Catalytic Enantioselective Friedel–Crafts Alkylation of Indoles with β,γ-Unsaturated α-Keto Phosphonates in the Presence of Chiral Palladium Complexes

Young Ku Kang, Ki Hyung Suh, Dae Young Kim*

Department of Chemistry, Soonchunhyang University, Asan, Chungnam 336-745, Korea
Fax +82(41)5301247; E-mail: dyoung@sch.ac.kr

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Abstract: The catalytic enantioselective Friedel–Crafts alkylation reaction promoted by chiral palladium complexes is described. The treatment of indoles with β,γ-unsaturated α-keto phosphonates under the mild reaction conditions afforded the corresponding Friedel–Crafts alkylation adducts with excellent enantioselectivities (up to 99% ee).

Key words: Friedel–Crafts reaction, asymmetric catalysis, chiral palladium catalysts, indoles, β,γ-unsaturated α-keto phosphonates

The Friedel–Crafts (FC) reaction is one of the most powerful C–C bond-forming processes in organic chemistry.[1] Indole derivatives are present in many substances commonly found in nature, as well as in many compounds that show pharmacological and biological activities. Thus, the development of FC reaction of indole derivatives is important in the synthesis of natural products[2] and pharmacological and biological activities.[3] Over the past decade, tremendous effort has been devoted to the development of catalytic enantioselective FC reaction of α,β-unsaturated carbonyl compounds using chiral metal complexes[4] as well as organocatalysts.[7] Simple alkenyl esters have proven to be difficult substrates for effective chirality relay in asymmetric catalysis because of essentially low reactivity of α,β-unsaturated esters as Michael acceptors. α-Keto phosphonates, which have the ability of the phosphorus to function as a leaving group, were introduced as activated ester surrogates. Recently, several groups presented catalytic asymmetric FC reactions of indoles to β,γ-unsaturated α-keto phosphonates. Evans and Yamamoto groups have developed FC reaction catalyzed by chiral $Sc(OTf)_3$-pybox complexes[5] and chiral aluminium complexes.[6] Akiyama and Jørgensen groups have reported FC reaction using organocatalysts such as chiral phosphoric acid[7c] and chiral H-bonding catalysts.[7b] There are still some drawbacks in the previously reported procedures, such as low temperatures for high enantioselectivity, high catalyst loading, and unsatisfactory enantioselectivities. Therefore, the development of alternative catalysts for enantioselective FC reactions between indoles and β,γ-unsaturated α-keto phosphonates would be highly desirable. Recently, the efficient examples of the enantioselective reactions catalyzed by chiral palladium complexes were reported.[8] To the best of our knowledge, FC reaction of indoles with β,γ-unsaturated α-keto phosphonates catalyzed chiral palladium complexes has not been reported.

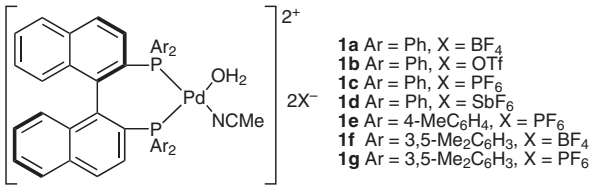
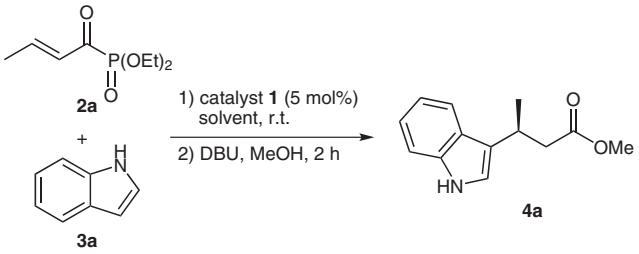


Figure 1 Structures of chiral palladium catalysts

Table 1 Optimization of the Reaction Conditions



Entry	Catalyst	Time	Solvent	Yield (%)[a]	ee (%)[b]
1	**1a**	2 h	CH_2Cl_2	70	89
2	**1b**	2 h	CH_2Cl_2	75	83
3	**1c**	2 h	CH_2Cl_2	70	93
4	**1d**	2 h	CH_2Cl_2	71	81
5	**1e**	2 h	CH_2Cl_2	73	89
6	**1f**	2 h	CH_2Cl_2	76	65
7	**1g**	2 h	CH_2Cl_2	79	39
8	**1c**	2 h	DCE	77	90
9	**1c**	1 h	THF	25	91
10	**1c**	1 h	EtOAc	50	90
11	**1c**	7 d	acetone	30	79
12	**1c**	7 d	MeCN	47	7
13	**1c**	7 d	toluene	39	85

[a] Yield of isolated product.
[b] Enantiomeric excess is determined by HPLC analysis with chiralcel OD-H.

