A Novel One-Step Diastereo- and Enantioselective Formation of *trans*-Azetidinones and Its Application to the Total Synthesis of Cholesterol Absorption Inhibitors

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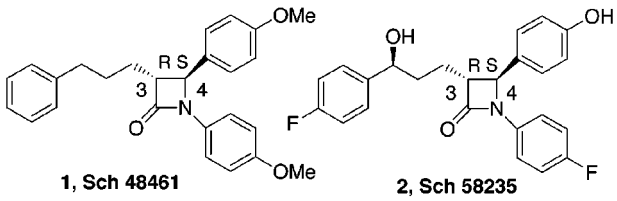
An efficient and practical asymmetric process was developed for the synthesis of azetidinone-based cholesterol absorption inhibitors. Key to this synthesis was the discovery of a novel one-step diastereo- and enantioselective formation of trans β-lactams starting from commercially available 3(*S*)-hydroxy-γ-lactone. Various trans β-lactams can be prepared in good yields and with better than 95:5 enantio- and diastereoselctivity. A Lewis acid-catalyzed aldol condensation and a highly enantioselective oxazaborolidine-catalyzed chiral reduction completes the side chain.

Introduction

Azetidinones are a very important class of compounds possessing a wide range of biological activities[1] and are also shown to be useful synthons for various pharmaceutical products.[2] Recently, trans azetidinones **1** and **2** have been found to be potent cholesterol absorption inhibitors (CAI) and have shown efficacy in clinical trials in reducing cholesterol levels.[3] Various synthetic methods have been developed to establish the two chiral centers on the β-lactam ring.[4] These include chiral auxiliary based chemistry,[5a] chiral pool derived methodologies,[5b] and catalytic asymmetric synthesis.[5c] For the synthesis of **1**, a variant of Evan's auxiliary-based chemistry was developed.[5a] In addition to the recovery of the auxiliary, this method required several steps to construct the β-lactam ring. For the synthesis of **2**, we designed and developed a short and practical process which provides an easy access for this type of β-lactam structure. Key to this synthesis was the discovery of a novel one-step diastereo- and enantioselective formation of trans β-lactams starting from commercially available 3(*S*)-hydroxy-γ-lactone.



Results and Discussion

Our synthetic strategy was to construct the β-lactam ring with the desired chiral centers followed by creation of needed side chain. The benzylic chiral center on the side chain could be obtained via an oxazaborolidine[6] or CBS-catalyzed reduction of a ketone precursor. For the synthesis of the β-lactam ring, we envisioned a one-step reaction between (*S*)-3-hydroxy-γ-lactone, **4**, and an appropriately substituted imine. A condensation reaction between an open-chain hydroxy ester and an imine are well documented but they give cis-β-lactams as the major product.[5b] Although condensation of lactone **4** with an aldehyde is known,[7] reaction with an imine has not been reported. However, this type of reaction offers an opportunity to form β-lactams in one step. Lactone **4** is readily derived from a glucose and is available commerciallly.[8] The existing hydroxy chiral center on the rigid lactone ring should induce the desired C-3 chiral center (Scheme 1).

Our early work started with generation of a dianion of lactone **4** with lithium diisopropylamide (LDA) at −35 °C in THF followed by addition of an imine and hexamethylphosporic triamide (HMPA) to give predominately the two adducts shown in Table 1. A warm up of the reaction did not drive the cyclization to completion. The low reactivity of the two intermediates is most likely due to the formation of stable lithium aggregates.[9] We speculated that an additional lithium salt may be able to form

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Scheme 1

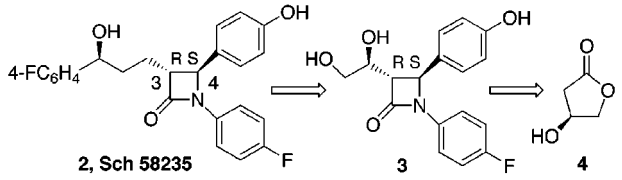
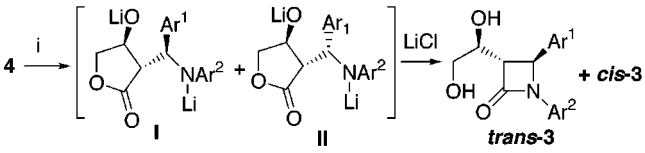


