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Catalytic Enantioselective Friedel–Crafts Alkylations of Indoles with α′-Phosphoric Enones

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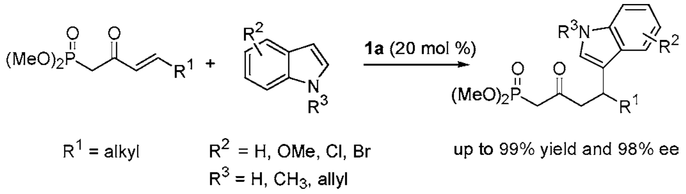
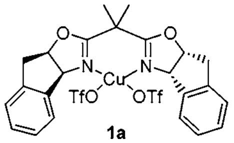
ABSTRACT





1a

The C_2-symmetric bis(oxazoline) copper(II) complex proves to be an excellent catalyst in the Friedel–Crafts alkylation of indoles with α′-phosphoric enones. The enantioselectivities of this reaction are obtained in up to 98% ee.

The Friedel−Crafts reactions are very important and useful for carbon−carbon bond formations. Their catalytic enantioselective reactions have attracted a great deal of recent attention owing to easy access to optically active aryl-substituted products from readily available starting materials.[1] Two approaches involving chiral secondary amine-catalyzed[2] and the chiral metal-catalyzed reactions are very promising. The latter process usually requires the substrates being capable of chelating to the chiral metal complexes. Previously reported templates for this purpose include β,γ-unsaturated α-ketoesters,[3] alkylidene malonates,[4] α,β-unsaturated acyl phosphates,[5] α′-hydroxy enones,[6] α,β-unsaturated 2-acylimidazoles,[7] and nitroalkenes.[8]

On the basis of the well-known synthetic usefulness of β-keto phosphonates,[9] we have been interested in utilizing β-keto phosphonate moieties for chelating to the chiral Lewis acids. Since the indole skeleton is an important substructure

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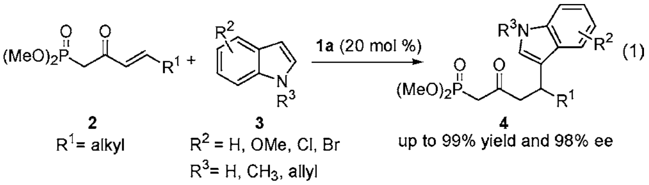
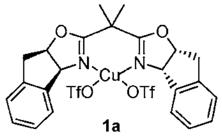
in both natural products[10] and therapeutic agents,[11] we studied the asymmetric Friedel−Crafts alkylation of indoles with α′-phosphoric enones using chiral catalyst [{(*S*)-In-Box}Cu-$(OTf)_2$] **1a**. This reaction exhibited good chemical yields and high enantioselectivities (up to 98% ee).





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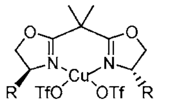
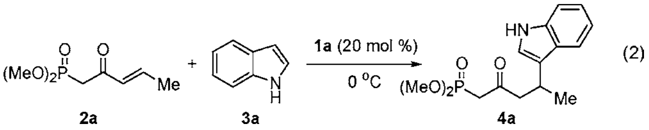


1b: R = Ph; **1c**: R = *t*-Bu

To search for highly efficient chiral metal complexes, the reaction was carried out with enone **2a** and indole in the presence of a variety of chiral bis(oxazoline)−metal complexes. It was found that **1a** gave the best result (at 0 °C, 98% yield, 86% ee) in terms of yield and enantioselectivity, whereas **1b** gave a low enantiomeric excess (at 0 °C, 95% yield, 35% ee). It is also noteworthy that the Friedel−Crafts reaction with **1c**[3,4a,12] slowed down dramatically. Treatment of **2a** with **3a** and **1c** in dichloromethane at 0 °C for 5 days afforded **4a** in 34% yield (31% ee) along with recovery of **2a** (59%).

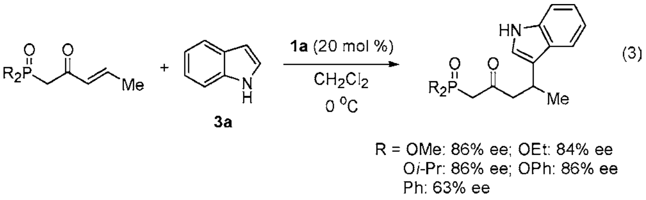
The effect of the solvent was briefly examined as shown in Table 1. Among the solvents employed in this study, dichloromethane gave the best result (entry 5) and toluene was also equally effective (entry 4). We next studied how structurally different phosphonate groups could influence the enantioselectivities of the reaction but found that the effect was not significant with the exception of a diphenylphosphine oxide derivative (63% ee) as shown in eq 3.

