

Pd(II)-Catalyzed Synthesis of Benzocyclobutenes by β -Methylene-Selective C(sp³)-H Arylation with a Transient Directing Group

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ABSTRACT: Methylene-selective C–H functionalization is a significant hurdle that remains to be addressed in the field of Pd(II) catalysis. In this paper, we report a Pd(II)-catalyzed synthesis of benzocyclobutenes by methylene-selective C(sp³)-H arylation of ketones. The reaction utilizes glycine as a transient directing group and an electron-poor pyridone ligand, which is expected to promote concerted metallation deprotonation, but also controls methylene selectivity by intimate molecular associations with the substrate. These reaction conditions are shown to be highly selective for intramolecular methylene C(sp³)-H arylation, thus enabling sequential C(sp³)-H functionalization.

A particularly important class of benzo-fused carbocycles is the benzocyclobutenes (BCBs). BCBs are reactive hydrocarbons with a proven utility in syntheses of myriad polycyclic compounds, complex natural products, and modified [60]fullerenes,^{1,2} as well as monomers for cross-linkable polymers.^{3,4} This utility primarily derives from the facile electrocyclic ring-openings of BCBs to *ortho*-quinodimethanes, which are primed for subsequent pericyclic reactions under the driving force of rearomatization.⁵ First synthesized by Finkelstein in 1909, and later confirmed by Cava and Napier in 1957,⁶ BCBs are also found in the structures of natural products.^{7,8} The importance of BCBs as progenitors to new polycyclic ring frameworks is reflected in the diverse methods that have been developed to achieve their syntheses.⁹ In this paper, we describe syntheses of benzocyclobutenes from keto aryl iodides in the course of intramolecular Pd(II)-catalyzed methylene C(sp³)-H arylations (Figure 1 C).

To date, the formation of the benzocyclobutene ring by Pd-catalyzed C(sp³)-H arylation has alone been demonstrated with the Pd(0/II) redox framework by Dyker and subsequently the Baudoin group.^{10–13} While efficient at BCB construction by methyl C(sp³)-H arylation, formation of the four-membered ring with the Pd(0/II) redox cycle suffers from kinetically competitive β -hydride elimination at methylene C–H bonds;¹² these processes also tend to select for 5-membered ring formation when possible.¹⁴ (Figure 1 B). Herein, we report the first examples of benzocyclobutene synthesis by methylene C(sp³)-H arylation, and this process is expected to proceed through a Pd(II/IV) catalytic redox manifold, also a first in the formation of this useful carbocycle. BCB formation by reductive elimination from Pd(IV) has been shown in stoichiometric studies of organometallic palladium complexes, but has proven elusive in catalysis.^{15–17}

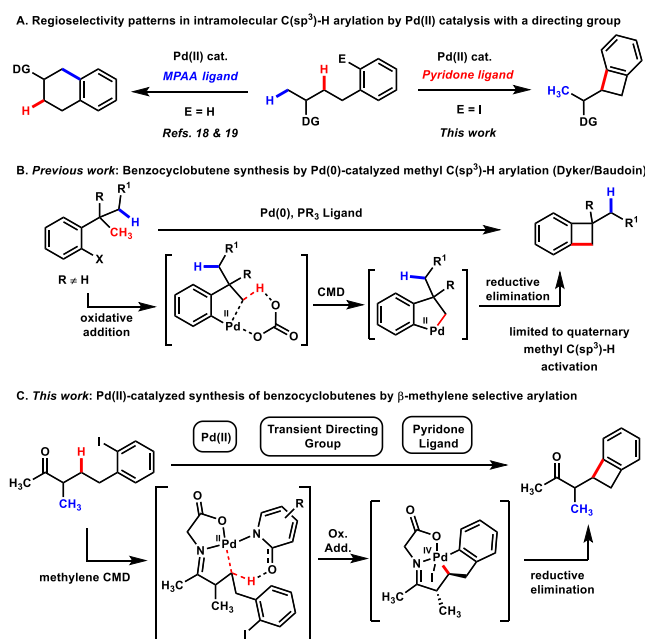


Figure 1. A. Comparing methyl/methylene regioselectivity patterns of intramolecular C(sp³)-H arylation in ligand-promoted Pd(II) catalysis. B. BCB synthesis by Pd(0) catalyzed C(sp³)-H arylation. C. Synthesis of benzocyclobutenes by methylene-selective Pd(II) catalyzed C(sp³)-H arylation.

