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Enantioselective Friedel–Crafts Alkylation of Indoles with (*E*)-1-Aryl-4-benzyloxybut-2-en-1-ones Catalyzed by an (*R*)-3,3′-Br_2BINOLate–Hafnium(IV) Complex

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Dedicated to the memory of Juan Fernández Torreblanca

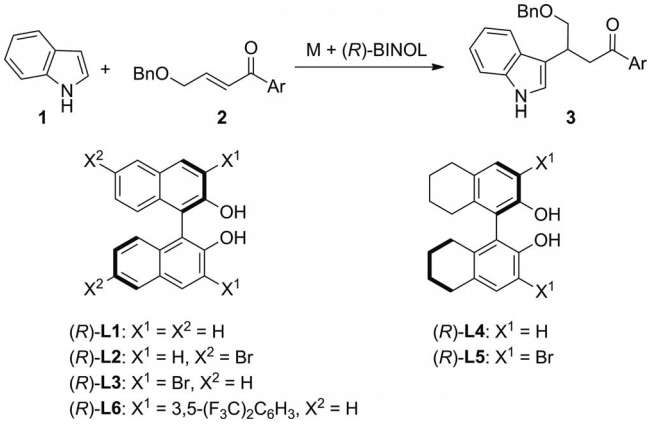
Keywords: Alkylation / Asymmetric catalysis / C–C coupling / Hafnium / Regioselectivity

A highly enantioselective Friedel–Crafts reaction of unprotected indoles with (*E*)-1-aryl-4-benzyloxybut-2-en-1-ones catalyzed by a new chiral [Hf{(*R*)-3,3′-Br_2-BINOL}($OtBu)_2]_2$ complex has been developed to functionalize the C-3 position of the indole nucleus with a side chain bearing a 1,4-difunctionalized moiety and a benzylic stereogenic center. The reaction proceeds in good to excellent yields and excellent enantioselectivities (up to 97 % *ee*). The usefulness of this approach was illustrated with the synthesis of a tryptophol derivative.

Introduction

The indole nucleus is present in many compounds of biological and pharmaceutical interest.[1] Consequently, there has been continuing interest in the development of new methods for the synthesis of indole derivatives. In the last years, several catalytic systems based on chiral metal complexes or organocatalysts have been developed and successfully applied to the enantioselective Friedel–Crafts alkylation of indoles with prochiral unsaturated electrophiles, leading to enantiomerically enriched alkylated indoles.[2] Most of the successful examples of such processes have been limited to the use of bidentate chelating substrates[3–15] and nitroalkenes,[16] whereas the use of nonchelating electrophile substrates is usually limited to structurally simple monofunctional α,β-unsaturated aldehydes[17] and enones.[18] The study of new electrophilic partners for the enantioselective Friedel–Crafts reaction that can provide access to a broader range of functionalized enantiomerically enriched indoles is of great interest for the development of new synthetic strategies toward drugs and bioactive compounds.

In this paper we report the enantioselective Friedel–Crafts reaction of indoles **1** with (*E*)-1-aryl-4-benzyloxybut-2-en-1-ones **2**[19] catalyzed by a new chiral (*R*)-3,3′-Br_2-BINOLate–hafnium(IV) *tert*-butoxide complex as a new convenient procedure to functionalize the C-3 position of the indole nucleus with a side chain bearing a 1,4-difunctionalized moiety and a benzylic stereogenic center (Scheme 1).



Scheme 1. Enantioselective Friedel–Crafts reaction between indoles **1** and (*E*)-1-aryl-4-benzyloxybut-2-en-1-ones **2** and BINOL-derived ligands used in this study (M = group IV metal alkoxide).

Results and Discussion

Previously, we reported the enantioselective Friedel–Crafts reaction of indoles with simple α,β-unsaturated

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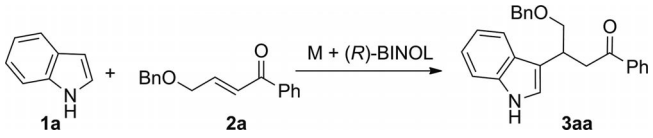
ketones and β-trifluoromethyl-α,β-unsaturated ketones catalyzed by a $[Zr_2\{(R)\text{-}3,3'\text{-}Br_2\text{-}BINOL\}_2(OtBu)_4]$ complex.[20] These reactions were carried out with 20 mol-% catalyst in dichloromethane at room temperature, giving the corresponding alkylated indoles with good yields and high enantioselectivities after 3.5 h. However, when these conditions were applied to the Friedel–Crafts alkylations of the indole (**1a**) with the new electrophile (*E*)-4-benzyloxy-1-phenylbut-2-en-1-one (**2a**), we observed a slower reaction, compared with our previous works, and the resulting product **3aa** was obtained with good enantioselectivity (89% *ee*), albeit with low yield (49%; Table 1, Entry 1). A modification of the reaction conditions was first explored to improve the efficiency of $[Zr(OtBu)_4]$ with other BINOL-derived ligands, (**L1**, **L2** and **L4**–**L6**). However, none of these ligands improved the results obtained with **L3** (the results are not included in the Table 1). The use of other group IV metal alkoxides with **L3** was then tested. Performing the reaction with $[Ti(OiPr)_4]$ resulted in a slow reaction rate, and the product **3aa** was obtained in low yield (24%) and enantioselectivity (6% *ee*; Table 1, Entry 2). Interestingly, when $[Hf(OtBu)_4]$ was used, the reaction product was obtained with good yield (90%) and excellent enantioselectivity (94% *ee*; Table 1, Entry 3). Ligands **L1**, **L2** and **L4**–**L6** were also tested with $[Hf(OtBu)_4]$, but they gave rise to lower enantioselectivities (Entries 4–8) than those obtained with **L3** (Entry 3). Next, a range of solvents were tested with $[(R)\text{-}\mathbf{L3}\text{-}Hf(OtBu)_4]$. The results indicated that the solvent plays an important role in governing the rate and enantioselectivity of the reaction. Coordinating and polar solvents such as dioxane and diethyl ether (Entries 9 and 10) had a negative influence on the catalytic activity of the $[(R)\text{-}\mathbf{L3}\text{-}Hf(OtBu)_4]$ complex. Other chlorinated solvents such as chloroform and 1,2-dichloroethane (Entries 11 and 12) were also investigated, but no superior results were obtained. When the reaction was carried out in toluene (Entry 13) good results were obtained, although they were somewhat lower than those obtained with dichloromethane as solvent. Reduction of the catalyst load to 10 mol-% had a deleterious effect on the reaction. Therefore, the optimal reaction conditions were established as follows: indole (**1a**; 0.15 mmol), enone **2** (0.125 mmol) and $[(R)\text{-}\mathbf{L3}\text{-}Hf(OtBu)_4]$ (20 mol-%, 1:1), in CH_2Cl_2 (1.8 mL) at room temperature.

