Direct Synthesis of Cyclopropanes from *gem*-Dialkyl Groups through Double C–H Activation

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Supporting Information Placeholder

ABSTRACT: Cyclopropanes are important structural motifs found in numerous bioactive molecules, and a number of methods are available for their synthesis. However, one of the simplest cyclopropanation reactions involving the intramolecular coupling of two C–H bonds on *gem*-dialkyl groups has remained an elusive transformation. We demonstrate herein that this reaction is accessible using aryl bromide or triflate precursors and the 1,4-Pd shift mechanism. The use of pivalate as the base was found to be crucial to divert the mechanistic pathway toward the cyclopropane instead of the previously obtained benzocyclobutene product. Stoichiometric mechanistic studies allowed the identification of aryl- and alkylpalladium pivalates, which are in equilibrium via a five-membered palladacycle. With pivalate, a second C(sp^3)–H activation leading to the four-membered palladacycle intermediate and the cyclopropane product is favored. A catalytic reaction was developed and showed a broad scope for the generation of diverse arylcyclopropanes, including valuable bicyclo[3.1.0] systems.

INTRODUCTION

Cyclopropanes are widespread structural motifs in natural products and bioactive molecules (see Figure 1 for examples).[1] Indeed, the cyclopropane ring can improve the pharmacological properties of active substances by reducing their lipophilicity, increasing their metabolic stability, or modifying their acido-basicity.[2] Although a great number of methods have been developed to synthesize cyclopropanes,[3] the cycloaddition of alkenes and carbenes or carbenoids largely prevails for applications to complex molecules.[4] In this context, one of the simplest ways to construct cyclopropanes, through C–C bond formation from two geminal alkyl groups (Scheme 1a), has remained an elusive transformation to this date. In 2006, Yu and co-workers reported the synthesis of cyclopropanes via a two-step sequence involving palladium(II)-catalyzed, oxazoline-directed C(sp^3)–H diiodination of *gem*-dimethyl groups followed by radical cyclization. (Scheme 1b).[5] Besides, cyclopropanes have been generated through domino reactions including olefin carbopalladation and C(sp^3)–H activation, leading to putative 4-membered palladacyclic intermediates (Scheme 1c).[6,7]

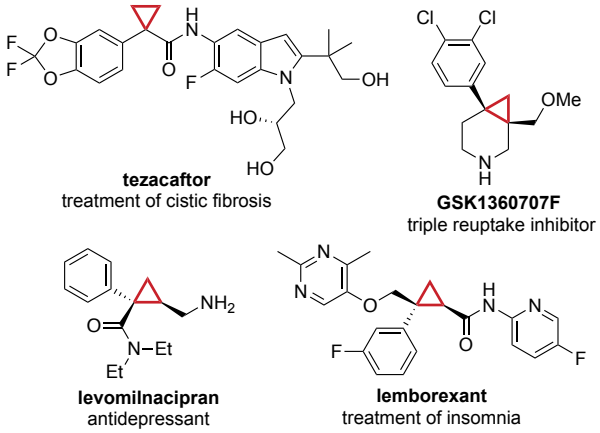


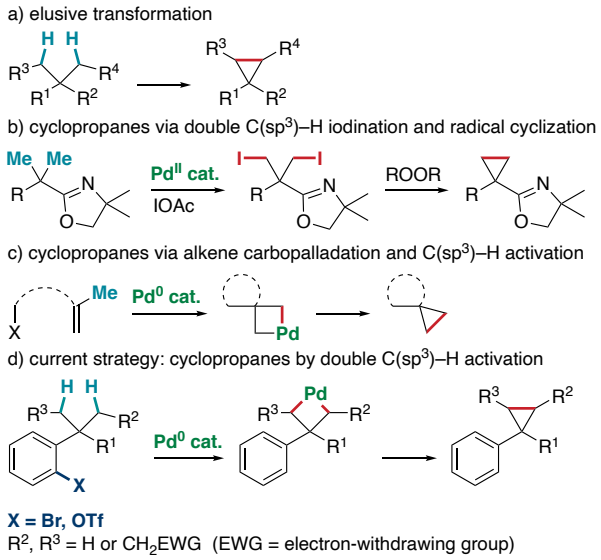
Figure 1. Examples of drugs or drug candidates containing an arylcyclopropane motif relevant to this study.

