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Pd-Catalyzed C(sp^3)–H Functionalization/Carbenoid Insertion: All-Carbon Quaternary Centers via Multiple C–C Bond Formation

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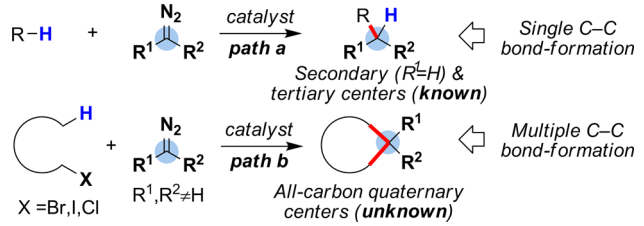
Supporting Information

ABSTRACT: A Pd-catalyzed C(sp^3)–H functionalization/carbenoid insertion is described. The method allows for the rapid synthesis of bicyclic frameworks, generating all-carbon quaternary centers via multiple C–C bond formations in a straightforward manner.

Over the past few years, there has been a growing consensus that C–H functionalization has profoundly changed the landscape of organic synthesis while establishing new paradigms in retrosynthetic analysis.[1] While spectacular advances have been realized, this area of expertise primarily relies on the utilization of directing groups, particularly via C(sp^2)–H functionalization. Indeed, a close inspection into the literature data reveals that the preparation of all-carbon quaternary centers[2] via C(sp^3)–H functionalization in the absence of directing groups still remains rather elusive.[3,4]

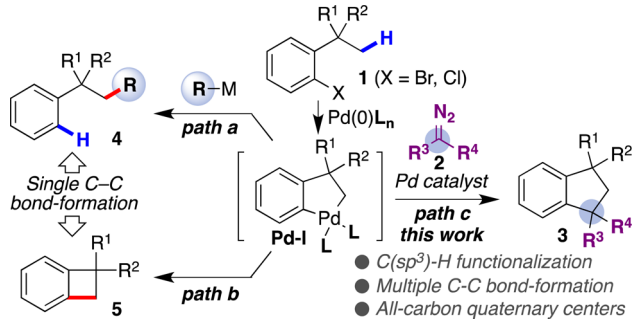
While originally designed for cyclopropanation events, carbenoid species have shown to be superb synthons in a myriad of relevant transformations.[5] Indeed, these reagents have successfully been employed in C–H insertion reactions without the need for directing groups, allowing for installing secondary or tertiary carbon centers via single C–C bond formation (Scheme 1, path a).[6] To the best of our knowledge,

Scheme 1. C(sp^3)–H Functionalization/Carbenoid Insertion



all-carbon quaternary centers derived from the corresponding carbenoid species are beyond reach in C–H functionalization.[7,8] Undoubtedly, the ability to promote multiple C–C bond formations initiated by C(sp^3)–H functionalization, while installing all-carbon quaternary centers would be of particular interest (Scheme 1, path b).[9] If successful, such a protocol would not only represent an unconventional, yet powerful, technique for our synthetic arsenal but also a unique opportunity to improve our ever-growing knowledge in C–H functionalization. However, the difficulty for effecting C(sp^3)–H functionalization in the absence of directing groups[3] and the inherent propensity of carbenoids toward competitive dimerization[5,6] constitute serious drawbacks to be overcome. To such end, we hypothesized that the intermediacy of *in situ*-generated **Pd-I**[10] via C(sp^3)–H functionalization would be critical for success (Scheme 2). At the outset of our investigations, it was

Scheme 2. Intermediacy of Pd-I in C–H Functionalization



unclear whether such scenario could ever be conducted given the known proclivity of **Pd-I** toward C–C reductive elimination (path b)[11,12] or competitive [1,4]-shifts en route to **4** (path a).[13] Herein, we report a mild catalytic C(sp^3)–H functionalization/carbenoid insertion en route to indanes **3** bearing all-carbon quaternary centers (path c). This protocol is distinguished by a wide scope and excellent chemoselectivity profile, thus constituting a unique tool to rapidly build up molecular complexity.

