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Platinum(0)-Catalyzed Indolyne Insertion into Bis(pinacolato)diboron Followed by Site-Selective Suzuki–Miyaura Cross-Coupling

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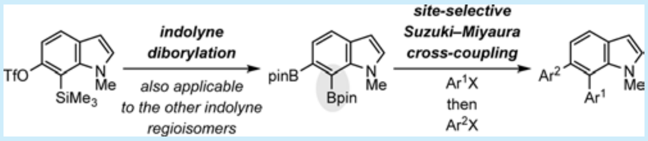
S *Supporting Information*

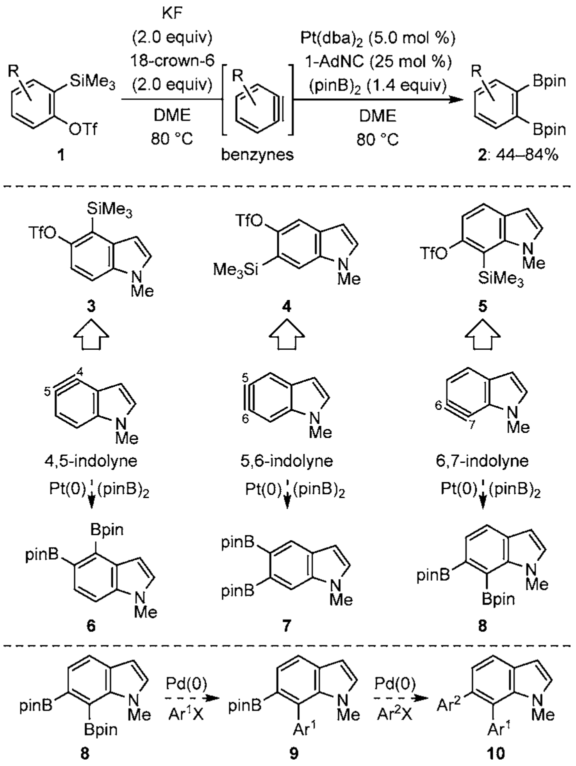
ABSTRACT: Indolynes are converted into previously unprecedented indole building blocks by platinum(0)-catalyzed insertion into a symmetrically substituted boron–boron bond. The two boron sites in these indoles must be differentiated in a subsequent step, and the 6,7-bis[(pinacolato)boryl]indole was shown to undergo site-selective Suzuki–Miyaura cross-coupling with perfect C7 selectivity. The net reaction is the regioselective installation of two different substituents in the C6 and C7 positions of a 6,7-indolyne precursor.



Transition-metal-catalyzed benzyne insertion into E–E interelement bonds[1,2] is one facet of the flourishing field of synthetic aryne chemistry.[3−6] For example, benzynes generated from **1** by Kobayashi's method[7] react with bis(pinacolato)diboron under platinum(0) catalysis to form two carbon–boron bonds in a one-pot sequence (**1** → **2**, Scheme 1, top).[1c,8] The boron sites in **2** serve as linchpins for subsequent carbon–carbon bond formations, but to date, regioselective Suzuki–Miyaura cross-couplings (R ≠ H) have not been accomplished. For cross-coupling reactions involving multiply functionalized substrates, regiochemical differentiation is generally achieved at the oxidative addition stage with respect to the halide (or pseudohalide) components, the basis of control being either the nature of the substrate or the catalyst system.[9] Attaining regioselectivity at the transmetalation stage is an emerging challenge. The use of alternately protected diboronates was demonstrated,[10] but examples of discrimination between identically protected boronates remains very rare, particularly for aryl boronates.[11]