Under the optimized reaction conditions (Table 1, Entry 3), several (*E*)-1-aryl-4-benzyloxybut-2-en-1-ones **2a**–**h** and indole (**1a**) were screened, giving the desired alkylated indoles with high to excellent enantioselectivities (up to 97% *ee*). It is noteworthy that the electronic nature as well as the position of the substituent on the phenyl ring of the enone had little influence on the enantioselectivity or yield of the reaction (Table 2, Entries 2–6). However, (*E*)-4-benzyloxy-1-(*p*-methoxyphenyl)but-2-en-1-one (**2e**) reacted

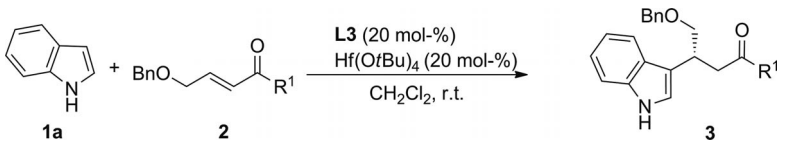
Table 1. Screening of ligands, metal alkoxides and solvents for the Friedel–Crafts reaction of **1a** and enone **2a**.[a]



Entry	Solvent	*t* [h]	$M(OR)_4$	L	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	7	$Zr(OtBu)_4$	**L3**	49	89
2	CH_2Cl_2	20	$Ti(OiPr)_4$	**L3**	24	6
3	CH_2Cl_2	2	$Hf(OtBu)_4$	**L3**	90	94
4	CH_2Cl_2	1.5	$Hf(OtBu)_4$	**L1**	98	33
5	CH_2Cl_2	21	$Hf(OtBu)_4$	**L2**	55	4
6	CH_2Cl_2	3	$Hf(OtBu)_4$	**L4**	94	33
7	CH_2Cl_2	20	$Hf(OtBu)_4$	**L5**	12	52
8	CH_2Cl_2	22	$Hf(OtBu)_4$	**L6**	19	67
9	dioxane	–	$Hf(OtBu)_4$	**L3**	–	–
10	Et_2O	21	$Hf(OtBu)_4$	**L3**	58	67
11	$CHCl_3$	3	$Hf(OtBu)_4$	**L3**	60	54
12	$(CH_2Cl)_2$	24	$Hf(OtBu)_4$	**L3**	48	72
13	toluene	4.5	$Hf(OtBu)_4$	**L3**	87	92

[a] Reaction conditions: **1a** (0.15 mmol, 1.2 equiv.), enone **2a** (0.125 mmol, 1 equiv.), (*R*)-BINOL ligand (20 mol-%), metal alkoxide (20 mol-%), solvent (1.8 mL), room temp., N_2. [b] Isolated yield of **3aa** after flash chromatography. [c] Determined by HPLC analysis on a Chiralcel OD-H column.

Table 2. Catalytic enantioselective Friedel–Crafts alkylation of indole (**1a**) with (*E*)-1-aryl-4-benzyloxybut-2-en-1-ones **2a**–**h** catalyzed by $[(R)\text{-}\mathbf{L3}\text{-}Hf(OtBu)_4]$.[a]



Entry	2	R^1	*t* [h]	3	Yield [%][b]	*ee* [%][c]
1	**2a**	Ph	2	**3aa**	90	94
2	**2b**	*p*-MeC_6H_4	3	**3ab**	86	92
3	**2c**	*m*-MeC_6H_4	2	**3ac**	98	97
4	**2d**	*o*-MeC_6H_4	2	**3ad**	81	84
5	**2e**	*p*-$MeOC_6H_4$	24	**3ae**	45	87
6	**2f**	*p*-BrC_6H_4	2	**3af**	78	86
7	**2g**	2-thienyl	1	**3ag**	90	92
8	**2h**	2-furyl	2	**3ah**	93	84

[a] Reaction conditions: indole **1a** (0.15 mmol, 1.2 equiv.), enones **2a**–**h** (0.125 mmol, 1.0 equiv.), $(R)\text{-}\mathbf{L3}\text{-}Hf(OtBu)_4$ complex (0.025 mmol, 20 mol-%; 1:1), CH_2Cl_2 (1.8 mL) room temp., N_2. [b] Isolated yield after flash chromatography. [c] Determined by chiral HPLC analysis.

slower, giving product **3ae** with only 45% yield. In addition, the heteroaromatic substrates **2g** and **2h** could also serve as substrates for this reaction, giving the corresponding alkylated indoles with excellent yields and enantioselectivities (Entries 7 and 8).

