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Communication

Pd(II)-Catalyzed Synthesis of Benzocyclobutenes by β-Methylene-Selective C(sp^3)−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. We report a Pd(II)-catalyzed synthesis of benzocyclobutenes by methylene-selective C(sp^3)−H arylation of ketones. The reaction utilizes glycine as a transient directing group and a 2-pyridone ligand, which may govern the methylene selectivity by making intimate molecular associations with the substrate during concerted metalation−deprotonation. This reaction is shown to be highly selective for intramolecular methylene C(sp^3)−H arylation, thus enabling sequential C(sp^3)−H functionalization.

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A particularly important class of benzo-fused carbocycles are the benzocyclobutenes (BCBs). BCBs are reactive hydrocarbons with proven utility in the syntheses of myriad polycyclic compounds, complex natural products,[1] and modified [60]fullerenes[2,3] and as monomers for cross-linkable polymers.[4,5] This utility primarily derives from the facile electrocyclic ring openings of BCBs to give *o*-quinodimethanes, which are primed for subsequent pericyclic reactions under the driving force of rearomatization.[6] First synthesized by Finkelstein in 1909 and later confirmed by Cava and Napier in 1957,[7] BCBs are also found in the structures of natural products.[8,9] The importance of BCBs as progenitors of new polycyclic ring frameworks is reflected in the diverse methods that have been developed to achieve their syntheses.[10]

The formation of the BCB ring by Pd-catalyzed C(sp^3)−H arylation was demonstrated with the Pd(0/II) redox framework by Dyker[11] and subsequently by the Baudoin group.[12−14] Although this method is efficient at BCB construction by methyl C(sp^3)−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;[14] these processes also tend to select for five-membered-ring formation when possible[15] (Figure 1 B). Herein we report the first examples of BCB synthesis by methylene C(sp^3)−H arylation via a Pd(II/IV) catalytic redox manifold, a first in the formation of these useful carbocycles. BCB formation by reductive elimination (RE) from Pd(IV) has been shown in stoichiometric studies of organometallic palladium complexes but has proven to be elusive in catalysis.[16−18]

We previously demonstrated a Pd(II/IV) system to achieve the synthesis of indanes,[19] and in the course of that study we sought to create benzo-fused carbocycles with different ring sizes using homologous iodoaryl ketones. As shown in Figure 1A, previous examples of monoprotected amino acid (MPAA)-ligand-promoted intramolecular C(sp^2)−H/C(sp^3)−H coupling with a monodentate directing group (DG) revealed an exclusive reactivity pattern of methyl C(sp^3)−H activation leading to six-membered tetralins.[20,21] In the cyclization

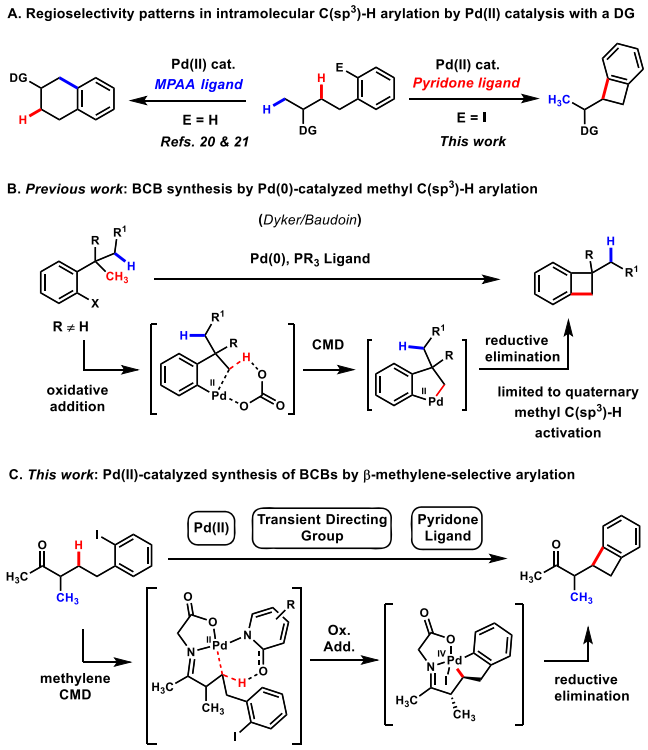

Figure 1. (A) Comparison of methyl/methylene regioselectivity patterns of intramolecular C(sp^3)−H arylation in ligand-promoted Pd(II) catalysis. (B) Benzocyclobutene (BCB) synthesis by Pd(0)-catalyzed C(sp^3)−H arylation. (C) Synthesis of BCBs by methylene-selective Pd(II)-catalyzed C(sp^3)−H arylation.