The current work reports the first single-step synthesis of cyclopropanes via coupling between two geminal methyl groups or one methyl and one activated methylene group (Scheme 1d). This reaction is based on the propension of the arylpalladium halide, generated in the initial oxidative addition step, to undergo 1,4-Pd shift[8] to generate an alkylpalladium intermediate which is able to perform a second C(sp^3)–H activation.[9] This mechanism allows cleavage of two primary C–H bonds within the same reaction, despite the fact that these are theoretically the strongest types of C–H bonds in organic molecules.[10]

RESULTS AND DISCUSSION

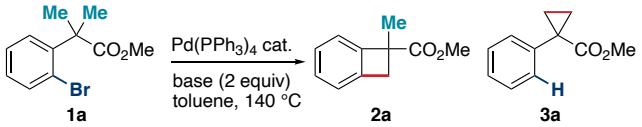
Initial Work and Mechanistic Study. The origin of this work stems from our initial studies on the generation of benzocyclobutenes (BCBs) by Pd^0-catalyzed C(sp^3)–H activation.[11] Recent re-investigations pointed to a spectacular influence of the base on the reaction outcome (Scheme 2).

Scheme 1. Synthesis of Cyclopropanes by Pd-Catalyzed C(sp^3)–H Activation



As initially reported, using potassium carbonate as the base in the intramolecular C–H arylation of substrate **1a** under the shown conditions provided BCB **2a** as the sole observable C–H activation product (entry 1), together with the proto-dehalogenated byproduct (not shown). Replacing carbonate with pivalate led to a complete change of selectivity, with cyclopropane **3a** becoming the sole C–H activation product (entry 2). The ligand also had a noticeable effect on the selectivity, with the bulky P(*t*-Bu)$_3$ favoring the BCB product, as previously reported (entry 3).[11]

Scheme 2. Influence of the Base on the Formation of Benzocyclobutene vs. Cyclopropane



entry	base	**2a** (%)[a]	**3a** (%)[a]
1	K_2CO_3	46%	0%
2	KOPiv	0%	75%
3	KOPiv[b]	36%	22%

[a] NMR yield using CH_2Br_2 as internal reference. [b] Using Pd_2dba_3 (5 mol%)/P(*t*-Bu)$_3$ (20 mol%) instead of $Pd(PPh_3)_4$.

Following these initial observations, and inspired from a study by Martin and co-workers,[12] we decided to reinvestigate the reaction mechanism by following each step through stoichiometric experiments (see the Supporting Information for details). A tentative mechanism, represented in qualitative energy profile format, is displayed in Figure 2. The oxidative addition of prototypical aryl bromide **1b** to $Pd(PPh_3)_4$ gives rise to complex **A**, which undergoes bromide substitution with pivalate, producing complex **B^1**. The latter is in equilibrium with complex **B^2**, containing one phosphine ligand and pivalate coordinated in the κ^2 mode,[13c] which undergoes base-mediated C(sp^3)–H activation via the concerted metalation–deprotonation mechanism[11,13] to give five-membered palladacycle **C^1**.

