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Review

Recent progress in copper catalyzed asymmetric Henry reaction

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ABSTRACT

Henry reaction is one of the most classical reactions to construct synthetically useful product nitro alcohol, which as a privileged skeleton is widely distributed in various pharmaceuticals. This review summarizes the recent progress of copper-catalyzed asymmetric Henry reaction from 2011 to 2016. The significant progress that has been made in this area will be highlighted and some of challenges that the author believes may be hindering further progress will be revealed.

1. Introduction

The Henry or nitroaldol reaction represents a highly attractive synthetic method, which provides a facile and direct access to versatile building block β-nitroalcohol [1]. The difunctional group of β-nitroalcohol can be readily converted into other functional groups *via* a variety of transformations (Scheme 1) [2]. For the nitro group, it can be easily reduced to amino group under mild conditions (Path a). Additionally, the Nef reaction of nitroalkanes provides an alternative route to carbonyl compounds (Path b). With a radical condition, the nitro group can also be replaced with a hydrogen atom (Path c). With respect to the hydroxyl group, the dehydration process can be employed to prepare nitroolefin (Path d), which is one of the most popular Michael acceptors.

Due to the versatility of nitroalcohol, the Henry reaction has been widely applied in numerous synthetic ventures with the tremendous development of asymmetric Henry reaction (Fig. 1) [3]. For instance, the Henry reaction has been employed as a key step in the total synthesis of nucleoside antibiotics tunicamycin developed by Suami and coworkers [3a]. The synthesis of natural product tetrodotoxin starting from D-glucose was also achieved by using two-step Henry reactions in Sato group [3b]. Recently, an efficient method to construct marine alkaloid manzamine A, involving Henry and aza-Henry reaction, was reported by Dixon *et al.* [3c,3d].

The above facts serve to emphasize that the great utility of Henry reaction in the practical synthesis. Consequently, considerable efforts have been devoted to the asymmetric Henry reaction since the pioneering work of Shibasaki in the first enantioselective Henry reaction [4]. Among the enormous reports, the copper catalyzed Henry reaction has occupied an important place for the advantages of flexible coordination mode, economical accessibility and the good tolerance for air and moisture [5]. Accordingly, in this respect, numerous chiral ligands were developed and tremendous progress was achieved. However, to the best of our knowledge, there was no specific review focused on the copper-catalyzed Henry reaction. Although Velmathi *et al.* summarized the transition metal catalyzed Henry reaction, covering some relative works on copper catalysis prior to 2011, a number of meaningful works dealing with new catalysts and concepts have recently emerged [6,7]. In this context, the recent advances in the field will be discussed in this digest and some previous papers will be introduced as background when necessary. To better illustrate the progress in the area, this review will be introduced according to the category of chiral ligands.

2. Chiral diamine ligands

Chiral 1,2-diaminocyclohexane as a privileged skeleton has been widely employed in the synthesis of chiral diamine ligands, which turned out to be effective ligands for many metal-catalyzed

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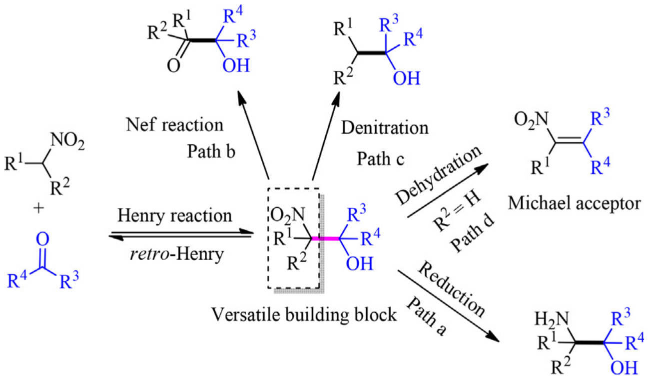


Scheme 1. The versatile building block nitroalcohol.

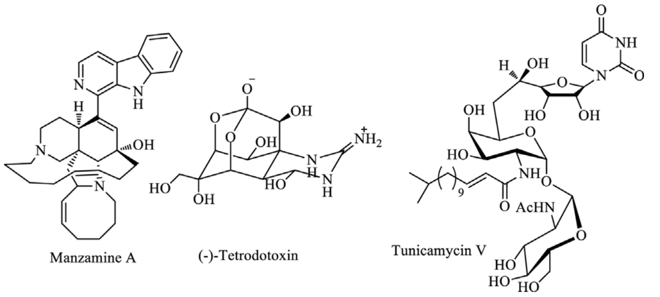
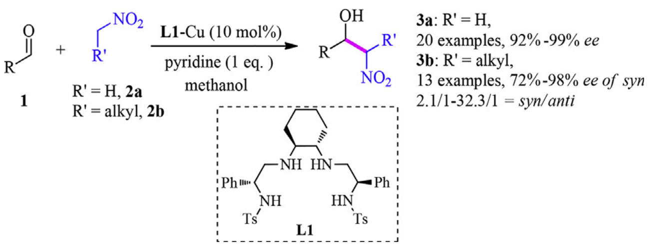


Fig. 1. The application of Henry reaction in natural products.

