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Synthesis of Functionalized Indoles with an α-Stereogenic Ketone Moiety Through an Enantioselective Friedel–Crafts Alkylation with (*E*)-1,4-Diaryl-2-butene-1,4-diones

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

[a] Departament de Química Orgànica, Facultat de Química, Universitat de València, C/Dr. Moliner, 50, 46100 Burjassot (València), Spain
Fax: (+34)-96-354-4328; phone: (+34)-96-354-4336; e-mail: jose.r.pedro@uv.es
[b] Departamento de Física Aplicada, Universidad Politécnica de Valencia, 46071 València, Spain

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Abstract: Chiral complexes of BINOL-based ligands with hafnium *tert*-butoxide catalyze the enantioselective Friedel–Crafts alkylation of indoles with (*E*)-1,4-diaryl-2-butene-1,4-diones at room temperature, with good yields and *ee* up to 94%. Hafnium(IV) was found to be a more effective Lewis acid than other frequently used metal ions such as titanium(IV) or zirconium(IV). Unlike the enantioselective Friedel–Crafts alkylation of indoles with α,β-unsaturated compounds where the stereogenic center is generated in the β-position to a carbonyl group, the Friedel–Crafts alkylation with 2-butene-1,4-diones described here generates an α-stereogenic center with respect to one of the carbonyl groups. This can be regarded as an inversion of the normal reactivity pattern or umpolung. The enantioselective Friedel–Crafts alkylation of indoles with (*E*)-4-oxo-4-phenylbutenoates using a zirconium(IV)-BINOL catalyst is also reported. This reaction takes place regioselectively at the carbon in the β-position to the ketone carbonyl group, generating an α-ester stereogenic center.

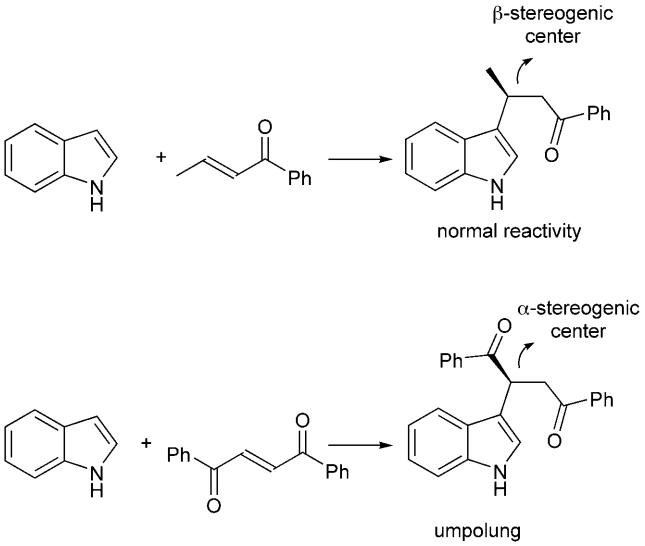
Keywords: asymmetric catalysis; enones; hafnium; O ligands; umpolung; zirconium