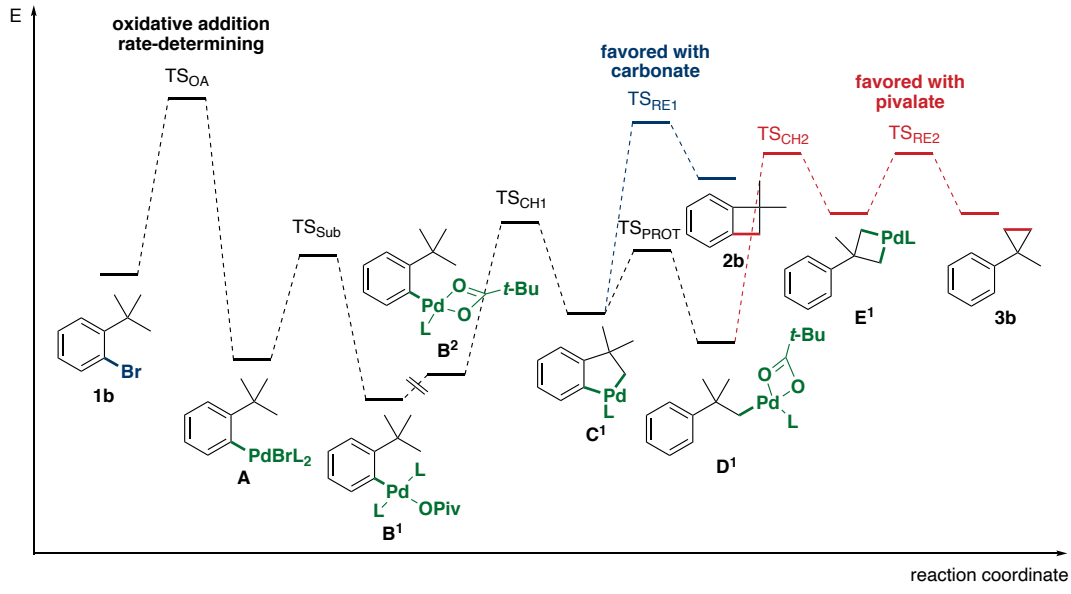
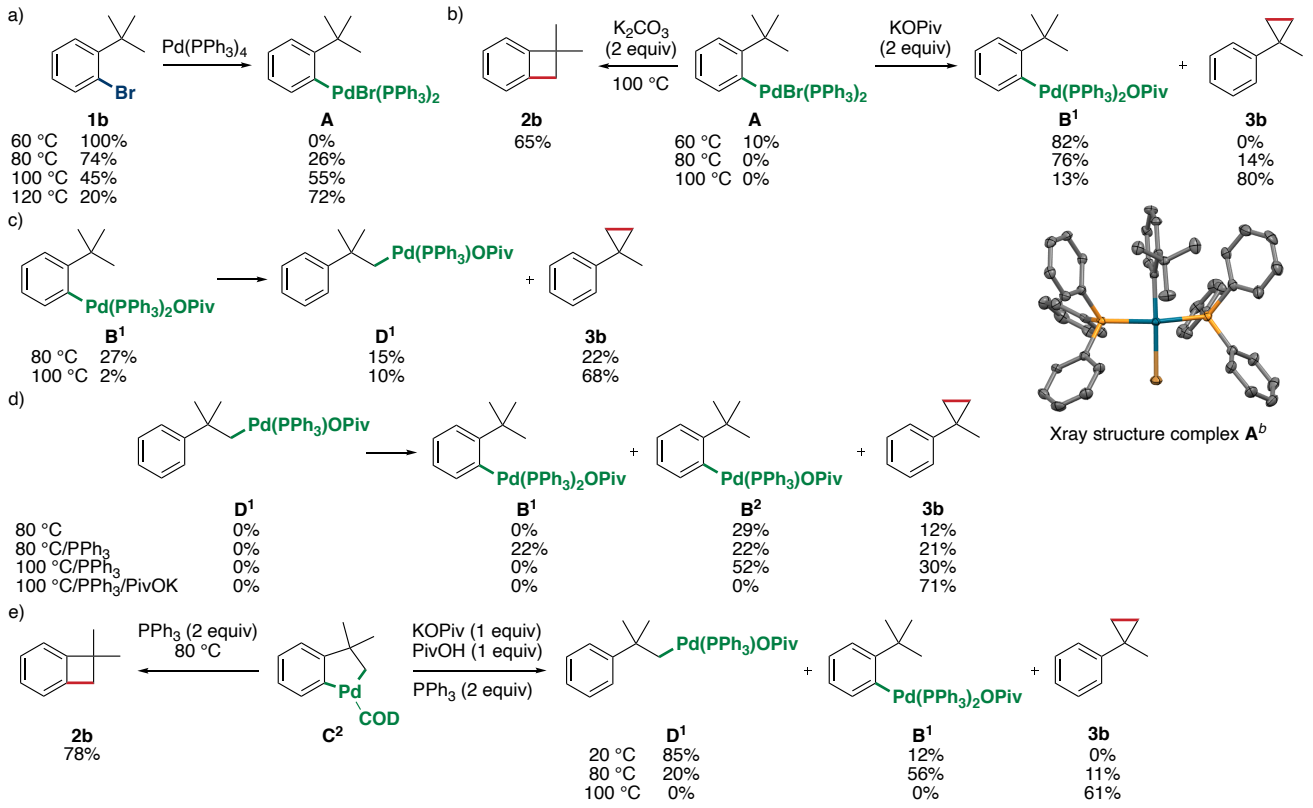


