Facile preparation of CF_3-substituted carbinols with an azine donor and subsequent kinetic resolution through stereoselective Si–O coupling†‡

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A number of CF_3-substituted carbinols decorated with an azine donor are efficiently prepared from fluoral and kinetically resolved in a reagent-controlled, Cu–H-catalysed Si–O coupling with a chiral silane. Selectivity factors are high, indicating a larger steric effect than CH_3 or C_6H_5 groups.

Introduction

Stereodefined α-CF_3-substituted alcohols are common linchpins for the synthesis of chiral fluorine-containing molecules, and the preparation of these important building blocks is a continuously evolving area of asymmetric catalysis.[1] Out of the many methods available today for enantioselective formation of these alcohols,[2,3] kinetic resolution of racemic mixtures might be a reasonable alternative, in particular when processing prochiral CF_3-containing precursors turns out to be complicated. While enzymatic kinetic resolution of CF_3-substituted alcohols is well-developed,[4] non-enzymatic acylation procedures are still limited to a handful of examples.[5] Interestingly, CF_3-substituted carbinols failed to react in palladium(II)-catalysed oxidative kinetic resolution.[6]

Both enzymatic and non-enzymatic kinetic resolutions of alcohols often hinge upon acylation.[7] Conversely, a related yet long-overlooked strategy, kinetic resolution through stereoselective Si–O coupling,[8] has just recently attracted considerable attention.[9] On the one hand, Hoveyda *et al.* elaborated a remarkably selective, catalyst-controlled protocol, in which an organocatalysed Si–O bond formation using a chlorosilane allows for the discrimination of enantiomeric 1,2-diols.[10] On the other hand, our reagent-controlled approach is based on a Cu–H-catalysed, dehydrogenative Si–O coupling using a silicon-stereogenic silane.[11,12] Diastereocontrol in this kinetic resolution originates from the stereochemical information at the silicon atom and is good for secondary[11] and tertiary[12] γ-donor-functionalised alcohols *rac*-**A** and *rac*-**B** with privileged cyclic silane (^{Si}S)-**1**[13] (Fig. 1) and a cognate strained silane (not shown), respectively.[14]

Superior diastereoselectivities (dr > 90:10) and selectivity factors (s > 15) were usually observed with an aryl rather than an alkyl group attached to the carbinol carbon atom. For example, poor performance is seen for CH_3-substituted *rac*-**A** (R = CH_3),[11] which is why we had previously excluded the CF_3 substituent in *rac*-**A** (R = CF_3) from our work. Its steric demand is however expected to increase, even more pronounced than that of a flat phenyl group in *rac*-**A** (R = C_6H_5).[15] Differences might also arise from the electronegativity of the fluorine atom and the highly polarised C–F bond, and interaction of fluorine and silicon atoms is at least conceivable.[16] We therefore decided to test γ-donor-functionalised, α-CF_3-substituted alcohols *rac*-**A** (R = CF_3) in our Cu–H-catalysed, dehydrogenative Si–O coupling. In this paper, we disclose the efficient kinetic resolution of several CF_3-substituted carbinols with an azine donor[17] and their facile preparation from trifluoroacetaldehyde (fluoral).

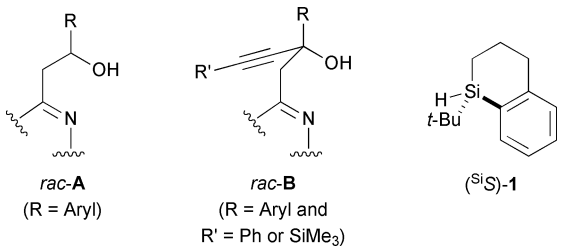

Fig. 1 Privileged γ-donor-functionalised alcohols and chiral silane.

Preparation of the CF_3-substituted carbinols

We envisioned the direct synthesis of the target compounds *rac*-**2**–*rac*-**9** from fluoral by nucleophilic addition of metallated CH_3-substituted azines (Scheme 1). To our surprise, we learned that such a disconnection is rarely used in the preparation of α-CF_3-substituted alcohols.[18,19] We note though that an expedient synthesis of the corresponding ketones is known.[20]

By the procedure outlined in Scheme 1, we were able to make alcohols derived from pyridine (*rac*-**2**, *rac*-**5** and *rac*-**9**), (iso)quinoline (*rac*-**3** and *rac*-**4**), pyridazine (*rac*-**6**), pyrimidine (*rac*-**7**) and pyrazine (*rac*-**8**). For this, fluoral (obtained as its hydrate) was dried over P_4O_{10} in di-*n*-butyl ether[21] and then condensed in a separate flask at −78 °C. Chemical yields (51–84%) are therefore based on the CH_3-substituted azine.

