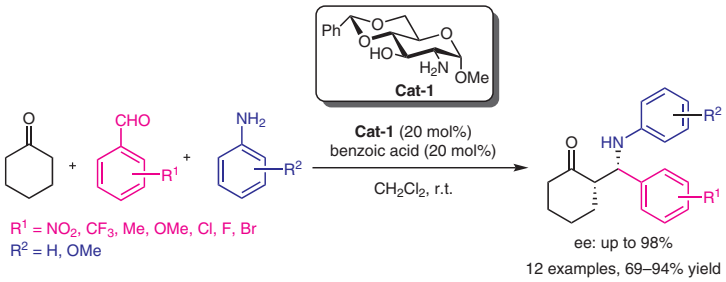
Synlett A. Sharma, R. K. Peddinti Letter

Direct Asymmetric Mannich Reaction Catalyzed by a D-Glucosamine-Derived Organocatalyst

Arun Sharma
Rama Krishna Peddinti*

Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee -247667, Uttarakhand, India
rkpedfcy@iitr.ac.in
ramakpeddinti@gmail.com



Received: 11.08.2017
Accepted after revision: 17.11.2017
Published online: 02.01.2018
DOI: 10.1055/s-0036-1591740; Art ID: st-2017-d0621-l

Abstract Sugar-based primary amines have been employed as organocatalysts for the direct asymmetric Mannich reaction. By catalyst-screening experiments, we observed that catalysts bearing a hydroxy function at C-3 actively participated in the reaction, possibly through hydrogen bonding with the imine generated in situ, to provide β-amino carbonyl compounds with better diastereoselectivity and enantioselectivity. All the products were obtained in good to excellent enantiomeric excess.

Key words aldimines, sugar amines, asymmetric catalysis, organocatalysis, amino carbonyl compounds, Mannich reaction

Carbohydrates are naturally abundant molecules that play significant roles as energy sources, biosynthetic resources, and energy-storage devices. Furthermore, these molecules have been used as key structural elements to access a plethora of natural products and molecules with potential biological activities, and they have been modified by organic chemists in several ways to obtain many useful skeletons. The complex structures and biological activity of aryl *O*-glycosides make them very attractive subjects.[1]

Owing to their ready availability and the presence of contiguous stereocenters in their structures, glucosamines are attractive entities in the field of asymmetric synthesis as catalysts, ligands, or chiral auxiliaries.[2] In recent decades, novel asymmetric organocatalysts have been developed by combining carbohydrate scaffolds with chiral molecules such as cinchona alkaloids, chiral cyclohexane-1,2-diamines, or proline for use in asymmetric transformations, including aldol reactions,[3] Michael additions,[4] Reformatsky reactions,[5] Henry reactions,[6] arylations,[7] allylations,[8] and other reactions.[9] The best-known carbohydrate-derived catalysts are synthesized from glucosamine. The amine functional group present in glucosamine can be functionalized to form various groups, thereby changing the mode of activation of the catalyst in a desired manner.[10] Although many asymmetric transformations catalyzed by carbohydrates and derivatives have been described, to the best of our knowledge there are no reports regarding Mannich reactions catalyzed by the free sugar amine. We therefore examined the use of sugar-based amine catalysts in the direct enantioselective Mannich reaction.

Generally, for the synthesis of such nitrogen-containing compounds, use of an imine as an electrophile is the most promising and convenient approach.[11] Furthermore, α-amino carbonyl compounds are valuable intermediates for the synthesis of many natural products with useful biological properties.[12]

In this report, we disclose a protocol that involves an enantioselective Mannich reaction catalyzed by a sugar-based primary amine. Initially, by following a procedure developed in our laboratory, we synthesized four sugar amine catalysts **1**–**4** from commercially available *N*-acetyl-D-glucosamine hydrochloride (Figure 1).[13]

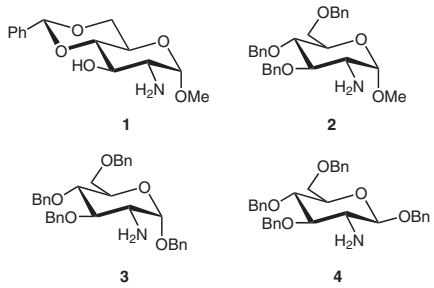
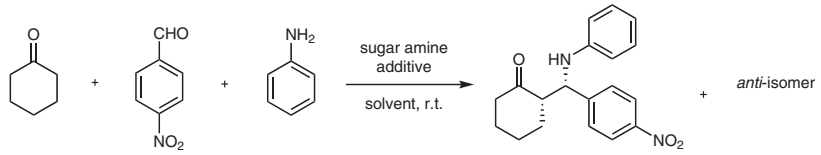


