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A Transition-Metal-Free Suzuki-Type Cross-Coupling Reaction of Benzyl Halides and Boronic Acids via 1,2-Metallate Shift

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Supporting Information Placeholder

ABSTRACT: Cross-coupling of organoboron compounds with electrophiles (Suzuki-Miyaura reaction) have greatly advanced C-C bond formation and well received in medicinal chemistry. During the last 50 years, transition metals play a central role throughout the catalytic cycle of this important transformation. In this process, chemoselectivity among multiple carbon-halogen bonds is a familiar challenge. In particular, selective oxidative addition of transition metals to alkyl halides rather than aryl halides is difficult due to unfavorable transition states and bond strengths. We describe a new approach that uses a single organic sulfide catalyst to activate both C(sp^3)-halides and aryl boronic acids *via* a zwitterionic boron "ate" intermediate. This "ate" species undergoes a 1,2-metallate shift to afford Suzuki coupling products using benzyl chlorides and aryl boronic acids. Various diaryl methane analogues can be prepared, including those with complex and biologically active motifs. The reactions proceed under transition-metal-free conditions and C(sp^2)-halides, including aryl bromides and iodides, are unaffected. The orthogonal chemoselectivity is demonstrated in the streamlined synthesis of highly functionalized diaryl methane scaffolds using multi-halogenated substrates. Preliminary mechanistic experiments suggest both the sulfonium salt and the sulfur ylide are involved in the reaction, with the formation of sulfonium salt being the slowest step in the overall catalytic cycle.

INTRODUCTION

Transition-metal-catalyzed cross-coupling of carbon-halides and carbon-boronic acids/esters is a dominant strategy for carbon-carbon bond synthesis in modern chemistry.[1] Over 60% carbon-carbon bond forming processes in medicinal chemistry are now accomplished using the Suzuki-Miyaura cross-coupling reaction.[2] Palladium and nickel are the most effective metals in this remarkable transformation, which has three sequential catalytic segments: oxidative addition (OA), transmetallation (TM) and reductive elimination (RE).[3] The procedure, however, has several limitations. In order to maintain appreciable concentrations of low-valent transition metals throughout the course of these reactions, an oxidative environment, such as ambient atmosphere, is often avoided.[3c, 4] More significantly, OA into C(sp^2)-X bonds is more facile than with their C(sp^3) counterparts[5] and as a result, cross-coupling reactions involving alkyl halides have limited tolerance of C(sp^2)-X bonds, especially aryl iodides and bromides. This inadequacy presents a difficult problem for syntheses using substrates containing several halogen atoms and extra steps are often needed to replace halogens with more distinguishable groups. Mechanistically, OA into C(sp^2)-halide bonds is concerted and generally facile, while metallation of C(sp^3)-halides is disfavored both for electronic reasons such as low reduction potential of alkyl halides[6] and stereochemical reasons, specifically steric hindrance and lack of orbital stabilization from neighboring sp^3-carbons (**Fig. 1a**).[7] A general solution to these limitations associated with OA requires a distinct mechanistic approach that does not involve an OA step.

Unlike transition metals, organic nucleophiles are inherently selective towards alkyl halides in S_N2 substitution reactions. Analogous reactions with aryl halides (S_NAr) are far more difficult. This textbook chemistry is an excellent example of complementary activation of C(sp^3)-halide bonds using organic molecules, and would be an ideal entry point towards an transition-metal-free cross-coupling strategy that does not require an OA step. So far, no such strategy for cross-coupling reactions has been reported.[8] The approach described here is redox-neutral throughout the catalytic cycle. It replaces toxic and expensive late transition metals with more environmentally sustainable small molecule catalysts that introduce complementary selectivity for carbon-carbon bond synthesis and potentially reverse the selectivity of C(sp^3) over C(sp^2).

In addition to OA, transition metals are also essential for the remaining catalytic cycle of cross-coupling reactions.[3a] Subsequent to OA, a new carbon-carbon bond is constructed following a sequence of TM followed by RE. Organic boron compounds are the most general partners with a carbon-metal bond for TM, due to well-balanced reactivity and wide tolerance to functional groups.[3b] Interestingly, organoboron compounds are known to form carbon-carbon bonds *via* a non-transmetallation pathway.[9] Boronic acids and esters are mild Lewis acids that are able to accept a lone pair of electrons from carbon anions to form anionic boron-centered "ate" complexes (**Fig. 1b**). When the carbon anion also contains a leaving group X, the resulting "ate" complex undergoes a stereospecific 1,2-metallate shift forming a new C-C bond.[10] This 1,2-carbon shift was first discovered in 1956 by Brown et al. in the hydroboration- oxidation reaction[11] and was subsequently reported in 1968 by Hooz and Linke for C-C bond synthesis.[12] We hypothesized that this unique reactivity of boron could be harnessed to replace the TM and RE steps in transition-metal-catalyzed cross-coupling reactions.

