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Electroreductive Intramolecular Coupling of Chiral α-Imino Esters: Stereoselective Synthesis of Mixed Ketals of *cis*-2,4-Disubstituted Azetidine-3-ones

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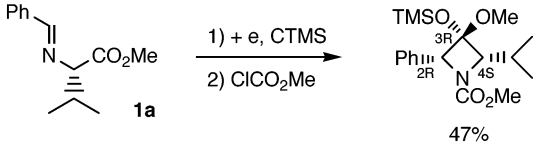
Abstract: The electroreduction of chiral aromatic α-imino esters prepared from (*S*)-α-amino acids, such as (*S*)-valine, (*S*)-leucine, and (*S*)-phenylalanine, in the presence of chlorotrimethylsilane and triethylamine afforded four-membered cyclized products, mixed ketals of *cis*-2,4-disubstituted azetidine-3-ones, stereospecifically (>99% de, 85−99% ee). The best result of the electroreductive cyclization was obtained using Bu_4NClO_4 as a supporting electrolyte and a Pt cathode. The absolute stereochemistry of the obtained single stereoisomers was confirmed to be 2*R*,3*R*,4*S* by X-ray crystallography. Calculations for the transition states of the cyclization support the stereospecific formation of the (2*R*,3*R*,4*S*)-isomers.

Introduction

Reductive cross-coupling of imines with carbonyl compounds is a promising method for the synthesis of functionalized amino compounds such as β-amino alcohols. Indeed, reductive intermolecular coupling of aromatic imines with aldehydes or ketones has been successfully realized using $NbCl_3(DME)$[1] and SmI_2[2] as a reducing agent. On the other hand, we have reported that electroreduction is also a useful tool for the reductive cross-coupling of aromatic imines with a variety of carbonyl compounds.[3] To the best of our knowledge, reductive intramolecular coupling of imino esters has so far been achieved only by the electrochemical method. In particular, the electroreduction of the chiral α-imino ester **1a** prepared from (*S*)-valine methyl ester and benzaldehyde gave a four-membered cyclized product, a mixed ketal of (2*R*,3*R*,4*S*)-2-isopropyl-4-phenylazetidine-3-one, stereospecifically (Scheme 1). Because this result is very interesting and is only one example, we decided to scrutinize this type of reaction in more detail. Azetidine-containing natural products are rare apart from β-lactams, although some azetidine alkaloids[4] have been known. However, a number of synthetic multisubstituted azetidines have been reported and utilized as chiral ligands.[5] Most of the methods that have so far been reported for the stereoselective synthesis of multisubstituted azetidines are based on intramolecular nucleophilic substitution.[5,6] In this paper, we report our further study on the electroreductive intramolecular coupling of chiral α-imino esters derived from readily available (*S*)-α-amino acids and aromatic aldehydes. The conditions for the electroreduction were optimized, the scope and limitations of the reductive cyclization were explored, and the stereostructure of the stereospecifically formed azetidines was confirmed by X-ray crystallography. Furthermore, the transition states for the electroreductive intramolecular coupling were calculated with semiempirical, ab initio, and DFT methods to explain theoretically the stereospecific formation of the multisubstituted azetidines.

Scheme 1

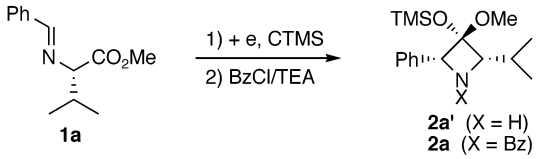


Results and Discussion

Conditions for the electroreduction of *N*-benzylidene (*S*)-valine methyl ester (**1a**) were investigated as summarized in Table 1. To verify the reproducibility of the previously reported results,[3] we initially carried out the electroreduction of **1a** in

(1) Roskamp, E, J.; Pedersen, S. F. *J. Am. Chem. Soc*. **1987**, *109*, 6551.
(2) (a) Machrouhi, F; Namy, J.-L. *Tetrahedron Lett*. **1999**, *40*, 1315. (b) Tanaka, Y; Taniguchi, N.; Uemura, M. *Org. Lett*. **2002**, *4*, 835.
(3) Shono, T.; Kise, N.; Kunimi, N.; Nomura, R. *Chem. Lett*. **1991**, 2191.
(4) (a) Kobayashi, J.; Cheng, J.; Ishibashi, M.; Walchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135. (b) Alvi, K. A.; Jaspars, M.; Crews, P. *Bioorg. Biomed. Chem. Lett*. **1994**, *4*, 2447.
(5) (a) Couty, F.; Prim, D. *Tetrahedron: Asymmetry* **2002**, *13*, 2619. (b) Hermsen, P. J.; Cremers, J. G. O.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett*. **2001**, *42*, 4243. (c) Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **2001**, *12*, 605. (d) Wilken, J.; Erny, S.; Wassmann, S.; Martens, J. *Tetrahedron: Asymmetry* **2000**, *11*, 2143. (e) Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 1673.
(6) For recent reports for the diastereoselective synthesis of racemic multisubstituted azetidines by nucleophilic substitution, see: (a) Salgado, A.; Dejaegher, Y.; Verniest, G.; Boeykens, M.; Gauthier, C.; Lopin, C.; Tehrani K. A.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 2231. (b) Salgado, A.; Boeykens, M.; Gauthier, C.; Declercq, J.-P.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 2763. By selenium-induced cyclization of homoallylamines, see: (c) Pannecoucke, X.; Outurquin, F.; Paulmier, C. *Eur. J. Org. Chem*. **2002**, 995. By bromo-amination of *N*-cinnamyl tosylamides, see: (d) Robin, S.; Rousseau, G. *Eur. J. Org. Chem*. **2000**, 3007. Recent reports for the asymmetric synthesis of multisubstituted azetidines by nucleophilic substitution, see: (e) Yoda, H.; Uemura, T.; Takabe, K. *Tetrahedron Lett*. **2003**, *44*, 977. (f) Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2002**, *13*, 297. (g) Agami, C.; Couty, F.; Rabasso, N. *Tertrahedron Lett*. **2002**, *43*, 4633. (h) Concellón, J. M.; Riego, E.; Bernad, P. L. *Org. Lett*. **2002**, *4*, 1299. (i) Concellón, J. M.; Bernad, P. L.; Pérez-Andrés, J. A. *Tetrahedron Lett*. **2000**, *41*, 1231. (j) Liu, D.-G.; Lin, G.-Q. *Tetrahedron Lett*. **1999**, *40*, 337.