Table 1. Metal and Temperature Effects on Diastereoselectivity



i = 1) 2.2 eq. LDA; 2) $Ar^1CH{=}NAr^2$; Ar^1 = 4-$BnOC_6H_4$, Ar^2 = 4-F-C_6H_4

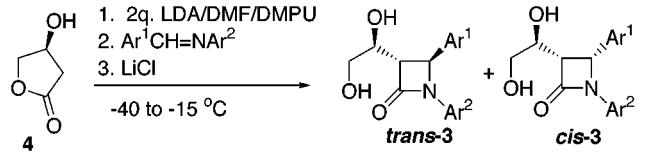
no.	base	temp, °C	convn, %	I:II	*trans*-**3**:*cis*-**3**[a]	yield, %[b]
1	Et_2Zn/LDA (1:1)	−25	80	11:89	40:60	7
2	LDA	−25	99	73:23	87:13	76
3	NaHMDA/LiHMDA	−25	65	86:14	99:1	46
4	LDA	−15	98	69:31	90:10	68
5	LDA	−35	99	79:21	90:10	78

[a] These are the ratios in reaction mixture. [b] These are total yield of *trans*- and *cis*-**3** as determined by HPLC.

mixed aggregates and increase the reactivity.[10] To our delight, addition of LiCl does accelerate the cyclization of these adducts to give a mixture of two β-lactams in 35% isolated yield. The imine condensation reaction gives exclusive control over C-3 but only moderate diastereoselectivity at the C-4 (or benzylic) position with an initial ratio of 73:27 (I:II) in favor of the desired *SSS* intermediate. The intermediate ratio was determined by HPLC on the quenched samples. We also observed that in this reaction the rate of cyclization of intermediate I to *trans*-**3** is about four times as fast as that of II to *cis*-**3**, enhancing the ratio of trans to cis from 73:27 (I:II) to 87:13 (*trans*-**3**:*cis*-**3**). To improve both the selectivity and the yield, this reaction was studied carefully using different metals, solvents, additives, concentrations, and temperatures. Examination of the cation effect on the diastereoselectivity indicated that the weaker the coordination ability the better the selectivity as shown in Table 1. For example, a 1:1 ratio of Et_2Zn/LDA gave an 11:89 ratio of I:II while 1:1 ratio of NaHMDA/LiHMDA reversed the ratio to 86:14. Hence, either the trans or the cis isomer can be obtained from this condensation reaction depending upon which metal is used. Chelation with either the enolate anion or the alkoxy anion may have played a role in the change of the selectivity.

Next we optimized the reaction conditions using LDA because it gave the best yield. *N*,*N*′-Dimethylpropyleneurea (DMPU) was introduced to replace the toxic HMPA. In the absence of either HMPA or DMPU, no addition takes place. It was also found that polar solvents, such as DMF, increased the reaction rate significantly. The selectivity could be further improved by carrying out the reaction at −35 °C. Reaction temperatures below −35 °C resulted in poor solubility of imines and slow reaction rate. A simple precipitation

Table 2. One-Step Formation of Trans β-Lactams



item	Ar^1	Ar^2	*trans*-**3**:*cis*-**3** in solution	HPLC yield, %	isolated yield, %[a]
3a	4-BnOPh-	4-MeOPh-	90:10	n/a	23
3b	4-BnOPh-	Ph-	86:14	70	70
3c	Ph-	Ph-	99:1	75	70
3	4-BnOPh-	4-FPh-	90:10	70	64
3d	Ph-	4-FPh-	92:8	68	62
3e	4-FPh-	4-FPh-	97:3	57	51

[a] In all cases, the ratios of *trans*-**3**:*cis*-**3** in isolated products were better than 95:5.

procedure was developed to further enhance the diastereomeric ratio in isolated **3** from 90:10 to better than 95:5. Under the optimized conditions, the reaction was scaled up to 300 g smoothly and the isolated yield improved from 35% to 64%. This reaction represents the first one-step enantio- and diastereoselective, high yielding, and practical synthesis of trans β-lactams starting from (*S*)-3-hydroxy-γ-lactone.

This one-step azetidinone formation is quite general for arylimines, and various trans β-lactams can be prepared as shown in Table 2. Three salient features deserve mention. First, the reaction works well with both electron-withdrawing and -donating substituents on the aromatic rings. Second, the diastereoselectivity of six reactions ranges from 86:14 to 99:1 in crude products. The ratios are further enhanced after crystallization. Third, good isolated yields were achieved for all examples except **3a** where solubility of the imine was poor. It is interesting to compare our results with a previous report where an open-chain 3-hydroxybutyrate was used as a starting material.[11] The predominant products in both cases have the same absolute stereochemistry for the β-lactam ring despite the opposite stereochemistry for the side-chain alcohols. This clearly demonstrates the effect of the butyrolactone ring on the dianion configuration and reactivity. A brief investigation indicated that this reaction does not work well with imines bearing alkyl groups.