The key issue is to identify a catalyst capable of linking the halide activation step, an S_N2 substitution, with a carbon-carbon bond formation step, a 1,2-metallate shift. The essential boron "ate" complex is the link between these two steps. Boron "ate"

complexes are normally generated by nucleophilic addition of a carbon anion to a organoboron and this particular carbon also should be electrophilic so as to trigger subsequent 1,2-migration. Besides halide-substituted anions, typical donor/acceptor species are carbenes[12, 13] and ylides.[14] Organic sulfides are both good nucleophiles and effective leaving groups. They react with alkyl halides in the presence of a base to give sulfur ylides,[15] and reaction of a sulfur ylide with boron will generate a zwitterionic boron "ate" complex. Pioneering work by Aggarwal and co-workers demonstrated that the 1,2-metallate shift occurs readily in electron-rich borane "ate" complexes with sulfide as the leaving group.[14, 16] However, carbon migration from less electron-rich "ate" complexes, those derived from boronic acids or esters for example, has not been reported.[17] Our primary mission therefore is to identify a sulfide that is sufficiently nucleophilic to generate boron "ate" complexes from boronic acids, and also competent to trigger subsequent 1,2-shifts. The migratory product, alkyl boronic acids, would undergo *in situ* protodeboronation to give the final cross-coupled product. We believe fine tuning the electronics of the sulfide might yield a competent catalyst for this purpose.

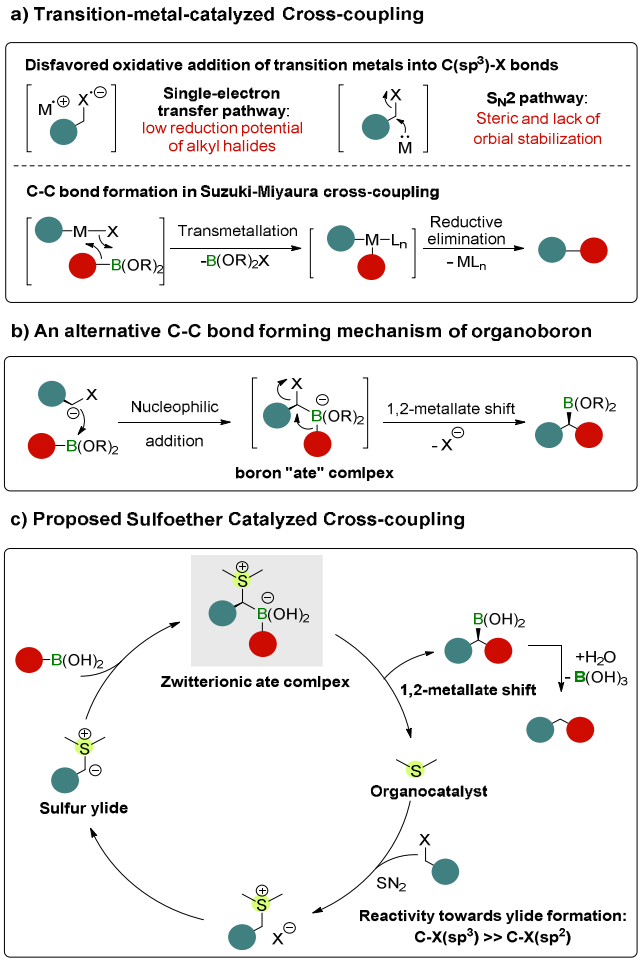


Figure 1. Transition-metal-catalyzed vs Sufide-Catalyzed Suzuki cross-coupling. M = transition metal; X = halogen.

RESULTS AND DISCUSSION

We began our investigation with benzyl bromide (**1a**) and 4-methoxyl boronic acid (**2a**) as coupling partners (**Fig. 2**). The desired diaryl methane cross-coupling product (**3aa**) was obtained in 22% GC yield, when tetrahydrothiophene (**cat. 1**) and $K_4P_2O_7$ were tested as the catalyst and the base, respectively. Among most inorganic bases examined (see Supplementary Information for details), $K_4P_2O_7$ exhibits the best overall balance of activity and basicity. A major side-product of this reaction was decomposition of **1a** as a result of hydrolysis by the boronic acid (**2a**) and the base. Significant quantities of the corresponding benzyl alcohol and dibenzyl ether were observed. In addition, the α-carbons of **cat. 1** are susceptible to deprotonation upon sulfonium formation. This can be followed by [2.3]-sigmatropic rearrangement to cause decomposition and deactivation of the catalyst.[15a] A similar behavior was observed for the six membered cyclic sulfide (**cat. 2**). The acyclic dialkyl sulfide (**cat. 3**) showed poor catalytic activity and triphenylphosphine sulfide (**cat. 4**), thiourea (**cat. 5** and **6**) and carbamimidothioate (**cat. 7**) led to poor conversions due to the instability of those sulfides under the reaction conditions. (For detailed discussions, see Supplementary Information). Next, in order to avoid α-deprotonation, diaryl sulfides were examined. Although diphenyl sulfide (cat. **8**) yielded merely 10% of the cross-coupling product (**3aa**), side reactions such as the decomposition of benzyl bromide and the sulfide catalyst were suppressed. Increased catalytic activity was observed for cyclic diaryl sulfides. Use of dibenzothiophene (**cat. 9**) yielded 21% of **3aa** with 40% of the halide remaining. We hypothesized that the low yield was a result of attenuated nucleophilicity of **cat. 9** due to aromaticity that tends to delocalize electron lone pairs on the sulfur atom. Generally a more nucleophilic sulfide would favor the sulfonium salt formation. Molecules such as thianthrene (**cat. 10**) are not fully aromatic and a transannular heteroatom further increases the nucleophilicity of such compounds. Indeed, an improved yield was obtained for **cat. 10**-**cat. 13**. N-benzylation was observed for catalysts containing a NH group, and more nucleophilic selenium analogues failed to catalyze the cross-coupling reaction. **Cat. 14** decomposed rapidly under the conditions of the reaction.

