Highlight Review

Sulfoximines: Synthesis and Catalytic Applications

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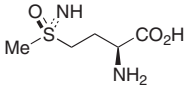
Abstract

Chiral sulfoximines have a stereogenic center at the sulfur atom and their use in asymmetric synthesis is well established. Recently, sulfoximines have been recognized as an interesting new class of chiral ligands, which can be applied in various asymmetric metal catalyses. This review summarizes the latest progress in synthetic methods towards sulfoximines and the application of chiral derivatives in catalytic asymmetric reactions.

♦ 1. Introduction

The chemistry of sulfoximines started in the late 1940's with the search for a toxic substance, which was formed during the bleaching of wheat with NCl_3.[1] In 1949, a methionine derivative with a highly oxidized stereogenic sulfur atom (methionine sulfoximine, Figure 1) was isolated and identified as the key component.[1d] The first enantiopure sulfoximine was prepared in 1965.[2] Subsequently, many asymmetric reactions using chiral sulfoximines have been developed,[3] and intensive biological and physiological studies have been performed.[4]



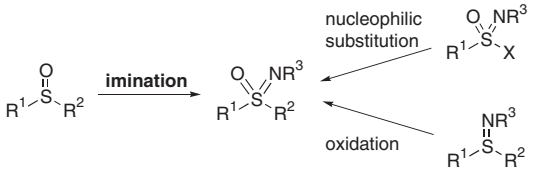
Methionine sulfoximine

Figure 1.

The first use of a chiral sulfoximine in a catalytic asymmetric reaction was reported in 1992.[5] Since then the research in this area has significantly been intensified, and enantioselectivities of up to 99% ee have been achieved.[6] Because several excellent overviews covering the work on sulfoximines until the 1990's have already been published,[3] this review will only focus on recent progress in synthetic studies and applications in asymmetric catalysis initiated in the late 1990's.

♦ 2. Synthesis of Sulfoximines

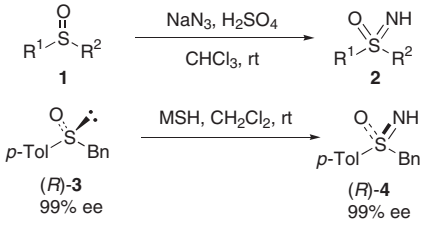
Three different approaches have been developed for the synthesis of sulfoximines (Scheme 1). The most direct and widely used one is the oxidative imination of sulfoxides. Since the other two methods involving nucleophilc substitutions and sulfilimine oxidations have already been well covered in the former reviews[3] and no significant improvements have been reported since then, this chapter only highlights recent progress made in sulfoxide imination reactions.



Scheme 1.

2.1 Non-catalytic Methods

The oldest but most frequently used method for the imination of sulfoxides to give sulfoximines utilizes mixtures of sodium azide and sulfuric acid.[7] These toxic reagents and the harsh reaction conditions can be avoided by using *O*-mesitylenesulfonylhydroxylamine (MSH) as iminating agent.[8] One of the major advantages of this method is that the stereochemistry at sulfur is retained allowing to convert optically active sulfoxides into the corresponding sulfoximines with retention of configuration (Scheme 2).[8b]



Scheme 2.

An interesting electrochemical oxidation was recently developed by Yudin.[9] This method is also applicable for iminations of chiral sulfoxides, and the resulting *N*-phthalimide sulfoximines are formed stereospecifically. Noteworthy is the fact that the products can be transformed into synthetically valuable *N*–H sulfoximines by a subsequent electrochemical reductive N–N-bond cleavage (Scheme 3).

