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Synthesis of pentasubstituted 2-aryl pyrroles from boryl and stannyl alkynes *via* one-pot sequential Ti-catalyzed [2 + 2 + 1] pyrrole synthesis/cross coupling reactions†

Yukun Cheng, Channing K. Klein and Ian A. Tonks *

Multisubstituted pyrroles are commonly found in many bioactive small molecule scaffolds, yet the synthesis of highly-substituted pyrrole cores remains challenging. Herein, we report an efficient catalytic synthesis of 2-heteroatom-substituted (9-BBN or SnR_3) pyrroles *via* Ti-catalyzed [2 + 2 + 1] heterocoupling of heteroatom-substituted alkynes. In particular, the 9-BBN-alkyne coupling reactions were found to be very sensitive to Lewis basic ligands in the reaction: exchange of pyridine ligands from Ti to B inhibited catalysis, as evidenced by *in situ* ^{11}B NMR studies. The resulting 2-boryl substituted pyrroles can then be used in Suzuki reactions in a one-pot sequential fashion, resulting in pentasubstituted 2-aryl pyrroles that are inaccessible *via* previous [2 + 2 + 1] heterocoupling strategies. This reaction provides a complementary approach to previous [2 + 2 + 1] heterocouplings of TMS-substituted alkynes, which could be further functionalized *via* electrophilic aromatic substitution.

Introduction

Pyrroles are important heterocycles found in diverse applications from pharmaceuticals to conducting materials.[1–6] However, their ubiquity belies significant challenges in the facile synthesis of highly substituted pyrrole cores. Many of the synthetic routes such as the Paal–Knorr condensation require multi-steps backbone synthesis, which add difficulties to late-stage substituent diversification.[7,8] Multicomponent reactions provide a shortcut to the construction of structures with high complexity. A series of pioneering studies has been reported by Odom on Ti-catalyzed multicomponent pyrrole synthesis based on hydroamination and iminoamination.[9–11] Following a slightly different strategy, we recently developed a multicomponent [2 + 2 + 1] Ti-catalyzed pyrrole forming reaction that yields the heterocycle in a single step.[12] Chemo- and regioselective intermolecular reactions can be achieved *via* the heterocoupling of trialkylsilyl-protected alkynes, which selectively engage in migratory insertion into a key azatitanacyclobutene [2 + 2] cycloadduct intermediate.[13] (Fig. 1, top).

Although the TMS-substituted pyrrole heterocoupling products were good candidates for further diversification through electrophilic aromatic substitution of the electron-rich silylpyrrole, we were not able to directly install aryl groups into either the 2- or 5-position around the pyrrole. This limitation arises from the polarization of the Ti-imido bond in [2 + 2] cycloaddition, as well as the limited utility of TMS-substituted arenes in C_{sp^2}–C_{sp^2} bond forming reactions. Thus, we envisioned that the development of other heteroatom-substituted alkyne heterocoupling reactions would lead to alternative strategies for pyrrole diversification.

Given the enormous library of well-established group to metal-catalyzed cross coupling reactions, we were interested in the direct synthesis of pyrroles with heteroatoms that could potentially serve as good transmetallation partners.[14–21] Herein, we report the application of B-alkynyl 9-borabicyclo[3,3,1]

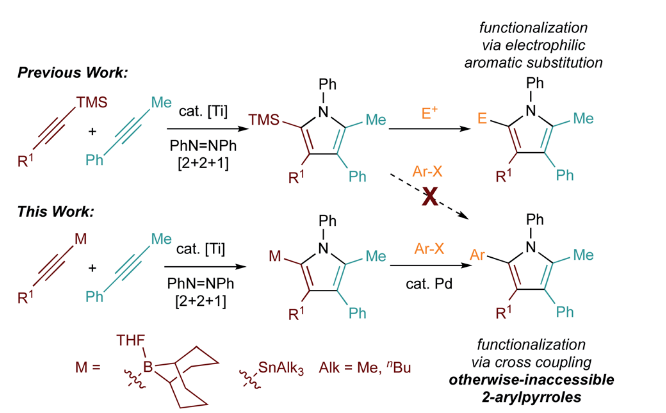

Fig. 1 Heterocoupling strategies for selective [2 + 2 + 1] pyrrole synthesis.