Introduction

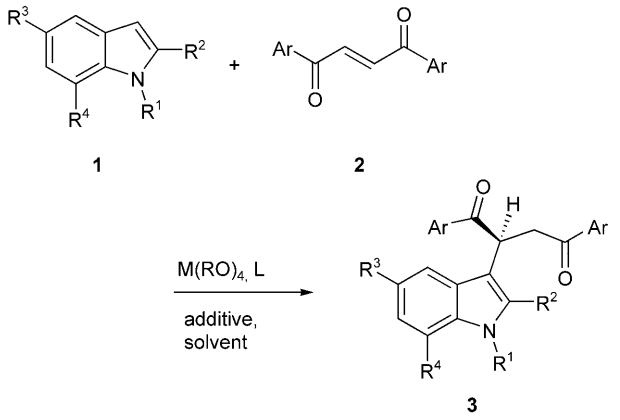
The indole nucleus is present in a large number of compounds of biological and/or pharmaceutical interest.[1] Because of this, chemical methods for its synthesis have been developed for more than a hundred years. In the last years, several catalytic system based on metal catalysis or organocatalysis have been developed and successfully applied to the enantioselective Friedel–Crafts alkylation of indoles with prochiral unsaturated compounds as electrophiles leading to enantiomerically enriched alkylated indoles.[2] To date, most of the successful examples of such processes have been limited to the use of bidentate chelating carbonyl substrates[3–13] and nitroalkenes,[14] whereas the use of non.chelating electrophilic substrates still remains rare and limited to structurally simple monofunctional α,β-unsaturated aldehydes[15] and enones.[16] 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 describe the enantioselective Friedel–Crafts reaction of indoles **1** with (*E*)-1,4-diaryl-2-butene-1,4-diones **2** as a new convenient procedure to functionalize the C-3 position of indoles with a side chain bearing a 1,4-dicarbonyl moiety and a stereogenic center. While the Friedel–Crafts alkylations with α,β-unsaturated substrates through a conjugate addition result in the formation of a stereogenic center in the β-position to a carbonyl group, the reaction with 2-butene-1,4-diones generates an α-stereogenic center with respect to one of the carbonyl groups. According to Tan,[17] as this α-stereogenic center is obtained through the action of a nucleophile (the indole nucleus) on an unsaturated ketone, this can be considered as an inversion of the normal reactivity pattern or umpolung reactivity[18] (Scheme 1).

To date, only two reports on asymmetric nucleophilic additions (Michael reactions) to 1,4-dicarbonyl-



Scheme 1. Friedel–Crafts alkylation of indole with enones and enediones.



Scheme 2. Friedel–Crafts alkylation of indoles **1** with (*E*)-1,4-diaryl-2-butene-1,4-diones **2**.

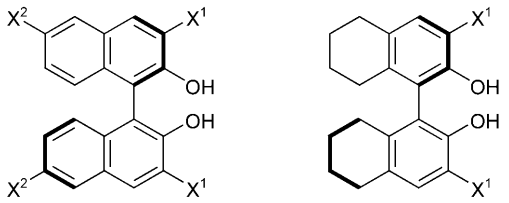


Figure 1. Structure of BINOL-type ligands used in this study.

but-2-enes have been published;[17,19] one of them involving arylboronic acids and the other 1,3-dicarbonyl compounds as nucleophiles, while the Friedel–Crafts reaction of nucleophilic heterocycles with this kind of acceptors has not been described so far. (*E*)-1,4-Diaryl-2-butene-1,4-diones **2** are challenging substrates on account of their functionalization with two carbonyl groups conjugate to a common *trans*-double bond. Because of these structural features it is expected that compounds **2** acts as non-chelating substrates, similarly to simple α,β-unsaturated ketones, but with reduced reactivity toward nucleophiles.[20]

Results and Discussion

In a recent paper we reported the enantioselective Friedel–Crafts reaction of indoles with simple α,β-unsaturated ketones catalyzed by a chiral BINOL-Zr(IV) complex.[21] This reaction was achieved with good yields and high enantioselectivities. Therefore, we intended to use this catalytic system in the reaction of indoles **1** with enediones **2** (Scheme 2). First, we applied our previously optimized reaction conditions to the Friedel–Crafts reaction of indole (**1a**) with (*E*)-1,4-diphenyl-2-butene-1,4-dione (**2a**) using ligand **L3** (Figure 1) and Zr(*t*-BuO)$_4$ in dichloromethane at room temperature. As anticipated, the reaction of **1a** with **2a** was slow and required 20 h to go to completion, much longer than the time required (3 h) for the reaction of **1a** and the enone (*E*)-1-phenyl-2-buten-1-one in our previous work.[21] The resulting product **3aa** was obtained in moderate 59% yield and with low enantioselectivity (23% *ee*) (Table 1, entry 3).

