C–H Activation

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Palladium-Catalyzed Amidation of Unactivated C(sp^3)–H Bonds: from Anilines to Indolines**

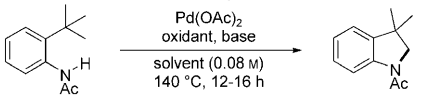
*Julia J. Neumann, Souvik Rakshit, Thomas Dröge, and Frank Glorius**

Amines, amides, and nitrogen-containing heterocycles are ubiquitous motifs[1] of biologically active compounds, such as alkaloids. Consequently, the formation of carbon–nitrogen bonds is of utmost importance, and many classical methods exist, such as reductive amination. Furthermore, powerful metal-catalyzed cross-coupling reactions, for example the palladium-catalyzed amination of aryl halides (Buchwald–Hartwig reaction)[2] or the copper-catalyzed amidation of aryl halides,[3] have recently been added to the armory of the synthetic chemist. However, these methods rely on the presence and elaboration of functional groups in each of the two reaction partners, which is a common feature in organic synthesis.

The activation and transformation of C–H bonds is a powerful exception to this requirement, and provides a more direct route to complex products from simpler starting materials. Many ground-breaking contributions have been made to this field in the last few years,[4] with the activation of C(sp^2)–H bonds and activated C(sp^3)–H bonds being far more facile and common than the activation of unactivated[5] C(sp^3)–H bonds.[6] Whereas the activation of C(sp^2)–H bonds is most often triggered by an interaction between the π electrons and the catalyst, the activation mode for unactivated C(sp^3)–H bonds is less understood. The combination of these C–H activation steps with C–N bond formation is a promising entry to nitrogen-containing compounds, and consequently, numerous C–N bond formations based on C(sp^2)–H bond activations have been developed.[7,8] However, to our knowledge, the activation of an unactivated C(sp^3)–H bond[5] followed by carbon–nitrogen bond formation has only been reported using nitrenes.[9] As part of our ongoing research into cross-coupling reactions,[10,11] we have been attempting the development of a C(sp^3)–H bond activation/C–N bond formation cascade without the involvement of nitrenes. Herein we report on the first realization of this strategy in a palladium-catalyzed synthesis of valuable indoline[12] products from many differently substituted anilides.

Our study commenced with the oxidative cyclization of readily available *N*-(2-*tert*-butylphenyl)acetamide (**1a**) to the corresponding indoline **2a** using AgOAc as oxidant and K_2CO_3 as base. No product was obtained using polar solvents, such as DMSO (Table 1, entry 1), DMF, or MeCN.[13] In contrast, the reaction proceeded to some extent in less polar aromatic solvents (Table 1, entries 2–4), and was found to be water-sensitive (entry 5). Variation of the oxidant showed that AgOAc is superior to other silver(I) and copper(II) salts and over hypervalent iodine reagents (Table 1, entries 6,7).[13] A major improvement was achieved by changing the base to Na_2CO_3. Under these optimized conditions, practically full conversion (>98%) was reached after 4 h, and the desired product was obtained in 80% yield of isolated product (Table 1, entry 9). This activation of the C(sp^3)–H bond is especially remarkable, because the competing C(sp^2)–H bond activation of acetanilides at the 6-position of the aromatic ring has previously been reported.[14] A scale-up of this reaction led to a virtually unchanged result (Table 1, entry 10).

Table 1: Optimization of the reaction parameters.[a]



Entry	Oxidant (equiv)	Base	Solvent	Yield[b] of **2a** [%]
1	AgOAc (3.0)	K_2CO_3	DMSO	1
2	AgOAc (3.0)	K_2CO_3	toluene	32
3	AgOAc (3.0)	K_2CO_3	chlorobenzene	41
4	AgOAc (3.0)	K_2CO_3	mesitylene	53
5	AgOAc (3.0)	K_2CO_3	mesitylene + H_2O[c]	8
6	$Cu(OAc)_2$ (3.0)	K_2CO_3	mesitylene	11
7	$PhI(OAc)_2$ (3.0)	Na_2CO_3	mesitylene	<1
8	AgOAc (3.0)	–	mesitylene	(48)
9	**AgOAc (3.0)**	**Na_2CO_3**	**mesitylene**	**89 (80)**
10[d]	AgOAc (3.0)	Na_2CO_3	mesitylene	(77)
11	AgOAc (2.1)	Na_2CO_3	mesitylene	76 (73)
12[e]	AgOAc (3.0)	Na_2CO_3	mesitylene	88 (79)