Department of Chemistry, University of Minnesota – Twin Cities, 207 Pleasant St SE, Minneapolis, Minnesota 55455, USA. E-mail: itonks@umn.edu

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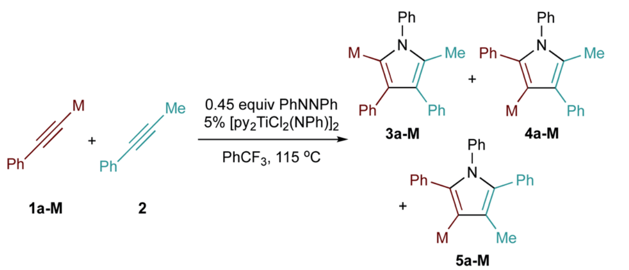
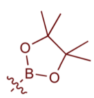
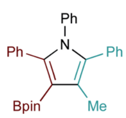
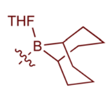
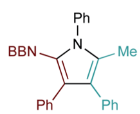
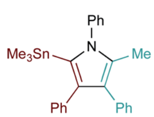
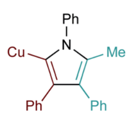
nonanes and alkynyl stannanes in selective Ti-catalyzed [2 + 2 + 1] pyrrole synthesis (Fig. 1, bottom). These reactions provide efficient methods for the construction of versatile poly-substituted pyrrole building blocks, and also provide the opportunity for further diversification into otherwise-inaccessible 2-arylpyrroles through one-pot alkyne cyclization/Suzuki coupling reactions. Preliminary results with other heteroatom-substituted alkynes such as B-alkynyl pinacolborane and copper acetylides are also presented.

Results and discussion

First, several potential heteroatom-substituted alkynes were examined as candidates for the [2 + 2 + 1] reaction, focusing on heteroatomic groups that could later be good transmetallation partners in cross-coupling catalysis (Table 1). The functional groups involved in the initial screen included boronic acid pinacol ester (Table 1, entry 1, **1a-Bpin**) and the THF adduct of 9-borabicyclo[3,3,1]nonane (Table 1, entry 2, **1a-BBN**), $SnMe_3$ (Table 1, entry 3, **1a-SnMe₃**), and Cu (Table 1, entry 4, **1a-Cu**). Initial reaction conditions were based off from previously successful conditions for TMS-substituted alkyne substrates,[13] using chloride-based Ti catalysts that are typically most robust for [2 + 2 + 1] reactions.[22,23] All new heteroatom-substituted reactions resulted in significantly lower yields than the corresponding TMS-substituted alkyne reactions, highlighting the challenges of conserving a reactive transmetallating agent through another organometallic transformation.

Table 1 Examination of potential heteroatom-substituted alkyne partners in Ti-catalyzed [2 + 2 + 1] heterocoupling[a]

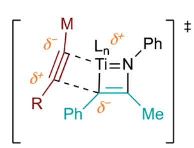


Entry	X	Product	Yield	Selectivity[b]
1[d]	 1a-Bpin	 5a-Bpin	19%	2.5 : 1 (1.1 : 1)[c]
2[e]	 1a-BBN	 3a-BBN	7%	22.3 : 1 (12.5 : 1)
3[e]	 1a-SnMe₃	 3a-SnMe₃	51%	6.4 : 1 (4.5 : 1)
4[d]	 1a-Cu	 3a-Cu	7%	n.d.[f]

[a] Conc. = 0.2 M. [b] Selectivity with respect to all heterocoupling pyrrole regioisomer products. Selectivity = **3a-M**/(**4a-M** + **5a-M**). In parenthesis: selectivity with respect to all possible pyrrole products. Selectivity in parenthesis = **3a-M**/(**4a-M** + **5a-M** + homocoupled products of **2**). [c] Selectivities calculated for major heterocoupling product **5a-M** instead of **3a-M**. [d] t = 16 h. [e] t = 20 h. [f] Other pyrrole products cannot be quantified due to their low yield and peak overlapping.

