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Enantioselective Organocatalytic Approach to the Synthesis of α,α-Disubstituted Cyanosulfones

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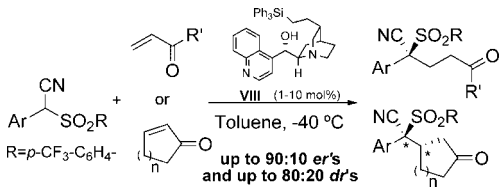

Optically pure cyano *tert*-alkyl sulfones have been obtained by organocatalytic enantioselective Michael addition of α-substituted cyanosulfones to vinyl ketones using cinchona alkaloids as catalysts. The best results were obtained for *p*-trifluorophenylsulfones by using **VIII** as catalyst in toluene at −40 °C. Reactions proved to be applicable for a variety of α,*β*-unsaturated ketones, affording α,α-disubstituted cyanosulfones in excellent yields with er's up to 90:10.

Sulfones are gaining an increasing importance in medicinal chemistry since they are considered as mimics of the carbonyl moieties in the transition state.[1] According to the World Drug Index, there are more than 40 sulfonyl-containing structures internationally recognized as drugs for a great variety of illness.[2] Chiral sulfonyl compounds have shown interesting activities in diseases such as glaucoma[3] or Alzheimer's.[4] A significant number of functionalized *tert*-alkyl sulfones[4,5] have been recently recognized as new chemical entities with a wide range of biological activities. However, to our knowledge, enantioselective methods to prepare this kind of compounds have not been described.

During the past few years, asymmetric organocatalysis has emerged as a powerful strategy in organic synthesis.[6] In this field, Michael addition has been extensively studied as one of the most versatile strategies in C−C bond formation.[7] In particular, when cinchona alkaloids are used as chiral bases, α-substituted dicarbonylic compounds[8] and cyanoesters[9] are mainly employed as the nucleophiles due to the strong acidity of their methylene protons. This strategy has allowed the formation of all-carbon quaternary stereocenters.[10]

At this point, we envisioned that α-cyanosulfones would be suitable starting materials to prepare enantioenriched *tert*-alkyl sulfones by using a similar strategy. In this paper, we describe the results obtained in the Michael addition of α-substituted α-cyanosulfones to α,*β*-unsaturated ketones catalyzed by cinchona alkaloids.[11] It is noteworthy that, in contrast with the wide use of vinyl sulfones as electrophiles in asymmetric organocatalysis,[12] there are few examples where α-sulfonyl carbanions have been used as nucleophiles,[13] in spite of the high acidity of the sulfonylated compounds and the large chemical versatility of the sulfones.

We first tried the efficiency of a variety of cinchona alkaloids (Figure 1) as catalysts to promote the enantioselective Michael addition of α-phenyl-α-cyano-*p*-tolylsulfone **1a**[14] to the commercially available methyl vinyl ketone (MVK) **2a** (Table 1).

(1) See, for example: (a) Lovejoy, B.; Welch, A. R.; Carr, S.; Luong, C.; Broka, C.; Hendricks, R. T.; Campbell, J. A.; Walker, K. A. M.; Martin, R.; Van Wart, H.; Browner, M. F. *Nat. Struct. Biol.* **1999**, *6*, 217.

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(7) For reviews on organocatalytic enanatioselective Michael reactions, see: (a) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (c) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, *14*, 2065.

(8) (a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *46*, 4057. (b) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796. (c) Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672. (d) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105. (e) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 947. (f) Elsner, P.; Bernardi, L.; Dela Salla, G.; Overgaard, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 4897.

(9) See, for example: (a) Liu, T.-Y.; Li, R.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem.—Eur. J.* **2007**, *13*, 319. (b) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed* **2006**, *45*, 947. For other uses of cyanoacetates, see: (c) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896. (d) López-Cantarero, J.; Cid, M. B.; Poulsen, T. B.; Bella, M.; García Ruano, J. L.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 7062.

