Catalytic Asymmetric Electrophilic α-Amination of β-Ketoesters in the Presence of Chiral Nickel Complexes

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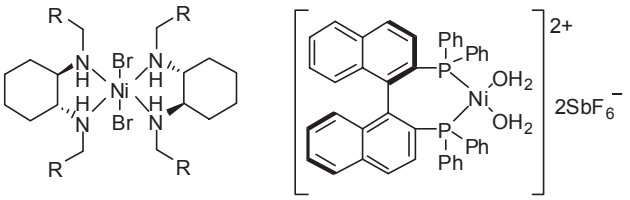
Amino acids are used as pharmaceuticals, agrochemicals, and fundamental synthetic building blocks for preparation of an assortment of biologically valuable molecules.[1] The development of stereoselective synthetic methods for the preparation of natural and non-natural α-amino acid derivatives has attracted considerable attention over the past decades.[2] The most popular methods for the catalytic asymmetric synthesis of α-amino acids are catalytic hydrogenation of α-dehydroamino acids,[3] alkylation of a *tert*-butyl glycinate-benzophenone Schiff base[4] using phase-transfer catalysts and cyanide addition to imines using Strecker[5] and Mannich reactions[6] with chiral Lewis acids or organocatalysts. Recently, enantioselective amination of carbonyl compounds emerged as a new method for the chiral α-amino acids. The catalytic enantioselective electrophilic amination of carbonyl compounds represents an efficient and the simplest procedures to generate stereogenic carbon center attached to a nitrogen atom.[7] Recently, several groups presented the direct enantioselective amination of 1,3-dicarbonyl compounds catalyzed by chiral Lewis acids[8] and organocatalysts.[9] While several efficient asymmetric amination reactions using chiral Lewic acids have been developed, a drawback is that most Lewis acids are unstable in the presence of water and even sensitive to moisture. Therefore, the development of electrophilic amination reaction using moisture stable chiral Lewis acid is still in great demand.



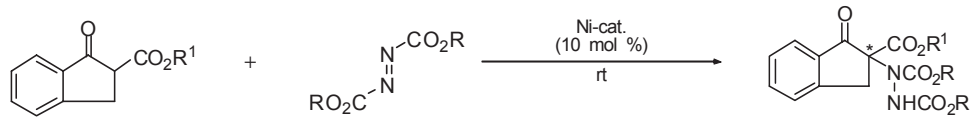
1a : R = Ph
1b : R = 4-F-Ph
1c : R = 1-naphthyl

1d

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

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[10] we reported the catalytic enan-