As shown in Figure 1 A, previous examples of MPA (mono-protected amino acid) ligand-promoted intramolecular C(sp²)-H/C(sp³)-H coupling with a monodentate directing group reveal an exclusive reactivity pattern of methyl C(sp³)-H activation leading to the six-membered tetralins.^{18,19} In the cyclization reaction in Figure 1 C, 2-pyridone-promoted C(sp³)-H activation in concert with a bidentate transient directing group induce selective intramolecular methylene C(sp³)-H arylation to form the alternate ring isomer, the benzocyclobutene. We reason that the 4-

membered ring outcome is influenced by the enhanced reactivity of 2-pyridone concerted metallation deprotonation (CMD) at methylene centers, as well as strain build-up in the critical Pd(IV) intermediate during oxidative addition in the pathway leading to tetralin formation.

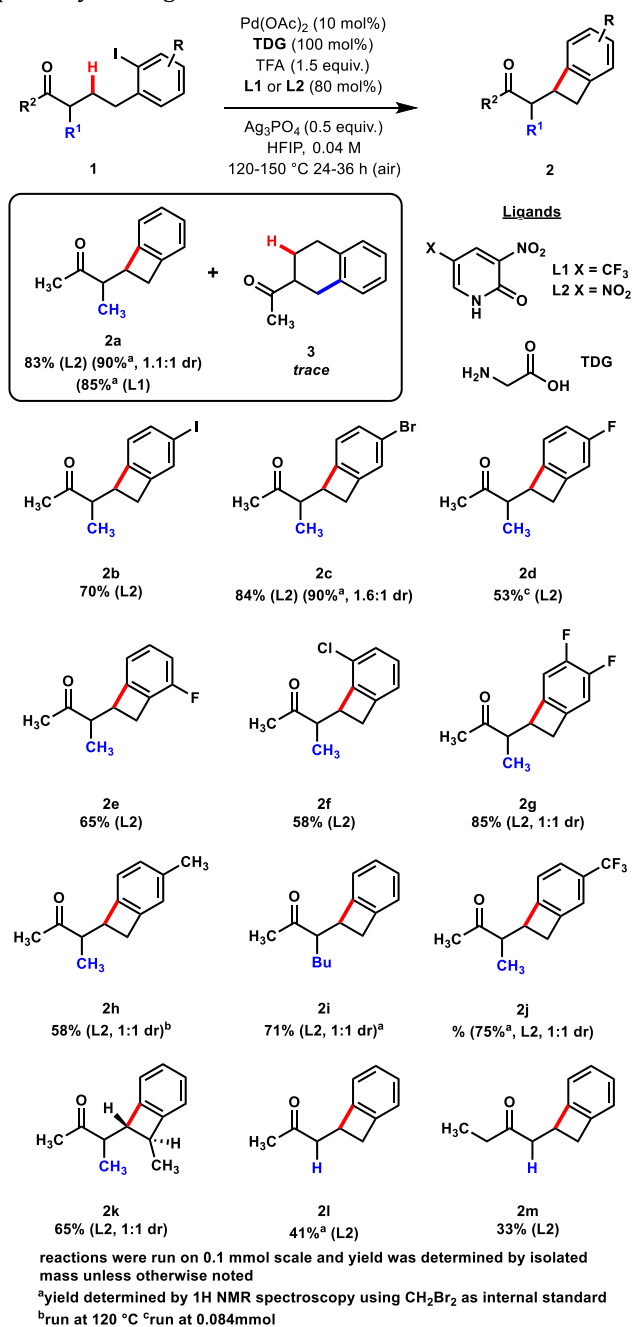


Table 1. Scope of benzocyclobutene formation by methylene-selective arylation.

