Redox-Neutral Coupling between Two C(sp^3)–H Bonds Enabled by 1,4-Palladium Shift for the Synthesis of Fused Heterocycles

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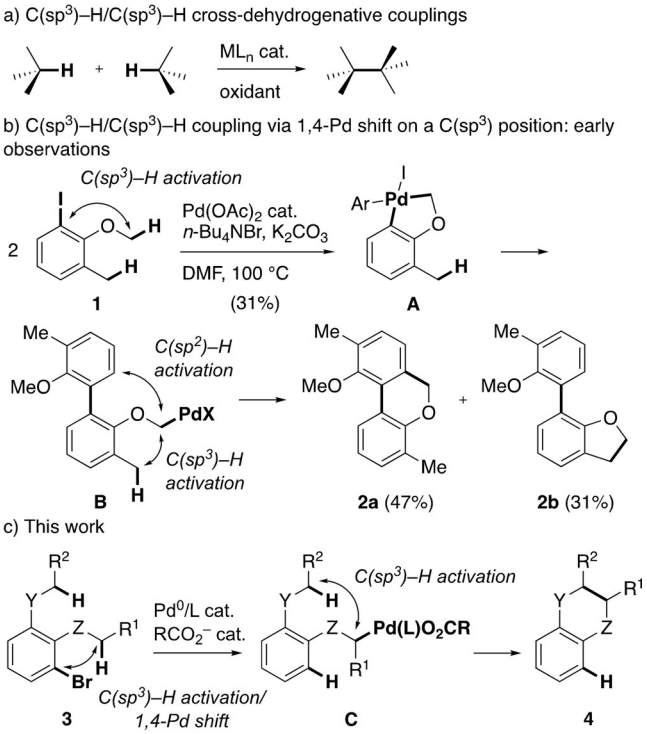
Abstract: *The intramolecular coupling of two C(sp^3)–H bonds to forge a C(sp^3)–C(sp^3) bond is enabled by 1,4-Pd shift from a trisubstituted aryl bromide. Contrary to most C(sp^3)–C(sp^3) cross-dehydrogenative couplings, this reaction operates under redox-neutral conditions, with the C–Br bond acting as an internal oxidant. Furthermore, it allows the coupling between two moderately acidic primary or secondary C–H bonds, which are adjacent to an oxygen or nitrogen atom on one side, and benzylic or adjacent to a carbonyl group on the other side. A variety of valuable fused heterocycles were obtained from easily accessible ortho-bromophenol and aniline precursors. The second C–H bond cleavage was successfully replaced with carbonyl insertion to generate other types of C(sp^3)-C(sp^3) bonds.*

Transition-metal-catalyzed C–C bond formation by double C–H bond cleavage, often termed cross-dehydrogenative coupling (CDC) has emerged as a promising transformation in organic synthesis.[1] However, in contrast to C(sp^2)–C(sp^2) and C(sp^2)–C(sp^3) bond formation, the construction of C-(sp^3)–C(sp^3) bonds through CDC is still very limited (Scheme 1 a). So far, most of the existing methods involve oxidative conditions and outer-sphere mechanisms which require two weak C–H bonds, with a low bond dissociation energy or high acidity. 1,*n*-Palladium shift, pioneered by Heck,[2] represents a redox-neutral alternative to construct C–C bonds by double C–H activation, thanks to an initial oxidative addition of a C–X bond to a Pd^0 catalyst.[3,4] Recently, we have exploited this concept to generate remote C(sp^2)–C(sp^3) bonds by 1,4-Pd shift into a C(sp^2) position and C(sp^3)–H activation.[5,6] However, using palladium shift to form C(sp^3)–C(sp^3) bonds is arguably more challenging, due to the propensity of σ-alkylpalladium species to undergo protodemetallation or β-hydride elimination, especially at high temperatures. Yet, early work from Dyker showed that alkylpalladium intermediates, generated from C(sp^3)–H activation at methoxy groups, are competent to perform subsequent C(sp^2)–H or C(sp^3)–H activation.[7] In particular, when iodoarene **1** was reacted with catalytic $Pd(OAc)_2$ and stoichiometric carbonate in DMF, the dimeric products **2a** and **2b** were isolated (Scheme 1 b).[7d] Mechanistically, a first C–I oxidative addition to an in situ-generated Pd^0 complex triggers C(sp^3)–H activation at the *ortho* methoxy group to give a 5-membered palladacycle, that undergoes oxidative addition of a second molecule of substrate **1** to give the palladium(IV) intermediate **A**.[8] Reductive elimination from **A** forges the biaryl bond and leads to the alkylpalladium(II) intermediate **B**. The latter furnishes dibenzopyran **2a** upon C(sp^2)–H activation at the *ortho* aryl group and reductive elimination, and dihydrobenzofuran **2b** upon C(sp^3)–H activation at the *ortho* methyl group and reductive elimination. We surmised that, if the second oxidative addition leading to palladacycle **A** could be avoided, substrates similar to **1** could give rise to simpler dihydrobenzofurans through 1,4-Pd shift and C(sp^3)–H/C-(sp^3)–H coupling.