In this context, we have become fascinated with the rich chemistry of hetarynes recently developed by Garg and coworkers.[12−14] These reactive intermediates have not been implemented into the above platinum(0)-catalyzed insertion into the boron–boron bond yet. However, application of this methodology to the three indolynes generated from **3**–**5** would provide access to attractive indole building blocks **6**–**8** (Scheme 1, middle). The use of a symmetric boron–boron reagent shifts the problem of regiochemical control[14] to a later stage where differentiation between the boron sites must be achieved in a Suzuki–Miyaura cross-coupling. We report here the successful transformation of indolyne precursors **3**–**5** into the unprecedented difunctionalized indoles **6**–**8**. Moreover, we demonstrate for the 6,7-disubstituted isomer that site-selective Suzuki–Miyaura cross-coupling is indeed possible (**8** → **9** → **10**, Scheme 1, bottom).

Scheme 1. Platinum(0)-Catalyzed Insertion of Benzynes (top) and Three Regioisomeric Indolynes (middle) into the Boron–Boron Bond of $(pinB)_2$ and Planned Site-Selective Suzuki–Miyaura Cross-Coupling (bottom)



We prepared the indolyne precursors **3**–**5** following the procedures reported by Garg and co-workers[12c,14a] and selected easy-to-make **3** as the test substrate for platinum(0)-catalyzed insertion into bis(pinacolato)diboron. Adopting Yoshida's setup[1c] (cf. Scheme 1, top) afforded desired **6** albeit with moderate conversion and in rather poor yield. Improvements

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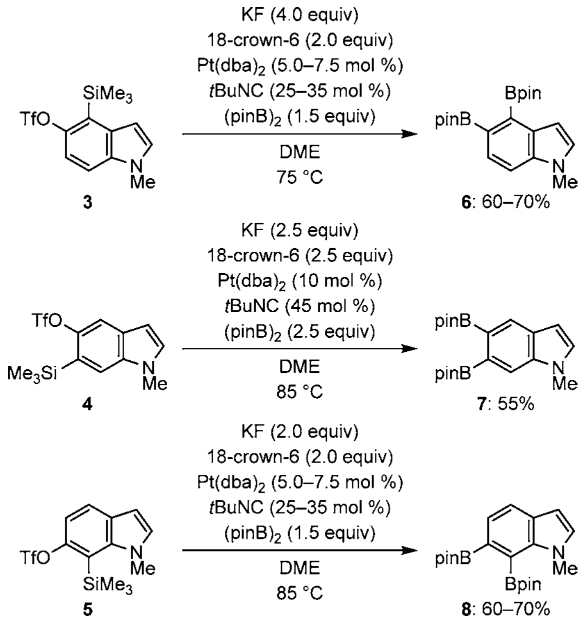
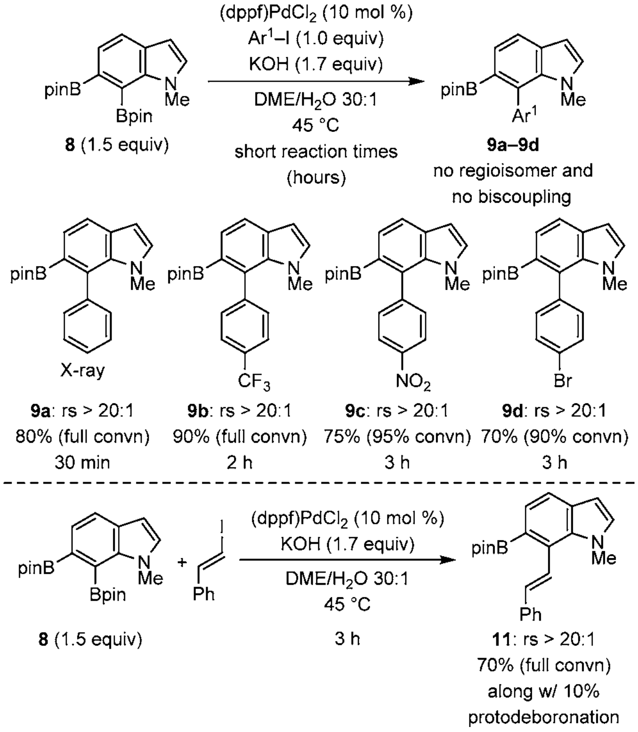
were made by doubling the amount of catalyst and ligand but not to a satisfactory level. Variation of the various reaction parameters then revealed the crucial role of the isonitrile (isocyanide) ligand.[15] CyNC and *t*OcNC (Walborsky's reagent) were less effective than 1-AdNC and *t*BuNC, which emerged as the optimal isonitrile ligand for this transformation (see the Supporting Information for details). With this protocol in hand, we were able to obtain good yields depending on the scale of the reactions (**3** → **6**, Scheme 2).[16] Application of this catalyst system to the other regioisomers **4** and **5** did work, requiring less potassium fluoride in both cases (**4** → **7** and **5** → **8**, Scheme 2). The reaction of **4** was sluggish and not optimized further due to the laborious preparation of the 5,6-isomer **4**. Conversely, precursor **5** participated in this reaction similar to its isomer **3**. We were able to make significant amounts of both **6** and **8** to continue with a systematic study of site-selective Suzuki–Miyaura cross-couplings.

