 (m, 2H), 7.32-7.20 (m, 5H), 7.04-7.00 (m, 2H), 5.19 (d, *J* = 7.9 Hz, 1H), 4.65-4.59 (m, 1H), 3.88 (s, 3H), 3.37 (s, 3H), 3.28-3.10 (m, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 160.3, 155.3, 146.6, 137.2, 135.8, 131.2, 129.7, 128.5, 128.2, 127.7, 127.6, 126.5, 114.6, 79.3, 57.4, 55.4, 44.1, 38.1, 28.3; IR (neat, cm^{-1}) 3385, 2929, 1519, 1249; MS (CI, *m/z*) 509 (MH$^+$); HRMS of $[M-C_4H_9O]^+$: Calcd. 435.1379; found 435.1379.

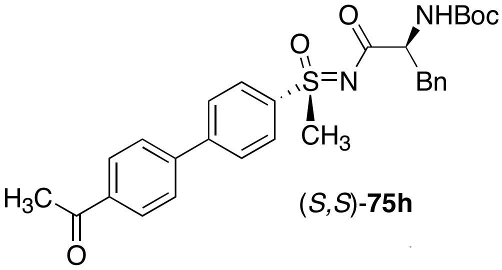
8-2-7-7. The synthesis of 75g



(*S*,*S*)-**75g**

Following GP 2 using (*S*,*S*)-**70** and 2,6-dimethylphenylboronic acid gave 76.1 mg (75%) of **75g** as a white solid and as a mixture of diastereomers (8:1). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.40-7.35 (m, 2H), 7.31-7.20 (m, 6H), 7.16-7.13 (m, 2H), 5.21 (d, *J* = 7.9 Hz, 1H), 4.68-4.61 (m, 1H), 3.44/3.37 (s, 3H), 3.30-3.13 (m, 2H), 2.02/2.01 (s, 6H), 1.43 (s, 9H) (signal pairs of diastereomers are indicated by /); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 179.9, 155.3, 147.6, 139.5, 137.2, 136.6, 135.4, 130.4, 129.7, 128.2, 128.0, 127.6, 127.4, 126.5, 79.3, 57.5, 44.1, 38.6, 28.3, 20.8; IR (neat, cm^{-1}) 3428, 2928, 1711, 1364; MS (CI, m/z) 507 (MH$^+$); HRMS of [M]$^+$: Calcd. 506.2239; found 506.2239.

8-2-7-8. The synthesis of 75h



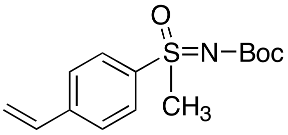
(*S*,*S*)-**75h**

Following GP 2 using (*S*,*S*)-**70** and 4-acetylphenylboronic acid gave 75.4 mg (70%) of **75h** as a white solid and as a mixture of diastereomers (>10:1). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.09-8.05 (m, 2H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.79-7.75 (m, 2H), 7.71-7.67 (m, 2H), 7.30-7.19 (m, 5H), 5.17 (d, *J* = 7.7 Hz, 1H), 4.63-4.56 (m, 1H), 3.36/3.30 (s, 3H) 3.26-3.08 (m, 2H), 2.64 (s, 3H), 1.41 (s, 9H) (signal pairs of diastereomers are indicated by /); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 197.4, 180.0, 155.3, 145.6, 143.3, 137.7, 137.1, 137.0, 129.7, 129.1, 128.4, 128.2, 127.9, 127.6, 126.6, 79.3, 57.4, 44.1, 38.6, 28.3, 26.7; IR (neat, cm^{-1}) 3378, 2925, 1685, 1516; MS (CI, *m/z*) 521 (MH$^+$); HRMS of [M-C$_4$H$_9$O]$^+$: Calcd. 447.1379; found 447.1379.

8-2-8. General Procedure (GP 3) for Palladium-Catalyzed Stille Coupling of *rac*-69 and (*S*,*S*)-70

Under argon (*S*,*S*)-**70** (96.0 mg, 0.2 mmol) or *rac*-**69** (100.0 mg, 0.3 mmol), $Pd_2(dba)_3$ (1 mol%) and *rac*-BINAP (2.2 mol%) were dissolved in toluene (2 mL). After adding the stannane (1.2 equiv), the mixture was heated to reflux until the starting material was completely consumed (TLC analysis). The solution was concentrated in vacuo, and the resulting product was isolated by column chromatography (SiO_2).

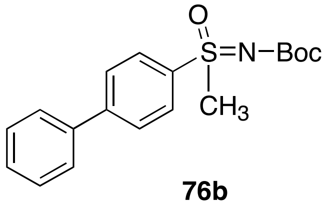
8-2-8-1. The synthesis of *rac*-76a



76a

Following GP 3 using *rac*-**69** and tributylvinyltin gave 82.3 mg (98%) of *rac*-**76a** as a white solid. Mp. 112-113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93-7.89 (m, 2H), 7.60-7.57 (m, 2H), 6.76 (dd, *J* = 11.0, 17.6 Hz, 1H), 5.55 (d, *J* = 17.6 Hz, 1H), 5.46 (d, 1H, *J* = 11.0 Hz), 3.22 (s, 3H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.4, 142.8, 137.0, 135.0, 127.7, 127.1, 118.1, 80.6, 44.8, 28.1; IR (neat, cm^{-1}) 3445, 2932, 1666, 1274; MS (CI, *m/z*) 282 (MH^+); HRMS of $[M-C_4H_9O]^+$: Calcd. 208.0432; found 208.0433.

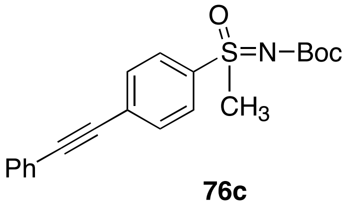
8-2-8-2. The synthesis of *rac*-76b



76b

Following GP 3 using *rac*-**69** and tributylphenyltin gave 95.0 mg (96%) of *rac*-**76b** as a white solid. Mp. 128-129 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05-8.02 (m, 2H), 7.81-7.78 (m, 2H), 7.63-7.60 (m, 2H), 7.52-7.42 (m, 3H), 3.28 (s, 3H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.4, 146.7, 138.9, 137.1, 129.0, 128.6, 128.2, 127.8, 127.3, 80.6, 44.9, 28.1; IR (neat, cm^{-1}) 2979, 1662, 1591, 1284; MS (CI, *m/z*) 332 (MH^+); Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.42; H, 6.71; N, 4.08.

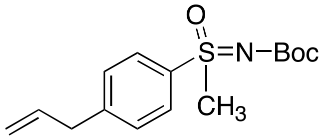
8-2-8-3. The synthesis of *rac*-76c



76c

Following GP 3 using *rac*-**69** and tributylphenylethynyltin gave 99.4 mg (94%) of *rac*-**76c** as a white solid. Mp. 125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96-7.93 (m, 2H), 7.74-7.70 (m, 2H), 7.56-7.53 (m, 2H), 7.39-7.36 (m, 3H), 3.25 (s, 3H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.3, 137.8, 132.4, 131.7, 129.2, 129.1, 128.4, 127.3, 93.6, 87.5, 80.7, 44.7, 28.1; IR (neat, cm^{-1}) 3440, 1665, 1389, 1287; MS (CI, *m/z*) 356 (MH$^+$); Anal. Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.95; N, 3.94. Found: C, 67.80; H, 5.85; N, 3.95.

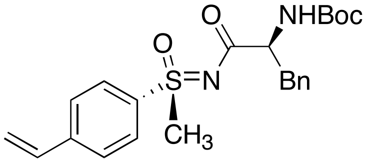
8-2-8-4. The synthesis of *rac*-76d



76d

Following GP 3 using *rac*-**69** and allytributyltin gave 78.8 mg (89%) of *rac*-**76d** as a white solid. Mp. 66 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.00-5.87 (m, 1H), 5.16-5.09 (m, 2H), 3.48 (d, *J* = 6.7 Hz, 2H), 3.22 (s, 3H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.6, 146.7, 136.3, 135.6, 129.8, 127.5, 117.3, 80.5, 44.8, 39.9, 28.0; IR (neat, cm^{-1}) 3450, 3019, 2979, 2929, 1665; MS (CI, *m/z*) 296 (MH$^+$); Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.80; H, 7.39; N, 4.50.

8-2-8-5. The synthesis of (*S,S*)-76e

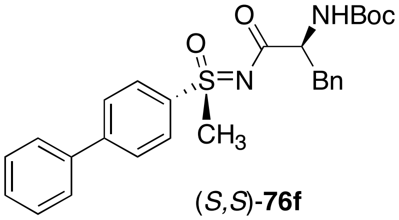


(*S,S*)-**76e**

Following GP 3 using (*S*,*S*)-**70** and tributylvinyltin gave 86.4 mg (97%) of (*S,S*)-**76e** as a white solid and as a single isomer. Mp.153-154 °C; $[\alpha]_D$ –41.4 (*c* 1.26, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.29-7.20 (m, 5H), 6.76 (dd, *J* = 11.0, 17.6 Hz, 1H), 5.92 (d, *J* = 17.6 Hz, 1H), 5.48 (d, *J* = 11.0 Hz, 1H), 5.16

(d, J = 7.4 Hz, 1H), 4.61-4.56 (m, 1H), 3.33 (s, 3H), 3.25-3.08 (m, 2H), 1.41(s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 155.3, 143.2, 137.2, 136.9, 135.0, 129.7, 128.2, 127.5, 127.1, 126.5, 118.4, 79.2, 57.4, 44.1, 38.6, 28.4; IR (neat, cm^{-1}) 3384, 2930, 1623, 1525; MS (CI, *m/z*) 429 (MH^+); Anal. Calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.33; H, 6.70; N, 6.48.

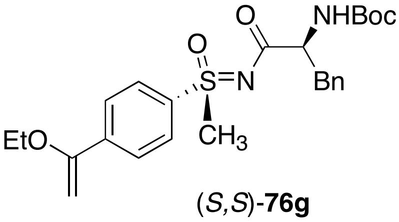
8-2-8-6. The synthesis of (*S,S*)-76f



(*S,S*)-**76f**

Following GP 3 using (*S*,*S*)-**70** and tributylphenyltin gave 97.4 mg (98%) of (*S,S*)-**76f** as a white solid and as a single isomer. Mp. 126-127 °C; $[\alpha]_D$ –36.6 (*c* 1.43, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, J = 8.4 Hz, 2H), 7.70-7.66 (m, 2H), 7.55-7.51 (m, 2H), 7.46-7.35 (m, 3H), 7.24-7.13 (m, 5H), 5.11 (d, J = 7.7 Hz, 1H), 4.57-4.51 (m, 1H), 3.30 (s, 3H), 3.20-3.03 (m, 2H), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.0, 155.3, 147.1, 138.9, 137.2, 136.7, 129.7, 129.1, 128.8, 128.2, 127.7, 127.4, 126.5, 79.3, 57.4, 44.1, 38.6, 28.3 (one signal could not be detected); IR (neat, cm^{-1}) 3428, 2927, 1693, 1364; MS (CI, *m/z*) 479 (MH^+); Anal. Calcd for $C_{27}H_{30}N_2O_4S$: C, 67.76; H, 6.32; N, 5.85. Found: C, 67.92; H, 6.65; N, 5.64.

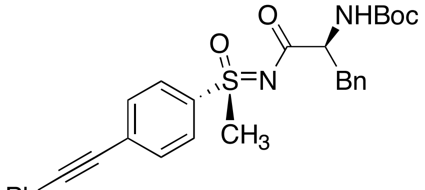
8-2-8-7. The synthesis of (*S,S*)-76g



(*S,S*)-**76g**

Following GP 3 using (*S*,*S*)-**70** and tributyl(1-ethoxyvinyl)tin gave 85.3 mg (87%) of (*S,S*)-**76g** as a colorless oil. $[\alpha]_D$ –41.0 (*c* 1.10, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84-7.78 (m, 4H), 7.32-7.22 (m, 5H), 5.19 (d, J = 7.7 Hz, 1H), 4.81 (d, J = 3.0 Hz, 1H), 4.64-4.58 (m, 1H), 4.40 (d, J = 3.0 Hz, 1H), 3.97 (dd, J = 7.1, 14.0 Hz, 2H), 3.35 (s, 3H), 3.28-3.10 (m, 2H), 1.49-1.39 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 157.8, 155.2, 142.2, 137.4, 137.1, 129.7, 128.2, 127.0, 126.5, 126.4, 85.0, 79.2, 63.7, 57.4, 41.0, 38.6, 28.3, 14.6; IR (neat, cm^{-1}) 3371, 2930, 1681, 1628, 1530; MS (EI, *m/z*) 472 (M$^+$); Anal. Calcd for $C_{25}H_{32}N_2O_5S$: C, 63.54; H, 6.82; N, 5.93. Found: C, 63.55; H, 6.43; N, 5.82.

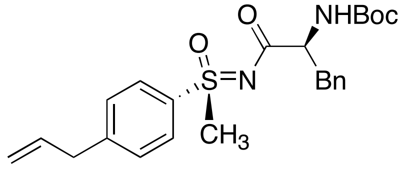
8-2-8-8. The synthesis of (*S,S*)-76h



(*S,S*)-**76h**

Following GP 3 using (*S*,*S*)-**70** and tributylphenylethynyltin gave 89.5 mg (86%) of (*S,S*)-**76h** as a white solid and as a single isomer. Mp. 160-161 °C; [α]$_D$ 13.8 (*c* 1.88, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.70-7.65 (m, 2H), 7.58-7.57 (m, 2H), 7.42-7.37 (m, 3H), 7.32-7.21 (m, 5H), 5.17 (d, *J* = 7.9 Hz, 1H), 4.61-4.59 (m, 1H), 3.35 (s, 3H), 3.26-3.09 (m, 2H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.0, 155.2, 137.2, 137.1, 132.4, 131.8, 129.7, 129.5, 129.2, 128.5, 128.2, 127.2, 126.5, 122.1, 93.8, 87.4, 79.3, 57.4, 44.0, 38.6, 28.3; IR (neat, cm^{-1}) 3377, 2926, 2219, 1696; MS (CI, *m/z*) 503 (MH$^+$); Anal. Calcd for $C_{29}H_{30}N_2O_4S$: C, 69.30; H, 6.02; N, 5.57. Found: C, 69.35; H, 6.26; N, 5.32.

