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Chiral Pd-catalyzed enantioselective Friedel–Crafts reaction of indoles with γ,δ-unsaturated β-keto phosphonates

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ABSTRACT

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

The Friedel–Crafts (FC) alkylation is important reaction for the formation of C–C bonds.[1] The asymmetric FC reaction can afford enantiomerically enriched alkylated arene products. The chemistry of indole derivatives that are present in many substances commonly found in nature is a rapidly developing area because of their importance in biochemical and medicinal application. Thus, the development of asymmetric FC reaction of indole derivatives is important in the synthesis of natural products[2] and pharmacological and biological active compounds.[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[1a–d] and organocatalysts.[1e–g] Chiral metal-catalyzed process usually required the bidentate chelating substrates such as β,γ-unsaturated α-ketoesters, glyoxylates, alkylidene malonates and pyruvates, acyl phosphonates, 2-acyl imidazoles, α′-hydroxy enones, enoylpyridine 1-oxide and thioesters.[4] In 2007, Kim and co-workers reported enantioselective FC reaction of indoles with γ,δ-unsaturated β-keto phosphonates catalyzed by chiral $Cu(OTf)_2$–Box complexes.[5] There are still some drawbacks in the previously reported procedures, such as high catalyst loading and low temperatures for high enantioselectivity. Therefore, the development of alternative catalysts for enantioselective FC reactions between indoles and γ,δ-unsaturated β-keto phosphonates would be highly desirable. Recently, the efficient examples of the enantioselective reactions catalyzed by chiral palladium complexes were reported.[6] To the best of our knowledge, FC reaction of indoles with γ,δ-unsaturated β-keto phosphonates catalyzed by chiral palladium complexes has not been reported.

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[7] we recently reported the catalytic electrophilic amination, fluorination, Mannich reaction and Michael reaction of active methines promoted by chiral palladium complexes with excellent enantioselectivities.[8] In this letter, we wish to describe the enantioselective FC reaction of indoles with γ,δ-unsaturated β-keto phosphonates catalyzed by air- and moisture-stable chiral palladium complexes (Fig. 1).

To determine suitable reaction conditions for the catalytic enantioselective FC reaction of indoles, we first examined FC reaction of indole **3a** with γ,δ-unsaturated β-keto phosphonates **2** in the presence of 5 mol % of dicationic palladium complexes **1** in CH_2Cl_2 at room temperature (Table 1). We surveyed the effect of structure of palladium complexes **1**. High yields with good to excellent enantioselectivities (85–96% ee) were observed for structurally variable palladium catalysts (entries 1–6). Under the

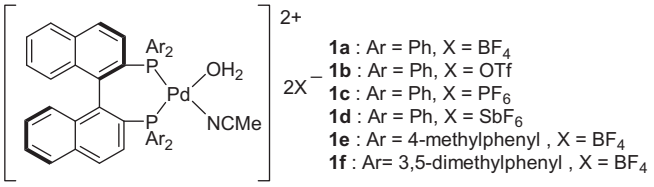

Figure 1. Structures of chiral palladium catalysts.

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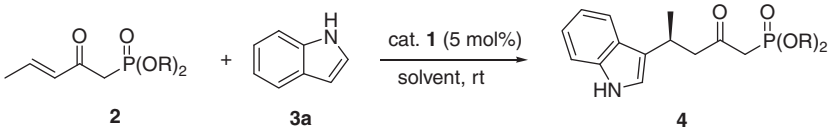
Table 1
Optimization of the reaction conditions

