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Regioselective Suzuki couplings of non-symmetric dibromobenzenes: alkenes as regiochemical control elements†

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The regiochemical outcome of Suzuki couplings of non-symmetric dibromobenzenes is investigated. Selectivities are dependent on the proximity of the bromine atom to alkene substituents, not on steric or electronic effects. Extension to a one-pot three-component Suzuki reaction leads to efficient terphenyl syntheses.

Suzuki cross-coupling has emerged as a mainstay of organic synthesis, and it is especially useful for the construction of Csp^2–Csp^2 bonds. The traditional application of the Suzuki reaction is the coupling of a halide with a boron reagent (Scheme 1, eqn (1)).[1]

Substantial efforts have expanded the Suzuki reaction, and they include many examples of chemoselective couplings that exploit the reactivity differences of the halogens (eqn (2)).[2] In addition to benzene systems, such chemoselective Suzuki reactions are also known in polycyclic aromatic molecules such as quinolines,[3] napthalenes,[4] and indoles.[5] Additionally there are many examples of tandem couplings of polyhalides (eqn (3)) where the coupling rate of the different halogen atoms is inconsequential.[6] Regioselectivity in the cross-coupling reactions of polybrominated heteroaromatic systems is also well studied (eqn (4)).[7,8] In such cases, the selectivities are attributed to either steric or electronic effects: the more electron deficient or less hindered bromine atom reacts faster.[7]

In heteroaromatic molecules, the carbon positions are inherently different (*e.g.* C2 *vs.* C3 in pyrrole, pyridine, and furan), and bromine atoms at these positions have predictable reactivity trends in Suzuki couplings.[9]

Examples of regioselective couplings of polybrominated (monocyclic) benzenes are rare.[10,11] The regioselectivity in these reactions is usually attributed to steric or electronic effects of the substituents. We know of only one case where a carboxylate was implicated as a directing group (eqn (5)).[10d]

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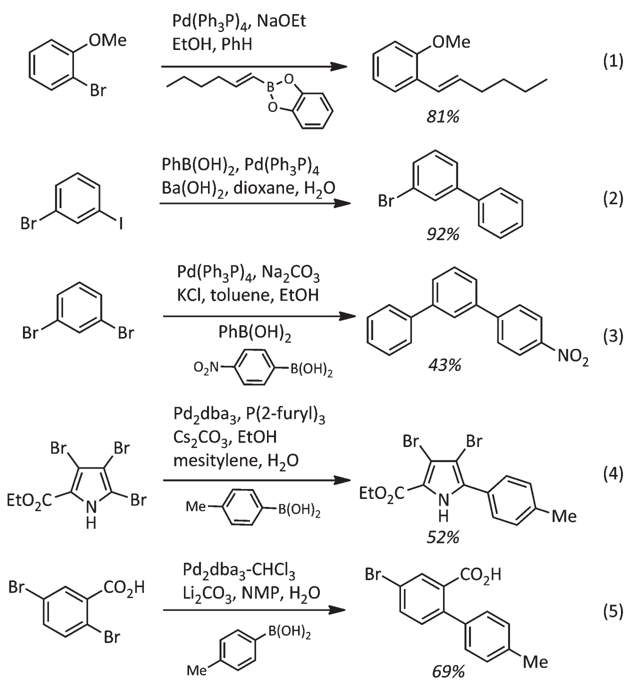

Scheme 1 Selected Suzuki reactions.

Such substituent effects on benzenes can be more subtle and are not always immediately predictable.

In this manuscript, we describe the discovery of a new regiochemical control element that is coordinative in nature; not a result of electron withdrawing groups or steric effects. Specifically, vinyl groups proximal to carbon–bromine bonds significantly decrease the rate at which such bromides undergo Suzuki coupling. This allows predictable and reliable design of sequential Suzuki reactions of alkene-substituted dibromobenzenes (*i.e.* dibromostyrenes).

