

# Enantioselective Direct $\alpha$ -Amination of Aromatic Ketones Catalyzed by Binaphthyl-Modified Primary Amine

Young Jo Lim and Dae Young Kim\*

Department of Chemistry, Soonchunhyang University, Asan, Chungnam 336-745, Korea. \*E-mail: dyoung@sch.ac.kr  
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Optically active  $\alpha$ -aminated carbonyl compounds are important synthetic building blocks for the synthesis of a large number of biologically active compounds.<sup>1</sup> The enantioselective electrophilic amination of carbonyl compounds represents a powerful and the simplest procedures to generate  $\alpha$ -amino carbonyl compounds possessing a nitrogen moiety attached to a stereogenic center.<sup>2</sup> The catalytic enantioselective direct  $\alpha$ -amination of active methine compounds such as 1,3-dicarbonyl compounds,<sup>3</sup>  $\beta$ -keto phosphonates<sup>4</sup> and  $\alpha$ -cyano carbonyl compounds<sup>5</sup> has been extensively studied. Since the first report for proline-catalyzed  $\alpha$ -amination of aldehydes,<sup>6</sup> a number of organocatalytic electrophilic  $\alpha$ -aminations of simple aliphatic aldehydes and ketones have been reported.<sup>7</sup> Recently, a organocatalytic enantioselective direct  $\alpha$ -amination of aromatic ketones has been reported by Chen *et al.*<sup>8</sup> 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  $\alpha$ -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,<sup>9</sup> we recently reported the catalytic enantioselective Michael-type reactions using chiral primary amine organocatalysts.<sup>10</sup> In this letter, we wish to report the catalytic enantioselective electrophilic  $\alpha$ -amination of aromatic ketones in the presence of chiral binaphthyl-modified organocatalysts.<sup>11</sup>

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

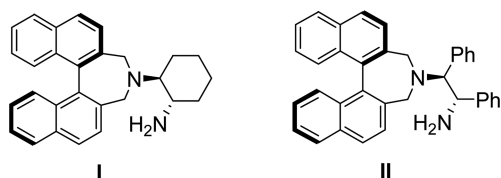
binaphthyl-modified chiral primary amines **I** and **II** as catalysts (Figure 1). Catalyst **I** exhibited better enantioselectivity (75% ee, entry 1). Among the solvents probed, the best results were achieved when the reaction was conducted in *i*-PrOH (entry 3). We examined our investigations by 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  $\alpha$ -amination of aromatic ketones **1** by using binaph-

**Table 1.** Optimization of the reaction conditions

Entry	Cat.	Additive	Solvent	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	<b>I</b>	<i>p</i> -TsOH	EtOH	54	75
2	<b>II</b>	<i>p</i> -TsOH	EtOH	56	37
3	<b>I</b>	<i>p</i> -TsOH	<i>i</i> -PrOH	64	85
4	<b>I</b>	<i>p</i> -TsOH	MeCN	30	73
5	<b>I</b>	<i>p</i> -TsOH	DMSO	35	55
6	<b>I</b>	<i>p</i> -TsOH	CH <sub>2</sub> Cl <sub>2</sub>	32	71
7	<b>I</b>	<i>p</i> -TsOH	CHCl <sub>3</sub>	33	60
8	<b>I</b>	<i>p</i> -TsOH	PhMe	25	73
9	<b>I</b>	HCO <sub>2</sub> H	<i>i</i> -PrOH	70	80
10	<b>I</b>	MeSO <sub>3</sub> H	<i>i</i> -PrOH	60	87
11	<b>I</b>	(-)-CSA	<i>i</i> -PrOH	55	81
12	<b>I</b>	TfOH	<i>i</i> -PrOH	75	97
13 <sup>c,f</sup>	<b>I</b>	TfOH	<i>i</i> -PrOH	70	97
14 <sup>d,f</sup>	<b>I</b>	TfOH	<i>i</i> -PrOH	71	97
15 <sup>e,f</sup>	<b>I</b>	TfOH	<i>i</i> -PrOH	70	97

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



**Figure 1.** Structures of various chiral primary amine catalysts.

**Table 2.** Catalytic enantioselective  $\alpha$ -amination of aromatic ketone

Entry	1, Ar, R	Time (d)	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	<b>1a</b> , Ph, Me	1	<b>3a</b> , 70	97
2	<b>1b</b> , Ph, Et	1	<b>3b</b> , 76	97
3	<b>1c</b> , 4-MeC <sub>6</sub> H <sub>4</sub> , Me	1	<b>3c</b> , 70	95
4	<b>1d</b> , 4-OMeC <sub>6</sub> H <sub>4</sub> , Me	1	<b>3d</b> , 68	97
5	<b>1e</b> , 4-F C <sub>6</sub> H <sub>4</sub> , Me	1	<b>3e</b> , 70	93
6	<b>1f</b> , 4-Cl C <sub>6</sub> H <sub>4</sub> , Me	1	<b>3f</b> , 73	97
7 <sup>c</sup>	<b>1g</b> , 2-Cl C <sub>6</sub> H <sub>4</sub> , Me	4	<b>3g</b> , 65	85
8 <sup>c</sup>	<b>1h</b> , 2-thienyl, Me	4	<b>3h</b> , 62	83

<sup>a</sup>Isolated yield. <sup>b</sup>Enantiopurity was determined by HPLC analysis using Chiralpak AS column. <sup>c</sup>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  $\alpha$ -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  $\alpha$ -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.<sup>8</sup>

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

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