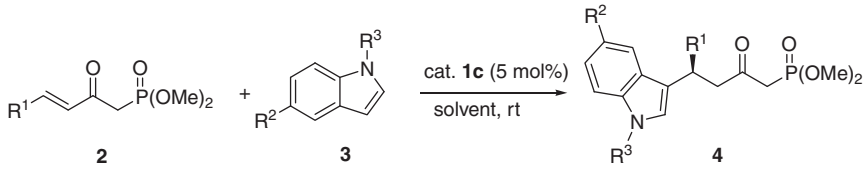


2 3a 4

Entry	Cat.	Solvent	2, R	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1a**	CH_2Cl_2	**2a**, Me	2	**4a**, 95	93
2	**1b**	CH_2Cl_2	**2a**, Me	2	**4a**, 92	91
3	**1c**	CH_2Cl_2	**2a**, Me	2	**4a**, 98	96
4	**1d**	CH_2Cl_2	**2a**, Me	2	**4a**, 93	85
5	**1e**	CH_2Cl_2	**2a**, Me	2	**4a**, 90	91
6	**1f**	CH_2Cl_2	**2a**, Me	2	**4a**, 94	86
7	**1c**	CH_2Cl_2	**2b**, Et	2.5	**4b**, 94	93
8	**1c**	CH_2Cl_2	**2c**, *i*-Pr	4	**4c**, 96	85
9	**1c**	MeOH	**2a**, Me	24	**4a**, 95	73
10	**1c**	AcOEt	**2a**, Me	60	**4a**, 70	95
11	**1c**	Acetone	**2a**, Me	48	**4a**, 60	81
12	**1c**	THF	**2a**, Me	48	**4a**, 71	99
13	**1c**	Toluene	**2a**, Me	36	**4a**, 74	95

[a] Isolated yield.
[b] Enantiopurity was determined by chiral HPLC analysis using chiral column (Chiralpak AS for **4a** and **4c** Chiralcel OD–H for **4b**).

Table 2
Catalytic enantioselective Friedel–Crafts reaction of indoles with γ,δ-unsaturated β-keto phosphonates



2 3 4

2a, R^1 = Me
2b, R^1 = Et
2c, R^1 = *n*-Pr
2d, R^1 = CH_2CH_2Ph
2e, R^1 = Ph

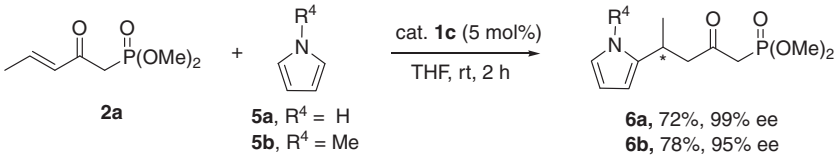
3a, R^2 = H, R^3 = H
3b, R^2 = Me, R^3 = H
3c, R^2 = OMe, R^3 = H
3d, R^2 = Br, R^3 = H
3e, R^2 = H, R^3 = Me
3f, R^2 = Br, R^3 = Me

Entry	2	3	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	**2a**	**3a**	THF	48	**4a**, 71	99
2	**2a**	**3b**	Toluene	96	**4d**, 79	99
3	**2a**	**3c**	THF	20	**4e**, 92	93
4	**2a**	**3d**	THF	72	**4f**, 75	99
5[c]	**2a**	**3e**	THF	72	**4g**, 71	93
6[c]	**2a**	**3f**	THF	72	**4h**, 86	93
7	**2b**	**3a**	CH_2Cl_2	20	**4i**, 94	85
8[c]	**2b**	**3c**	CH_2Cl_2	96	**4j**, 95	93
9	**2b**	**3d**	Toluene	34	**4k**, 98	93
10[c]	**2b**	**3e**	CH_2Cl_2	72	**4l**, 95	85
11	**2c**	**3a**	THF	24	**4m**, 78	90
12	**2d**	**3a**	THF	36	**4n**, 68	99
13	**2e**	**3a**	THF	72	N.R.	—

[a] Isolated yield.
[b] Enantiopurity was determined by HPLC analysis using chiral columns (Chiralpak AS for **4a**, **4i** and **4h**, Chiralpak AS–H for **4k** and **4l**, Whelk-01 for **4d**, Chiralcel OD–H for **4e**, Chiralhyun–Leu for **4j**, Chiralpak AD–H for **4f** and **4g**, IA for **4m** and **4n**).
[c] Cat. **1a** was used instead of cat. **1c**.

standard reaction conditions, catalyst **1c** gave better enantioselectivity (96% ee, entry 3). We studied the effect of the ester group of phosphonates **2** using Pd catalyst **1c** in CH_2Cl_2 (entries 3, 7 and 8). Dimethyl 2-oxo-pent-3-enylphosphonate (**2a**) showed the best enantioselectivity (entry 3). Next, we examined the reaction in various solvents (entries 3 and 9–13). The use of CH_2Cl_2, THF, toluene and EtOAc gave the good results, whereas the FC reaction in MeOH and acetone gave lower enantioselectivities (entries 3 and 9–13). 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 condition in hand, we studied the generality of the enantioselective FC reaction of various indoles **3** with γ,δ-unsaturated β-keto phosphonates **2**.[9] As it can be seen by the results summarized in Table 2, the corresponding alkylated products **4a**–**4n** were obtained in high yields with enantioselectivities



Scheme 1.