With a good trans β-lactam method in hand, we turned our attention to elaborating the side chain of desired chirality. We envisioned an oxidation of the diol to an aldehyde followed by an aldol condensation to complete the side-chain framework (Scheme 2). Thus, the 95:5 ratio of **3** was first subjected to an oxidative cleavage with $NaIO_4$ to form aldehyde **5**. The cis isomer was not stable under the reaction conditions and epimerized at C-3 to give the opposite enantiomer of the desired product, resulting in a 100% trans β-lactam (90% ee.). LDA-promoted direct condensation of 4-fluoroacetophenone with aldehyde **5** gave a complex mixture, presumably due to enolate exchange. We solved this problem by carrying out the reaction under Mukaiyama aldol condensation conditions. First, enolization of 4-fluoroacetophenone with LDA followed by trapping with TMSCl gave enol trimethylsilyl ether in 95% yield. A $TiCl_4$-catalyzed reaction of enol trimethylsilyl ether with **5** afforded both diastereomers of hydroxy ketone **6**. The condensation

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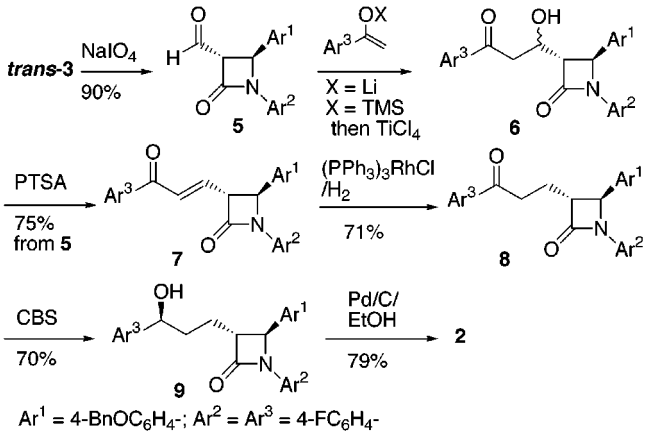
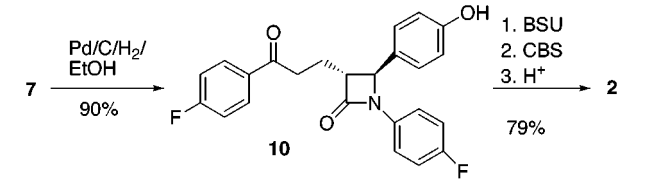
Scheme 2



Scheme 3



mixture must be quenched at low temperature to avoid any retro-aldol reaction. Without isolation, the reaction mixture was subjected directly to the dehydration conditions using PTSA and molecular sieves to give enone **7** in 75% isolated yield over two steps.

At this point, two different pathways were examined. The first began with reduction of the double bond in enone **7** with Wilkinson's catalyst to give saturated ketone **8** in 71% yield. A highly enantioselective reduction of ketone **8** with borane and CBS reagent gave alcohol **9** with a 98:2 selectivity of *S*:*R* at the benzylic position. Crystallization of this product removed 5% of the *SSR* diastereomer arising from *cis*-**3**. A catalytic hydrogenative removal of the benzyl group and crystallization was sufficient to purge the undesired *RRS* isomer and provide the final product **2** in 79% yield and excellent chiral purity (>99% ee).

Alternatively, a palladium-catalyzed double reduction in EtOH of both the double bond the benzyl group in enone **7** produced free phenol **10** in 90% yield. A direct chiral reduction of **10** with CBS reagent gave only 84% ee. Therefore, a three-step one-pot procedure was developed to convert the free phenol **10** to the final product (Scheme 3). Thus, the phenol was protected in situ as its trimethylsilyl ether using bis-trimethylsilyl urea (BSU) followed by a highly selective CBS reduction of the ketone group to give the required alcohol in 97% ee. The trimethylsilyl group was removed during the acidic workup, and the product crystallized to afford **2** in 79% overall yield from **10** and 99.7% ee.

In summary, we have discovered and developed an efficient, high-yielding, one-step process for the diastereo- and enantioselective formation of trans β-lactams and applied it successfully to the total synthesis of a novel cholesterol absorption inhibitor.

Experimental Section

All reactions were carried out under nitrogen. ^{1}H and ^{13}C NMR spectra (300 and 400 MHz) were recorded in $CDCl_3$ and are referenced to TMS unless otherwise noted. All starting materials were purchased commercially. Melting points are not corrected.

