A Catalytic Enantioselective Aza-Michael Reaction: Novel Protocols for Asymmetric Synthesis of β-Amino Carbonyl Compounds

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β-Amino carbonyl functionalities are ubiquitous motifs in natural and nonnatural products such as alkaloids and polyketides. Among the reactions for the synthesis of β-amino carbonyl compounds and β-substituted β-amino acids, aza-Michael reactions using catalytic amounts of chiral Lewis acids might provide the best methods for the generation of optically active β-amino carbonyl compounds. During the last five years, the asymmetric aza-Michael reaction has emerged as a very powerful tool for the synthesis of chiral β-amino carbonyl compounds, as will be discussed in this microreview.

1. Introduction

Among the traditional methodologies for generating chiral β-amino carbonyl compounds, Mannich-type reactions and other asymmetric additions to carbon–nitrogen double bonds are classical and powerful methods for the synthesis of these moieties through carbon–carbon bond formation.[1] However, owing to simplicity and atom economy, 1,4-addition of a nitrogen nucleophile to the β-carbon vinylogously attached to an electron-withdrawing group, the so-called aza-Michael reaction, is a convenient way to introduce an amine function.[2] Aza-Michael addition of a nitrogen-centered source is a convenient way to introduce an amine-based functionality to a β-carbon attached to an electron-withdrawing group.[3,4] Sometimes, hydroamination of an activated olefin (1,2-addition) is also represented as special aza-Michael reaction. Hydroamination is the direct reaction of alkene and alkynes with N–H bonds, which is a highly attractive route for the synthesis of nitrogen-containing compounds.[5] It is recognized that metal activation of either the olefinic/acetylenic bond or the amine is generally required as a preliminary step in catalytic hydroamination reactions.[6] In the aza-Michael reaction, single transition metal based Lewis acids, which coordinate with α,β-unsaturated carbonyl compounds (activated olefins), are often competitively displaced by the amine.[7] In the past few years, the development of novel and efficient synthetic methods leading to chiral β-amino ketones, β-amino acids, and their derivatives has attracted much attention in organic synthesis, and much effort has been expended on seeking transition metal catalysts for aza-Michael reactions.[8] However, the catalytic, enantioselective

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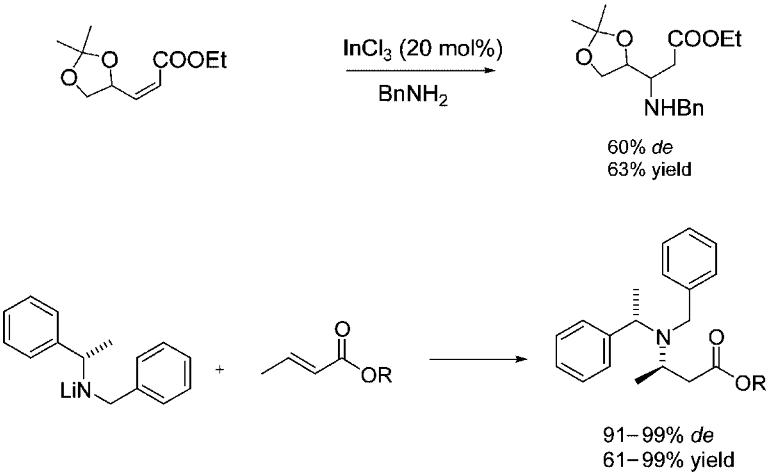
aza-Michael reaction is still one of the major challenges in synthetic organic and organometallic chemistry.

