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Diastereoselective Arylithium Addition to an α-Trifluoromethyl Imine. Practical Synthesis of a Potent Cathepsin K Inhibitor

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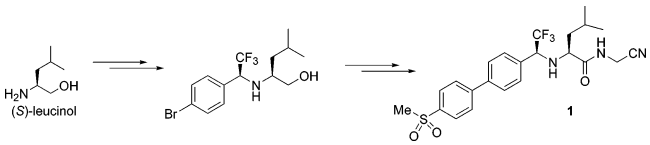

A practical, chromatography-free synthesis of potent cathepsin K inhibitor **1** is described. The addition of 4-bromophenyllithium to an α-trifluoromethylimine derived from commercially available (*S*)-leucinol was accomplished in a highly diastereoselective manner (97.6% de, 91% yield). Subsequent Suzuki cross-coupling afforded biaryl **7**. Oxidation of the alcohol and sulfide functionalities led to the formation of carboxylic acid **8**. Crystallization of **7** and acid **8** as its dicyclohexylamine salt gave excellent impurity rejection. The final amide coupling with commercially available aminoacetonitrile hydrochloride afforded **1** in excellent purity (99.6A% by HPLC, 100% de, <3 ppm Pd, W, Cr).

Osteoporosis is a disease characterized by low bone mass, resulting in skeletal fragility and a greater risk of fracture. It is known as the "silent disease", as bone loss often progresses over a number of years without showing any symptoms. In the United States alone, 10 million individuals are reported to already have osteoporosis and another 34 million are estimated to have low bone mass, placing them at an increased risk for osteoporosis. Each year, this disease is also responsible for more than 1.5 million fractures.[1] Cathepsin K, a member of the papain superfamily of cysteine proteases and one of a growing number of cysteinyl cathepsins (B, H, L, S, C, K, O, F, V, X, and W),[2] has been shown to be abundantly and selectively expressed in osteoclasts,[3] the cells that are responsible for bone resorption. Because of this unique and selective cellular distribution, it is believed that cathepsin K plays a key role in the osteoclast-mediated degradation of bone matrix. It has also been reported that cathepsin K can attack the collagen of adult human bone, which constitutes 90% of the organic matrix in bone.[4] It is postulated that molecules capable of selectively inhibiting cathepsin K may serve as useful therapeutic agents against diseases such as osteoporosis and other bone disorders involving excessive bone loss.

As part of an ongoing drug discovery program at our laboratories, compound **1**[5] was identified as a highly potent and selective inhibitor of cathepsin K. To enable further study of the pharmacological properties of **1**, we sought a scaleable chromatography-free synthesis suitable for the preparation of this compound in multigram quantities. A notable feature of **1** is the chiral, nonbasic α-trifluoromethylbenzylamine moiety ($pK_a \sim 1.5$). Stereoselective methods for the synthesis of perfluoroalkylamines have been the subject of recent reviews,[6] and several approaches were envisioned to achieve the synthesis of **1**. However, we were particularly interested in exploring synthetic routes from (*S*)-leucine derivatives given their commercial availability and the possibility of using the stereocenter to install the α-trifluoromethylamine center of **1** in a diastereoselective manner.

Our retrosynthetic analysis of **1** is illustrated in Scheme 1. We envisioned that the key (*S*)-α-trifluoromethylamine stereocenter could be set via diastereoselective addition of 4-bromophenyllithium to imine **4**. Subsequent Suzuki cross-coupling followed by sulfur and carbon oxidations would afford biaryl acid **8**. Amide coupling with commercially available aminoacetonitrile hydrochloride would complete the synthesis of **1**.

The condensation of (*S*)-leucinol **2** with trifluoroacetaldehyde methyl hemiacetal **3** in toluene in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) with the azeotropic removal of water/MeOH did not yield the desired imine **4**. Instead oxazolidine **5** was obtained as an ~2:1 mixture

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(1) *About Osteoporosis*, Fast Facts Sheet; National Osteoporosis Foundation: Washington, DC, October, 2004 (www.nof.org.).

(2) Drake, F. H.; Dodds, R. A.; James, I. E.; Connor, J. R.; Debouck, C.; Richardson, S.; Lee-Rykaczewski, E.; Coleman, L.; Rieman, D.; Barthlow, R.; Hastings, G.; Gowen, M. *J. Biol. Chem.* **1996**, *271*, 12511.

