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Synthesis of Functionalized Indoles with a Trifluoromethyl-Substituted Stereogenic Tertiary Carbon Atom Through an Enantioselective Friedel–Crafts Alkylation with β-Trifluoromethyl-α,β-enones

Gonzalo Blay,[a] Isabel Fernández,[a] M. Carmen Muñoz,[b] José R. Pedro,*[a] and Carlos Vila[a]

Dedicated to Professor Pelayo Camps on occasion of his 65th birthday

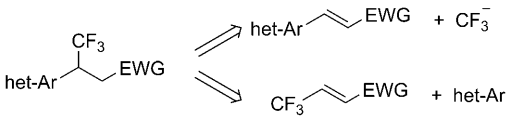
Abstract: Chiral complexes of BINOL-based ligands with zirconium *tert*-butoxide catalyze the Friedel–Crafts alkylation reaction of indoles with β-trifluoromethyl-α,β-unsaturated ketones to give functionalized indoles with an asymmetric tertiary carbon center attached to a trifluoromethyl group. The reaction can be applied to a large number of substituted α-trifluoromethyl enones and substituted indoles. The expected products were obtained with good yields and *ee*s of up to 99%.

Keywords: alkylation · aromatic substitution · asymmetric catalysis · enones · fluorinated compounds

Introduction

It is known that the introduction of a trifluoromethyl moiety to an organic structure can greatly modify its physicochemical features and consequently its biological properties. Because of this, trifluoromethylated compounds have played a unique and significant role in agricultural and medicinal chemistry.[1] This fact explains the continuing interest in developing general methods for the synthesis of this kind of compound and especially in the enantioselective construction of stereogenic centers bearing a CF_3 group. Among these compounds, molecules having an asymmetric tertiary carbon center attached to a trifluoromethyl group without any heteroatom substituent have been shown to be challenging synthetic targets.[2]

In this context, two general strategies for the asymmetric synthesis of this type of stereogenic tertiary carbon center could be used (Scheme 1). The first route is the conjugated nucleophilic trifluoromethylation of α,β-unsaturated carbonyl compounds. This strategy seems to be straightforward and



Scheme 1. Retrosynthetic analysis to chiral trifluoromethylated indoles.

uses the Ruppert–Prakash (Me_3SiCF_3) reagent. However, although this reagent has found widespread application in the trifluoromethylation of C=O and C=N bonds,[3] its enantioselective addition to electron-deficient alkenes (Michael reaction) has remained virtually unexplored.[4] In fact, to the best of our knowledge, no enantioselective conjugate trifluoromethylation reaction of α,β-unsaturated ketones has been reported so far. A second strategy may be the addition of carbon nucleophiles to β-trifluoromethyl α,β-unsaturated carbonyl compounds. However, this reaction still constitutes a major challenge in synthetic chemistry. So far, the use of β-trifluoromethyl α,β-unsaturated carbonyl compounds as acceptors in conjugated addition reactions has been limited. A few examples of non-enantioselective reactions have been reported,[5] and the addition of arylboronic acids is the only enantioselective example of such a addition reported so far.[2]

[a] Dr. G. Blay, Dr. I. Fernández, Prof. Dr. J. R. Pedro, C. Vila
Departament de Química Orgànica,
Facultat de Química, Universitat de València
Dr. Moliner 59, 46100 Burjassot, València (Spain)
Fax: (+34) 963544328
E-mail: jose.r.pedro@uv.es

[b] Prof. Dr. M. C. Muñoz
Centro de Tecnologías Físicas
Universidad Politécnica de Valencia
Camí de Vera S/N, 46022 Valencia (Spain)

