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Organocatalytic and Highly Enantioselective Direct α-Amination of Aromatic Ketones

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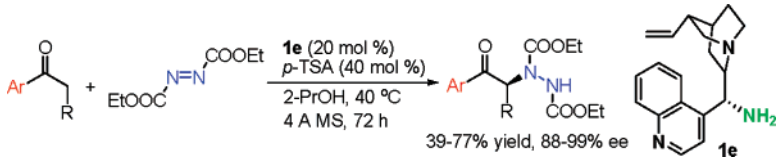
ABSTRACT



The first highly enantioselective direct α-amination of *aryl ketones* was reported to be catalyzed by organic primary amines derived from cinchona alkaloids. Excellent enantioselectivities (88–99% ee) have been achieved for a broad spectrum of aryl ketones. The presence of 4 Å molecular sieves was of great assistance for the high conversions and enantiocontrol.

The electrophilic amination reaction with simple and easily available materials is a very important protocol for the synthesis of nitrogenous molecules, and its asymmetric variants have received considerable interest in recent years.[1] Great progress has been made in the direct asymmetric amination of α-keto esters,[2] β-keto esters,[3] β-keto phosphates,[4] α-substituted cyanoacetates,[5] and alkylidene cyanoacetates[6] in the presence of chiral metal complexes or organic bases. On the other hand, excellent enantioselectivities have also been achieved in the direct α-amination of simple α-enolizable ketones or aldehydes by employing the well-established enamine catalysis.[7,8] However, the application of sterically more bulky aryl ketones as direct nucleophilic donors in the asymmetric amination reaction still remains to be explored. Since α-amino aryl ketones are chiral key elements and intermediates for many important compounds,[9]

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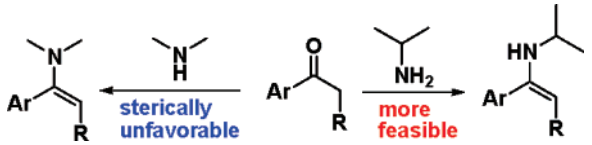
the development of a direct and efficient asymmetric synthetic method is highly desirable.

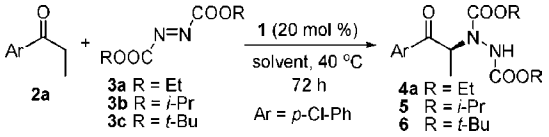
Most of the enamine catalysis of aliphatic ketones and aldehydes utilizes L-proline or its analogues as the organic catalysts. Only a very few organocatalytic examples have been presented for the direct asymmetric reaction of acetophenones,[10] while the direct construction of a chiral center at the α-position of aryl ketones was rarely reported in enamine catalysis.[10c] Encouraged by our experiences in the organocatalytic reactions of α,*β*-unsaturated ketones by iminium activation,[11] we envisaged that chiral *primary amines*,[12] in comparison with *secondary amines*, would be more suitable for the generation of nucleophilic enamines with aryl ketones, which could lead to the successful asymmetric α-amination of aryl ketones with electrophilic azodicarboxylates (Scheme 1).[13]

Scheme 1. Generation of Active Enamine from Aryl Ketone



Based on the above consideration, an array of amino acids and primary amines derived from natural cinchona alkaloids[11,14] were investigated in the asymmetric direct α-amination of *p*-chloropropiophenone **2a** and diethyl azodicarboxylate (DEAD) **3a**. As summarized in Table 1, no reaction occurred in the presence of L-proline **1a** or primary amino acids **1b** and **1c** (Table 1, entries 1−3, Figure 1). Fortunately, the desired α-amination product **4a** was isolated, albeit in low yield, catalyzed by the combination of 9-amino-9-deoxyepiquinine (ADQ) **1d** (20 mol %) and *p*-TSA (40 mol %) in THF at 40 °C for 72 h, and the ee value was quite promising (entry 4, 70%).[15] Slightly higher ee was obtained catalyzed by 9-amino-9-deoxyepicinchonine (ADC) **1e**, while the product has the opposite configuration (entry 5). Sub-