2. Asymmetric Aza-Michael Reactions

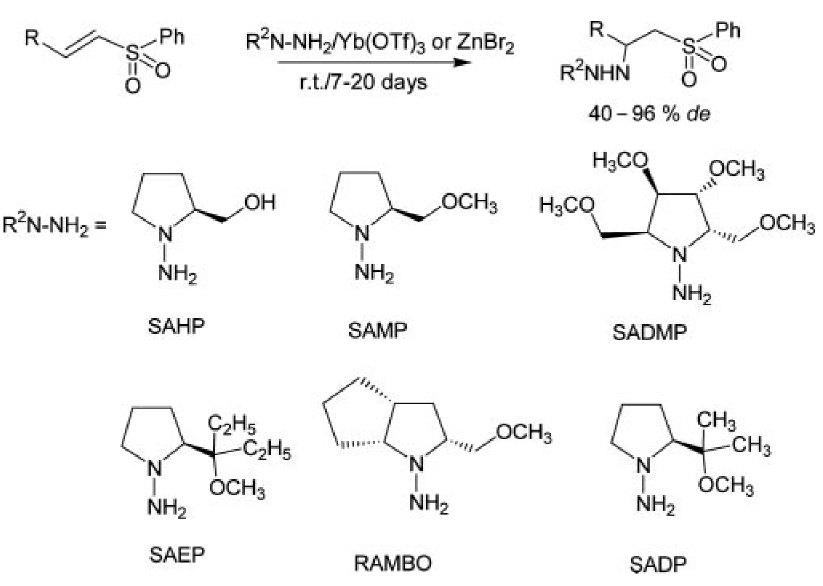
The impressive achievements in asymmetric aza-Michael reactions made to date rely on the use of chiral auxiliaries as the main stereochemical controllers. The enantioselective syntheses of β-amino carbonyl compounds use classical stoichiometric aza-Michael reactions with chiral auxiliaries or enantiomerically pure starting materials, as shown in large numbers of reports.[9] There are two major ways to achieve asymmetric induction: by using chiral amines or chiral acceptors (Scheme 1). Of these studies, one remarkable advance in the chiral-amine-controlled aza-Michael reaction was achieved by Enders and coworkers (Scheme 2).[10] This group developed the aza-Michael reaction of (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) and its derivatives with alkenyl sulfones to afford the corresponding β-amino sulfonates with high diastereomeric excesses (up to 96% *de*). The most exciting development in this area, however, was achieved by Tomioka et al., (Scheme 3) who developed efficient chiral-ether-mediated asymmetric conjugate addition of a lithium amide to enoates, which provides a powerful new methodology for the construction of chiral β-amino carbonyl moieties with high enantioselectivity (91–99% *ee*).[11] However, the development of efficient chiral catalysts for the aza-Michael reaction remains a significant challenge.

2.1. Catalytic Asymmetric Aza-Michael Reactions of Hydroxylamine Derivatives

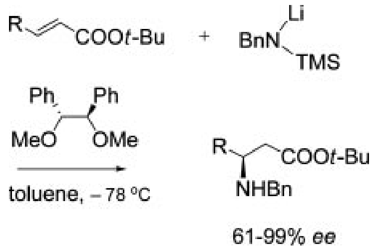
Undoubtedly the most elegant and most economically attractive way to introduce chirality into a molecule is by using a catalytic amount of a chiral controller to induce the enantioselective amine addition. To date, one of the most exciting applications of this strategy is the asymmetric aza-



Scheme 1. Asymmetric aza-Michael reaction of amines to enoates with chiral auxiliaries

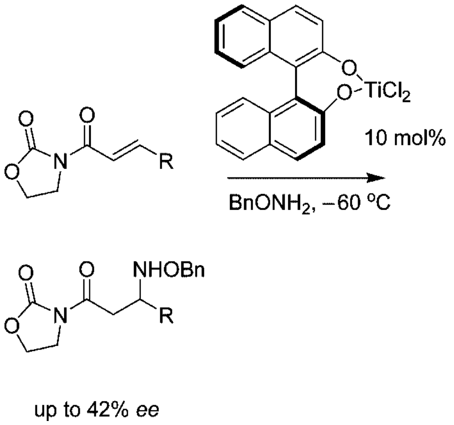


Scheme 2. Asymmetric aza-Michael reaction of amines to enoates with chiral auxiliaries, as reported by Enders and coworkers[10]



