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Highly Enantioselective Reactions of Cyclohexanone and β,γ-Unsaturated α-Keto Ester: The Tuning of Chemo-selectivities by Secondary and Primary Amine Catalysts†

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A series of of amphiphilic imidazole based secondary and primary amine catalysts were synthesized and shown to be very effective with an acid cocatalyst for the asymmetric reaction of cyclohexanone to β,γ-unsaturated α-keto ester. Interestingly, primary and secondary amine catalysts show different regio-selectivities in this reaction. Under the catalysis of secondary amine **1**, excellent enantioselectivities were observed for the products from direct 3+3 reactions of cyclohexanone with β,γ-unsaturated α-keto esters using water as the solvent. Moreover, the same reactants catalyzed by the primary amines **2** lead to the aldol reactions, affording the corresponding products with high diastereoselectivities and up to 97% *ee*. Theoretical studies on the transition states by using a model in gas phase revealed that steric effect plays an important role on different chemo-selective induction between the secondary amine **1** and primary amine **2**.

Keywords emulsion catalysis, asymmetric catalysis, organocatalysis

Introduction

Formation of enamine from the condensation of chiral amines catalysts with aldehydes or ketones can be used as an effective strategy for the acceleration of a wide variety of catalytic asymmetric reactions.[1] Since the proline was discovered to be an available catalyst in the intermolecular aldol reactions via the enamine mechanism by List and Barbas in 2000,[1b] various amines derived from natural amino acids and other chiral amines have been demonstrated to be effective enamine catalysts in a wide range of enantioselective organic reactions. Generally, secondary and primary amines represent two categories of chiral amine catalysts. Seconary amines with pyrrolidine core are regarded as the extremely powerful catalysts and dominated the field of enamine catalysis in early years. Recently, several primary amines derived from natural amino acids were found to be the effective enamine catalysts as the complementary of secondary amine catalysts.[2] Moreover, in contrast with the secondary amines, primary amine catalysts show distinct advantages in virtue of the presence of the hydrogen on the nitrogen atom, which can facilitate the formation of an active catalytic intermediate to control the enamine structure and selectivity of the reaction. For example, in 2007, Barbas reported a *syn*-selective aldol reaction between hydroxyketones and aromatic aldehydes catalyzed by the primary amine catalyst. Differed from the (*E*)-enamine in the C—C bond forming transition state formed by secondary amine, (*Z*)-enamine was induced by the hydrogen bonding interaction between the NH group in the primary amine and the OH group of hydroxyacetone, which leads to the formation of *syn*-aldol products.[3] Following the similar active model, several asymmetric 1,2-addition could realize fully diastereoselective control with primary amine and secondary amine catalysts[4] (Scheme 1.1).

Recently, our group developed a new amphiphilic proline-derived imidazole organocatalysts and has shown its effectiveness in the cascade reaction of α-ketoacids with aldehydes using water as the solvent.[5] The success on this type of catalyst motivated us to develop new amphiphilic imidazole-based organocatalysts.[6] Herein, we prepared a new class of imidazole derived seconary and primary catalysts from natural amino acid and tested the performance of them in the asymmetric reaction of cyclohexanone to β,γ-unsaturated α-keto ester. To our surprise, primary and secondary amine show the different chemo-selectivities in this reaction (Scheme 1.2). Secondary amine catalysts **1** can

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afford highly optically active 2-hydroxy-9-oxo-bicyclo [3.3.1] nonane derivatives with four stereo centers via formal 3+3 annulation reaction using water as solvent. The same reactants catalyzed by primary amines lead to the aldol reactions, affording the corresponding products bearing two adjacent chiral centers with high diastereoselectivities and up to 97% *ee*. Moreover, theoretical studies on the possible transition states of different catalyst in the control of regio-selectivities of the reaction of cyclohexanone to β,γ-unsaturated α-keto ester are also discussed.

