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Exploring the Oxidative Cyclization of Substituted *N*-Aryl Enamines: Pd-Catalyzed Formation of Indoles from Anilines

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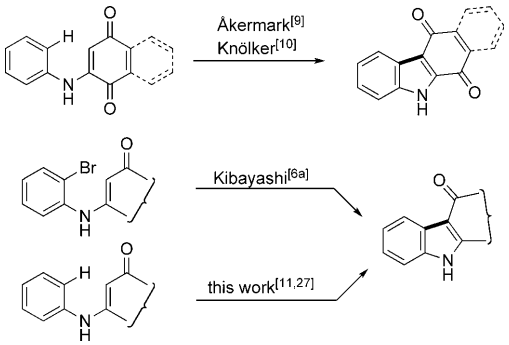
Abstract: The direct Pd-catalyzed oxidative coupling of two C–H-bonds within *N*-aryl-enamines **1** allows the efficient formation of differently substituted indoles **2**. In this cross-dehydrogenative coupling, many different functional groups are tolerated and the starting material *N*-aryl-enamines **1** can be easily prepared in one step from commercially available anilines. In addition, the whole sequence can also be run in a one-pot fashion. Optimization data, mechanistic insight, substrate scope, and applications are reported in this full paper.

Keywords: anilines · C–C coupling · C–H activation · indoles · palladium

Introduction

Indole derivatives are widely distributed in nature[1] and are known to be an important structural unit for the development of pharmaceuticals,[2] agrochemicals,[3] and materials sciences.[4] Generally, substituted indoles have been referred to as "privileged structures" since they are capable of binding to many receptors with high affinity.[5] Among many variations, 2,3-disubstituted indole substructures are widely distributed in nature as indole alkaloids and drugs, for example, vinblastine, reserpine, okaramines, and indomethacin. Over the last century, the synthesis of indoles has been an important area of research for organic chemists, and several powerful methods for the synthesis of indoles have been reported.[6] However, lack of starting material availability and functional-group tolerance often limits the generalization of a particular indole synthesis method. The development of mild, selective, and efficient methods for the synthesis of such compounds is highly desirable. In this context, direct oxidative C–C coupling by the selective activation of two C–H bonds is a promising synthetic strategy.[7] In contrast to established cross-coupling methods[8] prefunctionalization of the reaction centers is not required. Åkermark et al.[9] and Knölker et al.[10] have independently reported the formation of carbazoloquinone and carbazole derivatives by an exciting Pd-catalyzed and -mediated intramolecular oxidative Heck-type coupling (Scheme 1). Best results were obtained by employing electron-rich aniline substrates, since these reactions proceed by an electrophilic aromatic palladation mechanism. However, the need for acidic reaction media (HOAc), the rather harsh reaction conditions, and the limited scope restrict the applicability of these methods. By significantly changing the substrates and especially the reaction conditions, we recently developed an efficient method for the formation of indoles by Pd-catalyzed oxidative cyclization of *N*-aryl enaminones.[11] This oxidative Heck-type indole formation is more versatile than the standard Heck reaction, obviating the need for *ortho*-halo anilines (Scheme 1). In this full paper, we report on the details of this versatile cross-dehydrogenative coupling reaction (Scheme 1).



Scheme 1. Comparison of related strategies for indole formation.

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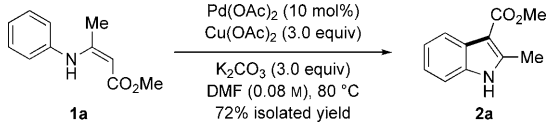
Results and Discussion

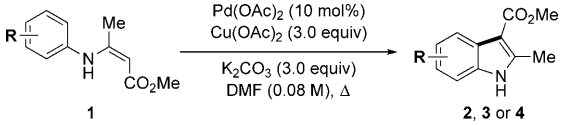
We commenced our investigation with the cyclization of methyl (*Z*)-3-(phenylamino)but-2-enoate (**1a**) to give the corresponding indole **2a**. Optimization reactions were carried out and the best results were obtained with a catalytic amount of $Pd(OAc)_2$, $Cu(OAc)_2$ as the oxidant, and K_2CO_3 as the base in DMF. Under these conditions, conversion was complete within 3 h at 80 °C or within less than 15 min at 140 °C, even when only 5 mol % of $Pd(OAc)_2$ was used (Scheme 2).[12] It is worth noting that **1a** can be prepared very easily in gram scale by condensation of methyl acetoacetate and aniline[13] (both are commercially available and cheap relative to the required starting materials necessary in other existing methods).