Scheme 1. 1,4-Pd shift for the formation of C(sp^3)–C(sp^3) bonds from two C(sp^3)–H bonds.

In the past years, we and others showed that the introduction of an appropriate ancillary ligand allows shutting down this unproductive oxidative addition pathway and generating a variety of ring systems by direct C(sp^2)–C(sp^3) reductive elimination.[9] Moreover, it was shown that aryl bromides **3** (Scheme 1 c) tend to undergo 1,4-Pd shift through carbonate or carboxylate-mediated proton transfer to generate alkylpalladium complex **C**.[10] Such alkylpalladium intermediates can be trapped with boronic acids or amines to give intermolecular C–C and C–N coupling products,[11] or

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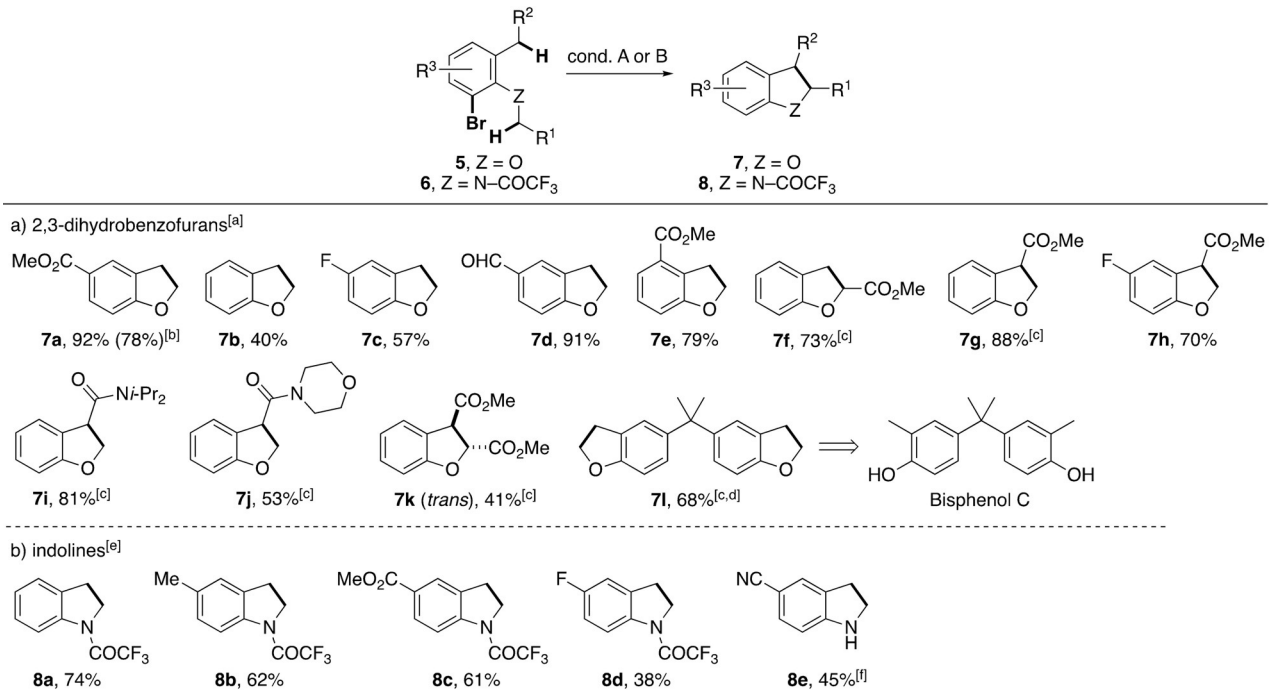
undergo β-H elimination to give olefins.[10b,12] Alternatively, we hypothesized that **C** might undergo a second C(sp^3)–H bond cleavage at an *ortho* alkyl group, similar to **B**, to provide cyclic product **4** upon reductive elimination from the corresponding palladacycle. This pathway, avoiding the undesired self-condensation described in Scheme 1b, could be potentially applicable to precursors containing diverse Y and Z groups as well as C(sp^3)–H bond types, to generate a variety of fused heterocycles of interest for medicinal chemistry. Herein, we report the development of this Pd shift-based C(sp^3)–C(sp^3) bond forming method.

