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Direct Access to Acylated Azobenzenes via Pd-Catalyzed C−H Functionalization and Further Transformation into an Indazole Backbone

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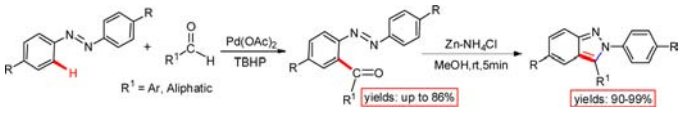
ABSTRACT



Azobenzenes were readily acylated at the 2-position through a Pd-catalyzed C−H functionalization from simple aromatic azo compounds and aldehydes in good yields. The obtained acylated azobenzenes could be efficiently converted into the corresponding indazole derivatives in nearly quantitative yields.

In the past decades, the emergence of transition-metal-catalyzed C−H activation dramatically shortened the pathway to the construction of C−C and C−heteroatom bonds, which led to much more efficient protocols for the desired substances.[1] A salient feature of the C−H activation strategy is not requiring stoichiometric organometallic reagents, and it has been widely used in organic synthesis.[1a,2] Undoubtedly, significant progress has been achieved in catalytic C−H activation and subsequent functionalization.[3] Generally, most of the developed approaches to regioselective C−H activation often involve using substrates containing heteroatoms as directing groups and direct oxidation to a specific C−H bond within molecules.[4] Hence, the suitable combination of transition metals and directing groups is key to realizing C−H activation and its further transformation. From recent elegant work on functional group-directed C−H activation, a variety of directing groups, such as pyridines, amides, oximes, alcohols, amines, carboxylic acids, esters, aldehydes, ketones, nitriles, and triazenes, have been developed for *ortho*-selective C−H activations and functionalizations.[5] To our knowledge, the azo group with a

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N−N double bond, as a directing group, is rarely studied in the C−H activation process.[6]

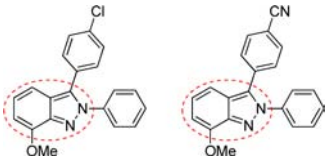

Figure 1. Representative biologically active indazoles as liver X receptor agonist.[13b]

Aromatic azo compounds have been extensively investigated for their photochromic properties, which were widely used as a light triggered switch in surface-modified materials,[7] polymers,[8] molecular machines,[9] and protein probes.[10] Additionally, azobenzene also frequently appears in food additives, industrial dyes, and nonlinear optical devices.[11] To date, many methodologies have been established for the synthesis of azobenzene and its derivatives, such as the coupling of diazo salts with aromatic compounds, the reduction of nitro compounds by reducing agents, the transition-metal-catalyzed aerobic oxidative dehydrogenation of aryl amines, etc.[12] However, the above-mentioned methodologies usually suffer from a narrow substrate scope and complex byproducts. Especially, it is worth noting that synthesis of the steric *ortho*-substituted azo compounds and their further transformations are often ignored. To make up for this deficiency, a transition metal-catalyzed C−H functionlization strategy with one-step transformation and simple operation is highly desirable.

It is well-known that indazole usually bears a benzo five-membered heterocycle unit, which has been broadly studied for its unique biological activity in medicinal chemistry (Figure 1).[13] Pursuing our interests in C−H activation,[14] herein we first report a novel approach to the acylated azobenzenes through Pd-catalyzed acylation of azobenzenes with aldehydes via azo-directed C−H activation. It is important to note that the obtained acylated azobenzenes can easily be converted into the corresponding indazoles via an intramolecular reductive cyclization process in nearly quantitative yields.

