ORGANIC LETTERS

2007
Vol. 9, No. 13
2601−2604

Highly Enantioselective Friedel–Crafts Alkylations of Indoles with Simple Enones Catalyzed by Zirconium(IV)–BINOL Complexes†

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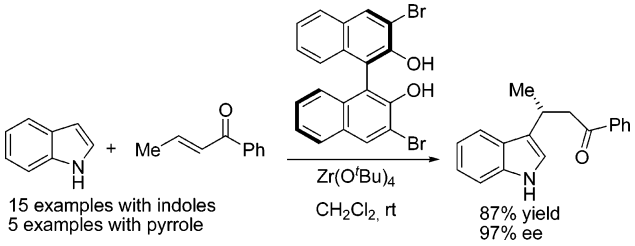
Received May 14, 2007

ABSTRACT



Complexes of BINOL-based ligands with $Zr(O^tBu)_4$ catalyze the Friedel–Crafts alkylation reaction of indoles and pyrrole with nonchelating β-substituted α,β-enones at room temperature affording the expected products with good yields and ee above 95% in most of the studied examples.

The Lewis acid-catalyzed Friedel−Crafts[1] alkylation reaction is a powerful carbon−carbon bond forming process in organic chemistry.[1] The asymmetric version of this reaction can provide a very useful approach to enantiomerically enriched alkylated arenes.[2] Of particular interest is the enantioselective Friedel−Crafts reaction of indoles due to the high relevance of the indole nucleus, as a privileged platform present in a wide range of natural products and pharmaceutical drugs.[3] To date most of the successful examples of such processes are limited to the use of bidentate chelating carbonyl substrates, including β,γ-unsaturated-α-ketoesters,[4] acyl phosphonates,[5] alkylidene malonates,[6] α-hydroxy enones,[7] 2-acyl imidazoles,[8] and other acyl-heterocyclecompounds[9] and nitroalkenes.[10] However, the use

† Dedicated to Prof. Ramón Mestres on the occasion of his retirement.

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10.1021/ol0710820 CCC: $37.00
Published on Web 05/25/2007

of simple nonchelating α,β-unsaturated carbonyl compounds as electrophiles represents a considerable synthetic challenge and has been less studied. MacMillan et al. have reported an organocatalytic alkylation of indole with α,β-unsaturated aldehydes.[11] Umani-Ronchi et al. have described the addition of indoles to α,β-unsaturated ketones using salen-Al complexes obtaining enantiomeric excesses in the 80% range for most of the reported substrates.[12] Recently an enantioselective Friedel−Crafts reaction of indole with electron-rich alkenes activated by a chiral Brønsted acid catalyst has been described.[13] Finally, two organocatalytic examples of asymmetric Friedel−Crafts alkylation of indoles with enones via ketiminine salts have been reported very recently.[14] The purpose of this Letter is to describe the enantioselective Friedel−Crafts reactions of α,β-unsaturated ketones **2** with indoles **1** catalyzed by a chiral BINOL-type−zirconium(IV) *tert*-butoxide complex.[15]

The reaction of indole (**1a**) with enone **2a** was chosen to optimize the reaction conditions. Several chiral Lewis acid catalysts generated in situ from metal salts and the ligand (*R*)-BINOL (**L1**) were evaluated as shown in the illustrated reaction (Scheme 1), and the results are summarized in Table 1. With use of 20 mol % of $Sc(OTf)_3$ or $Ti(O^iPr)_3$ and 20 mol % of ligand **L1** (entries 1 and 2) in CH_2Cl_2 at room temperature the reaction took place slowly, and the enantiomeric excess of the product was zero or low, while in the presence of $Zr(O^tBu)_4$ indole **1a** reacted fast (within 1 h) with enone **2a**, giving 3-(1-methyl-3-phenyl-3-propanone)-1*H*-indole (**3aa**) in good yield (85%) and enantioselectivity (74%) (entry 3). We further screened different solvents, temperature, and catalyst loading. With 1,2-dichloroethane the results were practically the same, but other solvents ($CHCl_3$, acetonitrile, ether, THF, toluene) had a negative influence on the catalytic activity. Increasing or diminishing the reaction temperature as well as the catalyst loading also had a negative effect on the enantioselectivity. Our efforts to optimize the reaction conditions were also aimed at exploring the effectiveness of $Zr(O^tBu)_4$ with other BINOL-type ligands (**L2**−**L5**) which contain electron-withdrawing groups at the 3,3′ and 6,6′ positions as well as a tetrahydrogenated ring. Ligand **L3** led to the best result (87% yield, 97% ee) (entry 5). A reduction of the catalyst load to 10 mol % had a deleterious effect on the reaction, compound **3aa** being obtained in 21% yield and 78% ee (entry 8)

