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Pd-Catalyzed Arylation/Aza-Michael Addition Cascade to C2-Spiroindolines and Azabicyclo[3.2.2]nonanones†

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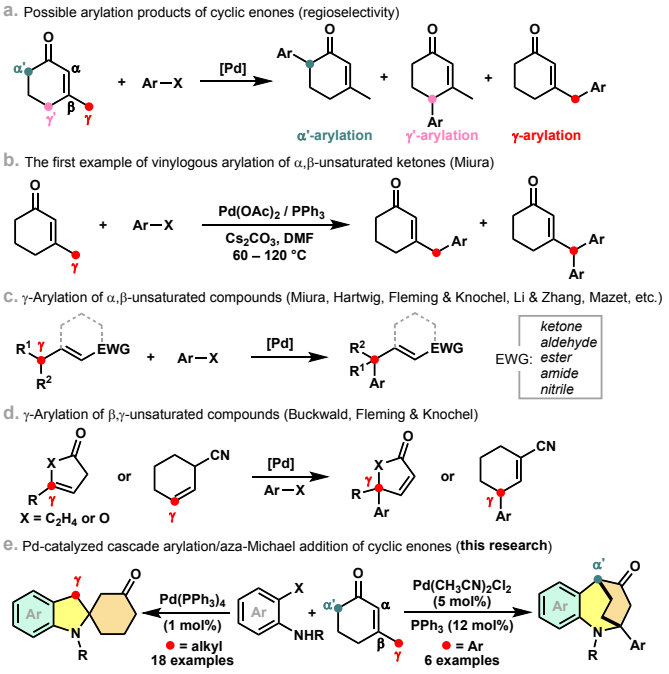
A palladium-catalyzed arylation/aza-Michael addition cascade reaction of β-substituted cyclic enones and 2-haloanilines is reported. Using 1 mol% $Pd(PPh_3)_4$ as a catalyst, C2-spiroindolines are accessed via an intermolecular vinylogous arylation of β-alkyl cyclic enones and 2-haloanilines followed by an intramolecular aza-Michael addition. Functional group tolerance of this transformation is examined by 18 examples in up to 93% yield. In the second part, we have developed an α'-arylation/aza-Michael addition cascade strategy to construct azabicyclo[3.2.2]nonanones catalyzed by $Pd(MeCN)_2Cl_2$•PPh_3. This study provides a quick route to complex and useful spiro- and bridged-heterocycles from readily available starting materials in good yields with high regioselectivity.

Transition-metal-catalyzed arylation of carbonyl derivatives is a powerful method for the formation of carbon–carbon bonds.[1] An increasing number of palladium-catalyzed α-arylation reactions of carbonyls have been developed[1] since the seminal work reported by Miura,[2] Buchwald,[3] and Hartwig.[4] In comparison, vinylogous arylation (γ-arylation) of α,β-unsaturated carbonyl compounds that can provide useful synthons (e.g., enones) for further diverse functionalization remains underdeveloped.

One of the main challenges of the vinylogous arylation is to control the regioselectivity of the multiple reactive sites (i.e., α'-, γ-, or γ'-arylation of cyclic enones, Scheme 1a). Moreover, double-arylation,[5] Heck-type side reaction,[6] and condensation of the enone substrates and/or products under basic conditions would also be problematic. In 1998, the first palladium-catalyzed vinylogous arylation was reported by Miura and coworkers (Scheme 1b).[7] Then the reactions of α,β-unsaturated ketones and aldehydes,[8] esters,[9] amides,[10] and nitriles,[11] were subsequently disclosed by Miura, Hartwig, Li and Zhang, Mazet, and others (Scheme 1c). Alternatively, Buchwald, Fleming and Knochel, and their coworkers successfully demonstrated the γ-arylation of β,γ-unsaturated ketones,[12] lactones,[13] and nitriles[11] for the construction of the corresponding γ-arylated α,β-unsaturated analogs (Scheme 1d).



Scheme 1. Pd-catalyzed arylation of α,β- and β,γ-unsaturated carbonyl compounds.

