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Original article

Asymmetric catalyzed intramolecular aza-Michael reaction mediated by quinine-derived primary amines

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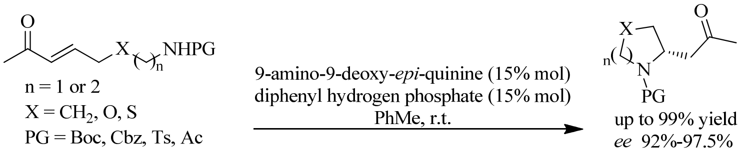
Graphical Abstract



An intramolecular organocatalytic enantioselective aza-Michael reaction of carbamates, sulfonamides and acetamides to α,β-unsaturated ketones has been developed with excellent enantioselectivity and very good yield.

ABSTRACT

An intramolecular organocatalytic enantioselective aza-Michael reaction of carbamates, sulfonamides and acetamides to α,β-unsaturated ketones was developed. This process is promoted by 9-amino-9-deoxy-epi-quinine and diphenyl hydrogen phosphate to afford a straightforward and expeditious synthesis of several synthetically useful five- and six-membered heterocycles with excellent enantioselectivity (92%-97.5% *ee*) and very good yields (up to 99%).

Keywords:
Asymmetric catalysis
Intramolecular aza-Michael reaction
Primary amine
Five- and six-membered heterocycles
Pyrrolidine and piperidine

Enantioselective organocatalytic

1. Introduction

The field of organocatalysis [1] has expanded in recent years, since the discovery of the proline-catalyzed aldol reaction [2]. During this period, an overwhelming number of novel, highly efficient organocatalysts have been reported in the literature. In particular, chiral secondary amines are extremely powerful reagents that have dominated the field of amino catalysis [3]. However, in spite of the tremendous success of the use of secondary amines in the asymmetric functionalization of aldehydes, only minor progress has been achieved in the corresponding transformations of ketones, because of the inherent difficulties in generating congested covalent intermediates between chiral secondary amines and ketones. Primary amine catalysis offers the unique possibility of participating in processes between sterically demanding partners [4] and chiral primary amines have also been demonstrated to be effective catalysts in a wide range of enantioselective organic reactions [5], especially for the activation of challenging substrates, such as α,α-disubstituted aldehydes [6] and ketones [7].

β-Amino carbonyl derivatives bearing heterocyclic nitrogen atoms have become attractive targets in organic and medicinal chemistry, as they are versatile synthetic intermediates that can be used in the preparation of a wide variety of heterocycles [8]. Among the β-amino carbonyl molecules, pyrrolidine and piperidine moieties are extremely valuable scaffolds due to their widespread occurrence in diverse biologically active natural products and pharmaceutical agents [9], as well as their utility as chiral auxiliaries and chiral ligands in asymmetric catalysis [10]. The aza-Michael reaction is the most direct method for selectively creating a