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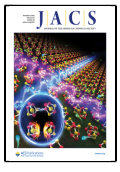

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reaction in Figure 1C, 2-pyridone-promoted C(sp^3)−H activation in concert with a bidentate transient directing group (TDG) induces selective intramolecular methylene C(sp^3)−H arylation to form the alternate ring isomer, the benzocyclobutene.

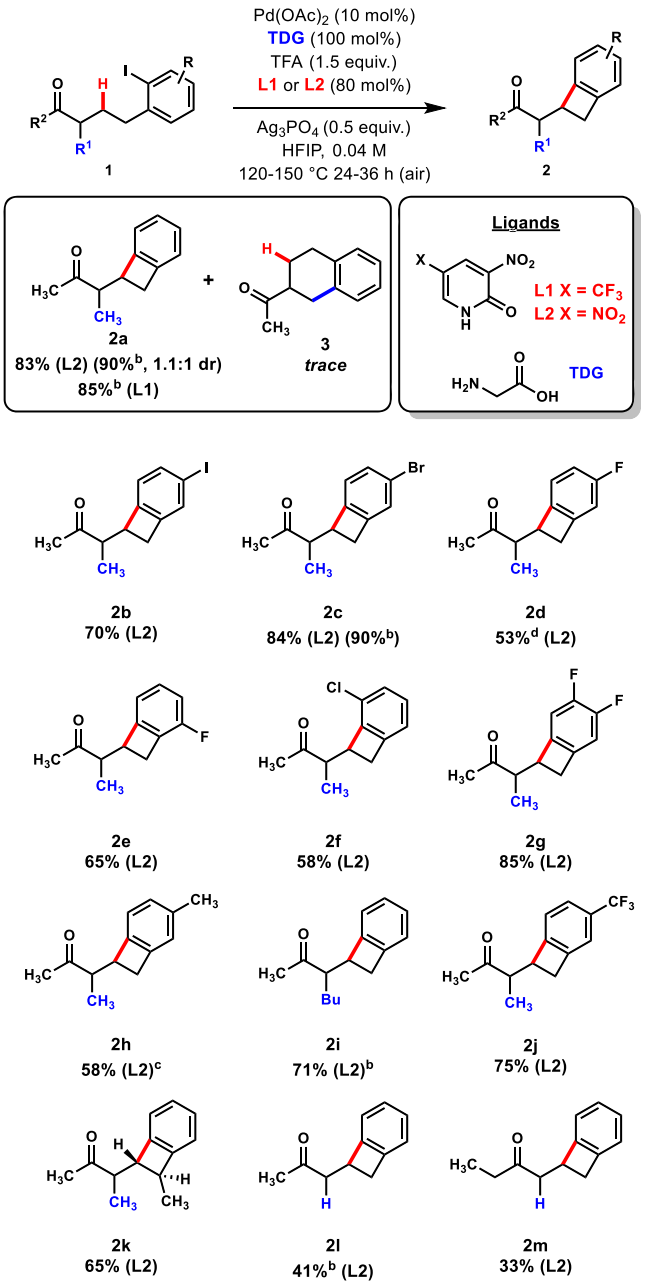
Selectivity is a significant question for any C−H functionalization because of the universality of C−H bonds in organic molecules. In cases where a DG is employed, the choice of which C(sp^3)−H bond will undergo activation at a Pd(II) center has been demonstrated numerous times: unless blocked,[22−24] C−H palladation typically proceeds through a five- or six-membered palladacycle[25] and preferentially occurs at a primary C−H bond over a secondary C−H bond equidistant to the DG.[26] A notable but isolated exception to the primary selectivity has been observed for cyclopropyl 2° C−H bonds, which may have higher reactivity at Pd(II) than 1° C−H bonds.[27] 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(sp^3)−H functionalization.