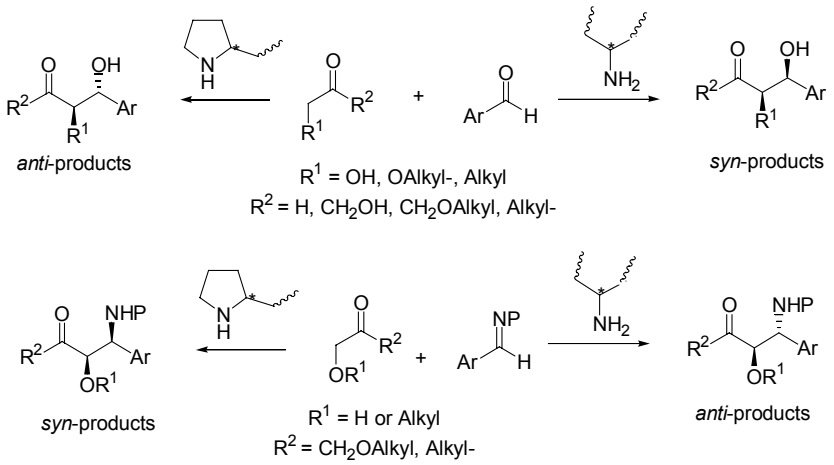
Results and Discussion

The synthesis of catalysts **1** and **2** was quite simple. The key intermediates, *N*-Cbz protected mercapto imidazoles were readily prepared by the condensation of mercapto imidazole with *N*-Cbz-protected amino bromide (see Supporting Information). A series of catalysts **1** and **2** were finally obtained after the grafting of hydrophobic alkyl chains with different lengths and the deprotection of Cbz group in good yields

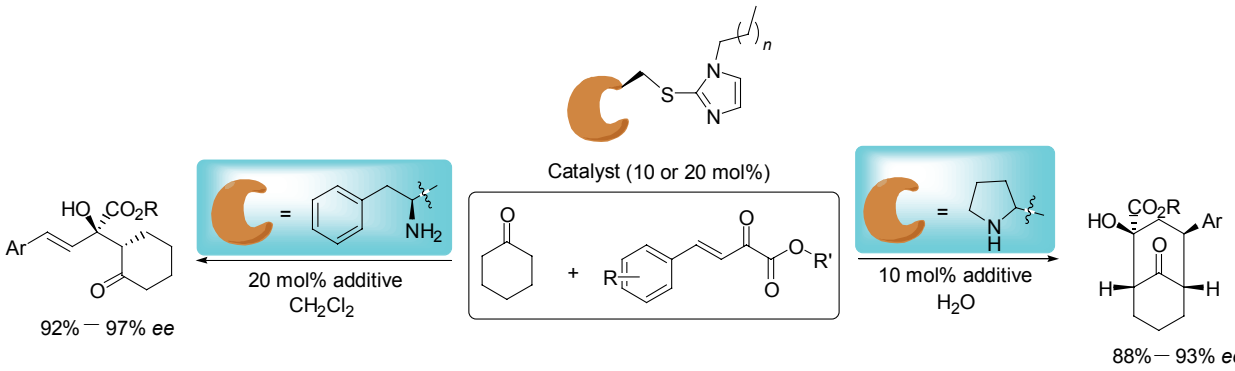
To explore the catalytic performance of **1** and **2**, we focused on the reactions of cyclohexanone with β,γ-unsaturated α-keto ester[7] which have been reported by three groups. These reactions can produce chiral [3,3,1] bicycle,[8] chiral alcohols[9] with two adjacent chiral centers and chiral fused dipyrans[10] via 3+3 annulation, aldol reaction and Hetero-Diels-Alder reaction separately. We began our investigation on the asymmetric reaction of cyclohexanone (**3a**) to β,γ-unsaturated α-keto ester (**4a**) in water[11] by using a 20 mol% catalyst loading at room temperature. Firstly, secondary amine catalysts **1a**—**1e** were screened and the results were listed in Entries 1—5 of Table 1. It was found that all the secondary amine catalysts **1a**—**1e** could promote the reaction with an additive of 4-methoxybenzoic acid (20 mol%), affording 2-hydroxy-9-oxo-bicyclo[3,3,1]nonane (**5a**) via 3+3 tandem annulation with 80%—90% *ee*. Judging from its appearance, the reaction mixture displayed stable emulsion[12] when catalysts **1a**—**1e** were added. Comparably, the emulsion could not form on adding non-carbon-chained catalyst **1a** or short carbon-chained catalyst **1b**. Accordingly, we found that reactivities were increasing as the emulsion of the reaction system became more stable. When 18 or 22-carbon chain com-