For the synthesis of enantiopure sulfoximines the MSH and the electrochemical method rely on the accessibility of the corresponding optically active sulfoxides. The latter, however, are often difficult to prepare in multi-grams quantities, and furthermore, none of the imination reactions are practical enough to

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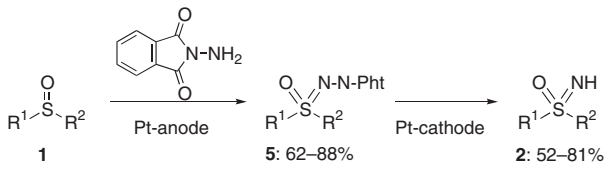
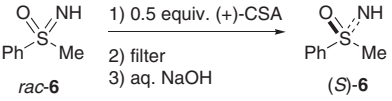


Scheme 3.

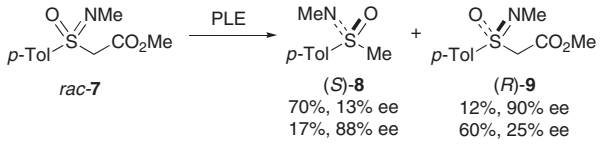
synthesize sulfoximines in enantiopure form on a large scale. For that reason many applications of optically active sulfoximines make use of a single starting material, *N*-methyl-*N*-phenylsulfoximine (**6**), which is easily prepared as a racemate on standard routes and resolved with camphorsulfonic acid (CSA) following well-established protocols. This sequence was first described by Fusco,[2] and after several improvements[10a–c] Gais developed a highly practical protocol, which now is applicable for almost mole-scale separations (Scheme 4).[10d]



Scheme 4.

Unfortunately, attempts to widen the substrate scope and to extend this CSA-based resolution to other chiral sulfoximines have remained unsuccessful to date.

Recently, Kielbasinski described the resolution of racemic sulfoximine **7** using an enzyme (Scheme 5).[11] Although products with high ee were only obtained at low conversion, this alternative approach appears promising and deserves particular attention in future work.

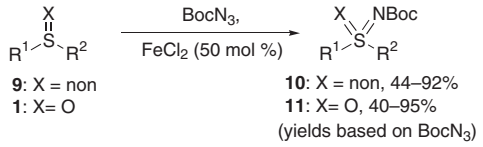


Scheme 5.

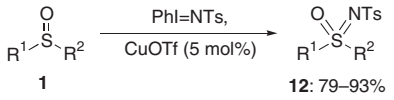
2.2 *Metal-catalyzed Methods*

Significant progress has recently been reported in metal-catalyzed oxidative iminations, which proceed under very mild reaction conditions and allow to stereospecifically convert chiral sulfoxides into sulfoximines. A copper(0)-catalyzed imination with tosylazide as nitrene source was already reported as early as 1967.[12] The efficiency of this process, however, was rather limited and an excess amount of metal was required to reach satisfactory yields. More than 30 years later, two research groups independently reported on major improvements of such metal-catalyzed imination reactions at almost same time. Bach described (on April 28, 1998) that $FeCl_2$ was capable to catalyze iminations of sulfoxides (and sulfides) with $BocN_3$.[13] Though the efficiency of this catalysis was not high, the resulting *N*-Boc sulfoximines could easily be converted into the synthetically useful *N*–H derivatives, which rendered this method most attractive (Scheme 6).

Müller reported (on April 29, 1998) that CuOTf was an efficient catalyst for the sulfoxide imination with PhI=NTs (Scheme 7).[14] Substrates having C–C double bonds were also nicely converted, providing sulfoximines in good yields.

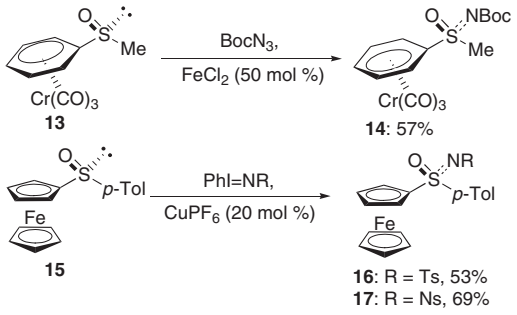


Scheme 6.



Scheme 7.

