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Highly enantioselective Michael-aldol-dehydration reaction for the synthesis of chiral 3,5-diaryl-cyclohexenones catalyzed by primary amine

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ABSTRACT

A simple organocatalytic Michael-aldol-dehydration domino approach to chiral 3,5-diaryl-cyclohexenones from acetone and α,β-unsaturated ketones was developed for the first time using a simple chiral primary amine as a catalyst. Moderate to good yields (up to 85%) and excellent enantioselectivities (88–98% *ee*) were obtained.

1. Introduction

Chiral cyclohexenones are important chiral scaffolds which have been widely used in the synthesis of asymmetric natural products and a broad spectrum of biologically active molecules.[1] Therefore, many useful strategies have been developed for the synthesis of this kind of compounds, including various multistep synthesis,[2] intramolecular aldol condensation reactions,[3] kinetic resolution of racemic substituted cyclohexenones by asymmetric catalytic reactions,[4] and enantioselective Robinson annulation, which consists of three consecutive processes: (I) the asymmetric Michael addition of a carbonyl compound to an α, β-unsaturated ketone/aldehyde, (II) an intramolecular aldol reaction, and (III) dehydration. Low cost starting materials are advantages for Robinson annulation strategy.[5]

In recent 20 years, asymmetric organocatalysis has emerged as a versatile strategy for the stereoselective preparation of valuable chiral compounds. Pure organic molecules are utilized as chiral catalysts providing a valuable complement to the traditional organometallic and biological approaches to asymmetric catalysis.[6] These stereo-controlled methods offer a practical pathway for the construction of a variety of enantio-enriched cyclohex-2-enones.[5] For instance, Jorgensen et al.[7] and Hayashi et al.[8] successfully used diarylprolinol silyl ether as an organocatalyst, and α,β-unsaturated aldehydes as the Michael acceptors to prepare various chiral cyclohexenones with excellent enantioselectivities. Deng and coworkers reported an asymmetric Michael addition for the synthesis of chiral cyclohexenones catalyzed by 9-amino-9-deoxyepiquinine.[9] Zhao et al. applied chiral primary-secondary diamine catalysts to catalyze the Michael-aldol-dehydration reaction between benzoylacetates, β-ketoamides and α,β-unsaturated ketones to form chiral cyclohexenones in high enantioselectivities with excellent yields.[10] However, the reports about synthesis of chiral 3,5-diaryl-cyclohexenones are very rare. In 2000, the Corey group reported the preparation of (**S**)-3,5-diaryl-cyclohexenones via a five step synthesis.[2c] Two straightforward procedures for the preparation of non-chiral 3,5-diaryl-cyclohexenones via Robinson annulation reaction of chalcones and acetone have been revealed. In 1998, Inanaga et al. synthesized non-chiral 3,5-diaryl-cyclohexenones via the reaction of chalcones and acetone catalyzed by lanthanoid salts.[11] In 2014, the Ghosh group reported the pyrrolidine-catalyzed direct synthesis of non-chiral 3,5-diaryl-cyclohexenones from acetone and chalcones.[12]

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However, to the best of our knowledge, the asymmetric version of the Robinson annulation of chalcones with acetone for the preparation of chiral 3,5-diaryl-cyclohexenones has not been reported yet.

In asymmetric catalysis, chiral secondary amines have been widely studied as highly versatile and extremely powerful catalysts. However, chiral primary amines as organocatalysts are relatively underutilized. In consideration of the advantage of primary amine catalysis for successfully dealing with major challenges in various sterically hindered carbonyl compounds, which many approaches hardly handle,[13] it is greatly desirable to develop more chiral primary amine catalysts in asymmetric organocatalysis. Moreover, for the choice of chiral catalysts for asymmetric synthesis, a combination of efficiency, availability, and economy is the core consideration. Enantiomerically pure *trans*-1,2-diaminocyclohexane is a structurally simple molecule which fits the requirements very well. As described in a review by Hanessian and coworker:[14] *trans*-1,2-diaminocyclohexane was first reported by Wieland et al. in 1926,[15] who prepared it from hexahydrophthalic acid through conversion to the hydrazide followed by a Curtius reaction. Nowadays, this diamine is readily available because it is a component in a byproduct amine stream produced during the purification of 1,6-hexanediamine, which is one of the materials for the manufacture of Nylon 66.[16] Its optical resolution can be easily done in aqueous medium by utilization of D- or L-tartaric acid to obtain the (R,R)- or the (S,S)- enantiomer in enantiopure form, respectively.[17] Fascinated by its features of ready availability and structural simplicity, our group has been paying much attention on development of new *trans*-1,2-diaminocyclohexane derived chiral catalysts for asymmetric organocatalysis.[18]

