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Synthesis of Monoacylated Derivatives of 1,2- Cyclohexanediamine. Evaluation of their Catalytic Activity in the Preparation of Wieland−Miescher Ketone†

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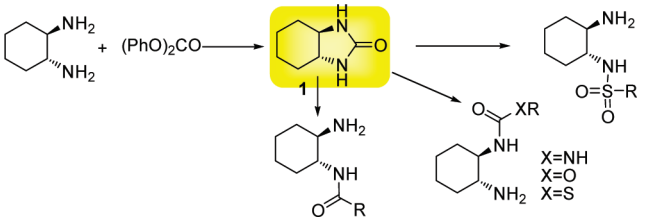


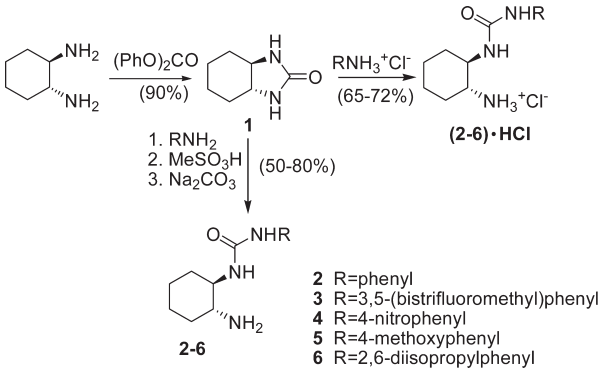
Ureas, carbamoyl derivatives, amides, and sulfonamides can be easily prepared from the strained (*R*,*R*)-cylohexanediamine urea (**1**) in high yield, leaving a free amino group that shows good catalytic activity in intramolecular aldol condensations. The preparation of Wieland−Miescher ketone has been studied with these catalysts.

Although the formation of amide bonds by reaction of amines with acid chlorides is a common procedure in organic synthesis, high-yield monoacylation of symmetrical diamines may be, in some cases, a difficult process. Several hypotheses have been proposed to explain these findings, such as an inefficient mixture of reagents or intramolecular catalysis by the first-formed amide group.[1] However, monoacylation has been shown to be possible by working with low reactivity compounds like esters,[2] by employing aggregation effects,[3] or by making use of steric hindrance.[4]

trans-Cyclohexanediamine is widely exploited as a source of chirality in many organic chemistry processes,[5] and numerous derived bifunctional catalysts have been prepared. Many of these organocatalysts combine the presence of the chiral primary amine group with another functionality (thiourea, urea, sulfonamide, etc.), so selective monoacylation is desired.[6]

Monoacylation of cyclohexanediamine can be achieved following the procedure of Kim et al.,[4] protecting both amines as their benzyloxycarbonyl derivatives, followed by reaction with Boc_2O and hydrogenolysis. Here, we develop an alternative procedure for monoacylation based on the reactivity of urea **1** (Scheme 1).

SCHEME 1. Preparation of Ureas Starting from (*R*,*R*)-Cyclohexanediamine



Cyclic urea **1** can be obtained when cyclohexanediamine is reacted with the gaseous and toxic carbonyl sulfide.[7] A simple and high-yield alternative synthesis is based on the use of diphenylcarbonate, which can also be employed when the starting material is the straightforwardly obtained enantiopure (*R*,*R*)-cyclohexanediamine tartrate salt.[8]

Owing to the *trans*-fused rings, under acidic conditions urea **1** shows suitable reactivity with nucleophiles.[9] Thus, aromatic amines can open the urea **1** ring in the presence of methanesulfonic acid to afford the corresponding aminoureas **2**−**6** after basic workup (Scheme 1). The reaction seems to be general for all anilines, including electron-poor (**3** and **4**)

† Dedicated to Professor Carmen Nájera on the occasion of her 60th birthday.