A number of BINOL-type ligands (**L1–L2** and **L4–L5)**, which contained electron-withdrawing groups and/or a tetrahydrogenated ring, were then screened (Figure 1).[22] Ligand **L2** gave the best result providing **3aa** in 89% yield and 69% *ee* (entry 2). A further improvement on the yield and reaction rate was obtained when dioxane was used as the solvent (entry 8); toluene and diethyl ether (entries 6 and 7) also increased the reaction rate but gave lower enantioselectivities than dichloromethane.

Other metal alkoxides[23] were also tested with **L2** in dioxane. In the presence of Ti(*i*-PrO)$_4$ (entry 10) the reaction took place slowly and compound **3aa** was obtained in low yield (32%) and with low *ee* (44%) while Hf(*t*-BuO)$_4$ gave a similar reactivity as Zr(*t*-BuO)$_4$, but the product **3aa** was obtained with somehow higher *ee* (73%) (entry 9).

Our efforts to optimize the reaction conditions were also aimed at exploring the effectiveness of Hf(*t*-BuO)$_4$ in the presence of alcohols with different chain lengths as additives.[24] After some experimentation we found that an 80 mol% amount of alcohol with respect to the enedione brought about an important increase of enantioselectivity. In general, we did not find a big influence of the alcohol chain length on the enantioselectivity, although it affected the yield of

Table 1. Screening of ligands, metal alkoxides, solvents and additives for the Friedel–Crafts reaction of **1a** ($R^1=R^2=R^3=R^4=H$) and **2a** (Ar = Ph) according to Scheme 2.[a]

Entry	$M(RO)_4$	L	Solvent	Additive	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Zr(*t*-BuO)$_4$	**L1**	CH_2Cl_2	–	20	93	57
2	Zr(*t*-BuO)$_4$	**L2**	CH_2Cl_2	–	16	89	69
3	Zr(*t*-BuO)$_4$	**L3**	CH_2Cl_2	–	20	59	−23[d]
4	Zr(*t*-BuO)$_4$	**L4**	CH_2Cl_2	–	18	84	−17[d]
5	Zr(*t*-BuO)$_4$	**L5**	CH_2Cl_2	–	22	45	19
6	Zr(*t*-BuO)$_4$	**L2**	Toluene	–	3	84	42
7	Zr(*t*-BuO)$_4$	**L2**	Et_2O	–	3.5	68	50
8	Zr(*t*-BuO)$_4$	**L2**	Dioxane	–	4	99	69
9	Hf(*t*-BuO)$_4$	**L2**	Dioxane	–	3.3	87	73
10	Ti(*i*-PrO)$_4$	**L2**	Dioxane	–	46	32	44
11	Hf(*t*-BuO)$_4$	**L2**	Dioxane	EtOH	22	59	88
12	Hf(*t*-BuO)$_4$	**L2**	Dioxane	*n*-PrOH	3	92	87
13	Hf(*t*-BuO)$_4$	**L2**	Dioxane	*n*-BuOH	5	74	83
14	Hf(*t*-BuO)$_4$	**L2**	Dioxane	*i*-BuOH	2.5	93	85

[a] *Conditions:* **1a** (0.30 mmol), **2a** (0.25 mmol), $M(RO)_4$ (0.05 mmol), **L** (0.05 mmol), solvent (2 mL), additive (0.2 mmol), room temperature.
[b] Isolated yield of **3aa**.
[c] Determined by chiral HPLC.
[d] The opposite enantiomer was obtained.

the reaction. The best result was obtained with 80 mol% *n*-propanol that allowed obtaining product **3aa** in 92% yield and 87% *ee* (entry 12).

To explore the scope and potential of the reaction, various 1,4-diaryl-2-butene-1,4-diones **2** containing electron-donating or electron-withdrawing groups on the phenyl group were reacted with indole (**1a**) (Table 2, entries 1–5). In all cases the corresponding alkylated products **3** were obtained in very good yields (74–92%) and with high enantioselectivities (85–90% *ee*). Unfortunately, neither the heteroaromatic enedione **2f** (entry 6) nor the aliphatic enedione **2g** (entry 14) reacted under the optimized conditions.

