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Diphenylamine-derived bis-hydroxyamide catalyzed asymmetric borane reduction of prochiral ketones

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ABSTRACT

A series of bis-hydroxyamides were synthesized from diphenylamine-2,2′-dicarboxylic acid and chiral aminoalcohols. Their catalytic activity in asymmetric borane reduction was investigated. After the fine optimization of solvents, temperature, amount of borane complex, and the length of catalyst generating period, good to excellent yields (55–99%) and enantioselectivities (79–97% ee) can be achieved in the reduction of aromatic and alkyl prochiral ketones. A transition state structure was proposed on the basis of absolute configuration and controlled experiment.

1. Introduction

Asymmetric borane reduction of prochiral ketones is one of the most important methods for the construction of chiral secondary alcohols.[1] After Itsuno et al.'s pioneering work in this field in the early 1980s,[2] a plethora of catalytic systems have been investigated. Among them, the CBS (Corey–Bakshi–Shibata) system developed by Corey et al. in 1987[3] attracts the most attention from the scientific community, for its excellent enantioselectivity and easy preparation from chiral amino alcohols. In addition to CBS system, other active catalysts derived from amino alcohols, such as chiral phosphinamido alcohols,[4] phosphoramido alcohols,[5] and sulfonamide alcohols,[6] have also been developed.

As important intermediates in the preparation of chiral oxazoline ligands,[7] thiazoline ligands,[8] and imidazoline ligands,[9] many chiral β-hydroxyamides have been synthesized from carboxylic acids and amino alcohols. Considering the potential coordination and H-bond donation ability of β-hydroxyamides, some of them have been applied to asymmetric catalysis as ligands or catalysts. A variety of enantioselective transformations, such as the alkylation of aldehydes,[10] alkynylation of aldehdyes,[11] Michael additions,[12] Nozaki–Hiyama reaction,[13] kinetic resolution of racemic alcohols,[14] conjugate radical addition,[15] hydrosilylation of imines,[16]and borane reduction of ketones,[17] can be catalyzed by C_1, C_2, or C_3 symmetric β-hydroxyamides. As part of our project on the development of diphenylamine-based chiral ligands,[8b,18] we synthesized chiral bis(β-hydroxyamide) compounds **1**–**4** (Fig. 1) from commercially available amino alcohols and tested their catalytic activity in the asymmetric borane reduction of prochiral ketones. Herein, we would like to document the recent results.

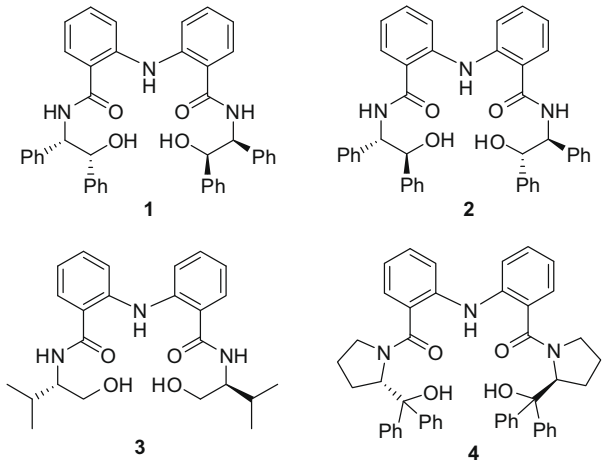

Figure 1. Diphenylamine-based bis(β-hydroxyamide) ligands.

2. Results and discussion

Chiral bis(β-hydroxyamide) ligands **1**–**3** have already been published.[8b,18c,d] Considering the privileged structure of (*S*)-2-diphenylhydroxymethylpyrrolidine in the CBS and related systems, we synthesized ligand **4** in two steps in 80% yield, as illustrated in Scheme 1.