We first explored the reactivity of aryl bromide **5a** in standard Pd^0/ligand-catalyzed C(sp^3)–H activation conditions (Scheme 2a). After a quick optimization,[13] we found that the use of the well-defined $Pd(PCy_3)_2$ complex and stoichiometric cesium pivalate as a mild stoichiometric base allowed formation of 2,3-dihydrobenzofuran **7a** in 92% yield. As hypothesized, we did not observe the formation of dimers analogous to **2a**,**b** (Scheme 1b) under these conditions. The reaction could be scaled up (78% yield on a tenfold scale) and extended to other aryl bromides, easily accessible from phenol precursors, to give dihydrobenzofurans **7b–e** in moderate to very good yields. The volatility of products **7b** and **7c** was likely responsible for their moderate yields. Of note, a carbaldehyde was well tolerated (**7d**), which is likely enabled using the mildly basic cesium pivalate as the stoichiometric base. Substitution was tolerated at the *ortho* position to the second activated methyl group (**7e**), but not at the *ortho* position to the bromine atom. Importantly, the reaction also proceeded when an ester or amide group was installed as R^1 (**7f**),[14] R^2 (**7g–j**) or both R^1 and R^2 (**7k**), with the latter being isolated as the *trans* diasteroisomer. Other R^1 and R^2 groups such as methyl led to a complete loss of reactivity under these conditions, thus showing that the current reaction is limited to primary and sufficiently acidic secondary C(sp^3)–H bonds. However, one should note that the synthesized dihydrobenzofurans **7a–k** are not accessible through direct Pd^0-catalyzed C(sp^3)–H arylation from aryl halides, which requires the presence of a quaternary center to favor the intramolecular C–H activation step.[15] Moreover, a double reaction was successfully conducted on a dibromo substrate (**5l**), easily derived from Bisphenol C through electrophilic bromination and methylation, to furnish bis(dihydrobenzofuran) **7l** in good yield. In this remarkable example, four C(sp^3)–H bonds were activated and two C(sp^3)–C(sp^3) bonds created.

Next, we considered the extension of the 1,4-Pd shift-induced coupling to sp^3 carbons adjacent to a nitrogen atom (Scheme 2b). We were motivated by prior observations that *o*-bromo-*N*-methylanilines tend to undergo demethylation under Pd^0/ligand-catalyzed conditions, presumably through 1,4-Pd shift and iminium formation.[16] Gratifyingly, this undesired demethylation could be avoided upon deactivation of the nitrogen atom with a trifluoroacetyl substituent (substrate **6a**), and after reoptimization of the reaction conditions (cat. $AdCO_2H$/stoich. Rb_2CO_3, 160 °C)[13] indoline **8a** was obtained in 74% yield. To the best of our knowledge, this is the first example of 1,4-Pd shift adjacent to a nitrogen atom leading to C–C bond formation. Substituents were well tolerated on the arene ring (**8b–e**), but unlike dihydrobenzofurans the indoline was not formed when substituents were introduced on the carbons undergoing C(sp^3)–H bond cleavage (R^1, R^2). Despite this limitation, this method is also complementary to indoline synthesis through direct Pd^0-



Scheme 2. Synthesis of 2,3-dihydrobenzofurans and indolines through C(sp^3)–H/C(sp^3)–H coupling. [a] Conditions A: $Pd(PCy_3)_2$ (10 mol%), CsOPiv (1.0 equiv), toluene, 140 °C (sealed tube). [b] Performed on a tenfold scale. [c] Performed at 160 °C. [d] Performed using 20 mol% Pd. [e] Conditions B: $Pd(PCy_3)_2$ (10 mol%), $AdCO_2H$ (30 mol%), Rb_2CO_3 (1.5 equiv), toluene, 160 °C (sealed tube). [f] The amide hydrolysis product was directly isolated.