A significant question for any ring-forming C–H functionalization reaction is the selectivity in ring size. In cases where a directing group (DG) is employed, the choice of which C(sp³)–H bond will undergo activation at a Pd(II) center has been demonstrated numerous times: unless blocked,^{20–22} C–H palladation typically proceeds through a five- or six-membered palladacycle and preferentially occurs at a primary C–H bond over a secondary C–H bond equidistant to the DG. A notable, but isolated exception to

primary selectivity has been observed for cyclopropyl 2° C–H bonds, which may have higher reactivity at Pd(II) than 1° C–H bonds.²³ Inverting this inherent reactivity pattern of primary selectivity to deliver alternate constitutional isomers is indeed a fundamental challenge to the field of palladium catalyzed C(sp³)–H functionalization, and such a discovery could also have significant impact on the strategic employment of C–H functionalization in chemical synthesis. For example, leaving a methyl intact may be necessary for the final molecule desired in a synthesis. The methyl functionality is especially important in bioactive compounds for the enhancement of potency and pharmacokinetics, which is known colloquially as the “magic methyl effect”.²⁴ Additionally, an intact methyl functionality allows for a broad array of other subsequent C–H functionalization reactions which are known to occur more readily at primary C–H bonds (oxygenation,²⁵ arylation,²⁶ alkynylation,²⁷ olefination,²⁸ amin(d)ation,^{29,30} halogenation,³¹ alkylation,³² carbonylation,³³ borylation,³⁴ among others³⁵). Indeed, recent advances in Pd catalyzed C(sp³)–H functionalization has vaulted this modest unreactive functionality to privileged status. Specific to this class of α-methyl ketone products, several auxiliaries provide opportunity for high-yielding elaboration via directed C(sp³)–H functionalization of the residual α-methyl in addition to TDG reactivity.^{25,31,36,37} Notwithstanding all of these reasons empowering its study, methylene C(sp³)–H functionalization inherently provides a more rapid buildup of molecular and stereochemical complexity than methyl C(sp³)–H functionalization.

In the pivotal example of this report, the benzocyclobutene **2a** was isolated in 83% yield (90% yield by ¹H NMR spectroscopy, Table 1), while tetralin **3** was coproduced in trace quantities. Table 1 shows the general scope of the reaction. Strikingly, this reaction is highly selective for consuming the C–I bond relevant to BCB formation, leaving intact the iodide found in BCB **2b**, which was isolated in a good yield of 70%. The products **2a**, **2c**, and **2g** are isolated in high yields, above 80%. Surprisingly, the 4-fluoro substituted product **2d** has a lower yield at 53%, while the yield improved for fluorine-containing **2e** (65%) and **2g** (85%). The selective formation of benzocyclobutene **2i** in favor of the constitutionally isomeric acetyltetralin indicates that the reaction is intrinsically selective for methylene arylation leading to a four membered ring. Methyl substituted substrates like **2h** must be run at 120 °C and thus form in slightly lower yield (58%); BCB ring-opened side products were observed at 150 °C. Formation of the simpler, unbranched benzocyclobutenes **2l** and **2m** proceeded in lower yields (41% and 33%, respectively), which is consistent with a lack of the Thorpe-Ingold effect. The substrate scope showcases how complementary this Pd(II/IV) catalyzed process is to the Dyker/Baudoin Pd(0/II) system: while the Pd(0) system can only generate gem-disubstituted BCBs (as in Figure 1B), monosubstituted and vicinal disubstituted BCBs (**2k**) are accessible by this reaction. Furthermore, reducible groups like iodo-, bromo- and chlorobenzene functionalities are unaltered, while they are commonly not tolerated under Pd(0/II) catalysis.