We next focused on fine tuning the structure of **cat. 12** in an attempt to further improve the nucleophilicity while avoiding *N*-benzylation of the catalyst. When a less nucleophilic *N*-Boc catalyst (**cat. 15**) was used, noticeably lower catalytic activity was observed. Introduction of electron-donating amino groups into the phenyl rings (**cat. 16**) failed to enhance the yield as ammonium salt formation was very rapid under the reaction conditions. The *N*-methylated catalyst (**cat. 17**) afforded 52% yield of **3aa**, but in this case, ammonium salt formation was still observed. The use of a less basic phenyl-substituted nitrogen (**cat. 18**) improved the yield to 62%. The best conversion was with **cat. 20**, which afforded 68% of the desired product. Under these optimized reaction conditions, hydrolysis of bromide (**1a**) could not be completely suppressed, but use of the corresponding chloride (**4a**) solved this problem and in this case, the cross-coupling occurred smoothly in 80% isolated yield. In the absence of **cat. 20**, no cross-coupling occurred, ruling out a possible direct S_N2 displacement mechanism.[18] **Cat. 20** belongs to a well-known family of photosensitizers,[19] and consequently, the reaction was tested in dark, but the cross-coupling was not affected.

With the optimized reaction conditions in hand, we surveyed the substrate scope of benzyl chlorides and aryl boronic acids (**table 1**). This transition-metal-free protocol tolerates various aromatic substituents in the benzyl chlorides and both electron-rich and electron-poor functional groups were tested, leading to moderate to good yields. Benzyl chlorides with electron-poor substituents react more slowly, despite being better electrophiles for S_N2 reactions. This observation is consistent with Aggarwal and Harvey's finding, that S_N2 substitution of these compounds with electron-neutral sulfides is slow.[20] Potassium bromide proved to be an effective co-catalyst that accelerates the formation of the sulfonium salt *via in situ* halogen exchange. Highly electron-deficient benzyl chlorides, including pentafluorobenzyl chloride, react smoothly with phenyl boronic acid using 20 mol% KBr. *Ortho*-, *meta*-, and *para*-methylbenzyl chlorides reacted with

similar efficiency, but the reaction was noticeably slower for 2,5-dimethylbenzyl chloride (**table 1**, product **3ga**), possibly due to steric effects.

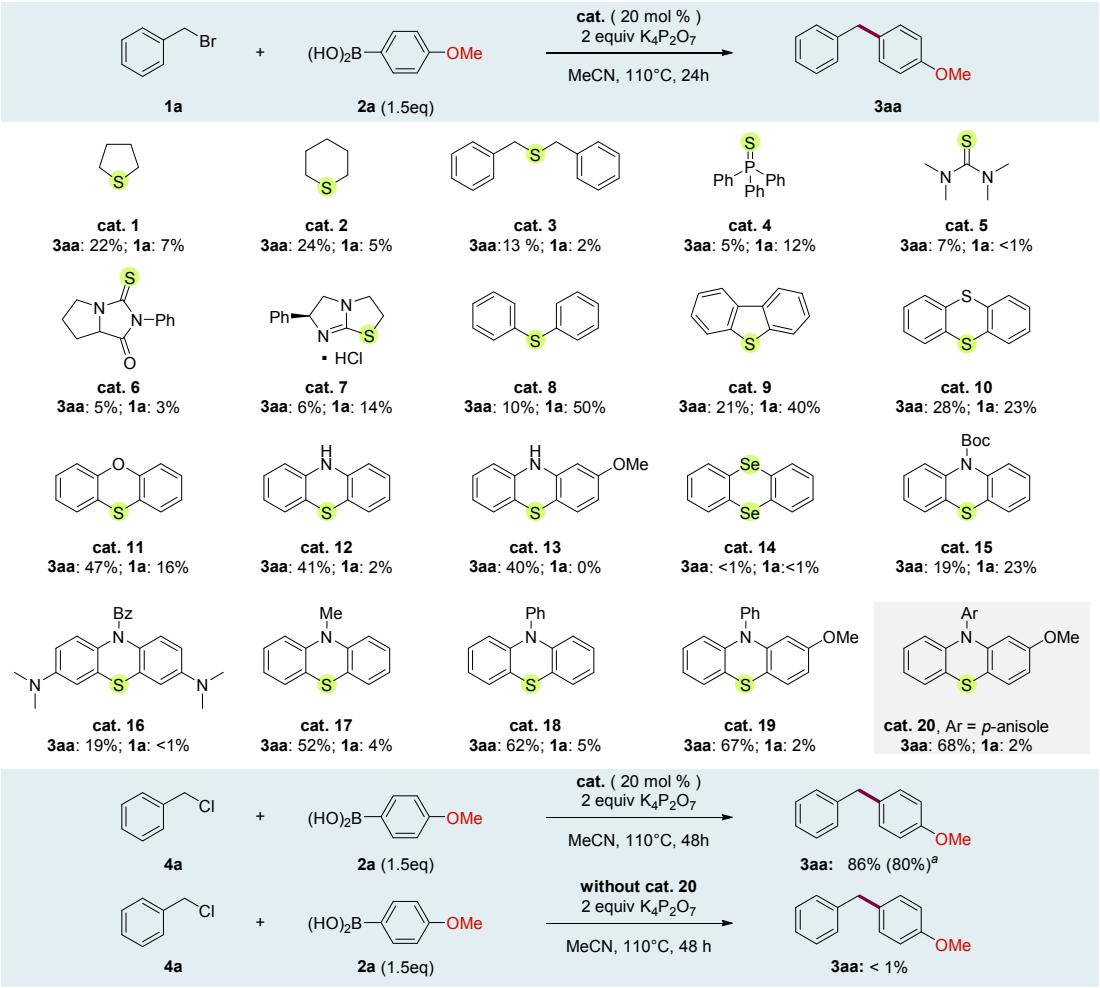
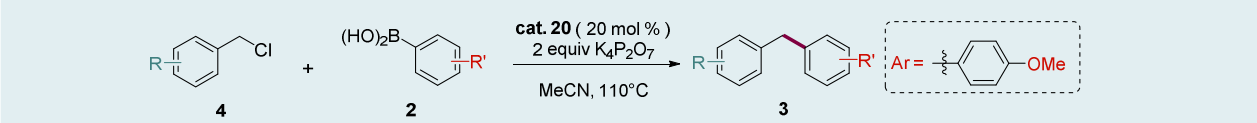