The indole partner was also amenable to modification. A number of C-5-substituted indoles were reacted with endione **2a** (entries 7–9). In general, the enantioselectivity of the reaction did not show a big dependence on the electronic features of the substituent,

Table 2. Enantioselective Friedel–Crafts reaction of indoles **1** and endiones **2** catalyzed by Hf(*t*-BuO)$_4$ and **L2** according to Scheme 2.[a]

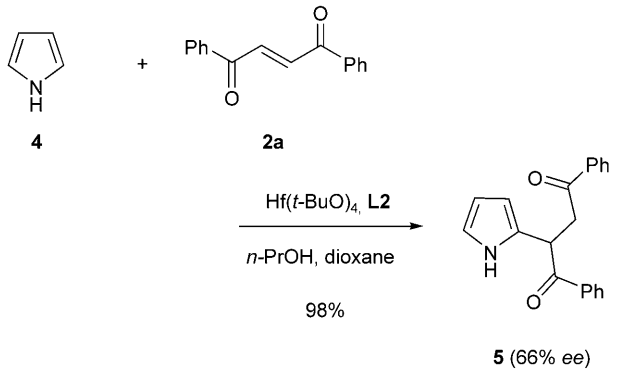
Entry	**1**	R^1	R^2	R^3	R^4	**2**	Ar	*t* [h]	**3**	Yield [%][b]	*ee* [%][c]
1	**1a**	H	H	H	H	**2a**	Ph	3	**3aa**	92	87
2	**1a**	H	H	H	H	**2b**	*p*-MeC_6H_4	22	**3ab**	74	90
3[d]	**1a**	H	H	H	H	**2c**	3,4-$Me_2C_5H_3$	3	**3ac**	88	90
4[d]	**1a**	H	H	H	H	**2d**	*p*-$MeOC_6H_4$	5	**3ad**	87	85
5	**1a**	H	H	H	H	**2e**	*p*-FC_6H_4	7	**3ae**	81	86
6	**1a**	H	H	H	H	**2f**	2-thienyl			n.r.	
7	**1b**	H	H	Me	H	**2a**	Ph	3	**3ba**	90	88
8	**1c**	H	H	MeO	H	**2a**	Ph	6	**3ca**	91	87
9	**1d**	H	H	Br	H	**2a**	Ph	24	**3da**	76	93
10[d]	**1d**	H	H	Br	H	**2b**	*p*-MeC_6H_4	5	**3db**	88	94
11	**1e**	H	H	H	Me	**2a**	Ph	5	**3ea**	91	85
12	**1f**	H	Me	H	H	**2a**	Ph	5	**3fa**	92	69
13	**1g**	Me	H	H	H	**2a**	Ph	3	**3ga**	97	86
14	**1a**	H	H	H	H	**2g**	Me			n.r.	

[a] *Conditions:* **1** (0.30 mmol), **2** (0.25 mmol), Hf(*t*BuO)$_4$ (0.05 mmol), **L2** (0.05 mmol), dioxane (2 mL), ^{n}PrOH (0.2 mmol), room temperature.
[b] Isolated yield of **3**.
[c] Major (*S*)-enantiomer. Determined by chiral HPLC.
[d] 40 mol% **L2** and 40 mol% Hf(*t*-BuO)$_4$ was used.

although the presence of the electron-withdrawing Br atom at the 5-position of indole decreased the reaction rate (entries 9 and 10). Also, 7-methylindole (**1e**) reacted with **2a** to give **3ea** (entry 11) in high yield and good *ee* (85%). However, the presence of a methyl group at the C-2 position (entry 12) brought about a decrease in the *ee*, compound **3fa** being obtained with only 69% *ee*, although in good yield (92%). Finally, 1-methylindole (**1g**), having a substituted nitrogen atom, reacted almost quantitatively (entry 13) with **2a** to give **3ga** with high enantioselectivity (86% *ee*). This result is remarkable since, in our previous work, we found that 1-methylindole (**1g**) reacted with (*E*)-1-phenyl-2-buten-1-one under catalysis with the **L3**-Zr(IV) system to give an almost racemic product.[25]