8-2-8-9. The synthesis of (*S,S*)-76i



(*S,S*)-**76i**

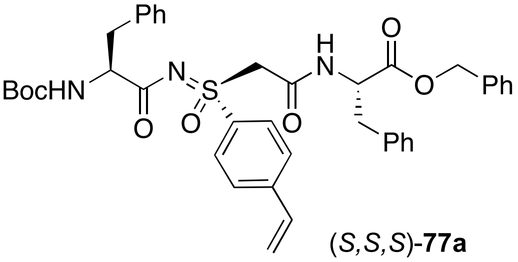
Following GP 3 using (*S*,*S*)-**70** and allytributyltin gave 83.5 mg (91%) of (*S,S*)-**76i** as a white solid and as a single isomer. Mp. 135 °C; [α]$_D$ –38.4 (*c* 1.88, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 7.9 Hz, 2H), 7.40-7.39 (m, 2H), 7.29-7.20 (m, 5H), 6.01-5.87 (m, 1H), 5.19-5.10 (m, 3H), 4.60-4.57 (m, 1H), 3.48 (d, *J* = 6.7 Hz, 2H), 3.33 (s, 3H), 3.24-3.07 (m, 2H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 155.3, 146.9, 137.1, 135.8, 135.4, 129.7, 129.6, 128.1, 127.2, 126.4, 117.3, 79.2, 57.4, 44.1, 40.0, 38.7, 28.4; IR (neat, cm^{-1}) 3382, 2927, 1681, 1527; MS (EI, *m/z*) 442 (M$^+$); HRMS of [M]$^+$: Calcd.

442.1926; found 442.1926. The product proved to be very unstable, and rapid decomposition occurred.

8-2-9. General Procedure (GP 4) for Palladium-Catalyzed Stille Coupling of *(S,S,S)*-71

Under argon (*S,S,S*)-**71** (99.0 mg, 0.13 mmol) $Pd_2(dba)_3$ (1 mol%) and P(*o*-Tol)$_3$ (2 mol%) were dissolved in toluene (2 mL). After adding the stannane (1.2 equiv), the mixture was heated to reflux until the starting material was completely consumed (TLC analysis). The solution was concentrated in vacuo, and the resulting product was isolated by column chromatography (SiO_2).

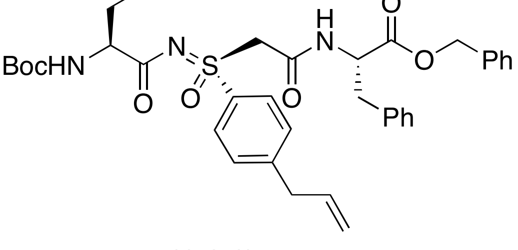
8-2-9-1. The synthesis of (*S,S,S*)-77a



(*S,S,S*)-**77a**

Following GP 4 using (*S,S,S*)-**71** and tributyl(vinyl)tin gave 75.5 mg (81%) of (*S,S*)-**77a** as colorless oil and as a single isomer. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.31-7.12 (m, 14H), 6.73 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.90 (d, *J* = 17.6 Hz, 1H), 5.40 (d, *J* = 11.0 Hz, 1H), 5.21-5.14 (m, 3H), 4.82-4.79 (m, 1H), 4.60-4.58 (m, 1H), 4.43-4.30 (m, 2H), 3.24-3.18 (m, 2H), 3.08-2.95 (m, 2H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.6, 170.5, 159.6, 155.5, 143.6, 136.9, 135.5, 135.0, 134.1, 129.4, 129.2, 128.5, 128.4, 128.2, 127.0, 126.9, 126.5, 118.5, 79.4, 67.3, 60.8, 57.8, 54.2, 38.0, 37.0, 28.4 (four signals could not be detected).

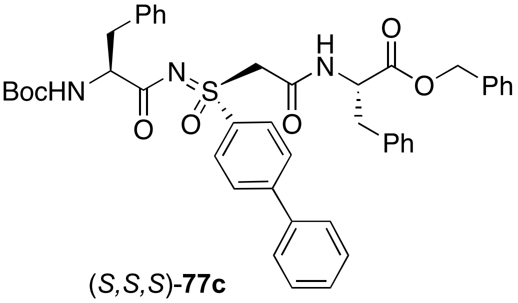
8-2-9-2. The synthesis of (*S,S,S*)-77b



(*S,S,S*)-**77b**

Following GP 4 using (*S,S,S*)-**71** and allyltributyltin gave 42.5 mg (45%) of (*S,S*)-**77b** as colorless oil and as a single isomer. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72-7.70 (m, 2H), 7.63-7.57 (m, 2H), 7.38-7.20 (m, 13H), 7.13-7.11 (m, 2H), 5.95-5.89 (m, 1H), 5.18-5.10 (m, 4H), 4.81-4.78 (m, 1H), 4.60-4.55 (m, 1H), 4.51-4.23 (m, 2H), 3.45 (d, *J* = 6.9 Hz, 2H), 3.23-3.17 (m, 2H), 3.07-2.92 (m, 2H), 1.61 (s, 9H).

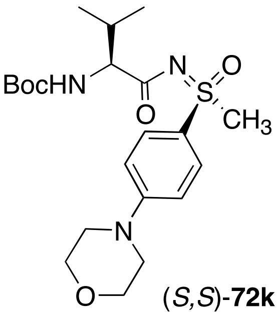
8-2-9-3. The synthesis of (*S,S,S*)-72c



(*S,S,S*)-**77c**

Following GP 4 using (*S,S,S*)-**71** and tributyl(vinyl)tin gave 70.2 mg (71%) of (*S,S*)-**77c** as colorless oil and as a single isomer. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, *J* = 8.24 Hz, 2H), 7.68-7.66 (m, 3H), 7.59-7.57 (m, 2H), 7.51-7.42 (m, 4H), 7.36-7.22 (m, 11H), 7.14-7.13 (m, 2H), 5.22-5.14 (m, 3H), 4.85-4.80 (m, 1H), 4.62-4.58 (m, 1H), 4.47-4.33 (m, 2H), 3.22-3.20 (m, 2H), 3.10-2.95 (m, 2H), 1.62 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.8, 170.6, 160.0, 155.6, 147.4, 138.8, 137.0, 135.6, 135.0, 134.0, 129.5, 129.3, 129.0, 128.8, 128.6, 128.6, 128.5, 128.3, 128.0, 127.4, 127.1, 126.6, 79.4, 67.3, 60.7, 57.7, 54.2, 37.9, 37.5, 28.3 (two signals could not be detected); IR (neat, cm^{-1}) 3342, 1743, 1673, 1217.

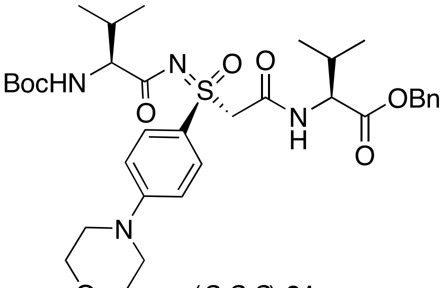
8-2-10. The synthesis of (*S,S*)-72k



(*S,S*)-**72k**

To a solution of TFA (1 mL) and dichloromethane (3 mL) was added (*S*)-**72b** (668.0 mg, 2 mmol), and the mixture was stirred at room temperature for 1 h. After the addition of H_2O (30 mL) the aqueous phase was neutralized with $NaHCO_3$ (solid) and extracted with dichloromethane several times. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Without further purification, the crude product was dissolved in dichloromethane (20 mL) under argon and the resulting solution was cooled to 0 °C. Then, DCC (433.0 mg, 2.1 mmol), HOBt (284.0 mg, 2.1 mmol) and N-Boc-Val-OH (434.0 mg, 2 mmol) were added and the reaction mixture was stirred over night. DCC urea was filtered off (celite), and the reaction mixture was concentrated. After column chromatography (SiO_2) (*S,S*)-**72k** (771.0 mg) was obtained as a colorless oil in 88% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, *J* = 9.2 Hz, 2H), 6.94 (d, *J* = 9.2 Hz, 2H), 5.19 (d, *J* = 9.2 Hz, 1H), 4.24 (dd, *J* = 4.0, 8.9 Hz, 1H), 3.87-3.83 (m, 4H), 3.34-3.30 (m, 7H), 2.27 (m, 1H), 1.44 (s, 9H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.7, 156.0, 154.5, 128.9, 126.1, 113,9, 79,0, 66.4, 61.4, 47.3, 44.6, 28.4, 19.6; IR (neat, cm^{-1}) 3426, 2969, 1711, 1593; MS (CI, *m/z*) 440 (MH^+); HRMS of $[M–C_9H_{18}NO_2]^+$: Calcd. 267.0803; found 267.0804.

8-2-11. The synthesis of (*S,S,S*)-81

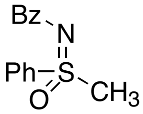


(*S,S,S*)-**81**

To a solution of cyclohexyl(isopropyl)amine (70 mL, 0.42 mmol) in THF (500 mL) at 0 °C under argon was added *n*-BuLi (15% in hexane, 0.42 mmol). The reaction mixture was stirred for 30 min at 0 °C and then cooled at –78 °C. A solution of (*S,S*)-**72k** (50.0 mg, 0.1 mmol) and THF (500 mL) was added dropwise at this temperature. After stirring for 30 min at –78 °C, dried CO_2 was bubbled through the solution for 10 min. The cooling bath was removed and the gas flow reduced. After 10 min the gas flow stopped, and the reaction mixture was warmed to room temperature. Under vigorous stirring water was added. The organic phase was separated and the aqueous phase extracted once with diethyl ether. The organic phases were discarded and to the aqueous phase NH_4Cl (solid) was added until a precipitate formed. The suspension was extracted with dichloromethane several times, the dichloromethane phase dried ($MgSO_4$), and the solvent removed under reduced pressure at room temperature (without heating!). After drying (and without further purification) the resulting crude product was dissolved in dichloromethane (1 mL) at 0 °C, and DMAP (1.8 mg, 0.01 mmol) and H-Val-OBn•Tos (38.0 mg, 0.1 mmol) were added under argon. After cooling to –12 °C, a solution of EEDQ (31.0 mg, 0.1 mmol) and dichloromethane (1 mL) was added, the reaction mixture was slowly warmed to room temperature and stirred over night. After evaporating the solvent under reduced pressure, purification by column chromatography (SiO_2) gave (*S,S,S*)-**81** (40.8 mg) as a colorless oil in 55% yield. $[\alpha]_D$ –31.1 (*c* 1.54, MeOH); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 9.2 Hz, 2H), 7.38-7.32 (m, 5H), 6.87 (d, *J* = 9.2 Hz, 2H), 5.27-5.15 (m, 3H), 4.51-4.29 (m, 4H), 3.85-3.81 (m, 4H), 3.32-3.16 (m, 4H), 2.35-2.20 (m, 2H), 1.45 (s, 9H), 1.01-0.86 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.5, 171.1, 160.4, 154.9, 135.4, 129.9, 128.7, 128.4, 123.3, 113.7, 79.2, 67.1, 66.4, 61.9, 61.7, 58.0, 47.1, 31.5, 31.1, 28.4, 19.7, 19.1, 17.7, 17.1; IR (neat, cm^{-1}) 3354, 2967, 1713, 1505; MS (CI, *m/z*) 673 (MH^+); Anal. Calcd for $C_{34}H_{48}N_4O_8S$: C, 60.69; H, 7.19; N, 8.33. Found: C, 61.03; H, 7.53; N, 8.33.

8-3. Palladium-catalyzed α-arylation of sulfoximines.

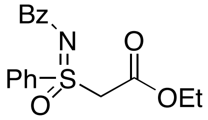
8-3-1. The synthesis of *N*-benzoyl methylphenyl sulfoximine (110)



110

rac-Sulfoximine **65** (1.55 g, 10 mmol) and NaH (60% in mineral oil, 600 mg, 15 mmol) were dissolved in anhydrous dichloromethane (50 mL) under argon at room temperature. Benzoyl chloride (1.28 mL, 11 mmol) was then added and the reaction mixture was stirred for two hours at room temperature. Subsequently water (30 mL) was added and the resulting mixture was extracted with dichloromethane several times. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification by crystallization (pentane and ethyl acetate) and column chromatography (SiO_2) gave 2.33 g (90%) of compound **110** as a white solid. Mp. 108-110 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, *J* = 7.2 Hz, 2H), 8.04 (d, *J* = 7.2 Hz, 2H), 7.69-7.38 (m, 6H), 3.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 138.8, 135.5, 133.7, 132.0, 129.6, 129.3, 127.9, 127.0, 44.2; IR (neat, cm^{-1}) 3019, 1617, 1447, 1214; MS (CI, *m/z*) 260 ($[M+1]^+$); Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; found C, 64.90; H, 5.11; N, 5.32.

8-3-2. The synthesis of *N*-benzoyl sulfoximine ethyl ester 111



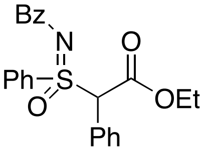
111

To a stirred solution of tetramethylpiperidine (2.4 mL, 14 mmol) in anhydrous THF (6 mL) was slowly added a solution of *n*-butyllithium (15% in hexane, 7.5 mL, 12mmol) at 0 °C. After 10 min, the reaction mixture was cooled to –78 °C and a solution of compound **110** (1.55 g, 6 mmol) in THF (10 mL) was added slowly via syringe. After stirring for 30 min at this temperature, ethyl chloroformate (1.4 mL, 12 mmol) was added dropwise at –78 °C and the strirring was continued for 2 hours without further control of temperature. The reaction mixture was quenched with saturated ammonium chloride (2 mL) and extracted with dichloromethane several times. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification by column chromatography gave 1.76 g (89%) of compound **111** as a pale yellow solid. Mp. 88-89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14-8.10 (m, 2H), 8.06-8.02 (m, 2H), 7.69-7.63 (m, 1H), 7.59-7.53 (m, 2H), 7.49-7.43 (m, 1H), 7.39-7.33 (m, 2H), 4.76 (d, *J* = 14.1 Hz, 1H), 4.56 (d, *J* = 14.1 Hz, 1H), 4.04-3.97 (m, 2H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.3, 162.1, 136.9, 135.4, 134.4, 132.4, 129.6, 129.5, 128.6, 128.1, 62.5, 59.5, 13.8; IR (neat, cm^{-1}) 3056, 2987, 2930, 1741; MS (CI, *m/z*) 332 ([M+1]$^+$); Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23; found C, 61.56; H, 4.94; N, 4.09.

8-3-3. General procedure for palladium-catalyzed α-arylation of *N*-benzoyl sulfoximine ethyl ester 111

A solution of *N*-benzoyl sulfoximine ethyl ester **111** (70.0 mg, 0.21 mmol), $Pd(OAc)_2$ or $Pd_2(dba)_3$ (3 mol%), PCy_3 (9 mol%), sodium *tert*-butoxide (60.0 mg, 0.63 mmol), and aryl bromide (1.2 equiv) in anhydrous dioxane (2 mL) was heated to reflux under argon until the starting material completely disappeared (ca. in 1 hour) by TLC analysis. After cooling to room temperature, 10 % HCl (aq.) and ethyl acetate were added, and the organic layer was separated, dried ($MgSO_4$), and concentrated. The product was purified by column chromatography (SiO_2).

