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A Novel Highly Selective Chiral Auxiliary for the Asymmetric Synthesis of L- and D-α-Amino Acid Derivatives via a Multicomponent Ugi Reaction

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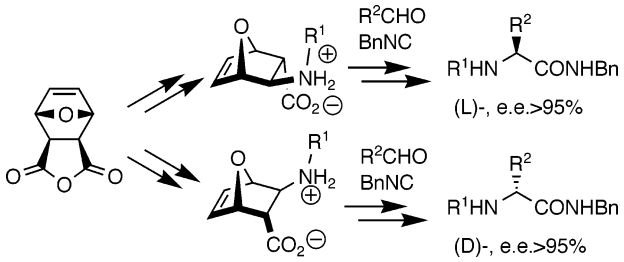

This paper describes the synthesis of a bicyclic β-amino acid scaffold in both pure enantiomeric forms and its application as chiral auxiliary in an intramolecular version of the Ugi multicomponent reaction (U-5C-4CR) to prepare α-amino acid derivatives of both D- and L-series in a straightforward and very stereoselective manner. The mild conditions required for the Ugi condensation and for the removal of the chiral auxiliary make this method very attractive to prepare a wide range of differently structured *N*-alkylated and unalkylated amino acid derivatives.

Introduction

Multicomponent reactions have become increasingly popular within the scientific community for their ability to generate valuable molecules in a very convergent manner. Among an increasing number of novel multicomponent condensations, the Ugi four-component reaction (U-4CR) remains by far the most widely used one. The reasons can be ascribed to the fact that by condensing an aldehyde, an amine, a carboxylic acid, and an isocyanide not only amino acid derivatives[1] but also many other classes of pharmacologically relevant molecules can be prepared in a very straightforward manner by an opportune choice of starting materials.[2] A new stereogenic center is usually generated in this reaction, and considerable efforts have been made to control its stereochemistry. For this purpose different chiral auxiliaries have been used; however, an acceptable degree of diastereoselectivity is generally observed only when chiral amines are employed, the most efficient ones being ferrocenylalkylamines and glycosylamines.[3] Although these two types of derivatives represent at the moment the auxiliaries of choice in Ugi reactions, their use still suffers from some drawbacks, such as the harsh conditions generally required to remove the auxiliary from the final adduct, the difficulties to prepare it in both enantiomeric forms, and the low temperatures necessary to achieve satisfactory control of the stereoselectivity.

Good diastereoselectivities have been observed also when α-amino acids are employed as bifunctional reagents in an intramolecular version of the Ugi reaction to give α,α′-iminodicarboxylic acid derivatives;[4] however, only when sterically hindered aldehydes and isocyanides are employed are the diastereomeric excesses higher than 90%.[5] Also in this case a limitation of the use of α-amino acids as chiral auxiliaries is represented by their removal

(1) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1700−1702.
(2) See, for example: (a) Dömling, A. *Comb. Chem. High Throughput Screening* **1998**, *1*, 1−22. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169−3210. (c) Ugi, I.; Dömling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647−658. (d) Ugi, I.; Heck, S *Comb. Chem. High Throughput Screening* **2001**, *4*, 1−34. (e) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306−313. (f) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53−66 and references therein.
(3) See, for example: (a) Marquarding, D.; Hoffmann, P.; Heitzer, H.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 1969−1971. (b) Kunz, H.; Pfrengle, W.; Rück, K.; Sager, W. *Synthesis* **1991**, 1039−1042. (c) Linderman, R. J.; Binet, S.; Petrich, S. R. *J. Org. Chem.* **1999**, *64*, 336−337. (d) Ross, G. F.; Herdtweck, E.; Ugi, I. *Tetrahedron* **2002**, *58*, 6127−6133.
(4) Demharter, A.; Horl, W.; Herdtweck, E.; Ugi, I. *Angew. Chem., Int. Ed.* **1996**, *35*, 173−175.
(5) Sung, K.; Chen, F.-L.; Chung, M.-J. *Mol. Div.* **2003**, *6*, 213−221.

