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A Diverted Aerobic Heck Reaction Enables Selective 1,3-Diene and 1,3,5-Triene Synthesis Through C−C Bond Scission

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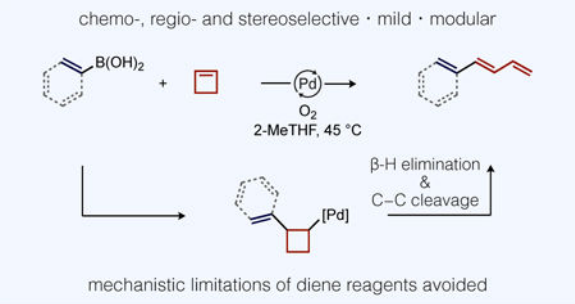
Abstract

Substituted 1,3-dienes are valuable synthetic intermediates used in myriad catalytic transformations, yet modern catalytic methods for their preparation in a highly modular fashion using simple precursors are relatively few. We report here an aerobic boron Heck reaction with cyclobutene that forms exclusively linear 1-aryl-1,3-dienes using (hetero)arylboronic acids, or 1,3,5-trienes using alkenylboronic acids, rather than typical Heck products (i.e., substituted cyclobutenes). Experimental and computational mechanistic data support a pericyclic mechanism for C−C bond cleavage that enables the cycloalkene to circumvent established limitations associated with diene reagents in Heck-type reactions.

Graphical Abstract



Substituted 1,3-dienes are common synthetic building blocks featured in a wide array of complexity-building catalytic transformations, including recently developed asymmetric hydrofunctionalizations,[1] difunctionalizations,[2] C−H functionalizations,[3] cycloadditions,[4] and cross-coupling.[5] Preparations of 1,3-dienes, 1-aryl-1,3-dienes being a particularly prevalent subset in modern catalytic methods, classically involve disconnections at the central sigma bond of the diene,[6] such as through Mizoroki-Heck reactions, cross-coupling,[7,8] and ene-yne metathesis,[9] or disconnection at the double bond in the case of Wittig-type

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ASSOCIATED CONTENT

Supporting Information

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Notes

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olefinations (Scheme 1, left).[10] Drawbacks of these approaches include functional group compatibility with strongly basic organometallic reagents or, more importantly, limited structural diversity in commercial starting materials (i.e., styrenyl halides or cinnamaldehydes). The development of single-step catalytic routes to substituted 1,3-dienes thus remains highly desirable, particularly if diverse and widely-available building blocks, such as boronic acids, could be used as substrates.[11] We report here a mild Pd-catalyzed aerobic coupling of (hetero)arylboronic acids or alkenylboronic acids with cyclobutene to generate substituted 1,3-dienes or 1,3,5-trienes, respectively, in a regio- and stereoselective fashion.

The focus on cyclobutene in this work was deliberate because direct synthesis of 1-aryl-1,3-dienes by arylation of butadiene suffers several established mechanistic limitations. The Pd-catalyzed reaction of aryl halides with butadiene (Scheme 1, upper right) was reported to occur in poor yields with competing formation of 1,4-diaryl-1,3-diene side products. Heck suggested this occurs because the immediate product (1-aryl-1,3-diene) is more reactive than butadiene in subsequent catalytic turnovers.[12] Another problem occurs immediately following migratory insertion of butadiene, which forms a stabilized (π-allyl)Pd intermediate that is reluctant to release diene by β-H elimination (Scheme 2).[13]

The kinetic problems noted above could potentially be avoided by the use of a butadiene surrogate. Rupture of strained rings by β-alkyl elimination[14] has been observed following migratory insertion of methylenecycloalkanes, which could provide an alternative path to diene formation (Scheme 2, top). While Larock did observe such β-alkyl elimination during reactions of anionic palladate complexes, facile “chain-walking”[15] also occurred that shuttled Pd back to the thermodynamically most stable intermediate – a π-allyl complex.[16] A ring opening reaction of cycloalkenes might nevertheless be a viable pathway to substituted dienes if chain-walking could be suppressed.

