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Pd-Catalyzed C–H activation/oxidative cyclization of acetanilide with norbornene: concise access to functionalized indolines†

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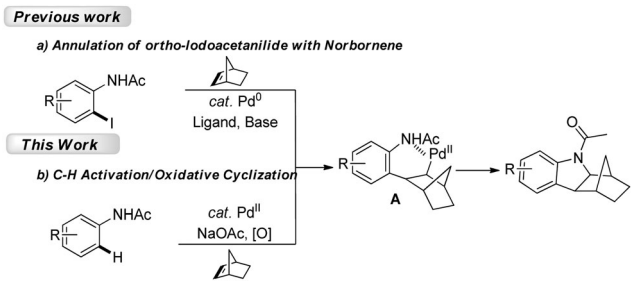
An efficient Pd-catalyzed oxidative cyclization reaction for the synthesis of functionalized indolines by direct C–H activation of acetanilide has been developed. The norbornylpalladium species formed *via* direct *ortho* C–H activation of acetanilides is supposed to be a key intermediate in this transformation.

In the past decades, metal-catalyzed C–H activation/coupling reactions have been widely explored and extensively employed in natural product synthesis, materials science and pharmaceutical chemistry.[1] Among them, the oxidative Heck reaction,[2] as pioneered by Fujiwara and Moritani,[3] has become one of the most important and distinct metal-catalyzed C–C bond-forming processes. In addition, metal-catalyzed C–H activation/alkyne cyclization for various useful heterocyclics, such as indoles,[4a–c] isoquinolines,[4d,e] pyrroles,[4f] isocoumarins,[4g] and pyridines,[4h] has attracted considerable attention. However, as for alkenes, the C–H activation/oxidative cyclization has been rarely realized since the comparative oxidative Heck reaction is usually the dominant process. In 2008, Booker-Milburn reported the first example employing 1,3-dienes in *ortho*-C–H activation of aryl urea to afford indolines.[5] Recently, in the work of Glorius[6a] and our related work,[6b] the coordinative saturation of the metal center has been shown to facilitate this chemical process. Considering that C–H activation/oxidative cyclization of alkene is still a great challenge, we devoted to develop a new strategy to fulfil this transformation. Notably, suppressing the β-hydride elimination and preventing the formation of Heck-type products is the key to the success of this reaction. We anticipated that the strained alkenes, such as norbornenes, could offer a solution to control the corresponding β-hydride elimination due to its strained structure and the intermediate A without *syn*-β-hydrogen could undergo reductive elimination to afford the oxidative cyclization products.



Scheme 1 Strategies for norbornene based indoline products.

On the other hand, norbornylpalladium species has been previously synthesized and its chemistry has been a widespread concern.[7] Catellani,[8a,b] Larock,[8c] Saito[8d] and Lautens[8e–g] *et al.* have reported several examples of the formation of nitrogen-containing heterocycles by the annulation of iodoanilines with norbornene compounds (Scheme 1a). However, most of these transformations are limited to the organohalide substrates, which always require multi-step procedures and generate a large amount of salt waste. Considering the atom economy and the importance of indoline products.[9] the development of a more direct C–H activation/oxidative cyclization process is urgently needed. Herein, we report an efficient Pd-catalyzed oxidative cyclization reaction for the synthesis of functionalized indolines by direct C–H bond activation of acetanilides (Scheme 1b).

Our initial investigations of this Pd-catalyzed C–H activation/oxidative cyclization reaction were commenced with acetanilide (**1a**) and norbornene (**2a**) as model substrates. Firstly, when **1a** and **2a** were treated with 10 mol% of $Pd(OAc)_2$ under 1 atm O_2 in DMSO at 120 °C, only a trace amount of expected product was detected (Table 1, entry 1). Considering that the oxidants might play an important role in this oxidative cyclization reaction, various frequently employed oxidants, such as 1,4-benzoquinone (BQ), silver and copper salts, were examined (see ESI† for details). To our delight, the yields were increased significantly when 2.0 equiv.

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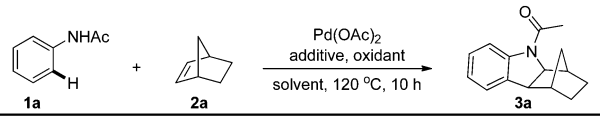
Table 1 Optimization of the reaction conditions[a]

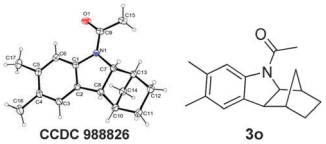


Entry	Oxidant (equiv.)	Additive[b]	Yield[c] (%)
1	1 atm O_2	—	<5
2	BQ (**2**)	—	10
3	Ag_2O (**2**)	—	30
4	AgOAc (**2**)	—	15
5	Ag_2CO_3 (**2**)	—	25
6	$Cu(OTf)_2$ (**2**)	—	38
7	$Cu(OAc)_2$ (**2**)	—	38
8	$Cu(OAc)_2$ (**1**) + 1 atm O_2	—	45
9	$Cu(OAc)_2$ (**1**) + 1 atm O_2	NaOAc	70 (66)
10	$Cu(OAc)_2$ (**1**) + 1 atm O_2	$TsOH{\cdot}H_2O$	21
11	$Cu(OAc)_2$ (**1**) + 1 atm O_2	CF_3COOH	8
12	$Cu(OAc)_2$ (**1**) + 1 atm O_2	PivOH	51