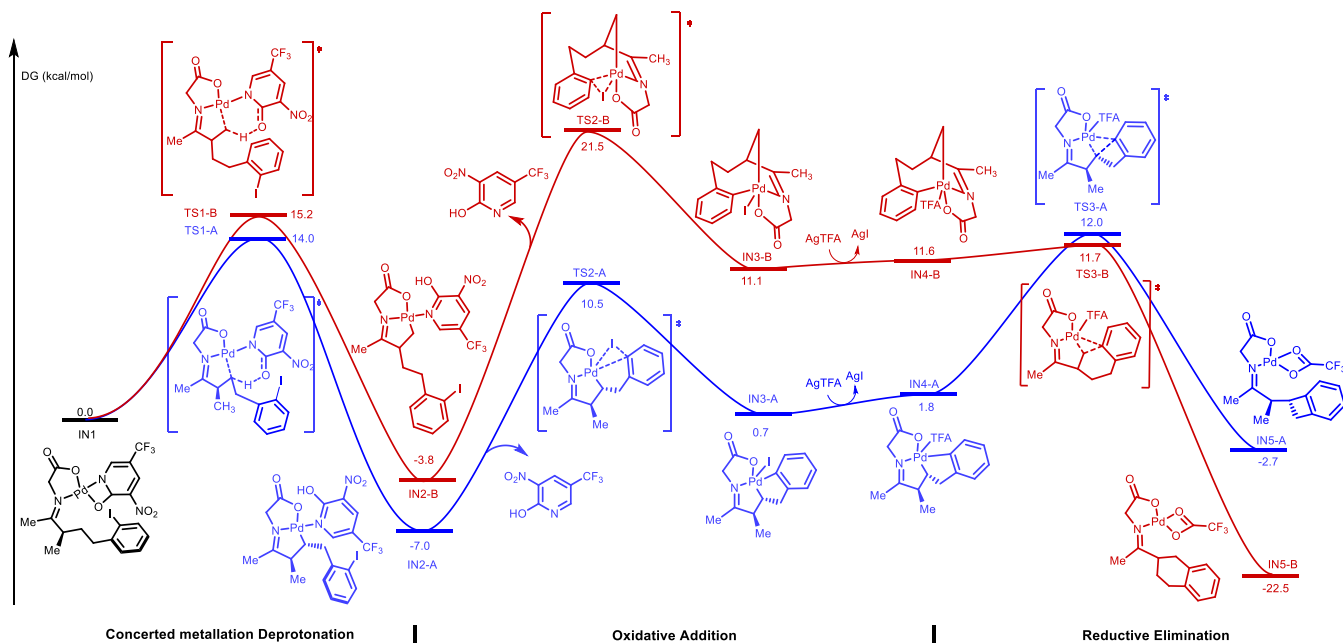
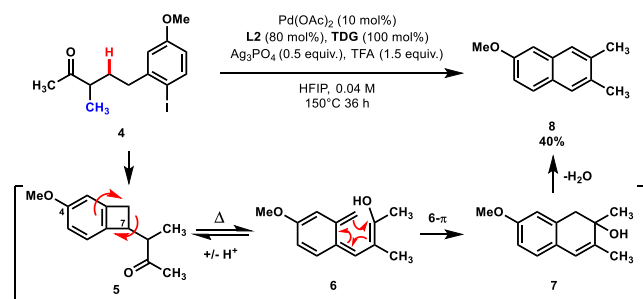


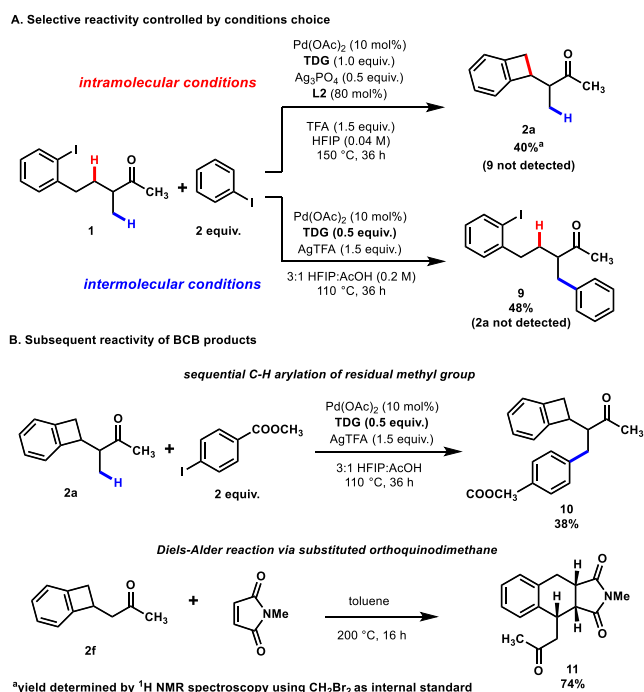
Figure 2. Comparing reaction pathways leading to benzocyclobutene INF-A and tetralin INS-B.



Scheme 1. An unexpected 6- π electrocyclization.