Scheme 2. Platinum(0)-Catalyzed Insertion of Three Regioisomeric Indolynes into the Boron–Boron Bond



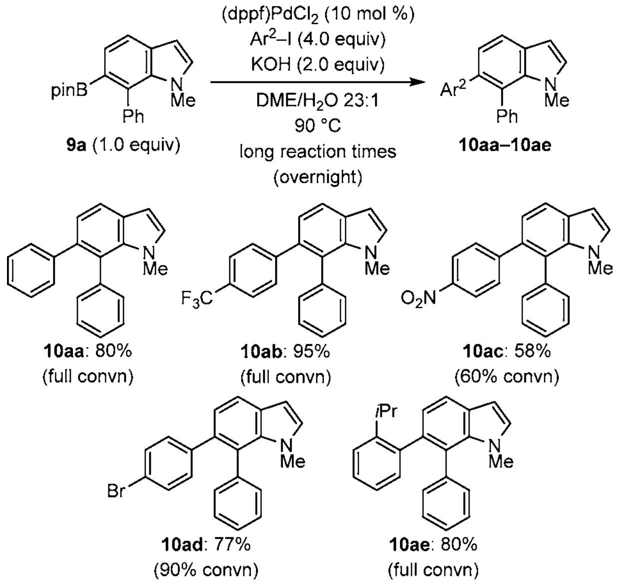
We quickly learned that Suzuki–Miyaura cross-couplings of 4,5-isomer **6** were neither regio- (position 4 vs position 5) nor chemoselective (mono- vs biscoupling) with typical catalyst systems (not shown). We were, however, delighted to find that the 6,7-isomer **8** converted cleanly into **9** with excellent site-selectivity (Scheme 3). Unexpectedly, it was the sterically more hindered boryl group at C7 that underwent the cross-coupling as unambiguously verified by X-ray analysis (see the Supporting Information for the molecular structure of **9a**). The cross-coupling was again not chemoselective when using equimolar amounts of precious **8** and the aryl iodide, affording mono/bis ratios of 2:1. Exclusive monocoupling was achieved with 1.5 equiv of **8**, and unreacted **8** could be reisolated during the purification by flash chromatography on silica gel. Arylation at C7 worked with several aryl iodides using (dppf)PdCl$_2$ as catalyst; alternative palladium sources such as (Ph$_3$P)$_4$Pd and Pd$_2$(dba)$_3$ led to longer reaction times and furnished lower yields, respectively. Protodeboronation as a minor side-reaction was observed with the *para*-nitro-substituted aryl iodide. The protocol was also applicable to a vinyl iodide but protodeboronation was more pronounced here (**8** → **11**, Scheme 3).

