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Reactivity of stable neopentyl-Pd intermediates in the absence of nucleophile

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Abstract—In the absence of any trapping agent, stable neopentyl-Pd intermediates can terminate a catalytic cycle by undergoing a regioselective C–H activation, leading to various spiro or fused cyclopropane derivatives in a straightforward manner. If the neopentyl-Pd intermediate contains a heteroatom at a suitable position, C–H activation does not occur and stable palladacycles are isolated.

In the course of preparing new ligands by means of an asymmetric sigmatropic rearrangement of allylic phosphinites,[1] we needed to functionalize phosphine oxide **1**. It appeared to us that an intramolecular *syn*-carbopalladation reaction would lead to a stable Pd intermediate that could be trapped by a nucleophile.[2] Such a strategy would lead to new, enantiomerically pure, useful ligands.[3] In a preliminary study, attempts to trap the Pd intermediate with a hydride source did not give the expected compound **2**. We reacted phosphine oxide **1** with $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), *n*-Bu_4NBr (1.3 equiv), $NaBH_4$ or HCOONa (3 equiv), and K_2CO_3 (5 equiv) in DMF at 120 °C for 16 h and observed the sole formation of tricyclic compound **3** (Table 1 and Scheme 1). Use of $NaBH_4$ as a trapping agent for intermediate **5** (Scheme 1 and entry 1) inhibited the reaction. With HCOONa, a high diastereoselectivity was achieved, but the conversion was too low to be synthetically useful (entries 2 and 3). As it was not possible to trap intermediate **5**, we decided to investigate this unexpected C–H activation pathway. When $Pd(OAc)_2$ was used as a catalyst, the optimal temperature was 120 °C (entry 8). Higher or lower temperatures (entries 9 and 10) led to lower diastereoselectivities or lower conversions. When Ag_2CO_3 was used as a base, high diastereoselectivities were achieved, but with low conversions (entries 4 and 5). At 120 °C, a high conversion was obtained, but the diastereoselectivity was poor (entry 6). Changing the Pd source to $Pd(PPh_3)_4$ led to no improvement (entry 7). Interestingly, compound **3** was formed at such a rate that the regioselective C–H activation pathway could occur, even in the presence of a *syn*-β-hydrogen. This is indicated by the fact that **3** was isolated as a mixture of diastereomers (Table 1). A suitably positioned *syn*-β-hydrogen is therefore necessarily present in one of the two isomers. Such pathways are unusual, as β-hydride elimination is often the fastest process to terminate a catalytic cycle.

The formation of **3** could be explained by a regioselective C–H activation of the Pd intermediate **5** (resulting from a 5-*endo-trig* intramolecular carbopalladation) into the methyl group geminal to the phosphorus moiety. Reductive elimination of the putative intermediate **6** leads to compound **3** (Scheme 1).

Although Pd-catalyzed C(sp^2)–H activation[4] is rather efficient and well documented, there are only very few reports dealing with C(sp^3)–H activation processes.[5]

As shown in Scheme 2, the C–H activation takes place very rapidly (more rapidly than the β-hydride elimination) and regioselectively into the methyl group attached to the more hindered position. We suspected a strong influence of the Thorpe–Ingold effect induced by the very bulky diphenylphosphinoyl group. In order to study the influence of the steric hindrance and the possibility to perform the reaction in the presence of a β-hydrogen, we submitted alkenes **7a**–**b** to the conditions described above (Scheme 2).

Keywords: Palladium; C–H activation; Cascade reactions.
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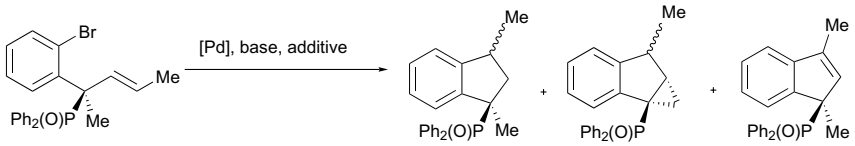
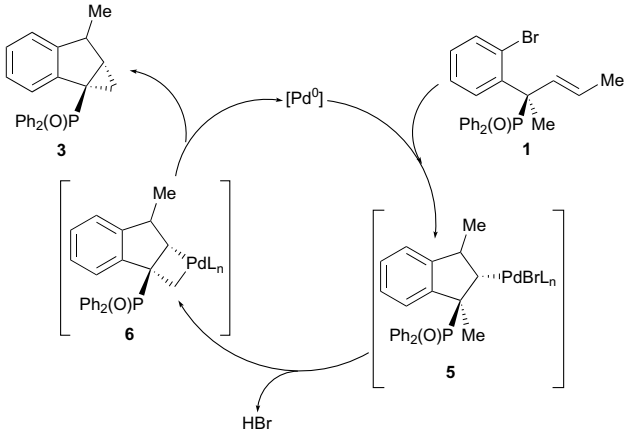
Table 1. Optimization of the reaction conditions



