Enantioselective Friedel–Crafts alkylation reaction of indoles with α,β-unsaturated acyl phosphonates catalyzed by chiral phosphoric acid†

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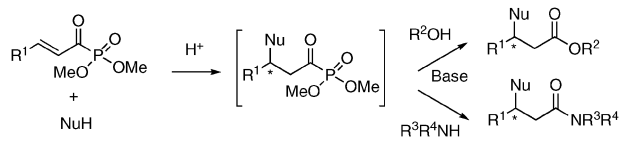
A variety of indoles underwent enantioselective Friedel–Crafts alkylation with α,β-unsaturated acyl phosphonates in the presence of 10 mol% chiral BINOL-based phosphoric acid and subsequent treatment with methanol and DBU to give methyl 3-(indol-3-yl)-propanoates in good yields and with high enantioselectivities.

The enantioselective carbon–carbon bond forming reaction has attracted much attention in both academia and industry because of its numerous potential advantages.[1] The formation of new carbon–carbon bonds *via* the Friedel–Crafts reaction[2] and the catalytic enantioselective variants has made a great impact on stereoselective synthesis. Those variants involve the addition of hetero-aromatic nucleophiles, such as indoles, to electron-deficient olefins, resulting in 3-substituted indole derivatives.[3] It has potential application in the synthesis of molecules with the indole framework or pharmacophore, which are found in a range of natural products and medicinal compounds of diverse therapeutic actions. The preparation of polyfunctional indoles is therefore an important topic of research.[4] Several chiral metal catalysts[5] as well as organo-catalysts[6] have been reported for the reactions with α,β-unsaturated carbonyl compounds.

The stereoselective addition of a nucleophile to an α,β-unsaturated esters is not a trivial issue because of the lower nature of the α,β-unsaturated ester as a Michael acceptor. Thus, we envisaged that employing an α,β-unsaturated acyl phosphonate to react with a nucleophile under organocatalytic conditions would allow us to produce a chiral intermediate. Under mild conditions, this intermediate can be converted to the corresponding ester or amide without affecting the enantiomerically enriched benzylic stereocenter (Scheme 1).

So far only metal catalyzed reactions have been reported in the conjugate addition of mainly protected indoles to α,β-unsaturated acyl phosphonates with limited scope.[5a,h]



Scheme 1 Chiral phosphoric acid catalyzed Friedel–Crafts alkylation reaction and subsequent transformation to ester or amide.

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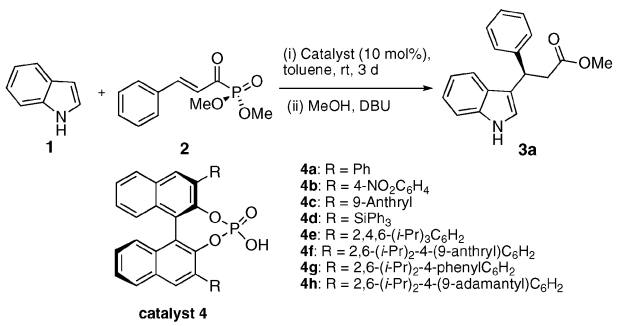
In the past few years, (*R*)-BINOL-derived phosphoric acids as chiral Brønsted acids have attracted considerable attention in organocatalyzed asymmetric organic transformations.[7,8] As part of our ongoing studies using chiral phosphoric acids as organocatalysts,[9] we investigated the chiral phosphoric acid catalyzed Friedel–Crafts alkylation reaction of unprotected indoles with α,β-unsaturated acyl phosphonate to afford Friedel–Crafts adducts with excellent enantioselectivities.[10]

First, we investigated the reaction of indole **1** with α,β-unsaturated acyl phosphonate **2** catalyzed by chiral phosphoric acid as the model reaction (Table 1). The reaction proceeded at room temperature in the presence of 10% catalysts (*R*)-**4a–h** in toluene. Due to the instability of the adduct, it was subsequently converted into methyl ester using methanol and DBU, as shown in Table 1. From this survey, we found that the use of sterically more hindered and bulkier phosphoric acids as catalysts gave higher enantioselectivities (Table 1, entries 6 and 7). The best result was obtained with (*R*)-**4f** as a catalyst, which afforded methyl ester **3a** in highest yield (72%) and enantioselectivity (92%).

