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Communication

# Modular Synthesis of Benzocyclobutenes via Pd(II)-Catalyzed Oxidative [2+2] Annulation of Arylboronic Acids with Alkenes

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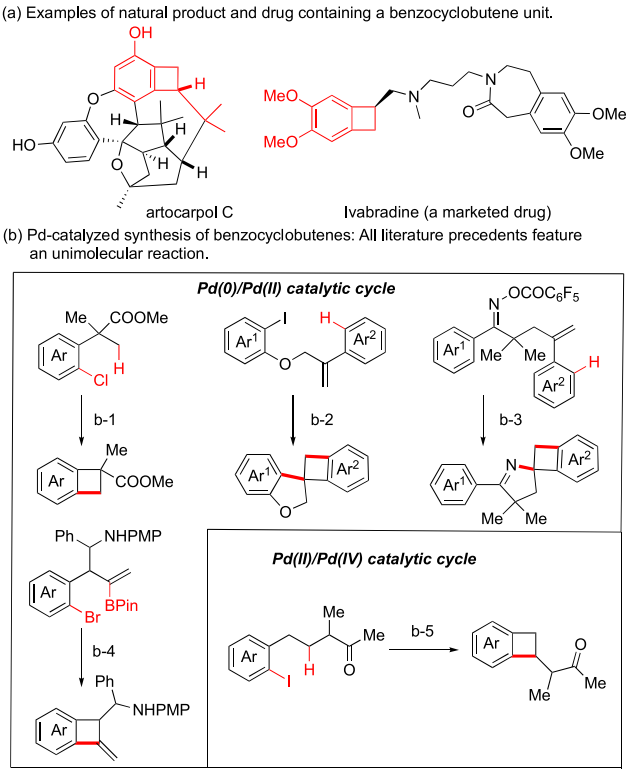
**ABSTRACT:** Benzocyclobutenes (BCBs) are highly valuable compounds in organic synthesis, medicinal chemistry, and materials science. However, catalytic modular synthesis of functionalized BCBs from easily accessible starting materials remains limited. We report herein an efficient synthesis of diversely functionalized BCBs by a Pd(II)-catalyzed formal [2+2] annulation between arylboronic acids and alkenes in the presence of *N*-fluorobenzenesulfonimide (NFSI). An intermolecular carbopalladation followed by palladium oxidation, intramolecular C($sp^2$)−H activation by a transient C($sp^3$)−Pd(IV) species, and selective carbon−carbon (C−C) bond-forming reductive elimination from a high-valent five-membered palladacycle is proposed to account for the reaction outcome. Kinetically competent oxidation of alkylPd(II) to alkylPd(IV) species is important to avoid the formation of a Heck adduct. The reaction forges two C−C bonds of the cyclobutene core and is compatible with a wide range of functional groups. No chelating bidentate directing group in the alkene part is needed for this transformation.



Benzocyclobutene (BCB) is an important bicyclic scaffold found in natural products such as artocarpol C[1] and marketed drugs as exemplified by ivabradine,[2] prescribed for the treatment of heart failure and heart-related chest pain (Scheme 1a). The propensity of BCBs to undergo thermal electrocyclic ring opening to afford reactive *o*-quinodimethanes also makes them important building blocks in organic synthesis,[3] and indeed, this chemistry has been extensively exploited in natural product synthesis[4] as well as in the field of polymer[5] and materials science.[6] Not surprisingly, diverse synthetic methodologies have been developed over the years,[7,8] and among them, Pd-catalyzed synthesis of BCBs involving an intramolecular C−H activation step has been a new addition to our synthetic toolbox. Baudoin and co-workers[9−11] developed an elegant cyclization of methyl 2-(2-halophenyl)-2-methylpropanoate based on the earlier observation of Dyker[12] (Scheme 1, b-1). Schoenebeck and Lautens[13] reported a domino intramolecular carbopalladation/C($sp^2$)−H activation sequence, while Liang and co-workers[14] described an azapalladation/C($sp^3$)−H functionalization cascade to access the spiro BCBs (Scheme 1, b-2 and b-3). Notwithstanding their high synthetic performance, these methods were applicable only to the synthesis of 7,7-disubstitued BCBs since $\beta$-hydride elimination leading to alkene would become a predominant pathway in the case of the C($sp^3$)−Pd(II) intermediate containing a $\beta$-hydrogen.[15] Alternatively, Procter et al. developed a modular synthesis of 7-methylene BCBs combining a Cu-catalyzed three-component coupling with an intramolecular Suzuki−Miyaura reaction (Scheme 1, b-4).[16] A Pd(0)/Pd(II) catalytic cycle is involved in all these transformations. Very recently, Sorensen and co-workers reported a synthesis of 7-monosubstituted BCBs involving a Pd(II)/Pd(IV) catalytic manifold (Scheme 1, b-5).[17]