Table 1. Electroreductive Coupling of **1a** to **2a**

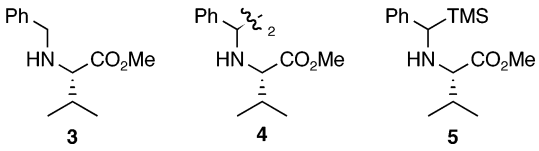


1a

entry	solvent[a]	additive[b]	cathode	yield (%) of **2a**[c]
1	Bu_4NClO_4/THF	CTMS/TEA	Pb	53
2	Bu_4NClO_4/THF	none	Pb	0[d]
3	Bu_4NClO_4/THF	CTMS	Pb	45
4	Bu_4NClO_4/DMF	CTMS/TEA	Pb	0[e]
5	Bu_4NBF_4/THF	CTMS/TEA	Pb	49
6	Bu_4NPF_6/THF	CTMS/TEA	Pb	54
7	Bu_4NBr/THF	CTMS/TEA	Pb	51
8	Bu_4NCl/THF	CTMS/TEA	Pb	43
9	$LiClO_4$/THF	CTMS/TEA	Pb	0[d]
10	Bu_4NClO_4/THF	CTMS/TEA	Pt	62
11	Bu_4NClO_4/THF	CTMS/TEA	Au	57
12	Bu_4NClO_4/THF	CTMS/TEA	Ag	54
13	Bu_4NClO_4/THF	CTMS/TEA	Cu	51
14	Bu_4NClO_4/THF	CTMS/TEA	Zn	48
15	Bu_4NClO_4/THF	CTMS/TEA	Sn	49
16	Bu_4NClO_4/THF	CTMS/TEA	Al	45

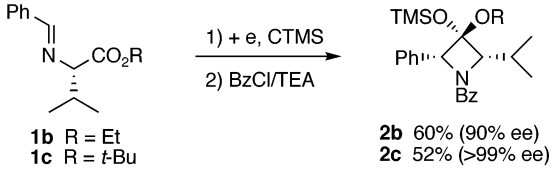
[a] 0.3 M electrolyte in solvent. [b] 5 equiv to **1a**. [c] Isolated yields. 85−88% ee. [d] Complex mixture was obtained with a small amount of **3**. [e] **1a** was recovered.

the presence of 5 equiv of chlorotrimethylsilane (CTMS) and triethylamine (TEA) in 0.3 M Bu_4NClO_4/THF (entry 1). Actually, (2*R*,3*R*,4*S*)-4-isopropyl-3-methoxy-2-phenyl-3-(trimethylsiloxy)azetidine (**2a′**) was produced as a single stereoisomer together with small amounts of simply reduced amine **3** (<5% yield), hydrodimer **4** (<5% yield),[7] and *N*-α-trimethysilylated product **5** (<10% yield). The cyclized product **2a′** was isolated as its *N*-benzoyl derivative **2a** in 53% yield and 88% ee (by ^{1}H NMR with Eu(hfc)$_3$) after treatment with BzCl−TEA, to simplify the purification of the somewhat unstable free azetidine **2a′**. The electroreduction of **1a** alone gave amine **3** (<20% yield) as only one isolatable product (entry 2). This result shows that CTMS is indispensable to promote the electroreductive intramolecular coupling. The addition of 5 equiv of CTMS to **1a** was the optimal condition (1 equiv of CTMS, 23% yield of **2a**; 2 equiv, 40%; 3 equiv, 47%; 8 equiv, 50%). Although the presence of TEA is not essential, the yield of **2a** decreased to some extent in the absence of TEA (entry 3). In DMF, the substrate **1a** was completely recovered (entry 4). Several tetrabutylammonium salts, which dissolve well in THF, were employed as a supporting electrolyte and gave comparable yields of **2a** (entries 1 and 5−8). The electroreduction with $LiClO_4$, however, produced a complex mixture in which a small amount of **3** (<10% yield) was detected (entry 9). In addition, the intramolecular coupling was less affected by the choice of cathode material; all cathode materials tested afforded **2a** in moderate yields (entries 11−16). Consequently, the best yield of **2a** (62% yield, 88% ee) was obtained with Bu_4NClO_4 as a supporting electrolyte and a Pt cathode (entry 10).



Next, we explored a range of substrates for this intramolecular coupling under the same conditions as entry 10 in Table 1. First,

Scheme 2



Scheme 3

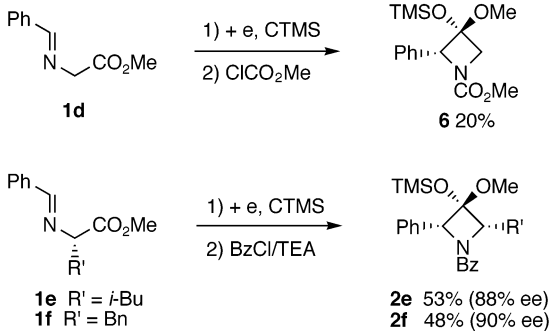
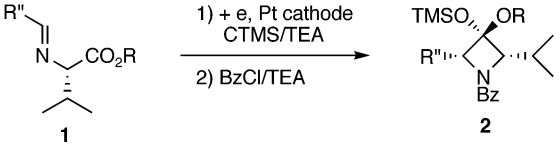


Table 2. Electroreductive Coupling of **1** to **2**[a]



1 **2**

entry	**1**	R″	R	**2**	yield (%)[b]
1	**1g**	*p*-$MeOC_6H_4$	Me	**2g**	60
2	**1h**	*m*-$MeOC_6H_4$	Me	**2h**	55
3	**1i**	*o*-$MeOC_6H_4$	Me	**2i**	41
4	**1j**	3,4-$(MeO)_2C_6H_3$	Me	**2j**	52
5	**1k**	*p*-FC_6H_4	Me	**2k**	47
6	**1l**	*p*-NCC_6H_4	Me	**2l**	34
7	**1m**	1-naphthyl	Me	**2m**	38
8	**1n**	2-naphthyl	Me	**2n**	60
9	**1o**	2-naphthyl	*t*-Bu	**2o**	52
10	**1p**	*t*-Bu	Me	**2p**	0[c]

[a] The electroreduction was carried out in 0.3 M Bu_4NClO_4/THF. [b] Isolated yields: **2g**−**2n** (85−90% ee), **2o** (>99% ee). [c] **1p** was recovered.