Figure 2. Qualitative energy profile of the reaction of substrate **1b** based on experimental observations. The relative stabilities of **B^2** and **D^1**, **C^1** and **E^1**, and **2b** and **3b** were calculated by DFT (see the Supporting Information for details). L = PPh_3. TS = transition state; OA = oxidative addition; Sub = substitution; CH = C–H activation; PROT = protonation; RE = reductive elimination.

Reductive elimination from $\mathbf{C^1}$ provides the BCB product **2b**. Alternatively, protonation of $\mathbf{C^1}$ with pivalic acid[11,13e] furnishes alkylpalladium complex $\mathbf{D^1}$. The sequence $\mathbf{B^1} \rightarrow \mathbf{C^1} \rightarrow \mathbf{D^1}$ results in an overall 1,4-Pd shift.[8,9b] A second base-induced C(sp^3)–H activation from $\mathbf{D^1}$ leads to the rare four-membered palladacycle $\mathbf{E^1}$,[6,7,14] already suggested by Martin,[12] which reductively eliminates to generate cyclopropane **3b**.

The oxidative addition of the bulky aryl bromide **1b** was followed by ^{1}H and ^{31}P NMR and was found to be slow using PPh_3 as the ligand, with only 26% of complex **A** formed at 80 °C after 16 h, and 72% at 120 °C together with 20% remaining starting material (Scheme 3a). Complex **A** was independently synthesized in 88% yield from **1b** and $Pd(PPh_3)_4$ (toluene, 120 °C), and its three-dimensional structure was confirmed by Xray diffraction analysis (Scheme 3). Consistent with results displayed in Scheme 2, heating **A** to 100 °C in the presence of K_2CO_3 furnished BCB **2b** in 65% yield (Scheme 3b). The substitution step was then analyzed by mixing complex **A** with KOPiv (Scheme 3b). This step was relatively easy, with σ-arylpalladium pivalate $\mathbf{B^1}$ being slowly formed at room temperature (25% after 16 h, not shown) and in 82% yield at 60 °C. Raising the temperature to 80 and 100 °C led to the formation of cyclopropane **3b** at the expense of complex $\mathbf{B^1}$. This result shows that the formation of the cyclopropane product is faster than the oxidative addition, and therefore that the latter is the slowest step of the reaction. The reaction of the known σ-alkylpalladium complex (PhC-Me_2CH_2)Pd(COD)Cl $\mathbf{D^2}$ (COD = cyclooctadiene)[15] in the presence of KOPiv and PPh_3 in toluene at room temperature led to alkylpalladium pivalate $\mathbf{D^1}$ in 88% yield (Scheme S1, see Figure 2 or Scheme 3 for the structure of $\mathbf{D^1}$). In contrast, at 60 °C arylpalladium pivalate $\mathbf{B^1}$ was formed from $\mathbf{D^2}$, thus showing that $\mathbf{B^1}$ is more stable than $\mathbf{D^1}$. The thermal decomposition of $\mathbf{B^1}$ was next analyzed at various temperatures (Scheme 3c). At 80 °C, both $\mathbf{D^1}$ and cyclopropane **3b** were formed, and the proportion of cyclopropane markedly increased at 100 °C. The reactivity of alkylpalladium pivalate $\mathbf{D^1}$ was also analyzed (Scheme 3d). At 80 °C, a new complex, which was assigned to arylpalladium species $\mathbf{B^2}$ containing one PPh_3 ligand and the κ^2-coordinated pivalate, was formed together with degradation products. Adding PPh_3 (1 equiv) led to a cleaner transformation, with both mono- and bis-ligated complexes $\mathbf{B^1}$-$\mathbf{B^2}$ and cyclopropane **3b** being formed in comparable amounts.