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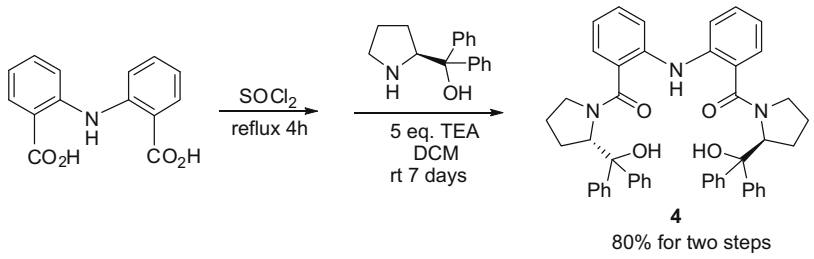
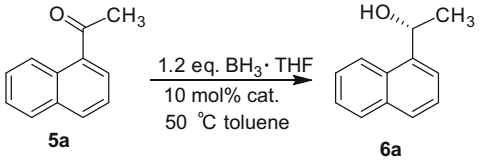


Scheme 1. Synthesis of ligand **4** from diphenyl-2,2′-dicarboxylic acid.

With the desired ligands in hand, we tested their catalytic activity in the asymmetric borane reduction of prochiral ketone. The reaction was conducted in toluene at 50 °C under the catalysis of 10 mol % ligand, using 1.2 equiv of BH_3–THF complex and 1-acetylnaphthalene **5a** as model substrate. The ligand and borane complex were stirred together under argon for 1 h at 50 °C in order to generate the active catalyst. The effect of the length of this period on enantioselectivity will be discussed later (vide infra). Full conversion of the substrate can be achieved in 3 h. As shown in Table 1, ligand **4** gave much better enantioselectivity as well as comparable yield, and was chosen for further optimization.

Table 1
Screening of ligands[a]



Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	**1**	87	23
2	**2**	93	51
3	**3**	92	46
4	**4**	92	91

[a] All the reactions were conducted on a 0.5 mmol scale in toluene at 50 °C using 10 mol % of ligand and 1-acetylnaphthalene as model substrate.
[b] Isolated yield.
[c] Determined by HPLC on Chiracel OJ-H column with *n*-hexane and 2-propanol 70:30 as eluents at 254 nm.

For further improvement of the enantioselectivity, we finely optimized the solvents and reaction temperature. 1-Acetylnaphthalene was also used as model substrate in this screening. The results are depicted in Table 2. Toluene, benzene, *n*-hexane, and *c*-hexane gave good yields and enantioselectivities (higher than 90%) at 50 °C. Though hexane isomers gave better results than toluene, the temperature optimization was conducted with all the three solvents. Benzene was abandoned for its toxicity. The temperature of the reaction mixture was raised or reduced to desired value after the 1 h catalyst generating period at 50 °C before the addition of substrate. When the temperature was varied from 0 °C to 65 °C (to 90 °C for toluene), the enantioselectivity was not affected significantly, except for the case of toluene at 0 °C. Generally, *n*- and *c*-hexane gave better results than toluene, and the best result can be achieved at 50 °C. Considering the better solubility of the substrates and ligands in *c*-hexane, it became the solvent of choice. No further optimization was observed when the borane source was changed to $BH_3{\cdot}SMe_2$ complex (90% yield and 86% ee). Another factor that can affect the enantioselectivity is the background reduction,[19] which is related to the amount of borane complex and the catalyst loading in the reaction, as well as the reaction temperature that we had optimized before. As depicted in Table 3, when the catalyst loading was reduced from 10 mol % to 5 mol % and 1 mol %, the enantioselectivity decreased drastically from 97% to 87% and 37%. Increasing the amount of borane complex from 1.2 to 1.4 equiv also caused a lower ee. The behavior of our system is in accord with the predictable effect of background reduction.

Table 2
Optimization of solvents and reaction temperature[a]

Entry	Solvent	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	THF	50	93	84
2	DCM	50	100	83
3	Benzene	50	95	90
4	Toluene	0	89	67
5	Toluene	25	90	91
6	Toluene	50	92	91
7	Toluene	70	90	93
8	Toluene	90	73	90
9	*c*-Hexane	0	90	88
10	*c*-Hexane	25	94	94
11	*c*-Hexane	50	94	97
12	*c*-Hexane	65	95	96
13	*n*-Hexane	0	90	92
14	*n*-Hexane	25	91	97
15	*n*-Hexane	50	89	97
16	*n*-Hexane	65	92	96

[a] All the reactions were conducted on a 0.5 mmol scale using 10 mol % of **4** as ligand and 1-acetylnaphthalene as model substrate.
[b] Isolated yield.
[c] Determined by HPLC on Chiracel OJ-H column with *n*-hexane and 2-propanol 70:30 as eluents at 254 nm.

