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Regio- and stereoselective synthesis of tetra- and triarylethenes by *N*-methylimidodiacetyl boron-directed palladium-catalysed three-component coupling

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The flexible synthesis of tetra- and triarylethenes bearing different aryl groups has been a long-standing challenge in organic synthesis. Here we report a palladium-catalysed *syn*-diarylation of arylethynyl *N*-methyliminodiacetyl (MIDA) boronates. The products, triarylalkenyl *N*-methyliminodiacetyl boronates, allow a step-economic and modular synthesis of tetra- or triarylethenes via a subsequent stereospecific Suzuki-Miyaura coupling reaction or base-promoted protodeborylation, respectively. Use of the sp^3-B(MIDA) masked aryl alkyne is the key factor for success by offering an exceptionally good regioselectivity for the boron-retentive coupling. The unusual regioselectivity is believed to arise from the stabilization due to the strong electron donation from the C—Pd σ bond to the p-orbital of boron in the transition state of migratory insertion. A broad range of differently substituted tetra- and triarylethenes are constructed in good yields and geometrical control. Synthetic manipulation of the C-B bond also enables the facile construction of several other types of tetra-substituted alkenes.

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Alkenes represent one of the most important classes of organic compounds. Although numerous methods exist for alkene preparation, the synthesis of polysubstituted alkenes in a regio- and stereochemically defined manner still poses a significant challenge to synthetic organic chemists[1–4]. In principle, six isomers exist for fully substituted alkenes with four different R groups. The control of regio- or stereoselectivity, therefore, is critical when planning a synthetic method. As an extended π-system, tetraarylethenes have been valuable targets of synthetic endeavor due to their useful physical, structural, and electronic properties[5–7]. Nevertheless, given the typically small electronic and steric differences between the individual aryl groups (compared to the difference between aryl and alkyl groups), the selective synthesis of tetraarylethenes bearing four different aromatic substituents is inherently challenging. While the classical double bond-forming methods such as olefin metathesis[8], Wittig[9] and McMurry[10] reactions are effective for tetraarylethene synthesis, the stereoselectivity of these protocols is typically a problem[1–4]. Platform synthesis is a powerful strategy to realize the synthesis of complex molecules in a programable and diversity-oriented format. In this regard, the advances of metal catalysis have inspired tremendous efforts towards modular tetraarylethene construction starting from alkenes[11–17] or alkynes[18–26]. Nevertheless, lengthy synthetic operations, the poor functional group tolerance arising from the participation of organolithium or Grignard reagents, and the often-encountered poor regioselectivity strongly limits their practical application.

A notable contribution by the Larock group revealed a straightforward tetraarylethene synthesis via a palladium-catalysed three-component coupling of readily available aryl iodides and arylboronic acids with internal alkynes (Fig. 1a)[27,28]. The ability to simultaneously introduce two aryl groups in one single synthetic operation makes this protocol appealing. Mechanistically, the three-component reaction proceeds via an oxidative addition/migratory insertion/reductive elimination sequence. While the stereoselectivity, derived from *cis*-arylpalladation, is generally excellent, the regioselectivity is problematic when unsymmetrical diaryl alkynes are employed. In addition, terminal alkynes are ineffective coupling partners due to the competitive Sonogashira coupling side reaction.

We considered a variation of Larock's protocol as a promising solution to the truly flexible tetraarylethene synthesis. To maximize the flexibility of the reaction, a high-degree control of the direction of the migratory insertion step should be realized. To this end, we envisioned that the use of an alkyne substrate pre-functionalized by attaching a transformable masking group to the triple bond is a promising approach. Ideally, the masking group should confer sufficient electronic bias to the triple bond, thereby rendering the migratory insertion regioselective. Nevertheless, the drastic alternation of the electron density on the triple bond should be avoided, otherwise the formation of biarenes via the direct Suzuki–Miyaura coupling of aryl iodide with arylboronic acid would compete as a side reaction. In addition, this masking group should be applicable to a follow-up cross-coupling reaction to install the final aryl group, but remain intact under the three-component coupling conditions with the palladium catalyst present. As such, the identification of proper reaction conditions to enable orthogonal reactivities is necessary but represents a challenge. Guided by the above-mentioned concept, we reasoned the sp^3-hybridized MIDA (*N*-methyliminodiacetyl) boron might be an optimal choice[29–32]. Early studies reveal the notable stability of MIDA boron towards diverse reaction conditions. Importantly, this moiety, as a protected form of boronic acid, is transformable to other functional groups under a one-pot deprotection/coupling reaction condition. Advances from us, and others have demonstrated that MIDA boron functionalized unsaturated systems (including alkenes[33–42] and alkynes[43–50]) are intriguing synthons for boron-retentive transformations[51–53]. Specifically, Yudin and Dudding[54], and Guérinot and Cossy[55], have independently observed the unique electronic directing effect of MIDA boron in palladium-catalysed Heck reactions and Wacker oxidations of alkenyl MIDA boronates, respectively (Fig. 1b). Computational analysis reveals a drastic electron donation from the C−Pd σ bond to a boron centered p-orbital the transition state due to the hemilabile nature of the MIDA B−N dative bond[56]. A similar regioselectivity trend was also observed in our previous rhodium

