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Nucleophilic displacements of non-racemic α-trifluoromethyl benzylic triflates

Greg Hughes *, Paul O'Shea, Julie Goll, Danny Gauvreau, Jennifer Steele

Department of Process Research, Merck Frosst Centre for Therapeutic Research, 16711 Route Transcanadienne, Kirkland, Québec, Canada H9H 3L1

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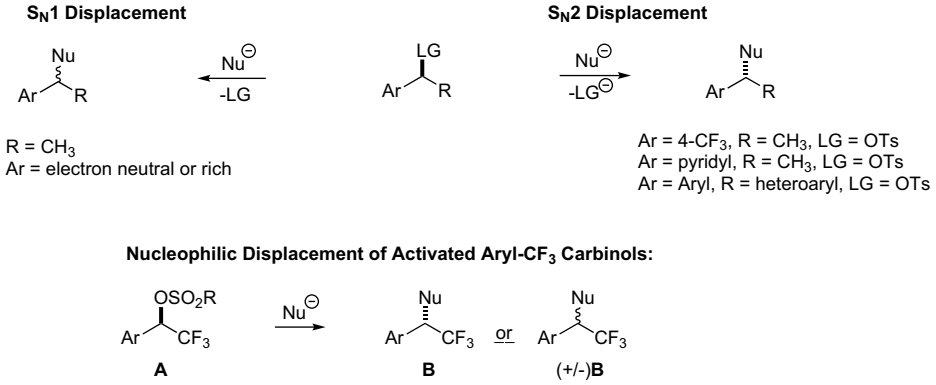
ABSTRACT

Effective protocols for the introduction of chiral α-trifluoromethyl benzyl moieties by nucleophilic displacement of enantiomerically enriched α-trifluoromethyl benzylic triflates are presented. The effects of substrate electronics, solvent polarity, temperature, and base are studied by measuring the diastereomeric or enantiomeric excesses of the displacement products formed by coupling a variety of α-trifluoromethyl benzylic triflates with a range of nucleophiles including amines, carboxylates, thiols, and malonates. Preliminary investigations to elucidate the mechanism(s) involved in the loss of stereochemical integrity at the benzylic center in the nucleophilic displacement reactions are also reported.

1. Introduction

The nucleophilic displacement of a leaving group from benzylic positions is a well studied classical transformation in organic chemistry.[1] While stereospecific S_N2 displacement could be a useful strategy for preparing optically active substrates, its use has been limited due to the propensity for racemization via competing S_N1 pathways (Scheme 1). This tendency has limited such displacements to highly electron deficient aromatic[2] or heteroaromatic[3] substrates where S_N1 pathways would require highly destabilized carbocationic intermediates. The stereospecific S_N2 displacement of particularly reactive diaryl carbinols following activation at low temperature has also been reported.[4]

We were particularly interested in an alternative class of nucleophilic displacements whereby carbocationic intermediates would be destabilized by a benzylic CF_3 substituent (compounds



Scheme 1. S_N2 versus S_N1 displacement of activated secondary benzylic alcohols.

A→**B**, Scheme 1). While the CF_3 functionality in **A** would be expected to retard S_N1 processes, it is also well known to impede S_N2 inversions and there are very few examples of this type of transformation being reduced to practice. Intramolecular

* Corresponding author. Tel.: +1 732 594 5204; fax: +1 732 594 0338.
E-mail address: greg_hughes@merck.com (G. Hughes).

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displacements allowing access to CF_3 substituted aziridines and cyclopropanes have been reported.[5] The displacement of tosylates derived from fluoral hemiacetals with aluminate complexes has also been shown to proceed with minimal (3–23%) racemization.[6] During the course of detailed studies of the solvolysis of 1-aryl-2,2,2-trifluoroethyl sulfonates, Tidwell et al. have shown that some inversion occurred in the solvolysis of 1-phenyl-2,2,2-trifluroethyl triflate in acetic acid.[7] The strongest precedent for the transformations we were interested in comes from the laboratories of Fuchikami who demonstrated S_N2 displacements of benzylic CF_3-mesylates using CsF as a base in DMF at 120 °C with reaction times of 3–4 days using benzoic acid (61% yield) as a nucleophile.[8] The only nitrogen nucleophile employed was phthalimide, which gave only 11% yield. Milder conditions (60 °C, 6 h) could be employed using 5 equiv of thiophenol (71% yield) as a nucleophile. The same authors have also shown that optically active α-trifluoromethyl alkyl triflates could be displaced under milder conditions (rt to 60 °C, 16–41 h) and in one case demonstrated the transformation to be stereoselective, giving complete inversion of the stereocenter using benzoic acid as a nucleophile. Unfortunately, no information is available regarding the stereoselectivity of the benzylic mesylate displacements.

As part of an ongoing preclinical program aimed at the development of selective Cathepsin K inhibitors for the treatment of osteoporosis,[9] we have been interested in the synthesis of fluorinated α-amino acids of general structure **C** (Scheme 2). While we have previously reported an approach to the related β-amino alcohols **D** using the diastereoselective addition aryllithiates to optically pure fluoral derived imines **E**,[10] accessing the desired amino acids would require a number of protecting group manipulations and oxidation state changes. We have also developed a diastereoselective reductive amination between 2,2,2-trifluoroacetophenones and α-aminoesters.[11]

We felt that the direct S_N2 displacement of a benzylic sulfonate **G** with an α-amino ester **H** would represent an attractive alternative as there are many proven methods for reducing aryl trifluoromethyl ketones to provide optically active aryl-trifluoromethyl carbinols (**I**).[12]

