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Novel bifunctional thiourea–ammonium salt catalysts derived from amino acids: application to highly enantio- and diastereoselective aza-Henry reaction

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ABSTRACT

The development of new efficient and easily accessible catalysts has been one of the focuses in asymmetric phase-transfer catalysis. In this paper, a novel class of chiral bifunctional thiourea–ammonium phase-transfer catalysts were synthesized from commercially available α-amino acids. The structural modularity of these catalysts permits facile tunings to achieve optimum results, which was demonstrated in catalyzing the aza-Henry reaction with excellent enantioselectivities (up to 99.5% ee) and diastereoselectivities (up to >25:1 dr).

1. Introduction

As an inexpensive and readily accessible chiral source, chiral α-amino acids have attracted much interest as an arsenal for the development of diverse organocatalysts, which have found extensive applications in asymmetric synthesis.[1] One of the recent remarkable advances in this field is the development of novel bifunctional or multifunctional organocatalysts based on simple chiral acyclic α-amino acids.[2] Representative catalysts including primary-secondary diamines,[3] tertiary amine-thioureas,[4] and aminophosphines[5] have been successfully applied to a variety of reactions. The success of these catalysts is closely related to the two obvious advantages endowed with chiral α-amino acids as a chiral pool: ready availability at affordable costs and modular structures enabling facile fine tunings.

The catalytic asymmetric phase-transfer catalysis has been well-established as one of the major commonly utilized methodology for the synthesis of kinds of organic compounds.[6] In this realm, while most catalysts are derived from cinchona alkaloids[6g,h] (Scheme 1, **I**), chiral binols[6i,j] (Scheme 1, II) or chiral guanidines[6k] (Scheme 1, III) with great success achieved, the development and applications of novel catalytic systems are still of key importance for the continuing advancement of this methodology.

Our group have focused on the development of novel bifunctional chiral organocatalysts from simple acyclic α-amino acid.[7] Bi- or multifunctionality, especially with an emphasis on H-bond interaction, has been one of the key concepts with great success in the design of new organocatalysts for asymmetric catalysis.[8] However, the application of such a concept in the development of new chiral phase-transfer catalysts has been still rather limited,[9] especially in the case of amino acid-based phase-transfer catalysts. Notably, Ooi and co-workers have developed a new family of chiral 1,2,3-triazoliums using α-amino acids over 10 steps, and applied them to some reactions with excellent results.[10] Our previous good results obtained with the bifunctional primary–tertiary diamine catalysts have inspired us to the development of structurally-related novel bifunctional ammonium salt phase-transfer catalysts (Fig. 1).[11] The highly modular structures of these bifunctional catalysts allow for easy fine tunings at different positions for efficiency improvement. To demonstrate the great potential of these new catalysts for applications in asymmetric phase-transfer catalysis, we applied them to catalyze the aza-Henry reaction as a model, which is an important method for the synthesis of numerous biologically active compounds and building blocks of natural products, such as vicinal diamines and α-amino acids.[12]

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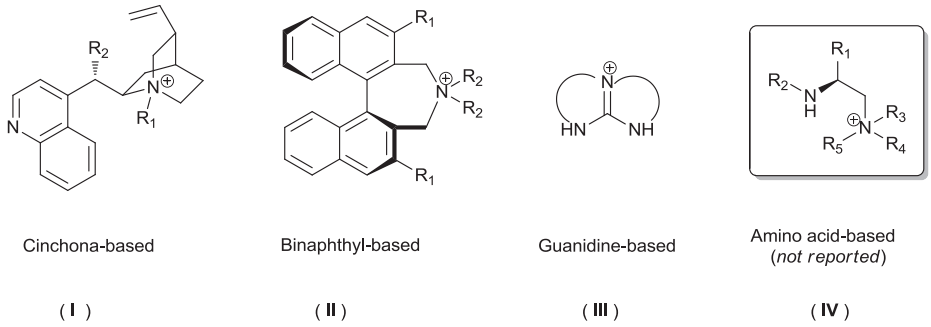


Scheme 1. Chiral quaternary ammonium catalysts (anions are omitted).

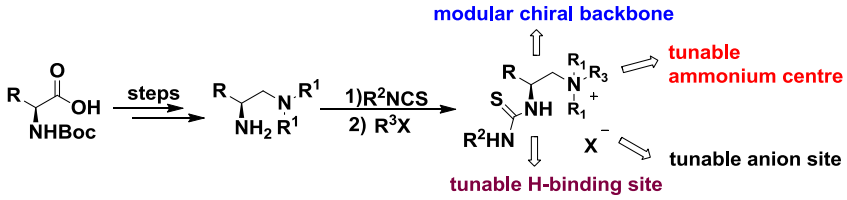


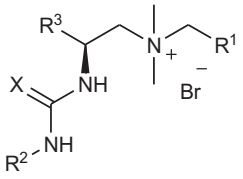
Fig. 1. Design and synthesis of bifunctional thiourea–ammonium salt catalysts.