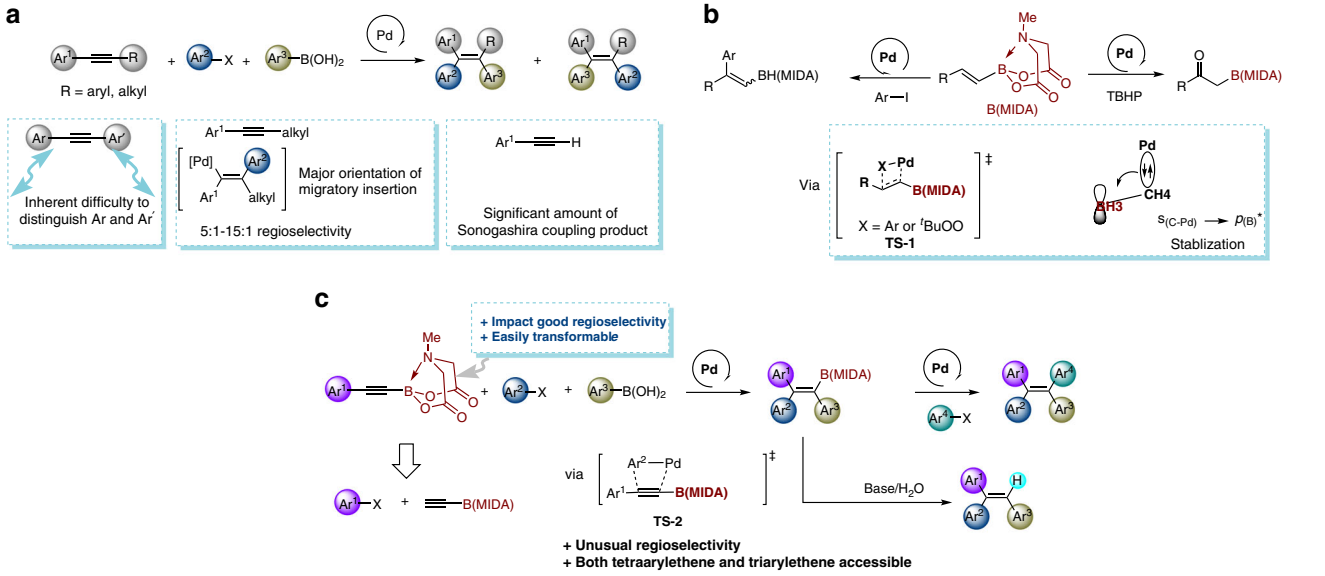


Fig. 1 Related work and reaction design. **a** Overview of Larock's three-component coupling reaction. **b** Palladium-catalysed functionalization of alkenyl MIDA boronates. **c** This work: palladium-catalysed *syn*-diarylation of arylethynyl MIDA (*N*-methyliminodiacetyl) boronates and its follow-up transformations

(III)-catalysed C–H annulation reaction with alkyne MIDA boronates[44].

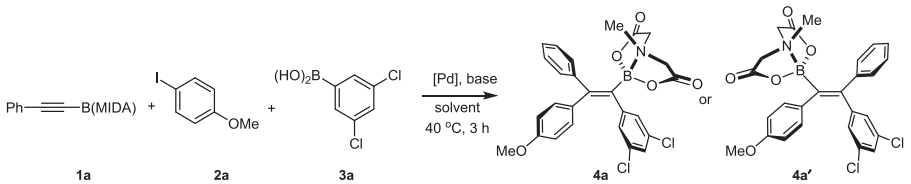
Herein, we report a palladium-catalysed regio- and stereoselective diarylation of arylethynyl MIDA boronates with aryl halides and arylboronic acids (Fig. 1c). The regioselectivity, guided by MIDA boron, is distinct from the previous observations when aryl alkyl acetylenes were used as substrates[27,28]. The starting arylethynyl MIDA boronates are readily accessible via a Sonogashira coupling of the corresponding aryl halides with commercially available ethynyl MIDA boronate. Synthetic manipulations of the MIDA boron moiety in the thus formed diarylated products via a stereospecific Suzuki–Miyaura coupling or base-promoted protodeborylation lead to a truly flexible and stereodefined synthesis of tetra- and triarylethenes.