Our initial studies focused on the model reaction of azobenzene (**1a**) and benzaldehyde (**2a**). The optimization of a Pd source and oxidant are summarized in Table 1. Considering the stability of **1a**, freshly distilled 1,2-dichloroethane (DCE) and dried *tert*-butyl hydroperoxide (TBHP) were necessary in the model reaction. We found that the combination of azobenzene (**1a**, 1.0 equiv) with benzaldehyde (**2a**, 1.1 equiv), TBHP (2.0 equiv), and Pd-$(PPh_3)_2Cl_2$ (5.0 mol %) in DCE at 80 °C for 12 h generated the acylated product **3a** in 26% yield (Table 1, entry 1). However, $Pd(PPh_3)_4$ did not work in the model reaction (Table 1, entry 2). When $PdCl_2$ was used as the catalyst in the reaction, **3a** was obtained in 42% yield (Table 1, entry 3). Meanwhile, acylation also proceeded in comparable yield and efficiency in the presence of $Pd(CH_3CN)_2Cl_2$ (Table 1, entry 4 vs 3). As expected, $Pd(OCOCF_3)_2$ gave **3a** in 69% yield (Table 1, entry 5). Gratifyingly, $Pd(OAc)_2$ showed excellent activity among the tested Pd sources (Table 1, entry 6). Further exploration of some commercially available oxidants in the model reaction indicated that dried TBHP was superior to the others, as also shown in Table 1. When TBHP (70% in H_2O) was used, **3a** was isolated in 56% yield (Table 1, entry 7). It is likely that the existing H_2O may be responsible for the partial decomposition of azobenzene, leading to the lower yield of **3a**. Other oxidants, such as α,α-dimethylbenzyl hydroperoxide (DBHP), di-*tert*-butyl peroxide (DTBP), dicumyl peroxide (DCP), 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), and *tert*-butyl perbenzoate (TBPB), generated the desired product **3a** in 23−66% yields (Table 1, entries 8−12). It is noteworthy to mention that inorganic oxidant $(NH_4)_2S_2O_8$

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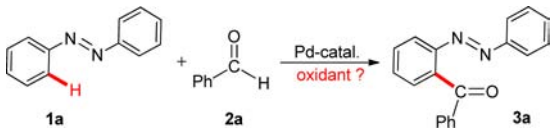
Table 1. Optimization of Pd Source and Oxidant[a]



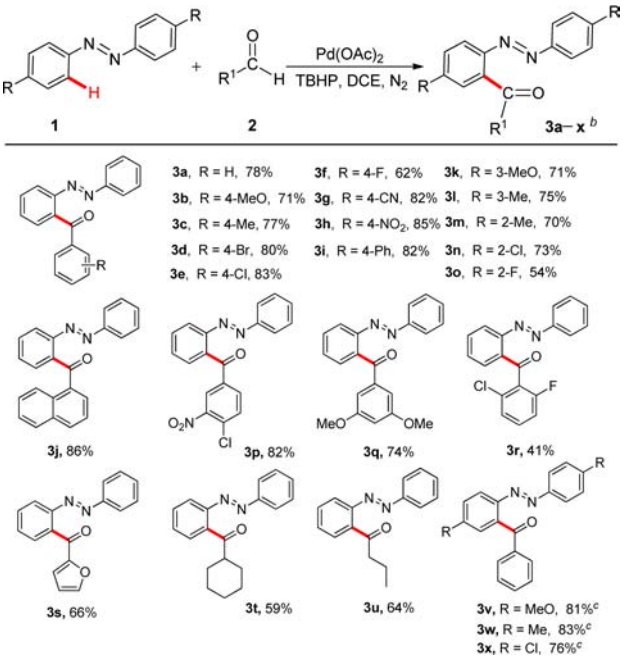
entry	Pd source	oxidant	yield (%)[b]
1	$Pd(PPh_3)_2Cl_2$	TBHP	26
2	$Pd(PPh_3)_4$	TBHP	0
3	$PdCl_2$	TBHP	42
4	$Pd(CH_3CN)_2Cl_2$	TBHP	46
5	$Pd(OCOCF_3)_2$	TBHP	69
6	$Pd(OAc)_2$	TBHP	78
7	$Pd(OAc)_2$	TBHP	56[c]
8	$Pd(OAc)_2$	DBHP	66
9	$Pd(OAc)_2$	DTBP	30
10	$Pd(OAc)_2$	DCP	43
11	$Pd(OAc)_2$	DDQ	23
12	$Pd(OAc)_2$	TBPB	57
13	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	0