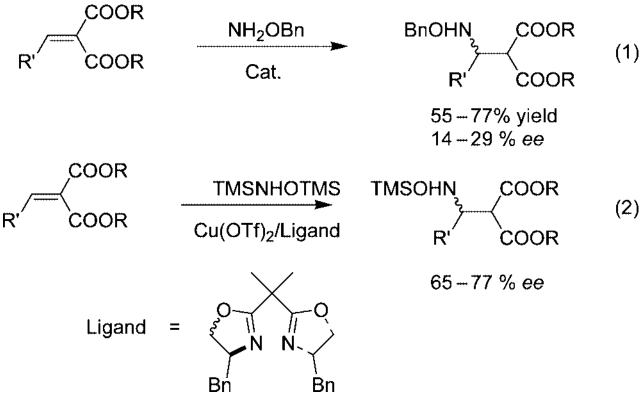
Scheme 3. Chiral-ether-controlled asymmetric aza-Michael addition of lithium amides to enoates

Michael reaction of hydroxylamine derivatives. The first example of enantioselective aza-Michael addition of hydroxylamines to acceptors was reported by Jørgensen et al. in 1996 (Scheme 4).[12] In a similar manner, Sibi et al.[13] have recently developed a highly enantioselective protocol for the aza-Michael addition of *O*-benzylhydroxylamine to 3,5-dimethylpyrazole-derived enoates using catalytic amounts of a chiral Lewis acid prepared from $MgBr_2{\cdot}OEt_2$ and a bisoxazoline [Equation (1) in Scheme 5]. Since they are more nucleophilic than *O*-substituted hydroxylamines, *N*-substituted hydroxylamines such as BnNHOH can undergo aza-Michael addition to α,β-unsaturated enoates to generate isoxazolidiones, which are precursors for β-amino carbonyl compounds. On the basis of previous studies, Sibi and coworkers later investigated a Mg-bisbox-based Lewis acid catalyst for the aza-Michael addition of BnNHOH to pyrazolidinone-derived acceptors.[14] Very recently, they extended the substrates to α,β-disubstituted imide-derived acceptors [Equation (2) in Scheme 5] and found that magnesium triflimide gave optimal enantioselectivity in the presence of the same bisoxazoline (up to 96% *ee*).[15]



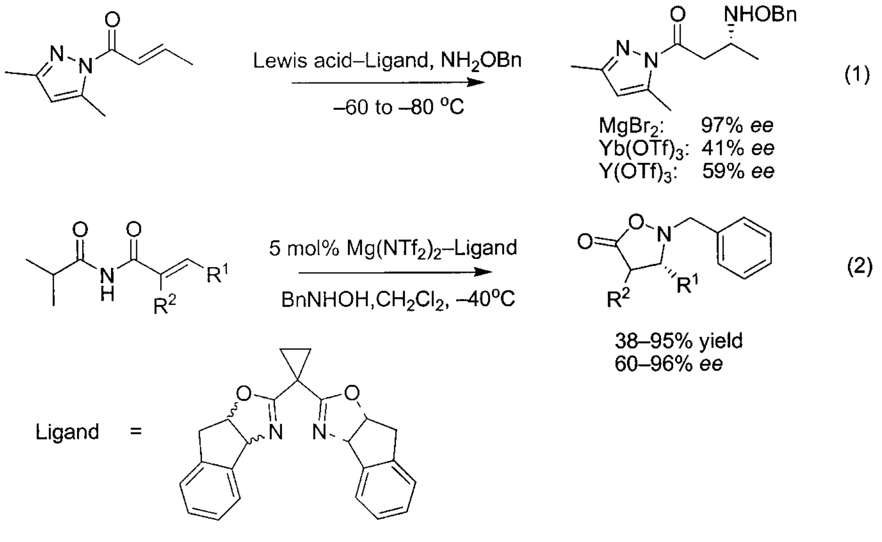
Scheme 4. Chiral Lewis acid catalyzed aza-Michael addition of amines

Independently, Cardillo and coworkers discovered that low to moderate *ee*'s (up to 29% *ee*) could be obtained in the aza-Michael addition of $BnONH_2$ to doubly activated acceptors in the presence of a Cu^{II}-box complex [Equation (1) in Scheme 6].[16a] They further improved the selectivity to up to 77% by use of a bulkier amine nucleophile, *N*,*O*-bis(trimethylsilyl)hydroxylamine [Equation (2) in Scheme 6].[16b]

