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Palladium-Catalyzed Direct Arylation of Indoles with Cyclohexanones

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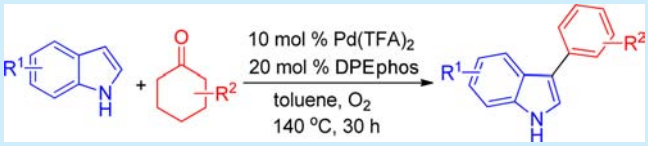
Supporting Information

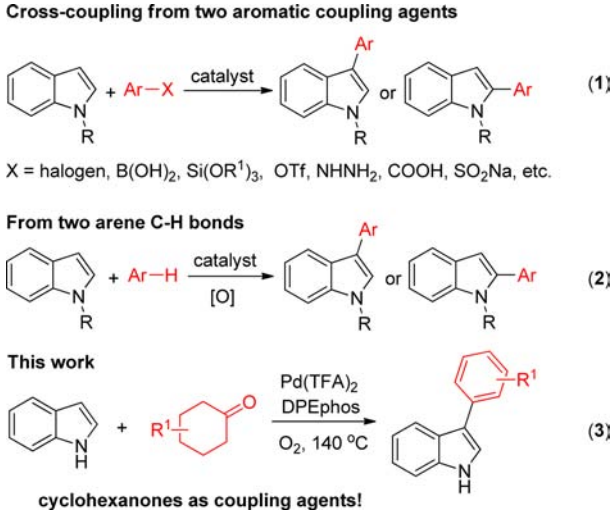
ABSTRACT: A novel palladium catalyzed approach to 3-arylindoles was developed from indoles and cyclohexanones. Various cyclohexanones acted as aryl sources via an alkylation and dehydrogenation sequence using molecular oxygen as the hydrogen acceptor. This method showed good regioselectivity and afforded 3-arylindoles as the sole products.



Indole and its derivatives are frequently found in natural products, functional materials, agrochemicals, and pharmaceuticals.[1] Among them, C-arylated indoles show great potential in pharmaceuticals, especially as anticancer drugs.[2] Since its discovery in 1869, great efforts have been made to develop efficient synthetic methodologies for the preparation and further functionalization of indole.[3] Recently, much focus has been devoted to the transition-metal-catalyzed direct arylation of indoles with activated arenes. This strategy avoids the prefunctionalization of indole derivatives and thus can potentially provide an efficient synthetic route to rapidly construct various biaryls containing an indole nucleus.[4] Aryl halides were the most commonly used coupling partners for direct C-arylation of indole derivatives promoted by transition-metal catalysts.[5] Apart from aryl halides, various aromatic coupling partners, including organoboranes,[6] aromatic hypervalent iodine chemicals,[7] arylsiloxanes,[8] arylhydrazines,[9] aryltriflates,[10] aromatic carboxylic acids,[11] and sodium sulfinates[12] have been successfully employed as arylation agents (Scheme 1, eq 1). More recently, nonactivated arenes were also used as coupling partners for arylated indole preparation via a cross-dehydrogenative-coupling (CDC) reaction under oxidative reaction conditions (Scheme 1, eq 2).[13,14] The CDC reaction avoids the prefunctionalization of both coupling partners and thus affords the most direct approach for the preparation of arylindoles. However, this method is mainly suitable for nonsubstituted or symmetrical substituted arenes.

However, all of the above-mentioned approaches require two aromatic coupling partners. The direct arylation of heteroarenes with readily available and cheap nonaromatic coupling partners is very rare. Cyclohexanone is cheap, readily available, and facile to convert into other important organic materials such as hexanedioic acid, which is an important precursor for the production of nylon.[15] Cyclohexanone also could be used as an alkylation reagent for indoles in trichloroacetic acid using triethylsilane as a reductant, selectively affording 3-cyclohexylindole in good yield.[16] Recently, the Stahl group found that

Scheme 1. Various Methods for C-Arylindoles



these compounds could be dehydrogenated under palladium catalyzed reaction conditions to afford the corresponding phenols or cyclohexenones using molecular oxygen as a hydrogen acceptor.[17] We and others successfully used cyclohexanones as aryl sources for C−C and C−heteroatom bond formation.[18] Similarly, phenothiazines could be prepared from cyclohexanones and 2-aminobenzenethiols via condensation−tautomerization reactions in the absence of transition metals.[19] We and others also developed methods for 2-arylsulfanylphenol formation from thiols and cyclohexanones using a catalytic amount of iodine as the catalyst under metal-free conditions.[20] In this transformation, cyclohexanones acted as phenol sources. It would be attractive and challenging to use cyclohexanones as aryl sources to prepare biaryls containing an indole moiety via