Scheme 3. Stepwise Study of the Reaction Mechanism through Stoichiometric Experiments[a]



[a] NMR yields using CH_2Br_2 as internal reference. All reactions were performed in C_6D_6 for 16 h. [b] Thermal ellipsoids at 50% probability, H atoms omitted for clarity. COD = 1,5-cyclooctadiene.

Heating this mixture to 100 °C furnished a higher proportion of **B²** and cyclopropane **3b**, and upon addition of 1 equiv of KOPiv the cyclopropane was formed exclusively. These results show that aryl- and alkylpivalate complexes **B¹**, **B²** and **D¹** are in equilibrium from 80 °C and are all competent intermediates en route to cyclopropane **3b**. Finally, since we did not observe the formation of five-membered palladacycles such as **C¹** (Figure 2) during the above studies, likely because they are higher-energy intermediates, we decided to prepare the known[16] five-membered COD-stabilized palladacycle **C²** and study its reactivity (Scheme 3e). In the presence of KOPiv, PivOH and PPh_3 at room temperature, complex **D¹** was formed as major product, together with minor amounts of **B¹**, thereby showing that the protonation with PivOH is kinetically favored on the aromatic vs. the alkyl ligand. Heating to 80 °C inversed the ratio between **D¹** and **B¹**, thus confirming the higher thermodynamic stability of **B¹**, and produced a minor amount of cyclopropane **3b**. At 100 °C, only the latter was formed (61% yield). In contrast, heating palladacycle **C²** to 80 °C in the presence of PPh_3 only provided BCB **2b** in good yield.[12]

