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Al(OTf)$_3$-catalyzed S$_N$2′ substitution of the β-hydroxy group in Morita–Baylis–Hillman adducts with indoles

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ABSTRACT

The Al(OTf)$_3$-catalyzed S$_N$2′-type substitution of the β-hydroxy group in Morita–Baylis–Hillman adducts with indoles is reported. The reaction proceeded efficiently with aryl-, heteroaryl-, aliphatic- and alicyclic-containing β-hydroxyketones and a variety of substituted indoles.

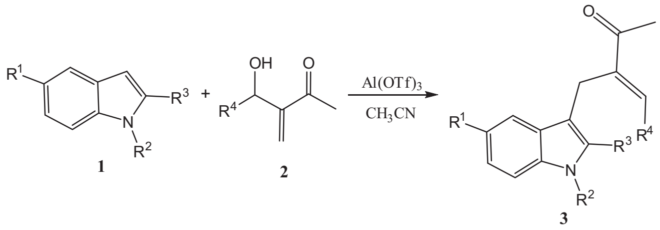
Indoles constitute a class of intensely studied heterocycles, members of which serve as potential scaffolds for many alkaloids and pharmaceutically important substances.[1,2] A plethora of methods are available for the preparation of diversely functionalized indoles,[3] especially 3-substituted indoles due to their significant biological activities.[4] 3-Substituted indoles are also important building blocks in the synthesis of various biologically active molecules.[5] Consequently, there is continued interest in the development of improved methods for the synthesis of 3-substituted indoles.

In our recent literature survey on the preparation of 3-substituted indoles, it was found that several reports described the direct nucleophilic substitution of the hydroxy group in propargylic, allylic, and benzylic alcohols with indoles,[6] but only a few methods have so far appeared for the preparation of the same skeleton based on an S$_N$2′ substitution approach.[7,8]

Very recently, Yao and co-workers[7b,8] disclosed an S$_N$2′ nucleophilic substitution reaction between hydroxyketones **2** derived from the Morita–Baylis–Hillman reaction (MBH) and indole **1**, in order to prepare diversely functionalized C3-alkylated indole derivatives. The products from these reactions were utilized to prepare important molecules of biological significance, but catalyst loadings were very high, that is, 30% of I$_2$, while the reactions also required prolonged reaction times. Moreover, a lack of versatility with regard to the functional groups on both the alcohols and indoles was observed. Thus, efficient and high yielding methods for the S$_N$2′ substitution of the hydroxy group in Baylis–Hillman (BH)[9] derived ketones with indoles in order to prepare interesting C-3 alkylated indoles are still required.

Despite being more affordable, and taking into consideration its unique Lewis acidity and stability in various solvents and in the presence of moisture,[10] Al(OTf)$_3$ has not been explored as extensively as other metal triflates.[11] Therefore, in continuation of our ongoing research[12] on developing efficient methodologies by applying Al(OTf)$_3$ as the catalyst, we herein disclose that Al(OTf)$_3$ can be used as an efficient catalyst for the S$_N$2′-type nucleophilic substitution of the hydroxy group in BH derived β-hydroxyketones to prepare interesting and diverse functionalized C3-substituted indoles (Scheme 1).

For optimization of the reaction conditions, initial experiments were carried out between indole **1** (R^1, R^2, R^3 = H) and the



Scheme 1. S$_N$2′-type substitution of the β-hydroxy group in Morita–Baylis–Hillman adducts with indoles. R^1 = H, Cl, OMe; R^2 = H, Me; R^3 = H, Me, Ph; R^4 = H, aryl, heteroaryl, benzyl, aliphatic alkyl, cycloalkyl.

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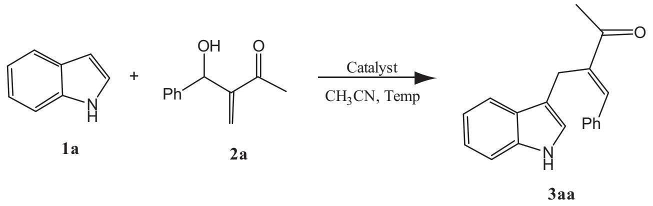
Table 1

Evaluation of Brønsted and Lewis acid catalysts and optimization of the $Al(OTf)_3$ conditions for the alkylation of indole **1a** with hydroxyketone **2a**



Entry	Catalyst (mol %)	Temp (°C)	Time (h)	Yield (%)[a]
1	PTSA (5)	80	1.5	66[b]
2	TfOH (5)	80	1.5	65[b]
3	$FeCl_3$ (5)	80	3	70
4	$Sc(OTf)_3$ (5)	80	1.5	88
5	$Yb(OTf)_3$ (5)	80	1.5	83
6	$Cu(OTf)_2$ (5)	80	1.5	85
7	$Al(OTf)_3$ (5)	80	1.5	89
8	$Al(OTf)_3$ (5)	rt	12	86
9	*p*-TsOH (2.5)	80	2	75
10	$Sc(OTf)_3$ (2.5)	80	2	80[c]
11	$Cu(OTf)_2$ (2.5)	80	2	70[c]
12	$Al(OTf)_3$ (2.5)	80	2	80
13	$Al(OTf)_3$ (2.5)	70	2	94
14	$Al(OTf)_3$ (1)	70	2.2	94
15	$Al(OTf)_3$ (0.5)	70	2.2	80[c]
16	–	70	24	–

[a] Isolated yield of **3aa** after column chromatography.

