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$B(C_6F_5)_3$-catalyzed Markovnikov addition of indoles to aryl alkynes: an approach toward bis(indolyl)alkanes†

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The first example of the metal- and solvent-free $B(C_6F_5)_3$-catalyzed Markovnikov addition of indoles to aryl alkynes was disclosed. Both *N*–H and *N*-protected indoles were tolerated, leading to a wide spectrum of versatile bis(indolyl)alkanes in moderate to good yields with high regioselectivities.

Introduction

The development of practical methodologies for the preparation of bis(indolyl)alkanes is an important issue in organic synthesis, owing to the prevalence of these derivatives as core structures in a wide range of biologically interesting natural products and pharmaceuticals (Fig. 1).[1] Among a myriad of methods to produce these structures,[2] the catalytic dihydroindolation of alkynes is the most efficient way to synthesize bis(indolyl)alkanes because this method does not require prefunctionalization of the reaction partners and exhibits high atom economy. To date, various metal-based catalysts, such as Pt,[3] Au,[4] Hg,[5] Re,[6] In,[7] and Ru,[8] have been reported for dihydroindolation reactions between *N*-protected indoles and alkynes in solutions (Scheme 1a), while a few of them could be applied in this kind of reaction employing *N*–H indoles as substrates (Scheme 1b).[9] In contrast, metal-free catalytic dihydroindolation has remained an unexplored field. With regard to the influences of trace metals on the efficiency of organic electronic devices and human consumption products as well as the costs associated with removing residual catalysts, the development of metal-free catalytic protocols for the efficient synthesis of bis(indolyl)alkanes is of great interest and importance.

Tris(pentafluorophenyl)-borane, as one component of FLPs,[10] has received much attention as metal-free alternatives to transition metal catalysis for the activation of small molecules and related transformations.[11] Alkynes are a class of important small molecules, considered as versatile building blocks, widely used in organic chemistry, materials science and pharmaceuticals.[12] The first example of $B(C_6F_5)_3$-promoted activation of alkynes was first achieved by Stephan's group, allowing the synthesis of alkynylborane or alkynylaluminium derivatives.[13] Following this fundamental work, numerous efforts have been devoted to reactions where stoichiometric $B(C_6F_5)_3$ activated alkynes toward cyclization to form heterocyclic and aromatic compounds.[14] Recently, the catalytic protocols of activation of alkynes have also been investigated, such as polymerization,[15] hydroamination,[16] cycloisomerization,[17] hydrofunctionalization,[18] oxoalkylation[19] and other transformations.[20] In general, as a strong π-Lewis acid, $B(C_6F_5)_3$ can activate the alkynes *via* π-coordination to the C–C triple bond. Accordingly, our design is to employ $B(C_6F_5)_3$ as a π-Lewis acid activating terminal alkynes to facilitate the double Markovnikov addition of indoles. Herein, we describe the first example of metal-free $B(C_6F_5)_3$-catalyzed dihydroindolation of aryl alkynes through double Markovnikov addition under solvent-free conditions, providing easy access to versatile bis(indolyl)alkanes (Scheme 1c).

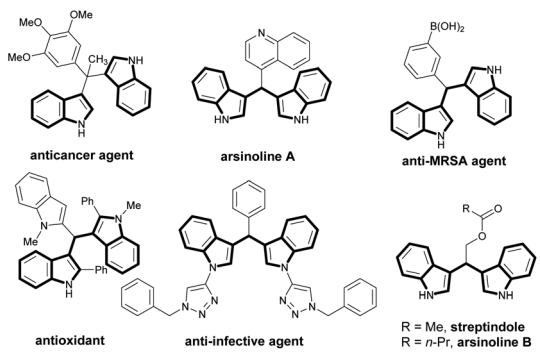

Fig. 1 Biological compounds containing a bis(indolyl)alkane core.

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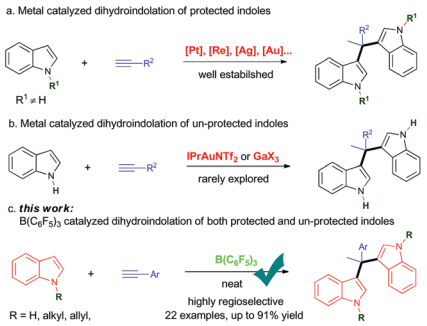


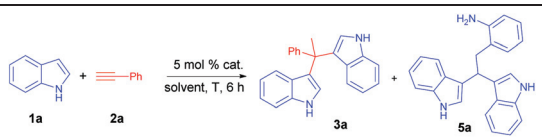
Scheme 1 Catalytic systems for dihydroindolation of alkynes.

