DOI: 10.1002/adsc.201000918

Asymmetric Friedel–Crafts Reaction of Indoles with Ethyl Trifluoropyruvate Using a Copper(I)-Bisoxazolidine Catalyst

Christian Wolf[a,*] and Peng Zhang[a]

[a] Department of Chemistry, Georgetown University, Washington, DC 20057, USA
Fax: (+1)-202-687-6209; phone: (+1)-202-687-3468; e-mail: cw27@georgetown.edu

Received: December 3, 2010; Revised: January 20, 2011; Published online: March 15, 2011

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000918.

Abstract: Bisoxazolidine **1** is an effective ligand in the copper(I)-catalyzed Friedel–Crafts reaction of alkyl trifluoropyruvates and indoles. A range of ethyl 2-(3′-indolyl)-3,3,3-trifluoro-2-hydroxypropanoates was produced in up to 99% yield and 94% *ee* within 30 min to 4 h. The effect of temperature on conversion and enantioselectivity proved to be substrate specific and was optimized individually. Of particular interest is that this method tolerates the presence of substituents in various positions in the indole ring. Yields ranging from 90–97% and *ee* values between 90 and 94% were obtained at optimized temperatures with substrates carrying substituents in position 1 or 7.

Keywords: asymmetric catalysis; bisoxazolidines; Friedel–Crafts reaction; indoles; trifluoropyruvates

Introduction

The increasing demand for chiral fluorinated compounds by the pharmaceutical and agrochemical industries has nourished the development of catalytic Friedel–Crafts reactions with trifluoromethyl ketones.[1] This reaction provides access to secondary and tertiary alcohols bearing a neighboring trifluoromethyl group as well as ether and ester derivatives thereof. This structural motif has become an important component in several drugs. Selected examples include anticonvulsants,[2] peptidomimetic matrix metalloproteinase (MMP) inhibitors,[3] CJ-17,493, a neurokinin 1 receptor antagonist,[4] and the anti-HIV agent Efavirenz[5] (Figure 1).

To date, indoles have been used extensively in asymmetric Friedel–Crafts reactions with a wide range of carbonyl electrophiles[6] but few examples of this reaction with methyl or ethyl trifluoropyruvate have been reported, Scheme 1.[7] Excellent results for the metal-catalyzed Friedel–Crafts reaction of indoles and trifluoropyruvates towards 2-(3′-indolyl)-3,3,3-trifluoro-2-hydroxypropanoates have been achieved with chiral copper(II) and titanium(IV) complexes but remaining drawbacks are either long reaction times[8] or a limited substrate scope, e.g., several procedures provide low *ee* values when *N*-alkylindoles are used as substrate.[9] The introduction of chiral Brønsted acids to this reaction has provided efficient alternatives.[10] The organocatalytic Friedel–Crafts variant generally tolerates substituents at position 5 but essentially racemic mixtures are obtained with *N*-methylindole and only moderate enantioselectivity is

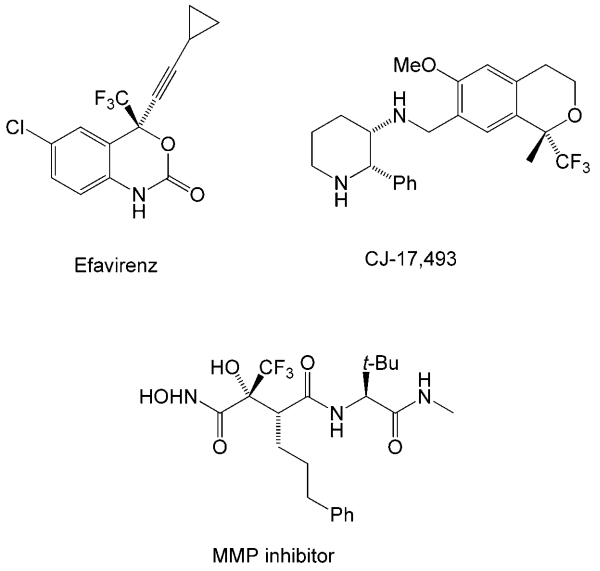
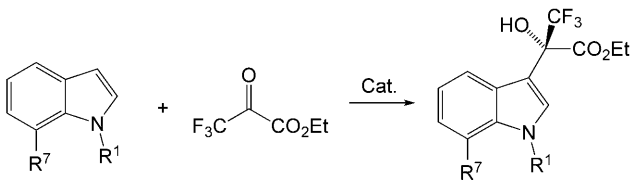


Figure 1. Structures of selected drugs containing a trifluoromethyl-derived alcohol, ether or ester group.

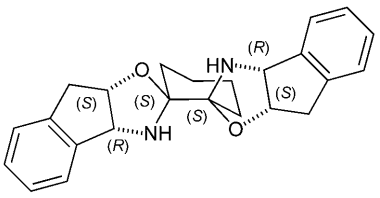


R^1, R^7 = H, alkyl

Scheme 1. Formation of 2-(3′-indolyl)-3,3,3-trifluoro-2-hydroxypropanoates by asymmetric Friedel–Crafts reaction with indoles and ethyl trifluoropyruvate.

observed when a methyl group is present at position 7. Accordingly, the development of a method that provides high yields and *ee* values with indoles carrying a substituent at the nitrogen atom or at carbon 7 is still desirable. Herein, we wish to report a copper(I)-catalyzed asymmetric Friedel–Crafts reaction using a bisoxazolidine ligand that overcomes the limitations mentioned above.

