Enantioselective Addition of a Trifluoromethyl Anion to Aryl Ketones and Aldehydes

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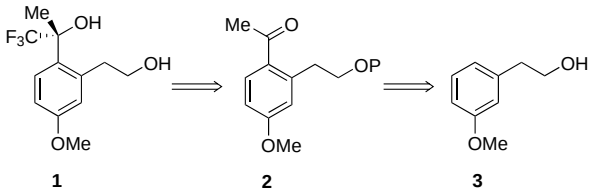
Abstract: The identification and development of a catalyst for the enantioselective nucleophilic addition of a trifluoromethyl anion to a ketone is described. An easily prepared cinchonine-derived catalyst was used in amounts as low as 4 mol% to afford enantiomeric excess as high as 92%.

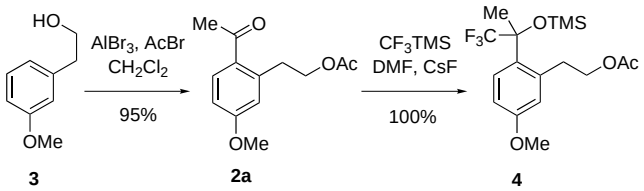
Key words: alkaloids, ketones, aldehydes, asymmetric catalysis, fluorine, nucleophilic additions, substituent effects

The nucleophilic addition of a trifluoromethyl group is not well precedented due to the difficulty generating a stable trifluoromethyl anion.[1–3] In 1989, Olah described a solution to this problem by using trimethylsilyltrifluoromethane (CF_3TMS) as a precursor to the anion, which was liberated by activation with a fluoride source.[4] This method has proven to be successful for addition to a number of electrophiles.[5,6] Furthermore, an asymmetric variation of this reaction, using a cinchonine-derived catalyst, has been described.[7] Unfortunately, the method yielded only modest enantiomeric excess. A chiral triaminosulfonium salt has also been reported for this transformation.[8] We recently were faced with the challenge of preparing diol **1** in enantiomerically-enriched form. While several approaches were considered and evaluated, we found that the desired product could be obtained by addition of a trifluoromethyl group to a suitably protected acetophenone **2**, derived from the corresponding phenethyl alcohol **3** (Scheme 1). Herein we describe the development of a catalyst to accomplish this transformation in a highly enantioselective fashion.



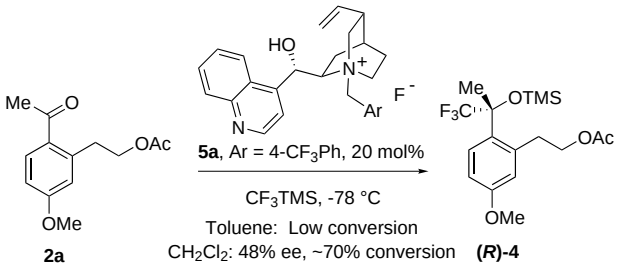
Scheme 1 Retrosynthesis to diol **1**

We initially prepared the known acetophenone **2a** from commercially available alcohol **3** in 95% yield by modifying a literature Friedel–Crafts acylation procedure.[9] The addition of the trifluoromethyl group was successfully achieved using CF_3TMS and CsF in DMF to provide the racemic silylated tertiary alcohol **4** in quantitative yield (Scheme 2).



Scheme 2

Initial investigations into an asymmetric variant of the trifluoromethyl addition began using a literature procedure[7] with cinchonine-derived catalyst **5a**. We observed a poor conversion in toluene, the recommended solvent, whereas CH_2Cl_2 was found to yield a 70% conversion and 48% ee[10] (Scheme 3).



Scheme 3

To further optimize the reaction, we studied the influence of the alcohol protecting group, the structure of the catalyst, and the reaction conditions. All factors affected the enantioselectivity of the reaction. The choice of protecting group of the primary alcohol altered the enantioselectivity and the rate of the reaction. The 3,4-dimethoxybenzoate derivative **2f**, a crystalline solid, provided the greatest level of enantioselectivity (78% ee, Table 1).[11]

Using 20 mol% of catalyst **5b** [Ar = 3,5-$(MeO)_2C_6H_3$], we surveyed the effects of reaction conditions. The addition did not proceed in DMAC, MeCN, toluene, THF or 2-MeTHF (Table 2, Entries 1–5). While the conversion was high in DMF, minimal chiral induction was observed (Entry 6). Fortunately, CH_2Cl_2 provided acceptable conversion and enantionselective excess up to 80% (Entries 7, 8). It appears that an electron rich protecting group maxi-

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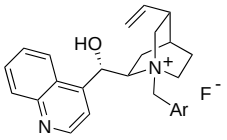
Table 1 Alcohol Protecting Group Effect Using Catalyst **5b** (20 mol%), CF_3TMS (2 equiv) in CH_2Cl_2 at –78 °C

Substrate	P	ee (%)[10,12]
2a	acetate	50
2b	pivalate	38
2c	benzoate	60
2d	4-bromobenzoate	24
2e	4-methoxybenzoate	62
2f	3,4-dimethoxybenzoate	78

mizes the interactions between catalyst and substrate, especially in a non-polar solvent. Temperature also played a role, as the % ee was eroded at temperatures above –40 °C (Entries 9, 10). Additionally, the % ee was slightly lower when less than one equivalent of CF_3TMS was used. However, the reaction concentration, order of reagent addition, and rate of CF_3TMS addition did not significantly impact the enantioselectivity.