Results and discussion

The initial assay was carried out by reacting 1*H*-indole (**1a**, 1 mmol) and ethynylbenzene (**2a**, 2 mmol) with 5 mol% of $B(C_6F_5)_3$ as a catalyst in toluene at 60 °C for 6 h (Table 1, entry 1). Pleasingly, the desired bis(indolyl)alkane **3a** was isolated in 78% yield. However, switching $B(C_6F_5)_3$ to Brønsted acid or less acidic boron acid failed to give the desired product (Table 1, entries 2 and 3). Next, a set of solvents were examined; while THF and *n*-hexane were capable of producing **3a** in 62% and 15% yields, along with the formation of the by-product **5a** in 10% and 23% yields, respectively, no product was obtained when using DCE or DMF as the solvent (Table 1, entries 4–7). Delightfully, **1a** reacted with **2a** smoothly under solvent-free conditions, delivering **3a** in 85% yield (Table 1, entry 8). Changing the reaction temperature did not improve the product yield (Table 1, entries 9 and 10). Moreover, decreasing the catalyst loading from 5 mol% to 1 mol% resulted in a reduced yield (Table 1, entry 11). It was noteworthy that the ratio of **1a** and **2a** is crucial for achieving a high yield; the reaction yield was sharply decreased to 35%, and the by-product **5a** was obtained in 54% yield when using 1.0 mmol of **2a**, while increasing the ratio from 1 : 2 to 1 : 4 had little influence on the yield (Table 1, entries 8, 12 and 13). In contrast, no product or by-product was observed in the absence of $B(C_6F_5)_3$ (Table 1, entry 14). Notably, this protocol could be easily conducted on a gram scale, producing **3a** in 1.36 g, 81% yield (Table 1, entry 15).

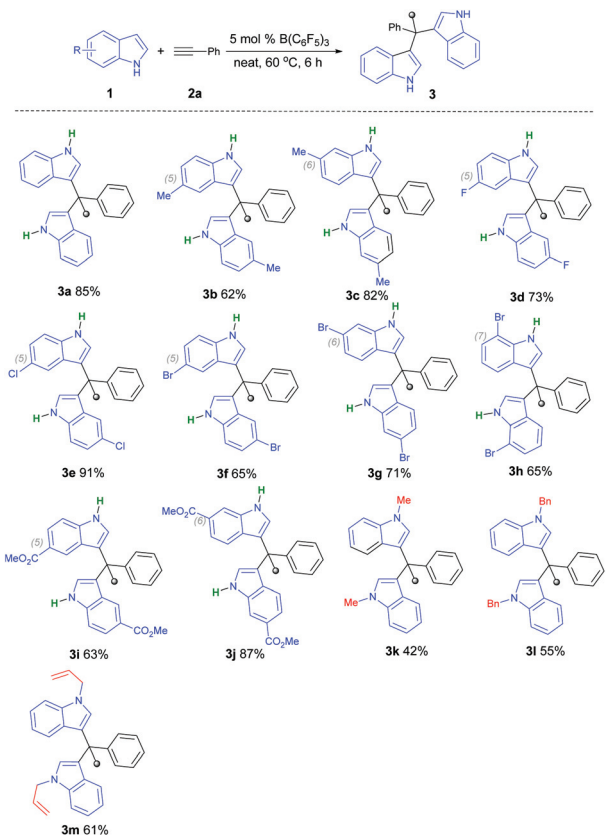
With the optimal conditions in hand, we set out to probe its versatility in the dihydroindolation of indoles and alkynes. The scope of this reaction was first explored with a range of indoles **1** with ethynylbenzene (**2a**) and the results are shown in Scheme 2. Both the electron-donating (–Me) and electron-withdrawing groups (–F, –Cl, –Br, and $–CO_2Me$) at the C4–C7 positions of the indole substrate reacted with ethynylbenzene smoothly to give the desired products in moderate to good yields. The substitution pattern had an influence on the reaction yield; 6-position-substituted indoles afforded the corresponding products (**3c**, **3g** and **3j**) in relatively higher yields than those bearing a substituent on the 5- or 7-position (**3b**, **3f**, **3h** and **3i**). In addition, the halogen groups were well

Table 1 Optimization of reaction conditions[a]