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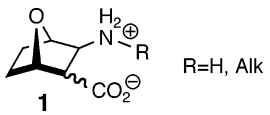
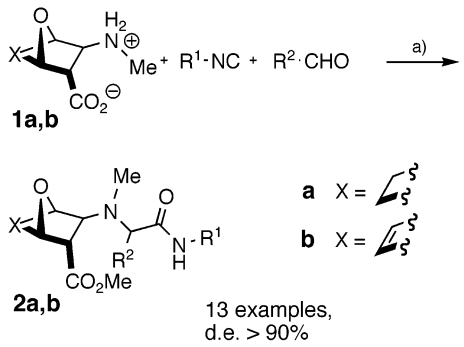


FIGURE 1. General formula for β-amino acid derivatives employed in an intramolecular version of the Ugi condensation.

SCHEME 1[a]



[a] Reagents and conditions: (a) MeOH, rt.

from the adducts and by the availability of both enantiomers.

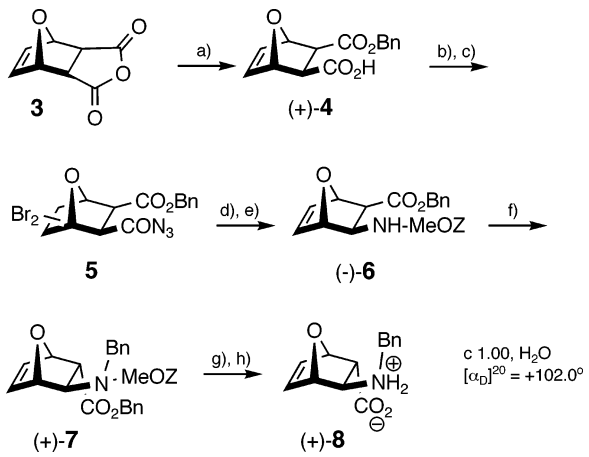
Recently, we have disclosed our results on the intramolecular Ugi reaction using β-amino acid derivatives of general formula **1**[6] (Figure 1) as bifunctional components and shown that the structure of **1** plays a fundamental role both on the product distribution and the stereochemical outcome of the reaction. In particular, we found that when the carboxylic group is in the *endo* position and the amino group is in the *exo* position and alkylated (compound**1a**), the path followed is an Ugi-5-center-4-component reaction (U-5C-4CR, Scheme 1) similar to that reported for α-amino acid derivatives:[4] esters **2a** were obtained as the main product (50−96% yield), and in all cases, even when unbulky aldehydes and isocyanides were employed, only one diastereoisomer could be detected when the reactions were performed at room temperature.

A similar behavior was found with the unsaturated amino acid **1b**. This was an even more interesting event, since in this case the adduct **2b** could be more easily manipulated and used as intermediate for further synthetic transformations. As a first application we anticipated that by removing the bicyclic moiety from **2b** the α-amino acid derivatives could be obtained as the final compounds, thus suggesting the possibility of using **1b** as a chiral auxiliary.

Obviously, to prove this hypothesis, an efficient synthesis of **1b** or its analogues in both enantiomeric forms had to be realized and conditions for removing the chiral auxiliary in a straightforward and enantiospecific manner had to be defined.

In this paper, we report the results of our efforts to prepare the unsaturated bicyclic *N*-benzyl β-amino acid **8** in both enantiomeric forms[7] and its use as a novel chiral auxiliary in the synthesis, through a multicomponent Ugi

SCHEME 2[a]



[a] Reagents and conditions: (a) (+)-quinine, benzyl alcohol, CCl_4, toluene, −55 °C, 95%; (b) ethyl chloroformate, Et_3N, THF, −30 °C, then NaN_3, H_2O, −10 °C to rt, 96%; (c) Br_2, CH_2Cl_2, 0 °C, quant; (d) toluene, reflux, then 4-MeO-benzyl alcohol, reflux to rt, 84%; (e) Zn powder, $TiCl_4$, THF, 0 °C, 95%; (f) NaH, benzyl bromide, DMF, 0 °C to rt, 90%; (g) trifluoroacetic acid, CH_2Cl_2, rt, 90%; h) NaOHaq, dioxane, rt, quant.

reaction, of α-amino acid derivatives of both L- and D-series.

Results and Discussion

To prepare **8**, we planned to start from the carboxylic acid **4**, easily obtainable by amine-mediated asymmetrization of meso anhydride **3**, following the elegant method recently described by Bolm,[8] and to perform a Curtius rearrangement of the corresponding acyl azide, followed by C−H epimerization, *N*-benzylation, and deprotection. With this aim, anhydride **3** was treated with benzyl alcohol in the presence of quinine to give the acid (+)-**4** which was transformed into the corresponding acyl azide via the chloroformate method. At this stage, protection of the double bond via bromine addition was fundamental to prevent competitive retro-Diels−Alder reaction during the Curtius rearrangement,[9,10] which was successfully performed in toluene at reflux in the presence of 4-methoxybenzyl alcohol on the diastereomeric mixture of dibromo derivatives **5**. Removal of double bond protection with Zn dust in the presence of a substoichiometric amount of $TiCl_4$[11] furnished the expected unsaturated carbamate (−)-**6** in an overall 80% yield from **3**.

