Synthetic Methods

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# Activation of a C($sp^3$)–H Bond by a Transient σ-Alkylpalladium(II) Complex: Synthesis of Spirooxindoles Through a Palladium-Catalyzed Domino Carbopalladation/C($sp^3$)–C($sp^3$) Bond-Forming Process**

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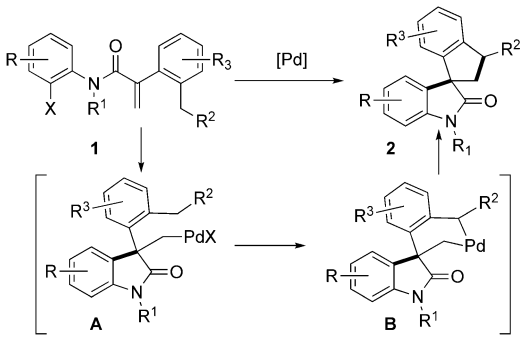
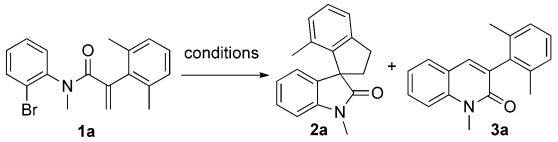
Catalytic C–H bond activation is an area of considerable current interest.[1] Whereas a plethora of methods for the metal-catalyzed functionalization of arenes and heteroarenes have been developed to allow the formation of C($sp^2$)–C($sp^2$) bonds,[2] methods dealing with C($sp^2$)–C($sp^3$) bond formation through activation of the less reactive C($sp^3$)–H bond are still an emerging research field.[3–6] An even less exploited subfield is the creation of a C($sp^3$)–C($sp^3$) bond through activation of a C($sp^3$)–H by a transient σ-alkylmetal complex.[7] In connection with our interest in the development of domino processes involving C–H functionalization as a key step[8] we became interested in the spirocyclization of **1** for the synthesis of spirooxindoles **2**.[9] The underlying principle is shown in Scheme 1. Intramolecular carbopalladation of **1** would give intermediate **A**, which has a neopentyl-type σ-alkylpalladium(II) function. The latter, being sufficiently stable and ideally positioned, should be able to activate the nearby C($sp^3$)–H bond, thus leading to six-membered palladacycle **B**. Reductive elimination from **B** would then afford spirooxindole **2** and regenerate the Pd° species.[10,8i] The realization of this unprecedented domino process is the subject of the present communication.

The easily accessible *N*-(2-bromophenyl)-2-(2,6-dimethylphenyl)-*N*-methylacrylamide (**1a**) was used as a substrate to test the feasibility of our projected domino process (Table 1).[11] Initial efforts employed the catalytic system reported by Guyonnet and Baudoin.[4o] Under these conditions, the desired spirooxindole **2a** was indeed obtained,[12] albeit accompanied by a significant amount of quinolinone **3a**, which resulted from a 6-*endo*-trig cyclization (**2a**/**3a** = 1:2, entry 1, Table 1). The predominant formation of **3a** was surprising, as a 5-*exo*-trig cyclization is generally overwhelmingly favored over a 6-*endo*-trig cyclization in the Heck reaction.[13] Systematic studies of the reaction conditions




