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COMMUNICATION

Frustrated Lewis pair-catalyzed double hydroarylation of alkynes with *N*-substituted pyrroles

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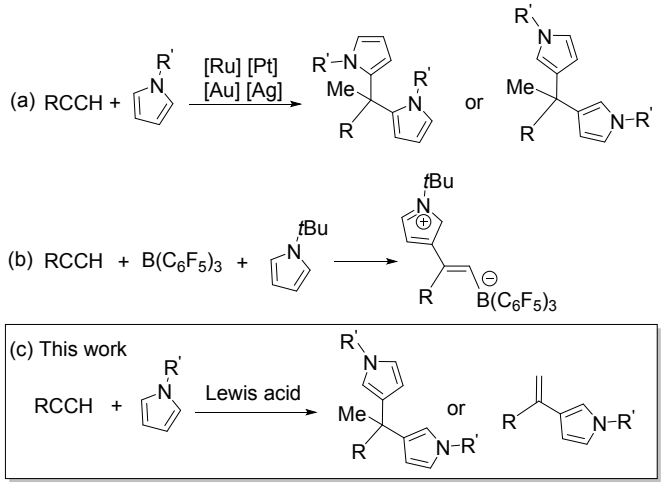
Metal-free hydroarylation of alkynes with *N*-substituted pyrroles is shown to be most efficiently mediated by $B(C_6F_5)_3$ to yield 12 varriants of dipyrrole-alkanes, a mono-hydroarylation product and a tetrahydroarylation product of a bis-alkyne. These products were generally obtained in good to excellent yields (up to 95%). Control experiments suggest a mechanism involving FLP addition of the borane and pyrrole to alkyne.

Frustrated Lewis pairs (FLPs) have garnered much attention in the areas of inorganic, organic and polymer chemistry since their discovery in 2006.[1] The breadth of applications of the concept of FLPs has expanded dramatically in the last decade.[2] To date, the major finding to emerge from this concept has been the development of metal-free hydrogenation.[3] This area has grown rapidly, not only in terms of substrate scope, but also in sophistication, with the development of highly enantioselective FLP catalysts. Another aspect of rapid growth has involved the use of FLPs in the capture of a wide range of small molecules, including alkynes, alkenes, dienes, CO_2, CO, SO_2, cyclopropanes, N_2O and NO, among a number of others.

This unique reactivity arising from combinations of Lewis acids and bases with a substrate molecule, has been demonstrated for a range of systems. Indeed, much of Lewis acid catalysis can be understood as FLP chemistry where the Lewis acid activates a molecule for nucleophilic attack by a third, (Lewis) basic component. For example, the well-established Piers protocol for borane mediated hydrosilylation of ketones[4] is now considered the first example of what has come to be known as an FLP mechanism.

Despite the broad potential beyond hydrogenation, the application of FLPs in organic chemistry is only beginning to emerge. Perhaps the most significant finding in this realm to date has been the discovery of FLP-mediated borylations by Fontaine et al.[5] Soós et al. have described the reductive etherification of aldehydes and ketones.[6] Wasa and colleagues have described the applications of FLPs in Mannich reactions,[7] Conia-Ene-type cyclizations and C–H functionalizations.[8]



Scheme 1 Recent methods for hydroarylation of alkynes with pyrroles and the present work.

In considering the potential for application in new bond formation, we note our earlier report of the stoichiometric addition of nucleophiles to alkynes.[9] We further exploited such FLP addition to alkynes, demonstrating that boranes can mediate the hydroamination of alkynes by sterically encumbered amines.[10] Subsequently, we reported borane mediated cyclizations of propargyl esters affording routes to unique allyl boron species.[11] Similarly, Melen et al. exploited FLP additions of propargyl amides, ureas, carbamates, and carbonates to generate heterocycles.[12]

In conceiving new applications of FLP additions to alkynes we noted that there is considerable interest in derivatizations of heteroaromatic species, due to their roles in natural products and pharmaceuticals.[13] We also noted that while a limited number of ruthenium[14, 15], platinum[16], silver and gold[17] based catalysts have been described to effect the double

