Synthetic Methods

Unveiling Reliable Catalysts for the Asymmetric Nitroaldol (Henry) Reaction**

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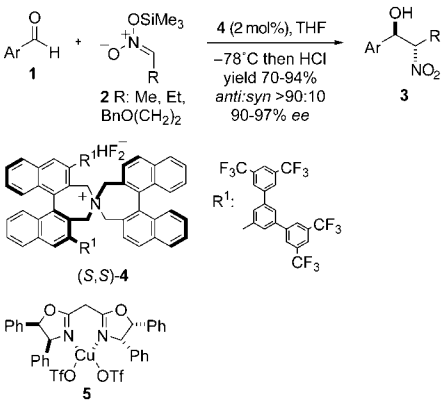
Keywords:
asymmetric catalysis · C–C bond formation · Henry reaction · nitroaldol reaction · synthetic methods

Dedicated to the memory of Juan Carlos del Amo

The addition reaction between nitroalkanes and carbonyl compounds to yield a nitroalcohol, namely the nitroaldol or Henry reaction, has long been known.[1] It constitutes a powerful C–C bond-forming process in organic chemistry,[2] providing efficient access to valuable functionalized structural motifs such as 1,2-amino alcohols and α-hydroxy carboxylic acids. [2,3] Because the reaction is so well known, it is conceivable that significant efforts may have been devoted over the years to implement asymmetric versions of the Henry reaction. Surprisingly no significant success has been achieved until the last few of years.[4] Stereocontrol in Henry reactions remains challenging: controlling the *syn*/*anti* stereochemistry is difficult,[5] and the use of covalently bonded chiral auxiliaries as a general strategy has not been much developed because of the lack of suitable attaching sites in both the pronucleophile nitroalkane and the aldehyde component.[6,7] Only recently, with the application of new concepts to catalyst design, have reliable catalytic systems appeared that significantly increase the current synthetic value of the Henry reaction. We highlight here the main concepts behind these developments and their impact in the field.

Relatively soon after the discovery of the Mukaiyama aldol reaction in 1973, chiral metal promoters and catalysts were steadily developed,[8] but no comparable progress followed the discovery by Seebach and Colvin[9] in 1978 of the fluoride-catalyzed reaction of silyl nitronates and aldehydes. Only quite recently—almost 25 years later—two independent groups have developed chiral catalysts.[10] Maruoka et al.[10a] have reported the addition of trimethylsilyl nitronates **2** to aromatic aldehydes **1** in the presence of 2 mol % of the chiral quaternary ammonium fluoride salt **4**, to give **3** with *anti*:*syn* ratios usually higher than 90:10 and with more than 90 % *ee* (Scheme 1). While poorer results are produced when aliphatic aldehydes are involved, the observed *anti* selectivity is explained on the basis of an acyclic extended transition-state model, which involves a chiral ammonium nitronate as the active species.



Scheme 1. Fluoride-promoted enantioselective nitroaldol reactions of silyl nitronates and aromatic aldehydes.

In a conceptually different design of the catalytic system, Jørgensen[10b] has reported the use of bis(oxazoline)copper(II) complexes such as **5** (20 mol %) in combination with tetrabutylammonium triphenylsilyl difluorosilicate (TBAT, 20 mol %). Again the *anti* adduct **3** is obtained preferentially, but in general both the yields (30–80 %) and enantioselectivities (40–65 % *ee*) are less impressive.

Perhaps the most impressive advance in the area came from the development of the first metal/chiral ligand complexes that are able to promote the direct reaction between unmodified nitroalkanes and aldehydes enantioselectively. Shibasaki et al.[4,11] reported the first efficient method of this type by making use of the general principle of two-center catalysis.[12] A metal/chiral ligand complex was designed possessing two sites of opposite character, a basic site and an acidic site, each capable of independently activating in close proximity the nitro compound and the aldehyde substrate, respectively. For example, as little as 1 mol % of the second-generation lithium/lanthanum polymetallic catalyst (complex **9** + 1.0 mol equiv H_2O + 0.9 mol equiv BuLi) can mediate the reaction between nitroalkanes **7** and aliphatic aldehydes **6** at −50/−30 °C within about 120 h in very high diastereo- and enantioselectivities (Scheme 2). Here, the *syn* adducts **8** are the major stereoisomers, thus complementing the silyl nitronate protocol mentioned above.

