ACS Catalysis

pubs.acs.org/acscatalysis Review

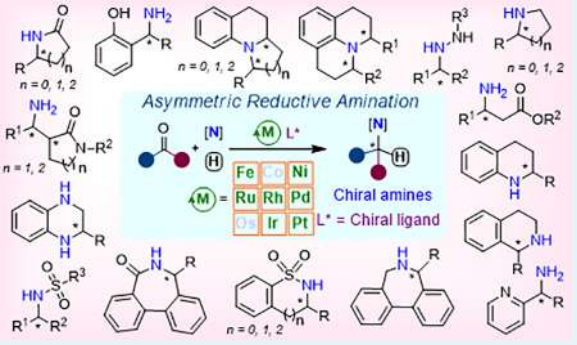
Recent Progress in Transition-Metal-Catalyzed Asymmetric Reductive Amination

Noor U Din Reshi,[§] Vitthal B. Saptal,[§] Matthias Beller, and Jitendra K. Bera*

Cite This: *ACS Catal.* 2021, 11, 13809–13837 Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Asymmetric reductive amination (ARA) of a prochiral carbonyl compound with an amine using a H_2/hydrogen surrogate is a concise and operationally simple method for the synthesis of chiral amines. ARA proceeds via condensation of a carbonyl group with an amine/ammonia followed by the enantioselective reduction of the generated intermediate. The activation of reductant and stereoselective transfer of hydrogen to intermediate imine/enamine is often mediated by a chiral transition metal catalyst. Considering the wide applications of enantiopure amines in pharmaceuticals, agrochemicals, and materials, the development of effective catalysts for ARA has been intensively pursued in the last two decades. Since the first report by Blaser in 1999, this key research area has grown significantly in recent years, as reflected by the advances in catalyst design, diversifying substrate scope and better mechanistic understanding. Several highly efficient and general ARA methodologies applicable to challenging carbonyl and amine partners have been demonstrated, providing ready access to a variety of enantiopure amines. In this Review, we present the recent progress in ARA featuring diverse carbonyl and amine partners employing transition metal-catalysts. This Review provides an organized and critical discussion on catalyst engineering and evolution, expanding susbstrate scope and mechanistic insights. To conclude, the remaining challenges and opportunities in ARA are also highlighted.



KEYWORDS: *chiral amines, transition-metal catalysts, reductive amination, asymmetric catalysis, chiral ligands*

1. INTRODUCTION

Chiral amines are ubiquitous in a broad range of pharmaceuticals, agrochemicals, natural products, and functional materials.[1−8] For example, nearly 50% of small-molecule pharmaceuticals among the top 200 drugs by retail sales in 2019 contain an enantiopure aliphatic amine as a key component.[9] Chiral amine moieties are present in approximately 40% of new chemical entities among drugs approved by the United States Food and Drug Administration (FDA).[10] Important pharmaceuticals containing chiral amine motifs include zoloft (depression), cinacalcet (secondary hyperparathyroidism), sitagliptin, flomax (enlarged prostate), rivastigmine (Alzheimer's and Parkinson's disease), selegiline (Parkinson's disease and depression), rotigotine (Parkinson's disease), and clopidogrel (antiblood clot, WHO essential medicine) (Scheme 1).

Because of the wide-ranging applications of enantiopure amines, several methods have been developed for their synthesis (Scheme 2).[6,11−16] Resolution of racemic mixtures to obtain optically pure amines is often inefficient. Hence, chiral amines are commonly synthesized via asymmetric hydrogenation/reduction of imines,[17−21] enamines,[22−24] and nitrogen-containing heteroaromatic compounds.[25,26] These methods require an initial preparation of unstable imines, which is tedious. Other methods include enantioselective C−C bond constructions via additions to imines,[27−36] addition of amines to alkenes/alkynes (hydroamination),[37−40] asymmetric amination of alcohols through a "borrowing hydrogen" strategy,[41] and asymmetric C−H amination.[42,43] An attractive method to prepare chiral amines is the asymmetric reductive amination (ARA) of a prochiral carbonyl compound with an amine in the presence of H_2 employing chiral catalysts.[44] It is the most straightforward and efficient protocol to prepare enantiopure amines from prochiral ketones. ARA proceeds via condensation of a carbonyl group with an amine to generate imine/iminium ion/enamine followed by its *in situ* reduction. This method alleviates the preparation and isolation of unstable ketimines containing C═N bonds.[45] Nevertheless, ARA is a challenging process, particularly for the syntheses of

Received: September 13, 2021
Revised: October 8, 2021
Published: October 29, 2021

https://doi.org/10.1021/acscatal.1c04208
ACS Catal. 2021, 11, 13809−13837