We initiated our study by investigating the reaction of **1a** with **2a** (Table 1). After considerable experimentation,[14] a protocol based on $PdCl_2(SMe_2)_2$, **L1**, PivOH, and Cs_2CO_3 in DMF at 80 °C provided the best results (entry 1). Although the structure of **3aa** was evident by NMR spectroscopy, we univocally assigned its structure by comparison with **3aa′**, derived from the hydrolysis of **3aa**, by X-ray crystallography.[14] Not surprisingly, the ligand backbone had a critical impact on both reactivity and selectivity (entries 2–6). While the significant lower reactivity of **L2** and **L3** might suggest an intimate interplay of steric and electronic effects, care must be taken when generalizing this since we found that **L4** was equally effective. The use of monodentate phosphines (entries 5 and 6) had a deleterious effect; strikingly, the utilization of P*t*Bu$_3$ resulted in a selectivity switch, obtaining exclusively **5a**.[11c]

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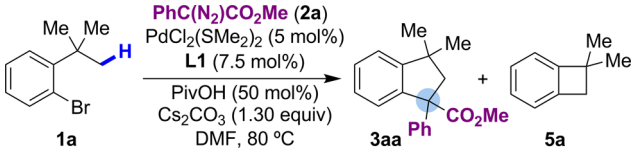
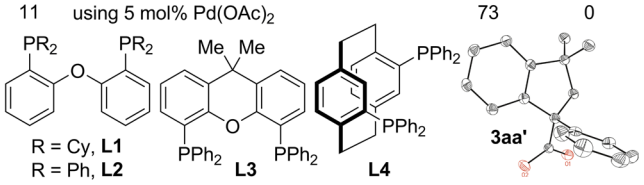
Table 1. Optimization of the Reaction Conditions[a]



Entry	Deviation from the standard conditions	3aa (%)[b]	5a (%)[b]
1	none	93 (80)[c]	0
2	using **L2** as the ligand	36	0
3	using **L3** as the ligand	0	0
4	using **L4** as the ligand	83	0
5	using $PtBu_3 \cdot HBF_4$ (15 mol%) as the ligand	0	58
6	using PCy_3 (15 mol%) as the ligand	0	0
7	using CsOPiv (1.30 equiv) as the base[d]	43	0
8	using CsOAc as the base	38	0
9	using PhMe instead of DMF	15	73
10	using DMA instead of DMF	49	0
11	using 5 mol% $Pd(OAc)_2$	73	0

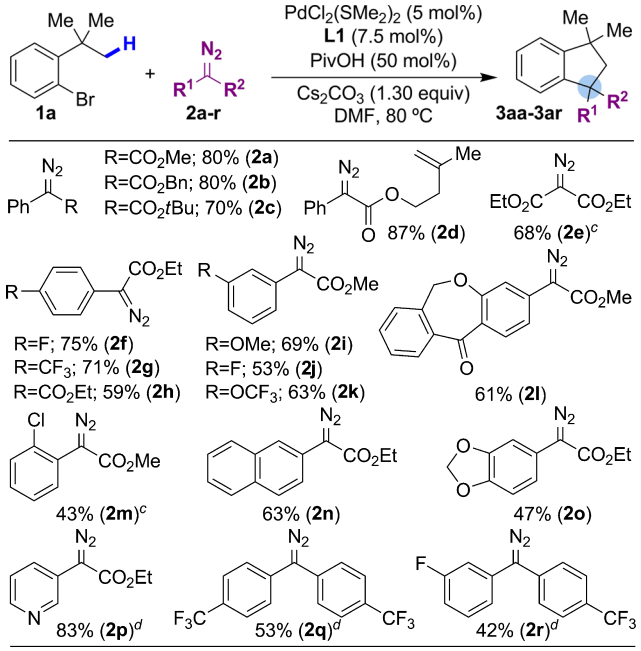


[a]**1a** (0.10 mmol), **2a** (0.18 mmol), $PdCl_2(SMe_2)_2$ (5 mol %), **L1** (7.50 mol %), PivOH (50 mol %), Cs_2CO_3 (0.13 mmol), DMF (0.25 M) at 80 °C. [b]GC yields using *o*-xylene as internal standard. [c]Isolated yield. [d]No PivOH was added.

Similarly, the base and the solvent exerted a profound influence on reactivity (entries 7−10), with toluene favoring the formation of **5a** (entry 9). Interestingly, inferior results were found for protocols based on $Pd(OAc)_2$ (entry 11). The higher reactivity of $PdCl_2(SMe_2)_2$ is tentatively attributed to its high solubility; at present, we cannot rule out that Me_2S facilitates the reduction to Pd(0) while forming DMSO. Additionally, otherwise related aryl chlorides, iodides, and triflate congeners failed to deliver **3aa**. As anticipated, control experiments univocally revealed that all parameters were essential for the reaction to occur.[14,15]