(1) Jacobson, A. R.; Makris, A. N.; Sayre, L. M. *J. Org. Chem.* **1987**, *52*, 2592.
(2) Tang, W.; Fang, S. *Tetrahedron Lett.* **2008**, *49*, 6003.
(3) Muñiz, F. M.; Simón, L.; Sáez, S.; Raposo, C.; Morán, J. R. *Tetrahedron Lett.* **2008**, *49*, 790.
(4) Kim, Y. K.; Lee, S. J.; Ahn, K. H. *J. Org. Chem.* **2000**, *65*, 7807.
(5) (a) Xue, F.; Zhang, S.; Duan, W.; Wang, W. *Adv. Synth. Catal.* **2008**, *350*, 2194. (b) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. (c) Uehara, H.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2009**, *48*, 9848. (d) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451. (e) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Chem. Pharm. Bull.* **2004**, *52*, 477. (f) Rasappan, R.; Reiser, O. *Eur. J. Org. Chem.* **2009**, 1305. (g) Peng, F.; Shao, Z. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1. (h) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074. (i) Mei, K.; Jin, M.; Zhang, S.; Li, P.; Liu, W.; Chen, X.; Xue, F.; Duan, W.; Wang, W. *Org. Lett.* **2009**, *11*, 2864. (j) Wang, J.; Wang, X.; Ge, Z.; Cheng, T.; Li, R. *Chem. Commun.* **2010**, 1751. (k) Ma, H.; Liu, K.; Zhang, F.- G.; Zhu, C.- L.; Nie, J.; Ma, J.- A. *J. Org. Chem.* **2010**, *75*, 1402. (l) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (m) Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923. (n) He, T.; Gu, Q.; Wu, X.-Y. *Tetrahedron* **2010**, *66*, 3195.
(6) Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431.
(7) Davies, S. G.; Mortlock, A. A. *Tetrahedron* **1993**, *49*, 4419.
(8) Schanz, H.-J.; Linseis, M. A.; Gilheany, D. G. *Tetrahedron: Asymmetry* **2003**, *14*, 2763.
(9) Hutchby, M.; Houlden, C. E.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 8721.

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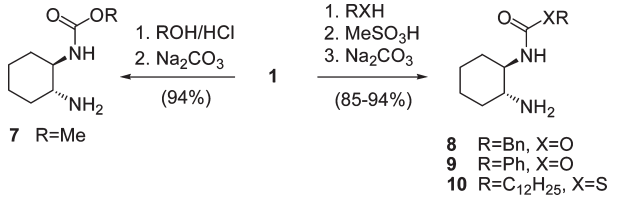
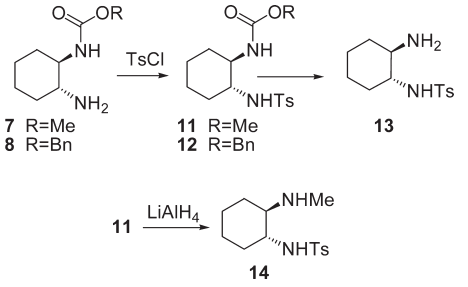
SCHEME 2. Monoprotection of Cyclohexanediamine as Carbamoyl (Carbamothioyl) Derivatives



SCHEME 3. Transformation of the Carbamoyl Derivatives into Sulfonamides



and electron-rich systems (**5**) and hindered amines (**6**). Ring opening can also be carried out without methanesulfonic acid when the hydrochloride salt of the aromatic amine is employed. In this case, the reaction also works well and the isolation of the corresponding ureas may be easily accomplished by precipitation upon addition of a proper solvent to the reaction medium (see the Supporting Information). By contrast, aliphatic amines failed to produce the desired ring opening under the above conditions.

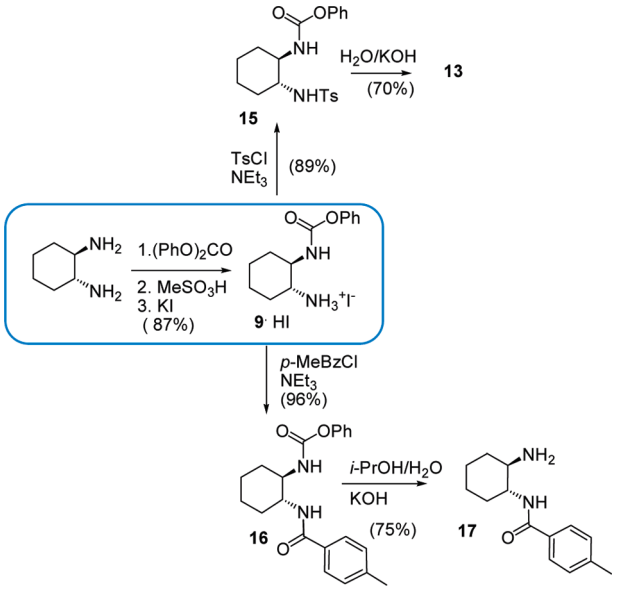
Monoamides and sulfonamides are other target compounds whose synthesis is achieved through the monocarbamoyl derivatives (see Schemes 3 and 4). Hence, the first step in the synthesis comprises the reaction of urea **1** with alcohols yielding the monocarbamates (Scheme 2). Compound **7** was obtained by reacting the cyclic urea **1** with MeOH/HCl, and the carbamoyl derivatives **8** and **9** were prepared by treatment with the corresponding alcohols and $MeSO_3H$. Under the same conditions, dodecanethiol afforded the monocarbamothioyl derivative **10**.