[a] Reaction conditions: **1a** (0.25 mmol), $Pd(OAc)_2$ (10 mol%), oxidant (0.75 mmol), base (0.75 mmol), solvent (3 mL), 140°C, 12 h. [b] Determined by GC-MS, with 1,3,5-tri-*tert*-butylbenzene as an internal standard. Yield of isolated **2a** (1 mmol scale reaction) in parentheses. [c] 6 μL of water added. [d] 10 mmol scale. [e] Reaction performed at 110°C.

[*] J. J. Neumann, S. Rakshit, T. Dröge, Prof. Dr. F. Glorius
Westfälische Wilhelms-Universität Münster
Organisch-Chemisches Institut
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-833-3202
http://www.uni-muenster.de/Chemie.oc/glorius/index.html
E-mail: glorius@uni-muenster.de

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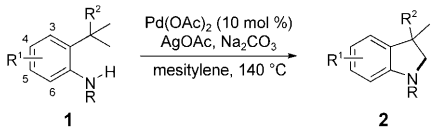
Furthermore, the amount of oxidant and the reaction temperature could be lowered without any substantial loss in product yield (Table 1, entries 11,12); however, significantly longer reaction times would be required, as conversion of the starting material was not complete after 12 h.

Under the optimized conditions, several differently substituted substrates **1** were investigated, providing the scope and limitations of this new method (Scheme 1). First, different substituents at the nitrogen atom, mostly electron-withdrawing ones, were tested.



1 2

Scheme 1. Synthesis of indolines by activation of a C(sp^3)–H bond.

The initially chosen *N*-acetyl group provided the best results. Whereas formyl, propionyl, and isobutyryl residues still gave the desired products (**2a′**, **2b**, **2c**) in significant, albeit reduced yields, hardly any product was observed for other acyl groups, such as pivaloyl, benzoyl, or trifluoroacetyl (Figure 1). Furthermore, neither carbamates nor sulfonamides nor free primary or secondary amines gave any of the desired cyclization products. It seems that a delicate balance between electronic and steric properties of the nitrogen substituent is required for the initiation of this reaction.

With the acetyl group being identified as the ideal *N*-substituent, the functional group tolerance was found to be extraordinarily broad. Many differently 4-substituted substrates were screened, and the reaction proceeded well both for electron-donating (**2d–k**) and electron-withdrawing (**2l–s**) substituents (Figure 1). Rather robust functional groups, such as ethers, sulfones, and carboxylic esters, less robust groups, such as thioethers, acetals, silanes, and ketones, and even bromide, olefin, and aldehyde groups were well-tolerated. These functional groups provide ample opportunity for further functional group manipulations, for example, by cross-coupling reactions. Substituents bearing acidic protons (R^1 = 4-OH, 4-COOH) and basic amines (R^1 = 4-NH_2, 5-NH_2, 4-NMe_2), however, did not yield the corresponding indoline products in significant amounts.[13] Substituents in the 5-position are also tolerated, but required higher reaction temperatures or catalyst loadings (**2t–v**), whereas 6-substituted substrates reacted under the standard conditions (**2w**,**x**). A phenyl substituent in the 6-position (**1y**) resulted in an insightful intramolecular competition experiment (sp^2 vs. sp^3; Scheme 2): Exclusive C(sp^2)–H activation at the phenyl group was observed for **1y**, leading to carbazole **3** as previously described,[7f,g] thus clearly demonstrating the challenge of C(sp^3)–H bond activation.[13]

