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$BF_3{\cdot}Et_2O$ catalyzed allylation of oxindoles with allyl trichloroacetimidate

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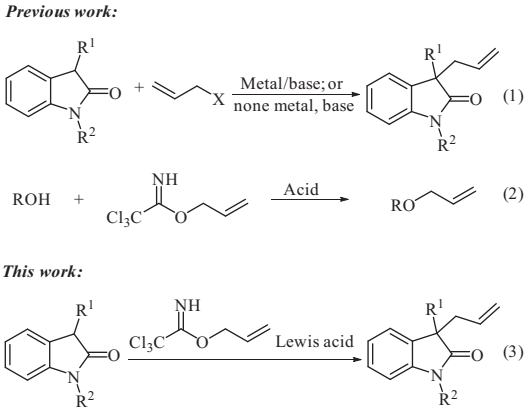
ABSTRACT

An efficient Lewis acid catalyzed allylation of 3-substituted oxindoles has been developed for the first time using allyl trichloroacetimidate as an electrophile under mild reaction conditions.

The 3,3′-disubstituted oxindole derivatives are structural motifs often found in a number of alkaloid natural products and pharmaceutically active compounds.[1,2] Therefore, many remarkable endevours have been made to develop general and efficient methods for the preparation of this structural motif.[3–9] Typically, synthesis of an all-carbon quaternary center at the C-3 of oxindole is attractive owing to its manifold bioactive properties and as the intermediate for the synthesis of other indole ring systems. To date, transition-metal-catalyzed allylic alkylation of 3-substituted oxindole has been shown to be the most efficient and synthetic useful method for the construction of quaternary carbon centers (Scheme 1, Eq. 1).[3,5] For example, Trost and co-workers developed Pd, Mo-catalyzed allylic alkylation of 3-substituted oxindoles.[6] On the other hand, organocatalytic allylic alkylation of 3-substituted oxindole has also been reported.[8,10] For example, Ooi and co-workers developed 1,2,3-triazoliums as cationic organic catalysts to realize asymmetric alkylation of 3-substituted oxindoles.[10] However, most of these reactions are performed under basic conditions.[3–11] Here we report the first Lewis acid catalyzed allylic alkylation of 3-substituted oxindoles by using allyl trichloroacetimidate as the electrophile (Scheme 1, Eq. 3).

Allyl trichloroacetimidate has been widely used as a convenient reagent for the O-allylation of hydroxyl groups under acidic conditions in oligosaccharide and natural products synthesis (Scheme 1, Eq. 2),[12] which is compatible with ester, imide, and acetal protecting groups. However, studies on the construction of C-allylation using this reagent are rare.[13] Inspired by the O-allylation reactions,[12] we envisage that a relative stable allylic carbocation ion intermediate may be generated from allyl trichloroacetimidate under acidic conditions, which may be captured by 3-substituted oxindoles to form a new carbon–carbon bond, leading to 3,3′-disubstituted oxindole derivatives bearing an allyl group.

To test this hypothesis, an acid catalyzed reaction of 1-methyl-3-benzylindolin-one (**1a**) with allyl trichloroacetimidate (**2**) was



Scheme 1. Allylation of oxindoles and alcohols.

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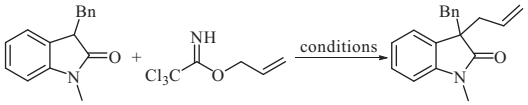
0040-4039/

Table 1
Optimization of the reaction conditions[a]



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

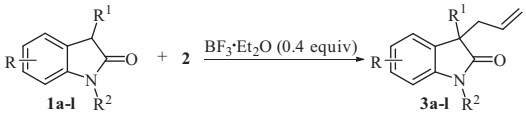
Entry	**2** (equiv)	Acid (equiv)	Solvent	Yield[b] (%)
1	1.2	CF_3CO_2H (0.4)	DCM	3
2	1.2	CF_3SO_3H (0.4)	DCM	7
3	1.2	$BF_3{\cdot}Et_2O$ (0.4)	DCM	30
4	1.2	$AlCl_3$(0.4)	DCM	—
5	1.2	$Cu(CF_3SO_2)_2$ (0.4)	DCM	Trace
6	1.2	$BF_3{\cdot}Et_2O$ (0.4)	THF	—
7	1.2	$BF_3{\cdot}Et_2O$ (0.4)	Toluene	4
8	1.2	$BF_3{\cdot}Et_2O$ (0.4)	ACN	Trace
9[c]	1.2	$BF_3{\cdot}Et_2O$ (0.4)	DCM	31
10	2.0	$BF_3{\cdot}Et_2O$ (0.4)	DCM	58
11	3.0	$BF_3{\cdot}Et_2O$ (0.4)	DCM	61
12	2.0	$BF_3{\cdot}Et_2O$ (0.8)	DCM	57
13	2.0	$BF_3{\cdot}Et_2O$ (0.2)	DCM	44
14[d]	1.0 * 2	$BF_3{\cdot}Et_2O$ (0.4)	DCM	63
15[d]	1.0 * 3	$BF_3{\cdot}Et_2O$ (0.4)	DCM	75
16[d]	0.5 * 6	$BF_3{\cdot}Et_2O$ (0.4)	DCM	80