Table 2 Solvent and Temperature Effects of CF_3TMS Addition (2 equiv) to Ketone **2f** Using 20 mol% of Catalyst **5b**



5b, Ar = 3,5-MeOPh

Entry	Solvent	Temp. (°C)	Conversion (%)	ee (%)
1	DMAC	–15	0	NA
2	MeCN	–40	0	NA
3	toluene	–78	0	NA
4	THF	–78	0	NA
5	2-MeTHF	–78	0	NA
6	DMF	–40	81	<1
7	CH_2Cl_2	–78	70	80
8	CH_2Cl_2	–40	66	80
9	CH_2Cl_2	–20	28	52
10	CH_2Cl_2	0	<5	42

We next studied the catalyst structure and loading amounts (Table 3). Protection of the secondary alcohol as a methyl or allyl ether resulted in no reaction (Entries 1, 2). Evaluation of the catalyst loading revealed that the use of a lower mol% of catalyst **5b** led to higher conversion and enantioselectivity (Entries 3–6). Higher catalyst loading may increase the potential for competitive enolization of the ketone by the basic fluoride anion. Finally, several catalysts were prepared and surveyed under the optimal conditions [CF_3TMS (1.5 equiv), CH_2Cl_2, –78 °C, catalyst (4 mol%)] (Entries 7–13). We were pleased to find that the 1-methylnaphthyl catalyst **5i** provided not only excellent conversion (97%) but also high enantioselectivity (92%) (Entry 12). The absolute stereochemistry was determined by X-ray analysis of the 4-bromobenzoate derivative (**6d**) which was obtained by hydrolysis of the silyl ether and 3,4-dimethoxybenzoate with NaOH and acylation with 4-bromobenzoyl chloride (Figure 1).

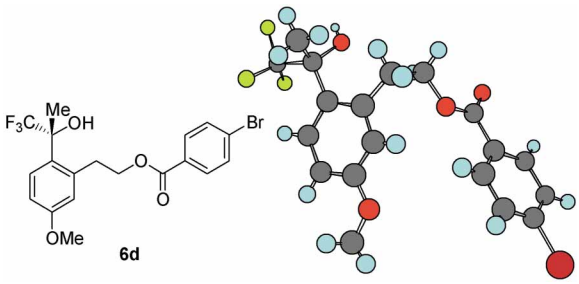
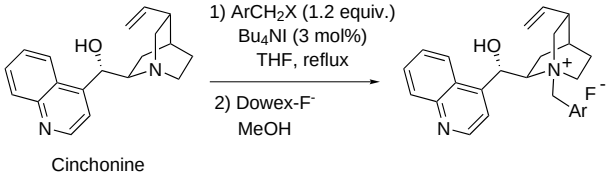


Figure 1 X-ray single crystal of **6d**

The preparation of these catalysts was straightforward (Scheme 4). These derivatives of *Cinchona* alkaloids have been used as catalysts in a number of important transformations.[13] We found that the best method for the formation of the ammonium salt was by treating cinchonine with 1.2 equiv of the benzyl halide in the presence of a catalytic amount of Bu_4NI (3 mol%) in refluxing THF. The advantage of using THF over the commonly-used toluene is that any unreacted cinchonine remains in solution. The ammonium salt is filtered followed by ion exchange using Dowex-F^- in MeOH.[14] The catalysts were isolated by filtration from methyl *tert*-butyl ether and proved to be air stable. In the case of catalysts **5c** and **5d**, the ether formation was performed prior to the ion exchange.[15]



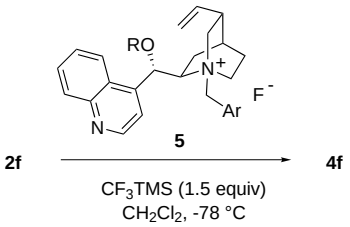
93% overall when Ar = 1-naphthyl (**5i**)

Scheme 4

Finally, we looked at different substrates using either catalysts **5b** and **5i** (Table 4). The enantioselectivity observed in these cases is not as high as for the substrate for which we optimized our catalyst. However, it is conceivable that for each substrate the catalyst could be optimized to provide an acceptable level of enantioselectivity in the CF_3 addition.

