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A Tandem Catalytic Approach to Methyleneindenes: Mechanistic Insights into *gem*-Dibromoolefin Reactivity†

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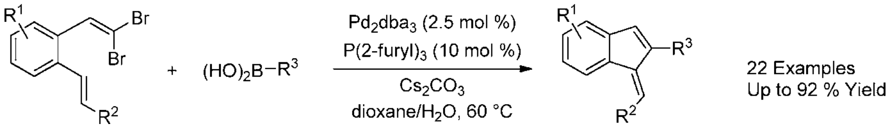
ABSTRACT



The methylenindene scaffold can be prepared from readily available *gem*-dibromoolefins using an efficient palladium-catalyzed tandem intermolecular Suzuki/intramolecular Heck reaction. The reaction is highly modular and proceeds under mild conditions. The choice of ligand was found to be crucial to control the selectivity of the reaction. Isolation of intermediates under different conditions provides insight into the mechanism.

The chemistry of *gem*-dihaloolefins, once almost entirely limited to alkyne synthesis, has undergone a renaissance through the application of palladium catalysis.[1,2] Of particular interest is the growing area of heterocycle synthesis through tandem catalysis, wherein the (*Z*)-bromide of a trisubstituted alkene undergoes an intramolecular cross coupling (cyclization) and the (*E*)-bromide participates in an orthogonal inter- or intramolecular coupling reaction which functionalizes or annulates the ring, respectively. This strategy has been applied to the synthesis of indoles,[3] benzothiophenes,[4] benzofurans,[5] isocoumarins,[6] and other heterocycles[7] and is characterized by its efficient and modular nature. Despite the utility of the methods which have been developed, only limited insight has been gained into their mechanisms.[8] In particular, it is in many cases unclear which coupling step occurs first.

Methyleneindenes have become highly sought after because of their ability to be converted into functionalized indenes, which are of interest as pharmaceutical agents,[9] as metallocene precursors in olefin polymerization,[10] and in material science applications.[11] A number of approaches to methyleneindenes have been reported, but these typically suffer from harsh reaction conditions, poor selectivity, or limited scope.[12−14] Herein, we disclose a mild, efficient method for the synthesis of methyleneindenes from *gem*-dibromoolefins and show how variation of reaction

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† In memory of Keith Fagnou.

[1] (a) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745. (b) Corey, E. J.; Fuchs, P. *Tetrahedron Lett.* **1972**, *36*, 3769.

[2] For a partial description of the catalytic reactions of dibromides, see: Wang, J. -R.; Matabe, K. *Synthesis* **2009**, 1405.

[3] (a) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, *7*, 3549. (b) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203. (c) Bryan, C. S.; Lautens, M. *Org. Lett.* **2008**, *10*, 4633. (d) Viera, T. O.; Meaney, L. A.; Shi, Y.-L.; Alper, H. *Org. Lett.* **2008**, *10*, 4899. (e) Arthuls, M.; Pontikis, R.; Florent, J.-C. *Org. Lett.* **2009**, *11*, 4608.

[4] Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064.

[5] (a) Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, 907. (b) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955.

[6] Shen, W.; Wang, L. *Tetrahedron Lett.* **1998**, *39*, 7625.

[7] (a) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152. (b) Sun, C.; Xu, B. *J. Org. Chem.* **2008**, *73*, 7361. (c) Chai, D.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 3054.

[8] Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538.

[9] (a) Clegg, N. J.; Paruthiyil, S.; Leitman, D. C.; Scanlan, T. S. *J. Med. Chem.* **2005**, *48*, 5989. (b) Maguire, A. R.; Papot, S.; Ford, A.; Touhey, S.; O'Connor, R.; Clynes, M. *Synlett* **2001**, 41. (c) Gao, H; Katzenellenbogen, J. A.; Garg, R.; Hansch, C. *Chem. Rev.* **1998**, *98*, 723.

[10] For a review on metallocenes in olefin polymerization, see: Leino, R.; Lehmus, P.; Lehtonen, A. *Eur. J. Inorg. Chem.* **2004**, 3201.

[11] (a) Barberá, J.; Rakitin, O. A.; Blanca Ros, M.; Torroba, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 296. (b) Yang, J.; Lakshmikanatham, M. V.; Cava, M. P. *J. Org. Chem.* **2000**, *65*, 6739.