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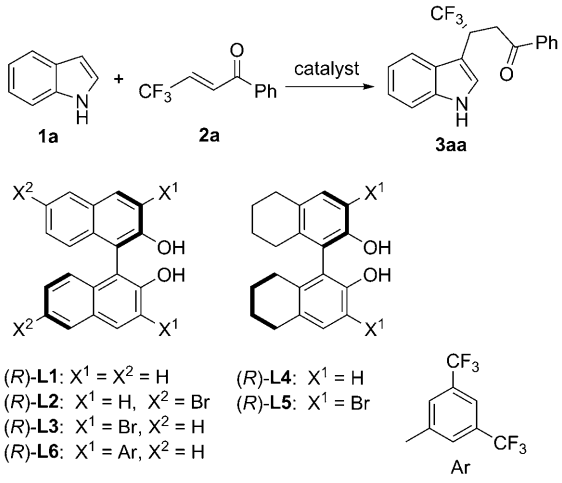
On the other hand, the indole nucleus is present in numerous compounds of biological and/or pharmaceutical interest, and new chemical methods for its synthesis have been developed for more than a hundred years.[6] Recently, the Lewis-acid-catalyzed Friedel–Crafts alkylation of indoles has proved to be one of the most efficient methods to obtain enantiomerically enriched alkylated indoles by using prochiral unsaturated compounds as electrophiles in the presence of chiral metal complexes.[7] To date, most of the successful examples of such processes are limited to the use of bidentate chelating carbonyl substrates[8] and nitroalkenes,[9] whereas the use of simple nonchelating α,β-unsaturated carbonyl compounds as electrophiles remains rare.[10] Very recently, during the preparation of this manuscript, Shibata et al. reported the enantioselective Friedel–Crafts reaction of β-trifluoromethylated acrylates with pyrroles and indole.[11]

Herein, we describe the enantioselective Friedel–Crafts reactions of β-trifluoromethyl-α,β-unsaturated ketones **2** with indoles **1** catalyzed by a chiral BINOL-type zirconium(IV) *tert*-butoxide complex as a new convenient method to functionalize the C3 position of the indole nucleus with a side chain bearing a stereogenic tertiary center attached to a trifluoromethyl group.[12]

Results and Discussion

Our initial studies were performed by using β-trifluoromethyl-α,β-enone **2a**, which is readily prepared according to a modified literature procedure,[13] and indole (**1a**) as shown in Scheme 2, Table 1. The first reactions were carried out in CH_2Cl_2 at room temperature and were aimed at exploring the effectiveness of $Zr(OtBu)_4$ with (*R*)-BINOL (**L1**) and other BINOL-type ligands (**L2**–**L5**), which contain electron-withdrawing groups at the 3,3′ and 6,6′ positions as well as a



Scheme 2. Friedel–Crafts reaction of indole (**1a**) with β-trifluoromethyl-α,β-enone **2a**, and the structure of the BINOL-type ligands used in this study.

Table 1. Ligand evaluation and optimization of the enantioselective Friedel–Crafts reaction of **1a** with **2a**.[a]

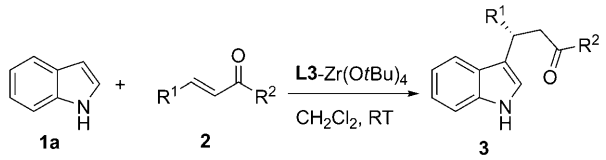
	Solvent	Catalyst	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	CH_2Cl_2	**L1**–$Zr(OtBu)_4$	5	62	12
2	CH_2Cl_2	**L2**–$Zr(OtBu)_4$	6	52	8
3	CH_2Cl_2	**L3**–$Zr(OtBu)_4$	3.5	87	96
4	CH_2Cl_2	**L4**–$Zr(OtBu)_4$	22	22	25
5	CH_2Cl_2	**L5**–$Zr(OtBu)_4$	22	32	50
6	CH_2Cl_2	**L6**–$Zr(OtBu)_4$	24	18	60
7	CH_2Cl_2	**L3**–$Ti(OiPr)_4$	44	78	15
8	CH_2Cl_2	**L3**–$Hf(OtBu)_4$	5	91	86
9	toluene	**L3**–$Zr(OtBu)_4$	20	23	80
10	THF	**L3**–$Zr(OtBu)_4$	24	–	–
11[d]	CH_2Cl_2	**L3**–$Zr(OtBu)_4$	24	64	86
12[e]	CH_2Cl_2	**L3**–$Zr(OtBu)_4$	4.5	80	99

[a] Reaction carried out with **1a** (0.15 mmol), **2a** (0.125 mmol), (*R*)-**L** (0.025 mmol), metal alkoxide (0.025 mmol) in solvent (2 mL) at RT. [b] Isolated yield of **3aa**. [c] Determined by chiral HPLC analysis. [d] 10 mol% catalyst used in this run. [e] Reaction carried out at 0°C.