Figure 2. Discovery of a Sulfide Catalyst Enabling Transition-Metal-Free sp^3-sp^2 cross-coupling. Reactions were conducted using 0.5 mmol benzyl halide **1a**, 0.75 mmol 4-methoxyphenylboronic acid **2a**, 20 mol% catalyst, 1 mmol $K_4P_2O_7$ in 1 mL acetonitrile under Ar at 110 °C for 24 h. Yield was determined by GC using biphenyl as internal standard. [a] 0.5 mL acetonitrile was used. The number in parentheses reflects the isolated yield.

Compatibility with halogens was surveyed next. Aryl fluorides, chlorides, bromides and iodides were all unaffected, regardless of their positions on the aromatic ring (**Table 1**, products **3ha-3na**). These results clearly demonstrate the complementary reactivity compared to transition-metal-catalyzed reactions.

We next studied the scope of arylboronic acids. The reaction shows preference to electron-rich arylboronic acids. *Para*-methoxy, *para*-diphenylamino, and 9-phenanthracenyl substrates afford the corresponding coupling products in 80%, 81% and 84% yield, respectively. Analogs with electron-donating methyl, phenyl and sulfide groups give moderate yields. For highly electron-rich arylboronic acids, K_2CO_3 sometimes works better as the base. Arylboronic acids with strong electron-withdrawing groups give low conversions, despite being stronger Lewis acids that would react faster with the sulfur ylide intermediate. Protodeboronation of the arylboronic acids and hydrolysis of the benzyl halides were predominant. During the cationotropic 1,2-metallate shift, these electron-deficient aryl groups are not nucleophilic enough to attack the sulfide leaving group on the adjacent, sp^3-hybridized carbon center. On the other hand, mildly electron-withdrawing halogen substituents are tolerated, providing additional handles for cross-coupling cascades with the help of transition metal catalysis. Aliphatic boronic acids, for example hexylboronic acid and cyclohexylboronic acid, are poor coupling partners under current conditions. Trace amounts of products were found by GC. We suspect the aromatic π-electrons of arylboronic acids participate and facilitate the 1,2-metallate shift process via a phenonium type intermediate. Although sp^3 C-B bonds are more nucleophilic than sp^2 C-B bonds, the lack of π-electrons might require significantly higher activation energy for 1,2-alkyl shift. In addition, alkylboronic acids are more prone to protodeboronation under the reaction conditions. Heteroaryl substrates containing basic nitrogens are not tolerated due to *N*-benzylation. Dihydrobenzofuran (**3ar**), indoline (**3as**), and quinolinone (**3at**) containing boronics gave the desired products in moderate to good yields. Structurally complex and biologically active motifs are well tolerated in this transition-metal-free sp^2-sp^3 C-C bond coupling reactions. For example, substrates containg bazedoxifene (**3wu**), celecoxib (**3yv**) and androsterone (**3rw**) as sidechains reacted with synthetically useful efficiency to yield novel drug analogues (Table 1, products **3wu**, **3yv** and **3rw**). Interestingly, ketones did not interfere with the sulfur ylide intermediate. The antilipidemic drug beclobrate was prepared using 4-chlorobenzyl chloride and the corresponding arylboronic acid.

Table 1. Substrate Scope of the Transition-Metal-Free C(sp^3)-C(sp^2) Cross-Coupling Reaction.