To further optimize the reaction conditions, we examined the solvent, temperature, and catalyst loading (Table 2). Toluene turned out to be the optimal solvent (Table 2, entry 5).

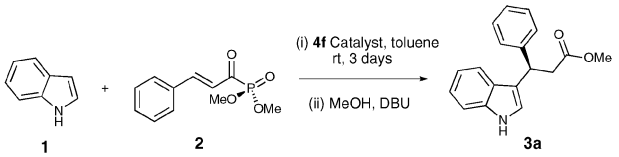
Table 1 Effect of the 3,3′-substituents of chiral phosphoric acid **4**[a]



Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**4a**	60	0
2	**4b**	62	20
3	**4c**	69	19
4	**4d**	62	30
5	**4e**	62	37
6	**4f**	73	92
7	**4g**	69	69
8	**4h**	75	43

[a] All the reactions were performed using **1** (0.10 mmol), **2** (0.11 mmol) and **4** (0.01 mmol) in solvent $c = 0.1$ M. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC.

Table 2 Effect of solvent and temperature[a]



Entry	T/°C	Solvent	**4f** (mol%)	Yield[b] (%)	ee[c] (%)
1	rt	THF	10	50	64
2	rt	CH_2Cl_2	10	46	82
3	rt	Benzene	10	54	89
4	rt	Mesitylene	10	50	88
5	rt	Toluene	10	73	92
6	rt	Toluene	5	61	86
7	−5	Toluene	10	50	92
8	−5	Toluene	5	31	90

[a] All the reactions were performed using **1** (0.10 mmol) and **2** (0.11 mmol) in solvent c = 0.1 M. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC.

Lowering the reaction temperature (Table 2, entries 7 and 8) and the catalyst loading (Table 2, entries 6 and 8) reduced the yield and did not improve the enantioselectivity.

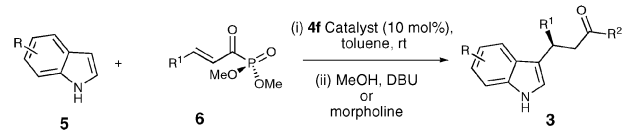
Experiments that probed the scope of the reaction of indoles having different substitution patterns with α,β-unsaturated acyl phosphonates catalyzed by chiral phosphoric acid **4f** revealed full conversion. The broad scope of the reaction is summarized in Table 3. Chiral phosphoric acid **4f** catalyst tolerates aromatic, heteroaromatic, and aliphatic substituents R^1 on the α,β-unsaturated acyl phosphonates. The ee values varied between 70% (entry 10) and 92% (entry 1); an exception is **3f**. The electron-withdrawing or -donating substituent at C(5) of the indoles is a competent substrate (entries 2–5 and 7). The 5-cyanoindole gave a corresponding adduct **3g** with good enantioselectivity (entry 7, 75% ee, 52% yield), although a long reaction time was necessary to obtain good yields. In terms of a product elaboration, amide **3h** was efficiently produced by treating the phosphonate adduct *in situ* with morpholine, and the ee was excellent (entry 7, 88% ee, 73% yield). On the other hand, 7-methylindole yielded **3f** with low ee (entry 9, 19% ee, 75% yield), presumably due to steric inhibition of the attendant Brønsted acid catalyst. It is noteworthy that the aromatic variation in the steric contribution of the olefin substituent R^1 can be accomplished with good results in contrast to previous reports.[5a,h]