N-benzylidene (*S*)-valine ethyl ester (**1b**) and *tert*-butyl ester (**1c**) were subjected to electroreduction (Scheme 2). The corresponding azetidine derivatives were produced stereospecifically in moderate yields even from sterically hindered *tert*-butyl ester (**2c**: 52% yield). It is noted that the enantiomeric excess of **2c** was determined to be >99% by ^{1}H NMR with Eu(hfc)$_3$, while **2a** (88% ee) and **2b** (90% ee) were obtained in slightly lower ee values. This fact shows that *tert*-butyl ester **1c** entirely resists racemization under the conditions of electroreduction. Second, *N*-benzylideneamines prepared from some other α-amino acid methyl esters were employed (Scheme 3). As previously reported,[3] *N*-benzylidene glycine methyl ester (**1d**) brought about poor results (**6**: 20% yield), probably due to the instability of the starting imine **1d**. On the other hand, chiral *N*-benzylideneamines **1e** and **1f** derived from (*S*)-leucine and (*S*)-phenylalanine methyl ester, respectively, also gave azetidines **2a** and **2f** stereospecifically in yields similar to that obtained with **1a**. Finally, the effect of aryl-substitution on **1a** was examined as exhibited in Table 2. Whereas para- and meta-

(7) We have already reported the reductive dimerization of **1a** to **5** with Zn−MsOH: Kise, N.; Oike, H.; Okazaki, E.; Yoshimoto, M.; Shono, T. *J. Org. Chem.* **1995**, *60*, 3980.

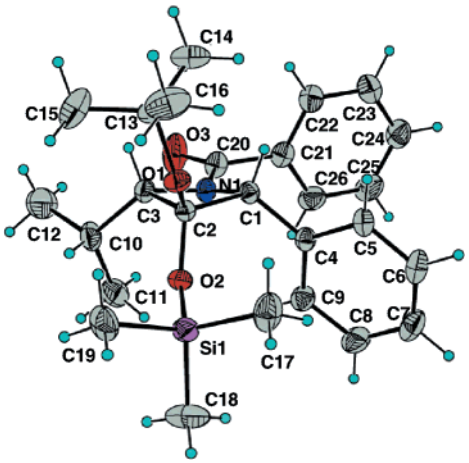


Figure 1. X-ray crystal structure of **2c**.

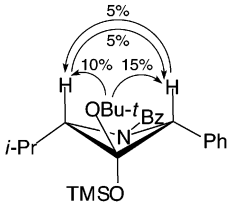


Figure 2. NOE enhancements in **2c**.

substitutions of an electron-donating group did not hinder the cyclization (entries 1, 2, 4, 8, and 9), ortho-substitution and a para-substituted electron-withdrawing group inhibited it (entries 3 and 5−7). All of the azetidines **2** were obtained as single stereoisomers. Unfortunately, aliphatic imine **1p** was not reduced under the same conditions (entry 10).

In the preliminary report,[3] the stereostructure of **2a′** was assigned by NOE experiments of its *N*-methoxycarbonylated analogue (Scheme 1). To ascertain the stereoconfiguration, we tried an X-ray crystallographic analysis of **2**. Fortunately, only **2c** crystallized among **2a**−**c** and **2e**−**o**, and its 2*R*,3*R*,4*S* configuration was confirmed conclusively (Figure 1). Additionally, reasonable NOE enhancements were observed in the ^{1}H NMR spectrum of **2c** (Figure 2). These results imply that the other azetidines **2** derived from chiral (*S*)-**1** also possess 2*R*,3*R*,4*S* configuration, although each stereoconfiguration could not be determined directly.

The presumed reaction mechanism of the electroreductive cyclization is illustrated in Scheme 4. The formation of an imine

Table 3. ^{1}H NMR Chemical Shifts of **1a** in the Presence of CTMS

CTMS (eq)	CH═N (δ)	NCHCO (δ)
0	8.24	3.67
0.5	8.53	4.15
1.0	8.77	4.47
2.0	8.82	4.53
3.0	8.85	4.56
5.0	8.91	4.62
5.0[a]	8.22	3.65

[a] 5 equiv of TEA was added.