All the aforementioned Pd-catalyzed transformations are unimolecular reactions producing BCBs via formation of one

**Scheme 1. Benzocyclobutenes: Biological Importance and Pd-Catalyzed Synthesis**

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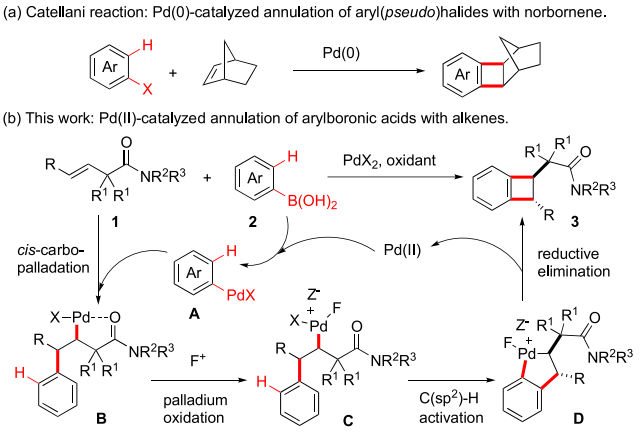
single C−C bond.[18,19] The Pd(0)-catalyzed Catellani reaction allows, on the other hand, the construction of BCBs via concurrent formation of two C−C bonds (Scheme 2a). Since

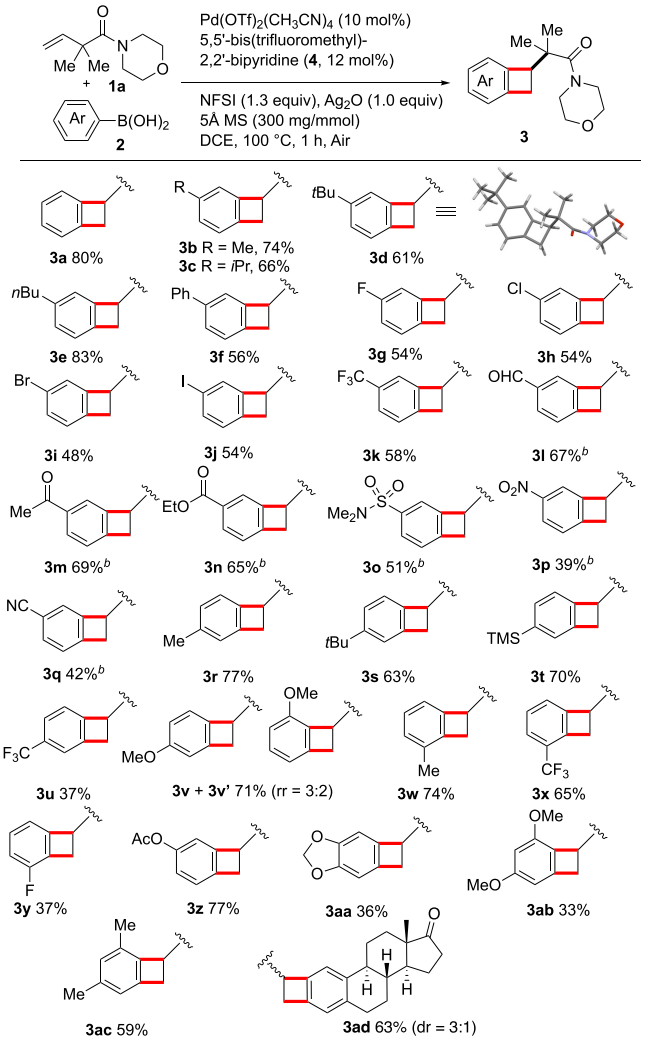
**Scheme 2. Modular Synthesis of Benzocyclobutenes**