Leaving a methyl intact may be necessary for the final molecule desired in a synthesis. The methyl functionality is important in bioactive compounds for the enhancement of potency and pharmacokinetics, which is known as the "magic methyl effect".[28] Additionally, an intact methyl functionality could enable other subsequent C−H functionalization reactions, which are known to occur more readily at primary C−H bonds (oxygenation,[29] arylation,[30] alkynylation,[31] olefination,[32] amidation,[33] amination,[34] halogenation,[35] alkylation,[36] carbonylation,[37] and borylation,[38] among others[39]). Indeed, recent advances in Pd-catalyzed C(sp^3)−H functionalization have vaulted this modest unreactive functionality to privileged status. Specific to the class of α-methyl ketone products produced in this report, several auxiliaries and TDGs provide opportunities for high-yielding elaboration via directed C(sp^3)−H functionalization of the residual α-methyl.[29,35,40,41] We anticipated that such transformations could be part of an attractive overall strategy for constructing structurally diverse frameworks via iterative functionalizations of methylene and methyl groups. Our development of this process is described herein.

Under the reaction conditions shown in Table 1, we found that iodoaryl ketones of type **1** could be directly converted to diverse BCBs. By this method, benzocyclobutene **2a** was generated in 83% yield (90% yield by ^{1}H NMR spectroscopy) (Table 1), while tetralin **3** was coproduced in trace quantities. Strikingly, this reaction selectively consumes the C−I bond required for BCB formation, leaving intact the iodine atom found in BCB **2b**, which was isolated in 70% yield. Products **2a**, **2c**, and **2g** were isolated in yields exceeding 80%. The selective formation of **2i** in favor of the constitutionally isomeric acetyltetralin indicates that the reaction is intrinsically selective for methylene arylation leading to four-membered-ring formation. Relatively electron-rich products such as **2h** require lower temperatures (e.g., 120 °C) to avoid electrocyclic ring openings (vide infra). Unbranched benzocyclobutenes **2l** and **2m** may also be produced by this method, although the yields of these products were moderate.

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 generate only *gem*-disubstituted BCBs (as in Figure 1B), monosubstituted and vicinally disubstituted BCBs (**2k**) are accessible by this

Table 1. Scope of Benzocyclobutene Formation by Methylene-Selective Arylation[a]



[a]Reactions were run on a 0.1 mmol scale. Yields were determined from isolated masses unless otherwise noted, and the dr was 1:1 unless otherwise noted. [b]The yield was determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [c]The reaction was run at 120 °C. [d]The reaction was run on an 0.084 mmol scale.

reaction. Product **2k** was isolated as a mixture of both *trans*-BCB diastereomers in a combined yield of 65%. Furthermore, reducible moieties like iodo-, bromo-, and chloroarenes are unaltered, whereas they are commonly not tolerated under Pd(0/II) catalysis.

When we subjected the challenging methoxy-bearing substrate **4** to the reaction conditions shown in Scheme 1, naphthalene **8** was isolated from the mixture of products. We reason that BCB **5** undergoes conrotatory electrocyclic ring opening to yield the isomeric *o*-quinodimethane and that

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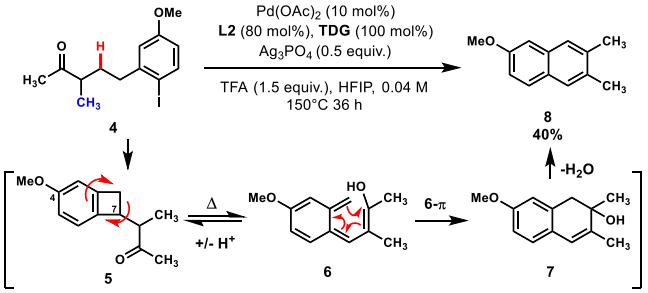
Scheme 1. An Unexpected 6-π Electrocyclization



formation of the fused six-membered ring subsequently occurs by 6π electrocyclization via enol tautomer **6**.