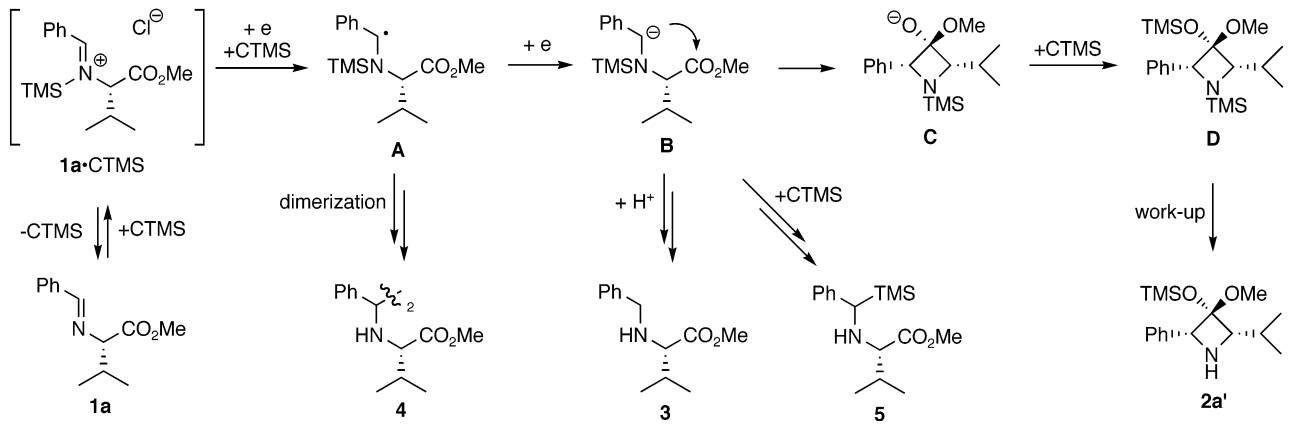
1a·CTMS complex was obvious from ^{1}H NMR analysis of **1a**; a lower field shift was measured in the imino and carbonyl-α methyne protons of **1a** by addition of CTMS to a solution of **1a** in $CDCl_3$ (Table 3). The formation of the **1a**·CTMS complex seems to not be necessary for the reductive coupling, because it dissociated into free **1a** by addition of TEA. Nevertheless, the reduction can be caused from **1a**·CTMS by the equilibrium of the formation of **1a**·CTMS even in the presence of TEA. The reduction potential of the iminium salt **1a**·CTMS is estimated to be less negative than that of **1a**, although reproducible data could not be obtained from the CV measurement of **1a**·CTMS. The radical **A** is generated by one-electron transfer to **1a**·CTMS and subsequent *N*-silylation, and then undergoes further one-electron transfer to form anion **B**. The carbanion in **B** attacks the ester carbonyl intramolecularly, and the following *O*-silylation of the resulting *O*-anion **C** yields **D**. After *N*-desilylation of **D** during workup, the product **2a′** is obtained.

Of the four possible isomers of **2a**, the 2*R*,3*R*,4*S*-isomer was formed predominantly as described above. The stereochemistry is determined kinetically in the cyclization step from anion **B** to **C**. Therefore, we calculated the transition states for the cyclization to compare their energies by semiempirical, ab initio, and DFT methods.[8] All calculations reveal that the transition state (*R*,*R*,*S*)-**TS** giving (2*R*,3*R*,4*S*)-**2a** is the most stable of the four transition states (Figure 3, Table 4).[9] These computational results support the stereospecificity in the electroreductive cyclization of **2**.

Conclusion

This paper describes a novel electroreductive intramolecular coupling of aromatic α-imino esters to give four-membered nitrogen heterocycles, azetidines. The presence of CTMS is essential for the electroreductive coupling. The present reaction provides a new method for the stereospecific synthesis of the

Scheme 4



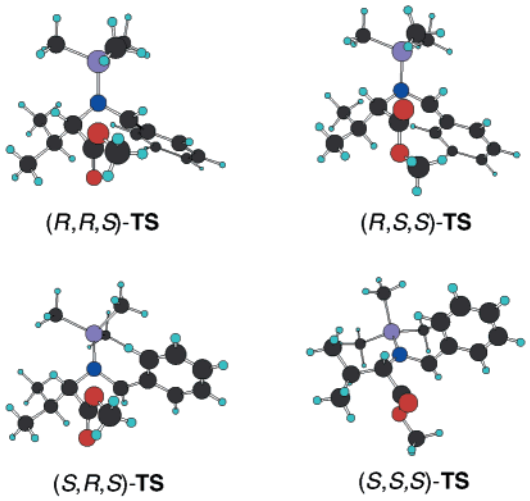


Figure 3. Optimized structures (RB3LYP/6-31G*) of transition states for the intramolecular coupling of **1a**.

Table 4. Relative Energies (kcal/mol) between Stereoisomers of Transition States for the Intramolecular Coupling of **1a**

method	(*R*,*R*,*S*)-**TS**	(*R*,*S*,*S*)-**TS**	(*S*,*R*,*S*)-**TS**	(*S*,*S*,*S*)-**TS**
RHF/AM1	0	0.94	1.42	2.64
RHF/PM3	0	1.42	3.50	6.79
RHF/6-31G*	0	1.78	5.75	5.09
RB3LYP/6-31G*	0	1.80	3.63	5.10

(2*R*,3*S*,4*S*)-isomers of the mixed ketals of *cis*-2,4-disubstituted azetidine-3-ones from (*S*)-α-amino acids. The 2*R*,3*R*,4*S* stereochemistry was confirmed with certainty by X-ray crystallography. Calculations for the transition states of the reductive cyclization gave convincing explanations for the stereospecific formation of the (2*R*,3*R*,4*S*)-azetidines.

Experimental Section

General. All ^{1}H and ^{13}C NMR spectra were measured on a JEOL GX-270 spectrometer with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Shimadzu FTIR-8300 infrared spectrometer. Optical rotations were obtained on a Jasco DIP-360 digital polarimeter. Column chromatography was performed on silica gel 60 or neutral alumina (Activity III). THF was distilled from sodium benzophenone ketyl radical. CTMS, TEA, and DMF were distilled from CaH_2. Aromatic α-imino esters **1** were synthesized by treatment of α-amino acid esters with aromatic aldehydes in dichloromethane in the presence of magnesium sulfate at room temperature and isolated by distillation in vacuo (**1a**, **1b**, **1e**−**n**, and **1p**) or by recrystallization from hexanes−ethyl acetate (**1c** and **1o**). Only **1d** was used without purification, because **1d** decomposed during distillation.