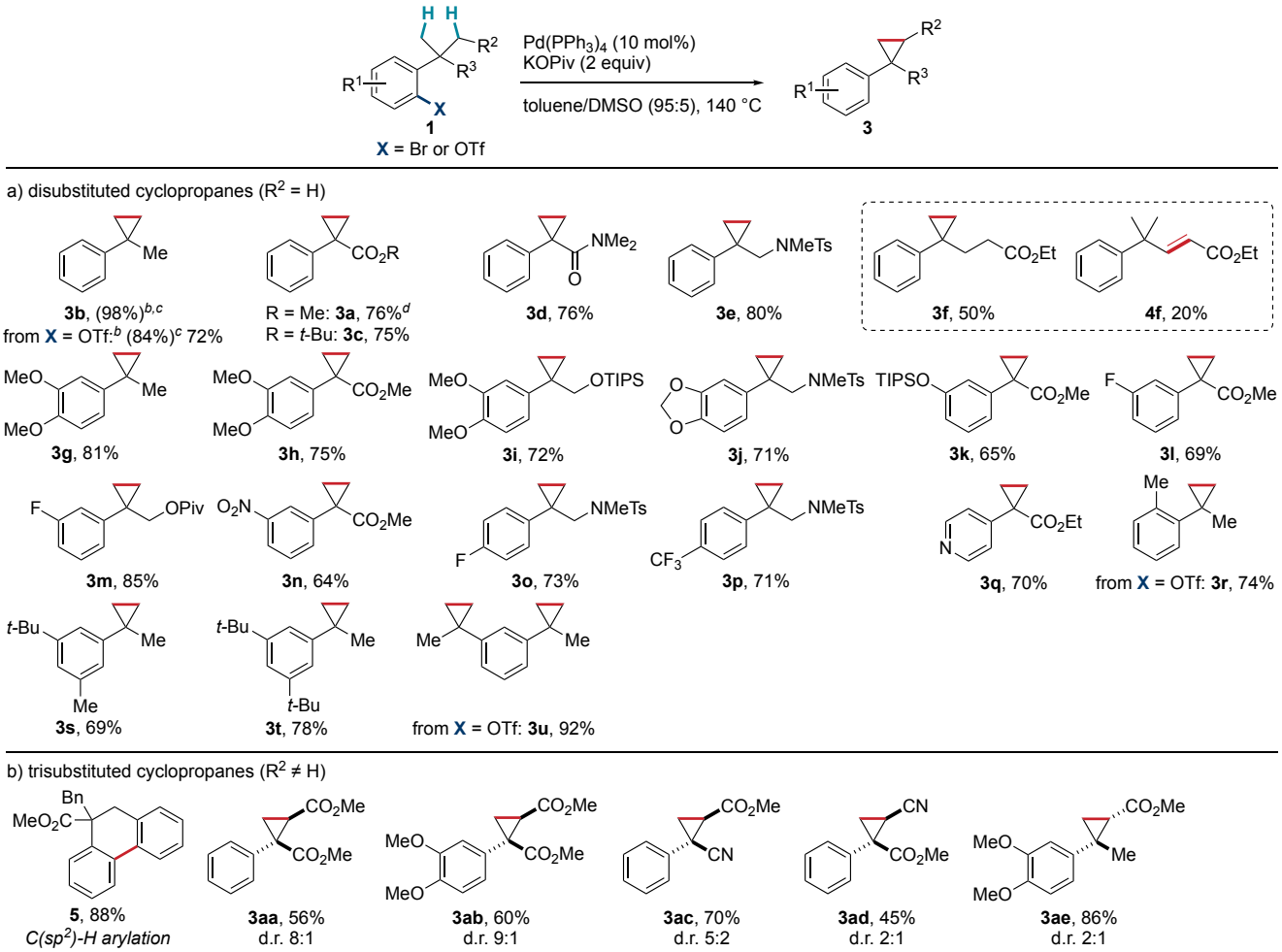
Taken together, these experimental observations allow to deduce the following relative stabilities for organopalladium complexes: **B¹ > B² > D¹ > C¹**. In addition, DFT calculations indicated that the four-membered palladacycle **E¹** is less stable than the five-membered isomer **C¹** by ca. 7 kcal mol^{-1}, hence establishing the stability order **B¹ > B² > D¹ > C¹ > E¹**. Furthermore, cyclopropane **3b** was found to be more stable than BCB **2b** by 1.7 kcal mol^{-1}. Figure 2 provides a qualitative overview of the reaction profile summarizing all experimental results and calculations. The oxidative addition is the highest kinetic barrier, which arises from the fact that the relatively electronically neutral PPh_3 was employed as ligand. In the presence of carbonate and the absence of pivalate, reductive elimination from five-membered palladacycle **C¹** occurs preferentially to give BCB product **2b**. In contrast, pivalate promotes the formation of cyclopropane **3b** via C(sp^3)–H activation of a second methyl group producing the four-membered palladacycle intermediate **E¹**. Both bicarbonate[17] and pivalic acid are able to open up palladacycle **C¹** to give alkylpalladium intermediates, and therefore the unique ability of pivalate to promote the second C(sp^3)–H activation event leading to cyclopropanation remains unclear, and will be the object of later studies.