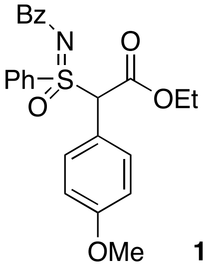
8-3-3-1. The synthesis of compound 112a



112a

Following the general procedure using $Pd(OAc)_2$ and bromobenzene (0.026 mL, 0.24 mmol) gave 67.4 mg (79%) of compound **112a** as a white solid and as a mixture of diastereomers. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.21-8.18 (m, 1H), 8.16-8.13 (m, 1H), 7.69-7.67 (m, 1H), 7.63-7.61 (m, 2H), 7.53-7.50 (m, 1H), 7.45-7.25 (m, 7H), 7.20-7.18 (m, 2H), 6.27/6.17 due to diastereomers (s, ds, 1H), 4.39-4.07 (m, 2H), 1.33/1.13 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1/174.0, 164.8/164.5, 135.5, 135.5, 134.1, 134.0, 133.2, 133.0, 132.2, 132.1, 130.6, 130.4, 130.3, 130.1, 129.8, 129.4, 128.3, 128.3, 127.9, 127.3, 126.9, 74.5/72.7, 62.7/62.4, 14.0/13.9; IR (neat, cm^{-1}) 3067, 2975, 1731, 1629, 1576; MS (CI, *m/z*) 408 ($[M+1]^+$); Anal. Calcd for $C_{23}H_{21}NO_4S$: C, 67.79; H, 5.19; N, 3.44; found C, 67.73; H, 5.27; N, 3.35.

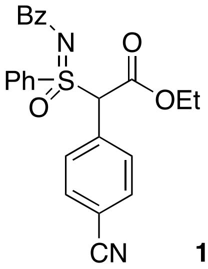
8-3-3-2. The synthesis of compound 112b



112b

Following the general procedure using $Pd(OAc)_2$ and 4-bromoanisole (0.032 mL, 0.25 mmol) gave 76.0 mg (83%) of compound **112b** as a white solid and as a mixture of diastereomers. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.20-8.18 (m, 1H), 8.16-8.14 (m, 1H), 7.71-7.68 (m, 1H), 7.65-7.61 (m, 2H), 7.54-7.49 (m, 1H), 7.46-7.39 (m, 4H), 7.22-7.18 (m, 1H), 7.13-7.09 (m, 1H), 6.79-6.75 (m, 1H), 6.72-6.68 (m, 1H), 6.12/6.11 (s, 1H), 4.40-4.05 (m, 2H), 3.79/3.74 (s, 3H), 1.32/1.12 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0/173.8, 164.9/164.7, 160.7/160.7, 135.5, 135.5, 134.0, 133.9, 133.3, 133.0, 132.1, 132.0, 131.6, 130.4, 130.1, 129.3, 128.3, 128.2, 127.9, 119.0, 118.5, 113.8, 113.7, 73.9/72.2, 62.6/62.3, 55.3/55.2, 14.0/13.9; IR (neat, cm^{-1}) 3016, 1739, 1633, 1310, 1280; MS (CI, *m/z*) Anal. Calcd for $C_{24}H_{23}NO_5S$: C, 65.89; H, 5.30; N, 3.20; found C, 65.58; H, 5.34; N, 3.19.

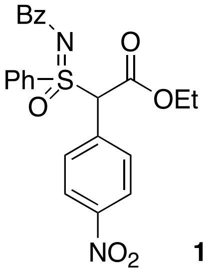
8-3-3-3. The synthesis of compound 112c



112c

Following the general procedure using $Pd_2(dba)_3$ and 4-bromobenzonitrile (45.0 mg, 0.25 mmol) gave 80.0 mg (88%) of compound **112c** as colorless oil and as a mixture of diastereomer. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18-8.11 (m, 2H), 7.72-7.64 (m, 3H), 7.59-7.34 (m, 9H), 6.50/6.29 (s, 1H), 4.42-4.09 (m, 2H), 1.34/1.10 (t, J = 7.17 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 164.1, 135.2, 134.7, 132.9, 132.6, 132.5, 132.3, 132.0, 131.5, 131.1, 130.3, 130.2, 129.5, 128.8, 128.7, 128.2, 128.1, 118.0, 113.8, 73.4/71.9, 63.2/62.9, 13.9/13.7; IR (neat, cm^{-1}) 3260, 3019, 2231, 1740, 1634; MS (CI, *m/z*) 433 ($[M+1]^+$); HRMS of $[M]^+$: Calcd. 432.1144; found 432.1143.

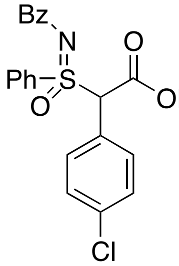
8-3-3-4. The synthesis of compound 112d



112d

Following the general procedure using $Pd(OAc)_2$ and 4-bromo nitrobenzene (51.0 mg, 0.25 mmol) gave 69.6 mg (73%) of compound **112d** as yellow oil and as a mixture of diastereomers. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.19-8.12 (m, 3H), 8.05-8.03 (m, 1H), 7.74-7.66 (m, 3H), 7.57-7.41 (m, 7H), 6.49/6.37 (s, 1H), 4.42-4.07 (m, 2H), 1.35/1.10 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0/173.8, 164.0/163.9, 148.5, 135.1, 135.0, 134.7, 134.4, 134.1, 132.7, 132.6, 132.5, 131.8, 131.4, 130.2, 130.1, 129.4, 128.7, 128.7, 128.1, 128.1, 123.3, 73.1/71.6, 63.3/63.0, 14.0/13.8; IR (neat, cm^{-1}) 2934, 1740, 1635, 1526, 1348, 1278; MS (CI, *m/z*) 453 ($[M+1]^+$); Anal. Calcd for $C_{18}H_{14}N_2O_5S_2$: C, 61.05; H, 4.46; N, 6.19; found C, 61.24; H, 4.46; N, 6.18.

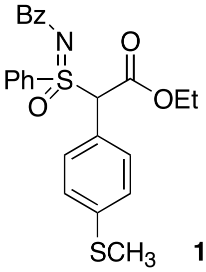
8-3-3-5. The synthesis of compound 112e



112e

Following the general procedure using $Pd_2(dba)_3$ and 4-bromo chlorobenzene (48.0 mg, 0.25 mmol) gave 62.5 mg (68%) of compound **112e** as a white solid and as a mixture of diastereomers. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.19-8.13 (m, 2H), 7.72-7.64 (m, 3H), 7.53-7.40 (m, 5H), 7.26-7.25 (m, 2H), 7.16-7.13 (m, 2H), 6.29/6.17 (s, 1H), 4.39-4.09 (m, 2H), 1.33/1.11 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0/173.8, 164.5/164.3, 136.2, 135.3, 134.3, 133.0, 132.9, 132.3, 132.3, 132.0, 131.6, 130.6, 130.4, 130.1, 129.4, 128.6, 128.5, 128.4, 128.0, 128.0, 125.9, 125.5, 73.5/71.8, 62.9/62.6, 14.0/13.8; IR (neat, cm^{-1}) 3018, 1739, 1634, 1491, 1279; MS (CI, *m/z*) 442 ($[M+1]^+$); HRMS of $[M]^+$: Calcd. 441.0802; found 441.0802.

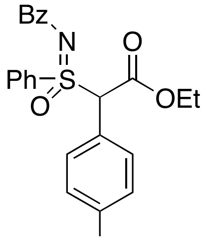
8-3-3-6. The synthesis of compound 112f



112f

Following general procedure using $Pd(OAc)_2$ and 4-bromothioanisole (51.0 mg, 0.25 mmol) gave 80.6 mg (85%) of compound **112f** as colorless oil and as a mixture of diastereomers. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.20-8.13 (m, 2H), 7.73-7.61 (m, 3H), 7.53-7.39 (m, 5H), 7.21-7.18 (m, 1H), 7.12-7.18 (m, 1H), 7.03-7.01 (m, 1H), 6.26/6.14 (s, 1H), 4.35-4.08 (m, 2H), 2.46/2.42 (s, 3H), 1.32/1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1, 164.9/164.7, 141.6, 135.6, 134.2, 133.3, 133.1, 132.3, 132.2, 131.0, 130.6, 130.5, 130.3, 129.5, 128.5, 128.4, 128.0, 125.6, 125.4, 123.5, 123.1, 74.0/72.3, 62.7/62.4, 15.1/15.0, 13.9/13.8; IR (neat, cm^{-1}) 3681, 3434, 3064, 2924, 2365, 1737, 1633; MS (CI, *m/z*) 454 ($[M+1]^+$); Anal. Calcd for $C_{24}H_{23}NO_4S_2$: C, 63.55; H, 5.11; N, 3.09; found C, 63.48; H, 5.46; N, 2.94.

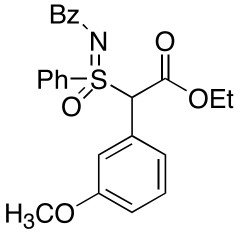
8-3-4-7. The synthesis of compound 112g



112g

Following the general procedure using Pd(OAc)$_2$ and 4-bromodiphenyl (59.0 mg, 0.25 mmol) gave 87.1 mg (86%) of compound **112g** as a white solid and as a mixture of diastereomers. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.22-8.17 (m, 2H), 7.76-7.74 (m, 1H), 7.69-7.62 (m, 2H), 7.58-7.36 (m, 13H), 7.28-7.26 (m, 1H), 6.35/6.25 (s, 1H), 4.19-4.12 (m, 2H), 1.35/1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 174.0/173.9, 164.8/164.6, 142.6/142.6, 139.8/129.6, 135.5/135.5, 134.1, 134.1, 133.3, 133.0, 132.2, 132.2, 131.0, 130.7, 130.5, 130.2, 129.4, 128.8, 128.8, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 127.0, 126.9, 126.9, 126.2, 125.8, 74.2, 72.5, 62.8, 62.5, 14.0, 13.9; IR (neat, cm^{-1}) 3067, 2973, 1738, 1633, 1578, 1312, 1283; MS (EI, *m/z*) 483 ([M]$^+$); HRMS of [M]$^+$: Calcd. 483.1504; found 483.1503.

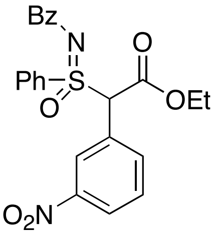
8-3-3-8. The synthesis of compound 112h



112h

Following the general procedure using Pd(OAc)$_2$ and 3-bromoanisole (0.032 mL, 0.25 mmol) gave 72.3 mg (79%) of compound **112h** as colorless oil and as a mixture of diastereomers. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.21-8.18 (m, 1H), 8.16-8.14 (m, 1H), 7.73-7.71 (m, 1H), 7.67-7.62 (m, 2H), 7.53-7.50 (m, 1H), 7.47-7.39 (m, 4H), 7.19-7.05 (m, 1H), 6.93-6.80 (m, 2H), 6.74-6.72 (m, 1H), 4.36-4.10 (m, 2H), 1.33/1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 174.1/173.9, 164.8/164.5, 159.2/159.2, 135.5, 135.5, 134.1, 133.0, 132.2, 132.2, 130.5, 130.3, 129.4, 129.4, 129.3, 129.2, 128.9, 128.6, 128.5, 128.3, 128.1, 127.9, 127.9, 123.2, 122.6, 116.6, 116.4, 115.2, 114.6, 74.4/72.2, 62.7/62.4, 55.2/55.0, 14.0/13.9; IR (neat, cm^{-1}) 3065, 3011, 2963, 2838, 1739, 1449, 1281; MS (CI, *m/z*) 438 ([M+1]$^+$); Anal. Calcd for $C_{24}H_{23}NO_5S$: C, 65.89; H, 5.30; N, 3.20; found C, 65.89; H, 5.58; N, 3.12.

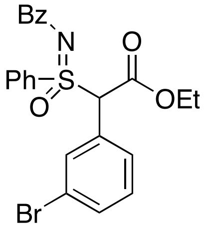
8-3-3-9. The synthesis of compound 112i



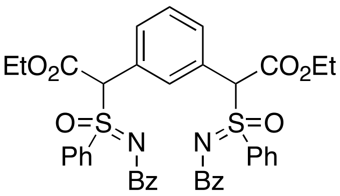
112i

Following the general procedure using $Pd_2(dba)_3$ and 3-bromonitrobenzene (50.5 mg, 0.25 mmol) gave 48.6 mg (51%) of compound **112i** as yellow oil and as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26-8.06 (m, 4H), 7.79-7.64 (m, 4H), 7.55-7.41 (m, 6H), 6.39/6.30 (s, 1H), 4.39-4.11 (m, 2H), 1.34/1.11 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0/174.0, 164.1/163.9, 147.9/147.8, 137.1, 136.4, 136.4, 135.2, 135.1, 134.8, 132.7, 132.6, 132.5, 130.2, 130.1, 129.7, 129.5, 129.3, 128.9, 128.8, 128.1, 125.6, 125.4, 124.7, 73.0/71.8, 63.3/63.0, 13.9/13.7; IR (neat, cm^{-1}) 3068, 3019, 1740, 1635, 1533, 1448, 1278; MS (CI, *m/z*) 453 ([M+1]$^+$); Anal. Calcd for $C_{23}H_{20}N_2O_6S$: C, 61.05; H, 4.46; N, 6.19; found C, 61.32; H, 4.62; N, 6.22.

8-3-3-10. The synthesis of compound 112j



112j-A



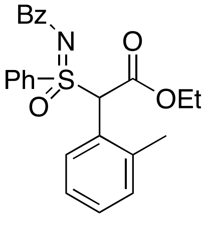
112j-B

Following the general procedure using compound **111** (119.0 mg, 0.36 mmol), 1,3-dibromobenzene (0.02 mL, 0.17 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), PCy_3 (8.4 mg, 0.03 mmol) and sodium *tert*-butoxide (103.0 mg, 1.1 mmol) gave 33.4 mg (41%) of monocoupled compound **112j-A** and 50.4 mg (41%) of dicoupled compound **112j-B** as a white solid each as a mixture of diastereomers.

Compound 112j-A: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20-8.13 (m, 2H), 7.70-7.18 (m, 12H), 6.27/6.26/6.17/6.13 (s, 1H), 4.43-4.03 (m, 2H), 1.36-1.31/1.16-1.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.1/174.0, 164.9, 164.6, 164.5, 135.6, 135.4, 134.5, 134.1, 133.5, 133.3, 133.1, 133.0, 132.3, 132.2, 130.7, 130.5, 130.4, 130.3, 130.2, 129.9, 129.9, 129.6, 129.5, 129.2, 129.1, 128.5, 128.5, 128.4, 128.3, 128.0, 128.0, 127.4, 127.0, 122.3, 74.4, 73.6, 72.7, 71.9, 62.9, 62.7, 62.6, 62.4, 13.9, 13.8; IR (neat, cm^{-1}) 3016, 2966, 1739, 1312, 1279; MS (CI, *m/z*) 486/488 ([M+1]$^+$); HRMS of [M-$C_{10}H_{10}O_2Br$]$^+$: Calcd. 244.0432; found 244.0432.

