

## Enantioselective Electrophilic $\alpha$ -Amination of $\alpha$ -Cyanoketones Catalyzed by Chiral Nickel Complexes

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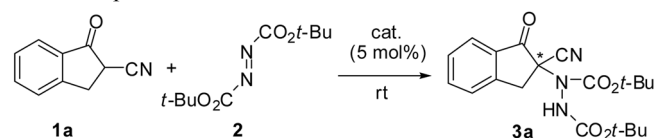
The efficient synthetic construction of  $\alpha$ -amino carbonyl compounds is one of the most intensely studied areas in organic synthesis.<sup>1</sup> Chiral  $\alpha$ -amino nitriles are very useful bifunctional compounds for a large number of synthetic applications.<sup>2</sup> The most popular and wide use of chiral  $\alpha$ -amino nitrile involves hydrolysis of the nitrile group to generate chiral  $\alpha$ -amino acids<sup>3</sup> which are often used as key building blocks in pharmaceuticals. In addition, since cyano group is easily converted to other functional groups, chiral  $\alpha$ -substituted  $\alpha$ -amino nitriles would be versatile synthetic intermediates for the synthesis of chiral 1,2-diamine derivatives which are employed as medicinal agents or chiral ligands.<sup>4</sup> The catalytic asymmetric cyanation of imines, Strecker reaction, represents one of the most popular methods for the synthesis of chiral  $\alpha$ -amino nitrile derivatives. Several successful achievements in catalytic asymmetric Strecker reaction were reported.<sup>5</sup> However, most of the known asymmetric Strecker reactions rely on the use of toxic and anhydrous cyanide reagents. The catalytic enantioselective electrophilic amination of  $\alpha$ -substituted nitriles seems to be alternate method for the synthesis of chiral  $\alpha$ -amino nitrile derivatives. The catalytic, enantioselective, direct C-N bond formation reaction of active methine compounds represents an efficient and the simplest procedures to generate stereogenic carbon center attached to a nitrogen atom.<sup>6</sup> Recently, several groups presented the direct enantioselective amination of active methine compounds such as  $\beta$ -ketoester,<sup>7</sup>  $\beta$ -ketophosphonates,<sup>8</sup> and  $\alpha$ -cyanoacetates<sup>9</sup> in the presence of chiral metal complexes or organocatalysts.

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,<sup>11</sup> we report the catalytic enantio-

selective functionalization of ester derivatives promoted by air- and moisture-stable chiral catalysts.<sup>12</sup> In this note, we wish to report the direct  $\alpha$ -amination of cyclic and acyclic  $\alpha$ -cyanoketones catalyzed by chiral nickel complexes **I-V**<sup>13</sup> with azodicarboxylates as the electrophilic nitrogen source.<sup>10</sup>

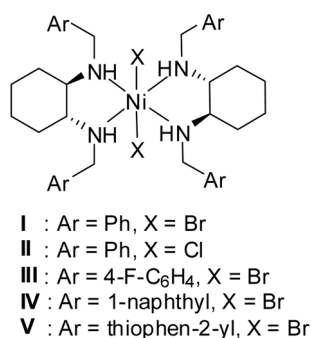
To determine optimum reaction conditions for the catalytic enantioselective electrophilic amination of  $\alpha$ -cyanoketones, we initially investigated the reaction of 2-cyanoindanone (**1a**) with azodicarboxylates **2** as the electrophilic aminating agent in the presence of 5 mol% of catalyst in toluene at room temperature. We first examined the impact of the structure of catalysts **I-V** on enantioselectivity (Table 1, entries 1-5). The best results have been obtained with catalysts **III**, which is prepared from (*R,R*)-*N,N'*-bis(4-fluorobenzyl)-cyclohexane-1,2-diamine. We examined the impact

