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Catalytic enantioselective Friedel–Crafts alkylation at the 2-position of indole with simple enones

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Abstract—A procedure for the enantioselective alkylation of indole at the 2-position with simple non-chelating enones is described for the first time. Reaction between 4,7-dihydroindole and enones in the presence of zirconium(IV)–BINOL complexes, followed by a *p*-benzoquinone oxidation gives indoles alkylated at the 2-position with good yields and moderate enantioselectivities.

The indole nucleus has long been of great interest to synthetic chemists owing to its ubiquity in a large number of biologically active alkaloids and pharmaceutical agents.[1] Since the 3-position of indole is the preferred site for the electrophilic substitution reaction, the introduction of functionalized alkyl frameworks at this position by means of a Friedel–Crafts reaction involving the use of various electrophilic reagents constitutes a well established strategy.[2] Only recently Saraçoglu et al. have described the functionalization of the less reactive 2-position by means of a Friedel–Crafts reaction.[3] The access to the 2-position of the indole nucleus is achieved by using 4,7-dihydroindole as the nucleophilic reaction component followed by a *p*-benzoquinone oxidation to regenerate the aromaticity of the indole nucleus. The use of 4,7-dihydroindole instead of indole explains the observed change of regioselectivity as it is known that indole undergoes substitution at the 3-position, whereas pyrrole derivatives give reaction at the 2-position.[4]

In the last years, attention has been focused on the catalytic enantioselective functionalization of the indole nucleus. Taking advantage of the reactivity of the 3-position of the indole nucleus several electrophiles have been introduced at this position via a Friedel–Crafts reaction using both bidentate chelating carbonyl substrates[5] as well as the most challenging non-chelating simple α,β-unsaturated carbonyl compounds.[6,7] However, only very recently, Evans et al. have reported an enantioselective functionalization of the less reactive 2-position.[8] Following the methodology of Saraçoglu,[3] these authors have used 4,7-dihydroindole as the nucleophilic reaction component and α,β-unsaturated 2-acyl imidazoles as bidentate chelating electrophile, followed by a *p*-benzoquinone oxidation.

In this Letter, we wish to present our results on the functionalization of the indole nucleus at the 2-position by an enantioselective Friedel–Crafts reaction of α,β-unsaturated ketones with 4,7-dihydroindole[9] catalyzed by a chiral BINOL–zirconium(IV) *tert*-butoxide complex,[10] followed by a *p*-benzoquinone oxidation.

The reaction of 4,7-dihydroindole (**1**) with enone **2a** was chosen to optimize the reaction conditions. Several chiral Lewis acid catalysts, generated in situ from metal alkoxides and (*R*)-BINOL type ligands, were evaluated as shown in the illustrated reaction (Scheme 1), and the results are summarized in Table 1.

All (*R*)-BINOL ligands (**L1**–**L5**) were able to catalyze the reaction at acceptable rates and in good yield but with variable enantioselectivities. Using 20 mol % of $Ti(O^iPr)_3$ and 20 mol % of ligand **L1** (entry 1), in CH_2Cl_2 at room temperature the reaction between 4,7-dihydroindole (**1**) with enone **2a**, took place in 2.5 h giving 2-(1-methyl-3-phenyl-3-propanone)-1*H*-indole (**3a**) in good yield (85%) but with a low enantiomeric excess (19%), while in the presence of $Zr(O^tBu)_4$ 4,7-dihydroindole (**1**) reacted faster (within 0.75 h) with enone **2a**,