Table 1. Screening Studies of Organocatalytic α-Amination of *p*-Chloropropiophenone **2a** with Azodicarboxylates **3**[a]



entry	cat. **1**	solvent	additive	yield[b] (%)	ee[c] (%)
1−3	**1a**−**c**	THF	–	–	–
4	**1d**	THF	*p*-TSA	40	−70
5	**1e**	THF	*p*-TSA	76	75
6	**1e**	THF	L-CSA	28	64
7	**1e**	THF	$PhCO_2H$	–	–
8	**1e**	THF	AcOH	–	–
9	**1e**	CH_3CN	*p*-TSA	70	67
10	**1e**	2-PrOH	*p*-TSA	26	82
11	**1e**	DMF	*p*-TSA	30	58
12[d]	**1e**	**2-PrOH**	***p*-TSA**	**76**	**98**
13[d]	**1e**	THF	*p*-TSA	70	86
14[d]	**1d**	**2-PrOH**	***p*-TSA**	**51**	**−96**
15[d,e]	**1e**	2-PrOH	*p*-TSA	99	80
16[d,f]	**1e**	2-PrOH	*p*-TSA	99	11

[a] Unless otherwise noted, the reaction was performed with 0.2 mmol of **2**, 0.1 mmol of **3a**, 20 mol % of **1**, and 40 mol % of additive, in 0.3 mL of solvent at 40 °C for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Adding 20 mg of 4 Å MS. [e] With **3b**. [f] With **3c**.

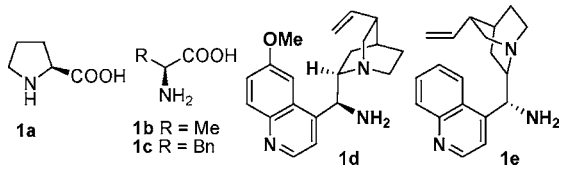


Figure 1. Structures of various amine catalysts.

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(15) Using 20 mol % of *p*-TSA resulted in very low yield (< 10%).

sequently, a variety of conditions were systematically explored with **1e** in order to improve the results. Lower enantioselectivity was observed when L-CSA was used as the acidic additive (entry 6), and no product was found utilizing carboxylic acids (entries 7 and 8). Then solvents were studied (entries 9−11), and higher ee was attained in 2-propanol (entries 10).[16] We ascribed the low yield of α-amination reaction in 2-propanol to the difficult formation of enamine intermediate; the addition of 4 Å molecular sieves (extraction of water) might be helpful for the promotion of the equilibrium. To our delight, outstanding enantioselectivity (98% ee) was gained in the presence of 4 Å MS, and the yield was also dramatically raised (entry 12). Beneficial effects on ee were also noted in THF (entry 13). Moreover, excellent ee was achieved with ADQ **1d** under the optimal conditions (entry 14). Therefore, both enantiomers of the α-amination product could be prepared. Nevertheless, this catalytic system seems to be rather sensitive to the bulkiness of the electrophilic azodicarboxylates. While diisopropyl azodicarboxylate **3b** gave significantly reduced enantioselectivity under the optimal conditions (entry 15), very poor ee was unluckily obtained when di-*tert*-butyl azodicarboxylate **3c** was applied (entry 16), though quantitative yields were isolated for the amination products **5** and **6**.[17] In addition, the α-amination reaction was found to be very sluggish when 10 mol % of primary aminocatalyst **1e** was used.

With the screening conditions in hand, we then examined a variety of aryl ketones (Figure 2) to establish the general

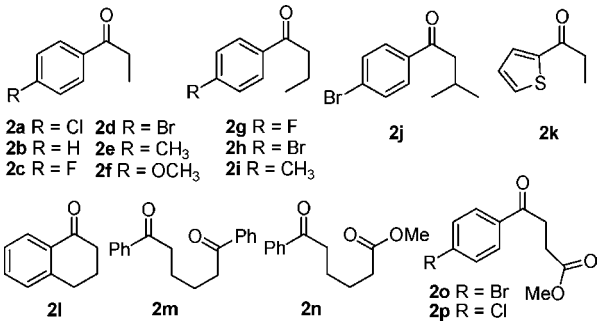


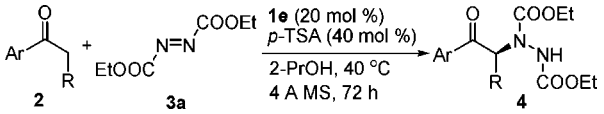
Figure 2. Structures of aryl ketones **2**.

efficacy of the catalytic transformation. The α-amination reaction was commonly conducted with 20 mol % of **1e** and 40 mol % of *p*-TSA in the presence of 4 Å MS at 40 °C for 72 h. As illustrated in Table 2, excellent enantioselectivities with good isolated yields were obtained for propiophenones **2a**−**f** bearing electron-withdrawing or -donating substitutions (Table 2, entries 1−6). High ee values were also attained for diverse *n*-butyrophenones **2g**−**i** (entries 7−9), and even aryl ketone **2j** with a bulky α-isopropyl group could be

(16) Similar solvent effects have been reported in enamine catalysis, see: Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369.