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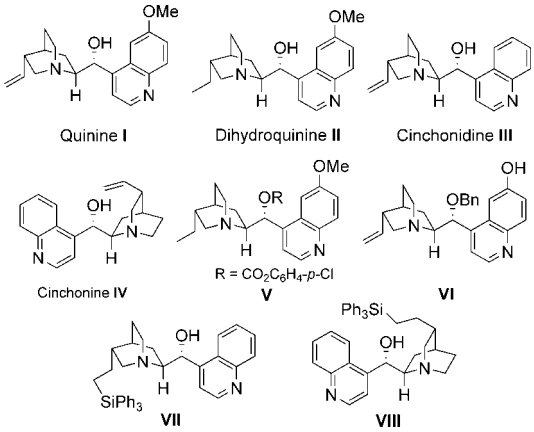
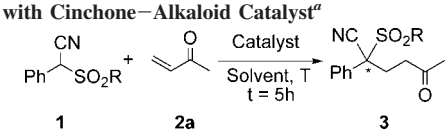


FIGURE 1. Structure of cinchona alkaloids used in this paper.

TABLE 1. Asymmetric Michael Addition of Cyanosulfones 1 to MVK 2a with Cinchone−Alkaloid Catalyst[a]



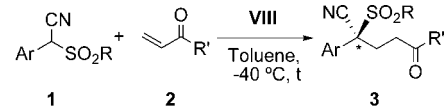
1a R=Tol, **1b** R=Me, **1c** R=Mesityl, **1d** R=*p*-MeO-C_6H_4, **1e** R=*p*-CF_3-C_6H_4, **1f** R=*o*-CF_3-C_6H_4, **1g** R=CH_2Tol, **1h** R=2-Py

entry	1	cat.	solvent	T (°C)	3	conv (%)	er[b]
1	**1a**	**I**	CH_2Cl_2	25	**3a**	100	47:53
2	**1a**	**I**	CH_2Cl_2	−20	**3a**	100	34:66
3	**1a**	**II**	CH_2Cl_2	−20	**3a**	100	32:68
4	**1a**	**III**	CH_2Cl_2	−20	**3a**	<70	30:70
5	**1a**	**IV**	CH_2Cl_2	−20	**3a**	50	70:30
6	**1a**	**V**	CH_2Cl_2	−20	**3a**	<5	50:50
7	**1a**	**VI**	CH_2Cl_2	−20	**3a**	<50	49:51
8	**1a**	**VIII**	CH_2Cl_2	−20	**3a**	91	73:27
9	**1b**	**III**	CH_2Cl_2	−20	**3b**	70	30:70
10	**1c**	**III**	CH_2Cl_2	25	**3c**	<20	36:64
11	**1d**	**III**	CH_2Cl_2	−20	**3d**	57	27:73
12	**1e**	**III**	CH_2Cl_2	−20	**3e**	100	31:69
13	**1f**	**III**	CH_2Cl_2	−20	**3f**	60	29:71
14	**1g**	**III**	CH_2Cl_2	−20	**3g**	100	44:66
15	**1h**	**III**	CH_2Cl_2	−20	**3h**	66	30:70
16	**1e**	**III**	toluene	−20	**3e**	100	27:73
17	**1e**	**III**	toluene	−40	**3e**	>80	27:73
18	**1e**	**VIII**	toluene	−40	**3e**	100	85:15
19	**1e**	**VII**	toluene	−40	**3e**	100	32:68

[a] The reaction was performed on a 0.1 mmol scale of **1** with 2 equiv of **2a** and 10 mol % of catalyst (0.14 M in the indicated solvent referred to **1**). [b] Enantiomeric ratio determined by HPLC.