A cinchonine-derived catalyst **5i** was developed for the enantioselective addition of a trifluoromethyl anion to ketone **2f** to generate a quaternary center in 92% ee using only 4 mol% of catalyst. This reaction represents the high-

Table 3 Optimization of the Catalyst and Catalyst Loading



	Ar	R	Catalyst	Quantity (mol%)	Conversion (%)	ee (%)[12]
1	3,5-$(MeO)_2C_6H_3$	Me	**5c**	20	0	NA
2	3,5-$(MeO)_2C_6H_3$	Allyl	**5d**	20	0	NA
3	3,5-$(MeO)_2C_6H_3$	H	**5b**	50	27	69
4	3,5-$(MeO)_2C_6H_3$	H	**5b**	20	71	77
5	3,5-$(MeO)_2C_6H_3$	H	**5b**	10	96	82
6	3,5-$(MeO)_2C_6H_3$	H	**5b**	4	98	83
7	4-$MeOC_6H_4$	H	**5e**	4	88	58
8	3-$MeOC_6H_4$	H	**5f**	4	86	74
9	3,5-$(CF_3)_2C_6H_3$	H	**5g**	4	21	70
10	4-$CF_3C_6H_4$	H	**5a**	4	77	69
11	9-anthracyl	H	**5h**	4	95	85
12	1-naphthyl	H	**5i**	4	97	92
13	4-biphenyl	H	**5j**	4	86	68

est enantioselectivity in the addition of a trifluoromethyl anion to a carbonyl using organocatalysis. While this catalyst did not prove to be generally applicable to a variety of ketones it demonstrated that highly enantioselective CF_3 anion additions to ketones are feasible with the properly designed catalyst.

All starting materials were obtained from commercial suppliers and used without further purification. Solvents were purchased from Aldrich in Sure/Seal™ bottles. Reactions were performed under an anhyd N_2 atmosphere. Silica gel chromatography was carried out with J.T.Baker 40 μm silica gel according to Still's procedure.[17] Mps were measured in open capillary tubes. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) were measured in $CDCl_3$ unless otherwise indicated. *J* values are given in Hz. IR spectra were recorded as thin films using a Nicolet Avatex 300 FTIR.

Acetic Acid 2-(2-Acetyl-5-methoxyphenyl)ethyl Ester (2a)

To $AlBr_3$ (51.15g, 191.8 mmol) in CH_2Cl_2 (80 mL) at 0 ºC was slowly added acetyl bromide (17.0 mL, 230 mmol). The solution was allowed to warm to 15 ºC and alcohol **3** (11.68g, 76.75 mmol) was added in CH_2Cl_2 (20 mL + 10 mL rinse) over 35 min. The orange solution was allowed to stir for 1 h and was poured over ice (100mL) and aq HCl (1 M; 100 mL). The product was extracted with CH_2Cl_2 (2 × 50 mL) and the organic extracts were washed with aq NaOH (1 M; 50 mL). The organic layer was filtered through Celite and concentrated.

Yield 16.96g (94%) as a 10:1 mixture of regioisomers; oil.

IR: 1737, 1674, 1604, 1567, 1358, 1290, 1037 cm^{-1}.

^{1}H NMR: δ = 2.05 (s, 3 H), 2.59 (s, 3 H), 3.29 (t, 2 H, *J* = 6.8), 3.89 (s, 3 H), 4.33 (t, 2, *J* = 6.8), 6.81 (d, 1 H, *J* = 2.5), 6.85 (dd, 1 H, *J* = 8.6, 2.6), 7.82 (d, 1 H, *J* = 8.6).

^{13}C NMR: δ = 22.28, 30.37, 3536, 56.63, 66.11, 101.21, 112.63, 119.17, 131.00, 134.24, 142.90, 163.24, 172.32.

Anal. Calcd for $C_{13}H_{22}O_4$: C, 65.71; H, 7.21. Found: C, 66.09; H, 6.83.

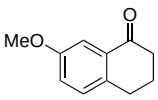
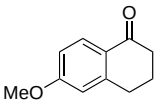
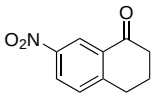
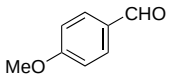
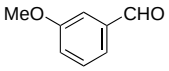
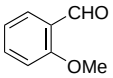
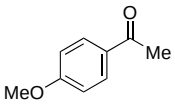
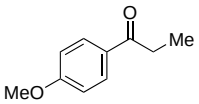
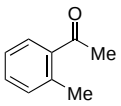
Acetic Acid 2-[5-Methoxy-2-(2,2,2-trifluoro-1-methyl-1-trimethylsilanyloxyethyl)phenyl]ethyl Ester [(*R*)-4]

To ketone **2a** (7.21g, 30.5 mmol) in DMF (40.0 mL) was added CsF (0.550g, 3.62 mmol). The solution was cooled to 0 ºC and CF_3TMS (5.90mL, 39.9 mmol) was added dropwise. After 40 min, no starting material was detected by GC–MS. For characterization purposes, the reaction mixture was poured into H_2O and extracted with methyl *tert*-butyl ether (MTBE) (100 mL). The organic layer was washed with H_2O (2 × 75 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated to provide acetic acid 2-[5-methoxy-2-(2,2,2-trifluoro-1-methyl-1-trimethylsilanyloxyethyl)phenyl]ethyl ester as a crude oil.