[a] Reactions were carried out with **1a** (0.20 mmol), catalyst and **2** in solvent (1.0 mL) at room temperature for 36 h.
[b] Isolated yield.
[c] Reaction time is 115 h.
[d] Compound **2** was added portionwise over a 5 h interval.

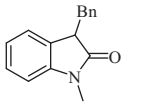
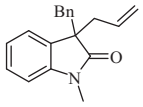
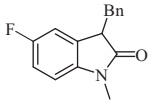
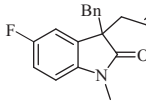
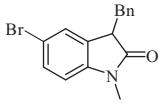
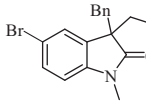
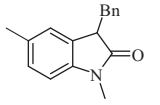
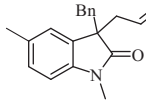
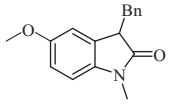
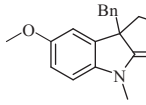
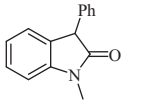
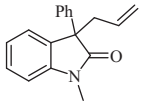
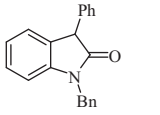
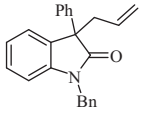
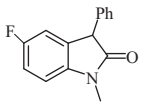
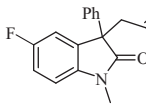
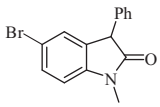
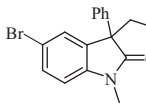
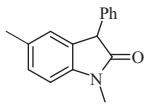
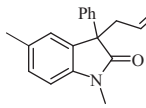
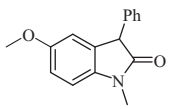
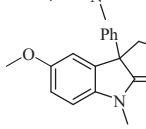
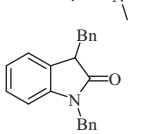
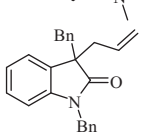
examined (Table 1). As expected, the desired 3-allyl-3-benzyl-1-methylindolin-2-one (**3a**) was obtained. Treatment of **1a** with **2** in the presence of 0.4 equiv of trifluoromethanesulfonic acid in CH_2Cl_2 at room temperature gave **3a** in 7% yield (Table 1, entry 2). A variety of Lewis acids were evaluated in the model reaction (Table 1, entries 1–5), and $BF_3{\cdot}OEt_2$ was found to give the desired **3a** in 30% yield (Table 1, entry 3). Other Brønsted acids (H_3PO_4, H_2SO_4) and Lewis acids ($SnCl_4$, $FeCl_3$, $ZnCl_2$) all resulted in only a trace amount of product. Other solvents such as toluene, THF, and acetonitrile diminished the reaction clearly (Table 1, entries 6–8). Notably, the starting material **1a** was always recovered during the process. So the reaction time was prolonged, however, similar results were obtained (Table 1, entry 9). To our delight, the yields were clearly increased when 2.0 equiv of **2** was employed (Table 1, entry 10). The reason may be ascribed to the corresponding allylic carbocation intermediate being unstable. Indeed, using a large excess of **2** resulted in a higher yield (Table 1, entries 10, 11 vs entry 3). In contrast, no improvement was achieved by changing the catalyst amount (Table 1, entry 12 vs entry 10). Further optimization of the reaction conditions revealed that addition of 3.0 equiv of **2** by 6 times dramatically enhanced the yield to 80% (Table 1, entry 16).

Having identified the optimized conditions, we next examined this new method in a range of substrates with different substitution patterns. The results are summarized in Table 2. Overall, a variety of 3-allyl-3′-substituted oxindole derivatives were successfully prepared, and various substituents on the aromatic ring were found to be tolerable in this process. Substrates with electron-deficient or electron-rich substitutions at the aromatic ring offered good yields (Table 2, entries 2–5), indicating that the electron effect plays little role in this reaction. Reaction of 1,3-dimethylindolin-2-one with **2** under the optimal conditions gave the desired product in only 24% yield. It seemed that the reaction started from an acid catalyzed enolization of oxindole at 3-position, thus a 3-aryl substituted group will be beneficial to such a ketone-enol equilibrium through π–π conjugation. Then 3-phenyl substituted oxindole substrates were prepared and subjected to this reaction.

