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Organocatalytic Enantioselective Friedel−Crafts Alkylation of 4,7-Dihydroindoles with α,β-Unsaturated Aldehydes: An Easy Access to 2-Substituted Indoles

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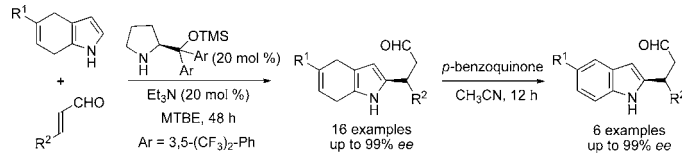
ABSTRACT



An enantioselective Friedel−Crafts alkylation of 4,7-dihydroindoles and α,β-unsaturated aldehydes has been developed. The process is promoted by diphenylprolinol ether to afford 2-substituted 4,7-dihydroindoles in high yields and enantioselectivities. After a subsequent oxidation of the products, the optically active 2-substituted indoles could be obtained smoothly in high yields without any loss of enantioselectivity.

Indole structures are found in many natural products, pharmaceutical agents, and material polymers.[1] The interesting chemical properties of indoles have inspired chemists to design and synthesize a variety of indole derivatives.[2] Although many synthetic methods have been developed for the synthesis of indoles, due to the dramatic difference in reactivity between the 2- and 3-position of indole, most of the successful examples are limited to the formation of 3-substituted indoles.[3] In sharp contrast, the synthesis of optically active 2-substituted indole derivatives represents a considerable challenge and has been less studied.[4] Therefore, a new simple access to 2-functionalized indoles might further contribute to the chemistry and pharmacology of indole compounds.

It is well-known that indoles undergo electrophilic substitution at the 3-position, whereas pyrrole derivatives give reaction at the 2-position.[5] 4,7-Dihydroindoles, which can be considered as disubstituted pyrroles, due to their easy aromatization, are good intermediates to synthesize 2-substituted indoles (Scheme 1). Recently, Saraçoğlu et al. have utilized this strategy in the racemic conjugate addition of 4,7-dihydroindole to enones followed by a *p*-benzoquinone oxidation to provide the 2-substituted indoles in moderate yields.[6] Following the methodology of Saraçoğlu, Evans et al. and Pedro et al. have realized the asymmetric version of

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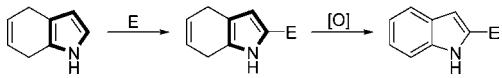
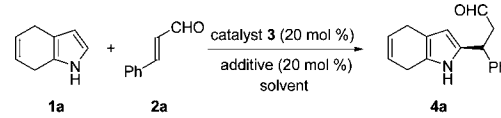
Scheme 1. Strategy To Synthesize 2-Substituted Indoles

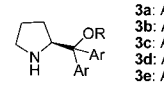


this reaction by utilizing chiral Lewis acid catalysts, providing easy access to enantioenriched 2-substituted indole derivatives.[7] More recently, an enantioselective Friedel−Crafts alkylation[8] of 4,7-dihydroindoles with imines and β,γ-unsaturated α-keto esters activated by a chiral phosphoric acid has been described by You et al.[9] Interesting as the optically pure 2-substituted indole derivatives are, their catalytic asymmetric synthesis is still rather limited. For instance, the use of α,β-unsaturated aldehydes as electrophilic reagents has not been reported yet, although the aldehyde group in the products would offer facile conversions to versatile functionalities. In this paper, we present our results on the functionalization of the indole nucleus at the 2-position by a highly enantioselective Friedel−Crafts reaction of 4,7-dihydroindoles with α,β-unsaturated aldehydes catalyzed by diphenylprolinol ether, followed by a *p*-benzoquinone oxidation.

We initially investigated the reaction of the 4,7-dihydroindole **1a** with cinnamaldehyde **2a** in the presence of the readily available diphenylprolinol trimethylsilyl ether **3a** (20 mol %) in toluene.[10] The Friedel−Crafts alkylation proceeded smoothly to afford desired product **4a** in 74% yield and 70% ee (Table 1, entry 1). Encouraged by this, we surveyed the organocatalysts[11] **3a**−**f** for the reaction under the same reaction conditions (Table 1, entries 1−6). The results showed that **3f** was an effective organocatalyst for

Table 1. Catalyst Screening and Reaction Optimization[a]





3a: Ar = Ph, R = TMS
3b: Ar = Ph, R = TES
3c: Ar = Ph, R = TBS
3d: Ar = Ph, R = H
3e: Ar = Ph, R = Me
3f: Ar = 3,5-$(CF_3)_2$Ph, R = TMS

entry	catalyst	solvent	additive	yield[b] (%)	ee[c] (%)
1	**3a**	toluene	none	74	70
2	**3b**	toluene	none	<10	n.d.[d]
3	**3c**	toluene	none	<10	n.d.[d]
4	**3d**	toluene	none	53	31
5	**3e**	toluene	none	61	43
6	**3f**	toluene	none	74	83
7	**3f**	toluene	PhCOOH	58	56
8	**3f**	toluene	Et_3N	89	88
9	**3f**	toluene	2,6-lutidine	78	69
10	**3f**	toluene	iPr_2EtN	81	87
11	**3f**	toluene	Et_3N-HCl	80	71
12	**3f**	THF	Et_3N	84	89
13	**3f**	ether	Et_3N	81	91
14	**3f**	MTBE	Et_3N	87	96
15	**3f**	DMSO	Et_3N	<10	n.d.[d]
16	**3f**	CH_2Cl_2	Et_3N	78	81
17	**3f**	CH_3CN	Et_3N	73	78

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.36 mmol) and **2a** (0.30 mmol) in the presence of an organocatalyst **3** (0.06 mmol), additive (0.06 mmol), and solvent (1.0 mL) for 48 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralpak OD-H column after $NaBH_4$ reduction. [d] Not determined.