Table 1. Optimization of the reaction conditions

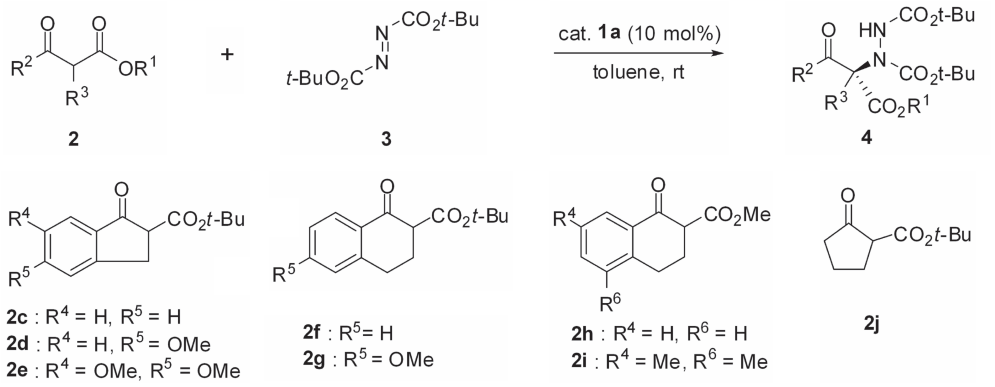


2 **3** **4**

entry	R^1	R	cat.	solvent	time (h)	yield (%)	ee[a] (%)
1	**2a**, Me	*t*-Bu	**1a**	toluene	0.5	**4aa**, 90	59
2	**2a**, Me	*t*-Bu	**1b**	toluene	0.5	**4aa,** 91	55
3	**2a**, Me	*t*-Bu	**1c**	toluene	0.5	**4aa,** 86	57
4	**2a**, Me	*t*-Bu	**1d**	toluene	0.5	**4aa,** 87	31
5	**2a**, Me	Et	**1a**	toluene	0.2	**4ab,** 85	31
6	**2a**, Me	*i*-Pr	**1a**	toluene	0.5	**4ac,** 80	43
7	**2a**, Me	*t*-Bu	**1a**	CH_2Cl_2	0.5	**4aa,** 86	45
8	**2a**, Me	*t*-Bu	**1a**	*i*-PrOH	0.5	**4aa,** 93	49
9	**2a**, Me	*t*-Bu	**1a**	acetone	0.5	**4aa,** 95	49
10	**2a**, Me	*t*-Bu	**1a**	acetonitrile	2	**4aa,** 85	53
11	**2a**, Me	*t*-Bu	**1a**	xylene	2	**4aa,** 82	51
12	**2a**, Me	*t*-Bu	**1a**	THF	2	**4aa,** 87	47
13	**2b**, Bn	*t*-Bu	**1a**	toluene	0.5	**4ba,** 95	63
14	**2c**, *t*-Bu	*t*-Bu	**1a**	toluene	0.5	**4ca,** 90	69

[a]Enantiopurity of **4** was determined by HPLC analysis with Chiralpak AD-H columns.

Table 2. Catalytic enantioselective amination of β-ketoesters **2**



entry	**2**	time (h)	yield (%)	ee[a] (%)
1	**2c**	0.5	**4ca**, 90	69
2	**2d**	7	**4da**, 95	82
3	**2e**	5	**4ea**, 90	80
4	**2f**	5	**4fa**, 92	88
5	**2g**	5	**4ga**, 90	86
6	**2h**	5	**4ha**, 93	80
7	**2i**	5	**4ia**, 95	82
8	**2j**	5	**4ja**, 90	84 (*S*)[b]

[a]Enantiopurity of **4** was determined by HPLC analysis with Chiralpak AD-H (for **4ca**, **4ea**, **4fa**, **4ga**, **4ha, 4ia,** and **4ja**), and (*S,S*)-Whelk-01 (for **4da**) columns. [b]Absolute configuration was determined by comparison of the optical rotation and the HPLC retention time of the corresponding ester with literature value.[8e]

tioselective amination of ester derivatives promoted by chiral palladium complexes.[8d,10f] In this communications, we wish to report the direct α-amination of cyclic and acyclic β-ketoesters **2** catalyzed by air- and moisture-stable chiral nickel complexes **1**[11] with azodicarboxylates **2** as the electrophilic nitrogen source.

A survey of some reaction parameters was performed, and some representative results are presented in Table 1. Our investigation began with enantioselective electrophilic amination of indanone carboxylate **2** with *tert*-butyl azodicarboxylate **3** as the electrophilic aminating reagent in toluene at room temperature in the presence of 10 mol% of catalysts (Fig.1). High yields with moderate enantioselectivities (31-59% ee) were observed for structurally variable chiral nickel catalysts (entries 1-4). Under the standard reaction conditions, catalyst **1b** was more effective than other catalysts. Varying the structure of the azodicarboxylates **3** had an impact on asymmetric induction (entries 1 and 5-6). The best results have been obtained with *tert*-butyl azodicatboxylates. Concerning the solvent (entries 1, 7-12), there is a little influence on the stereochemical outcome of the process but a significant impact on the reaction time. The nature of ester group of β-ketoesters **2** has also a significant impact on the selectivity (enteries 1, 13-14). The highest enantioselectivity was achieved with sterically hindered, *tert*-butyl ester of indanone carboxylate **2c**, aminated adduct **4** was isolated with 69% ee (entry 14).

To examine the generality of the catalytic enantioselective amination of β-ketoesters **2** by using chiral nickel catalyst **1a**, we studied the amination of various β-ketoesters **2**. As it can be seen by the results summarized in Table 2, the corresponding α-aminated β-ketoesters **4** were obtained in high to excellent yields and enantioselectivities. The cyclic β-ketoesters **2c-j** reacted with *tert*-butyl azodicarboxylate (**3**) to give the corresponding α-aminated β-ketoester **4ca-ja** in 90-95% yields and 69-88% ee.