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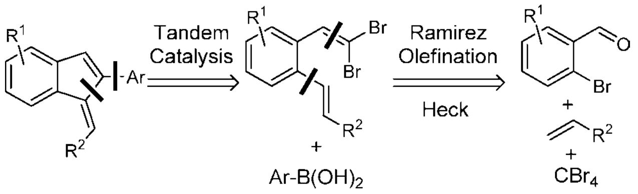
conditions alters the course of the reaction. This strategy provides three points of diversity; a boronic acid, a monosubstituted alkene Heck acceptor, and an *o*-bromobenzaldehyde can be varied to provide a high degree of modularity (Scheme 1).

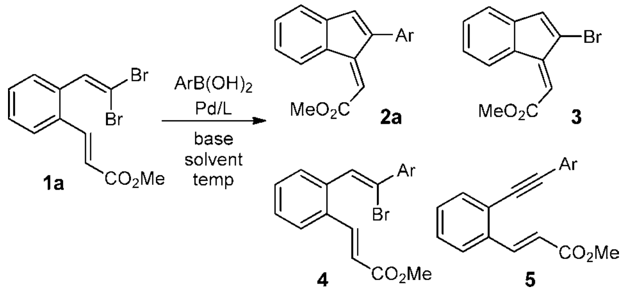
Scheme 1. Retrosynthetic Analysis



We used substrate **1a** to explore conditions for the tandem reaction (see Table 1). We began with the conditions previously developed for tandem Suzuki/amination and Suzuki/Heck couplings of *gem*-dihaloolefins;[3a,b] in both cases, conversion was poor, though a single product was isolated and identified as **3** (entries 1 and 2). Although previous reports have indicated that intermolecular coupling of a trisubstituted *gem*-dihaloolefin occurs selectively at the (*E*)-bromide,[15] it has been demonstrated that a coordinating group such as an alkyne or heteroatom can direct oxidative addition of Pd to the (*Z*)-bromide, leading to a reversal of selectivity for certain intramolecular couplings.[16] Interestingly, the indenyl bromide **3** does not undergo Suzuki coupling despite the presence of a boronic acid.

In an attempt to alter the selectivity, we investigated a mixed solvent system using trifurylphosphine (TFP) as ligand, as first described by Shen.[17] We were pleased to discover that not only can selectivity be reversed to give **4** (**3** is no longer observed) but also the desired tandem product **2a** can be obtained simply by increasing the reaction time (entries 3 and 4). Screening of various parameters led us to our optimal conditions: boronic acid (1.5 equiv), Pd_2dba_3 (2.5 mol %), TFP (10 mol %), and Cs_2CO_3 (4 equiv) in dioxane/water 5:2 at 60 °C. We also discovered that enhanced yields of **3** are obtained when $^tBu_3PHBF_4$ was used as the ligand (entry 6). Further studies are in progress to explain the nature of this selectivity.

Table 1. Screening of Reaction Parameters (Selected Entries)[a]



entry	ligand	base	temp (°C)	**2a**:**3**:**4**:**5**[b]
1	SPhos	K_3PO_4	110	0:15:0:0
2	Bu_4NBr[c]	K_3PO_4/Et_3N	110	0:24:0:0
3[d,e]	TFP	Na_2CO_3	60	31:0:55:nd
4[e]	TFP	Na_2CO_3	60	64:0:0:nd
5[e]	TFP	Cs_2CO_3	60	77:0:0:16
6	$^tBu_3PHBF_4$	Cs_2CO_3	110	0:45:0:0

[a] Reactions were run using 0.2 mmol of **1a**, 1.0 equiv of 3,4-dimethoxypheylboronic acid, 2.5 mol % of Pd_2dba_3, 10 mol % of ligand, and 4.0 equiv of base in 1 mL of dioxane overnight. [b] Isolated yields. [c] 1.0 equiv of Bu_4NBr was used instead of 10 mol % of ligand. [d] Reaction was run for 3 h. [e] 0.4 mL of water were added. Ar = 3,4-dimethoxyphenyl.