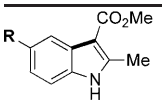
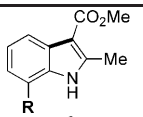
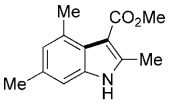


Scheme 2. Optimized reaction conditions.

With these optimized conditions in hand, we examined the substrate scope with different substituents on the aryl group of the enaminone (Table 1). Substrates with a variety of electron-withdrawing and -donating substituents were successfully converted directly into the indole products. Sensitive groups like nitro, nitrile, acetyl, ester, amide (3°), and a trifluoromethyl group can be used on the aromatic part of the enaminone derivative in moderate to good yield. Halo-substituents on the aryl part of the enaminone were also tolerated under mild conditions (**2j**). However, debrominated indole (**2a**) was also formed in small amount under these reaction conditions. The formation of a brominated indole derivative (**2j**) is attractive because these bromoindoles are key intermediates in the preparation of biologically active compounds by Suzuki–Miyaura cross-coupling reactions.[14] Interestingly, *ortho*-alkyl substituted enaminones led to comparably higher yields than *para*-alkyl substituted enaminones (Table 1, for example, **3e** compared to **2k**). Similarly, a bulky alkyl substituent at the *ortho*-position of the enaminone gave a good yield (Table 1, **3g**, **3h**). Although the free amine (NH_2) and hydroxyl (OH)-substituted enaminones decomposed (not shown), pivalyl-protected amine and acetyl-protected hydroxyl-substituted enaminones gave good yields under our optimized reaction conditions (Table 1, **2l**, **2m**), whereas TBS-protected hydroxyl-substituted enaminone provided the corresponding deprotected free hydroxyl-substituted indole under these basic conditions in good yield (Table 1, **2n**). Furthermore, methoxy-substituted enaminones performed well under our reaction conditions (Table 1, **2o**, **3i**). The ability to vary the aniline moiety so broadly is a noticeable attractive feature of this indole synthesis.

Table 1. Variation on the aromatic part of enaminones.[a]



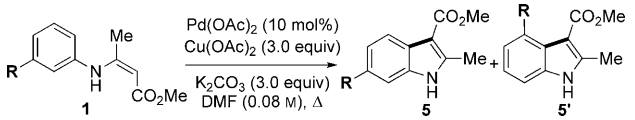
Compounds **2**		Compounds **3** and **4**	
	R = NO_2: **2b**, 42%[b] CN: **2c**, 65% Ac: **2d**, 52% CO_2Et: **2e**, 64% $CONEt_2$: **2f**, 70% CF_3: **2g**, 60%[c] F: **2h**, 74%[d] Cl: **2i**, 64%[e] Br: **2j**, 56%[f] Me: **2k**, 72%[e] NHPiv: **2l**, 76%[c] OAc: **2m**, 63%[d] OH: **2n**, 52%[c,h] OMe: **2o**, 68% NMe_2: **2p**, 24%[b]		R = CF_3: **3a**, 86%[g] F: **3b**, 78%[d] Cl: **3c**, 53%[e] Ph: **3d**, 32% Me: **3e**, 82%[c] Et: **3f**, 83%[c] *i*Pr: **3g**, 82%[c] *t*Bu: **3h**, 81%[c] OMe: **3i**, 64%
			**4**, 62%[c]