Bolm applied these metal-catalyzed imination reactions in syntheses of sulfoximines having benchrotrene and ferrocene skeletons.[15] Although benchrotrene sulfoxide **13** was unstable under oxidative conditions, the transformation of **13** with $FeCl_2$-$BocN_3$ proceeded well to give sulfoximine **14** in good yield. The imination of the less reactive ferrocene sulfoxide **15** was achieved by using a Cu(I) catalyst and PhI=NR. A combination of $CuPF_6$ and PhI=NNs proved to be even more efficient (Scheme 8).



Scheme 8.

The advantage of the imination with $CuPF_6$ and PhI=NR was also recognized by other groups. Thus, Nakayama reported that this combination was effective for the imination of the relatively unstable thiophene sulfoxide **18**.[16] Tye found that the Cu(I)-catalyzed imination proceeded well even with substrates such as **20** and **22**, which were not converted by MSH (Scheme 9).[17]

Tye also described efficient deprotections of *N*–Ns (Ns = nosyl) and *N*–Ses (Ses = trimethylsilylethylsulfonyl) sulfoximines. Since most *N*–Ts sulfoximines were difficult to transform into their *N*–H counterparts, this improvement expanded the synthetic utility of *N*-sulfonylated sulfoximines significantly (Scheme 10).[17]

In 2002, Malacria found that $Cu(OTf)_2$ was an active catalyst for this type of imination (Scheme 11).[18] Even rather complex sulfoxides including those having triple bonds and a sterically hindered substituent were efficiently converted into the corresponding sulfoximines.

Recently, we reported a new oxidative imination using

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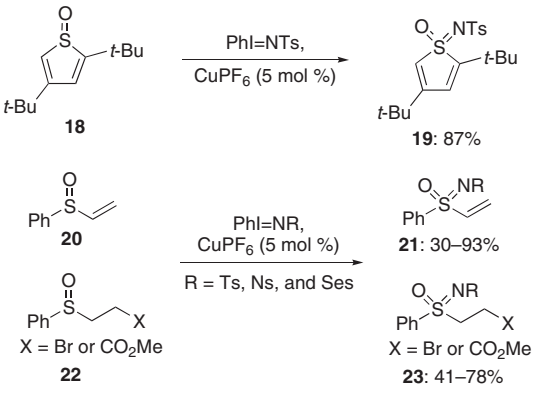
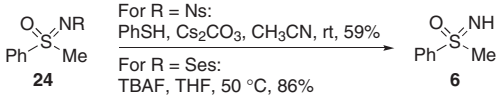
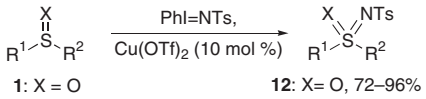


Scheme 9.

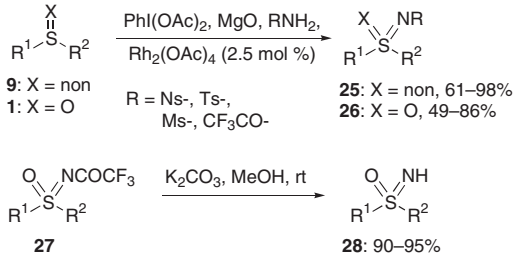


Scheme 10.



Scheme 11.