Typical Procedure for Electroreduction of 1. A 0.3 M solution of Bu_4NClO_4 in THF (15 mL) was placed in the cathodic chamber of a divided cell (40 mL beaker, 3 cm diameter, 6 cm height) equipped with a platinum cathode (5 × 5 cm^2), a platinum anode (2 × 1 cm^2), and a ceramic cylindrical diaphragm (1.5 cm diameter). A 0.3 M solution of Bu_4NClO_4 in DMF (4 mL) was placed in the anodic chamber (inside the diaphragm). Imino ester (**1a**) (219 mg, 1 mmol), CTMS (0.64 mL, 5 mmol), and triethylamine (0.70 mL, 5 mmol) were added to the cathodic chamber. After 300 C of electricity was passed at a constant current of 100 mA at room temperature, the catholyte was evaporated in vacuo. To the residue were added Et_2O (30 mL) and 1 M $NaHCO_3$ (30 mL). Insoluble Bu_4NClO_4 was filtered off, and the filtrate was extracted with Et_2O three times. After removal of the solvent, the residue was dissolved in THF (5 mL). To the solution were added benzoyl chloride (0.12 mL, 1 mmol) and TEA (0.21 mL, 1.5 mmol) at room temperature. The suspended mixture was stirred for 6 h, diluted with 1 M $NaHCO_3$ (10 mL), and then extracted with Et_2O three times. The crude mixture was purified by column chromatography on silica gel (hexanes−ethyl acetate, 50:1) to give **2a** in 62% yield. The enantiomeric excess of **2a** was measured by ^{1}H NMR with Eu(hfc)$_3$. The products **2a**, **2b**, and **2e**−**o** were isolated as colorless pastes or amorphous solids. Only **2c** was obtained as a single crystal by recrystallization from hexanes−ethyl acetate.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-isopropyl-3-methoxy-2-phenyl-3-(trimethylsiloxy)azetidine (2a). 88% ee. Colorless paste. R_f 0.61 (hexanes−ethyl acetate, 5:1). $[\alpha]^{25}_D$ −14.5 (c = 1.03, $CHCl_3$). IR (neat): 1653, 1603, 1580, 1497, 881, 843, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ −0.26 (s, 9H), 1.06 (d, 3H, J = 6.2 Hz), 1.18 (d, 3H, J = 6.8 Hz), 2.27−2.42 (m, 1H), 4.35 (d, 1H, J = 11.1 Hz), 4.90 (s, 1H), 7.05−7.12 (m, 2H), 7.21−7.44 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 0.95 (q), 19.71 (q), 20.11 (q), 29.50 (d), 50.19 (q), 75.02 (d), 79.63 (d), 100.48 (s), 127.47 (d), 128.12 (d), 128.16 (d), 128.37 (d), 128.92 (d), 130.63 (d), 133.48 (s), 138.13 (s), 175.67 (s). Anal. Calcd for $C_{23}H_{31}NO_3Si$: C, 69.48; H, 7.86; N, 3.52. Found: C, 69.63; H, 7.88; N, 3.36.

5. R_f 0.58 (hexanes−ethyl acetate, 10:1). $[\alpha]^{25}_D$ −109 (c = 1.47, $CHCl_3$). IR (neat): 1736, 1601, 839, 752, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ −0.03 (s, 9H), 0.89 (d, 3H, J = 7.0 Hz), 0.96 (d, 3H, J = 7.0 Hz), 1.74−1.92 (m, 1H), 2.91 (d, 1H, J = 6.2 Hz), 3.69 (s, 3H), 7.03−7.27 (m, 5H). ^{13}C NMR ($CDCl_3$): δ −3.89 (q), 18.63 (q), 19.61 (q), 31.72 (d), 50.94 (q), 54.90 (d), 66.19 (d), 125.05 (d), 126.84 (d), 127.62 (d), 142.06 (s), 175.80 (s). Anal. Calcd for $C_{16}H_{27}NO_2Si$: C, 66.48; H, 9.27; N, 4.77. Found: C, 69.63; H, 7.88; N, 3.36.

(2*R*,3*R*,4*S*)-1-Benzoyl-3-ethoxy-4-isopropyl-2-phenyl-3-(trimethylsiloxy)azetidine (2b). 90% ee. Colorless solid. R_f 0.54 (hexanes−ethyl acetate, 5:1). $[\alpha]^{23}_D$ 11.4 (c = 0.98, $CHCl_3$). IR (KBr): 1720, 1643, 1602, 1578, 1500, 934, 916, 881, 843, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ −0.27 (s, 9H), 1.04 (d, 3H, J = 6.5 Hz), 1.18 (d, 3H, J = 7.0 Hz), 1.22 (t, 3H, J = 7.3 Hz), 2.27−2.42 (m, 1H), 3.44−3.56 (m, 1H), 3.60−3.72 (m, 1H), 4.36 (d, 1H, J = 10.8 Hz), 4.94 (s, 1H), 7.05−7.12 (m, 2H), 7.22−7.43 (m, 8H). ^{13}C NMR ($CDCl_3$): δ −1.00 (q), 15.06 (q), 19.75 (q), 20.09 (q), 29.55 (d), 57.92 (t), 75.31 (d), 79.81 (d), 99.89 (s), 127.47 (d), 128.09 (d), 128.16 (d), 128.34 (d), 128.92 (d), 130.64 (d), 133.46 (s), 138.23 (s), 175.69 (s). Anal. Calcd for $C_{24}H_{33}NO_3Si$: C, 70.03; H, 8.08; N, 3.40. Found: C, 70.12; H, 8.12; N, 3.19.

(2*R*,3*R*,4*S*)-1-Benzoyl-3-*tert*-butoxy-4-isopropyl-2-phenyl-3-(trimethylsiloxy)azetidine (2c). >99% ee. Colorless solid. R_f 0.56 (hexanes−ethyl acetate, 5:1). mp 97−98 °C. $[\alpha]^{21}_D$ −8.7 (c = 1.0, $CHCl_3$). IR (KBr): 1647, 1495, 880, 843, 766, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ −0.24 (s, 9H), 1.07 (d, 3H, J = 6.2 Hz), 1.19 (d, 3H, J = 7.0 Hz), 1.40 (s, 3H), 2.40−2.55 (m, 1H), 4.84 (d, 1H, J = 10.0 Hz), 4.97 (s, 1H), 7.05−7.13 (m, 2H), 7.21−7.39 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 1.34 (q), 20.07 (q), 30.19 (d), 30.45 (q), 76.28 (s), 76.55 (d), 82.74 (d), 99.52 (s), 127.44 (d), 127.77 (d), 127.91 (d), 128.64 (d), 130.25 (d), 130.43 (d), 133.80 (s), 138.38 (s), 175.69 (s). Anal.