N-Benzylation of **6** accompanied by epimerization[6] of the benzyl ester at C-2 and double cleavage of the 4-methoxybenzyloxycarbonyl (MeOZ) and of the benzyl ester yielded almost quantitatively the desired β-amino acid derivative (+)-**8** $[\alpha_D] = +102.0$ (*c* 1.00, H_2O) (Scheme 2). A similar procedure, using quinidine instead of quinine in the asymmetrization of **3**, furnished (−)-**8** with $[\alpha_D] = -99.8$ (*c* 0.30, H_2O). At this stage, the optical

(6) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron Lett.* **2004**, *45*, 587−590.

(7) *N*-benzyl analogous of **1b** was selected in order to have a removable protection on the NH_2 of the final amino acid derivative.

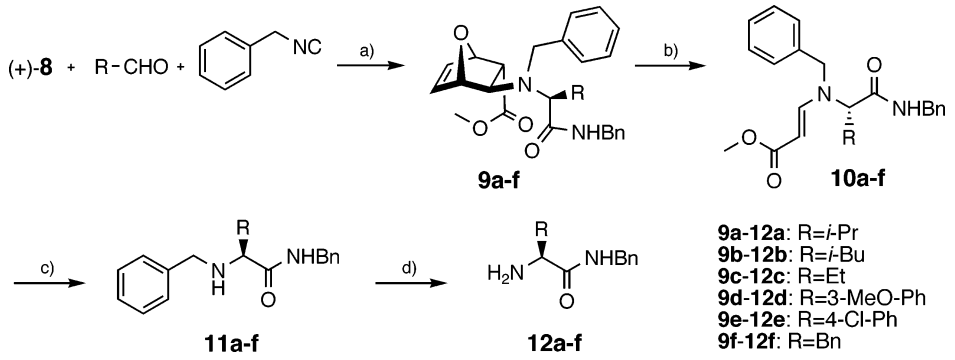
(8) Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455−3467.

(9) Akssira[10] reported the Curtius rearrangement of the racemic azide of the bicyclic monomethyl ester in 84% yield; however, even after several attempts, we could not reproduce his results.

(10) Canonne, P.; Akssira, M.; Dahdouh, A.; Kasmi, H.; Boumzebra, M. *Tetrahedron* **1993**, *49*, 1985−1992.

(11) Sato, F.; Akiyama, T.; Iida, K.; Sato, M. *Synthesis* **1982**, 1025−1026.

SCHEME 3[a]



[a] Reagents and conditions: (a) MeOH, rt; (b) toluene, reflux; (c) HCl, dioxane, rt; (d) Pd black, formic acid, MeOH, rt.

TABLE 1. Summary of the Results of the Ugi Condensation and the Subsequent Elaborations As Outlined in Scheme 3[a]

entry	aldehyde	yield (**9**)	yield (**11**)	yield (**12**)	config (ee, %)	$[\alpha]^{20}_D$ (12)[b]
a	isobutyric	78	91	90	(*S*) (>95)	−23.3 (0.70)[c]
b	isovaleric	76	92	71	(*S*) (>95)	+6.8 (1.45)
c	propionic	70	78	96	(*S*) (>95)	+12.2 (1.20)
d	3-MeO-phenyl	57	88	83	(*S*) (>95)	+47.3 (1.10)
e	4-Cl-phenyl	58	90	76	(*S*) (>95)	+57.4 (1.65)
f	phenylacetic	66	87	88	(*S*) (>95)	−69.4 (0.50)[d]
g	isovaleric	75	92	87	(*R*) (>95)	−7.0 (1.50)

[a] The Ugi reactions were performed in MeOH at room temperature for 3−5 days. All compounds were purified by column chromatography and fully characterized. [b] Optical rotatory powers are measured in MeOH, *c* is reported in parentheses. [c] Measured in $CHCl_3$ stabilized with 0.5−1.0% ethanol. [d] Measured in $CHCl_3$ stabilized with amylenes; lit.[14b] −70.6.

purity of the two enantiomeric β-amino acids was verified by reacting them with (+)-phenylethylamine. The corresponding diastereomeric amides were analyzed by NMR and HPLC, and no cross-contamination peaks were observed by either of the two methods.