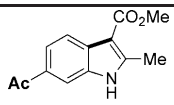
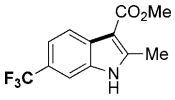
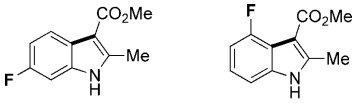
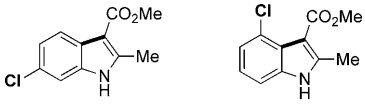
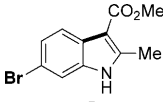
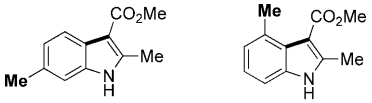
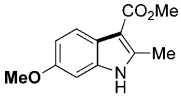
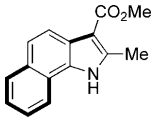
[a] **1** (1.0 mmol), $Cu(OAc)_2$ (3.0 mmol), K_2CO_3 (3.0 mmol), $Pd(OAc)_2$ (10 mol %), DMF (12 mL), 140 °C, 30 min, isolated yield given. [b] 140 °C, 14 h. [c] 110 °C, 14 h. [d] 110 °C, 5 h. [e] 80 °C for 12 h. [f] 60 °C, 8 min, debrominated indole **2a** as the byproduct. [h] Starting material was TBS-protected hydroxyl-enaminone. [g] 80 °C, 14 h.

The presence of a *meta*-substituent on the aniline fragments can afford two regioisomeric indole products **5** and **5′**. Intriguingly, exclusive formation of the 6-substituted indole regioisomer was observed with both the electron-withdrawing acetyl and the electron-donating methoxy substituent (Table 2, entries 1, 7). Similarly, good regioselectivities were observed with trifluoromethyl, chloro, bromo, and methyl substituents (Table 2, entries 2, 4, 5, 6). The presence of the small fluoro substituent led to the nonselective formation of the 4- and 6-substituted indole regioisomers (Table 2, entry 3). It seems that the steric demand of the substituents is responsible for the levels of regioselectivity obtained in this transformation rather than their electronic character. Interestingly, the substrate derived from α-naphthylamine containing both available α and β C–H bonds underwent the desired reaction to give only one regioisomer (**5h**) in excellent yield (Table 2, entry 8).

The enaminone moiety was also varied successfully with the efficient formation of different carbonyl derivatives. Ethyl and *tert*-butyl ester-derived enaminones formed the corresponding indole products smoothly under our optimized reaction conditions (Table 3, entries 1–4). Interestingly, ethyl (*Z*)-3-(phenylamino)-but-2-enoate also gave a good yield when using cheap $Cu(OAc)_2$ hydrate as an oxidant. Concurrently, we have demonstrated a gram scale (10.0 mmol) synthesis of **6a** by using 2.0 mol % $Pd(OAc)_2$ as catalyst and $Cu(OAc)_2$ hydrate as an oxidant in reasonable yield. Besides ester-substituted enaminones, some nitrile- and ketone-substituted enamines also reacted to indole products in good yield (Table 3, entries 5, 6). Electronically different β-substituted (CF_3, *i*Pr, OEt) enaminones were also smoothly converted to the products under our optimized reaction conditions (Table 3, entries 7–9). Notably, no

Table 2. Regioselective aromatic C–H bond activation.[a]



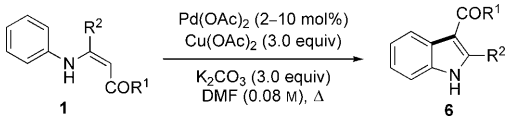
Entry	Product	Yield[b] [%]
1	 **5a**	54
2[c]	 **5b**	54
3[d]	 6-F (**5c**)/4-F (**5c'**) = 53:47	74[e]
4[c]	 6-Cl (**5d**)/4-Cl (**5d'**) = 88:12	75
5[f]	 **5e**	43
6[g]	 6-Me (**5f**)/4-Me (**5f'**) = 92:8	68
7[b]	 **5g**	64
8[c]	 **5h**	85