When we subjected the expectedly challenging methoxy-bearing substrate **4** to the reaction conditions shown in Scheme 1, the product that could be isolated from the mixture of products was naphthalene **8**. We theorize that BCB **5** undergoes conrotatory electrocyclic ring opening to yield the isomeric *o*-quinodimethane, and formation of the fused six-membered ring subsequently occurs by 6- π electrocyclization via enol tautomer **6**. Based on earlier reports from the Houk lab concerning the torquoselectivity of this ring opening,³⁸ their model predicts that donor substituents bound to C-7 in intermediate **5** would electronically bias towards the “outward” geometry by stabilizing the LUMO.

In this example, the enol form of **5** may be fully formed and constitute a donor group before ring opening occurs, indicating that this reversible process captures a minor “inward opening” species in the equilibrium formed by reversible ring opening of **5**. Once the 6- π electrocyclization takes place from **5**, acid-catalyzed elimination of water from **7** would give rise to **8**. The formation of **8** indicates that BCB **5** is more prone to ring-opening due to the electron-rich methoxy substituent.



Scheme 2. A. Competition experiments: high selectivity for inter- and intramolecular reactivity. **B.** Subsequent reactivity of scaffold includes sequential C-H arylation and Diels-Alder reactivity.

In competition experiments, we discovered that intermolecular and intramolecular C-H arylation could be highly selective. As shown in Scheme 2 A, when two equivalents of iodobenzene were present in the reaction mixture developed for intramolecular arylation, the only identifiable product in the resulting mixture was BCB **2a** along with a trace amount of starting material; no intermolecular arylation product was observed. Alternatively, when **1** was subjected to conditions for intermolecular arylation,²⁰ the major product isolated was intermolecular methyl arylation product **9**; signals indicating the presence of **2a** or other BCBs were not

observed in the ^1H NMR spectrum of the crude mixture. Though previously we had observed that insoluble Ag_3PO_4 was inefficient at promoting intermolecular $\text{C}(\text{sp}^3)\text{-H}$ arylation,³⁹ high selectivity for intermolecular arylation has now been achieved with the use of AgTFA and co-solvent AcOH . One conclusion could be that acetate is slow to activate methylene C-H bonds by CMD, which is consistent with the formation of the “kinetic” product **9**, while the pyridone CMD more easily facilitates linear methylene $\text{C}(\text{sp}^3)\text{-H}$ cleavage by CMD,³⁹ enabling exclusive access to BCB **2a**. Fagnou⁴⁰ and Deboef⁴¹ demonstrated that regioselectivity in indole $\text{C}(\text{sp}^2)\text{-H}$ arylation could be controlled by oxidant choice, but in this example regiocontrol, chemoselectivity (methyl/methylene) and inter/intramolecularity of $\text{C}(\text{sp}^3)\text{-H}$ functionalization can all be controlled.

Due to the exceptional methylene selectivity of this reaction, the product can undergo sequential $\text{C}(\text{sp}^3)\text{-H}$ functionalization. This reactivity was demonstrated on BCB **2a**, which could undergo methyl $\text{C}(\text{sp}^3)\text{-H}$ arylation with methyl 4-iodobenzoate to form **10** in 38% yield, as shown in Scheme 2B. As expected, the BCB substrates obtained from this reaction are also prone to undergoing ring-opening to substituted *o*-quinodimethanes and efficiently participating in the Diels-Alder reaction, highlighting the versatility of these BCB intermediates. Heating a mixture of **2f** and *N*-methylmaleimide in toluene at 200 °C for 16 h afforded *endo*-cycloadduct **11** in 74% yield (Scheme 2B).

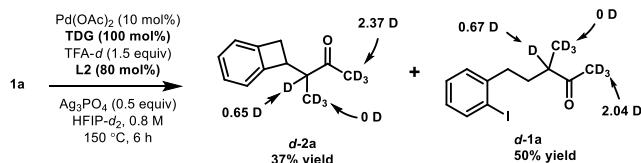


Figure 3. Isotope-incorporation experiment indicating an irreversible CMD process.