We hypothesized that electrophilic, rather than the electron-rich Pd complexes previously studied, could offer a potential solution because the former has been shown to form kinetic product distributions (i.e., no chain-walking) during oxidative Heck reactions.[17,18] An electrophilic organo-Pd intermediate might then react with cyclobutene by either of two conceivable pathways for C−C cleavage (Scheme 2, bottom) to form 1-substituted 1,3-dienes without leading to (π-allyl)Pd intermediates. We thus studied the boron Heck reaction to test this idea.

An optimization campaign identified suitable conditions for the aerobic reaction of phenylboronic acid with cyclobutene in the presence of $Pd(OAc)_2$. In the best case using 5 mol% Pd with added acetic acid and water, a near quantitative yield (99%) of *trans*-1-phenyl-1,3-butadiene (**1**) was generated after 72 h at 45 °C (Table 1). The absence of detectable quantities of the typical Heck product (3-phenylcyclobutene) or 1,4-diphenyl-1,3-butadiene indicates surprisingly high selectivity in this catalytic process. Additionally, absence of 2-phenyl-1,3-butadiene highlights the complementary regioselectivity compared to (neocuproine)Pd-catalyzed aerobic Heck reactions developed by Stahl that favor branched products.[19] Substitution of butadiene for cyclobutene led to complete suppression of reactivity (entry 1), which is consistent with the hypothesis that reaction pathways leading to

(π-allyl)Pd intermediates are detrimental to catalysis. The use of lower O_2 pressure in a balloon (14 psig) also generated 69% of **1**, which should be attractive for applications without pressure equipment (entry 2). The use of 10% O_2 in N_2 mixture, close to the limiting oxygen concentration of 2-methyltetrahydrofuran (2-MeTHF),[20] also produced **1** in 80% yield at the same oxygen partial pressure as the standard conditions (entry 3).

Several alternative boron reagents were also effective nucleophiles in the model reaction, such as the pinacol ester or trifluoroborate analogues of phenylboronic acid (entries 4 and 5), producing **1** in 83% and 79% yield, respectively. The inclusion of a radical inhibitor, butylated hydroxytoluene (BHT), was important in all cases for stabilizing the 1,3-diene products under the aerobic conditions. High yield of **1** (90%) is still possible with a five-fold reduction in catalyst loading with increased time (entries 6 and 7). Catalytic *p*-benzoquinone (BQ) enhances the yield of **1** but is not required for aerobic turnover (entry 8). The importance of added water and acetic acid on product yield are more pronounced (entries 9−11), which we speculate could promote transmetalation[21] and/or catalyst turnover from a [Pd]−H or Pd0 species.[22] The use of an industrially preferred solvent (2-MeTHF),[23] molecular oxygen as terminal oxidant, and the generation of benign byproducts (e.g., boric acid and water) are several attractive features of this method. Organoboron reagents also complement the substrates used in existing methods to prepare dienes and trienes, such as aldehydes[10–11] or haloarenes,[11b] while also avoiding the need for harsh oxidants or bases.

We next examined a series of other (hetero)arylboronic acids to establish the generality of this transformation. 1-Aryl-1,3-dienes derived from arylboronic acids with *para*- or *meta*-withdrawing substituents (**2**, **6**, **8**, **9**, and **11**−**13**) formed in good isolated yield (56%−91%). Arylboronic acids with electron-releasing substituents (**3**−**5**) were obtained in slightly reduced yet reasonable yields (60%−79%). The compatibility of the catalyst with free phenol, carboxylic acid, Weinreb's amide, and coordinating thioether functional groups is very good. Reactions with 3-benzothienyl, 3-(2-fluoro)pyridyl, and 3-(2,6-difluoro)pyridyl boronic acids also generated 1-heteroaryl-1,3-dienes **14**−**16** in reasonable isolated yields (57%−62%). The fluoropyridine units in **15** and **16** are notable for their utility in medicinal chemistry for further elaboration by S_NAr reactions.