We recently completed a synthesis of the bisbibenzyl natural product, cavicularin using two separate Suzuki reactions for the construction of the C12′–C14 and C10′–C3′ bonds (Scheme 2, cavicularin numbering).[12] Suzuki reaction of **1** with

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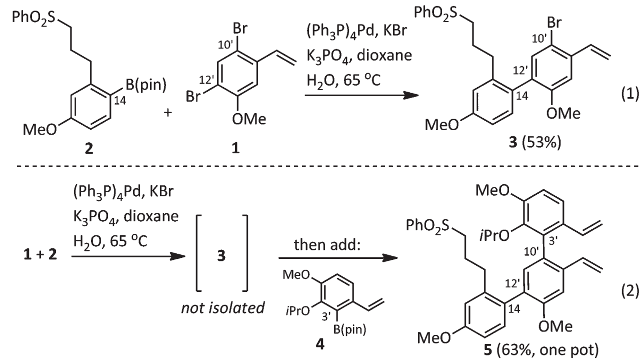
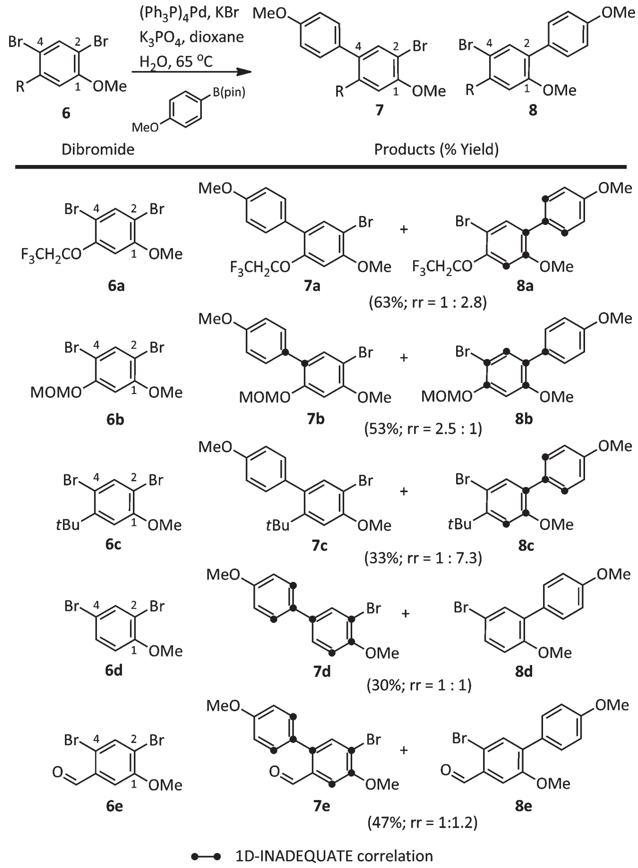


Scheme 2 Suzuki reactions for cavicularin.



Scheme 3 Suzuki reactions of dibromobenzenes.

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boronic ester **2** gave **3** as a single regioisomer that was isolated and characterized (eqn (1)). We also found that **1**, **2**, and **4** react sequentially in a one-pot three-component Suzuki reaction[13] to give **5** (eqn (2)). Although this reaction was pivotal in our cavicularin synthesis, it was unclear which structural features led to the regioselectivity in the Suzuki reaction of **1**, **2**, and **4**.

The high regioselectivity of dibromide **1** for reaction of the C12′ bromide was not immediately attributable to steric or electronic properties of the substrate. The steric difference of the methoxy and vinyl substituents is not sufficient to explain the formation of a single observable regioisomer. Moreover, consideration of the ^{1}H NMR chemical shifts of the non-halogenated congener (*i.e.* 3-vinylanisole) revealed that the more shielded position (C12′) was reacting selectively, opposite the trend observed in heteroaromatic systems.[9] Finally, as both bromine atoms were positioned *ortho* to one substituent and *para* to the other, both the vinyl and methoxy substituents could be electronically influencing both bromine atoms simultaneously. Since it was difficult to identify what properties were leading to the regioselectivity in the reaction of **1**, we decided to prepare additional non-symmetric *meta*-dibromobenzenes (**6**) to interrogate their regiochemical preference under our standard Suzuki reaction conditions to give **7** or **8** (Scheme 3). Regioisomers **7** and **8** display very similar ^{1}H- and ^{13}C-NMR spectra with multiple contiguous carbons that lack hydrogen atoms, and distinguishing between these structures, even with modern 2D-NMR techniques (*e.g.* HMBC[14]) is difficult. We commonly determined the molecular structure using 1D-INADEQUATE[14] to assign the connectivity of the contiguous carbon atoms that lack hydrogen (see annotations in Schemes).