General Method Preparation of 3. To a dry 5-L three-necked flask equipped with a mechanical stirrer, thermometer, and addition funnel were added sequentially 500 mL of THF, 400 mL of DMPU, and 120 mL (0.92 mol) of diisopropylamine. To the cooled mixture at −40 to −45 °C was added dropwise 368 mL (0.92 mol) of 2.5 M *n*-BuLi hexane solution. After 20 min, 47 g (0.46 mol) of lactone **4** diluted in 250 mL of THF was introduced and the reaction was agitated at −40 to −45 °C for 2 h. To the resulting mixture was added dropwise a solution of 100 g (0.33 mol) of imine in 1 L of DMF over a period of 30 min. The reaction was maintained at −25 to −30 °C for 14−18 h and warmed to −13 to −17 °C for another 4 h. To the reaction mixture was added 14 g of LiCl dissolved in 400 mL of DMF. After another 2 h at −15 °C, 200 mL of HOAc was added to the reaction mixture.

The reaction mixture was poured slowly into a 10-L extractor containing 2 L of 3 N HCl, 1 L of ice, and 2.5 L of EtOAc. The mixture was stirred for 15 min and separated into layers. The aqueous layer was extracted with 2 × 1.0 L of EtOAc. The combined organic layers were washed with 4 × 2 L of brine and concentrated. Addition of 250 mL of toluene crystallized the *trans*-**3**. The solid was filtered and dried at 50 °C to give 85.5 g (64% yield) of *trans*-**3**. Mp: 119−120 °C. $[\alpha]^{24}_D = -69.78$ (*c* 0.12, THF). ^{1}H NMR: δ 7.45−7.28 (m, 5H), 7.28−7.18 (m, 4H), 6.95−6.85 (m, 4H), 5.04 (d, J = 2.0 Hz, 1H), 5.02 (s, 2H), 4.26−4.16 (m, 1H), 3.75−3.70 (m, 1H), 3.70−3.60 (m, 1H), 3.52 (d, J = 5.0 Hz, 1H), 3.15 (dd, J = 5.2, 2.0 Hz, 1H), 2.85 (t, J = 5.3 Hz, 1H). ^{13}C NMR: δ 165.6, 158.9, 160.2 & 157.8 (J = 244 Hz), 136.5, 133.4 and 133.3 (J = 2.0 Hz), 129.2, 128.6, 128.0, 127.4, 127.3, 118.6 & 118.5 (J = 7.8 Hz), 115.9 and 115.8 (J = 22.6 Hz), 115.4, 70.0, 69.3, 64.9, 62.7, 56.6. HRMS: 408.1619 ($M^+ + H$), calcd for $C_{24}H_{23}FNO_4$ 408.1611. Anal. Calcd for $C_{24}H_{23}FNO_4$: C, 70.75; H, 5.44; N, 3.44. Found: C, 70.57; H, 5.56; N, 3.41. IR (Nujol): 3330, 2920, 2870, 1740, 1520 cm^{-1}. ***cis*-3**. ^{1}H NMR δ 7.44−7.36 (m, 4H), 7.35−7.25 (m, 5H), 7.02−6.94 (m, 4H), 5.26 (d, J = 2.0 Hz, 1H), 5.05 (s, 2H), 3.95−3.85 (m, 1H), 3.72 (bs, 2H), 2.51 (t 1H). Also confirmed by NOE. Anal. Calcd for $C_{24}H_{23}FNO_4$: C, 70.75; H, 5.44; N, 3.44. Found: C, 70.54; H, 5.47; N, 3.56.

3a. The above general method was followed. The ratio of *trans*-**3a** to *cis*-**3a** isomer was 90:10, and the isolated yield of pure *trans*-**3a** was 23%. Mp: 135−136 °C. $[\alpha]^{23}_D = -63.8$ (*c* 0.54, MeOH). ^{1}H NMR: δ 7.45−7.35 (m, 5H), 7.30 (d, J = 8.7 Hz, 1H), 7.23 (d, J = 9.1 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 9.1 Hz, 1H), 5.06 (d, J = 2.4 Hz, 1H), 5.05 (s, 2H), 4.25 (dt, J = 3.8, 6.0 Hz, 1H), 3.79 (dd, J = 3.8, 11.3 Hz, 1H), 3.75 (s, 2H), 3.70 (dd, J = 6.0, 11.3 Hz, 1H), 3.19 (dd, J = 2.4, 6.0 Hz, 1H). ^{13}C NMR: δ 164.5, 158.5, 155.6, 136.2, 130.4, 129.2, 128.2, 127.6, 127.1, 126.9, 118.1, 114.9, 113.8, 69.6, 69.2, 64.6, 62.2, 56.3, 54.9. Anal. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 72.04; H, 6.48; N, 3.50. IR (Nujol): 3320, 2920. 2870, 1730, 1540 cm^{-1}.