Compound 112j-B: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.18-8.11 (m, 4H), 7.72-7.31 (m, 18H), 7.23-7.10 (m, 2H), 6.14/6.06/5.95/5.93/5.84 (s, 2H), 4.40-3.85 (m, 4H), 1.37-1.27/1.15-1.04 (m, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 173.5, 163.8, 134.9, 133.9, 133.8, 132.7, 131.9, 131.6, 131.5, 131.4, 129.9, 129.8, 129.7, 129.3, 129.1, 129.1, 129.1, 128.4, 128.3, 128.2, 128.1, 127.6, 127.3, 73.4, 73.2, 72.4, 65.4, 62.5, 62.1, 62.0, 13.5, 13.3; IR (neat, cm^{-1}) 3438, 3066, 2973, 1736, 1635, 1449, 1279; MS (CI, *m/z*) 737 ([M+1]$^+$); Anal. Calcd for $C_{40}H_{36}N_2O_8S_2$: C, 65.20; H, 4.92; N, 3.80; found C, 65.08; H, 5.16; N, 3.58.

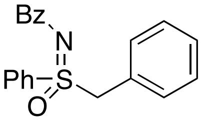
8-3-3-11. The synthesis of compound 112k



112k

Following the general procedure using Pd(OAc)$_2$ and 2-bromotoluene (0.03 mL, 0.25 mmol) gave 64.4 mg (73%) of compound **112k** as a white solid and as a mixture of diastereomers. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.22-8.14 (m, 2H), 7.77-7.39 (m, 8H), 7.30-7.22 (m, 2H), 7.16-7.00 (m, 1H), 6.91-6,90 (m, 1H), 6.70/6.06 (s, 1H), 4.37-4.02 (m, 2H), 2.66/2.05 (s, 1H), 1.35-1.30/1.14-1.09 (m, 3H); ^{13}C NMR (CDCl$_3$, 400 MHz) δ 174.1/173.6, 165.1/164.4, 139.8, 138.4, 135.5, 134.1, 133.9, 133.0, 132.1, 132.1, 130.9, 130.7, 130.4, 130.4, 129.8, 129.7, 129.5, 129.4, 129.4, 128.8, 128.2, 127.9, 126.0, 125.7, 125.4, 125.2, 69.6/69.5, 62.7/62.3, 20.4/19.5, 14.0/13.8; IR (neat, cm^{-1}) 2968, 1734, 1630, 1312, 1276, 1229; MS (CI, *m/z*) 422.0 ([M+1]$^+$); Anal. Calcd for $C_{24}H_{23}NO_4S$: C, 68.39; H, 5.50; N, 3.32; found C, 68.16; H, 5.81; N, 3.23.

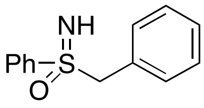
8-3-4. Hydrolysis of compound 112a to give *N*-benzoyl benzylphenyl sulfoximine (118)



118

To a solution of 1 N NaOH (aq, 3 mL) and methanol (6 mL) was added compound **112a** at room temperature and the reaction mixture was stirred for 2 hours. 10 % HOAc was added to the reaction mixture and the product was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification by column chloromatography (SiO_2) gave 75.5 mg (98%) of *N*-benzoyl benzylphenyl sulfoximine (**118**) as a white solid. Mp. 132-133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20-8.17 (m, 2H), 7.72-7.69 (m, 2H), 7.65-7.59 (m, 1H), 7.55-7.40 (m, 5H), 7.32-7.17 (m, 3H), 7.02-7.00 (m, 2H), 4.95 (d, *J* = 13.6 Hz, 1H), 4.87 (d, *J* = 13.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.3, 135.7, 135.4, 133.7, 132.0, 131.1, 129.3, 129.0, 128.9, 128.4, 127.9, 127.2, 62.1; IR (neat, cm^{-1}) 3455, 3060, 1627, 1447, 1279; MS (CI, *m/z*) 336.0 ([M+1]$^+$); Anal. Calcd for $C_{20}H_{17}NO_2S$: C, 71.62; H, 5.11; N, 4.18; found C, 71.33; H, 5.45; N, 4.04.

8-3-5. Removal of benzoyl protecting group to give NH-benzylphenyl sulfoximine (119)



119

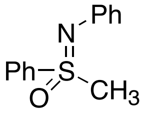
BH_3-THF (1.0 M in THF, 0.3 mL, 0.3 mmol) was slowly added to a solution of *N*-benzoyl benzylphenyl sulfoximine (32.0 mg, 0.1 mmol) at 0 °C. After stirring for 3 hours at this temperature, the reaction mixture was quenched carefully with MeOH-H_2O (1:1, 3 mL), extracted with dichloromethane, dried over $MgSO_4$ and concentrated. Purification by column chromatography (SiO_2) gave 13.7 mg (62%) of NH-free benzylphenyl sulfoximine (**119**) as a white solid. Mp. 112-113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77-7.75 (m, 2H), 7.60-7.53 (m, 1H), 7.47-7.41 (m, 2H), 7.34-7.23 (m, 3H), 7.12-7.09 (m, 2H), 4.39 (d, *J* = 13.4 Hz, 1H), 4.30 (d, *J* = 13.4 Hz, 1H), 2.75 (bs, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 140.3, 133.0, 129.9, 128.7, 128.6, 128.5, 128.4, 64.5; IR (neat, cm^{-1}) 3972, 3317, 3056, 2923, 1445, 1217, 1110; MS (CI, *m/z*) 232.0 ([M+1]$^+$); Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06; found C, 67.33; H, 5.91; N, 6.06.

8-4. Cu-mediated N-arylation of sulfoximines.

8-4-1. General procedure for *N*-arylations of sulfoximines

Under an argon atmosphere a dry Schlenk tube was charged with sulfoximine **65** (1.0 equiv), aryl halide (2.0 equiv), CuI (1.0 equiv) and base [2.5 equiv, Cs_2CO_3 (method A) or CsOAc (method B) as indicated in Table 9; in method C the reagents were as follows: sulfoximine **65** (2.0 equiv), aryl halide (1.0 equiv), CuI (1.0 equiv), CsOAc (2.5 equiv)]. The mixture was dissolved in degassed DMSO (1 M). After heating to 90 °C for 12 h, the mixture was cooled to room temperature and neutralized with HCl. The aqueous layer was extracted with dichloromethane three times. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the N-arylated sulfoximines.

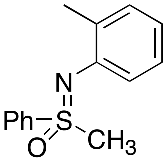
8-4-1-1. The synthesis of *rac*-*N*-(phenyl)-*S*-methyl-*S*-phenylsulfoximine (131a)



131a

The general procedure (method A) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 78.2 mg, 0.51 mmol) and iodobenzene (204.0 mg, 1.01 mmol) gave 109.0 mg (94%) of **131a** as a light brown solid. Mp. 100-101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95-7.99 (m, 2H), 7.54-7.58 (m, 1H), 7.47-7.53 (m, 2H), 7.08-7.14 (m, 2H), 6.99-7.03 (m, 2H), 6.83-6.88 (m, 1H), 3.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.9, 139.4, 133.2, 129.5, 129.0, 128.6, 123.3, 121.7, 46.1; IR (neat, cm^{-1}) 3060, 3021, 2921, 1592, 1484 1198, 1095; MS (EI, *m/z*) 231 ([M]$^+$) Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06; found C, 67.42; H, 5.51; N, 5.84.

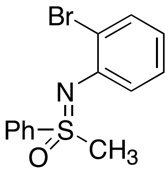
8-4-1-2. The synthesis of *rac*-*N*-[2-(methyl)phenyl]-*S*-methyl-*S*-phenylsulfoximine (131b)



131b

The general procedure (method A) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 84.1 mg, 0.54 mmol) and 1-iodo-2-methylbenzene (238.1 mg, 1.09 mmol) gave 111 mg (84%) of **131b** as a brown solid. Mp. 61-62 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97-8.00 (m, 2H), 7.56-7.61 (m, 1H), 7.50-7.55 (m, 2H), 7.10-7.13 (m, 1H), 6.99-7.02 (m, 1H), 6.88-6.93 (m, 1H), 6.79-6.84 (m, 1H), 3.22 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.0, 132.9, 132.1, 130.2, 129.3, 128.2, 126.1, 121.7, 121.6, 45.4, 18.6; IR (neat, cm^{-1}) 3012, 2921, 1591, 1486, 1263, 1188, 1094; MS (EI, *m/z*) 245 ($[M]^+$); Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71; found C, 68.71; H, 5.99; N, 5.42.

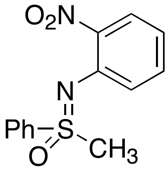
8-4-1-3. The synthesis of *rac-N*-[2-(bromo)phenyl]-*S*-methyl-*S*-phenylsulfoximine (131c)



131c

The general procedure (method A) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 81.3 mg, 0.52 mmol) and 1-bromo-2-iodobenzene (67.5 mg, 1.05 mmol) gave 110.0 mg (68%) of **131c** as a light brown solid. Mp. 63-64 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05-8.09 (m, 2H), 7.57-7.63 (m, 1H), 7.48-7.56 (m, 3H), 7.18-7.22 (m, 1H), 7.00-7.05 (m, 1H), 6.73-6.78 (m, 1H), 3.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2, 138.8, 133.3, 132.8, 129.3, 128.4, 127.7, 123.4, 122.9, 119.1, 45.4; IR (neat, cm^{-1}) 3011, 2920, 1577, 1197, 1124, 684; MS (EI, *m/z*) 309, 311 ($[M]^+$); Anal. Calcd for $C_{14}H_{12}BrNOS$: C, 50.33; H, 3.90; N, 4.52; found C, 50.18; H, 4.12; N, 4.26.

8-4-1-4. The synthesis of *rac-N*-[2-(nitro)phenyl]-*S*-methyl-*S*-phenylsulfoximine (131d)

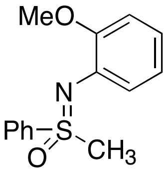


131 d

The general procedure (method A) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 86.2 mg, 0.56 mmol) and 1-iodo-2-nitro-benzene (276.5 mg, 1.11 mmol) gave 127.1 mg (83%) of **131d** as a yellow solid.

The general procedure (method B) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 40.4 mg, 0.26 mmol) and 1-bromo-2-nitro-benzene (105.0 mg, 0.52 mmol) gave 56.0 mg (78%) of **131d** as a yellow oil. Mp. 77-79 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.15-8.11 (m, 2H), 7.73-7.60 (m, 4H), 7.36-7.26 (m, 2H), 7.03-6.97 (m, 1H), 3.33 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 145.3, 139.1, 138.6, 133.9, 132.6, 129.8, 128.6, 124.5, 124.4, 121.4, 45.8; IR (neat, cm^{-1}) 1521, 1287, 1209, 1100, 749; MS (EI, *m/z*) 276 ([M]$^+$); Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14; found C, 56.24; H, 4.85; N, 10.22.

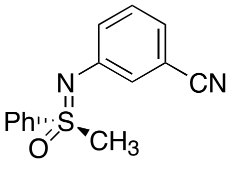
8-4-1-5. The synthesis of *rac*-*N*-[2-(methoxy)phenyl]-*S*-methyl-*S*-phenylsulfoximine (131e)



131e

The general procedure (method A) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 81.6 mg, 0.52 mmol) and 1-iodo-2-methoxybenzene (250.6 mg, 1.07 mmol) gave 99 mg (72%) of **131e** as a brown oil. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.00-8.05 (m, 2H), 7.46-7.59 (m, 3H), 7.06-7.10 (m, 1H), 6.84-6.91 (m, 1H), 6.78-6.83 (m, 1H), 6.66-6.73 (m, 1H), 3.83 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 153.0, 140.0, 133.8, 133.1, 129.4, 128.5, 124.3, 122.8, 120.8, 111.4, 55.7, 46.2; IR (neat, cm^{-1}) 3060, 3004, 2928, 2834, 1586, 1496 1237, 1200, 1122, 1095, 1026; MS (EI, *m/z*) 261 ([M]$^+$); Anal. Calcd for $C_{14}H_{15}NO_2S$: HRMS of [M]$^+$: Calcd. 261.0824; found 261.0827.

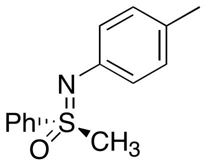
8-4-1-6. The synthesis of *rac*-*N*-[3-(cyano)phenyl]-*S*-methyl-*S*-phenylsulfoximine (131g)



131g

The general procedure (method A) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 82.1 mg, 0.53 mmol) and 3-iodo-benzonitrile (241.8 mg, 1.06 mmol) gave 127.0 mg (94%) of **131g** as a light brown solid. Mp. 74-76 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93-7.98 (m, 2H), 7.60-7.67 (m, 1H), 7.52-7.60 (m, 2H), 7.10-7.27 (m, 4H), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.1, 138.4, 133.7, 129.8, 129.8, 128.5, 127.6, 126.1, 125.0, 119.0, 112.7, 46.2; IR (neat, cm^{-1}) 3064, 3022, 2928, 2579, 1732, 1590, 1211, 1095; MS (EI, *m/z*) 256 ([M]$^+$); Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93; found C, 65.36; H, 4.85; N, 10.69.

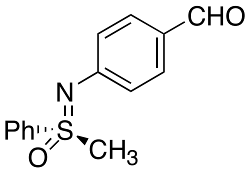
8-4-1-7. The synthesis of *rac-N*-[4-(methyl)phenyl]-*S*-methyl-*S*-phenylsulfoximine (131h)



131h

The general procedure (method A) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 103.4 mg, 0.66 mmol) and 1-iodo-4-methylbenzene (291.3 mg, 1.34 mmol) gave 151.0 mg (93%) of **131h** as a light yellow solid. Mp. 113-114 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95-8.00 (m, 2H), 7.47-7.61 (m, 3H), 6.92-6.93 (m, 4H), 3.22 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.1, 139.4, 133.1, 131.0, 129.6, 129.5, 128.6, 123.2, 45.8, 20.7; IR (neat, cm^{-1}) 3023, 2999, 2920, 1609, 1506, 1189, 1088; MS (EI, *m/z*) 245 ([M]$^+$); Calcd. for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71; found C, 68.61; H, 6.36; N, 5.54.

8-4-1-8. The synthesis of *rac-N*-[4-formyl(phenyl)]-*S*-methyl-*S*-phenylsulfoximine (131i)

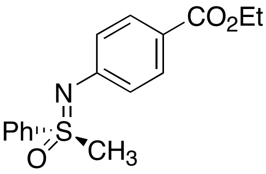


131i

The general procedure (method C) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 152.3 mg, 0.98 mmol) and 4-iodobenzaldehyde (115.7 mg, 0.50 mmol) gave 151.0 mg (85%) of **131i** as a light yellow solid. Mp. 92-94 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.78 (br s, 1H), 7.94-7.99 (m, 2H), 7.61-7.67 (m, 3H), 7.52-7.59 (m, 2H), 7.05-7.11 (m, 2H), 3.31 (s, 3H); ^{13}C

NMR ($CDCl_3$, 75 MHz) δ 191.1, 151.9, 138.5, 133.9, 131.2, 130.1, 129.8, 128.4, 122.9, 46.5; IR (neat, cm^{-1}) 3001, 2921, 2836, 1688, 1595; MS (EI, *m/z*) 259 ($[M]^+$); Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; found C, 64.71; H, 4.93; N, 5.20.