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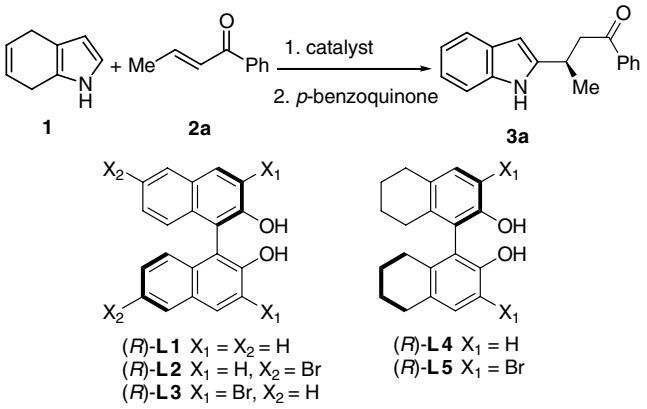


Scheme 1. Friedel–Crafts reaction of 4,7-dihidroindole (**1**) with enone **2a** and structure of BINOL-type ligands used in this study.

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

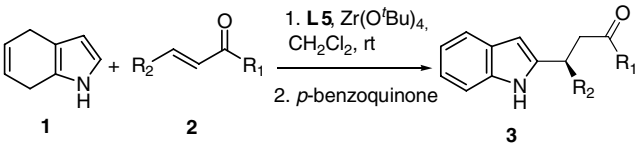
Entry	Ligand	Metal alkoxide	Time (h)	Yield (%)[b]	ee (%)[c]
1	**L1**	$Ti(O^iPr)_4$	2.5	85	19
2	**L1**	$Zr(O^tBu)_4$	0.7	74	59
3	**L2**	$Zr(O^tBu)_4$	0.5	81	14
4	**L3**	$Ti(O^iPr)_4$	2.5	93	2
5	**L3**	$Zr(O^tBu)_4$	0.5	80	8
6	**L4**	$Zr(O^tBu)_4$	0.5	71	19
7	**L5**	$Zr(O^tBu)_4$	1	79	71

[a] 20 mol % of (*R*)-ligand and 20 mol % of metal alkoxide, in dichloromethane at room temperature.
[b] Isolated yield of **3a**.
[c] Determined by chiral HPLC analysis. (*R*)-configuration tentatively assigned on the assumption of a uniform mechanistic pathway with regard to indole and pyrrole (see Ref. 6g).

giving the reaction product in good yield (74%) and a better enantiomeric excess (59 %) (entry 2). **L2**–**L5** BINOL-type ligands, which contain electron-withdrawing groups at the 3,3′ and 6,6′ positions as well as a tetrahydrogenated ring were evaluated also in the presence of $Zr(O^tBu)_4$. Ligand **L5** led to the best result (79% yield, 71% ee) (entry 7). Different solvents ($ClCH_2CH_2Cl$, $CHCl_3$, ether, THF, and toluene) temperatures and catalyst loadings were screened. However all these changes had a negative influence on the catalytic activity,[11] especially on the enantioselectivity.

With this set of reaction conditions[12] in hand the applicability of the reaction with other α,β-unsaturated ketones was investigated (Table 2). Enones **2** with a sterically demanding aromatic group bound to the carbonyl group and an aliphatic group linked to the C–C double bond produced alkylated indoles in excellent yields and moderate enantioselectivities (entries 1 and 2). The reaction with related enones containing an electron-donating group on the phenyl group had a lower reaction rate than with enones containing an electron-withdrawing group (entries 3–6 vs entries 7 and 8). In all cases the yields were good but the enantioselectivities were moderates. The best result was obtained with enone **2c**, bearing a *p*-MeC_6H_4-substituent on the carbonyl group, which gave the reaction product **3c** in good yield

Table 2. Enantioselective Friedel–Crafts reaction of 4,5-dihidroindole (**1**) with enones **2** catalyzed by **L5**–$Zr(O^tBu)_4$[a]