With regard to the substituent effect on the indole nucleus, the reactions of a range of indoles **1a**–**i** with enones **2a**, **2b** and **2f** were examined (Table 3). Neither electron-donating groups (CH_3, CH_3O) nor electron-withdrawing groups (Br) at the 5-position of indole affected the enantioselectivity of the reaction, although the reaction rate and yield were indeed unfavorably influenced in the case of 5-bromoindole (**1e**), which required a reaction time of 22 h at room temperature (Entry 7). Similarly, 2-methylindole (**1g**) reacted slowly with **2a** to give **3ga** with good yield and enantioselectivity (92% *ee*). However, the presence of a methyl group at C-7 brought about a decrease in the reaction rate, yield, and enantioselectivity, with compound **3ha** being obtained with only 48% yield and 51% *ee* (Entry 10). Finally, 1-methylindole (**1i**) gave the corresponding alkylated product **3ia** in a 65% yield and 5% *ee* (Entry 11).

The absolute configuration of the stereogenic center in compound **3bf** was determined to be (*R*) on the basis of X-ray crystallographic analysis (Figure 1); the configurations of the rest of the products were assigned on the assumption of a uniform mechanistic pathway.[21]

A plausible catalytic cycle for the [(*R*)-**L3**-Hf(O*t*Bu)$_4$]-catalyzed Friedel–Crafts reaction between indoles and benzyloxyenones is outlined in Scheme 2. Based on our recent experimental and theoretical studies on the structure of complexes derived from (*R*)-3,3′-Br$_2$-BINOL ligand and group IV metal alkoxides,[22] the catalytic species generated from stoichiometric quantities of (*R*)-3,3′-Br$_2$-BINOL and *tert*-butoxide of Hf (without elimination of the *t*BuOH released) is a dimer at room temperature consisting of a doubly bridged [Hf^{IV}{μ-(*R*)-3,3′-Br$_2$BINOL}]$_2$ motif, in which each BINOL ligand acts as bridge between the metal centers, and all the *tert*-butoxide groups are terminal (Figure 2; for ^{1}H and ^{13}C NMR spectra of the complex see the Supporting Information).[23]

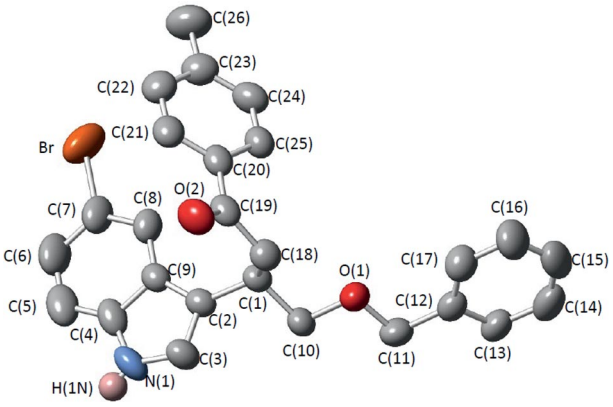
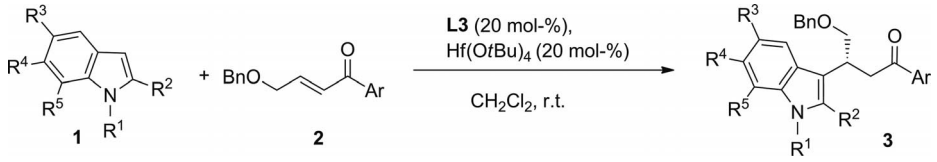


Figure 1. X-ray structure of compound **3bf**. Hydrogen atoms (except N–H) have been omitted for clarity.

Activation of the benzyloxyenone **2** by Hf^{IV} coordination forms a substrate–catalyst complex **B**, which undergoes H-bond-assisted (**C**) nucleophilic addition of the indole to the double bond of the enone to provide the Friedel–Crafts adduct **D**. Subsequent H-transfer and decoordination of the chiral enolate **E** afford the Friedel–Crafts product and regenerate the catalyst **A** (Scheme 2). In this case, the use of additional alcohol to facilitate the catalyst turnover[24] is not necessary, because the 2 equiv. of *t*BuOH released after generation of the complex seems to be enough to carry out catalyst regeneration.