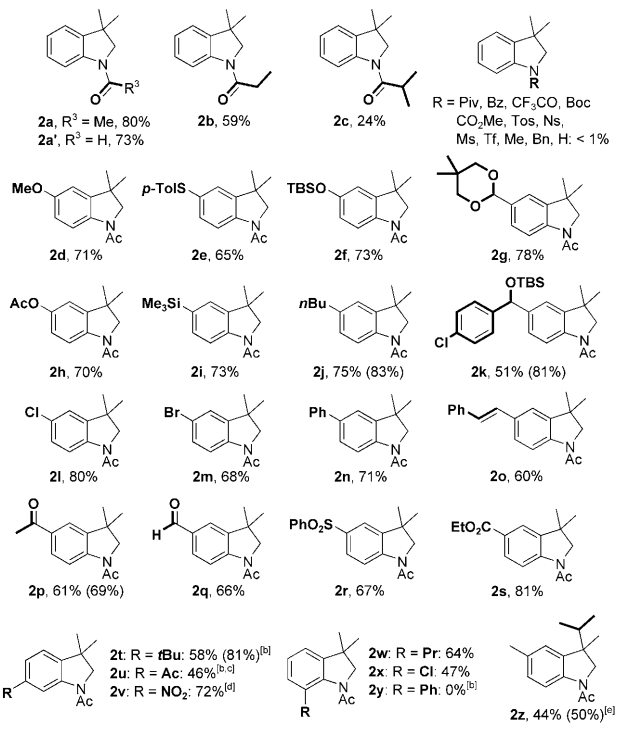
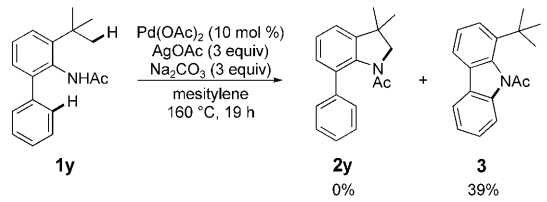
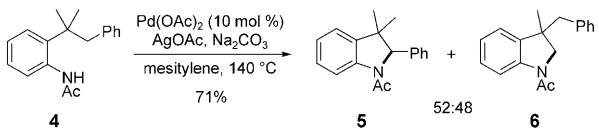


Figure 1. Investigation of the reaction scope[a] (see Scheme 1). [a] Reaction conditions: **1** (1.0 mmol), Pd($OAc)_2$ (10 mol%), AgOAc (3.0 mmol), Na_2CO_3 (3.0 mmol), mesitylene (12 mL), 140°C, 12–36 h.[13] Yield of isolated **2** given; yield based on recovered starting material is given in parentheses. [b] Reaction at 160°C. [c] 20 mol% Pd($OAc)_2$. [d] 30 mol% Pd($OAc)_2$. [e] 0.5 mmol scale (**1**).



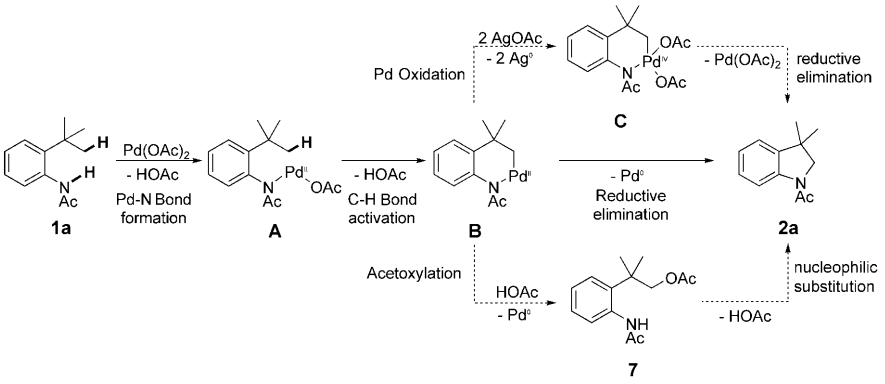
Scheme 2. Intramolecular competition experiment: C(sp^2)–H versus C(sp^3)–H.