[a] Reaction conditions: azobenzene (**1a**, 0.20 mmol), benzaldehyde (**2a**, 0.22 mmol), Pd source (5.0 mol %), TBHP (0.40 mmol) dried over 4 Å MS prior to use, DCE (1.0 mL), 80 °C, sealed tube, N_2, 12 h. [b] Isolated yields. [c] TBHP (70% in H_2O).

was ineffective in the reaction (Table 1, entry 13). In addition, the solvent also played an important role and the results demonstrated that DCE was the best reaction medium among the solvents tested in the model reaction (see Table S1, Supporting Information).

Based on the optimized reaction conditions, the scope of the oxidative acylation of azobenzenes was examined. As can be seen from Scheme 1, the reactions of azobenzenes with various aldehydes could proceed well and generate the desired acylated products in good yields. A wide range of aromatic aldehydes bearing substituents on the benzene rings were investigated. The results demonstrated that both electron- and electron-withdrawing groups were tolerated in the acylation reactions. The *para*-substituted benzaldehydes with electron-donating groups, such as MeO and Me, reacted with azobenzene smoothly and afforded the corresponding acylated products **3b** and **3c** in 71 and 77% yields respectively. Meanwhile, with the exception of F, electron-withdrawing groups such as Br, Cl, CN, and NO_2 also reacted with azobenzene well and generated **3d**, **3e**, **3g**, and **3h** in 80−85% yields. When [1,1′-biphenyl]-4-carbaldehyde and 1-naphthaldehyde were used to couple with azobenzene, **3i** and **3j** were obtained in 82 and 86% yields respectively. A slight steric effect was observed when *meta*- and *ortho*-substitued benzaldehydes (**2l** and **2m** vs **2c**, **2n** vs **2e**, and **2o** vs **2f**) as coupling reagents reacted with azobenzene, and inferior yields of the products **3k**−**o** were obtained. Similarly, disubstituted benzaldehydes including 4-chloro-3-nitrobenzaldehyde (**2p**), 3,5-dimethoxybenzaldehyde (**2q**), and 2-chloro-6-fluorobenzaldehyde(**2r**) also coupled with azobenzene smoothly to afford the acylated product **3p**, **3q**, and **3r** in 82, 74, and 41% yields, respectively.

Scheme 1. Scope of the Acylation of Azobenzenes with Aldehydes[a]

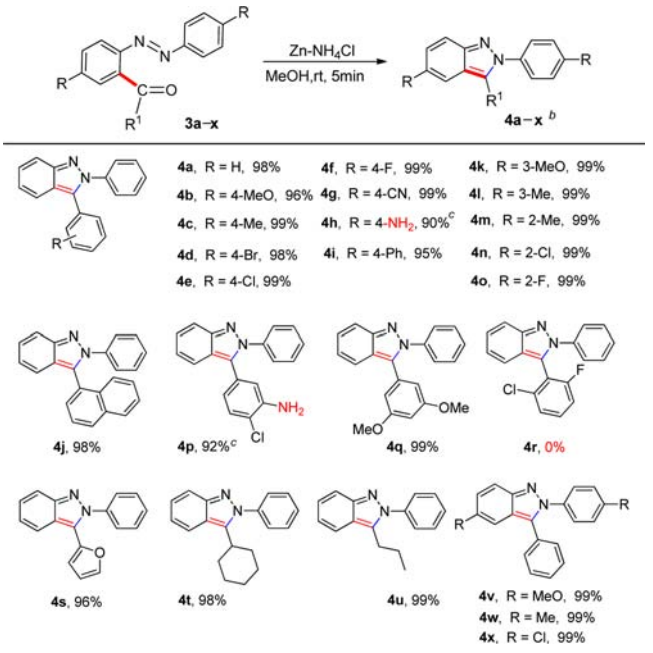


[a] Reaction conditions: azobenzene (**1**, 0.20 mmol), aldehyde (**2**, 0.22 mmol), $Pd(OAc)_2$ (5.0 mol %), TBHP (0.40 mmol, dried over 4 Å MS prior to use), DCE (1.0 mL), 80 °C, sealed tube, N_2, 12 h. [b] Isolated yields. [c] 18 h.

