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

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Multisubstituted pyroles 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 SnBu) pyroles 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 11B NMR studies. The resulting 2-boryl substituted pyroles can then be used in Suzuki reactions in a 1-pot sequential fashion, resulting in pentasubstituted 2-aryl pyroles 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. However, their ubiquity belies significant challenges in the facile synthesis of highly substituted pyrrole cores. Many of the synthtic routes such as the Paal-Knorr condensation require multi-steps backbone synthesis, which add difficulties to late-stage substituent diversification. We recently developed a multicomponent [2+2+1] Ti-catalyzed pyrrole forming reaction that yields the heterocycle in a single step using an earth-abundant metal as catalyst. 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. (Figure 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=C-C=Si bond forming reactions. Thus, we envisioned the development of other heteroatom-substituted alkene heterocoupling reactions that 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 pyroles with heteroatoms that could potentially serve as 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 (THF) adduct of 9-borabicyclo[3,3,1]nonane (Table 1, entry 2, 1a-BBN), SnMe3 (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 alkylene substrates. All new heteroatom-substituted reactions resulted in significantly lower yields than the corresponding TMS-substituted alkylene reactions, highlighting the challenges of conserving a reactive transmetallating agent through another organometallic transformation.

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 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), SnMe3 (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 alkylene substrates. All new heteroatom-substituted reactions resulted in significantly lower yields than the corresponding TMS-substituted alkylene reactions, highlighting the challenges of conserving a reactive transmetallating agent through another organometallic transformation.

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

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

| Entry | X         | Product | Yield (20 h) | Selectivity (20 h) |
|-------|-----------|---------|--------------|--------------------|
| 1a    | 1a-Bpin   | 5a-Bpin | 19%          | 2.5:1 (1:1:1)      |
| 2a    | 1a-BBN    | 3a-BBN  | 7%           | 22.3:1 (12.5:1)    |
| 3a    | 1a-SnMe₂  | 3a-SnMe₂| 51%          | 6.4:1 (4:5:1)      |
| 4a    | 1a-Cu     | 3a-Cu   | 7%           | n.d.               |

aConc. = 0.2 M. bSelectivity 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). cSelectivities calculated for major heterocoupling product 5a-M instead of 3a-M. d*t = 16 h. e*t = 20 h. fOther pyrrole products cannot be quantified due to their low yield and peak overlapping.

The reaction of PhCCBpin (1a-Bpin) with PhCCMe yielded 3bpin-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, leading us to speculate that oxophilic Ti may be transmetallating or otherwise reacting with the Bpin B-O bonds.19 Further optimization attempts with Bpin-substituted alkynes were unsuccessful (Figure S11). 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.20-25 In fact, there are no reports of organometallic reactions of 9-BBN-substituted alkyne that retain the 9-BBN group. Similar to 1a-BBN, reaction of PhCCSnMe₃ (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 alkenes another attractive candidate class for optimization and method development. Regioselectivity in these reactions results from the polarized C-C triple bond (Figure 2).26-28 In the case of 9-BBN, polarization is a result of the B mesomeric effect,29 while for SnMe₃ polarization results from hyperconjugation between σSn-R and π*C in a manner similar to TMS-protected alkenes.10

[PhCCCu]ₙ (1a-Cu) exhibited excellent regioselectivity for the formation of 3a-Cu (Table 1, entry 4; Figure S10); however, the yield and overall chemoselectivity for the heterocoupled product was very low owing to the insolubility of polymeric 1a-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 hydromamination of NHC-Cu alkenes indicates that alkynylcuprates could yet be good candidates for [2+2+1] pyrrole synthesis.30

Having identified 9-BBN- and Sn-substituted alkenes 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-SnMe₃ (1a-SnMe₃) are presented in Table S2. Increasing Ti catalyst loading to 10% and changing the solvent from PhCF₃ to C₆D₅Br 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 (Figure 3). First, reaction of 1a-BBN with pyridine-free catalyst [TiCl₂(NPh)₅] (Figure S13) resulted in dramatically lower yields, indicating that pyridine is needed for productive catalysis (in part, at least, due to catalyst solubility). Excess 1a-BBN (Figure S5) resulted in a lower yield of 3a, and monitoring by ¹¹B NMR (Figure 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 (Figure S4). In situ ¹¹B NMR analysis of the optimized reaction of 1a-BBN (Table 2, entry 8) and the reaction of 1a-BBN-py are shown in Figure 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.