The reaction of PhCCBpin (**1a-Bpin**) with PhCCMe yielded 3-Bpin-substituted pyrrole **5a-Bpin** as the major product of the reaction (Table 1, entry 1); however, the heterocoupling selectivity with respect to **3a-Bpin** and **4a-Bpin** (2.5 : 1) and overall selectivity toward **5a-Bpin** (1.1 : 1) was poor. Additionally, there was obvious decomposition of the Bpin moiety, indicated by the observation of white Ti-oxo precipitates. This leads us to speculate that oxophilic Ti may be transmetallating or otherwise reacting with the Bpin B–O bonds.[24] Further optimization attempts with Bpin-substituted alkynes were unsuccessful (Fig. S11†). Although alkynyl borates exhibited compatibility issues with our catalytic system, a recent report from Schafer has demonstrated a borane-functionalized alkyne as a hydroamination substrate in Ti hydroamination catalysis.[25] Thus, we next examined PhCC-BBN·THF (**1a-BBN**) (Table 1, entry 2). Although **1a-BBN** gave a low yield of **3a-BBN** as the major product, both the heterocoupling selectivity and overall selectivity of the reaction were very high. Retention of the 9-BBN moiety in this reaction was encouraging, given the diverse modes of reactivity and transmetallation of the boryl unit with transition metals and unsaturated species.[26–31] In fact, there are no reports of organometallic reactions of 9-BBN-substituted alkynes that retain the 9-BBN group. Similar to **1a-BBN**, reaction of $PhCCSnMe_3$ (**1a-SnMe₃**) resulted in the chemo- and regioselective formation of **3a-SnMe₃** (Table 1, entry 3). **3a-SnMe₃** is also stable to aqueous workup, making stannyl alkynes another attractive candidate class for optimization and method development. Regioselectivity in these reactions results from the polarized C–C triple bond (Fig. 2).[32–34] In the case of 9-BBN, polarization is a result of the B mesomeric effect,[26] while for $SnMe_3$ polarization results from hyperconjugation between $\sigma_{Sn\text{-}R}$ and π^*_{C-C} in a manner similar to TMS-protected alkynes.[13]

$[PhCCCu]_n$ (**1a-Cu**) exhibited excellent regioselectivity for the formation of **3a-Cu** (Table 1, entry 4; Fig. S10†); however, the yield and overall chemoselectivity for the heterocoupled product was very low owing to the insolubility of polymeric **1a-**



M = 9-BBN, SnR'₃

Fig. 2 Alkyne polarization results in high regioselectivity for 2nd insertion into the putative azatitanacyclobutadiene intermediate.

Cu. Further, significant protodecupration occurred in all attempts with **1a-Cu**, hampering potential utility. Despite these initial challenges with Cu, a recent report from Schafer on Ti-catalyzed hydroamination of NHC-Cu alkynes indicates that alkynylcuprates could yet be good candidates for [2 + 2 + 1] pyrrole synthesis.[35]

Having identified 9-BBN- and Sn-substituted alkynes as potential heterocoupling candidates, we next optimized these reactions and explored their substrate scope. Optimization experiments for PhCC-BBN·THF (**1a-BBN**) are presented in Table 2, while optimization of PhCC-$SnMe_3$ (**1a-SnMe$_3$**) are presented in Table S2.† Increasing Ti catalyst loading to 10% and changing the solvent from $PhCF_3$ to C_6D_5Br resulted in significant increases to the yield of **3a** without erosion of the overall selectivity. Under these optimized conditions, the reactions were completed within 0.5 h (Table 2, entry 8).