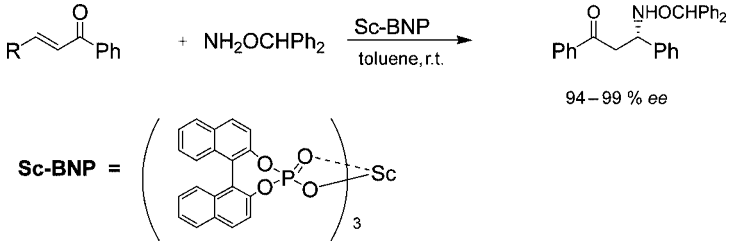


Scheme 6. Asymmetric catalytic aza-Michael addition of special hydroxylamine derivatives

In the presence of chiral rare-earth-metal complexes as the catalyst, *O*-alkylhydroxylamines can be reacted with α,β-unsaturated ketones to afford the corresponding chiral



Scheme 5. Asymmetric catalytic aza-Michael addition of hydroxylamine derivatives



Scheme 7. Chiral Lewis acid catalyzed asymmetric aza-Michael reaction of *O*-alkylhydroxylamines

β-amino ketones. The use of Sc-BNP catalyst and *O*-(diphenylmethyl)hydroxylamine as a nitrogen source under optimized conditions was found to provide the desired β-amino ketones with high enantioselectivity (up to 99% *ee*) in almost quantitative yield (Scheme 7).[17]

As described by Hartwig and coworkers,[7a] Lewis acids catalyze the addition of hydroxylamine derivatives to substituted acrylates, and provide chiral products in high enantiomeric excess. However, these Lewis acid catalysts are likely to be poisoned by alkyl and arylamine reagents.

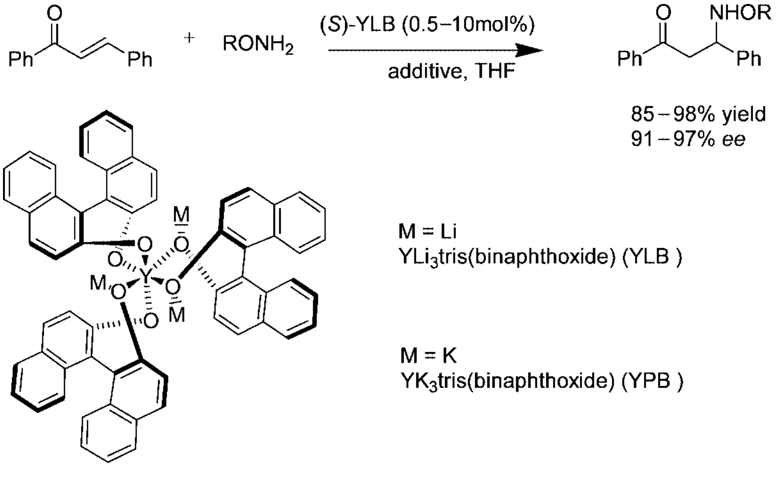
Shibasaki et al.[18] have developed an interesting heterobimetallic catalyst that contains rare-earth and alkali metals for the aza-Michael addition of *O*-alkylhydroxylamines to enones (Scheme 8). The YLi_3tris(binaphthoxide) species have chiral chelating binaphthyl groups in their coordination spheres and give the best reactivity and enantioselectivity (up to 97% *ee*). Although the substrate scope is somewhat limited, the results imply that neither amines nor products inhibit the heterobimetallic catalysis.