tetrahydrogenated ring. Ligand **L3**, with two bromine atoms at the 3,3′ positions, led to the best result and gave compound **3aa** with 87% yield and 96% *ee* (Table 1, entry 3). This result seemed to indicate that substitution at the 3,3′-positions of BINOL was essential to obtain high enantioselectivities. However, use of the highly hindered 3,3′-diaryl-BINOL ligand (**L6**) led to reaction product **3aa** with low yield (18%) and 60% *ee* (Table 1, entry 6). The use of other group IV metal alcoxides was also tested. Performing the reaction with $Ti(OiPr)_4$ and ligand **L3** resulted in a slow reaction rate, and product **3aa** was obtained with low *ee* (Table 1, entry 7), whereas by using $Hf(OtBu)_4$ (Table 1, entry 8) the reaction product was obtained with good yield (91%), albeit with a somewhat lower enantioselectivity (86% *ee*) than with $Zr(OtBu)_4$. The use of aromatic hydrocarbon solvents (toluene) or ethers (THF) resulted in lower yields and enantioselectivities (Table 1, entries 9 and 10). An attempt to decrease the catalyst loading to 10 mol% resulted in a lower yield and enantioselectivity (Table 1, entry 11). Finally, lowering the temperature to 0°C improved the enantioselectivity up to 99% *ee*, although the yield of product **3aa** was somewhat lower (84%; Table 1, entry 12).

With these optimized reaction conditions (Table 1, entries 3 and 12), we next investigated the Friedel–Crafts reaction of various β-trifluoromethyl-α,β-enones **2** with indole (**1a**). β-Trifluoromethyl enones **2** with a sterically demanding aromatic group bound to the carbonyl group produced trifluoroalkylated indoles **3aa**–**aj** in excellent yields and high enantioselectivities (up to 99% *ee*) in most cases (Table 2). The reaction with β-trifluoromethyl-α,β-enones containing weak electron-donating or electron-withdrawing groups on the aromatic ring gave better enantioselectivities than those containing strong electron-donating or electron-withdrawing groups on the aromatic ring (Table 2, entries 2 and 5 vs. entries 4 and 6). The *ortho* substitution on the aromatic ring of the β-trifluoromethyl-α,β-enone lowered the reaction rate and the yield of the trifluoroalkylation product dropped to

Table 2. Enantioselective Friedel–Crafts reaction of indole (**1a**) with β-trifluoromethyl-α,β-enones **2** catalyzed by **L3**–$Zr(OtBu)_4$.[a]



	Enone	R^1	R^2	*t* [h]	Product	Yield[b] [%]	*ee*[c] [%]
1	**2a**	CF_3	Ph	3.5 (4.5)	**3aa**	87 (80)	96 (99)
2	**2b**	CF_3	*p*-MeC_6H_4	2 (5)	**3ab**	95 (98)	97 (95)
3	**2c**	CF_3	*o*-MeC_6H_4	22	**3ac**	30	94
4	**2d**	CF_3	*p*-$MeOC_6H_4$	7 (23)	**3ad**	93 (99)	91 (97)
5	**2e**	CF_3	*p*-ClC_6H_4	1.5 (3)	**3ae**	89 (85)	93 (81)
6	**2f**	CF_3	*p*-$NO_2C_6H_4$	1.2 (4)	**3af**	97 (88)	64 (66)
7	**2g**	CF_3	2-naphthyl	6 (22)	**3ag**	97 (82)	76 (92)
8	**2h**	CF_3	2-thienyl	5 (23)	**3ah**	93 (90)	96 (98)
9	**2i**	CF_3CF_2	Ph	48	**3ai**	44	92
10	**2j**	CF_3CF_2	*p*-MeC_6H_4	31	**3aj**	46	93

[a] Reaction carried out with **1a** (0.15 mmol), **2** (0.125 mmol), (*R*)-**L3** (0.025 mmol), $Zr(OtBu)_4$ (0.025 mmol) in CH_2Cl_2 (2 mL) at RT. Data in parenthesis are for the same reaction carried out at 0 °C. [b] Isolated yield of **3**. [c] Determined by chiral HPLC analysis. The (*R*)-configuration was assigned from X-ray crystallographic analysis of **3ae** and on the assumption of a uniform mechanistic pathway for the rest of products **3**.