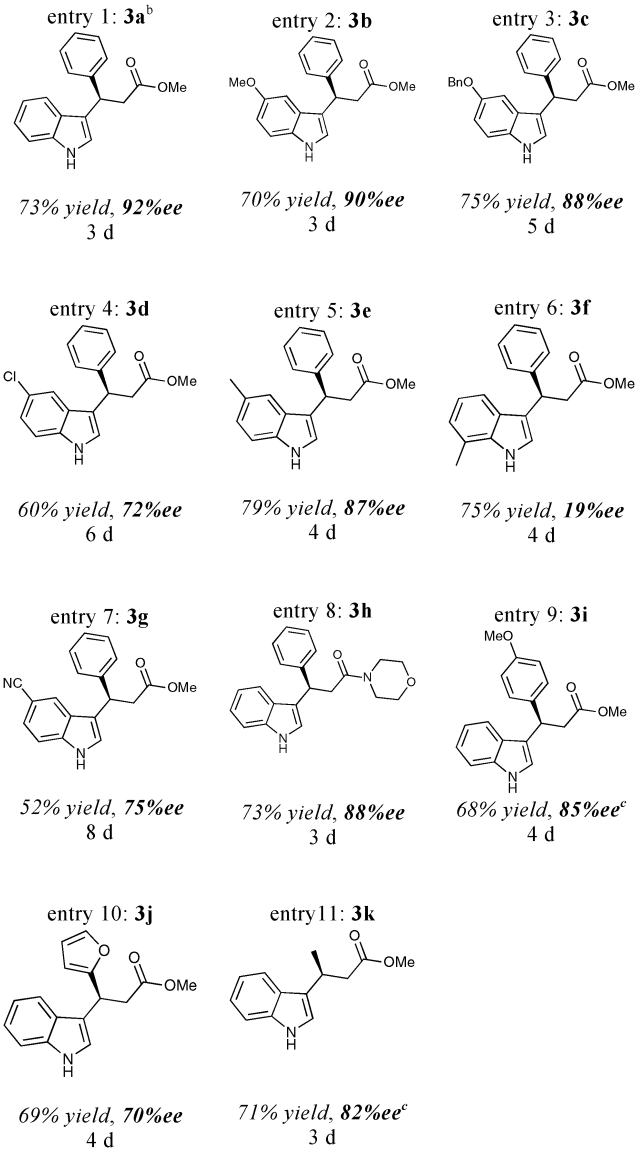
The absolute configurations of products **3** were correlated to the absolute configuration of **3k**, which was confirmed to be *S* by comparison with the literature.[10]

To rationalize the reaction mechanism, *N*-benzyl substituted indole was treated with α,β-unsaturated acyl phosphonate **2** under optimized conditions to afford the corresponding adduct in 5% yield with 0% ee. Thus, the presence of the N–H moiety of indole is essential to attain both high chemical yield and enantioselectivity. We assume that the phosphoric acid activates the carbonyl moiety and at the same time the phosphoryl oxygen atom forms a hydrogen bond with the hydrogen atom of the indole N–H moiety as previously proposed (Fig. 1).[9d,g]

In summary, chiral phosphoric acids are efficient catalysts for the Michael type Friedel–Crafts addition reaction of

Table 3 Results of the Friedel–Crafts alkylation reaction[a]





[a] All the reactions were performed using **5** (0.10 mmol), **6** (0.11 mmol) and **4f** (0.01 mmol), in solvent c = 0.1 M. [b] Isolated yields were obtained for all the compounds and enantiomeric excess was determined by chiral HPLC. [c] The reaction was carried out at −10 °C.

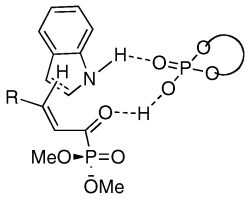


Fig. 1 Plausible transition state.

electron-rich indoles with α,β-unsaturated acyl phosphonates to generate adducts with excellent enantioselectivities and good yields at room temperature. The reaction was shown to be a general one for 5-substituted indoles and acyl phosphonates. Its application to the construction of the potentially bio-active natural products and their derivatives is under investigation.

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