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

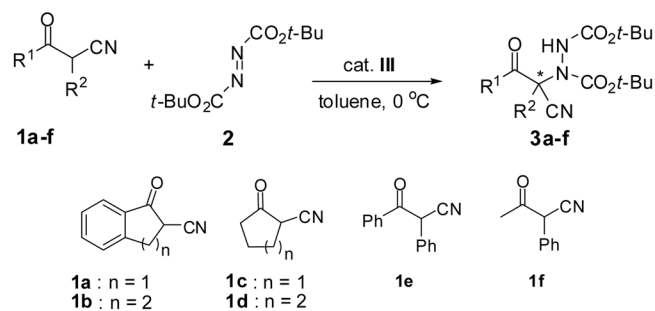


Entry	Cat.	Solvent	Yield (%)	Ee <sup>a</sup> (%)
1	<b>I</b>	Toluene	90	75
2	<b>II</b>	Toluene	92	33
3	<b>III</b>	Toluene	93	78
4	<b>IV</b>	Toluene	85	55
5	<b>V</b>	Toluene	87	37
6 <sup>b</sup>	<b>III</b>	Toluene	93	43
7 <sup>c</sup>	<b>III</b>	Toluene	88	68
8 <sup>d</sup>	<b>III</b>	Toluene	81	59
9	<b>III</b>	MeOH	91	47
10	<b>III</b>	Acetone	88	60
11	<b>III</b>	CH <sub>2</sub> Cl <sub>2</sub>	78	58
12	<b>III</b>	Et <sub>2</sub> O	67	65
13	<b>III</b>	THF	76	58
14	<b>III</b>	CH <sub>3</sub> CN	85	61
15 <sup>e</sup>	<b>III</b>	Toluene	91	81
16 <sup>f</sup>	<b>III</b>	Toluene	87	80

<sup>a</sup>Enantiopurity of **5** was determined by HPLC analysis using a Chiralpak AD column. <sup>b</sup>Reaction was carried out with diethyl azodicarboxylate. <sup>c</sup>Reaction was carried out with di-isopropyl azodicarboxylate. <sup>d</sup>Reaction was carried out with dibenzyl azodicarboxylate. <sup>e</sup>Reaction was carried out at 0 °C. <sup>f</sup>Reaction was carried out at -40 °C.



**Figure 1.** Structure of chiral Ni(II) complexes.

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

Entry	$\alpha$ -Cyanoketone	Time (h)	Yield <sup>a</sup> (%)	Ee <sup>b</sup> (%)
1	<b>1a</b>	0.5	<b>3a</b> , 91	81
2	<b>1b</b>	0.5	<b>3b</b> , 92	83
3	<b>1c</b>	1	<b>3c</b> , 93	73
4	<b>1d</b>	3	<b>3d</b> , 85	75
5	<b>1e</b>	12	<b>3e</b> , 84	78
6	<b>1f</b>	8	<b>3f</b> , 87	76

<sup>a</sup>Yield of isolated product. <sup>b</sup>Enantiopurity of **3** was determined by HPLC analysis using Chiralpak AD (for **3a** and **3c**), AS (for **3b**), Chiralcel OD-H (for **3e-f**) and (*S,S*)-Whelk-O1 (for **3d**) columns.

of the structure of azodicarboxylates **2** on enantioselectivity (Table 1, entries 3, 6-8). When employing sterically encumbered *tert*-butyl ester of azodicarboxylate **2**, the corresponding aminated adduct **3a** was isolated with high enantioselectivity of 78% ee (entry 3). Concerning the solvent (entries 3, 9-14), the use of toluene gave the best results in the yield and the enantiomeric excess (entry 3). Lowering the temperature to 0 ~ -40 °C with catalyst **V** improved the enantioselectivity (80-81% ee, entries 15-16).