Table 3
Effect of catalyst loading and amount of borane complex[a]

Entry	Loading (mol %)	Borane amount (equiv)	Yield[b] (%)	ee[c] (%)
1	10	1.2	94	97
2	5	1.2	93	87
3	1	1.2	93	37
4	10	1.4	97	88

[a] All the reactions were conducted on a 0.5 mmol scale at 50 °C in *c*-hexane using 10 mol % of **4** as ligand and 1-acetylnaphthalene as a model substrate.
[b] Isolated yield.
[c] Determined by HPLC on Chiracel OJ-H column with *n*-hexane and 2-propanol 70:30 as eluents at 254 nm.

We also tested the effect of the catalyst generating period. As shown in Table 4, when the length of the period was prolonged to 1.5 h or shortened to 0.5 h, the results were not affected, thus indicating the rapid generation of the active catalyst in our system.

With the optimized conditions in hand, we tested ligand 4 in the asymmetric borane reduction of differently substituted aromatic ketones. The results are listed in Table 5. Excellent yields

Table 4
Effect of the length of catalyst generating period[a]

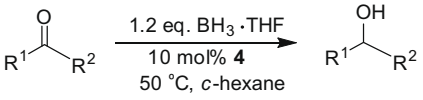
Entry	Catalyst generating period (h)	Yield[b] (%)	ee[c] (%)
1	0.5	94	95
2	1	94	97
3	1.5	95	94

[a] All the reactions were conducted in 0.5 mmol scale at 50 °C after the catalyst generating period in *c*-hexane, using 10 mol % of **4** as ligand and 1-acetylnaphthalene as model substrate.
[b] Isolated yield.
[c] Determined by HPLC on Chiracel OJ-H column with *n*-hexane and 2-propanol 70:30 as eluents at 254 nm.

and enantioselectivities can be achieved in the cases of both electron-donating groups and electron-withdrawing groups substituted onto the aromatic ketones. Generally, electron-deficient ketones gave better results than electron-rich ketones. Such a tendency can be interpreted through Hammond's hypothesis. Higher electron deficiency will cause larger $-\Delta H$ for the hydride transfer process, which is considered to be the rate-determining step. Thus, a starting-material-like transition state will be favored and the transfer of stereochemical information between material (the complex containing ligand **4**, ketone, and borane) and product will be better. In the case of propiophenone, 90% ee can still be obtained, although the stereochemical differences between phenyl and ethyl are smaller. The diaryl ketone and dialkyl ketone were also tested in this reaction. Moderate enantioselectivities were obtained. The absolute configuration of the products was determined to be (*R*) in most cases through comparison of the specific rotation values with the literature data.[5,6] The opposite configuration of diarylmethanol **6m** may be attributed to the π–π stacking effect between the naphthyl and the ligand skeleton which overwhelm the steric effect.

To obtain more information about the catalytic system, we prepared (*S*)-*N*-benzoyl-2-diphenylhydroxymethylpyrro-lidine **7** (Fig. 2). When this compound was used as a ligand (20 mol % was added to keep an equal amount of the pyrrolidine subunit to the original system) in the reduction of 1-acetylnaphthalene under the same conditions, the ee value decreased to 92%, which indicated the synergetic mode of interaction between the two pyrrolidine subunits. On the basis of the absolute configuration and our knowledge about the diphenylamine skeleton, a transition state was postulated to interpret the origin of the enantioselectivity. As illustrated in Figure 3, the active catalyst is generated from 1 equiv of borane and ligand **4**. Two equivalents of H_2 are extruded during this process. A molar of ketone and another molar of borane coordinate to the catalyst to form the reactive complex. In the transition state, the large group R_L directs to the outer side and the hydride attacks the carbonyl group from the *Si* face.