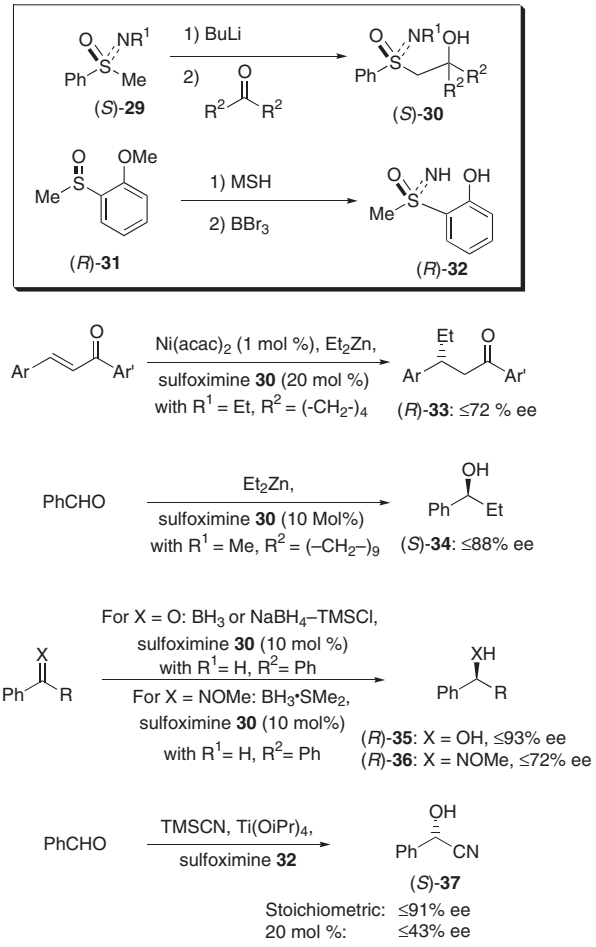
$Rh_2(OAc)_4$ as catalyst.[19] The reaction conditions are very mild, and with a combination of alkyl- or arylsulfonamides and iodobenzenediacetate the corresponding protected sulfoximines are formed in good yield. Noteworthy, the reaction with trifluoroacetamide as nitrene source also proceeds well. Since the resulting *N*–$COCF_3$ sulfoximines are easily deprotected, this reaction is a practical indirect method for the preparation of the synthetically useful *N*–H sulfoximines (Scheme 12).



Scheme 12.

♦ 3. Catalytic Applications

Despite the fact that the first asymmetric reaction using a chiral sulfoximine-based reagent (an enantioselective reduction of an alkylphenyl ketone with stoichiometric amounts of a β-hydroxysulfoximine borane complex) was reported by Johnson as early as 1979,[20] the progress in this area remained slow and no catalytic reactions with chiral sulfoximine ligands were reported in the 1980's. An intensive search for catalytic applications was initiated by Bolm in 1992, who first focused on asymmetric 1,4-additions to enones.[5] In these nickel-catalyzed reactions β-hydroxysulfoximines **30**, that can easily be prepared by addition of sulfoximine carbanions to ketones (and subsequent aqueous work-up), were applied. Later, the use of the same ligand type was studied in other nucleophilic addition reactions as shown in Scheme 13.[21–23] Phenolic sulfoximine **32** was then developed for the enantioselective formation of cyanohydrines.[24] The synthesis of **32** involved the intermediacy of optically pure anisylmethyl sulfoxide, which was prepared by Kagan's asymmetric sulfide oxidation.[25] Unfortunately, however, the catalytic efficiency of this phenolic sulfoximine was low, and in contrast to reactions with **30**, a stoichiometic amount of **32** was required for the achievement of high enantioselectivities.

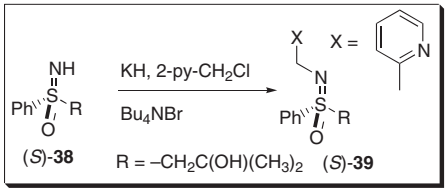


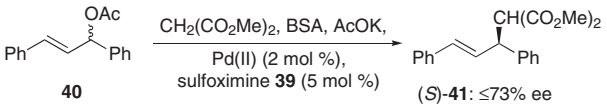
Scheme 13.