Figure 1 Sugar amine catalysts

For our initial studies, we chose cyclohexanone (**5**), aniline (**7a**), and 4-nitrobenzaldehyde (**6a**) as model substrates to optimize the reaction conditions. In a typical experimen-

tal procedure, a mixture of 4-nitrobenzaldehyde (**6a**) and aniline (**7a**) in dichloromethane was stirred at room temperature for ten minutes and then cyclohexanone (**5**), catalyst **1** (10 mol%), and benzoic acid (10 mol%) were added sequentially. The resulting reaction mixture was stirred at room temperature for 48 hours to afford the corresponding Mannich products **8a** and **8a′** in 78% yield as a 6:1 *syn*/*anti* diastereomeric mixture with a 59% enantiomeric excess of the major *syn*-diastereomer **8a** (Table 1, entry 1). The use of catalyst **2** under the same conditions gave a 36% yield of **8a** and **8a′** in a 3:1 dr and with a 47% enantiomeric excess of the *syn*-isomer. Catalyst **3** afforded **8a** and **8a'** in 79% yield, a slightly higher dr, and a 54% enantiomeric excess of major isomer **8a** (entry 3). When sugar amine **4** was used, the reaction was complete in 48 hours with a 64% combined yield of the diastereomers in 2.7:1 dr and a 34% ee of the *syn*-isomer (entry 4). We then examined the reaction under neat conditions with 10 mol% of catalysts **1**–**4**; however, no significant improvement in the yield or dr was observed, but a 76% enantiomeric excess was achieved with catalyst **1** (entries 5–8). In the hope that the use of a chiral additive might be helpful in improving the chiral induction in the asymmetric transformation, we carried out the reaction in the presence of a 20 mol% loading of camphor-10-sulfonic acid as an additive. In this case, the reaction proceeded smoothly and was complete within 24 hours, giving a 4:1 dr and an 84% yield, but with moderate enantioselectivity (entry 9). This might be explained on the basis of a mismatch between the camphor-10-sulfonic acid and the sugar amine in relation to the stereochemical outcome. In an attempt to improve the selectivity of the reaction, we screened 2,4-dinitrobenzoic acid and 4-bromobenzoic acid as additives (entries 10 and 11). Surprisingly, the use of simple benzoic acid as an additive along with 20 mol% catalyst **1** afforded

Table 1 : Evaluation of Conditions for the Asymmetric Mannich Reaction[a]



5 **6a** **7a** **8a** **8a'**

Entry	Catalyst	mol%	Solvent	Additive (mol%)	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] % (*syn*)
1	**1**	10	CH_2Cl_2	BzOH (10)	48	78	6:1	59
2	**2**	10	CH_2Cl_2	BzOH (10)	48	36	3:1	47
3	**3**	10	CH_2Cl_2	BzOH (10)	48	79	3.4:1	54
4	**4**	10	CH_2Cl_2	BzOH (10)	48	64	2.7:1	34
5	**1**	10	neat	BzOH (10)	48	55	3:1	76
6	**2**	10	neat	BzOH (10)	32	48	4:1	70
7	**3**	10	neat	BzOH (10)	48	51	3.3:1	69
8	**4**	10	neat	BzOH (10)	48	62	5:1	74
9	**1**	20	CH_2Cl_2	CSA (20)	24	84	4:1	39
10	**1**	20	CH_2Cl_2	2,4-$(O_2N)_2C_6H_3CO_2H$ (20)	24	79	5:1	45
11	**1**	20	CH_2Cl_2	4-$BrC_6H_4CO_2H$ (20)	48	57	6.5:1	68
12	**1**	20	CH_2Cl_2	BzOH (20)	48	77[e]	12:1	98
13	**1**	20	MeOH	BzOH (20)	30	69	5:1	72
14	**1**	20	toluene	BzOH (20)	120	64	4:1	76
15	**1**	20	DCE	BzOH (20)	48	77	7:1	57
16	**1**	20	MeCN	BzOH (20)	48	71	8:1	73
17[f]	**1**	20	CH_2Cl_2	BzOH (20)	120	59	9:1	92
18[g]	**1**	20	MeCN	BzOH (20)	120	66	7:1	93

[a] Reaction conditions: cyclohexanone (**5**, 0.4 mmol), aldehyde **6a** (0.2 mmol), aniline (**7a**, 0.22 mmol), catalyst, additive, solvent (0.5 mL), r.t.
[b] Combined yield of isolated diastereomers.
[c] Determined by ^{1}H NMR analysis of the crude product.
[d] Determined by HPLC analysis on a ChiralPAK AD(-H) column.
[e] The product was obtained with a negative specific rotation (see Supporting Information).
[f] At 0 °C.
[g] At –10 °C.