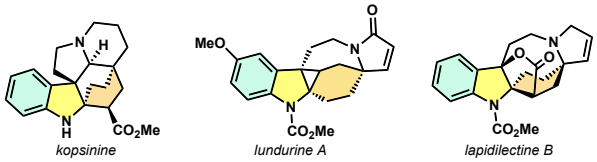


Figure 1. Representative natural products containing C2-spiroindolines.

With the interest of our group in the arylation chemistry and heterocycle synthesis,[14] we sought to develop a palladium-catalyzed selective vinylogous arylation of β-alkyl cyclic enones with 2-haloanilines (Scheme 1e, left). We envisaged that the arylation product could undergo a sequential aza-Michael addition leading to the formation of C2-spiroindolines[15] in a single operation. Similarly,

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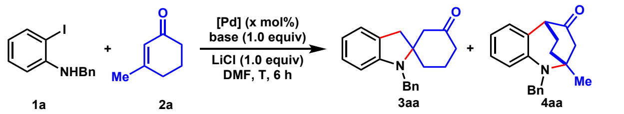
a cascade α′-arylation/aza-Michael addition reaction is also feasible, when β-aryl cyclic enones are employed, to access azabicyclo[3.2.2]nonanones (Scheme 1e, right).[16] This approach allows the rapid construction of molecular complexity from simple substrates, which is attractive given the vast abundance of those important scaffolds in alkaloids (Figure 1).[17]

To test our arylation/aza-Michael addition hypothesis, *N*-benzyl-2-iodoaniline **1a** and 3-methyl-2-cyclohexen-1-one **2a** were employed as the model substrates (Table 1 and Tables S1–S4 in the ESI). To our delight, C2-spiroindoline **3aa** was obtained in 37% yield with $Pd(OAc)_2$•PPh_3 as a catalyst, NaO^{t}Bu as a base, and LiCl as an additive in DMF at 100 °C (entry 1). Next, several bases were examined (Table 1, entries 2–7), and LiO^{t}Bu was proven to be the optimal base, producing the desired product **3aa** in 62% yield together with minor amount of azabicyclo[3.2.2]nonanone **4aa** (entry 5). In general, the reaction underwent well in polar aprotic solvent, such as DMF, NMP, and DMSO, delivering the desired product in moderate yields. However, no product was detected in THF, toluene, DME or 1,4-dioxane (Table S2). A brief investigation of catalysts revealed that the use of $Pd(PPh_3)_4$ resulted **3aa** in 71% yield (entries 8–9). Further extensive investigation of the reaction parameters (Table S4), including concentration, catalyst loading, temperature, and the equivalent of the base and the additive, led to the identification of the optimal reaction conditions, which employed only 1 mol% of $Pd(PPh_3)_4$ in DMF at 60 °C (entry 17). Control experiments demonstrated that no desired product was detected without either $Pd(PPh_3)_4$ or base (entries 18–19).

Table 1. Optimization of the reaction conditions.