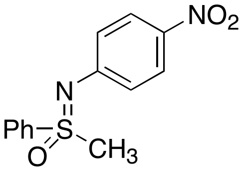
8-4-1-9. The synthesis of *rac-N*-[4-(ethyloxycarbonyl)phenyl]-*S*-methyl-*S*-phenylsulfoximine (131j)



131j

The general procedure (method A) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 85.2 mg, 0.55 mmol) and 4-iodobenzoic acid ethylester (313.5 mg, 1.14 mmol) gave 147.0 mg (88%) of **131j** as a white solid. Mp. 125 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94-7.97 (m, 2H), 7.78-7.84 (m, 2H), 7.59-7.65 (m, 1H), 7.51-7.59 (m, 2H), 6.99-7.05 (m, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 149.8, 138.3, 133.6, 130.8, 129.7, 128.5, 123.4, 122.4, 60.5, 46.3, 14.4; IR (neat, cm^{-1}) 3061, 2971, 1708, 1599, 1502, 1270, 1198, 1168, 1097; MS (EI, *m/z*) 303 ($[M]^+$); Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62; found C, 63.35; H, 5.65; N, 4.35.

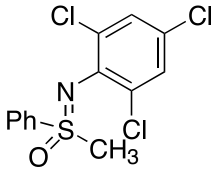
8-4-1-10. The synthesis of *rac-N*-[4-(nitro)phenyl]-*S*-methyl-*S*-phenylsulfoximine (131k)



131k

The general procedure (method A) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 71.3 mg, 0.46 mmol) and 1-iodo-4-nitrobenzene (227.7 mg, 0.91 mmol) gave 104 mg (82%) of **131k** as an orange solid. Mp. 151-154 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.93-8.03 (m, 4H), 7.63-7.70 (m, 1H), 7.54-7.61 (m, 2H), 6.99-7.05 (m, 2H), 3.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.6, 141.7, 138.2, 134.0, 129.9, 128.4, 125.2, 122.4, 46.6; IR (neat, cm^{-1}) 3078, 3006, 2922, 1585, 1499, 1336, 1269; MS (EI, *m/z*) 276 ($[M]^+$); Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14; found C, 56.66; H, 4.68; N, 9.96.

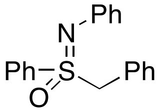
8-4-1-11. The synthesis of *rac-N*-[2,4,6-(trichloro)phenyl]-*S*-methyl-*S*-phenylsulfoximine (131n)



131n

The general procedure (method B) using *rac*-*S*-methyl-*S*-phenylsulfoximine (**65**, 77.6 mg, 0.50 mmol) and 1,3,5-trichloro-2-iodo-benzene (307.0 mg, 1.00 mmol) gave 100.0 mg (60%) of **131n** as a white solid. Mp. 101-103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22-8.18 (m, 2H), 7.70-7.56 (m, 3H), 7.32 (s, 2H), 3.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.1, 137.8, 133.6, 132.7, 129.4, 128.4, 128.3, 128.1, 45.1; IR (neat, cm^{-1}) 1444, 1298, 1218, 743; MS (EI, *m/z*) 334.9 ($[M]^+$); Anal. Calcd for $C_{10}H_{10}Cl_3NOS$: C, 46.66; H, 3.01; N, 4.19; found C, 46.38; H, 3.03; N, 3.99.

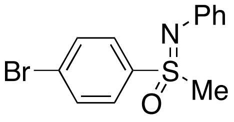
8-4-1-12. The synthesis of *rac-N*-(phenyl)-*S*-benzyl-*S*-phenylsulfoximine (132)



132

The general procedure (method A) using *S*-benzyl-*S*-phenylsulfoximine (**119**, 109.2 mg, 0.47 mmol) and phenyl iodide (200.5 mg, 0.983 mmol) gave 91.2 mg (63%) of **132** as a light brown solid. Mp. 148-151 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60-7.63 (m, 2H), 7.44-7.52 (m, 1H), 7.07-7.40 (m, 10H), 6.99-7.07 (m, 2H), 4.58 (d, *J* = 13.9 Hz, 1H), 4.52 (d, *J* =13.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.5, 136.1, 133.1, 131.1, 129.6, 128.8, 128.8, 128.6, 128.1, 127.9, 123.2, 121.6, 63.2; IR (neat, cm^{-1}) 3060, 2922, 1595, 1489,1289, 1263 1207, 1088; MS (EI, *m/z*) 307 ($[M]^+$); Anal. Calcd for $C_{19}H_{17}NOS$: C, 74.23; H, 5.57; N, 4.56; found C, 74.34; H, 5.52; N, 4.24.

8-4-1-13. The synthesis of *rac-N*-(phenyl)-*S*-4-bromo-phenyl-*S*-methylsulfoximine (133)



133

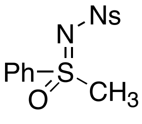
The general procedure (method A) using *p*-bromophenylmethyl sulfoximine **66** (117.0 mg, 0.50 mmol) and phenyl iodide (210.0 mg, 1.03 mmol) gave 82.0 mg (53%) of **133** as a yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.82-7.79 (m, 2H), 7.65-7.61 (m, 2H), 7.13-7.08 (m, 2H), 6.98-6.95 (m, 1H), 6.89-6.85 (m, 1H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.5, 138.4, 132.8, 130.2, 129.0, 128.4, 123.2, 121.9, 46.0; IR (neat, cm^{-1}) 3022, 2926, 1593, 1487, 1292, 1204, 1093; MS (EI, *m/z*) 309, 311 ([M]$^+$); Anal. Calcd for $C_{13}H_{12}BrNOS$: C, 50.33; H, 3.90; N, 4.52; found C, 50.11; H, 4.02; N, 4.80.

8-5. Silver-catalyzed and metal-free imination of sulfoxides and sulfides

8-5-1. General procedure for the imination of sulfoxides

To a suspension of the sulfoxide (0.25 mmol) or sulfide (0.25 mmol), sulfonylamide (0.3 mmol), PhI(OAc)$_2$ (121.0 mg, 0.37 mmol), AgNO$_3$ (3.4 mg, 0.02 mmol) and *t*Bu$_3$tpy (8.0 mg, 0.02 mmol) in CH$_3$CN (2 mL) was added at room temperature and the reaction mixture was stirred for overnight (16 h). The resulting mixture was concentrated under reduced pressure, and then the product purified by column chromatography to afford the corresponding sulfoximines.

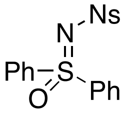
8-5-1-1. The synthesis of *N*-(4-nitro-benzenesulfonyl)methylphenylsulfoximine (180)[158]



180

Following the general procedure using methyl phenyl sulfoxide and NsNH$_2$ gave 71.1 mg (84%) of compound **180** as pale yellow solid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.32-8.27 (m, 2H), 8.17-8.13 (m, 2H), 8.03-7.99 (m, 2H), 7.77-7.71 (m, 1H), 7.66-7.60 (m, 2H), 3.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) d 149.7, 148.9, 137.7, 134.8, 129.9, 128.1, 127.3, 123.9, 46.8.

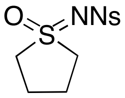
8-5-1-2. The synthesis of *N*-(4-Nitro-benzenesulfonyl)diphenylsulfoximine (194a)[158]



194a

Following the general procedure using phenyl sulfoxide and $NsNH_2$ gave 98.0 mg (98%) of compound **194a** as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30-8.27 (m, 2H), 8.18-8.14 (m, 2H), 8.02-7.98 (m, 4H), 7.65-7.61 (m, 2H), 7.58-7.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.7, 149.1, 139.4, 134.2, 129.7, 128.1, 127.6, 123.9.

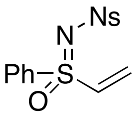
8-5-1-3. The synthesis of *N*-(4-nitro-benzenesulfonyl)tetramethylenesulfoximine (194b)



194b

Following the general procedure using tetramethylenesulfoxide and $NsNH_2$ gave 63.5 mg (84%) of compound **194b** as pale yellow solid. Mp. 222-225 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.44-8.41 (m, 2H), 8.15-8.12 (m, 2H), 3.80-3.73 (m, 2H), 3.58-3.40 (m, 2H), 2.29-2.16 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 150.2, 149.7, 128.5, 125.2, 54.7, 23.6; IR (neat, cm^{-1}) 3110, 2953, 1537, 1301, 1054; MS (CI, *m/z*) 305 ($[M+1]^+$); Anal. Calcd for $C_{10}H_{12}N_2O_5S_2$: C, 39.46; H, 3.97; N, 9.20; found C, 39.69; H, 4.37; N, 9.20.

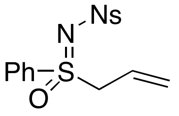
8-5-1-4. The synthesis of *N*-(4-nitro-benzenesulfonyl)methylvinylsulfoximine (194c)



194c

Following the general procedure using methylvinylsulfoxide and $NsNH_2$ gave 81.3 mg (92%) of compound **194c** as pale yellow solid. Mp. 150-151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32-8.30 (m, 2H), 8.16-8.14 (m, 2H), 7.98-7.96 (m, 2H), 7.74-7.70 (m, 1H), 7.64-7.60 (m, 2H), 6.85 (dd, *J* = 9.6, 16.2 Hz, 1H), 6.51 (dd, *J* = 1.7, 16.2 Hz, 1H), 6.26 (dd, *J* = 1.7, 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.0, 149.0, 137.2, 136.8, 134.7, 129.9, 129.8, 128.1, 127.9, 124.0; IR (KBr, cm^{-1}) 3114, 1792, 1523, 1158, 1104; MS (CI, *m/z*) 353 ($[M+1]^+$); Anal. Calcd for $C_{15}H_{15}N_2O_5S_2$ + $2H_2O$: C, 47.72; H, 3.43; N, 7.95; found C, 47.91; H, 3.80; N, 7.76.

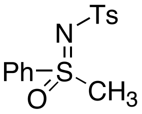
8-5-1-5. The synthesis of *N*-(4-nitro-benzenesulfonyl)allylmethylsulfoximine (194d)[158]



194d

Following the general procedure using allylmethyl sulfoxide and $NsNH_2$ gave 41.0 mg (91%) of compound **194d** as pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32-8.29 (m, 2H), 8.19-8.16 (m, 2H), 7.95-7.92 (m, 2H), 7.75-7.71 (m, 1H), 7.64-7.60 (m, 2H), 5.78-5.67 (m, 1H), 5.42 (d, *J* = 10.2 Hz, 1H), 5.21-5.17 (m, 1H), 4.35-4.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.6, 149.0, 134.7, 129.4, 128.5, 128.0, 127.3, 123.9, 122.7, 62.8.

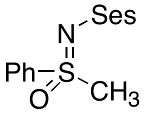
8-5-1-5. The synthesis of *N*-(*p*-toluenesulfonyl)methylphenylsulfoximine (194e)[158]



194e

Following the general procedure using methylphenylsulfoxide and $TsNH_2$ gave 60.9 mg (79%) of compound **194e** as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02-7.99 (m, 2H), 7.86-7.83 (m, 2H), 7.72-7.67 (m, 1H), 7.62-7.24 (m, 2H), 3.42 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.8, 140.6, 138.4, 134.3, 129.7, 129.3, 127.5, 126.6, 46.6, 21.5.

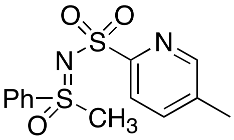
8-5-1-6. The synthesis of *N*-(trimethylsilylethylsulfonyl)methylphenylsulfoximine (194f)



194f

To a suspension of methylphenylsulfoxide (70.0 mg, 0.5 mmol), SES-NH_2[195] (108.0 mg, 0.6 mmol), $PhI(OAc)_2$ (242.0 mg, 0.8 mmol), $AgNO_3$ (3.4 mg, 0.02 mmol) and *t*-Bu_3tpy (8.0 mg, 0.02 mmol) in acetonitrile (4 mL) was added and the reaction mixture was heated to reflux for 90 min. The resulting mixture was concentrated under reduced pressure and purified by chromatography on silica gel to afford 119.5 mg (75%) of the desired compound **194f** as white solid. Mp. 106-108 °C; ^1H NMR ($CDCl_3$) δ 8.07-8.03 (m, 2H), 7.74-7.68 (m, 1H), 7.65-7.59 (m, 2H), 3.43 (s, 3H), 3.16-3.10 (m, 3H), 3.16-3.10 (m, 2H), 1.18-1.10 (m, 2H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 138.4, 134.4, 129.7, 127.4, 53.6, 46.5, 10.3, 1.9; MS (CI, *m/z*) 320 ($[M+1]^+$); Anal. Calcd for $C_{12}H_{21}NO_3S_2Si$: C, 45.11; H, 6.62; N, 4.38; found C, 45.21; H, 6.40; N, 4.29.

8-5-1-7. The synthesis of *N*-(*p*-methyl-2-pyridinylsulfonyl)methylphenylsulfoximine (194g)



194g

Following the general procedure using methylphenyl sulfoxide and *p*-methyl-2-pyridinyl sulfonyl amide gave 56.9 mg (73%) of compound **194g** as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.49-8.48 (m, 1H), 8.00-7.98 (m, 2H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.69-7.62 (m, 2H), 7.62-7.55 (m, 2H), 3.55 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.7, 149.9, 138.1, 137.8, 136.8, 134.2, 129.5, 127.3, 121.1, 46.3, 18.5; IR (KBr, cm^{-1}) 3015, 2924, 1453, 1326, 1166, 1059; MS (CI, *m/z*) 311 ($[M+1]^+$); Anal. Calcd for $C_{13}H_{14}N_2O_3S_2$: C, 50.30; H, 4.55; N, 9.03; found C, 50.33; H, 4.79; N, 9.10.

8-5-1-7. The synthesis of *N*-(aminophthalimido)methylphenylsulfoximine (194h)[156c]

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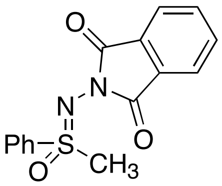
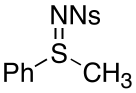
[195] For the synthesis of Ses-NH_2, see: Declerck, V.; Ribiere, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372.



194h

Following the general procedure using methylphenyl sulfoxide and *N*-aminophthalimide gave 64.1 mg (85%) of compound **194h** as a white solid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.21-8.18 (m, 2H), 7.72-7.68 (m, 2H), 7.64-7.58 (m, 3H), 7.56-7.52 (m, 2H), 3.32 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 166.8, 136.2, 134.2, 133.8, 130.5, 129.3, 129.2, 123.0, 42.5.