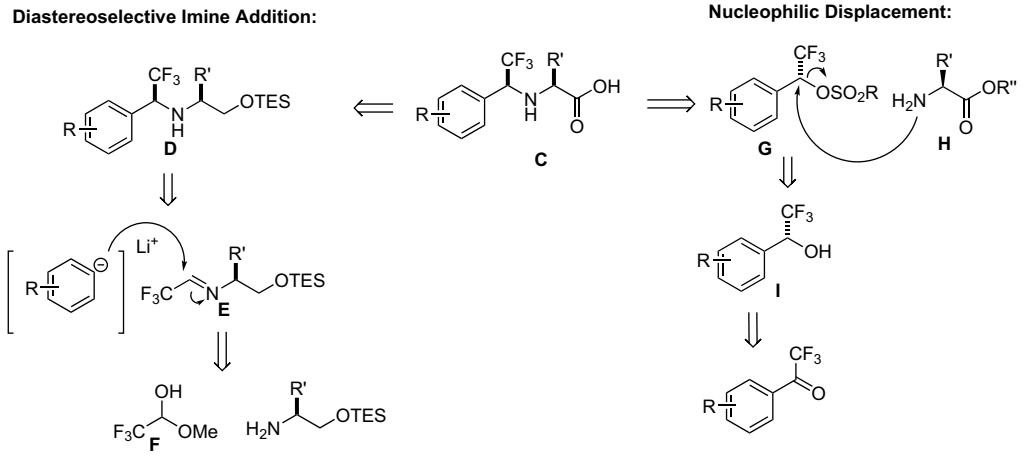
We report herein the development of mild conditions, which allow for the smooth S_N2 displacement of either electronically neutral or deficient secondary benzyl triflates with minimal erosion of optical activity at the benzylic stereocenter. We have also observed that even mildly electron donating substituents on the aromatic ring gives rise to a dramatic loss in optical activity at the benzylic center. This is consistent with the results of Tidwell's solvolysis studies, which revealed exceptionally large ρ^+ values for this class of substrates with values ranging from −6.7 in TFA to −11.9 in EtOH.[7]

2. Results

Our studies were initiated using mesylate **2a**, derived from alcohol **1a** with an ee of 90%.[13] Employing the ethyl ester of (*S*)-leucine (**3a**) as a nucleophile, we were unable to observe any of the desired product using Fuchikami's DMF/CsF protocol, with ~40% of alcohol **1a** being generated, presumably by attack of the amine at sulfur. Therefore, we were pleased to find that the desired product **4** could be obtained in 75% yield, albeit with partial racemization (10%) of the benzylic stereocenter, by mixing **3a** and triflate **2b** in THF with $^i Pr_2NEt$ as base (Table 1, entry 2).[14] Switching to a more polar solvent (acetonitrile) gave rise to a number of byproducts and more pronounced racemization (24%, entry 3). While the conversions were lower, similar yields and slightly higher diastereomeric excesses were observed in $^i PrOAc$, toluene, and n-Bu_2O (70–78% yield, 6–7% racemization, entries 4–6). The lower conversions in these solvents could be compensated for by increasing the reaction temperature to 75 °C. While more significant erosion in optical activity was observed at this temperature, the desired product was formed in 89% yield with a de of 72% (entry 7). Running the reaction in the absence of solvent at 45 °C further improved the de to 84% (entry 8). Alternatively, switching the base from $^i Pr_2NEt$ to K_2CO_3 in n-Bu_2O at 75 °C improved the yield and stereoselectivity such that **4** could be isolated in 94–96% yield and 83% de (entry 9). In order to simplify the work up of the reactions, the solvent was switched to *c*-hexane, which afforded the desired product in 98% yield and 86% de (entry 10).

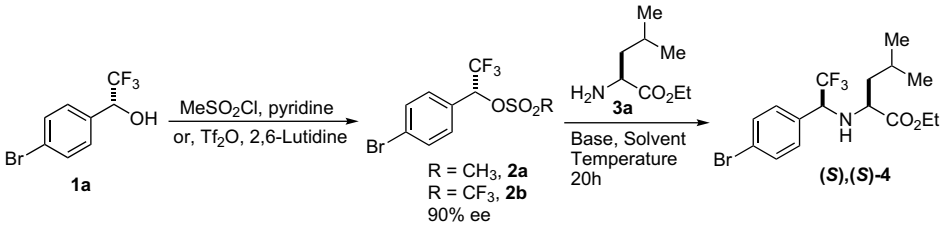
With these conditions in hand, we turned our attention to studying the influence of aromatic substituents on the stereoselectivity of the displacement reaction. A series of benzylic alcohols were subjected to the optimized S_N2 displacement conditions using **3b** as a nucleophile (Table 2). A dramatic dependence on the nature of the aromatic substituents was observed. While little or no erosion was seen with electron deficient or electron neutral substrates (0–11% erosion, entries 1–3), even a mildly electro-positive substituent (CH_3) gave significant erosion of optical activity at the displacement center (59% racemization, entry 4). The use of a biaryl benzylic alcohols resulted in extensive racemization, even with a very electron deficient substrate (entry 5).

The next issue to be addressed was the scope of the nucleophiles, which could be employed in the displacement reactions. The reactions were run using **2b** of >99.5% ee.[15] Primary amines such as amino diphenylmethane and α-methylbenzyl amine as well as secondary amines such as morpholine underwent clean



Scheme 2. Accessing fluorinated α-amino acids via nucleophilic displacement.

Table 1
Optimization of conditions for nucleophilic displacement of benzylic sulfates



Entry	Substrate[a]	Solvent	Base	Temp (°C)	Time (h)	% Conv (% yield)[b]	%de[c]
1	**2a**	DMF	CsF	120	18	40 (0)[d]	—
2	**2b**	THF	^{i}PrNEt$_2$	45	36	96 (75)	80
3	**2b**	CH_3CN	^{i}PrNEt$_2$	45	36	85 (47)	66
4	**2b**	^{i}PrOAC	^{i}PrNEt$_2$	45	36	83 (78)	83
5	**2b**	Toluene	^{i}PrNEt$_2$	45	36	83 (74)	84
6	**2b**	*n*-Bu$_2$O	^{i}PrNEt$_2$	45	36	78 (70)	84
7	**2b**	*n*-Bu$_2$O	^{i}PrNEt$_2$	75	18	100 (89)	72
8	**2b**	None	^{i}PrNEt$_2$	45	18	88 (66)	85
9	**2b**	*n*-Bu$_2$O	K_2CO_3	75	18	100 (95)	83
10	**2b**	*c*-Hexane	K_2CO_3	75	18	100 (98)	86

[a] All of the starting materials were 90% ee.
[b] Determined by calibrated HPLC analysis.
[c] Measured by ^{19}F NMR spectroscopic analysis.
[d] Compound **1** (~40%) was generated during the reaction.

displacement with minimal erosion of % ee under the optimized displacement conditions (Table 3, entries 1–4). We were surprised to find that using the K_2CO_3/*c*-hexane protocol with thiophenol as a nucleophile afforded only a moderate yield of the displacement product with significant erosion of ee (45% yield, 62% ee, entry 5). However, using the solvent free ^{i}Pr$_2$NEt protocol at 0 °C, the desired product could be isolated in 95% yield and 94% ee (entry 6). Similar behavior was observed with octanoic acid as a nucleophile. Using K_2CO_3 in *c*-hexane, the desired product was isolated in 75% yield and 82% ee (entry 7). However, the solvent free ^{i}Pr$_2$NEt protocol at 45 °C afforded the desired compound in 86% yield and 95% ee (entry 8). It was also possible to form carbon–carbon bonds by displacement with malonate anions at ambient temperature without any erosion of ee (entry 9).

