Asymmetric Catalytic Aminoalkylations: New Powerful Methods for the Enantioselective Synthesis of Amino Acid Derivatives, Mannich Bases, and Homoallylic Amines

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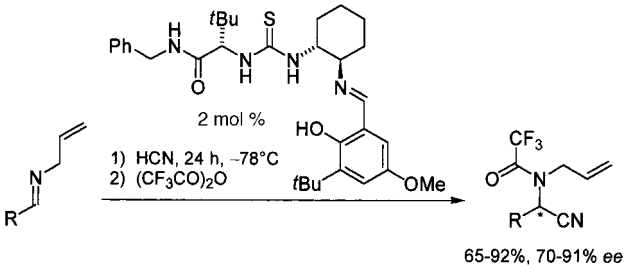
The economic importance of enantiomerically pure compounds has grown considerably during the last years and will increase even further.[1] Therefore, the development of efficient asymmetric syntheses with chiral catalysts is a main focus of modern industrial and basic research. As a result, there are meanwhile powerful asymmetric catalytic variants for many basic reactions.[2] However, until recently this did not include the important class of aminoalkylation reactions,[3] if one leaves aside aminoalkylations of Grignard, organolithium, or organozinc compounds catalyzed by chiral ligands (Lewis bases).[4]

Attempts to activate and to modify other nucleophiles such as ester enolates[5a,b] or HCN[5c] chirally with ligands or Lewis bases (diether,[5a,b] dipeptide[5c]) and to aminoalkylate them enantioselectively were only partly successful. These methods either require a stoichiometric amount of the chiral ligand or provide good *ee* values solely in special cases. However, recently it has been shown impressively that the potential of this methodology is definitely not exhausted yet. Thus, a relatively efficient and broadly applicable asymmetric variant of the Strecker synthesis could be developed by optimization of a Lewis base catalyst using combinatorial methods (Scheme 1).[5d]

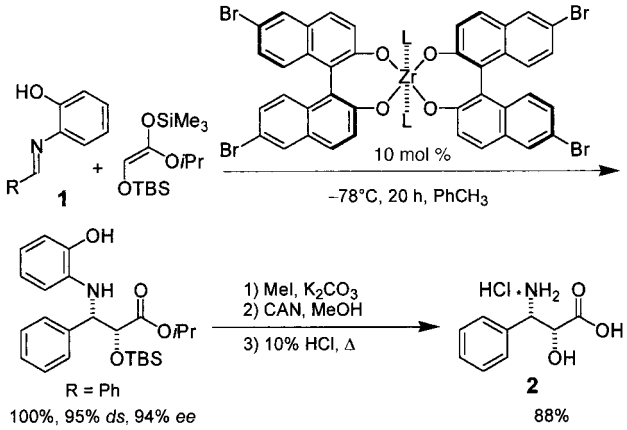


Scheme 1. Base-catalyzed enantioselective variant of the Strecker synthesis (R = alkyl, aryl).[5d]

More recent publications demonstrate the extraordinary potential of an alternative synthetic strategy: the use of chiral Lewis acid catalysts for the activation and chiral modification of Mannich reagents (generally imino compounds). In this way, not only HCN or its synthetic equivalents[6] but also numerous other nucleophiles could be aminoalkylated asymmetrically (e.g. trimethylsilyl enol ethers derived from esters[7–9a] or ketones,[9] alkenes,[10] allyltributylstannane,[11a] allyltrimethylsilanes,[9a, 11b] and ketones[12]). Thus, efficient routes for the enantioselective synthesis of a variety of valuable synthetic building blocks were created (e.g. α-aminonitriles,[6] α- or β-amino acid derivatives,[7–10] homoallylic amines,[9a, 10–11] or β-amino ketones[9, 12]).

Most of the hitherto published methods employ imino compounds that can act as bidentate ligands and form chelate complexes with the chiral Lewis acid catalysts. On the other hand, simple Mannich reagents usually furnish significantly lower *ee* values.[9c, 12] One can easily explain this by the restriction of the configurational diversity in the chelate complexes,[9d] favoring a stereochemically uniform course of the reaction.

Thus, *N*-(2-hydroxyphenyl)imines **1** (R = alkyl, aryl) together with zirconium catalysts (binaphthol derivatives) generated in situ were used successfully for the asymmetric synthesis of α-aminonitriles[6a] and simple β-amino acid derivatives[7a,c] or for the diastereo- and enantioselective preparation of α-hydroxy-β-amino acid derivatives.[7b] The advantages of the methodology include good yields and stereoselectivities, a relatively broad scope, and also the fact that the *N*-(2-methoxyphenyl) moiety is easily removed by oxidation with cerium ammonium nitrate (CAN).[6a, 7] A good example for the potential of this approach is depicted in Scheme 2.[7b] A related method employs *N*-4-trifluoromethylbenzoylhydrazones for the enantioselective aminoalkylation



