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$B(C_6F_5)_3$-Catalysed Alkylation of Imidazo[1,2-*a*]pyridines Using α,β-Unsaturated Ketones

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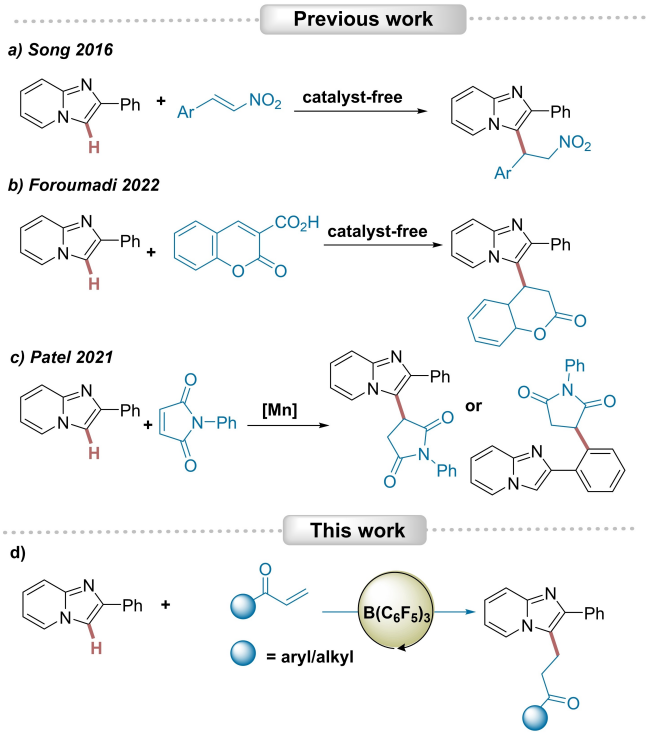
Fluorinated triarylboranes have shown a breadth of reactivity as catalysts for organic transformations, particularly in carbon-carbon bond forming reactions. Herein we report a facile, metal-free synthetic route for the addition of 2-phenylimidazo[1,2-*a*]pyridines to α,β-unsaturated ketones using $B(C_6F_5)_3$ as a metal-free catalyst. 25 examples of reactions leading to products in up to 97% yield are reported. DFT studies show the role of $B(C_6F_5)_3$ and hydrogen shuttling in the mechanism of this Michael alkylation.

Introduction

Among nitrogen-containing fused heterocyclic compounds, the imidazo[1,2-*a*]pyridine unit is an essential moiety contained in a wide range of pharmaceuticals, natural products, agrochemicals, and optical materials.[1–9] The functionalisation of imidazo[1,2-*a*]pyridines at the C3-position is an important transformation in synthetic chemistry leading to products with diverse biological properties including antiviral activity,[10,11] enzyme inhibition,[12] and anticancer activity.[13] The development of efficient methods for C3-functionalisation has gained interest in the synthetic organic community covering alkylation,[14–16] arylation,[17] carbonylation,[18] sulfenylation,[19] selenenylation,[20] phosphonation,[21] and halogenation reactions.[22] The direct alkylation at the C3 position using Michael acceptors has attracted much interest. There are a few examples in the literature of the conjugate addition to imidazo[1,2-*a*]pyridines. In 2016, Song *et al.* reported a catalyst-free alkylation using β-nitrostyrenes (Scheme 1a).[23] Carbon–carbon bond formation between imidazo[1,2-*a*]pyridines and coumarin carboxylic acid has been achieved through a catalyst-free decarboxylative Michael addition (Scheme 1b).[24] Besides the catalyst-free conjugate addition, Patel *et al.* reported the transition-metal catalysed reaction with maleimide using a manganese catalyst (Scheme 1c).[25] However, the alkylation of imidazo[1,2-*a*]pyridines using α,β-unsaturated ketones remains a challenge.



Scheme 1. Previous work on Michael reactions of imidazo[1,2-a]pyridines (a–c) and the work presented herein (d).