We found the standard conditions used for arylboronic acid coupling with cyclobutene are also directly applicable to alkenylboronic acids (Table 2), which extend the π-conjugation of the products. Competing 6π-electrocyclization was not observed, which allowed the formation of a range of substituted 1,3,5-trienes by this diverted aerobic Heck reaction. Formation of cyclohexyl- (**17**), *tert*-butyl- (**18**), and chloropropyl- (**19**) substituted (1*E*, 3*E*)-1,3,5-trienes occurred in good isolated yields (63%−72%) and as the only detectable stereoisomer. Alternatively, the use of a *Z*-alkenylboronic acid generated the 1*Z*-configured triene product **20** stereospecifically. Finally, a range of *trans*-styrenylboronic acids generated (1*E*,3*E*)-1-aryl-1,3,5-trienes **21**−**26** in 44%−75% isolated yields. Preliminary attempts using alkylboronic acids (e.g., Me, Bu, *i*-Pr, *c*-Pr) were not successful under the standard conditions.

We conducted DFT calculations to establish a mechanistic rationalization for the formation of linear 1,3-dienes rather than branched isomers (e.g., 2-aryl-1,3-dienes) or normal Heck

products (e.g., 3-arylcyclbutenes), the results of which are summarized in Figure 1. The phenyl-Pd species formed by transmetalation of $PhB(OH)_2$ to Pd(II) initially forms **27** upon coordination of cyclobutene. Migratory insertion through a Cossee-Arlman mechanism (**TS28**) generates a cyclobutyl-Pd intermediate **29**. This insertion reaction is more exoergic (−11 kcal/mol) than typical insertions of acyclic alkenes,[24] which reflects a conformationally-enforced, stabilizing η^2-arene interaction. Other plausible cyclobutyl-Pd species with alternative coordination modes of the acetate or 2-phenylcyclobutyl ligands were also evaluated (Figure S3), but these were less stable than **29** by 5.4−15.0 kcal/mol because the planar κ^2-OAc in **29** minimizes steric interactions with the Ph group. Two postulated reactions pathways bifurcate from this point.

One pathway to diene **1** from cyclobutyl-Pd complex **29** would proceed by C−C bond scission through β-C elimination, an elementary reaction that has ample precedent among the group 10 metals.[16,25] Cleavage of the C_α−$C_{\beta'}$ or $C_{\beta'}$−C_γ cyclobutyl bond by this mechanism would generate new alkyl-Pd intermediates **31** or **32**, respectively (Figure 1a). Formation of complex **31** is calculated to be exoergic by 14 kcal/mol and occurs through a lower energy transition state (**$TS30_{lin}$**) than the competing pathway toward the branched diene (**$TS30_{br}$**), possibly due to more favorable benzylic stabilization.[26] Product **1** is then formed by β-H elimination from **31** (not shown).

An alternative pathway that could advance the common intermediate **29** to diene **1** could occur initially by formation of a [Pd]−H species (**33**) through β-H elimination followed by reinsertion with the opposite regioselectivity to generate a new symmetric cyclobutyl-Pd intermediate **34** (Figure 1a). While β-C elimination from **34** could only lead to the linear diene product, which could rationalize the experimentally observed selectivity, **TS35** involving C_α−C_β scission is calculated to proceed with a higher barrier than the alternative β-C elimination pathways. These mechanisms thus do not adequately account for the exclusive linear selectivity for formation of **1** over 2-phenyl-1,3-butadiene given the calculated $\Delta\Delta G^‡$ of ca. 1 kcal/mol between linear and branched product formation.

Another pathway to diene formation could begin from the intermediate **33** formed after β-H elimination (Figure 1b). Exchange of coordinated 3-phenylcyclobutene (**37**) for BQ occurs with a barrier of 32 kcal/mol by a dissociative mechanism. While associative mechanisms for release of product **37** might occur with lower barriers, the fact that the dissociative mechanism is lower in energy than **$TS30_{lin}$** in the β-C elimination pathway is nonetheless informative. Subsequent BQ-promoted H−OAc reductive elimination to form Pd(0) is strongly exoergic and renders the process irreversible. Other pathways for oxidative turnover of Pd by O_2 or BQ are possible but were not considered here.[22,27] Linear product **1** can then be formed from free **37** by 4π-electrocyclic ring opening, which is calculated to occur with a considerable energy barrier ($\Delta G^‡$ = 29 kcal/mol).[28] This significant barrier to product formation suggests **37** could accumulate during the course of the catalytic reaction. To test this, we conducted a reaction with phenylboronic acid using low pressure of O_2 (14 psig) that facilitated periodic sampling for ^{1}H NMR analysis. A kinetic profile generated from these data (Figure S2) indeed revealed early accumulation of intermediate **37**, which peaks after ca. 12 h (92%). Product **1** grows in more slowly over 72 h to a final yield of 69%. With