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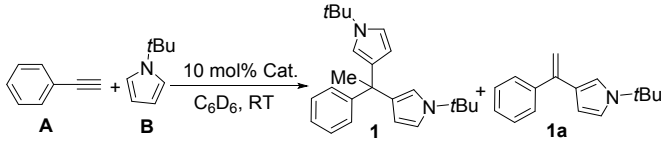
hydroarylation of alkynes with pyrroles (Scheme 1a), metal-free routes have remained less explored.[18] In 2010, our group described the stoichiometric addition of pyrroles and $B(C_6F_5)_3$ FLPs to alkynes affording the zwitterionic addition products of the form $(C_4H_3NtBu)C(R)=CH(B(C_6F_5)_3)$ (Scheme 1 b).[19] Herein, we exploit our early finding of C-C bond formation *via* the action of pyrrole/$B(C_6F_5)_3$ based FLPs, to develop a facile protocol for catalytic hydroarylations of alkynes, affording a range of dipyrrole-alkanes (Scheme 1c). Mono-hydroarylated products are obtained using poorer Lewis acids or sterically demanding alkynes. The mechanism of these reactions is considered.

A 1:2.5 ratio of phenylacetylene and *N*-*t*-butylpyrrole in C_6D_6 did not react (Table 1, entry 1). Similarly, addition of a catalytic quantity of the Lewis acid $BF_3{\cdot}Et_2O$ to the alkyne-pyrrole mixture had no impact (entry 2). The Brønsted acids TFA and TfOH also gave no reaction while the combination of anhydrous $B(C_6F_5)_3$ with H_2O (10 mol%) yielded only trace amounts of the double hydroarylated product (see ESI). Further survey of Lewis acids revealed that use of $Ga(C_6F_5)_3$ as a catalyst yielded a complex mixture of uncharacterized products (entry 3). $InCl_3$ and $GaCl_3$ furnished the mono-hydroarylated product, $PhC(CH_2)(C_4H_3NtBu)$ **1a** in 32% and 65% yields, respectively (entries 4 and 5). Other Lewis acids including $[Ph_3C][B(C_6F_5)_4]$ or the phosphorus(III) dication $[(terpy)PPh][B(C_6F_5)_4]_2$[20] gave no reaction (entries 6, 7). Using 10 mol% $B(C_6F_5)_3$, varied ratios of phenylacetylene and *N*-*t*-butylpyrrole was subsequently explored. Interestingly, with a 1:1 ratio of the reagents, a 35% yield of $PhCMe(C_4H_3NtBu)_2$ **1** was observed (entries 8, 9). Similarly, when the catalyst loading was decreased to 5 mol% and the reagent ratio was increased to 1:2.5 ratio, the product **1** was obtained in 68% yield (entry 10). However, the same mixture of phenylacetylene and *N*-*t*-butylpyrrole with 10 mol% $B(C_6F_5)_3$ afforded the double hydroarylated product **1** in 92% yield (entry 11).

Table 1 Optimization of reaction conditions.[a]



Entry[a]	Cat.	**A**:**B**	Yield (**1**[b])	Yield (**1a**[b])
1	-	1:2.5	0	-
2	$BF_3{\cdot}Et_2O$	1:2.5	0	-
3	$Ga(C_6F_5)_3$	1:2.5	0[c]	-
4	$InCl_3$	1:2.5	-	32
5	$GaCl_3$	1:2.5	-	65
6	$[Ph_3C][B(C_6F_5)_4]$	1:2.5	0	-
7	$[(terpy)PPh][B(C_6F_5)_4]_2$	1:2.5	0	-
8	$B(C_6F_5)_3$	1:1	35	-
9	$B(C_6F_5)_3$	1:2	82	-
10[d]	$B(C_6F_5)_3$	1:2.5	68	-
11	$B(C_6F_5)_3$	1:2.5	92	-

[a] All reactions were performed with phenylacetylene (**A**, 0.10 mmol, 1.0 equiv.), *N*-*t*-butylpyrrole (**B**, 0.25 mmol, 2.5 equiv.) and $B(C_6F_5)_3$ (10 mol%, 5.1 mg) in C_6D_6 (0.5 mL) at 25 °C for 5 hours. [b] Isolated yield. [c] The resulting reaction mixture was complex. [d] 5 mol% $B(C_6F_5)_3$.