(8) The calculations were carried out using the Gaussian 98W program: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J. Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98W*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

(9) It was confirmed that the optimized structures had only one imaginary frequency according to the vibration analysis. The imaginary frequency was verified to be consistent with the intramolecular coupling by displaying the vibrational mode using the Gauss View program.

Calcd for $C_{26}H_{37}NO_3Si$: C, 71.03; H, 8.48; N, 3.19. Found: C, 71.07; H, 8.48; N, 3.12.

3-Methoxy-1-methoxycarbonyl-2-phenyl-3-(trimethylsiloxy)azetidine (6). Colorless paste. R_f 0.37 (hexanes−ethyl acetate, 5:1). IR (neat): 1828, 1713, 1605, 1497, 941, 868, 845, 756, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.05 (s, 9H), 3.33 (s, 3H), 3.62 (s, 3H), 4.04 (dd, 1H, J = 1.1, 8.9 Hz), 4.19 (d, 1H, J = 8.9 Hz), 5.22 (s, 1H), 7.23−7.38 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 0.81 (q), 49.75 (q), 52.42 (q), 61.95 (t), 75.58 (d), 97.62 (s), 127.35 (d), 127.76 (d), 136.21 (s), 157.15 (s). Anal. Calcd for $C_{15}H_{23}NO_4Si$: C, 58.22; H, 7.49; N, 4.53. Found: C, 58.32; H, 7.53; N, 4.38.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-isobutyl-3-methoxy-2-phenyl-3-(trimethylsiloxy)azetidine (2e). 86% ee. Colorless solid. R_f 0.45 (hexanes−ethyl acetate, 5:1). $[\alpha]^{23}_D$ 0.02 (c = 1.06, $CHCl_3$). IR (KBr): 1649, 1601, 1580, 1495, 885, 845, 721, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.23 (s, 9H), 1.04 (d, 6H, J = 5.9 Hz), 1.73−1.86 (m, 3H), 3.33 (s, 3H), 4.70 (t, 1H, J = 6.8 Hz), 5.07 (s, 1H), 7.05−7.16 (m, 2H), 7.23−7.40 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 0.99 (q), 22.53 (q), 23.38 (q), 25.31 (d), 39.40 (t), 50.37 (q), 68.77 (d), 78.37 (d), 100.53 (s), 127.56 (d), 127.75 (d), 128.00 (d), 128.19 (d), 128.78 (d), 130.32 (d), 133.80 (s), 137.44 (s), 173.75 (s). Anal. Calcd for $C_{24}H_{33}NO_3Si$: C, 70.03; H, 8.08; N, 3.40. Found: C, 70.21; H, 8.13; N, 3.16.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-benzyl-3-methoxy-2-phenyl-3-(trimethylsiloxy)azetidine (2f). 88% ee. Colorless paste. R_f 0.39 (hexanes−ethyl acetate, 5:1). $[\alpha]^{26}_D$ −1.3 (c = 0.75, $CHCl_3$). IR (neat): 1645, 1602, 1578, 1495, 885, 841, 754, 721, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.28 (s, 9H), 2.80 (s, 3H), 3.27−3.50 (m, 2H), 4.80 (dd, 1H, J = 3.5, 10.5 Hz), 5.06 (s, 1H), 7.08−7.42 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 1.00 (q), 35.99 (t), 50.75 (q), 71.48 (d), 78.55 (d), 101.04 (s), 126.08 (d), 127.58 (d), 127.67 (d), 128.03 (d), 128.25 (d), 129.31 (d), 129.81 (d), 130.31 (d), 133.88 (s), 137.19 (s), 138.21 (s), 173.69 (s). Anal. Calcd for $C_{27}H_{31}NO_3Si$: C, 72.77; H, 7.01; N, 3.28. Found: C, 72.95; H, 7.12; N, 3.11.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-isopropyl-3-methoxy-2-(4-methoxyphenyl)-3-(trimethylsiloxy)azetidine (2g). 88% ee. Colorless paste. R_f 0.46 (hexanes−ethyl acetate, 5:1). $[\alpha]^{25}_D$ −7.5 (c = 1.00, $CHCl_3$). IR (neat): 3447, 1650, 1611, 1580, 1514, 984, 926, 883, 843, 797, 702, 675 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.23 (s, 9H), 1.06 (d, 3H, J = 6.5 Hz), 1.17 (d, 3H, J = 6.8 Hz), 2.25−2.40 (m, 1H), 3.32 (s, 3H), 3.86 (s, 3H), 4.31 (d, 1H, J = 10.8 Hz), 4.83 (s, 1H), 6.90−6.95 (m, 2H), 7.07−7.14 (m, 2H), 7.18−7.33 (m, 6H). ^{13}C NMR ($CDCl_3$): δ −0.99 (q), 19.70 (q), 20.11 (q), 29.54 (d), 50.16 (q), 55.27 (q), 74.70 (d), 79.20 (d), 100.53 (s), 113.79 (d), 127.42 (d), 128.17 (d), 130.27 (d), 130.36 (s), 130.57 (d), 133.58 (s), 159.51 (s), 175.72 (s). Anal. Calcd for $C_{24}H_{33}NO_4Si$: C, 67.41; H, 7.78; N, 3.28. Found: C, 67.48; H, 7.85; N, 3.23.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-isopropyl-3-methoxy-2-(3-methoxyphenyl)-3-(trimethylsiloxy)azetidine (2h). 87% ee. Colorless paste. R_f 0.42 (hexanes−ethyl acetate, 5:1). $[\alpha]^{23}_D$ 2.6 (c = 2.9, $CHCl_3$). IR (neat): 1651, 1603, 1585, 1491, 935, 845, 716, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.22 (s, 9H), 1.05 (d, 3H, J = 6.2 Hz), 1.18 (d, 3H, J = 6.8 Hz), 2.26−2.42 (m, 1H), 3.32 (s, 3H), 3.83 (s, 3H), 4.33 (d, 1H, J = 11.1 Hz), 4.88 (s, 1H), 6.85−6.94 (m, 3H), 7.08−7.15 (m, 2H), 7.26−7.34 (m, 4H). ^{13}C NMR ($CDCl_3$): δ −1.03 (q), 19.66 (q), 20.16 (q), 29.57 (d), 50.19 (q), 55.25 (q), 75.16 (d), 79.57 (d), 110.49 (s), 113.85 (d), 114.23 (d), 121.35 (d), 127.57 (d), 128.18 (d), 129.44 (d), 130.73 (d), 133.40 (s), 139.74 (s), 159.70 (s), 175.56 (s). Anal. Calcd for $C_{24}H_{33}NO_4Si$: C, 67.41; H, 7.78; N, 3.28. Found: C, 67.58; H, 7.90; N, 3.01.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-isopropyl-3-methoxy-2-(2-methoxyphenyl)-3-(trimethylsiloxy)azetidine (2i). 