To examine the generality of the catalytic enantioselective amination of  $\alpha$ -cyanoketones **1** by using new chiral nickel complex **III**, we studied the amination of various  $\alpha$ -cyanoketones **1a-f**. As it can be seen by the results summarized in Table 2, the corresponding  $\alpha$ -aminated  $\alpha$ -cyanoketones **3a-f** were obtained in high yields and enantioselectivities. The cyclic  $\alpha$ -cyanoketones **1a-d** reacted with *tert*-butyl azodicarboxylate (**2**) to give the corresponding  $\alpha$ -aminated  $\beta$ -ketoesters **3a-d** in 84-92% yields and 73-83% ee (Table 2, entries 1-4). Acyclic  $\beta$ -ketoesters **1e-f** reacted with *tert*-butyl azodicarboxylate (**2**) to afford the  $\alpha$ -aminated  $\beta$ -ketoesters **3e-f** with 76-78% ee (Table 2, entries 5-6).

In conclusion, we have developed a highly efficient catalytic enantioselective  $\alpha$ -amination of cyclic and acyclic  $\alpha$ -cyanoketones using air- and moisture-stable chiral nickel complexes. The desired  $\alpha$ -aminated products were obtained in high yields and enantioselectivities (75-83% ee). Further details and application of this amination will be presented in due course.

## Experimental Section

**Typical procedure for the amination of 2-cyano-1-indanone 1a:** To a stirred solution of 2-cyano-1-indanone **1a** (47.15 mg, 0.3 mmole) and catalyst **III** (2.64 mg, 0.003 mmol) in toluene (0.3 mL) was added dropwise the solution

of *tert*-butyl azodicarboxylate (103.6 mg, 0.45 mmol) in 0.3 mL of toluene at 0 °C. Reaction mixture was stirred for 30 min at 0 °C. The mixture was concentrated and purified by flash chromatography (EtOAc:hexane = 1:4) to afford the 105.7 mg (91%) of  $\alpha$ -aminated 2-cyano-1-indanone **3a**.

**Di-*tert*-butyl 1-(2-cyano-1-oxo-2,3-dihydro-1H-inden-2-yl)hydrazine-1,2-dicarboxylate 3a:**  $[\alpha]_D^{20}$  -18.1 (c 1.5, CHCl<sub>3</sub>, 81% ee); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  7.90-7.86 (m, 1H), 7.82-7.70 (m, 1H), 7.56-7.43 (m, 2H), 7.09-7.01 (s, 1H), 4.07-3.87 (m, 2H), 1.62-1.22 (m, 18H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  192.0, 155.5, 149.3, 136.9, 136.6, 132.2, 128.6, 126.5, 123.8, 115.6, 83.0, 82.6, 68.4, 40.0, 28.2, 27.8; MS (ESI): m/z 387 [M<sup>+</sup>], 356 (10), 332 (70), 275 (32), 232 (8), 213 (12), 188 (7.5), 158 (8); HRMS (ESI/[M]<sup>+</sup>) m/z calcd. for C<sub>20</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>: 387.1794, found: 387.1802; HPLC (hexane/*i*-PrOH = 80/20, 1.0 mL/min, 254 nm, Chiralpak AD column): *t*<sub>R</sub> = 5.8 min (minor), *t*<sub>R</sub> = 7.7 min (major).

**Di-*tert*-butyl 1-(2-cyano-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)hydrazine-1,2-dicarboxylate 3b:**  $[\alpha]_D^{17}$  0.3 (c 1.0, CHCl<sub>3</sub>, 83% ee); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  8.11-7.94 (m, 1H), 7.58-7.51 (m, 1H), 7.40-7.33 (m, 1H), 7.29-7.22 (m, 1H), 6.90 (s, 1H), 3.49-3.06 (m, 3H), 2.96-2.66 (m, 1H), 1.51-1.37 (m, 18H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  186.3, 152.9, 142.7, 134.8, 129.3, 129.0, 128.9, 127.5, 127.35, 114.3, 84.4, 83.9, 82.3, 32.4, 28.2, 28.0, 26.6; MS (ESI): m/z 401 [M<sup>+</sup>], 370 (10), 346 (65), 289 (31), 247 (20), 219 (9), 186 (8), 171 (7); HPLC (hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm, Chiralpak AS column), *t*<sub>R</sub> = 15.2 min (major), *t*<sub>R</sub> = 9.4 min (minor).