On the basis of reports concerning the torquoselectivity of this ring opening,[42] Houk predicted that donor substituents bound to C-7 in intermediate **5** would result in an electronic bias toward the "outward" geometry by stabilizing the LUMO. Here, 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**.

After 6π electrocyclization takes place, acid-catalyzed elimination of water from **7** would give rise to **8**. The formation of **8** suggests that the electron-rich arene renders BCB **5** more prone to ring opening. Transformations of analogous electron-rich aryl iodides could provide a useful synthesis of naphthalenes.[1,43−46]

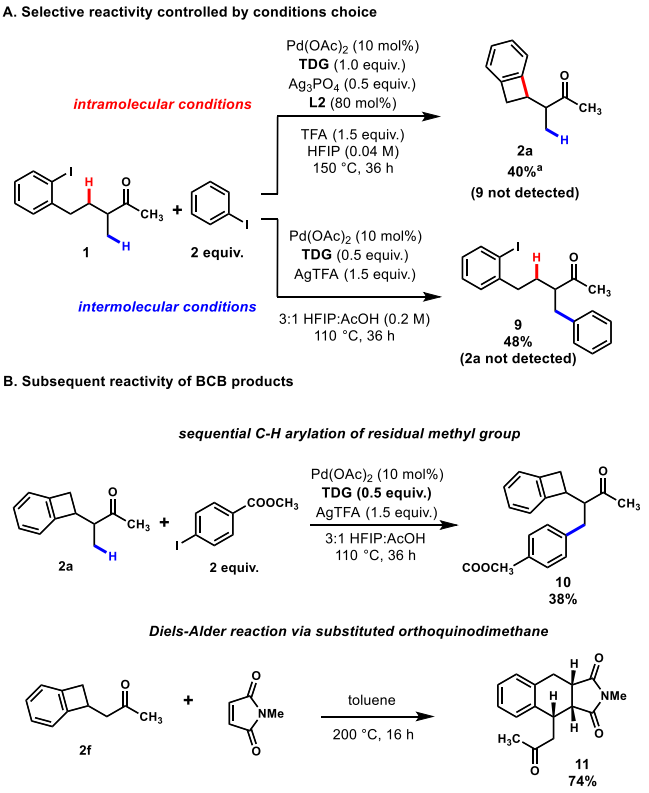
Through competition experiments, we discovered that intermolecular and intramolecular C−H arylation could be highly selective. As shown in Scheme 2A, when 2 equivalents of iodobenzene were present in the reaction mixture developed for intramolecular arylation, the only identifiable product was **2a**; no intermolecular arylation product was observed. Alternatively, when **1** was subjected to conditions for intermolecular arylation,[22] only **9** was isolated, and no BCB products were observed.

The inter/intramolecular selectivity switch between these two conditions apparently derives from the Ag(I) source and the acetate/2-pyridone ligand choice. One conclusion could be that acetate is slow to activate methylene C−H bonds by concerted metalation−deprotonation (CMD),[47] while the 2-pyridone-mediated CMD more easily facilitates linear methylene C(sp^3)−H cleavage,[19] enabling exclusive access to BCB **2a**. Fagnou[48] and Deboef[49] demonstrated that regioselectivity in indole C(sp^2)−H arylation could be controlled by the oxidant choice, but in this example the regioselectivity, chemoselectivity (methyl/methylene), and inter/intramolecularity of C(sp^3)−H functionalization can all be controlled.

Sequential site-selective C(sp^3)−H functionalizations are also possible. For example, compound **2a** was advanced to **10** via directed arylation of the residual methyl group (Scheme 2 B). As expected, the BCB substrates obtained by this method are capable of undergoing ring opening to give substituted *o*-quinodimethanes en route to Diels−Alder products. Heating a mixture of **2f** and *N*-methylmaleimide in toluene at 200 °C for 16 h afforded endo cycloadduct **11** in 74% yield (Scheme 2 B).