For the preparation of *rac*-**10** (Scheme 2) we had to follow the published route[20] because metallation of 2,4-lutidine was not completely regioselective (Scheme 1). The reduction step required the presence of $CeCl_3$, likely due to the distinct tendency towards enolisation.[20]

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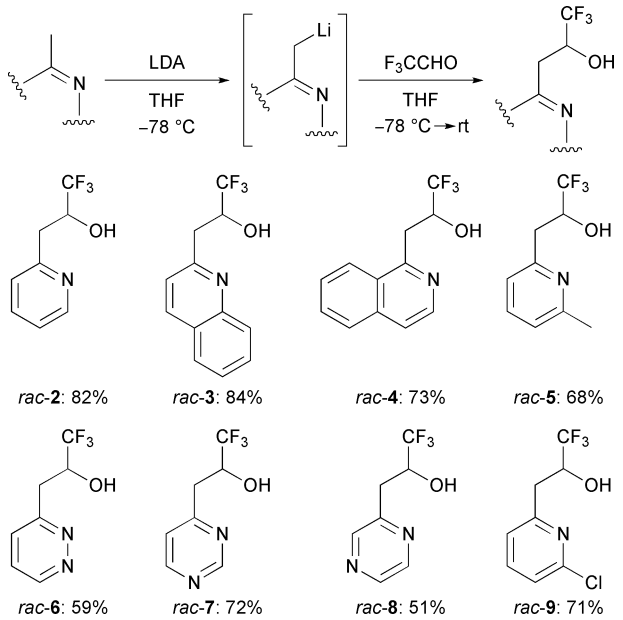
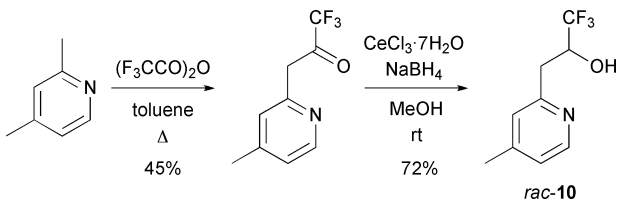
† Dedicated to Professor Günter Haufe on the occasion of his 60th birthday.

‡ Electronic supplementary information (ESI) available: Preparation of *rac*-**10**, characterisation data of (^{Si}R,*R*)-**11**–(^{Si}R,*R*)-**19** and (^{Si}R*,*R**)-**21** as well as ^1H, ^{13}C and ^{19}F NMR spectra of all new compounds. See DOI: 10.1039/b911534j



Scheme 1 Preparation of azine-containing, CF_3-substituted carbinols.



Scheme 2 Alternative route to CF_3- and azine-containing carbinols.[20]

Kinetic resolution through Si–O coupling

Our survey commenced with the reagent-controlled Si–O coupling of carbinols *rac*-**2**–*rac*-**10** with silane *rac*-**1** (Scheme 3 and Table 1). The diastereoselectivity is an unbiased measure for the selectivity factor of this kinetic resolution. The diastereomeric excess in the racemic series (de_{rac}) corresponds to the enantiomeric excess (ee) of the recovered alcohol in the enantiomeric series at exactly 50% conversion, provided that both follow identical kinetics (*cf.* footnote *c*, Table 1). Therefore, all reactions were initially performed in the racemic series. CF_3-substituted carbinol *rac*-**2** served as a reference point as the diastereomeric ratios for the related CH_3- and C_6H_5-substituted alcohols are known (dr = 78:22 *vs.* dr = 92:8). We were delighted to find that the standard CuCl–(3,5-xylyl)$_3$P–NaO*t*-Bu system[11a,11c] in toluene as solvent produced an excellent level of diastereoselection (dr = 94:6) at high reaction rate in almost quantitative chemical yield (97%). This data corresponds to a superb selectivity factor of 45.5 (Table 1, entry 1), thus exceeding our so far best results![11a,11c] Carbinols *rac*-**3**–*rac*-**5** and *rac*-**9**–*rac*-**10** containing an azine with just one nitrogen donor atom reacted almost equally well (Table 1, entries 2–4 and 8–9). In contrast to that, heteroarenes *rac*-**7**–*rac*-**8** (except for *rac*-**6**) with two nitrogen donor atoms markedly diminished the reaction rate (two days instead of a few hours) while diastereoselection remained at a decent level (Table 1, entries 5–7).