3b. The above general method was followed. The ratio of trans to cis was 86:14 in the crude product, and 70% pure *trans*-**3b** was isolated. Mp: 158−160 °C. $[\alpha]^{25}_D = -40.1$ (*c* 0.33, MeOH). ^{1}H NMR: δ 7.50−7.25 (m, 11H), 7.20−6.95 (m, 3H), 5.11 (d, J = 2.3 Hz, 1H), 5.06 (s, 2H), 4.27 (dt, J = 3.7, 6.1 Hz, 1H), 3.81 (dd, J = 3.7, 11.2 Hz, 1H), 3.73 (dd, J = 6.2, 11.2 Hz, 1H), 2.22 (dd, J = 2.3 6.1 Hz, 1H). ^{13}C NMR: δ 165.2, 158.4, 136.8, 136.2, 129.2, 128.6, 128.2, 127.6, 127.1, 126.9, 123.6, 116.7, 114.9, 69.6, 69.1, 64.6, 62.3, 56.2. Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.68; H, 6.29; N, 3.67. IR (Nujol): 3380, 2920, 1740, 1525 cm^{-1}.

3c. The above general method was followed. The ratio of trans to cis was observed as 99:1 in the crude product, and a 70% isolated yield of *trans*-**3c** was obtained. Mp: 204−206 °C. $[\alpha]^{23}_D = -89.6$ (*c* 0.17, MeOH). ^{1}H NMR: δ 7.40−7.20 (m, 10H), 5.14 (d, J = 2.5 Hz, 1H), 4.27 (dt, J = 3.8. 6.2 Hz, 1H), 3.81 (dd, J = 3.8, 11.2 Hz, 1H), 3.74 (dd, J = 6.2, 11.2 Hz, 1H), 3.22(dd, J = 2.5, 6.2 Hz, 1H). ^{13}C NMR: δ 165.9, 138.2, 137.0, 128.8, 128.5, 127.6, 126.0, 123.0, 116.1, 67.95, 63.61, 62.11, 54.6. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94.

Found: C, 71.95; H, 6.34; N, 5.04. IR (Nujol): 3370, 2920, 2870, 1690, 1460 cm^{-1}.

3d. The above general method was followed. The ratio of trans to cis was 92:8 in the crude product, and 62% pure *trans*-**3d** was isolated. Mp: 203−205 °C. $[\alpha]^{23.3}_D = -82.1$ (*c* 0.38, EtOH). ^1H NMR: δ 7.36−7.32 (m, 5H), 7.23 (dd, J = 4.7, 9.0 Hz, 1H), 6.92 (t, J = 9.0 Hz, 1H), 5.10 (d, J = 2.4 Hz, 1H), 4.25 (dt, J = 3.8, 6.2 Hz, 1H), 3.79 (dd, J = 3.8, 11.2 Hz, 1H), 3.70 (dd, J = 6.2, 11.2 Hz, 1H), 3.21 (dd, J = 2.4, 5.8 Hz, 1H). Anal. Calcd for $C_{17}H_{16}FNO_3$: C, 67.76; H, 5.35; N, 4.65. Found: C, 67.74; H, 5.14; N, 4.56. IR (Nujol): 3380, 2920, 2870, 1720, 1500, 1470 cm^{-1}.

3e. The above general method was followed. The ratio of trans to cis isomer was 97:3 in the crude produc, and 51% pure *trans*-**3e** was isolated. Mp: 135−137 °C. $[\alpha]^{24}_D = -61.2$ (*c* 0.43 MeOH). ^1H NMR: δ 7.33 (dd, J = 5.2, 8.6 Hz, 1H), 7.30 (dd, J = 4.7, 9.0 Hz, 1H), 7.03 (t, J = 8.6 Hz, 1H), 6.92 (t, J = 9.0 Hz, 1H), 5.10 (d, J = 2.4 Hz, 1H), 4.23 (dt, J = 3.6, 5.8 Hz, 1H), 3.76 (dd, J = 3.6, 11.3 Hz, 1H), 3.66 (dd, J = 5.8, 11.3 Hz, 1H), 3.17 (dd, J = 2.4, 5.8 Hz, 1H). Anal. Calcd for $C_{17}H_{15}F_2NO_3$: C, 63.95; H, 4.73; N,4.39. Found: C, 63.83; H, 5.03; N, 4.40. IR (Nujol): 3380, 2920, 1725, 1600, 1470 cm^{-1}.