IR: 2961, 1741, 1610, 1383, 1286, 1255, 1165, 1140, 1039, 864, 846 cm^{-1}.

^{1}H NMR: δ = 0.19 (s, 9 H), 1.93 (s, 3 H), 2.10 (s, 3 H), 3.23–3.33 (m, 1 H), 3.42–3.52 (m, 1 H), 3.83 (s, 3 H), 4.26–4.32 (m, 2 H), 6.77 (dd, 1 H, *J* = 8.9, 2.8), 6.86 (d, 1 H, *J* = 2.9), 7.32 (d, 1 H, *J* = 8.9).

Table 4 Alternative Substrates Using 4 mol% of Catalyst, CF_3TMS (1.5 equiv), in CH_2Cl_2 at –50 °C

Entry	Substrate	Catalyst	Conversion (%)	ee (%)[16]
1		**5b**	63	64
		5i	88	25
2		**5b**	78	30
		5i	65	39
3		**5b**	100	28
		5i	100	1
4		**5b**	88	58
		5i	100	9
5		**5b**	100	14
		5i	100	6
6		**5b**	100	11
		5i	100	9
7		**5b**	100	28
		5i	96	27
8		**5b**	96	32
		5i	96	43
9		**5b**	100	6
		5i	100	5

^{13}C NMR: δ = 2.03, 21.03, 24.64, 32.86, 55.11, 65.54, 78.90 (q, *J* = 30.3), 111.26, 117.44, 125.70 (q, *J* = 287), 129.56, 129.79, 139.77, 159.17, 171.09.

Anal. Calcd for $C_{17}H_{25}F_3O_4Si$: C, 53.95; H, 6.66. Found: C,53.72; H, 6.53.

Acylation of Alcohol 3; General Procedure

To a solution of an alcohol **3** in CH_2Cl_2 (10 volumes) at 0 °C was added Et_3N (1.1 equiv), the acid chloride (1.1 equiv) and DMAP (0.2 equiv). The reactions were followed by TLC and quenched with H_2O (10 volumes) upon disappearance of the starting material. The layers were separated and the organic layer was dried (Na_2SO_4), filtered and concentrated. The esters were used directly in the next step without further purification.

2,2-Dimethylpropionic Acid 2-(3-Methoxyphenyl)ethyl Ester

^1H NMR: δ = 1.20 (s, 9 H), 2.94 (t, 2 H, *J* = 7.0), 3.83 (s, 3 H), 4.30 (t, 2 H, *J* = 7.0), 6.79–6.86 (m, 3 H), 7.24 (dd, 1, *J* = 8.7, 7.5).

Benzoic Acid 2-(3-Methoxyphenyl)ethyl Ester

^1H NMR: δ = 3.09 (t, 2 H, *J* = 7.0), 3.83 (s, 3 H), 4.57 (t, 2 H, *J* = 7.0), 6.81–6.93 (m, 3 H), 7.29 (t, 1 H, *J* = 3.5), 7.44–7.50 (m, 2 H), 7.56–7.59 (m, 1 H), 8.07 (dd, 2 H, *J* = 8.4, 1.4).

4-Bromobenzoic Acid 2-(3-Methoxyphenyl)ethyl Ester

^1H NMR: δ = 3.10 (t, 2 H, *J* = 7.0), 3.85 (s, 3 H), 4.58 (t, 2 H, *J* = 7.0), 6.82–6.93 (m, 3 H), 7.26–7.32 (m, 1 H), 7.62 (d, 2 H, *J* = 8.9), 7.92 (d, 2 H, *J* = 8.9).

4-Methoxybenzoic Acid 2-(3-Methoxyphenyl)ethyl Ester

^1H NMR: δ = 3.10 (t, 2 H, *J* = 7.0), 3.84 (s, 3 H), 3.91 (s, 3 H), 4.55 (t, 2 H, *J* = 7.0), 6.82–6.98 (m, 3 H), 6.96 (d, 2 H, *J* = 8.9), 7.26–7.32 (m, 1 H), 8.03 (d, 2 H, *J* = 9.0).