(85–99% ee). The best enantioselectivity of FC adducts **4d** and **4k** was obtained in toluene, and FC adducts **4i**, **4j** and **4l** was obtained in CH_2Cl_2. On the other hand, dimethyl 2-oxo-4-phenyl-but-3-enylphosphonate (**2e**) could not be alkylated with indole (**3a**) under optimal reaction conditions (Table 2, entry 13).

Furthermore, indole derivatives **5** were also used as substrate in this FC reaction with dimethyl 2-oxo-pent-3-enylphosphonate (**2a**). It was found that the corresponding products **6** were obtained in high yields with excellent enantioselectivities (Scheme 1).

In conclusion, we have developed an efficient catalytic FC reaction of indoles to γ,δ-unsaturated β-keto phosphonates using air- and moisture-stable chiral palladium complexes at room temperature. The desired δ-indolyl β-keto phosphonates **4** were obtained in high yields, and excellent enantioselectivities (85–99% ee) were observed for all the substrates examined in this work. We believe that this report provides a practical method for the preparation of chiral γ-indolyl β-keto phosphonate derivatives, and the availability of these compounds should facilitate biochemical and medicinal studies in various fields.

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References and notes

1. For reviews on Friedel–Crafts alkylation, see: (a) Jrgensen, K. A. *Synthesis* **2003**, 1117; (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550; (c) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199; (d) Poulsen, T. B.; Jrgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903; (e) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701; (f) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190; (g) Terrasson, V.; de Figueiredo, R. M.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, 2635; Bandini, M.; Umani-Ronchi, A. *Catalytic Asymmetric Friedel–Crafts Alkylations*; Wiley-VCH: Weinheim, 2009; (i) Zeng, M.; You, S.-L. *Synlett* **2010**, 1289.
2. Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996; (b) Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, *15*, 327; (c) Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1998**, *61*, 1304; (d) Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120; (e) Mancini, I.; Guella, G.; Zibrowius, H.; Pietra, F. *Tetrahedron* **2003**, *59*, 8757; (f) Kam, T.-S.; Choo, Y.-M. *J. Nat. Prod.* **2004**, *67*, 547.
3. (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73; (b) Reddy, R.; Jaquith, J. B.; Neelagiri, V. R.; Saleh-Hanna, S.; Durst, T. *Org. Lett.* **2002**, *4*, 695; (c) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437; (d) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450.
4. (a) Lv, J.; Li, X.; Zhong, L.; Luo, S.; Cheng, J.-P. *Org. Lett.* **2010**, *12*, 1096; (b) Liu, Y.; Shang, D.; Zhou, X.; Zhu, Y.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2010**, *12*, 180; (c) Singh, P. K.; Singh, V. K. *Org. Lett.* **2008**, *10*, 4121; (d) Blay, G.; Fernandez, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, *9*, 2601; (e) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942; (f) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739; (g) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154; (h) Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843; (i) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Helv. Chim. Acta* **2003**, *86*, 3753; (j) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780; (k) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029; (l) Takenaka, N.; Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 742.
5. Yang, H.; Hong, Y.-T.; Kim, S. *Org. Lett.* **2007**, *9*, 2281.