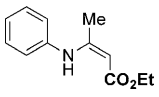
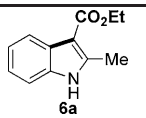
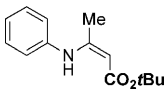
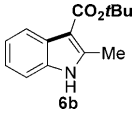
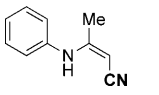
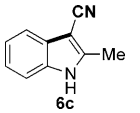
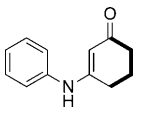
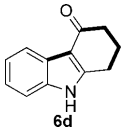
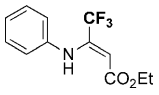
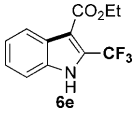
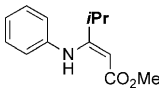
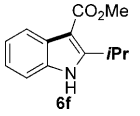
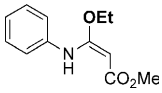
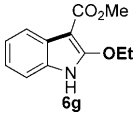
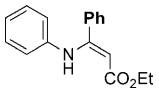
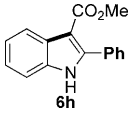
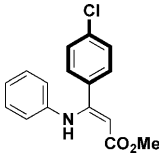
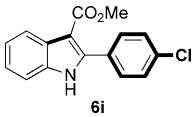
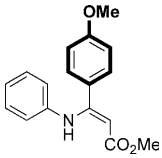
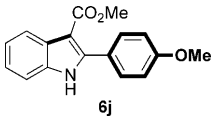
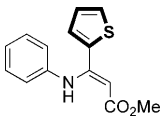
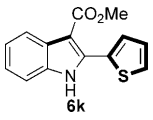
[a] **1** (1.0 mmol), $Cu(OAc)_2$ (3.0 mmol), K_2CO_3 (3.0 mmol), $Pd(OAc)_2$ (10 mol%), DMF (12 mL), 140 °C, 30 min; regioisomeric ratio was calculated by GC analysis. [b] Isolated yield of the major product. [c] 80 °C, 14 h. [d] 110 °C, 14 h. [e] Yield of inseparable regioisomeric mixture. [f] 60 °C, 8 min, debrominated indole **2a** as the byproduct;[g] 80 °C, 16 h.

base had to be used to achieve good conversion for electron-rich α-substituted enaminone (Table 3, entry 9).[15] Interestingly, when using aryl substituents on the β-position of enaminone derivatives higher temperatures and microwave irradiation were required to achieve reasonably good yields (Table 3, entries 10–12). Hetero biaryl compounds can also be efficiently synthesized in moderate yield (Table 3, entry 13).

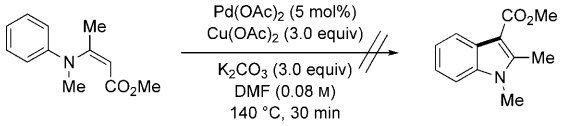
Apparently, the *N*-methyl derivative of **1a** decomposed under reaction conditions and no desired product was observed. This indicates the essential need of the free NH to achieve enough reactivity for this reaction (Scheme 3).

Table 3. Variation on enaminone part.



Entry	Enaminone	Product	Yield [%]
1[a]		 **6a**	71
2[b]			70
3[c]			62
4[a]		 **6b**	79
5[d]		 **6c**	69
6[e]		 **6d**	85
7[f]		 **6e**	80
8[f]		 **6f**	73
9[g]		 **6g**	73
10[h]		 **6h**	68
11[i]		 **6i**	58
12[i]		 **6j**	58
13[j]		 **6k**	59

[a] **1** (1.0 mmol), $Cu(OAc)_2$ (3.0 mmol), K_2CO_3 (3.0 mmol), $Pd(OAc)_2$ (5 mol%), DMF (12 mL), 140 °C, 15 min. [b] $Cu(OAc)_2{\cdot}H_2O$ instead of $Cu(OAc)_2$. [c] **1** (10.0 mmol), $Cu(OAc)_2{\cdot}H_2O$ (30.0 mmol), K_2CO_3 (30.0 mmol), $Pd(OAc)_2$ (2 mol%), DMF (120 mL), 140 °C, 17 h. [d] K_3PO_4 (1 equiv) instead of K_2CO_3, 125 °C, 12 h. [e] **1** (1.0 mmol), $Cu(OAc)_2$ (3.0 mmol), K_2CO_3 (3.0 mmol), $Pd(OAc)_2$ (10 mol%), DMF (12 mL), 140 °C, 24 h. [f] 140 °C, 1 h. [g] 110 °C, 1 h, no base was used. [h] 180 °C (microwave), 1 h. [i] 160 °C (microwave), 1 h. [j] 110 °C, 14 h.