Prompted by these results, we sought to examine the influence of the carbenoid species (Table 2). As shown, the scope was insensitive to electronic changes at the *para* and *meta* positions on the aromatic ring (**2f**−**l**). Likewise, the substitution pattern on the ester motif was inconsequential to the reactivity profile (**2a**−**c**), invariably leading to the targeted products in high yields. The chemoselectivity profile of our protocol is nicely illustrated by the fact that a wide variety of diazoester derivatives bearing aryl halides (**2f**, **2j**, and **2m**), esters (**2e** and **2h**), ketones (**2l**), or acetals (**2o**) were all well accommodated. Notably, nitrogen-containing heterocycles posed no problems (**2p**). Particularly interesting was the observation that the presence of an alkene on the side chain did not interfere, affording **3ad** in high yields without traces of intramolecular cyclopropanation being observed in the crude mixtures. Gratifyingly, the diazo compound derived from isoxepac (**2l**),[16] a nonsteroidal anti-inflammatory drug, could be employed with equal ease. Notably, this transformation was not limited to diazoester derivatives, as diaryldiazomethanes could also be coupled, albeit in lower yields (**2q** and **2r**). Unfortunately, donor/donor diazo compounds and monosubstituted carbene precursors could not participate in the targeted reaction, recovering starting material unaltered.

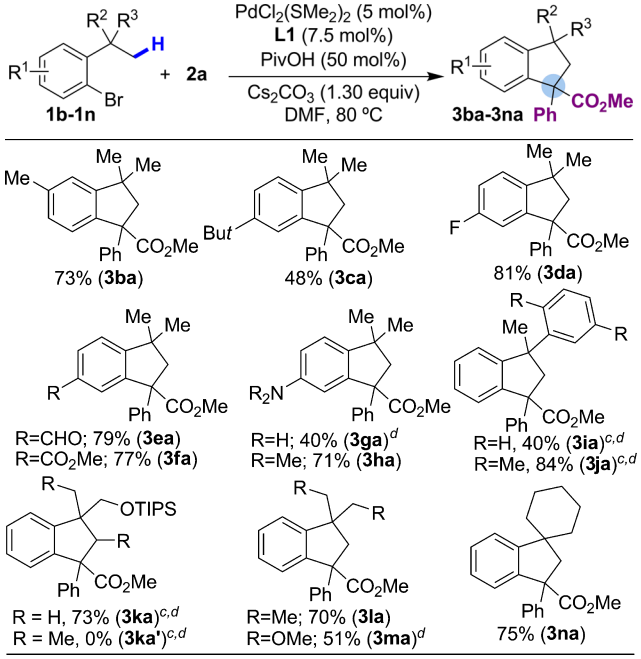
Table 2. Scope of Diazo Compounds[a,b]



[a]As Table 1 (entry 1), 0.50 mmol scale. [b]Isolated yields, average of at least two independent runs. [c]$PdCl_2(SMe_2)_2$ (10 mol %) at 100 °C. [d]$PdCl_2(SMe_2)_2$ (10 mol %).

Next, we turned our attention to study the substitution pattern on the aryl halide backbone (Table 3). As shown, the preparative scope was rather general regardless of whether electron-donating or electron-withdrawing groups were present

Table 3. Scope of Aryl Bromides[a,b]



[a]As for Table 1 (entry 1), but at 0.50 mmol scale. [b]Isolated yields, average of at least two independent runs. [c]1:1 diastereomeric ratio. [d]$PdCl_2(SMe_2)_2$ (10 mol %) at 100 °C.

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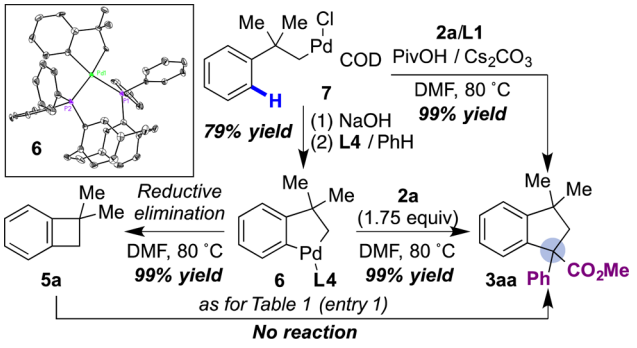
or not. Notably, a variety of aryl fluorides (**3da**), aldehydes (**3ea**), esters (**3fa**), amines (**3ga** and **3ha**), or silyl ethers (**3ka**) could perfectly be tolerated. Importantly, even free amines could be employed as substrates, albeit in lower yields (**3ga**). Although the presence of an *ortho* *t*-butyl group statistically accelerates the key C(sp^3)−H functionalization,[17] we found that a variety of *ortho* substituents other than *t*-butyl groups could be equally accommodated (**3ia**−**na**). In all cases analyzed, the targeted C(sp^3)−H functionalization occurred exclusively at the primary C(sp^3)−H bonds, leaving the corresponding methylene positions intact. In line with this notion, no reaction occurred when employing **3ka**′. Unfortunately, no diastereoselection was observed in the presence of *gem*-dimethyl groups (**3ia**−**ka**), even in the presence of bulky silyl or aromatic motifs (**3ja** and **3ka**).[18] Likewise, tertiary benzylic carbons (R^2 = H) resulted in *β*-hydride elimination, even with bulkier mesityl groups. Taken together, the results in Tables 2 and 3 show the prospective impact of our protocol for rapidly preparing indane skeletons bearing all-carbon quaternary centers.