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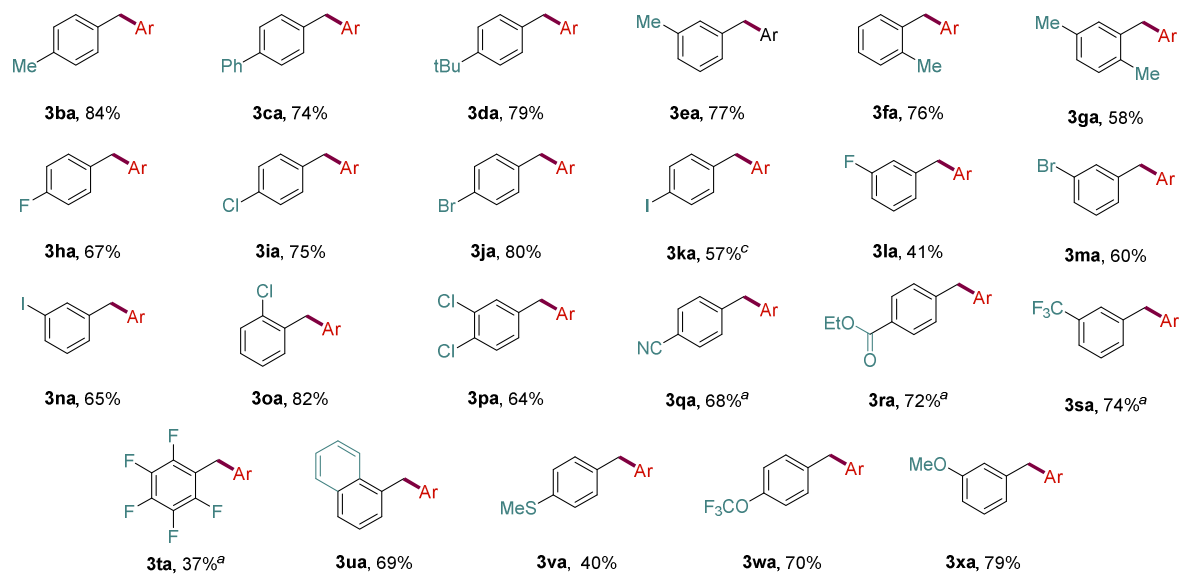
benzyl chlorides



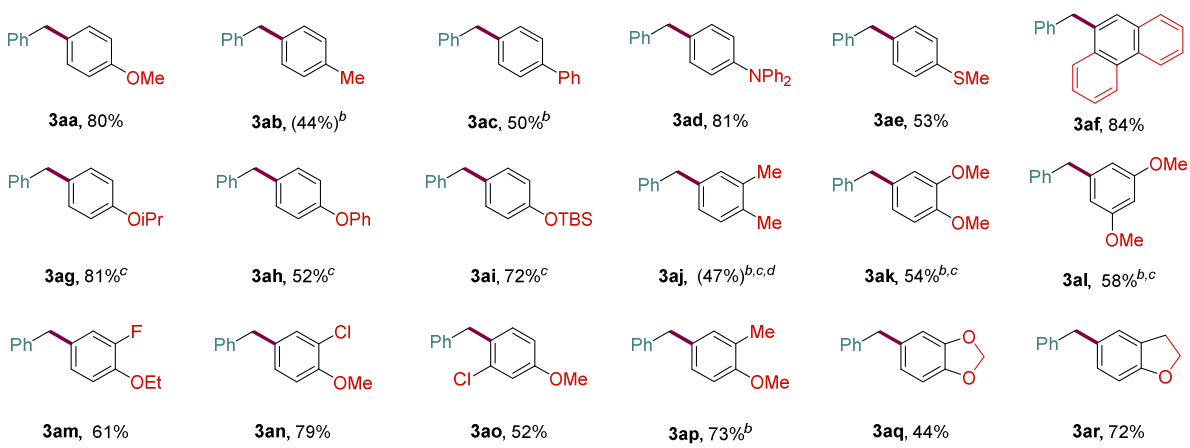
3ba, 84% **3ca**, 74% **3da**, 79% **3ea**, 77% **3fa**, 76% **3ga**, 58%

3ha, 67% **3ia**, 75% **3ja**, 80% **3ka**, 57%[c] **3la**, 41% **3ma**, 60%

3na, 65% **3oa**, 82% **3pa**, 64% **3qa**, 68%[a] **3ra**, 72%[a] **3sa**, 74%[a]

3ta, 37%[a] **3ua**, 69% **3va**, 40% **3wa**, 70% **3xa**, 79%

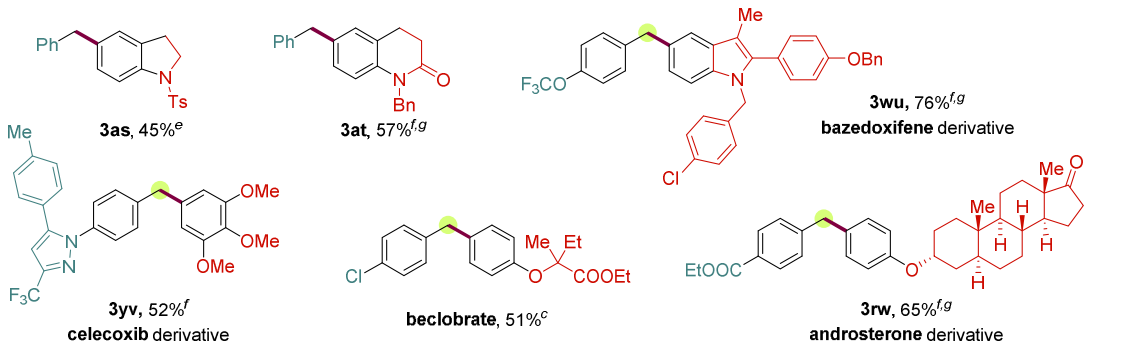
boronic acids



3aa, 80% **3ab**, (44%)[b] **3ac**, 50%[b] **3ad**, 81% **3ae**, 53% **3af**, 84%

3ag, 81%[c] **3ah**, 52%[c] **3ai**, 72%[c] **3aj**, (47%)[b,c,d] **3ak**, 54%[b,c] **3al**, 58%[b,c]