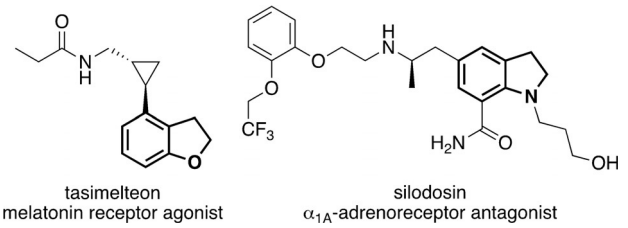


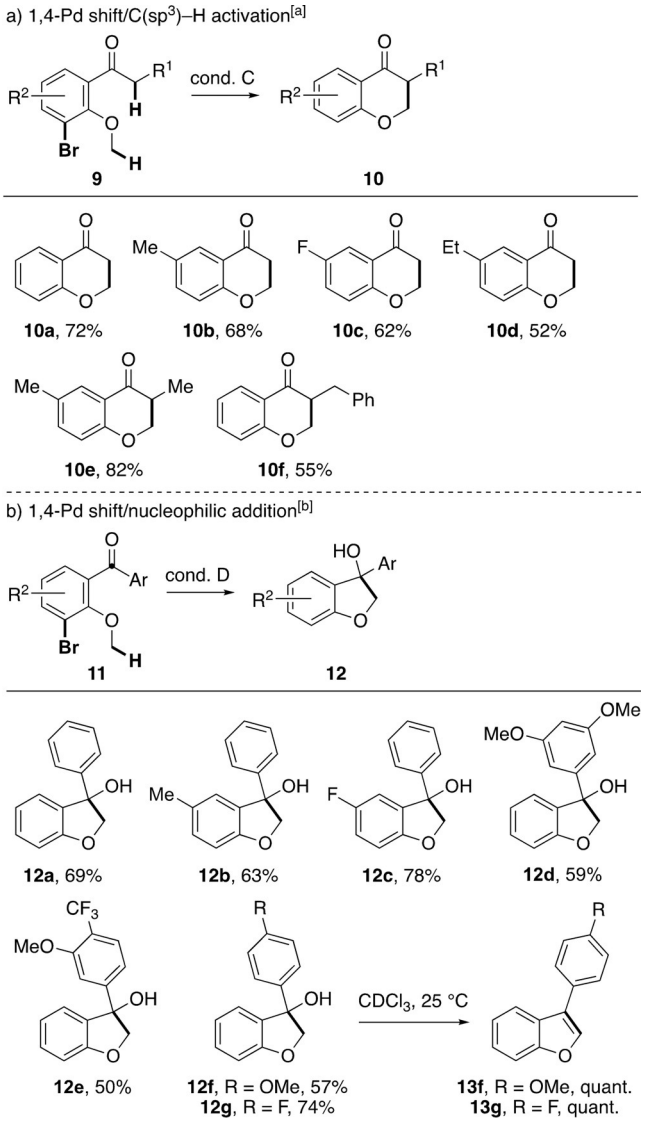
Figure 1. Bioactive molecules containing the 2,3-dihydrobenzofuran and indoline motifs.

catalyzed C(sp^3)–H arylation.[17,15b] As illustrated with the structures of tasimelteon[18] and silodosin (Figure 1),[19] the 2,3-dihydrobenzofuran and indoline motifs are important substructures found in many pharmaceuticals.