3,4-Dimethoxybenzoic Acid 2-(3-Methoxyphenyl)ethyl Ester

^1H NMR: δ = 3.08 (t, 2 H, *J* = 7.0), 3.82 (s, 3 H), 3.95 (s, 3 H), 3.97 (s, 3 H), 4.54 (t, 2 H, *J* = 7.0), 6.80 (dd, 1 H, *J* = 2.6, 0.8), 6.83 (dd, 1 H, *J* = 2.6, 0.8), 6.87 (t, 1 H, *J* = 1.9), 6.90 (d, 1 H, *J* = 8.6), 7.24 (d, 1 H, *J* = 7.8), 7.54 (d, 1 H, *J* = 1.9), 7.69 (dd, 1 H, *J* = 8.4, 2.0).

Friedel–Crafts Acylation of Esters; General Procedure

To a solution of the ester in CH_2Cl_2 (10 volumes) at 0 °C was added $TiCl_4$ (1.5 equiv) and AcCl (2.0 equiv). The reaction was followed by either TLC or HPLC. Upon disappearance of the starting material, the reaction was poured into ice and aq HCl (1 M; 10 volumes) was added. The layers were separated and the organic layer was washed with H_2O, dried (Na_2SO_4), filtered and concentrated. The product was purified by crystallization or chromatography.

2,2-Dimethylpropionic Acid 2-(2-Acetyl-5-methoxyphenyl)ethyl Ester (2b)

Yield: 70%; filtered through a SiO_2 pad, EtOAc–hexanes, 80:20.

IR: 2972, 1723, 1674, 1603, 1656, 1249, 1239, 1155 cm^{-1}.

^1H NMR: δ = 1.16 (s, 9 H), 2.58 (s, 3 H), 3.28 (t, 2 H, *J* = 6.5), 3.86 (s, 3 H), 4.32 (t, 2 H, *J* = 6.5), 6.80–6.84 (m, 2 H), 7.81 (d, 1 H, *J* = 8.4).

^{13}C NMR: δ = 27.40, 29.27, 34.45, 38.88, 55.55, 64.86, 111.64, 118.25, 139.80, 133.24, 142.13, 162.13, 178.67, 199.51.

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.84; H, 8.34.

Benzoic Acid 2-(2-Acetyl-5-methoxyphenyl)ethyl Ester (2c)

Yield: 90%; chromatography EtOAc–hexane, 30:70.

IR: 1717, 1673, 1603, 1567, 1275, 1251, 1115, 713 cm^{-1}.

^1H NMR: δ = 2.56 (s 3 H), 3.39 (t, 2 H, *J* = 6.6), 3.78 (s, 3 H), 4.56 (t, 2 H, *J* = 6.4), 6.79–6.83 (m, 2 H), 7.39 (d, 1 H, *J* = 7.3), 7.41 (d, 1 H, *J* = 7.9), 7.41–7.48 (m, 2 H), 7.79 (d, 1 H, *J* = 8.5), 7.99 (dd, 2 H, *J* = 8.3, 1.2).

^{13}C NMR: δ = 29.34, 34.56, 55.58, 65.61, 112.04, 118.08, 128.54, 129.81, 130.40, 130.74, 133.04, 133.28, 142.12, 162.29, 166.77, 199.60.

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.38; H, 6.34.

4-Bromobenzoic Acid 2-(2-Acetyl-5-methoxyphenyl)ethyl Ester (2d)

Yield: 95%; silica pad, EtOAc–hexanes, 30:70.

IR: 1715, 1670, 1591, 1565, 1267, 1235, 1102, 1068, 1011, 756 cm^{-1}.

^1H NMR: δ = 2.56 (s 3 H), 3.38 (t, 2 H, *J* = 6.6), 3.80 (s, 3 H), 4.55 (t, 2 H, *J* = 6.6), 6.80 (s, 1 H), 6.81 (dd, 1 H, *J* = 7.5, 2.9), 7.54 (d, 2 H, *J* = 8.7), 7.79–7.82 (m, 1 H), 7.85 (d, 2 H, *J* = 8.7).

^{13}C NMR: δ = 29.31, 64.54, 55.60, 65.85, 111.88, 118.23, 128.13, 129.64, 129.94, 131.33, 131.89, 133.37, 141.90, 162.31, 165.98, 199.50.

Anal. Calcd for $C_{18}H_{17}BrO_4$: C, 57.31; H, 4.54. Found: C, 57.09; H, 4.39.

4-Methoxybenzoic Acid 2-(2-Acetyl-5-methoxyphenyl)ethyl Ester (2e)
Yield: 95%; silica pad, EtOAc–hexanes, 30:70; mp 99–100 °C.

IR: 1706, 1671, 1602, 1248, 1166, 1101, 1027, 770 cm^{-1}.