Surprisingly, the yield of **3a** dropped from 74% to 65% upon increasing the catalyst loading from 10 mol% to 15 mol% (Table 2, entries 3 and 4). We hypothesized that B and Ti may be undergoing dative ligand (THF or py) exchange and that the resulting B-L/Ti-L speciation may be impacting catalysis. Thus, several experiments were conducted where the L donor identities and molar ratios were changed (Fig. 3). First, reaction of **1a-BBN** with pyridine-free catalyst $[TiCl_2(NPh)]_n$ (Fig. 3A) resulted in dramatically lower yields, indicating that pyridine is needed for productive catalysis (in part, at least, due to catalyst solubility). Excess **1a-BBN** (Fig. 3B) resulted in a lower yield of **3a**, and monitoring by ^{11}B NMR (Fig. S73†) indicated that remaining **1b** had abstracted pyridine from the catalyst forming PhCC-BBN·py (**1a-BBN-py**). Reaction of preformed **1a-BBN-py** resulted in very slow conversion to **3a** (Fig. 3C). *In situ* ^{11}B NMR analysis of the optimized reaction of **1a-BBN** (Table 2, entry 8) and the reaction of **1a-BBN-py** are shown in Fig. 4. In both cases, **1a-BBN-py** is evident at $t = 0$ and is not fully consumed at the end of the reaction at $t = 0.5$ h. These results indicate that a careful stoichiometric balance of pyridine must be struck with these Lewis acidic substrates: the Ti catalyst needs py bound for productive catalysis, but py-bound **1a-BBN-py** undergoes significantly slower reaction than THF-bound **1a-BBN** or free PhCC-BBN (Fig. 3D).

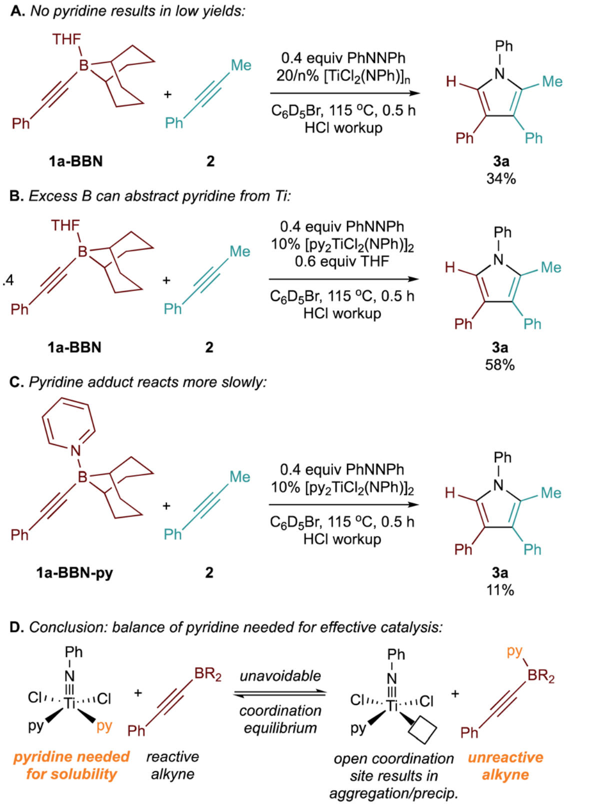
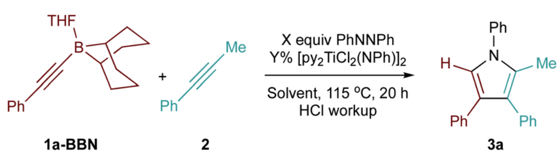


Fig. 3 Control reactions studying the effect of L donor on the Ti-catalyzed [2 + 2 + 1] heterocoupling of **1a-BBN** with **2**. (A) Reaction with 0 equiv. pyridine. (B) Excess **1a-BBN** acts as a pyridine scavenger. (C) Pyridine-bound **1a-BBN-py** reacts significantly slower than **1a-BBN**. (D) Schematic demonstrating pyridine coordination equilibrium effects.

