Organocatalytic C3-selective Friedel–Crafts alkylations of indoles with α,β-unsaturated ketones†

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The use of an equimolar amount of pyrrolidine and $HClO_4$ (30 mol%) was found to be effective in promoting the conjugate addition of indoles to (*E*)-α,β-unsaturated ketones, affording the corresponding β-indolyl ketones in excellent yields.

The indole framework represents important structural units frequently found in natural products, pharmaceuticals, and other synthetics.[1] The preparation of polyfunctional indoles is therefore an important research field. Indole serves as an ambient nucleophile, and selective targeting of C–H bonds in the presence of a reactive N–H functionality represents a challenging goal. The selective alkylation at C-2 or C-3 position will be complementary to the known N-alkylation methodology[2] and holds significant synthetic potential. In particular, regioselective Friedel–Crafts alkylation at the 3-position of indoles represents one of the most straightforward methods for the synthesis of many naturally occurring alkaloids.[3] The elegant method for the synthesis of 3-alkylated indoles involves the conjugate addition of indoles to α,β-unsaturated compounds in the presence of protic acids,[4] Lewis acids,[5] transition-metal catalysts[6] or molecular iodine.[7] However, many of these methods involve strong acidic conditions, expensive reagents, complex handling, and low yields of products. Thus, it was necessary to develop an alternate synthetic procedure.

Recently, MacMillan[8] and King[9] have published new methods to generate a variety of 3-(indol-3-yl)propionaldehydes and 2-(indol-3-yl)cyclopentanecarbaldehydes, respectively, based on MacMillan's LUMO-lowering activation of α,β-unsaturated aldehydes using the imidazolidinone catalyst. In this communication, we extend this organocatalytic strategy to the activation of α,β-unsaturated ketones using an equimolar amount of pyrrolidine and $HClO_4$ as the catalytic system. In this context, we document the first organocatalytic C3-selective Friedel–Crafts alkylations of indoles with simple ketone electrophiles, resulting in β-indolyl-ketones in high yields.

In a preliminary experiment, treatment of indole (**1a**) with 5-methyl-3-hexen-2-one (**2a**) in the presence of pyrrolidine (30 mol%) and *p*-TsOH (30 mol%) in CH_2Cl_2 at an ambient temperature for 5 days afforded the 3-substituted indole adduct **3a** in 14% isolated yield. Encouraged by this result, we then examined the variation in the reaction conditions (Table 1).

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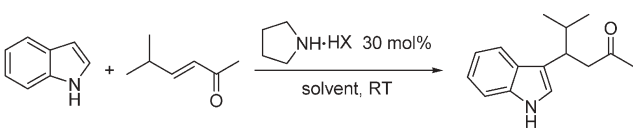
As revealed in Table 1, both co-catalyst and solvent have a dramatic influence on the reaction efficiency. It was found that a number of pyrrolidine acid salts were found to catalyze the formation of 4-(3-indolyl)-5-methyl-2-hexanone (entries 1–5, Table 1), while the $HClO_4$ salt is most effective in dichloromethane at room temperature (entry 5, Table 1). A survey of solvents showed that dichloromethane was more efficient than other solvents such as MeOH, $CHCl_3$, toluene and THF (entries 5–10, Table 1). The superior level of the reaction efficiency exhibited by pyrrolidine-$HClO_4$ salt in dichloromethane prompted us to select this catalytic system and solvent for further exploration.

The scope of the organocatalytic Friedel–Crafts alkylation of various indoles with α,β-unsaturated ketones has been investigated and the results are summarized in Table 2.

The reaction appears quite general with respect to the indole structure (entries 1–4 in Table 2, 83–92% yield). Incorporation of methyl substituent at the C(2)-indole position reveals that electronic and steric modification of the indole ring can be accomplished with little influence on the reaction yields (entries 5 and 6 in Table 2); however, as revealed in entry 7, the reaction of 1,2-dimethylindole took several days to go completion with moderate yield. Structural variation in α,β-unsaturated ketones can also be realized. There appears to be significant latitude in the steric demands of the β-olefin substituent (entries 4, 8, and 9 in Table 2) to enable access to a broad variety of 4,4′-disubstituted butan-2-ones. The reactions were clean and the products were

Table 1 Effect of co-catalyst and solvent on the Friedel–Crafts alkylation of indole **1a** with 5-methyl-3-hexene-2-one **2a**[a]

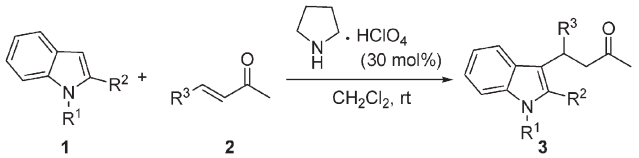


1a **2a** **3a**

Entry	Solvent	HX-co-catalyst	Time	Yield (%)[b]
1	CH_2Cl_2	TFA	5 day	14
2	CH_2Cl_2	$Cl_2CHCOOH$	5 day	33
3	CH_2Cl_2	HCl	4 day	40
4	CH_2Cl_2	*p*–TsOH	10 h	90
5	CH_2Cl_2	$HClO_4$	6 h	92
6	CH_3OH	$HClO_4$	7 h	89
7	$CHCl_3$	$HClO_4$	50 h	82
8	toluene	$HClO_4$	30 h	85
9	THF	$HClO_4$	15 h	88
10	$CHCl_3$–^{i}PrOH[c]	$HClO_4$	72 h	65

[a] All reactions were carried out in the wet solvent using 30 mol% of pyrrolidine and 30 mol% of co-catalyst. [b] Isolated yield. [c] A mixture of $CHCl_3$/^{i}PrOH (85 : 15 V/V) was used.