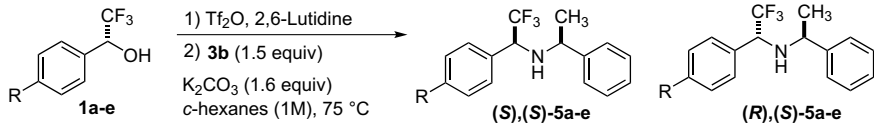
3. Discussion

There are a number of possible mechanisms by which the racemization observed in this study could be occurring (Scheme 3). They include: **Ia** The racemization of triflate via an S_N1 process followed by stereospecific S_N2 displacement; **Ib** The racemization of triflate via an S_N2 process, followed by stereospecific S_N2 displacement; **II** Competing S_N1 and S_N2 displacement with the nucleophilic coupling partner; **IIIa** Base mediated epimerization of triflate; **IIIb** Deprotonation of the triflate, followed by α-elimination and N–H insertion of the resulting carbene; **IIIc** Base mediated epimerization of the product.

The base mediated pathways **IIIa–c** are unlikely as they would be expected to lead to more pronounced racemization of electron deficient substrates. Additionally, upon reaching 100% conversion, no further racemization of the displacement products was observed. Furthermore, stirring the triflates in the presence of base at elevated temperatures in the absence of nucleophiles actually retards the rate of racemization (and chemical degradation) compared to a solution, which is warmed in the absence of base.

With displacement reactions involving electron deficient substrates such as **2b**, the % de/ee of the product decreases over the course of the reaction, but at a rate, which is slower than the erosion of % ee of residual triflate. For example, coupling **3a** with **2b**

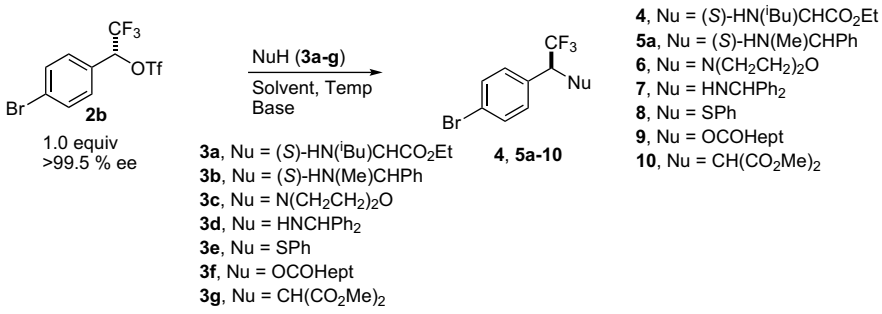
Table 2
Substituent effects on the displacement of 1-phenyl-2,2,2-trifluoroethyl triflates



Entry	Starting material	R	% ee[a]	Yield[b]	% de[c]	% Racemization
1	**1a**	CF_3	83	66	83	0
2	**1b**	Br	>99	95	94	6
3	**1c**	H	92	79	82	11
4	**1d**	CH_3	86	68	35	59
5[d,e]	**1e**	4-MeSO$_2$Ph	>99	65	56	44

[a] Measured by HPLC analysis of **1a–e**.
[b] HPLC.
[c] Measured by ^{19}F NMR spectroscopic analysis.
[d] Compound **3b** (4 equiv) was employed in a one-pot process.
[e] DCE was used as solvent, and the reaction was run at 23 °C.

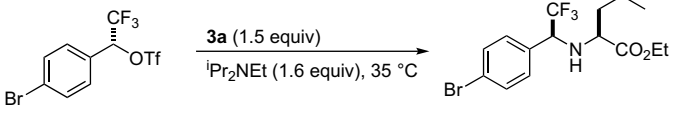
Table 3
Scope of the nucleophile in the S_N2 displacement of α-trifluoromethyl benzyl triflates



Entry	NuH	Product	Solvent	Base	Temp (°C)	Time (h)	Yield (%)[a]	de[b]/ee[c] (%)
1	**3a**	**4**	*c*-Hexane	K_2CO_3	75	12	94	95
2	**3b**	**5a**	*c*-Hexane	K_2CO_3	75	6	90	97
3	**3c**	**6**	*c*-Hexane	K_2CO_3	75	6	83	96
4	**3d**	**7**	*c*-Hexane	K_2CO_3	75	6	82	93
5	**3e**	**8**	*c*-Hexane	K_2CO_3	50	5	45	62
6	**3e**	**8**	None	$^iPr_2NEt$	0	0.5	95	98
7	**3f**	**9**	*c*-Hexane	K_2CO_3	75	18	75	82
8	**3f**	**9**	None	$^iPr_2NEt$	45	2	86	95
9	**3g**	**10**	THF	NaH	23	18	82	>99.5

[a] Isolated yields.
[b] Determined by ^{19}F NMR spectroscopic analysis.
[c] Measured by chiral HPLC analysis.

(90% ee) in neat $^iPr_2NEt$ at 35 °C gave 65% conversion after 6 h (Eq. 1). The product formed at this point had a de of 89%, while the residual triflate had an ee of 87%. After 18 h and 87% conversion, the product had a de of 87% and the residual triflate had an ee of 76%. These results suggest that the S_N1 pathway **II** is not playing a dominant role in the racemization of this type of substrate, as one would expect the % de of the product to be lower than the % ee of the residual triflate if that were the case.