More recent work by Trost et al.[13] has revealed a novel family of dinuclear zinc complexes such as **10**, which apparently function along a similar principle of cooperative activation. Thus, 5 mol %

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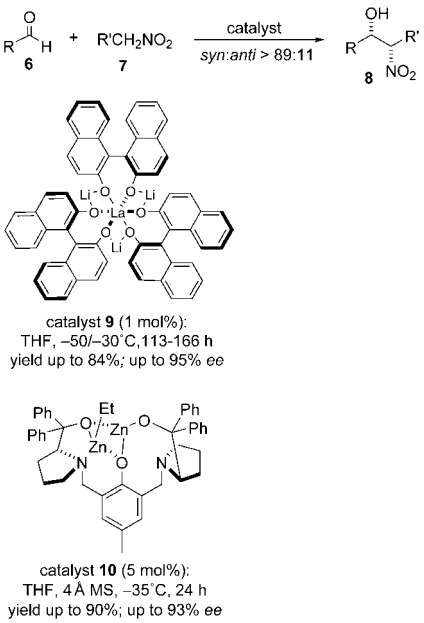
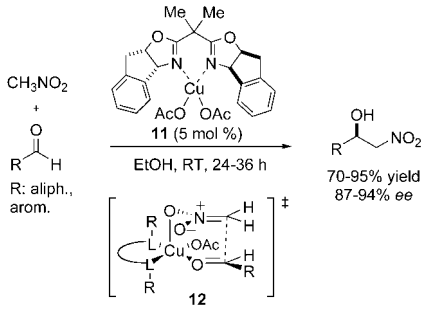


Scheme 2. The enantioselective, direct Henry reaction catalyzed by polymetallic complexes of bifunctional character.

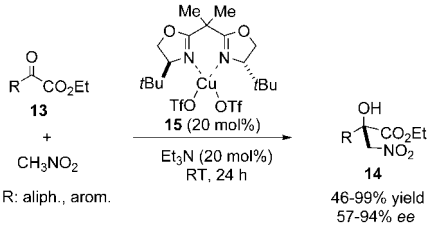
of complex **10** catalyzes the reaction between nitromethane and either aromatic or aliphatic aldehydes at −35 °C within about 24 h to produce nitroaldols **8** (R′ = H) in yields in the 56 to 90 % range and up to 93 % *ee*. Zinc-based catalysts are especially interesting because they might be compatible with aqueous systems in the light of the fact that zinc enolates have been identified as intervening species in aldol reactions catalyzed by type II aldolases.[14] To date, a few other zinc complexes bearing amino alcohol ligands[15] and macrocyclic thioaza ligands[16] have been described for the Henry reaction. Because the results are still poor, future developments in the area can be expected.

In an important recent report, Evans et al.[17] have formulated that weakly Lewis acidic metal complexes bearing moderately basic, charged ligands may facilitate the deprotonation of nitroalkanes. A catalyst based on this novel design, the copper acetate catalyst **11**, was found to catalyze the nitroaldol reaction between nitromethane and either aromatic or aliphatic aldehydes to afford nitroaldols with very high enantioselectivity (Scheme 3). Although not conclusive, transition-state model **12** is invoked for the catalyzed reaction, where apparently chelation between the copper metal and a bidentate substrate[18] is not a prerequisite for effective asymmetric induction.



Scheme 3. A bis(oxazoline)copper(II) acetate complex as a monometallic catalyst of the enantioselective nitroaldol reaction.