Table 5
Asymmetric borane reduction of aromatic ketones[a]



Entry	R^1	R^2	Product	Yield[b] (%)	ee[c] (%)
1	1-Naphthyl	Me	**6a**	94	97 (*R*)
2	C_6H_5	Me	**6b**	87	96 (*R*)
3	4-MeC_6H_4	Me	**6c**	93	90 (*R*)
4	4-$MeOC_6H_4$	Me	**6d**	93	93 (*R*)
5	3-$MeOC_6H_4$	Me	**6e**	95	95 (*R*)
6	2-$MeOC_6H_4$	Me	**6f**	95	90 (*R*)
7	4-FC_6H_4	Me	**6g**	85	97 (*R*)
8	4-ClC_6H_4	Me	**6h**	90	95 (*R*)
9	4-BrC_6H_4	Me	**6i**	84	97 (*R*)
10	2-BrC_6H_4	Me	**6j**	96	90 (*R*)
11	4-$NO_2C_6H_4$	Me	**6k**	99	91 (*R*)
12	C_6H_5	Et	**6l**	85	90 (*R*)
13	1-Naphthyl	C_6H_5	**6m**	86	81 (*S*)
14	*c*-C_6H_{11}	Me	**6n**	55	79 (*R*)

[a] All the reactions were conducted on a 0.5 mmol scale at 50 °C in *c*-hexane under the catalysis of 10 mol % **4**.
[b] Isolated yield.
[c] Determined by HPLC on Chiracel columns with chiral stationary phase. For **6n**, transformation to its carbamate is needed for HPLC analysis.

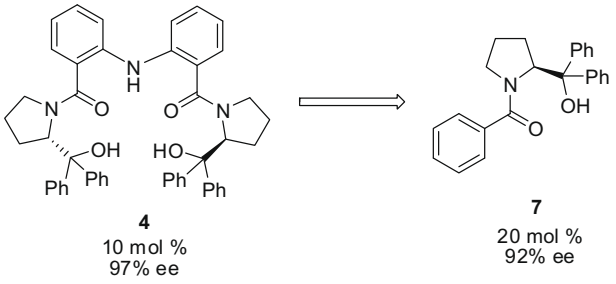


Figure 2. Control experiment using mono-β-hydroxyamide ligand.

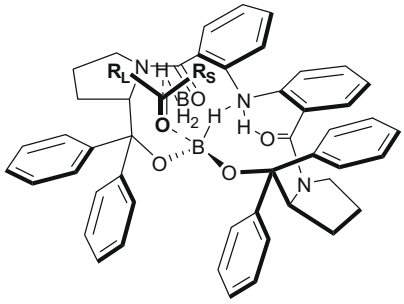


Figure 3. Proposed transition state of the reaction.

3. Conclusion

In conclusion, we have developed a novel diphenylamine-derived bis(β-hydroxyamide) ligand **4** which can be easily prepared from diphenylamine-2,2′-dicarboxylic acid and (*S*)-2-diphenylhydroxymethylpyrrolidine in two steps. This ligand show high catalytic activity in the asymmetric borane reduction of aromatic prochiral ketones. Excellent yields and enantioselectivities can be achieved after the optimization solvent, reaction temperature, amount of borane complex, and the length of catalyst generating period. The transition state of the hydride transfer step was postulated on the basis of absolute configuration of the products, and the result of control experiment using ligand **7**. Further development of diphenylamine derived chiral ligands is ongoing in our laboratory.

4. Experiment

4.1. General

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Column chromatography was carried out using silica gel (200–300 mesh). Melting points were measured on a Yanaco melting point apparatus and were uncorrected. The ^1H NMR spectra were recorded on Bruker 300 MHz spectrometer, while the ^{13}C NMR spectra were recorded at 75 MHz. Infrared spectra were obtained on a Nicolet AVATAR 330 FT-IR spectrometer. Mass spectra were obtained on a Bruker Apex IV (ESI) mass spectrometer. Optical

rotations were measured on a Perkin–Elmer 341 LC spectrometer. The enantiomeric excesses (ee) of the products were determined by chiral HPLC analysis using Aglient HP 1100 instrument (*n*-hexane/2-propanol as eluent).