^1H NMR: δ = 2.55 (s 3 H), 3.38 (t, 2 H, *J* = 6.6), 3.78 (s, 3 H), 3.83 (s, 3 H), 4.52 (t, 2 H, *J* = 6.6), 6.78–6.82 (m, 2 H), 6.88 (d, 2 H, *J* = 9.1), 7.78 (d, 1 H, *J* = 8.3), 7.94 (d, 2 H, *J* = 9.1).

^{13}C NMR: δ = 29.35, 34.55, 55.55, 55.62, 65.27, 111.95, 113.74, 117.98, 123.10, 129.93, 131.77, 133.21, 142.17, 162.20, 163.47, 166.49, 199.58.

Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.13; H, 6.14.

3,4-Dimethoxybenzoic Acid 2-(2-Acetyl-5-methoxyphenyl)ethyl Ester (2f)
Yield: 89%; mp 110–111 °C; *i*-PrOH–hexanes, 6:1.

IR: 1709, 1672, 1602, 1270, 1223, 1031, 533 cm^{-1}.

^1H NMR: δ = 2.57 (s, 3 H), 3.39 (t, 2 H, *J* = 6.6), 3.79 (s, 3 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 4.54 (t, 2 H, *J* = 6.6), 6.81 (dd, 1 H, *J* = 8.3, 2.5), 6.84 (d, 1 H, *J* = 2.5), 6.86 (d, 1 H, *J* = 8.3), 7.49 (d, 1 H, *J* = 2.1), 7.64 (dd, 1 H, *J* = 8.7, 2.1), 7.80 (d, 1 H, *J* = 8.7).

^{13}C NMR: δ = 29.33, 34.56, 55.52, 56.13, 56.20, 65.37, 110.37, 111.62, 112.10, 118.37, 123.17, 123.72, 129.90, 133.30, 142.13, 148.71, 153.04, 162.16, 166.47, 199.53.

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 67.27; H, 6.27.

Preparation of the Catalysts; General Procedure
To cinchonine (1.0 equiv) in THF (15 volumes) was added the benzyl halide (1.2 equiv) and Bu_4NI (0.03 equiv). The mixture was heated at reflux for 18 h (until disappearance of the cinchonine by HPLC analysis). The reaction was cooled to r.t., filtered and the solid washed with THF to provide a white solid. To the solid in MeOH (5 volumes) was added Dowex F^- (equal weight as the alkaloid, Dowex F^- was prepared by neutralizing Dowex 66 HO^- with aqueous HF followed by wash with MeOH and MTBE). The suspension was stirred for 10 h, filtered, and washed with MeOH and MTBE. The filtrate was concentrated to a low volume and MTBE was added to provide a white solid, which was filtered.

{1-(3,5-Dimethoxybenzyl)-5-vinyl-1-azabicyclo[2.2.2]oct-2-yl}-quinolin-4-ylmethanol Chloride
IR: 3029, 1601, 1462, 1206, 1156, 859 cm^{-1}.

^1H NMR: (DMSO-d_6): δ = 0.99–1.05 (m, 1 H), 1.67–1.83 (m, 3 H), 2.22–2.28 (m, 1 H), 2.61–2.65 (m, 1 H), 2.98 (q, 1 H, *J* = 10.0), 3.49–3.55 (m, 1 H), 3.75–3.84 (m, 1 H), 3.81 (s, 6 H), 3.89–3.94 (m, 1 H), 4.03–4.24 (m, 1 H), 4.92–5.01 (m, 2 H), 5.19–5.23 (m, 2 H), 5.98 (ddd, 1 H, *J* = 17.8, 10.0, 6.6), 6.45 (br s, 1 H), 6.67 (t, 1 H, *J* = 2.1), 6.90–6.92 (m, 2 H), 7.10 (d 1 H, *J* = 4.1), 7.69–7.73 (m, 1 H), 7.79 (d, 1 H, *J* = 4.1), 7.79–7.83 (m, 1 H), 8.08 (d, 1 H, *J* = 7.9), 8.27 (d, 1 H, *J* = 8.3), 8.95 (d, 1 H, *J* = 4.1).

^{13}C NMR: (DMSO-d_6) δ 21.35, 23.73, 26.91, 37.43, 54.54, 56.19, 56.98, 62.85, 65.00, 68.03, 102.16, 112.57, 117.64, 120.81, 124.45, 125.05, 127.86, 130.00, 130.47, 130.62, 137.90, 145.88, 148.29,150.84, 161.18.

Anal. Calcd for $C_{28}H_{33}ClN_2O_6$: C, 69.91; H, 6.91, N, 5.82. Found: C, 69.59; H, 6.90, N, 5.84.

Catalyst 5b
Yield: 86% from cinchonine.