With these optimized conditions in hand, we set out to test the scope of our method (see Scheme 2). The reaction tolerated a wide range of boronic acids, including electron-rich, electron-poor, sterically crowded, and heteroaryl species (entries **2a**−**h**). Both electron-deficient alkenes and styryl derivatives could be used as Heck acceptors (entries **2i**−**n**). The efficiency was improved as the electron density on the aryl ring increased: a substrate bearing an electron-donating methoxy group (entry **2p**) led to higher yields than the electron-neutral system, while electron-poor substrates gave reduced yields (entries **2q**−**s**). Incorporation of a sterically demanding substituent *ortho* to the Heck acceptor greatly decelerated the Heck reaction: under normal conditions, only the Suzuki coupling occurs (entry **2t**). A thiophenyl substrate reacted sluggishly, giving the desired product in only 18% yield (entry **2u**). This could be due to coordination of the

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(12) For selected recent methyleneindene syntheses, see: (a) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Synlett* **2010**, 97. (b) Furuta, T.; Asakawa, T.; Iinuma, M.; Fujii, S.; Tanaka, K.; Kan, T. *Chem. Commun.* **2006**, 3648. (c) Abdur Rahman, S. M.; Sonoda, M.; Ono, M.; Miki, K.; Tobe, Y. *Org. Lett.* **2006**, *8*, 1197. (d) Basurto, S.; García, S.; Neo, A. G.; Torroba, T.; Marcos, C. F.; Miguel, D.; Barberá, J.; Blanca Ros, M.; de la Fuente, R. *Chem.—Eur. J.* **2005**, *11*, 5362. (e) Bekele, T.; Christian, C. F.; Lipton, M. A.; Singleton, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 9216. (f) Schmittel, M.; Vavilala, C. *J. Org. Chem.* **2005**, *70*, 4865. (g) Kovalenko, S. V.; Peabody, S.; Manoharan, M.; Clark, R. J.; Alabugin, I. V. *Org. Lett.* **2004**, *6*, 2457. (h) Singer, R. A.; McKinley, J. D.; Barbe, G.; Farlow, R. A. *Org. Lett.* **2004**, *6*, 2357. (i) Gilbertson, R. D.; Wu, H.-P.; Gorman-Lewis, G.; Weakley, T. J. R.; Weiss, H. -C.; Boese, R.; Haley, M. M. *Tetrahedron* **2004**, *60*, 1215. (j) Schreiner, P. R.; Prall, M.; Lutz, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5757.

(13) For an efficient approach to chlorinated derivatives, see: Ye, S.; Gao, K.; Zhao, H.; Wang, X.; Wu, J. *Chem. Commun.* **2009**, 5406.

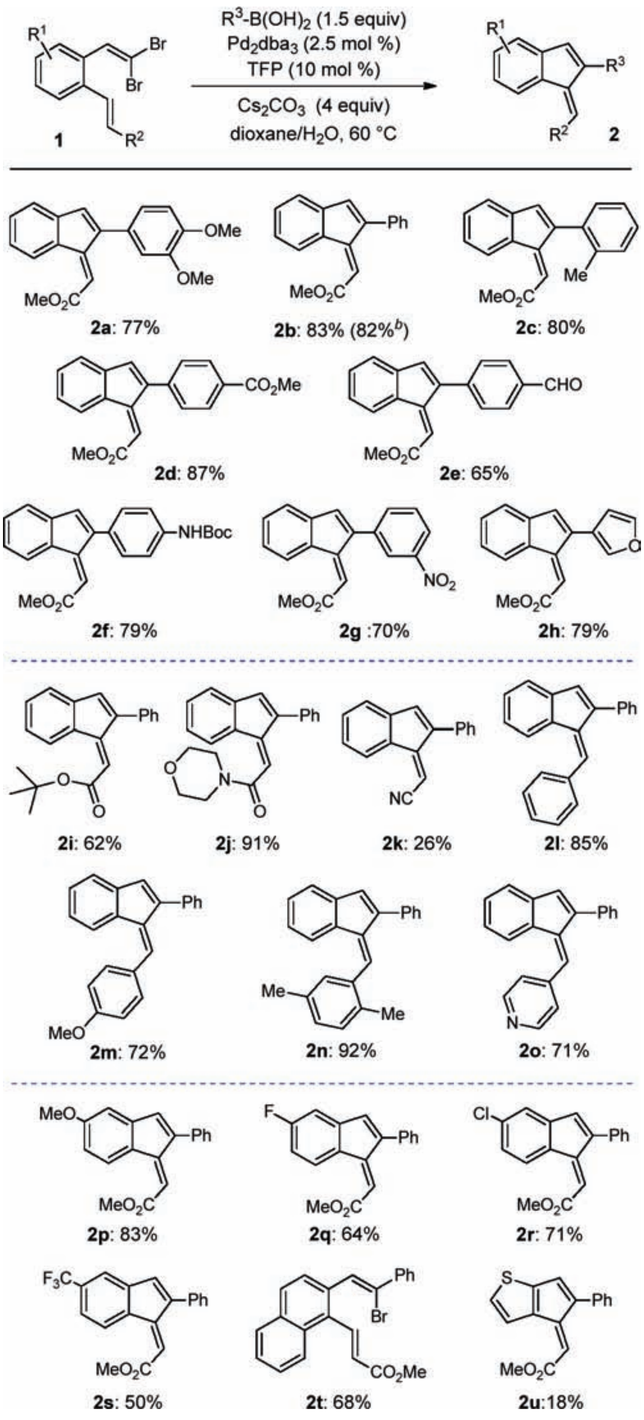
(14) During preparation of this manuscript, an alternative route to methyleneindenes from alkynyl *gem*-dibromoolefins was described: Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 2950.