Asymmetric catalysis with chiral oxazolidine ligands has received increasing attention during the last decade. Current applications of this relatively unexplored class of ligands include asymmetric alkylations, alkynylations, allylic alkylations, cycloadditions, and aldol reactions.[11] We have demonstrated the general usefulness of the aminoindanol-derived bisoxazolidine **1** in several asymmetric carbon-carbon bond forming reactions, Figure 2.[12] This ligand catalyzes the enantioselective alkynylation of aromatic and aliphatic aldehydes, generating chiral propargylic alcohols in high yield and *ee*.[13] Excellent results have also been obtained for the alkylation of aldehydes with Me_2Zn and Et_2Zn.[14] Bisoxazolidine **1** proved to be a versatile ligand in the asymmetric nitroaldol reaction. We found that it catalyzes the reaction between aromatic and aliphatic aldehydes with nitroalkanes in the presence of dimethylzinc, which generates the reactive zinc nitronate in situ.[15] A wide range of Henry products was obtained with yields and *ee* values of up to 99% yield and 95% *ee*, respectively. Alternatively, the Cu(I)OAc-catalyzed variant proceeds with similar efficiency but shows the opposite sense of asymmetric induction.[16] Most recently, we have extended the use of **1** to the nitroaldol reaction with trifluoromethyl ketones and α-keto esters.[17]



(+)-**1**

Figure 2. Structure of bisoxazolidine (+)-**1**.

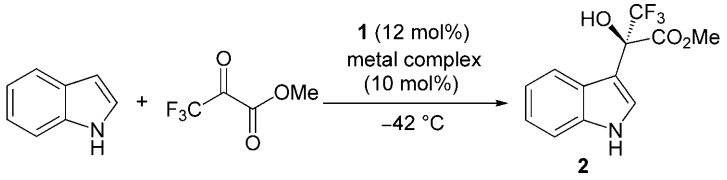
Results and Discussion

We initiated this study by screening the effect of metal salt, catalyst loading, solvent, temperature etc. on the conversion, reaction time, and enantioselectivity of the Friedel–Crafts reaction between methyl trifluoropyruvate and indole. Using 10 mol% of bisoxazolidine (+)-**1** and either $Cu(OTf)_2$ or $(CuOTf)_2$-toluene complex in dichloromethane, chloroform, toluene, tetrahydrofuran, diethyl ether, *tert*-butyl methyl ether, ethanol, and combinations thereof with hexane at −42 °C, we found that methyl 2-(3′-indolyl)-3,3,3-trifluoro-2-hydroxypropanoate, **2**, is formed in up to 92% yield and 79% *ee*, Table 1. In particular, results obtained with dichloromethane and diethyl ether were encouraging, see entries 1, 5 and 8. The performance of several copper, silver, zinc, and magnesium salts in dichloromethane was then evaluated, entries 13–17. Since **2** was obtained in only moderate *ee* values under these conditions, $Cu(OTf)_2$ or $(CuOTf)_2$-toluene complex were tested in dichloromethane at −78 °C (entries 18 and 19). The latter gave superior results and furnished **2** in 97% yield and 88% *ee* when diethyl ether was used as solvent (entry 20).

A decrease in the catalyst loading to 5 mol% of $(CuOTf)_2$-toluene complex and 6 mol% of ligand **1** did not affect the results and we were pleased to find that the copper(I)-catalyzed asymmetric Friedel–Crafts reaction proceeds with 95% yield and 89% *ee* in diethyl ether at −78 °C. Importantly, the reaction was complete after 1 hour. We realized that comparable results are obtained with ethyl trifluoropyruvate and therefore decided to screen several indoles with this ketone.

The Friedel–Crafts reaction between indole and ethyl trifluoropyruvate gave ethyl 2-(3′-indolyl)-3,3,3-trifluoro-2-hydroxypropanoate, **3**, in 98% yield and 91% *ee* within 30 min, see entry 1 in Table 2. Introduction of electron-donating and electron-withdrawing groups to position 5 in the indole ring revealed that yields and *ee* values slightly decrease with 5-fluoro- and 5-bromoindole even when the reaction was conducted at −98 °C (entries 2–5). However, excellent results were obtained with unprotected 5-hydroxyindole at −60 °C and the corresponding Friedel–Crafts reaction product **8** was isolated in 96% yield and 85% *ee* (entry 6). With this substrate, the *ee* values decreased at lower temperatures to 79% at −78 °C and 58% at −98 °C. This observation prompted us to look more closely at temperature effects, and we found a similar trend for the Friedel–Crafts reaction with *N*-methylindole, see below. Our reaction protocol also tolerates indole substrates carrying a methyl group in position 6 and, more importantly, in position 7 (entries 7 and 8). The synthesis of **10** from 7-methylindole and ethyl trifluoropyruvate was accomplished with 97% yield and 94% *ee* at −98 °C

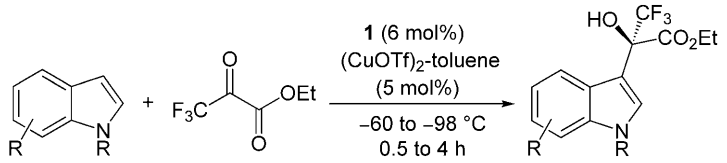
Table 1. Optimization of the enantioselective Friedel–Crafts reaction with indole.