Table 1 Kinetic resolution of γ-donor-functionalised, α-CF_3-substituted carbinols by diastereoselective Si–O coupling with *rac*-**1** (racemic series)

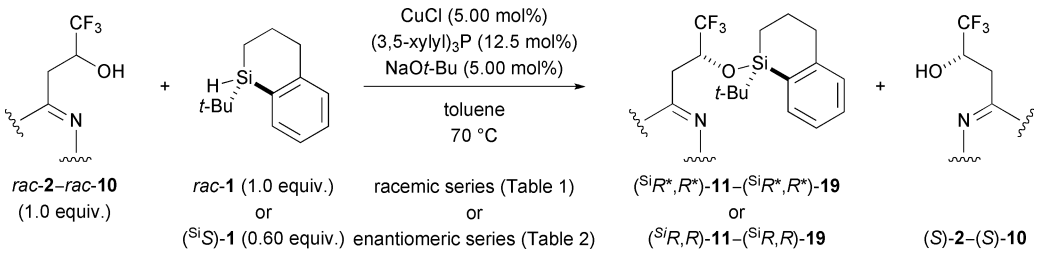
Entry	Racemic alcohol	Silyl ether	Yield[a] (%)	dr[b]	*s*[c]
1	*rac*-**2**	($^{Si}R^*,R^*$)-**11**	97	94:6	45.5
2	*rac*-**3**	($^{Si}R^*,R^*$)-**12**	96	90:10	21.9
3	*rac*-**4**	($^{Si}R^*,R^*$)-**13**	95	93:7	36.6
4	*rac*-**5**	($^{Si}R^*,R^*$)-**14**	98	89:11	18.9
5	*rac*-**6**	($^{Si}R^*,R^*$)-**15**	95	88:12	16.6
6	*rac*-**7**	($^{Si}R^*,R^*$)-**16**	54	91:9	25.5
7	*rac*-**8**	($^{Si}R^*,R^*$)-**17**	33	88:12	16.6
8	*rac*-**9**	($^{Si}R^*,R^*$)-**18**	93	86:14	13.0
9	*rac*-**10**	($^{Si}R^*,R^*$)-**19**	97	93:7	36.6

[a] Yield of analytically pure silyl ether isolated by flash chromatography on silica gel. [b] Determined by GLC analysis as well as ^{19}F NMR spectroscopy prior to purification by integration of the baseline-separated (resonance) signals of the diastereomers. [c] Selectivity factor calculated from $s = \ln[(1 - 0.5) \times (1 - de_{rac})]/\ln[(1 - 0.5) \times (1 + de_{rac})]$.[22]

Kinetic resolution of *rac*-**2** with enantiopure (^{Si}S)-**1** (>99% ee) afforded the slow-reacting enantiomer (*S*)-**2** with 95% ee and the silyl ether of the fast-reacting enantiomer (^{Si}R,*R*)-**11** with dr = 88:12 at 53% conversion (Scheme 3, Table 2, entry 1). The absolute and relative configurations of (*S*)-**2** and (^{Si}R,*R*)-**11** were assigned unambiguously by comparison with reported values for (*S*)-**2**[17] and (^{Si}S)-**1**;[13] these are in agreement with other diastereoselective Si–O couplings of *rac*-**A**.[11a,11c]

As predicted from the data obtained in the racemic series (Table 1), quinolinyl- and isoquinolinyl-substituted carbinols *rac*-**3** and *rac*-**4** were resolved at high reaction rate with selectivity factors comparable to that of *rac*-**2** (Table 2, entries 2 and 3). The same is true for picolinyl-substituted *rac*-**5** and *rac*-**10** (Table 2, entries 4 and 9). Out of the substrates decorated with an azine donor with two nitrogen atoms (Table 2, entries 5–7), it was only *rac*-**6** that reacted particularly sluggishly (Table 2, entry 5). A chloro substituent in the 6-position of the pyridine (*cf.* 6-picolinyl-substituted *rac*-**5**) was tolerated as well (Table 1, entry 8).

A control experiment, namely the Si–O coupling of *rac*-**1** and unfunctionalised carbinol *rac*-**20**,[23] again corroborated the decisive role of the tethered nitrogen donor (*rac*-**20** → *rac*-**21**, Scheme 4). As in previous projects,[11a,11c] the chelation ability of

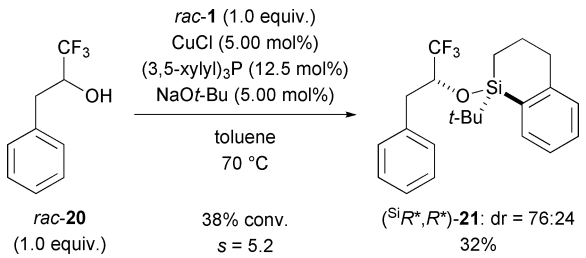


Scheme 3 Kinetic resolution of γ-donor-functionalised, α-CF_3-substituted carbinols by diastereoselective Si–O coupling.