Table 2 Reactions of alkynes with *N*-*t*-butylpyrrole [a]

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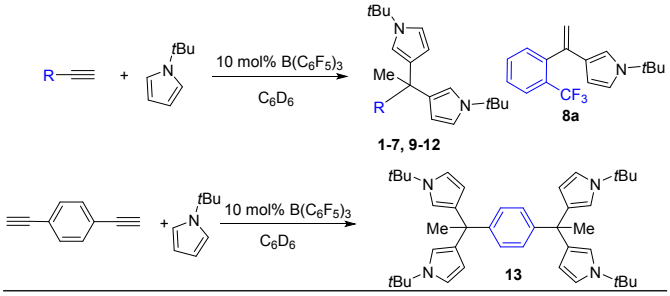


Entry	Alkyne	Time (h)	T (°C)	Product	Yield (%)
1	PhCCH	5	25	**1**	92
2[b]	PhCCH	12	25	**1**	94
3	4-MeC_6H_4CCH	5	25	**2**	76
4	$4\text{-}t\text{BuC}_6H_4CCH$	5	25	**3**	86
5	4-ClC_6H_4CCH	5	25	**4**	89
6	4-BrC_6H_4CCH	5	25	**5**	89
7	$4\text{-CF}_3C_6H_4CCH$	6	25	**6**	89
8	$3\text{-CF}_3C_6H_4CCH$	6	25	**7**	95
9	$2\text{-CF}_3C_6H_4CCH$	12	25	**8a**	64
10	2-MeC_6H_4CCH	5	25	[c]	[c]
11	2-BrC_6H_4CCH	5	25	[d]	tr
12	$2,4\text{-F}_2C_6H_3CCH$	5	25	**9**	80
13	1-decyne	12	25	**10**	34
14	1-decyne	24	50	**10**	52
15	1-octyne	48	50	**11**	56
16	cyclopropylacetylene	24	50	**12**	38
17	1,4-diethynylbenzene	12	25	**13**	53
18	PhCCH	5	25	**14**[e]	85

All reactions were performed with alkynes (0.10 mmol, 1.0 equiv.), *N*-*t*-butylpyrrole (0.25 mmol, 2.5 equiv.) and $B(C_6F_5)_3$ (10 mol%, 5.1 mg) in C_6D_6 (0.5 mL). [b] The reaction of phenylacetylene (0.51 g, 5 mmol) with *N*-t-butylpyrrole (1.54 g, 12.5 mmol) in the presence of 10 mol% $B(C_6F_5)_3$ afforded 1.64 g of **1** in a 94% isolated yield. [c] 7.4:1 mixture of bis and mono-hydroarylated product observed by NMR spectroscopy; the products were not separable. [d] only traces of the mono-hydroarylated product seen. [e] *N*-adamantyl pyrrole was used to yield $PhCMe(C_4H_3NAd)_2$.

Using the optimal reaction conditions, the reactivity of a series of alkynes with *N*-*t*-butylpyrrole in C_6D_6 was investigated. Double hydroarylation of phenylacetylene or alkynes with electron-donating substituents in the presence of 10 mol% of $B(C_6F_5)_3$ proceeded in 5 hours at room temperature to give the corresponding products $RC_6H_4CMe(C_4H_3NtBu)_2$ (R = 4-Me **2**, 4-*t*Bu **3**) (Table 2, entries 3 and 4) in 76% and 86% yields, respectively. Moreover, various alkynes with electron-withdrawing substituents reacted to provide the corresponding double hydroarylated products $RC_6H_4CMe(C_4H_3NtBu)_2$ (R = 4-Cl **4**, 4-Br **5**, 4-CF_3 **6**, 3-CF_3 **7**) (Table 2, entries 5–8) in good to excellent yield (89–95%) in 5–6 h. Employing the more sterically demanding alkyne $2\text{-CF}_3C_6H_4CCH$ as a substrate under standard conditions, only the mono-hydroarylated product $2\text{-}(CF_3)C_6H_4C(CH_2)(C_4H_3NtBu)$ **8a** was detected even with prolonged reaction time (12 h) (Table 2, entry 9). When the less sterically demanding alkyne 2-MeC_6H_4CCH was used as a substrate, a 7.4:1 ratio of double hydroarylated product $2\text{-MeC}_6H_4CMe(C_4H_3NtBu)_2$ and *mono*-hydroarylated product 2-

$MeC_6H_4(CH_2)(C_4H_3NtBu)$ (Table 2, entry 10) was observed as evidenced by ^1H NMR data. In contrast, the alkyne 2-BrC_6H_4CCH yielded only trace amounts of the *mono*-hydroarylated product with no sign of the bis-hydroarylated species (Table 2, entry 11). Nonetheless, the use of 2,4-$F_2C_6H_3CCH$, afforded the double hydroarylated product 2,4-$F_2C_6H_3CMe(C_4H_3NtBu)_2$ **9** in 80% yield (Table 2, entry 12). The alkyl-substituted alkynes 1-decyne, 1-octyne and cyclopropylacetylene also reacted with *N*-*t*-butylpyrrole in the presence of $B(C_6F_5)_3$ to give the products $RCMe(C_4H_3NtBu)_2$ (R = C_8H_{17} **10**, C_6H_{13} **11**, C_3H_5 **12**) albeit in reduced yield of 38–56% (Table 2, entries 13–16). Raising the reaction temperature to 60 °C and lengthening the reaction time did not improve these yields.