Reaction Optimization and Scope. Taking advantage of the above mechanistic study, a catalytic version of this transformation was successfully developped (see the Supporting Information for details). Unsubstituted cycloproprane **3b** was obtained from both aryl bromide and triflate precursors in good yield using 10 mol% $Pd(PPh_3)_4$ and 2 equiv potassium pivalate in toluene at 120 °C (Scheme 4a). However, this volatile product was best isolated from the triflate precursor in 72% yield. For functionalized cyclopropanes, a temperature of 140 °C was essential to ensure complete conversion, presumably because these substrates are less reactive towards oxidative addition. Besides, the addition of DMSO (5% vol.) was found to diminish the formation of the proto-dehalogenated side-product, presumably by increasing the solubility of pivalate.

With these standard conditions in hand, the versatility of this double C(sp^3)–H activation-based cyclopropanation was inspected. Substrates bearing an ester (**3a**, **3c**), amide (**3d**), protected amine (**3e**) or protected alcohol (**3i**, **3m**) on the quaternary benzylic carbon worked well under the optimized conditions (72-85% yields). Of note, the reaction producing cyclopropane **3a** was successfully scaled up to 1 mmol. In addition, substrate **1f** bearing a substituted linear alkyl chain provided a mixture of the desired cyclopropane **3f** (50% yield) and olefin **4f** arising from methylene C–H activation and β-H elimination, consistent with previous work.[18,13e] Reactants containing various electron-donating groups on the aromatic ring such as dimethoxy (**3g-i**), methylenedioxy (**3j**) or TIPS-protected phenol (**3k**) gave the desired cyclopropanes in good yields (65-81%). Likewise, electron-withdrawing groups such as fluoro (**3l**, **3m**, **3o**), nitro (**3n**) and trifluoromethyl (**3p**) were found to be compatible. The position of the substituent on the aromatic ring (*meta* or *para*) did not have a significant influence on the reaction outcome. In addition, the pyridinylcyclopropane **3q** was generated in 70% yield, hence indicating the compatibility of heteroarenes. Moreover, substrates functionalized in *ortho* position to the quaternary carbon (**1r**) or to the bromine atom (**1s**, **1t**) provided the corresponding cyclopropane products **3r-t** in good yields (69-78%). Remarkably, a twofold cyclopropanation reaction was successfully carried out, allowing formation of bis-cyclopropane **3u** in 92% yield via two consecutive cyclopropanations including four C(sp^3)–H activation steps.

As expected, substrates bearing benzyl instead of methyl groups did not undergo C(sp^3)–H activation and cyclopropanation, but rather direct C(sp^2)–H arylation, as illustrated with the 6-membered ring product **5** (Scheme 4b). In contrast, in the case of substrates bearing a quaternary carbon with one methyl and one methylene adjacent to an ester or nitrile group, the construction of trisubstituted cyclopropanes was possible. First, cyclopropanes **3aa** and **3ab** containing two esters were synthesized in average yields and good diastereoselectivity, probably arising from thermodynamic control. The positional isomers **3ac** and **3ad** containing nitrile groups were also produced, albeit with a reduced diastereoselectivity. Finally, the trisubstituted cyclopropane **3ae** was generated in 86% combined yield and with a weak, but opposite diastereoselectivity compared to **3ab**.

Scheme 4. Reaction Scope[a]