(3) (a) Bromme, D.; Okamoto, K.; Wang, B. B.; Biroc, S. *J. Biol. Chem.* **1996**, *271*, 2126. (b) Bossard, M. J.; Tomaszek, T. A.; Thompson, S. K.; Amegadzie, B. Y.; Hanning, C. R.; Jones, C.; Kurdyla, J. T.; McNulty, D. E.; Drake, F. H.; Gowen, M.; Levy, M. A. *J. Biol. Chem.* **1996**, *271*, 12517. (c) Tezuka, K.; Tezuka, Y.; Maejima, A.; Sato, T.; Nemoto, K.; Kamioka, H.; Hakeda, Y.; Kumegawa, M. *J. Biol. Chem.* **1994**, *269*, 1106.

(4) Garnero, P.; Borel, O.; Byrjalsen, I.; Ferras, M.; Drake, F. H.; McQueney, M. S.; Fogged, N. T. Delmas, P. D.; Delaisse, J. M. *J. Biol. Chem.* **1998**, *273*, 32347.

(5) Li, C. S.; Deschênes, D.; Desmarais, S.; Falgueyret, J.-P.; Gauthier, J. Y.; Kimmel, D. B.; Léger, S.; Massé, F.; McKay, D. J.; Percival, M. D.; Riendeau, D.; Rodan, S. B.; Somoza, J. R.; Thérien, M.; Truong, V.-L.; Wesolowski, G.; Zamboni, R.; Black, W. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1985.

(6) (a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999. (b) *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications and Future Directions*; Ramachandran, P. V., Ed.; American Chemical Society; Washington, DC, 1999. (c) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2436. (d) Wang, Y.; Mosher, H. S. *Tetrahedron Lett.* **1991**, *32*, 987. (e) Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 313. (f) Sakai, T.; Yan, F.; Kashino, S.; Uneyama, K. *Tetrahedron* **1996**, *52*, 233. (g) Enders, D.; Funabiki, K. *Org. Lett.* **2001**, *3*, 1575. (h) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P.; Van Meervelt, L.; Mischenki, N. *Tetrahedron Lett.* **1997**, *38*, 4671. (h) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847. (i) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589.

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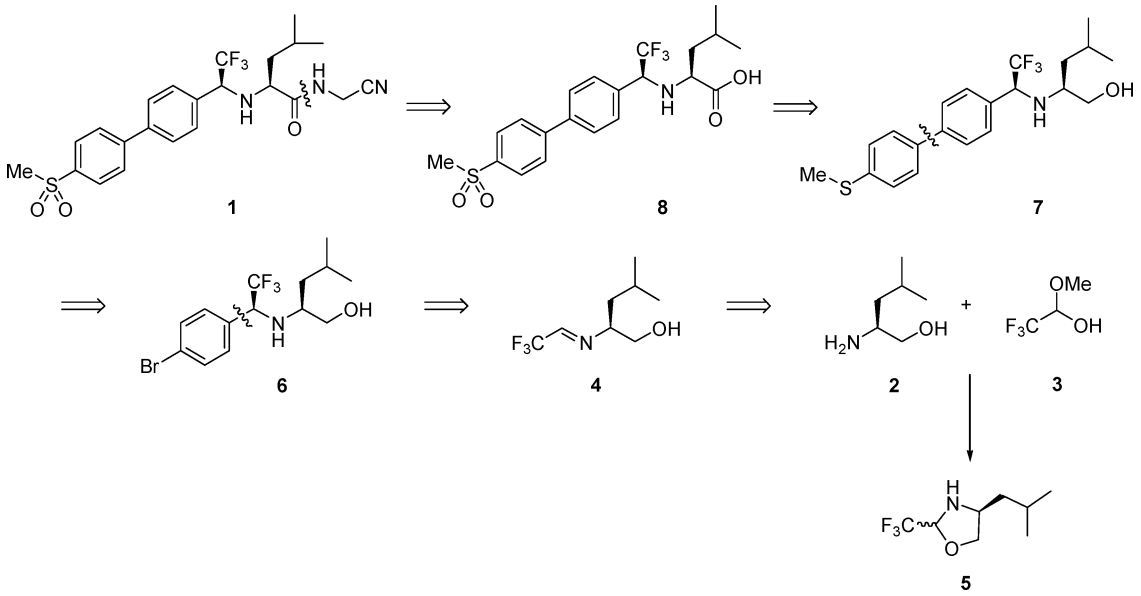
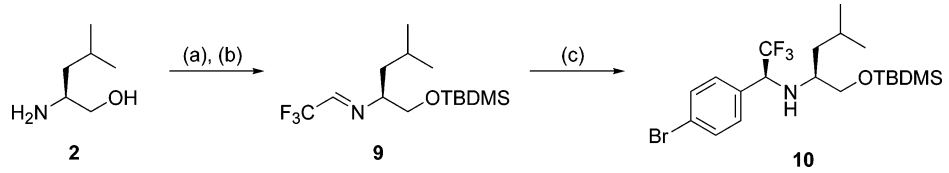
SCHEME 1. Retrosynthetic Analysis of 1