The strongly Lewis acidic borane, tris(pentafluorophenyl)borane $[B(C_6F_5)_3]$, can efficiently activate α,β-unsaturated carbonyl compounds through coordination of the Lewis basic carbonyl group to the boron centre, facilitating the conjugate addition by a nucleophile.[26] For example, Werner and co-workers reported the $B(C_6F_5)_3$-catalysed Michael addition of dialkyl aniline derivatives and indoles to α,β-unsaturated carbonyl compounds.[26e] Ooi *et al.* have reported that similar

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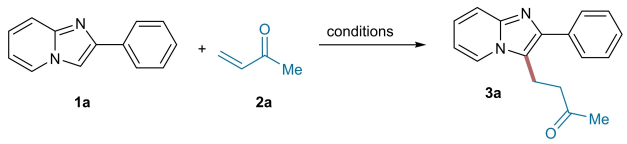
reactions can be achieved *via* a radical pathway in the presence of light where $B(C_6F_5)_3$ acts as a single-electron redox catalyst. In the presence of *N*,*N*-dialkylanilines, an α-aminomethyl radical is formed which then adds to the unsaturated ketone.[27] Herein, we investigate the catalytic behaviour of $B(C_6F_5)_3$ as an effective metal-free catalyst to achieve the conjugate addition of α,β-unsaturated ketones to 2-phenylimidazo[1,2-*a*]pyridines (Scheme 1d).

Results and Discussion

We initially optimised the reaction conditions using 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and commercially available methyl vinyl ketone (**2a**) as model substrates (Table 1). In the absence of any catalyst (Table 1, entry 1), the desired product (**3a**) was obtained in only 15% yield (at 80 °C for 24 h, in toluene). Using 5 mol% of $B(C_6F_5)_3$ as a catalyst improved the yield to 57% (Table 1, entry 2). Based on this result, the catalytic loading was increased to 10 mol% and 15 mol% (Table 1, entries 3 and 4), showing an improvement in the product yields to 79% and 95%, respectively. We then explored the feasibility of the reaction using different fluorinated triaryl boranes. $B(3,4,5\text{-}C_6H_2F_3)_3$ afforded the desired product in 79% yield (Table 1, entry 5), while employing the slightly less Lewis acidic borane $B(2,4,6\text{-}C_6H_2F_3)_3$ showed a lower yield of 64% (Table 1, entry 6). In contrast, the commercially available triphenylborane (BPh_3) gave a significantly reduced yield of 23% (Table 1, entry 7). The highly Lewis acidic boron trihalides $BF_3{\bullet}OEt_2$ and BCl_3 were also investigated, but neither of them was found to be an effective catalyst giving just 19% and 15% yields, respectively (Table 1, entries 8 and 9). Using $B(C_6F_5)_3$ as the catalyst, variation of solvent, temperature and reaction time did not afford better results (Table 1, entries 10–15). Reaction with trifluoroacetic acid as Bronsted acid gave poor result (Table 1, entry 16).

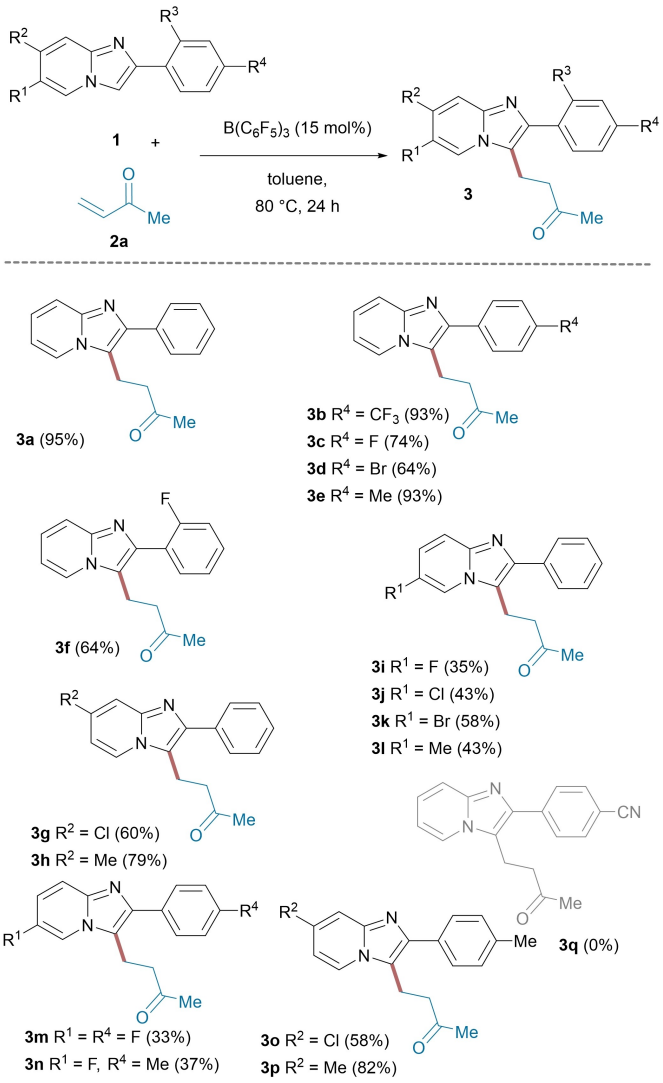
Using the optimised conditions, the substrate scope with different 2-phenylimidazo[1,2-*a*]pyridines and methyl vinyl ketone (**2a**) was explored (Scheme 2). First, we surveyed the scope of imidazo[1,2-*a*]pyridines **1** with a series of substituents