Table 2
Substrate scope of allylation of 3-substituted oxindoles[a]

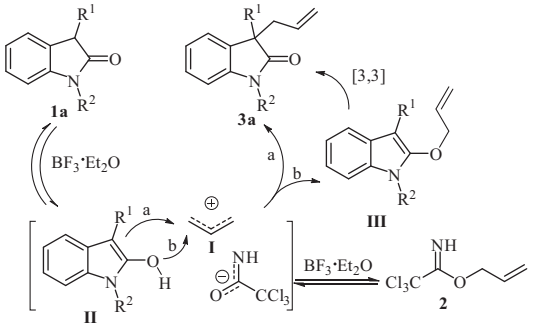


1a-l **3a-l**

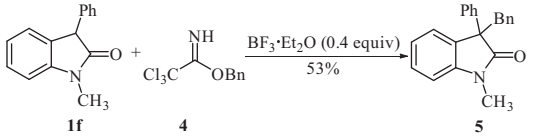
Entry	Substrate	**1**	Product	**3**	Yield[b] (%)
1		**1a**		**3a**	81[c]
2		**1b**		**3b**	78
3		**1c**		**3c**	75
4		**1d**		**3d**	74
5		**1e**		**3e**	76
6		**1f**		**3f**	93
7		**1g**		**3g**	89
8		**1h**		**3h**	90
9		**1i**		**3i**	87
10		**1j**		**3j**	85
11		**1k**		**3k**	86
12		**1l**		**3l**	73

[a] Reactions were carried out with **1a–l** (0.20 mmol), $BF_3{\cdot}Et_2O$ (0.08 mmol, 0.4 equiv) and **2** (0.60 mmol, 3.0 equiv) in DCM (1.0 mL) at room temperature for 36 h.
[b] Isolated yield.
[c] 2.0 mmol scale.

Generally, the desired 3-allylation oxindole products were obtained with higher yields than those of 3-benzyl substituted oxindole substrates (Table 2, entries 6–11 vs entries 1–5). Similar to a previous observation, electron-deficient or electron-rich substituted 3-phenyl oxindole substrates all gave the desired ally-



Scheme 2. Proposed mechanism.



Scheme 3. Benzylation of **1f**.

lation products with excellent yields. Notably, the steric size of the *N*-protecting group does not seem to be important as benzyl (**1g**) and gave essentially identical results as methyl (**1f**). Other *N*-protecting groups such as Ts and Boc gave no positive results, only complex mixtures were observed. Substrates with the free NH group resulted in the desired product in low yield (30% for 3-phenylindolin-2-one). Additionally, crotylation of **1a** by using (*E*)-2-butenyl trichloroacetimidate has also been attempted, ^{1}H NMR revealed the presence of a mixture of products maybe including regio- and diastereoisomers,[14] while cinnamylation of **1a** by using cinnamyl trichloroacetimidate resulted in no desired product. Finally, the reaction was readily scalable without losing any efficiency (Table 2, entry 1).

The proposed mechanism is shown in Scheme 2. Imidate **2** was transformed to the allylic carbocation intermediate **I** with the assistance of $BF_3{\cdot}Et_2O$; at the same time, $BF_3{\cdot}Et_2O$ catalyzed enolization of **1a** to give enol **II**. Next nucleophilic attack of **I** by enol **II** through a pathway followed by deprotonation with trichloroacetimidate ion to generate C-allylation product **3a**. On the other hand, this reaction may follow the other possible pathway (Scheme 2, pathway b): O-allylation of **II** to give **III**, followed by [3,3]-Claisen rearrangement promoted by $BF_3{\cdot}Et_2O$ to give the desired product **3a**. To further probe the mechanism, benzylation of **1f** with benzyl trichloroacetimidate (**4**) under the optimal conditions was attempted. Interestingly, the desired product **5** was obtained in 53% yield (Scheme 3), suggesting the reaction mechanism may follow our proposal that involves a direct C-allylation.

In summary, we have developed an efficient allylation of 3-substituted oxindoles with allyl trichloroacetimidate catalyzed by $BF_3{\cdot}Et_2O$ for the first time. This method allows for the facile synthesis of 3-allyl-3′-substituted oxindoles which are fundamental units of many pharmaceutically important molecules. Further investigation to extend the scope of this acid catalyzed allylation reaction, and to develop new applications is underway.

Acknowledgments

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Supplementary data

Supplementary data (experiment details, copies of ^{1}H and ^{13}C NMR spectra for products. This material is available free of charge via the Internet at doi.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.155. These data include MOL files and InChiKeys of the most important compounds described in this article.

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