To understand what drove the selective formation of BCB **2a** instead of the isomeric **3** under conditions shown in Table 1, we undertook a computational study of the two competing pathways in conjunction with some limited experimentation. This proposed mechanism is based on the presumption that Ag_3PO_4 first slowly converts to AgTFA before is operative as an iodide abstractor.³⁹ Calculations indicate that oxidative addition (OA) presents the largest energy difference between transition states leading to the alternate products. As shown in Figure 2, towards BCB **2a**, **TS2-A** is 11 kcal lower in energy than **TS2-B**, which leads to **3**. In **TS2-B**, the planar geometry of the 5,5 palladacycle undergoes greater disturbance in order to accommodate oxidation by the approaching aryl iodide, leading to the strained seven-membered $\text{Pd}(\text{IV})$ metallacycle **IN3-B**. Approach to $\text{Pd}(\text{II})$ by an oxidant is favored from the equatorial aspect as in **TS2-A**, while approach from the axial aspect is disfavored, as in **TS2-B**. Based on the calculated potential energy surface, we expected the methyl CMD proceeding through **TS1-B** to be reversible, and thus reveal methyl deuterium incorporation in the Figure 3 experiment *via* H/D scrambling. However, it appears that the methyl $\text{C}(\text{sp}^3)\text{-H}$ activation process at **L2**/ $\text{Pd}(\text{II})$ does not take place and betrays the high selectivity in this reaction for methylene $\text{Pd}(\text{II})$ /**L2**-activation. In the favored process leading to BCB **2a**, reductive elimination (RE) is likely rate-determining with a total energy barrier of 19.0 kcal/mol from **IN2-A** to **TS3-A**, while

the minor tetralin product **3** is formed through a disfavored process where the rate is determined by OA. There is a significant barrier (10.2 kcal from **IN4-A** to **TS3-A**) to the ultimate carbocyclic ring formation by RE due to the buildup of strain, and yet it is computed that the CMD transition state is higher in energy. The readiness with which this challenging ring formation occurs highlights the favorable $\text{Pd}(\text{IV}/\text{II})$ redox cycle for RE.

Thus, calculations would suggest that the productive CMD step is irreversible and that the product distribution reflective of the difference in barriers between **TS1-A** and **TS2-B**. A simple H/D scrambling experiment (Figure 3) demonstrated strong evidence that the CMD step is irreversible for this reaction. We anticipate that the deuterium incorporation in the α -position is due to enol/enamine formation and deuteration by acid/base chemistry. Analysis of the competing transition states revealed two contributing factors resulting in this phenomenon (Figure 4). First, an attractive $\pi\text{-}\pi$ interaction between the arene and pyridone during may stabilize the preferred **TS1-A**. Secondly, steric repulsion between the phenylene moiety and pyridone ligand may disfavor **TS1-B**. In any case, this is a rare example of ligand control to effect linear methylene C-H activation in the presence of equidistant methyl C-H bonds. While previous reports have demonstrated that the CMD under similar conditions is reversible,^{39,42} this isotopic labelling study is consistent with accounts of mechanistic labelling caused by small changes in substrate.⁴³ Broadening this result to achieve general, ligand-controlled selectivity requires more experimental study and is ongoing in our lab.

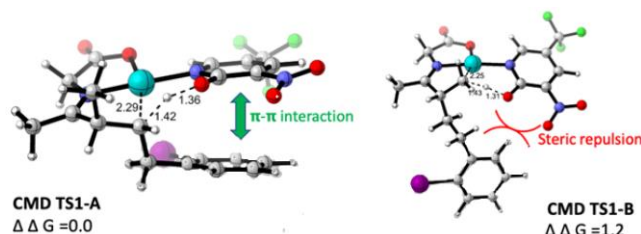


Figure 4. Ligand-control in competing transition states

In conclusion, we have developed an efficient process for synthesizing benzocyclobutenes by $\text{Pd}(\text{II})$ -catalyzed methylene $\text{C}(\text{sp}^3)\text{-H}$ arylation with a transient directing group. This reaction is highly selective for forming four-membered BCBs by methylene arylation, and the intramolecular process outcompetes intermolecular reactivity. Due to the high selectivity for methylene arylation, an intact methyl group is available for subsequent $\text{C}(\text{sp}^3)\text{-H}$ arylation. Ongoing studies in our laboratory will reveal how these carbocycles derived in this way can lead to efficient syntheses of natural products and how to expand this result to induce a general methylene selectivity.

ASSOCIATED CONTENT

Compound characterization data for all new compounds and data for computations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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