Results

Screening of reaction conditions. We first investigated the feasibility of the palladium-catalysed coupling reaction of phenylethynyl MIDA boronate **1a** with iodide **2a** (2.0 equiv.) and boronic acid **3a** (2.0 equiv.). Complexity may arise due to the presence of two different organoborons (the chemoselectivity issue), the possible competing direct Suzuki–Miyaura coupling, and the unclear regio- as well as stereoselectivity issues. Gratifyingly, with 5 mol % $PdCl_2(PhCN)_2$ as catalyst and $KHCO_3$ as base in DMF at 40 °C[27], the diarylated alkene product **4a** was formed as a single regio- and stereoisomer in 42% yield (Table 1, entry 1). Interestingly, structural elucidation revealed that the phenyl and the 3,5-dichlorophenyl group resides *trans* to each other across the resulting carbon–carbon double bond, which is in contrast to the previous observations that the aryl group derived from the boronic acid preferentially locates at the position proximal to the aryl substituent of the alkyne, indicating the unique directing effect of MIDA boron. Biaryl derived from direct Suzuki–Miyaura coupling was detected as the major byproduct. The screening of different palladium-based catalysts proved that $PdCl_2(MeCN)_2$ to be ideal, giving a higher yield of 46% (entries 2–6). Switching from $KHCO_3$ to Ag_2CO_3 led to a higher conversion of **1a** (entries 7–10).The attempt to employ a variety of metal ligands in this reaction was proven to be unfruitful (see Supplementary Table 1). Other solvents were also screened (entries 12–14), with acetonitrile being a better choice (75% yield). It is worth to mention that a significant amount regioisomer **4a'** was formed in acetone (entry 13). Consistent with the previous observations, the use of H_2O (15 equiv) as additive further improved the yield to 94% (entry 15). Interestingly, decreasing the catalyst loading to 1 mol % also deliverd the product in 63% yield (entry 16). Unlike the previous three-component coupling reaction wherein 100 °C was used, a temperature of 40 °C was sufficient for the reaction to proceed efficiently, demonstrating the mildness of our reaction. As a comparison, the reaction of three congeners of phenylethynyl MIDA boronate, including the corresponding pinacol boronate **I**, trifluoroboronate **II**, and B(dan) **III** all resulted in a rapid decomposition, with no boron-retentive diarylated products being found (Fig. 2). Interestingly, the silicon protected alkyne **IV** showed trivial reactivity in this reaction. **IV** was largely recovered after the reaction. Moreover, phenyl ethyl alkyne is applicable to our reaction conditions, but a low yield of 11% was obtained. The regioselectivity of this reaction is identical to Larock's observation [27].

Synthesis of triarylalkenyl MIDA boronates. With the optimized conditions in hand, the scope on the aryl group of alkynyl MIDA boronates was first examined (Fig. 3a). Both electron-rich and electron-poor aryl substituents are compatible with the

Table 1 Optimization studies[a]



Entry	[Pd] (5 mol %)	Base	Solvent	Yield[b]	Ratio[c]
1	$PdCl_2(PhCN)_2$	$KHCO_3$	DMF	42%	>20:1
2	$Pd(OAc)_2$	$KHCO_3$	DMF	26%	>20:1
3	$PdCl_2(MeCN)_2$	$KHCO_3$	DMF	46%	>20:1
4	$PdCl_2$	$KHCO_3$	DMF	27%	>20:1
5	$Pd(OCOCF_3)_2$	$KHCO_3$	DMF	ND	–
6	$PdCl_2(PPh_3)_2$	$KHCO_3$	DMF	ND	–
7	$PdCl_2(MeCN)_2$	Na_2CO_3	DMF	20%	>20:1
8	$PdCl_2(MeCN)_2$	Cs_2CO_3	DMF	ND	-
9	$PdCl_2(MeCN)_2$	Ag_2CO_3	DMF	56%	>20:1
10	$PdCl_2(MeCN)_2$	DBU	DMF	ND	-
12	$PdCl_2(MeCN)_2$	Ag_2CO_3	DMSO	Trace	-
13	$PdCl_2(MeCN)_2$	Ag_2CO_3	Acetone	70%	4:1
14	$PdCl_2(MeCN)_2$	Ag_2CO_3	MeCN	75%	>20:1
15[d]	$PdCl_2(MeCN)_2$	Ag_2CO_3	MeCN	94%[e]	>20:1
16[f]	PdCl2(MeCN)2	Ag2CO3	MeCN	63%	>20:1

ND not detected
[a]**1a** (0.1 mmol), **2a** (0.2 mmol), **3a** (0.2 mmol), [Pd] (5 mol %), base (0.1 mmol) in 1 mL solvent at 40 °C for 3 h
[b]^{1}H-NMR yield
[c]Ratio of **4a**:**4a'**
[d]With H_2O (15 equiv)
[e]Isolated yield
[f]1 mol % [Pd] was used

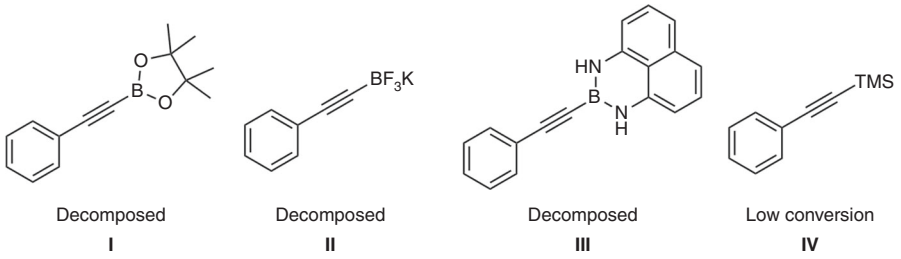


Fig. 2 Unsuccessful substrates in palladium-catalysed three-component reaction. For I–III no boron-containing diarylated products were obtained