***Scheme 1.*** Domino carbopalladation/C($sp^3$)–C($sp^3$) bond-forming process. Ligands on Pd are omitted for clarity.

***Table 1:*** Survey of reaction conditions for the cyclization of **1a**.[a]




| Entry | Ligand | Base | Additive | **2a**/**3a**[b] | Yield [%][c] |
|---|---|---|---|---|---|
| 1[d] | $PCy_3 \cdot HBF_4$ | $Na_2CO_3/K_2CO_3$ | PivOH | 1:2 | n.d. |
| 2 | $PCy_3 \cdot HBF_4$ | $Cs_2CO_3$ | – | 1:2 | n.d. |
| 3 | $PtBu_3 \cdot HBF_4$ | $Cs_2CO_3$ | – | 2.2:1 | n.d. |
| 4 | $PPh_3$ | $Cs_2CO_3$ | – | 2.2:1 | 67 |
| 5 | $P(2\text{-furyl})_3$ | $Cs_2CO_3$ | – | 2.5:1 | 71 |
| 6 | XantPhos | $Cs_2CO_3$ | – | 2.8:1 | 73 |
| 7 | dppe | $Cs_2CO_3$ | – | 3.6:1 | n.d. |
| 8[e] | dppp | $Cs_2CO_3$ | – | 12:1 | 85 |
| 9[f] | dppp | $Cs_2CO_3$ | – | 3.3:1 | n.d. |
| 10[g] | dppp | $Na_2CO_3$ | – | n.d. | n.d. |
| 11 | dppp | $K_2CO_3$ | – | 32.7:1 | 94 |
| 12 | dppp | $RbCO_3$ | – | 17.1:1 | 85 |

[a] **1a** (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), ligand (0.2 equiv), and base (1.3 equiv) in mesitylene (0.15 M) at 140 °C, under argon for 1–2 h. [b] Determined by $^1H$ NMR analysis of the crude material. [c] Yield of isolated **2a**. [d] Reaction was performed using PivOH (0.3 equiv), $Na_2CO_3$ (0.3 equiv), and $K_2CO_3$ (1.3 equiv). [e] $nBu_4NCl$ (1.0 equiv) was used. [f] Reaction was performed at 120 °C. [g] Incomplete conversion after 24 h. Cy = cyclohexyl, dppe = ethylenebis(diphenylphosphine), dppp = 1,3-bis(diphenylphosphino)propane, n.d. = not determined, OAc = acetate, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

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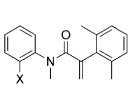
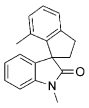
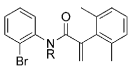
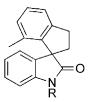
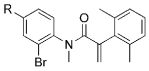
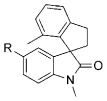
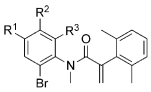
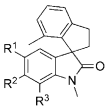
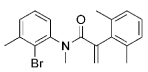
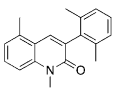
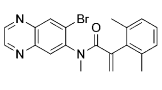
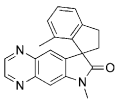
revealed that the ligand, the base, and the temperature exerted a dramatic influence on the regioselectivity of the reaction. Some representative results are summarized in Table 1.[14] Overall, the optimized conditions consisted of $Pd(OAc)_2$ (OAc = acetate; 0.1 equiv), 1,3-bis(diphenylphosphino)propane (dppp; 0.2 equiv), $K_2CO_3$ (1.3 equiv) in mesitylene (0.15 M) at 140 °C. Under these conditions, the domino 5-*exo* carbopalladation/C($sp^3$)–C($sp^3$) bond-forming process occurred smoothly to provide spirooxindole **2a** in 94% yield (entry 11). Attempts to render this reaction enantioselective through the use of chiral bidentate ligands such as (*R*,*R*)-BINAP or (*S*,*S*)-DIOP failed to produce any significant chiral induction (see the Supporting Information).

With the optimized conditions in hand, the scope of the domino process was next evaluated. The influence of the haloaniline subunit on the reaction outcome was examined first (Table 2). Whereas the iodoanilide (**1b**, X = I) afforded the spirooxindole **2a** in 92% yield, the chloroanilide (**1c**, X = Cl) failed to undergo the spirocyclization (Table 2, entry 1 vs. 2). The use of a tertiary amide was mandatory to ensure the occurrence of the domino reaction, as treatment of secondary amide **1d** failed to produce the spirocycle (entry 3). Cyclizations of *N*-benzyl, *N*-*para*-methoxybenzyl and *N*-phenyl anilide took place smoothly to provide the spirooxindoles (**2e–g**) in excellent yields (entries 4–6). In these cases, the direct aromatic C($sp^2$)–H activation was not observed.[15] The *N*-2-(trimethylsilyl)ethoxy)methyl group was compatible as shown in the synthesis of **2h** (entry 7). Electron-donating or electron-withdrawing groups were well tolerated (entries 8–12), and substrates bearing substituents *meta*- and *para*- to the halide furnished spirooxindoles in excellent yields (entries 13–14). In contrast, the presence of a substitutent *ortho* to the halide preferentially underwent a 6-*endo*-Heck cyclization to afford the quinolinone **3p** in 60% yield, together with a 37% yield of the desired spirooxindole **2p** (entry 15). Finally, heterocycles such as benzopyrazine underwent cyclization without difficulty to afford **2q** in excellent yield (entry 16).