Scheme 2. Asymmetric catalytic aminoalkylation as the key step in the diastereo- and enantioselective synthesis of (2*R*,3*S*)-3-phenylisoserine hydrochloride (**2**).[7b] TBS = *tert*-butyldimethylsilyl, L = 1,2-dimethylimidazole.

of ketene acetals. The resulting hydrazine derivatives are obtained in moderate yields, but in part with good *ee* values, and can be transformed into β-amino acid esters without racemization by cleavage of the N–N bond with samarium(II) iodide.[8]

The imines **3** (X = 4-$H_3CC_6H_4SO_2$ (Ts),[9a,b,d, 10] aryl[9c]) derived from glyoxylic acid, preformed[9b–d, 10] or generated in situ from N,O-acetals,[9a] can also form chelate complexes

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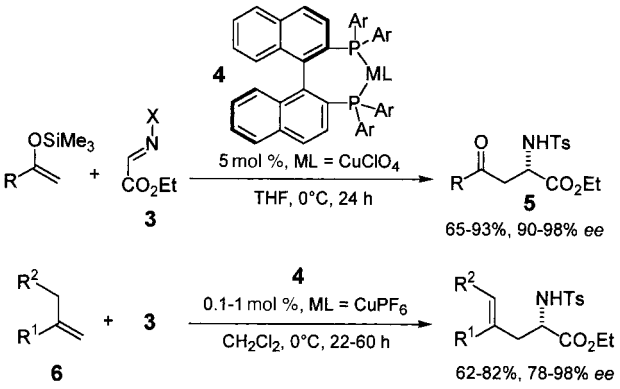
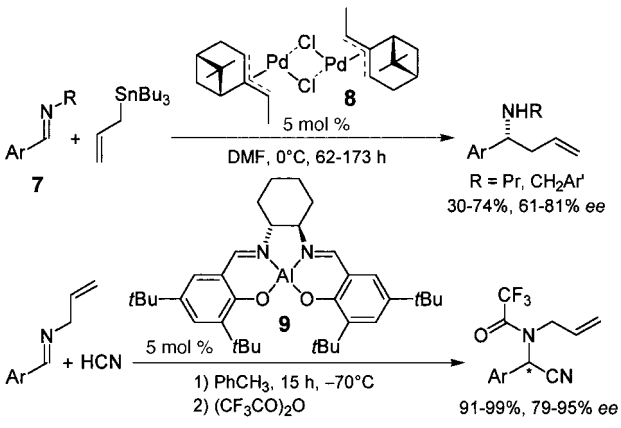
with chiral Lewis acids. Among other things, excellent results were obtained in the enantioselective aminoalkylation of silyl enol ethers with the 2,2′-bis(diarylphosphanyl)-1,1′-binaphthyl (BINAP) catalysts **4** (usually copper complexes).[9] A typical example is the synthesis of Mannich bases **5** depicted in Scheme 3.[9d] Because of their comparatively high electrophilicity imines **3** could even be used successfully for the asymmetric aminoalkylation of unactivated alkenes **6** (ene reactions, see Scheme 3).[10]



Scheme 3. Enantioselective catalytic aminoalkylation of silyl enol ethers[9d] and alkenes[10b] with imines **3** (X = Ts) and BINAP catalysts **4** (Ar = 4-MeC_6H_4).

All methods discussed so far employ special Mannich reagents (bidentate ligands) and BINAP-derived Lewis acids, which generally count among the most powerful chiral catalysts.[13] However, preliminary experiments show that in principle simple imines **7** can also be used successfully for asymmetric catalytic aminoalkylations. Nevertheless, BINAP catalysts such as **4** do not seem to be suitable for this kind of reaction.[9c, 11a] On the other hand, the asymmetric allylation of the simple imines **7** with allyltrimethylsilane[11b] or allyltributylstannane[11a] (Scheme 4) catalyzed by the β-pinene derivative **8** furnished comparatively good results. Moreover, it was demonstrated on the basis of Strecker syntheses[6b,c] that other catalysts such as the chiral salen complex **9**[6b] (Scheme 4) are also well suited for enantioselective aminoalkylations with simple imines.

During the past two years impressive progress has been made in the field of catalytic asymmetric aminoalkylation.



Scheme 4. Asymmetric catalytic aminoalkylation of allyltributylstannane[11a] and HCN[6b] with simple imines. Al represents $Al^{III}Cl$.

Nevertheless, this chemistry is still in its infancy. An important reason for this is that in many cases the common techniques (even if they have been applied successfully to formally closely related reactions such as aldol additions) are only imperfectly or not at all applicable to aminoalkylations.[3b, 12] Hence, the hitherto known methods for asymmetric aminoalkylation are mostly limited to special cases. Furthermore, they often require low reaction temperatures, relatively large amounts of the catalyst, or long reaction times to give good yields or *ee* values. However, it can be assumed that in the future both the scope and efficiency of enantioselective aminoalkylations can be enhanced considerably by the development of tailor-made catalysts. There is no doubt that modern methodologies such as the design of chiral catalysts using combinatorial techniques will play a key role in this process.[5d, 6c, 14]

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