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# Communications

## Asymmetric Organocatalytic Friedel-Crafts Alkylation–Cyclization Cascade Reaction of Indoles with *o*-Hydroxyaromatic α,β-Unsaturated Aldehydes

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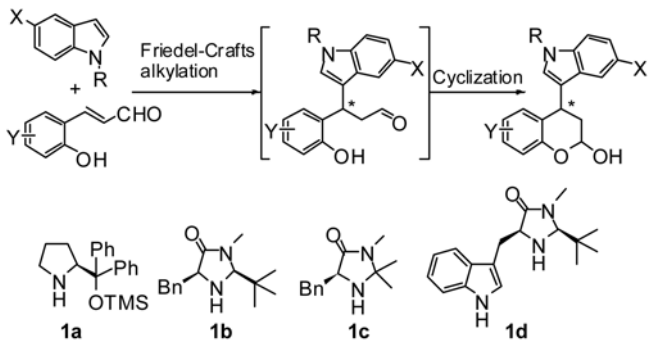
The indole molecular scaffold is the most widely distributed heterocycle found in nature.[1] In addition, substituted indoles are important in drug discovery because of their presence in numerous biologically active natural products and their high-affinity binding to many receptors.[2] Functionalization of indole rings is therefore an important branch of organic chemistry and various synthetic approaches have been reported.[3] Friedel-Crafts alkylation is one of the most powerful methods for the construction of substituted indole ring especially when applied to catalytic asymmetric transformations.[4] Nowadays, asymmetric organocatalysis has been new paradigm for the catalytic enantioselective Friedel-Crafts alkylation of indoles.[5]

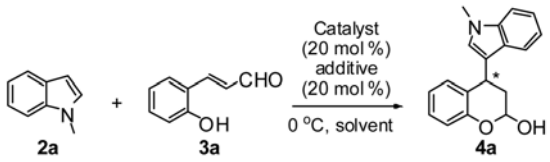
As part of our continuing interest in exploring the organocatalytic reaction using *o*-hydroxyaromatic α,β-unsaturated aldehydes as an electrophile,[6] we recently discovered that imidazolidinone organocatalysts are efficient for the Friedel-Crafts alkylation of indoles with *o*-hydroxyaromatic α,β-unsaturated aldehydes. During this reaction, the indole reacts through conjugate addition with *o*-hydroxyaromatic α,β-unsaturated aldehyde to give a chiral β-substituted aldehyde, which can be hemiacetalized to a chiral 4-substituted chroman-2-ol (Scheme 1). Here we report our preliminary results from this discovery. The obtained chroman-2-ol can easily be transform to chroman and derivatives that are ubiquitously found in numerous biologically active natural products. Molecules containing chroman scaffolds exhibit a broad range of biological functions, such as antiviral, antitumor, and antimicrobial activities.[7] Their importance has led to many methods being developed for their synthesis.[8]




**Scheme 1.** Organocatalytic Friedel-Crafts alkylation-cyclization cascade reactions of indoles with *o*-hydroxyaromatic α,β-unsaturated aldehydes.

We initially investigated the reaction of *N*-methylindole (**2a**) with *o*-hydroxycinnamaldehyde (**3a**) in the presence of readily available diphenylprolinol trimethylsilyl ether (**1a**, 20 mol %) in $CH_2Cl_2$ at 0 °C (Table 1).[9] However, the reaction did not produced corresponding chroman-2-ol **4a**, despite the starting material **3a** being completely disappeared (entry 1). Next, we examined MacMillan imidazolidinone catalysts,[10] which have been used in many Friedel-Crafts alkylations of α,β-unsaturated aldehydes, in this reaction. Imidazolidinone catalyst **1b** with $CF_3CO_2H$ additive pro-

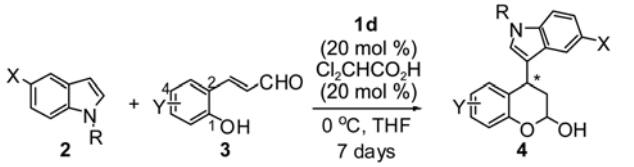
**Table 1.** Asymmetric Friedel-Crafts alkylation of *N*-methylindole (**2a**) with *o*-hydroxycinnamaldehyde (**3a**) by organocatalyst[a]