SCHEME 2. Organometallic Addition to *O*-TBDMS-Protected Imine 9[a]



[a] Reagents and conditions: (a) TBDMSCl, Et_3N, DMAP (cat.), toluene, rt (77%); (b) trifluoroacetaldehyde methyl hemiacetal **3**, ppts (cat.), toluene, reflux (70%); (c) 1,4-dibromobenzene, *n*-BuLi, THF, −78 °C then **9** (94%, 31:1 dr).

of diastereomers in high yield, and imine **4** was never observed. However, several groups have reported that the addition of organometallic species to 1,3-oxazolidine mixtures bearing an alkyl or aryl group at the 2-position gave the desired adducts in moderate to excellent yields and diastereoselectivities.[7] In our case, a preliminary investigation of the addition of aryllithium species at −78 °C to 2-trifluoromethyl-1,3-oxazolidine **5** gave good conversion to the desired adduct **6** but with no diastereoselectivity. Indeed, a 2:1 mixture of adduct **6** was obtained from a 2:1, *nonseparable* mixture of oxazolidine **5**. When Grignard reagents were employed, the reaction only took place at higher temperature (0 °C), and many byproducts were formed. In an analogous manner, the use of $BF_3{\cdot}OEt_2$ has been reported to promote the nucleophilic addition of aryl species to chiral 2-trifluoromethyl-1,3-oxazolidine through the corresponding trifluoromethyl-iminium ion.[8] When oxazolidine **5** was submitted to a variety of such reaction conditions, disappointingly low conversion or decomposition of the reaction mixture was observed, along with no diastereoselectivity.

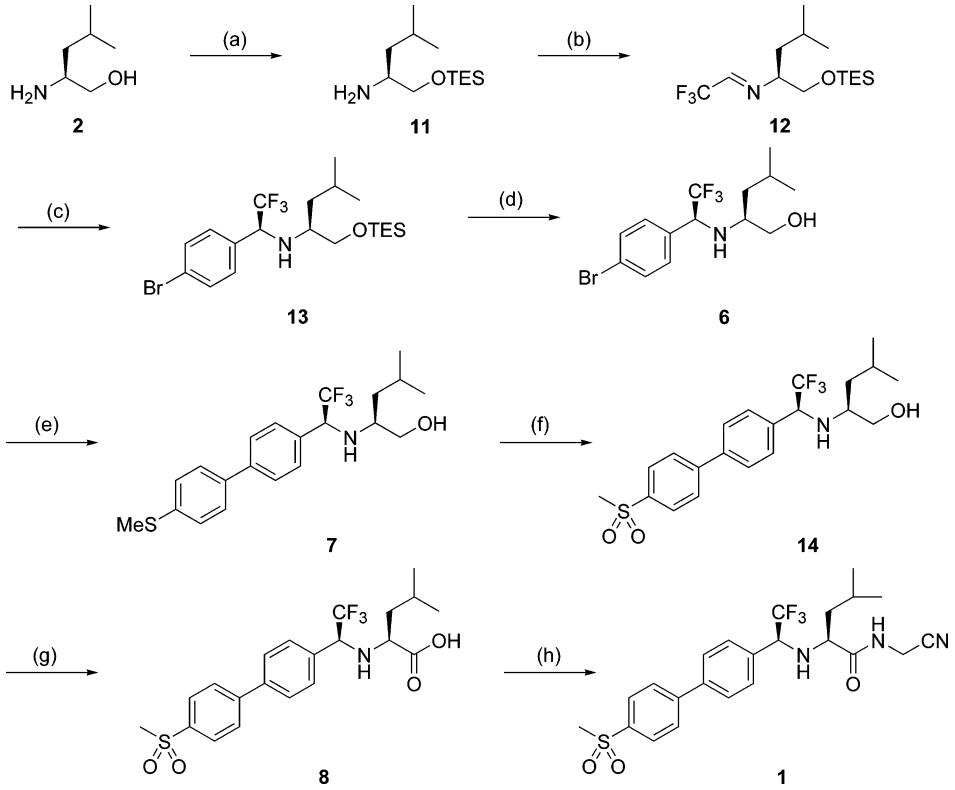
On the basis of our observed results, we postulated that the highly electron-withdrawing CF_3 group at the 2-position of **5** greatly enhances the electrophilicity of the imine carbon, thus, greatly shifting the equilibrium completely to the oxazolidine tautomer. We reasoned that installing a protecting group (PG) on the oxygen of (*S*)-leucinol would prevent the ring closure and thus enable preparation of the desired imine. A diastereoselective aryl addition to this imine would give access to the key 1-aryl-2,2,2-trifluoroethylamine intermediate **6** after deprotection. Thus, *tert*-butyldimethylsilyl (TBDMS) was employed as a PG, and the subsequent reaction of the protected adduct with trifluoroacetaldehyde methyl hemiacetal **3** furnished imine **9** in high yield as a single geometric *E* isomer by ^{1}H NMR (Scheme 2). The addition of 4-bromophenyllithium in THF at −78 °C cleanly and reproducibly provided adduct **10** in 94% yield and with 94% de (determined by HPLC) in favor of the desired (*S*,*S*)-diastereomer. The diastereoselectivity was similar in THF, THF/toluene, or MTBE. Confident that this approach would rapidly give us access to **1**, we began the development of a process suitable for a multigram-scale synthesis.