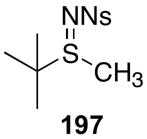
8-5-1-8. The synthesis of *N*-(4-nitro-benzenesulfonyl)methylphenylsulfilimine (196)[158]



196

Following the general procedure using methylphenylsulfide and NsNH$_2$ gave 67.2 mg (83%) of compound **196** as white solid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.22-8.18 (m, 2H), 8.01-7.98 (m, 2H), 7.71-7.68 (m, 2H), 7.60-7.55 (m, 1H), 7.53-7.49 (m, 2H), 2.92 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 149.7, 149.1, 135.0, 133.0, 130.2, 127.4, 125.9, 123.9, 39.1.

8-5-1-9. The synthesis of *N*-(4-nitro-benzenesulfonyl)-*tert*-butylmethylsulfilimine (197)[158]



197

Following the general procedure using *tert*-butylmethylsulfoxide and NsNH$_2$ gave 58.8 mg (77%) of compound **197** as white solid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.31-8.26 (m, 2H), 8.09-8.05 (m, 2H), 2.49 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 150.1, 149.1, 127.5, 124.0, 55.7, 28.0, 23.4.

8-5-2. Deprotection of *N*-(4-nitro-benzenesulfonyl)methylphenylsulfoximine (180) to give *NH*-methylphenylsulfoximine (65)

To a solution of compound **180** (170.0 mg, 0.5 mmol) in acetonitrile (4 mL) was added Cs_2CO_3 (293.0 mg, 0.9 mmol) and thiophenol (83.0 mg, 0.8 mmol) at room temperature and the reaction mixture was stirred overnight. Water was added to the reaction mixture and the product was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification by silica column chromatography gave 58.8 mg (76%) of compound **65** as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.05-8.01 (m, 2H), 7.68-7.55 (m, 3H), 3.12 (s, 3H), 2.78 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.3, 132.8, 129.0, 127.5, 46.1.

8-5-3. Representative procedure for the metal-free imination of sulfoxides

To the solution of sulfoxide (1.0 equiv) in anhydrous acetonitrile (0.15 M) was added $NsNH_2$ (1.2 equiv) and $PhI(OAc)_2$ (1.5 equiv) at rt under argon, and the reaction mixture was then heated to reflux for 16 h. Subsequently, the mixture was cooled to ambient temperature and concentrated under reduced pressure. Purification of the remaining product by column chromatography gave the corresponding *N*-nosyl sulfoximine in 75% yield (128.0 mg).

9. Appendix

9-1. Abbreviations

acac	acetylacetonate
BINAP	2,2’-bis(diphenylphosphanyl)-1,1’-binaphthyl
BINOL	2,2’-dihydroxy-1,1’-binaphthyl
BHC	*tert*-butylhypochlorite
Boc	*tert*-butoxycarbonyl
BOX	bisoxazoline
CHP	cumene hydroperoxide
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	dibenzylidenacetone
DBU	1,8-Diazabicyclo[5,4,0]-7-undecene
DCC	*N,N’*-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DET	diethyltartrate
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	dimethylforamide
DPPA	diphenylphosphoryl azide
DPPF	1,1´-bis(diphenylphosphino)ferrocene
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline ethyl 1,2-dihydro-2-ethoxy-1-quinolinecarboxylate
HBTU	*O*-benzotriazol-1-yl-*N,N,N’,N”*-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazide
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high performance/pressure liquid chromatography
LCHIPA	lithium(cyclohexyl)isopropyl amine
MSH	*O*-mesitylenesulfonylamine
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
Ns	*p*-nitrobenzenesulfonylamide

PPTS	pyridinum *p*-toluenesulfonate
Pfp	pentafluorophenyl
Py	pyridine
PyBox	2,2-bis(2-oxazolin-2-yl)pyridine
Ses	trimethylsilylethyl sulfonyl amide
TADDOL	α,α,α',α''-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethyanol
TBAF	tetrabutylammoniumfluoride
TBHP	*tert*-butylhydroperoxide
TBDMS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TMS	tetramethylsilyl
tpy	terpyridine
Ts	*p*-toluenesulfonylamide

9-2. Curriculum Vitae

Personal data

Name: Gae Young Cho
Date of birth: 02.04.1976
Nationality: Korean
Gender: Female

Education

Jul. 2002 - present	RWTH Aachen University, PhD student in organic chemistry, Supervisor : Prof. Dr. Carsten Bolm
Mar. 2001 – Feb. 2002	Ewha Womans University, graduate research student in organic chemistry, Supervisor : Prof. Dr. Soo Young Ko
Mar. 1999 – Feb. 2001	Ewha Womans University, M.S. degree in Molecular Life Sciences (organic chemistry)
Mar. 1995 – Feb. 1999	Ewha Womans University, B.S. degree in Chemistry

Work Experience

Jul. 2002 – Apr. 2006	Research Assistant to Prof. Dr. Carsten Bolm, RWTH Aachen University

Research Topic : Synthesis of New Sulfoximines for Asymmetric Synthesis and Pseudopeptides

Jul. 1998 – Feb. 2002	Research Assistant to Prof. Dr. Soo Young Ko, Ewha Womans University

Research Topic : Synthetic Methodology: Conversion of syn-Diols to syn-Amino Alcohols and aPNA Synthesis

Mar. 1995- Nov. 1999	Mathematics and Science Teacher in Educational Institution

Publications

(1) **Cho, G. Y.**; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 8007.
„ Metal-free Imination of sulfoxides and sulfides“
(2) **Cho, G. Y.**; Bolm, C. *Org. Lett*. **2005**, *7*, 4983.

„ Silver-catalyzed imination of sulfoxides and sulfides“

(3) **Cho, G. Y.**; Bolm, C. *Org. Lett.* **2005**, *7*, 1351.

„ Palladium-catalyzed α-arylation of sulfoximines“

(4) **Cho, G. Y.**; Okamura, H.; Bolm, C. *J. Org. Chem.* **2005**, *70*, 2346.

„ Palladium-catalyzed cross coupling reaction of enantiopure *p*-bromophenyl methyl sulfoximine“

(5) **Cho, G. Y.**; Remy, P.; Jansson, J.; Moessner, C.; Bolm, C. *Org. Lett.* **2004**, *6*, 3293.

„ Copper-mediated N-arylation of sulfoximines“

(6) **Cho, G. Y.**; Choi, J. Y.; Ko, S. Y. *Bulletin of the Korean Chemical Society* **2002**, *23*, 11.

„ The Cyclic Iminocarbonate Rearrangement: The Scope and Limitation of the N-Substituents“

(7) **Cho, G. Y.**; An, K. M.;Ko, S. Y. *Bulletin of the Korean Chemical Society* **2001**, *22*, 432.

„ Improving the Regioselectivity in the Cyclic Iminocarbonate Rearrangement: Enantioselective Synthesis of the Paclitaxel Side Chain“

(8) **Cho, G. Y.**; Park, J. N.; Ko, S. Y. *Tetrahedron Letters* **2000**, *41*, 1789.

„ Reversal of Regioselection in the Rearrangement of Cinnamate Diol Cyclic Iminocarbonates“

(9) **Cho, G. Y.**; Ko, S. Y. *Journal of Organic Chemistry* **1999**, *64*, 8745.

„ Expanding Synthetic Utilities of Asymmetric Dihydroxylation Reaction: Conversion of *syn*-Diols to *syn*-Amino Alcohols“

Representative Poster Presentations

1. “Silver-Catalyzed Imination of Sulfoxides and Sulfides”
   Cho, G. Y.; Bolm, C. NATO ASI Symposium, Siena, Italy, 2005
2. “Palladium-Catalyzed α-Arylation of Sulfoximines”
   Cho, G. Y.; Bolm, C. OMCOS Symposium, Geneva, Switzerland, 2005
3. “Palladium-Catalyzed α-Arylation of Sulfoximines”
   Cho, G. Y.; Bolm, C. Namur Meeting, Namur, Belgium, 2004
4. “Synthesis and Palladium Coupling Reaction of Enantiopure *p*-Bromophenyl Methyl Sulfoximine”
   Cho, G. Y.; Okamura, H.; Bolm, C. SFB Symposium, Jülich, Germany, 2003
5. “Synthetic Application of Cyclic Iminocarbonate Rearrangment: Enantioselective Syntheses of Chloramphenicol and 4-*Epi*-cytoxazone”

Park, J. N.; Gwan, S. J.; Cho, G. Y.; Ko, S. Y. American Chemical Society Meeting, San Diego, USA, 2001

6. “Enantioselective Synthesis of the Paclitaxel Side Chain”

Cho, G. Y.; Ko, So. Y. National Symposium of the Korean Chemical Society, Seoul, Korea, 2000

7. “Expanding Synthetic Utilities of Asymmetric Dihydroxylation Reaction: Conversion of *syn*-Diols to *syn*-Amino Alcohols”

Cho, G.Y.; Ko, S. Y. Peptide Symposium, Seoul, Korea, 1999

9-3. Acknowledgement

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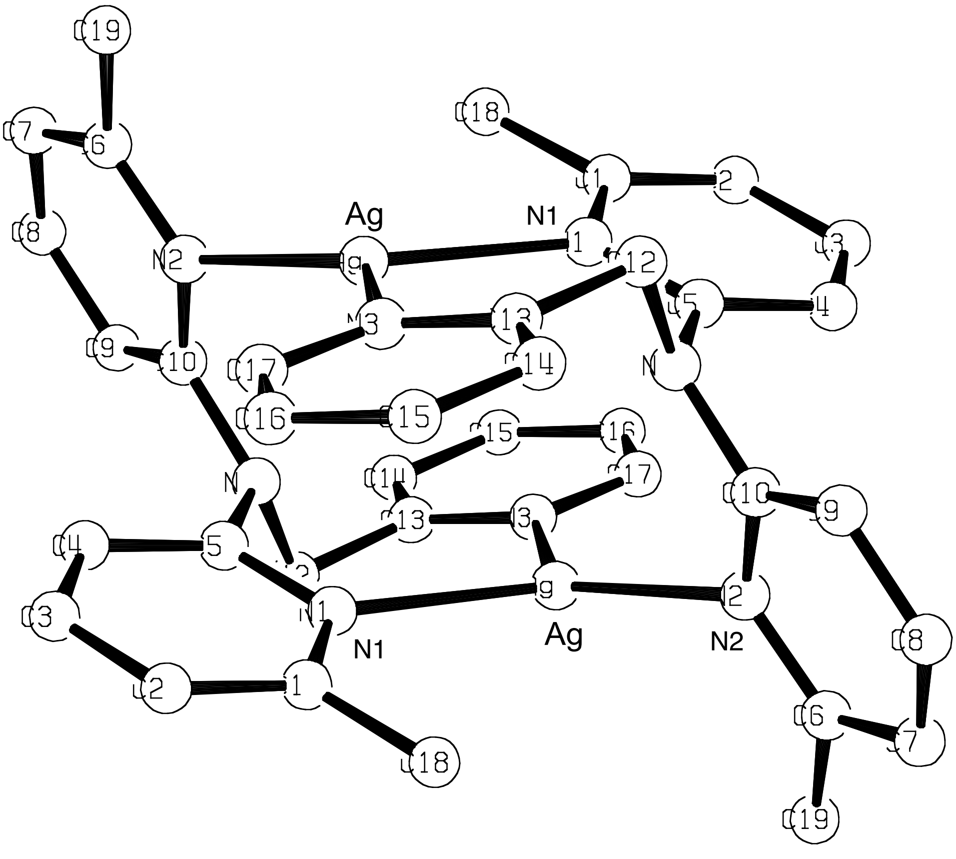
9-4. X-ray crystallographic data

Structure report No. AC/315

Internal code: GR0567

Date: 28.11.2005

(Datensammlung durch Dr. Lehmann MPI für Kohlenforschung Mülheim/Ruhr)



Experimental Details

Crystal data:

Chemical formula : $C_{18}H_{18}N_5O_3\cdot 1/2H_2O^{b)}$

formula weight : 568.76

Crystal system : monoclinic

Space group (No.) : *C*2/*c* (15)

Z : 8

a (Å) : 17.7955(2)

b (Å) : 14.6780(1)

c (Å) : 15.1056(1)

α (°) : 90.0

β (°) : 111.313(0)

γ (°) : 90.0

cell volume : 3675.77(5)$Å^3$

Density calc. : 1.696 g/cm^3

Radiation : MoKα (0.71073Å)

Range for lattice parameters : E<Θ<E

Absorption coefficient : 1.13mm^{-1}

Temperature : 100K

Crystal source : recrystallized from

Crystal colour : colourless

Crystal shape : irregular

Crystal size : ca.0.3x0.3x0.3mm

Data Collection

Diffractometer type : Bruker AXS Kappa CCD

collection method :

Absorption correction : SADABS

No. of reflections measured : 220142

No. of independent reflections: 11514

No. of observed reflections : 11029

Θ max (E)	40.23
hmin 6 hmax	-32 **6** 32
kmin 6 kmax	-26 **6** 26
lmin 6 lmax	-27 **6** 27
Criterion for observed	$I > 2\sigma(I)$
R_{int}	0.045(27)
Standard reflections	
Variation	
Refinement:	
On	F
Treatment of hydrogens	Located in part. Rest calculated in idealized positions. Us fixed at 1.5_U of the corresponding heavy atom. No refinement of hydrogen parameters
R	0.041
R_w	0.054
Weighting scheme	$w=1/[\sigma^2(F)+0.0004F^2]$
No. of parameters refined	254
No. of reflections in refmnt.	11029
Residual electron density	-1.44/1.82e/Å^3
r*[1]	not refined
XABS[2]	
Goodness of fit	1.787
Solution	XTAL3.7[3]
Remarks	[a)]From separate calculation [b)]The NO_3^- anion is disordered in that two of the three oxygen atoms occur in three positions. The disorder could be resolved and refined isotropically. The oxygen of the water molecule hydrogen-bonded

to the NO_3^- anion has been refined isotropically.

The water molecule occurs in two orientations and is hydrogen-bonded to the NO_3^- anion.Oxygen refinined isotropically. One hydrogen in a special position (_, 0.7519, _).

Definitions:

$$U_{eq} = 1/3\sum_i\sum_j U_{ij}a_i^*a_j^*\boldsymbol{a_i}\,\boldsymbol{a_j}$$

The anisotropic displacement factor in the structure factor expression is:

$$t = \exp[-2\pi^2(\sum_i\sum_j U_{ij}h_ih_ja_i^*a_j^*)]$$

Literature:

[1] a)A.C.Larson; Crystallographic Computing. F.R.Ahmed, S.R. Hall, C.P.Huber, eds., Munksgaard. Copenhagen: 291-294, (1970).
b)W.H.Zachariasen; Acta Cryst. 23, 558-564(1967).

[2] H.D.Flack; Acta Cryst. A39, 876-881(1983)

[3] S.R.Hall, D.J. du Boulay and R.Olthof-Hazekamp; Eds. XTAL3.7 System. University of Western Australia. Perth (2000).