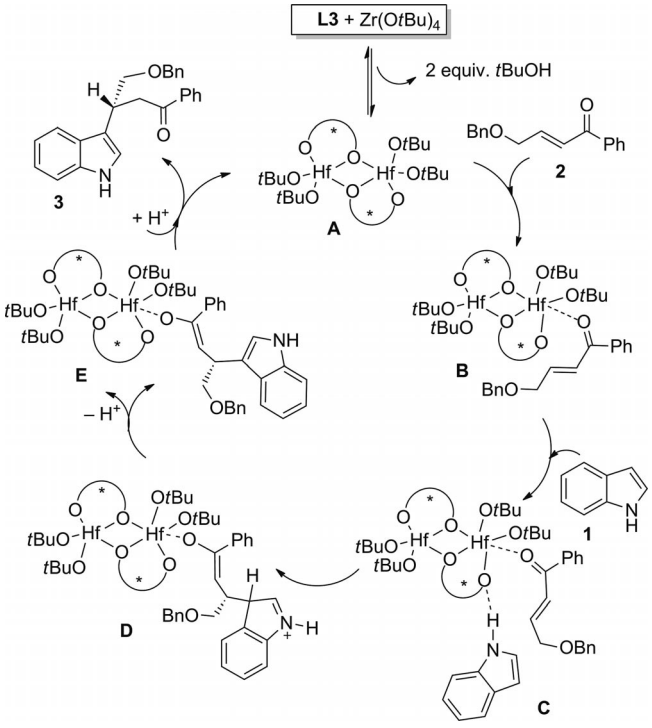
Our working model to account for the stereoselectivity of the reaction is shown in Figure 3. The benzyloxyenone

Table 3. Catalytic enantioselective Friedel–Crafts alkylation of indoles **1a**–**i** with (*E*)-1-aryl-4-benzyloxybut-2-en-1-ones **2a**, **2b** and **2f** catalyzed by [(*R*)-**L3**-Hf (O*t*Bu)$_4$].[a]



Entry	1	R^1	R^2	R^3	R^4	R^5	2	Ar	*t* [h]	3	Yield [%][b]	*ee* [%][c]
1	**1a**	H	H	H	H	H	**2a**	Ph	2	**3aa**	90	94
2	**1b**	H	H	Me	H	H	**2a**	Ph	3	**3ba**	94	97
3	**1b**	H	H	Me	H	H	**2f**	*p*-BrC$_6$H$_4$	2	**3bf**	54	83
4	**1c**	H	H	MeO	H	H	**2a**	Ph	3	**3ca**	80	94
5	**1d**	H	H	F	H	H	**2a**	Ph	5	**3da**	93	92
6	**1d**	H	H	F	H	H	**2b**	*p*-MeC$_6$H$_4$	3	**3db**	85	93
7	**1e**	H	H	Br	H	H	**2b**	*p*-MeC$_6$H$_4$	22	**3eb**	52 (24)[d]	67 (98)[d]
8	**1f**	H	H	H	F	H	**2a**	Ph	24	**3fa**	70	68
9	**1g**	H	Me	H	H	H	**2a**	Ph	30	**3ga**	74	92
10	**1h**	H	H	H	H	Me	**2a**	Ph	30	**3ha**	48	51
11	**1i**	Me	H	H	H	H	**2a**	Ph	2	**3ia**	65	5

[a] Reaction conditions: indoles **1a**–**i** (0.15 mmol, 1.2 equiv.), (*E*)-1-aryl-4-benzyloxybut-2-en-1-ones **2a**, **2b** and **2f** (0.125 mmol, 1.0 equiv.), [(*R*)-**L3**-Hf(Bu*t*O)$_4$] complex (0.025 mmol, 20 mol-%; 1:1), CH_2Cl_2 (1.8 mL), room temp., N_2. [b] Isolated yield of **3**. [c] Determined by chiral HPLC analysis. [d] Yield and enantiomeric excess after crystallization are given in parentheses.



Scheme 2. Proposed catalytic cycle for the Friedel–Crafts alkylation of indole with 4-benzyloxy-α,β-unsaturated ketones catalyzed by [Hf{(*R*)-3,3′-Br_2BINOL}($OtBu)_2$]$_2$.

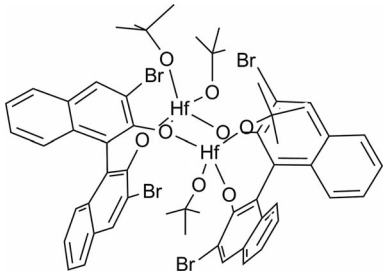


Figure 2. Dimeric structure of the hafnium complex [Hf{(*R*)-3,3′-Br_2BINOL}($OtBu)_2$]$_2$.

coordinates to the hafnium atom in an approximately octahedral geometry in complex **B**. The attack of indole on (*E*)-1-aryl-4-benzyloxybut-2-en-1-one (**2**) takes place preferably from the *Re* face, leading to formation of the predominant (*R*)-configured adduct. The model shows also that the H atom of the N–H group of the indole must form a hydrogen bond with the basic oxygen atom of one 3,3′-Br_2-BINOLate ligand, which plays an important role in stabilizing the transition state of the process. Accordingly, the absence of the hydrogen-bond interaction in the case of *N*-methylindole (**1i**) might explain why a lower enantiomeric excess was obtained for product **3ia** (65% yield, 5% *ee*). A bifunctional mode of action of catalyst [Hf{(*R*)-(3,3′-Br_2-BINOL)}-($OtBu)_2$]$_2$ is therefore proposed with simultaneous activation of the benzyloxyenone by one hafnium atom and of the indole through BINOLate oxygen coordination with the N–H group.[25]

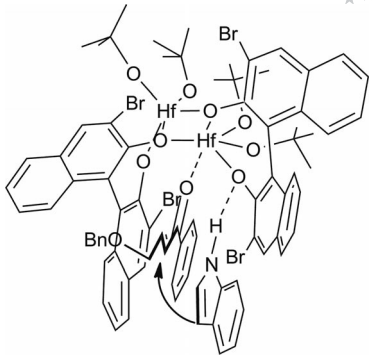
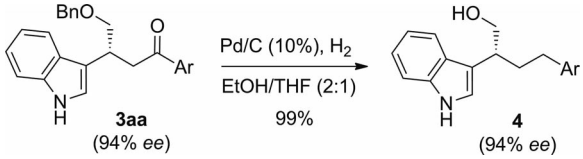


Figure 3. Proposed working stereomodel for the bifunctional mode of action of the catalyst.