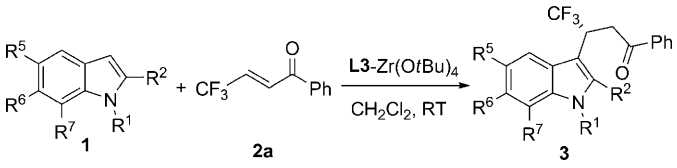
30% (94% *ee*), which indicates the existence of a steric effect of the *ortho* substituents on the reactivity (Table 2, entry 3). In addition, the 2-naphthyl- and the heteroaromatic β-trifluoromethyl-α,β-enones **2g** and **2h** can also serve as substrates in this reaction, giving the corresponding trifluoroalkylated indoles in excellent yields and high enantioselectivities (Table 2, entries 7 and 8). The influence of the size of the fluoroalkyl group (CF_3 or CF_3CF_2)[14] at the β position was also investigated. In the case of CF_3CF_2, a diminished reactivity and lower yield were observed (Table 2, entries 9–10), but the reactions proceeded with high enantioselectivities (92–93% *ee*). Finally, we studied the indole scope of the reaction. Indoles bearing electron-donating groups (CH_3, CH_3O) or electron-withdrawing groups (Br) at the 5-position of the indole ring (**1b–d**) were treated with β-trifluoromethyl-α,β-enone **2a** to provide the corresponding trifluoroalkylated indoles **3aa–da** in good to excellent yields and enantioselectivities (Table 3, entries 2–4). With regard to the substituent effect on the indole ring (Table 3), neither the presence of electron-donating groups (CH_3, CH_3O) nor electron-withdrawing groups (Br) at the 5-position of the indole nucleus affected the enantioselectivity of the reaction, but the reaction rate was indeed unfavorably influenced in the case of 5-bromoindole (**1d**), which required a reaction time of 27 h at room temperature (Table 3, entries 1–4). Also, 2-methylindole (**1e**) and 7-methylindole (**1f**) reacted with **2a**, although with decreased reactivity, to give **3ea** and **3fa**, respectively, with yields and enantioselectivities somewhat lower (Table 3, entries 5–6). Finally, 1-methylindole (**1g**), with a substituted nitrogen atom, gave the corresponding alkylated product **3ga** with low yield and enantioselectivity (Table 3, entry 7).

The absolute configuration of the stereogenic center in compound **3ae** was determined by X-ray crystallographic analysis (Figure 1) to be *R*, and for the rest of the products it was assigned on the assumption of a uniform mechanistic pathway.[15]

Compounds **3** could be transformed into several CF_3-containing building blocks by chemical transformation of the carbonyl group (Scheme 3). For example, we have carried out an interesting reduction of the carbonyl group of compounds **3aa**, **3ab**, **3ai**, and **3ba** to methylene to give compounds **4aa**, **4ab**, **4ai**, and **4ba** in almost quantitative yield.

Considering the usefulness of pyrroles as pharmaceuticals, we have also attempted to expand the scope of the reaction to include pyrrole (**5**) as a nucleophilic heteroarene (Scheme 4). When the set of reaction conditions used in the Friedel–Crafts reaction of indoles **1** with β-trifluoromethyl-α,β-enones **2** was applied to the reaction with pyrrole (**5**; 10 equiv to avoid the formation of dialkylated products), the reaction was complete in 1 h and gave the 2-trifluoroalkylated-pyrrole **6a** in excellent yield (99%) although with a low *ee* (27%). Unfortunately, further attempts to optimize the reaction with pyrrole led to modest results, the best result was obtained with ligand **L6**, which afforded the tri-

Table 3. Enantioselective Friedel–Crafts reaction of indole (**1a**) with β-trifluoromethyl-α,β-enones **2** catalyzed by **L3**–$Zr(OtBu)_4$.[a]



	Indole	R^1	R^2	R^5	R^6	R^7	*t* [h]	Product	Yield[b] [%]	*ee*[c] [%]
1	**1a**	H	H	H	H	H	3.5 (4.5)	**3aa**	87(80)	96 (99)
2	**1b**	H	H	Me	H	H	5.5 (23)	**3ba**	95 (69)	90 (94)
3	**1c**	H	H	MeO	H	H	4 (22)	**3ca**	99 (76)	85 (82)
4	**1d**	H	H	Br	H	H	27	**3da**	89	94
5	**1e**	H	Me	H	H	H	27	**3ea**	76	82
6	**1f**	H	H	H	H	Me	22	**3fa**	64	70
7	**1g**	Me	H	H	H	H	22	**3ga**	34	24
8	**1h**	H	H	H	Me	H	5	**3ha**	90	90

[a] Reaction carried out with **1** (0.15 mmol), **2** (0.125 mmol), (*R*)-**L3** (0.025 mmol), $Zr(OtBu)_4$ (0.025 mmol) in CH_2Cl_2 (2 mL) at RT. Data in parenthesis are for the same reaction carried out at 0 °C. [b] Isolated yield of **3**. [c] Determined by chiral HPLC analysis. (*R*)-Configuration was assigned on the assumption of a uniform mechanistic pathway for products **3**, cf. **3ae**.