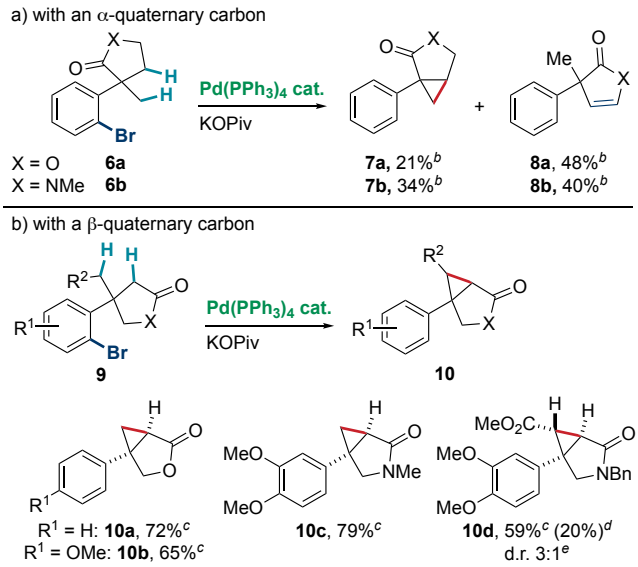
[a] Reactions were performed on a 0.2 mmol scale. The aryl bromide precursor was employed unless otherwise noted. Yields refer to the isolated product or mixture of diastereoisomers. Diastereomeric ratios (d.r.) were determined by ^{1}H NMR of the crude mixture. Relative configurations were determined by NOESY NMR. [b] Performed at 120 °C without DMSO. [c] NMR yield using CH_2Br_2 as internal reference. [d] Performed on a 1 mmol scale.

Molecules containing an aryl-substituted [3.1.0] bicyclic system show interesting biological activities,[2] but only a few methods have been developped for their synthesis.[19-22] The access to these attractive scaffolds was investigated by applying our newly developped Pd-catalyzed double C(sp^3)–H activation reaction (Scheme 5). Starting from lactone **6a**, the cyclopropane-fused product **7a** was formed in low yield and the major product was the butenolide **8a** resulting from β-hydrogen elimination (Scheme 5a). A similar result was obtained from lactam **6b**. To supress the olefin formation, the reaction was conducted with γ-lactones and lactams **9** bearing the quaternary carbon in β position to the carbonyl group (Scheme 5b). Gratifyingly, this modification led to the cyclopropane-fused lactones **10a-b** and lactam **10c** in 65-79% yields. To further increase the complexity, a more substituted substrate bearing a CH_2CO_2Me instead of the CH_3 group was employed. A separable 3:1 diastereomeric mixture of fused γ-lactams was obtained in 79% combined yield, with the major diastereoisomer **10c** having the aryl and ester groups in *cis* relationship. This example shows that our methodology can also be employed to couple two activated methylene groups for the synthesis of tetrasubstituted cyclopropanes.

CONCLUSIONS

The elusive intramolecular cyclopropanation reaction cleaving two C–H bonds and forging a C–C bond has been developed by taking advantage of the 1,4-Pd shift mechanism. Stoichiometric studies indicated that oxidative addition is the rate-limiting step with the employed substrates and catalyst. The characterization of intermediate Pd complexes allowed the delineation of a mechanistic pathway including σ-aryl- and σ-alkylpalladium pivalates, which are in equilibrium via the five-membered diorganopalladacycle.

Scheme 5. Synthesis of Cyclopropane-Fused Lactones and Lactams



[a] Conditions: $Pd(PPh_3)_4$ (10 mol%), KOPiv (2 equiv), toluene/DMSO (95:5), 140 °C, 16 h. [b] NMR yield. [c] Yield of the isolated product. [d] Yield of the isolated minor diastereoisomer. [e] Ratio determined by ^1H NMR of the crude mixture, relative configuration determined by NOESY NMR.

With pivalate as the base and PPh_3 as the ligand, the reductive elimination from this palladacycle is disfavored and the activation of a second C(sp^3)–H bond is favored, leading to a high-energy four-membered palladacycle which reductively eliminates to give the cyclopropane product. A catalytic version was developed, which enabled the generation of an array of arylcyclopropanes in good yields, including fused ring systems, from simple aryl bromide or triflate precursors. This work further illustrates that tuning the catalyst and base in Pd-catalyzed C–H activation reactions may allow to divert mechanistic pathways toward the formation of high value-added products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: Full optimization tables, crystallographic, procedural and spectral data.

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Notes

The authors declare no competing financial interest.

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