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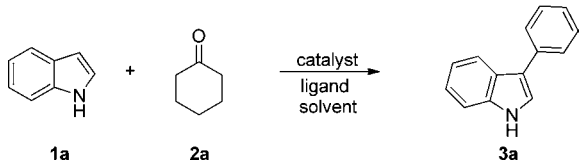
direct arylation of free indole C(sp^2)−H bonds. Herein, we describe a palladium-catalyzed 3-arylindole formation from cyclohexanones and free indoles using oxygen as the hydrogen acceptor (Scheme 1, eq 3).

Initially, we examined the reaction of indole (**1a**) and cyclohexanone (**2a**) in toluene under an oxygen atmosphere. No arylated indole product was observed when the reaction was carried out at 140 °C using 5 mol % $PdCl_2$ as the catalyst as determined by GC analysis (Table 1, entry 1). Under these

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a**

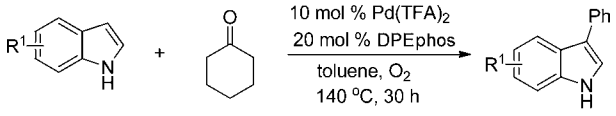
entry	catalyst	ligand	solvent	temp (°C)	yield[b] (%)
1	$PdCl_2$		toluene	140	trace
2	$PdBr_2$		toluene	140	trace
3	$Pd(COD)Cl_2$		toluene	140	trace
4	$Pd(acac)_2$		toluene	140	3
5	$Pd(OAc)_2$		toluene	140	5
6	$Pd(TFA)_2$		toluene	140	32
7	$Pd(TFA)_2$	1,10-phen	toluene	140	11
8	$Pd(TFA)_2$	DMAP	toluene	140	15
9	$Pd(TFA)_2$	PPh_3	toluene	140	38
10	$Pd(TFA)_2$	X-phos	toluene	140	28
11	$Pd(TFA)_2$	DPEphos	toluene	140	45
12	$Pd(TFA)_2$	DPEphos	*p*-xylene	140	23
13	$Pd(TFA)_2$	DPEphos	mesitylene	140	12
14	$Pd(TFA)_2$	DPEphos	NMP	140	0
15	$Pd(TFA)_2$	DPEphos	toluene	140	56
16[c]	$Pd(TFA)_2$	DPEphos	toluene	140	66
17[c]	$Pd(TFA)_2$	DPEphos	toluene	130	58
18[c,d]	$Pd(TFA)_2$	DPEphos	toluene	140	85
19[c,e]	$Pd(TFA)_2$	DPEphos	toluene	140	5

[a]Conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (5 mol %), ligand (5 mol %) solvent (2.0 mL), 24 h, under oxygen unless otherwise noted. For entries 15−19, 0.75 mmol of **2a** was used. [b]GC yield based on **2a** using dodecane as internal standard. [c]10 mol % catalyst and 20 mol % ligand were used. [d]30 h. [e]Under argon.

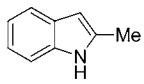
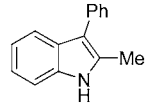
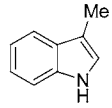
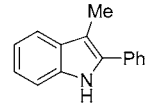
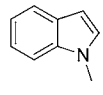
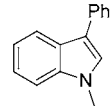
conditions, several other palladium salts were screened in the absence of any ligand and proved to be ineffective for this type of arylation reaction (entries 2−5). Fortunately, the expected product 3-phenylindole (**3a**) was detected in 32% yield when $Pd(TFA)_2$ was used as the catalyst (entry 6). Various ligands were then screened in the presence of $Pd(TFA)_2$ (entries 7−11). Nitrogen-containing ligands such as 1,10-phenanthroline and DMAP (4-dimethylaminopyridine) were ineffective, and their use resulted in lower yields (entries 7 and 8). Among the phosphine ligands investigated, DPEphos ((bis{2-diphenylphosphino}phenyl)ether) exhibited the best reactivity, and **3a** could be formed in 45% yield (entry 11). The choice of solvent was pivotal, and the use of other solvents such as *p*-xylene, mesitylene and NMP all resulted in lower yields (entries 12−14). Increasing the catalyst and ligand loading increased the reaction yield while decreasing the reaction temperature decreased the reaction yield (entries 16 and 17). The reaction yield could be further improved to 85% when the reaction time was prolonged to 30 h (entry 18). Oxygen acted as an efficient hydrogen acceptor, and replacement of it with inert argon significantly decreased the reaction yield to 5% (entry 19).