consideration of these computational and experimental mechanistic data, we conclude that the most likely reaction pathway involves an initial Heck process to generate a 3-substituted cyclobutene followed by pericyclic ring opening to reveal the final diene or triene product. Control of alkene geometry would be expected by this mechanism because C−C cleavage would be stereospecific through a pericyclic process. The high regioselectivity can also be rationalized because the Pd-catalyzed reaction can only form 3-substituted cyclobutenes by stereospecific *syn*-migratory insertion and *syn*-β-H elimination in the absence of chain walking.

In summary, a mild and modular route to synthetically versatile 1-aryl-1,3-dienes and substituted 1,3,5-trienes has been developed. The normal, aerobic Heck reaction in these cases diverts through a pathway involving C−C bond scission by pericyclic ring opening. This mechanism allows cyclobutene to function as a masked form of butadiene thereby circumventing mechanistic liabilities associated with the latter in Heck-type reactions. The reported method complements disconnections in classic synthetic routes to 1,3-dienes, such as by Wittig olefination or Pd-catalyzed cross-coupling, and also benefits from the wide availability of commercial organoboron reagents. The applicability of other nucleophiles and cycloalkenes to this reaction manifold will be the foci of future efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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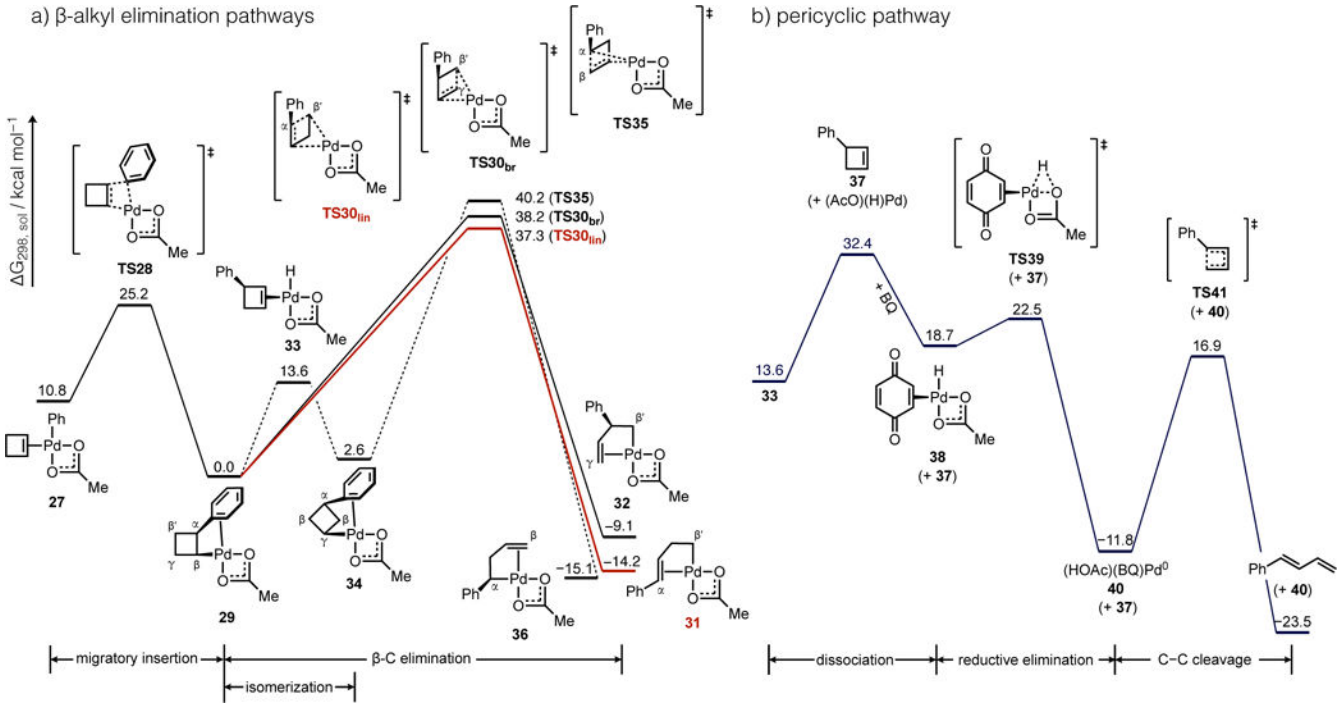
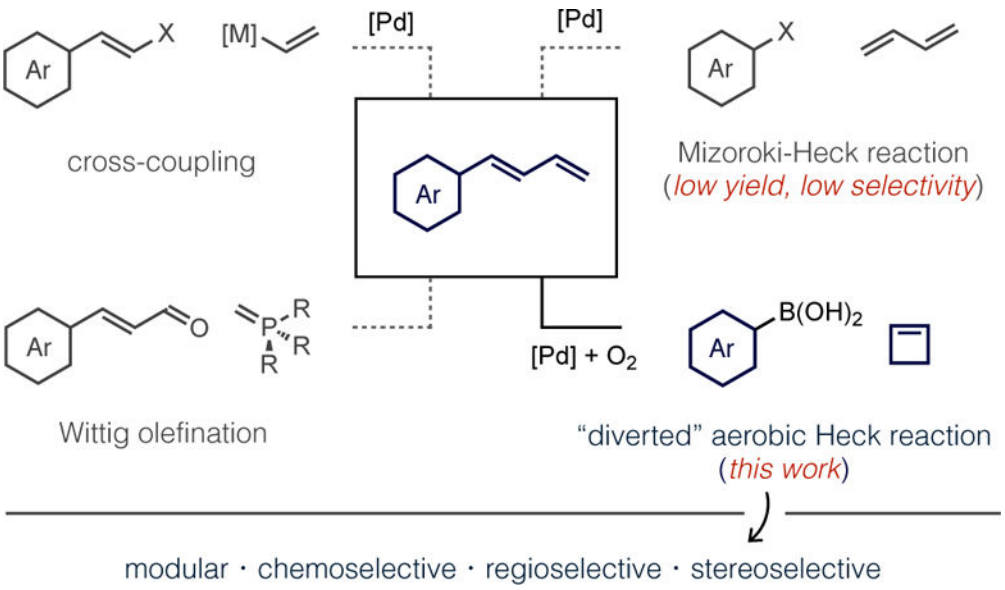
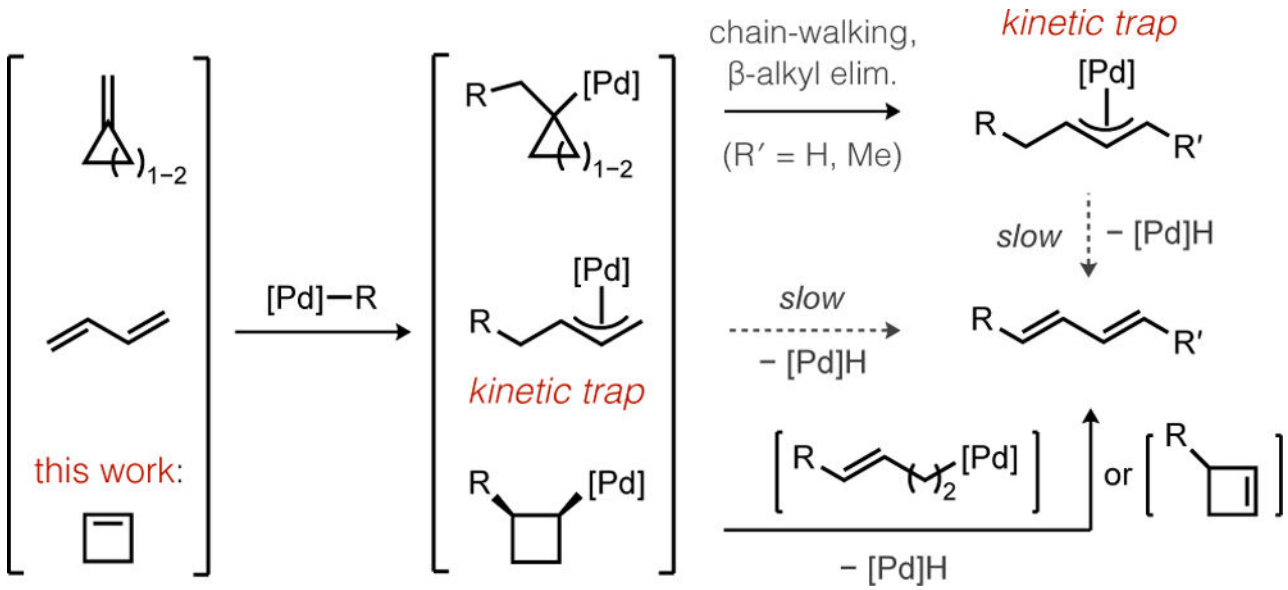