To demonstrate the scope and potential of this reaction, we next examined a series of indole derivatives **1** and enones **2**. Enones with a sterically demanding aromatic group bound to the carbonyl group and an aliphatic chain linked to the C−C double bond produced alkylated indoles in excellent yields and very high enantioselectivities, above 95% ee in most of the cases (Table 2). The size of the alkyl group at the β-position (Me, Et, Pr) did not seem to influence the reaction (entries 1−3) although in the case of chalcone (phenyl group at the β-position) a diminished reactivity was observed (entry 4). The reaction with enones containing an electron-donating group on the phenyl group had a slightly lower reaction rate than that with enones containing an

Scheme 1. Friedel−Crafts Reaction of Indole **1a** with Enone **2a** and Structure of BINOL-Type Ligands Used in This Study

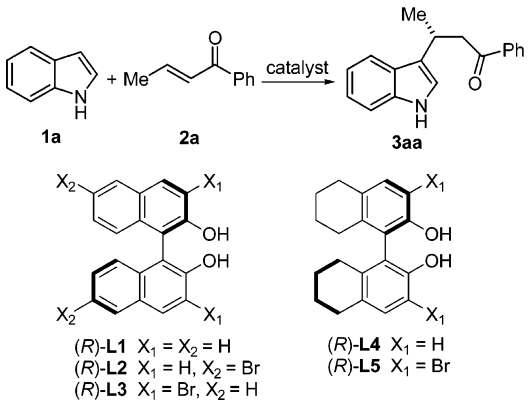

Table 1. Ligand Evaluation and Optimization of the Enantioselective Friedel−Crafts Reaction of **1a** with **2a**[a]

entry	solvent	catalyst	time (h)	yield (%)[b]	ee (%)[c]
1	CH_3CN	**L1**-$Sc(OTf)_3$	6	71	2
2	CH_2Cl_2	**L1**-$Ti(O^iPr)_4$	21	60	25
3	CH_2Cl_2	**L1**-$Zr(O^tBu)_4$	1	85	74
4	CH_2Cl_2	**L2**-$Zr(O^tBu)_4$	1	84	74
5	CH_2Cl_2	**L3**-$Zr(O^tBu)_4$	3	87	97
6	CH_2Cl_2	**L4**-$Zr(O^tBu)_4$	22	41	75
7	CH_2Cl_2	**L5**-$Zr(O^tBu)_4$	96	trace	
8[d]	CH_2Cl_2	**L3**-$Zr(O^tBu)_4$	46	21	78

[a] 20 mol % of (*R*)-ligand and 20 mol % of metal salt. [b] Isolated yield of **3aa**. [c] Determined by chiral HPLC analysis. (*R*) configuration assigned by comparison of the optical rotation sign with literature data (ref 12). [d] 10 mol % catalyst was used in this run.

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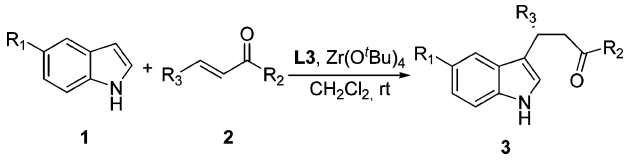
Table 2. Enantioselective Friedel−Crafts Reaction of Indole Derivatives **1** with Enones **2** Catalyzed by **L3**-Zr(O^{t}Bu)$_4$[a]