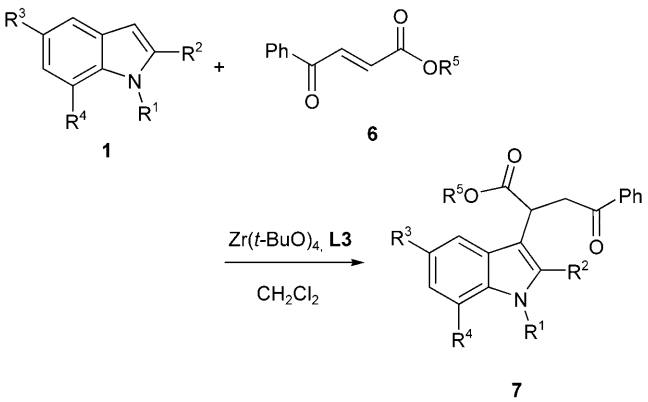
Considering the synthetic value of pyrroles, we have also studied the reaction of pyrrole (**4**) with compound **2a** under the optimized conditions for indoles (Scheme 3). The alkylated pyrrole **5** was thus obtained in almost quantitative yield and in moderate *ee* (66%) after 1 h of reaction at room temperature.

Finally, we tried to expand the scope of our catalytic system to other 1,4-dicarbonyl-but-2-enes such as



4 2a 5 (66% *ee*)

Scheme 3. Friedel–Crafts alkylation of pyrrole **4** with (*E*)-1,4-diphenyl-2-butene-1,4-dione **2a**.



Scheme 4. Friedel–Crafts alkylation of indoles (**1**) with alkyl (*E*)-4-oxo-4-phenylbutenoates **6**.

(*E*)-4-oxo-4-arylbutenoates **6**, which will generate α-ester stereogenic centers (Scheme 4). However, under the optimized conditions for enediones, ethyl (*E*)-4-oxo-4-phenylbutenoate (**6a**) did not react with indole (**1a**). In spite of this, the reaction could be carried out with Zr(*t*-BuO)$_4$/**L3** in dichloromethane in the absence of an alcohol additive (conditions of entry 3 in Table 1). Under these conditions, ethyl (*E*)-4-oxo-4-phenylbutenoate (**6a**) reacted with indole (**1a**) to give compound **7aa** as the sole product in 50% yield and 79% *ee* (Table 3, entry 1). Although the yield was moderate, the reaction took place with fair enantioselectivity and total regioselectivity, the only product being observed was that derived from the β-attack of the indole to the enone moiety present in the starting material, so generating an α-ester stereogenic center. A further improvement could be achieved by changing the ester group. Thus, the reaction of indole (**1a**) with methyl ester **6b** provided the Friedel–Crafts product **7ab** in 80% yield with a high 93% *ee*. Other 5-substituted indoles reacted with **6b** to give the corresponding products **7bb** and **7cb** with high enantioselectivity (entries 5 and 6), while indoles **1e** and **1f**

Table 3. Enantioselective Friedel-Crafts reaction of indoles **1** and alkyl (*E*)-4-oxo-4-phenylbutenoates **6** catalyzed by Zr(*t*-BuO)$_4$ and **L3** according to Scheme 4.[a]