Table 2 Optimization of the Ti-catalyzed [2 + 2 + 1] heterocoupling of 1a-BBN with 2[a]



Entry	% [Ti][b]	Solvent	[py] equiv.[c]	Yield[d] (selectivity[e])
1	5	$PhCF_3$	0.2	7% (12.5 : 1)
2	5	C_6D_5Br	0.2	22% (6.2 : 1)
3	10	C_6D_5Br	0.4	74% (17.1 : 1)
4	15	C_6D_5Br	0.6	65% (13.2 : 1)
5	10	$PhCH_3$	0.4	67% (19.6 : 1)
6	10	$PhCF_3$	0.4	55% (15.7 : 1)
7	10	$PhOCH_3$	0.4	20% (9.6 : 1)
8[f]	10	C_6D_5Br	0.4	66% (22.7 : 1)

[a] Conc. = 0.2 M. [b] [PhNNPh] was adjusted coordinatingly to the change in [Ti] to keep the nitrene equivalent as 1, on basis of the relationship [nitrene] = [Ti] + 2[PhNNPh]. [c] Total equivalent of pyridine in the reaction. [d] Yield determined by GC-FID. [e] Selectivity with respective to all possible pyrrole products. [f] $t = 0.5$ h.

Next, a small scope of 9-BBN-substituted and SnR_3-substituted alkynes was examined in heterocoupling with **2** (Table 3). Reactions of the alkynes examined resulted in good selectivity and yield of the corresponding 2-borylpyrroles and 2-stannylpyrroles, which were hydrolyzed with HCl in methanol to simplify analysis. Neither electronics or sterics on the arylalkyne significantly impacted yield and selectivity: electron-rich (**1b-BBN**, **1b-SnMe$_3$**) and electron-deficient (**1c-BBN**, **1c-SnMe$_3$**) arylalkynylboranes reacted equally well, as did the more sterically encumbered *o*-tolyl-alkynylborane (**1d-BBN**, **1d-SnMe$_3$**). Lastly, the reaction of alkyl-substituted alkynes ^{n}BuCC-BBN·THF (**1e-BBN**) and MeCC-Sn^{n}Bu$_3$ (**1f-Sn^{n}Bu$_3$**) were also highly selective.

Further, we investigated the [2 + 2 + 1] heterocoupling reactions with different hydrocarbon alkynes (Table 4). Various symmetric internal alkynes (**2g–j**) demonstrated productive heterocoupling reactivity. The non-polarized nature of the C≡C

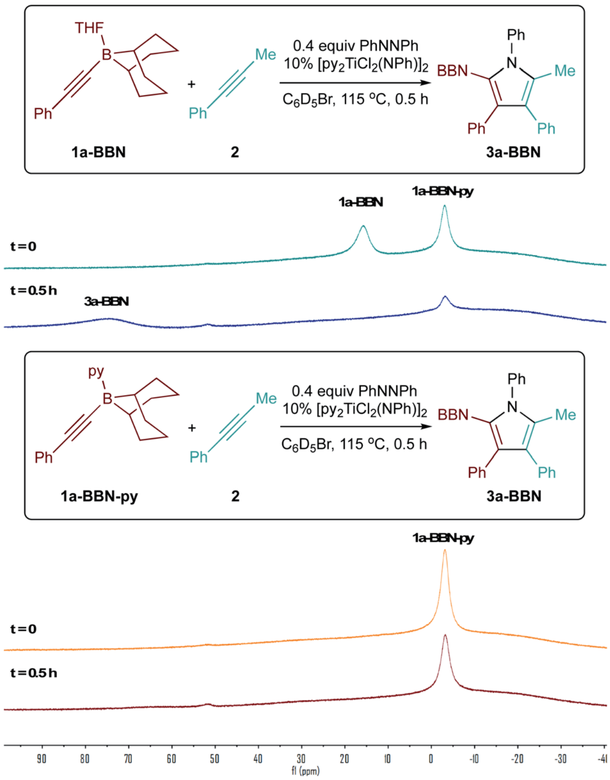
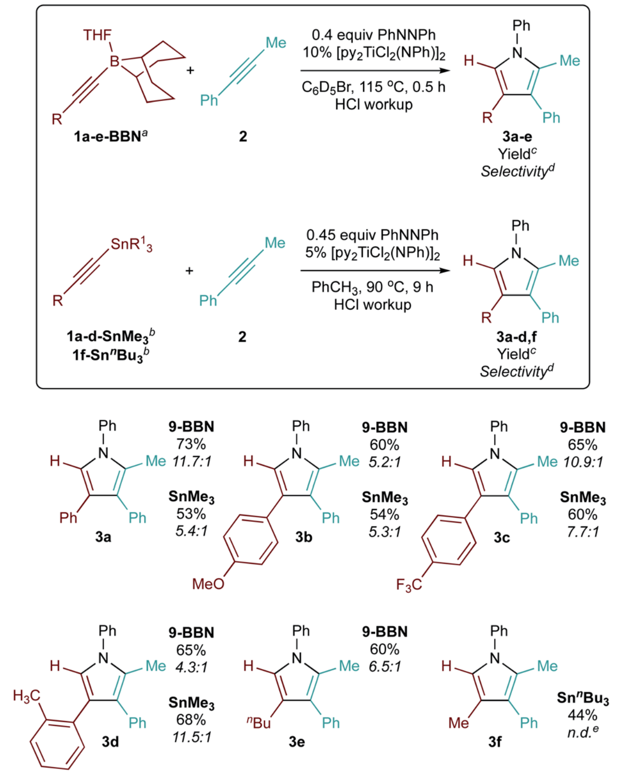