its initial discovery, this reaction has been examined by several groups.[20−25] However, the scope of this annulation reaction remains limited, as only norbornene and its derivatives can be used as the alkene inputs. In connection with our research program dealing with the Pd(II)[26−28] and Pd(IV) chemistry,[29] we became interested in developing a modular synthesis of BCBs from alkenes **1** and arylboronic acids **2**. The underlying principle is depicted in Scheme 2b. Transmetalation of $PdX_2$ with arylboronic acids would afford arylPdX species **A**, which upon coordination to the double bond of **1** followed by migratory insertion would afford the C($sp^3$)−Pd(II) intermediate **B**. A sequence of palladium oxidation and C($sp^2$)−H activation of the neighboring aromatic ring by the resulting C($sp^3$)−Pd(IV) species **C** would produce the five-membered palladacycle **D**. Selective C−C bond-forming reductive elimination would then produce BCBs **3** with concurrent regeneration of the Pd(II) catalyst. The realization of this unprecedented Pd(II)-catalyzed domino process is the subject of the present communication.

To realize this domino process, one has to address the potential pitfalls including (a) avoiding the facile $\beta$-hydride elimination of Pd(II) intermediate **B**, which would lead to the classic Heck adduct; rapid oxidation of Pd(II) to Pd(IV) (**B** to **C**) would be an obvious option, as the latter is known to be less prone to undergo the $\beta$-hydride elimination; (b) identifying an oxidant that could chemoselectively oxidize $\sigma$-C($sp^3$)−Pd(II) species **C** without prematurely oxidizing the C($sp^2$)−Pd(II) intermediate **A**; (c) controlling the selectivity of the reductive elimination process.[30] Indeed, Sanford, Zimmerman, and co-workers have shown that the selectivity of C−C vs $Csp^2$−F or $Csp^3$−F bond-forming reductive elimination from isolated high-valent five-membered palladacycles is condition-dependent, and an additive can drive the reaction toward one or the other direction.[31,32] To begin our study, the reaction between 2,2-dimethyl-1-morpholinobut-3-en-1-one (**1a**) and phenylboronic acid (**2a**) was chosen to test the feasibility of the process. To our delight, the reaction in the presence of a catalytic amount of $Pd(OAc)_2$ and Selectfluor led indeed to the formation of the desired BCB **3a** (Scheme 3). After an extensive screening of reaction parameters by varying systematically the palladium sources, the oxidants, the ligands,

**Scheme 3. Condition Optimization and Scope of Arylboronic Acids**[a]




[a]Standard conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $Pd(OTf)_2(MeCN)_4$ (10 mol %), 5,5′-bis(trifluoromethyl)-2,2′-bipyridine (**4**, 12 mol %), MS (30 mg), DCE (1.0 mL), 100 °C. [b]Reaction was performed at 80 °C. Yields refer to isolated pure products. Abbreviations: NFSI = *N*-fluorobenzenesulfonimide, MS = molecular sieves; DCE = dichloroethane, TMS = trimethylsilyl, dr = diastereomeric ratio, rr = regioisomeric ratio.