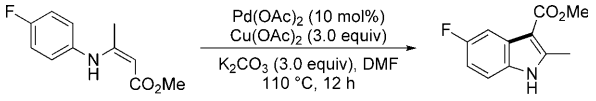


Scheme 3. Cyclization of the *N*-methyl derivative of **1a**.

In our previous optimization, we had observed that a less polar solvent like toluene is less efficient for this transformation relative to an aprotic polar solvent like DMF.[11] But, no study was performed with other bases (except carbonates) when using DMF to get better reactivity towards the desired indole product. In addition, the carbonate base leads to a buildup of pressure (CO_2), which might pose a significant danger for large-scale reactions. Thus, we commenced our reoptimization study to find other suitable solvents and cheaper oxidants and bases. To optimize the reaction (*Z*)-methyl 3-[(4-fluorophenyl)amino]but-2-enoate (**1h**) was used as the starting material and quantitative reaction control by ^{19}F NMR spectroscopy was performed based on 5-fluoro-substituted indole derivative **2h**. Firstly, DMA (*N*,*N*-dimethylacetamide) and NMP (*N*-methylpyrrolidone) showed reactivity similar to the standard reaction conditions (Table 4, entries 2, 3), whereas other coordinating polar solvents, such as *i*PrCN, dioxane, or DMSO, gave only very poor yields (Table 4, entries 4–6).[16] Replacing $Cu(OAc)_2$ by other Fe and Cu-based oxidants also did not work well, but $CuBr_2$ gave moderate yield. The role of the base is essential; strong bases like NaOH gave comparable yields, whereas KO*t*Bu was not efficient under these conditions. The best result was obtained with K_3PO_4 (73% NMR yield). To show the efficiency of this reaction, we performed a 5.0 mmol scale reaction with methyl **1h** by using 5.0 mol% $Pd(OAc)_2$ as the catalyst and K_3PO_4 as the base in 79% isolated yield. Surprisingly, the combination of $CuBr_2$ and K_3PO_4 did not give any detectable amount of the desired product.

A few attempts were made to lower the amount of $Cu(OAc)_2$ and to use air or oxygen as the terminal oxidant.[17] However, unfortunately none of these experiments met with success.[12] Finally, we intended to use mono-hydrated $Cu(OAc)_2$ as a cheaper oxidant with K_3PO_4 (1.0 equiv) as the base and 5.0 mol% $Pd(OAc)_2$ as the catalyst under air without any moisture precaution. Under these conditions, we have successfully shown the formation of our desired indole product in good yield (Scheme 4).

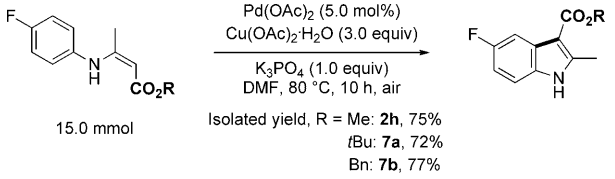
Table 4. Reoptimization of the reaction conditions.[a]



1h **2h**

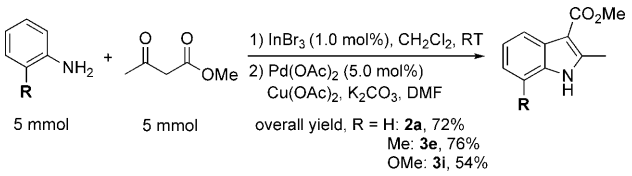
Entry	Variation from standard conditions	Yield [%]
1	none	58
2	DMA instead of DMF	57
3	NMP instead of DMF	56
4	*i*PrCN instead of DMF	1[16]
5	Dioxane instead of DMF	3
6	DMSO instead of DMF	13
7[b]	$Fe(acac)_3$ instead of $Cu(OAc)_2$	2
8[b]	$FeCl_3$ instead of $Cu(OAc)_2$	0
9[b]	$Cu(acac)_2$ instead of $Cu(OAc)_2$	3
10[b]	$CuBr_2$ instead of $Cu(OAc)_2$	48
11[b]	CuO instead of $Cu(OAc)_2$	2
12[b]	NaOH instead of K_2CO_3	69
13[b]	KO*t*Bu instead of K_2CO_3	18
14[b]	K_3PO_4[c] instead of K_2CO_3	73 (79)[d]
15[b]	$CuBr_2$ as oxidant and K_3PO_4[c] as base	0