2.2. Catalytic Asymmetric Aza-Michael Reactions of Aromatic and Aliphatic Amines

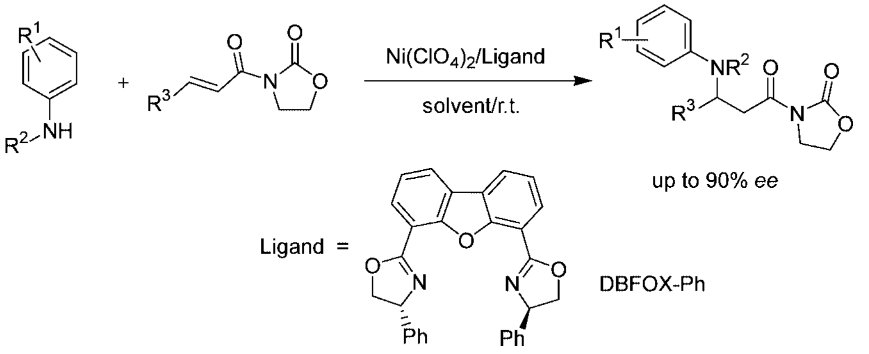
The first stereoselective aza-Michael addition of secondary aromatic amines to an acyl pyrrolidine was investigated by Jørgensen et al. (Scheme 9). The reaction of *N*-methylaniline with *N*-alkenoyl oxazolidinones proceeds well in the presence of $Ni(ClO_4)_2{\cdot}6H_2O$/DBFOX-Ph as the Lewis acid catalyst.[19] The selectivity and chemical efficiency were found to be dependent on the reaction conditions, including solvents, catalyst, and other metal-salt-based Lewis acids. The absolute configuration of the product was determined to be *S*. Sundararajan and Prabagaran have utilized a novel polymer-supported chiral catalyst in the aza-Michael addition of $BnNH_2$ to ethyl cinnamate for the synthesis of chiral β-aryl-β-amino esters with high enantioselectivity (81% *ee*).[20] It should be noted that the work-up of this reaction is simple: only a filtration step is needed for purification of the final product, and the catalyst can be easily recovered by washing with acid (Scheme 10).

In 2003 Togni et al.[21] reported the hydroamination of α,β-unsaturated carbonyl compounds catalyzed by Ni^{2+}-phosphane complexes (Scheme 11), and later that same year Hii et al. described their new findings with excellent enantioselectivity using Pd^{2+}-Binap for the addition of aromatic amines.[22,23] Hii found that the reaction with electron-rich amines did not achieve a synthetically useful level. This phenomenon may be due to the basic character of amines, which causes deactivation of the Lewis acid catalysts by coordination to the metal center and results in uncontrolled reactions.

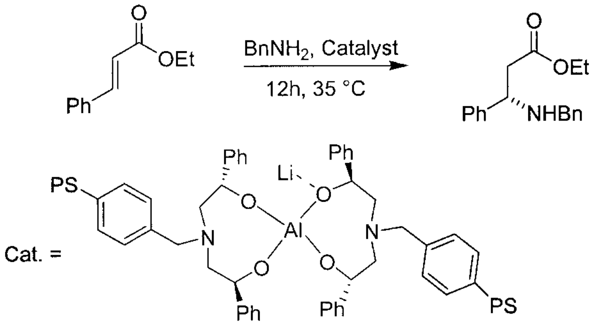
Very recently, Sodeoka et al.[24] have introduced a more robust, binuclear Pd catalyst for such processes. In this reaction, appropriate regulation of the amino functionality was achieved by the combined use of Pd-BINAP and an amine salt ($RNH_2{\cdot}TfOH$, Scheme 12). As a result, both decomposition of the catalyst by amine and the uncontrolled spontaneous reaction were considerably suppressed. Furthermore, the reported aza-Michael reactions with both aromatic and alkyl amines were not sensitive to either air or water, and



Scheme 8. Heterobimetallic catalysis in asymmetric reaction of *O*-alkylhydroxylamines to enones

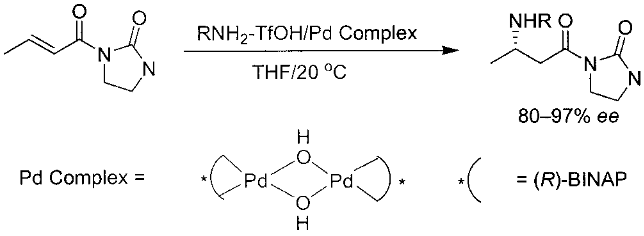


Scheme 9. Chiral Lewis acid catalyzed aza-Michael addition of aromatic amines to enones



