Tetrahedron Letters 55 (2014) 551–558

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Catalytic asymmetric α-C(sp^3)–H functionalization of amines

Yan Qin, Jian Lv, Sanzhong Luo *

Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China
Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, China

ARTICLE INFO

Article history:
Received 3 October 2013
Revised 8 November 2013
Accepted 13 November 2013
Available online 21 November 2013

Keywords:
Asymmetric catalysis
Chiral amine
C(sp^3)–H activation
α-Functionalization
α-Amino intermediates

ABSTRACT

In this digest review, we aim to give a brief overview of catalytic asymmetric α-C(sp^3)–H functionalization of amines, mainly via internal *tert*-aminocyclization, intermolecular C–H oxidative couplings, and redox neutral metal insertion C–H bond.

Amines are abundant chemicals with rich synthetic potentials. In particular, chiral amines are versatile and ubiquitous motif in many bioactive compounds and chiral reagents. Accordingly, enantioselective preparation of chiral amines has been a central topic in organic synthesis and this trend continues echoing the evolution of synthetic concepts and methodologies.[1,2] Typical approaches along this line include chiral resolution of racemic amine and asymmetric transformation via amination, nitrogenation and reactions with imines. Recently, there appears another strategy that involves direct α-C–H activation and functionalization of amines. This type of transformations is synthetically appealing provided with a large number of readily available amines either enantiopure or achiral and any methods for chemo- and stereoselective transformations of these compounds would generate enormous synthetic potentials. On the other hand, such reactions pose significant challenges, particularly for catalytic asymmetric versions, as the reactions target on direct activation and selective functionalization of rather inert sp^3 C–H bonds. In fact, to achieve catalytic asymmetric functionalization of inert C–H bonds in general remains elusive and successful examples on catalytic C(sp^3)–H functionalization are quite limited. Recently, notable progresses have been achieved in catalytic asymmetric α-C(sp^3)–H functionalization of amines, showing significant potentials of the C–H activation strategy in complementing or even by-passing the typical synthetic strategies such as asymmetric imine reactions to access chiral amines.

Direct α-C–H functionalization of amines is not a new concept and previous efforts can be traced back to 1980s[3] when the reaction of chiral amino anion (**I**) (Fig. 1) was pursued. In these cases, stoichiometric amount of chiral ligands such as (–)-sparteine were required to achieve decent enantioselective controls (Scheme 1).[4] Another notable precedent is the catalytic asymmetric carbenoid insertion,[5–7] wherein chiral rhodium complexes have been reported to promote highly enantioselective insertion to α-C–H of cyclic amines such as *N*-Boc-pyrrolidine (Scheme 1).[7] These advances have been covered in a number of review articles.[8]

In this digest article, we aim to give a brief overview on asymmetric α-C–H functionalization of amines wherein the redox properties of nitrogen are actively pursued. Mechanistically, catalytic α-C–H functionalization of amines can be classified into four catagories via α-amino cation (iminium **II**), α-amino radical (**III**) or C-M intermediates (**IV**) (Fig. 1). The past few years have witnessed tremendous advances in methodology studies involving any of the three types of intermediates. However, progresses on catalytic asymmetric versions have been largely lagged behind, and successes have been mainly achieved in iminium ion-based processes. The variation in this regard lies in the way of iminium intermediate generated and the strategy of the stereoselectivity controlled. Both metal complexes and chiral organocatalysts were used to achieve catalytic asymmetric α-functionalization of tertiary amines. Prominent examples on asymmetric α-C–H functionalization of amines via C-M intermediate (Fig. 1, **IV**) is also included in this digest article.

---

* Corresponding author.
E-mail address: luosz@iccas.ac.cn (S. Luo).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.11.051

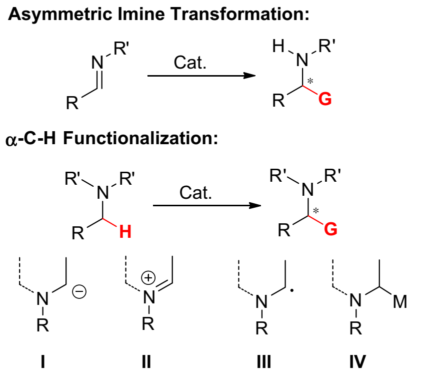
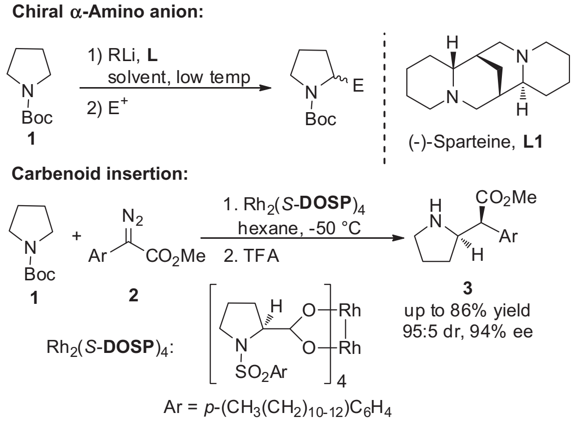


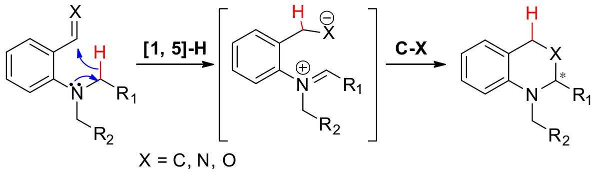
Figure 1. Four type reactive intermediates in C(sp^3)–H activation of tertiary amine.



