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Enantioselective Direct α-Amination of Aromatic Ketones Catalyzed by Binaphthyl-Modified Primary Amine

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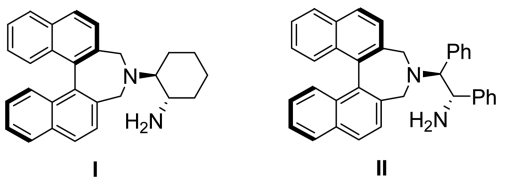
Optically active α-aminated carbonyl compounds are important synthetic building blocks for the synthesis of a large number of biologically active compounds.[1] The enantioselective electrophilic amination of carbonyl compounds represents a powerful and the simplest procedures to generate α-amino carbonyl compounds possessing a nitrogen moiety attached to a stereogenic center.[2] The catalytic enantioselective direct α-amination of active methine compounds such as 1,3-dicarbonyl compounds,[3] β-keto phosphonates[4] and α-cyano carbonyl compounds[5] has been extensively studied. Since the first report for proline-catalyzed α-amination of aldehydes,[6] a number of organocatalytic electrophilic α-aminations of simple aliphatic aldehydes and ketones have been reported.[7] Recently, a organocatalytic enantioselective direct α-amination of aromatic ketones has been reported by Chen *et al*.[8] However, this synthetic method suffered some drawbacks such as the high catalyst loading and long reaction time. To overcome these drawbacks, the development of alternative catalysts for the organocatalytic enantioselective direct α-amination of aromatic ketones is highly desirable.

As part of our effort to demonstrate the development of catalytic synthetic methods for the enantioselective construction of stereogenic carbon centers,[9] we recently reported the catalytic enantioselective Michael-type reactions using chiral primary amine organocatalysts.[10] In this letter, we wish to report the catalytic enantioseletive electrophilic α-amination of aromatic ketones in the presence of chiral binaphthyl-modified organocatalysts.[11]

A survey of some reaction parameters was performed, and some representative results are presented in Table 1. Our investigation began with the catalytic enantioselective electrophilic amination of propiophenone (**1a**) with ethyl azodicarboxylates (**2**) as the electrophilic aminating reagent in ethanol at room temperature in the presence of 20 mol % of catalysts and 40 mol % of *p*-TsOH as additive. We surveyed binaphthyl-modified chiral primary amines **I** and **II** as catalysts (Figure 1). Catalyst **I** exhibited better enantioselectivity (75% ee, entry 1). Among the solvents probed, the best results were achieved when the reaction was conducted in *i*-PrOH (entry 3). We examined our investigations by examining the reactivity and selectivity with organocatalyst **I** in the presence of different acids, such as formic acid and various sulfonic acid derivatives as additives (entries 3 and 9-12). Among the additives probed, the best results were achieved when the reaction was conducted in trifluoromethanesulfonic acid (75% yield and 97% ee, entry 12). The present catalytic system tolerates catalyst loading down to 10, 5, or 2.5 mol % without compromising the yield or the enantioselectivity (entries 13-15).

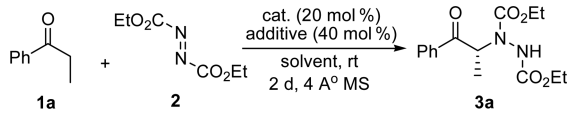
To examine the generality of the catalytic enantioselective direct α-amination of aromatic ketones **1** by using binaph-



I II

Figure 1. Structures of various chiral primary amine catalysts.

Table 1. Optimization of the reaction conditions

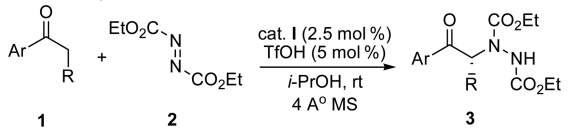


1a **2** **3a**

Entry	Cat.	Additive	Solvent	Yield (%)[a]	ee (%)[b]
1	**I**	*p*-TsOH	EtOH	54	75
2	**II**	*p*-TsOH	EtOH	56	37
3	**I**	*p*-TsOH	*i*-PrOH	64	85
4	**I**	*p*-TsOH	MeCN	30	73
5	**I**	*p*-TsOH	DMSO	35	55
6	**I**	*p*-TsOH	CH_2Cl_2	32	71
7	**I**	*p*-TsOH	$CHCl_3$	33	60
8	**I**	*p*-TsOH	PhMe	25	73
9	**I**	HCO_2H	*i*-PrOH	70	80
10	**I**	$MeSO_3H$	*i*-PrOH	60	87
11	**I**	(−)-CSA	*i*-PrOH	55	81
12	**I**	TfOH	*i*-PrOH	75	97
13[c,f]	**I**	TfOH	*i*-PrOH	70	97
14[d,f]	**I**	TfOH	*i*-PrOH	71	97
15[e,f]	**I**	TfOH	*i*-PrOH	70	97

[a]Isolated yield. [b]Enantiopurity was determined by HPLC analysis using Chiralpak AS column. [c]10 mol % of catalyst and 20 mol % of additive loading. [d]5 mol % of catalyst and 10 mol % of additive loading. [e]2.5 mol % of catalyst and 5 mol % of additive loading. [f]Reaction was carried for 24 h.

Table 2. Catalytic enantioselective α-amination of aromatic ketone



1 2 3

Entry	**1**, Ar, R	Time (d)	Yield (%)[a]	ee (%)[b]
1	**1a**, Ph, Me	1	**3a**, 70	97
2	**1b**, Ph, Et	1	**3b**, 76	97
3	**1c**, 4-MeC_6H_4, Me	1	**3c**, 70	95
4	**1d**, 4-OMe C_6H_4, Me	1	**3d**, 68	97
5	**1e**, 4-F C_6H_4, Me	1	**3e**, 70	93
6	**1f**, 4-Cl C_6H_4, Me	1	**3f**, 73	97
7[c]	**1g**, 2-Cl C_6H_4, Me	4	**3g**, 65	85
8[c]	**1h**, 2-thienyl, Me	4	**3h**, 62	83

[a]Isolated yield. [b]Enantiopurity was determined by HPLC analysis using Chiralpak AS column. [c]10 mol % of catalyst loading.

thyl-modified chiral primary amine organocatalyst **I**, we studied the amination of various aromatic ketones **1**. As it can be seen by the results summarized in Table 2, the corresponding α-aminated aromatic ketones **3** were obtained in high to moderate yields and excellent enantioselectivities. A range of electron-donating and electron-withdrawing substitutions on the aryl ring of the aromatic ketones **1** provided reaction products in high to moderate yields and excellent enantioselectivities (85-97% ee, entries 1-7). The heteroaryl ketone **1h** provided the α-aminated products with moderate yield and high selectivity (83% ee, entry 8). The absolute configuration of **3** was established by comparison of the optical rotation and chiral HPLC analysis with previously reported values.[8]

In conclusion, we have developed an efficient catalytic enantioselective direct α-amination of aromatic ketones promoted by 2.5 mol % of binaphthyl-modified chiral primary amine catalyst **I**. The desired α-aminated products were obtained in high to moderate yields, and excellent enantioselectivities (83-97% ee) were observed.

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