the bases, the solvents, the additives, and temperature (see the Supporting Information), the optimum conditions consisted of heating a solution of **1a** and **2a** (2.0 equiv) in dichloroethane (*c* 0.1 M) in the presence of $Pd(OTf)_2(MeCN)_4$ (10 mol %), 5,5′-bis(trifluoromethyl)-2,2′-bipyridine (**4**, 12 mol %), *N*-fluorobenzenesulfonimide (NFSI, 1.3 equiv), $Ag_2O$ (1.0 equiv), and 5 Å molecular sieves at 100 °C under an air atmosphere for 1 h. Under these conditions, compound **3a** was isolated in 80% yield. Experimental observations pertinent to the optimization process are summarized as follows: (a) Other Pd(II) sources such as $Pd(OAc)_2$, $Pd(TFA)_2$, and $Pd(acac)_2$ can also catalyze the reaction, affording **3a** in about 50% yield; however, $PdCl_2$ was completely inefficient; (b) the ligand was of utmost importance, with **4** being optimum; in its absence, biphenyl was formed exclusively at the expense of **3a**; (c) while Selectfluor was a competent oxidant, PIDA and peroxide (TBHP, $Na_2CO_3{\cdot}1.5H_2O_2$) were ineffective; (d) adding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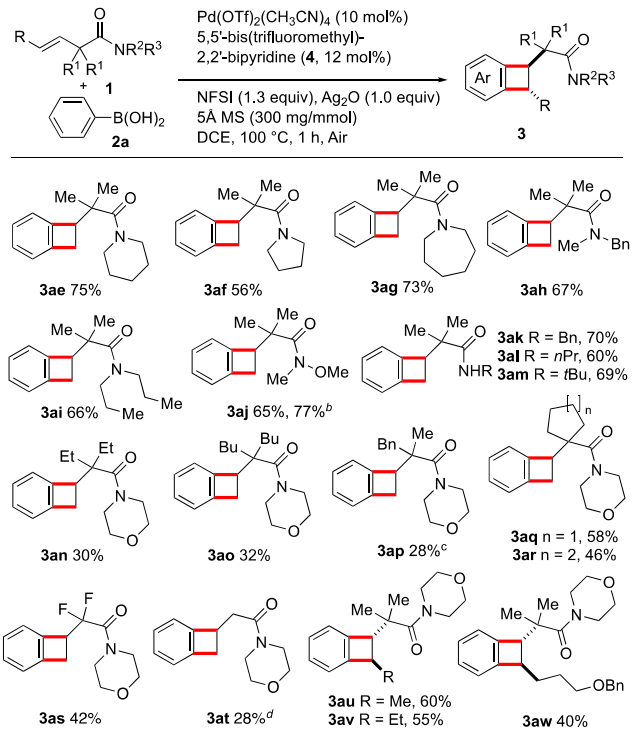
$Me_4NNTf_2$, known to promote the C−C bond reductive elimination from the Pd(IV) intermediate,[32] reduced the yield of **3a** (68%). We note that under optimized conditions, C−F bond-forming reductive elimination was not observed.