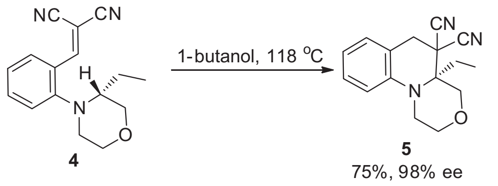
Scheme 1. Alkylithium/chiral diamine-mediated asymmetric deprotonation of tertiary amines.

Internal redox–neutral reactions: *tert*-aminocyclization

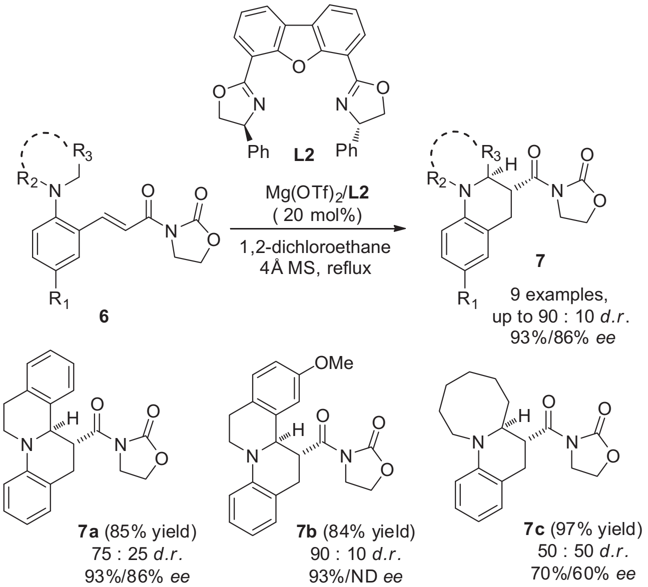
The α-C–H functionalization of *tert*-amines, for example *N*,*N*-disubstituted anilines, is well-known for the synthesis of heterocycles. In 1972, the intriguing amino effect in this type of reaction was summarized and coined as *tert*-amino effect.[9] The intramolecular *tert*-aminocyclization, a highly atom and redox economic process based on the *tert*-amino effect, represents a redox-neutral cascade sp^3 C–H activation/C–C formation process for the synthesis of heterocyclic compounds, especially for the synthesis of tetrahydroquinoline derivatives (Scheme 2). In 1980s, Reinhoudt and coworkers investigated extensively the thermal *tert*-aminocyclization reactions (Scheme 3).[10] In these studies, they have found that chiral *tert*-amino compounds can undergo the cyclization with complete reservation of the enantioselectivity without the participation of external reagents. In this process, the chirality is memorized via a stereoselective 1,5-suparafacial H-transfer in the zwitterionic intermediate, which dictates the subsequent C–C bond formation. These pioneering studies set basis for chiral induction with external chiral reagents, however, such a catalytic asymmetric version has not been realized until 30 years later.



Scheme 2. The *tert*-aminocyclization.



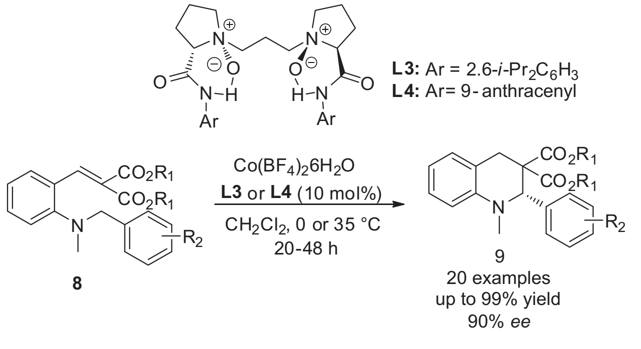
Scheme 3. Thermal *tert*-amino cyclization reactions.



Scheme 4. Magnesuim-catalyzed asymmetric *tert*-aminocyclization.

Based on the finding that Lewis/Brønsted acid could promote the *tert*-aminocyclization reaction,[11–13] Seidel and co-workers reported the first example of enantioselective reaction with substrates bearing an acyl oxazolidinone as accepter moiety in 2009.[14] Enantioselective hydride transfer/ring closure reaction was catalyzed by using $Mg(OTf)_2$/DBFox (**L2**) as a catalyst in dichloroethane under reflux conditions (Scheme 4). Polycyclic tetrahydroquinolines **7** were obtained with good yields and in excellent enantiselectivities. However, this catalytic protocol is limited to cyclic amines and requires refluxing conditions to achieve decent conversions.

In 2011, Feng and co-workers[15] reported a chiral *N*,*N*′-dioxide-Co(II) complex for the asymmetric cyclization of *o*-dialkylamino-substituted alkylidene malonates under mild conditions (Scheme 5). The reaction can be applied to acyclic benzyl amines



Scheme 5. Cobalt(II)-catalyzed asymmetric *tert*-aminocyclization.