Based on the optimized conditions, various indoles with substituents were screened to explore the scope and generality of this reaction (Table 2). The reaction was found to be

Table 2. Reaction of Various Indoles with 2a[a]



1 **2a** **3**

entry	indole		product		yield[b] (%)
1	R^1 = H	**1a**	**3a**		72
2	R^1 = 4-Me	**1b**	**3b**		81
3	R^1 = 7-Me	**1c**	**3c**		64
4	R^1 = 5-MeO	**1d**	**3d**		53
5	R^1 = 4-F	**1e**	**3e**		68
6	R^1 = 5-F	**1f**	**3f**		71
7	R^1 = 6-F	**1g**	**3g**		67
8	R^1 = 5-Cl	**1h**	**3h**		21
9	R^1 = 5-Br	**1i**	**3i**		trace
10	R^1 = 5-CN	**1j**	**3j**		70
11	R^1 = 6-CO_2Me	**1k**	**3k**		72
12		**1l**		**3l**	68
13		**1m**		**3m**	0
14		**1n**		**3n**	74

[a]Conditions: **1** (0.75 mmol), **2a** (0.5 mmol), $Pd(TFA)_2$ (0.05 mmol), DPEphos (0.1 mmol), toluene (2.0 mL), 140 °C, 30 h, under oxygen. [b]Isolated yield based on **2a**.

general, giving the desired 3-phenylindoles (**3**) in reasonable yields and excellent selectivity. Common functional substituents were compatible with the optimized conditions. The substituent position significantly affected the reaction yield, and the reaction yield decreased from 81% to 64% when the methyl substituent shifted from C-4 to C-7 (entries 2 and 3). Similar phenomena were observed when a fluoro substituent was located at a different position of indole (entries 5 and 6). No desired product could be obtained when a bromo substituent was presented in the indole moiety due to the cleavage of the carbon−bromo bond (entry 9). Active functional groups such as cyano and ester were well tolerated, and the C-arylation products **3j** and **3k** were obtained in 70% and 72% yields, respectively (entries 10 and 11). The reaction did not show much difference when a hindered methyl substituent was located at the C-2 position of indole, and the C-3 arylated product **3l** was isolated in 68% yield (entry 12). In all cases, the reaction showed very good selectivity and no 2-phenylindole or

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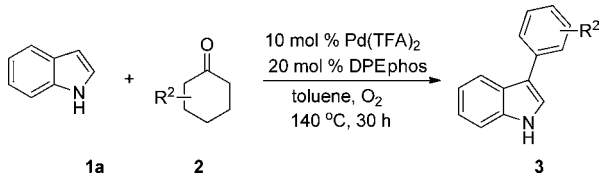
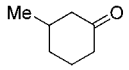
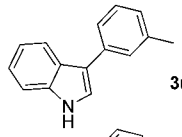
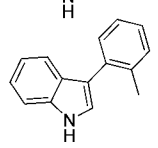
N-arylated byproducts were observed. When the C-3 position was occupied by a methyl group, no coupled product could be observed (entry 13). Protected 1-methylindole (**1n**) also could be employed for this reaction and gave 1-methyl-3-phenylindole (**3n**) in 74% yield (entry 14).

The scope of the reaction with cyclohexanones is outlined in Table 3. Cyclohexanones bearing alkyl substituents at the para

Table 3. Reaction of 1a with Various Cyclohexanones[a]