2. Results and discussion

The *N*-Boc imines used in the aza-Henry reaction for this study were in situ generated from amidosulfones.[9c,f,13] The results of the optimization of the reaction condition parameters, such as screenings of catalysts (Fig. 2), solvents were listed in Table 1. We chose the reaction between amidosulfone **2a** and nitromethane **4a** in the presence of 5 equiv of KOH at −20 °C in toluene as a model reaction for catalyst evaluation (entries 1–8). Firstly, catalysts **1a**–**e** derived from L-leucine and L-isoleucine with different substitutions at the ammonium centre (R^1) and thiourea moieties (R^2) were tested (entries 1–5). The enantioselectivity of the reaction seemed susceptible to changes on both sites and a suitable combination of the substituent groups was identified as in the catalyst **1d** (R^1=4-BrC_6H_4, R^2=4-$NO_2C_6H_4$, entry 4). Subsequent examination of the chiral backbones of these ammonium salts revealed a superior catalyst **1f** derived from *tert*-butyl leucine (entry 6). The ensuing investigation of solvent effect indicated that this reaction gave a higher level of enantiocontrol in CH_2Cl_2 (entry 9), with the best ee value (92%) obtained at −30 °C (entry 13). The use of weaker bases led to inferior results (entries 14–17).

tolerated in the reaction to give the desired products in high yields and with good to excellent enantioselectivities (entries 1–9). While substrates with electron-donating groups on the benzene ring are favoured over those with electron-withdrawing ones in terms of yield and ee value, the influence of the positions of these substituents seemed negligible. However, a significant drop in enantioselectivity was observed with the aliphatic substrate **2j**, while the yield remained excellent (entry 10). To our delight, the employment of nitroethane **4b** also provided excellent yields and ee values, although the dr values were sensitive to the substitution changes of the aryl groups, fluctuating between moderate to excellent (entries 11 and 13–15). The 1-nitropropane **4c** bearing a longer alkyl chain also gave an excellent yield, high ee value and a moderate dr value (entry 12). Notably, the reaction between **2a** and nitromethane **4a** could be performed on a gram-scale with only a slight decrease in the yield and enantioselectivity (entry 16).

To get some insights into the catalytic mechanism of the reaction, we performed two control experiments to test the role of the H-bond sites (the thiourea moiety) and the quaternary ammonium centre of the bifunctional phase-transfer catalysts (Scheme 2). When we employed the thiourea-tertiary amine cata-



1a : R^1 = Ph, R^2 = 4-$NO_2C_6H_3$, R^3 = *i*-Bu, X = S
1b : R^1 = 4-BrC_6H_4, R^2 = 3,5-$(CF_3)_2C_6H_3$, R^3 = *i*-Bu, X = S
1c : R^1 = 4-BrC_6H_4, R^2 = 3,5-$(CF_3)_2C_6H_3$, R^3 = *i*-Bu, X = O
1d : R^1 = 4-BrC_6H_4, R^2 = 4-$NO_2C_6H_4$, R^3 = *i*-Bu, X = S
1e : R^1 = 4-$NO_2C_6H_4$, R^2 = 4-$NO_2C_6H_4$, R^3 = 2-(*S*)-Bu, X = S
1f : R^1 = 4-BrC_6H_4, R^2 = 4-$NO_2C_6H_4$, R^3 = *t*-Bu, X = S
1g : R^1 = 4-BrC_6H_4, R^2 = 4-$NO_2C_6H_4$, R^3 = Bn, X = S
1h : R^1 = 4-BrC_6H_4, R_2 = 4-$NO_2C_6H_4$, R^3 = 2-(*S*)-Bu, X = S

Fig. 2. Catalysts screened in this study.

Under these optimized reaction conditions, we then surveyed the substrate scope of this reaction with different amidosulfones and nitroalkanes (Table 2). With nitromethane **4a**, in general, various amidosulfones with diverse aromatic groups (Rx) were well

lyst **1l**, which lacks the quaternary ammonium centre compared to **1b** (Table 1, entry 1), the enantioselectivity slumped to 3% ee, though the yield was excellent. Similarly, the use of catalyst **1m** with one blocked H-donor site also gave much inferior results.