[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.3 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%) in DMSO (2.0 mL) at 120 °C for 10 h. [b] 1.0 equiv. of additive was added. [c] Determined by GC based on **1a**. The value in parentheses is the yield of the isolated product.

of oxidants were employed in the reaction system (entries 2–8). Among them, $Cu(OAc)_2$ gave the best result and the yield of **3a** was increased from 5% to 38% (entry 7). Further attempts revealed that 1.0 equiv. of $Cu(OAc)_2$ and 1 atm O_2 was the optimal oxidation system. Then, different additives were also tested (entries 9–12). Strong acids ($TsOH{\cdot}H_2O$, TFA) did not show positive effects on the yields since side reactions of norbornene might occur under these conditions. However, when 1.0 equiv. of NaOAc was added as an additive, the yield of **3a** increased significantly to 70% and this result indicated that NaOAc might be beneficial for the C–H activation step. Thus, the optimal catalytic system for this reaction was: **1a** (0.3 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (1 equiv.), NaOAc (1 equiv.) in DMSO (2.0 mL) under 1 atm O_2 at 120 °C for 10 h. It should be noted that the reaction proved to be totally diastereoselective affording polysubstituted indoline branched in the configuration *exo* to the bicyclic unit (confirmed by X-ray crystallographic analysis).[10]

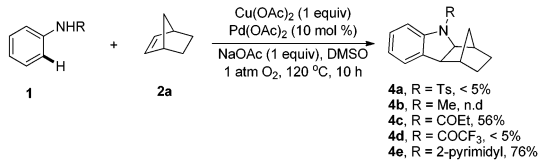
With the optimal reaction conditions in hand, we then examined the scope of this C–H activation/oxidative cyclization transformation. Generally, various acetanilides with different substituents were found to be suitable reaction partners for this process. A series of *para*-substituted acetanilides including some with electron-donating groups (Me, OMe, OCF_3, and OPh) and some with electron-withdrawing groups (F, Cl, and Br) were well tolerated and converted to the corresponding indoline products **3a–3h** in moderate to good yields. It should be noted that substituents on the aromatic ring of the acetanilide were found to influence the efficiency of the oxidative cyclization significantly. Electron-rich substrates tended to give relatively high yields, whereas electron-deficient substrates displayed a much lower reactivity. Moreover, *ortho*-Me, -OMe and -F substituted acetanilides proceeded smoothly to afford the desired products **3i–3k** with a slight increase in the yields. Notably, *N*-(naphthalen-1-yl)acetamide also displayed a similar reactivity. Next, *meta*-substituted acetanilides were tested. To our delight, good selectivity was observed with 3,4-dimethyl and 3-methoxy substituted acetanilides, leading to



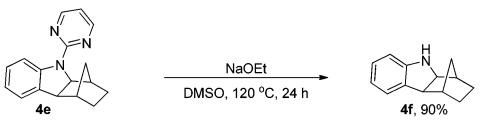
Scheme 2 X-ray crystallographic analysis of **3o**.

the formation of two indoline regioisomers with high selectivity, **3n** and **3o** were almost the exclusive products. In addition, the structure of **3o** was further confirmed by X-ray crystallographic analysis (Scheme 2).[10] Intriguingly, the reaction of *N*-(3,4-dichlorophenyl)-acetamide led to the formation of two regioisomers with decreased selectivity (a/a' = 5/1), while a 7/4 value was observed when using *N*-(3-fluorophenyl)acetamide as the substrate. Evidently, both the electronic character and steric demand of the substituents influenced the selectivity of this transformation. To further demonstrate the synthetic potential of this method, various norbornene derivatives were also introduced to this oxidative cyclization reaction and the corresponding indoline products **3r–3u** were obtained in moderate yields (46–66%). Moreover, this reaction showed a good selectivity to the C–C double bond of norbornene when tetrahydro-1*H*-4,7-methanoindene was employed as the substrate (Table 2).

To further highlight the versatility of this reaction, other directing groups were also tested (eqn (1)). We found that the 2-pyrimidyl and propionyl groups could be utilized as the directing group in addition to the acetyl group, and the desired oxidative cyclization products **4c** and **4e** were formed in 56% and 76% yields, respectively. However, tosyl, methyl and trifluoroacetyl did not serve as proper directing groups. It is important to note that the 2-pyrimidyl group was easily removed from indoline[11] and the corresponding *N*-free indoline product **4f** could be obtained in good yield (90%, eqn (2)).