Figure 1.

Potential energies of key steps in putative reaction pathways to 1-aryl-1,3-diene products involving C−C cleavage by either a (a) β-alkyl elimination or (b) pericyclic mechanism. Geometry optimizations were carried out at the B3LYP/LANL2DZ-6–31-G(d) and solvation corrections at the M06/SDD-6–311+G(d,p)/SMD(THF) level of theory.



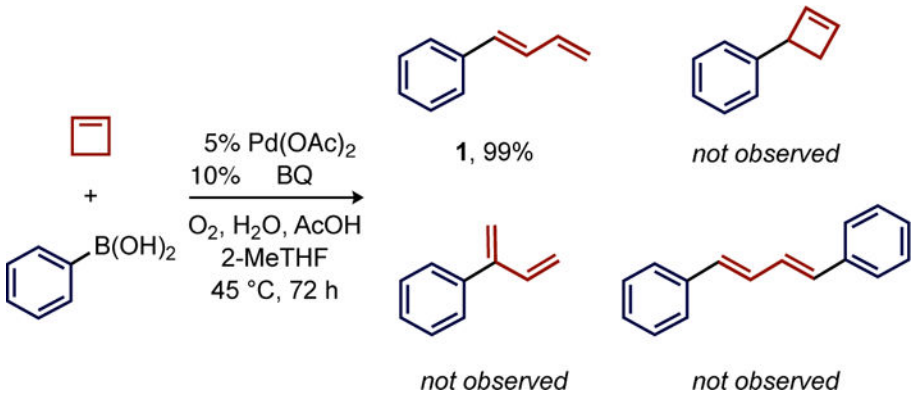
Scheme 1.
Representative Routes to 1-Aryl-1,3-Dienes.



Scheme 2.
Evolution of Intermediates Following Insertion of Butadiene or Related Alkenes.

Table 1.

Aerobic Boron Heck Reaction with Cyclobutene.[a]



entry	deviation from the standard conditions	yield 1 (%)[b]
1	butadiene instead of cyclobutene	0
2	O_2 balloon (14 psig)	69
3[c]	10% O_2, balance N_2 (500 psig)	80
4	PhBPin instead of $PhB(OH)_2$	83
5	$PhBF_3K$ instead of $PhB(OH)_2$	79
6	1 mol% Pd	43
7	1 mol% Pd, 96 h	90
8	omit BQ	84
9	omit AcOH	72
10	omit H_2O	43
11	omit AcOH and H_2O	31
12	omit Pd	0