A number of groups were evaluated for the protection of the (*S*)-leucinol alcohol. An initial screen indicated that TBDMS and trimethylsilyl protection gave mixtures of *N*- and *O*-protected products. However, using chlorotriethylsilane (TESCl) only *O*-protection was observed. Thus, 250 g of (*S*)-leucinol **2** was *O*-protected using TESCl in toluene with Et_3N and a catalytic amount of DMAP (Scheme 3). $Et_3N{\cdot}HCl$ was removed by filtration, and the toluene solution was used directly for the imine formation. In general, good results were obtained by

(7) Although this strategy works well with nonfluorinated alkyl or aryl groups at the 2-position,[7a−c] lower selectivities have been reported in the case of 2-trifluoromethyl-1,3-oxazolidines, unless the diastereomeric oxazolidines are separated by column chromatography prior to addition of the organometallic species.[7d,e] (a) Takahashi, H.; Chida, Y.; Yoshii, T.; Suzuki, T.; Yanaura, S. *Chem. Pharm. Bull.* **1986**, *34*, 2071. (b) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340. (c) Pridgen, L. N.; Mokhallalati, M. K.; Wu, M.-J. *J. Org. Chem.* **1992**, *57*, 1237. (d) Higashiyama, K.; Ishii, A.; Mikami, K. *Synlett* **1997**, 1381. (e) Higashiyama, K.; Ishii, A.; Miyamoto, F.; Mikami, K. *Tetrahedron Lett.* **1998**, *39*, 1199.

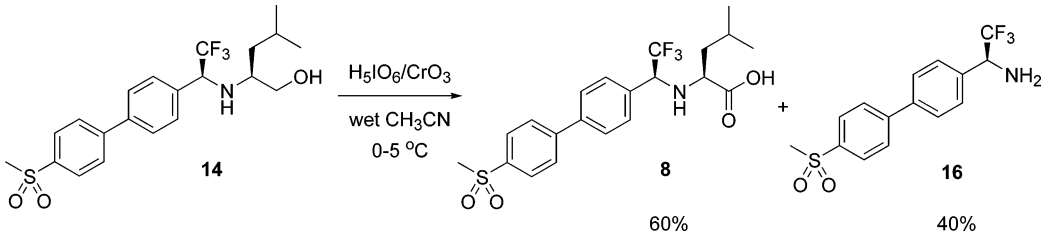
(8) Lebouvier, N.; Laroche, C.; Huguenot, F.; Brigaud, T. *Tetrahedron Lett.* **2002**, *43*, 2827.