Scheme 1 Different induced selectivities of the primary amine and secondary amine catalysts

1.1 The reported results: The diastereo-selective control with primary amine and secondary catalysts



1.2 This work: The chemo-selective control with primary amine and secondary catalysts



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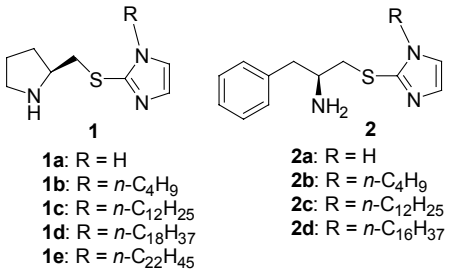
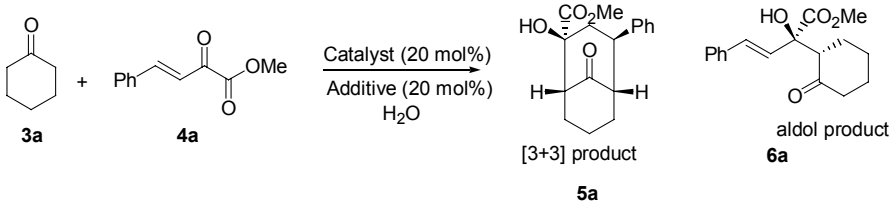


Figure 1 Amphiphilic amino acids-derived mercapto imidazole organocatalysts.

pound **1d** or **1e** was selected to be catalyst, it can achieve over 80% conversion and 90% *ee* (Entries 4, 5, Table 1). By using benzoic acid instead of 4-methoxybenzoic acid, almost the same result was achieved (Entry 6, Table 1). By prolonging the reaction time to 12 h, **1d** afforded a conversion of over 95% and enantioselectivity of 91% (Entry 7, Table 1). To prove the high efficiency of emulsion system, the model reaction was carried out with a reduced catalyst loading (5 mol%), thereby affording **5a** with a 90% conversion with the enantioselectivity as high as 91% by increasing the reaction time to 72 h (Entry 8). Amphiphilic primary catalyst **2d** was then investigated in the same reaction system. To our surprise, the different regio-selectivity was achieved which gave the aldol product **6a** with the complete conversion and 47% *ee* in 12 h. To further improve enantioselectivity, solvents, additives and catalysts have been screened and the results were summarized in Entries 10—15 of Table 1. Finally we found that using CH_2Cl_2 as the solvent could increase the enantioselectivity to 95% with the additive of 4-nitrophenol catalyzed by **2d** at the price of reactivity (Entry 13, Table 1).

Thus, two optimal conditions were set up for 3+3 reaction and aldol reaction separately. Various β,γ-unsaturated α-keto esters were examined to evaluate the reaction scope. **1d**-Catalyzed asymmetric reactions of cyclohexanone (**3a**) with different β,γ-unsaturated α-keto ester (**4**) afforded the corresponding 3+3 products with excellent *ee* values (88%—93%, Table 2, Entries 1—11). Substituted group situated at different positions on the phenyl ring and different ester group have little impact on the enantioselectivity of the reaction. Moreover, compared with the reported procedure (neat condition, 20 mol% catalyst loading and 24—168 h reaction time), emulsion catalytic system composed of **2d** and using water as solvent showed higher reactivity and efficiency. For the aldol 4-nitrophenol was proved to be effective. Under the optimized conditions, a variety of