In general, ketones react more slowly than aldehydes, and their Henry reactions with nitroalkanes tend to be reversible. In addition, enantioface differentiation is rather challenging because of the greater similarity of the two entities flanking the carbonyl group. Not surprisingly, general methodologies for catalytic Henry reactions are still lacking. A remarkable exception, however, is the Henry reaction of α-keto esters (pyruvates) **13** and nitromethane depicted in Scheme 4, which is promoted by the bis(oxazoline)copper complex **15** and triethylamine binary system.[19] When 20 mol % of both triethylamine and complex **15** are used, nitroaldols **14** are obtained in up to 94 % *ee*. Interestingly, in the absence of either catalyst partner the reaction does not occur, and the enantioselectivity is very sensitive to variation in their stoichiometry.



Scheme 4. Henry reaction of α-ketoesters catalyzed by a combination of triethylamine and a chiral bis(oxazoline)copper(II) triflate complex.

While in most of the above approaches the enantioselectivity results from the organizational ability of a metal center (chiral Lewis acid) to create an effective asymmetric environment, it appears that chiral Brønsted bases[20] are also suitable for this role. Thus, certain cinchona alkaloids[21] and guanidine bases[22] have been reported to promote direct catalytic asymmetric Henry reactions, although to date the enantioselectivities are still low, typically below 50 % *ee*. These incipient achievements are clearly limited, but improvements in the organocatalytic Henry reaction might be coming soon in light of quite recent work on the parent aza-Henry reaction.[23] In this latter context, the protonated chiral bisamidine ligand **16**[24] and chiral thiourea derivative **17**[25] (Figure 1) have been found to catalyze the addition reaction of nitroalkanes to *N*-Boc and *N*-phosphanoyl imines, respectively, in high enantioselectivities. Although the mechanistic rationale of these catalytic reactions is not yet established, the working hypothesis proposed for **17** (see Figure 1) is plausible and could be potentially extended to Henry reactions.

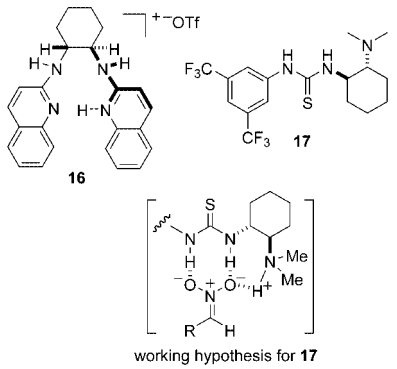


Figure 1. Recent chiral organocatalysts applied to enantioselective aza-Henry reactions.

A special case worth commenting on is the Henry reaction of α-aminoaldehydes **18** to provide nitroaldols **19** (Scheme 5), which represent precursors of medicinally important compounds. While some chiral catalysts have been used to enhance the inherent diastereoselectivity of the reaction,[7c,26] Matsumoto et al.[27] have found that no added catalyst is needed for the reaction to proceed in high diastereoselectivity and with no or little racemization if high pressure (8 kbar) is applied. The implicit concept of this development is that the substrate itself may act as a catalytic chiral base, an idea that might be extended to other types of reactions.

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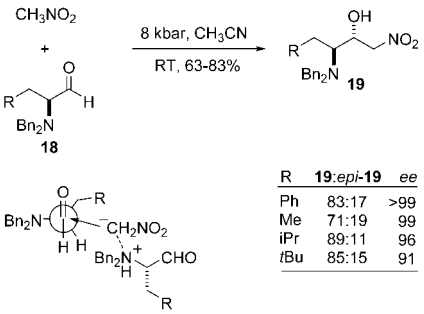

Scheme 5. Diastereoselective asymmetric nitroaldol reactions of α-amino aldehydes under high pressure.

The chemistry highlighted herein proves that the catalytic asymmetric nitroaldol (or Henry) reaction is already a practicable task. Some principles have been set to understand the mechanisms of reactant activation and reaction diastereo- and enantiocontrol, which may guide new developments. Yet, since some of these principles are too general and sometimes little supported, much effort will be needed to fully understand the basis of reactivity and selectivity. Much improvement is still needed in the reaction scope as well. For instance, reactions involving nitroalkanes other than nitromethane have been less studied, while the Henry reaction of ketones is essentially unexplored and challenging. Nevertheless, from the current degree of development, one can already anticipate for the near future extended synthetic applications of the catalytic asymmetric Henry reaction.

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