Starting from the hypothesis that the regiochemical preference was a result of the electronics of the system, we prepared trifluoroethyl-containing substrate **6a**. The bromine atoms in **6a** have similar steric environments, but the C4 bromine[15] is proximal to the more electron-deficient ether, and we anticipated that the C4 bromine would couple preferentially. To our surprise, there was little regiochemical preference and the C2 bromine was still the more reactive halogen. We wondered if the regioselectivity in the coupling of **1** was the result of the coordinating ability of the methoxy group. To test this, we prepared MOM ether **6b**. Again, the selectivity was only modest favoring the C4 bromine.

The regioselectivity in the cross-coupling of dihaloarenes has been interpreted based (in some cases) on steric considerations.[10] Three substrates were prepared that were designed to probe if the Suzuki reaction of dibromobenzenes correlated with the steric environment of the bromides. First, *tert*-butyl containing **6c** was subjected to the standard Suzuki conditions. The Suzuki reaction was modestly regioselective[16] and coupling of the less hindered C2 bromide was preferred, but even this sterically biased substrate did not exhibit the same level of regioselectivity as substrate **1**. Dibromoanisole **6d** showed no regioselectivity in the Suzuki reaction, despite having bromine atoms in different steric environments. Next, dibromobenzaldehyde **6e** was prepared. The aldehyde functional group has a similar steric size as the vinyl group in **1**; however, substrate **6e** showed very little regioselectivity in the coupling. On the basis of these results, it appears that the regioselectivity in the Suzuki coupling of **1** (and **6a**–**6e**) cannot be attributed to sterics alone. Moreover, these results highlight the difficulty in predicting steric effects on regioselectivity in these type of Suzuki reactions.

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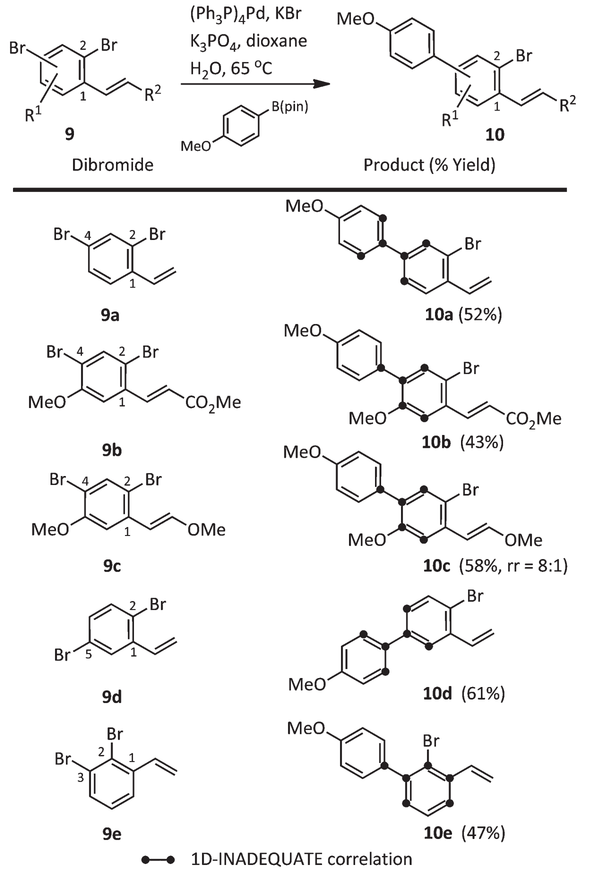
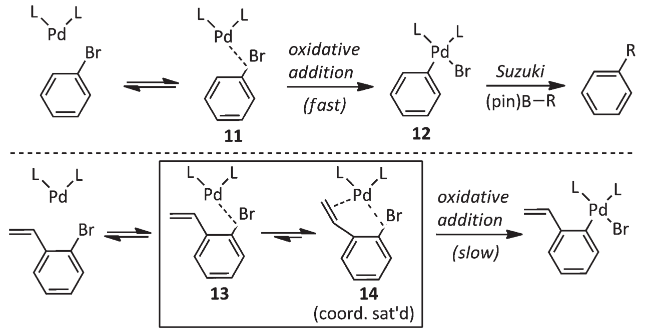