Entry	Metal Complex	Solvent	Yield [%][a]	*ee* [%]
1	$Cu(OTf)_2$	CH_2Cl_2	97	59
2	$Cu(OTf)_2$	$CHCl_3$	99	53
3	$Cu(OTf)_2$	EtOH	<5%	n.d.
4	$Cu(OTf)_2$	CH_2Cl_2:hexanes (1:1)	95	49
5	$(CuOTf)_2$-toluene	CH_2Cl_2	92	70
6	$(CuOTf)_2$-toluene	$CHCl_3$	99	65
7	$(CuOTf)_2$-toluene	toluene	91	45
8	$(CuOTf)_2$-toluene	Et_2O	92	79
9	$(CuOTf)_2$-toluene	THF	96	39
10	$(CuOTf)_2$-toluene	TBME	88	68
11	$(CuOTf)_2$-toluene	CH_2Cl_2:Et_2O (1:1)	99	63
12	$(CuOTf)_2$-toluene	Et_2O:hexanes (4:1)	99	73
13	$Cu(ACN)_4PF_6$	CH_2Cl_2	86	34
14	CuOAc	CH_2Cl_2	82	14
15	$Cu(OAc)_2$	CH_2Cl_2	73	9
16	$AgClO_4$	CH_2Cl_2	61	25
17	$Zn(OTf)_2$	CH_2Cl_2	91	10
18[b]	$Cu(OTf)_2$	CH_2Cl_2	98	60
19[b]	$(CuOTf)_2$-toluene	CH_2Cl_2	96	74
20[b]	$(CuOTf)_2$-toluene	Et_2O	97	88

[a] Isolated yields.
[b] −78 °C.

Table 2. Scope of the enantioselective Friedel–Crafts reaction with indoles.[a]



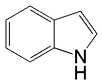
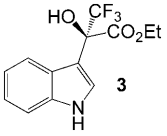
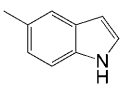
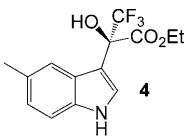
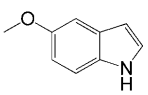
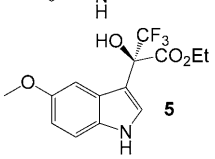
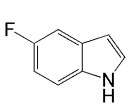
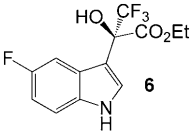
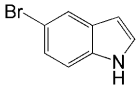
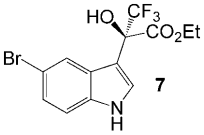
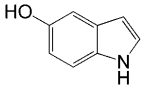
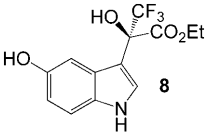
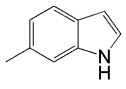
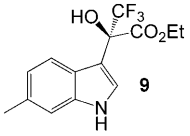
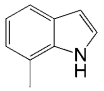
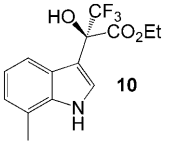
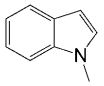
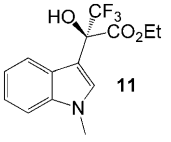
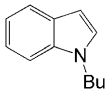
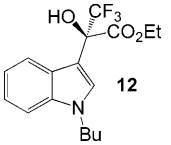
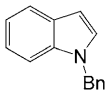
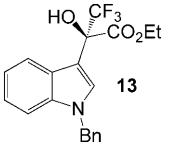
Entry	Substrate	Product	*T* [°C]	*t* [h]	Yield[b] [%]	*ee*[c,d] [%]
1		 3	−60	0.5	95	82 (*R*)
			−78	0.5	98	91
			−98	3.0	52	65
2		 4	−60	0.5	96	85 (*R*)
			−78	1.0	93	90
			−98	1.0	99	90
3		 5	−60	0.5	96	84 (*R*)
			−78	1.0	95	86
			−98	1.5	99	86

Table 2. (Continued)

Entry	Substrate	Product	T [°C]	t [h]	Yield[b] [%]	ee[c,d] [%]
4		 **6**	−60 −78 −98	0.5 2.0 3.0	92 94 90	72 (*R*) 77 86
5		 **7**	−60 −78 −98	1.0 1.0 4.0	99 90 86	59 (*R*) 70 81
6		 **8**	−60 −78 −98	3.0 3.0 4.0	96 92 87	85 (*R*) 79 58
7		 **9**	−60 −78 −98	0.5 1.0 4.0	99 95 75	90 (*R*) 91 92
8		 **10**	−60 −78 −98	0.5 0.5 2.0	98 96 97	84 (*R*) 90 94
9		 **11**	−60 −78 −98	0.5 1.0 3.0	95 93 87	89 (*R*) 90 77
10		 **12**	−60 −78 −98	0.5 0.5 0.5	99 92 90	86 (*R*) 90 91
11		 **13**	−60 −78 −98	0.5 2.0 2.0	96 93 90	84 (*R*) 88 92

[a] All reactions were performed on a 0.5 mmol scale using 6 mol% of ligand **1**, 5 mol% of $(CuOTf)_2$-toluene complex, and 1.1 equiv. of ethyl 3,3,3-trifluoropyruvate in 6 mL of Et_2O.
[b] Isolated yields.
[c] The *ee* values were determined by chiral HPLC on Chiralcel OD, Chiralcel OJ, Chiralpak AS, Chiralpak AD.
[d] The absolute configuration was determined by comparison of the elution order as described in ref.[9] or by analogy.

within 2 h. The same reaction is complete after 30 min when it is performed at −78 °C and **10** was prepared in 96% yield and 90% *ee* under these conditions. The general substrate scope of the Cu(I)-bisoxazolidine-catalyzed reaction is further highlighted by the results obtained with *N*-substituted indoles. Products **11**–**13** were generated in unprecedented yields and *ee* values and in very short reaction times (entries 9–11). A significant decrease in the enantioselectivity of the Friedel–Crafts reaction of *N*-methylindole was observed when the temperature was reduced to −98 °C, and **11** was obtained in 87% yield and 77% *ee*. The opposite trend was found with *N*-benzylindole: while **13** was produced in 93% yield and 88% *ee* at −78 °C, the results improved to 90% and 92% *ee* at −98 °C.