Preparation of 5. To a 2-L three-necked flask equipped with a mechanical stirrer, thermometer, and addition funnel were added sequentially 100 g (0.25 mmol) of *trans*-**3** and 800 mL of CH_3CN. To the cooled mixture at 10 °C was added dropwise over a period of 20 min 63 g (0.30 mmol) of $NaIO_4$ dissolved in 800 mL of water while maintaining the temperature below 20 °C. The reaction mixture was allowed to warm to rt and stirred for 2 h as followed by NMR. The reaction was poured into a 6-L extractor containing 1.5 L of ice−brine and 1.5 L of toluene. The layers were stirred and separated, and the aqueous layer was extracted with 500 mL of toluene. The combined organic layer was washed with 2 × 500 mL brine and concentrated to about 500 mL for the next reaction. The aldehyde is not very stable and gets hydrated quickly. An analytical sample can be obtained by concentrating the extract to dryness. $[\alpha]^{20}_D = +45°$ (*c* 1.9, $CHCl_3$). Mp: 76−78 °C. HRMS: 376.1348 ($M + H^+$), calcd for $C_{23}H_{19}FNO_3$ 376.1349. ^1H NMR: δ 9.82 (d, J = 1.3 Hz, 1H), 7.38−7.25 (m, 5H), 7.25−7.15 (m, 4H), 6.95−6.82 (m, 4H), 5.32 (d, J = 2.4 Hz, 1H), 4.98 (s, 2H), 4.15 (dd, J = 2.4, 1.3 Hz, 1H). Anal. Calcd for $C_{23}H_{18}FNO_3 \cdot 1/2H_2O$: C, 71.86; H, 4.98; H, 3.64. Found: C, 72.04; H, 5.06; N, 3.74. IR: 2920, 1745, 1730, 1620, 1520 cm^{-1}.

Preparation of 7. To a 1-L three-necked flask equipped with a mechanical stirrer, thermometer, and addition funnel were added at rt a solution of 100 g (0.27 mmol) of aldehyde **6** in 500 mL of toluene and 32 mL (0.27 mmol) of BF_3 etherate. To the cooled mixture at −30 °C was added dropwise 56 g (0.27 mmol) of enol ether. After stirring at −30 °C for 5 min, the aldol mixture was added dropwise into an ice-cold quench solution containing 1 L of saturated $NaHCO_3$, 2 L of *t*-BuOMe, and 150 mL of hydrogen peroxide (30%). The resulting mixture was allowed to warm to 15 to 20 °C, and the layers were separated. The aqueous layer was extracted with 1 L of toluene. The combined organic layer was washed with 2 × 500 mL of brine and concentrated to about 1 L for dehydration. An analytical sample was purified on a silica gel column eluting with EtOAc/hexanes (1:1) to give a diastereomeric mixture of **6** as a solid. ^1H NMR: δ 8.0−7.90 (m, 2H), 7.40−7.15 (m, 9H), 7.15 (t, J = 8.5 Hz, 2H), 7.02−6.90 (m 4H), 5.05 (d, J = 2.4 Hz, 1H), 5.00 (s, 2H), 4.65−4.55 (m, 1H), 3.65−3.57 (m, 1H), 3.42 (dd, J = 17.8, 2.4 Hz, 1H), 3.20−3.05 (m, 2H). Anal. Calcd for $C_{31}H_{25}F_2NO_3$: C, 72.50; H, 4.91; N, 2.73. Found: C, 72.32; H, 5.24; N, 2.80.

To the above 1 L toluene solution of aldol product were added 200 g of molecular sieves and 25 g (0.13 mmol) of *p*-toluenesulfonic acid monohydrate. This mixture was heated to 40−50 °C and monitored by proton NMR for about 2−4 h. The reaction was cooled to 0 °C and filtered through a pad of $MgSO_4$ and 100 g silica gel. The filtrate was concentrated for the next step. Alternatively, the concentrated solution was added to 400 mL of heptane to precipitate enone **7** (99 g, 75% overall yields). The compound is not stable on silica gel. HRMS: 496.1706 ($M + H^+$), calcd for $C_{31}H_{24}F_2NO_3$ 496.1724. ^1H NMR: δ 8.01 (dd, J = 8.6, 5.5 Hz, 1H), 7.50−7.25 (m, 7H), 7.25 (m, 6H), 7.18 (m, 2H), 7.22 (d, J = 8.5 Hz, 1H), 6.98 (t, J = 8.5 Hz, 1H), 5.08 (s, 2H), 4.88 (d, J = 2.4 Hz, 1H), 4.04−3.98 (m, 1H).