The alkylated indoles **3** prepared by this methodology can be used to synthesize tryptophol derivatives by reduction of their carbonyl group and deprotection of the benzyl ether. Thus, the hydrogenation of **3aa** with Pd/C as catalyst gave 2-(2-phenylethyl)-2-(3-indolyl)ethanol, [2-(2-phenylethyl)tryptophol] (**4**) quantitatively, without any appreciable loss of the enantiomeric excess of the starting material (Scheme 3). Tryptophols are a class of indoles bearing a 3-(hydroxyethyl) side chain substituted or not in the α- and/or β-positions. Tryptophol and a number of its derivatives have been isolated from a variety of natural sources, and some are known to possess biological activity; thus, for example, esters of 5-methoxytryptophol possess anticholinergic activity.[26] Compared with previous established methods for the synthesis of tryptophols,[27] our methodology is simple to conduct and delivers tryptophol derivatives with high yields in enantiomerically pure form.



Scheme 3. Synthesis of [2-(2-phenylethyl)tryptophol] (**4**).

Conclusions

We have shown that the [Hf_2\{(*R*)-3,3′-Br_2-BINOL\}$_2$-($OtBu)_4$] complex is a very effective catalyst for the enantioselective Friedel–Crafts alkylation of unprotected indole derivatives with a number of nonchelating (*E*)-1-aryl-4-benzyloxybut-2-en-1-ones to give chiral indoles with a side chain bearing a 1,4-difunctionalized moiety and a benzylic stereogenic center. The reaction proceeds with yields and enantioselectivities ranging from good to excellent. The use of ligands that are commercially available in both enantiomeric forms and a simple experimental procedure at room temperature constitutes additional advantages of this method. Furthermore, the use of *N*-protecting groups can be avoided in this indole alkylation, which enhances the efficiency by which substituted indoles can be synthesized. Finally, the alkylated indoles prepared by this methodology

can be efficiently transformed into tryptophol derivatives by reduction of their carbonyl group and deprotection of the benzyl ether without any appreciable loss of stereochemical integrity.

Experimental Section

General Methods: All catalytic reactions were carried out in glassware dried at 120 °C overnight. All air- and moisture-sensitive manipulations were performed under nitrogen by using standard techniques. Reactions were monitored by using TLC (Merck Silica gel 60 F254). Flash column chromatography was performed on silica gel 60, 0.040–0.063 mm. Melting points were measured with a Büchi M-560 instrument and are uncorrected. NMR spectra for the characterization of the Friedel–Crafts products were recorded at 300 MHz for ^{1}H and at 75 MHz for ^{13}C nuclei with a Bruker Avance 300 spectrometer. NMR studies of the catalytic species were conducted at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei with a Bruker Avance 400 spectrometer. Residual non-deuterated solvent was used as internal standard in all cases (δ = 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C in the case of $CDCl_3$, δ = 5.35 ppm for ^{1}H and 53.5 ppm for ^{13}C NMR in the case of CD_2Cl_2). The carbon multiplicity was determined by DEPT experiments. Specific optical rotations were measured by using sodium light (D line, 589 nm) and a 1 dm cell; concentrations (*c*) are given in g/100 mL. Chiral HPLC analyses were performed with an Agilent 1100 series instrument equipped with a refraction index detector or in a Hitachi Elite Lachrom instrument equipped with a Hitachi UV diode-array L-4500 detector by using chiral stationary columns from Daicel. Mass spectra (EI) were recorded at 70 eV, and mass spectra (FAB) were carried out at 30 kV in an MNBA matrix with a Fisons Instruments VG Autospec GC 8000 series. ESI mass spectra were recorded with a Q-TOF premier mass spectrometer with an electrospray source. Nitrogen was used as the drying as well as the nebulizing gas. CH_2Cl_2 was distilled from P_2O_5 and stored over molecular sieves (4 Å). THF was freshly distilled from Na/benzophenone under nitrogen. All BINOL-type ligands, all indoles, LDA, NEt_3, methanesulfonyl chloride, aryl methyl ketones and 2-benzyloxyacetaldehyde were commercially available and used as purchased without further purification; [Zr(O*t*Bu)$_4$] and [Hf(O*t*Bu)$_4$] were purchased from Fluka or Strem Chemicals and [Ti(O*i*Pr)$_4$] from Aldrich. (*E*)-1-Aryl-4-benzyloxy-2-buten-1-ones **2** were synthesized by aldol reaction followed by dehydration (see the Supporting Information).