Table 2 Kinetic resolution of γ-donor-functionalised, α-CF_3-substituted carbinols by diastereoselective Si–O coupling with (^{Si}S)-**1** (enantiomeric series)

		Silyl ether of fast-reacting alcohol			Slow-reacting alcohol				
Entry	Racemic alcohol	No.	Yield[a] (%)	dr[b]	No.	Yield[a](%)	ee[c] (%)	Conv[d] (%)	s[e]
1	*rac*-**2**	($^{Si}R,R$)-**11**	53	88:12	(*S*)-**2**[f]	38	95	53	43.0
2	*rac*-**3**	($^{Si}R,R$)-**12**	51	77:23	(*S*)-**3**	42	89	53	25.0
3	*rac*-**4**	($^{Si}R,R$)-**13**	50	84:16	(*S*)-**4**	43	88	51	34.5
4	*rac*-**5**	($^{Si}R,R$)-**14**	55	80:20	(*S*)-**5**	38	93	56	21.2
5	*rac*-**6**	($^{Si}R,R$)-**15**	29	80:20	(*S*)-**6**	61	35	30	13.9
6	*rac*-**7**	($^{Si}R,R$)-**16**	52	79:21	(*S*)-**7**	25	91	54	24.6
7	*rac*-**8**	($^{Si}R,R$)-**17**	53	85:15	(*S*)-**8**	38	87	55	16.4
8	*rac*-**9**	($^{Si}R,R$)-**18**	58	76:24	(*S*)-**9**	36	91	59	13.4
9	*rac*-**10**	($^{Si}R,R$)-**19**	55	76:24	(*S*)-**10**	36	98	56	34.3

[a] Yield (based on starting racemic alcohol) of analytically pure silyl ether and recovered alcohol, respectively isolated by flash chromatography on silica gel. [b] Determined by GLC analysis as well as ^{19}F NMR spectroscopy prior to purification by integration of the baseline-separated (resonance) signals of the diastereomers. [c] Determined by HPLC analysis using Daicel Chiralpak columns providing baseline separation of enantiomers. [d] Determined by GLC analysis as well as ^{19}F NMR spectroscopy prior to purification by integration of the baseline-separated (resonance) signals of the diastereomers and the slow-reacting alcohol. [e] Selectivity factor calculated from $s = \ln[(1 - \text{conv.}) \times (1 - \text{ee})]/\ln[(1 - \text{conv.}) \times (1 + \text{ee})]$.[22] [f] Absolute configuration secured by comparison with reported optical rotation.[17]



Scheme 4 Diastereoselective Si–O coupling of an unfunctionalised, α-CF_3-substituted carbinol.

the alcohol decided on the efficiency of the kinetic resolution in terms of reactivity and diastereoselectivity. Nevertheless, a diastereomeric ratio of 76:24 is somewhat higher than that of corresponding C_6H_5-substituted carbinol (dr = 60:40).[11a]

Conclusion

To summarise, we elaborated a straightforward method for the synthesis of γ-donor-functionalised, α-CF_3-substituted carbinols by nucleophilic addition of metallated methylazines to fluoral. Compared with α-CH_3- and α-C_6H_5-substituted carbinols, their subsequent kinetic resolution by dehydrogenative Cu–H-catalysed Si–O coupling with our silicon-stereogenic silane[13] turned out to be unexpectedly selective (dr = 86:14–96:4 and s = 13.0–45.5). Moreover, a number of these carbinols are relatively reactive. Both of these experimental observations might suggest a Lewis acid–base interaction of a fluorine atom in *rac*-**2**–*rac*-**10** and the silicon atom in *rac*-**1**.[16] The resulting enantiomerically enriched alcohols might be further processed in enantiospecific C–C bond-forming reactions.[24]