Entry	**1**	R^1	R^2	R^3	R^4	**6**	R^5	*t* [h]	**7**	Yield [%][b]	*ee* [%][c]
1	**1a**	H	H	H	H	**6a**	Et	22	**7aa**	50	79
2	**1a**	H	H	H	H	**6b**	Me	4	**7ab**	80	93
3	**1a**	H	H	H	H	**6c**	*i*-Pr	7	**7ac**	88	88
4	**1a**	H	H	H	H	**6d**	*t*-Bu	18	**7ad**	35	34
5	**1b**	H	H	Me	H	**6b**	Me	8	**7bb**	56	87
6	**1c**	H	H	MeO	H	**6b**	Me	7	**7cb**	84	95
7	**1e**	H	H	H	Me	**6b**	Me	10	**7eb**	67	65
8	**1f**	H	Me	H	H	**6b**	Me	7	**7fb**	89	71
9	**1g**	Me	H	H	H	**6b**	Me	24	**7gb**	47	30

[a] *Conditions:* **1** (0.30 mmol), **6** (0.25 mmol), Zr(*t*-BuO)$_4$ (0.05 mmol), **L3** (0.05 mmol), CH_2Cl_2 (2 mL), room temperature.
[b] Isolated yield of **7**.
[c] Determined by chiral HPLC.

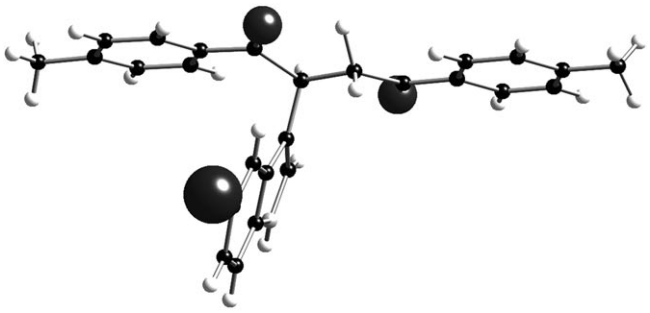


Figure 2. X-ray structure of compound **3db**. Flack parameter 0.01 (2).

bearing substituents respectively at the 7 and 2 positions, close to the nitrogen atom (entries 7 and 8) reacted to provide the Friedel–Crafts products with more moderate enantiomeric excesses. Finally, indole **1g** substituted at the nitrogen atom reacted with low enantioselectivity (entry 9) as we have observed in other Friedel–Crafts reactions using this catalytic system.[21,25]

The absolute configuration of compound **3db** (Table 2, entry 10) was determined to be *S* by X-ray crystallographic analysis (Figure 2),[26] and for the rest of the products it was assigned on the assumption of a uniform reaction mechanism. The stereochemistry of the products indicates the preference of the indole to approach the enedione from the *re* face of the double bond.

To gain some insight into the mechanistic aspects of the reaction, we investigated the relationship between the enantiopurity of ligand **L2** and the enantiopurity of the Friedel–Crafts product **3aa**, looking for possible non-linear effects (NLE). For this purpose, we conducted the reaction using ligand with low *ee* (0%, 20%, 40%, 60% and 80% *ee*). As it can be seen in Figure 3 we found a moderate positive non-linear effect. These results suggest the presence of various BINOL-Hf(IV) species of non-monomeric nature with different thermodynamic stabilities and kinetic reactivities.[27]

A mechanistic proposal for this reaction is outlined in Scheme 5. In the first step, the chiral hafnium catalyst, formed from BINOL, Hf(*t*-BuO)$_4$ and *n*-PrOH, might coordinate with the 1,4-diaryl-2-butene-1,4-dione **2** because of its oxophilicity. Then the indole would attack the *re* face of the double bond to give a cationic intermediate **8**, which after deprotonation and exchange of the chiral enolate by alkoxide would provide the Friedel–Crafts product and regenerate the catalyst.