As ligands for asymmetric transition metal catalysts *N*,*N*-bidentate sulfoximines were designed. Because of the low nucleophilicity of the sulfoximine nitrogen, only reactive electrophiles could be applied. Among several derivatives, *N*-2-pyridylmethyl sulfoximine **39** was found to be a good ligand for Pd-catalyzed *C*-allylation reactions (Scheme 14).[26]

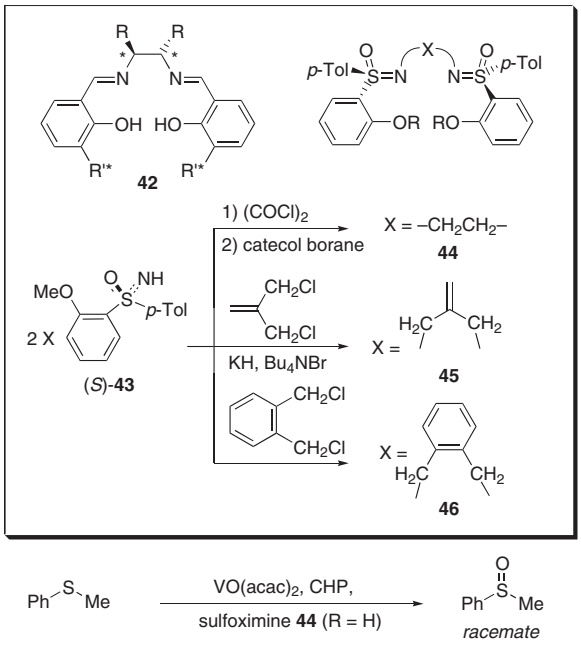
Subsequently, C_2-symmetric bissulfoximine **44**–**46**, which are reminiscent of chiral salens **42**, were prepared and examined in vanadium-catalyzed sulfide oxidations. However, only racemic products were obtained (Scheme 15).[27]

C_2-Symmetric bissulfoximine **47**, which was prepared by an acylation-reduction sequence,[28] was used in the Pd-catalyzed *C*-



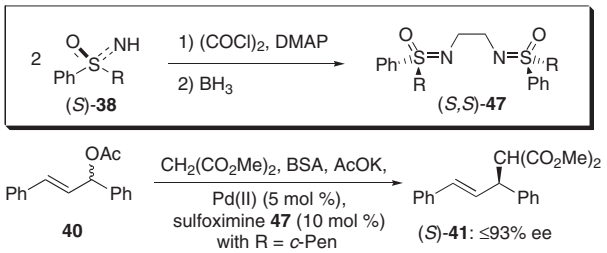


Scheme 14.



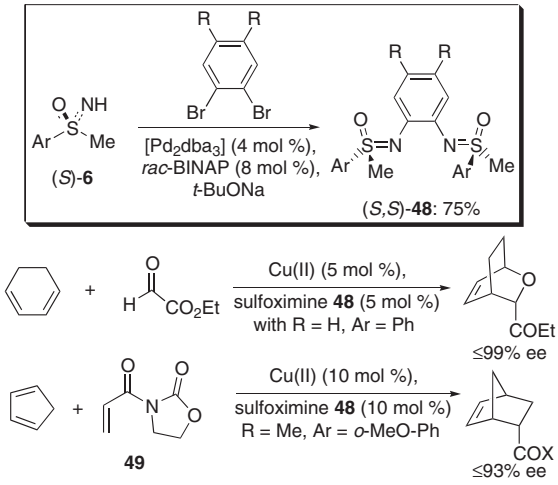
Scheme 15.

allylation of **40** to give **41** (Scheme 16).[29] The reaction proceeded with high enantioselectivity (up to 93% ee) and prompted further examinations of C_2-symmetric sulfoximine ligands.



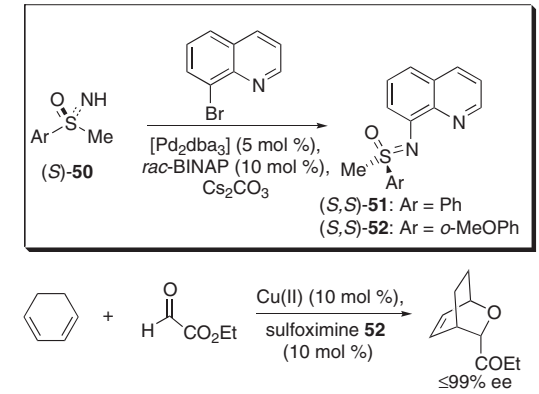
Scheme 16.