Conclusions

In conclusion, we have shown that bisoxazolidine **1** is an effective ligand in the Cu(I)-catalyzed asymmetric

Friedel–Crafts reaction of indoles with 3,3,3-trifluoropyruvates. High yields and *ee* values were achieved with a wide range of substrates in relatively short reaction times. In particular, the reaction between indoles carrying a substituent in position 1 or 7 and ethyl 3,3,3-trifluoropyruvate gave yields and *ee* values that compare favorably with previously reported methods. The use of bisoxazolidine **1** in other asymmetric reactions is currently explored in our laboratories.

Experimental Section

All commercially available reagents and solvents were used without further purification. Anhydrous diethyl ether was used as purchased and not dried any further. NMR spectra were obtained at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). Chemical shifts are reported in ppm relative to TMS. Reaction products were purified by column chromatography on silica gel (particle size 32–63 μm).

General Friedel–Crafts Reaction Procedure

The bisoxazolidine ligand (11.2 mg, 0.03 mmol) and $(CuOTf)_2$-toluene complex (12.9 mg, 0.025 mmol) were dissolved in 4 mL of anhydrous Et_2O under nitrogen at room temperature. After 30 min, ethyl 3,3,3-trifluoropyruvate (96.4 mg, 0.55 mmol) dissolved in 1 mL of Et_2O was added, and the solution was stirred for an additional 10 min. It was then cooled to the optimized reaction temperature shown in Table 2 and kept for another 10 min. Finally, the indole (0.5 mmol) dissolved in 1 mL of Et_2O was added. After completion of the reaction, the crude residue was loaded directly onto a silica gel column and purified by flash chromatography as described below.

(*R*)-Methyl 3,3,3-trifluoro-2-hydroxy-2-(indol-3′-yl)propanoate:[9a] Chromatographic purification (Et_2O:hexanes = 2:3) gave a colorless oil; yield: 133 mg (0.49 mmol, 97%, 88% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H), 4.41 (bs, 1H), 7.11–7.25 (m, 4H), 7.82 (d, J = 7.9 Hz, 1H), 8.15 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.4, 76.8 (q, $J_{C,F}$ = 31.6 Hz), 108.2, 111.5, 120.6, 120.7, 122.7, 123.6 (q, $J_{C,F}$ = 286.3 Hz), 124.4, 125.0, 136.2, 169.9. The *ee* was determined by HPLC on Chiralpak AD using IPA:hexanes (10:90) as mobile phase: t_1 (major) = 16.5 min, t_2 (minor) = 20.4 min, α = 1.29.

(*R*)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(indol-3′-yl) propanoate:[9c] Chromatographic purification (Et_2O:hexanes = 2:3) gave a colorless oil; yield: 141 mg (0.49 mmol, 98%, 91% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 3H), 4.30 (dq, J = 3.5 Hz, 7.1 Hz, 1H), 4.41 (dq, J = 3.5 Hz, 7.1 Hz, 1H), 4.45 (s, 1H), 7.12–7.24 (m, 3H), 7.28 (d, J = 2.4 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 8.23 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 64.2, 76.8 (q, $J_{C,F}$ = 31.5 Hz), 108.4, 110.4, 120.5, 121.0, 122.6, 123.5 (q, $J_{C,F}$ = 286.3 Hz), 124.5, 125.1, 136.3, 169.4. The *ee* was determined by HPLC on Chiralcel OD using IPA:hexanes (10:90) as mobile phase: t_1 (major) = 19.8 min, t_2 (minor) = 23.3 min, α = 1.21.

(*R*)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5′-methylindol-3′-yl)propanoate:[9c] Chromatographic purification (Et_2O:hexanes = 2:3) gave a white solid; yield: 145 mg (0.47 mmol, 93%, 90% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.1 Hz, 3H), 2.43 (s, 3H), 4.32 (dq, J = 3.5 Hz, 7.1 Hz, 1H), 4.41 (s, 1H), 4.43 (dq, J = 3.5 Hz, 7.1 Hz, 1H), 7.03 (dd, J = 1.2 Hz, 8.3 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 2.6 Hz, 1H). 7.66 (s, 1H), 8.12 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 21.5, 64.1, 76.7 (q, $J_{C,F}$ = 31.5 Hz), 107.8, 110.9, 120.4, 123.5 (q, $J_{C,F}$ = 286.2 Hz), 124.2, 124.3, 125.2, 129.7, 134.5, 169.4. The *ee* was determined by HPLC on Chiralcel OJ using IPA:hexanes (15:85) as mobile phase: t_1 (major) = 27.7 min, t_2 (minor) = 37.7 min, α = 1.40.

(*R*)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5′-methoxyindol-3′-yl)propanoate:[9c] Chromatographic purification (Et_2O:hexanes = 2:3) gave a colorless oil; yield: 151 mg (0.48 mmol, 95%, 86% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.1 Hz, 3H), 3.82 (s, 3H), 4.32 (dq, J = 3.6 Hz, 7.1 Hz, 1H), 4.43 (dq, J = 3.6 Hz, 7.2 Hz, 1H), 4.45 (s, 1H), 6.85 (dd, J = 2.5 Hz, 8.9 Hz, 1H), 7.15 (d, J = 8.9 Hz, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 8.27 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.9, 55.7, 64.1, 76.8 (q, $J_{C,F}$ = 31.5 Hz), 102.7, 108.0, 112.1, 113.1, 123.5 (q, $J_{C,F}$ = 286.4 Hz), 125.0, 125.6, 131.4, 154.4, 169.3. The *ee* was determined by HPLC on Chiralcel OD using IPA:hexanes (10:90) as mobile phase: t_1 (major) = 30.4 min, t_2 (minor) = 43.0 min, α = 1.46.