**Di-*tert*-butyl 1-(1-cyano-2-oxocyclopentyl)hydrazine-1,2-dicarboxylate 3c:**  $[\alpha]_D^{18}$  6.2 (c 0.3, CHCl<sub>3</sub>, 73% ee); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  6.78 (s, 1H), 2.72-2.58 (m, 2H), 2.51-2.42 (m, 1H), 2.38-2.22 (m, 1H), 2.19-1.81 (m, 2H), 1.49-1.37 (m, 18H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  202.4, 153.3, 153.0, 115.1, 84.0, 82.5, 69.3, 34.9, 34.0, 28.2, 28.0, 18.7; MS (ESI): m/z 339 [M<sup>+</sup>], 308 (6), 295 (6), 283 (12), 263 (4), 228 (28), 184 (4); HPLC (hexane/*i*-PrOH = 95/5, 1 mL/min, detection 220 nm, Chiralpak AD column): *t*<sub>R</sub> = 12.8 min (major), *t*<sub>R</sub> = 21.3 min (minor).

**Di-*tert*-butyl 1-(1-cyano-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate 3d:**  $[\alpha]_D^{20}$  -12.2 (c 1.13, CHCl<sub>3</sub>, 75% ee); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  6.83-5.59 (br, 1H), 3.15-2.70 (m, 1H), 2.69-2.40 (m, 2H), 2.39-2.05 (m, 2H), 2.04-1.79 (m, 3H), 1.52-1.46 (s, 18H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  199.5, 155.4, 154.4, 116.4, 84.6, 82.3, 67.9, 38.1, 37.2, 28.7, 27.9, 21.1, 19.5; MS (ESI): m/z 353 [M<sup>+</sup>], 337 (12), 298 (85), 291 (4), 241 (29), 199 (5), 170 (3); HPLC (hexane/*i*-PrOH = 90/10, 216 nm, 1.0 mL/min, (*S,S*)-Whelk-O1 column): *t*<sub>R</sub> = 15.8 min (major), *t*<sub>R</sub> = 18.9 min (minor).

**Di-*tert*-butyl 1-(1-cyano-2-oxo-1,2-diphenylethyl)hydrazine-1,2-dicarboxylate 3e:**  $[\alpha]_D^{22}$  -78.4 (c = 1.7, CHCl<sub>3</sub>, 78% ee); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  7.9-7.71 (m, 2H), 7.69-7.56 (m, 2H), 7.55-7.36 (m, 4H), 7.35-7.27 (m, 2H), 6.40-6.33 (br, 1H), 1.54-1.21 (m, 18H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  188.9, 154.2, 133.6, 133.3, 130.6, 130.2, 129.8, 129.7, 129.5, 129.2, 128.9, 128.3, 117.4, 84.3, 82.5, 81.2, 27.9, 27.8; MS (ESI): m/z 451 [M<sup>+</sup>], 408 (4), 396 (26), 352

(20), 325 (30), 295 (28), 252 (3), 225 (14); HPLC (hexane/*i*-PrOH = 98/2, 254nm, 1.0 mL/min, Chiralcel OD-H column):  $t_R$  = 9.97 min (major),  $t_R$  = 12.2 min (minor).

**Di-*tert*-butyl 1-(1-cyano-2-oxo-1-phenylpropyl)hydrazine-1,2-dicarboxylate 3f:**  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.8-7.42 (m, 5H), 6.18-5.86 (br, 1H), 2.42 (s, 3H), 1.62-1.30 (m, 18H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  194.5, 155.0, 154.3, 130.5, 130.2, 129.4, 128.5, 127.5, 118.1, 80.1, 79.7, 73.3, 28.0, 26.1; MS (ESI):  $m/z$  389 [ $\text{M}^+$ ]; HPLC (hexane/*i*-PrOH = 95/5, 254 nm, 1.0 mL/min, Chiralcel OD-H column):  $t_R$  = 5.31 min (major),  $t_R$  = 4.86 min (minor).

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