Atomic Positional, Isotropic Displacement and Site Occupation Parameters

Atom	x/a	y/b	z/c		U_{eq} Å^2	PP
Ag	0.63727(1)	0.76874(1)	0.44399(1)	*	0.01986(6)	
O1a	0.5027(2)	0.6470(3)	0.5729(3)		0.032(1)	0.3340(-)
O1b	0.4903(2)	0.6154(3)	0.5469(3)		0.034(1)	0.3330(-)
O1c	0.5098(2)	0.7069(3)	0.6055(3)		0.031(1)	0.3330(-)
O2a	0.4802(2)	0.7454(3)	0.4590(2)		0.0190(-)	0.3340(-)
O2b	0.4922(5)	0.7531(5)	0.5022(7)		0.070(2)	0.3330(-)
O2c	0.4908(2)	0.7186(3)	0.4544(3)		0.024(1)	0.3330(-)
O3	0.38341(7)	0.68551(8)	0.49251(9)	*	0.0305(6)	
O	0.5340(3)	0.7560(3)	0.7343(4)		0.071(1)	0.5000(-)
N	0.72625(6)	0.59269(7)	0.55250(7)	*	0.0153(4)	
N1	0.69670(7)	0.73288(6)	0.60684(8)	*	0.0168(5)	
N2	0.86401(6)	0.57850(7)	0.58678(7)	*	0.0167(4)	
N3	0.61694(6)	0.64199(7)	0.35208(7)	*	0.0177(4)	
N4	0.45689(8)	0.6951(1)	0.5127(1)	*	0.0288(7)	
C1	0.69833(8)	0.79008(9)	0.67752(9)	*	0.0201(6)	
C2	0.7395(1)	0.7677(1)	0.7726(1)	*	0.0262(7)	
C3	0.77879(9)	0.6854(1)	0.79588(9)	*	0.0265(7)	
C4	0.77554(8)	0.62541(9)	0.72350(9)	*	0.0212(6)	
C5	0.73387(7)	0.65212(8)	0.62996(8)	*	0.0153(5)	
C6	0.93146(7)	0.52797(9)	0.6051(1)	*	0.0206(6)	
C7	0.92857(9)	0.4330(1)	0.5970(1)	*	0.0268(7)	
C8	0.85416(9)	0.39006(9)	0.5663(1)	*	0.0252(7)	
C9	0.78427(8)	0.44113(8)	0.54882(9)	*	0.0198(5)	
C10	0.79228(7)	0.53553(7)	0.56278(8)	*	0.0150(5)	
C12	0.64397(7)	0.55876(8)	0.49919(8)	*	0.0162(5)	
C13	0.62576(7)	0.55912(8)	0.39360(8)	*	0.0159(5)	
C14	0.61680(7)	0.47871(9)	0.34203(9)	*	0.0197(5)	
C15	0.59827(8)	0.4834(1)	0.24429(9)	*	0.0232(6)	
C16	0.58842(9)	0.5680(1)	0.20120(9)	*	0.0243(6)	
C17	0.59797(8)	0.64554(9)	0.25755(9)	*	0.0218(6)	
C18	0.6560(1)	0.8793(1)	0.6494(1)	*	0.0301(8)	
C19	1.01033(9)	0.5775(1)	0.6346(1)	*	0.0301(8)	
H8	0.8547(-)	0.3150(-)	0.5548(-)	*	0.038(-)	
H4	0.7918(-)	0.5719(-)	0.7275(-)	*	0.032(-)	
H17	0.6001(-)	0.7004(-)	0.2371(-)	*	0.032(-)	
H15	0.6001(-)	0.4297(-)	0.2120(-)	*	0.035(-)	
H9	0.7311(-)	0.4107(-)	0.5297(-)	*	0.027(-)	
H12a	0.6144(-)	0.5849(-)	0.5141(-)	*	0.024(-)	
H3	0.8079(-)	0.6669(-)	0.8645(-)	*	0.039(-)	
H14	0.6278(-)	0.4194(-)	0.3731(-)	*	0.030(-)	
H18c	0.6463(-)	0.9188(-)	0.7046(-)	*	0.045(-)	
H18a	0.6806(-)	0.9040(-)	0.6456(-)	*	0.045(-)	
H16	0.5787(-)	0.5763(-)	0.1394(-)	*	0.036(-)	
H7	0.9880(-)	0.3969(-)	0.6074(-)	*	0.041(-)	
H19a	1.0124(-)	0.6109(-)	0.6067(-)	*	0.045(-)	
H19c	1.0515(-)	0.5355(-)	0.6388(-)	*	0.045(-)	
H19b	1.0206(-)	0.6040(-)	0.6959(-)	*	0.045(-)	
H18b	0.6122(-)	0.8744(-)	0.5900(-)	*	0.045(-)	
H2	0.7416(-)	0.8083(-)	0.8232(-)	*	0.039(-)	
H12b	0.6398(-)	0.4975(-)	0.5188(-)	*	0.024(-)	
H02	0.5107(-)	0.7508(-)	0.6760(-)		0.250(-)	0.500(-)
H01	1/2	0.7519(-)	3/4		0.250(-)	

Atomic Displacement Parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Ag	0.02137(5)	0.01450(5)	0.02200(5)	0.00027(3)	0.00585(4)	0.00116(3)
N	0.0140(3)	0.0150(3)	0.0149(3)	0.0010(3)	0.0031(3)	-0.0020(3)
N1	0.0163(4)	0.0162(4)	0.0180(4)	0.0015(3)	0.0064(3)	-0.0021(3)
N2	0.0158(4)	0.0162(4)	0.0175(4)	0.0018(3)	0.0056(3)	0.0012(3)
N3	0.0159(4)	0.0188(4)	0.0174(4)	-0.0002(3)	0.0048(3)	0.0011(3)
N4	0.0297(6)	0.0313(6)	0.0290(6)	0.0105(5)	0.0150(5)	0.0071(5)
O1a	0.032(1)					
O2a	0.0190(-)					
O1c	0.031(1)					
O2b	0.070(2)					
O1b	0.034(1)					
O2c	0.024(1)					
O	0.071(1)					
O3	0.0300(5)	0.0230(4)	0.0391(6)	-0.0044(4)	0.0131(5)	-0.0025(4)
C1	0.0204(5)	0.0202(5)	0.0211(5)	0.0020(4)	0.0092(4)	-0.0045(4)
C2	0.0289(7)	0.0304(7)	0.0198(5)	0.0020(5)	0.0093(5)	-0.0084(4)
C3	0.0285(6)	0.0342(7)	0.0150(5)	0.0037(5)	0.0058(4)	-0.0035(4)
C4	0.0229(5)	0.0237(5)	0.0154(4)	0.0040(4)	0.0048(4)	0.0001(4)
C5	0.0143(4)	0.0159(4)	0.0153(4)	0.0003(3)	0.0051(3)	-0.0020(3)
C6	0.0174(5)	0.0205(5)	0.0249(5)	0.0035(4)	0.0087(4)	0.0014(4)
C7	0.0229(6)	0.0204(5)	0.0388(7)	0.0064(4)	0.0133(5)	0.0007(5)
C8	0.0264(6)	0.0169(5)	0.0329(7)	0.0044(4)	0.0116(5)	-0.0019(4)
C9	0.0211(5)	0.0148(4)	0.0224(5)	0.0010(4)	0.0066(4)	-0.0010(4)
C10	0.0161(4)	0.0141(4)	0.0144(4)	0.0022(3)	0.0052(3)	0.0007(3)
C12	0.0151(4)	0.0174(4)	0.0162(4)	-0.0014(3)	0.0056(3)	-0.0011(3)
C13	0.0138(4)	0.0176(4)	0.0152(4)	-0.0004(3)	0.0039(3)	-0.0011(3)
C14	0.0195(5)	0.0191(5)	0.0182(4)	-0.0016(4)	0.0040(4)	-0.0030(4)
C15	0.0241(5)	0.0253(6)	0.0186(5)	0.0008(4)	0.0058(4)	-0.0046(4)
C16	0.0237(5)	0.0311(6)	0.0173(5)	0.0011(5)	0.0063(4)	-0.0011(4)
C14	0.0195(5)	0.0191(5)	0.0182(4)	-0.0016(4)	0.0040(4)	-0.0030(4)
C17	0.0215(5)	0.0249(5)	0.0181(5)	0.0014(4)	0.0062(4)	0.0038(4)
C18	0.0371(7)	0.0222(6)	0.0327(7)	0.0065(5)	0.0148(6)	-0.0057(5)
C19	0.0184(5)	0.0272(6)	0.0447(8)	0.0015(5)	0.0115(5)	0.0037(6)
H8	0.038(-)	0.038(-)	0.038(-)	0.000(-)	0.014(-)	0.000(-)
H4	0.032(-)	0.032(-)	0.032(-)	0.000(-)	0.012(-)	0.000(-)
H17	0.032(-)	0.032(-)	0.032(-)	0.000(-)	0.012(-)	0.000(-)
H15	0.035(-)	0.035(-)	0.035(-)	0.000(-)	0.013(-)	0.000(-)
H9	0.027(-)	0.027(-)	0.027(-)	0.000(-)	0.010(-)	0.000(-)
H12a	0.024(-)	0.024(-)	0.024(-)	0.000(-)	0.009(-)	0.000(-)
H3	0.039(-)	0.039(-)	0.039(-)	0.000(-)	0.014(-)	0.000(-)
H14	0.030(-)	0.030(-)	0.030(-)	0.000(-)	0.011(-)	0.000(-)
H18c	0.045(-)	0.045(-)	0.045(-)	0.000(-)	0.016(-)	0.000(-)
H18a	0.045(-)	0.045(-)	0.045(-)	0.000(-)	0.016(-)	0.000(-)
H16	0.036(-)	0.036(-)	0.036(-)	0.000(-)	0.013(-)	0.000(-)
H7	0.041(-)	0.041(-)	0.041(-)	0.000(-)	0.015(-)	0.000(-)
H19a	0.045(-)	0.045(-)	0.045(-)	0.000(-)	0.016(-)	0.000(-)
H19c	0.045(-)	0.045(-)	0.045(-)	0.000(-)	0.016(-)	0.000(-)
H19b	0.045(-)	0.045(-)	0.045(-)	0.000(-)	0.016(-)	0.000(-)
H18b	0.045(-)	0.045(-)	0.045(-)	0.000(-)	0.016(-)	0.000(-)
H2	0.039(-)	0.039(-)	0.039(-)	0.000(-)	0.014(-)	0.000(-)
H12b	0.024(-)	0.024(-)	0.024(-)	0.000(-)	0.009(-)	0.000(-)
H02	0.250(-)					
H01	0.250(-)					

Bond Distances	(Angstroms)
O3-N4	1.238(2)
N4-O2b	1.103(9)
N4-O1a	1.203(4)
N4-O2a	1.273(4)
N4-O2c	1.284(5)
N4-O1b	1.328(4)
N4-O1c	1.386(4)
O1a-O1b	.596(6)
O1a-O1c	.992(6)
O2a-O2c	.453(5)
O2a-O2b	.62(1)
O1c-H02	1.240(4)
O1c-O1b	1.575(6)
O1c-O2b	1.62(1)
O2b-O2c	.87(1)
O-H01	.728(7)
O-H02	.830(5)
O-O	1.45(1)
Ag-N3	2.270(1)
N2-C10	1.350(2)
N2-C6	1.351(2)
N1-C5	1.340(1)
N1-C1	1.350(2)
N-C10	1.406(2)
N-C5	1.426(2)
N-C12	1.478(1)
C5-C4	1.392(2)
C10-C9	1.401(2)
C12-H12a	.749(1)
C12-H12b	.957(1)
C12-C13	1.508(2)
C13-N3	1.351(2)
C13-C14	1.391(2)
N3-C17	1.344(2)
C2-H2	.960(2)
C2-C3	1.376(2)
C2-C1	1.393(2)
C16-H16	.894(1)
C16-C15	1.384(2)
C16-C17	1.394(2)
C9-H9	.990(1)
C9-C8	1.393(2)
C14-H14	.975(1)
C14-C15	1.393(2)
C1-C18	1.494(2)
C6-C7	1.399(2)
C6-C19	1.497(2)
C17-H17	.869(1)
C15-H15	.933(1)
C4-H4	.831(1)
C4-C3	1.388(2)
C3-H3	1.013(1)
C7-H7	1.142(2)
C7-C8	1.385(2)
C8-H8	1.116(1)
C18-H18a	.587(2)
C18-H18b	.953(1)
C18-H18c	1.080(2)
C19-H19a	.656(2)
C19-H19c	.943(2)
C19-H19b	.959(2)

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Bond Angles        (degrees)

 O2b-N4-O1a             107.3(5)
 O2b-N4-O3              131.1(4)
 O2b-N4-O2a              29.1(5)
 O2b-N4-O2c              42.1(6)
 O2b-N4-O1b             122.5(5)
 O2b-N4-O1c              80.6(5)
 O1a-N4-O3              119.0(3)
 O1a-N4-O2a             122.3(3)
 O1a-N4-O2c             108.5(3)
 O1a-N4-O1b              26.6(2)
 O1a-N4-O1c              44.4(3)
 O3-N4-O2a              117.9(2)
 O3-N4-O2c              125.4(2)
 O3-N4-O1b              106.3(2)
 O3-N4-O1c              122.2(2)
 O2a-N4-O2c              20.4(2)
 O2a-N4-O1b             123.7(3)
 O2a-N4-O1c             108.2(2)
 O2c-N4-O1b             104.4(3)
 O2c-N4-O1c             110.1(3)
 O1b-N4-O1c              70.9(2)
 O1b-O1a-O1c            165.2(7)
 O1b-O1a-N4              88.5(5)
 O1c-O1a-N4              77.6(3)
 O2c-O2a-O2b            108(1)
 O2c-O2a-N4              81.1(7)
 O2b-O2a-N4              60.0(9)
 O1a-O1c-H02            147.7(5)
 O1a-O1c-N4              58.0(3)
 O1a-O1c-O1b              5.5(3)
 O1a-O1c-O2b             87.0(5)
 H02-O1c-N4             136.4(3)
 H02-O1c-O1b            148.9(4)
 H02-O1c-O2b            123.1(4)
 N4-O1c-O1b              52.8(2)
 N4-O1c-O2b              42.1(3)
 O1b-O1c-O2b             83.7(4)
 O2a-O2b-O2c             29.4(6)
 O2a-O2b-N4              90.9(9)
 O2a-O2b-O1c            144(1)
 O2c-O2b-N4              80.1(7)
 O2c-O2b-O1c            119.3(7)
 N4-O2b-O1c              57.4(5)
 O1a-O1b-N4              64.9(5)
 O1a-O1b-O1c              9.3(4)
 N4-O1b-O1c              56.3(2)
 O2a-O2c-O2b             42.2(7)
 O2a-O2c-N4              78.5(8)
 O2b-O2c-N4              57.8(7)
 H01-O-H02              100.6(6)
 H01-O-O                  4.7(3)
 H02-O-O                101.0(5)
 O-H02-O1c              143.5(4)
 O-H01-O                170.6(5)
 C10-N2-C6              118.8(1)
 C5-N1-C1               118.5(1)
 C10-N-C5               116.62(9)
 C10-N-C12              118.8(1)
 C5-N-C12               115.7(1)
 N1-C5-C4               122.9(1)
 N1-C5-N                115.88(9)
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C4-C5-N	121.1(1)
N2-C10-C9	122.5(1)
N2-C10-N	114.9(1)
C9-C10-N	122.6(1)
H12a-C12-H12b	104.3(2)
H12a-C12-N	109.2(1)
H12a-C12-C13	114.3(1)
H12b-C12-N	108.69(9)
H12b-C12-C13	108.6(1)
N-C12-C13	111.4(1)
N3-C13-C14	122.2(1)
N3-C13-C12	116.0(1)
C14-C13-C12	121.8(1)
C17-N3-C13	118.0(1)
C17-N3-Ag	122.74(8)
C13-N3-Ag	119.21(8)
H2-C2-C3	118.2(1)
H2-C2-C1	121.9(1)
C3-C2-C1	119.9(1)
H16-C16-C15	123.8(2)
H16-C16-C17	117.5(2)
C15-C16-C17	118.6(1)
H9-C9-C8	120.4(1)
H9-C9-C10	121.6(1)
C8-C9-C10	118.0(1)
H14-C14-C13	121.8(1)
H14-C14-C15	118.9(1)
C13-C14-C15	119.1(1)
N1-C1-C2	121.3(1)
N1-C1-C18	117.2(1)
C2-C1-C18	121.5(1)
N2-C6-C7	121.8(1)
N2-C6-C19	117.5(1)
C7-C6-C19	120.7(1)
H17-C17-N3	112.8(1)
H17-C17-C16	123.4(1)
N3-C17-C16	123.0(1)
H15-C15-C16	122.3(1)
H15-C15-C14	118.2(1)
C16-C15-C14	118.9(1)
H4-C4-C3	128.9(1)
H4-C4-C5	112.5(1)
C3-C4-C5	118.4(1)
H3-C3-C2	121.3(1)
H3-C3-C4	119.7(1)
C2-C3-C4	118.9(1)
H7-C7-C8	124.0(1)
H7-C7-C6	116.6(1)
C8-C7-C6	118.9(1)
H8-C8-C7	116.1(1)
H8-C8-C9	124.0(1)
C7-C8-C9	119.8(1)
H18a-C18-H18b	109.8(2)
H18a-C18-H18c	94.5(2)
H18a-C18-C1	104.5(2)
H18b-C18-H18c	117.5(2)
H18b-C18-C1	110.9(1)
H18c-C18-C1	117.1(1)
H19a-C19-H19c	108.0(3)
H19a-C19-H19b	106.2(2)
H19a-C19-C6	115.9(2)
H19c-C19-H19b	109.3(1)
H19c-C19-C6	109.0(1)