(*R*)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5′-fluoroindol-3′-yl)propanoate:[9c] Chromatographic purification (Et_2O:hexanes = 2:3) gave a colorless oil; yield: 135 mg (0.45 mmol, 90%, 86% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.2 Hz, 3H), 4.35 (dq, J = 3.5 Hz, 7.2 Hz, 1H), 4.44 (dq, J = 3.5 Hz, 7.2 Hz, 1H), 4.46 (s, 1H), 6.94 (ddd, J = 2.5 Hz, 9.0 Hz, 9.0 Hz, 1H), 7.20 (dd, J = 4.3 Hz, 4.5 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.57 (dd, J = 2.2 Hz, 10.4 Hz, 1H), 8.34 (bs, 1H): ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 64.4, 76.7 (q, $J_{C,F}$ = 31.7 Hz), 106.3 (d, $J_{C,F}$ = 25.2 Hz), 108.6 (d, $J_{C,F}$ = 4.6 Hz), 111.2 (d, $J_{C,F}$ = 26.5 Hz), 112.0 (d, $J_{C,F}$ = 9.8 Hz), 123.5 (q, $J_{C,F}$ = 286.2 Hz), 125.5 (d, $J_{C,F}$ = 10.8 Hz), 126.0, 132.8, 158.0 (d, $J_{C,F}$ = 234.8 Hz), 169.1. The *ee* was determined by HPLC on Chiralcel OD using IPA:hexanes (5:95) as mobile phase: t_1 (major) = 23.4 min, t_2 (minor) = 27.1 min, α = 1.19.

(*R*)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5′-bromoindol-3′-yl)propanoate:[9c] Chromatographic purification (Et_2O:hexanes = 2:3) gave a colorless oil; yield: 156 mg (0.43 mmol, 86%, 81% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.1 Hz, 3H), 4.34 (dq, J = 3.5 Hz, 7.2 Hz, 1H), 4.43 (dq, J = 3.5 Hz, 7.2 Hz, 1H), 4.51 (bs, 1H), 7.25 (d, J = 8.7 Hz, 1H), 7.31 (dd, J = 1.8 Hz, 8.7 Hz, 1H), 7.48 (d, J = 2.7 Hz, 1H), 8.05 (s, 1H), 8.40 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 64.5, 76.7 (q, $J_{C,F}$ = 31.8 Hz), 108.0, 112.8, 113.7, 123.5 (q, $J_{C,F}$ = 286.4 Hz), 123.7, 125.5, 125.7, 126.7, 135.0, 169.0. The *ee* was determined by HPLC on Chiralpak AS using IPA:hexanes (10:90) as mobile phase: t_1 (minor) = 11.2 min, t_2 (major) = 13.3 min, α = 1.27.

(*R*)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5′-hydroxyindol-3′-yl)propanoate: Chromatographic purification (Et_2O:hexanes = 2:3, gradually changed to 4:1) gave a white solid; yield: 145 mg (0.48 mmol, 96%, 85% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.2 Hz, 3H), 4.35 (bs,

1H), 4.36 (dq, $J=3.6$ Hz, 7.1 Hz, 1H), 4.46 (dq, $J=3.6$ Hz, 7.1 Hz, 1H), 4.64 (bs, 1H), 6.82 (dd, $J=2.4$ Hz, 8.7 Hz, 1H), 7.22 (d, $J=8.7$ Hz, 1H), 7.32 (d, $J=2.1$ Hz, 1H), 7.43 (d, $J=2.7$ Hz, 1H), 8.18 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.9$, 64.2, 76.7 (q, $J_{C,F}=31.6$ Hz), 105.5, 108.0, 112.0, 112.6, 123.5 (q, $J_{C,F}=286.3$ Hz), 125.2, 126.0, 131.5, 150.0, 169.2. The *ee* was determined by HPLC on Chiralpak AD using IPA:hexanes (15:85) as mobile phase: t_1 (major)=34.2 min, t_2 (minor)=40.8 min, $\alpha=1.21$. Anal. calcd. for $C_{13}H_{12}F_3NO_4$: C 51.49, H 3.99, N 4.62, found: C 51.31, H 4.13, N 4.47.

(*R*)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(6′-methylindol-3′-yl)propanoate:[10a] Chromatographic purification (Et_2O:hexanes=2:3) gave a slightly yellow oil; yield: 142 mg (0.48 mmol, 95%, 91% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.29$ (t, $J=7.2$ Hz, 3H), 2.42 (s, 3H), 4.32 (dq, $J=3.6$ Hz, 7.2 Hz, 1H), 4.38 (bs, 1H), 4.44 (dq, $J=3.6$ Hz, 7.2 Hz, 1H), 6.95-6.99 (m, 2H), 7.20 (d, $J=2.5$ Hz, 1H), 7.73 (d, $J=8.6$ Hz, 1H), 8.02 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.9$, 21.5, 64.2, 76.7 (q, $J_{C,F}=31.6$ Hz), 108.2, 111.4, 120.5, 122.3, 122.8, 123.7 (q, $J_{C,F}=286.2$ Hz), 123.8, 132.5, 136.8, 169.4. The *ee* was determined by HPLC on Chiralcel OD using IPA:hexanes (4:96) as mobile phase: t_1 (minor)=21.8 min, t_2 (major)=24.9 min, $\alpha=1.16$.