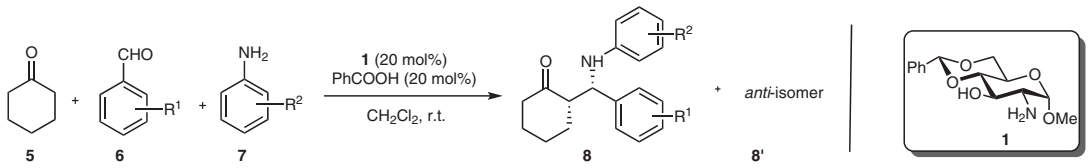
the product in 77% yield in 12:1 dr and 98% ee of the *syn*-product. The additive loading had a marked effect on the yield of this reaction (entry 12).

The reaction was then investigated with a range of polar and nonpolar solvents, including methanol, toluene, acetonitrile, and dichloroethane, at various temperatures (Table 1, entries 13–18), but no improvement in the yield, dr, or ee was observed. Of all the reaction conditions studied, the optimum results were obtained with 20 mol% of catalyst **1** and benzoic acid (20 mol%) in CH_2Cl_2 at room temperature.

The relative stereochemistries of the stereogenic centers were determined on the basis of the mutual coupling constants between the two adjacent protons attached to the stereogenic centers. These protons can be *syn* or *anti* to each other. An analysis of the ^{1}H NMR spectra of the products revealed that the major isomer of the product had a coupling constant J = 4.0–4.5 Hz, whereas that of the minor isomer was in the range J = 5.0–6.0 Hz. It is well known that in this system, *anti* protons show higher coupling constants than do *syn* diastereomeric protons. This was supported by a comparison of the HPLC analyses with previous reports that the major product exhibits *syn*-stereochemistry.[14]

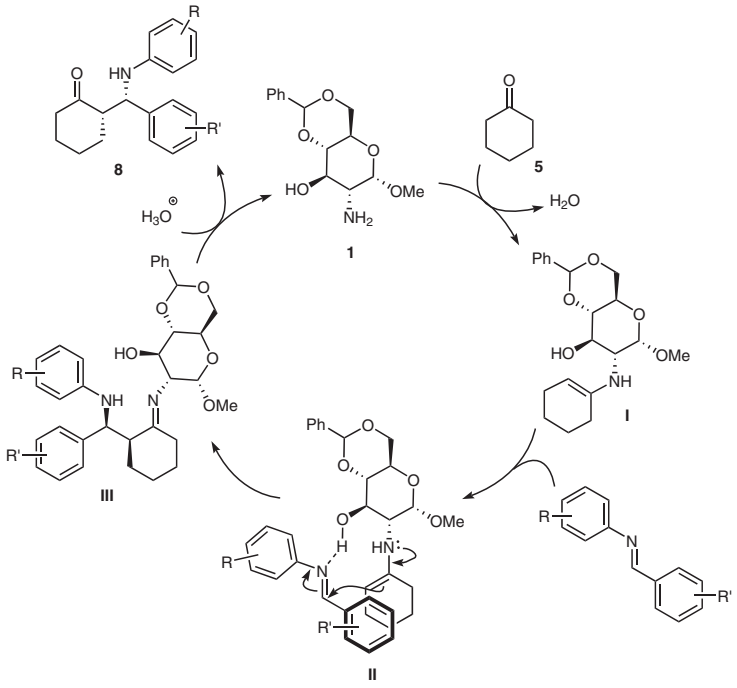
Having determined the optimal reaction conditions, we applied the method to a variety of aldehydes **6a–k** with aniline or *p*-anisidine to examine the scope of the reaction (Table 2).[15] We observed that aldehydes **6a** and **6c** bearing electron-withdrawing substituents at the *para*-position afforded the corresponding Mannich products **8c** and **8d** smoothly in 48 hours with good to excellent diastereo- and enantioselectivity (Table 2, entries 1 and 3). 3-Nitrobenzaldehyde (**6b**) afforded product **8b** in 83% yield with an acceptable diastereoselectivity of 8.5:1 and an excellent 95% ee for the *syn*-isomer. Similarly, 4-bromo- and 4-chlorobenzaldehyde derivatives furnished products **8d** and **8e**, respectively, in high yields, good diastereoselectivities, and excellent enantiomeric excesses (entries 4 and 5). The stereochemical outcome significantly depended on the electronic nature of the substituents on both the benzaldehyde and the aniline. 4-Methoxy- and 4-methylbenzaldehyde derivatives were less effective in terms of optical induction and the corresponding products **8f** and **8g** were obtained with 20% and 60% enantioselectivity, respectively, for the *syn*-diastereomer, whereas the *anti*-isomer was almost racemic (entries 6 and 7). Similar trends have also been reported for Mannich-type reactions that involve imines bearing electron-donating groups.[16] Benzaldehydes **6i** and