(15) (a) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257. (b) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509. (c) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965. (d) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2732.

(16) (a) Nuss, J. M.; Rennels, R. A.; Levine, B. H. *J. Am. Chem. Soc.* **1993**, *115*, 6991. (b) Torii, S.; Okumoto, H.; Tadokoro, T.; Nishimura, A.; Rashid, M. A. *Tetrahedron Lett.* **1993**, *34*, 2139. We have also described reactions of *gem*-dibromoolefins wherein the (*Z*)-bromide must react first; see: (c) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653. (d) Newman, S. G.; Aureggi, V.; Bryan, C. S.; Lautens, M. *Chem. Commun.* **2009**, 5236.

(17) Shen, W. *Synlett* **2000**, 737.

Scheme 2. Scope of Tandem Reaction

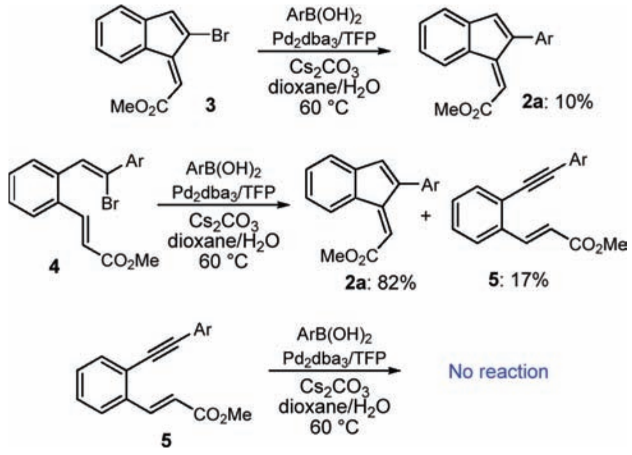


^{a} Reactions carried out using 0.2 mmol of **1**, 1.5 equiv of boronic acid, 2.5 mol % of Pd_2dba_3, 10 mol % of TFP, and 4 equiv of Cs_2CO_3 in 1,4-dioxane (1 mL)/H_2O (0.4 mL) at 60 °C for 18 h. ^{b} 1.0 mmol scale.

sulfur to the vinylpalladium intermediate, which would slow the Heck process.[18]

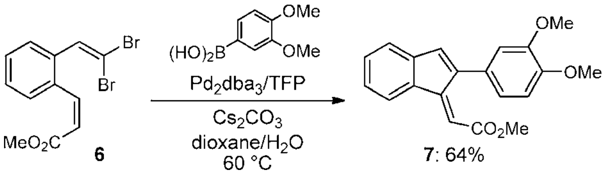
To study the mechansim further, potential intermediates **3** and **4** were subjected to the reaction conditions (Scheme 3). Intermediate **3** gave poor conversion and low yield, even after prolonged reaction times, while intermediate **4** gave exactly the product distribution obtained from the tandem reaction. This supports the idea that under the optimized conditions it is the (*E*)-bromide that undergoes oxidative addition first. The alkyne byproduct **5** was also subjected to the reaction conditions but was found to be completely unreactive.

Scheme 3. Investigation of Potential Reaction Intermediates^a



^{a} Conditions are identical to those in Table 2. Ar = 3,4-dimethoxyphenyl.