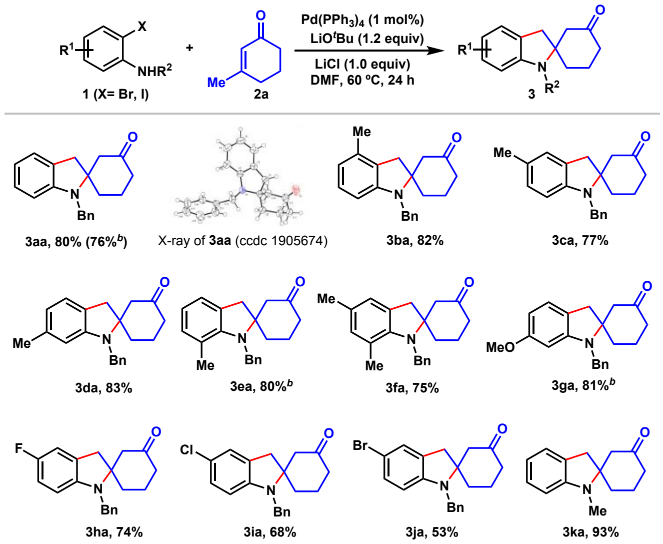


entry[a]	[Pd] (x mol%)	T (°C)	base	3aa/4aa (%)[b]
1	$Pd(OAc)_2$ (5)/PPh_3 (12)	100	NaO^{t}Bu	37/–
2	$Pd(OAc)_2$ (5)/PPh_3 (12)	100	NaOMe	–
3	$Pd(OAc)_2$ (5)/PPh_3 (12)	100	NaOH	10/–
4	$Pd(OAc)_2$ (5)/PPh_3 (12)	100	NaHMDS	27/–
5	$Pd(OAc)_2$ (5)/PPh_3 (12)	100	LiO^{t}Bu	62/5
6	$Pd(OAc)_2$ (5)/PPh_3 (12)	100	KO^{t}Bu	43/8
7	$Pd(OAc)_2$ (5)/PPh_3 (12)	100	Cs_2CO_3	–
8	$Pd_2(dba)_3$ (2.5)/PPh_3 (12)	100	LiO^{t}Bu	68/6
9	$Pd(PPh_3)_4$ (5)	100	LiO^{t}Bu	71/–
10[c]	$Pd(PPh_3)_4$ (5)	100	LiO^{t}Bu	76/5
11[c]	$Pd(PPh_3)_4$ (2)	100	LiO^{t}Bu	73/–
12[c]	$Pd(PPh_3)_4$ (1)	100	LiO^{t}Bu	80/–
13[c]	$Pd(PPh_3)_4$ (1)	120	LiO^{t}Bu	71/5
14[c]	$Pd(PPh_3)_4$ (1)	80	LiO^{t}Bu	76/5
15[c,d]	$Pd(PPh_3)_4$ (1)	60	LiO^{t}Bu	79/–
16[c,d]	$Pd(PPh_3)_4$ (1)	40	LiO^{t}Bu	62/–
17[c,d,e]	**$Pd(PPh_3)_4$ (1)**	**60**	**LiO^{t}Bu**	**81 (80)/–**
18[c,d,e]	–	60	LiO^{t}Bu	–
19[c,d]	$Pd(PPh_3)_4$ (1)	60	–	–

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol) in 1 mL of DMF. [b] Determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard with isolated yield in the parentheses. [c] With 2 mL of DMF. [d] For 24 h. [e] With 1.2 equiv of LiO^{t}Bu.

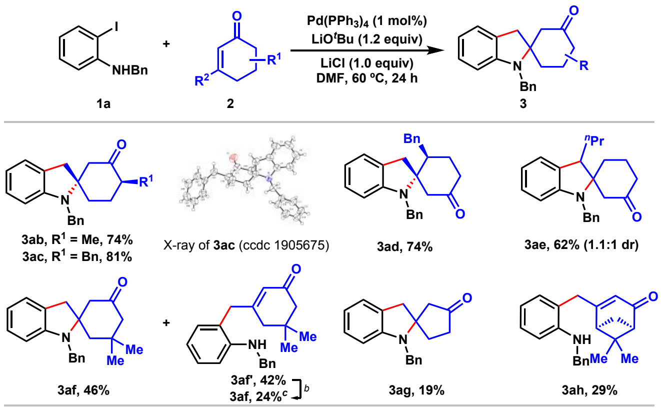
With the optimal conditions in hand, the scope of 2-iodoanilines was first investigated with cyclic enone **2a** as the coupling partner (Table 2). Substrates with electron-rich substituents (Me- and MeO-), notably with methyl group substituted at each position, were tolerated in this transformation affording the corresponding products **3aa**–**3ga** in 75–83% yields. Remarkably, 2-iodoaniline containing F-, Cl-, and Br- substituents were suitable substrates in this reaction delivering the corresponding products **3hg**, **3ia**, and **3ja** in 53–74% yields without the observation of dehalogenation. The reaction with *N*-methyl-2-iodoaniline gave spirocyclic product **3ka** in a slightly increased yield (93%). In contrast, the use of less nucleophilic *N*-Ac-protected 2-iodoaniline under the standard conditions did not lead to the occurrence of the reaction. To our delight, 2-bromoanilines were tolerated despite requiring 5 mol% of the catalyst and elevated temperature to achieve good yields (**3aa**, **3ea**, and **3ga**, 76–81%).