To understand what drove the selective formation of **2a** instead of isomer **3** under the conditions shown in Table 1, we undertook a computational study of the two competing pathways at the PBE0-D3(BJ)[50,51]/6-311++G(d,p),[52] SDD-(Pd,I),[53,54] SMD[55] (generic, eps = 16.7, ep-sinf = 1.625625)//

Scheme 2. (A) Competition Experiments Showing High Selectivity for Inter- and Intramolecular Reactivity; (B) Subsequent Reactivity of the Scaffold Including Sequential C−H Arylation and Diels-Alder Reactivity



[a]Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard

B3LYP-D3[56−59]/6-31G(d), LANL2DZ(Pd,I)[60−62] level with conformational searches[63−68] (see the Supporting Information) in conjunction with some experimentation. This proposed mechanism is based on the presumption that Ag_3PO_4 is first slowly converted to AgTFA before it operates as an iodide abstractor.[19]

TS1-A is favored over **TS1-B** by 2.4 kcal/mol as a result of two contributing factors (Figure 2B). First, an attractive $\pi-\pi$ interaction between the substrate arene and the pyridone ligand during CMD stabilizes the preferred **TS1-A**. Second, steric repulsion between the phenylene moiety and pyridone ligand disfavors **TS1-B**. In calculations, when the iodoarene substituent was replaced with a hydrogen atom, diminished energy differences between **TS1-A** and **TS1-B** were observed because of the missing $\pi-\pi$ stacking interaction and pyridone−phenylene steric repulsion (Figure S76).

As shown in Figure 2, **TS2-A** is 10.1 kcal lower in energy than **TS2-B**. 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 Pd(IV) metallacycle **IN3-B**. The approach of an oxidant to Pd(II) is favored from the equatorial aspect, as in **TS2-A**, while approach from the axial aspect is disfavored, as in **TS2-B**. This large energy difference between oxidative addition (OA) transition states leads to the alternate products. The reductive elimination (RE) step via **TS3-B** is favored by 2.7 kcal/mol over that via **TS3-A** because of the stability of **IN5-B**.

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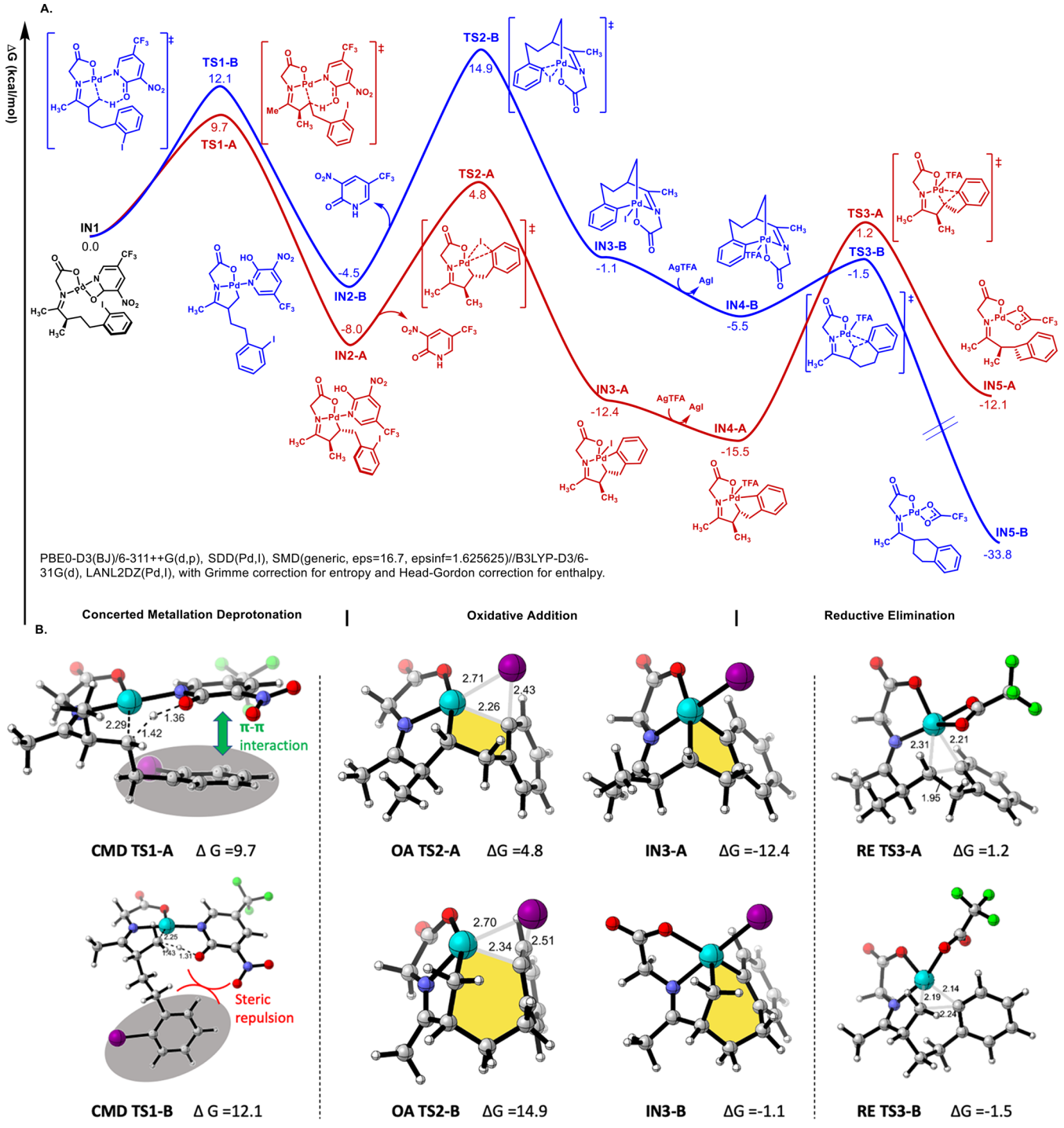