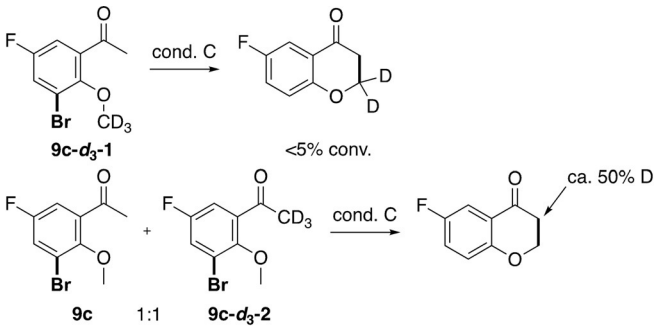
Next, we set out to extend this method to the construction of 6-membered rings (Scheme 3a). Keeping in mind the above reactivity limitation to primary and acidic secondary C–H bonds, we found that aryl bromide **9a**, containing an acetyl instead of methyl group in *ortho* position to the methoxy group which undergoes 1,4-Pd shift, furnished chroman-4-one **10a** in 72% yield, after further tuning the reaction conditions (cat. $AdCO_2H$/stoich. Cs_2CO_3, 120°C).[13] The reaction was successfully extended to arylalkylketones bearing substituents on the aromatic ring (**10b–d**), as well as other alkyl groups (**10e**,**f**). Of note, such chroman-4-ones are valuable heterocycles for drug discovery.[20]

In the absence of an enolizable position, the organopalladium intermediate arising from 1,4-Pd shift could potentially attack the ketone to give a tertiary alcohol.[21] Indeed, under more forcing conditions arylketones **11a–g** underwent 1,4-Pd shift/nucleophilic addition to give the corresponding 2,3-dihydrobenzofuran-3-ols **12a–g** in average to good yields, thereby providing a conceptually simple extension of the current method to a different type of C(sp^3)–C(sp^3) bond formation (Scheme 3b). In principle, this reaction requires a stoichiometric reductant to recycle Pd^0 after the carbonyl insertion step.[21] Given that cesium pivalate is the only stoichiometric reagent in our case, we hypothesize that the catalyst turnover is provided by anionic ligand exchange with pivalate, giving rise to palladium(II) pivalate, which regenerates Pd^0 through homocoupling of toluene.[22] The 2,3-dihydrobenzofuran-3-ol products were moderately stable and underwent facile dehydration when left in $CDCl_3$ at room temperature to give the corresponding benzofurans, as illustrated with **13f** and **13g**, hence providing a new entry into this biologically important motif.[23]

Preliminary mechanistic investigations were conducted with deuterated substrates. First, compound **9c**-d_3-**1** was submitted to the standard conditions forming chromanones (Scheme 4). Surprisingly, no reaction occurred even after prolonged heating, in contrast to its protiated isotopomer **9c**.[24] At first glance, this result seems to translate a very large kinetic isotope effect (KIE), typically observed in tunneling.[25] Further investigations on this singular behavior are ongoing. In addition, equimolar mixtures of **9c** and **9c**-d_3-**2** led to the corresponding chromanone with a 50% deuterium content on the α-carbonyl position at various conversions, diagnostic of an absence of primary KIE at this position.[26]



Scheme 3. Divergent behavior of *o*-methoxyphenylketones. [a] Conditions C: $Pd(PCy_3)_2$ (10 mol%), $AdCO_2H$ (30 mol%), Cs_2CO_3 (1.0 equiv), toluene, 120°C (sealed tube). [b] Conditions D: $Pd(PCy_3)_2$ (10 mol%), CsOPiv (3.0 equiv), toluene, 160°C (sealed tube).



Scheme 4. Deuterium isotope effect.

These two experiments indicate that the first C(sp^3)–H bond cleavage is turnover-limiting, in agreement with the relative acidities of the corresponding C–H bonds.

In conclusion, we have successfully achieved the intramolecular coupling of two C(sp^3)–H bonds to forge a C(sp^3)–C(sp^3) bond using the 1,4-Pd shift strategy. A variety of valuable fused heterocycles were obtained from easily accessible *ortho*-bromo phenol and aniline precursors. This reaction is so far limited to moderately acidic C–H bonds, adjacent to an oxygen or nitrogen atom on one side and benzylic or adjacent to a carbonyl group on the other side, but extensions to less reactive C–H bonds are foreseen.

Acknowledgements

This work was financially supported by the University of Basel, Università degli Studi di Perugia and MIUR. We thank Prof. L. Vaccaro for supporting the visiting studentship of I.A., Dr. D. Häussinger for NMR experiments, Dr. M. Pfeffer for MS analyses, and Dr. A. Clémenceau for fruitful discussions.

Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H activation · domino reactions · heterocycles · palladium

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