To explain the stereochemical outcome of the reaction we propose the TS model shown in Figure 4 which would be formed after coordination of the substrate to an apical position of the catalytic species. Before this stage, the remaining *tert*-butoxide groups

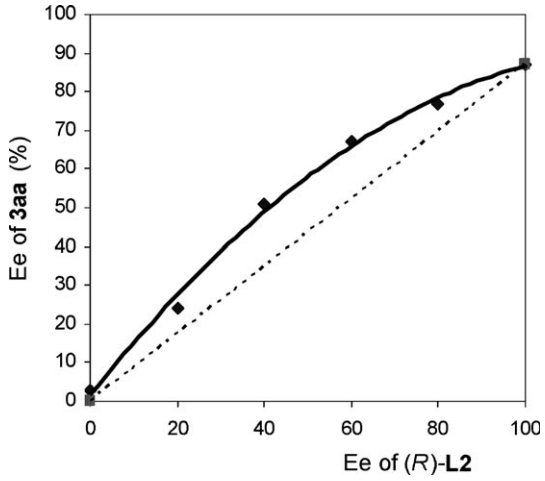
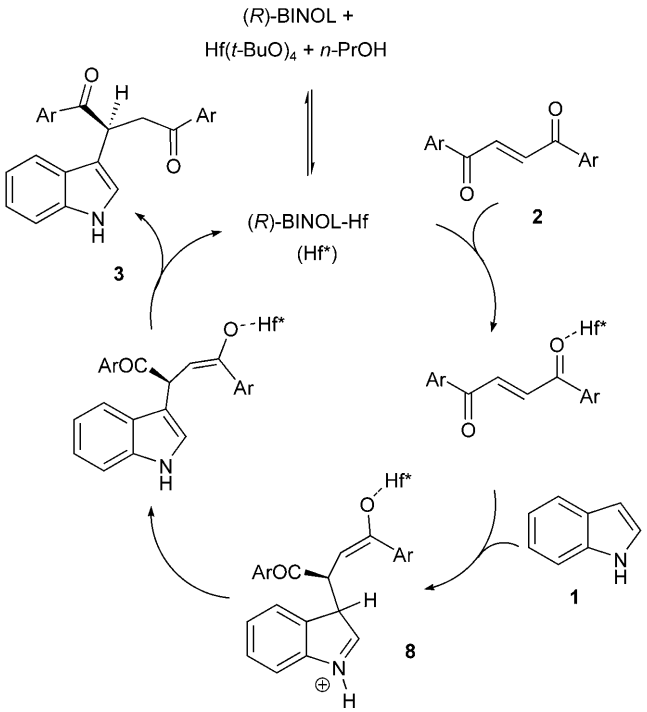


Figure 3. Positive NLE observed in the **L2**-Hf(IV)-*n*-PrOH-catalyzed reaction of indole (**1a**) and **2a**.



Scheme 5. Proposed mechanism for the catalytic cycle of the Friedel–Crafts alkylation of indoles with (*E*)-1,4-diaryl-2-butene-1,4-diones.

in the coordination sphere of the Hf atom would have been exchanged for the primary *n*-propyl alcohols, releasing the crowding in the environment around the Hf(IV) ion. In this octahedrical Hf complex[28] the C-1−C-2 bond of the substrate would prefer an *s-trans* conformation to avoid the steric repulsion of the rest of the molecule and one of the ligand naphthyl groups, exposing the *re* face of the double bond to the nucleophile, while the *si* face is shielded by the other naphthyl group.

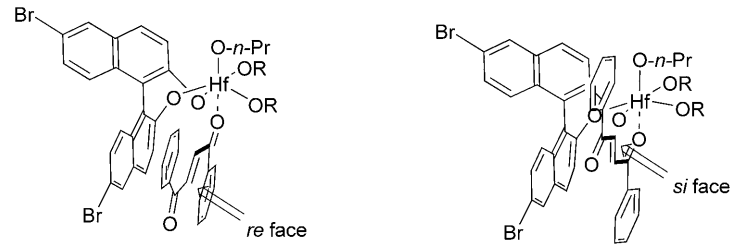


Figure 4. Stereochemical models for the Friedel-Crafts reaction.