[a] Standard reaction conditions: **1h** (0.25 mmol), $Cu(OAc)_2$ (0.75 mmol), K_2CO_3 (0.75 mmol), $Pd(OAc)_2$ (10 mol%), DMF (3 mL), the yield was determined by ^{19}F NMR spectroscopy. [b] 120°C was used. [c] The K_3PO_4 employed was pestled and dried. [c] **1h** (5.0 mmol), $Cu(OAc)_2$ (15.0 mmol), K_3PO_4 (15.0 mmol), $Pd(OAc)_2$ (5.0 mol%), DMF (60 mL), 80°C for 66 h, isolated yield given.



Scheme 4. Reoptimized reaction.

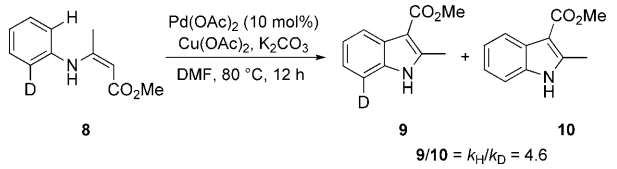
From a synthetic point of view, to make this overall approach to indoles even more attractive, we explored their formation through a one-pot reaction sequence that omits the isolation of the enaminone intermediates.[18] Thus, substituted anilines were condensed at room temperature with methyl acetoacetate in the presence of $InBr_3$ (1.0 mol%) to give the corresponding enamine carboxylates,[19] which underwent subsequent cyclization under the standard conditions to give the desired indole products in good yield (Scheme 5).



Scheme 5. One-pot synthesis of indole from aniline.

To probe the role of the Cu^{II} salt, the reaction was performed by using $Pd(OAc)_2$ (20 mol%) as the catalyst with K_2CO_3 (3.0 equiv) as the base at 110°C for 1 h (without Cu^{II} salt) leading to 15% ^1H NMR spectroscopic yield. After this time, addition of $Cu(OAc)_2$ (3.0 equiv) to the mixture and prolonged heating for 12 h at 110°C resulted in continued turnover and 43% yield determined by ^1H NMR spectroscopy.[12] This experiment suggests that $Cu(OAc)_2$ does not play a crucial role in the direct formation of the product. $Cu(OAc)_2$ just acts as a terminal oxidant to achieve the turnover in the catalytic cycle.[20]

To learn about the C–H activation step, an intramolecular kinetic isotope effect of enaminone (**8**) was determined.



Scheme 6. Determination of the intramolecular kinetic isotope effect.

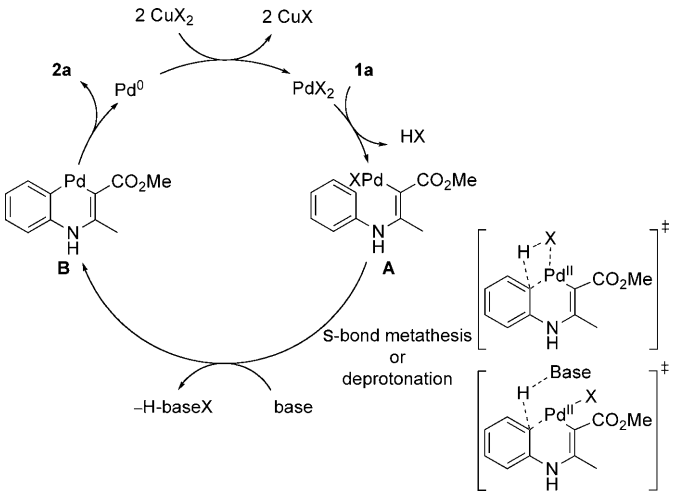
This intramolecular kinetic isotope effect $k_H/k_D = 4.6$ suggested that the C–H activation step does not proceed through an electrophilic aromatic palladation (Scheme 6).