The conjugate addition proceeded smoothly to give the desired product **3a** using CH_2Cl_2 in a quite clean fashion using catalysts **I**−**IV** (Table 1, entries 1−5). However, very low conversion degrees and enantioselectivities were observed with **V** and **VI**[15] (entries 6 and 7) as well as with dimeric catalysts such as $(DHQ)_2$Pyr, $(DHQ)_2$PHAL, or $(DHQ)_2$AQN not included in Table 1. These observations suggest a significant role of the free hydroxyl group at C9.[16] Silylated catalyst **VIII** afforded higher conversion and enantioselectivities than its precursor **IV** (entry 8).[17]

TABLE 2. Reaction Scope of α-Substituted Cyanosulfones 1 and Unsubstituted Vinyl Ketones 2[a]



R = *p*-CF_3-C_6H_4
R' = Me(**a**), Et(**b**), Pent(**c**)

entry	Ar	2	t (h)	3	yield (%)	er[b]
1	Ph (**1e**)	**2a**	3	**3e**	97	85:15
2	*p*−Cl-C_6H_4 (**1i**)	**2a**	3	**3i**	93	85:15
3	*o*−Cl-C_6H_4 (**1j**)	**2a**	48	**3j**	97	87:13
4	*p*-MeO-C_6H_4 (**1k**)	**2a**	24	**3k**	85	89:11
5	*p*−F-C_6H_4 (**1l**)	**2a**	1.5	**3l**	90	66:34
6	Ph (**1e**)	**2b**	5	**3m**	98	86:14[c]
7	Ph (**1e**)	**2c**	5	**3n**	98	86:14[c]

[a] Unless otherwise specified, the reaction was performed at a 0.1 mmol scale (**1**) with 2 equiv of **2** and 1 mol % of catalyst (0.14 M in the indicated solvent referred to **1**). [b] er determined by HPLC. [c] 5 mol % of catalyst was employed.

Next, we studied the influence of the group joined to the sulfonyl moiety. Yields and enantioselectivities have been evaluated for aliphatic substituents [**1b** (R = Me) and **1g** (CH_2Tol)], aromatic substituents with different sizes and electronic properties [**1c** (R = mesityl), **1d** (R = *p*-MeO-C_6H_4), **1e** (R = *p*-CF_3-C_6H_4), and **1f** (R = *o*-CF_3-C_6H_4)], and heteroaromatic substituents bearing coordinative heteroatoms [**1h** (R = 2-Py)] by using the commercially available catalyst **III** (entries 9−15). Although the *p*-methoxyphenyl substituent (entry 11) afforded the highest enantiomeric ratio, the best enantioselectivity/reactivity balance was found for *p*-trifluoromethyl sulfone **1e** (entry 12). Taking into account that about 20−25% of drugs in the pharmaceutical pipelines contain at least one fluorine atom,[18] we chose the *p*-trifluoromethyl sulfones for our studies.[19]

The influence of the temperature and the solvent was also explored (entries 16 and 17).[20] The higher conversion and enantiomeric ratio (85:15) was obtained from **1e** in toluene at −40 °C by using catalyst **VIII** (entry 18). The corresponding pseudoenantiomer derivative **VII** (entry 19) affords opposite selectivity but significantly lower enantiomeric ratio (entry 18).

It is remarkable that under the conditions optimized for compounds **1e** and **2a** (Table 1, entry 18) the catalyst loading can be reduced to 1 mol% (Table 2, entry 1) without erosion on the enantioselectivity. The scope of the reaction was studied (Table 2) and a wide range of substituents are allowed in both

(14) All cyanosulfones **1** have been prepared following the general procedure previously described in: (a) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210. (b) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Vakulenko, A. V.; Tau, H. *J. Org. Chem.* **2005**, *65*, 9191. For details of each compound, see the Supporting Information.

(15) This catalyst afforded high levels of enantioselectivity in the same reaction but using β-ketoesters as nucleophiles: (a) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 947–950.

(16) This effect has also been observed in other examples described in the literature: (a) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417. See also ref 9d and references cited therein.

(17) Catalyst **VIII** has been previously used in (a) Bell, M.; Frisch, K.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 5407. It was prepared from cinchonine following the experimental procedure described for the preparation of the corresponding cinchonidine derivative **VII** in: (b) Lindholm, A.; Mäki-Arvela, P.; Toukoniitty, E.; Pakkanen, T. A.; Hirvi, J. T.; Salmi, T.; Murzin, D. Y.; Sjöholm., R.; Leino, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2605–2612. (c) Busygin, I.; Toukoniitty, E.; Sillanpää, R.; Murzin, D. Y.; Leino, R. *Eur. J. Org. Chem.* **2005**, 2811.