3am, 61% **3an**, 79% **3ao**, 52% **3ap**, 73%[b] **3aq**, 44% **3ar**, 72%



3as, 45%[e] **3at**, 57%[f,g] **3wu**, 76%[f,g] **bazedoxifene** derivative

3yv, 52%[f] **celecoxib** derivative **beclobrate**, 51%[c] **3rw**, 65%[f,g] **androsterone** derivative

Unless otherwise specified, reactions were performed using 0.5 mmol substituted benzyl chlorides, 0.75 mol arylboronic acid, 1 mmol $K_4P_2O_7$ and 0.1 mmol **cat. 20** in 0.5 mL acetonitrole at 110 ºC for 48 h. Isolated yield. The number in parentheses reflects the GC yield. [a] 0.1 mmol KBr was used as co-catalyst. [b] 1 mmol arylboronic acid was used. [c] 1 mmol K_2CO_3 was used as base instead of $K_4P_2O_7$. [d] Run at 130 ºC. [e] 0.25 mmol benzyl chloride, 0.375 mmol boronic acid and 40% **cat. 20** was used in 0.3M MeCN. [f] 30% **cat. 20** was used. [g] 0.25 mmol boronic acid and 0.375 mmol benzyl chloride was used in 0.4 mL acetonitrile/1,4-dioxane (v/v=1/1)

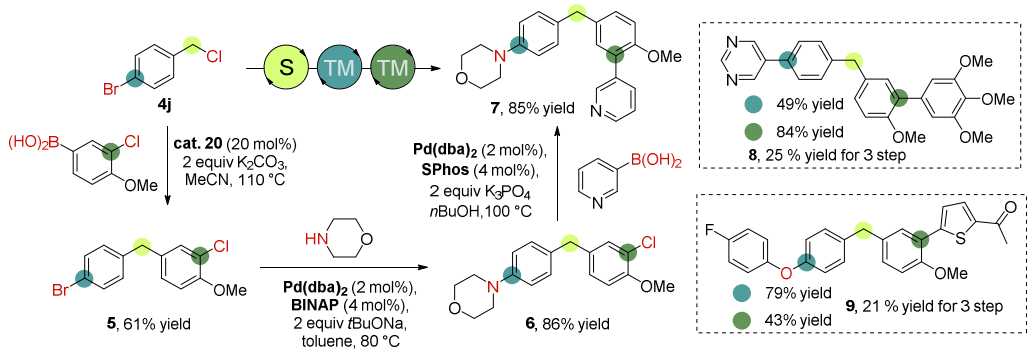
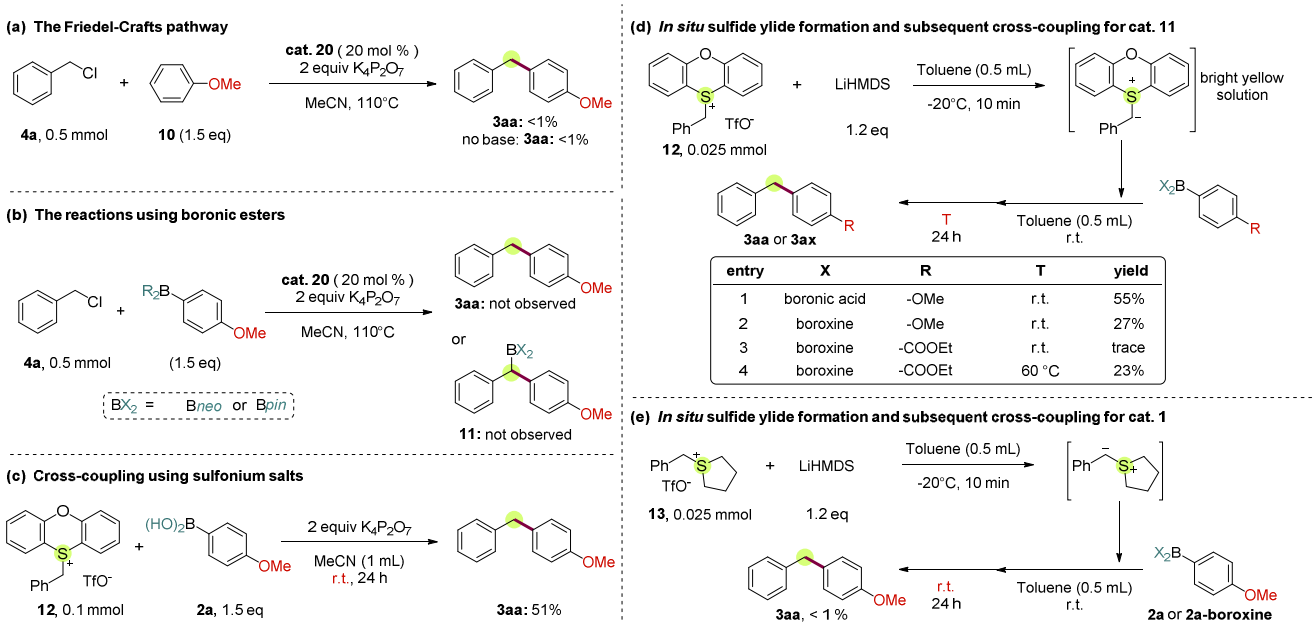


Figure 3. Modular synthesis of diaryl methane scaffolds using sequential cross-coupling reactions.