6. For recent selected examples of the enantioselective reactions catalyzed by chiral palladium complexes, see: (a) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708; (b) Sodeoka, M.; Hamashima, Y. *Chem. Commun.* **2009**, 5787; (c) Hamashima, Y.; Sasamoto, N.; Umebayashi, N.; Sodeoka, M. *Chem. Asian J.* **2008**, *3*, 1443; (d) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525; (e) Smith, A. M. R.; Rzepa, H. S.; White, A. J. P.; Billen, D.; Hii, K. K. *J. Org. Chem.* **2010**, *75*, 3085; (f) Smith, A. M. R.; Billen, D.; Hii, K. K. *Chem. Commun.* **2009**, 3925; (g) Phua, P. H.; Mathew, S. P.; White, A. J. P.; de Vries, J. G.; Blackmond, D. G.; Hii, K. K. *Chem. Eur. J.* **2007**, *13*, 4602.
7. (a) Yoon, S. J.; Kang, Y. K.; Kim, D. Y. *Synlett* **2011**, 420; (b) Moon, H. W.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2011**, *32*, 291; (c) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847; (d) Kang, S. H.; Kim, D. Y. *Adv. Synth. Catal.* **2010**, *352*, 2783; (e) Lee, J. H.; Kim, D. Y. *Synthesis* **2010**, 1860; (f) Moon, H. W.; Kim, D. Y. *Tetrahedron Lett.* **2010**, *51*, 2906; (g) Lee, J. H.; Kim, D. Y. *Adv. Synth. Catal.* **2009**, *351*, 1779; (h) Kang, Y. K.; Kim, D. Y. *J. Org. Chem.* **2009**, *74*, 5734; (i) Moon, H. W.; Cho, M. J.; Kim, D. Y. *Tetrahedron Lett.* **2009**, *50*, 4896; (j) Kwon, B. K.; Kim, S. M.; Kim, D. Y. *J. Fluorine Chem.* **2009**, *130*, 259; (k) Oh, Y.; Kim, S. M.; Kim, D. Y. *Tetrahedron Lett.* **2009**, *50*, 4674; (l) Kang, S. H.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 1439; (m) Kwon, B. K.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 1441; (n) Mang, J. Y.; Kwon, D. G.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 249; (o) Kim, S. M.; Lee, J. H.; Kim, D. Y. *Synlett* **2008**, 2659; (p) Jung, S. H.; Kim, D. Y. *Tetrahedron Lett.* **2008**, *49*, 5527; (q) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897; (r) Kim, D. Y.; Choi, Y. J.; Park, H. Y.; Joung, C. U.; Koh, K. O.; Mang, J. Y.; Jung, K.-Y. *Synth. Commun.* **2003**, *33*, 435; (s) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545; (t) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299; (u) Kim, D. Y.; Huh, S. C. *Tetrahedron* **2001**, *57*, 8933.
8. (a) Kang, S. H.; Kang, Y. K.; Kim, D. Y. *Tetrahedron* **2009**, *65*, 5676; (b) Kim, E. J.; Kang, Y. K.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 1437; (c) Lee, N. R.; Kim, S. M.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 829; (d) Kang, Y. K.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2008**, *29*, 2093; (e) Lee, J. H.; Bang, H. T.; Kim, D. Y. *Synlett* **2008**, 1821; (f) Kang, Y. K.; Cho, M. J.; Kim, S. M.; Kim, D. Y. *Synlett* **2007**, 1135; (g) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4265; (h) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115; (i) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309.
9. *Typical procedure:* To a stirred solution of (*E*)-dimethyl 2-oxopent-3-enylphosphonate (**2a**, 57.6 mg, 0.3 mmol), Pd-catalyst **1c** (16.2 mg, 0.015 mmol) in THF (1.5 mL) was added indole (**3a**, 41.1 mg, 0.36 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. The reaction was diluted with EtOAc (10 mL), then washed with sat. NH_4Cl. The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (EtOAc/Hex:15/1) to afford (*S*)-dimethyl 4-(1*H*-indol-3-yl)-2-oxopentylphosphonate (**4a**, 71%, 65.9 mg). $[\alpha]_D^{26.3} = -55.4$ ($c = 1.0$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (d, $J = 6.9$ Hz, 3H), 2.89 (dd, $J = 8.1$, 16.1 Hz, 1H), 3.00 (d, $J = 22.4$ Hz, 2H), 3.12 (dd, $J = 5.9$, 16.1 Hz, 1H), 3.55–3.66 (m, 1H), 3.70 (d, $J = 11.6$ Hz, 3H), 3.73 (d, $J = 10.8$ Hz, 3H), 6.99 (d, $J = 2.4$ Hz, 1H), 7.07–7.24 (m, 2H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.64 (d, $J = 7.6$ Hz, 1H), 8.30 (br s, 1H); ^{13}C MNR (50 MHz, $CDCl_3$) δ 21.1, 26.7, 41.6 ($J = 127.5$ Hz), 51.7, 53.0 (d, $J = 6.1$ Hz), 111.3, 119.1, 119.3, 120.4, 121.3, 122.0, 126.2, 136.5, 201.5 ($J = 7.0$ Hz); MS (ESI): $m/z = 310.1$ $[M+H]^+$; HPLC (80:20, *n*-hexane/*i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AS column, $t_R = 20.0$ (minor), 21.5 min (major), 99% ee.