Scheme 3. Site-Selective Suzuki–Miyaura Cross-Coupling

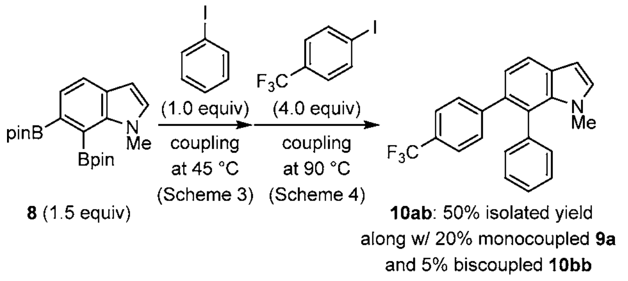


The reaction setup for the Suzuki–Miyaura cross-coupling of the remaining boryl site at C6 was essentially identical to the previous one, just requiring higher temperature and longer reaction time. Starting from monocoupled **9a**, we performed the second cross-coupling with the same set of aryl iodides as well as a sterically more hindered aryl iodide (**9a** → **10aa**–**10ae**, Scheme 4). When used in excess (4.0 equiv), conversions and yields were high.

Scheme 4. Suzuki–Miyaura Cross-Coupling of the Remaining Boron Site



Scheme 5. One-Pot Sequential Suzuki–Miyaura Cross-Couplings with Different Aryl Iodides



The fact that both Suzuki–Miyaura cross-couplings are promoted by the same catalyst system at different temperatures prompted us to try sequential addition of the two aryl iodides in one pot (Scheme 5). We chose to combine **8** → **9a** using iodobenzene (Scheme 3) and **9a** → **10ab** using 1-iodo-4-(trifluoromethyl)benzene (Scheme 4) as the individual reactions went to completion. However, the one-pot approach was far less efficient, affording **10ab** in 50% rather than 75% (or more) isolated yield. To our surprise, the second coupling did not proceed without the addition of another batch of (dppf)PdCl$_2$ and KOH, and significant amounts of monocoupled **9a** still remained after prolonged reaction times. Moreover, the formation of biscoupled **10bb** (formed from unreacted **8** and two molecules of the trifluoromethylated aryl iodide) complicated the purification of **10ab**.

To summarize, we accomplished the implementation of a member of the hetaryne family into Yoshida's transition-metal-catalyzed aryne insertion into symmetrically substituted interelement bonds.[1] Three regioisomeric indolynes were transformed into the corresponding bis[(pinacolato)boryl]-indoles that constitute new difunctionalized indole building blocks. The differentiation of the boron sites in these molecules poses a challenge as site-selective Suzuki–Miyaura cross-couplings are basically unprecedented.[11] We were nevertheless able to show for the 6,7-bis[(pinacolato)boryl]indole that it is possible to selectively address the C7 boryl group. Another aryl group was then subsequently introduced at C6 by an almost identical procedure. The overall sequence allows for the regioselective formation of two new carbon–carbon bonds at the aryne carbon atoms of an indolyne.[17] The origins of regioselectivity in this process remains a fascinating open question.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General procedures, experimental details, crystallographic data (CIF), characterization data, and ^{1}H, ^{11}B, ^{13}C, and ^{19}F NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2003**, *125*, 6638–6639 (Si–Si). (b) Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5052–5055 (Sn–Sn). (c) Yoshida, H.; Okada, K.; Kawashima, S.; Tanino, K.; Ohshita, J. *Chem. Commun.* **2010**, *46*, 1763–1765 (B–B).

(2) For general reviews of interelement bond activation, see: (a) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320–2354. (b) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221–3256.

(3) For a review of arynes in transition metal catalysis, see: Dyke, A. M.; Hester, A. J.; Lloyd-Jones, G. C. *Synthesis* **2006**, 4093–4112.

(4) For reviews of aryne chemistry in total synthesis, see: (a) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550–3577. (b) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766–3778.