Experimental‡

General procedure for the preparation of the CF_3-substituted carbinols

In a flame-dried Schlenk flask, a solution of freshly distilled *i*-Pr_2NH (1.45 mL, 1.05 g, 10.4 mmol, 1.30 equiv.) in anhydrous THF (10 mL) is cooled to −78 °C followed by slow addition of *n*-BuLi (6.00 mL, 9.60 mmol, 1.20 equiv., 1.6 M solution in hexanes). The reaction mixture is then allowed to warm to room temperature and is maintained at this temperature for 30 minutes. After recooling to −78 °C, a solution of the requisite CH_3-substituted azine (8.00 mmol, 1.00 equiv.) in anhydrous THF (10 mL) is added in one portion and stirred at this temperature for further 30 minutes. The deeply coloured mixture is added to fluoral (prepared from its hydrate by drying over P_4O_{10} in di-*n*-butyl ether,[21] approximately 1.00 equiv.) *via* syringe. After warming to room temperature, the reaction mixture is quenched with H_2O (10 mL) and diluted with *t*-butyl methyl ether (10 mL). The pH is adjusted to 7–8 by adding aqueous HCl (2 M), and the organic phase is separated. Extraction of the aqueous phase with dichloromethane (3 × 25 mL) and washing of the combined organic extracts with brine (20 mL) is followed by drying of the organic phase over $MgSO_4$. The solvents are evaporated under reduced pressure and the resulting residue is purified by flash column chromatography on silica gel using dicholoromethane–methanol mixtures as eluent, affording the desired alcohol as off-white or amber-yellow solids.

Representative procedure for the Cu–H-catalysed Si–O coupling

A flame-dried Schlenk tube was charged with CuCl (2.0 mg, 20 μmol, 5.0 mol%), tris(3,5-xylyl)phosphine (17.3 mg, 50.0 μmol, 12.5 mol%) and degassed toluene (1.5 mL) followed by addition of solid NaO*t*-Bu (1.9 mg, 20 μmol, 5.0 mol%). At room temperature, the pre-catalyst was then successively treated with a solution of alcohol *rac*-**2** (76.4 mg, 400 μmol) in toluene (2.0 mL) and a solution of silane (^{Si}S)-**1** (49.1 mg, 240 μmol, 0.600 equiv., >99% ee) in toluene (0.5 mL). The reaction mixture was maintained at 70 °C until GLC analysis of an aliquot indicated full conversion (after approximately 12 h) of (^{Si}S)-**1** into ($^{Si}R,R$)-**11** (dr = 88:12). The crude mixture was directly loaded onto silica gel, and the solvent was evaporated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane–*t*-butyl methyl ether = 95:5 and dichloromethane–methanol = 30:1) gave ($^{Si}R,R$)-**11** (88.2 mg, 58%, dr = 88:12) as a colorless oil, as well as

enantioenriched alcohol (*S*)-**2** (29.0 mg, 38%, 95% ee) as a white solid.

1,1,1-Trifluoro-3-pyridin-2-ylpropan-2-ol (2)

Analytical data for *rac*-**2**: Yield: 82%. $R_f = 0.17$ (dichloromethane–methanol = 40:1). M.p. 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.02 (dd, J = 15.6, 8.5 Hz, 1H), 3.09 (dd, J = 15.6, 3.4 Hz, 1H), 4.48 (dqd, J = 8.4, 3.5, 3.4 Hz, 1H), 6.39 (br s, 1H), 7.27–7.35 (m, 2H), 7.68 (ddd, J = 5.9, 5.9, 1.8 Hz, 1H), 8.45 (ddd, J = 4.3, 4.3, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.5 (m), 69.7 (q, J = 31 Hz), 122.4, 124.1, 125.0 (q, J = 281 Hz), 137.5, 148.4, 157.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ −79.2. IR (ATR) 3745 (br, O–H), 1268 (m, C–F) cm^{-1}. HRMS (ESI) calcd for $C_8H_8F_3NONa$ (M + Na$^+$): 214.0450; found: 214.0439. Anal. calcd for $C_8H_8F_3NO$ (191.15): C, 50.27; H, 4.22; N, 7.33; found: C, 50.20; H, 3.92; N, 7.21.

Analytical data for (*S*)-**2** (95% ee, Table 2, entry 1,): Yield: 38%. $[\alpha]_D^{20} = -16.1$, $[\alpha]_{578}^{20} = -17.0$, $[\alpha]_{546}^{20} = -18.8$, $[\alpha]_{436}^{20} = -28.0$, $[\alpha]_{365}^{20} = -123$ (*c* 0.935, $CHCl_3$). HPLC (Daicel Chiralpak IA column, column temperature 20 °C, solvent *n*-heptane–*i*-propanol = 95:5, flow rate 0.80 mL/min, λ = 230 nm): t_R = 10.54 min for (*R*)-**2**, t_R = 11.76 min for (*S*)-**2**.