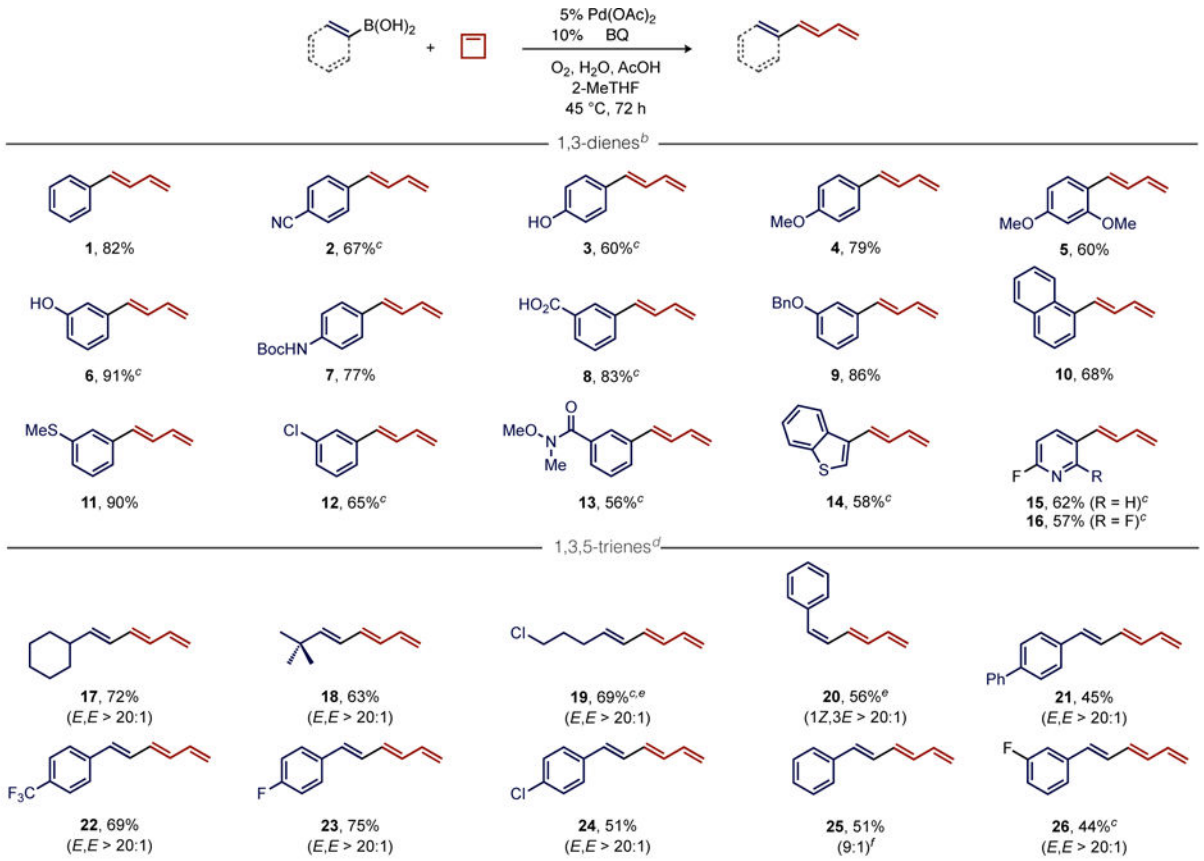
[a]Conditions: boronic acid (0.25 mmol, 0.2 M), cyclobutene (2.7 equiv), AcOH (4 equiv), H_2O (10 equiv), $Pd(OAc)_2$, BQ, and BHT inhibitor (1000 ppm) in 2-MeTHF at 45 °C under O_2 (50 psig).

[b]Yield determined by NMR versus Bn_2O as standard. Pin = pinacolato.

[c]After additional heating at 75 °C for 6 h.

Table 2.

Applicable (Hetero)Aryl and Alkenyl Boronic Acids to Aerobic Heck Reaction with Cyclobutene.[a]



[a]Isolated yields shown. Conditions: boronic acid (0.25 mmol, 0.2 M), cyclobutene (2.7 equiv), AcOH (4 equiv), H_2O (10 equiv), $Pd(OAc)_2$, BQ, and BHT inhibitor (1000 ppm) in 2-MeTHF at 45 °C under O_2 (50 psig). [b]>20:1 *E*:*Z* in all cases. [c]After additional heating at 75 °C for 6 h. [d]Geometric isomer indicated for each triene was the only detectable isomer, unless noted otherwise. [e]BPin reagent used. [f](1*E*, 3*E*)/(1*Z*, 3*E*); isomerization occurred during isolation.

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