Table 1. Optimisation results for the Michael addition of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) to methyl vinyl ketone (**2a**).



entry	Catalyst [15 mol %]	Solvent	Temp [°C]	Time [h]	Yield [%][a]
1	–	toluene	80	24	15
2	$B(C_6F_5)_3$[b]	toluene	80	24	57
3	$B(C_6F_5)_3$[c]	toluene	80	24	79
4	$B(C_6F_5)_3$	toluene	80	24	95
5	$B(3,4,5\text{-}C_6H_2F_3)_3$	toluene	80	24	79
6	$B(2,4,6\text{-}C_6H_2F_3)_3$	toluene	80	24	64
7	BPh_3	toluene	80	24	23
8	$BF_3{\bullet}OEt_2$	toluene	80	24	19
9	BCl_3	toluene	80	24	15
10	$B(C_6F_5)_3$	α,α,α-trifluorotoluene (TFT)	80	24	87
11	$B(C_6F_5)_3$	1,2-dichloroethane	80	24	76
12	$B(C_6F_5)_3$	CH_2Cl_2	40	24	23
13	$B(C_6F_5)_3$	toluene	80	20	83
14	$B(C_6F_5)_3$	toluene	80	16	72
15	$B(C_6F_5)_3$	toluene	70	16	77
16	TFA	toluene	70	16	15

All the reactions were carried out on a 0.1 mmol scale using 3 equivalents of methyl vinyl ketone (**2a**). [a] isolated yields. [b] 5 mol% catalyst loading. [c] 10 mol% catalyst loading.



Scheme 2. Scope of imidazo[1,2-*a*]pyridines. Reactions were carried out on a 0.1 mmol scale using 3 equivalents of methyl vinyl ketone.

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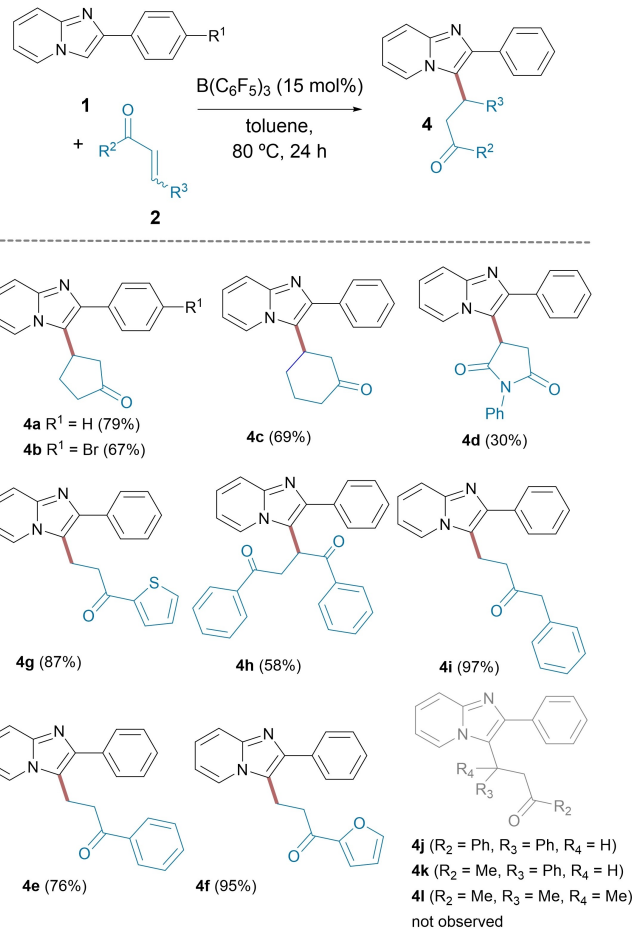
on the phenyl ring, 4-CF_3 (**1b**), 4-F (**1c**), 4-Br (**1d**), 4-Me (**1e**). All substrates led to the formation of the C3-alkylated product in good to excellent yields (**3b–e**, up to 93%). 2-Phenylimidazo[1,2-*a*]pyridines bearing an *ortho*-substituted fluorine atom (**1f**) also afforded the product in good yield (**3f**, 64%). Next, we investigated the effect of the substituent on the imidazopyridine framework. The 2-phenylimidazo[1,2-*a*]pyridines bearing an electron-withdrawing substituent (Cl) and a methyl group at the C7 position (**1g** and **1h**) also underwent the Michael addition yielding **3g** and **3h** in 60% and 79% yields, respectively. Functional groups at the C6 position (**1i–l**) led to less efficient reactions affording the products in lower yields (**3i–l**).