Table 2 Substrate Scope of the Reaction[a]



Entry	R^1	R^2	Time (h)	Product	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d,e] (% *syn*)
1	4-NO_2 (**6a**)	H	48	**8a**	77	12:1	98
2	3-NO_2 (**6b**)	H	48	**8b**	83	8.5:1	95
3	4-CF_3 (**6c**)	H	48	**8c**	76	12:1	96
4	4-Br (**6d**)	H	48	**8d**	84	12:1	98
5	4-Cl (**6e**)	H	48	**8e**	83	12:1	94
6	4-OMe (**6f**)	H	48	**8f**	91	1:4	20
7	4-Me (**6g**)	H	48	**8g**	81	1:1.8	60
8	4-F (**6h**)	H	48	**8h**	83	1.5:1	76
9	3-Br (**6i**)	H	48	**8i**	88	8:1	93
10	3-F (**6j**)	H	48	**8j**	69	6:1	nd
11	3-OMe (**6k**)	H	48	**8k**	72	20:1	98
12	4-NO_2 (**6a**)	4-OMe	48	**8l**	83	20:1	80
13	4-CF_3 (**6c**)	4-OMe	48	**8m**	77	1.5:1	60
14	3-NO_2 (**6b**)	4-OMe	48	**8n**	94	2.2:1	99

[a] Reaction conditions: cyclohexanone (**5**, 0.4 mmol), aldehyde **6** (0.2 mmol), aniline (**7**, 0.22 mmol), catalyst **1** (20 mol%), BzOH (20 mol%), CH_2Cl_2 (0.5 mL), r.t.
[b] Combined yield of isolated diastereomeric products.
[c] Determined by ^{1}H NMR spectroscopic analysis of a crude sample.
[d] Determined by HPLC analysis on a chiral stationary phase.
[e] All products were obtained with a negative specific rotation (see Supporting Information).



Scheme 1 Plausible reaction mechanism

6k with substituents at the *meta*-position produced the corresponding Mannich product with good diastereoselectivity and excellent ee (entries 9 and 11).

The use of *p*-anisidine instead of aniline had a significant influence on both the dr and enantioselectivity. Under the optimized conditions, benzaldehyde derivatives **6b** and **6c** gave products **8m** and **8n**, respectively, with moderate diastereoselectivity and enantioselectivities of 60 and 99%, respectively (Table 2, entries 13 and 14). In the reaction of 4-nitrobenzaldehyde (**6a**) with *p*-anisidine, the corresponding Mannich adduct **8l** was obtained in an excellent dr of 20:1 and 80% ee (entry 12). Unfortunately, reactions of *p*-anisidine with other benzaldehydes **6** bearing electron-donating groups or halogen substituents were slow and afforded the Mannich products with poor dr. Furthermore, the isolated products were unstable in air, undergoing oxidation. It was therefore difficult to isolate the pure compounds for further analysis. The configurations of the products were assigned as (2*S*,1′*S*) by comparing the retention times in HPLC analysis with reported data[14] (see Supporting Information).