Table 1 The catalytic asymmetric reactions of **3a** and **4a**[a]

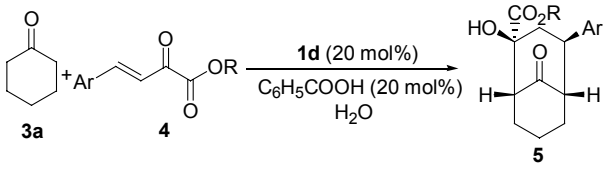


Entry	Cat.	Additive	Time/h	Conv.[b]/%	Prod.	*ee*[c]/%
1	**1a**	4-MeO-BA	6	19	**5a**	80
2	**1b**	4-MeO-BA	6	45	**5a**	90
3	**1c**	4-MeO-BA	6	78	**5a**	90
4	**1d**	4-MeO-BA	6	84	**5a**	90
5	**1e**	4-MeO-BA	6	87	**5a**	90
6	**1d**	BA	6	84	**5a**	91
7	**1d**	BA	12	>95	**5a**	91
8[d]	**1d**	BA	72	90	**5a**	91
9	**2d**	BA	12	>95	**6a**	47
10[e]	**2a**	4-Nitro-P	36	>95	**6a**	94
11[e]	**2b**	4-Nitro-P	36	>95	**6a**	91
12[e]	**2c**	4-Nitro-P	36	>95	**6a**	93
13[e]	**2d**	4-Nitro-P	36	>95	**6a**	95
14[e]	**2d**	BA	36	>95	**6a**	89
15[e]	**2d**	4-MeO-BA	36	>95	**6a**	89

[a] Unless otherwise noted, the reaction was conducted in solvent H_2O (0.5 mL for catalyst **1**, 0.05 mL for catalyst **2**) by using **3a** (124 μL, 1.2 mmol), **4a** (38 mg, 0.2 mmol), and catalyst **1** (0.04 mmol) in the presence of 20 mol% additive at room temperature; [b] determined by crude ^{1}H NMR; [c] determined by chiral HPLC; [d] catalyst loading: 5 mol%; [e] CH_2Cl_2 as the solvent; BA: benzoic acid; P: phenol.

β,γ-unsaturated α-keto esters (**4**) were reacted with cyclohexanone (**3a**) to afford the corresponding aldol products with high diastereoselectivities and excellent enantioselectivities (Table 3, Entries 1—14).

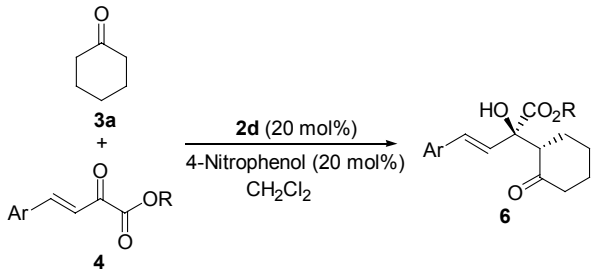
Table 2 Substrates scope of the [3+3] annulation reaction[a]



Entry	Ar	R	Time/h	Yield[b]/%	*ee*[c]/%
1	C_6H_5	Me	12	80	91
2	C_6H_5	Et	12	80	90
3	C_6H_5	Bn	12	60	91
4	C_6H_5	*t*-Bu	12	80	93
5	*m*-MeC_6H_4	*t*-Bu	12	99	89
6	*p*-MeC_6H_4	*t*-Bu	12	99	92
7	*p*-$MeOC_6H_4$	*t*-Bu	24	67	88
8	*p*-FC_6H_4	*t*-Bu	12	99	90
9	*m*-BrC_6H_4	*t*-Bu	12	90	91
10	*p*-$CF_3C_6H_4$	*t*-Bu	12	77	90
11	*p*-ClC_6H_4	*t*-Bu	12	75	92

[a] Unless otherwise noted, the reaction was conducted in solvent H_2O (0.5 mL) by using **3** (1.2 mmol), **4** (0.2 mmol), and catalyst **1d** (0.04 mmol) in the presence of 20 mol% of C_6H_5COOH at room temperature; [b] isolated yield; [c] determined by chiral HPLC.