90% ee. Colorless paste. R_f 0.38 (hexanes−ethyl acetate, 5:1). $[\alpha]^{21}_D$ −1.6 (c = 1.26, $CHCl_3$). IR (neat): 1720, 1651, 1603, 1580, 1493, 932, 883, 843, 754, 719, 704 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.24 (s, 9H), 1.04 (d, 3H, J = 6.8 Hz), 1.18 (d, 3H, J = 7.0 Hz), 2.48−2.63 (m, 1H), 3.33 (s, 3H), 3.58 (s, 3H), 4.32 (d, 1H, J = 11.1 Hz), 5.47 (s, 1H), 6.82 (dd, 1H, J = 0.8, 8.4 Hz), 7.05−7.13 (m, 3H), 7.23−7.36 (m, 4H), 7.65 (dd, 1H, J = 1.9, 7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 0.71 (q), 19.78 (q), 20.12 (q), 29.35 (d), 50.29 (q), 55.02 (q), 72.17 (d), 75.36 (d), 100.80 (s), 110.35 (d), 120.72 (d), 126.56 (s), 127.33 (d), 127.88 (d), 129.16 (d), 129.74 (d), 130.35 (d), 133.66 (s), 156.82 (s), 175.66 (s). Anal. Calcd for $C_{24}H_{33}NO_4Si$: C, 67.41; H, 7.78; N, 3.28. Found: C, 67.52; H, 7.88; N, 3.10.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-isopropyl-3-methoxy-2-(3,4-dimethoxyphenyl)-3-(trimethylsiloxy)azetidine (2j). 90% ee. Colorless paste. R_f 0.61 (hexanes−ethyl acetate, 2:1). $[\alpha]^{27}_D$ −8.0 (c = 0.88, $CHCl_3$). IR (neat): 1651, 1605, 1593, 1580, 1516, 924, 845, 799, 733, 712, 696 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.21 (s, 9H), 1.07 (d, 3H, J = 6.5 Hz), 1.18 (d, 3H, J = 6.8 Hz), 2.25−2.41 (m, 1H), 3.32 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 4.32 (d, 1H, J = 10.5 Hz), 4.83 (s, 1H), 6.80 (dd, 1H, J = 1.6, 8.4 Hz), 6.88 (d, 1H, J = 8.4 Hz), 6.92 (d, 1H, J = 1.6 Hz), 7.08−7.16 (m, 2H), 7.24−7.34 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 0.98 (q), 19.43 (q), 20.10 (q), 29.55 (d), 50.08 (q), 55.68 (q), 55.88 (q), 74.68 (d), 79.30 (d), 100.43 (s), 110.96 (d), 111.94 (d), 121.54 (d), 127.39 (d), 128.09 (d), 130.55 (d), 130.73 (s), 133.39 (s), 148.85 (s), 175.46 (s). Anal. Calcd for $C_{25}H_{35}NO_5Si$: C, 65.61; H, 7.71; N, 3.06. Found: C, 65.78; H, 7.80; N, 2.90.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-isopropyl-3-methoxy-2-(4-fluorophenyl)-3-(trimethylsiloxy)azetidine (2k). 87% ee. Colorless paste. R_f 0.4 (hexanes−ethyl acetate, 5:1). $[\alpha]^{23}_D$ 27.0 (c = 1.1, $CHCl_3$). IR (neat): 1651, 1603, 1508, 928, 883, 853, 719, 704 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.23 (s, 9H), 1.06 (d, 3H, J = 6.5 Hz), 1.17 (d, 3H, J = 7.0 Hz), 2.22−2.38 (m, 1H), 3.33 (s, 3H), 4.34 (d, 1H, J = 10.8 Hz), 4.86 (s, 1H), 7.06−7.15 (m, 4H), 7.18−7.22 (m, 2H), 7.24−7.34 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 1.05 (q), 19.70 (q), 20.11 (q), 29.65 (d), 50.34 (q), 74.84 (d), 78.79 (d), 100.38 (s), 115.36 (d, J_{CCF} = 21.7 Hz), 127.56 (d), 128.06 (d), 130.72 (d, J_{CCCF} = 8.4 Hz), 130.74 (d), 133.55 (d), 134.19 (s, J_{CCCCF} = 2.8 Hz), 162.56 (s, J_{CF} = 245.4 Hz), 175.82 (s). Anal. Calcd for $C_{26}H_{37}NO_6Si$: C, 64.04; H, 7.65; N, 2.87. Found: C, 64.08; H, 7.70; N, 2.71.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-isopropyl-3-methoxy-2-(4-cyanophenyl)-3-(trimethylsiloxy)azetidine (2l). 85% ee. Colorless paste. R_f 0.63 (hexanes−ethyl acetate, 2:1). $[\alpha]^{24}_D$ −39.7 (c = 0.88, $CHCl_3$). IR (neat): 2230, 1734, 1701, 1655, 1609, 1580, 935, 881, 847, 733, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.24 (s, 9H), 1.05 (d, 3H, J = 6.5 Hz), 1.17 (d, 3H, J = 6.8 Hz), 2.16−2.34 (m, 1H), 3.34 (s, 3H), 4.39 (d, 1H, J = 10.8 Hz), 4.95 (s, 1H), 7.08−7.20 (m, 3H), 7.29−7.36 (m, 2H), 7.41−7.46 (m, 2H), 7.69−7.74 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 1.05 (q), 19.56 (q), 19.93 (q), 29.53 (d), 50.44 (q), 75.11 (d), 78.54 (d), 100.28 (s), 111.92 (s), 118.31 (s), 127.67 (d), 127.72 (d), 129.41 (d), 130.85 (d), 132.08 (d), 133.22 (s), 143.47 (s), 175.50 (s). Anal. Calcd for $C_{24}H_{30}N_2O_3Si$: C, 68.21; H, 7.16; N, 6.63. Found: C, 68.27; H, 7.20; N, 6.45.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-isopropyl-3-methoxy-2-(1-naphthyl)-3-(trimethylsiloxy)azetidine (2m). 90% ee. Colorless paste. R_f 0.51 (hexanes−ethyl acetate, 5:1). $[\alpha]^{26}_D$ 1.2 (c = 0.89, $CHCl_3$). IR (neat): 1719, 1651, 1599, 1578, 1512, 941, 885, 845, 799, 779, 733, 712 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.55 (s, 9H), 1.03 (d, 3H, J = 6.5 Hz), 1.26 (d, 3H, J = 6.8 Hz), 2.25−2.41 (m, 1H), 3.37 (s, 3H), 4.47 (d, 1H, J = 10.8 Hz), 5.88 (s, 1H), 6.93−7.01 (m, 2H), 7.13−7.21 (m, 1H), 7.35−7.51 (m, 4H), 7.58−7.66 (m, 1H), 7.71−7.78 (m, 1H), 7.84−8.00 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 0.80 (q), 19.83 (q), 20.05 (q), 29.58 (d), 50.29 (q), 75.57 (d), 75.75 (d), 100.97 (s), 123.21 (d), 125.44 (d), 125.60 (d), 126.01 (d), 127.60 (d), 127.75 (d), 128.31 (d), 128.51 (d), 130.62 (d), 131.11 (s), 133.03 (s), 133.57 (s), 133.95 (s), 175.31 (s). Anal. Calcd for $C_{27}H_{33}NO_3Si$: C, 72.44; H, 7.43; N, 3.13. Found: C, 72.54; H, 7.47; N, 2.99.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-isopropyl-3-methoxy-2-(2-naphthyl)-3-(trimethylsiloxy)azetidine (2n). 88% ee. Colorless solid. R_f 0.5 (hexanes−ethyl acetate, 5:1). $[\alpha]^{23}_D$ −74.8 (c = 3.6, $CHCl_3$). IR (KBr): 1647, 845, 733, 712 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.36 (s, 9H), 1.08 (d, 3H, J = 6.8 Hz), 1.25 (d, 3H, J = 7.0 Hz), 2.35−2.52 (m, 1H), 4.42 (d, 1H, J = 10.8 Hz), 5.09 (s, 1H), 6.98−7.06 (m, 2H), 7.20−7.29 (m, 3H), 7.47−7.58 (m, 3H), 7.67 (s, 1H), 7.77−7.84 (m,