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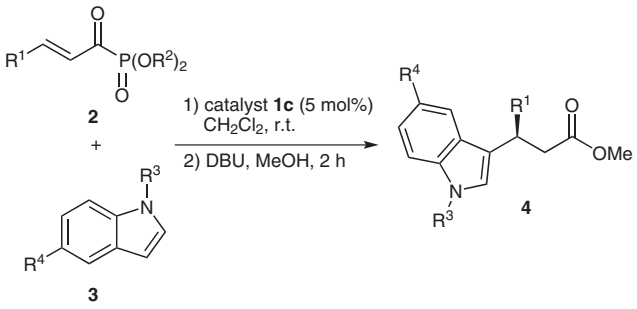
As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[9] we recently reported the catalytic electrophilic amination, fluorination, Mannich reaction, and Michael reaction of active methines promoted by chiral palladium complexes with excellent enantioselectivities.[10] Herein, we wish to describe the enantioselective FC reaction of indoles with β,γ-unsaturated α-keto phosphonates catalyzed by air- and moisture-stable chiral palladium complexes (Figure 1).

To determine suitable reaction conditions for the catalytic enantioselective FC reaction of indoles, we first examined the FC reaction of indole **3a** with β,γ-unsaturated α-keto phosphonate **2a** in the presence of 5 mol% of dicationic palladium complexes **1** in CH_2Cl_2 at room temperature (Table 1). The intermediate γ-indolyl-α-keto phosphonate, which is unstable, was converted to the corresponding methyl ester by direct addition of MeOH and DBU. We surveyed the effect of the structures of palladium complexes **1**. High yields with moderate to high enantioselectivities (39–93% ee) were observed for structurally variable palladium catalysts (Table 1, entries 1–7). Under the standard reaction conditions, catalyst **1c** exhibited better enantioselectivity (93% ee, Table 1, entry 3). Next, we examined the reaction in various solvents (Table 1, entries 3 and 8–13). The use of CH_2Cl_2 gave the best results, whereas the FC reaction in 1,2-dichloroethane, tetrahydrofuran, ethyl acetate, acetone, acetonitrile, and toluene led to lower yields and enantioselectivities (Table 1, entries 3 and 8–13). The absolute configuration of **4a** was established by comparison of the optical rotation and chiral HPLC analysis with previously reported values.[5]

With optimal reaction conditions in hand, we studied the generality of the enantioselective FC reaction of various indoles **3** with β,γ-unsaturated α-keto phosphonates **2**.[11] As shown in the results summarized in Table 2, the corresponding alkylated products **4** were obtained in good to high yields with enantioselectivities (up to 99% ee). In most cases, the reaction gave the desired products in excellent enatioselectivities but the reactions of *N*-methyl indole derivatives **3b** and **3e** with α-keto phosphonates gave relatively low enantioselectivities (Table 2, entries 4 and 8). Unfortunately, FC reaction of γ-phenyl-substituted α-keto phosphonate **2e** with indole gave the desired product **4i** in moderate yield and low enantioselectivity (31% ee, Table 2, entry 11).

Although the reason for the observed enantioselectivity is still unclear, we believe that β,γ-unsaturated α-keto phosphonate **2** is activated by the palladium catalyst **1** in a bidentate fashion. Then, indole **3** attacks the double bond as shown in Figure 2. Because the *Re* face of the double bond of phosphonate **2** was blocked preferentially by one of the phenyl group of (*R*)-BINAP, the addition of indole proceeded from the *Si* face in a highly enantioselective manner (Figure 2).[12]

Table 2 Catalytic Enantioselective Friedel–Crafts Reaction of Indoles with β,γ-Unsaturated α-Keto Phosphonates