With the optimum conditions in hand, we examined first the scope of the arylboronic acids (Scheme 3). A broad range of functional groups regardless of their electronic nature and positions were well accommodated in this catalytic system. The reaction of 4-alkyl- and 4-phenyl-substituted boronic acids with **1a** afforded the corresponding BCBs (**3b**−**3f**) in good to high yields. The structure of **3d** was confirmed by single-crystal X-ray diffraction analysis. The presence of halogens such as fluorine, chlorine, bromine, and even iodine (**3g**−**3j**) was tolerated in this Pd(II)/Pd(IV) redox cycle. Trifluoromethyl (**3k**) and a number of functionalities such as aldehyde, ketone, ethoxycarbonyl, sulfonamide, nitro, and cyano groups can be successfully incorporated into the structures of BCBs with moderate to good yields (**3l**−**3q**). 3-Alkyl-substituted as well as 3-silylated phenylboronic acids participated in the reaction to afford one single regioisomer (**3r**−**3u**) in good yields for obvious steric reasons. As expected, reaction of **1a** with 3-methoxyphenylboronic acid afforded a mixture of two regioisomers (**3v** and **3v′**, rr = 3:2), a direct consequence of the interplay between steric and coordinating capability of the methoxy group.[33] 2-Methyl, 2-trifluoromethyl, and 2-fluorophenylboronic acids were converted to BCBs **3w**, **3x**, and **3y**, respectively. The moderate yield of **3y** might be related to the reduced efficiency of transmetalation between the electron-poor phenylboronic acids and the Pd(II) salt. Although electron-rich 4-methoxyphenylboronic acid was incompatible with the reaction conditions, the 4-acetoxy counterpart participated in the reaction to afford **3z** in 77% yield. Reaction of **1a** with benzo[*d*]dioxo-5-ylboronic acid and 3,5-dimethoxyphenylboronic acid afforded BCBs **3aa** and **3ab**, respectively, albeit with moderate yields. The uncatalyzed reaction of the electron-rich arenes with NFSI could account for the reduced reaction efficiency. Indeed, BCB **3ac** was isolated in 59% yield from less electron rich 3,5-dimethylphenylboronic acid. The reaction of 3-(dihydroxyboryl)estrane-1(10),2,4-triene-17 one (**2ad**) with **1a** afforded one regioisomer (**3ad**) in 63% yield as a mixture of two diastereomers (dr = 3:1). Finally, 4-pyridinylboronic acid failed to participate in this reaction.

The scope of the alkene part was next investigated (Scheme 4). Tertiary amides derived from piperidine, pyrrolidine, and azepane as well as linear secondary amines, i.e., *N*-methyl-1-phenylmethanamine and dipropylamine, participated in the reaction to afford the corresponding BCBs (**3ae**−**3ai**) in good yields. Importantly, the less coordinating Weinreb amide was an appropriate substrate, affording **3aj** in 65% yield.[34] We note that the yield of **3aj** increased to 77% when the reaction was performed on a 5 mmol scale, showcasing the practicality of the protocol. Secondary amides were compatible with the reaction conditions to afford the corresponding BCBs (**3ak**−**3am**) in good yields. The competitive reaction pathway leading to *β*-lactam was not observed under these conditions.[35,36] The *gem*-dimethyl group can also be replaced, although the reaction efficiency seemed to be sensitive to the steric effect of these substituents (**3an**−**3ar**). Importantly, 2,2-difluoro-1-morpholinobut-3-en-1-one and 1-morpholinobut-3-en-1-one participated in the reaction to provide BCBs **3as** and **3at**, respectively, albeit in moderate yields. In the latter case, the reaction turned out to be quite complex and the competitive *β*-hydride elimination is not responsible for the low yield of **3at**.

**Scheme 4. Scope of Alkenes**[a]




[a]Standard conditions: **1** (0.1 mmol), **2a** (0.2 mmol), Pd(OTf)$_2$(MeCN)$_4$ (10 mol %), 5,5′-bis(trifluoromethyl)-2,2′-bipyridine (**4**, 12 mol %), MS (30 mg), DCE (1.0 mL), 100 °C. [b]Reaction was performed with 5 mmol of alkene. [c]Only one diastereomer was isolated. [d]Reaction was performed under the following conditions: Pd(OPiv)$_2$ (10 mol %), Selectfluor (1.5 equiv), HFIP (*c* 0.1 M).