1a 2 3

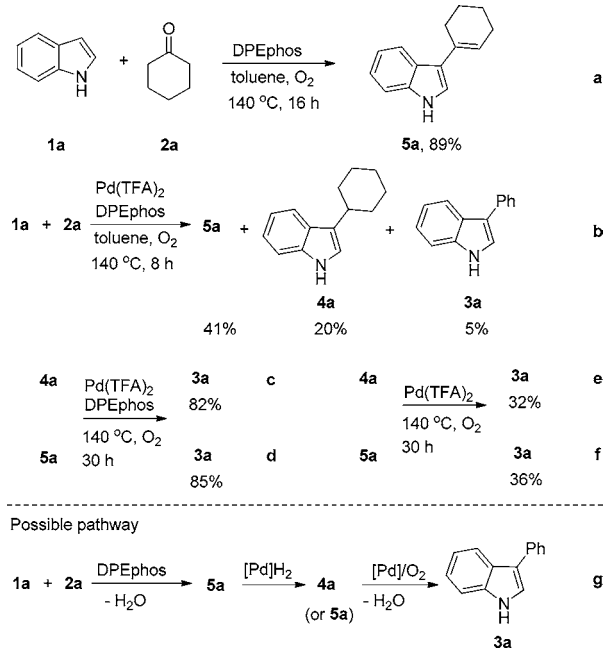
entry	cyclohexanone	product	yield[b] (%)
1	R^2 = Me	**2b** **3o**	66
2	R^2 = Et	**2c** **3p**	71
3	R^2 = *n*-pentyl	**2d** **3q**	55
4	R^2 = *tert*-pentyl	**2e** **3r**	71
5	R^2 = Ph	**2f** **3s**	63
6	R^2 = CO_2Et	**2g** **3t**	77
7		**2h**  **3u**	72
8		**2i**  **3v**	trace

[a]Conditions: **1a** (0.75 mmol), **2** (0.5 mmol), $Pd(TFA)_2$ (0.05 mmol), DPEphos (0.1 mmol), toluene (2.0 mL), 140 °C, 30 h, under oxygen. [b]Isolated yield based on **2**.

position were able to smoothly couple with **1a** to give the corresponding biaryls in good yields (entries 2−4). When 4-phenylcyclohexanone (**2f**) was employed to react with **1a**, product **3s** was obtained in 63% yield (entry 5). To our delight, the ester functional group was well tolerated in this reaction, and the corresponding arylated product was obtained in 77% yield (entry 6). The substituent position in cyclohexanone significantly affected the reaction yield. When 3-methylcyclohexanone (**2h**) was used, 3-(*m*-tolyl)-1*H*-indole (**3u**) was obtained in 72% yield (entry 9). However, no desired product **3v** could be isolated when 2-methylcyclohexanone (**2i**) was used as a coupling partner (entry 8).

To gather more information about the reaction mechanism, some control experiments were carried out under different conditions (Scheme 2). An intermediate **5a** (determined by GC-MS, not isolable) was observed in 89% GC yield when the reaction of indole (**1a**) and cyclohexanone (**2a**) was carried out in the absence of $Pd(TFA)_2$ (Scheme 2a). DPEphos played an important role in this transformation, and only a trace amount of **5a** was observed in the absence of it. When the reaction was stopped after 8 h using $Pd(TFA)_2$/DPEphos as the catalyst, **5a**

Scheme 2. Control Experiments and Possible Pathway



could be smoothly transferred into stable 3-cyclohexylindole (**4a**) using the hydrogen generated from the cyclohexanone dehydrogenation step (Scheme 2b). Further treatment of **5a** or **4a** with the standard conditions afforded the corresponding product **3a** in 85% and 82% yields, respectively (Scheme 2c and d). However, treatment of **5a** and **4a** in the absence of DPEphos only gave the target product **3a** in 36% and 32% yields, respectively (Scheme 2e and f). Both $Pd(TFA)_2$ and DPEphos were necessary to give the final biaryl product in a satisfactory yield. Although we could not trap more important intermediates between the starting material and the final product to elucidate the exact reaction mechanism, the first step should be the direct alkylation of indole under neutral conditions. The second step should be the dehydrogenation of alkylated intermediates (**4a** or **5a**) using oxygen as the hydrogen acceptor (Scheme 2g). It is very interesting that DPEphos could significantly improve the direct alkylation of indole with cyclohexanone under neutral conditions (Scheme 2a), which is usually carried out under acidic conditions.[16,21,22]

In summary, we have developed a novel approach for the synthesis of 3-arylindoles using cyclohexanones as the aryl source. The palladium-catalyzed coupling reaction of cyclohexanones with an indole $C(sp^2)$−H bond and subsequent dehydrogenation−tautomerization reactions were realized in one pot. Molecular oxygen was used as an efficient hydrogen acceptor in this transformation. The reaction showed good selectivity, and no 2-arylindole byproduct was observed. Since cyclohexanones are readily available starting materials, this method can afford an efficient and environmentally benign approach for the preparation of biaryls and other arylated heteroarenes. The generality, exact reaction mechanism, and synthetic applications of this methodology are under investigation.

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■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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