Fig. 4 ^{11}B NMR study demonstrating pyridine-bound **1a-BBN-py** (bottom) reacts more slowly than **1a-BBN** (top).

bond of these symmetric alkynes led to lower reactivity in [2 + 2] cycloaddition, resulting in lower yields. However, these less reactive alkynes were also less prone to competitive insertion chemistry, contributing to the higher overall selectivity (>50 : 1 in the case of **3j**) of these reactions. Lastly, a terminal alkyne (**2k**) was also tested, which resulted in mostly alkyne trimerization instead of productive reactivity (see ESI pg S126†).

Though 9-BBN is frequently used in Suzuki cross coupling reactions between C_{sp^3}-9-BBN and various C–X electrophiles,[36–40] the sp^2–sp^2 Suzuki cross coupling of aryl-9-BBN nucleophiles is rare.[41] Nonetheless, we sought to develop a one-pot sequential [2 + 2 + 1] pyrrole synthesis and arylation procedure (Table 5). Reaction of **1a-BBN** with **2** in $PhCH_3$ *in situ* produces **3a-BBN**; after formation of the pyrrole, addition of *p*-iodofluorobenzene (**6a**), 10% $Pd(PPh_3)_4$, and 2.5 equiv. NaO^{t}Bu generates the pentasubstituted pyrrole product **7aa** in good (58%) overall yield. Since these Ti redox catalytic reactions are tolerant of aryl halide functional groups, the reaction can also be carried in the desired aryl halide solvent in similar overall yield (40% for **7aa**) and shorter [2 + 2 + 1] reaction time. This one-pot procedure provides convenient access to unsymmetrical pentasubstituted 2-aryl pyrroles that cannot be accessed *via* previous [2 + 2 + 1] heterocoupling protocols, which could only install aryl groups at the *N*-, 3-, and 4-positions. Further exploration on the scope of the one-pot pyrrole synthesis/arylation revealed that productive chemistry can be performed on a broad scope of alkynylborane substrates and aryl halides, giving moderate to good yields over the two-step sequence. In general, the substrate