(*R*)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(7′-methylindol-3′-yl)propanoate:[10b] Chromatographic purification (Et_2O:hexanes=2:3) gave a white solid; yield: 144 mg (0.49 mmol, 97%, 94% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.30$ (t, $J=7.1$ Hz, 3H), 2.40 (s, 3H), 4.30 (dq, $J=3.6$ Hz, 7.1 Hz, 1H), 4.42 (bs, 1H), 4.43 (dq, $J=3.6$ Hz, 7.1 Hz, 1H), 6.95 (d, $J=7.1$ Hz, 1H), 7.06 (dd, $J=7.2$ Hz, 7.9 Hz, 1H), 7.38 (d, $J=2.5$ Hz, 1H), 7.72 (d, $J=8.0$ Hz, 1H), 8.19 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.9$, 16.4, 64.2, 76.7 (q, $J_{C,F}=31.5$ Hz), 109.0, 118.7, 120.5, 120.6, 123.1, 123.5 (q, $J_{C,F}=286.2$ Hz), 124.1, 124.6, 135.9, 169.4. The *ee* was determined by HPLC on Chiralpak AD using IPA:hexanes (10:90) as mobile phase: t_1 (major)=17.5 min, t_2 (minor)=23.7 min, $\alpha=1.44$.

(*R*)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(1′-methylindol-3′-yl)propanoate:[9c] Chromatographic purification (Et_2O:hexanes=1:10) gave a colorless oil; yield: 141 mg (0.49 mmol, 97%, 90% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.33$ (t, $J=7.1$ Hz, 3H), 3.75 (s, 3H), 4.33 (dq, $J=3.6$ Hz, 7.2 Hz, 1H), 4.36 (s, 1H), 4.45 (dq, $J=3.6$ Hz, 7.2 Hz, 1H), 7.14 (dd, $J=6.9$ Hz, 8.1 Hz, 1H), 7.24 (dd, $J=6.9$ Hz, 8.2 Hz, 1H), 7.31 (d, $J=8.0$ Hz, 1H), 7.33 (s, 1H), 7.88 (d, $J=8.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.9$, 33.0, 64.2, 76.7 (q, $J_{C,F}=31.2$ Hz), 106.8, 109.5, 120.1, 121.2, 122.2, 123.5 (q, $J_{C,F}=286.2$ Hz), 125.8, 128.9, 137.3, 169.5. The *ee* was determined by HPLC on Chiralcel OD using IPA:hexanes (10:90) as mobile phase: t_1 (major)=9.2 min, t_2 (minor)=14.3 min, $\alpha=1.88$.

(*R*)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(1′-butylindol-3′-yl)-propanoate: Chromatographic purification (Et_2O:hexanes=1:10) gave a white solid; yield: 157 mg (0.46 mmol, 92%, 90% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.92$ (t, $J=7.2$ Hz, 3H), 1.28–1.38 (m, 5H), 1.79 (m, 2H), 4.07 (t, $J=7.2$ Hz, 2H), 4.33 (dq, $J=3.4$ Hz, 7.2 Hz, 1H), 4.39 (s, 1H), 4.44 (dq, $J=3.4$ Hz, 7.2 Hz, 1H), 7.12 (dd, $J=7.1$ Hz, 8.0 Hz, 1H), 7.22 (dd, $J=7.2$ Hz, 7.9 Hz, 1H), 7.32 (d, $J=8.2$ Hz, 1H), 7.36 (s, 1H), 7.89 (d, $J=8.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.6$, 13.9, 20.1, 32.1, 46.4, 64.1, 76.8 (q, $J_{C,F}=31.6$ Hz), 106.7, 109.8, 120.0, 121.4, 122.4, 123.8 (q, $J_{C,F}=286.2$ Hz), 125.9, 128.0, 136.6, 169.5. The *ee* was determined by HPLC on Chiralcel OD using IPA:hexanes (10:90) as mobile phase: t_1 (major)=7.8 min, t_2 (minor)=15.6 min, $\alpha=2.63$. Anal. calcd. for $C_{17}H_{20}F_3NO_3$: C 59.47, H 5.87, N 4.08; found: C 59.04, H 5.86, N 4.12.

(*R*)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(1′-benzylindol-3′-yl)propanoate: Chromatographic purification (Et_2O:hexanes=1:5) gave a colorless oil; yield: 170 mg (0.45 mmol, 90%, 92% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.30$ (t, $J=7.2$ Hz, 3H), 4.33 (dq, $J=3.6$ Hz, 7.2 Hz, 1H), 4.39 (s, 1H), 4.44 (dq, $J=3.6$ Hz, 7.2 Hz, 1H), 5.28 (s, 2H), 7.08–7.31 (m, 8H), 7.39 (s, 1H), 7.93 (d, 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.9$, 50.3, 64.2, 76.8 (q, $J_{C,F}=31.6$ Hz), 107.5, 110.0, 120.3, 121.5, 122.4, 123.6 (q, $J_{C,F}=287.2$ Hz), 126.0, 126.8, 127.8, 128.4, 128.8, 136.6, 136.9, 169.4. The *ee* was determined by HPLC on Chiralpak AD using IPA:hexanes (10:90) as mobile phase: t_1 (major)=13.8 min, t_2 (minor)=20.1 min, $\alpha=1.58$. Anal. calcd. for $C_{20}H_{18}F_3NO_3$: C 63.66, H 4.81, N 3.71; found: C 63.41, H 4.59, N 3.61.