Time (h)	Conv (%)	% ee **2b**	% de **4a**
0	0	90	-
6	35	89	87
18	87	87	76

(1)

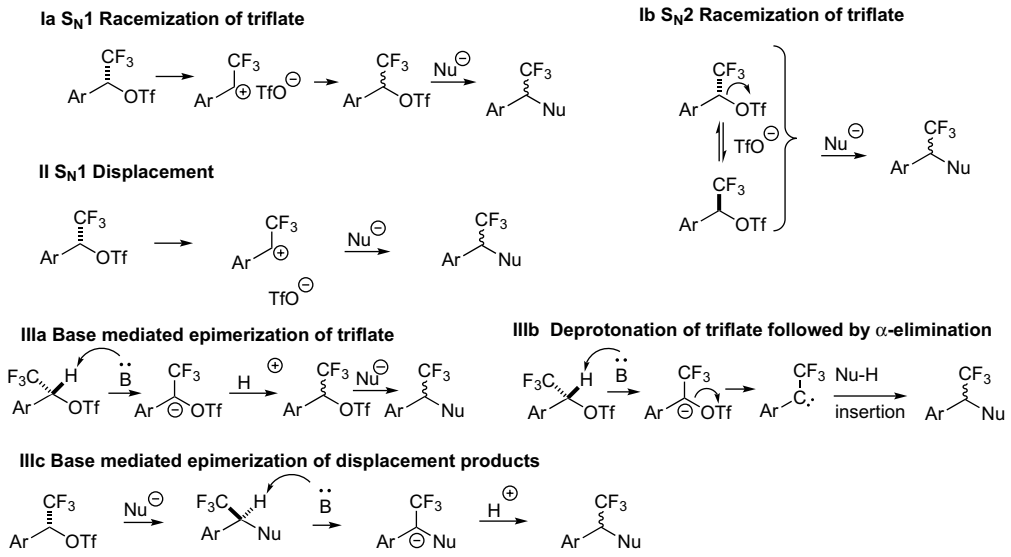
While the presence of S_N1 type racemization of triflate (path **Ia**) cannot be ruled out completely, the following observations lead us to believe that electron deficient substrates racemize predominantly via path **IIb**. During an initial screen of solvents and bases for the displacement reactions, a correlation was noted between the solubility of the triflate salts of the bases employed and extent of erosion of optical activity (Table 4). For instance, using dichloroethane (DCE) as solvent, the product formed upon coupling **2b** with **3b** was produced in higher % de with K_2CO_3 (89%, Table 4, entry 1) and 2,2,6,6-tetramethylpiperidine (TMP) (83%, Table 4, entry 2) as base than with either $^iPr_2NEt$ (68%, Table 4, entry 3) or 2,6-lutidine (64%, Table 4, entry 4). The conjugate acids of the first two bases (KOTf and TMP·HOTf) were highly insoluble, where as the conjugate acids of 2,6-lutidine and $^iPr_2NEt$ (2,6-lutidine·HOTf and $^iPr_2NEt$·HOTf) have considerable solubility in DCE at 70 °C. This led us to speculate that solvated triflate ion might be undergoing S_N2 displacement of the starting triflate.

As further evidence of the effects of solvated triflate, a series of reactions between **2b** and **3b** were run in DCE at 75 °C using either DIPEA or TMP as base with various amounts of added DIPEA·HOTf. After >99% conversion, the % de of the product was measure by ^{19}F NMR and the results are represented graphically in Figure 1. With no added DIPEA·HOTf, there was 17% erosion of de with TMP and a loss of 32% with DIPEA. As the amount of added DIPEA·HOTf was increased to a full equivalent, the extent of erosion increased to 45 and 50%, respectively.

The mechanism of racemization of more reactive substrates appears to be different. In contrast to the displacement of **2b** described above, the biphenylsulphone derived triflate of **11** undergoes displacement to give a product **12** whose % de lowers very little throughout the course of the reaction. In addition, the residual triflate at partial conversion was found to have a higher % ee than the % de of the displacement product. For example, after 72 h at 25 °C in *t*-BuOMe (TBME), HPLC showed 80% conversion. The product formed to this point had a de of 67%, while the % ee of the residual triflate had only dropped from >99.5% to 78% as determined by chiral HPLC analysis (Eq. 2). These observations suggest that with substrates, which are better able to stabilize benzylic cations, there is a significant portion of the erosion of stereochemical integrity, which can be attributed to S_N1 displacement.

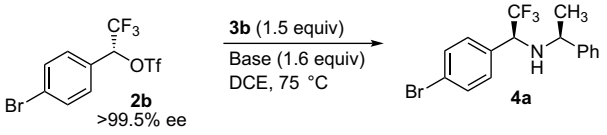
4. Conclusion

We have described rare examples of practical intermolecular S_N2 displacements of a leaving group positioned α to a CF_3 substituent.[16] We have shown that a wide range of nucleophiles including nitrogen, oxygen, and carbon based examples undergo displacement in good yields and with excellent stereoselectivity with electron deficient substrates. A strong correlation between the electronic properties of the electrophilic partners and the stereoselectivity of the displacements has been established, and mechanistic rationale for different modes of racemization for electron poor and electron rich substrates has been discussed.



Scheme 3. Possible mechanisms of racemization.

Table 4
Influence of base on the stereoselectivity of the displacement reactions



Entry	Base	Conversion[a] (%)	Yield[a] (%)	de[b] (%)
1	K_2CO_3	>99	94	89
2	TMP	>99	88	83
3	DIPEA	>99	59	68
4	2,6-Lutidine	>99	82	64

[a] Measured by calibrated HPLC analysis.
[b] Measured by ^{19}F NMR spectroscopic analysis.

5. Experimental

5.1. General

Unless otherwise noted all reactions were run under an inert atmosphere, and solvents and reagents were transferred by syringe. Anhydrous DMF, cyclohexane, 1,2-dichloroethane (DCE), and isopropylacetate (IPAC) were purchased from A&C Chemicals Ltd, anhydrous grade methanol was purchased from Acros, and anhydrous acetonitrile, tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), *n*-butyl ether (DBE), and *tert*-butyl methyl ether (MTBE) were purchased from Aldrich in Sure/Seal™ bottles and used as received. Diisopropylethylamine (DIPEA), 2,2,6,6-tetramethylpiperidine (TMP), and K_2CO_3 were purchased from Aldrich and used as received. Unless otherwise noted, ^1H NMR (500 MHz), ^{13}C NMR (125 MHz), and ^{19}F NMR spectra (376.5 MHz) were recorded in acetone-d_6, chloroform-d_1, or benzene-d_6 purchased from CDN isotopes. The ^1H and ^{13}C spectra were referenced to residual solvent. ^{19}F NMR spectra were referenced to added benzotrifluoride (−67.73 ppm). Coupling constants are reported in hertz (Hz). Multiplicities are as follows: s=singlet, d=doublet, t=triplet, q=quartet. Chiral SFC was run on a Berger SFC system, reverse phase HPLC's were run on an Agilent 1100 series system. Infrared (IR) spectra were recorded on an Applied Systems Inc. ReactIR 1000, optics model. Optical rotations were obtained on a Perkin Elmer 241 polarimeter. Melting points are uncorrected. High resolution mass spectrometry was performed by Merck Analytical Research. Elemental analysis was performed by Prevalere Life Sciences in Whitesboro, NY.