Preparation of sulfonamides **11** and **12** was carried out in two steps, starting from the related carbamoyl derivatives. For the obtention of sulfonamides, compounds **7** and **8**, respectively, were reacted with tosyl chloride. These sulfonamides may be deprotected yielding the primary amine **13** (Scheme 3). Deprotection can be carried out under basic conditions, nucleophilic displacement in the case of the methyl group,[10] or hydrogenolysis for the benzyl group. Additionally, the tosyl derivative **11** was converted to the corresponding methylamine **14** through reduction of the carbamoyl group with $LiAlH_4$.

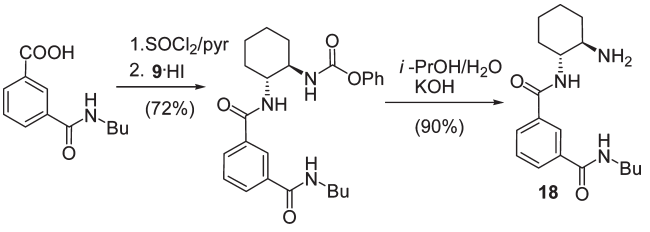
The one-pot synthesis of the monocarbamate **9** starting from the cyclohexanediamine tartrate salt offers an attractive possibility to achieve the monoprotected compounds (Scheme 4). Since urea **1** can be obtained from diphenyl carbonate, generating two phenol equivalents in situ, the addition of methanesulfonic acid led to ring opening, directly affording the

(10) Elsinger, F.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1960**, *43*, 113.

SCHEME 4. One-Pot Synthesis of Carbamate 9 and Preparation of Amides and Sulfonamides



SCHEME 5. Preparation of Catalyst 18



monocarbamoylated compound **9**. This compound is highly water-soluble as its methanesulfonate salt but readily crystallizes as the hydroiodide. Tosylation or benzoylation, for example, can be carried out in chloroform in the presence of triethylamine to yield compounds **15** and **16**. Hydrolysis of the phenylcarbamoyl group can be readily achieved under mild basic conditions to yield the sulfonamide **13** and the amide **17** (Scheme 4).

The "oxyanion hole" properties of isophthalic derivatives[11] inspired us to prepare compound **18**, which incorporates an extra amide functionality. This cyclohexanediamine derivative is obtained starting from the isophthalic acid monobutyl amide,[12] according to the synthetic procedure depicted in Scheme 5 (see the Supporting Information).

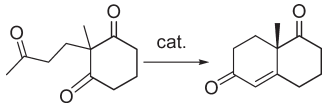
Chiral amines derived from diaminocyclohexane have proved to be efficient organocatalysts for the aldol reaction.[13] Due to

(11) (a) Dixon, R. P.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1992**, *114*, 365. (b) Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 191. (c) Muñiz, F. M.; Montero, V. A.; Fuentes de Arriba, A. L.; Simón, L.; Raposo, C.; Morán, J. R. *Tetrahedron Lett.* **2008**, *49*, 5050.

(12) Oliva, A. I.; Simón, L.; Muñiz, F. M.; Sanz, F.; Morán, J. R. *Tetrahedron* **2004**, *60*, 3755.

(13) (a) Raj, M.; Parashari, G. S.; Singh, V. K. *Adv. Synth. Catal.* **2009**, *351*, 1284. (b) Nakayama, K.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 17666. (c) Luo, S.; Xu, H.; Chen, L.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 1775. (d) Luo, S. Z.; Xu, H.; Li, J. Y.; Zhang, L.; Cheng, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 3074. (e) Mei, K.; Zhang, S.; He, S.; Li, P.; Jin, M.; Xue, F.; Luo, G.; Zhang, H.; Song, L.; Duan, W.; Wang, W. *Tetrahedron Lett.* **2008**, *49*, 2681. (f) Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, *130*, 5654.