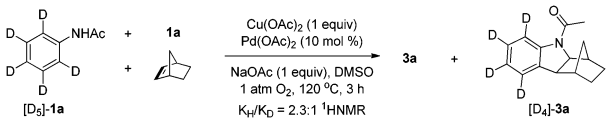


(1)



(2)

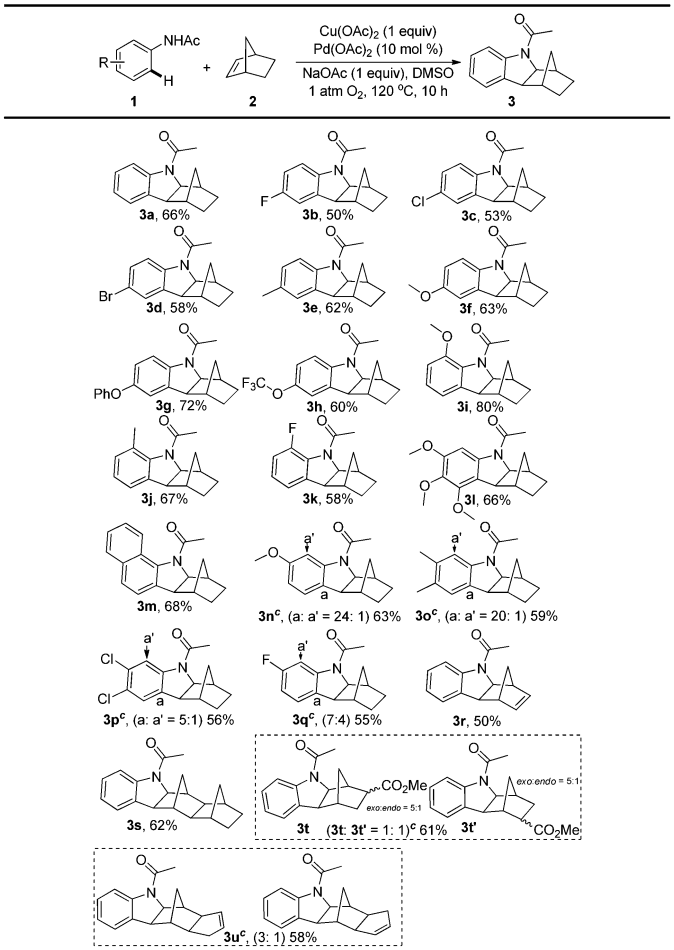
To gain more insight into the mechanism of these reactions, we performed a deuterium competition experiment between substrate **1a** and $[D_5]$-**1a**, and a kinetic isotope effect (KIE) of $k_H/k_D \approx 2.3$ (eqn (3)) was observed, which indicated that the C–H activation of arenes was the rate-determining step.



(3)

A tentative mechanism for the Pd-catalyzed intermolecular oxidative cyclization of acetanilides and norbornenes is proposed

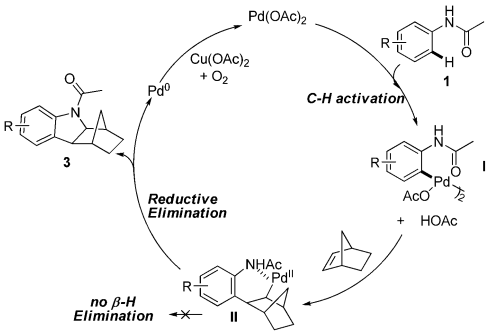
Table 2 Substrate scope of various acetanilides and norbornenes[a,b]



[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.3 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (1 equiv.), NaOAc (1 equiv.) under 1 atm O_2 in DMSO (2.0 mL) at 120 °C for 10 h. [b] Isolated yield. [c] Determined by ^1H NMR.

on the basis of the above-mentioned results and previous reports[12] (Scheme 2). With the assistance of directing groups, intermediate I is formed through Pd-catalyzed *ortho*-C(sp^2)–H activation of acetanilide,[12] subsequent coordination with norbornene and then 1,2-migratory insertion to generate intermediate II which can suppress the β-hydride elimination due to the lack of *syn*-β-hydrogen. Finally, the indoline product is formed *via* C(sp^3)–N bond reductive elimination, and Pd(II) active species is regenerated in the presence of $Cu(OAc)_2$ and 1 atm O_2 (Scheme 3).

In conclusion, we have developed an efficient Pd-catalyzed oxidative cyclization reaction for the synthesis of functionalized indolines by direct C–H bond activation of acetanilide. Compared to the oxidative Heck reaction, this oxidative cyclization suppresses the β-hydride elimination and prevents the formation of Heck-type products. The norbornylpalladium species formed *via* direct aryl C–H activation may provide a new approach to the study of the Catellani reaction.[7a] The detailed reaction mechanism and further synthetic applications of the indoline products are under investigation in our laboratory, and the results will be reported in due course.



Scheme 3 Possible reaction mechanism.

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