5.2. General procedure for triflation of aryl-2,2,2-trifluoroethanols

*5.2.1. (1R)-1-(4-Bromophenyl)-2,2,2-trifluoroethyl trifluoromethanesulfonate (**2b**)*

Trifluoromethanesulfonic anhydride (1.43 mL, 8.52 mmol) was added to a −15 °C solution of 1*R*-(4-bromophenyl)-2,2,2-trifluoroethanol **1a** (1.45 g, 5.68 mmol, >99.5% ee, Chiralcel OJ 4.6 mm×25 cm column; eluants: A, 2-propanol; B, CO_2; 2 mL/min;

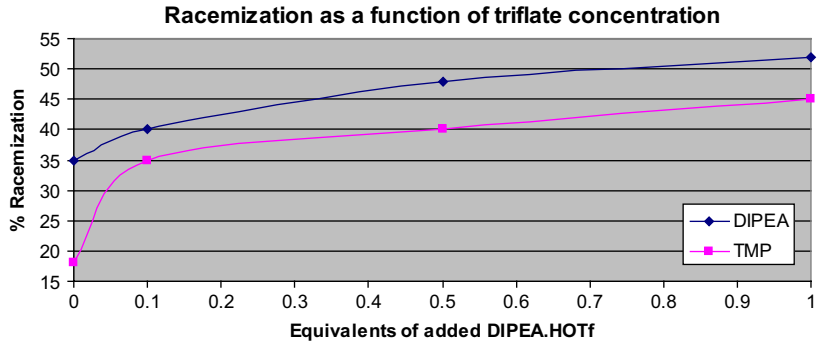
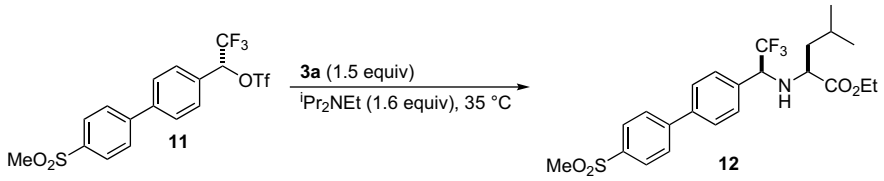


Figure 1. Influence of added DIPEA·HOTf on the extent of racemization.



(2)

Time (h)	Conv (%)	% Ee **11**	% De **12**
0	0	>99.5	-
72	80	78	67

gradient: A/B 1:99 for 4 min to 20:80 over 12.7 min; λ=220 nm; temperature 35 °C; t_R: (*R*)-**2a**=10.2 min, (*S*)-**2a**=10.9 min) and 2,6-lutidine (1.05 mL, 9.08 mmol) in *c*-hexane (5.7 mL). After 30 min, water (50 mL) and *c*-hexane (50 mL) were added. The organic layer was washed with water (2×25 mL) and concentrated. The residue was diluted with *c*-hexane to give a solution whose total mass was 5.2 g. Quantitative HPLC analysis showed the material to be 40 wt % (95% yield). This solution was stable and can be frozen and stored for up to 6 months without decomposition or erosion of % ee. Chiral HPLC analysis of the crude material showed it to be >99.5% ee (Chiralpak® AD, 100% hexanes, 1 mL/min, 25 °C). Samples could be chromatographed (5% EtOAc/hexanes) to obtain pure samples by ^{1}H NMR, but the pure material decomposes within a few days at ambient temperature and after a few weeks at −20 °C. The triflate also underwent racemization on silica gel and material, which was >99.5% ee prior to chromatography was 80% ee after. ^{1}H NMR (400 MHz, acetone): δ 7.83–7.79 (m, 2H), 7.70 (d, *J*=8.4 Hz, 2H), 6.74 (q, *J*=5.9 Hz, 1H); ^{13}C NMR (126 MHz, benzene): δ 132.6, 129.4, 126.9, 126.2, 121.7 (q, *J*=282 Hz), 118.7 (q, *J*=320 Hz), 82.0 (q, *J*=36 Hz); ^{19}F NMR (377 MHz, acetone): δ −80.33 (s, 3F), −81.77 (d, *J*=6 Hz, 3F); IR (neat, cm^{-1}) 1602, 1327, 1247, 1197, 1135, 1073.

5.3. General K_2CO_3/*c*-hexane displacement conditions

*5.3.1. (1S)-1-(4-Bromophenyl)-2,2,2-trifluoro-N-[(1S)-1-phenylethyl]ethanamine (**5a**)*

Potassium carbonate (1.26 g, 9.08 mmol) and **3b** (1.08 mL, 8.52 mmol) were added to 5.5 g of a 40 wt % solution of **2b** (5.68 mmol) in *c*-hexane and the mixture was warmed to 75 °C and aged for 18 h. The mixture was cooled to ambient temperature and partitioned between cyclohexane (50 mL) and 1 M HCl (50 mL). The organic layer was washed with water (2×25 mL). The organic layer was concentrated to dryness. The residue was purified by flash chromatography (5% ethylacetate/hexane) to afford the desired compound as a colorless oil (1.83 g, 90%). ^{1}H NMR (400 MHz, acetone): δ 1.41 (d, *J*=6.6 Hz, 3H), 2.66 (t, *J*=6.7 Hz, 1H), 4.02 (quint, *J*=6.3 Hz, 1H), 4.28 (quint, *J*=7.6 Hz, 1H), 7.19–7.24 (m, 1H), 7.25–7.32 (m, 4H), 7.36 (d, *J*=8.3 Hz, 2H), 7.52 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (126 MHz, acetone): δ 23.7, 56.9, 61.7 (q, *J*=19.4 Hz), 122.9, 126.8 (q, *J*=283 Hz), 127.3, 127.7, 129.0, 131.1, 132.2, 135.6, 145.6; ^{19}F NMR (377 MHz, acetone): δ −78.37 (d, *J*=7.5 Hz); IR (neat, cm^{-1}): 3350, 3030, 2968, 1594, 1490, 1366, 1258, 1119, 814, 702. Anal. Calcd for $C_{16}H_{15}BrF_3N$: C, 53.65; H, 4.22; N, 3.91. Found: C, 53.63; H, 4.28; N, 4.21.