TABLE 1. Preparation of the Wieland−Miescher Ketone in $CDCl_3$ (1.0 M) with 10 mol % of Catalyst at 20 °C



entry	catalyst	conversion[a] (%)	yield[b] (%)	time (h)	ee[c] (%)
1	**2**[d]	95	76	22	85
2	**3**	94	82	30	89
3	**4**	81	63	117	75
4	**8**	76	59	117	65
5	**13**	3	n.d.	161	61
6	**14**	24	n.d.	161	−11
7	**17**	94	77	44	91
8	**18**[d]	100	85	16	95

[a]Determined by integration of the corresponding signals in the ^1H NMR spectra. [b]Isolated yield after silica gel chromatography. [c]Determined by chiral HPLC (Daicel Chiralpak IC column). [d]2.0 M concentration of the ketone, 10 mol % catalyst. Higher concentrations of the ketone yielded reduced enantioselectivities.

our interest in this reaction,[14] we decided to explore the ability of these compounds in the preparation of the Wieland−Miescher ketone.[15] Ureas **2**−**4** are good organocatalysts for this reaction, showing high enantioselectivities (Table 1, entries 1−3). The catalytic activity of the carbamoyl derivative **8** was also evaluated (entry 4, Table 1), but enantioselectivity was reduced in comparison with that obtained with the urea compounds.

Considering enantioselectivity, sulfonamide **13** proved to be a similar catalyst to the carbamoyl derivative **8** (entries 4 and 5, Table 1), although the conversion rate was considerably reduced. To test the influence of a secondary amine in the conversion and enantioselectivity, we prepared the sulfonamide **14** with a methylamino group (entry 6, Table 1). This catalyst showed the lowest enantioselectivity with the opposite enantiomer as the major product.

When amide **17** was used, enantioselectivity was increased up to 91% ee (entry 7, Table 1). The isophthalic derivative **18**, which resembles the oxyanion hole geometry, gave the best enantioselectivity (95% ee) with a complete conversion within 16 h (entry 8, Table 1). This catalyst has also been tested in the preparation of the Hajos−Wiechert ketone; however, in this case, the reaction was much slower (only 20% conversion to the ketone after 94 h and 81% ee), which limits its use for preparative purposes.

In summary, an alternative approach to the synthesis of monofunctionalized 1,2-cyclohexanediamines has been described, starting from the readily available (*R*,*R*)-cyclohexanediamine urea and taking advantage of the reactivity provided by the *trans* ring junction. In addition, we have explored the possibilities of these compounds as catalysts in the intramolecular aldol condensation yielding the Wieland−Miescher ketone, with the best results being obtained for ureas and amides, reaching up to 95% ee.

Experimental Section

(3a*R*,7a*R*)-Hexahydro-1*H*-benzo[*d*]imidazol-2(3*H*)-one (1). Enantiopure (*R*,*R*)-cyclohexanediamine tartrate salt was readily obtained starting from the racemic *trans*-cyclohexane-1,2-diamine and L-tartaric acid.[8] This tartrate salt (40.0 g, 150.8 mmol) and KOH (17.0 g, 303.6 mmol) were dissolved in H_2O (30 mL) to generate the free diamine. The reaction mixture was heated until all of the solid was dissolved. Then, 2-propanol (100 mL) was added, and the solution was stirred and cooled (ice bath) to yield a potassium tartrate precipitate. To complete the precipitation and remove the water, powdered sodium sulfate (40.0 g) was added and the precipitate was filtered off. The solid was washed with more 2-propanol (2 × 20 mL), diphenyl carbonate (35.0 g, 163 mmol) was added to the filtrate, and the mixture was refluxed for 30 min. Steam distillation and water evaporation allowed us to obtain a crude urea which could be further purified by recrystallization from EtOH/H_2O (1:1) to yield 18.8 g (90% yield) of a compound with the same physical properties as those described in the literature.[16]

General Procedure for the Preparation of Monoureas (2−6) with Methanesulfonic Acid (Procedure A). To a mixture of the urea **1** (2.2 mmol) and the aromatic amine (2.2 mmol) in diglyme (2 mL) was added methanesulfonic acid (0.15 mL) was added, and the reaction mixture was heated at 120 °C for ∼1 h with stirring under argon atmosphere. After the mixture was cooled to room temperature, H_2O (10 mL) and Na_2CO_3 (2.0 g, 19 mmol) were added, and a crystalline solid precipitated that was filtered to afford the desired compound. If the urea did not crystallize spontaneously, diethyl ether (2 mL) was added to assist the precipitation. This procedure has been carried out on a 2−15 mmol scale.