Scheme 4 Suzuki reactions of dibromostyrenes.



Scheme 5 Mechanistic considerations.

We began to suspect that the regioselectivity displayed by substrate **1** was attributable to a rate decrease in the C10′ bromide because of its proximity to the adjacent vinyl group. A series of *meta*-dibromostyrenes were prepared to test whether the alkene was the regiochemical control element. Three *meta*-substituted dibromobenzenes were prepared, and all of the substrates showed good regioselectivity for reaction at the bromide distal to the alkene (Scheme 4). The yields are intentionally unoptimized: the Suzuki conditions (from Scheme 2) were held constant so that a direct correlation in selectivity could be measured.[17] Substrates **9a** and **9b** showed complete regioselectivity, giving **10a** and **10b**, respectively. The electron-rich alkene in **9c** gave slightly lower levels of regioselectivity (rr = 8 : 1) compared with **1**. *para*-Dibromostyrene (**9d**) was prepared, and it showed complete regioselectivity for the C5 bromide (distal to the alkene). Finally, *ortho*-dibromostyrene (**9e**) was prepared, and it was also completely selective for the C3 bromide.

The regioselectivity can be attributed to the relative rates of oxidative addition of the two bromides (Scheme 5). Mechanistically, $[Pd^0(PPh_3)_2]$ first forms an agostic interaction with the C–Br bond (**11**). In the absence of a neighboring alkene, oxidative addition occurs to give the Pd(II) intermediate **12**, which participates in the Suzuki coupling. However, in the case of styrene **13** where the bromine atom is flanked by an alkene, reversible coordination may take place, leading to coordinatively saturated complex **14**. Complex **14** lacks open coordination sites required for oxidative addition. The complexation removes the reactive species **13**, which decreases the rate of the oxidative addition and leads to the observed regioselectivity.

Olefin effects on oxidative addition are well known.[18] Oxidative addition of $[Pd^0(PPh_3)_2]$ to PhI is slowed considerably by the addition of olefin additives.[19] Moreover, oxidative addition is slower when electron-poor alkene ligands are present and relatively faster when electron-rich alkenes are present.[20] This is fully consistent with the lower regioselectivity observed with substrate **9c** compared with **9b**. When the alkene is electron-poor (a better ligand) as in **9b**, the adjacent C2 bromide undergoes relatively slow oxidative addition, leading to high regioselectivity. When the alkene is electron-rich (a poorer ligand) as in **9c**, the adjacent C2 bromide undergoes relatively fast oxidative addition and regioselectivity is lower.

Good regioselectivity in a Suzuki reaction of a dibromobenzene suggests that a one-pot three-component Suzuki reaction is possible. We decided to showcase such a one-pot three-component Suzuki reaction in the synthesis of a target terphenyl (Scheme 6). Recently, Hamilton investigated terphenyl **21** as a proteomimetic compound.[21] The synthesis of **21** involved the sequential Negishi coupling of **22**, **23**, and **24**. Overall, the sequence to **21** took 7 chemical steps. We selected **21** as a target to demonstrate the utility of the regioselective one-pot three-component Suzuki reaction.