Entry	Cat.	Solvent	T (°C)	Yield (%) **3a**/**5a**
1	$B(C_6F_5)_3$	Toluene	60	78/trace
2	CF_3CO_2H	Toluene	60	—
3	$(2,6\text{-}F_2C_6H_3)_3B$	Toluene	60	Trace
4	$B(C_6F_5)_3$	THF	60	62/10
5	$B(C_6F_5)_3$	*n*-Hexane	60	15/23
6	$B(C_6F_5)_3$	DCE	60	—
7	$B(C_6F_5)_3$	DMF	60	—
8	$\mathbf{B(C_6F_5)_3}$	**Neat**	**60**	**85/trace**
9	$B(C_6F_5)_3$	Neat	80	71/trace
10	$B(C_6F_5)_3$	Neat	40	62/trace
11[b]	$B(C_6F_5)_3$	Neat	60	43/trace
12[c]	$B(C_6F_5)_3$	Neat	60	35/54
13[d]	$B(C_6F_5)_3$	Neat	60	80/trace
14	—	Neat	60	0/0
15[e]	$B(C_6F_5)_3$	Neat	60	81/trace

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), and catalyst (5 mol%) in solvent (2 mL) for 6 h under air. [b] With 1 mol% of $B(C_6F_5)_3$. [c] With **2a** (1.0 mmol). [d] With **2a** (4.0 mmol). [e] Gram-scale experiment with 10 mol of **1a**.

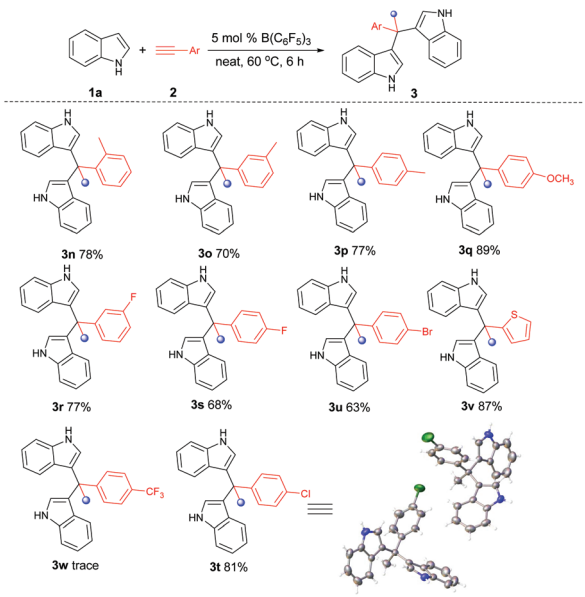


Scheme 2 Substrate scope of indoles **1**.

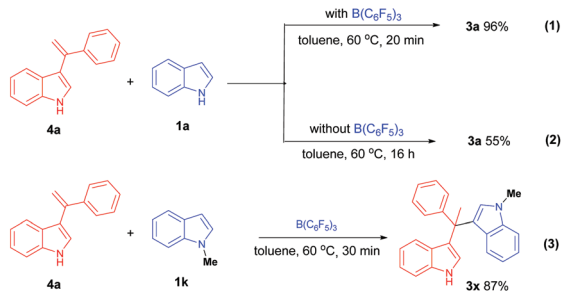
tolerated to produce the corresponding products **3d–3h** in 65–91% yield. Importantly, the *N*-methyl indole reacted with **2a** smoothly to give the desired product **3k** in 42% yield. Notably, the *N*-protected indoles were also compatible with this reaction, affording the expected products **3l** and **3m** in 55% and 61% yields, respectively.

Next, the scope of this reaction was examined with a range of aryl alkynes **2** with 1*H*-indole (Scheme 3). The substitution pattern of aryl moieties had a slight effect in this reaction; for the electron-donating group, *meta*-substituted alkyne gave a lower yield than those with *ortho*- and *para*-substituents (**3o** *vs.* **3n** and **3p**), while an opposite result was observed when using fluoro-substituted alkynes (**3r**, 77% yield *vs.* **3s**, 68% yield). Moreover, the best result was obtained when using 1-ethynyl-4-methoxybenzene as a substrate, producing **3q** in 89% yield. In addition, this process was compatible with Br and Cl, leading to the desired products **3u** and **3t** in moderate to good yields. Notably, the structure of **3t** was unambiguously determined by single-crystal X-ray analysis. Remarkably, the thienyl group still reacted with **1a** efficiently to yield the targeted product **3v** in 87% yield. Unfortunately, a strong electron-withdrawing aryl alkyne was unable to deliver the expected product **3w**.