(17) Dibenzyl azodicarboxylate was also tested, but only a trace amount of the desired α-amination product was isolated due to some side reactions catalyzed by **1e** salt.

Table 2. Asymmetric Direct α-Amination of Aryl Ketones **2** with DEAD **3a**[a]



entry	2	4	yield[b] (%)	ee[c] (%)
1	**2a**	**4a**	76	98
2	**2b**	**4b**	65	94[d]
3	**2c**	**4c**	52	93
4	**2d**	**4d**	62	98
5	**2e**	**4e**	62	94
6	**2f**	**4f**	77	94
7	**2g**	**4g**	77	96
8	**2h**	**4h**	54	99
9	**2i**	**4i**	49	98
10	**2j**	**4j**	52	97
11	**2k**	**4k**	63	96
12[e]	**2l**	**4l**	74	90
13	**2m**	**4m**	51	88
14	**2n**	**4n**	39	96
15	**2o**	**4o**	65	91
16	**2p**	**4p**	63	91

[a] Unless otherwise noted, the reaction was performed with 0.2 mmol of **2**, 0.1 mmol of **3a**, 20 mg of 4 Å MS, 20 mol % of **1e**, and 40 mol % of *p*-TSA, in 0.3 mL of 2-PrOH at 40 °C for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configuration of **4b** was determined by comparison with reported optical rotation; see ref 13a. The other products were assigned accordingly. [e] Mesitylsulfonic acid as additive.

smoothly converted to the desired α-amination product with remarkable ee (entry 10). Heteroaryl ketone **2k** is also a proper substrate (entry 11). Good enantioselectivity could be achieved for cyclic 1-tetralone **2l** when a more bulky additive mesitylsulfonic acid was applied (entry 12). Moreover, we also investigated some functionalized aryl ketones. Only monoaminated product **4m** was isolated for symmetric dione **2m** with high ee (entry 13). Outstanding ees were also gained for aryl ketones **2n**−**p** with an ester group (entries 14−16). Therefore, assorted multifunctional chiral amine compounds could be attainable.

Based on the absolute configuration of **4b**, we proposed a plausible catalytic mode for the amination reaction (Figure 3). The in situ formed enamine between propiophenone **2b**

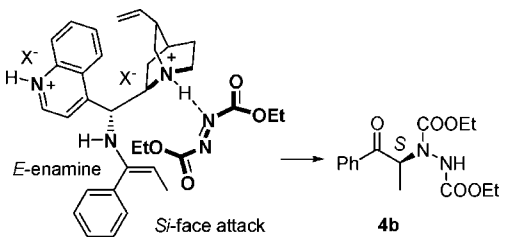


Figure 3. Proposed catalytic reaction mode through concerted activation.

and catalyst **1e** may adopt the *E*-conformation, which directs the α-methyl group away from the catalyst. Like other well-developed diamine−protonic acid-catalyzed reactions,[18] the protonated quinuclidine moiety of **1e** would act as a synergistic Brønsted acid for the activation of electrophilic azodicarboxylate through hydrogen bonding (the quinoline nitrogen might also be protonated in the presence of 2 equiv of *p*-TSA).[19] Then the preferred chiral product would be produced by the *Si* face attacking the enamine intermediate. Because of the crowded nature of the active enamine structure, the expected concerted hydrogen-bonding interaction might not be readily engendered when bulky di-*tert*-butyl azodicarboxylate was employed, which would account for the observed poor enantiocontrol in the amination reaction. Nevertheless, the real catalytic mechanism still needs further investigation.

In conclusion, we have successfully demonstrated that 9-amino-9-deoxyepicinchona alkaloids are excellent enamine organocatalysts for the direct enantioselective α-amination of aryl ketones for the first time. The reaction scopes were substantial, and excellent enantioselectivities (88−99% ee) were achieved for aryl ketones bearing a number of substituents. Therefore, further applications of aryl ketones in a range of challenging asymmetric reactions would be expected through primary amine activation reported in this presentation. Current studies are underway to investigate the synthetic utility of the amination products and expand this catalytic system in other asymmetric transformations.

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Supporting Information Available: Experimental procedures, structural proofs, NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Apart from the promotion of enamine formation, the presence of 4 Å MS may also be helpful for this hydrogen-bonding activation to improve the enantioselectivity.