Entry	2	R^1	R^2	3	R^3	R^4	Time (h)	Yield (%)[a]	ee (%)[b]
1	**2a**	Me	Et	**3a**	H	H	2	**4a** 70	93
2	**2b**	Me	Me	**3a**	H	H	2	**4a** 75	89
3	**2c**	Me	*i*-Pr	**3a**	H	H	1	**4a** 82	90
4	**2c**	Me	*i*-Pr	**3b**	Me	H	2	**4b** 65	83
5	**2c**	Me	*i*-Pr	**3c**	H	Br	3	**4c** 80	99
6	**2c**	Me	*i*-Pr	**3d**	H	OMe	3	**4d** 75	93
7	**2d**	Et	*i*-Pr	**3a**	H	H	1	**4e** 74	97
8	**2d**	Et	*i*-Pr	**3e**	Me	Br	2	**4f** 68	85
9	**2d**	Et	*i*-Pr	**3c**	H	Br	2	**4g** 79	97
10	**2d**	Et	*i*-Pr	**3d**	H	OMe	2	**4h** 71	97
11	**2e**	Ph	Et	**3a**	H	H	36	**4i** 67	31

[a] Yield of isolated product.
[b] Enantiometic excess is determined by HPLC analysis with Chiralcel OD-H (for **4a**–**b**,**f**,**g**) and Chiralpak AD-H (for **4c**–**e**,**h**–**i**).

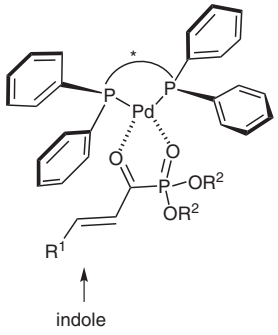


Figure 2 Plausible transition-state model

In conclusion, we have developed an efficient catalytic FC reaction of indoles to β,γ-unsaturated α-keto phosphonates using air- and moisture-stable chiral palladium complexes at room temperature. The intermediate γ-indolyl α-keto phosphonates were easily converted into the desired methyl esters and the alkylated products were obtained in good yields (65–82%) with excellent enantioselectivities (up to 99% ee).

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(11) **Typical Procedure**
To a stirred solution of (*E*)-diethyl 1-oxobut-2-enylphosphonate (**2a**, 20.6 mg, 0.1 mmol), Pd catalyst **1c** (5.4 mg, 0.005 mmol) in CH_2Cl_2 (1 mL) was added indole (**3a**, 14.0 mg, 0.12 mmol) at r.t. The reaction mixture was stirred for 2 h at r.t. Then MeOH (0.15 mL), followed by DBU (0.03 mL), was added directly to the reaction mixture. The reaction was allowed to stir for 2 h at r.t. The reaction was diluted with EtOAc (10 mL), then washed with sat. NH_4Cl. The organic layer was dried over anhyd $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (EtOAc–hexane, 1:5) to afford (*S*)-methyl 3-(1*H*-indol-3-yl)butanoate (**4a**, 70%, 15.2 mg). $[\alpha]_D^{28}$ 7.3 (*c* 0.7, $CHCl_3$, 93% ee). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.99 (br s, 1 H), 7.63 (d, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 7.23–7.05 (m, 2 H), 6.90 (d, *J* = 2.5 Hz, 1 H), 3.65–3.47 (m, 1 H), 3.62 (s, 3 H), 2.82 (dd, *J* = 14.8, 6.0 Hz, 1 H), 2.56 (dd, *J* = 14.7, 8.7 Hz, 1 H), 1.39 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.0, 136.1, 125.9, 121.5, 120.2, 119.7, 118.8, 118.7, 110.9, 51.1, 41.9, 27.6, 20.6. ESI-MS: *m/z* = 217.9 $[M + H]^+$, 117.0, 120.9, 123.0 147.0, 176.9. HPLC (hexane–*i*-PrOH = 90:10, 220 nm, 0.8 mL/min) Chiralcel OD-H column, t_R = 9.0 min(minor), t_R = 13.8 (major).

(12) The two-site-binding interaction between substrate and palladium catalyst is crucial to guarantee reactivity as well as stereocontrol. In fact, when the monodentate ethyl (*E*)-but-2-enoate was reacted with indole under the same reaction conditions, no reaction occurred.