reaction conditions, providing the desired products in generally moderate to good yields. In addition, broad functional group tolerance was found, as evident by the survival of valuable methoxy (**4n**), bromo (**4d**), acetyl (**4g**, **4o**), ester (**4k**, **4l**, **4q**), nitrile (**4i**), nitro (**4h**), trifluoromethyl (**4j**, **4u**), and trifluoromethoxy (**4m**) groups in the reaction. The sterically hindered *ortho*-substituent (**4p-4r**) does not hamper the reactivity. Heterocycles, such as isoxazole (**4w**), thiophene (**4x**), indole (**4y**), thiozole (**4z**), benzothiophene (**4aa**), and carbozole (**4ab**) were also tolerated, although the electron-rich ones gave relatively lower yields. In all the cases, clean *cis*-addition to the alkyne was observed. However, in some cases, the formation of a minor amount of the regioisomer was found. The scope on the aryl iodides is also noteworthy. A variety of electron-rich or -neutral (hetero)aryl iodides, including the one bearing a free hydroxyl substituent (**4ae**), the one which is sterically shielded (**4aj**), were successfully employed. More interestingly, alkenyl bromides (**4ap**, **4aq**) were also effective coupling partners to provide the desired 1,3-diene products in reasonable yields. The easy availability of arylboronic acids offered tremendous chances for the structural diversity of the product. Interestingly, in addition to the electron-neutral and electron-rich arylboronic acids, the electron-deficient ones (**4as**, **4at**, **4av**, **4az**, **4ba, 4be**, **4bg**), which were poor coupling partners in Larock's protocol, also worked very well in this chemistry. An alkenyl MIDA boronate (**4bl**) substituted with three heteroarenes was also constructed in reasonable yield. Unfortunately, the employment of arylboronic acids bearing an *ortho*-substituent (**4bm**) resulted in low yield using our present reaction conditions, revealing a limitation of the protocol. The structure of **4ba** was unambiguously assigned by X-ray crystallographic analysis. In accordance to the observations mentioned above, an additive-based robustness screen demonstrated the broad functional group tolerance of the reaction conditions (Fig. 3b)[57,58]. A variety of synthetically important moieties,such as a ketone, aldehyde, free alcohol, amide, aryl bromide, acetal, or even challenging additives like aniline or a nitrile, were well tolerated. However, the screen indicated that terminal alkynes and alkenes along with sterically unshielded *N*-heterocycles are not compatible with the reaction conditions (see Supplementary Methods).

Synthesis of tetraarylethenes. Having established the regio- and stereoselective synthesis of triarylalkenyl MIDA boronates, we set out to explore their capacity to be engaged in metal-catalysed cross-coupling reactions. As shown in Fig. 4a, we were pleased to find that under Burke's slow-release reaction conditions, a series of triarylalkenyl MIDA boronates underwent Suzuki–Miyaura coupling smoothly with diverse (hetero)aryl iodides to deliver the tetraarylethenes in good to excellent yields. As expected, this reaction is stereospecific, thereby leading to a truly simple and flexible construction of differently substituted tetraarylethenes. A representative while interesting example is the effective synthesis of **5t** bearing four heterocycles. To maximize the reaction efficiency, a telescoped synthesis was conducted. Thus, the arylethynyl MIDA boronate was first reacted with an aryl iodide and an arylboronic acid. After the consumption of alkyne, the reaction mixture was subjected directly to the follow-up Suzuki–Miyaura coupling with the second aryl iodide. To highlight the power of this protocol, three tetraarylethenes were obtained in reasonable yields over two steps upon one single purification (Fig. 4b) (See Supplementary Methods).

Synthesis of triarylethenes. Larock's three-component coupling reaction is not applicable to triarylethenes synthesis since terminal alkynes are not viable substrates. We envisoned the lability of C–B bond towards hydrolysis may offer a chance to construct triarylethenes starting from triarylalkenyl MIDA boronates via protodeborylation. In other words, the MIDA boron moiety could be considered as a transient protecting group for terminal alkynes. As expected, our trials showed that by simple treatment of the alkenyl MIDA boronate products with K_3PO_4 (2.5 M, 7.5 equiv) in DMF at 40 °C, the corresponding triarylethenes could be obtained in high efficiency (Fig. 5a). This process is highly stereospecific with no isomerization of the double bond being found. The simplicity of the reaction conditions also rendered the telescoped synthesis of triarylethenes possible. Thus, by following a two-step, one-purification procedure, four triarylethenes were synthesized in moderate yields with good regio- and stereocontrol (Fig. 5b) (See Supplementary Methods).

A gram-scale synthesis of **4a** (1.5 g, 75%) was successful under the standard reaction conditions (Fig. 6a), demonstrating the potential utility of the reaction. Apart from the synthesis of tetraarylethenes and triarylethenes, other synthetic manipulation of the MIDA boron moiety in the cross-coupling products also allowed the stereodefined synthesis of diverse tetra-substituted alkenes (Fig. 6b). For instance, both alkenyl and alkynyl bromides were efficiently coupled with 4aa to give the corresponding extended π-systems (**7** and **8**)[59]. By treating with KHF_2, the corresponding potassium trifluoroboronates **9** could be obtained[60]. In another vein, ligand exchange with pinacol under acidic conditions provided the pinacol boronate **10** in quantitative yield[61]. This sp^2-B species **10** could then react with aliphatic halides under palladium catalysis to give a methylated (**11**) or benzylated (**12**) product[62]. In addition, a palladium-catalysed oxidative alkoxycarbonylation with carbon monoxide in MeOH allowed the construction of a fully substituted α,β-unsaturated ester **13**[63]. Finally, a phenanthrene product (**14**) was obtained via a Suzuki–Miyaura coupling/oxidative cyclization cascade[64].