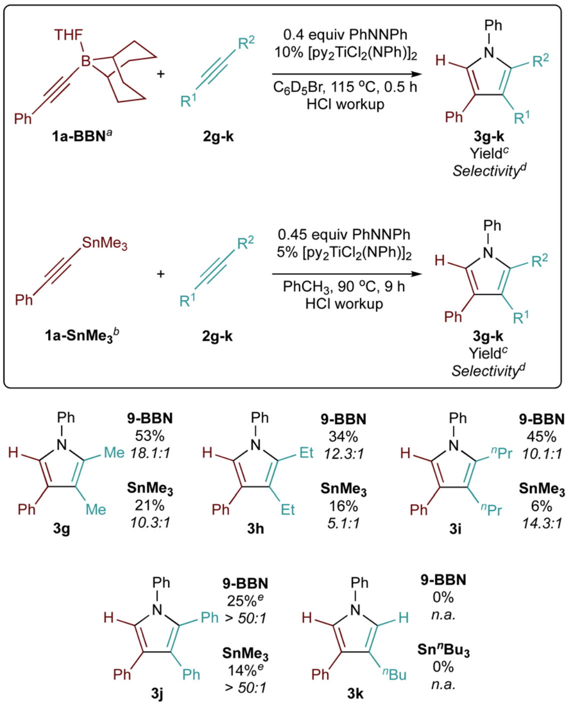
Table 3 Substrate scope of 9-BBN- and R_3Sn-alkynes in [2 + 2 + 1] pyrrole synthesis



^{a} Conc. = 0.2 M. ^{b} Conc. = 0.8 M. ^{c} Yield determined by NMR. ^{d} Selectivity with respect to all possible pyrrole products. ^{e} Other regioisomers cannot be quantified due to their low yield.

scope revealed limited effect on the yield of [2 + 2 + 1] step (as seen in Table 3), but large effects on the arylation step. For example, the arylation step is very sensitive to steric hindrance: formation of **7da**, which requires transmetallation[42] of a sterically encumbered 3-tolyl-2-(9-BBN)pyrrole, resulted in large amount of protodeborylated **3d** (Fig. S123†) and only 19% **7da**. In contrast, in the formation of **7ac** (where the aryl and tolyl groups are transposed, resulting in a less bulky 3-tolyl-2-(9-BBN) pyrrole), there was a smaller amount of protodeborylated **3a** observed (Fig. S141†). Similarly, the arylation to form **7ea** is much higher yielding, with only trace amount of **3e** formed (Fig. S130†). The aryl ether substrate **6b** underwent coupling to form **7ab** with moderate yield, although some demethoxylation was evident. Other oxygenated substrates such as **6d** and **6e** were poor cross coupling partners. Although nitro groups and esters are commonly tolerated in Suzuki reactions, ^{11}B NMR spectroscopic evidence indicates that deleterious chemistry with the 9-BBN group may be taking place (Fig. S150†). In addition to sp^2–sp^2 Suzuki cross coupling, we also attempted C_{sp^3}–C–X cross couplings with aryl-9-BBN. These reactions are also rarely studied, although Fu has several demonstrations with aryl and vinyl 9-BBN substrates.[18,43] Unfortunately, rapid protodemetallation of the 9-BBN pyrrole was observed in all attempts.

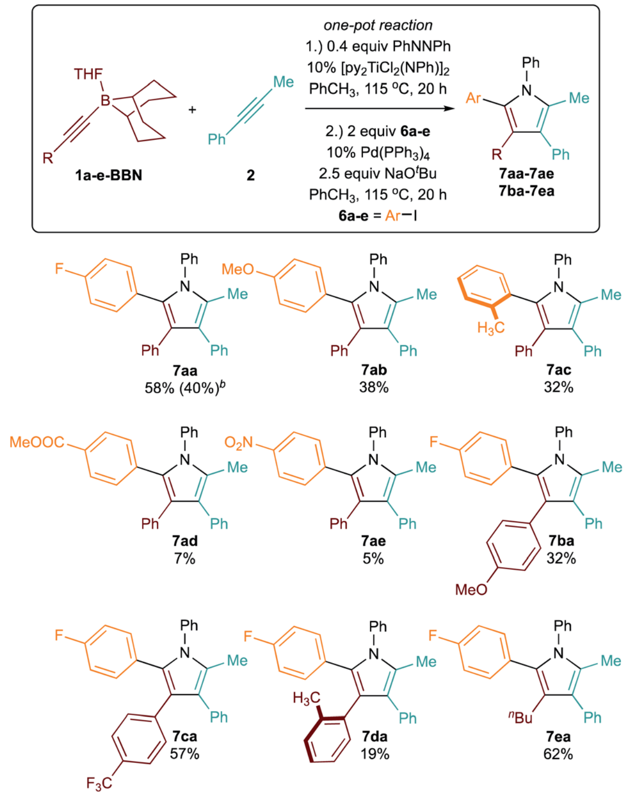
Table 4 Alkyne scope in B- and Sn-functionalized [2 + 2 + 1] pyrrole synthesis



[a] Conc. = 0.2 M. [b] Conc. = 0.8 M. [c] Yield determined by NMR. [d] Selectivity with respect to all possible pyrrole products. [e] Yield determined by GC.