The development of a Pd-catalyzed *N*-arylation reaction was a major breakthrough for the alternation of the sulfoximine nitrogen.[30] Following Diver's modified Hartwig–Buchwald protocol,[31] which involves a strong base and [Pd_2dba_3] as catalyst, a double coupling starting from 1,2-dibromobenzene proceeded well affording C_2-symmetric bissulfoximine **48** in good yield.[32] This compound proved to be a highly effective ligand in Cu(II)-catalyzed Diels–Alder and hetero Diels–Alder reactions, where products with up to 99% ee were obtained (Scheme 17).[32,33] Noteworthy, excellent results were also achieved with only 0.5 mol % of the catalyst, which led to products with 98% ee in the hetero Diels–Alder reaction.



Scheme 17.

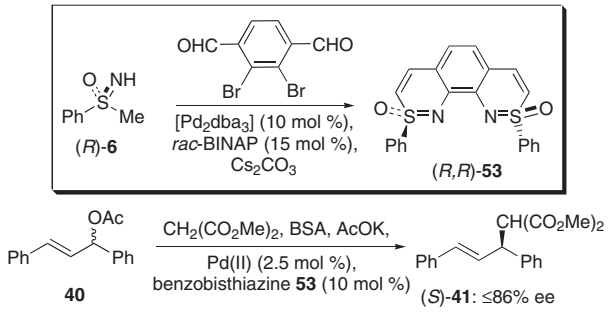
The structural analysis of the intermediate obtained from bissulfoximine **48**, $Cu(OTf)_2$, and substrate **49** showed an unsymmetrical distorted square-planar arrangement, which suggested that the C_2-symmetry of the ligand was not essential for achieving a high enantioselectivity in this reaction.[34] On the basis of this finding, simple C_1-symmetric monosulfoximines were synthesized, and also with them good enantioselectivities, which compared well with those obtained with C_2-symmetric **48**, were achieved in hetero Diels–Alder reactions (Scheme 18).[35] Interestingly, ligands having an *ortho*-methoxy substituent at the sulfoximine aryl (Ar) gave the best results, which suggested that the metal was close to this aryl moiety. Indeed, an X-ray crystal structure analysis of the $Cu(OTf)_2$ complex of **52** confirmed this assumption.[35]



Scheme 18.

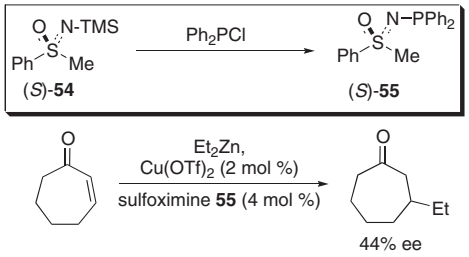
Other C_2-symmetric sulfoximine-derived ligands[6] were prepared by Harmata, who focused on the synthesis of 1,2-benzothiazines.[36] An efficient one-pot cyclization reaction involving

a Pd-catalyzed *N*-arylation and subsequent base-mediated intramolecular condensation of the sulfoximine group with the carbonyl substituent gave rise to unique C_2-symmetric bisbenzothiazine **53**, which showed good enantioselectivity in a Pd-catalyzed *C*-allylation reaction (Scheme 19).[37]



Scheme 19.

Tye reported the synthesis of *N*-phosphinated sulfoximines and their application in Cu-catalyzed asymmetric 1,4-additions.[38] Though the enantioselectivity of this reaction was not high, phosphine/sulfoximine combinations appear to be promising (Scheme 20).