In conclusion, we have developed a highly efficient catalytic enantioselective α-amination of cyclic β-ketoesters using air- and moisture-stable chiral nickel complexes. The desired α-aminated products were obtained in good to high yields with moderate to high level of enantioselectivities (69-88% ee). We believe that this method provides an efficient route for the preparation of chiral α-amino acid derivatives, which could facilitate various kind of medicinal chemical studies. Further study of these air- and moisture-stable chiral nickel catalysts in asymmetric reactions is being under investigation.

Experimental Section

General procedure for the amination of β-ketoesters 2: To a stirred solution of β-ketoester **2** (0.3 mmole) and catalyst **1a** (2.64 mg, 0.003 mmol) in toluene (0.3 ml) was added dropwise the solution of *tert*-butyl azodicarboxylate (**3**, 103.6 mg, 0.45 mmol) in 0.3 mL of toluene at room temperature. Reaction mixture was stirred for 0.5-7 h, concentrated and purified by flash chromatography (EtOAc : hexane = 1 : 4) to afford the α-aminated β-ketoester **4**.

***N′,N*-Bis(*tert*-butoxycarbonyl)-1-hydrazino-2-oxo-indanone carboxylic acid *tert*-butyl ester (4ca)**: $[\alpha]_D^{24}$ = -60.50 (c

= 0.55, $CHCl_3$, 69% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.41 (s, 9H), 1.49 (s, 9H), 3.48-4.45 (m, 2H), 6.74 (br, 1H), 7.30 -7.73 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.6, 28.0, 37.0, 78.6, 81.2, 82.6, 83.8, 124.8, 126.2, 127.4, 133.5, 135.3, 135.8, 154.5, 154.7, 167.0, 197.1; R_t HPLC (90:10, *n*-hexane : EtOH, 254 nm, 0.25 mL/min) Chiralpak AD-H, t_R = 22 min (major), t_R = 30 min (minor)

***N′,N*-Bis(*tert*-butoxycarbonyl)-1-hydrazino-2-oxo-5-methoxyindanone carboxylic acid *tert*-butyl ester (4da)**: $[\alpha]_D^{22}$ = -93.24 (c = 1.80, $CHCl_3$, 82% ee); ^{1}H NMR (200 MHz, $CDCl_3$) 1.24 (s, 9H), 1.42 (s, 9H), 1.49 (s, 9H), 3.52-4.19 (m, 2H), 3.87 (s, 1H), 6.86 (br, 1H), 6.90 (s, 2H), 7.63 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 27.3, 27.6, 27.7, 34.4, 55.8, 81.4, 81.9, 82.7, 83.2, 108.6, 115.1, 115.4, 115.6, 126.2, 154.6, 157.3, 163.3, 165.4, 192.7; R_t HPLC (90:10, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) (S,S)-Whelk-01, t_R = 6.5 min (major), t_R = 9.2 min (minor)

***N′,N*-Bis(*tert*-butoxycarbonyl)-1-hydrazino-2-oxo-5,6-dimethoxyindanone carboxylic acid *tert*-butyl ester (4ea)**: $[\alpha]_D^{25}$ = -113.92 (c = 1.50, $CHCl_3$, 80% ee); ^{1}H NMR (200 MHz, $CDCl_3$) 1.31 (s, 9H), 1.42 (s, 9H), 1.49 (s, 1H), 3.60-3.68 (m, 1H), 3.89 (s, 3H), 3.98 (s, 3H), 4.06-4.17 (m, 1H), 6.76 (br, 1H), 6.88 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 27.7, 28.1, 38.1, 56.1, 56.3, 71.7, 81.1, 82.5, 86.4, 105.0, 107.2, 123.4, 126.2, 149.5, 156.6, 156.9, 158.3, 172.1, 192.6; R_t HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 7.2 min (major), t_R = 11.8 min (minor)