H19b-C19-C6	108.2(2)

Dihedral Angles	(degrees)
O3-N4-O1a-O1c	-107.7(4)
O3-N4-O1a-O1b	67.0(7)
O2a-N4-O1a-O1c	83.3(5)
O2a-N4-O1a-O1b	-101.9(7)
O1c-N4-O1a-O1c	-.0(4)
O1c-N4-O1a-O1b	174.8(9)
O2b-N4-O1a-O1c	55.7(7)
O2b-N4-O1a-O1b	-129.5(8)
O1b-N4-O1a-O1c	-174.8(9)
O1b-N4-O1a-O1b	.0(7)
O2c-N4-O1a-O1c	100.1(4)
O2c-N4-O1a-O1b	-85.1(7)
O3-N4-O2a-O2b	125(1)
O3-N4-O2a-O2c	-117.3(5)
O1a-N4-O2a-O2b	-66(1)
O1a-N4-O2a-O2c	51.7(6)
O1c-N4-O2a-O2b	-19(1)
O1c-N4-O2a-O2c	98.7(6)
O2b-N4-O2a-O2b	0(1)
O2b-N4-O2a-O2c	117(1)
O1b-N4-O2a-O2b	-97(1)
O1b-N4-O2a-O2c	19.9(6)
O2c-N4-O2a-O2b	-117(1)
O2c-N4-O2a-O2c	.0(6)
O3-N4-O1c-O1a	100.1(4)
O3-N4-O1c-O2b	-133.0(5)
O3-N4-O1c-O1b	97.6(3)
O3-N4-O1c-H02	-42.0(6)
O1a-N4-O1c-O1a	.0(5)
O1a-N4-O1c-O2b	126.9(6)
O1a-N4-O1c-O1b	-2.5(4)
O1a-N4-O1c-H02	-142.1(7)
O2a-N4-O1c-O1a	-117.8(4)
O2a-N4-O1c-O2b	9.0(5)
O2a-N4-O1c-O1b	-120.3(3)
O2a-N4-O1c-H02	100.1(5)
O2b-N4-O1c-O1a	-126.9(6)
O2b-N4-O1c-O2b	-.0(7)
O2b-N4-O1c-O1b	-129.3(6)
O2b-N4-O1c-H02	91.0(7)
O1b-N4-O1c-O1a	2.5(4)
O1b-N4-O1c-O2b	129.3(6)
O1b-N4-O1c-O1b	.0(3)
O1b-N4-O1c-H02	-139.6(6)
O2c-N4-O1c-O1a	-96.3(4)
O2c-N4-O1c-O2b	30.5(5)
O2c-N4-O1c-O1b	-98.8(3)
O2c-N4-O1c-H02	121.6(5)
O3-N4-O2b-O2a	-73(1)
O3-N4-O2b-O1c	124.9(5)
O3-N4-O2b-O2c	-100.5(7)
O1a-N4-O2b-O2a	126.2(8)
O1a-N4-O2b-O1c	-35.9(4)
O1a-N4-O2b-O2c	98.8(6)
O2a-N4-O2b-O2a	-.0(5)
O2a-N4-O2b-O1c	-162(1)
O2a-N4-O2b-O2c	-27.5(6)
O1c-N4-O2b-O2a	162(1)
O1c-N4-O2b-O1c	.0(3)
O1c-N4-O2b-O2c	134.6(6)
O1b-N4-O2b-O2a	102.0(8)

O1b-N4-O2b-O1c	-60.1(5)
O1b-N4-O2b-O2c	74.6(7)
O2c-N4-O2b-O2a	27.5(6)
O2c-N4-O2b-O1c	-134.6(6)
O2c-N4-O2b-O2c	.0(3)
O3-N4-O1b-O1a	-123.0(7)
O3-N4-O1b-O1c	-119.1(3)
O1a-N4-O1b-O1a	-.0(7)
O1a-N4-O1b-O1c	3.9(6)
O2a-N4-O1b-O1a	95.8(7)
O2a-N4-O1b-O1c	99.6(3)
O1c-N4-O1b-O1a	-3.9(6)
O1c-N4-O1b-O1c	-.0(3)
O2b-N4-O1b-O1a	61(1)
O2b-N4-O1b-O1c	64.8(7)
O2c-N4-O1b-O1a	102.8(7)
O2c-N4-O1b-O1c	106.7(3)
O3-N4-O2c-O2a	74.5(6)
O3-N4-O2c-O2b	114.6(6)
O1a-N4-O2c-O2a	-135.6(6)
O1a-N4-O2c-O2b	-95.5(7)
O2a-N4-O2c-O2a	-.0(5)
O2a-N4-O2c-O2b	40.0(8)
O1c-N4-O2c-O2a	-88.4(6)
O1c-N4-O2c-O2b	-48.4(7)
O2b-N4-O2c-O2a	-40.0(8)
O2b-N4-O2c-O2b	-.0(9)
O1b-N4-O2c-O2a	-163.0(5)
O1b-N4-O2c-O2b	-123.0(6)
N4-O1a-O1c-N4	-.0(1)
N4-O1a-O1c-O2b	-32.5(4)
N4-O1a-O1c-O1b	21(3)
N4-O1a-O1c-H02	127.6(8)
O1b-O1a-O1c-N4	-21(3)
O1b-O1a-O1c-O2b	-53(4)
O1b-O1a-O1c-O1b	0(3)
O1b-O1a-O1c-H02	107(3)
N4-O1a-O1b-N4	.0(1)
N4-O1a-O1b-O1c	-20(3)
O1c-O1a-O1b-N4	20(3)
O1c-O1a-O1b-O1c	0(1)
N4-O2a-O2b-N4	.0(1)
N4-O2a-O2b-O1c	26(1)
N4-O2a-O2b-O2c	68(1)
O2c-O2a-O2b-N4	-68(1)
O2c-O2a-O2b-O1c	-42(2)
O2c-O2a-O2b-O2c	.0(8)
N4-O2a-O2c-N4	.00(8)
N4-O2a-O2c-O2b	-54(1)
O2b-O2a-O2c-N4	54(1)
O2b-O2a-O2c-O2b	0(1)
N4-O1c-O2b-N4	-.0(1)
N4-O1c-O2b-O2a	-32(2)
N4-O1c-O2b-O2c	-53.5(7)
O1a-O1c-O2b-N4	42.8(5)
O1a-O1c-O2b-O2a	11(2)
O1a-O1c-O2b-O2c	-11(1)
O1b-O1c-O2b-N4	38.3(4)
O1b-O1c-O2b-O2a	7(2)
O1b-O1c-O2b-O2c	-15.2(9)
H02-O1c-O2b-N4	-124.6(5)
H02-O1c-O2b-O2a	-156(2)
H02-O1c-O2b-O2c	-178.1(8)

N4-O1c-O1b-N4	.0(1)
N4-O1c-O1b-O1a	158(4)
O1a-O1c-O1b-N4	-158(4)
O1a-O1c-O1b-O1a	0(4)
O2b-O1c-O1b-N4	-31.4(4)
O2b-O1c-O1b-O1a	126(4)
H02-O1c-O1b-N4	120.2(6)
H02-O1c-O1b-O1a	-82(4)
N4-O1c-H02-O	165.3(7)
O1a-O1c-H02-O	62(1)
O2b-O1c-H02-O	-141.6(8)
O1b-O1c-H02-O	73(1)
N4-O2b-O2c-N4	.0(1)
N4-O2b-O2c-O2a	110(1)
O2a-O2b-O2c-N4	-110(1)
O2a-O2b-O2c-O2a	0(1)
O1c-O2b-O2c-N4	43.4(6)
O1c-O2b-O2c-O2a	153(2)
H01-O-H02-O1c	-125.3(6)
O-O-H02-O1c	-130.1(6)
H02-O-H01-O	-96(3)
O-O-H01-O	0(3)
H02-O-O-H01	85(3)
H01-O-O-H01	-.0001
O-H01-O-O	0(3)
C6-N2-C10-N	175.0(1)
C6-N2-C10-C9	-5.2(2)
C10-N2-C6-C7	2.1(2)
C10-N2-C6-C19	-178.1(1)
C1-N1-C5-N	176.6(1)
C1-N1-C5-C4	-1.4(2)
C5-N1-C1-C2	1.9(2)
C5-N1-C1-C18	-179.7(1)
C10-N-C5-N1	147.0(1)
C10-N-C5-C4	-34.9(2)
C12-N-C5-N1	-65.9(2)
C12-N-C5-C4	112.2(1)
C5-N-C10-N2	-52.5(2)
C5-N-C10-C9	127.8(1)
C12-N-C10-N2	161.5(1)
C12-N-C10-C9	-18.2(2)
C5-N-C12-C13	138.4(1)
C5-N-C12-H12a	11.2(2)
C5-N-C12-H12b	-101.9(1)
C10-N-C12-C13	-75.3(1)
C10-N-C12-H12a	157.5(1)
C10-N-C12-H12b	44.4(2)
N1-C5-C4-C3	-.2(2)
N1-C5-C4-H4	174.5(1)
N-C5-C4-C3	-178.1(1)
N-C5-C4-H4	-3.5(2)
N2-C10-C9-C8	4.0(2)
N2-C10-C9-H9	-178.5(1)
N-C10-C9-C8	-176.2(1)
N-C10-C9-H9	1.2(2)
N-C12-C13-N3	-70.1(1)
N-C12-C13-C14	111.4(1)
H12a-C12-C13-N3	54.3(2)
H12a-C12-C13-C14	-124.3(1)
H12b-C12-C13-N3	170.2(1)
H12b-C12-C13-C14	-8.3(2)
C12-C13-N3-Ag	3.6(1)
C12-C13-N3-C17	-177.8(1)

C14-C13-N3-Ag	-177.9(1)
C14-C13-N3-C17	.8(2)
C12-C13-C14-C15	178.6(1)
C12-C13-C14-H14	-6.9(2)
N3-C13-C14-C15	.1(2)
N3-C13-C14-H14	174.6(1)
Ag-N3-C17-C16	177.5(1)
Ag-N3-C17-H17	6.9(2)
C13-N3-C17-C16	-1.1(2)
C13-N3-C17-H17	-171.7(1)
C3-C2-C1-N1	-.8(3)
C3-C2-C1-C18	-179.1(2)
H2-C2-C1-N1	179.2(2)
H2-C2-C1-C18	.8(3)
C1-C2-C3-C4	-.9(3)
C1-C2-C3-H3	-178.4(2)
H2-C2-C3-C4	179.2(2)
H2-C2-C3-H3	1.7(3)
C15-C16-C17-N3	.5(2)
C15-C16-C17-H17	170.1(1)
H16-C16-C17-N3	-176.4(1)
H16-C16-C17-H17	-6.8(3)
C17-C16-C15-C14	.4(2)
C17-C16-C15-H15	-170.9(1)
H16-C16-C15-C14	177.1(2)
H16-C16-C15-H15	5.8(3)
C10-C9-C8-C7	.3(2)
C10-C9-C8-H8	-177.5(1)
H9-C9-C8-C7	-177.2(2)
H9-C9-C8-H8	5.0(3)
C13-C14-C15-C16	-.7(2)
C13-C14-C15-H15	170.9(1)
H14-C14-C15-C16	-175.4(1)
H14-C14-C15-H15	-3.7(2)
N1-C1-C18-H18c	167.4(1)
N1-C1-C18-H18a	-89.6(2)
N1-C1-C18-H18b	28.7(2)
C2-C1-C18-H18c	-14.2(2)
C2-C1-C18-H18a	88.8(3)
C2-C1-C18-H18b	-152.9(2)
N2-C6-C7-C8	2.1(3)
N2-C6-C7-H7	174.6(1)
C19-C6-C7-C8	-177.7(2)
C19-C6-C7-H7	-5.3(2)
N2-C6-C19-H19a	-51.9(3)
N2-C6-C19-H19c	-174.0(2)
N2-C6-C19-H19b	67.2(2)
C7-C6-C19-H19a	127.9(2)
C7-C6-C19-H19c	5.9(3)
C7-C6-C19-H19b	-112.9(2)
C5-C4-C3-C2	1.3(2)
C5-C4-C3-H3	178.8(1)
H4-C4-C3-C2	-172.3(2)
H4-C4-C3-H3	5.2(3)
C6-C7-C8-C9	-3.2(3)
C6-C7-C8-H8	174.7(1)
H7-C7-C8-C9	-175.1(2)
H7-C7-C8-H8	2.9(3)