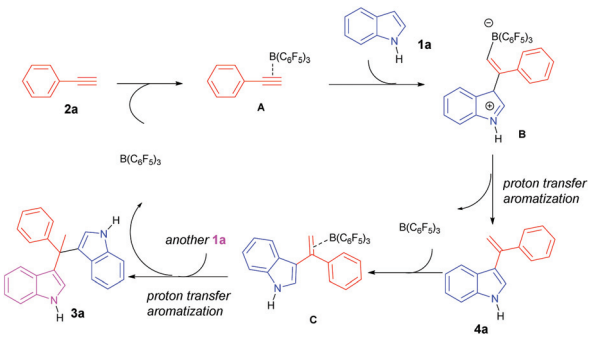
In order to get an insight into the reaction mechanism, several control experiments were conducted (Scheme 4). Initially, we synthesized 3-(1-phenylvinyl)-1*H*-indole (**4a**),[21] which is a key intermediate according to the previous literature. Reacting **4a** with 1*H*-indole (**1a**) and $B(C_6F_5)_3$ in toluene at 60 °C for 20 min resulted in the full conversion of **4a** to give **3a** in 96% yield (Scheme 4, eqn (1)). However, without $B(C_6F_5)_3$ as a catalyst, the reaction became inefficient and only 55% yield of **3a** was obtained after 16 h (Scheme 4, eqn (2)). These results indicated that 3-(1-phenylvinyl)-1*H*-indole (**4a**)



Scheme 3 Substrate scope of alkynes **2**.



Scheme 4 Control experiments.



Scheme 5 Proposed mechanism.

might be involved in this process and $B(C_6F_5)_3$ could promote the second hydroindolation of **4a** and **1a**. Interestingly, 3-(1-phenylvinyl)-1*H*-indole reacted with 1-methyl-1*H*-indole (**1k**) smoothly to give unsymmetrical bis(indolyl)alkane **3x** in 87% yield (Scheme 4, eqn (3)).

Based on the control experiments and the previous work on $B(C_6F_5)_3$-catalyzed activation of alkynes,[14–20] a proposed mechanism for this dihydroindolation is described in Scheme 5 using 1*H*-indole (**1a**) and ethynylbenzene (**2a**) as template substrates. Coordination of $B(C_6F_5)_3$ with alkyne **2a** affords intermediate **A**. Subsequent nucleophilic attack of **1a** on the internal carbon of the C–C triple bond results in the zwitterionic boron derivative **B**, which undergoes protodeborylation[15,16] and aromatization to yield the intermediate 3-(1-phenylvinyl)-1*H*-indole (**4a**) with concomitant regeneration of the borane catalyst. Next, $B(C_6F_5)_3$ further coordinates with **4a** to afford intermediate **C**, which is attacked by another **1a** to produce the final Markovnikov product **3a** along with the release of $B(C_6F_5)_3$.

Conclusions

In conclusion, the first metal-/solvent-free procedure for the intermolecular Markovnikov addition of indoles to aryl alkynes was successfully developed *via* $B(C_6F_5)_3$ catalysis. This protocol was compatible with both *N*–H indoles and *N*-protected indoles, thus providing a wide spectrum of versatile bis(indolyl)alkanes with excellent selectivity.

Experimental section

General information

All commercial materials were used as received unless otherwise noted. Commercially available chemicals were obtained from Energy Chemical, TCI, Alfa Aesar, and J&K. ^{1}H NMR spectra were recorded at 400 MHz and 600 MHz using TMS as an internal standard, and ^{13}C NMR spectra were recorded at 100 MHz, 125 MHz and 150 MHz using TMS as an internal standard. The multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), multiplet (m), triplet (t) and broad resonances (br). The mass spectroscopy data of the products were collected on an HRMS-TOF instrument.

General procedure for the synthesis of 3. A mixture of 1*H*-indole (**1a**, 117.0 mg, 1.0 mmol), ethynylbenzene (**2a**, 204.2 mg, 2.0 mmol) and $B(C_6F_5)_3$ (25.6 mg, 0.05 mmol) was heated at 60 °C for 6 hours. After the reaction was completed, the residue was purified by chromatography on silica gel (*n*-hexane/EtOAc = 20 : 1) to obtain the product **3a** (142.9 mg, 85%) as a white solid. **3b–w** were synthesized in a similar way.

Conflicts of interest

There are no conflicts to declare.

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