Dibromide **9d** was coupled with boronic ester **25**[22] using our standard conditions. When TLC indicated the consumption of the starting material, boronic ester **26**[22] was added to the mixture and the reaction was allowed to proceed to completion (TLC). In this one-pot process, terphenyl **27** was isolated in 54% overall yield as a single regioisomer. Hydrogenation reduced the alkene and removed the benzyl group to give **21** in high chemical yield.

In summary, non-symmetric dibromobenzenes undergo regioselective Suzuki reactions if one bromine atom is adjacent to an alkene. This discovery allows reliable prediction of bromide reactivity that does not require analysis of electronic or steric environments. The alkene slows the rate of oxidative addition of palladium through coordinative saturation of the

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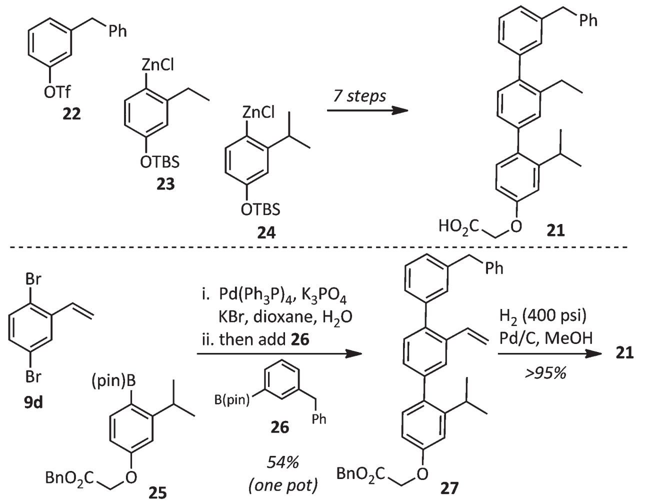

Scheme 6 One-pot three-component Suzuki for proteomimetic **27**.

agostic Pd(0) complex. The regioselectivity is observed in *ortho*-, *meta*-, and *para*-dibromobenzenes. The regioselectivity enables the application of the reaction in one-pot three-component Suzuki reactions to form terphenyl target molecules.