Table 2 Organocatalytic Friedel–Crafts alkylation of indole with α,β-enones[a]



1 2 3

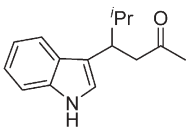
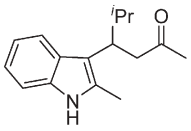
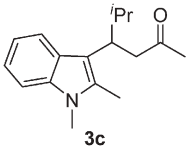
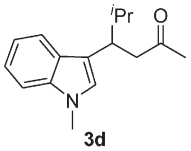
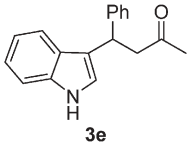
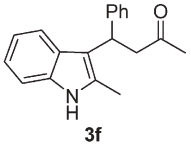
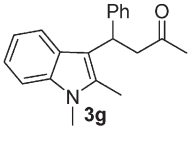
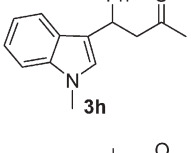
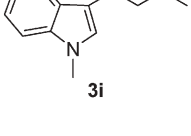
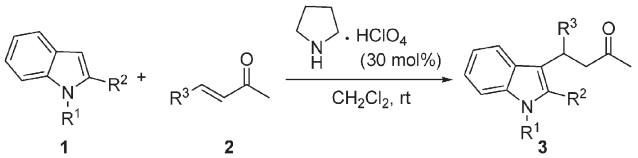
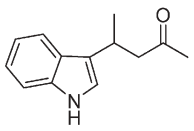
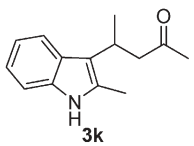
Entry	1	2	Time	3	Yield (%)[b]
1	**1a** R^1 = H, R^2 = H	**2a** R^3 = ^{i}Pr	6 h	 **3a**	92
2	**1b** R^1 = H, R^2 = Me	**2a** R^3 = ^{i}Pr	10 h	 **3b**	90
3	**1c** R^1 = Me, R^2 = Me	**2a** R^3 = ^{i}Pr	15 h	 **3c**	87
4	**1d** R^1 = Me, R^2 = H	**2a** R^3 = ^{i}Pr	20 h	 **3d**	83
5	**1a** R^1 = H, R^2 = H	**2b** R^3 = Ph	12 h	 **3e**	80
6	**1b** R^1 = H, R^2 = Me	**2b** R^3 = Ph	18 h	 **3f**	87
7	**1c** R^1 = Me, R^2 = Me	**2b** R^3 = Ph	4 days	 **3g**	69
8	**1d** R^1 = Me, R^2 = H	**2b** R^3 = Ph	2 days	 **3h**	79
9	**1d** R^1 = Me, R^2 = H	**2c** R^3 = Me	15 h	 **3i**	90

Table 2 Organocatalytic Friedel–Crafts alkylation of indole with α,β-enones[a] (*Continued*)



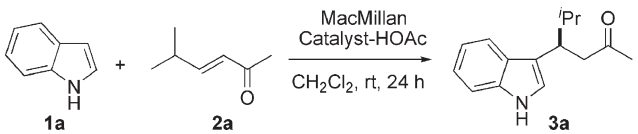
1 2 3

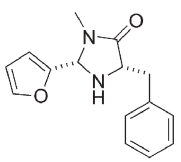
Entry	1	2	Time	3	Yield (%)[b]
10	**1a** R^1 = H, R^2 = H	**2c** R^3 = Me	10 h	 **3j**	82
11	**1d** R^1 = Me, R^2 = H	**2c** R^3 = Me	14 h	 **3k**	89

[a] All reactions were carried out using 1 equiv. of indole, 3 equiv. of α,β-enone in the presence pyrrolidine (30 mol%) and $HClO_4$ (30 mol%) in 1.0 ml of CH_2Cl_2 at room temperature. [b] Isolated yield after column chromatography.

obtained in high yields without the formation of any side products such as dimers or trimers, which are normally observed under the influence of strong acids. Remarkably, no *N*-alkylation or C2-alkylation products were detected at all. This result provided a strong contrast to similar reactions under palladium catalysis, where N- or C2-alkylation was sometimes predominant.[10] Furthermore, it is noteworthy that all of the reactions described in this study were performed under an aerobic atmosphere, using wet solvents and a readily available bench-stable catalyst, highlighting the operation advantages of this methodology.

An initial attempt to carry out the organocatalytic asymmetric version of this reaction has also been examined. The MacMillan second generation organocatalyst **4**, originally developed for enantioselective Diels–Alder reaction of unsaturated ketones,[11] was employed in the reaction of indole and **2a** (Scheme 1). The reaction gave promising results with 52% isolated yield and 28% ee.





4
MacMillan Organocatalyst

Scheme 1

In conclsion, we have demonstrated that pyrrolidine-$HClO_4$ salt is an efficient catalyst for the C3-selective Friedel–Crafts alkylation of indoles with α,β-enones. The development of asymmetric variants for these reactions is now in progress in this laboratory.

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