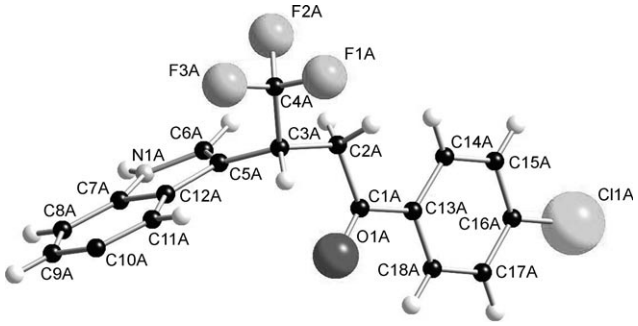
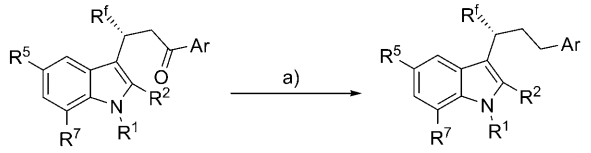
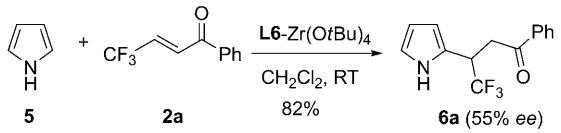


Figure 1. X-ray structure for compound **3ae**. Flack parameter 0.03 (10).



3aa: $R^1=R^2=R^5=R^7=H$, Ar=Ph, $R^f=CF_3$ — **4aa** (99%)
3ab: $R^1=R^2=R^5=R^7=H$, Ar=*p*-MeC_6H_4, $R^f=CF_3$ — **4ab** (89%)
3ai: $R^1=R^2=R^5=R^7=H$, Ar=Ph, $R^f=CF_3CF_2$ — **4ai** (99%)
3ba: $R^1=R^2=R^7=H$, R^5=Me, Ar=Ph, $R^f=CF_3$ — **4ba** (99%)

Scheme 3. Hydrogenation of compounds **3**. a) H_2, 10% Pd/C, EtOH/THF.



5 + **2a** → **6a** (55% *ee*)

Scheme 4. Enantioselective Friedel–Crafts reaction of pyrrole **5** with β-trifluoromethyl-α,β-enone **2a**. The reaction was carried out by using **5** (1.25 mmol), **2a** (0.125 mmol), (*R*)-**L6** (0.025 mmol), $Zr(OtBu)_4$ (0.025 mmol) in CH_2Cl_2 (2 mL) at RT.

fluoroalkylated pyrrole with 82% yield and 55% *ee* of the opposite enantiomer.

Conclusion

In conclusion, we have shown that chiral BINOL-type/$Zr(OtBu)_4$ complexes are very effective catalysts for the enantioselective Friedel–Crafts reaction of indole derivatives with a number of β-trifluoromethyl-α,β-unsaturated ketones. The reaction proceeds with good yields and excellent enantioselectivities (up to 99%) and gives functionalized indoles with an asymmetric tertiary carbon center attached to a trifluoromethyl group. The conditions are of application to a large number of substituted β-trifluoromethyl aryl enones and indoles. The use of ligands that are commercially available in both enantiomeric forms (thus providing access to both enantiomeric products) and a simple experimental procedure at room temperature constitute additional advantages of this method.