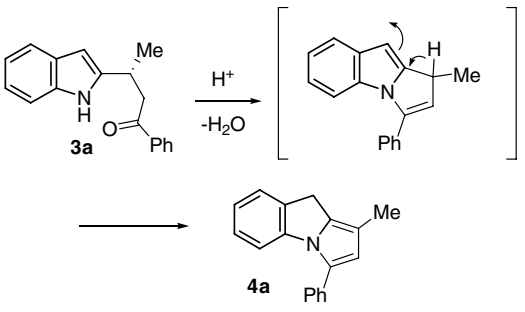


Entry	2	R_1	R_2	Time (h)	3	Yield (%)[b]	ee (%)[c]
1	**2a**	Ph	Me	1	**3a**	79	71
2	**2b**	Ph	Et	2.5	**3b**	89	60
3	**2c**	*p*-Me-C_6H_4	Me	2	**3c**	73	78
4	**2d**	*m*-MeC_6H_4	Me	2	**3d**	69	51
5	**2e**	*p*-MeO-C_6H_4	Me	2	**3e**	88	64
6	**2f**	3,4-$Me_2C_6H_3$	Me	2	**3f**	89	58
7	**2g**	*p*-F-C_6H_4	Me	0.75	**3g**	86	53
8	**2h**	*p*-Br-C_6H_4	Me	0.75	**3h**	79	50
9	**2i**	2-Naphthyl	Me	1	**3i**	79	40
10	**2j**	2-Thienyl	Me	1.5	**3j**	95	69
11	**2k**	2-Furyl	Me	0.5	**3k**	72	59

[a] 20 mol % of (*R*)-**L5** and 20 mol % of $Zr(O^tBu)_4$, in dichloromethane at room temperature.
[b] Isolated yield of **3**.
[c] Determined by chiral HPLC analysis. (*R*)-configuration tentatively assigned on the assumption of a uniform mechanistic pathway with regard to indole and pyrrole (see Ref. 6g).

(73%) and with enantioselectivity (78%). In addition, 2-naphthalene **2i** and heteroaromatic **2j**, **2k** enone derivatives can also serve as substrates in this reaction, giving the corresponding 2-alkylated indoles in good yields and with moderate enantioselectivities (entries 9–11). Unfortunately, the reaction is limited to enones with R_1 aromatic or heteroaromatic groups. Enones **2** bearing an R_1 aliphatic group ($R_1 = Me$, $R_2 = Ph$, or $R_1 = Me$, $R_2 = i$-Pr) reacted very slowly with 4,7-dihydroindole (**1**) under the optimized conditions.

The structures of products **3** were determined by ^1H NMR, ^{13}C NMR, and HRMS.[13] An interesting structural feature of these 2-alkylated indoles **3** is the 1,5-disposition between the carbonyl carbon of the side chain and the nitrogen atom of the indole ring, which could allow an intramolecular reaction to give pyrrolo[1,2-*a*] indole compounds[14] (Scheme 2). In fact conversion of compound **3a** into compound **4a** took place spontaneously and was complete within 24 h in $CDCl_3$ in the NMR tube.[15] The structure of this compound was perfectly established by spectroscopic data.[16]



Scheme 2. Cyclization of compound **3a** to **4a**.

In summary, we have developed an efficient strategy to access 2-substituted indole derivatives in enantioenriched form. This strategy is based on the one-pot catalytic asymmetric Friedel–Crafts reaction between 4,7-dihydroindole as nucleophilic reaction component and an α,β-unsaturated carbonyl compound as electrophilic partner followed by a *p*-benzoquinone oxidation. The enantioselective reaction is based on the use of BINOL-type-Zr(O^tBu)$_4$ complexes as catalyst and the reaction proceeds in good yields and moderate enantioselectivities. The use of ligands that are commercially available in both enantiomeric forms, and a simple experimental procedure at room temperature constitute additional advantages of this method.