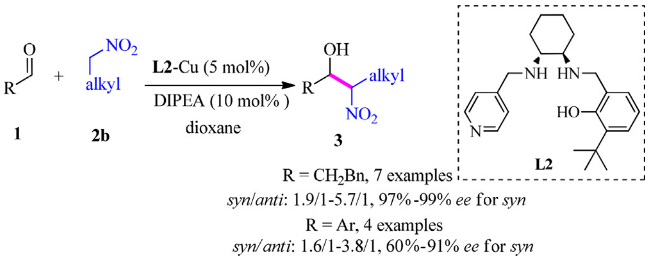
asymmetric transformations [8]. For the Henry reaction, this catalytic system was first introduced by Arai in 2006 [9].

Recently, a chiral ligand bis(sulfonamide)-diamine **L1** with multiple coordination sites was prepared by Wan and coworkers, which could readily coordinate with Cu(I) to form an active chiral catalyst (Scheme 2) [10]. This chiral copper catalyst was effective not only in the Henry reaction involving nitromethane but also for the reaction of substituted nitroalkanes. In particular, with the assistance of pyridine, the corresponding *syn*-selective adducts could be obtained with moderate to good diastereoselectivities (Scheme 2).

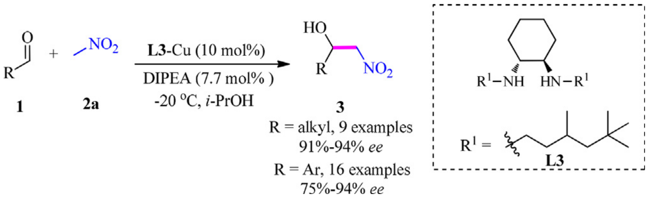
In 2011, a range of C_1-symmetrical diamine ligands were reported by Woggon to address the challenging diastereoselectivity issue in the nitroaldol reaction of aliphatic aldehydes (Scheme 3) [11]. In order to find the optimal conditions for the reaction, a screening was performed using more than 60 chiral diamines-copper complexes. With the optimal ligand **L2**, various prochiral nitro compounds could react smoothly with 3-phenylpropionaldehyde giving the *syn*-selective product with 1.9/1-5.7/1 *dr* values and 90-99% *ee* values (Scheme 3). However, the shortcoming of this method was that a lower stereoselectivity was observed in the cases of aromatic aldehydes.



Scheme 2. The chiral bis(sufonamide)-diamine ligand in the Henry reaction.



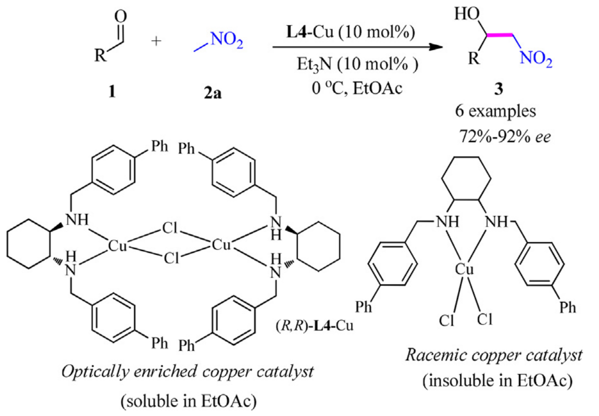
Scheme 3. The C_1-symmetrical copper catalyzed diastereo-selective Henry reaction.



Scheme 4. Chiral branched diamine ligand in the asymmetric Henry reaction.

Further investigation on the chiral diamine ligand structure showed that the alkyl substituent significantly affected the stereoselectivity in the Henry reaction [12]. The study of Gou *et al.* showed that branched diamine **L3** was the optimal ligand in terms of the yield and enantioselectivity (Scheme 4). With this optimal ligand in hand, the generality of the substrate scope was examined in the presence of the corresponding copper complexes. Specifically, better enantioselectivities with 91%-94% *ee* were observed for the aliphatic aldehydes compared with the aromatic counterparts (Scheme 4). Despite the admirable results in the Henry reaction of nitromethane, other nitroalkanes had not been tried in the report with the optimal catalyst.

Very recently, the chirality induction mechanism in the diamine-copper catalyzed Henry reaction was investigated by Tanaka (Scheme 5) [13]. Interestingly, a significant positive nonlinear effect was observed when the reaction was performed in EtOAc, while a similar effect could not be detected in MeOH. This solvent-dependent nonlinear effect might originate from the difference solubility between the optically pure catalyst (*R*,*R*)-**L4**-Cu and the racemic one, especially in the aprotic organic solvents (Scheme 5). To the best of our knowledge, the strong solvent-dependent asymmetric amplification in Henry reaction was unprecedented in the literature.



Scheme 5. The nonlinear effect in the diamine-copper cataly-zed Henry reaction.