Mechanistic proposal. The following reaction mechanism is proposed for this process (Fig. 6). Initially, Pd(II) is reduced to Pd (0), probably by arylboronic acid (Fig. 7a). The oxidative addition of aryl iodide to Pd(0) furnishes arylpalladium species **A**, which then undergoes *cis*-carbopalladation with arylethynyl MIDA boronate to deliver intermediate **B**. The regioselectivity, which is different from Larock's observation, may arise from the

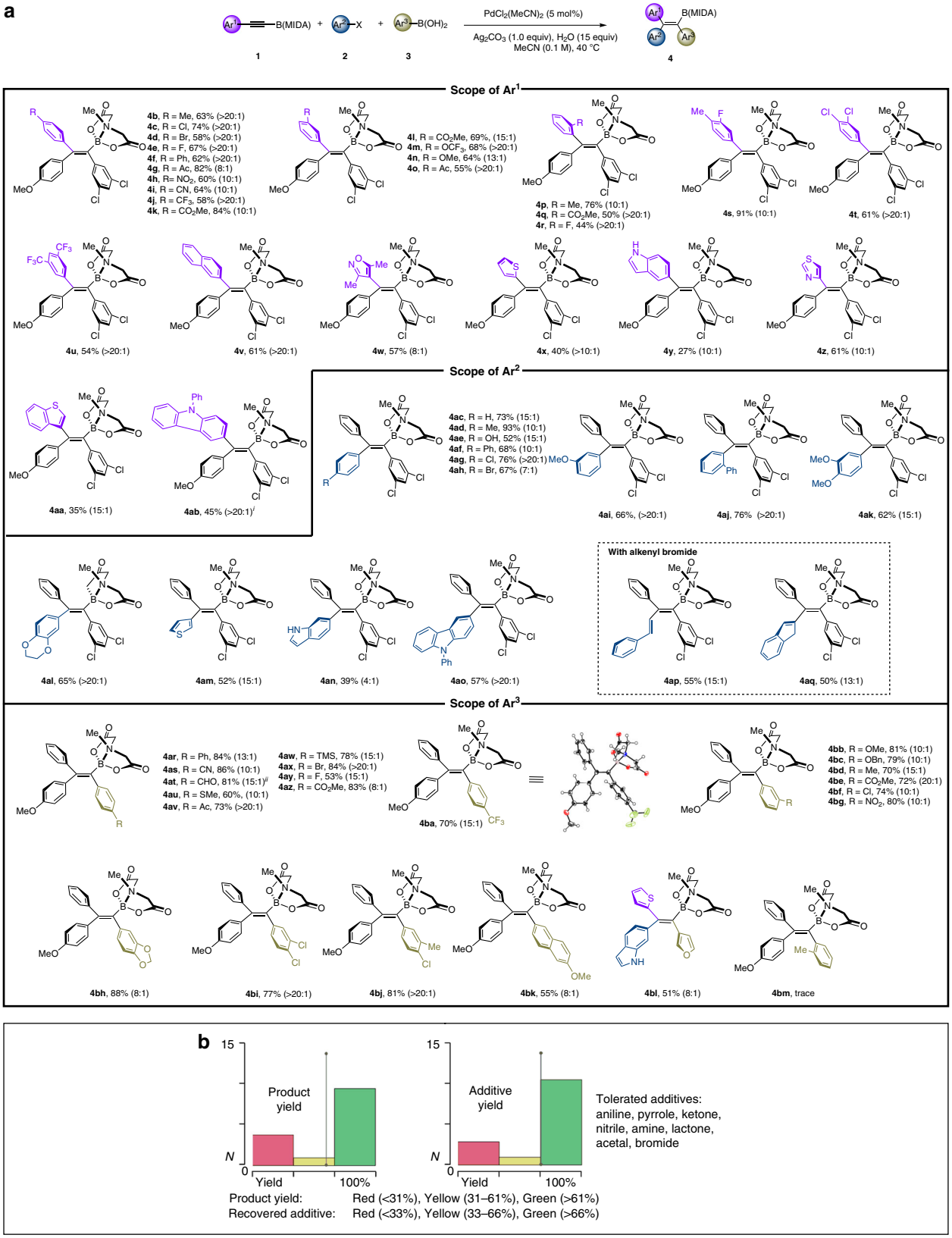


Fig. 3 Synthesis of triarylalkenyl MIDA boronates. **a** Substrate scope. **b** Robustness screen. Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.4 mmol), $PdCl_2(MeCN)_2$ (5 mol %), Ag_2CO_3 (0.2 mmol), H_2O (3 mmol) in 2 mL MeCN at 40 °C for 3–5 h; ratio of regioisomers is determined by crude ^{1}H-NMR and shown in the parentheses. [i] at 30 °C. [ii] at 25 °C