With the two optically pure β-amino acid derivatives in hand, we moved on to study the Ugi reaction. As the first aldehyde we used isobutyraldehyde which was allowed to react in methanol at room temperature with equimolar amounts of benzyl isocyanide and amino acid (+)-**8**. After 3 days, the almost complete consumption of the isocyanide prompted us to stop the reaction by evaporation of the solvent. Analysis of the crude material showed that the Ugi adduct (+)-**9a** was formed as a single diastereoisomer, which was isolated by column chromatography in 78% yield. Retro-Diels−Alder reaction in toluene at reflux and enamine (−)-**10a** deprotection with HCl in dioxane proceeded smoothly and furnished (−)-*N*-benzylvaline benzylamide (−)-**11a**, which by hydrogenolysis with Pd black and formic acid[12] provided (−)-valine benzylamide (−)-**12a** in almost quantitative yield (Scheme 3).

The enantiomeric excess was determined reacting **12a** respectively with (*R*)- and (*S*)-Mosher's chlorides in dichloromethane/triethylamine. Comparison of the ^{1}H NMRs of the two Mosher's amides indicated that the enantiomeric excess of (−)-**12a** was higher than 95%, confirming our strategy to be completely stereoselective and proving also that no racemization had occurred in the course of the subsequent synthetic manipulations. To test the generality of this method, we reacted *N*-benzylamino acid (+)-**8** and benzyl isocyanide with different aldehydes, and the results are reported in Table 1. All of the reactions were clean and almost complete within 5 days at room temperature, and in all cases only one diastereoisomer was found, within the limits of the ^{1}H NMR sensitivity. After removal of the chiral auxiliary from **9b**−**f**, the enantiomeric excess was determined on the amides **12b**−**f** as described above for **12a** and resulted in all cases higher than 95%.[13]

Finally, to determine the absolute configuration of the reaction products, we compared the optical rotatory power of **12b** and **12f** with that reported in the literature.[14] The data indicate that, using (+)-**8** as chiral auxiliary, the obtained α-amino acid derivatives have the absolute configuration (*S*) and therefore belong to the L-series.

To prove the validity of this methodology to prepare also α-amino acid derivatives of the opposite configuration, we repeated the Ugi reaction using isovaleraldehyde, benzyl isocyanide, and the amino acid (−)-**8**. Following the same procedure previously described, the expected D-leucine benzylamide **12g** was isolated as the final compound with an enantiomeric excess higher than 95% (by the Mosher's amide method) and with an $[\alpha_D]$ = −7.0 (*c* 1.50, MeOH).

(12) ElAmin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442−3444.

(13) Each amino acid derivative was separately reacted with (*R*)- and (*S*)-Mosher's chlorides and the resulting product were analyzed by ^{1}H NMR in order to check the presence of a single diastereoisomer. In all cases the α-methoxy group could be univocally distinguished between the two diastereoisomers, as illustrated by the δ frequencies reported below. Mosher's amides: from **12a**, (*R*) = 3.42, (*S*) = 3.33; from **12b**, (*R*) = 3.39, (*S*) = 3.31; from **12c**, (*R*) = 3.41, (*S*) = 3.33; from **12d**, (*R*) = 3.53, (*S*) = 3.36; from **12e**, (*R*) = 3.35, (*S*) = 3.51; from **12f**, (*R*) = 3.28, (*S*) = 3.23; from **12g**, (*R*) = 3.31, (*S*) = 3.39.

(14) (a) Giordano, C.; Gallina, C.; Ottaviano, V.; Consalvi, V.; Scandurra, R. *Eur. J. Med. Chem.* **1992**, *27*, 865−873. (b) Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieux, R.; Schonholzer, P.; Spiegler, C.; Muller, K. *Helv. Chim. Acta* **1995**, *78*, 563−580.

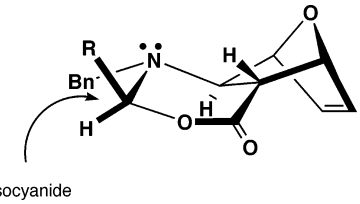


FIGURE 2. Low-energy conformation of the cyclic intermediate.