IR: 2950, 1598, 1462, 1206, 1156, 738 cm^{-1}.

^1H NMR: (DMSO-d_6): δ = 0.82–0.95 (m, 1 H), 1.59–1.81 (m, 3 H), 2.19–2.25 (m, 1 H), 2.57 (q, 1 H, *J* = 8.3), 2.95 (q, 1 H, *J* = 9.5), 3.45 (t, 1 H, *J* = 11.2), 3.74 (s, 6 H), 3.81–3.87 (m, 1 H), 4.28 (t, 1 H, *J* = 9.5), 4.86 (d, 1 H, *J* = 12.0), 5.11 (d, 1 H, *J* = 12.0), 5.17 (d, 1 H, *J* = 18.7), 5.18 (d, 1 H, *J* = 9.5), 5.98 (ddd, 1 H, *J* = 17.4, 10.4, 7.1), 6.34 (br s, 1 H), 6.55 (t, 1 H, *J* = 2.1), 6.81–6.84 (m, 2 H), 7.63 (t, 1 H, *J* = 7.9), 7.75 (d, 1 H, *J* = 4.1), 7.73–7.78 (m, 1 H), 8.03 (d, 1 H, *J* = 7.9), 8.15 (d, 1 H, *J* = 8.3), 8.87 (d, 1 H, *J* = 4.1).

^{13}C NMR: (DMSO-d_6): δ = 21.32, 23.79, 26.97, 37.47, 54.34, 56.05, 56.88, 62.77, 65.21, 68.29, 101.98, 112.42, 117.57, 120.81, 124.22, 125.11, 127.66, 129.78, 130.40, 130.59, 137.89, 146.41, 146.24,150.71, 161.09.

(1-Naphthalen-1-ylmethyl-5-vinyl-1-azabicyclo[2.2.2]oct-2-yl)-quinolin-4-ylmethanol Chloride
IR: 3067, 2953, 1591, 1510, 1267, 781, 739 cm^{-1}.

^1H NMR: (DMSO-d_6): δ = 0.95–1.07 (m, 1 H), 1.67–1.79 (m, 3 H), 2.25–2.31 (m, 1 H), 3.00 (q, 1 H, *J* = 10.0), 3.22 (t, 1 H, *J* = 10.8), 4.03–4.17 (m, 2 H), 4.31–4.36 (m, 1 H), 5.09 (d, 1 H, *J* = 17.0), 5.15 (d, 1 H, *J* = 10.4), 5.45 (d, 1 H, *J* = 12.9), 5.77 (d, 1 H, *J* = 13.3), 5.95 (ddd, 1 H, *J* = 17.4, 10.4, 7.0), 6.69 (br s, 1), 7.45 (d, 1 H, *J* = 4.1), 7.61–7.65 (m, 1 H), 7.68–7.77 (m, 4 H), 7.81–7.89 (m, 2 H), 8.03 (d, 1 H, *J* = 7.1), 8.09 (t, 2 H, *J* = 8.3), 8.17 (d, 1 H, *J* = 8.3), 8.45–8.48 (m, 2 H), 8.99 (d, 1 H, *J* = 4.1).

^{13}C NMR: (DMSO-d_6): δ = 21.62, 23.85, 37.52, 55.13, 56.97, 59.15, 65.58, 67.70, 117.70, 120.89, 124.60, 124.69, 125.14, 126.10, 126.98, 127.88, 128.15, 129.89, 130.11, 130.47, 132.00, 133.85, 134.47, 135.17, 137.80, 145.94, 148.33, 150.91.

Catalyst 5i
Yield: 93% from cinchonine.

IR: 3414, 2947, 2834, 1663, 1032, 746 cm^{-1}.

^1H NMR: δ = 0.50–0.59 (m, 1 H), 1.50–1.66 (m, 3 H), 1.95–2.05 (m, 2 H), 2.59–2.66 (m, 1 H), 2.88 (t, 1 H, *J* = 11.2), 3.95–4.06 (m, 2 H), 4.61 (t, 1 H, *J* = 10.4), 4.96 (d, 1 H, *J* = 17.4), 5.05 (d, 1 H, *J* = 10.4), 5.76 (ddd, 1 H, *J* = 17.4, 10.4, 7.5), 5.86 (d, 1 H, *J* = 12.5), 6.16–6.20 (m, 1 H), 6.35 (br s, 1 H), 6.75 (t, 1 H, *J* = 7.5), 7.12–7.29 (m, 5 H), 7.37–7.43 (m, 2 H), 7.55 (d, 1 H, *J* = 4.2), 7.60–7.65 (m, 2 H), 8.14–8.16 (m, 1 H), 8.40 (d, 1 H, *J* = 8.7), 8.56 (d, 1 H, *J* = 4.6).