Preparation of 8. To crude **7** (ca. 80 mmol) dissolved in 120 mL of CH_2Cl_2 was added 2.2 g (2.4 mmol) of the catalyst, $(Ph_3P)_3RhCl$. The mixture was subjected hydrogenation at 60 psi for 18 h. Concentration of the reaction gave a residue of the product, which was separated by column with hexane and EtOAc (90:10) to give 27.5 g (71%) **8** as a solid. ^1H NMR: δ 7.98 (dd, J = 8.5, 5.5 Hz, 1H), 7.41 (m, 5H), 7.25 (m, 4H), 7.12 (t, J = 8.5 Hz, 2H), 6.55 (m, 4H), 5.04 (s, 2H), 4.68 (d, J = 2.1, 1H), 3.65 (m, 1H), 3.28 (m, 1H), 3.16 (m, 1H), 2.40 (m, 1H), 2.28 (m, 1H).

CBS Reduction to 9. The chiral catalyst was made by following the standard procedure: trimethylboroxine (28 mg, 0.22 mmol) was added into a solution of diphenylprolinol (75 mg, 0.3 mmol) in toluene (5 mL) and the resultant solution was heated until refluxing. Toluene was distilled, and another 5 mL of toluene was added and distilled out. The residue was used directly in the following reaction.

To a 250 mL oven-dried flask with a magnetic stirrer were added 6.2 g (12.5 mmol) of **8** and 60 mL of CH_2Cl_2. To the resulting solution at −20 °C were added sequentially 0.1 equiv of the chiral catalyst and 6.3 mL (12.5 mmol) of 2.0 N $BH_3 \cdot Me_2S$ over 2 h. The reaction mixture was allowed to warm to 0 °C for 1 h and quenched with methanol. The quenched solution was concentrated and extracted with CH_2Cl_2. The organic layer was concentrated, and the residue was recrystallized from EtOAc and hexanes to give 4.1 g (70%) of product **9**. The ee was determined by chiral HPLC. Mp: 132−134 °C. ^1H NMR: δ 7.45−7.20 (m, 11H), 7.05−6.90 (m, 6H), 5.05 (s, 2H), 4.72−4.69 (m, 1H), 4.57 (d, J = 2.2 Hz, 1H), 3.07 (dd, J = 7.6, 2.2 Hz, 1H), 2.36 (bs, 1H), 2.05−1.85 (m, 4H). ^{13}C NMR: δ 167.6, 163.4, 160.9, 160.1, 159.1, 157.8, 140.1, 140.0, 136.6, 133.9, 133.8, 129.6, 128.6, 128.1, 127.44, 127.40, 127.3, 127.1, 118.4, 118.3, 115.9, 115.6, 115.5, 115.4, 115.2, 73.0, 70.1, 61.1, 60.3, 36.6, 25.0. Anal. Calcd for $C_{31}H_{27}F_2NO_3$: C, 74.53; H, 5.45; N, 2.80. Found: 74.10; H, 5.43; N, 2.98. IR: 3490, 2920, 2850, 1720 cm^{-1}.

