Enantioselective Electrophilic α-Amination of α-Cyanoketones Catalyzed by Chiral Nickel Complexes

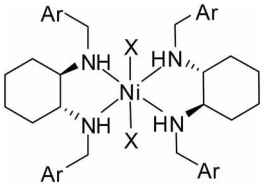
Dae Young Kim

Department of Chemistry, Division of Applied Science, Soonchunhyang University, Asan, Chungnam 336-745, Korea
E-mail: dyoung@sch.ac.kr
Received June 25, 2008

Key Words : Electrophilic amination, Asymmetric catalysis, Chiral nickel catalysts, α-Cyanoketones

The efficient synthetic construction of α-amino carbonyl compounds is one of the most intensely studied areas in organic synthesis.[1] Chiral α-amino nitriles are very useful bifunctional compounds for a large number of synthetic applications.[2] The most popular and wide use of chiral α-amino nitrile involves hydrolysis of the nitrile group to generate chiral α-amino acids[3] which are often used as key building blocks in pharmaceuticals. In addition, since cyano group is easily converted to other functional groups, chiral α-substituted α-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.[4] The catalytic asymmetric cyanation of imines, Strecker reaction, represents one of the most popular methods for the synthesis of chiral α-amino nitrile derivatives. Several successful achievements in catalytic asymmetric Streker reaction were reported.[5] However, most of the known asymmetric Strecker reactions rely on the use of toxic and anhydrous cyanide reagents. The catalytic enantioselective electrophilic amination of α-substituted nitriles seems to be alternate method for the synthesis of chiral α-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.[6] Recently, several groups presented the direct enantioselective amination of active methine compounds such as β-ketoester,[7] β-ketophosphonates,[8] and α-cyanoacetates[9] 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,[11] we report the catalytic enantioselective functionalization of ester derivatives promoted by air- and moisture-stable chiral catalysts.[12] In this note, we wish to report the direct α-amination of cyclic and acyclic α-cyanoketones catalyzed by chiral nickel complexes **I-V**[13] with azodicarboxylates as the electrophilic nitrogen source.[10]

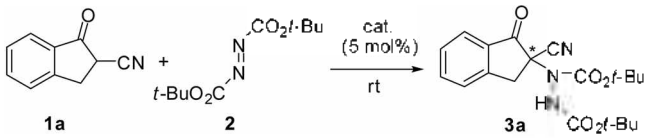


I : Ar = Ph, X = Br
II : Ar = Ph, X = Cl
III : Ar = 4-F-C_6H_4, X = Br
IV : Ar = 1-naphthyl, X = Br
V : Ar = thiophen-2-yl, X = Br

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

To determine optimum reaction conditions for the catalytic enantioselective electrophilic amination of α-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 preparped from (*R*,*R*)-*N*,*N*'-bis(4-fluorobenzyl)-cyclohexane-1,2-diamine. We examined the impact

Table 1. Optimization of the reaction conditions

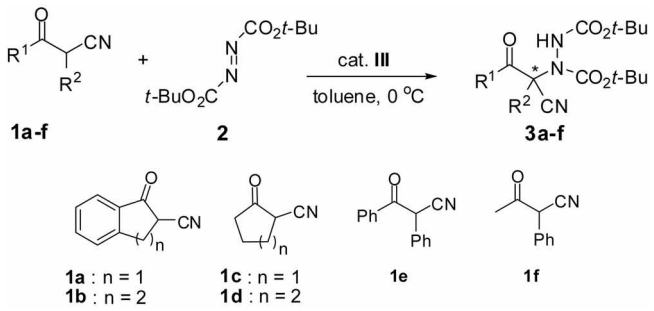


1a **2** **3a**

Entry	Cat.	Solvent	Yield (%)	Ee[a] (%)
1	**I**	Toluene	90	75
2	**II**	Toluene	92	33
3	**III**	Toluene	93	78
4	**IV**	Toluene	85	55
5	**V**	Toluene	87	37
6[b]	**III**	Toluene	93	43
7[c]	**III**	Toluene	88	68
8[d]	**III**	Toluene	81	59
9	**III**	MeOH	91	47
10	**III**	Acetone	88	60
11	**III**	CH_2Cl_2	78	58
12	**III**	Et_2O	67	65
13	**III**	THF	76	58
14	**III**	CH_3CN	85	61
15[e]	**III**	Toluene	91	81
16[f]	**III**	Toluene	87	80

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

Table 2. Catalytic enantioselective amination of α-cyanoketones



Entry	α-Cyanoketone	Time (h)	Yield[a] (%)	Ee[b] (%)
1	**1a**	0.5	**3a**, 91	81
2	**1b**	0.5	**3b**, 92	83
3	**1c**	1	**3c**, 93	73
4	**1d**	3	**3d**, 85	75
5	**1e**	12	**3e**, 84	78
6	**1f**	8	**3f**, 87	76