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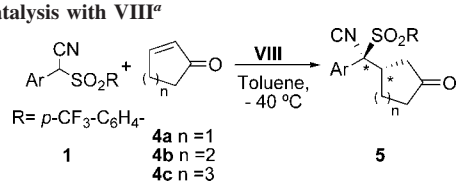
(20) Several solvents were used: $CHCl_3$, THF, acetone, acetonitrile, CH_2Cl_2, PhI, xylene, toluene, Tol/CH_2Cl_2, $C_2H_4Cl_2$, and Tol/$CHCl_3$ = 3:1.

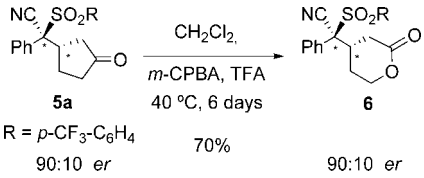
TABLE 3. Reaction of Cyanosulfones 1 with Cyclic Enones 4 under Catalysis with VIII[a]



entry	Ar	4	5	dr[b]	yield[c] (%)	er[d]
1	Ph (**1e**)	**4a**	**5a**	80:20	75	90:10
2	Ph (**1e**)	**4b**	**5b**	80:20	79	89:11
3	Ph (**1e**)	**4c**	**5c**	65:35	58	80:20
4	p-Cl-C_6H_4 (**1i**)	**4a**	**5d**	72:28	62	85:15
5	p-MeO-C_6H_4 (**1k**)	**4a**	**5e**	90:10	81	88:12

[a] Unless otherwise specified, the reaction was performed at a 0.1 mmol scale (**1**) with 2 equiv of **4** and 1−10 mol % of catalyst (0.14 M in the indicated solvent referred to **1**). [b] dr determined by ^{1}H NMR or HPLC (see the Supporting Information). [c] Major diastereomer. [d] er determined by HPLC. For complete reaction details, such as times and catalyst loading, see the Supporting Information.

SCHEME 1. Reaction of Cyclopentanone 5a with *m*-CPBA



reacting partners, sulfone (**1**) and ketone (**2**). Yields of the corresponding cyano *tert*-alkyl sulfones **3** are usually very high in all the cases. The nature and position of the substituents introduced at the aromatic ring of the sulfone determine a different reactivity (see reaction times in entries 2−5). The enantioselectivity ranges between 89:11 and 85:15 er's except for the case of the fluorinated compound **1l** where was found a significant variation (entry 5). On the other hand, the increase in the size of the substituent at the ketone had scarce influence in the enantioselectivity although it produced a decrease on the reactivity and 5 mol% of catalyst had to be employed (entries 6 and 7).

The reaction also proved to be applicable to cyclic unsaturated ketones (Table 3), where two stereocenters are simultaneously created. The stereoselectivity control at the carbon ring ranged between moderate to good for cyclopentenones (entries 1, 4, and 5) and cyclohexenone (entry 2), but it slightly decreased for cycloheptenone (entry 3), which in its turn showed a lower reactivity. After separation, the major diastereoisomers were obtained in high yields and er's similar to those observed for acyclic ketones (up to 90:10 er). The presence of substituents at the aromatic ring of the sulfone determined significant changes in the diastereoselectivity (larger for electron donating groups) but had scarce influence on the er's of the major diastereoisomers (entries 4 and 5).

Interestingly, compounds **3** and **5** are crystalline and can be converted into enantiomerically pure compounds by symple crystallization. Hence, **3i** and **5b** were easily obtained in enantiomerically pure form, and the absolute configuration of their stereocenters was determined by X-ray analysis. It allowed us to unequivocally assign the (*S*) and (*S*,*S*) configurations of the major enantiomers of **3i** and **5b**, respectively. All compounds **3** and **5** should have the same configuration since a similar stereochemical evolution should be expected for all the cyanosulfonyl compounds.