Remarkably, the *tetra*-hydroarylation transformation with 1,4-diethynylbenzene and *N*-*t*-butylpyrrole proceeds, affording the *tetra*-hydroarylated product 2,4-$C_6H_4(CMe(C_4H_3NtBu)_2)_2$ **13** in 53% yield (Table 2, entry 17). All products were isolated *via* standard workup, and fully characterized spectroscopically. In addition, compounds **5** and **13** were characterized by single crystal X-ray crystallography (Figure 1). Gratifyingly, these double hydroarylation reactions could also be performed on a gram-scale. For example, a reaction of 0.51 g of phenylacetylene with 1.54 g of *N*-*t*-butylpyrrole in the presence of 10 mol% $B(C_6F_5)_3$ afforded 1.64 g of **1** in a 94% isolated yield (Table 2, entry 2).

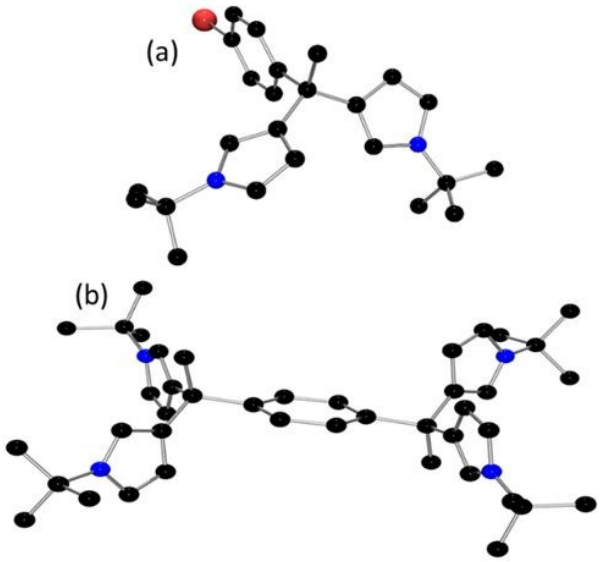
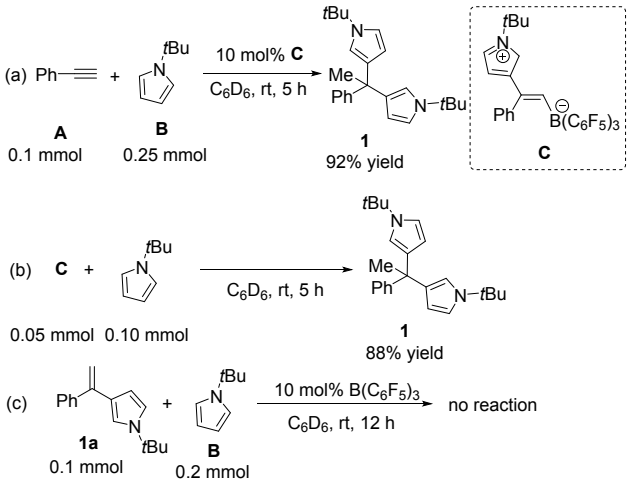


Figure 1 POV-Ray depictions of the molecular structures of (a) **5** and (b) **13;** hydrogen atoms are omitted for clarity. Colour scheme: C: black, N: blue, Br: red-brown.

Efforts to effect the corresponding $B(C_6F_5)_3$ mediated hydroarylation of phenylacetylene using furan, thiophene or the unsubstituted pyrrole were unsuccessful. *N*-methyl pyrrole, *N*-*iso*-propyl pyrrole and *N*-iPr_3Si pyrrole yielded only trace amounts of the double hydroarylated product, while use of N-Boc pyrrole only led to deprotection of the pyrrole. However, use of bulky N-adamantyl pyrrole afforded $PhCMe(C_4H_3NAd)_2$ **14** in 85% yield (Table 2 entry 18). These observations suggest that the binding of donors to the Lewis acid $B(C_6F_5)_3$ precludes catalysis. This thus limits hydroarylation to pyrrole / $B(C_6F_5)_3$ that are FLPs. These results are also consistent with our previous work demonstrating stoichiometric C-C bond formation in FLP addition reactions of sterically encumbered pyrroles and $B(C_6F_5)_3$ to alkynes to afford zwitterionic species of the form $(C_4H_3NtBu)C(Ar)=CH(B(C_6F_5)_3)$.