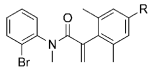
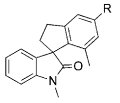
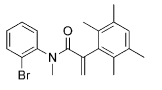
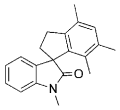
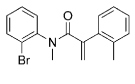
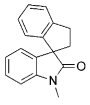
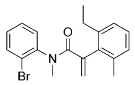
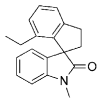
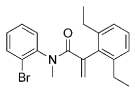
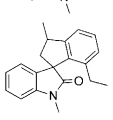
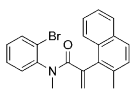
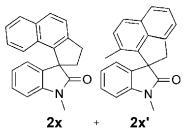
Variation of the α-aryl substitutent on the acrylate was next evaluated (Table 3). Substituents such as *tert*-butyl, methyl, and methoxy groups were tolerated, providing the corresponding spirooxindoles (**2r–2t**) in excellent yields (Table 3, entries 1–3). On the other hand, 2-(*o*-tolyl)acrylamide (**1u**) failed to produce the desired oxindole, **2u** (entry 4). In the case of unsymmetrical 2,5-disubstituted derivative **1v**, the cyclization proceeded chemoselectively on the methyl group to produce compound **2v** in 97% yield (entry 5). However, when anilide **1w**, which bears a 2,5-diethylbenzene moiety, was submitted to the reaction conditions, cyclization by activation of the methylene C($sp^3$)–H group took place to provide spirooxindole **2w** as a mixture of two diastereomers (68%, d.r. = 2:1, entry 6). This result is

***Table 2:*** Reaction scope: varying the aniline.[a]

| Entry | Substrate (**1**) | Product (**2** or **3**) | Yield [%][b] |
|---|---|---|---|
| 1[c] |  |  **2a** | 92 |
| 2[d,e] | | **2a** | trace |
| 3 |  |  **2d**, R = H | 0 |
| 4 | | **2e**, R = Ph | 99 |
| 5 | | **2f**, R = Bn | 96 |
| 6 | | **2g**, R = PMB | 89 |
| 7 | | **2h**, R = SEM | 85 |
| 8 |  |  **2i**, R = $CO_2$Me | 85 |
| 9 | | **2j**, R = F | 78 |
| 10 | | **2k**, R = CN | 79 |
| 11 | | **2l**, R = OMe | 96 |
| 12 | | **2m**, R = Me | 98 |
| 13 |  |  **2n**, $R^2$ = H, $R^1$,$R^3$ = Me | 97 |
| 14 | | **2o**, $R^2$ = Me, $R^1$,$R^3$ = H | 97 |
| 15[f] |  |  **3p** | 60 |
| 16 |  |  **2q** | 97 |

[a] **1** (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), dppp (0.2 equiv), $K_2CO_3$ (1.3 equiv) in mesitylene ($c$ = 0.15 M) at 140 °C under argon for 1–5 h. [b] Yield of isolated product. [c] X = I. [d] 24 h. [e] X = Cl. [f] Oxindole **2p** (structure not shown) was isolated in 37% yield. Bn = benzyl, PMB = *p*-methoxybenzyl ether, SEM = 2-(trimethylsilyl)ethoxy)methyl.