Table 1. Effect of Solvent in the Friedel−Crafts Alkylations



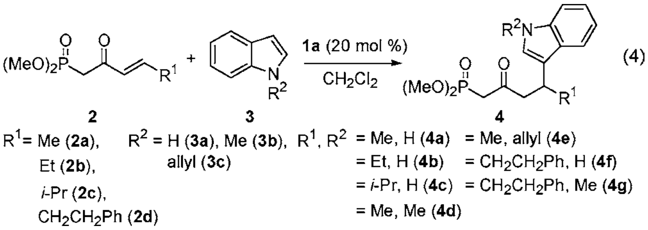
entry	solvent	time [h]	yield [%]	ee [%][b]
1	Et_2O	18	95	78
2	$CHCl_3$	8	93	66
3	THF	18	46	78
4	toluene	18	83	84
5	CH_2Cl_2	8	98	86

[a] All reactions were carried out on a 0.1 mmol scale with 20 mol % catalyst. [b] Enantiomeric excesses were determined by chiral HPLC.



The enantioselective Friedel−Crafts alkylations of indoles with several structurally different α′-phosphoric enones **2** using **1a** (20 mol %) in dichloromethane are summarized in Table 2. In most cases, the reaction gave the desired products in high yields and excellent enantioselectivities but the reactions with isopropyl-substituted α′-phosphoric enone **2c** (entry 6) and *N*-allyl-substituted indole **3c** (entry 8) were slow and gave the products in low yields. The enantioselectivities ranged from 82% ee to 97% ee and the use of molecular sieves 4 Å as an additive increased the enantiomeric excess to a small extent (entries 2 and 11).[13]

Table 2. Cu(II)-Catalyzed Friedel−Crafts Alkylations of Indoles with α′-Phosphoric Enone **2**[a]



entry	2	3	temp [°C]	time [h]	yield [%]	ee [%][b]
1	**2a**	**3a**	0	8	98 (**4a**)	86
2	**2a**	**3a**	0	8	98 (**4a**)	88[c]
3	**2a**	**3a**	−40	72	98 (**4a**)	94
4	**2a**	**3a**	−78	120	98 (**4a**)	95
5	**2b**	**3a**	0	24	98 (**4b**)	90
6	**2c**	**3a**	0	120	62 (**4c**)	86
7	**2a**	**3b**	0	60	98 (**4d**)	86
8	**2a**	**3c**	0	144	39 (**4e**)	82
9	**2d**	**3a**	0	18	95 (**4f**)	86
10	**2d**	**3a**	−40	72	96 (**4f**)	96
11	**2d**	**3a**	−40	72	98 (**4f**)	97[c]
12	**2d**	**3a**	−78	120	99 (**4f**)	96
13	**2d**	**3b**	0	96	90 (**4g**)	88
14	**2d**	**3b**	−40	504	95 (**4g**)	94

[a] All reactions were carried out on a 0.1 mmol scale with 20 mol % catalyst. [b] Enantiomeric excesses were determined by chiral HPLC. [c] The reaction was carried out in the presence of MS 4 Å.

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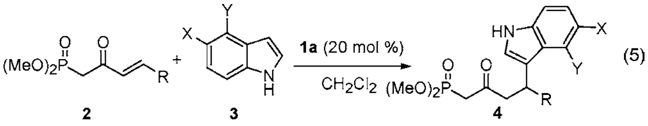
The effect of indole derivatives was next evaluated under similar conditions. The enantioselectivity was influenced by either substituents of enone **2** or the reaction temperature. Generally, 5-methoxy-1*H*-indole **3d** reacted with enone **2** to give **4** in excellent yields and high enantiomeric excesses (Table 3). Indoles substituted with electron-donating substituents (**3d** and **3g**) reacted with enone **2** in a highly enantioselective manner and the rate of reaction was accelerated (entries 1 and 6). Indoles substituted with electron-withdrawing substituents (**3e** and **3f**) also gave the desired products in high yields, but the reaction slowed down (entries 3 and 4). As compared to indole **3d** (entry 1), indole **3g** with a methoxy group at C(4) was somewhat less reactive but a good level of enantioselectivity was still observed (entry 5). The use of 4 Å molecular sieves was found to be marginal (entry 8) and the temperature effect was more noticeable. Furthermore, *N*-methylpyrrole worked as efficiently as indole derivatives (eq 6).