Preparation and Characterization of the Chiral Metal Complex [Hf$_2${(*R*)-3,3′-Br$_2$-BINOL}$_2$(O*t*Bu)$_4$]: [Hf(O*t*Bu)$_4$] (11 μL, 0.025 mmol) was added by using a syringe to a solution of ligand **L3** (11.1 mg, 0.025 mmol) in CD_2Cl_2 (0.5 mL) under nitrogen at room temp. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.27 (s, 1 H, 4-H), 8.06 (s, 1 H, 4′-H), 7.91 (dd, *J* = 8.1, 0.5 Hz, 1 H, 5′-H), 7.88 (d, *J* = 8.2 Hz, 1 H, 5-H), 7.42 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1 H, 6-H), 7.33 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1 H, 6′-H), 7.25 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1 H, 7-H), 7.18 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.08 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1 H, 7′-H), 6.86 (dd, *J* = 8.5, 0.4 Hz, 1 H, 8′-H), 0.95 (s, 9 H, *t*Bu), 0.94 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100.1 MHz, CD_2Cl_2): δ = 154.0 (C), 151.9 (C), 132.5 (C), 132.6 (CH), 132.5 (C), 130.8 (C), 130.7 (CH), 130.1 (C),127.5 (CH), 127.4 (CH), 127.1 (CH), 126.8 (CH), 126.4 (CH), 125.3 (CH), 125.1 (CH), 123.5 (CH), 122.6 (C), 119.3 (C), 117.5 (C), 117.2 (C), 78.4 (C), 78.0 (C), 32.3 (CH_3), 31.8 (CH_3) ppm.

General Procedure for the Catalytic Enantioselective Friedel–Crafts Reaction: To a solution of ligand **L3** (11.1 mg, 0.025 mmol) in anhydrous CH_2Cl_2 (0.8 mL) at room temperature under nitrogen was added [Hf(O*t*Bu)$_4$] (10 μL, 0.025 mmol). The mixture was stirred for 1 h, then a solution of indole **1** (0.15 mmol) and (*E*)-1-aryl-4-benzyloxy-2-buten-1-one **2** (0.125 mmol) in anhydrous CH_2Cl_2 (0.8 mL) were added by using a syringe. After completion of the reaction (TLC), the mixture was filtered through a short pad of silica gel eluting with diethyl ether. The solvents were removed under reduced pressure, and the Friedel–Crafts products **3** were isolated directly by flash chromatography on silica gel (hexane/EtOAc).

Experimental Procedure for the Synthesis of (*R*)-2-(2-Phenylethyl)tryptophol (4): Alkylated indole **3aa** (50 mg, 0.136 mmol) was dissolved in a mixture of EtOH/THF (2:1, 3 mL) in a two-necked flask; 10% Pd/C (10 mg) was added, and the reaction mixture was stirred under hydrogen at atmospheric pressure. After completion of the reaction (TLC), the mixture was filtered through a short pad of silica gel eluting with diethyl ether. The solvents were removed under reduced pressure to give (*R*)-2-(2-phenylethyl)tryptophol (**4**; 35.9 mg, 99%) as an oil. $[a]_D^{25}$ = –5.9 (*c* = 1.25, $CHCl_3$) (94% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (br. s, 1 H), 7.66 (d, *J* = 7.9 Hz, 1 H), 7.40 (d, *J* = 8.1 Hz, 1 H), 7.30–7.12 (m, 7 H), 7.09 (d, *J* = 2.3 Hz, 1 H), 3.92–3.81 (m, 2 H), 3.22–3.13 (m, 1 H), 2.72–2.56 (m, 2 H), 2.15 (t, *J* = 7.8 Hz, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 142.3 (C), 136.7 (C), 128.4 (CH), 128.3 (CH), 126.9 (C), 125.7 (CH), 122.2 (CH), 122.1 (CH), 119.4 (CH), 119.3 (CH), 115.9 (C), 111.3 (CH), 66.5 (CH_2), 39.5 (CH), 33.7 (CH_2), 33.3 (CH_2) ppm. HRMS (ESI): calcd. for $C_{18}H_{20}NO$ [M + H$^+$] 266.1545; found 266.1544. The enantiomeric excess (94%) was determined by chiral HPLC analysis (Chiralpack AD-H; 2-propanol/hexane, 20%; 1.0 mL/min): t_R = 13.7 [(*R*), major], 11.2 [(*S*), minor] min.

Supporting Information (see footnote on the first page of this article): Experimental procedures, synthesis and characterization of enones **2**, characterization data for compounds **3** and **4**; copies of ^{1}H and ^{13}C NMR spectra for compounds **3** and **4**; chiral HPLC chromatograms for compounds **3** and **4**; ^{1}H and ^{13}C NMR spectra of (*R*)-3,3′-Br$_2$BINOL (**L3**) and the complex [Hf(O*t*Bu)$_4$-(*R*)-**L3**].