Acknowledgements

Funding from the National Science Foundation (CHE-0848301) is gratefully acknowledged.

References

[1] a) T. B. Poulsen, K. A. Jorgensen, *Chem. Rev.* **2008**, *108*, 2903–2915; b) G. Blay, I. Fernandez, A. Monleon, J. R. Pedro, C. Vila, C. *Org. Lett.* **2009**, *11*, 441–444; c) J. Nie, G.-W. Zhang, L. Wang, A. Fu, Y. Zheng, J.-A. Ma, *Chem. Commun.* **2009**, 2356–2358; d) F. Tur, J. Mansilla, V. J. Lillo, J. M. Saa, *Synthesis* **2010**, 1909–1923.

[2] H. A. Schenck, P. W. Lenkowski, I. Choudhury-Mukherjee, S.-H. Ko, J. P. Stables, M. K. Patel, M. L. Brown, *Bioorg. Med. Chem.* **2004**, *12*, 979–993.

[3] M. Sani, D. Belotti, R. Giavazzi, W. Panzeri, A. Volonterio, M. Zanda, *Tetrahedron Lett.* **2004**, *45*, 1611–1615.

[4] S. Caron, N. M. Do, J. E. Sieser, P. Arpin, E. Vazquez, *Org. Process Res. Dev.* **2007**, *11*, 1015–1024.

[5] N. Y. Rakhmanina, J. N. van den Anker, *Expert Opin. Drug Metab. Toxicol.* **2010**, *6*, 95–103.

[6] For asymmetric Friedel–Crafts reactions of indoles and carbonyl electrophiles other than trifluoropyruvates, see refs.[1a,c] and: a) W. Zhuang, T. B. Poulsen, K. A. Jorgensen, *Org. Biomol. Chem.* **2005**, *3*, 3284–3289; b) H. Li, Y.-Q. Wang, L. Deng, *Org. Lett.* **2006**, *8*, 4063–4065; c) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2007**, *5*, 816–821; d) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403–1405; e) H.-M. Dong, H.-H. Lu, L.-Q. Lu, C.-B. Chen, W.-J. Xiao, *Adv. Synth. Catal.* **2007**, *349*, 1597–1603; f) G. Blay, I. Fernandez, J. R. Pedro, C. Vila, *Org. Lett.* **2007**, *9*, 2601–2604; g) G. Desimoni, G. Faita, M. Toscanini, M. Boiocchi, *Chem. Eur. J.* **2008**, *14*, 3630–

3636; h) L. Hong, L. Wang, C. Chen, B. Zhang, R. Wang, *Adv. Synth. Catal.* **2009**, *351*, 772–778; i) G. Blay, I. Fernandez, A. Monleon, M. C. Munoz, J. R. Pedro, C. Vila, *Adv. Synth. Catal.* **2009**, *351*, 2433–2440; j) Y.-J. Sun, N. Li, Z.-B. Zheng, L. Liu, Y.-B. Yu, Z.-H. Qin, B. Fu, *Adv. Synth. Catal.* **2009**, *351*, 3113–3117; k) S. Adachi, F. Tanaka, K. Watanabe, T. Harada, *Org. Lett.* **2009**, *11*, 5206–5209; l) Y. Hui, Q. Zhang, J. Jiang, L. Lin, X. Liu, X. Feng, *J. Org. Chem.* **2009**, *74*, 6878–6880; m) J. Deng, S. Zhang, P. Ding, H. Jiang, W. Wang, J. Li, *Adv. Synth. Catal.* **2010**, *352*, 833–838; n) W. Wang, X. Liu, W. Cao, J. Wang, L. Lin, X. Feng, *Chem. Eur. J.* **2010**, *16*, 1664–1669; o) M. Zeng, S.-L. You, *Synlett* **2010**, 1289–1301; p) T. Tsubogo, Y. Kano, Y. Yamashita, S. Kobayashi, *Chem. Asian J.* **2010**, *5*, 1974–1977; q) S. Sasaki, T. Yamauchi, K. Higashiyama, *Tetrahedron Lett.* **2010**, *51*, 2326–2328; r) S. Adachi, F. Tanaka, K. Watanabe, A. Watada, T. Harada, *Synthesis* **2010**, 2652–2669; s) Y. Qian, G. Ma, A. Lv, H.-L. Zhu, J. Zhao, V. H. Rawal, *Chem. Commun.* **2010**, *46*, 3004–3006; t) S. Jin, C. Li, Y. Ma, Y. Kan, Y. J. Zhang, W. Zhang, *Org. Biomol. Chem.* **2010**, *8*, 4011–4015; u) T. Sakamoto, J. Itoh, K. Mori, T. Akiyama, *Org. Biomol. Chem.* **2010**, *8*, 5448–5454; v) N. Li, X.-H. Chen, S.-M. Zhou, S.-W. Luo, J. Song, L. Ren, L.-Z. Gong, *Angew. Chem.* **2010**, *122*, 6522–6525; *Angew. Chem. Int. Ed.* **2010**, *49*, 6378–6381; w) G. Blay, I. Fernandez, M. C. Munoz, J. R. Pedro, C. Vila, *Chem. Eur. J.* **2010**, *16*, 9117–9122.