1 2 3 4

Entry	[Pd]	Base	Additive	T (°C)	1[a]	2[a]	3[a]	4[a]
1	$Pd(OAc)_2$	K_2CO_3	$NaBH_4$	120	90	0	0	10
2	$Pd(OAc)_2$	K_2CO_3	HCOONa	120	60	0	20 (dr > 99/1)	10
3	$Pd(OAc)_2$	Ag_2CO_3	HCOONa	100	60	0	0	40
4	$Pd(OAc)_2$	Ag_2CO_3	None	80	94	0	6 (dr > 99/1)	0
5	$Pd(OAc)_2$	Ag_2CO_3	None	100	60	0	20 (dr > 99/1)	15
6	$Pd(OAc)_2$	Ag_2CO_3	None	120	0	0	90 (dr = 60/40)	10
7	$Pd(PPh_3)_4$[c]	Et_3N	None	80	100	0	0	0
8	$Pd(OAc)_2$	K_2CO_3	None	120	0	0	75 (dr = 80/20)[b]	25[b]
9	$Pd(OAc)_2$	K_2CO_3	None	80	30	0	58 (dr = 60/40)	12
10	$Pd(OAc)_2$	K_2CO_3	None	140	0	0	63 (dr = 65/35)	12

[a] Ratios and diastereoselectivities were measured by ^{31}P NMR of the crude mixture.
[b] Isolated yields.
[c] No additional PPh_3 was added.



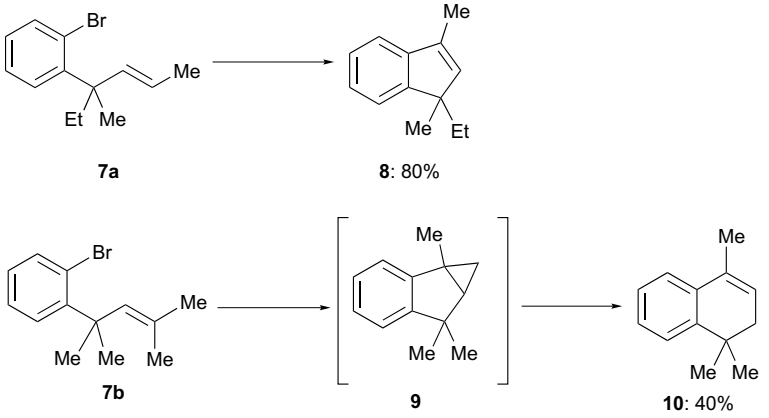
Scheme 1. Reagents and conditions: $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), n-Bu_4NBr (1.3 equiv), K_2CO_3 (5 equiv), DMF, 120 °C, overnight.

Alkenes **7a**–**b** were reacted under the described conditions (Scheme 2). Alkene **7a**[6] underwent β-hydrogen elimination to produce indene **8**, showing the crucial importance of a large steric hindrance to favor C–H activation over β-hydride elimination. Alkene **7b**, possessing no β-hydride underwent a regioselective C–H activation, but we could only isolate dihydronaphthalene **10** instead of the expected tricyclic compound **9**.

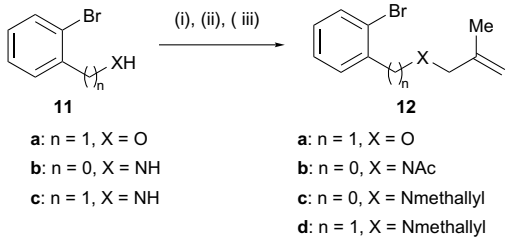
We then turned our attention to using this reaction to prepare heterocycles. The required amides, amines, and ethers were prepared according to described methods (Scheme 3).[7]

We first reacted amide **12b** under the conditions described above and both the expected spirocyclopropane **13a** and compound **13b** were isolated (Scheme 4). These results contrast with those recently reported by Larock et al., who reported a $C(sp^2)$–H activation under slightly different conditions.[8]