5.4. General method for triflation/displacement through process

*5.4.1. (1S)-2,2,2-Trifluoro-N-[(1S)-1-phenylethyl]-1-[4-(trifluoromethyl)phenyl]ethanamine (**5b**)*

Tf_2O (252 μL, 1.50 mmol) was added drop-wise to a −10 °C solution of **1b** (244 mg, 1.00 mmol, 83% ee) and 2,6-lutidine (185 μL, 1.60 mmol) in *c*-hexane (1 mL). After 30 min, the mixture was diluted with water (10 mL) and *c*-hexane (10 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in *c*-hexane (1 mL) and K_2CO_3 (221 mg, 1.6 mmol) and **3b** (193 μL, 1.50 mmol) were added. The reaction mixture was warmed to 75 °C for 18 h, then cooled to ambient temperature and partitioned between *c*-hexane and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography. ^{1}H NMR (400 MHz, acetone): δ 7.69 (d, *J*=8 Hz, 2H), 7.63 (d, *J*=8 Hz, 2H), 7.17–7.27 (m, 5H), 4.39 (quint, *J*=8 Hz, 1H), 3.98 (quint, *J*=6.5 Hz, 1H), 2.87 (t, *J*=6.5 Hz, 1H), 1.37 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (126 MHz, acetone): δ 145.7, 141.0, 130.8 (q, *J*=32 Hz), 130.1, 129.1, 127.8, 127.4, 127.1 (q, *J*=237 Hz), 126.0 (q, *J*=3.5 Hz), 124.9 (q, *J*=226 Hz), 62.0 (q, *J*=28.5 Hz), 57.2, 23.7; ^{19}F NMR (377 MHz, acetone): δ −67.73 (s, 3F), −78.14 (d, *J*=7 Hz, 3F).

5.4.2. (1S)-2,2,2-Trifluoro-1-phenyl-N-[(1S)-1-phenylethyl]ethanamine

Alcohol **1c** (92% ee) was subjected to the general conditions for triflation/displacement to afford the title compound in 79% yield and 82% de. The spectral data were consistent with the literature values.[17]

*5.4.3. (1S)-2,2,2-Trifluoro-1-(4-methylphenyl-N-[(1S)-1-phenylethyl]ethanamine) (**5d**)*

Alcohol **1d** (86% ee, Chiralpak® AD, 3% isopropanol/hexanes, 1 mL/min, 25 °C) was subjected to the general method for triflation/displacement through process affording the title compound as a colorless oil in 68% yield (35% de). ^{1}H NMR (400 MHz, acetone): δ 7.20–7.30 (m, 7H), 7.17 (d, *J*=8 Hz, 2H), 4.16 (quint, *J*=8 Hz, 1H, (*S*,*S*) diastereomers); ^{13}C (126 MHz, acetone): δ 146.0, 139.0, 133.3, 129.9, 129.1, 129.0, 127.8, 127.4, 127.8 (q, *J*=282 Hz), 62.0 (q, *J*=28 Hz), 56.7, 23.6, 21.1; ^{19}F NMR (377 MHz, acetone): δ −78.33 (d, *J*=7 Hz).

*5.4.4. (1S)-2,2,2-Trifluoro-1-(4-(4-methylsulfonylphenyl)phenyl-N-[(1S)-1-phenylethyl]ethanamine) (**5e**)*

Alcohol **1e** (>99.5% ee) was subjected to the general method for triflation/displacement through process, except that 1,2-dichloroethane (DCE) was used in place of *c*-hexane in order to improve solubility. The displacement was also run at ambient temperature, affording the title compound as a colorless oil in 68% yield (56% de). ^{1}H NMR (500 MHz, acetone): δ 8.03 (d, *J*=8.5 Hz, 2H), 7.93 (d, *J*=8.5 Hz, 2H), 7.74 (d, *J*=8.3 Hz, 2H), 7.57 (d, *J*=7.9 Hz, 2H), 7.35–7.19 (m, 5H), 4.35–4.29 (m, 1H), 4.02–3.96 (m, 1H), 3.16 (s, 3H), 1.36 (d, *J*=6.6 Hz, 3H); ^{19}F NMR (377 MHz, acetone): δ −78.05 (d, *J*=7 Hz). Anal. Calcd for $C_{23}H_{22}F_3NO_2S$: C, 63.73; H, 5.12; N, 3.23. Found: C, 63.77; H, 5.00; N, 3.12.

*5.4.5. Ethyl 2-{[(1S)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]amino}-4-methylpentanoate (**4**)*

The general K_2CO_3/*c*-hexane procedure was employed. The product was purified by flash chromatography (10% EtOAc/

hexanes) to afford the desired compound as a colorless oil in 94% yield. ^{1}H NMR (400 MHz, acetone): δ 0.90 (d, J=6.5 Hz, 3H), 0.92 (d, J=6.5 Hz, 3H), 1.10 (t, J=7 Hz, 3H), 1.41–1.54 (m, 2H), 1.88 (nonet, J=6.5 Hz, 1H), 2.48 (dd, J=9, 5.5 Hz, 1H), 3.43–3.50 (m, 1H), 3.90–3.97 (m, 2H), 4.33–4.39 (m, 1H), 7.44 (d, J=8.4 Hz, 2H), 7.58 (d, J=8.5 Hz, 2H); ^{13}C NMR (126 MHz, acetone): δ 14.3, 22.1, 23.1, 25.3, 43.3, 60.2, 61.1, 63.5 (q, J=29 Hz, 1H), 123.3, 126.6 (q, J=281 Hz), 131.5, 132.4, 135.7, 175.3; ^{19}F NMR (377 MHz, acetone): δ −79.15 (d, J=8 Hz); IR (neat, cm^{-1}): 3343, 2961, 1729, 1490, 1262, 1151, 1123, 1011, 814. Anal. Calcd for $C_{16}H_{21}BrF_3NO_2$: C, 48.50; H, 5.34; N, 3.53. Found: C, 48.51; H, 5.27; N, 3.62.