Table 2. Scope of 2-haloanilines.[a]



[a] Reactions conducted with 0.2 mmol of **1** and 0.4 mmol of **2a** in 2 mL of DMF. Unless otherwise stated, X= I. [b] X = Br and with 5 mol% of $Pd(PPh_3)_4$ at 100 °C for 2 h.

Table 3. Scope of cyclic enones.[a]



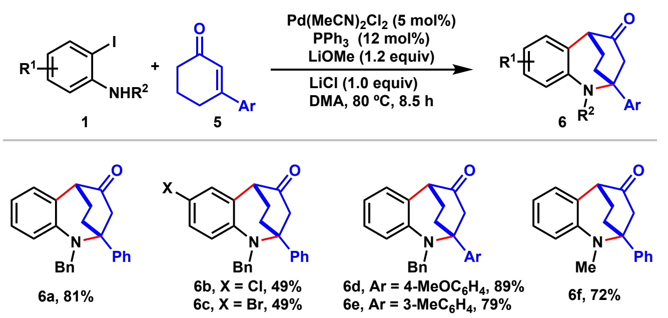
[a] Reactions conducted with 0.2 mmol of **1a** and 0.4 mmol of **2** in 2 mL of DMF. [b] With 20 mol% LiO^{t}Bu. [c] NMR yield.

Next, we applied this catalytic system to the arylation/aza-Michael addition of a range of cyclic enones (Table 3). Reactions with α′- and γ′-substituted cyclic enones proceeded smoothly delivering products **3ab**, **3ac**, and **3ad** bearing two stereogenic centers with perfect diastereoselectivities. 3-Butylcyclohex-2-en-1-one (**2e**) was viable

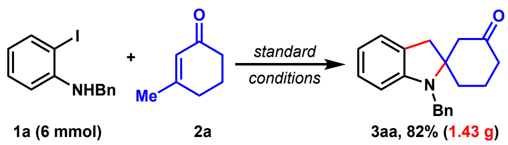
substrate delivering a 1.1:1 mixture of diastereoisomers (**3ae**) in 62% yield. Interestingly, 5,5-dimethyl-2-cyclohexen-1-ones **2f** produced the desired spirocyclic product **3af** in 46% yield together with the vinylogous arylation product **3af'** in 42% yield. Treatment of **3af'** with catalytic amount of LiO^{t}Bu could form the aza-Michael adduct **3af** albeit in low yield. Surprisingly, a complicated reaction with multiple condensation byproducts was observed resulting in a significantly lower yield of **3ag** when 3-methylcyclopent-2-en-1-one **2g** was used as the substrate. The reaction with enantioenriched (–)-verbenone **2h** provided γ-arylation product **3ah** exclusively, possibly due to the steric hindrance of the bridged substrate. The reactions with acyclic β-substituted enones, including α,β-unsaturated ketones and aldehydes, were carried out, but resulted in an inseparable mixture of arylation and homo-condensation products (Scheme S1).

The choice of β-substituents of the cyclic enones proved to be crucial to the product formation. When β-aryl cyclic enones **5** were employed, a selective α'-arylation[18] followed by intramolecular aza-Michael addition forming azabicyclo[3.2.2]nonanones **6** was achieved (Table 4). After careful optimization of the reaction conditions (Table S6–S8 in ESI), we found the use of a palladium catalyst derived from Pd(MeCN)$_2$Cl$_2$ and PPh$_3$ showed superior reactivity. A variety of azabicyclo[3.2.2]nonanones (**6a–6f**) were obtained in moderate to good yields. Efforts toward asymmetric α'-arylation/aza-Michael addition reaction employing chiral phosphine ligands resulted in little enantioselectivity (Table S9).