(5) For reviews of hetaryne chemistry, see: (a) Goetz, A. E.; Shah, T. K.; Garg, N. K. *Chem. Commun.* **2015**, *51*, 34–45. (b) Goetz, A. E.; Garg, N. K. *J. Org. Chem.* **2014**, *79*, 846–851.

(6) For a summary of multicomponent reactions involving arynes, see: Yoshida, H. In *Multicomponent Reactions in Organic Synthesis*; Zhu, J., Wang, Q., Wang, M., Eds.; Wiley-VCH: Weinheim, Germany, 2015; pp 39–72.

(7) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214.

(8) For the transmetalation approach catalyzed by copper(I) alkoxides, see: Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 235–238.

(9) For recent reviews, see: (a) Kapdi, A. R.; Prajapati, D. *RSC Adv.* **2014**, *4*, 41245–41259. (b) Wang, J.-R.; Manabe, K. *Synthesis* **2009**, 1405–1427.

(10) (a) Noguchi, H.; Shioda, T.; Chou, C.-M.; Suginome, M. *Org. Lett.* **2008**, *10*, 377–380. (b) Iwadate, N.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 2548–2549.

(11) For terminal-selective couplings of 1,2-bis(boryl)alkanes, see: (a) Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234–18235. (b) Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. *Nature* **2014**, *505*, 386–390. For terminal-selective couplings of 1,2-bis(boryl)alk-1-enes, see: (c) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Lett.* **1996**, 1117–1118. We found a single report of regioselective couplings of 2-substituted 1,4-bis(boryl)tetralins: (d) Iannazzo, L.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C.; Gandon, V. *Eur. J. Org. Chem.* **2011**, 3283–3292. For 1,1-bis(boryl)alk-1-enes, see: (e) Shimizu, M.; Shimono, K.; Schelper, M.; Hiyama, T. *Synlett* **2007**, 1969–137. (f) Jiao, J.; Nakajima, K.; Nishihara, Y. *Org. Lett.* **2013**, *15*, 3294–3297. For 1,1,2-tris(boryl)alkanes, see: (g) Coombs, J. R.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 16140–16143.

(12) For the seminal work, see: (a) Buszek, K. R.; Luo, D.; Kondrashov, M.; Brown, N.; VanderVelde, D. *Org. Lett.* **2007**, *9*, 4135–4137. (b) Brown, N.; Luo, D.; VanderVelde, D.; Yang, S.; Brassfield, A.; Buszek, K. R. *Tetrahedron Lett.* **2009**, *50*, 63–65. (c) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007–1010.

(13) For recent applications in total synthesis, see: (a) Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797–15799. (b) Fine Nathel, N. F.; Shah, T. K.; Bronner, S. M.; Garg, N. K. *Chem. Sci.* **2014**, *5*, 2184–2190.

(14) For experimental and quantum-chemical investigations toward the origin of regioselectivities, see: (a) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G-Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.*

2010, *132*, 1267−1269. (b) Im, G-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933−17944.

(15) For the critical role of these ligands in the oxidative addition of silicon−silicon bonds to palladium(0), see: (a) Ito, Y.; Suginome, M.; Murakami, M. *J. Org. Chem.* **1991**, *56*, 1948−1951. (b) Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G.; Ito, Y. *J. Am. Chem. Soc.* **1993**, *115*, 6487−6498. For a review, see: (c) Suginome, M.; Ito, Y. *J. Chem. Soc., Dalton Trans.* **1998**, 1925−1934.

(16) We experienced issues with reproducibility on <0.5 mmol scales, but results were consistently reliable on larger scales using a higher catalyst/ligand loading.

(17) This distinguishes our approach from the elegant palladium(0)-catalyzed three-component couplings developed by Greaney and co-workers where two new carbon−carbon bonds are formed with no regiocontrol using nonsymmetrically substituted benzyne intermediates: (a) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426−7427. (b) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 5589−5592.