Finally, variation of the *tert*-butyl group of substrates **1** allows the formation of chiral products. For example, employing a (1,1,2-trimethyl)propyl substituent resulted in the cyclization to indoline **2z**. Further variation of the *t*Bu group allowed the reactivity of the unactivated C(sp^3)–H bonds to be compared with activated bonds. An intramolecular competition between an activated benzylic position and two unactivated methyl groups in acetanilide **4** resulted in the formation of the corresponding indolines **5** and **6** in 71% yield[15] and a ratio of 52:48,[16] thus showing only a slight preference for the activation of the benzylic position (Scheme 3).



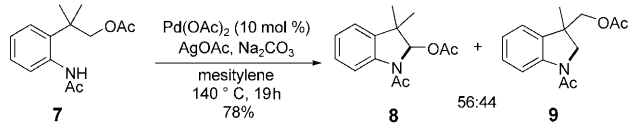
Scheme 3. Intramolecular competition experiment: benzylic versus unactivated C(sp^3)–H bond.[13]

A possible reaction mechanism for the cyclization of *N*-(2-*tert*-butylphenyl)acetamide **1** is shown in Scheme 4. The acetanilide moiety is a well-known directing group that can readily coordinate to the palladium(II) catalyst, replacing one



Scheme 4. Proposed mechanism for the oxidative cyclization of **1**.

acetate ligand (**A**). Once the palladium is in close proximity to the unactivated C–H bond of an alkyl group, C–H bond activation can take place to give intermediate **B**. Subsequent reductive elimination of palladium(0), which can be reoxidized to palladium(II) by the silver(I) salt that is present, leads to the formation of indoline product **2**. Alternatively, the reaction could proceed through a silver(I)-promoted oxidation of intermediate **B** to a more highly oxidized palladium species **C**, facilitating reductive elimination of palladium(II).[17] A third possible pathway involves acetoxylation of intermediate **B** to generate ester **7**. The acetate may then be replaced in an intramolecular S_N-type reaction without participation of a palladium species to form indoline **2**. This latter C(sp^3)–H bond acetoxylation[6n,p]/nucleophilic substitution[7i] pathway was readily investigated by subjection of the acetoxylated anilide **7** to the optimized conditions (Scheme 5). The substitution product **2a** could not be



Scheme 5. Mechanistic investigation of the amidation pathway and intramolecular competition experiment: activated versus unactivated C(sp^3)–H bond. **2a** is not formed in this reaction.[13]

detected in the crude reaction mixture neither by GC-MS, ESI-MS, nor ^{1}H NMR. Instead, reaction of the acetoxylated substrate **7** proceeded smoothly to provide the C–H functionalized products **8** and **9** in 78% yield[15] and a ratio of 56:44, again showing a slight preference for functionalization of the activated position. Heating of **7** under the same conditions in the absence of $Pd(OAc)_2$ also failed to afford indoline **2a**.[13] These observations strongly argue against a sequential acetoxylation/amidation pathway in this reaction. Furthermore, intermolecular competition experiments using differently 4-substituted anilides did not show any significant effect of the electronic properties of the aromatic ring on the reaction rate.[13]

These latter three examples (**1z**, **4**, **7**) round out the investigation of the scope of this reaction by demonstrating different variations of the *t*Bu group. In conclusion, we have developed an unprecedented process in which an unactivated C(sp^3)–H bond is activated by the aid of an amide directing group that subsequently acts as a reaction partner in the same process. This reaction is one of the first unactivated C(sp^3)–H bond activation/C–N bond-forming processes, and arguably the first example that does not involve nitrenes. A number of intra- and intermolecular competition experiments have provided insights into the reaction mechanism. An exceptionally broad tolerance of functional groups permits the formation of numerous valuable indolines in good yields. The investigation of intermolecular and asymmetric variants is currently ongoing in our laboratories.

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