Direct Catalytic Asymmetric Addition of Various Nucleophiles to N-Unprotected Ketimines

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PURPOSE OF THE ABSTRACT
Enantioselective nucleophilic addition to ketimines is one of the most straightforward approaches to synthesize optically active tetrasubstituted amines. Although various methodologies using stoichiometric amounts of metal reagents have been developed, in terms of atom economy, direct catalytic asymmetric reactions are more ideal pathway. Therefore, such direct reactions using N-protected imines have been explored including our Rh-catalysis.[1] To obtain N-unprotected amines, however, they require additional deprotection steps, which limit their synthetic utilities. A prominent way to address these issues is using N-unprotected ketimines; however, there are only limited success using N-unprotected ketimines as an electrophile. Herein, we disclose direct catalytic asymmetric addition of various nucleophiles, such as terminal alkynes, 1,3-dicarbonyl compounds, and heteroaromatics, to N-unprotected ketimines.

By proper choice of catalysts, such as metal catalysts and organocatalysts, for each of reactions, the reaction of various nucleophiles proceeded smoothly to afford the corresponding N-unprotected tetrasubstituted amines in high yield with good to high ee (up to 98% ee) (Scheme1).

For example, Zn catalyst efficiently promoted the addition of various aryl- and alkyl-substituted alkynes to ketimines[2]. Compatibility with a variety of functional groups, such as unprotected aniline, alkyl chloride and acetal, highlighted the broad functional group tolerance of the catalytic system. Very surprisingly, under our reaction conditions, Zn-catalyzed alkynylation selectively proceeded with N-unprotected ketimines over the N-PMP-protected ketimines and aldimines. It is notable that alkynylation of N-PMP-protected aldimine predominantly proceeded in the presence of Cu(I) catalyst, which is commonly used for alkynylation of imines (Scheme 2).
FIGURES

**FIGURE 1**
direct catalytic asymmetric addition of various nucleophiles
Scheme 1

**FIGURE 2**
Chemoselective reaction of NH-ketimines over N-PMP-aldimines
Scheme 2

KEYWORDS
NH-Ketimine | Green Chemistry | Protecting Group-Free | Chemoselectivity

BIBLIOGRAPHY
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