***N′,N*-Bis(*tert*-butoxycarbonyl)-1-hydrazino-2-oxo-tetralone carboxylic acid *tert*-butyl ester (4fa)**: $[\alpha]_D^{23}$ = -20.37 (c = 0.85, $CHCl_3$, 88% ee); ^{1}H NMR (200 MHz, $CDCl_3$) 1.10 (s, 9H), 1.39 (s, 9H), 1.43 (s, 9H), 2.44-2.55 (m, 1H), 2.80-2,89 (m, 2H), 2.80-3.29 (m, 1H), 6.21 (br, 1H), 7.09-7.22 (m, 2H), 7.26-7.48 (m, 1H), 7.75-7.98 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 25.4, 25.7, 27.3, 27.7, 27.9, 80.4, 80.7, 82.4, 83.0, 126.3, 127.4, 128.4, 131.8, 133.1, 144.4, 154.0, 155.3, 167.6, 191.3; R_t HPLC (90:10, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 5.4 min (minor), t_R = 7.9 min (major)

***N′,N*-Bis(*tert*-butoxycarbonyl)-1-hydrazino-2-oxo-5-methoxytetralone carboxylic acid *tert*-butyl ester (4ga)**: $[\alpha]_D^{26}$ = -26.05 (c = 1.50, $CHCl_3$, 86% ee); ^{1}H NMR (200 MHz, $CDCl_3$) 1.20 (s, 9H), 1.48 (s, 9H), 1.52 (s, 9H), 2.21-2.65 (m, 1H), 2.84-2.94 (m, 2H), 3.27-3.69 (m, 1H), 3.69 (s, 3H), 6.31 (br, 1H), 6.64-6.84 (m, 2H), 7.82-8.00 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 25.9, 26.5, 27.9, 28.0, 55.4, 75.4, 80.6, 82.5, 83.1, 111.7, 112.1, 112.5, 113.3, 113.7, 130.0, 130.4, 147.3, 163.6, 196.7; R_t HPLC (90:10, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 8.9 min (minor), t_R = 19.5 min (major)

***N′,N*-Bis(*tert*-butoxycarbonyl)-1-hydrazino-2-oxo-tetralone carboxylic acid methyl ester (4ha)**: $[\alpha]_D^{28}$ = -11.20 (c = 2.00, $CHCl_3$, 80% ee); ^{1}H NMR (200 MHz, $CDCl_3$) 1.47 (s, 9H), 1.24 (s, 9H), 2.57-2.79 (m, 1H), 2.89-3.11 (m, 1H), 3.28-3.52 (m, 2H), 3.83 (s, 3H), 6.34 (br, 1H), 7.19-7.28 (m, 2H), 7.43-7.50 (m, 1H), 7.91 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 25.8, 28.2, 31.3, 52.9, 75.6, 81.1, 83.0, 126.6, 128.0, 128.7, 131.8, 133.7, 144.4, 154.9, 155.6, 170.0, 191.2; R_t HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 10.6 min (minor), t_R = 11.5 (major)

***N′,N*-Bis(*tert*-butoxycarbonyl)-1-hydrazino-2-oxo-1,5-dimethytetralone carboxylic acid methyl ester (4ia)**: $[\alpha]_D^{23}$ = -23.17 (c = 1.70, $CHCl_3$, 82% ee); ^{1}H NMR (200 MHz, $CDCl_3$) 1.24 (s, 9H), 1.56 (s, 9H), 2.27 (s, 3H), 2.28 (s, 3H), 2.63-3.35 (m, 4H), 3.81 (s, 3H), 6.30 (br, 1H), 7.15 (s, 1H), 7.51 (s, 1H); R_t HPLC (90:10, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 7.2 min (major), t_R = 10.4 min (minor)

(*S*)-*N′,N*-Bis(*tert*-butoxycarbonyl)-1-hydrazino-2-oxo-cyclopentanecarboxylic acid *tert*-butyl ester (4ja): $[\alpha]_D^{25}$ = -4.76 (c = 1.10, CH_2Cl_2, 84% ee); ^{1}H NMR (200 MHz, $CDCl_3$) 1.36-1.54 (m, 27H), 1.78-2.05 (m, 2H), 2.05-2.37 (m, 2H), 2.63 (br, 2H), 6.50 (br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 6.3, 18.6, 27.8, 28.0, 35.8, 79.6, 82.3, 82.5, 85.2, 154.5, 155.1, 167.1, 209.9; R_t HPLC (95:5, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 6.5 min (major), t_R = 8.2 min (minor)

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