entry	X	R	T	yield
1	boronic acid	-OMe	r.t.	55%
2	boroxine	-OMe	r.t.	27%
3	boroxine	-COOEt	r.t.	trace
4	boroxine	-COOEt	60 °C	23%

Figure 4. Mechanistic experiments

Unsymmetrical diarylmethanes are prevalent structural motifs in natural products and pharmaceutical agents.[21] Consequently, the sulfide catalyzed cross-coupling reactions were applied in the synthesis of several structurally sophisticated diarylmethane scaffolds The exclusive selectivity of alkyl chloride over aryl bromide and aryl iodide led us to test modular cross-coupling reactions using cascades of organo and transitional metal catalysis (**Figure 3**). Substrates containing multiple halogens were employed. The sulfide-catalyzed C(sp^3)-C(sp^2) cross-coupling was carried out first. The remaining C(sp^2)-halide bonds are further functionalized using transition metal catalysis. The reaction between halide (**4j**) and 3-chloro-4-methoxy-phenylboronic acid affords, in 61% yield, compound **5**, which contains one aryl bromide and one aryl chloride. Selective functionalization of the aryl bromide was accomplished using palladium-catalyzed Buchwald-Hartwig amination/ether formation or Suzuki coupling.[22] The less reactive aryl chloride was converted to aryl and heteroaryl groups by Suzuki coupling. The highly functionalized diarylmethane analogs (**7**, **8**, **9**) were prepared in a three-step sequence, a modular approach which allows rapid generation of diversified libraries of diarylmethanes using multi-halogenated substrates.

An alternative mechanism for this benzyl chloride-aryl boronic acid coupling reaction would be Friedel-Crafts benzylation by an arene that could be generated by protodeboronation. This possible reaction pathway was tested using benzyl chloride and anisole. It was found that only less than 1% of the cross-coupling product was detected, regardless as to whether or not a base or a sulfide was used (**Figure 4a**). These negative results suggest that neither benzyl chloride nor its sulfonium salt is electrophilic enough to react with anisole directly. Arylboronic esters were commonly used to generate boron "ate" complexes by reacting with lithium or Grignard reagents. These substrates fail to react under our standard cross-coupling conditions (**Figure 4b**). The increased steric effect and decreased Lewis acidity might prevent addition of a soft nucleophilic such as a sulfur ylide.

In order to further understand the mechanistic details of this sulfur ylide mediated transformation, a number of experiments were carried out. The sulfonium salts of **cat. 20** is unstable. The corresponding benzyl sulfonium salt of **cat. 11** (compound **12**) was prepared by heating the sulfide and excess benzyl bromide in the presence of TMSOTf. Interestingly, treating compound **12** with *p*-methoxyphenylboronic acid (**2a**) and $K_4P_2O_7$ led to the desired cross-coupling product **3aa** in 51% yield at room temperature. In sharp contrast, the reaction between **2a** and benzyl bromide only afforded 1% of product **3aa** using **cat. 20** at room temperature. These results suggest the sulfonium is likely involved in

the catalytic cycle and its formation is the slowest step that requires heating. The sulfur ylide formation, boron "ate" complex formation, 1,2-metallate shift and protodeboronation are all facile steps that occur smoothly at room temperature. HRMS of the reaction mixture also suggests the concentration of the sulfonium is very low (see SI).

The sulfur ylide of compound **12** can be obtained by using LiHMDS -20 ºC in toluene, which appears as a bright yellow solution. Isolation of the pure ylide was unsuccessful and self-dimerization to stilbene was the major decomposition pathway. Direct transfer of the crude ylide solution into a suspension of **2a** in toluene led to immediate color quenching. The cross-coupling product **3aa** slowly formed in 55% yield after 24 hours at room temperature. (**Figure 4d, entry 1, 2**). Stilbene was formed in 14% yield based on compound **12**. When boroxine was used, **3aa** was obtained in 27% yield. We propose that the reduced yield was due to the increased stereo effect of boroxine. These results suggest the sulfide ylide is likely the key intermediate, and the rapid color fading indicates the formation of the "ate" complex is very fast at room temperature. During our substrate scope survey (Table 1), no stilbene formation was observed, indicating the sulfur ylide was formed in low concentration. This observation is consistent with our proposal that the sulfonium salt formation is the rate-limiting step for this reaction. The final protodeboronation has been reported to be facile for diarylmethyl boronic acids.[13]

Employing electron deficient boroxines resulted in low conversion at room temperature. Moderate yield (22%) of **3ax** was obtained at 60 ºC (**Figure 4d, entry 3, 4**), indicating higher activation energy is required to promote the migration of electron-deficient aryl groups compared to their electron-rich counterparts. Sulfur ylide generated from tetrahydrothiophene (**cat. 1**) gave very low yield of the cross-coupling product **3aa** at room temperature (**Figure 4e**). Although **cat 1** is a better nucleophile than **cat. 20**. It is a poor leaving group and might disfavor the 1,2-metallate shift. At elevated temperature, decomposition of **cat. 1**, involving multiple α-Hs of the sulfide, is rapid. In comparison, the reduced nucleophilicity of **cat. 20** is compensated by facilitating the 1,2-metallate shift as a better leaving group. The lack of α-Hs of this sulfide also improves catalyst stability.