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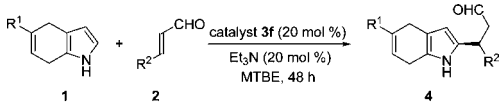
the reaction in terms of the yield and enantioselectivity (Table 1, entry 6). No reaction occurred for the more sterically bulky catalyst **3b** and **3c** (Table 1, entries 2 and 3). Screening additives including acid (Table 1, entry 7), bases (Table 1, entries 8−10), and salt (Table 1, entry 11) revealed that they had an effect on the process, and the use of Et_3N gave the best result (Table 1, entry 8). To further optimize the process, examination of the reaction medium led to the selection of *tert*-butyl methyl ether (Table 1, entry 14).

Having established optimal reaction conditions, we explored the scope of this Friedel−Crafts alkylation. Thus, 4,7-dihydroindoles **1** were treated with α,β-unsaturated aldehydes **2** in the presence of **3f** (20 mol %) and Et_3N (20 mol %) in MTBE at room temperature. In general, the Friedel−Crafts alkylation products were obtained in high yields and excellent enantioselectivities. Significant structural variation of α,β-unsaturated aldehydes could be tolerated (Table 2). The

Table 2. Scope of the Enantioselective Friedel−Crafts Alkylation of 4,7-Dihydroindoles with α,β-Unsaturated Aldehydes[a]



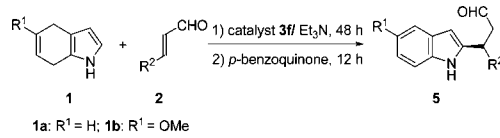
entry	1	2, R^2	product	yield[b] (%)	ee[c] (%)
1	**1a**	**2a**, Ph	**4aa**	87	96
2	**1a**	**2b**, 2-MeOPh	**4ab**	78	98
3	**1a**	**2c**, 2-ClPh	**4ac**	85	99
4	**1a**	**2d**, 3-MeOPh	**4ad**	81	97
5	**1a**	**2e**, 3-ClPh	**4ae**	88	98
6	**1a**	**2f**, 4-MeOPh	**4af**	61	96
7	**1a**	**2g**, 4-FPh	**4ag**	93	99
8	**1a**	**2h**, 4-ClPh	**4ah**	90	99
9	**1a**	**2i**, 4-BrPh	**4ai**	89	95
10	**1a**	**2j**, 4-NO_2Ph	**4aj**	91	96
11	**1a**	**2k**, Me	**4ak**	83	92
12	**1a**	**2l**, Pr	**4al**	80	97
13	**1a**	**2m**, *i*Pr	**4am**	76	99
14	**1b**	**2l**, Pr	**4bl**	73	96
15	**1b**	**2a**, Ph	**4ba**	82	93
16	**1b**	**2h**, 4-ClPh	**4bh**	86	95

[a] The reaction conditions were the same as those in Table 1, entry 14. [b] Isolated yield. [c] For analysis of the ee values of the products, see the Supporting Information.

electronic nature of the aromatic rings of α,β-unsaturated aldehydes had limited influence on the stereochemical outcome. It demonstrated that the electron-withdrawing (Table 2, entries 3, 5 and 7−10), electron-donating (Table 2, entries 2, 4 and 6), and neutral (Table 2, entry 1) systems can participate in the reactions. In the case of less reactive aliphatic enals, excellent enantioselectivities were obtained (Table 2, entries 11−13). Finally, substituted 4,7-dihydroindole **1b** was tested, and good results were also attained (Table 2, entries 14−16).

To demonstrate the suitability of the current methodology for the synthesis of 2-functionalized indoles, the oxidation of 2-substituted 4,7-dihydroindoles was tested. To our delight, in all cases, the corresponding 2-substituted indole derivatives were obtained smoothly in good overall yields and excellent enantioselectivities (Table 3).

Table 3. Synthesis of 2-Functionalized Indoles[a]



entry	1	2, R^2	product	yield[b] (%)	ee[c] (%)
1	**1a**	**2l**, Pr	**5al**	76	97
2	**1a**	**2a**, Ph	**5aa**	79	96
3	**1a**	**2h**, 4-ClPh	**5ah**	83	99
4	**1b**	**2l**, Pr	**5bl**	68	96
5	**1b**	**2a**, Ph	**5ba**	74	93
6	**1b**	**2h**, 4-ClPh	**5bh**	81	95

[a] Reaction conditions: see the Supporting Information for details. [b] Isolated yield. [c] For analysis of the ee values of the products, see the Supporting Information.

Finally, the absolute configuration of the products was determined by X-ray analysis. Suitable crystals of compound **4ai** which enabled assignment of the absolute configuration were obtained, and a single-crystal analysis revealed the configuration to be *R* (Figure 1).

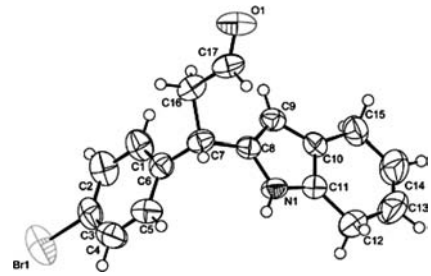


Figure 1. X-ray structure of (*R*)-**4ai**.

In summary, we have developed an enantioselective Friedel−Crafts alkylation of 4,7-dihydroindoles with α,β-unsaturated aldehydes in high yields and excellent enantioselectivies. The corresponding 4,7-dihydroindole products could be subsequently transformed to 2-functionalized indoles by the oxidation of *p*-benzoquinone without any loss

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in the enantioselectivies. Further applications of the current methodology are ongoing in our laboratory.

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Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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