(1*R*,2*R*)-1,2-Diaminocyclohexane 3,5-bis(trifluoromethyl) phenylurea (3). Urea **1** (2.0 g, 14.2 mmol), 3,5-bis(trifluoromethyl)aniline (3.4 g, 14.8 mmol), and methanesulfonic acid (1 mL) were dissolved in diglyme (2 mL), and the mixture was heated at 120 °C for 30 min. Then, H_2O (30 mL) and Na_2CO_3 (7 g, 66 mmol) were added. The product was extracted with ethyl acetate (2 × 20 mL), and the solvent was evaporated. The crude residue was purified by recrystallization from ether−hexane at 0 °C to afford 3.5 g (66% yield) of compound **3**, whose properties are in agreement with those published.[5e]

General Procedure for the Preparation of Monoureas (2−6) Starting from the Hydrochloride Salts of the Amines (Procedure B). Urea **1** (3.5 mmol) and the amine hydrochloride (3.5 mmol) were heated in diglyme (2 mL) at 120 °C. After the mixture was heated for ∼1 h, a solid precipitated from the reaction medium. NMR ^1H analysis of an aliquot confirmed that the reaction had finished. The mixture was cooled to room temperature, and diethyl ether (10 mL) was added. The solid was filtered and dried under vacuum (0.1 mmHg) heating at 90 °C to remove completely the traces of diglyme, affording the monoureas as their hydrochloride salts.

This procedure has been carried out on a 1−5 mmol scale.

(14) (a) Fuentes de Arriba, Á. L.; Simón, L.; Raposo, C.; Alcázar, V.; Morán, J. R. *Tetrahedron* **2009**, *65*, 4841. (b) Fuentes de Arriba, Á. L.; Simón, L.; Raposo, C.; Alcázar, V.; Sanz, F.; Muñiz, F. M.; Morán, J. R. *Org. Biomol. Chem.* **2010**, *8*, 2979.

(15) (a) Almasi, D.; Alonso, D. A.; Balaguer, A.-N.; Nájera, C. *Adv. Synth. Catal.* **2009**, *351*, 1123. (b) Almasi, D.; Alonso, D. A.; Nájera, C. *Adv. Synth. Catal.* **2008**, *350*, 2467. (c) Bradshaw, B.; Etxebarría-Jardi, G.; Bonjoch, J.; Viózquez, S. F.; Guillena, G.; Nájera, C. *Adv. Synth. Catal.* **2009**, *351*, 2482. (d) Davies, S. G.; Sheppard, R. L.; Smith, A. D.; Thomson, J. E. *Chem. Commun.* **2005**, 3802. (e) Lacoste, E.; Vaique, E.; Berlande, M.; Pianet, I.; Vincent, J.-M.; Landais, Y. *Eur. J. Org. Chem.* **2007**, 167. (f) He, L. *Hecheng Huaxue* (*Chin. J. Synth. Chem.*) **2007**, *15*, 231. (g) Akahane, Y.; Inage, N.; Nagamine, T.; Inomata, K.; Endo, Y. *Heterocycles* **2007**, *74*, 637. (h) Akahane, Y.; Inomata, K.; Endo, Y. *Heterocycles* **2009**, *77*, 1065. (i) D'Elia, V.; Zwicknagl, H.; Reiser, O. *J. Org. Chem.* **2008**, *73*, 3262. (j) Guillena, G.; Hita, M. d. C.; Nájera, C.; Viózquez, S. F. *J. Org. Chem.* **2008**, *73*, 5933. (k) Kanger, T.; Kriis, K.; Laars, M.; Kailas, T.; Muurisepp, A.-M.; Pehk, T.; Lopp, M. *J. Org. Chem.* **2007**, *72*, 5168. (l) Davies, S. G.; Russell, A. J.; Sheppard, R. L.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3190. (m) Guillena, G.; Nájera, C.; Viózquez, S. F. *Synlett* **2008**, *19*, 3031. (n) Kriis, K.; Kanger, T.; Laars, M.; Kailas, T.; Muurisepp, A.-M.; Pehk, T.; Lopp, M. *Synlett* **2006**, *11*, 1699. (o) Nozawa, M.; Akita, T.; Hoshi, T.; Suzuki, T.; Hagiwara, H. *Synlett* **2007**, *4*, 661. (p) Zhang, X.-M.; Wang, M.; Tu, Y.-Q.; Fan, C.-A.; Jiang, Y.-J.; Zhang, S.-Y.; Zhang, F.-M. *Synlett* **2008**, *18*, 2831. (q) Agami, C.; Meynier, F.; Puchot, C.; Guilhem, J.; Pascard, C. *Tetrahedron* **1984**, *40*, 1031. (r) Bui, T.; Barbas, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951.