Experimental Section

General methods: Glassware was oven-dried overnight at 120°C. Reactions were monitored by TLC analysis by using Merck silica gel 60 F-254 thin-layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040–0.063 mm. NMR spectra were run by using a Bruker Avance 300 spectrometer with residual nondeuterated solvent as the internal standard. Specific optical rotations were measured by using a Perkin–Elmer polarimeter using sodium light (D line 589 nm). EI mass spectra were recorded by using a Fisons Instruments VG Autospec GC 8000 series at 70 eV. ESI mass spectra were recorded by using a Waters Q-TOF premier mass spectrometer with an electrospray source and a capillary voltage of 3.3 kV. Chiral HPLC analyses were performed by using an Agilent 1100 series instrument equipped with a refraction index detector or by using a Hitachi Elite Lachrom instrument equipped with a Hitachi UV diode-array L-4500 detector and chiral stationary columns from Daicel. CH_2Cl_2 and toluene were dried over CaH_2 prior to use. All BINOL-type ligands and all indoles **1** were commercially available and used as purchased without further purification.

General procedure for the synthesis of β-trifluoromethyl-α,β-enones (2a–h): Pyrrolidine (0.6 mL, 7 mmol), trifluoroacetaldehyde hemiacetal (1.29 mL, 10 mmol) and the corresponding acetophenone (10 mmol) were dissolved in toluene. The mixture was heated at reflux until the starting material was completely reacted (monitored by TLC). Then, the solvent was removed under reduced pressure and the resulting product was chromatographed on silica gel by eluting with hexane/EtOAc (97:3 to 95:5) to afford the desired β-trifluoromethyl-α,β-enones **2a–h**.

*(*E*)-4,4,4-Trifluoro-1-phenylbut-2-en-1-one (**2a**)*:[16] Yellow liquid, 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.98$ (dd, $J=7.2$, 1.5 Hz, 2H), 7.65 (t, $J=7.4$ Hz, 1H), 7.58–7.49 (m, 3H), 6.82 ppm (dq, $J=15.5$, 6.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=188.0$ (C), 136.1 (C), 134.1 (CH), 131.0 (q, J(C,F)=5.6 Hz; CH), 130.2 (q, J(C,F)=35.0 Hz; CH), 129.0 (CH), 128.8 (CH), 122.5 ppm (q, J(C,F)=268.5 Hz; CF_3).

General procedure for the synthesis of β-pentafluoro enones (2i–j): Pyrrolidine (0.21 mL, 2.5 mmol), pentafluoropropionaldehyde monohydrate (950 mg, 5 mmol), and acetic acid (0.21 mL, 2.5 mmol) were dissolved in the corresponding acetophenone (2.5 mL). The mixture was heated at reflux until starting material was completely reacted (monitored by TLC). Then the solvent was removed under reduced pressure and the resulting product was chromatographed on silica gel by eluting with hexane/EtOAc (97:3 to 9:1) to afford the β-hydroxyketones. These β-hydroxyketones were dissolved in toluene (15 mL) and *p*-toluenesulfonic acid (15 mol%) was added. The mixture was heated at reflux until the starting material was completely reacted (monitored by TLC). Then, the solvent was removed under reduced pressure and the product was chromatographed on silica gel by eluting with hexane/EtOAc (97:3) to afforded the desired enone (**2i–j**).

*(*E*)-4,4,5,5,5-Pentafluoro-1-phenylpent-2-en-1-one (**2i**)*:[16] Yellow liquid, 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.98$ (dd, $J=8.4$, 1.2 Hz, 2H), 7.65 (tt, $J=7.6$, 1.8 Hz, 1H), 7.60 (dt, $J=15.7$, 2.1 Hz, 1H), 7.53 (t, $J=7.5$ Hz, 1H), 6.85 ppm (tq, $J=15.7$, 11.9, 0.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=187.5$ (C), 136.1 (C), 134.2 (CH), 133.0 (t, J(C,F)=7.1 Hz, CH), 129.4 (t, J(C,F)=24.7 Hz, CH), 129.0 (CH), 128.8 (CH), 118.6 (qt, J(C,F)=284.0, 36.5 Hz, CF_3), 112.1 ppm (tq, J(C,F)=250.0, 39.0 Hz, CF_2).

General procedure for the catalytic enantioselective Friedel–Crafts reaction: $Zr(OtBu)_4$ (10 μL, 0.025 mmol) was added with a microsyringe to a solution of ligand **L3** (11.1 mg, 0.025 mmol) in dry CH_2Cl_2 (1 mL) under N_2 at RT. After 1 h, a solution of indole **1** (0.15 mmol) and enone **2** (0.125 mmol) in dry CH_2Cl_2 (1 mL) was added and the mixture stirred at RT. After completion of the reaction (monitored by TLC), the mixture was filtered through a short pad of silica gel (eluent: Et_2O). The solvents were removed under reduced pressure and products **3** were directly isolated by flash chromatography on silica gel (hexane/EtOAc or hexane/CH_2Cl_2 mixtures).