(*E*)-1,2-Disubstituted alkenes were reactive enough to afford 7,8-*trans* disubstituted BCBs **3au**−**3aw** in good yields. The observed diastereoselectivity is the direct consequence of the highly selective *cis*-carbopalladation step. The trisubstituted alkene **1s**, pyridin-2-ylmethanamine-derived amide **1t**,[37] and 8-aminoquinoline (AQ)-coupled amide **1u**[38−41] failed to participate in the reaction, while the reaction of *N*-methoxy-*N*,3,3-trimethylpent-4-enamide (**1v**) with **2a** afforded a complex mixture (Figure 1). The amide function is essential

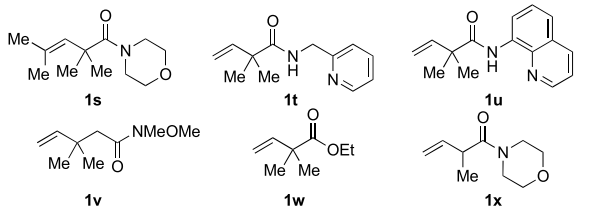



**Figure 1.** Substrates failed to participate in the annulation reaction.

to ensure the occurrence of the desired domino process, as reaction of phenylboronic acid (**2a**) with ethyl 2,2-dimethylbut-3-enoate (**1w**) failed to produce the corresponding BCB. Finally, reaction of 2-methyl-1-morpholinobut-3-en-1-one (**1x**) with **2a** provided the 1,2-fluorophenylation product in moderate yield (25%).[42]

We have also briefly examined the catalytic enantioselective version of this reaction (see the SI for the chiral ligands screened). Using pyridine-dihydroquinoline ligand **5**[43] under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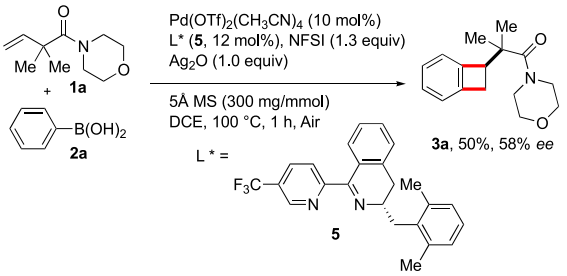
otherwise standard conditions, the reaction between **1a** and **2a** afforded **3a** in 50% yield with 58% ee (Scheme 5). Although enantioselectivity remained moderate, it did illustrate the feasibility of rendering this synthesis of BCBs enantioselective.

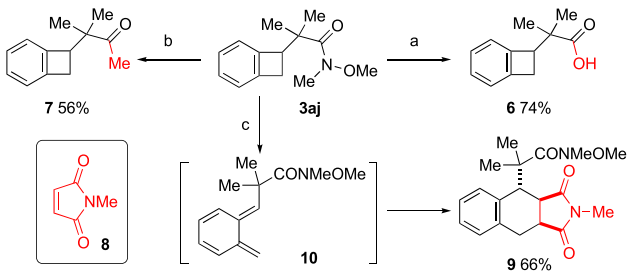
**Scheme 5. Catalytic Enantioselective Synthesis of 3a**[a]




[a]The absolute configuration of **3a** was not determined.

The presence of halogens and other functional groups on the aromatic ring of BCBs provides handles for postfunctionalization. Some representative transformations, taking advantage of the reactivity of Weinreb amide and the cyclobutene unit, are shown in Scheme 6. Hydrolysis of **3aj** (NaOH in EtOH)

**Scheme 6. Post-transformations of BCB 3aj**

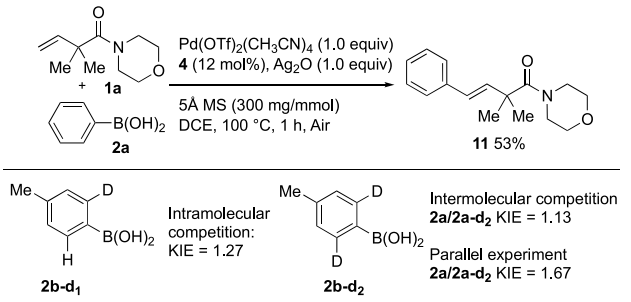



[a]Reagents and conditions: NaOH (1.5 mmol, 15.0 equiv) in EtOH (1.0 mL, *c* 0.1 M), 80 °C, 24 h, 74%. [b]MeLi (1.3 equiv), THF (*c* 0.1 M), −78 °C to rt, 3 h, 56%. [c]*N*-Methylmaleimide (2.0 equiv), *o*-dichlorobenzene (*c* 0.5 M), μw, 250 W, 180 °C, 6 h, 66%.