(16) Davies, S. G.; Mortlock, A. A. *Tetrahedron* **1993**, *49*, 4419.

(1*R*,2*R*)-1,2-Diaminocyclohexane Phenylurea (2). Urea **1** (495 mg, 3.5 mmol) and aniline hydrochloride (460 mg, 3.5 mmol) were heated in diglyme (2 mL) at 120 °C. After the mixture was heated for ~1 h, a solid precipitated from the reaction medium. ^{1}H NMR analysis of an aliquot confirmed that the reaction had finished. The mixture was cooled to room temperature, and diethyl ether (10 mL) was added. The solid was filtered and dried under vacuum (0.1 mmHg) heating at 90 °C to remove completely the traces of diglyme. The urea **2** as its hydrochloride salt (621 mg, 66%) was obtained. Spectral and physical data of the free amine (liberated with aqueous KOH (3.3 mL, 6 mM) and extracted with diethyl ether) were in agreement with those published.[17]

Phenyl (1*R*,2*R*)-2-Aminocyclohexylcarbamate 9. Initially, (*R*,*R*)-cyclohexane-1,2-diamine tartrate salt (10.02 g, 37.9 mmol) was reacted under the same conditions described for the preparation of urea **1**. After the mixture was refluxed with diphenyl carbonate (8.11 g, 37.9 mmol) in 2-propanol, the solvent was evaporated under reduced pressure, and the crude residue was dried through azeotropic destillation with benzene (100 mL). To this mixture of phenol and the urea **1** was added 1 equiv of methanesulfonic acid (2.5 mL), and the reaction was heated at 110 °C with stirring for 1 h under Ar atmosphere. Then the solution was cooled, water (30 mL) was added, and the phenol was extracted with ethyl acetate (2 × 30 mL). To the aqueous layer, cooled to 0 °C, was added KI (7.0 g, 42 mmol), and a precipitate of the hydroiodide salt of compound **9** (12 g, 87% yield) was obtained: mp 187−189 °C; $[\alpha]^{20}_D$ −6.33 (*c* 0.6, CH_3OH); ^{1}H NMR (200 MHz, $CDCl_3$/CD_3OD) δ 7.22−7.15 (2H, m), 7.06−6.97 (3H, m), 3.38 (1H, m), 3.03 (1H, m), 1.94−1.84 (2H, m), 1.65−1.55 (2H, m), 1.30−1.16 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$/CD_3OD) δ 155.9 (C), 150.9 (C), 129.3 (CH), 125.6 (CH), 121.8 (CH), 54.6 (CH), 53.1 (CH), 31.7 (CH_2), 29.9 (CH_2), 24.4 (CH_2), 23.7 (CH_2); IR (film) 3565, 3318, 1729, 1599, 1462 cm^{-1}. Anal. Calcd for $C_{13}H_{19}IN_2O_2$: C, 43.11; H, 5.29; N, 7.73. Found: C, 42.89; H, 5.38; N, 7.83.

(17) Bied, C.; Moreau, J. J. E.; Wong Chi Man, M. *Tetrahedron: Asymmetry* **2001**, *12*, 329.

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Supporting Information Available: Synthesis of catalysts, characterization data (including ^{1}H and ^{13}C spectra of the new compounds), and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.