Table 3. Cu(II)-Catalyzed Friedel−Crafts Alkylations of Substituted Indoles with **2**

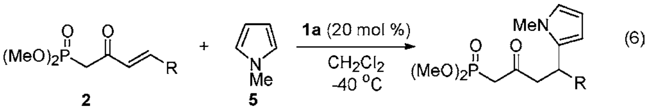


X, Y = OMe, H (**3d**)
= Cl, H (**3e**)
= Br, H (**3f**)
= H, OMe (**3g**)

R^1, X, Y = Me, OMe, H (**4h**)
= Me, Cl, H (**4i**)
= Me, Br, H (**4j**)
= Me, H, OMe (**4k**)
= CH_2CH_2Ph, OMe, H (**4l**)

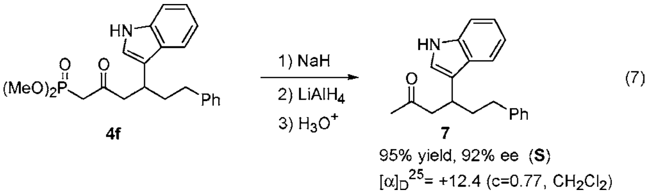
entry	2	3	temp [°C]	time [h]	yield [%]	ee [%][a]
1	**2a**	**3d**	0	5	90 (**4h**)	90
2	**2a**	**3d**	−40	48	90 (**4h**)	95
3	**2a**	**3e**	0	48	86 (**4i**)	88
4	**2a**	**3f**	0	48	85 (**4j**)	86
5	**2a**	**3g**	0	48	95 (**4k**)	90
6	**2d**	**3d**	0	8	99 (**4l**)	91
7	**2d**	**3d**	−40	18	95 (**4l**)	97
8	**2d**	**3d**	−40	18	92 (**4l**)	98[b]

[a] Enantiomeric excesses were determined by chiral HPLC. [b] The reaction was carried out in the presence of MS 4 Å.



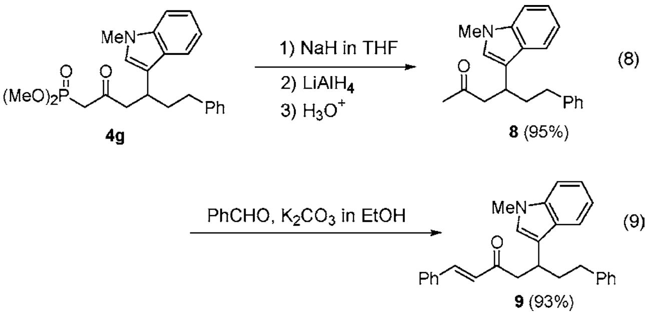
2a: R = Me
2d: R = CH_2CH_2Ph
6a: 81%, 82% ee
6b: 90%, 89% ee

To establish the absolute configuration of the Friedel−Crafts adduct **4**, we examined a chemical correlation between the Friedel−Crafts adduct **4f** having 92% ee and the previously known compound **7**.[6] Treatment of **4f** with sodium hydride (1.1 equiv) in THF followed by the addition of lithium aluminum hydride (3 equiv) afforded **7** (eq 7).[14] Compared with the optical rotation value of **7** and the previously known compound, the absolute configuration could be assigned as (*S*), indicating that the stereocenter was not affected during transformations.[6]



Similarly, **4g** was converted into **8** in 95% yield. The dephosphonylation method makes the present approach very attractive. The Friedel−Crafts alkylation with α′-phosphoric enones complements those of simple aliphatic enones, which have difficulty in achieving high enantiomeric excesses.[15] The Horner−Emmons reaction of the Friedel−Crafts adduct **4** was performed by the known method.[16] Treatment of **4g** with benzaldehyde and potassium carbonate in ethanol at room temperature for 9 h afforded enone **9** in 93% yield (Scheme 1).

Scheme 1. Conversion of *β*-Keto Phosphonate **4g** into Ketone **8** and Enone **9**



The mechanism for chiral Cu(II)-bis(oxazoline)-catalyzed enantioselective reactions has been well studied.[17] The asymmetric induction observed in the present Friedel−Crafts

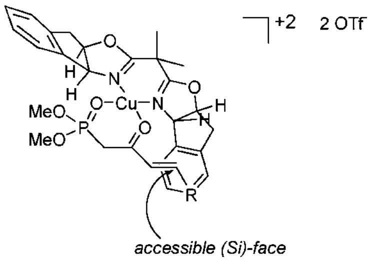


Figure 1. Stereochemical model for the substrate−catalyst complex.

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reactions is consistent with the model shown in Figure 1, which assumes a distorted square-planar geometry around copper. Apparently, the indanyl ring would block the (*Re*)-face approach by indole derivatives.

In summary, the α′-phosphoric enones, which have *β*-keto phosphate as a template, are highly efficient for the enantioselective Friedel−Crafts alkylations catalyzed by catalyst [{(*S*)-In-Box}Cu(OTf)$_2$] **1a** and complement the previously reported templates. The Friedel−Crafts adducts can be converted into the corresponding methyl ketones and α,*β*-unsaturated ketones. Further studies on the catalytic enantioselective Michael reactions associated with α′-phosphoric enone templates are in progress.

Acknowledgment. We are grateful to the CMDS, KEPCO, and BK21 for financial support.

Supporting Information Available: General experimental procedures and full characterization of compounds **2**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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