Table 4. Synthesis of azabicyclo[3.2.2]nonanones.[a]



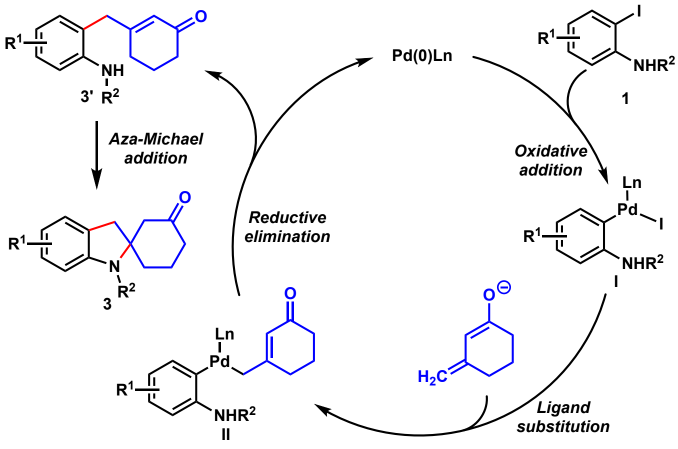
[a] Reactions conducted with 0.4 mmol of **1** and 0.2 mmol of **5** in 2 mL of DMA.



Scheme 2. Gram-scale synthesis.

To showcase the robustness of this strategy, a gram-scale reaction with 2-iodoaniline **1a** and 3-methyl-2-cyclohexen-1-one **2a** was carried out (Scheme 2). With 1 mol% of Pd(PPh$_3$)$_4$ as the catalyst, 1.43 gram of C2-spiroindoline **3aa** was successfully obtained without erosion of the yield.

A plausible catalytic cycle for the palladium-catalyzed cascade reaction is proposed analogous to the mechanism of α-arylation provided in the literature (Scheme 3).[1d] Oxidative addition of a Pd(0) species with 2-iodioaniline **1** forms aryl-Pd(II) iodide **I**, which undergoes nucleophilic substitution of the coordinated iodide by sterically less hindered enolate generates intermediate **II**. The subsequent reductive elimination of **II** provides the vinylogous arylation product **3'**, as evidenced by the observation of **3ag** with the sterically congested substrate, and regenerates the Pd(0) catalyst. Recently, a computational study of γ-arylation of α,β-unsaturated aldehydes by Poblador-Bahamonde et al. identified several palladium species in equilibrium existing after the nucleophilic substitution step, and the formation of vinylogous arylation product is both thermodynamically and kinetically favored.[19] Finally, under basic conditions, an off-cycle intramolecular aza-Michael addition[20] of **3'** delivers the desired C2-spiroindoline **3**.



Scheme 3. Proposed mechanism of vinylogous arylation/aza-Michael addition.

In summary, we have demonstrated a highly efficient palladium-catalyzed vinylogous arylation/aza-Michael addition cascade reaction of 2-haloanilines and β-alkyl cyclic enones. An array of valuable C2-spiroindolines were efficiently synthesized in good yields. This strategy is scalable and features readily available starting materials and low Pd(PPh$_3$)$_4$ catalyst loading. A gram-scale reaction was conducted successfully. Additionally, under slightly modified conditions, azabicyclo[3.2.2]nonanones were accessed from β-aryl cyclic enones and 2-haloanilines via an α'-arylation/aza-Michael addition process.

Conflicts of interest

The authors declare no competing financial interest.

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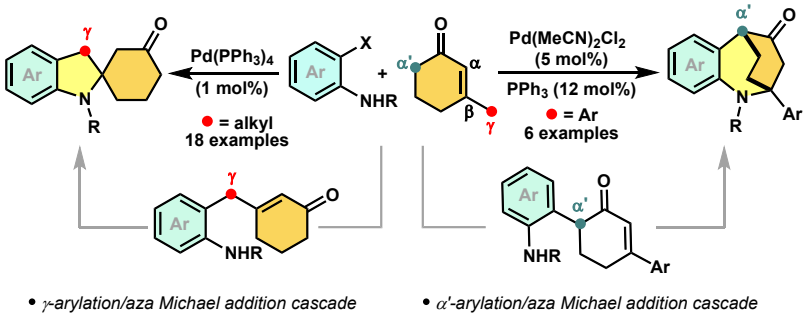

• *γ-arylation/aza Michael addition cascade* • *α'-arylation/aza Michael addition cascade*

Construction of spiro- and bridged heterocycles by a palladium-catalyzed arylation/aza-Michael cascade reaction