[b] Impurities were observed, probably due to side reactions.

[c] Starting material was not completely consumed as observed by TLC [EtOAc-hexane (2:8)] and GC–MS analysis.

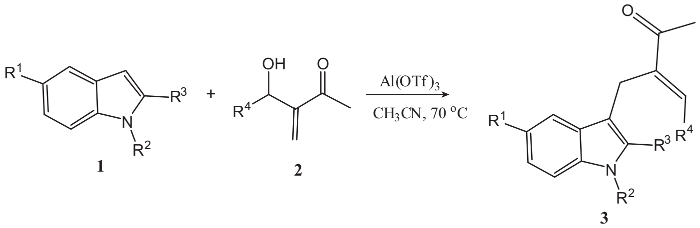
unsaturated β-hydroxyketone **2** (R^4 = Ph) in various solvents such as EtOH, THF, CH_2Cl_2, CH_3CN, etc., with $Al(OTf)_3$ (5 mol %). Acetonitrile (CH_3CN) was found to be the solvent of choice in terms of conversion and duration of the reaction. Although the reaction proceeded slowly at room temperature (12 h), the rate increased significantly at 80 °C and an excellent yield (89%) of the corresponding product **3** was obtained in a short period of time (ca. 1.5 h). Although the reaction also proceeded under solventless conditions, unexpected impurities that had a negative impact on the yield (as monitored by TLC and GC–MS) were found.

In order to evaluate the catalytic activity of various acid catalysts commonly used in direct nucleophilic substitution reactions,[6] triflic acid (TfOH), *p*-toluenesulfonic acid (*p*-TsOH), $FeCl_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, and $Cu(OTf)_2$, were also tested in the substitution of the hydroxy function in β-hydroxyketone **2a** (R^4 = Ph) with indole **1a** (Table 1). While it was found that the $Al(OTf)_3$-catalyzed reactions proceeded well even at concentrations as low as 1 mol % (entry 14), 2.5 mol % or higher catalyst concentrations were required for completion of the reactions with the other catalysts tested (entries 1–6 and 9–11). Moreover, most of the other catalysts gave yields that were considerably lower than those obtained with $Al(OTf)_3$, probably due to decomposition of the product, the acid-sensitive hydroxyketone **2**, or side reactions during the course of the reaction. Decreasing the $Al(OTf)_3$ catalyst concentration from 5 to 0.5 mol % led to extended reaction times, which also had a negative effect on the yields (entries 7 and 12–15). As expected, no reaction was observed in the absence of any catalyst (entry 16). It was therefore decided to study this reaction using 1 mol % of $Al(OTf)_3$ in CH_3CN at 70 °C.

To investigate the scope and general applicability of the reaction, indoles with electron-withdrawing (**1c**, Table 2, entry 3) and electron-donating groups (**1b**, Table 2, entry 2) on the benzene ring were reacted with β-hydroxyketone **2a** to give the desired 3-substituted indole products (**3ca** and **3ba**, respectively). The reaction of *N*-methyl- (**1d**), 2-methyl- (**1e**), and 1,2-dimethyl- (**1f**) substituted indoles with β-hydroxyketone **2a** were successful and led to the expected 3-substituted indoles in excellent yields

Table 2

Reactions between indoles **1** and β-hydroxyketones **2**



Entry	Indole	R^1	R^2	R^3	Hydroxyketone	R^4	Time (min)[a]	Product[b]	Yield (%)[c]
1	**1a**	H	H	H	**2a**	Ph	140	**3aa**[7b]	93
2	**1b**	OMe	H	H	**2a**	Ph	130	**3ba**	90
3	**1c**	Cl	H	H	**2a**	Ph	150	**3ca**	92
4	**1d**	H	Me	H	**2a**	Ph	100	**3da**	93
5	**1e**	H	H	Me	**2a**	Ph	90	**3ea**	93
6	**1f**	H	Me	Me	**2a**	Ph	120	**3fa**	92
7	**1g**	H	H	Ph	**2a**	Ph	130	**3ga**	90
8	**1a**	H	H	H	**2b**	$4-ClC_6H_4$	120	**3ab**	93
9	**1a**	H	H	H	**2c**	$4-MeOC_6H_4$	140	**3ac**	70
10	**1a**	H	H	H	**2d**	$4-O_2NC_6H_4$	130	**3ad**	92
11	**1a**	H	H	H	**2e**	2-thienyl	150	**3ae**	94
12	**1a**	H	H	H	**2f**	2-furyl	160	**3af**	78
13	**1a**	H	H	H	**2g**	CH_2Ph	90	**3ag**	85
14	**1a**	H	H	H	**2h**	Me	90	**3ah**	78
15	**1a**	H	H	H	**2i**	*n*-Pr	120	**3ai**	75
16	**1a**	H	H	H	**2j**	$c-C_6H_{11}$	110	**3aj**	90
17	**1a**	H	H	H	**2k**	H	120	**3ak1**[14]+**3ak2**[13]	40+50[d]

[a] Time needed for complete consumption of **1** as determined by TLC and GC–MS analysis.

[b] Literature references to known compounds are provided.

[c] Isolated yield.

[d] Bisindolyl ketone **3ak2**.