1,1,1-Trifluoro-3-quinolin-2-ylpropan-2-ol (3)

Analytical data for *rac*-**3**: Yield: 84%. $R_f = 0.14$ (dichloromethane–methanol = 50:1). M.p. 153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30 (dd, J = 15.9, 7.7 Hz, 1H), 3.35 (dd, J = 15.9, 4.3 Hz, 1H), 4.63 (dqd, J = 7.7, 4.4, 4.3 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.56 (ddd, J = 8.1, 6.3, 1.1 Hz, 1H), 7.74 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.83 (dd, J = 8.1, 1.0 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.6 (m), 69.8 (q, J = 31 Hz), 122.0, 125.0 (q, J = 285 Hz), 126.4, 126.8, 127.8, 128.3, 130.4, 137.8, 146.5, 152.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ −79.1. IR (ATR) 3057 (br, O–H), 1267 (m, C–F) cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{10}F_3NONa$ (M + Na$^+$): 264.0611; found: 264.0602. Anal. calcd for $C_{12}H_{10}F_3NO$ (241.21): C, 59.75; H, 4.18; N, 5.81; found: C, 59.74; H, 4.06; N, 5.77.

Analytical data for (*S*)-**3** (89% ee, Table 2, entry 2): Yield: 42%. $[\alpha]_D^{20} = -26.7$, $[\alpha]_{578}^{20} = -17.1$, $[\alpha]_{546}^{20} = -44.9$ (*c* 0.595, $CHCl_3$). HPLC (Daicel Chiralpak IA column, column temperature 20 °C, solvent *n*-heptane–*i*-propanol = 90:10, flow rate 0.80 mL/min, λ = 230 nm): t_R = 8.77 min for (*R*)-**3**, t_R = 13.32 min for (*S*)-**3**.

1,1,1-Trifluoro-3-isoquinolin-1-ylpropan-2-ol (4)

Analytical data for *rac*-**4**: Yield: 73%. $R_f = 0.10$ (dichloromethane–methanol = 30:1). M.p. 108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.54 (dd, J = 16.6, 9.5 Hz, 1H), 3.71 (dd, J = 16.6, 2.8 Hz, 1H), 3.74 (ddq, J = 9.5, 2.8, 2.4 Hz, 1H), 6.31 (br s, 1H), 7.62–7.65 (m, 1H), 7.66–7.70 (m, 1H), 7.75 (ddd, J = 7.7, 6.9, 1.2 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.38 (d, J = 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.6 (m), 69.5 (q, J = 31 Hz), 120.6, 124.5, 125.2 (q, J = 281 Hz), 127.0, 127.7, 128.1, 131.0, 136.3, 140.2, 157.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −79.0. IR (ATR) 3054 (br, O–H), 1269 (m, C–F) cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{11}F_3NO$ (M + H$^+$): 242.0787; found: 242.0771. Anal. calcd for $C_{12}H_{10}F_3NO$ (241.21): C, 59.75; H, 4.18; N, 5.81; found: C, 59.79; H, 4.02; N, 5.66.

Analytical data for (*S*)-**4** (88% ee, Table 2, entry 3): Yield: 43%. $[\alpha]_D^{20} = -47.8$, $[\alpha]_{578}^{20} = -50.5$, $[\alpha]_{546}^{20} = -57.7$, $[\alpha]_{436}^{20} = -93.5$ (*c* 0.650, $CHCl_3$). HPLC (Daicel Chiralpak IB column, column temperature 20 °C, solvent *n*-heptane–*i*-propanol = 90:10, flow rate 0.80 mL/min, λ = 230 nm): t_R = 7.66 min for (*R*)-**4**, t_R = 8.58 min for (*S*)-**4**.

1,1,1-Trifluoro-3-(6-methylpyridin-2-yl)propan-2-ol (5)

Analytical data for *rac*-**5**: Yield: 68%. $R_f = 0.13$ (dichloromethane–methanol = 30:1). M.p. 102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 3H), 3.03 (dd, J = 15.3, 7.8 Hz, 1H), 3.11 (dd, J = 15.3, 4.2 Hz, 1H), 4.41 (ddq, J = 7.8, 4.2, 4.0 Hz, 1H), 7.00 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 34.8 (m), 70.1 (q, J = 31 Hz), 120.9, 122.0, 125.0 (q, J = 281 Hz), 137.8, 156.9, 157.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ −79.2. IR (ATR) 3073 (br, O–H), 1267 (m, C–F) cm^{-1}. HRMS (ESI) calcd for $C_9H_{10}F_3NONa$ (M + Na$^+$): 228.0607; found: 228.0609.