5.4.6. 4-[(1S)-1-(4-Bromophenyl)-2,2,2-trifluoroethyl]-morpholine (**6**)

The general K_2CO_3/*c*-hexane procedure was employed. The product was purified by flash chromatography (0→10% EtOAc/hexanes) to afford the desired compound as a colorless oil in 83% yield. Chiral HPLC analysis (Chiralpak® AD, 1% IPA/CO_2^{sc}, hold 4 min, then to 20% IPC/CO_2^{sc} at 1.3%/min, hold 5 min, 1.5 mL/min, 220 nm, 50 °C, retention times: 10.4 min, 11.0 min) showed the material to be 96% ee. ^{1}H NMR (400 MHz, acetone): δ 7.63 (d, J=8.5 Hz, 2H), 7.42 (d, J=8.4 Hz, 2H), 4.35 (q, J=9 Hz, 1H), 3.60 (t, J=4.7 Hz, 4H), 2.59–2.65 (m, 2H), 2.49–2.57 (m, 2H); ^{13}C NMR (126 MHz, acetone): δ 132.4, 132.3, 132.1, 126.7 (q, J=284 Hz), 123.3, 70.2 (q, J=27.5 Hz), 67.5, 51.9; ^{19}F NMR (377 MHz, acetone): δ −72.18 (d, J=8.5 Hz); IR (neat, cm^{-1}) 2964, 2856, 1490, 1455, 1254, 1150, 1188, 1011, 872, 726; $[\alpha]_D^{589}$ +40 (*c* 11.3 mg/mL, $CHCl_3$).

5.4.7. (1S)-1-(4-Bromophenyl)-N-(diphenylmethyl)-2,2,2-trifluoroethanamine (**7**)

The general K_2CO_3/*c*-hexane procedure was employed. The reaction mixture was purified by flash chromatography (0→5% EtOAc/hexanes) to afford the title compound in 82% yield as a colorless oil. ^{1}H NMR (400 MHz, acetone): δ 7.62 (d, J=8.5 Hz, 2H), 7.45 (dd, J=7, 5 Hz, 4H), 7.34 (dd, J=16, 8 Hz, 4H), 7.52 (t, J=7.5 Hz, 3H), 7.18 (t, J=7.5 Hz, 1H), 4.76 (d, J=3.7 Hz, 1H), 4.17 (quint, J=8 Hz, 1H), 3.22 (dd, J=10, 3.5 Hz, 1H); ^{13}C NMR (126 MHz, acetone): δ 144.4, 143.2, 134.8, 132.6, 131.6, 129.5, 129.2, 128.3, 128.2, 128.0, 127.9, 126.4 (q, J=281 Hz), 123.4, 64.6, 62.1 (q, J=29 Hz); ^{19}F NMR (377 MHz, acetone): δ −78.49 (d, J=8 Hz); IR (neat, cm^{-1}) 1490, 1258, 1170, 1123, 702; $[\alpha]_D^{589}$ +89 (*c* 13.4 mg/mL, $CHCl_3$). Anal. Calcd for $C_{21}H_{17}BrF_3N$: C, 60.02; H, 4.08; N, 3.33. Found: C, 59.83; H, 4.34; N, 3.37.

5.5. General neat ^{i}PrNEt displacement reactions

5.5.1. (1S)-1-(4-Bromophenyl)-2,2,2-trifluoroethyl octanoate (**9**)

Octanoic acid (307 μL, 1.94 mmol) was added to a 25 °C mixture of **2b** (500 mg, 1.29 mmol) and ^{i}Pr$_2$NEt (368 μL, 2.06 mmol). The mixture was warmed to 45 °C for 2 h. HPLC analysis showed 100% conversion. The mixture was diluted with TBME (25 mL) and washed with 1 N HCl (25 mL) and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (100% hexanes) to afford the desired product as a colorless oil (423 mg, 86%). Chiral HPLC analysis (SFC, Chiralpak® AD, 1% ^{i}PrOH/CO_2^{sc}, hold 4 min, then to 20% ^{i}PrOH at 1.3%/min, hold 5 min, 220 nm, 2.0 mL/min, retention times: 5.4 min, 8.7 min) showed the product to be 95% ee. ^{1}H NMR (CD_3COCD_3): δ 0.86 (t, J=7.0 Hz, 3H), 1.22–1.34 (m, 8H), 1.59–1.68 (m, 2H), 2.53 (t, J=7.5 Hz, 2H), 6.33 (q, J=7 Hz, 1H), 7.54 (d, J=8.4 Hz, 2H), 7.66 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.0, 22.5, 24.7, 28.8, 28.9, 31.6, 33.9, 71.1 (q, J=33 Hz), 122.9 (q, J=280 Hz), 124.2, 129.6, 130.4, 131.9, 171.4; ^{19}F NMR (377 MHz, CD_3COCD_3): δ −73.10 (d, J=8.2 Hz); IR (neat, cm^{-1}) 2930, 1760, 1355, 1266, 1181, 1135, 1011, 811; $[\alpha]_D^{589}$ +63 (*c* 11.8 mg/mL, $CHCl_3$). Anal. Calcd for $C_{16}H_{20}BrF_3O_2$: C, 50.41; H, 5.29. Found: C, 50.39; H, 5.17.

5.5.2. (1S)-1-(4-Bromophenyl)-2,2,2-trifluoroethyl phenyl sulfide (**8**)

The general protocol for neat ^{i}Pr$_2$NEt displacement reactions was followed except that the reaction was carried out at 0 °C for 30 min. The crude reaction mixture was purified to flash chromatography (0→2% EtOAc/hexanes) to afford the desired compound in 95% yield. Chiral HPLC analysis (SFC, Chiralpak® OD-H, 1% MeOH/CO_2^{sc}, hold 4 min, then to 20% MeOH/CO_2^{sc} at 1.3%/min, hold 5 min, 2.0 mL/min, 220 nm, 50 °C, retention times: 9.9 min, 10.5 min) showed the product to be 98% ee. Mp (TBME)=58–59 °C; ^{1}H NMR (CD_3COCD_3): δ 5.20 (q, J=8.7 Hz, 1H), 7.33–7.35 (m, 3H), 7.44–7.50 (m, 4H), 7.59 (d, J=8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 55.1 (q, J=29 Hz), 123.4, 126.6 (q, J=279 Hz), 129.5, 130.1, 131.9, 132.7, 132.9, 133.9, 134.0; ^{19}F NMR (CD_3COCD_3): δ −72.96 (d, J=11.5 Hz); $[\alpha]_D^{589}$ +261 (17.1 mg/mL, $CHCl_3$). Anal. Calcd for $C_{14}H_{10}BrF_3S$: C, 48.43; H, 2.90. Found: C, 48.48; H, 3.05.