Debenzylation to 2. To a flask were added 1 g of Pd−C (5% by w/w), 11.4 g (181 mmol) of ammonium formate, 18.1 g (36.3 mmol) of **9**, and 250 mL of MeOH carefully at rt under N_2. HOAc was added to adjust the pH to 3−5, and the resultant mixture was heated at 45−55 °C until the reaction was finished as determined by TLC (about 2 to 3 h). During the reaction, the pH was controlled in the range of 3−5 by adding HOAc. The reaction was filtered and the solvent evaporated. The residue was dissolved in *t*-BuOMe and washed with water. After drying over Na_2SO_4 and evaporation the solvent, the product was purified by recrystallization in *t*-BuOMe/heptane and MeOH/water to give 11.75 g (79%) product with 99.4% ee. Mp: 155−157 °C. $[\alpha]^{24}_D = -32.6$ (*c* 0.34, MeOH). ^1H NMR: (DMSO-d_6) δ 9.54 (s, 1H), 7.32 (dd, J = 8.3, 5.7 Hz, 2H), 7.21 (m, H), 7.35 (m, 4H), 6.77 (d, J = 8.3 Hz, 2H), 5.3 (d, J = 4.6 Hz, 1H), 4.82 (d, J = 2.1 Hz, 1H), 4.50 (m, 1H), 3.10 (m, 1H), 1.70−1.90 (m, 4H). ^{13}C NMR: (DMSO-d_6) δ 167.4, 162.3 & 159.3 (J = 304.8 Hz), 159.9 and 156.9 (J = 303.3 Hz), 157.5, 142.3 and 142.3 (J = 2.9 Hz), 134.1 and 134.0 (J = 2.3 Hz), 128.0, 127.7, 127.7 and 127.6 (J = 7.1 Hz), 118.4 and 118.3 (J = 7.9 Hz), 116.0 and 115.8 (J = 22 Hz), 115.8, 114.9 and 114.7 (J = 21 Hz), 71.2, 59.7, 59.5, 36.5, 24.6. Anal. Calcd for $C_{24}H_{21}F_2NO_3$: C, 70.40; H, 5.14; N, 3.42; F 9.28. Found: C, 70.14; H, 5.21; N, 3.53; F 9.34. IR (Nujol): 3260, 2920, 1860, 1715, 1510 cm^{-1}.

Preparation of 10. To a 1-L Parr pressure bottle were added 0.8 g of palladium on carbon (10%), 1.6 g (19.0 mmol) of $NaHCO_3$, 16 g (32.3 mmol) of compound **6** in 80 mL of EtOAc, and 80 mL of methanol. The bottle was shaken under 30 psi of hydrogen pressure for 2 to 3 h and followed by TLC and HPLC. The reaction mixture was filtered through a pad of Celite and washed with 200 mL of toluene. The filtrate was washed with 200 mL of brine and 2 mL of 3 N HCl. After separation of the layers, the organic layer was concentrated to give 11.8 g (90% yield) of **10**. Mp: 60−62 °C. ^1H NMR: δ

7.95 (dd, J = 8.6, 5.5 Hz, 2H), 7.13−7.22 (m, 4H), 7.09 (t, J = 8.6 Hz, 2H), 6.91 (t, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.65 (d, J = 2.1 Hz, 1H), 3.26 (m, 1H), 2.33 (d, 1H), 2.25 (m, 1H)., ^{13}C NMR: δ 197.8, 167.7, 167.7 and 164.3 (J = 256 Hz), 160.7 and 157.5 (J = 243 Hz), 156.3, 133.8, 133.0, 130.9 and 130.8 (J = 9.4 Hz), 129.0, 127.5, 118.6 and 118.5 (J = 7.7 Hz), 116.2, 116.1 and 115.8 (J = 23 Hz), 116.0 and 115.7 (J = 22 Hz), 61.3, 59.7, 35.6, 23.3. Anal. Calcd for $C_{24}H_{19}NF_2O_3 \cdot 1/2H_2O$: C, 69.23; H, 4.80; N, 3.36; F, 9.13; O, 13.45. Found: C, 69.75; H, 4.47; N, 2.95; F, 9.11; O, 13.44. IR (Nujol): 3370, 2920, 2860, 1735, 1720, 1680, 1520 cm $^{-1}$.

One-Pot Reaction to 2. To a 50 mL oven-dried flask with a magnetic stirrer were added 2.4 g (5.9 mmol) of compound **10**, 10 mL of CH_2Cl_2, and 0.62 g (3.0 mmol) of bistrimethylsilyl urea (BSU). After 0.5 h, the reaction was filtered directly into another 50 mL oven-dried flask containing 0.05 equiv of the chiral catalyst at −20 °C. To this was added 2.3 mL (4.7 mmol) of 2 N $BH_3 \cdot Me_2S$. The reaction mixture was stirred at −15 to −20 °C for 3−5 h as monitored by TLC and HPLC. The reaction was quenched with 10 mL of methanol/HCl, and the resulting solution was concentrated to a residue. To the residue were added water and *t*-BuOMe. The layers were separated. Concentration of *t*-BuOMe layer lead to a recovery of >50% catalyst as the HCl salt after filtration. Crystallization of crude product from 2-propanol/H_2O afforded 1.9 g (79%) of **2** with >99.4% ee as determined by HPLC on a Chiralcel ODH column.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and IR spectra for **2**, **3**, **3a**, **3b**, **3c**, **3d**, **3e**, **5**, **7**, **8**, **9**, and **10**, also chiral HPLC chromatogram for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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