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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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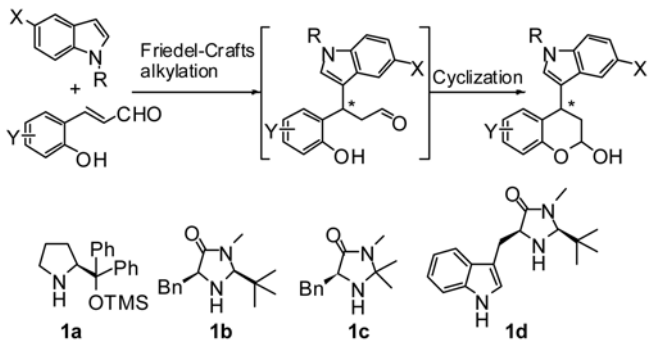
The indole molecular scaffold is the most widely distributed heterocycle found in nature.[1] In addition, substituted indoles are important in drug discovery because of their presence in numerous biologically active natural products and their high-affinity binding to many receptors.[2] Functionalization 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]

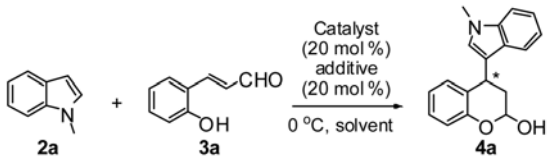
As part of our continuing interest in exploring the organocatalytic reaction using *o*-hydroxyaromatic α,β-unsaturated aldehydes as an electrophile,[6] we recently discovered that imidazolidinone organocatalysts are efficient for the Friedel-Crafts alkylation of indoles with *o*-hydroxyaromatic α,β-unsaturated 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-

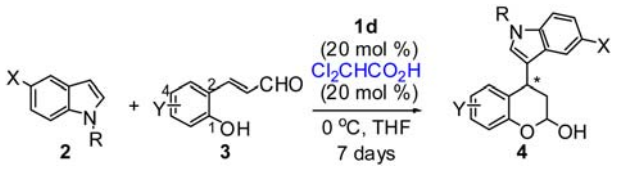
Table 1. Asymmetric Friedel-Crafts alkylation of *N*-methylindole (**2a**) with *o*-hydroxycinnamaldehyde (**3a**) by organocatalyst[a]



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**	$ClCHCO_2H$	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



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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