Analytical data for (*S*)-**5** (93% ee, Table 2, entry 4): Yield: 38%. $[\alpha]_D^{20} = -15.6$, $[\alpha]_{578}^{20} = -13.9$, $[\alpha]_{546}^{20} = -16.1$, $[\alpha]_{436}^{20} = -22.8$, $[\alpha]_{365}^{20} = -26.6$ (*c* 0.180, $CHCl_3$). HPLC (Daicel Chiralpak IB column, column temperature 20 °C, solvent *n*-heptane–*i*-propanol = 99:1, flow rate 0.80 mL/min, λ = 230 nm): t_R = 7.73 min for (*R*)-**5**, t_R = 12.22 min for (*S*)-**5**.

1,1,1-Trifluoro-3-pyridazin-3-ylpropan-2-ol (6)

Analytical data for *rac*-**6**: Yield: 59%. $R_f = 0.12$ (dichloromethane–methanol = 30:1). M.p. 60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25 (dd, J = 15.5, 9.3 Hz, 1H), 3.75 (dd, J = 15.5, 2.8 Hz, 1H), 4.53 (br s, 1H), 4.69 (dqd, J = 9.3, 3.1, 2.8 Hz, 1H), 7.46 (dd, J = 8.5, 2.0 Hz, 1H), 7.51 (dd, J = 8.4, 4.7 Hz, 1H), 9.09 (dd, J = 4.6, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.0 (m), 69.2 (q, J = 32 Hz), 125.1 (q, J = 282 Hz), 127.4, 128.6, 150.1, 159.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −79.2. IR (ATR) 3134 (br, O–H), 1274 (m, C–F) cm^{-1}. HRMS (ESI) calcd for $C_7H_7F_3N_2ONa$ (M + Na$^+$): 215.0403; found: 215.0409. Anal. calcd for $C_7H_7F_3N_2O$ (192.14): C, 43.76; H, 3.67; N, 14.58; found: C, 43.66; H, 3.36; N, 14.18.

Analytical data for (*S*)-**6** (35% ee, Table 2, entry 5): Yield: 61%. $[\alpha]_D^{20} = +2.88$ (*c* 0.504, $CHCl_3$). HPLC (Daicel Chiralpak IA column, column temperature 20 °C, solvent *n*-heptane–*i*-propanol = 90:10, flow rate 0.80 mL/min, λ = 230 nm): t_R = 12.00 min for (*R*)-**6**, t_R = 15.51 min for (*S*)-**6**.

1,1,1-Trifluoro-3-pyrimidin-4-ylpropan-2-ol (7)

Analytical data for *rac*-**7**: Yield: 72%. $R_f = 0.13$ (dichloromethane–methanol = 30:1). M.p. 79 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.08 (dd, J = 15.3, 8.9 Hz, 1H), 3.18 (dd, J = 15.3, 2.7 Hz, 1H), 4.54 (dqd, J = 8.9, 3.3, 2.7 Hz, 1H), 5.00 (br s, 1H), 7.29 (d, J = 5.2 Hz, 1H), 8.67 (d, J = 5.1 Hz, 1H), 9.10 (d, J = 6.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.2 (m), 69.2 (q, J = 32 Hz), 121.9, 124.8 (q, J = 280 Hz), 157.4, 158.0, 165.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −79.2. IR (ATR) 3103 (br, O–H), 1278 (m, C–F) cm^{-1}. HRMS (ESI) calcd for $C_7H_7F_3N_2ONa$ (M + Na$^+$): 215.0403; found: 215.0405. Anal. calcd for $C_7H_7F_3N_2O$ (192.14): C, 43.76; H, 3.67; N, 14.58; found: C, 43.74; H, 3.53; N, 14.35.

Analytical data for (*S*)-**7** (91% ee, Table 2, entry 6): Yield: 25%. $[\alpha]_D^{20} = +15.7$, $[\alpha]_{578}^{20} = +20.0$, $[\alpha]_{546}^{20} = +26.1$, $[\alpha]_{436}^{20} = +35.0$

(c 0.230, $CHCl_3$). HPLC (Daicel Chiralpak IA column, column temperature 20 °C, solvent n-heptane–i-propanol = 95:5, flow rate 0.80 mL/min, λ = 230 nm): t_R = 7.77 min for (*R*)-**7**, t_R = 9.51 min for (*S*)-**7**.