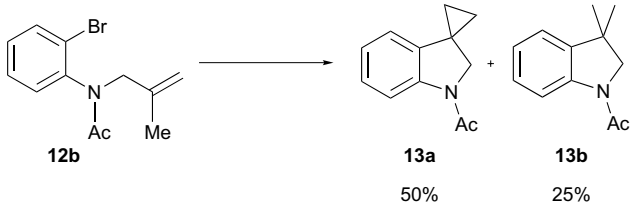
We then treated amines **12c** and **d** under the conditions described above and isolated, besides unreacted starting material, Pd complexes **14a**–**b**. Complexation of the Pd



Scheme 2. Reagents and conditions: $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), n-Bu_4NBr (1.3 equiv), K_2CO_3 (5 equiv), AcOH (3 equiv), DMF, 120 °C, overnight.



Scheme 3. Reagents and conditions: (i) Acetylation reaction: acetyl chloride (1 equiv), Et_3N, CH_2Cl_2, rt, 2 h (80%); (ii) allylation of amides: amide (1 equiv), NaOH (5 equiv), *n*-Bu_4NHSO_4 (0.1 equiv), methallyl chloride (7 equiv), H_2O, 80 °C, overnight (70%); (iii) allylation of amines and ether: amine or ether (1 equiv), NaH (1 equiv), methallyl chloride (2–3 equiv), DMF, 80 °C, overnight (80–90%).



Scheme 4. Reagents and conditions: $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), *n*-Bu_4NBr (1.3 equiv), K_2CO_3 (5 equiv), AcOH (3 equiv) where relevant, DMF, 120 °C, overnight.

atom by the lone pair of nitrogen prevents this intermediate to react further, either in a second carbopalladation reaction or in the expected C–H activation mode. Ether **12a** was also reacted and led after 24 h to a mixture of the expected spirocyclopropane derivative **16a** and *gem*-dimethyl compound **16b**. In this latter case, conversion reached only 50% (Scheme 5).[9]

As can be seen from our results, this reaction is very sensitive to various parameters such as the nature of the protecting groups and the nature of the base.

In summary, we reported herein a novel intramolecular carbopalladation/C–H activation cascade reaction. Such pathways allow the preparation of spiro or fused cyclopropane derivatives selectively and are unprecedented in the literature. Further developments will be reported in due course.

Acknowledgements

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Supplementary data

Experimental procedures and full characterization data for all the compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.018.

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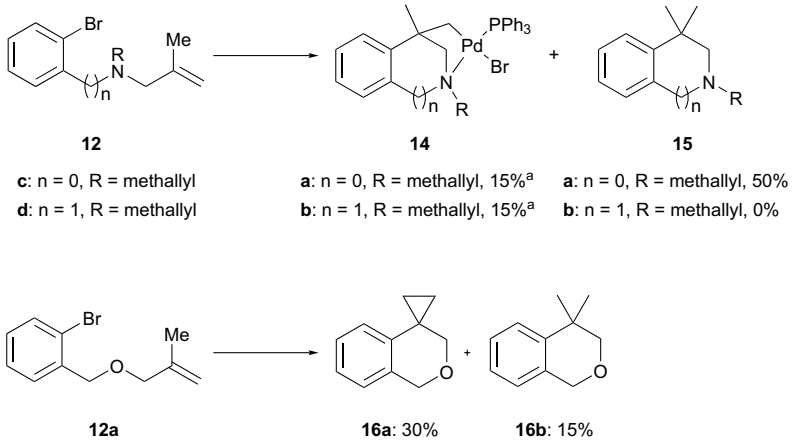

Scheme 5. Reagents and conditions: $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), *n*-Bu_4NBr (1.3 equiv), K_2CO_3 (5 equiv), DMF, 120 °C, overnight; [a] 75% based on Pd loading.

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9. *Typical procedure*: An argon-flushed flask was charged with $Pd(OAc)_2$ (0.4 mmol, 0.2 equiv), PPh_3 (0.8 mmol, 0.4 equiv), *n*-Bu_4NBr (2.6 mmol, 1.3 equiv), K_2CO_3 (10 mmol, 5 equiv), the substrate (2.0 mmol, 1.0 equiv), and DMF (5 mL). The mixture was heated to 120 °C overnight. After cooling to rt, it was quenched with water (20 mL) and extracted (Et_2O). The organic layer was dried over $MgSO_4$, concentrated in vacuo, and chromatographed on silica gel, leading to the pure compounds.