Table 3 Substrates scope of the cross-aldol reaction[a]



Entry	Ar	R	*t*/h	Yield[b]/%	*dr*[c]	*ee*[d]/%
1	Ph	Me	48	60	5∶1	95
2	Ph	Et	72	62	5∶1	97
3	Ph	*i*-pr	72	58	4∶1	97
4	Ph	Bn	72	60	6∶1	93
5	*p*-FC_6H_4	Me	48	75	5∶1	94
6	*p*-ClC_6H_4	Me	48	76	5∶1	96
7	*p*-BrC_6H_4	Me	48	74	6∶1	96
8	*o*-ClC_6H_4	Me	48	75	5∶1	97
9	*m*-ClC_6H_4	Me	48	77	5∶1	95
10	*p*-$CF_3C_6H_4$	Me	48	78	5∶1	94

Continued

Entry	Ar	R	*t*/h	Yield[b]/%	*dr*[c]	*ee*[d]/%
11	*p*-$CH_3C_6H_4$	Me	48	60	5∶1	97
14	2-Thienyl	Me	96	60	6∶1	92

[a] Unless otherwise specified, the reaction was conducted in CH_2Cl_2 (0.5 mL) by using **3a** (62 μL, 0.6 mmol), **4** (0.1 mmol), and catalyst **2d** (0.02 mmol) in the presence of 20 mol% of 4-nitrophenol at room temperature; [b] isolated yield of the major isomers; [c] determined by crude ^{1}H NMR; [d] determined by chiral HPLC.

A question is posed regarding why the secondary amine and primary amine catalyst induce the different chemoselectivities. To further understand the factors of controlling the chemoselectivity, two kinds of enamine models catalyzed by secondary amine and primary amine, which represent the intermediates of 3+3 reaction and aldol reaction separately, were studied by theoretical calculations with the Gaussian 09 program. Geometries were fully optimized and characterized by frequency analysis method by using hybrid density functional theory (B3LYP) and the 6-31G(d) basis set. As shown in Figure 2, using the primary amine **2** as the catalyst, the intermediate enamine-I was predicted to be a little more favorable than the enamine-II with a slightly lower enthalpy of about 0.48 kcal/mol in the gas phase for the best two different intermediates (enamine-1 and enamine-2), which means that the aldol reaction has an advantage on the competition with 1,4-addition. On the other hand, perhaps owing to the steric affection between secondary amine and substrates, the intermediate enamine-IV, which represents the formation of the 1,4-addtion adduct was predicted to be a little more favorable than the enamine-III with lower enthalpy of about 0.66 kcal/mol under the catalysis of secondary amine **1**.

Conclusions

In conclusion, a series of amphiphilic imidazole derived seconary and primary amines from natural amino acids have been synthesized and applied in the reaction of cyclohexanone to β,γ-unsaturated α-keto ester. The secondary amine catalysts **1** were demonstrated to be efficient catalysts for the 3+3 reaction. In the presence of 5—20 mol% of the catalyst, excellent enantioselectivities ranging from 88% to 92% *ee* and high chemo-selectivities were observed for the products from direct 3+3 reactions of cyclohexanone with a broad scope of β,γ-unsaturated α-keto esters using water as the solvent. Moreover, the same reactants catalyzed by the primary amines **2** lead to the aldol reactions, affording the corresponding products bearing two adjacent chiral centers with high diastereoselectivities and up to 97% *ee*. Theoretical studies on the transition states by using a model in gas phase revealed that steric effect plays an important role on the different chemo-selective induc-