We have initiated the study of the transformations of the resulting cyanosulfones. Interestingly, the Baeyer−Villiger reaction of the cyclic ketone **5a** produce the regioselective oxidative cleavage of the methylene group far away from the chiral tertiary carbon yielding lactone **6** with reasonable yield with no erosion of the enatiomeric ratio.

In conclusion, we have developed a straightforward organocatalytic enantioselective aproach to the synthesis of fluorinated *tert*-alkyl sulfones by Michael addition of α-substituted cyanosulfones to vinyl ketones using cinchona alkaloids as catalysts. A useful transformation underlines the utility of the methodology.

Experimental Section

General Procedure for the Catalytic Michael Addition of α-Aryl-α-cyanosulfones 1 to Vinyl Ketones 2 and 4. A vial equipped with a magnetic stirring bar was charged with the α-aryl-α-cyanosulfone **1** (0.2 mmol) and dissolved in toluene (1.5 mL, M = 0.14 mmol/mL). The vial was placed at −40 °C, and the corresponding vinyl ketone **2** or **4** (0.4 mmol) and catalyst **VIII** (1−10 mol %, see Tables 1 and 2) were sequentially added. No precautions were taken to exclude moisture or air. The reactions were followed by TLC (see Tables 1 and 2 for times) and charged onto a silica gel column when finished. After the column was washed with hexane, the products **3** or **5** were obtained by flash chromatography using hexane/AcOEt mixtures (from 4:1 to 2:1).

(*S*)-5-Oxo-2-phenyl-2-(4-(trifluoromethyl)phenylsulfonyl)hexanenitrile (3e). The title compound was obtained as a white solid according to the general procedure (97% yield): mp 124−126 °C; ^{1}H NMR (300 MHz) δ 7.66 (s, 4H), 7.47−7.32 (m, 5H), 3.03−2.72 (m, 3H), 2.46−2.32 (m, 1H), 2.11 (s, 3H); ^{13}C NMR (75 MHz) δ 204.8 (CO), 137.2 (C), 136.3 (q, J = 33.6 Hz, C), 131.2 (2CH), 130.6 (CH), 129.2 (2CH), 128.3 (2CH), 127.9 (C), 125.8 (q, J = 3.8 Hz, 2CH), 122.8 (q, J = 273 Hz, CF_3), 115.8 (CN), 71.5 (C), 38.7, 29.8, 25.8; MS (FAB) m/z 396 (M + 1, 34), 186 (100); HRMS (FAB) calcd for $C_{19}H_{17}F_3NO_3S$ [M + 1] 396.0881, found 396.0870; $[\alpha]^{20}D$ −71 (c 1.0, $CHCl_3$); IR (KBr) 2200, 1716, 1336, 1157, 1129 cm^{-1}. Anal. Calcd for $C_{19}H_{16}F_3NO_3S$: C, 57.72; H, 4.08; N, 3.54; S, 8.11. Found: C, 57.93; H, 3.99; N, 3.65; S, 8.07. The enantiomeric ratio was determined by HPLC using a Chiralpak AD column [hexane/*i*-PrOH = 80:20]; flow rate 1.0 mL/min; τ_{major} = 8.1 min, τ_{minor} = 9.8 min (85:15 er).