Scheme 10. Polymer-supported-catalyst-mediated aza-Michael reaction of amines

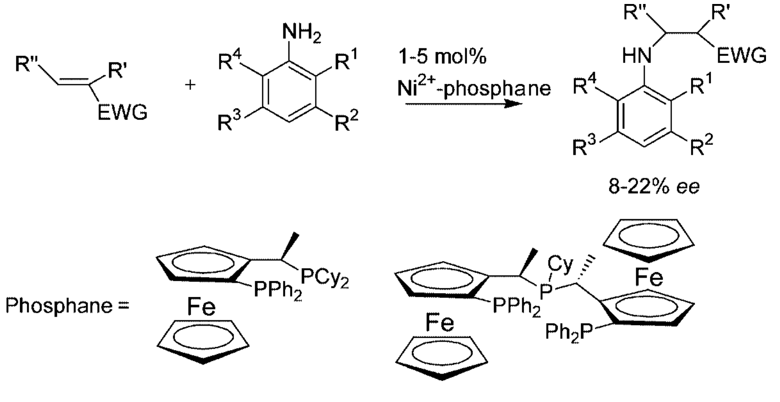
could be conducted without any particular precautions. Although the exact reaction mechanism has not been established, they speculate that the monomeric Pd complex could activate alkenoyl oxazolidinones in a bidentate fashion, and then the concomitantly formed free amine would attack the activated double bond. Because the *re*-face of the double bond is blocked preferentially by one of the phenyl groups of (*R*)-BINAP, the addition of amine proceeds from the *si*-face in a highly enantioselective manner to give the Pd enolate. Subsequent protonation of this Pd enolate, followed by dissociation of the product as the salt, would complete the catalytic cycle. In this step, protonation of the product might contribute to preventing the product from coordinating to the metal center.



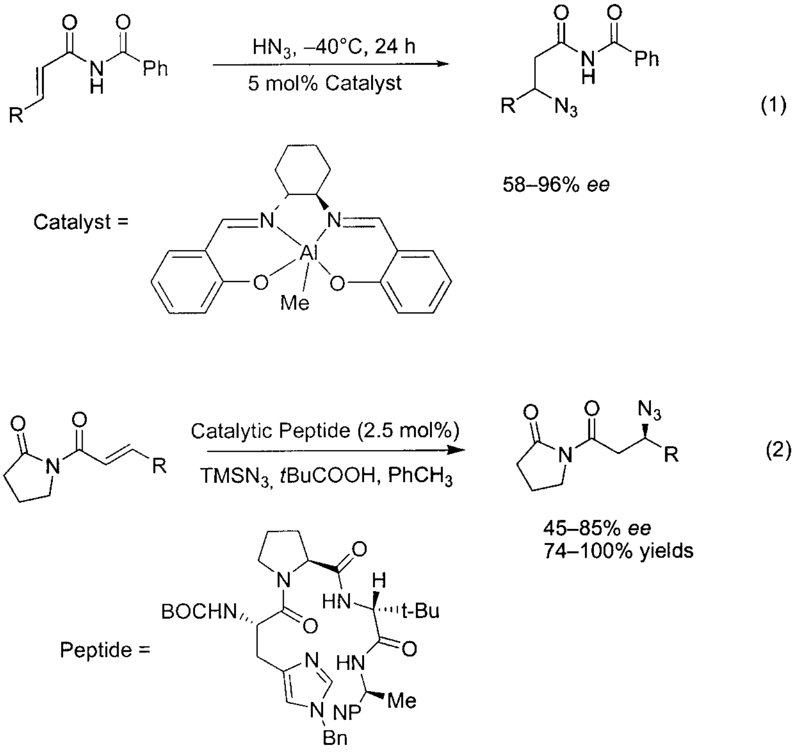
Scheme 12. Pd-BINAP-catalyzed aza-Michael reaction of amines in the presence of TfOH