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

| Entry | %[Ti] | Solvent | [py] equiv | Yield (Selectivity) |
|-------|-------|---------|------------|---------------------|
| 1     | 5     | PhCF₃   | 0.2        | 7% (12.5:1)         |
| 2     | 5     | C₅D₅Br  | 0.2        | 22% (6.2:1)         |
| 3     | 10    | C₅D₅Br  | 0.4        | 74% (17.1:1)        |
| 4     | 15    | C₅D₅Br  | 0.6        | 65% (13.2:1)        |
| 5     | 10    | PhCH₃   | 0.4        | 67% (19.6:1)        |
| 6     | 10    | PhCF₃   | 0.4        | 55% (15.7:1)        |
| 7     | 10    | PhOCH₃  | 0.4        | 20% (9.6:1)         |
| 8⁺    | 10    | C₅D₅Br  | 0.4        | 66% (22.7:1)        |

⁺Conc. = 0.2 M. ²[PhNNPh] was adjusted coordinately to the change in [Ti] to keep the nitrene equivalent as 1, on basis of the relationship [Nitrene] = [Ti] + 2[PhNNPh]. ³Total equivalent of pyridine in the reaction. ⁴Yield determined by GC-FID. ⁵Selectivity with respect to all possible pyrrole products. ⁶t = 0.5 h.

Next, a small scope of 9-BBN-substituted and SnR₃-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 steric on the arylalkyne significantly impacted yield and selectivity: electron-rich (1b-BBN, 1b-SnMe₃) and electron-deficient (1c-BBN, 1c-SnMe₃) arylalkynylboranes reacted equally well, as did the more sterically encumbered o-toly-alkynylborane (1d-BBN, 1d-SnMe₃). Lastly, the reaction of alkyl-substituted alkynes ³BuCC-BBN-ThF (1e-BBN) and MeCC-SnBu₃ (1f-SnBu₃) were also highly selective.
Table 3. Substrate scope of 9-BBN- and R$_2$Sn-alkynes in [2+2+1] pyrrole synthesis.

![Diagram of pyrrole synthesis](image)

4Conc. = 0.2 M. 5Conc. = 0.8 M. 6Yield determined by NMR. 7Selectivity with respect to all possible pyrrole products. 8Other regioisomers cannot quantified due to their low yield.

Though 9-BBN is frequently used in sp$^3$-sp$^3$ Suzuki cross coupling reactions, the sp$^3$-sp$^3$ Suzuki cross coupling of aryl-9-BBN nucleophiles is rare. Nonetheless, we sought to develop a one-pot sequential [2+2+1] pyrrole synthesis and arylation procedure (Table 4). Reaction of 1a-e-BBN with 2 in PhCH$_2$ N$_2$ 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$_2$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 pyroles 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 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$^{12}$ of a sterically encumbered 3-tolyl-2-(9-BBN)pyrrole, resulted in large amount of protodeborylated 3d (Figure 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 (Figure S141). Similarly, the arylation to form 7ea is much higher yielding, with only trace amount of 3e formed (Figure 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 (Figure S150).

Table 4. One-pot sequential pyrrole synthesis/arylation.

![Diagram of one-pot reaction](image)

$^{*}$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).

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 (Figure 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 $\beta$-hyperconjugative stabilization of putative vinyl carbocation intermediates increases Si $<$ Ge $<$ Sn,$^{34}$ which could potentially also stabilize the building $\delta^*$ on the $\beta$-C during 1,2 insertion of the alkyne into the Ti-C bond of the azatitanacylclobutadiene 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 (Figure 5, top), while reaction of TMSCCSnBu3 (1g-SnBu3) with 2 resulted in the formation of 6\% 3g-SnBu3 and 12\% 4g-SnBu3 (Figure 5, bottom). Thus, TMS is a stronger directing group for insertion than both 9-BBN and SnBu3, resulting product 5 was obtained in 6\% yield, whereas reactions of 1g-BBN and SnBu3 furnished only trace amounts of the corresponding 3g-SnBu3 and 4g-SnBu3. This finding indicates that the Sn group is more effective for the insertion of the reactive alkynie than both 9-BBN and SnBu3, as evidenced by the increased yield of the desired product. However, in the case of 1g-BBN and SnBu3, the yield of the product was only trace amounts, indicating that the Sn group is more effective than 9-BBN and SnBu3 for the insertion of the reactive alkynie.

**Conclusions**

In summary, both alkynie boranes and stannanes are efficient alkynie heterocoupling partners in titanium-catalyzed [2+2+1] pyrrole synthesis, generating the corresponding heteroatom-substituted pyroles with high chemoselectivity and regioselectivity. The resulting products are candidates for further functionalization through cross coupling, as evidenced by a 1-pot sequential [2+2+1] boryl pyrrole synthesis/Suzuki coupling reaction. These 1-pot sequential reactions provide access to highly decorated pentasubstituted pyroles that are otherwise inaccessible via [2+2+1] heterocoupling protocols.

**Conflicts of interest**

There are no conflicts to declare.

**Acknowledgements**

Financial support was provided by the National Institutes of Health (1R35GM119457), and the Alfred P. Sloan Foundation (I.A.T. is a 2017 Sloan Fellow). Instrumentation for the University of Minnesota Chemistry NMR facility was supported from a grant through the National Institutes of Health (S10OD011952). We thank B. J. Foley and Prof. O. V. Ozerov (Texas A&M University) for providing an iridium catalyst used for the synthesis of Bpin-substituted alkynes.

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