Although there are numerous asymmetric aldol reactions reported, aliphatic ketones and aldehydes are mainly concerned; to the best of our knowledge, there is scarcely any reported example for the aromatic ketones without any other assisted functional group participating asymmetric (domino) aldol reactions with other aliphatic ketones. For the Robinson annulation reaction (the sequential asymmetric Michael addition/intramolecular aldol reaction/dehydration) as shown in Scheme 1, generally when R^1 and R^2 are both aliphatic groups or R^1 aromatic while R^2 aliphatic, the initial (metal free organocatalytic) Michael reaction and subsequent aldol reactions may readily take place, while when both R^1 and R^2 are aromatic substituted groups such as chalcone, the enantioselectivity and reactivity of the first Michael addition is difficultly to be controlled due to steric hindrance and the minor differences between the two groups. To the best of our knowledge, there has been only one example on the asymmetric Michael addition of acetone to chalcone which was reported in 2014 and a chiral benzoylthiourea–pyrrolidine was used as a catalyst; only 53% yield with 50% *ee* was obtained without subsequent aldol reaction.[19]

Based on double catalysis: enamine/imine-hydrogen bonding mechanism such as Noyori's chiral ligand *N*-[(1R,2R)-2-amino-1,2-diphenylethyl]-4-methylbenzenesulfonamide (Ts-DPEN),[20] a chiral primary amine bifunctional catalyst, which has been successfully used for the highly enantioselective Michael addition of acetone to nitroalkenes,[21] (1S,2S)-diaminocyclohexane and its benzoyl derivatives were chosen as very simple bifunctional organocatalysts. In this work, a highly enantioselective Robinson annulation of chalcones with acetone was developed using a chiral primary amine as a catalyst to construct (R)-3,5-diaryl-cyclohexenones.

2. Results and discussion

Initially, the domino reaction of chalcone **1a** and acetone **2** was used as a model reaction at 30 °C in PhMe, and a variety of optically active primary amines shown in Fig. 1 were screened as catalysts. As can be seen from the results in Table 1, when **3a** was used in the reaction, only a trace amount of product **4a** was detected (Table 1, entry 1). Catalysts **3b-3f** could promote the model reaction, giving the desired product with high enantioselectivities (92–96% *ee*, the absolute configuration of **3a** was determined as **R** by comparison of HPLC with literature.[3e, 10a]) but in low yields (10–31%) (Table 1, entries 2–6). Taking into consideration of both yield and enantiomeric excess, **3f** was chosen as the catalyst for the cascade reaction. We speculated that the low yields may be due to the evaporation of acetone. Thus, we attempted to improve the yield by adding acetone (20 eq.) in two portions (10 eq. each portion) at the beginning and after 2 days into the reaction mixture, which gave the product in a better yield of 42% with 96% *ee* (Table 1, entry 7). Therefore, the amount of acetone (10 equiv. + 10 equiv./2d) was adopted in the following investigation.

Different solvents were tested for the model reaction catalyzed by **3f** at 30 °C (Table 2). The results revealed that the solvent had a significant effect on the rate and the enantioselectivity of the reaction. In polar solvents, such as DMF, MeCN, MeOH, and EtOH, the reaction resulted in poor yields (Table 2, entries 1–4). By contrast, in non-polar solvents or solvents with low polarity, such as PhMe, PhBr, and xylene, the reaction gave better yields (42–56%) and better enantioselectivities (90–97% *ee*, Table 2, entries 10–12). Among them, the reaction in xylene provided product with an excellent enantioselectivity (96% *ee*) in a relatively good yield (52%) (Table 2, entry 12). Thus, xylene was selected for further optimization. Next, the influence of temperature on the model reaction in xylene was investigated at 20, 40, and 50 °C, respectively. The results indicated that the yield improved from 36% to 60% when the temperature was increased from 20 to 50 °C (Table 2, entries 12–15), however the enantioselectivity decreased from 96% *ee* to 90% *ee*. Therefore, in view of both yield and stereoselectivity, 30 °C was selected as the suitable temperature for the domino reaction.

Other parameters, including the amount of acetone, the catalyst loading and the volume of solvent, were also investigated (Table 3). No superior results were obtained by screening of the amount of acetone and catalyst loading (Table 3, entries 1–7). However, when the volume of the solvent (xylene) was reduced from 1.0 mL to 0.50 mL, the reaction gave a better yield of 62% with high stereoselectivity of 94% *ee* after 4 d (Table 3, entry 9). Through these

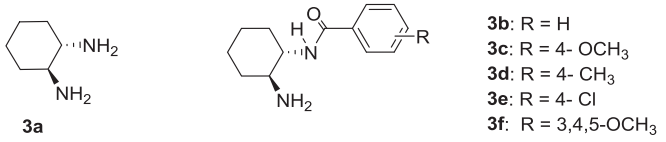
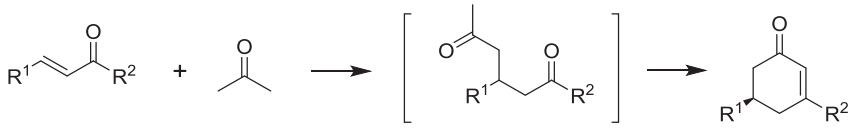


Fig. 1. Structures of the catalysts.



Scheme 1. Robinson annulation reaction.