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[1] For examples of relevant natural products and potential medicinal agents, see: a) R. D. Dillard, N. J. Bach, S. E. Draheim, D. R. Berry, D. G. Carlson, N. Y. Chirgadze, D. K. Clawson, L. W. Hartley, L. M. Johnson, N. D. Jones, E. R. McKinney, E. D. Mihelich, J. L. Olkowski, R. W. Schevitz, A. C. Smith, D. W. Snyder, C. D. Sommers, J.-P. Wery, *J. Med. Chem.* **1996**, *39*, 5119–5136; b) D. M. Leonard, K. R. Shuler, C. J. Poulter, S. R. Eaton, T. K. Sawyer, J. C. Hodges, T.-Z. Su, J. D. Scholten, R. Gowan, S. Judith, J. S. Sebolt-Leopold, A. M. Doherty, *J. Med. Chem.* **1997**, *40*, 192–200; c) U. Huber, R. E. Moore, G. M. L. Patterson, *J. Nat. Prod.* **1998**, *61*, 1304–1306; d) S. K. Rabindran, H. He, M. Singh, E. Brown, K. I. Collins, T. Annable, L. M. Greenberger, *Cancer Res.* **1998**, *58*, 5850–5858; e) D. J. Rawson, K. N. Dack, R. P. Dickinson, K. James, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 125–128; f) T. Nickelsen, A. Samel, M. Vejvoda, J. Wenzel, B. Smith, R. Gerzer, *Chronobiol. Int.* **2002**, *19*, 915–936; g) . I. Mancini, G. Guella, H. Zib-

rowius, F. Pietra, *Tetrahedron* **2003**, *59*, 8757–8762; h) T. Kam, Y. Choo, *J. Nat. Prod.* **2004**, *67*, 547–552; i) A. C. Kinsman, M. A. Kerr, *J. Am. Chem. Soc.* **2003**, *125*, 14120–14125; j) J. Chang-Fong, J. B. Rangisetty, M. Dukat, V. Setola, T. Raffay, B. Roth, R. Glennon, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1961–1964; k) J. Croonenberghs, A. Wauters, D. Deboutte, R. Verkerk, S. Scharpe, M. Maes, *Neuroendocrinol. Lett.* **2007**, *28*, 449–455; l) H. Pessoa-Mahana, C. U. Nunez, R. Araya-Maturana, C. S. Barria, G. Zapata-Torres, C. D. Pessoa-Mahana, P. Iturriaga-Vasquez, J. Mella-Raipan, M. Reyes-Parada, C. Celis-Barros, *Chem. Pharm. Bull.* **2012**, *60*, 632–638; m) M. M. Ismail, M. M. Kamel, L. W. Mohamed, S. I. Faggal, *Molecules* **2012**, *17*, 4811–4823; n) H. Nakano, N. Saito, L. Parker, Y. Tada, M. Abe, K. Tsuganezawa, S. Yokoyama, A. Tanaka, H. Kojima, T. Okabe, N. Tetsuo, *J. Med. Chem.* **2012**, *55*, 5151–5164; o) N. Kaila, A. Huang, A. Moretto, B. Follows, K. Janz, M. Lowe, J. Thomason, T. S. Mansour, C. Hubeau, K. Page, P. Morgan, S. Fish, X. Xu, C. Williams, E. Saiah, *J. Med. Chem.* **2012**, *55*, 5088–5109.

[2] For a review on Friedel–Crafts reactions, see: a) G. A. Olah, R. Krishnamurti, G. K. S. Prakash, *Friedel–Crafts Alkylations*, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 3, pp. 293–339. For reviews on enantioselective Friedel–Crafts reactions, see: b) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 560–566; *Angew. Chem. Int. Ed.* **2004**, *43*, 550–556; c) *Catalytic Asymmetric Friedel–Crafts Alkylations* (Eds.: M. Bandini, A. Umani-Ronchi), Wiley-VCH, Weinheim, Germany, **2009**; d) T. B. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903–2915; e) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; f) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190–2201; g) A. Zamfir, S. Schenker, M. Freund, S. B. Tsogoeva, *Org. Biomol. Chem.* **2010**, *8*, 5262–5267; h) M. Zeng, S.-L. You, *Synlett* **2010**, 1289–1301.

[3] K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 164–167; *Angew. Chem. Int. Ed.* **2001**, *40*, 160–163.

[4] a) D. A. Evans, K. A. Scheidt, K. R. Frandrick, H. W. Wu, J. Lam, *J. Am. Chem. Soc.* **2003**, *125*, 10780–10781; b) H. Yang, Y.-T. Hong, S. Kim, *Org. Lett.* **2007**, *9*, 2281–2284.

[5] a) W. Zhuang, T. Hausen, K. A. Jørgensen, *Chem. Commun.* **2001**, 347–348; b) J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030–9031; c) J. Zhou, Y. Tang, *Chem. Commun.* **2004**, 432–433; d) J. Zhou, M.-C. Ye, Z.-Z. Huang, Y. Tang, *J. Org. Chem.* **2004**, *69*, 1309–1320.

[6] C. Palomo, M. Oiarbide, B. G. Kardak, J. M. Garcia, A. Linden, *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155.

[7] a) D. A. Evans, K. R. Fandrick, H. J. Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942–8943; b) N. Takenaka, J. P. Abell, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 742–743.

[8] M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Helv. Chim. Acta* **2003**, *86*, 3753–3763.

[9] P. K. Singh, V. K. Singh, *Org. Lett.* **2008**, *10*, 4121–4124.

[10] C. Cao, Y. Zhou, X. Sun, Y. Tang, *Tetrahedron* **2008**, *64*, 10676–10680.

[11] M. P. Sibi, J. Coulomb, L. M. Stanley, *Angew. Chem.* **2008**, *120*, 10061–10063; *Angew. Chem. Int. Ed.* **2008**, *47*, 9913–9915.

[12] A. J. Boersma, B. L. Feringa, G. Roelfes, *Angew. Chem.* **2009**, *121*, 3396–3398; *Angew. Chem. Int. Ed.* **2009**, *48*, 3346–3348.

[13] Y. Liu, D. Shang, X. Zhou, X. Liu, X. Feng, *Chem. Eur. J.* **2009**, *15*, 2055–2058.