afforded carboxylic acid **6**, while addition of methyllithium to **3aj** furnished methyl ketone **7**. Heating a solution of **3aj** and *N*-methylmaleimide (**8**) in *o*-dichlorobenzene under microwave irradiation at 180 °C provided tricyclic compound **9** as the only isolable diastereomer.[44] The observed diastereoselectivity could be accounted for by an outward torquoselectivity of the 7-alkyl substituent in the electrocyclic ring opening of **3aj** followed by *endo*-selective Diels−Alder cycloaddition between the resulting (*E*)-*o*-quinodimethane **10** and dienophile **8** (Scheme 6).[45]

Several experiments were performed to gain insight on the reaction mechanism. The reaction of **1a** with **2a** in the presence of one equivalent of $Pd(OTf)_2(MeCN)_4$ without NFSI afforded Heck adduct **11** in 53% yield (Scheme 7). This result indicated the importance of the rapid oxidation of Pd(II) to Pd(IV) intermediate **C** in order to avoid the competitive *β*-elimination process. Stopping the reaction of **2b-d$_1$** with **1a** at 14% conversion allowed us to determine the intramolecular KIE value of 1.27. An intermolecular competition experiment using an equimolar amount of **2b** and its 2,6-dideuterated derivative **2b-d$_2$** provided a KIE value of 1.13. In a side-by-side

**Scheme 7. Control Experiments and KIE Studies**




kinetic experiment, the reaction of **1a** with **2b** and **2b-d$_2$**, respectively, provided a KIE value of 1.67. The results of these experiments indicated that the C−H activation might not be a catalyst turnover-limiting step. Indeed, a kinetically competent C(sp$^2$)−H activation by the Pd(IV) species could be important to channel the reaction toward the formation of BCBs since the Pd(IV) intermediate **C** can also undergo the *β*-elimination, although less likely relative to Pd(II) species.[46] We note that products resulting from C−F bond-forming reductive elimination were not observed under our reaction conditions.[27,47−51]

The reaction of **1a** with **2a** was computed at the PBE0-D3(BJ)/Def2-TZVP//M06/Def2-SVP level, accounting for solvent effects (dichloroethane, DCE) with the SMD model (Figure 2, see the SI for computational details). Migratory insertion of the metal-coordinated alkene **A·1a** into the Pd−Ph bond proceeds with a low barrier (15 kcal/mol), affording the square-planar C(sp$^3$)−Pd(II) intermediate **B** (cf. Scheme 2b). Two pathways were investigated for C(sp$^2$)−H activation. In the first one, oxidation of **B** to the octahedral complex **C** was found to be both kinetically and thermodynamically favorable ($\Delta\Delta G^{\ddagger}$ = −1.8 kcal/mol), overriding the competitive *β*-H elimination ($\Delta\Delta G^{\ddagger}$ = 22.3 kcal/mol, see the SI). Inner-sphere concerted metalation−deprotonation (CMD) with triflate occurs with a barrier of 35 kcal/mol, which at 373 K corresponds to an acceptable rate (ca. 2 mmol day$^{-1}$).[52] Conversely, external base-assisted C(sp$^2$)−H activation of **B**[53,54] yielding Pd(II)-five-membered palladacycle **G** has a prohibitively higher barrier of 47 kcal/mol, suggesting that palladium oxidation is necessary for this reaction to occur. Finally, reductive elimination (RE) proceeds with another relatively high barrier (33 kcal/mol), likely related to the formation of the four-membered ring. Degree of turnover frequency (TOF)-control analysis[55] predicts **TSC-D** to be rate-determining. However, the small energy difference between the C(sp$^2$)−H activation and RE barriers (2 kcal/mol) is within the error expected for DFT; given that many ligand arrangements in the octahedral **C** and **TSC-D** complexes are possible and performing an exhaustive conformational sampling is not straightforward,[56] RE might, in fact, be a catalyst turnover-limiting step.