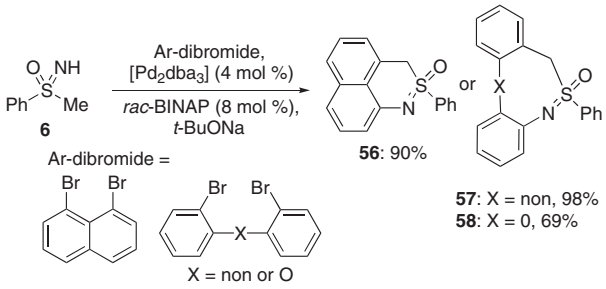
Scheme 20.

♦ 4. Novel Synthetic Applications of Sulfoximines and Future Catalytic Use

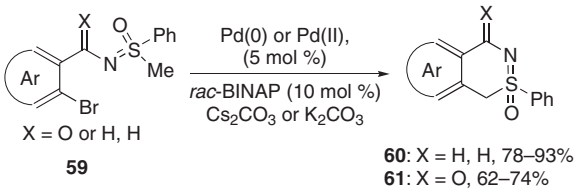
"New" reactions are needed for the development of "new" chiral ligands to be used in "new" catalytic reactions. Because of their unique properties sulfoximines open preparative opportunities, which might eventually lead to major breakthroughs in synthesis and asymmetric catalysis. The Pd-catalyzed heterocyclization of 1,8-dibromonaphthalene or 2,2′-dibromobiphenyl derivatives is an interesting example reported by Bolm.[39] Originally, the authors intended to synthesize C_2-symmetric bissulfoximines by double *N*-arylations. However, the resulting products were six to eight membered heterocycles obtained from successive Pd-catalyzed *N*- and *C*-arylations (Scheme 21).

Further studies of this novel heterocyclization revealed that *N*-2-bromobenzyl- and *N*-2-bromobenzoylsulfoximines **59** were suitable starting materials as well. Both substrates were smoothly converted into the corresponding six membered heterocycles (Scheme 22).[40]

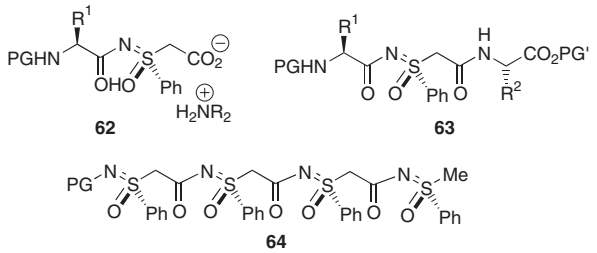
Finally, conceptually based on the structural similarity between α-carboxysulfoximines and β-amino acids, pseudo-peptides with sulfoximine units have been prepared. Bolm established efficient syntheses of various pseudo-di- and -tripeptides as



Scheme 21.



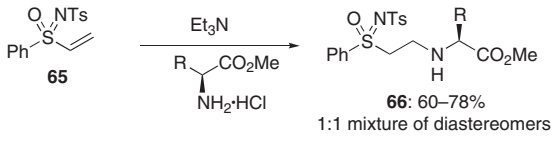
Scheme 22.



Scheme 23.

well as homo-oligomers (Scheme 23).[41] Besides having interesting physiological properties, they might eventually serve as chiral ligands due to their appropriate array of multiple nitrogen atoms and the steric impact of the amino acids.

A different type of sulfoximine/amino acid combination was reported by Tye.[42] In this case, β-aminosulfoximines **66** were prepared by conjugated additions of the amino acids to vinylsulfoximine **65** following a protocol, which was originally introduced by Annunziata[43] (Scheme 24).



Scheme 24.

In summary, catalytic applications of sulfoximines have only recently been studied in greater detail, and the initial results reveal an enormous potential of these chiral sulfur reagents in catalytic asymmetric synthesis. The recent progress with respect to their preparative methods allow them now to be synthesized in enantiopure form on a large scale, and with this improved accessibility new horizons in sulfoximine-based catalytic reactions have been opened.

♦ Acknowledgement

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Dedicate in memory to Dr. Anne Giese.

References and Notes

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