When functionalised 2-phenylimidazo[1,2-*a*]pyridines were employed (**1m** and **1n**), the yield of the corresponding products was not improved (**3m** and **3n**: 33% and 37%, respectively). With a methyl group at both C7 and the *para*-position of the phenyl ring (**1p**), the expected product **3p** was formed in high yield (82%), while replacing the methyl group at the C7 position with a halogen substituent (**1o**) decreased the yield to 58% (**3o**). Crystals of products **3g** and **3m** suitable for X-ray diffraction analysis could be obtained from evaporation of the solvent from a saturated solution of the compounds in CH_2Cl_2 (Figure 1). Electron-withdrawing CN substituent on the phenyl ring of 2-phenylimidazo[1,2-a]pyridines did not produce the desired product **3q**. This might be due to the withdrawal effect of -CN group which did not help to proceed with the product formation.

Encouraged by the applicability of this methodology, we also investigated the scope of α,β-unsaturated ketones (Scheme 3). The cyclic ketones, 2-cyclopentenone (**2b**) and 2-cyclohexenone (**2c**), provided the corresponding products in good yields (67–79%, **4a–c**). *N*-Phenyl maleimide (**2d**) was also used but provided the C3-alkylated product **4d** in low yield (30%). In addition to the cyclic ketones, unsaturated ketones bearing a phenyl (**2e**), furane (**2f**), or thiophene (**2g**) substituent were also compatible under the reaction conditions (**4e–g**, yields up to 95%). Reaction with (*E*)-1,4-diphenylbut-2-ene-1,4-dione also gave the expected product in moderate yield (**4h**, 58%). Unsaturated ketones bearing a benzyl group (**2i**) afforded the desired product in excellent yield (**4i**, 97%). Unfortunately, the reaction with unsaturated ketones having substituents at the β-position failed to afford the alkylated products **4j–4l** which might be due to to the restricted nucleophilic attack caused by steric bulk originating from methyl and phenyl groups.



Scheme 3. Scope of α,β-unsaturated ketones. Reactions carried out on a 0.1 mmol scale using 3 equivalents of α,β-unsaturated ketone **2**.

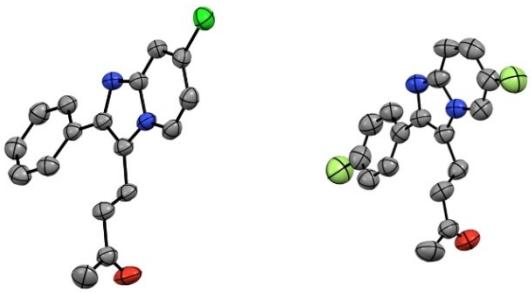


Figure 1. Solid-state crystal structures of compound **3g** (left, CCDC = 2294604) and **3m** (right, CCDC = 2294605). Thermal ellipsoids drawn at 50% probability. H atoms are omitted for clarity. Carbon: grey; oxygen: red; nitrogen: blue; chlorine: dark green; fluorine; light green.

To understand how the Lewis acid $B(C_6F_5)_3$ catalyses the alkylation of imidazo[1,2-*a*]pyridine **1a** using α,β-unsaturated ketone **2a**, we conducted density functional theory (DFT) calculations in toluene using the SMD/M06-2X-D3/def2-TZVP//SMD/M06-2X/6-31G(d) level of theory (Figures 2a and 2b). According to our calculations, the reaction begins with the coordination of the borane catalyst to the α,β-unsaturated ketone **2a**, forming the adduct **2a·B(C_6F_5)$_3$**. This coordination activates the π-bond in **2a**, facilitating the C–C coupling reaction to generate intermediate **int1** *via* transition state **TS1**, which has an energy barrier of 12.7 kcal mol^{-1}. Our calculations reveal that the hydrogen transfer mechanism for the formation of the final product **3a** is not feasible due to the high energy barrier of 34.5 kcal mol^{-1} at transition state **TS2′**. However, with the assistance of an additional **2a** molecule, hydrogen transfer in two steps (deprotonation of C^a and protonation of C^b) becomes favourable through the transition state **TS2**, leading to the formation of **int2** with an energy barrier of 25.8 kcal mol^{-1}. According to our computational results, the deprotonation of C^a