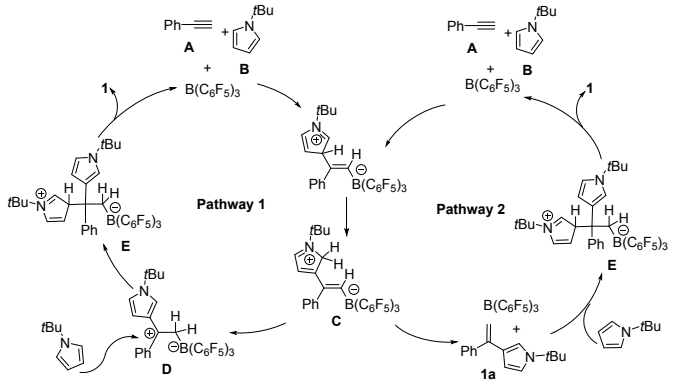


Scheme 2 Control experiments involving the hypothetical intermediates **C** and **1a** under the standard reaction conditions.

In considering the mechanism of these hydroarylations reactions, we speculated that the product of stoichiometric FLP addition could be an intermediate in the present catalytic cycle. To probe this possibility, the zwitterion $(C_4H_3NtBu)C(Ph)=CH(B(C_6F_5)_3)$ (**C**) was prepared by our literature method.[19] Compound **C** is known to undergo a 1,1-carboboration on standing affording a bicyclic product,[19] however immediate addition of stoichiometric *N*-t-butylpyrrole gives the double hydroarylated product $PhCMe(C_4H_3NtBu)_2$ in 88% yield (Scheme 2b). Moreover, 10 mol% of **C** catalyses the double hydroarylation of phenylacetylene with *N*-*t*-butylpyrrole providing **1** in same yield (92 %) after 5 hours at room temperature (Scheme 2a) as described above. These observations together with the inability of Brønsted acids to catalyze these hydroarylations support the view that the Lewis acid initiates addition of *N*-*t*-butylpyrrole and alkyne affording **C**. The acidity of the pyrrole protons in this zwitterionic intermediate **C** prompts proton migration to the acetylenic carbon adjacent boron with concurrent rearomatization of the pyrrole fragment, affording the intermediate **D**. A subsequent addition of the pyrrole to the intermediate **D** affords an intermediate **E** and proton migration yields the double hydroarylated product with the liberation of borane for further catalysis (Scheme 3, pathway 1).

An alternative possibility involves the liberation of the borane and the intermediate olefin. To probe this, the mono-hydroarylated product **1a** was isolated from the reactions of $InCl_3$ and $GaCl_3$. Subsequent reaction with pyrrole in the presence of $B(C_6F_5)_3$ (Scheme 2c) showed no double-hydroarylated product. Similarly, attempts to use 2-vinylpyridine, styrene or 1,1-diphenylethylene as surrogates for **1a** yielded none of the expected hydroarylated products. The

reaction of **1a** with pyrrole in the presence of **C** or $B(C_6F_5)_3$/**C** showed no double hydroarylation product. These observations discount this alternative mechanism (Scheme 3, pathway 2), in favour of pathway 1. The formation of the mono-hydroarylated product **8a** is presumably the result of unfavourable steric demands, precluding further substitution in the *ortho*-CF_3-substituted analogue of intermediate **D**.



Scheme 3 Proposed reaction pathways for the double hydroarylation of alkyne by *N*-*t*-butylpyrrole.

Conclusions

In summary, we have developed a facile and efficient metal-free method for the hydroarylation of alkynes with sterically encumbered pyrroles affording the products **1-14**. Mechanistically these reactions proceed *via* an FLP addition reaction of the Lewis acid $B(C_6F_5)_3$ and the Lewis base pyrroles to the alkyne. This methodology tolerates electron-rich and electron-poor substituents on arylalkynes as well as alkyl alkynes. The protocol employs mild reaction conditions and is effective on gram-scales. The wider application of FLP and main group Lewis acid reactivity in organic chemistry is a focal point of our on-going efforts.

Conflicts of interest

There are no conflicts to declare.

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