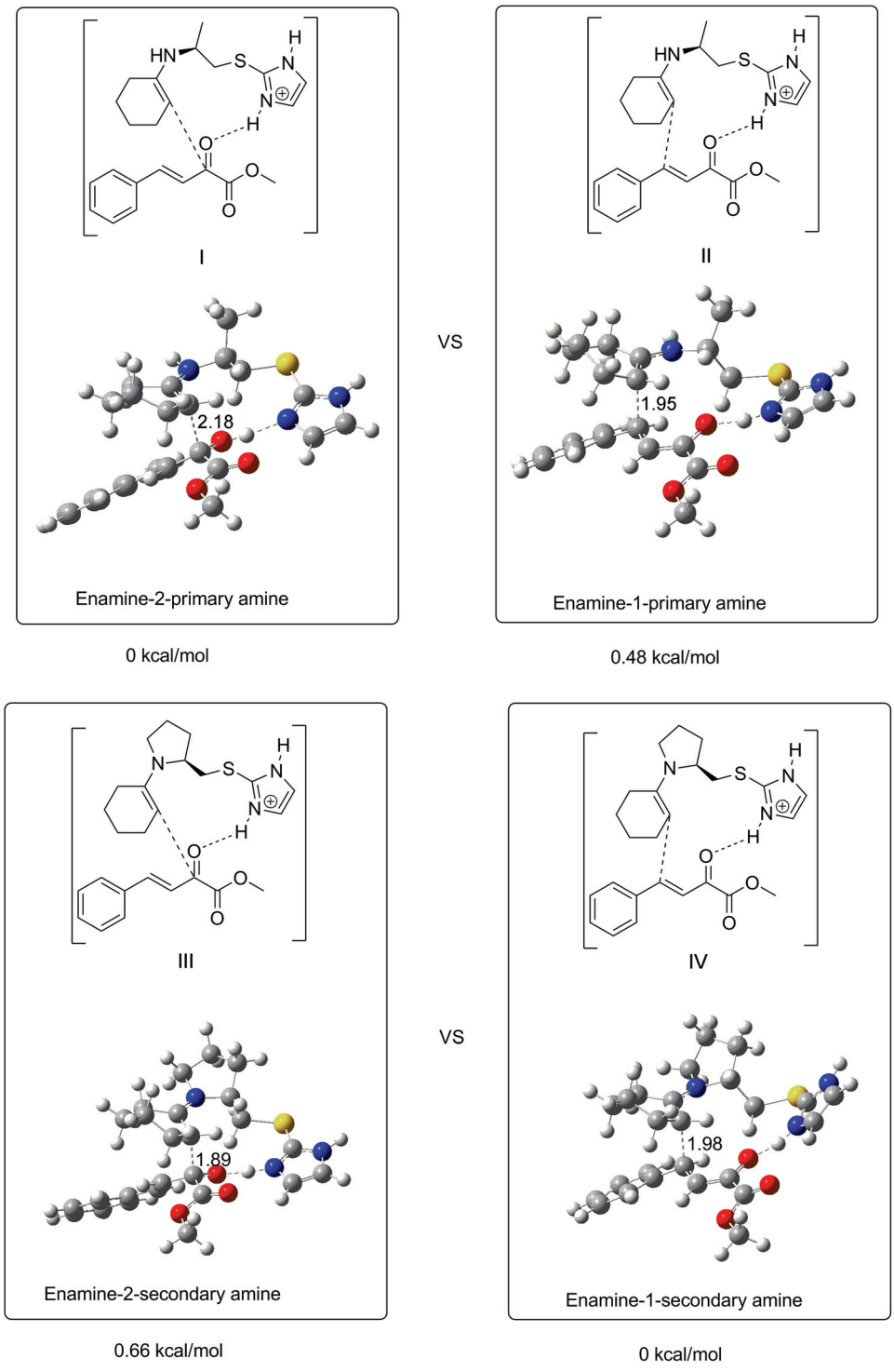


Figure 2 Intermediates and different reaction pathways.

tion between the secondary amine **1** and primary amine **2**.

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