Acknowledgments

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11. For instance, when the reaction was carried out using 20 mol % catalyst load at 0 °C the alkylation product was obtained in 51% yield and 72% ee, after 4 h, while when the catalyst load was decreased to 10 mol % at rt the expected product was obtained in 58% yield and 66% ee.
12. *Typical experimental procedure*: Zr(O^tBu)$_4$ (10 μL, 0.025 mmol) was added via syringe to a solution of ligand **L5** (11,.3 mg, 0.025 mmol) in dichloromethane (0.8 mL) under nitrogen atmosphere at rt. After 1 h, a solution of enone **2** (0.125 mmol) and 4,7-dihydroindole (0.15 mmol) in dichloromethane (0.8 mL) was added, stirring was continued until completion of the reaction (TLC) and *p*-benzoquinone (40 mg, 0.375 mmol) was added. After 2 h, the reaction mixture was diluted with diethyl ether (30 mL), washed with 0.5 M aqueous sodium thiosulfate (25 mL), 2 M aqueous NaOH (2 × 25 mL) and brine (25 mL), and was dried over $MgSO_4$. After removal of the solvent under reduced pressure, product **3** was obtained by column chromatography eluting with hexane:dichloromethane mixtures.
13. *Compound* **3a**: mp 117–120 °C (Hexane–^{i}PrOH); enantiomeric excess was determined by HPLC (Chiralcel OD-H), hexane–^{i}PrOH 85:15, 1 mL/min, major enantiomer $t_r = 12.2$ min, minor enantiomer $t_r = 10.4$ min, to be 71%; $[\alpha]_D^{25} - 16.7$ (c 0.87, CH_2Cl_2,ee 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (br s, 1H), 7.96 (dd, $J =$ 7.5, 1.5 Hz, 1H), 7.58 (tt, $J = 7.5$, 1.5 Hz, 1H), 7.54 (d, $J = 7.5$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 2H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.12 (td, $J = 7.5$, 1.2 Hz, 1H), 7.05 (td, $J = 7.5$, 1.2 Hz, 1H), 6.29 (dd, $J = 1.2$, 0.9 Hz, 1H), 3.80 – 3.69 (m, 1H), 3.42 (dd, $J = 18.0$, 7.8 Hz, 1H), 3.31 (dd, $J = 18.0$, 5.0 Hz, 1H), 1.52 (d, $J = 6.9$ Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.1 (C), 144.2 (C), 136.7 (C), 135.6 (C), 133.4 (CH), 128.6 (CH), 128.2 (C), 128.0 (CH), 121.2 (CH), 119.8 (CH), 119.4 (CH), 110.6 (CH), 97.4 (CH), 46.9 (CH_2), 27.9 (CH), 19.9 (CH_3). MS (EI) m/z (%): 263 (M^+, 77), 158 (100), 144 (32). HRMS: 263.1298 (M^+), $C_{18}H_{17}NO$ required 263.1310.

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15. This cyclization is most probably catalyzed by residual HCl present in $CDCl_3$. In fact it is avoided if $CDCl_3$ is previously filtered through a pad of basic alumina.
16. *Compound* **4a**: Oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, $J = 7.2$, 1.2 Hz, 2H), 7.43 (t, $J = 6.8$ Hz, 2H), 7.39 (dt, $J = 7.2$, 1.0 Hz, 1H), 7.35 (tt, $J = 7.4$, 1.6 Hz, 1H), 7.10 (d, $J = 3.9$ Hz, 1H), 7.03 (dq, $J = 7.6$, 4.0 Hz, 1H), 6.19 (s, 1H), 3.81 (s, 2H), 2.17 (d, $J = 1.60$ Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 141.9 (C), 135.4 (C), 133.9 (C), 133.2 (C), 128.8 (CH), 128.2 (CH), 127.8 (C), 127.0 (CH), 126.9 (CH), 125.8 (CH), 122.5 (CH), 115.2 (CH), 111.9 (C), 111.6 (CH), 27.7 (CH_2), 11.2 (CH_3). MS (EI) m/z (%): 245 (M^+, 94), 244 (36), 230 (100). HRMS: 245.1209 (M^+), $C_{18}H_{15}N$ required 245.1205.