CONCLUSION

In summary, after nearly half a century of domination of transition metals in the Suzuki reaction, an alternative transition-metal-free strategy is developed for $C(sp^3)$-$C(sp^2)$ cross-coupling reactions between benzyl chlorides and arylboronic acids. The exclusive chemoselectivity of alkyl over aryl halides is complementary to transition-metal-catalyzed processes. The reaction proceeds through a novel catalytic cycle: sulfonium salt, sulfur ylide, boron "ate" complex, 1,2-metallate shift and protodeboronation. This approach eliminates possible $C(sp^2)$-$C(sp^2)$ coupling reactions for substrates with multiple aryl halide substituents and enables a modular synthesis of unsymmetrical diarylmethanes using a sequential cross-coupling technique. We anticipate this new strategy will significantly widen the paradigm for cross-coupling reactions.

Supporting Information

Experimental procedures, analytical and spectroscopic data for new compounds, copies of NMR spectra. 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 interests.

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REFERENCES

(1). (a) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9047. (b) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722.

(2). Schneider, N.; Lowe, D. M.; Sayle, R. A.; Tarselli, M. A.; Landrum, G. A. *J. Med. Chem.* **2016**, *59*, 4385.

(3). (a) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis* (University Science Books, Sausalito, CA, 2010). (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270.

(4). Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829.

(5). (a) Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674. (b) Kambe, N.; Iwasaki, T.; Terao, J. *Chem. Soc. Rev.* **2011**, *40*, 4937. (c) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299.

(6). (a) Rondinini, S.; Mussini, P. R.; Muttini, P.; Sello, G. *Electrochim. Acta.* **2001**, *46*, 3245. (b) Hu, X. *Chem. Sci*. **2011**, *2*, 1867.

(7). (a) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910. (b) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

(8). Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219.

(9). For selected recent review see: (a) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535. (b) Leonori, D.; Aggarwal, V. K. *Acc. Chem. Res.* **2014**, *47*, 3174.

(10) For selected example for 1,2-metallate shift to sp^3 carbon, see: (a) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7491. (b) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778. (c) Schmidt, F.; Keller, F.; Vedrenne, E.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1149. (d) Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 4025. (e) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096. (f) Partridge, B. M.; Chausset-Boissarie, L.; Burns, M.; Pulis, A. P.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 11795. (g) Pulis, A. P.; Blair, D. J.; Torres, E.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 16054. (h) Rasappan, R.; Aggarwal, V. K. *Nat. Chem.* **2014**, *6*, 810. (i) Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature* **2014**, *513*, 183. (j) Watson, C. G.; Balanta, A.; Elford, T. G.; Essafi, S.; Harvey, J. N.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2014**, *136*, 17370. (k) Balieu, S.; Hallett, G. E.; Burns, M.; Bootwicha, T.; Studley, J.; Aggarwal, V. K. *J. Am.Chem. Soc.* **2015**, *137*, 4398. (l) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken J. P. *Science* **2016**, *351*, 70. For selected example for 1,2-metallate shift to sp^2 carbon, see: (m) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal V. K. *Nat. Chem.* **2014**, 6, 584. (n) Llaveria, J.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 10958. (o) Wang, Y.; Noble, A.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 4270. (p) Odachowski, M.; Bonet, A.; Essafi, S.; Conti-Ramsden, P.; Harvey, J. N.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2016**, *138*, 9521. (q) Armstrong, R. J.; García-Ruiz, C.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2017**, *56*, 786.

(11) Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956**, *78*, 5694.

(12). Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936.

(13) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 494.

(14). (a) Aggarwal, V. K.; Fang, G. Y.; Schmidt, A. T. *J. Am. Chem. Soc.* **2005**, *127*, 1642. (b) Robiette, R.; Fang, G. Y.; Harvey, J. N.; Aggarwal, V. K. *Chem. Commun.* **2006**, 741. (c) Fang, G. Y.; Wallner, O. A.; Blasio, N. D.; Ginesta, X.; Harvey, J. N.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2007**, *129*, 14632. (d) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem.,*

Int. Ed. **2007**, *46*, 359.

(15) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. For selected review, see: (b) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841. (c) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611. (d) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341.

(16) Aggarwal, V. K.; Harvey, J. N.; Robiette, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 5468.

(17) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412.

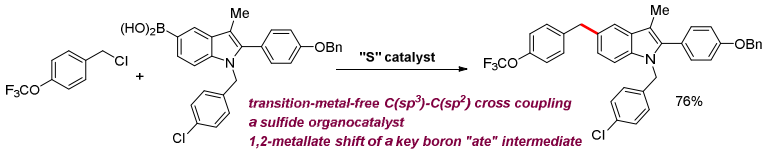
(18) Li, C.; Zhang, Y.; Sun, Q.; Gu, T.; Peng, H.; Tang, W. *J. Am. Chem. Soc.* **2016**, *138*, 10774.

(19) Treat, N. J.; Sprafke, H.; Kramer, J. W.; Clark, P. G.; Barton, B. E.; Read de Alaniz, J.; Fors, B. P.; Hawker, C. J. *J. Am. Chem. Soc.* **2014**, *136*, 16096.

(20) Robiette, R.; Trieu-Van, T.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2016**, *138*, 734.

(21) Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J. A.; Hall, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 9694.

(22) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (c) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555. (d) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.



transition-metal-free $C(sp^3)$-$C(sp^2)$ cross coupling
a sulfide organocatalyst
1,2-metallate shift of a key boron "ate" intermediate
exclusive selectivity of alkyl over aryl halides
60 examples, up to 84% yield