*(*R*)-4,4,4-Trifluoro-3-(1*H*-indol-3-yl)-1-phenylbutan-1-one (**3aa**)*: The *ee* (99%) was determined by HPLC analysis, Chiralcel OD-H, *i*PrOH/

hexane (1:9), flow rate = 1.0 mL min^{-1}, major enantiomer (*R*) t_r = 14.9 min, minor enantiomer (*S*) t_r = 13.9 min; m.p. 117–120 °C (CH_2Cl_2/hexane); $[\alpha]_D^{25}$ +57.5 (*c* = 0.74 in $CHCl_3$, 99% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (brs, 1H), 7.92 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.76 (dd, *J* = 6.9, 1.2 Hz, 1H), 7.56 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.35 (dd, *J* = 6.9, 2.4 Hz, 1H), 7.24–7.15 (m, 3H), 4.70–4.56 (m, 1H), 3.75 (dd, *J* = 17.6, 8.3 Hz, 1H), 3.66 ppm (dd, *J* = 17.4, 4.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 195.9 (C), 136.3 (C), 136.0 (C), 133.5 (CH), 128.7 (CH), 128.0 (CH), 127.4 (q, *J*(C,F) = 277.5 Hz, CF_3), 126.5 (C), 123.4 (CH), 122.4 (CH), 120.1 (CH), 119.2 (CH), 111.4 (CH), 109.7 (q, *J*-(C,F) = 2.3 Hz; C), 38.3 (q, *J*(C,F) = 1.5 Hz; CH_2), 36.7 ppm (q, *J*(C,F) = 28.8 Hz, CH); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −70.59 ppm (s, CF_3); EI MS: *m/z* (%): 297 $[M]^+$ (81), 297 (34), 212 (58), 198 (55), 105 (100), 77 (32); HRMS: *m/z* calcd for $C_{18}H_{14}F_3NO$: 317.1027 $[M]^+$; found: 317.1019.

General procedure for the reduction of the carbonyl group: Compound **3** was dissolved in a mixture of EtOH/THF (2:1) on a two-necked flask. After that, 10% Pd/C (20 mg) was added, and the mixture was stirred under H_2 at atmospheric pressure. After completion of the reaction (monitored by TLC), the mixture was filtered through a short pad of silica gel (eluent: Et_2O). The solvents were removed under reduced pressure to give compound **4**.

*(R)-3-(1,1,1-Trifluoro-4-phenylbutan-2-yl)-1*H*-indole (**4aa**)*: The product was isolated as an oil. The *ee* (98%) was determined by HPLC analysis, Chiralpak AD-H, *i*PrOH/hexane (1:9), flow rate = 1.0 mL min^{-1}, major enantiomer (*R*) t_r = 8.1 min, minor enantiomer (*S*) t_r = 13.5 min; $[\alpha]_D^{25}$ −12.3 (*c* 1.23, $CHCl_3$, 98% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (brs, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.42 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.30–7.15 (m, 6H), 7.09 (dd, *J* = 8.1, 1.5 Hz, 2H), 3.75 (dqd, *J* = 19.1, 9.5, 4.3 Hz, 1H), 2.68 (ddd, *J* = 13.8, 9.0, 5.4 Hz, 1H), 2.58–2.25 ppm (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.9 (C), 136.2 (C), 128.5 (CH), 128.4 (CH), 127.4 (q, *J*(C,F) = 277.8 Hz; CF_3), 127.2 (C), 126.1 (CH), 123.4 (CH), 122.5 (CH), 120.0 (CH), 119.2 (CH), 111.3 (CH), 109.6 (q, *J*-(C,F) = 2.5 Hz; C), 40.8 (q, *J*(C,F) = 27.9 Hz; CH), 32.8 (CH_2), 30.3 ppm (q, *J*(C,F) = 1.7 Hz; CH_2); ^{19}F NMR (282 MHz, $CDCl_3$): δ = −70.74 ppm (s, CF_3); ESI HRMS: *m/z* calcd for $C_{19}H_{17}F_3N$: 304.1313 $[M+H]^+$; found: 304.1310.

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