(*S*)-2-((*S*)-3-Oxocyclopentyl)-2-phenyl-2-(4-(trifluoromethyl)phenylsulfonyl) acetonitrile (5a). This compound was obtained as the major diastereoisomer (80:20 dr) following the general procedure (75% yield). Diastereomeric and enantiomeric ratios were determined by HPLC with a Chiralpak AD column [Hex/*i*-PrOH (90:10)]; flow rate 1.0 mL/min, T = 25 °C; minor diastereoisomer, τ_{major} = 11.4 min, τ_{minor} = 12.3 min (50:50 er); major diastereoisomer, τ_{major} = 15.1 min, τ_{minor} = 17.7 min (89:11 er). White solid: mp 144−146 °C; $[\alpha]^{20}_D$ −118 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.56 (m, 4H, pCF$_3$-Ar), 7.43−7.32 (m, 5H, Ph), 3.76−3.68 (m, 1H, H_3), 3.11 (dd, J = 18.7, 7.4 Hz, 1H), 2.78 (ddd, J = 18.7, 11.6, 1.2 Hz, 1H), 2.37 (dd, J = 18.6, 8.7 Hz, 1H), 2.22 (ddd, J = 18.6, 12.1, 8.7 Hz, 1H), 1.92−1.80 (m, 1H), 1.65 (m, 1H); ^{13}C NMR (75 MHz) δ 214.4 (CO), 137.8 (C), 136.2 (q, J = 32.9 Hz, C), 130.7 (4CH), 130.6 (2CH), 129.2 (CH), 128.7 (C), 125.7 (q, J = 3.3 Hz, 2CH), 122.7 (q, J = 277 Hz, CF_3), 114.4 (CN), 76.5 (C), 42.5, 39.2, 36.8, 26.7; MS (FAB) m/z 408 (M+1, 9), 198 (100); HRMS (FAB) calcd for $C_{20}H_{17}F_3NO_3S$ [M + 1] 408.0881, found 408.0893; IR (film) 2242, 1739, 1322, 1154 cm^{-1}. Anal. Calcd for $C_{20}H_{16}F_3NO_3S$: C, 58.96; H, 3.96; N, 3.44; S, 7.87. Found: C, 58.76; H, 3.93; N, 3.51; S, 7.74.

(*S*)-2-((*S*)-2-Oxotetrahydro-2*H*-pyran-4-yl)-2-phenyl-2-(4-(trifluoromethyl)phenylsulfonyl)acetonitrile (6). *m*-CPBA (60−75% in water, 169 mg, 0.98 mmol, 10 equiv) was dissolved in 7 mL of CH_2Cl_2, dried over magnesium sulfate, and filtered and the resulting solution added at room temperature to a flask charged with

cyanosulfone **5a** (40 mg, 0.098 mol). Eight drops of TFA were then added to this mixture, and the reaction was stirred at 40 °C for 6 days whereupon it was cooled to room temperature and quenched by addition of a saturated Na_2SO_3 solution (6 mL). The organic layer was washed with a $NaHCO_3$ solution (6 mL × 2) and with brine (6 mL), dried over magnesium sulfate, and filtered and the solvent removed under vacuo. The crude product was purified by flash column chromatography [SiO_2, hexane/EtOAc= 4:1 to 1.5:1] to afford the title compound **6a** as a white solid (29 mg, 70% yield). White solid: mp 181−183 °C; ^{1}H NMR (300 MHz) δ 7.55 (s, 4H), 7.42−7.30 (m, 5H), 4.45−4.23 (m, 2H), 3.69−3.57 (m, 2H), 3.24−3.13 (m, 1H), 1.77−1.65 (m, 2H); ^{13}C NMR (75 MHz) δ 168.1 (CO), 138.2 (C), 136.2 (q, J = 33.3 Hz, C), 130.8 (2CH), 130.5 (2CH), 129.6 (2CH), 128.7 (CH), 128.0 (C), 125.8 (q, J = 3.8 Hz, 2CH), 122.7 (q, J = 272 Hz, CF_3), 114.2 (CN), 75.8, 66.8, 36.1, 33.8, 25.8; MS (FAB) m/z 436 (M + 1, 25), 226 (95), 57 (100); $[\alpha]^{20}_D$ −83 (c 0.5, $CHCl_3$); IR (film) 2240, 1743, 1451, 1405, 1323, 1157 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{17}F_3NO_4S$ [M + H$^+$] 424.0824, found 424.0827. The enantiomeric ratio was determined by HPLC using a Chiralpak AD column [hexane/i-PrOH = 80:20]; flow rate 0.8 mL/min; T^a = 25 °C. τ_{major} = 29.3 min, τ_{minor} = 31.0 min (90:10 er).

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Supporting Information Available: Experimental procedures and characterization data for catalyst **VIII** and compounds **1a−l**, **3e−n**, **5a−e**, and **6** as well as X-ray ORTEP of **3i** and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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