5.5.3. Dimethyl [(1S)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]malonate (**10**)

A solution of **2b** (500 mg, 1.29 mmol) in *c*-hexane (1 mL) was added to a rt mixture of NaH (103 mg of 60 wt % NaH, 2.58 mmol) and dimethyl malonate (221 μL, 1.94 mmol) in THF (5 mL). After warming to 23 °C and aging 18 h, HPLC analysis showed 100% conversion. The mixture was diluted with TBME (25 mL) and quenched carefully with 1 N NaOH (10 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (5→20% EtOAc/Hexanes) to afford the desired compound as a white solid (390 mg, 82%). Chiral HPLC analysis (Chiralpak OD-H, 1% ^{i}PrOH/CO_2^{sc}, hold 4 min, then to 20% ^{i}PrOH at 1.3%/min, hold 5 min, retention times: 5.8 min, 6.6 min) showed >99.5% ee. Mp (TMBE): 101–102 °C; ^{1}H NMR (CD_3COCD_3): δ 3.46 (s, 3H), 3.78 (s, 3H), 4.28 (d, J=11.3 Hz, 1H), 4.32–4.40 (m, 1H), 7.45 (d, J=8.3 Hz, 2H), 7.59 (d, J=8.5 Hz, 2H); ^{13}C NMR (C_6D_6): δ 49.2 (q, J=27.5 Hz), 52.3 (br peak), 52.4, 52.8, 123.3, 126.1 (q, J=281 Hz), 131.3, 131.4, 132.0, 165.8, 166.9; ^{19}F (CD_3COCD_3): δ 81.26 (d, J=6.9 Hz); IR (film, cm^{-1}) 1752, 1733, 1489, 1432, 1309, 1161, 1112, 1077, 1011, 973, 930, 814; $[\alpha]_D^{589}$ +28 (*c* 13.6, $CHCl_3$). Anal. Calcd for $C_{13}H_{12}BrF_3O_4$: C, 42.30; H, 3.28. Found: C, 42.51; H, 3.36.

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References and notes

1. (a) Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 4513; (b) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1383 and references therein.
2. Lim, C.; Kim, S.-H.; Yoh, S.-D.; Fujio, M.; Tsuno, Y. *Tetrahedron Lett.* **1997**, *38*, 3243.
3. Uenishi, J.; Hamada, M.; Aburatani, S.; Matsui, K.; Yonemitsu, O.; Tsukube, H. *J. Org. Chem.* **2004**, *69*, 6781.
4. Bolshan, Y.; Chen, C.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111.
5. (a) Katagiri, T.; Ihara, H.; Takahashi, M.; Kashino, S.; Furuhashi, K.; Uneyama, K. *Tetrahedron: Asymmetry* **1997**, *8*, 2933; (b) Katagiri, T.; Irie, M.; Uneyama, K. *Tetrahedron: Asymmetry* **1999**, *10*, 2583.
6. (a) Matsutani, H.; Poras, H.; Kusumoto, T.; Hiyama, T. *Synlett* **1998**, 1353; (b) Matsutani, H.; Kusumoto, T.; Hiyama, T. *Chem. Lett.* **1999**, 529.
7. Allen, A. D.; Ambidge, A. I.; Che, C.; Micheal, H.; Muir, R. J.; Tidwell, T. T. *J. Am. Chem. Soc.* **1983**, *105*, 2343.
8. (a) Hagiwara, T.; Tanaka, K.; Fuchikami, T. *Tetrahedron Lett.* **1996**, *37*, 8187; (b) Hagiwara, T.; Ishizuka, M.; Fuchikami, T. *Nippon Kagaku Kaishi* **1998**, *11*, 750.
9. (a) Gauthier, J. Y.; Chauret, N.; Cromlish, W.; Desmarais, S.; Duong, L. T.; Falgueyret, J.-P.; Kimmel, D. B.; Lamontagne, S.; Leger, S.; LeRiche, T.; Li, C. S.; Masse, F.; McKay, D. J.; Nicoll-Griffith, D. A.; Oballa, R. M.; Palmer, J. T.; Percival, M. D.; Riendeau, D.; Robichaud, J.; Rodan, G. A.; Rodan, S. B.; Seto, C.; Therien, M.; Truong, V.-L.; Venuti, M. C.; Wesolowski, G.; Young, R. N.; Zamboni, R.; Black, W. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 923; (b) Black, W. C.; Bayly, C. I.; Davis, D. E.; Desmarais, S.; Falgueyret, J.-P.; Léger, S.; Li, C. S.; Massé, F.; McKay, D. J.; Palmer, J.

T.; Percival, M. D.; Robichaud, J.; Tsou, N.; Zamboni, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4741; (c) Li, C. S.; Deschenes, D.; Desmarais, S.; Falgueyret, J.-P.; Gauthier, J. Y.; Kimmel, D. B.; Léger, S.; Massé, F.; McKay, D. J.; Percival, M. D.; Riendeau, D.; Sevgi, B. R.; McGrath, M. E.; Thérien, M.; Truong, V.-L.; Wesolowski, G.; Zamboni, R.; Black, W. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1985.

10. Gosselin, F.; Roy, A.; O'Shea, P. D.; Chen, C.; Volante, R. P. *Org. Lett.* **2004**, *6*, 641.
11. Hughes, G.; Devine, P. N.; Naber, J. R.; O'Shea, P.; Foster, B.; McKay, D. J.; Volante, R. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 1839.
12. (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611; (b) Fujisawa, T.; Ichikawa, K.; Shimizu, M. *Tetrahedron: Asymmetry* **1993**, *4*, 1237; (c) Matsuda, T.; Harada, T.; Nakajima, N.; Itoh, T.; Nakamura, K. *J. Org. Chem.* **2000**, *65*, 157.
13. The benzylic alcohols were prepared by the oxazaborolidine ((*S*)-Bu-OAB) catalyzed catacholborane reduction of the corresponding ketones described in Ref. 12a.
14. That the nucleophilic displacement occurs with inversion was determined by hydrolyzing ester (*S*),(*S*)-**4a** to the corresponding carboxylic acid and comparing its spectral data to the literature values. Roy, A.; O'Shea, P. D.; Cheng, C.-y. *J. Org. Chem.* **2006**, *71*, 4320. Authentic samples of all four stereoisomer were prepared and HPLC analysis confirms that the racemization in this process is occurring at the benzylic stereocenter with the stereochemical integrity of the epimerizable α-amino ester stereocenter remaining intact.
15. Alcohol **1a** formed in 90% ee was recrystallized from hexanes with 80% recovery as a single isomer as determined by chiral HPLC analysis.
16. As a testament to the robustness of this methodology, the displacement of **2b** with an α-amino ester has been performed on 2 kg scale, affording the desired product in 94% yield with only 3% racemization of the benzylic stereocenter.
17. Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2436.