We propose that this asymmetric Mannich reaction proceeds through an enamine pathway, as nucleophilic addition of the enamine generated in situ would be faster on an imine than on an aldehyde. As shown in Scheme 1, the sequence commences with formation of an enamine **I** from cyclohexanone and the sugar amine **1**; this reacts with an imine to form **III** via the transition state **II**. The last step is hydrolysis to afford product **8**. The catalyst **1** is regenerated in a subsequent step. The stereochemical outcome can be explained by the plausible transition state **II**. The hydroxy group of the sugar moiety activates the imine by hydrogen bonding and also allows the *Re* face of the enamine to attack on the *Si* face of the imine, leading to a *syn*-stereochemistry between the two stereogenic centers.

In summary, we have accomplished the first sugar amine-catalyzed direct asymmetric Mannich reaction using cyclohexanone, an aniline derivative, and a benzaldehyde derivative, through generation of an imine in situ.

Funding Information

This work was supported by the SERB [research grant No. SR/S1/OC-38/2011], New Delhi. A.S. thanks the CSIR for a research fellowship.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591740.

References and Notes

(1) (a) Boons, G.-J.; Hale, K. *Organic Synthesis with Carbohydrates*; Sheffield Academic Press **2000**. (b) *Carbohydrate Synthons in Natural Product Chemistry*; Witczak, Z. J.; Tatsuta, K., Eds.; ACS Symposium Series 841: Washington, **2002**. (c) Bowen, M. L.;

Orvig, C. *Chem. Commun.* **2008**, 5077. (d) Ernst, B.; Magnani, J. L. *Nat. Rev. Drug Discov.* **2009**, *8*, 661. (e) Mastsuo, I.; Ito, Y. US 7879766, **2011**.

(2) (a) Coll, M.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2014**, *356*, 2293. (b) Minuth, T.; Boysen, M. M. K. *Beilstein J. Org. Chem.* **2010**, *6*, 23. (c) D'Onofrio, A.; Copey, L.; Jean-Gérard, L.; Goux-Henry, C.; Pilet, G.; Andrioletti, B.; Framery, E. *Org. Biomol. Chem.* **2015**, *13*, 9029. (d) Nishioka, T.; Shibata, T.; Kinoshita, I. *Organometallics* **2007**, *11*, 1126. (e) Benessere, V.; Lega, M.; Silipo, A.; Ruffo, F. *Tetrahedron* **2011**, *67*, 4826. (f) Mata, Y.; Claver, C.; Diéguez, M.; Pàmies, O. *Tetrahedron: Asymmetry* **2006**, *17*, 3282. (g) Shen, C.; Xia, H.; Zheng, H.; Zhang, P.; Chen, X. *Tetrahedron: Asymmetry* **2010**, *21*, 1936. (h) Goyard, D.; Telligmann, S. M.; Goux-Henry, C.; Boysen, M. M. K.; Framery, E.; Gueyrard, D.; Vidal, S. *Tetrahedron Lett.* **2010**, *51*, 374.

(3) (a) De Nisco, M.; Pedatella, S.; Bektaş, S.; Nucci, A.; Caputo, R. *Carbohydr. Res.* **2012**, *356*, 273. (b) Singh, N.; Pandey, J.; Tripathi, R. P. *Catal. Commun.* **2008**, *9*, 743. (c) Shen, C.; Liao, H.; Shen, F.; Zhang, P. *Catal. Commun.* **2013**, *41*, 106. (d) Agarwal, J.; Peddinti, R. K. *J. Org. Chem.* **2011**, *76*, 3502. (e) Otsuka, Y.; Sasaki, A.; Teshima, T.; Yamada, K.; Yamamoto, T. *Org. Lett.* **2016**, *18*, 1338. (f) Han, X.; Wang, Y.; Gai, X.; Zeng, X. *Synlett* **2015**, 2858. (g) Agarwal, J. *Org. Biomol. Chem.* **2016**, *14*, 10747.

(4) (a) Agarwal, J.; Peddinti, R. K. *Tetrahedron: Asymmetry* **2010**, *21*, 1906. (b) Shen, C.; Shen, F.; Xia, H.; Zhang, P.; Chen, X. *Tetrahedron: Asymmetry* **2011**, *22*, 708.

(5) Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923.

(6) Pu, X.-W.; Peng, F.-Z.; Zhang, H.-B.; Shao, Z.-H. *Tetrahedron* **2010**, *66*, 3655.

(7) Emmerson, D. P. G.; Hems, P.; Davis, B. G. *Tetrahedron: Asymmetry* **2005**, *16*, 213.

(8) Robak, J.; Kryczka, B.; Świerczyńska, B.; Zawisza, A.; Porwański, S. *Carbohydr. Res.* **2015**, *404*, 83.