In summary, we have developed an efficient synthesis of benzocyclobutenes by Pd(II)-catalyzed formal [2+2] annulation between arylboronic acids and alkenes. The chemoselective oxidation of alkylPd(II) at the expense of arylPd(II) species by NFSI, followed by intramolecular C(sp$^2$)−H activation by the transient alkylPd(IV) intermediate, is key to the success of this domino process. The reaction tolerates a broad range of functional groups providing BCBs that are ready for further transformations.



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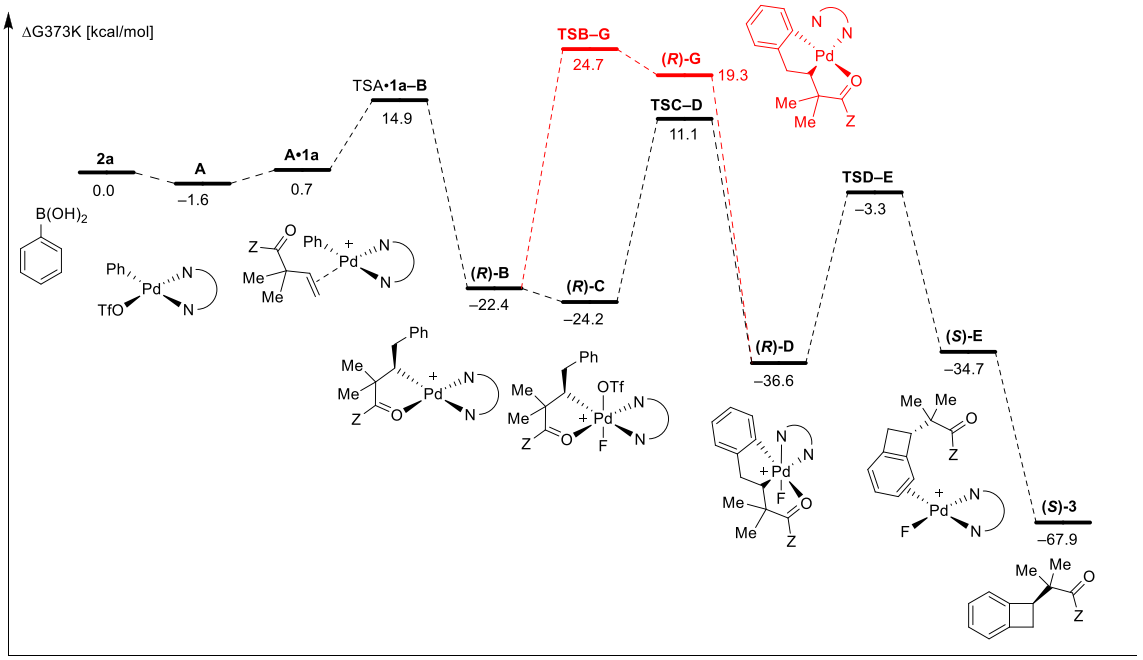


**Figure 2.** Reaction profile for the annulation of **1a** and **2a** to **3a**. Values are Gibbs free energies at 373 K, in kcal/mol, computed at the SMD(DCE)/PBE0-D3(BJ)/Def2-TZVP//M06/Def2-SVP level of theory. N^N = 5,5′-bis(trifluoromethyl)-2,2′-bipyridine; Z = morpholinyl.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c03565.

Experimental procedures and characterization data; copies of $^{1}H$ and $^{13}C$ NMR spectra (PDF)
xyz file (XYZ)

### Accession Codes

CCDC 2094813 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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