2.3. Catalytic Asymmetric Aza-Michael Reactions of Azides

Jacobsen et al.[25] have reported that a chiral SalenAl^{III} complex catalyzes the aza-Michael reaction of hydrazoic acid (HN_3) with α,β-unsaturated imides. This procedure provides access to a variety of enantiopure β-alkyl-β-azido compounds [Equation (1) in Scheme 13]. Recently, Miller et al. have developed a milder, metal-free version of this aza-Michael or azidation reaction in which the azide is generated from $TMSN_3$ and *t*BuCOOH in toluene.[26] Simple β-tripeptide-mediated aza-Michael addition of azides to enoates yields β-amino acid derivatives in up to 85% *ee* [Equation (2) in Scheme 13]. The perturbation of the catalyst conformational equilibria with this approach could represent a general strategy for catalyst design, not only with small peptides but with other types of open-chain catalysts as well.



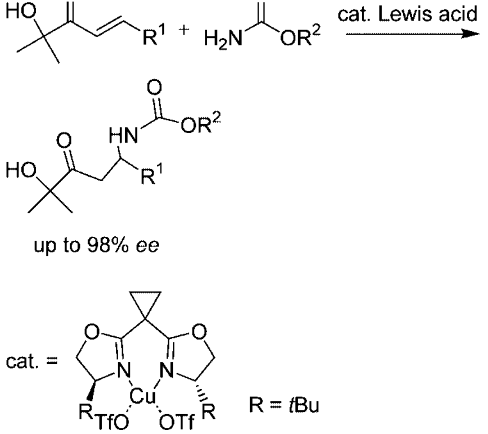
Scheme 11. Ni^{2+}-phosphane-catalyzed hydroamination of α,β-unsaturated carbonyl compounds with amines



Scheme 13. Asymmetric aza-Michael reaction of hydrazoic acid with α,β-unsaturated carbonyl compounds

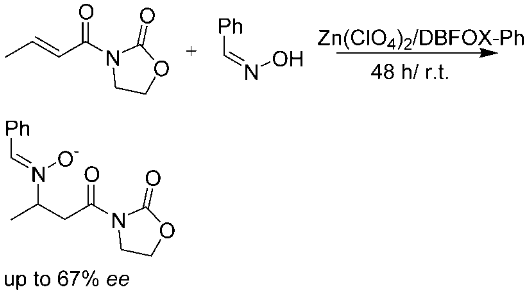
2.4. Catalytic Asymmetric Aza-Michael Reactions of Other Nitrogen Nucleophile Sources

Very recently Palomo and coworkers reported the first highly enantioselective conjugate addition reactions of carbamate enones catalyzed by chiral Lewis acids.[27] Their chiral bis(oxazoline)copper complexes catalyze the aza-Michael addition of carbamates and α′-hydroxy enones to yield products with high *ee*'s, uniformly above 92% (Scheme 14).



Scheme 14. Chiral Lewis acid catalyzed aza-Michael reactions of carbamates

The aza-Michael addition reactions of aldoximes can be successfully accelerated by a catalytic amount of Lewis acid when using acceptor substrates containing β-substituents (Scheme 15). The aqua complex derived from (*R*,*R*)-DBFOX-Ph and zinc(II) perchlorate hexahydrate is an especially active catalyst with the best enantioselectivity (up to 67% *ee*).[28] Although the enantioselectivities are only modest, this work presents a new asymmetric nitrone-forming reaction by *N*-alkylation through the aza-Michael addition of aldoximes to α,β-unsaturated carbonyl compounds in the presence of Lewis acid catalysts.



Scheme 15. Chiral Lewis acid catalyzed aza-Michael reaction of aldoximes

Conclusion

The highly enantioselective aza-Michael reaction is one of the major challenges in synthetic organic and organometallic chemistry. Even at such an advanced stage of modern chiral chemistry, the catalytic enantioselective aza-Michael reaction has found no general solution. The examples shown herein are certainly only the beginning and have limited applications. The search for efficient and highly enantioselective catalysts in aza-Michael reactions will most likely follow in the near future and yield new information in this exciting area.

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