Among the various mechanisms proposed for these multicomponent reactions,[15] we argued that a stepwise pathway, similar to that suggested by Ugi and others[4,16] for the classical Ugi reaction, involving a six member cyclic intermediate formed after condensation of the aldehyde with **8**, followed by displacement of the carboxylate by the isocyanide, could account for our experimental results. To explain the complete stereoselectivity of the reaction, preliminary conformational calculations[17] have indicated that the preferred conformation of the cyclic intermediate is the one illustrated in Figure 2, with the *N*-benzyl group *trans* with respect to the aldehyde side chain and *cis* with respect to the bicycle C-3 hydrogen. The isocyanide should attack this intermediate from the side opposite to the carboxylic oxygen, thus generating, in the case of (+)-**8**, an amino acid derivative of the L-series.

Although this mechanism is in accordance with the observed stereochemistry of the final compounds, more detailed studies[18] are required for better understanding the reasons of the strong stereocontrol and to rule out other possible hypotheses.

Conclusions

In conclusion, we have reported the synthesis and application of a novel chiral auxiliary for the preparation of optically pure α-amino acid derivatives via the Ugi reaction. The availability of a large number of aldehydes and of both enantiomers of **8**, the mild conditions used in the Ugi reaction and in the cleavage of the auxiliary, make this methodology extremely useful for the preparation of a wide range of differently structured *N*-alkylated and not alkylated L- and D-amino acid derivatives. Other synthetic elaborations of intermediate **9** as well as the use of a convertible isocyanide to obtain free α-amino acids are under study in our laboratory, and the results will be reported in due course.

(15) (a) Ugi, I.; Kaufhold, G. *Liebigs Ann. Chem.* **1967**, *709*, 11−28. (b) Ugi, I.; Offermann, K.; Herlinger, H.; Marquarding, D. *Liebigs Ann. Chem.* **1967**, *709*, 1−10.

(16) (a) Flanagan, D. M.; Joullié, M. M. *Synth. Commun.* **1989**, *19*, 1−12. (b) Bock, H.; Ugi, I. *J. Prakt. Chem.* **1997**, *339*, 385−389.

(17) The four possible isomers of the postulated cyclic intermediate were minimized using MM2 (ChemBats3D software) and the energies compared, furnishing, as most stable isomer, the one reported in Figure 2.

(18) Attempts to prove the involvement of the cyclic postulated intermediate were performed, but without success. When the bicyclic amino acid **8** was mixed with benzaldehyde using MeOH-d_4 as the solvent, neither transient peaks nor any stable intermediate was observed by NMR, even after several days; however, after addition of the isocyanide, the reaction proceeded smoothly to give the desired Ugi adduct. A parallel experiment was conducted mixing compound **8** with benzyl isocyanide, but also in this case no transformation was observed until benzaldehyde was added to the mixture. These experiments do not prove but do not exclude the involvement of the postulated intermediate as metastable species in the reaction.

Experimental Section

Compound (+)-4. Benzyl alcohol (3.7 mL, 36.0 mmol) was added dropwise to a stirred suspension of *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride (2.0 g, 12.0 mmol) and quinine (4.8 g, 13.2 mmol) in a 1:1 mixture of toluene and carbon tetrachloride (240 mL) at −55 °C under nitrogen. The reaction mixture was stirred at this temperature for 5 days and then extracted with 2 N HCl (2 × 200 mL). The combined water phase was then extracted with ethyl acetate (2 × 100 mL), and the combined organics were anhydrified and dried under vacuo. The crude material was purified via flash chromatography (eluent EtOAc/PE 1:1 + 1% AcOH), yielding 3.1 g (95%) of pure product. R_f = 0.34 (eluent: DCM/Et_2O = 1:1, 1% AcOH). Mp: 120−121 °C dec. $[\alpha]^{20}_D$: +30.0 (*c* 1.00, MeOH). ^{1}H NMR (300 MHz): δ 2.88 [2H, s]; 5.06 [1H, d, *J* 12]; 5.17 [1H, d, *J* 12]; 5.27 [1H, broad s]; 5.34 [1H, broad s]; 6.46 [1H, dd, *J* 9, 1]; 6.48 [1H, dd, *J* 9, 1]; 7.30−7.35 [5H, s]. ^{13}C NMR (75 MHz): δ 46.9 (CH); 47.3 (CH); 67.2 (CH_2); 80.4 (CH); 80.7 (CH); 128.4 (CH); 128.5 (CH); 128.6 (CH); 135.5 (C); 136.4 (CH); 136.8 (CH); 171.1 (C); 176.8 (C). Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.82; H, 5.28.