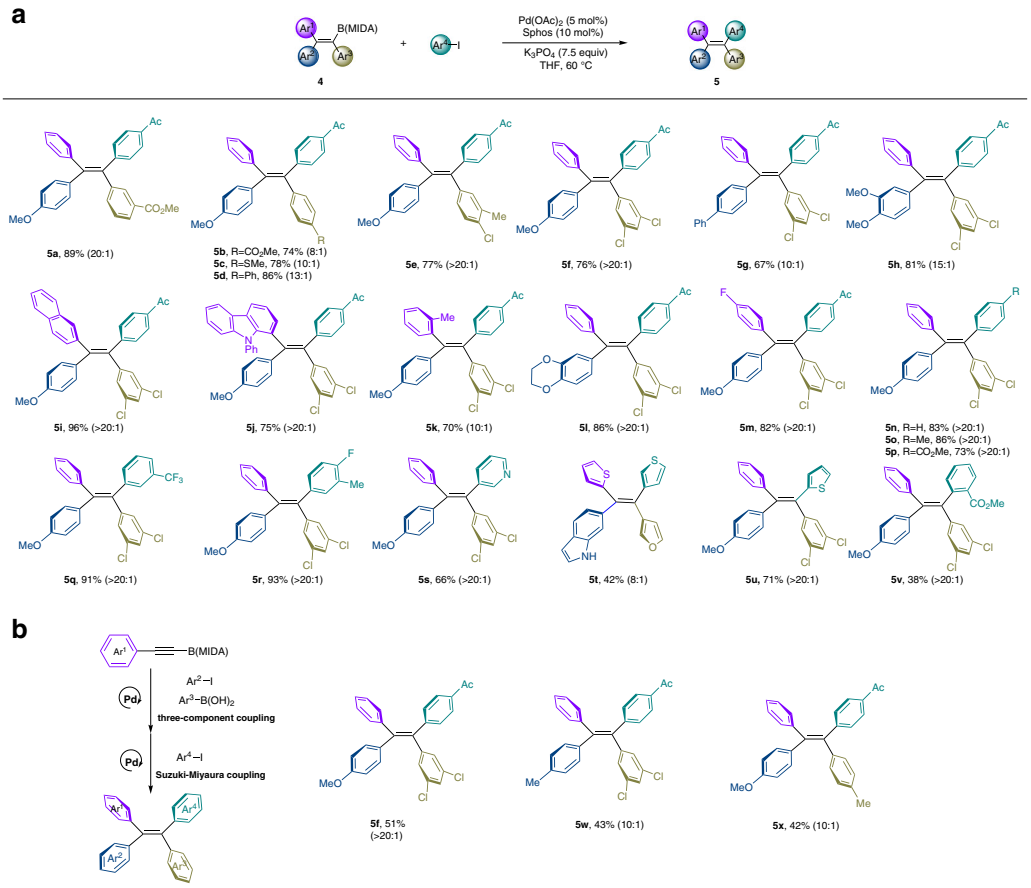


Fig. 4 Synthesis of tetraarylethenes. **a** Pd-catalysed Suzuki-Miyaura coupling reaction to synthesize tetraarylethenes. **b** Synthesis of tetraarylethenes in one pot

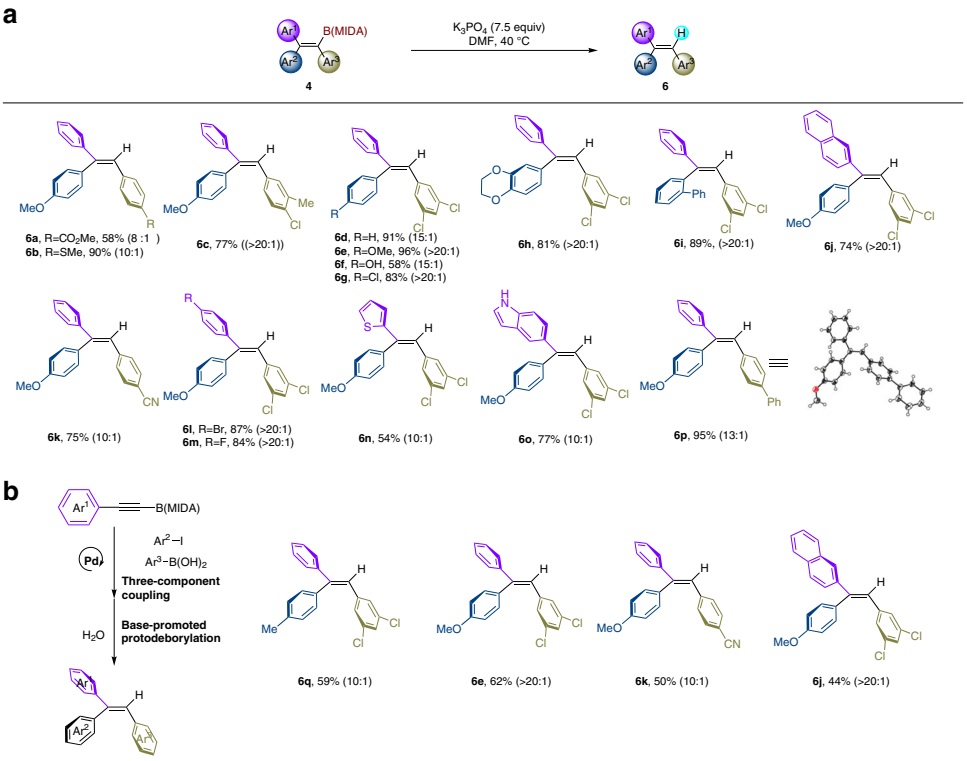


Fig. 5 Synthesis of triarylethenes. **a** Base-promoted protodeborylation to synthesize triarylethenes. **b** Synthesis of triarylethenes in one pot