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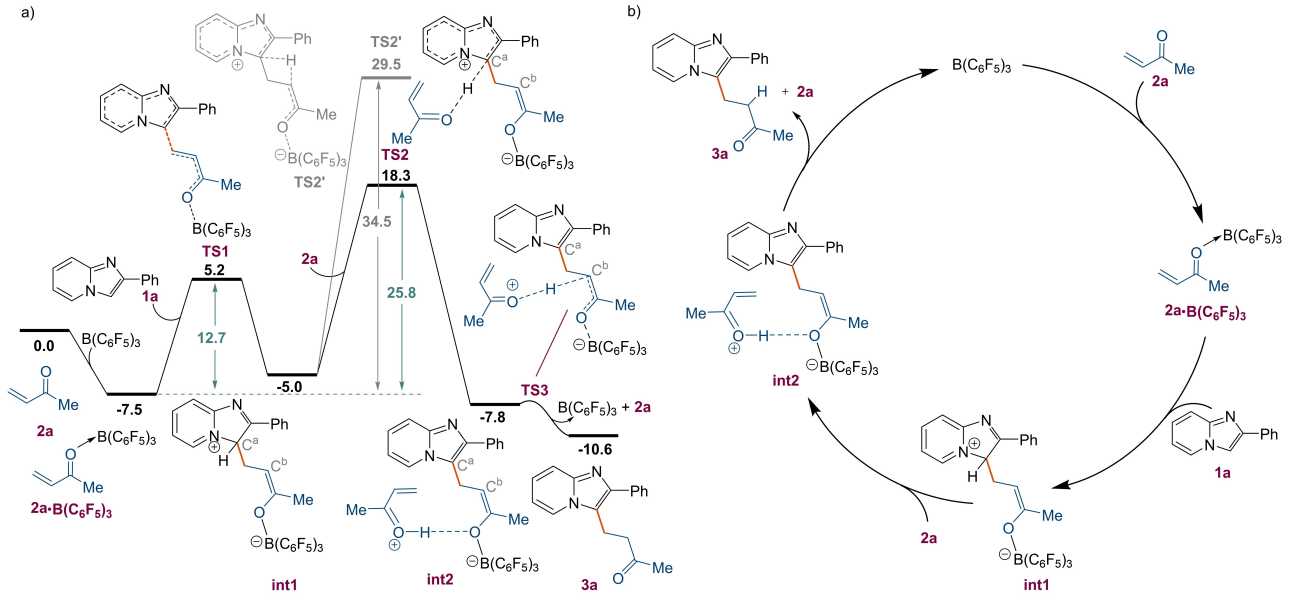

Figure 2. a) DFT calculated reaction pathways for the formation of **3 a** from the borane catalysed reaction of imidazo[1,2-*a*]pyridine **1 a** using α,β-unsaturated ketone **2 a** in toluene using SMD/M06-2X-D3/def2-TZVP//SMD/M06-2X/6-31G(d) level of theory. The relative free energies are given in kcal mol^{-1}. b) Proposed reaction mechanism.

is predicted to be the rate determining step. The relatively high barrier elucidates the experimental requirement for an elevated temperature (80 °C) to facilitate the reaction. Once the intermediate **int2** has formed, C^b will be protonated by formed ylidene-oxonium intermolecularly in a barrierless way, leading to the formation of product **3 a** and regeneration of catalyst in an exergonic fashion. The barrierless nature of the C^b protonation *via* ylidene-oxonium is confirmed by relaxed Potential Energy Surface (PES) scan (see supporting information, Figure ESI1).

According to our experimental results (Table 1), the use of excess ketone **2 a** can be justified by recognising its vital role in the hydrogen transfer process, which explains the experimental observation that the reaction does not progress when only one equivalent of ketone **2 a** is used.

Additionally, we performed DFT calculations to examine this reaction in the absence of the borane catalyst. Here, the energy barrier required for the first step of the uncatalysed reaction is 35.3 kcal mol^{-1}, suggesting that the presence of the borane catalyst is essential for this reaction to occur (see supporting information, Figure ESI2).

Conclusions

In summary, we have shown that $B(C_6F_5)_3$ is a highly effective catalyst for the C3-alkylation of 2-phenylimidazo[1,2-*a*]pyridines using α,β-unsaturated ketones as Michael acceptors. A variety of substrates were investigated giving the C3-alkylated products in good to high yield (25 examples, up to 95 % yield). This work adds to the series of transformations that can be catalysed by the strong Lewis acid $B(C_6F_5)_3$. Further applications of this Lewis acid are ongoing in our group.

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Conflict of Interests

There are no conflicts to declare.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: $B(C_6F_5)_3$ catalysis · alkylation · 2-phenylimidazo[1,2-*a*]pyridine · methyl vinyl ketone

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