^{13}C NMR: δ = 21.70, 24.30, 38.60, 54.86, 56.68, 58.44, 65.94, 68.04, 117.92, 119.77, 123.09, 123.54, 124.02, 124.43, 124.51, 125.80, 127.29, 127.74, 128.60, 128.67, 129.30, 130.96, 133.14, 133.27, 134.76, 135.94, 145.58, 147.20, 149.69.

(1*R*)-3,4-Dimethoxybenzoic Acid 2-[5-Methoxy-2-(2,2,2-trifluoro-1-methyl-1-trimethylsilanyloxyethyl)phenyl]ethyl Ester (4f)
To a solution of ketone **2f** (200 mg, 0.558 mmol) and catalyst **5i** (10.1 mg, 4 mol%) in CH_2Cl_2 (2.0 mL) at –50 °C was added CF_3TMS (0.12 mL, 8.1 mmol). The solution was stirred at –50 °C for 3 h and allowed to warm to r.t. overnight. HPLC analysis showed a 97% conversion and 92% ee. The mixture was poured into H_2O and extracted with CH_2Cl_2. The organic extract was concentrated to provide an oil. For analytical purposes, the material was purified by chromatography (SiO_2; EtOAc–hexanes, 20:80).

IR: 1711, 1604, 1515, 1270, 1223, 1174, 1134, 1027, 861, 846, 763 cm^{-1}.

^1H NMR: δ = 0.22 (s, 9 H), 1.96 (s, 3 H), 3.42 (ddd, 1 H, *J* = 13.4, 8.4, 6.5), 3.56–3.65 (m, 1 H), 3.81 (s, 3 H), 3.97 (s, 3 H), 3.98 (s, 3 H), 4.44–4.59 (m, 2 H), 6.78 (dd, 1 H, *J* = 9.0, 2.8), 6.94 (d, 1 H, *J* = 8.4), 6.96 (d, 1 H, *J* = 2.8), 7.34 (d, 1 H, *J* = 9.0), 7.60 (d, 1 H, *J* = 1.9), 7.74 (dd, 1 H, *J* = 8.4, 1.9).

^{13}C NMR: δ = 2.31, 24.84, 33.40, 55.29, 56.13, 56.20, 66.09, 79.24 (q, *J* = 30.1), 110.45, 111.53, 112.13, 117.92, 123.10, 123.79,

124.18 (q, J = 286), 129.76, 130.05, 140.09, 148.80, 153.15, 159.43, 166.56.

Anal. Calcd for $C_{24}H_{31}F_3O_6Si$: C, 57.58; H, 6.24. Found: C, 57.16; H, 6.30.

(1*R*)-4-Bromobenzoic Acid 2-[5-Methoxy-2-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)phenyl]ethyl Ester (6d)
IR: 3461, 1702, 1271, 1247, 1158, 1105, 1070, 1012, 757 cm^{-1}.

^1H NMR: δ = 1.84 (s, 3 H), 2.79–2.91 (m, 1 H), 3.13 (dt, 1 H, J = 13.3, 7.5), 3.69 (dq, 1 H, J = 7.5, 6.2), 3.76 (s, 3 H), 4.48–4.63 (m, 2 H), 6.75 (dd,1 H, J = 8.7, 2.9), 6.84 (d, 1 H, J = 2.9), 7.28 (d, 1 H, J = 9.1), 7.55 (d, 2 H, J = 8.7), 7.85 (d, 2 H, J = 8.7).

^{13}C NMR: δ = 26.05, 34.78, 55.38, 67.28, 111.91, 118.70, 128.29, 128.39, 129.42, 129.87, 126.16 (q, J = 286), 131.30, 131.92, 139.79 159.50, 166.23.

Supporting Information Available
The author has deposited atomic coordinates for structure **6d** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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(10) The enantiomeric excess was determined by evaluation of the corresponding diol (obtained by treating the silyl ether with TBAF followed by NaOH) by HPLC (Chiracel OD, 4.6 × 250 mm; 40 °C; 1.5 mL/min; 230 nm; hexanes–*i*-PrOH–TFA, 90:10:0.1). The absolute configuration was determined single crystal X-ray analysis of 4-bromobenzoate(**6d**).
(11) The starting material was obtained by esterificaton of alcohol **3** with 3,4-dimethoxybenzoyl chloride (CH_2Cl_2, Et_3N, DMAP, 100%) and Friedel–Crafts acylation (AcCl, $TiCl_4$, CH_2Cl_2, 89%).
(12) The enantiomeric excess was determined by evaluation of the corresponding tertiary alcohol (obtained by treating the silyl ether with TBAF) by HPLC (Chiracel OD, 4.6 × 250 mm; 40 °C; 1.5 mL/min; 230 nm; hexanes–*i*-PrOH–TFA, 80:20:0.2).
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