To establish that cyclization was occurring via a Heck-type mechanism, (*Z*)-alkene starting material **6** was synthesized. When this alkene was subjected to the reaction conditions, the alternate product isomer was obtained (eq 1). This demonstrates that the textbook Heck reaction mechanism (*syn*-carbopalladation followed by bond rotation and *syn*-β-hydride elimination) is operative in the tandem process.[19]



(1)

An overview of the proposed mechansim is displayed in Scheme 4. Path I is followed exclusively when small monodentate phosphines are used as ligands. In this pathway, oxidative addition of Pd^0 to the (*E*)-bromide occurs, followed by transmetalation with a boronate and reductive elimination of intermediate **4** to regenerate a

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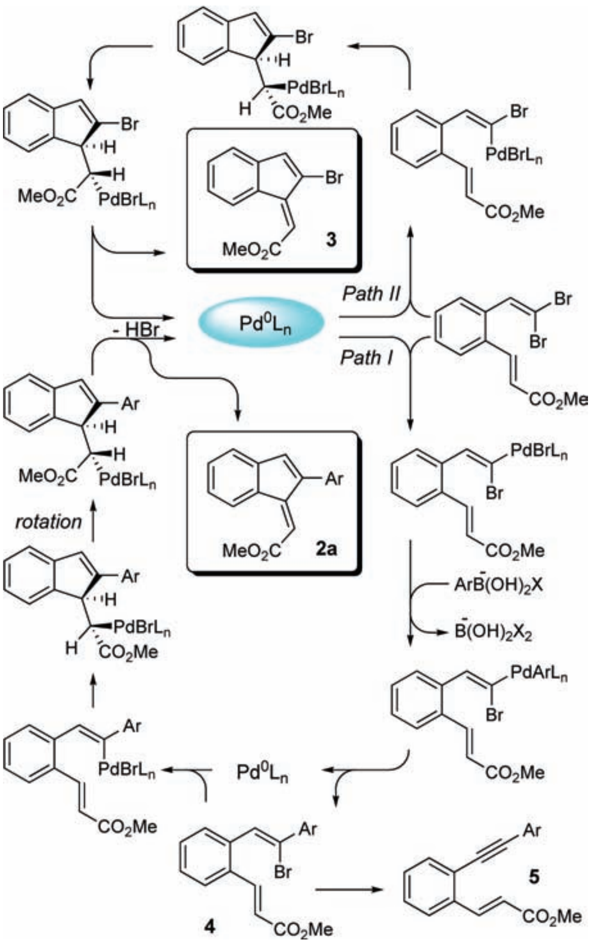
[18] Sulfur-containing compounds display strongly coordinating and absorbtive properties; see: (a) Alvaro, E.; Hartwig, J. *J. Am. Chem. Soc.* **2009**, *131*, 7858. (b) Hutton, A. T. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, 1984; Vol. 5, p 1131.

[19] For a thorough account of Heck reaction mechanisms, see: Jutand, A. In *The Mizoroki−Heck Reaction*; Oestreich, M., Ed.; John Wiley and Sons: Hoboken, 2009; p 1.

Scheme 4. Mechanism of the Tandem Reaction[a]



[a] Ligands omitted for clarity. X = Br or other Lewis base.

Pd^0 species. This intermediate may then undergo an E2 elimination to give alkyne byproduct **5** or reenter the catalytic cycle through oxidative addition to the remaining alkenyl bromide. In the latter case, the alkenylpalladium undergoes carbopalladation, followed by bond rotation and β-hydride elimination to give the (*Z*)-methyleneindene **2a**. When an electron-rich, sterically crowded ligand such as ^{t}Bu$_3$P or SPhos is used, Path II is followed. In this case, apparent oxidative addition to the (*Z*)-bromide occurs, and the Heck reaction proceeds as expected giving product **3**. Under the conditions conducive to Path I, product **3** does not undergo subsequent Suzuki coupling despite the presence of a boronic acid. Whether the (*Z*)-alkenylpalladium intermediate indeed arises from a selective oxidative addition, possibly directed by the olefin of the Heck acceptor, or is in fact obtained by an isomerization of the (*E*)-alkenylpalladium bromide is a question we are currently studying in our laboratories.

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Supporting Information Available: Full experimental details and characterization including ^{1}H and ^{13}C NMR spectra for all new compounds, along with X-ray crystal structures of compounds **2a** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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