1,1,1-Trifluoro-3-pyrazin-2-ylpropan-2-ol (8)

Analytical data for *rac*-**8**: Yield: 51%. R_f = 0.15 (dichloromethane–methanol = 30:1). M.p. 61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.12 (dd, J = 15.2, 9.3 Hz, 1H), 3.22 (dd, J = 15.2, 3.2 Hz, 1H), 4.49 (dqd, J = 9.3, 3.2, 3.1 Hz, 1H), 4.81 (br s, 1H) 8.45–8.56 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.0 (m), 69.6 (q, J = 32 Hz), 124.8 (q, J = 281 Hz), 143.4, 143.5, 145.4, 153.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −79.2. IR (ATR) 3150 (br, O–H), 1278 (m, C–F) cm^{-1}. HRMS (ESI) calcd for $C_7H_7F_3N_2ONa$ (M + Na^+): 215.0403; found: 215.0385. Anal. calcd for $C_7H_7F_3N_2O$ (192.14): C, 43.76; H, 3.67; N, 14.58; found: C, 43.68; H, 3.39; N, 14.32. Analytical data for (*S*)-**8** (87% ee, Table 2, entry 7): Yield: 38%. $[\alpha]_D^{20}$ = −34.3, $[\alpha]_{578}^{20}$ = −35.4, $[\alpha]_{546}^{20}$ = −40.0, $[\alpha]_{436}^{20}$ = −44.0, $[\alpha]_{365}^{20}$ = −88.9 (c 0.350, $CHCl_3$). HPLC (Daicel Chiralpak IB column, column temperature 20 °C, solvent n-heptane–i-propanol = 90:10, flow rate 0.80 mL/min, λ = 230 nm): t_R = 9.70 min for (*R*)-**8**, t_R = 11.56 min for (*S*)-**8**.

3-(6-Chloropyridin-2-yl)-1,1,1-trifluoropropan-2-ol (9)

Analytical data for *rac*-**9**: Yield: 71%. R_f = 0.11 (dichloromethane–methanol = 30:1). M.p. 84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.99 (dd, J = 15.2, 9.2 Hz, 1H), 3.09 (dd, J = 15.2, 3.1 Hz, 1H), 4.42 (dqd, J = 9.2, 3.2, 3.0 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.2 (m), 69.8 (q, J = 32 Hz), 122.7, 123.0, 124.8 (q, J = 281 Hz), 139.8, 150.8, 158.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −79.2. IR (ATR) 3179 (br, O–H), 1269 (m, C–F) cm^{-1}. HRMS (ESI) calcd for $C_8H_7F_3NClONa$ (M + Na^+): 248.0060; found: 248.0047.

Analytical data for (*S*)-**9** (91% ee, Table 2, entry 8): Yield: 36%. $[\alpha]_D^{20}$ = −22.5, $[\alpha]_{578}^{20}$ = −23.3, $[\alpha]_{546}^{20}$ = −24.9, (c 0.510, $CHCl_3$). HPLC (Daicel Chiralpak IA column, column temperature 20 °C, solvent n-heptane–i-propanol = 90:10, flow rate 0.80 mL/min, λ = 230 nm): t_R = 7.65 min for (*R*)-**9**, t_R = 9.40 min for (*S*)-**9**.

1,1,1-Trifluoro-3-(4-methylpyridin-2-yl)propan-2-ol (10)

For details of preparation see the ESI‡. Analytical data for *rac*-**10**: Yield: 72%. R_f = 0.42 (cyclohexane–t-butyl methyl ether = 1:2). M.p. 111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.03 (dd, J = 15.4, 8.2 Hz, 1H), 3.10 (dd, J = 15.3, 3.6 Hz, 1H), 4.41 (dqd, J = 8.2, 3.7, 3.4 Hz, 1H), 6.42 (br s, 1H), 7.04–7.05 (m, 2H), 8.13 (d, J = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 35.1 (m), 70.0 (q, J = 31 Hz), 123.4, 124.4, 125.0 (q, J = 282 Hz), 148.0, 149.1, 157.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ −79.2. IR (ATR) 3057 (br, O–H), 1267 (m, C–F) cm^{-1}. HRMS (ESI) calcd for $C_9H_{10}F_3NONa$ (M + Na^+): 228.0607; found: 228.0604. Anal. calcd for $C_9H_{10}F_3NO$ (205.18): C, 52.68; H, 4.91; N, 6.83; found: C, 52.78; H, 4.83; N, 6.49.

Analytical data for (*S*)-**10** (98% ee, Table 2, entry 9): Yield: 36%. $[\alpha]_D^{20}$ = −22.7, $[\alpha]_{578}^{20}$ = −23.8, $[\alpha]_{546}^{20}$ = −32.4, $[\alpha]_{436}^{20}$ = −42.2 (c 0.184, $CHCl_3$). HPLC (Daicel Chiralpak IB column, column temperature 20 °C, solvent n-heptane–i-propanol = 99:1, flow rate 0.80 mL/min, λ = 230 nm): t_R = 10.40 min for (*R*)-**10**, t_R = 16.88 min for (*S*)-**10**.

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