4.2. Synthesis of 1,1′-(diphenylamine-2,2′-dicarbonyl)-bis[(2*S*)-α,α-diphenyl-2-pyrrolidinemethanol] 4

To a 50 mL round-bottomed flask were added diphenylamine-2,2′-dicarboxylic acid (2.57 g, 10 mmol) and thionyl chloride (10 mL). After being refluxed for 4 h, the excess thionyl chloride was removed under vacuum. The yellowish solid residue (diphenylamine-2,2′-dicarbonyl dichloride) was dissolved in dichloromethane (DCM) (70 mL). To another 250 mL round-bottomed flask were added (*S*)-2-diphenylhydroxymethylpyrrolidine (6.08 g, 24 mmol), Et_3N (7.0 mL, 50 mmol), and DCM (30 mL). After being cooled to 0 °C, the solution of the dichloride in DCM was added dropwise. After the addition, the temperature was allowed to reach 25 °C and the mixture was stirred at this temperature for further 7 days for the full conversion of material (monitored by TLC). The reaction was quenched by water. The mixture was washed with satd $NaHCO_3$ (aq) and water, dried with Na_2SO_4, and concentrated under vacuum. The product was purified by column chromatography using DCM/methanol 400:1 (*V*/*V*) as eluent. The pure bis(β-hydroxyamide) **4** was obtained as a white solid (5.82 g, 80% yield). Mp 178–180 °C. $[\alpha]_D^{20} = -98.0$ (*c* 0.5, DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30–1.40 (m, 2H), 1.46–1.58 (m, 2H), 1.92–2.02 (m, 2H), 2.14–2.20 (m, 2H), 2.84 (dd, J_1 = 17.1 Hz, J_2 = 9.9 Hz, 2H), 3.33 (t, J = 8.1 Hz, 2H), 5.53 (t, J = 8.1 Hz, 2H), 6.64 (s, 2H), 6.76–6.83 (m, 4H), 7.16–7.37 (m, 16H), 7.49 (d, J = 6.9 Hz, 4H), 7.63 (d, J = 6.3 Hz, 4H), 8.52 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2, 29.5, 51.7, 66.7, 82.4, 117.6, 120.0, 125.0, 127.1, 127.2, 127.4, 127.8, 127.9, 128.0, 128.5, 130.4, 140.5, 143.1, 145.2, 172.0. IR: 3289, 3058, 1613, 1580, 1508, 1448, 1411, 1306, 1200, 1161, 1031, 751, 702 cm^{-1}. HRMS (ESI) calcd for $C_{48}H_{46}N_3O_4$ (M+H): 728.34828, found: 728.35103.

4.3. General procedure for the asymmetric borane reduction of prochiral ketones 5a–k

To a flame-dried Schlenk tube were added ligand **4** (36 mg, 0.05 mmol), BH_3–THF complex (1 M solution in THF, 0.6 mL, 0.6 mmol), and anhydrous cyclohexane (*c*-hexane) (1.5 mL). The mixture was heated to 50 °C and was stirred at this temperature for 1 h. Then, the solution of prochiral ketone (0.5 mmol) in *c*-hexane (1.5 mL) was added in one portion. After being stirred at the same temperature for a further 3 h, the reaction was quenched by methanol. After removing the solvent, the product was purified by column chromatography using petroleum ether/ethyl acetate 5:1 (*V*:*V*) as eluent. The ee value was determined by HPLC.

Product **6a** was obtained as a colorless oil (81 mg, 94% yield). The ee was determined by HPLC on Chiracel OJ-H column (*n*-hexane: 2-propanol 70:30, 1.0 mL/min, 254 nm, t_{minor} = 6.8 min, t_{major} = 7.9 min). $[\alpha]_D^{20} = +34.9$ (*c* 2.3, DCM, 97% ee).

Product **6b** was obtained as a colorless oil (53 mg, 87% yield). The ee was determined by HPLC on Chiracel OB column (*n*-hexane: 2-propanol 95:5, 0.8 mL/min, 254 nm, t_{minor} = 10.0 min, t_{major} = 12.7 min). $[\alpha]_D^{20} = +44.1$ (*c* 2. 2, DCM, 96% ee).

Product **6c** was obtained as a colorless oil (63 mg, 93% yield). The ee was determined by HPLC on Chiracel OB column (*n*-hexane: 2-propanol 95:5, 1.0 mL/min, 254 nm, t_{minor} = 9.0 min, t_{major} = 12.9 min). $[\alpha]_D^{20} = +18.5$ (*c* 4.0, DCM, 90% ee).