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

In conclusion, we have developed a highly efficient catalytic enantioselective α-amination of cyclic and acyclic α-cyanoketones using air- and moisture-stable chiral nickel complexes. The desired α-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 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 α-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, $CHCl_3$, 81% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 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); ^{13}C NMR (50 MHz, $CDCl_3$) δ 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^+], 356 (10), 332 (70), 275 (32), 232 (8), 213 (12), 188 (7.5), 158 (8); HRMS (ESI/[M]$^+$) m/z calcd. for $C_{20}H_{25}N_3O_5$: 387.1794, found: 387.1802; HPLC (hexane/*i*-PrOH = 80/20, 1.0 mL/min, 254 nm, Chiralpak AD column): t_R = 5.8 min (minor), t_R = 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, $CHCl_3$, 83% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 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); ^{13}C NMR (50 MHz, $CDCl_3$) δ 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^+], 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_R = 15.2 min (major), t_R = 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, $CHCl_3$, 73% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 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); ^{13}C NMR (50 MHz, $CDCl_3$) δ 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^+], 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_R = 12.8 min (major), t_R = 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, $CHCl_3$, 75% ee); ^{1}H NMR (200 MHz, $CDCl_3$): δ 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); ^{13}C NMR (50 MHz, $CDCl_3$): δ 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^-], 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-01 column): t_R = 15.8 min (major), t_R = 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, $CHCl_3$, 78% ee); ^{1}H NMR (200 MHz, $CDCl_3$): δ 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), ^{13}C NMR (50 MHz, $CDCl_3$): δ 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^+], 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}H NMR (200 MHz, $CDCl_3$) δ 7.8-7.42 (m, 5H), 6.18-5.86 (br, 1H), 2.42 (s, 3H), 1.62-1.30 (m, 18H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 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 [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).

Acknowledgments. This research was supported by Korea Research Foundation Grant founded by the Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2006-521-C00099).

References and Notes

1. Reviews on α-amino acids, see: (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (c) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. (d) Arend, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 2873. (e) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342. (f) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (g) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.
2. Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359.
3. (a) Matier, W. L.; Owens, D. A.; Comer, W. T.; Dietchman, D.; Ferguson, H. C.; Seidehamel, R. J.; Young, J. R. *J. Med. Chem.* **1973**, *16*, 901. (b) Weinstock, L. M.; Davis, P.; Handelsman, B.; Tull, R. *J. Org. Chem.* **1967**, *32*, 2823.
4. Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.
5. See, for example: (a) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279. (b) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibassaki, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 1650. (c) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. (d) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762.
6. For reviews on asymmetric α-amination reactions, see: (a) Greck, C.; Genet, J.-P. *Synlett* **1997**, 741. (b) Genet, J.-P.; Greck, C.; Lavergne, D. *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000; Ch. 3. (c) Duthaler, R. O. *Angew. Chem. Int. Ed.* **2003**, *42*, 975. (d) Greck, C.; Drouillat, B.; Thomassigng, C. *Eur. J. Org. Chem.* **2004**, 1377. (e) Erdik, E. *Tetrahedron* **2004**, *60*, 8742. (f) Janey, J. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4292.
7. For 1,3-dicarbonyl compounds: (a) Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420. (b) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1367. (c) Ma, S.; Jiao, N.; Zheng, Z.; Ma, Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, *6*, 2193. (d) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115. (e) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137. (f) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4565. (g) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (h) Comelles, J.; Pericas, A.; Moreno-Manas, M.; Vallribera, A.; Drudis-Sole, G; Lledos, A.; Parella, T.; Roglans, A.; Garcia-Grands, S.; Roces-Fernandez, L. *J. Org. Chem.* **2007**, *72*, 2077. (i) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342. (j) Jung, S. H.; Kim, D. Y. *Tetrahedron Lett.* **2008**, *49*, 5527.
8. For β-ketophosphonates: (a) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309. (b) Bernardi, L.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5772.
9. For α-cyano acetates: (a) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (b) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167. (c) Liu, Y.; Melgar-Fernandez, R.; Juaristi, E. *J. Org. Chem.* **2007**, *72*, 1522. (d) Hasegawa, Y.; Watanabe, M.; Gridnev, I. D.; Ikariya, T. *J. Am. Chem. Soc.* **2008**, *130*, 2158.
10. For catalytic asymmetric reaction of α-cyanoketones, see: (a) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (b) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (c) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 5630. (d) Lee, J. H.; Bang, H. T.; Kim, D. Y. *Synlett* **2008**, 1821.
11. (a) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545. (b) Kim, D. Y.; Choi, Y. J.; Park, H. Y.; Joung, C. U.; Koh, K. O.; Mang, J. Y.; Jung, K.-Y. *Synth. Commun.* **2003**, *33*, 435. (c) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897. (d) Park, E. J.; Kim, H. R.; Joung, C. W.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2004**, *25*, 1451. (e) Kim, D. Y.; Huh, S. C. *Bull. Korean Chem. Soc.* **2004**, *25*, 347. (f) Kang, Y. K.; Cho, M. J.; Kim, S. M.; Kim, D. Y. *Synlett* **2007**, 1135. (g) Cho, M. J.; Kang, Y. K.; Lee, N. R.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2191. (h) Kim, S. M.; Kang, Y. K.; Cho, M. J.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2435.
12. (a) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309. (b) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115. (c) Kim, S. M.; Kang, Y. K.; Lee, K.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 423.
13. (a) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958. (b) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583. (c) Fossy, J. S.; Matsubara, R.; Kiyohara, H.; Kobayashi, S. *Inorg. Chem.* **2008**, *47*, 781.