stabilization due to the strong electron donation from the C−Pd σ bond to the p-orbital of boron in the transition state (Fig. 7b), although a simple steric reason that Pd favor the bulky B(MIDA) end is also possible. Thereafter, the transmetalation of **B** with $Ar^3B(OH)_2$ generates **C**, which upon reductive elimination produces triarylalkenyl MIDA boronate with simultaneous regeneration of the Pd(0) catalyst.

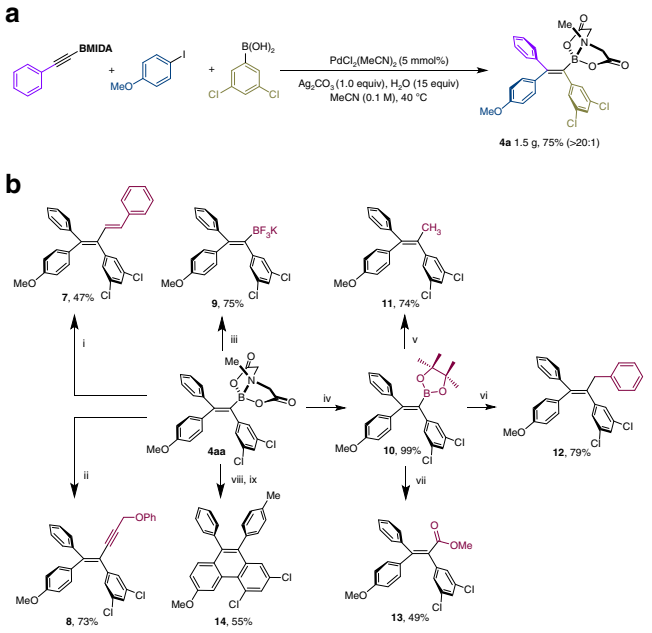


Fig. 6 Synthetic applications. **a** Gram-scale reaction **b** Other synthetic derivatizations of triarylalkenyl MIDA boronates. Reagents and conditions: i. beta-Bromostyrene (1.5 equiv), $Pd(dba)_2$ (10 mol %), SPhos (10 mol %), K_3PO_4 (7.5 equiv), 1,4-dioxane (0.1 M), 40 °C; ii. ((3-bromoprop-2-yn-1-yl) oxy)benzene(1.5 equiv), $Pd(dba)_2$ (10 mol %), SPhos (10 mol %), K_3PO_4 (7.5 equiv), 1,4-dioxane (0.1 M), 40 °C; iii. KHF_2 (5.0 equiv), MeOH (0.025 M), 50 °C; iv. 2 M H_2SO_4 (3.0 equiv), pinacol (5.0 equiv), THF (0.1 M), RT; v. MeI (3.0 equiv), $Pd(dba)_2$ (5 mol %), P(2-tol)$_3$ (10 mol %), K_2CO_3 (2.0 equiv), DMF/H_2O; vi. benzyl bromide (2.0 equiv), $Pd(dba)_2$ (5 mol %), P(2-tol)$_3$ (10 mol %), K_2CO_3 (2.0 equiv), DMF/H_2O; vii. $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), PBQ (2 equiv), K_3PO_4 (5.0 equiv), CO (1 atm), MeOH (0.1 M), 60 °C; viii. *p*-iodotoluene (1.2 equiv), $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), K_3PO_4 (7.5 equiv), THF (0.1 M), 60 °C; ix. DDQ (1 equiv), $MeSO_3H$ (1 mL), DCM (0.01 M), 0 °C

Discussion

The remarkable stability combined with the unique electronic and steric properties of sp^3-B MIDA boron renders arylethynyl MIDA boronates intriguingly competent substrates in palladium-catalysed three-component couplings with aryl iodides and arylboronic acids. The reaction offers a facile synthesis of triarylalkenyl borons in a regio- and stereoselective manner with a broad substrate scope under mild reaction conditions. Synthetic manipulation on the C−B bond in the product via the stereospecific Suzuki–Miyaura coupling and base-promoted protodeborylation reaction led to a step-economic and truly flexible synthesis of tetra- and triarylethenes, both of which are historically challenging synthetic targets. The value of the approach was further highlighted by the success of telescoped synthesis. Another notable feather is that all the starting materials, including arylethynyl MIDA boronates, are readily available. Other transformations of the formed triarylalkenyl MIDA boronates provided straightforward access to a number of tetra-substituted alkenes in good efficiency. Given the operational simplicity, the excellent control on regio- and stereoselectivity and the broad substrate scope of this method, we anticipate it will find numerous applications in organic synthesis.