Furthermore, competition experiments were carried out between electronically different *para*-substituted substrates **1** (Cl with H and Me with OMe). These set of experiments showed that electron-donating groups in the *para*-position slow down this transformation.[12] This observation is in agreement with a mechanism involving σ-bond metathesis or base-assisted deprotonation, but not with an electrophilic aromatic palladation.[21]

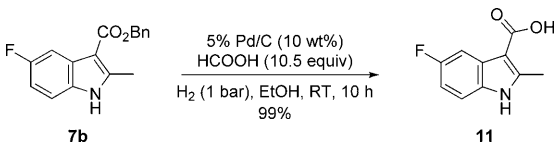
N-Aryl enamine carboxylates tend to react with electrophiles at the α-C atom;[22] similar reactivity was also reported recently for a palladium-catalyzed coupling of enaminones with aryl borates.[23] Therefore, a plausible mechanism begins with an electrophilic palladation of the nucleophilic enamine,[24] followed by deprotonation (Scheme 7). The resulting palladium complex **A** is suitable for intramolecular C–H activation, such as σ-bond metathesis[25] or base-assisted deprotonation.[26] Subsequent reductive elimination generates the indole product and a Pd^0 complex that can be reoxidized to the Pd^{II} complex by the terminal oxidant $Cu(OAc)_2$.

Furthermore, deprotection of the benzyl ester of **7b** proceeds under mild hydrogenolytic conditions to provide the free carboxylic acid in excellent yield (Scheme 8).

To further demonstrate the synthetic utility of the indole products, we carried out decarboxylation reactions with **2h**

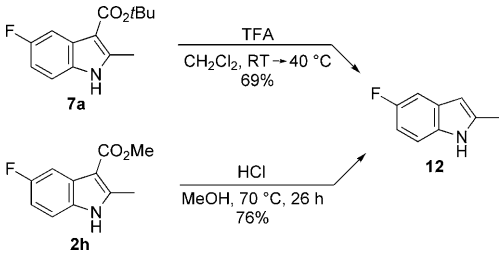


Scheme 7. Mechanism for palladium-catalyzed indole synthesis from enaminone.



Scheme 8. Synthesis of indole-derived free acid.

and **7b** to give 3-unsubstituted indole **12** (Scheme 9), which is a very valuable building block for medicinal chemistry and natural-product synthesis.[2,3] This further functional group modification shows the potential application of this method.



Scheme 9. Synthesis of 3-unsubstituted indole. TFA = trifluoroacetic acid.

Conclusion

We have developed an efficient and broadly applicable direct oxidative synthesis of indoles from commercially available anilines. This concept is broadly applicable in different systems towards the synthesis of 2,3-disubstituted indoles. In the aftermath of our communication,[11] this strategy was skillfully utilized by the groups of Jiao, Zhao, Cacchi, and Liang.[27] Their reported methods represent attractive indole formations with attractive features, such as using no toxic Pd catalyst or utilizing oxygen as the terminal oxidant.[27] All these studies provide new or improved synthetic routes to valuable indoles and new preparative applications for biologically active indole-based molecules. Furthermore, a one-pot reaction sequence enables rapid access to indoles from commercially available anilines.

Experimental Section

General procedure: Methyl (*Z*)-3-(phenylamino)-but-2-enoate (**1a**; 191 mg, 1 mmol) was stirred in DMF (12 mL) together with $Pd(OAc)_2$ (22.5 mg, 10 mol%), $Cu(OAc)_2$ (545 mg, 3 mmol), and K_2CO_3 (415 mg, 3 mmol) at 80 °C under an atmosphere of argon. After completion of the reaction (as indicated by TLC, GC, or GCMS), the reaction mixture was cooled to room temperature, diluted with EtOAc (15 mL), and filtered through a short pad of silica, which was then washed with EtOAc (60 mL). Removal of the solvent in vacuo and purification of the residue by flash chromatography (SiO_2, pentane/EtOAc 5:1) provided indole **2a** (136 mg, 0.72 mmol, 72%) as an orange solid.

Acknowledgements

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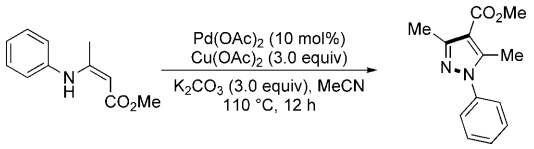

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