Product **6d** was obtained as a colorless oil (71 mg, 93% yield). The ee was determined by HPLC on Chiracel OB column (*n*-hexane: 2-propanol 95:5, 1.0 mL/min, 254 nm, t_{minor} = 15.1 min, t_{major} = 16.8 min). $[\alpha]_D^{20} = +34.4$ (*c* 3.4, DCM, 93% ee).

Product **6e** was obtained as a colorless oil (72 mg, 95% yield). The ee was determined by HPLC on Chiracel OB column (*n*-hexane: 2-propanol 95:5, 1.0 mL/min, 254 nm, t_{minor} = 15.1 min, t_{major} = 20.1 min). $[\alpha]_D^{20} = +27.2$ (*c* 3.8, DCM, 95% ee).

Product **6f** was obtained as a colorless oil (72 mg, 95% yield). The ee was determined by HPLC on Chiracel OB column (*n*-hexane: 2-propanol 98:2, 0.8 mL/min, 254 nm, t_{minor} = 15.0 min, t_{major} = 15.6 min). $[\alpha]_D^{20} = +20.3$ (*c* 3.0, DCM, 90% ee).

Product **6g** was obtained as a colorless oil (59 mg, 85% yield). The ee was determined by HPLC on Chiracel OB column (*n*-hexane: 2-propanol 98:2, 0.8 mL/min, 254 nm, t_{minor} = 13.5 min, t_{major} = 14.4 min). $[\alpha]_D^{20} = +26.5$ (*c* 3.2, DCM, 97% ee).

Product **6h** was obtained as a colorless oil (70 mg, 90% yield). The ee was determined by HPLC on Chiracel OB column (*n*-hexane: 2-propanol 98:2, 0.8 mL/min, 254 nm, t_{minor} = 14.2 min, t_{major} = 14.6 min). $[\alpha]_D^{20} = +36.6$ (*c* 2.6, DCM, 96% ee).

Product **6i** was obtained as colorless oil (84 mg, 84% yield). The ee was determined by HPLC on Chiracel OB column (*n*-hexane: 2-propanol 98:2, 0.8 mL/min, 254 nm, t_{minor} = 15.2 min, t_{major} = 15.6 min). $[\alpha]_D^{20} = +31.6$ (*c* 3.9, DCM, 97% ee).

Product **6j** was obtained as a colorless oil (97 mg, 96% yield). The ee was determined by HPLC on Chiracel OB column (*n*-hexane: 2-propanol 98:2, 0.8 mL/min, 254 nm, t_{minor} = 11.2 min, t_{major} = 13.8 min). $[\alpha]_D^{20} = +39.3$ (*c* 4.3, DCM, 90% ee).

Product **6k** was obtained as colorless oil (83 mg, 99% yield). The ee was determined by HPLC on Chiracel OB column (*n*-hexane: 2-propanol 98:2, 0.8 mL/min, 254 nm, t_{minor} = 54.0 min, t_{major} = 55.6 min). $[\alpha]_D^{20} = +23.8$ (*c* 3.5, DCM, 91% ee).

Product **6l** was obtained as a colorless oil (57 mg, 85% yield). The ee was determined by HPLC on Chiracel OD-H column (*n*-hexane: 2-propanol 95:5, 1.0 mL/min, 254 nm, t_{major} = 7.1 min, t_{minor} = 8.4 min). $[\alpha]_D^{20} = +20.2$ (*c* 1.0, DCM, 90% ee).

Product **6m** was obtained as a colorless oil (100 mg, 86% yield). The ee was determined by HPLC on Chiracel OD-H column (*n*-hexane: 2-propanol 90:10, 1.0 mL/min, 254 nm, t_{major} = 12.0 min, t_{minor} = 24.5 min). $[\alpha]_D^{20} = -46.0$ (*c* 1.0, DCM, 90% ee).

Product **6n** was obtained as colorless oil (35 mg, 55% yield). The ee was determined by HPLC on Chiracel OD-H column (*n*-hexane: 2-propanol 98:2, 1.0 mL/min, 254 nm, t_{major} = 7.0 min, t_{minor} = 7.8 - min) after being transformed to the carbamate using phenylisothiocyanate in the presence of stoichiometric amount of NaH in THF for 10 h. $[\alpha]_D^{20} = -7.2$ (*c* 1.0, DCM, 79% ee).

Acknowledgments

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