Conclusions

In summary, we have described the first catalytic enantioselective Friedel-Crafts reaction of indoles using 1,4-diaryl-2-butene-1,4-diones as electrophiles. This kind of compound is a challenging substrate on account of the non-chelating character and reduced reactivity toward nucleophiles. Besides, the new stereogenic center in the resulting dicarbonyl indole derivative is generated in the α-position to one of the carbonyl group and therefore this reaction can be considered as an inversion of the normal reactivity pattern or umpolung. (*E*)-4-Oxo-4-arylbutenoates can also be used as electrophiles. In this case, a stereogenic center is regioselectively formed in an α poisition to the ester group, with good enantioselectivity. The success of the reaction is sustained on the use of chiral Hf(IV) complexes that have been little studied in asymmetric catalysis.

Experimental Section

General Procedures

Glassware was oven-dried overnight at 120 °C. Reactions were monitored by TLC analysis 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. ^{1}H NMR were run at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR in a Bruker Avance 300 spectrometer, in $CDCl_3$ using residual non-deuterated solvent ($CHCl_3$) as internal standard ($\delta =$ 7.26 and 77.0 ppm), unless otherwise stated. Specific optical rotations were measured in a Perkin–Elmer polarimeter using sodium light (D line 589 nm). Mass spectra were recorded on a Fisons Instruments VG Autospec GC 8000 series. Mass spectra (EI) were run at 70 eV. Mass spectra (FAB) were carried out at 30 kV in a MNBA matrix. Chiral HPLC analyses were performed in 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, using chiral stationary columns from Daicel. Dioxane was dried over Na-benzophenone prior to use. All BINOL-type ligands and all indoles **1** were commercially available and used as purchased without further purification. Endiones **2** were prepared according procedures from the literature.[29]

Procedure for the Catalytic Enantioselective Friedel–Crafts Reaction

Hf(*t*-BuO)$_4$ (21 μL, 0.05 mmol) and *n*-PrOH (16 μL, 0.2 mmol) were successively added *via* microsyringe to a solution of **L2** (22 mg, 0.05 mmol) in dry dioxane (1 mL) under nitrogen at room temperature. After 1 h, a solution of **1a** (35 mg, 0.30 mmol) and enedione **2a** (59 mg, 0.25 mmol) in dry dioxane (1 mL) was added and the mixture stirred at room temperature. After 3 h, the reaction mixture was filtered through a short pad of silica gel eluting with diethyl ether. The solvents were removed under reduced pressure and the residue chromatographed on silica gel eluting with hexane/EtOAc (88:12) to give compound **3aa**; yield: 81.2 mg (92%). The enantiomeric excess (87%) was determined by HPLC [Chiralpak AD-H (4.6×250 mm), hexane:*i*-PrOH 85:15, 1 mL min^{-1}]: (+)-major $t_r = 35.5$ min, (−)-minor $t_r = 33.3$ min; oil; $[\alpha]_D^{25}$: +305.4 (*c* 0.8, $CHCl_3$, 87% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.13$ (br s, 1H), 8.06 (dd, $J = 6.9$, 1.5 Hz, 2H), 7.98 (dd, $J = 7.2$, 1.2 Hz, 2H), 7.79 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.55 (tt, $J = 7.4$, 1.5 Hz, 1H), 7.49–7.34 (m, 6H), 7.25–7.15 (m, 2H), 7.01 (d, $J = 2.4$ Hz, 1H), 5.62 (dd, $J = 10.2$, 3.6 Hz, 1H), 4.26 (dd, $J = 18.1$, 10.2 Hz, 1H), 3.45 (dd, $J = 18.2$, 3.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.1$ (C), 198.2 (C), 136.5 (C), 136.4 (C), 133.2 (CH), 132.7 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 126.0 (C), 122.8 (CH), 122.5 (CH), 120.0 (CH), 118.7 (CH), 113.2 (C), 111.4 (CH), 42.8 (CH_2), 39.6 (CH); MS (EI): *m/z* (%): 353 (M^+, 27), 335 (14), 248 (37), 105 (100), 77 (34); HR-MS: *m/z* = 353.1414 (M^+), calcd. for $C_{24}H_{19}NO_2$: 353.1416.

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