1H), 7.85−7.93 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 0.97 (q), 19.78 (q), 20.16 (q), 29.57 (d), 50.29 (q), 75.20 (d), 79.76 (d), 100.60 (s), 126.13 (d), 126.18 (d), 126.23 (d), 127.53 (d), 127.83 (d), 128.16 (d), 128.21 (d), 129.91 (d), 130.71 (d), 133.02 (s), 133.08 (s), 133.36 (s), 135.58 (s), 175.81 (s). Anal. Calcd for $C_{27}H_{33}NO_3Si$: C, 72.44; H, 7.43; N, 3.13. Found: C, 72.52; H, 7.43; N, 3.04.

(2*R*,3*R*,4*S*)-1-Benzoyl-4-isopropyl-3-*tert*-butoxy-2-(2-naphthyl)-3-(trimethylsiloxy)azetidine (2o). >99% ee. Colorless paste. R_f 0.57 (hexanes−ethyl acetate, 5:1). $[\alpha]^{23}_D$ −75.3 (c = 1.0, $CHCl_3$). IR (neat): 1651, 1601, 1580, 1508, 1468, 934, 895, 845, 797, 754, 708 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ −0.33 (s, 9H), 1.09 (d, 3H, J = 6.2 Hz), 1.26 (d, 3H, J = 6.5 Hz), 1.43 (s, 9H), 2.46−2.66 (m, 1H), 4.90 (d, 1H, J = 10.3 Hz), 6.98−7.05 (m, 2H), 7.20−7.27 (m, 3H), 7.44−7.60 (m, 4H), 7.74−7.81 (m, 1H), 7.84−7.90 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 1.39 (q), 20.15 (q), 20.18 (q), 30.31 (d), 30.55 (q), 76.47 (s), 76.78 (d), 82.94 (d), 99.75 (s), 125.81 (d), 125.91 (d), 126.44 (d), 127.56 (d), 127.70 (d), 127.75 (d), 128.00 (d), 130.55 (d), 132.84 (s), 132.89 (s), 133.80 (s), 136.07 (s), 175.86 (s). Anal. Calcd for $C_{30}H_{39}NO_3Si$: C, 73.58; H, 8.03; N, 2.86. Found: C, 73.64; H, 8.04; N, 2.79.

X-ray Crystallographic Analysis of 2c. All measurements were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods with SIR92 and expanded using Fourier techniques with DIRDIF99. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement on F^2 was based on 5876 observed reflections and 317 variable parameters and converged with unweighted and weighted agreement factors of R_1 = 0.059 and wR_2 = 0.195. All calculations were performed using the CrystalStructure crystallographic software package.

Crystal Data of 2c. $C_{26}H_{37}O_3NSi$, FW = 439.67, monoclinic, $P2_1$ (No. 4), colorless block, a = 10.3906 Å, b = 9.6213(1) Å, c = 13.4593(5) Å, β = 95.347(2)°, V = 1339.69(3) Å^3, T = 298 K, Z = 2, D_{calcd} = 1.090 g/cm^3, μ = 1.12 cm^{-1}, GOF = 1.002.

Supporting Information Available: A crystallographic CIF file for **2c**. A drawing of the electrolysis cell, ^{1}H and ^{13}C spectra of **2c**, and the results of calculations for the transition states (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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