Finally, given that 9-BBN and Sn alkynes undergo coupling with similar chemo- and regioselectivity to TMS-protected alkynes,[13] intramolecular competition experiments were conducted to determine the relative directing ability of the two functional groups compared to TMS (Fig. 5). There are few points of comparison for the regioselectivity of insertion into these types of doubly-functionalized alkynes. Studies of protodemetallation of TMS–CC–M (M = Si, Ge, Sn) indicate that β-hyperconjugative stabilization of putative vinyl carbocation intermediates increases Si < Ge ≪ Sn,[44] which could potentially also stabilize the building δ^+ on the β-C during 1,2 insertion of the alkyne into the Ti–C bond of the azatitanacyclobutadiene intermediate. If this were the dominant mechanism of regiocontrol, Sn would be a stronger director than Si. Reaction of TMSCC-BBN·THF (**1g-BBN**) with **2** resulted in formation of 10% **3g-BBN** and 25% **4g-BBN** (Fig. 5, top), while reaction of $TMSCCSn^nBu_3$ (**1g-Sn^{n}Bu$_3$**) with **2** resulted in the formation of 6% **3g-Sn^{n}Bu$_3$** and 12% **4g-Sn^{n}Bu$_3$**. Thus, TMS is a stronger directing group for insertion than both 9-BBN and Sn^nBu_3 (Fig. 5, bottom). Thus, the β-stabilization from the alkyne substituent does not play a dominant role in determining relative selectivity, and other factors such as the relative strength of the forming Ti–C_{Si} bond *vs.* Ti–C_M bond may also be involved: for example, Micalizio has demonstrated that insertion into 2-silyl-3-stannyltitanacyclopropenes will occur on the Ti–C_{Sn} bond compared to the Ti–C_{Si} bond.[45,46]

Table 5 One-pot sequential pyrrole synthesis/arylation[a]



[a] Conc. = 0.2 M. Yields determined by ^{1}H NMR. [b] In parenthesis: reaction solvent = **6a**, time = 0.5 h (1st step), 20 h (2nd step).

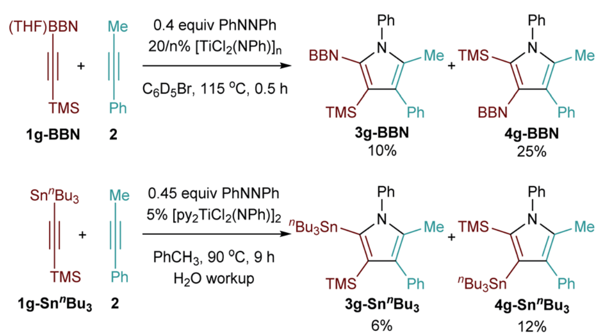


Fig. 5 Directing group strength comparisons.

Conclusions

In summary, both alkynyl boranes and stannanes are efficient alkyne heterocoupling partners in titanium-catalyzed [2 + 2 + 1] pyrrole synthesis, generating the corresponding heteroatom-substituted pyrroles with high chemo- and regioselectivity. The resulting products are candidates for further functionalization through cross coupling, as demonstrated by a one-pot sequential [2 + 2 + 1] boryl pyrrole synthesis/Suzuki coupling reaction. These one-pot sequential reactions provide access to unique, highly decorated pentasubstituted pyrroles that are otherwise inaccessible *via* [2 + 2 + 1] heterocoupling protocols or classical pyrrole synthetic strategies.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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