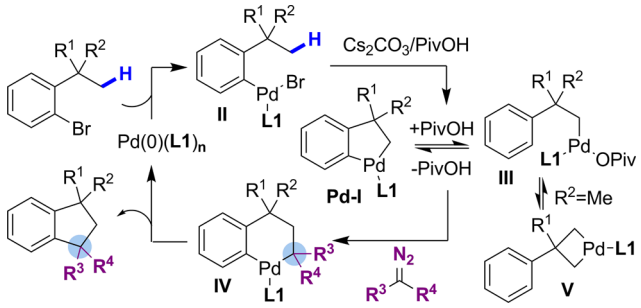
Next, we decided to gather indirect evidence on the mechanism by examining the reactivity of **1a** with PivOD. Interestingly, a non-negligible deuteration at *ortho* position of **3aa** was observed, suggesting that **Pd-I** (Scheme 2) might coexist in equilibrium with homobenzylic Pd(II) intermediates generated upon protonolysis with PivOD via [1,4]-shift.[10c,11c,13,14] Next, we studied the reactivity of the putative metallacycle **Pd-I**. Following the methodology described by Cámpora,[10b] we prepared **6** from **7** in high yield (Scheme 3, top), which was fully characterized by X-ray structure analysis.[14] Interestingly, while **6** rapidly underwent reductive elimination en route to **5a** in the absence of **2a**,[11] **3aa** was exclusively obtained with **2a** (Scheme 3, bottom).[19,20] Notably, **3aa** was not obtained from **5a**, thus ruling out the possibility of a C−C cleavage event. We believe these results reinforce a scenario consisting of **Pd-I** via concerted metalation−deprotonation from **II** (Scheme 4).[11,21] While **Pd-I** might coexist in equilibrium with **III** upon protonolysis with PivOH, a 1,2-insertion of a diazo compound[10a,22,23] might generate **IV** that ultimately delivers the targeted product via reductive elimination. At present, we cannot rule out the intermediacy of **V** via rapid equilibration with **III** and **Pd-I**,[24] as traces of cyclopropane derivatives via reductive elimination from **V** were detected in reactions of aryl bromides possessing bulky groups at the geminal position.[25]

In conclusion, we have developed a mild and robust Pd-catalyzed C(sp^3)−H functionalization/carbenoid insertion event. This technique represents a unique synthetic tool in the C(sp^3)−H functionalization arena for building up bicyclic frameworks in which the all-carbon quaternary center is derived from carbenoid species.

Scheme 3. Mechanistic Experiments



Scheme 4. Mechanistic Hypothesis



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02867.

Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Experimental details and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(14) See SI for details.

(15) The use of tosyl hydrazones as carbenoid precursors resulted in dehalogenation while not observing even traces of **3aa**.

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(18) DFT calculations (B3LYP and M06) showed that the energy difference of the transition states leading to the two possible diastereoisomers (**IV**, Scheme 4) is negligible (0.3−2.3 kcal·mol^{-1}). Additionally, the overall energy barrier for [1,2]-insertion was found to be 1.7−3.3 kcal·mol^{-1} (ref 14).

(19) Although **6-L1** could be isolated and characterized by X-ray crystallography (see ref 14), its insolubility prevented its characterization by NMR spectroscopy. Still, **6-L1** could be converted into either **5a** or **3aa** in quantitative yields.

(20) **6** and **7** were found to be catalytically competent on the conversion of **1a** into **3aa** (see ref 14).

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(22) We propose the intermediacy of Pd carbenoid species from **Pd-I** prior 1,2-insertion at the C(sp^3)−Pd bond en route to **IV**. Preliminar DFT calculations (B3LYP and M06) revealed that 1,2-insertion at C(sp^2)−Pd bond was less favorable by 12−15 kcal·mol^{-1} (ref 14).

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(25) 0% ee was observed by reacting diethyl 2-diazomalonate with aryl halides containing *gem*-dimethyl groups. See SI for a mechanistic rationale.

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