1 **2** **3**

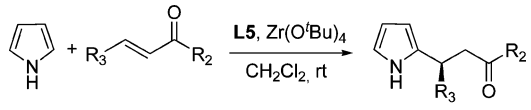
entry	**1**	R_1	**2**	R_2	R_3	time (h)	**3**	yield (%)[b]	ee (%)[c]
1	**1a**	H	**2a**	Ph	Me	3	**3aa**	87	97
2	**1a**	H	**2b**	Ph	Et	20	**3ab**	87	94
3	**1a**	H	**2c**	Ph	Pr	24	**3ac**	82	97
4	**1a**	H	**2d**	Ph	Ph	96	**3ad**	25	96
5	**1a**	H	**2e**	*p*-Me-C_6H_4	Me	20	**3ae**	91	95
6	**1a**	H	**2f**	*m*-MeC_6H_4	Me	4	**3af**	84	92
7	**1a**	H	**2g**	*o*-Me-C_6H_4	Me	22	**3ag**	73	72
8	**1a**	H	**2h**	*p*-MeO-C_6H_4	Me	18	**3ah**	54	95
9	**1a**	H	**2i**	*p*-F-C_6H_4	Me	2	**3ai**	92	96
10	**1a**	H	**2j**	*p*-Br-C_6H_4	Me	2	**3aj**	95	97
11	**1a**	H	**2k**	2-naphthyl	Me	2	**3ak**	89	98
12	**1a**	H	**2*l***	2-thienyl	Me	20	**3a*l***	87	96
13	**1b**	Me	**2a**	Ph	Me	4	**3ba**	97	95
14	**1c**	MeO	**2a**	Ph	Me	4	**3ca**	95	97
15	**1d**	Cl	**2a**	Ph	Me	30	**3da**	74	95

[a] 20 mol % of (*R*)-**L3** and 20 mol % of Zr(O^{t}Bu)$_4$. [b] Isolated yield. [c] Determined by chiral HPLC analysis (see the Supporting Information). (*R*) configuration assigned by comparison of the optical rotation signs of **3aa** and **3ca** with literature data (ref 12), and on the assumption of a uniform mechanistic pathway for the rest of products **3**.

electron-withdrawing group (entries 5−8 vs entries 9 and 10). The *ortho* substitution on the phenyl of the enone lowered the reaction rate and the enantiomeric excess of the alkylation product dropped to 72% (entry 7), implying the existence of a steric effect of the *ortho* substituents on the reactivity and enantioselectivity of the reaction (entries 5−7). In addition, the 2-naphthalene **2k** and the heteroaromatic **2*l*** enone derivatives can also serve as substrates in this reaction, giving the corresponding alkylated indoles in excellent yields and high enantioselectivities (entries 11 and 12). With regard to the substituent effect on the indole ring neither the electron-donating groups (CH_3, CH_3O) nor the electron-withdrawing groups (Cl) at the 5-position of indole affected the enantioselectivity of the reaction, but the reaction rate was indeed influenced unfavorablely in the case of 5-chloro-indole (entries 13−15). Unfortunately, the reaction is limited to enones with R_2 aromatic or heteroaromatic groups. Enones **2** bearing an R_2 aliphatic group (R_2 = Me, R_3 = Ph, or R_2 = Me, R_3 = *i*-Pr) reacted very slowly with **1a** under the optimized conditions.

Considering the value of pyrroles as useful synthons and as pyrrolidine surrogates,[16] we have expanded the reaction scope to include pyrrole (**4**) as a nucleophilic heteroarene. The reaction was carried out under similar optimized conditions as for the Friedel−Crafts reaction of indoles but with 10 equiv of pyrrole to avoid the formation of dialkylated products. A screening of ligands indicated that **L5** was the best choice in terms of enantioselection and yield (Table 3).