| Entry | Catalyst | Additive | Solvent | Time (h) | Yield (%)[b] | er[c] |
|---|---|---|---|---|---|---|
| 1 | **1a** | $PhCO_2H$ | $CH_2Cl_2$ | 48 | -[d] | - |
| 2 | **1b** | $CF_3CO_2H$ | $CH_2Cl_2$ | 24 | 35 | 51:49 |
| 3 | **1b** | $CF_3CO_2H$ | Toluene | 48 | 52 | 52:48 |
| 4 | **1b** | $CF_3CO_2H$ | $CH_3CN$ | 48 | 82 | 54:46 |
| 5 | **1c** | $CF_3CO_2H$ | $CH_3CN$ | 116 | 91 | 54:46 |
| 6 | **1b** | HCl | $CH_3CN$ | 48 | -[d] | - |
| 7 | **1c** | HCl | $CH_3CN$ | 48 | -[d] | - |
| 8 | **1d** | $CF_3CO_2H$ | $CH_3CN$ | 24 | 75 | 60:40 |
| 9 | **1d** | $CF_3CO_2H$ | EtOAc | 48 | 86 | 61:39 |
| 10 | **1d** | $CF_3CO_2H$ | THF | 36 | 82 | 63:37 |
| 11 | **1d** | $CF_3CO_2H$ | 1,4-Dioxane | 100 | 53 | 65:35 |
| 12 | **1d** | $CCl_3CO_2H$ | THF | 7 days | 70 | 70:30 |
| 13 | **1d** | $Cl_2CHCO_2H$ | THF | 7 days | 61 | 73:27 |

[a]Unless otherwise specified, the reaction was carried out in solvent (0.3 M) with 1.3 equiv of *N*-methylindole (**2a**) relative to the *o*-hydroxycinnamaldehyde (**3a**) in the presence of 20 mol % catalyst and additive. [b]Isolated yield after chromatographic purification. [c]Determined by HPLC using chiral column AD-H after oxidation. [d]The desired product was not obtained.

**Table 2.** Asymmetric organocatalytic Friedel-Crafts alkylation-cyclization reaction of *o*-hydroxyaromatic α,β-unsaturated aldehydes to representative indoles




**2** **3** **4**

| Entry | R | X | Y | Yield (%)[a] | er[b] | dr[c] |
|---|---|---|---|---|---|---|
| 1 | Me | H | H | 61 | 73:27 | 3:1 |
| 2 | allyl | H | H | 40 | 70:30 | 3:1 |
| 3 | Bn | H | H | 53 | 67:33 | 3:1 |
| 4[d] | H | H | H | 65 | 67:33 | 6:1 |
| 5 | Bn | OMe | H | 55 | 81:19 | 3:1 |
| 6 | Bn | OBn | H | 63 | 78:22 | 3:1 |
| 7 | Bn | H | 4-Me | 46 | 58:42 | 4:1 |
| 8 | Bn | H | 4-OMe | 32 | 61:39 | 3:1 |
| 9 | Bn | H | 5-OMe | 36 | 63:37 | 3:1 |
| 10 | Bn | H | 4-Cl | 69 | 71:29 | 4:1 |
| 11 | Bn | H | 4-Br | 60 | 69:31 | 4:1 |
| 12 | Bn | H | 4-$NO_2$ | 85 | 74:26 | 5:1 |

[a]Isolated yield after chromatographic purification. [b]Determined by HPLC using chiral column AD-H after oxidation. [c]Determined by 1H NMR analysis. [d]TFA was used as additive.

duced the corresponding chroman-2-ol **4a** in moderate yield with poor level of enantioselectivity (entry 2). This result led to other imidazolidinone catalysts, acid additives and solvents being tested to improve the reactivity and enantioselectivity. The tryptophan-derived imidazolidinone catalyst **1d** showed increased reactivity and enantioselectivity (entry 8).

After the reaction conditions were optimized, we found that the superior level of enantioselectivity and yield were obtained using catalyst **1d** (20 mol %) in THF at 0 °C with $Cl_2CHCO_2H$ (20 mol %) (61% yield, 73:27 er, entry 13).

Having established the optimal reaction conditions, we next investigated the scope of this asymmetric catalytic reaction (Table 2). Variation of the indoles' *N*-substituents (R=Me, allyl, Bn, H, entries 1-4) was shown to be possible, though with moderate yields and enantioselectivity. Incorporation of electron-donating substituent (X=OMe, OBn) at the C(5)-indole position increased enantioselectivity (81:19 er and 78:22 er, entries 5 and 6, respectively). This reaction was also compatible with a variety of *o*-hydroxyaromatic α,β-unsaturated aldehydes **3**; moderate to good yields and enantioselectivities observed in all tested cases (Table 2). In particular, 4-nitro-substituted *o*-hydroxyaromatic α,β-unsaturated aldehyde afforded a chroman-2-ol product in the best yield and with the highest regioselectivity (85% yield, 74:26 er, 5:1 dr, entry 12).

In summary, an asymmetric organocatalytic Friedel-Craft alkylation-cyclization cascade reaction of indoles with *o*-hydroxyaromatic α,β-unsaturated aldehydes was developed to produce chiral 4-substituted chroman-2-ols in moderate to good yields with up to 81:19 er. A variety of chroman derivatives can be readily obtained through the subsequent transformation of these products having the biologically useful molecular scaffolds of indole and chroman.[6,11] Further study of this reaction's applicability with other substrates to facilitate the preparation of more biologically relevant compounds is underway.

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