Compound (−)-**4** was obtained analogously by quinidine-mediated asymmetrization. $[\alpha]^{20}_D$: −29.7 (*c* 3.22, MeOH).

Compound (−)-6. Compound (+)-**4** (1.3 g, 4.74 mmol) was dissolved in dry THF (25 mL) under nitrogen, together with triethylamine (1.3 mL 9.48 mmol). The solution was cooled to −30 °C, and ethylchloroformate (0.7 mL, 7.11 mmol) was added dropwise. The solution was allowed to warm to −10 °C, and then sodium azide (0.77 g, 11.8 mmol) dissolved in water (5 mL) was added and the solution was let warm to room temperature. The solution was then diluted with ethyl acetate (25 mL) and washed with brine (2 × 20 mL). The organic phase was dried over magnesium sulfate, concentrated in vacuo, and redissolved in methylene chloride (30 mL). The resulting solution, containing a small amount of triethylammonium chloride, was put in the dark at 0 °C, and bromine (5.14 mmol, 0.26 mL) dissolved in methylene chloride (20 mL) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. Solvent and excess bromine were removed under vacuo, and crude material was taken up in diethyl ether (40 mL) and anhydrified with sodium sulfate. Filtration of sodium sulfate and triethylammonium chloride and evaporation of the solvents yielded almost pure **5** as an inseparable 1:1 mixture of diastereoisomers. Crude **5** was then dissolved in toluene (40 mL) and heated at reflux for 30 min until the release of nitrogen ceased. 4-Methoxybenzyl alcohol (1.2 mL, 9.36 mmol) was then added, and the solution was allowed to cool to room temperature overnight. The crude material was partially crystallized, and the mother waters were purified by flash chromatography (eluent: gradient from EtOAc/PE 2:8 to EtOAc/PE 3:7). The solid and the product of the chromatography were combined, yielding 2.1 g (3.62 mmol, 81%) of product as two diastereoisomers. This mixture was finally dissolved in dry THF (40 mL) and cooled to 0 °C. A substechiometric amount of $TiCl_4$ dissolved in methylene chloride (approximately 0.5 mL of a 1.8 M solution) and Zn dust (0.71 g, 10.9 mmol) were added in this sequence. The resulting suspension was stirred overnight, while three more aliquots of catalyst were added at regular intervals. The solid was then filtered over Celite and the crude material extracted with 1 M HCl (20 mL) and brine (20 mL). The organic phase was dried over magnesium sulfate, concentrated in vacuo, and purified by flash chromatography (eluent: gradient from EtOAc/PE 3:7 to EtOAc/PE 1:1) yielding 1.4 g (95%) of pure product. R_f = 0.49 (eluent: EtOAc/PE = 1:1). Mp: 105 °C. $[\alpha]^{20}_D$: −4.40 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz): δ 2.85 [1H, d, *J* 8]; 3.78 [3H, s]; 4.29 [1H, dd, *J* 10, 8]; 4.74 [1H, s]; 4.93 [1H, d, *J* 12]; 4.94 [1H, d, *J* 12]; 5.01 [1H, d, *J* 12]; 5.12 [1H, s]; 5.14 [1H, d, *J* 12]; 5.43 [1H, d, *J* 10]; 6.44 [2H, broad s]; 6.85 [2H, d, *J* 8]; 7.20−7.40 [7H, m]. ^{13}C NMR (75 MHz): δ 47.1 (CH); 52.7 (CH); 55.2 (CH_3); 66.7 (CH_2); 66.8 (CH_2); 80.1 (CH); 83.9 (CH); 113.8 (CH); 128.3 (CH); 128.4 (CH); 128.5

(CH); 129.9 (CH); 130.1 (C); 135.2 (CH); 135.4 (C); 137.9 (CH); 156.0 (C); 159.5 (C); 171.6 (C). Anal. Calcd for $C_{23}H_{23}NO_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.38; H, 5.56; N, 3.37.

Compound (+)-**6** was obtained analogously. $[\alpha]^{20}_D$: +3.63 (*c* 2.00, $CHCl_3$).