Table 3. Enantioselective Friedel−Crafts Reaction of Pyrrole (**4**) with Enones **2** Catalyzed by **L5**-Zr(O^{t}Bu)$_4$[a]



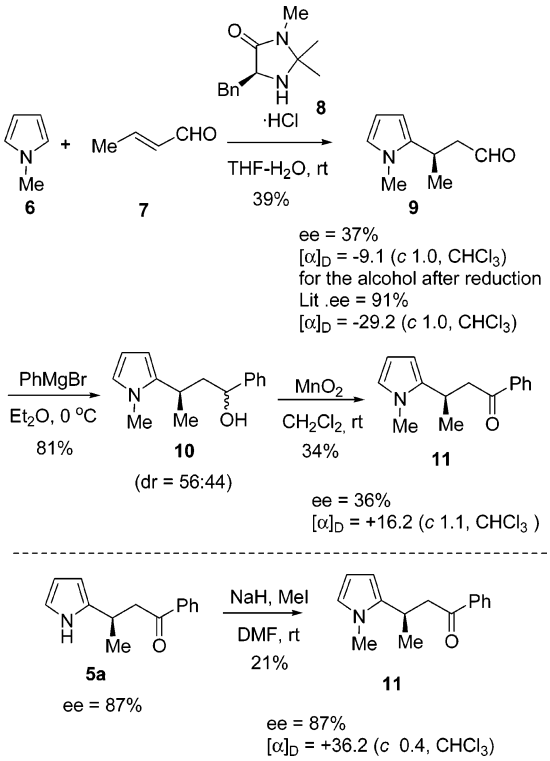
4 **2** **5**

entry	**2**	R_2	R_3	time (h)	**5**	yield (%)[b]	ee (%)[c]
1	**2a**	Ph	Me	4	**5a**	84	83
2	**2e**	*p*-Me-C_6H_4	Me	1	**5e**	97	96
3	**2h**	*p*-MeO-C_6H_4	Me	1	**5h**	89	99
4	**2j**	*p*-Br-C_6H_4	Me	0.75	**5j**	95	65
5	**2*l***	2-thienyl	Me	0.75	**5*l***	96	98

[a] 20 mol % of (*R*)-**L5** and 20 mol % of Zr(O^{t}Bu)$_4$. [b] Isolated yield. [c] Determined by chiral HPLC or GLC analysis (see the Supporting Information).

The establishment of the absolute configuration of the alkylated pyrroles **5** was achieved by chemical correlation following Bandini's methodology (Scheme 2).[12a] Following the asymmetric organo-catalyzed Friedel−Crafts alkylation described by MacMillan,[11a] we prepared the (*R*)-pyrrolyl

Scheme 2. Absolute Configuration Assignment for **5a**



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aldehyde **9** in 39% yield and 37% ee by reacting *N*-methylpyrrole **6** with acrolein **7** in the presence of the hydrochloride of imidazolidinine **8** at room temperature. Then, compound **9** was reacted with PhMgBr at 0 °C affording a 56:44 mixture of two diastereomeric alcohols **10** in 81% yield. The diasteromeric mixture was oxidized with MnO_2 to give (*R*)-**11** in 34% yield and 36% ee.

On the other hand, *N*-methylation of compound **5a** could be achieved, after some experimentation, by treatment with NaH/MeI in DMF in the presence of tetrabutylammonium iodide. By this method, a compound with identical spectral features as **11** in 21% yield and 87% ee was obtained from an 87% ee sample of compound **5a**. Comparison of both the optical rotation values and chiral HPLC retention times allowed us to establish the absolute sterochemistry of the product prepared from **5a** to be *R* as well. The absolute stereochemistry of all pyrrolyl ketones **5** was assigned by analogy.

In summary we have shown that BINOL-type-$Zr(O^tBu)_4$ complexes are very effective catalysts for the enantioselective Friedel−Crafts reaction of indole and pyrrole derivatives with a number of nonchelating β-substituted α,β-unsaturated ketones. The reaction proceeds with good yields and excellent enantioselectivities, superior to those obtained with salen-Al complexes, and does not require the use of additives. Additional advantages are the use of ligands that are commercially available in both enantiomeric forms, and a simple experimental procedure at room temperature.

Acknowledgment. Financial support from the Ministerio de Educación y Ciencia (Grant CTQ 2006-14199) and the Universitat de València (Grant UV-AE-20060244) is acknowledged. C.V. thanks the Generalitat Valenciana for a grant.

Supporting Information Available: Representative experimental procedures, characterization data, ^1H and ^{13}C NMR spectra, and chiral analysis for all compounds **3**, **5**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0710820