[7] For asymmetric Friedel–Crafts reactions of trifluoropyruvates and aromatic compounds other than indole, see: a) N. Gathergood, W. Zhuang, K. A. Jorgensen, *J. Am. Chem. Soc.* **2000**, *122*, 12517–12522; b) A. Corma, H. Garcia, A. Moussaif, M. J. Sabater, R. Zniber, A. Redouane, *Chem. Commun.* **2002**, 1058–1059; c) K. A. Jorgensen, *Synthesis* **2003**, 1117–1125; d) K. Mikami, K. Aikawa, S. Kainuma, Y. Kawakami, T. Saito, N. Sayo, H. Kumobayashi, *Tetrahedron: Asymmetry* **2004**, *15*, 3885–3889; e) J.-L. Zhao, L. Liu, Y. Sui, Y.-L. Liu, D. Wang, Y.-J. Chen, *Org. Lett.* **2006**, *8*, 6127–6130; f) J.-L. Zhao, L. Liu, C.-L. Gu, D. Wang, Y.-J. Chen, *Tetrahedron Lett.* **2008**, *49*, 1476–1479.

[8] W. Zhuang, N. Gathergood, R. G. Hazell, K. A. Jorgensen, *J. Org. Chem.* **2001**, *66*, 1009–1013.

[9] a) M. P. A. Lyle, N. D. Draper, P. D. Wilson, *Org. Lett.* **2005**, *7*, 901–904; b) H.-M. Dong, H.-H. Lu, L.-Q. Lu, C.-B. Chen, W.-J. Xiao, *Adv. Synth. Catal.* **2007**, *349*, 1597–1603; c) S. Nakamura, K. Hyodo, Y. Nakamura, N. Shibata, T. Toru, *Adv. Synth. Catal.* **2008**, *350*, 1443–1448.

[10] a) B. Torok, M. Abid, G. London, J. Esquibel, M. Torok, S. C. Mhadgut, P. Yan, G. K. S. Prakash, *Angew. Chem.* **2005**, *117*, 3146–3149; *Angew. Chem. Int. Ed.* **2005**, *44*, 3086–3089; b) J. Nie, G. W. Zhang, L. Wang, D.-H. Zheng, Y. Zheng, J.-A. Ma, *Eur. J. Org. Chem.* **2009**, 3145–3149; c) W. Kashikura, J. Itoh, K. Mori, T. Akiyama, *Chem. Asian J.* **2010**, *5*, 470–472.

[11] Selected examples of asymmetric catalysis with oxazolidine ligands: a) M. J. Jin, J. A. Jung, S. H. Kim, *Tetrahedron Lett.* **1999**, *40*, 5197–5198; b) Y. Okuyama, H. Nakano, H. Hongo, *Tetrahedron: Asymmetry* **2000**, *11*, 1193–1198; c) A. L. Braga, H. R. Appelt, P. H. Schneider, O. E. D. Rodriguez, C. C. Silveira, L. A. Wessjohann, *Tetrahedron* **2001**, *57*, 3291–3295; d) O. E. D. Rodriguez, M. W. Paixao, H. R. Appelt, C. C. Silveira, D. P. Bottega, *Synlett* **2002**, 2338–2340; e) H. Nakano, Y. Okuyama, Y. Suzuki, R. Fujita, C. Kabuto, *Chem. Commun.* **2002**, 1146–1147; f) A. L. Braga, H. R. Appelt, C. C. Silveira, L. A. Wessjohann, P. H. Schneider, *Tetrahedron* **2002**, *58*, 10413–10416; g) P. H. Schneider, H. S. Schrekker, C. C. Silveira, L. A. Wessjohann, A. L. Braga, *Eur. J. Org. Chem.* **2004**, 2715–2722; h) H. Nakano, K. Takahashi, Y. Okuyama, C. Senoo, N. Tsugawa, Y. Suzuki, R. Fujita, K. Sasaki, C. Kabuto, *J. Org. Chem.* **2004**, *69*, 7092–7100; i) Y.-F. Kang, R. Wang, L. Liu, C.-S. Da, W.-J. Yan, Z.-Q. Xu, *Tetrahedron Lett.* **2005**, *46*, 863–865; j) Y.-F. Kang, L. Liu, R. Wang, Y.-F. Zhou, W.-J. Yan, *Adv. Synth. Catal.* **2005**, *347*, 243–247; k) R. W. Parrott, S. R. Hitchcock, *Tetrahedron: Asymmetry* **2007**, *18*, 377–382; l) Z. Szakonyi, A. Hetenyi, F. Fulop, *Tetrahedron* **2008**, *64*, 1034–1039; m) Z. Xu, J. Mao, Y. Zhang, *Org. Biomol. Chem.* **2008**, *6*, 1288–1292; n) J. Mao, J. Guo, *Synlett* **2009**, 2295–2300; o) H. Nakano, K. Osone, M. Takeshita, E. Kwon, C. Seki, H. Matsuyama, N. Takano, Y. Kohari, *Chem. Commun.* **2010**, *46*, 4827–4829.

[12] This ligand is commercially available at Strem (catalogue no. 07–0488), *US Patent*, 11/737,371, **2007**.

[13] C. Wolf, S. Liu, *J. Am. Chem. Soc.* **2006**, *128*, 10996–10997.

[14] S. Liu, C. Wolf, *Org. Lett.* **2007**, *9*, 2965–2968.

[15] S. Liu, C. Wolf, *Org. Lett.* **2008**, *10*, 1831–1834.

[16] K. Y. Spangler, C. Wolf, *Org. Lett.* **2009**, *11*, 4724–4727.

[17] a) H. Xu, C. Wolf, C. *Chem. Commun.* **2010**, *46*, 8026–8028; b) H. Xu, C. Wolf, *Synlett* **2010**, 2765–2770.