(9) (a) Wouters, A. D.; Trossini, G. H. G.; Stefani, H. A.; Lüdtke, D. S. *Eur. J. Org. Chem.* **2010**, 2351. (b) Appelt, H. R.; Limberger, J. B.; Weber, M.; Rodrigues, O. E. D.; Oliveira, J. S.; Lüdtke, D. S.; Braga, A. L. *Tetrahedron Lett.* **2008**, *49*, 4956. (c) Kong, S.; Fan, W.; Wu, G.; Miao, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 8864.

(10) (a) Puglisi, A.; Benaglia, M.; Raimondi, L.; Poletti, L. *Org. Biomol. Chem.* **2011**, 3295. (b) Pinheiro, D. L. J.; Batista, G. M. F.; Gonçalves, J. R.; Duarte, T. N.; Amarante, G. W. *Eur. J. Org. Chem.* **2016**, 459. (c) Bauer, T.; Smoliński, S. *Appl. Catal. A.* **2010**, *375*, 247. (d) Shen, C.; Shen, F.; Zhou, G.; Xia, H.; Chen, X.; Liu, X.; Zhang, P. *Catal. Commun.* **2012**, *26*, 6. (e) Del Litto, R.; Benessere, V.; Ruffo, F.; Moberg, C. *Eur. J. Org. Chem.* **2009**, 1352. (f) Ge, X.; Qian, C.; Chen, Y.; Chen, X. *Tetrahedron: Asymmetry* **2014**, *25*, 596. (g) Sawada, D.; Sasayama, S.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2008**, *64*, 8780.

(11) (a) Bauer, T.; Tarasiuk, J.; Paśniczek, K. *Tetrahedron: Asymmetry* **2002**, *13*, 77. (b) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 355. (c) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (d) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (e) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(12) Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **2004**, Suppl. 1, Chap. 29.5 143.

(13) Agarwal, J.; Peddinti, R. K. *Eur. J. Org. Chem.* **2012**, 6390.

(14) Zheng, X.; Qian, Y.-B.; Wang, Y. *Eur. J. Org. Chem.* **2010**, 515.

(15) **Mannich Adducts 8a–n; General Procedure**

To a stirred solution of the appropriate benzaldehyde derivative **6** (0.2 mmol) and aniline derivative **7** (0.22 mmol) in dry CH_2Cl_2 were added, sequentially, cyclohexanone (**5**; 0.4 mmol), catalyst **1** (20 mol%), and BzOH (20 mol%). The resulting mixture was stirred at 20 °C for 48 h until the reaction was complete (TLC). The mixture was then concentrated, and the product was purified by column chromatography [silica gel, EtOAc–hexanes (10–25%)].

(2*S*)-2-[(*S*)-(4-Nitrophenyl)(phenylamino)methyl]cyclohexanone (8a)

Reaction time: 48 h. Pale-yellow solid; yield: 50 mg (77%); mp 119–120 °C, $[\alpha]_D^{20}$ –62.7 (*c* = 0.20, $CHCl_3$). IR (KBr): 3360, 2926, 1698, 1599, 1513, 1344, 747, 693 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.5 Hz, 2 H), 7.56 (d, *J* = 8.5 Hz, 2 H), 7.08 (t, *J* = 7.5 Hz, 2 H), 6.71 (t, *J* = 7.0 Hz, 1 H), 6.54 (d, *J* = 7.0 Hz, 2 H), 4.86 (d, *J* = 4.0 Hz, 1 H), 2.93–2.83 (m, 1 H), 2.44 (d, *J* = 13.5 Hz, 1 H), 2.38–2.28 (m, 1 H), 2.15–2.05 (m, 2 H), 1.95–1.88 (m, 1 H), 1.70–1.55 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.6, 149.4, 147.0, 146.5, 129.1, 128.5, 123.6, 118.4, 114.0, 57.2, 56.1, 42.4, 29.0, 27.0, 24.9.

(16) (a) Gu, Q.; Jiang, L.-X.; Yuan, K.; Zhang, L.; Wu, X.-Y. *Synth. Commun.* **2008**, *38*, 4198. (b) Takech, S.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2013**, *15*, 2632. (c) Rachwalski, M.; Leenders, T.; Kaczmarczyk, S.; Kiełbasiński, P.; Leśniak, S.; Rutjes, F. P. J. T. *Org. Biomol. Chem.* **2013**, *11*, 4207.