SCHEME 3. Large-Scale Diastereoselective Synthesis of 1[a]



[a] Reagents and conditions: (a) TESCl, Et_3N, DMAP (cat), toluene, rt (100%); (b) trifluoroacetaldehyde methyl hemiacetal **3**, DMAP·HCl, toluene, reflux (80%); (c) 1,4-dibromobenzene, *n*-BuLi, THF, −78 °C then **12** (91%, 97.6% de); (d) TFA, THF/H_2O, 0 °C to room temperature (88%, 97.6% de); (e) 4-(methylthio)phenylboronic acid, $Pd(OAc)_2$, PPh_3, Na_2CO_3, *n*-PrOH/H_2O, 90 °C (78%, 100% de); (f) 30% H_2O_2, $Na_2WO_4 \cdot 2H_2O$ (cat.), Bu_4NHSO_4, toluene, rt (94%); (g) H_5IO_6, CrO_3 (cat.), CH_3CN, 5 °C (79%); (h) aminoacetonitrile·HCl, HATU, Et_3N, DMF, 0 °C (79%).

SCHEME 4



heating compound **11** in toluene with azeotropic removal of water/MeOH in the presence of a catalytic amount of acid. Interestingly, a cleaner reaction was obtained using residual DMAP·HCl in the toluene solution in place of PPTS. We also found that the order of operations had an influence on the yield of imine **12**. Indeed, adding hemiacetal **3** over 30 min to a refluxing solution of *O*-TES-leucinol **11** and DMAP·HCl in toluene prevented the formation of impurities and reproducibly afforded imine **12** in 80% yield over two steps.

An investigation of the halogen−metal exchange of 1,4-dibromobenzene indicated that the formation of 4,4′-dibromobiphenyl became significant when the *n*-BuLi addition time and age time after addition was greater than 30 min. Moreover, thorough degassing of the reaction mixture was required prior to the addition of *n*-BuLi to reduce the formation of oxidation byproducts.[9] The addition of 4-bromophenyllithium to imine **12** at −78 °C in THF proceeded smoothly and afforded clean aryl bromide **13** in 91% yield and 97.6% de.[10] It is noteworthy that similar diastereoselectivities were observed using *O*-TBDMS-, *O*-TES-, or *O*-Me-protected leucinol, suggesting that the diastereoselectivity is not influenced by the size or the complexing ability of the PG. Indeed, our results support the hypothesis that the nucleophile attacks the imine face flanked by the CH_2OPG group, rather than the larger *i*-Bu group. A number of conditions were investigated for the deprotection of TES ether **13**. The best results were obtained using 1.2 equiv of TFA in THF/H_2O from 0 °C to room temperature. Using this protocol, compound **13** was deprotected to yield alcohol **6** in 88% yield and 97.6% de. Interestingly, we observed that if the TFA was not quenched with a base prior to the workup, significant amounts (∼20%) of TES-protected adduct **13** were recovered, presumably due to reprotection during the workup.

(9) Bromophenol was identified and characterized as one of the impurities.

(10) Further improvements have been made to the diastereoselective organometallic addition sequence and are described in the following reference: Gosselin, F.; Roy, A.; O'Shea, P. D.; Chen, C.-y.; Volante, R. D. *Org. Lett.* **2004**, *6*, 641.

The use of aqueous NaOH as a quenching agent eliminated this side reaction.

4-(Methylthio)phenylboronic acid was prepared in 93% yield via halogen−metal exchange of 4-bromothioanisole in THF at −70 °C followed by quenching with triisopropyl borate. Among many conditions investigated for the Suzuki cross-coupling, the most effective protocol involved the use of $Pd(OAc)_2$ (2.5 mol %), PPh_3 (7.5 mol %), and Na_2CO_3 (2.7 equiv) as a base in *n*-propanol/water. After an aqueous workup, biaryl **7** was crystallized as a tan solid in 78% yield, with complete rejection of the undesired diastereomer. Initial attempts to oxidize sulfide **7** to sulfone **14** using OXONE were not successful, leading to decomposition of the starting sulfide. However, the oxidation proceeded smoothly at room temperature using 1 mol % $Na_2WO_4 \cdot 2H_2O$ in the presence of H_2O_2 in toluene under phase-transfer catalysis conditions to furnish sulfone **14** in excellent yield (94%).[11] Oxidation of the primary alcohol to the corresponding carboxylic acid **8** was performed with H_5IO_6 in the presence of a catalytic amount of CrO_3. Initial attempts using published conditions[12] (2.5 equiv of H_5IO_6, 1.2 mol % CrO_3, wet CH_3CN, 0−5 °C) gave complete consumption of starting material, however, a low yield (∼60%) of acid **8** was obtained. A closer examination of the reaction indicated that 2-aryl-2,2,2-trifluoroethylamine **16** was formed in significant quantity, presumably through oxidative cleavage of amino-alcohol **14** under the reaction conditions (Scheme 4). Increasing the quantity of oxidant to 5 equiv and conducting the oxidation in anhydrous CH_3CN minimized formation of **16** (10%), which could be readily rejected in the workup, and increased the yield to 79% for acid **8**. Moreover, no *N*-oxide product was seen under any oxidation conditions. Purification of the acid was achieved by crystallization of the dicyclohexylamine (DCHA) salt from isopropyl acetate.