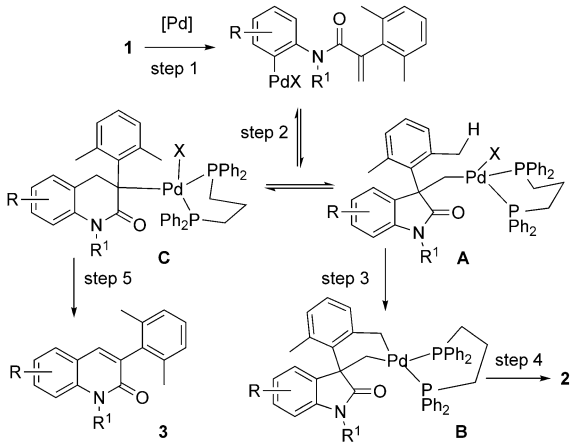
***Table 3:*** Reaction scope: varying the α-aryl substituent.[a]

| Entry | Substrate (**1**) | Product (**2**) | Yield [%][b] |
|---|---|---|---|
| 1 |  |  **2r**, R = OMe | 92 |
| 2 | | **2s**, R = *t*Bu | 91 |
| 3 |  |  **2t** | 97 |
| 4 |  |  **2u** | 0 |
| 5 |  |  **2v** | 97 |
| 6 |  |  **2w**[c] | 68 |
| 7 |  |  **2x** + **2x'** | **2x**+**2x'**[d] 89 |

[a] **1** (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), dppp (0.2 equiv), $K_2CO_3$ (1.3 equiv) in mesitylene (0.15 M) at 140 °C under argon for 1–5 h. [b] Yield of isolated product. [c] d.r. = 2:1. [d] **2x**/**2x'** = 1:3.

a rare example of C($sp^3$)–H bond activation/C($sp^3$)–C($sp^3$) bond formation of a methylene group. When the phenyl group was replaced by a naphthalene derivative (**1x**), activation of the naphthyl C($sp^2$)–H bond dominated over the methyl C($sp^3$)–H bond, which is consistent with the notion that activation of C($sp^2$)–H bonds is generally favored over C($sp^3$)–H bonds.

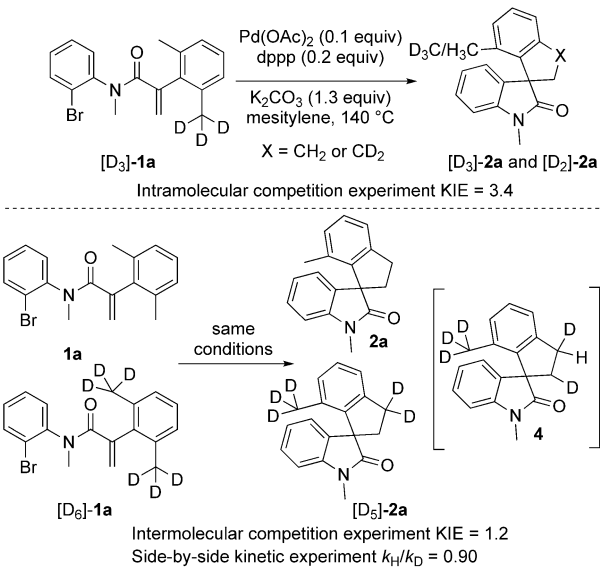
Although bidentate ligands have been used in Pd-catalyzed C($sp^2$)–H bond activation for the formation of aryl–aryl bonds,[16] bulky and electron-rich monodentate ligands are generally the ligand of choice for C($sp^3$)–H activation processes. Considering the reversibility of the carbopalladation step, an appealing rational for the beneficial effect of dppp in the present domino transformation could be that it chelates strongly to Pd and therefore: 1) favors the formation of the less sterically congested neopentyl-type σ-alkyl $Pd^{II}$ complex (5-*exo* cyclization) over the tertiary σ-alkyl $Pd^{II}$ complex **C** (6-*endo* cyclization; Scheme 2) owing




***Scheme 2.*** Regioselectivity of the domino process.

to the increased effective size of metal coordination sphere;[17] 2) disfavors the β-hydride elimination as the 14-electron $Pd^{II}$ complex **C** has no vacant coordination site available to accommodate the β-hydride elimination (Scheme 2, step 5);[18] 3) enforce the *cis* geometry of the two alkyl groups in intermediate **B**, facilitating therefore the reductive elimination process.[19] The low selectivity displayed by XantPhos, might indicate that dissociation was occurring with this ligand.[20] Indeed, the similar selectivity observed with XantPhos and with a monophosphine ligand was in agreement with this assumption (entries 3–6, Table 1).