[14] H. J. Lee, D. Y. Kim, *Synlett* **2012**, *23*, 1629–1632.

[15] L. Liu, H. Ma, Y. Xiao, F. Du, Z. Qin, N. Li, B. Fu, *Chem. Commun.* **2012**, *48*, 9281–9283.

[16] a) W. Zhuang, R. G. Hazell, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 2566–2571; b) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem.* **2005**, *117*, 6734–6737; *Angew. Chem. Int. Ed.* **2005**, *44*, 6576–6579; c) Y. X. Jia, S. F. Zhu, Y. Yang, Q. L. Zhou, *J. Org. Chem.* **2006**, *71*, 75–80; d) S.-F. Lu, D.-M. Du, J. Xu, *Org. Lett.* **2006**, *8*, 2115–2118; e) H. Liu, J. Xu, D.-M. Du, *Org. Lett.* **2007**, *9*, 4725–4728; f) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2008**, *120*, 4080–4082; *Angew. Chem. Int. Ed.* **2008**, *47*, 4016–4018; g) H. Liu, S.-F. Lu, J. Xu, D.-M. Du, *Chem. Asian J.* **2008**, *3*, 1111–1121; h) H. Liu, D.-M. Du, *Adv. Synth. Catal.* **2010**, *352*, 1113–1118; i) E. Marques-Lopez, A. Alcaine, T. Tejero, R. P. Herrera, *Eur. J. Org. Chem.* **2011**, 3700–3705.

[17] a) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371; b) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173; c) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894–7895; d) L. Hong, L. Wang, C. Chen, B. Zhang, R. Wang, *Adv. Synth. Catal.* **2009**, *351*, 772–778.

[18] a) M. Bandini, M. Fagioli, M. Garavelli, A. Melloni, V. Trigari, A. Umani-Ronchi, *J. Org. Chem.* **2004**, *69*, 7511–7518; b) M. Bandini, M. Fagioli, P. Melchiorre, A. Melloni, A. Umani-Ronchi, *Tetrahedron Lett.* **2003**, *44*, 5843–5846; c) M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 292–293; d) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403–1405; e) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2007**, *5*, 816–821; f) Q. Cai, Z.-A. Zhao, S.-L. You, *Angew. Chem.* **2009**, *121*, 7564–7567; *Angew. Chem. Int. Ed.* **2009**, *48*, 7428–7431; g) J.-W. Zhang, Q. Cai, X.-X. Shi, W. Zhang, S.-L. You, *Synlett* **2011**, 1239–1242; h) D. Lyzwa, K. Dudzinski, P. Kwiatkowski, *Org. Lett.* **2012**, *14*, 1540–1543.

[19] The (*E*)-1-aryl-4-benzyloxybut-2-en-1-ones (**2**) were synthesized by aldol reaction followed by dehydratation, see the Supporting Information.

[20] a) G. Blay, I. Fernández, J. R. Pedro, C. Vila, *Org. Lett.* **2007**, *9*, 2601–2604; b) G. Blay, I. Fernández, M. C. Muñoz, J. R. Pedro, C. Vila, *Chem. Eur. J.* **2010**, *16*, 9117–9122.

[21] CCDC-911096 (for **3bf**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[22] G. Blay, J. Cano, L. Cardona, I. Fernández, M. C. Muñoz, J. R. Pedro, C. Vila, *J. Org. Chem.* **2012**, *77*, 10545–10556.

[23] a) T. L. Boyle, D. L. Barnes, J. A. Heppert, *Organometallics* **1992**, *11*, 1112–1126; b) T. J. Boyle, N. W. Eilerts, J. A. Heppert, F. Takusagawa, *Organometallics* **1994**, *13*, 2218–2229; c) H. Z. Tang, P. D. Boyle, B. M. J. Novak, *J. Am. Chem. Soc.* **2005**, *127*, 2136–2142.

[24] a) S. Yamasaki, M. Kanai, M. Shibasaki, *Chem. Eur. J.* **2001**, *7*, 4066–4072; b) Y. Yamashita, H. Ishitani, H. Shimizu, S. Kobayashi, *J. Am. Chem. Soc.* **2002**, *124*, 3292–3302; c) H. Bao, J. Zhou, Z. Wang, Y. Guo, T. You, K. Ding, *J. Am. Chem. Soc.* **2008**, *130*, 10116–10127; d) G. Blay, I. Fernández, A. Monleón, M. C. Muñoz, J. R. Pedro, C. Vila, *Adv. Synth. Catal.* **2009**, *351*, 2433–2440.

[25] For reviews on bifunctional catalysts, see: a) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290–1311; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236–1256; b) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187–2210; c) M. Shibasaki, S. Matsunaga, *Chem. Soc. Rev.* **2006**, *35*, 269–279.

[26] I. N. Fernando, P. L. Francis, I. Smith, *J. Neural Transm.* **1983**, *56*, 33–41.

[27] a) H. Kotsuki, M. Teraguchi, N. Shimomoto, M. Ochi, *Tetrahedron Lett.* **1996**, *37*, 3727–3730; b) S. J. Garden, R. B. da Silva, A. C. Pinto, *Tetrahedron* **2002**, *58*, 8399–8412; c) V. Khedkar, A. Tillack, M. Michalik, M. Beller, *Tetrahedron* **2005**, *61*, 7622–7631.

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