Several coupling reagents were screened for the final amide coupling. While CDI did not afford any of the desired product, EDC·HCl showed complete conversion but with a maximum yield of 60%. Similarly, PyBOP gave good conversion but led to the formation of an impurity that proved difficult to remove. The amide coupling was finally performed with HATU and Et_3N in DMF at 0 °C, without necessitating the protection of the less-nucleophilic α-trifluoromethylamine. After a sodium bicarbonate quench and extractive workup, the product was crystallized from isopropyl acetate and heptane to give **1** in 79% yield and excellent purity (99.6A% by HPLC, <3 ppm Pd, W, Cr).

In conclusion, the discovery of a highly diastereoselective addition of 4-bromophenyllithium to imine **12** derived from commercially available (*S*)-leucinol allowed the rapid development of a scaleable synthesis of a potent and selective cathepsin K inhibitor. Crystallization of biphenyl adduct **7** and acid **8** as its DCHA salt gave excellent impurity rejection, and no chromatography was required in the process. Thus, **1** was prepared in 9 steps and with a 31% overall yield.

Experimental Section

[(1*S*)-1-(4-Bromophenyl)-2,2,2-trifluoroethyl]-((1*S*)-3-methyl-1-triethylsilanyloxymethylbutyl)amine (13). A 22-L 4-neck round-bottom flask equipped with a mechanical stirrer, a thermocouple, an addition funnel, and a N_2 inlet/outlet was charged with THF (6 L). 1,4-Dibromobenzene (439 g, 1.86 mol) was added in one portion, followed by additional THF (1.5 L). The mixture was degassed by bubbling N_2 through the solution for about 15 min. The mixture was then cooled to −74 °C using a MeOH/dry ice bath, and *n*-BuLi (1.6 M hexanes, 1.12 L, 1.79 mol) was added over 25 min via the addition funnel. The white slurry was aged at −74 °C for 15 min. Imine **4** (463.40 g, 1.49 mol) in THF (1.2 L) was then added over 45 min to the reaction mixture while keeping the temperature below −70 °C. The reaction mixture was stirred at −75 °C for 1 h. The mixture was quenched by the addition of saturated aqueous NH_4Cl (2 L) at −75 °C, followed by water (2 L), and the mixture was warmed to 20−25 °C. The batch was transferred to a 50-L extractor. Toluene (10 L) was added, and after agitation, the layers were cut. The organic layer was washed with water (2 L) and concentrated under reduced pressure (<40 °C). The residue was flushed with toluene (4 L) to give an orange oil containing the desired bromide (700 g at 91 wt % in toluene = 637 g, 91% yield, 97.6% de). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, 2H, J = 8.4 Hz), 7.25 (d, 2H, J = 8.3 Hz), 4.19 (m, 1H), 3.56 (dd, 1H, J_1 = 3.7 Hz, J_2 = 10.0 Hz), 3.35 (dd, 1H, J_1 = 7.3 Hz, J_2 = 9.9 Hz), 2.56 (m, 1H), 2.23 (br s, 1H), 1.57 (m, 1H), 1.21 (m, 2H), 0.89 (t, 9H, J = 7.9 Hz), 0.86 (d, 3H, J = 6.6 Hz), 0.78 (d, 3H, J = 6.6 Hz), 0.53 (q, 6H, J = 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.3, 131.7, 130.1, 125.3 (q, J = 281 Hz), 122.8, 65.2, 61.4 (q, J = 29 Hz), 54.8, 40.6, 24.9, 23.2, 22.6, 6.6, 4.3; HRMS calcd for $C_{20}H_{33}BrF_3NOSi$, 467.1467; found, 468.1544 [M + 1]; IR ($CDCl_3$, cm^{-1}) 2961, 2914, 2880, 1262, 1173, 907, 730; $[\alpha]^{20}_D$ +39.0 (c = 10.5, $CHCl_3$). Anal. Calcd for $C_{20}H_{33}BrF_3NOSi$: C, 51.28; H, 7.10; N, 2.99. Found: C, 51.55; H, 6.90; N, 2.89.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X.-Q.; Noyori, R. *Tetrahedron* **2001**, *57*, 2469.

(12) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323.