A kinetic study determined that the reaction is zero order in **1a** (see the Supporting Information), indicating a fast oxidative addition in which the Pd catalyst is saturated as a $Pd^{II}$–aryl species, and ruled out the possibility of oxidative addition being the rate-determining step. To gain further insight into the reaction mechanism, the kinetic isotope effect was examined next (Scheme 3).[21] Submitting [$D_3$]-**1a** to our standard spirocyclization conditions afforded [$D_3$]-**2a**/[$D_2$]-**2a** in a ratio of 3.4:1, hence with an intramolecular KIE value of 3.4. This result indicated that the C–H cleavage is directly




***Scheme 3.*** Kinetic isotope effect experiments.

involved in the C($sp^3$)–H activation step leading to palladacycle **B**. An intermolecular competition experiment using an equimolar amount of **1a** and its hexadeuterated derivative [$D_6$]-**1a** provided an intermolecular KIE value of 1.2. More significantly, side-by-side kinetic experiments using **1a** and [$D_6$]-**1a** provided an intermolecular KIE ($k_H/k_D$, initial rate constant) value of 0.90. The inverse KIE observed in this last experiment might indicate that reductive elimination, rather than C–H activation, was the turnover-limiting step of the domino process, and that the observed inverse intermolecular KIE is in fact a secondary kinetic isotope effect. To the best of our knowledge, this is the first time an inverse KIE was observed for a palladium-catalyzed C($sp^3$)–H functionalization reaction.[22] By invoking the Curtin–Hammett principle,[23] these mechanistic considerations also explain the failure encountered in developing an enantioselective variant of this domino process.

As the biphosphine-chelated Pd intermediate is essential for the efficacy of the present transformation, we speculated that the intramolecular base-assisted concerted metalation-deprotonation (CMD) mechanism may not be operating in our case, as this would implicate a pentacoordinated $Pd^{II}$ intermediate. Alternatively, an intermolecular base-assisted CMD mechanism could be advanced to account for the reaction outcome. The fact that compound **4** (which would result from deuterium scrambling) was not observed when [$D_6$]-**1a** was subjected to the spirocyclization conditions also allowed us to speculate that the C–H activation was irreversible (Scheme 3).

In summary, we have reported an efficient one-pot synthesis of spirooxindoles using a novel palladium(0)-catalyzed domino carbopalladation/C($sp^3$)–C($sp^3$) bond-forming process. The strategically positioned double bond allows the remote C($sp^3$)–H bond to be activated by a transient σ-alkylmetal complex. We believe that this reaction provides a new means for the elaboration of domino reactions by including a C($sp^3$)–C($sp^3$) bond-forming

reaction as an elementary step, and offers an unusual bond disconnection logic.

## Experimental Section

Anilide **1** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol, 0.1 equiv), dppp (0.02 mmol, 0.2 equiv), and $K_2CO_3$ (0.13 mmol, 1.3 equiv) were added to a screw-cap vial equipped with a magnetic stir bar. The vial was purged with argon for 10 min. Degassed mesitylene (0.50 mL) was added and the mixture was stirred at 140 °C until TLC monitoring indicated the complete disappearance of the starting material. After being cooled to room temperature, ethyl acetate was added and the reaction mixture was filtered through a short pad of Celite. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography ($SiO_2$, petroleum ether/ethyl acetate; see the Supporting Information for details) to provide the desired spirooxindole **2**.

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