Compound (+)-7. Compound (−)-**6** (0.35 g, 0.85 mmol) was dissolved in dry *N*,*N*-dimethylformamide (5 mL) at 0 °C. Sodium hydride (60% in mineral oil, 51 mg, 1.28 mmol) was added in small portions over a time of 30 min, and then benzyl bromide (0.25 mL, 2.14 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction was then quenched with HCl 1 N (20 mL) and the water phase extracted with diethyl ether (3 × 15 mL). The combined organic phase was dried over magnesium sulfate, concentrated in vacuo, and purified by flash chromatography (eluent: gradient from EtOAc/PE 3:7 to EtOAc/PE 1:1) yielding 0.38 g of pure product (yield 90%) as a colorless oil. R_f = 0.49 (eluent: EtOAc/PE = 3:7). $[\alpha]^{20}_D$: +54.0 (*c* 1.40, $CHCl_3$). ^{1}H NMR (CD_3CN, 300 MHz): δ 2.93 [1H, t, *J* 4]; 3.78 [3H, s]; 4.55−4.80 [4H, m]; 4.90−5.20 [5H, m]; 6.31 [1H, broad s]; 6.41 [1H, broad s]; 6.82 [2H, broad s]; 7.00−7.40 [12H, m]. ^{13}C NMR (CD_3CN, 75 MHz): δ 46.9 (CH); 48.8 (CH_2); 55.9 (CH_3); 60.7 (CH); 67.2 (CH_2); 67.9 (CH_2); 79.5 (CH); 84.7 (CH); 114.7 (CH); 127.2 (CH); 127.7 (CH); 129.0 (CH); 129.1 (CH); 129.4 (CH); 129.5 (CH); 130.6 (C); 136.7 (CH); 137.0 (CH); 137.2 (C); 140.5 (C); 157.7 (C); 160.5 (C); 171.7 (C). Anal. Calcd for $C_{30}H_{29}NO_6$: C, 72.13; H, 5.85; N, 2.80. Found: C, 72.15; H, 5.86; N, 2.67.

Compound (−)-**7** was obtained analogously. $[\alpha]^{20}_D$: −51.8 (*c* 1.02, $CHCl_3$).

Compound (+)-8. Compound (+)-**7** (1.35 g, 2.70 mmol) was dissolved in chloroform (15 mL), and trifluoroacetic acid (1.5 mL) was added at room temperature. After 1 h, the reaction was diluted with HCl 1 N (25 mL) and the phases were separated. The water phase was neutralized with solid sodium carbonate and extracted with methylene chloride (2 × 20 mL). The combined organics were dried over magnesium sulfate and concentrated in vacuo, yielding 0.81 g (90%) of secondary amine.

This product (0.81 g, 2.43 mmol) was dissolved in dioxane (8 mL), and NaOH 1 M (4 mL) was added. After 1 h, the dioxane was removed under reduced pressure, the resulting solution was diluted with water (5 mL), and ion-exchange resin DOWEX X8 (H^+) (5 g, 5mequiv/g) was added. The resin was then filtered and washed with water (30 mL) and then treated with NH_3 5% (40 mL) and filtered again. The ammonia solution was then lyophilized, yielding 0.60 g (2.43 mmol, quant.) of product as a white solid. Mp: 160 °C dec. $[\alpha]^{20}_D$: +102.1 (*c* 0.18, H_2O). ^{1}H NMR (D_2O, 300 MHz): δ 2.92 [1H, dd, *J* 5, 3]; 3.40 [1H, d, *J* 3]; 4.13 [2H, s]; 4.65 [2H, broad s]; 5.03 [1H, broad s]; 5.06 [1H, d, *J* 5]; 6.35 [1H, dd, *J* 6, 2]; 6.40 [1H, d, *J* 6, 2]; 7.29 [5H, s]. ^{13}C NMR (D_2O, 75 MHz): δ 50.6 (CH_2); 51.8 (CH); 61.4 (CH); 79.9 (CH); 81.1 (CH); 129.4 (CH); 129.8 (CH); 130.0 (CH); 130.8 (C); 133.7 (CH); 137.7 (CH); 175.9 (C). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.68; H, 6.06; N, 5.67.

Compound (−)-**8** was obtained analogously. $[\alpha]^{20}_D$: −99.8 (*c* 0.30, H_2O).

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Supporting Information Available: Detailed experimental procedures and complete product characterization data for compounds **9a**−**g**, **10a**−**g**, and **11a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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