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Notes and references

1 (*a*) N. Miyaura and A. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1979, 866; (*b*) N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.*, 1979, **20**, 3437.
2 For selected recent examples of chemoselective Suzuki reactions, see: (*a*) A. Voituriez and A. B. Charette, *Adv. Synth. Catal.*, 2006, **348**, 2363; (*b*) A. F. Littke, C. Y. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020; (*c*) A. H. Roy and J. F. Hartwig, *Organometallics*, 2004, **23**, 194; (*d*) T. Kamikawa and T. Hayashi, *Tetrahedron Lett.*, 1997, **38**, 7087.
3 Z. Khaddour, O. A. Akrawi, A. M. Hamdy, A. Suleiman, K. Jamous, A. Villinger and P. Langer, *Tetrahedron Lett.*, 2015, **56**, 554.
4 Z. Hassan, M. Hussain, A. Villinger and P. Langer, *Tetrahedron*, 2012, **68**, 6305.
5 M. F. Ibad, D. S. Zinad, M. Hussain, A. Ali, A. Villinger and P. Langer, *Tetrahedron*, 2013, **69**, 7492.
6 For examples, see: (*a*) F. Beaumard, P. Dauban and R. H. Dodd, *Org. Lett.*, 2009, **11**, 1801; (*b*) N. Eleya, T. Patonay, A. Villinger and P. Langer, *Helv. Chim. Acta*, 2013, **96**, 408; (*c*) S. Reimann, P. Ehlers, A. Petrosyan, S. Kohse, A. E. Spannenberg, T. V. Surkus, A. S. Ghochikyan, S. L. Saghyan, O. Kühn, R. Ludwig and P. Langer, *Adv. Synth. Catal.*, 2014, **356**, 1987.
7 For reviews, see: (*a*) S. Schröter, C. Stock and T. Bach, *Tetrahedron*, 2005, **61**, 2245; (*b*) M. Schnurch, R. Flaski, A. F. Khan, M. Spina, M. D. Mihovilovic and P. Stanetty, *Eur. J. Org. Chem.*, 2006, 3283.
8 (*a*) S. Schröter and T. Bach, *Synlett*, 2005, 1957; (*b*) I. Kaswasaki, M. Yamashita and S. Ohta, *J. Chem. Soc., Chem. Commun.*, 1994, 2085; (*c*) S. T. Handy and J. J. Sabatini, *Org. Lett.*, 2006, **8**, 1537.
9 The relative reactivity in polybrominated heteroaromatic systems can be predicted based on ^{1}H NMR considerations: the less shielded position in the non-halogenated congener predicts the more reactive bromide. See: S. T. Handy and Y. Zhang, *Chem. Commun.*, 2006, 299.
10 For regioselective Suzuki reactions of dibromobenzenes, see: (*a*) I. Ullah, M. Nawaz, A. Villinger and P. Langer, *Synlett*, 2011, 1895; (*b*) M. Sharif, M. Zeeshan, S. Reimann, A. Villinger and P. Langer, *Tetrahedron Lett.*, 2010, **51**, 2810; (*c*) K. Manabe and M. Yamaguchi, *Catalysts*, 2014, **4**, 307; (*d*) I. N. Houpis, C. Huang, U. Nettekoven, J. G. Chen, R. Liu and M. Canters, *Org. Lett.*, 2008, **10**, 5601; (*e*) M. Sharif, A. Maalik, S. Reimann, H. Feist, J. Iqbal, T. Patonay, A. Villinger and P. Langer, *J. Fluorine Chem.*, 2013, **146**, 19; (*f*) I. Ali, B. Siyo, Z. Hassan, I. Malik, I. Ullah, A. Ali, M. Nawaz, J. Iqbal, T. Patonay, A. Villinger and P. Langer, *J. Fluorine Chem.*, 2013, **145**, 18.
11 For Suzuki reactions of bis(trifluoromethanesulfonyl)benzenes, see: (*a*) M. Nawaz, I. Ullah, O. Abid, A. Ali, T. Patonay, A. S. Saghyan, T. V. Ghochikan, A. Villinger and P. Langer, *Can. J. Chem.*, 2013, **91**, 1048; (*b*) Z. Hassan, T. Patonay and P. Langer, *Synlett*, 2013, 412.
12 (*a*) P. Zhao and C. M. Beaudry, *Org. Lett.*, 2013, **15**, 402; (*b*) P. Zhao and C. M. Beaudry, *Angew. Chem., Int. Ed.*, 2014, **53**, 10500.
13 For related transformations in heteroaromatic systems, see: (*a*) S. Varello and S. T. Handy, *Synthesis*, 2009, 138; (*b*) A. Piala, D. Mayi and S. T. Handy, *Tetrahedron*, 2011, **67**, 4147.
14 S. Braun, H.-O. Kalinowski and S. Berger, *150 and More Basic NMR Experiments: A Practical Course*, Wiley-VCH, Weinheim, 1998.
15 We consistently number the dibromobenzenes as 2,4-dibromoanisoles.
16 Regioselectivities were measured by NMR of the crude reaction mixture.
17 The mass balance of the reactions was an intractable mixture of by products. Simply adding excess of one reactant or performing portion-wise additions of reactants often improves the reaction yield.
18 J. B. Johnson and T. Rovis, *Angew. Chem., Int. Ed.*, 2008, **47**, 840.
19 (*a*) C. Amatore, A. Jutand, F. Khalil, M. A. M'Barki and L. Mottier, *Organometallics*, 1993, **12**, 3168; (*b*) C. Amatore, G. Broeker, A. Jutand and F. Khalil, *J. Am. Chem. Soc.*, 1997, **119**, 5176.
20 Y. Macé, A. R. Kapdi, I. J. S. Fairlamb and A. Jutand, *Organometallics*, 2006, **25**, 1795.
21 B. P. Orner, J. T. Ernst and A. D. Hamilton, *J. Am. Chem. Soc.*, 2001, **123**, 5382.
22 See ESI† for preparation.