Methods

General procedure for stereodefined synthesis of triarylalkenyl MIDA boronates. To a 15-mL Schlenk tube equipped with a stirring bar, were added **1** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), **3** (0.4 mmol, 2.0 equiv), silver carbonate (55.2 mg, 0.2 mmol, 1.0 equiv), and $PdCl_2(MeCN)_2$ (2.6 mg, 5 mol %) in glove box. The reaction vessel was taken out, and 54 μL H_2O and MeCN (2 mL) was added under N_2 protection. The reaction mixture was stirred at 40 °C until **1** were consumed completely (about 3 h). The mixture was concentrated and directly subjected to flash column chromatography on silica gel (DCM/EtOAc 32:1 v/v) to afford the desired product.

General procedure for stereodefined synthesis of tetra-aryl substituted alkenes. To a 15-mL Schlenk tube, were added **4** (51.0 mg, 0.1 mmol, 1.0 equiv), aryl iodide **5** (0.11 mmol, 1.1 equiv), $Pd(OAc)_2$ (1.1 mg, 0.005 mol), and SPhos (4.1 mg, 0.01 mmol), the reaction vial was sealed with a rubber septum. K_3PO_4 (3 M, 0.25 mL) and THF (0.75 mL) were added through syringe. The reaction mixture was stirred at 60 °C until **4** were completely consumed. After cooling to room temperature, the reaction mixture was concentrated in vacuo. Purification by flash chromatography (Petroleum ether/EtOAc 64:1 v/v) afforded the desired products **5**.

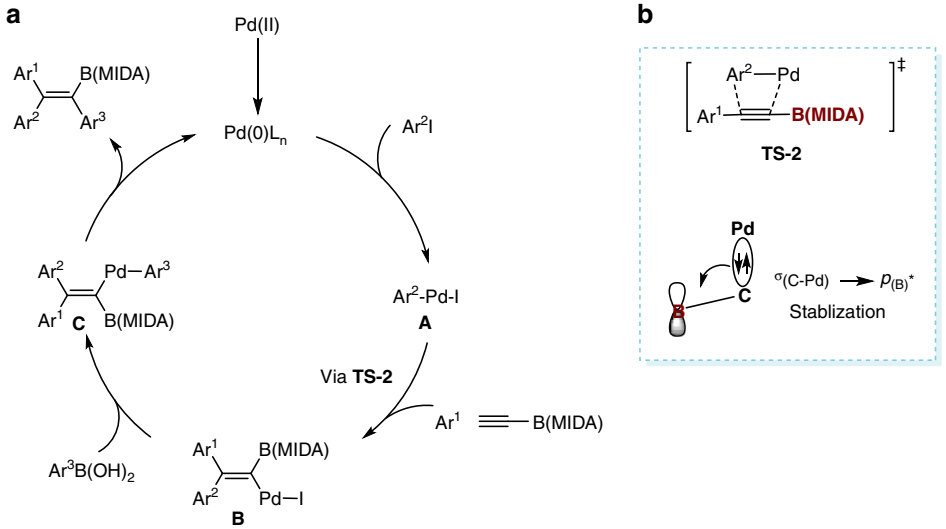


Fig. 7 Mechanistic hypothesis. **a** Possible reaction mechanism. **b** Rationale of regioselectivity

General procedure for stereodefined synthesis of tri-aryl substituted alkenes. To an oven-dried flask were added **4** (51.0 mg, 0.1 mmol, 1.0 equiv), K_3PO_4 (3 M, aq. 0.25 mL), and DMF (1.0 mL) through syringe. The solution was stirred at 40 °C until **4** was completely consumed. After cooling to room temperature, the reaction mixture was quenched with water (10 mL), extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) and dried with Na_2SO_4 and concentrated in vacuo to give a crude residue. The crude product was subsequently loaded onto a silica gel column and purified by flash column chromatography (Petroleum ether/EtOAc 100:1 v/v) to afford the desired compound **6**.

Synthetic transformations. Full procedures for synthetic transformations of compounds **7–14** are available in the Supplementary Methods and Supplementary Figs. 1-16.

Robustness screen. Please see Supplementary Table 2 and Supplementary Figures 17-18.

NMR spectra. ^{1}H, ^{13}C, and ^{19}F NMR spectra of purified compounds are available in Supplementary Figs. 19–130.

Crystallography. X-ray crystallographic CIF files for compounds **4ba** and **6p** are available in Supplementary Data 1 and 2.

Data availability

The authors declare that all the data supporting the findings of this study are available within the article and Supplementary Information files, and also are available from the corresponding author upon reasonable request. The X-ray crystallographic coordinates for structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC1862138 (**4ba**) and CCDC 1862136 (**6p**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

E.L. and J.W. planned and performed the experiments and prepared Supplementary Information. S.F. performed the robustness screen. X.S., K.W., and J.L. prepared some of the starting materials. Y.C. determined the X-ray crystal structure of compound **4ba** and **6p**. X.Z., H.T, Q.L., and T.O. revised the manuscript. F.G. and H.W. conceived and directed the project and wrote the manuscript.

Additional information

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