Figure 2. (A) Comparison of reaction pathways leading to benzocyclobutene IN5-A and tetralin IN5-B. (B) Optimized structures.

On the basis of the calculated potential energy surface (Figure 2A, blue trace), we expected the methyl CMD proceeding through **TS1-B** to be reversible, and as shown in Figure 3, the H/D scrambling experiment confirmed a reversible methyl CMD, as indicated by significant H/D scrambling. Furthermore, the higher rate at which intramolecular methylene arylation takes place compared with methyl H/D scrambling is congruent with the indication by the calculations that the methylene CMD is irreversible (Figure 2A, red trace). However, as we continue to study methyl/methylene control by the ligand, we expect more mechanistic experimentation to be necessary.

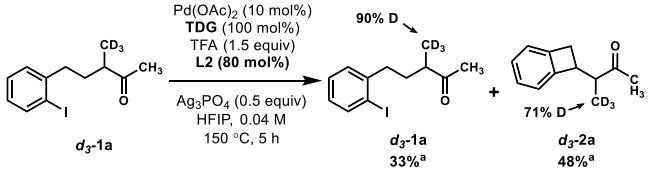

Figure 3. H/D scrambling experiment. [a]Yields were determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

While previous reports have demonstrated that CMD under similar conditions is reversible,[19,69] calculations and an isotopic

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labeling study are consistent with accounts of mechanistic variations caused by small changes in the substrate.[70] In this case, the methylene selectivity may be due to two factors: (1) ligand−substrate interactions that promote methylene selectivity and (2) the geometry of Pd at the competing OA transition states. This result is distinct from our earlier publication that described indane cyclizations by reversible CMD.[19] Work on broadening this result to achieve general ligand-controlled methylene selectivity is ongoing in our laboratory.

In conclusion, we have developed an efficient process for synthesizing BCBs by Pd(II)-catalyzed methylene C(sp^3)−H arylation with a transient directing group. This reaction is highly selective for the formation of four-membered rings by methylene arylation. Because of the high selectivity for methylene arylation, an intact methyl group is available for subsequent C(sp^3)−H functionalization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c09368.

Compound characterization data for all new compounds and data for computations (PDF)

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Notes

The authors declare no competing financial interest.

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