When azobenzene was treated with furaldehyde (**2s**) under the present reaction conditions, **3s** was isolated in 66% yield. Pleasingly, aliphatic aldehydes, for example cyclohexanecarbaldehyde and *n*-butyraldehyde, also reacted with azobenzene to generate the corresponding products **3t** and **3u** in 59 and 64% yields. In order to expand the scope of azobenzenes, three representative 4,4′-disubstituted azobenzenes, 4,4′-dimethoxyazobenzene (**1b**), 4,4′-dimethylazobenzene (**1c**), and 4,4′-dichloroazobenzene (**1d**) were surveyed. It was found that the oxidative acylation reactions of **1b**, **1c**, and **1d** with benzaldehyde were clean and gave the corresponding **3v**, **3w**, and **3x** in 81, 83, and 76% yields, respectively.

With the obtained acylated azobenzenes (**3a**−**x**) in hand, their further transformation into important substances is desirable. Having the unique biological activity of indazoles in mind, we tried to construct the backbone of indazole using acylated azobenzenes as starting materials. To our delight, most of them (**3a**−**q** and **3s**−**x**) could be efficiently transformed into the indazoles (**4a**−**q** and **4s**−**x**) through a Zn/NH_4Cl/MeOH reducing system at rt within 5 min in nearly quantitative yields (results listed in Scheme 2). It should be noted that although the nitro group on the benzene ring remarkably influenced the transformation, excellent yields of **4h** and **4p** were also obtained in the mixed solvent MeOH/DCM (3:1) along with the reduction of NO_2 into NH_2. However, the more steric acylated azobenzene **3r** could not be transformed into the corresponding product **4r**. Compared to the

Scheme 2. Synthesis of Indazoles from Acylated Azobenzenes[a]

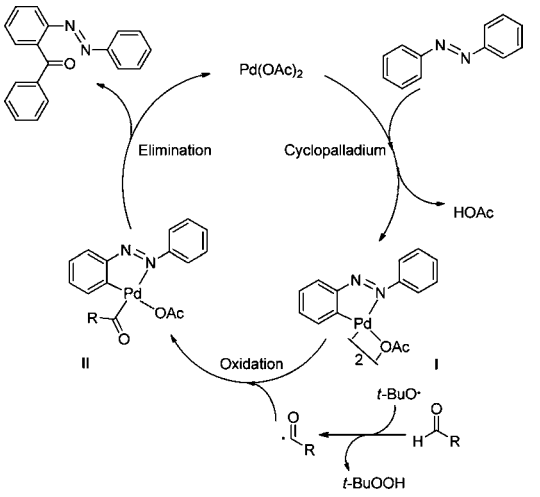


[a] Reaction conditions: acylated azobenzenes (**3**, 0.20 mmol), zinc dust (0.40 mmol), NH_4Cl (0.60 mmol), CH_3OH (0.50 mL), room temperature, 5 min. [b] Isolated yields. [c] MeOH/DCM (3:1, v/v), 50 °C, 6 h.

well-established method for the synthesis of indazole derivatives,[15] this transformation is more efficient and economical.

A possible mechanism for the Pd-catalyzed C−H functionalization is proposed in Scheme 3. Initially, a five-membered cyclopalladated intermediate **I** was generated through chelate-directed C−H activation of azobenzene. In fact, a similar metalocycle was obtained through the use of a coordinating group that helps direct the subsequent transition-metal C−H bond insertion.[6b,16] In contrast, the reaction of benzaldehyde with TBHP generated a reactive benzoyl radical, which next reacted with intermediate **I** to realize the oxidation of Pd(II) to dimeric Pd(III) or Pd(IV) **II**.[17] Finally, the Pd(II) species was regenerated through

Scheme 3. Proposed Reaction Mechanism



the reductive elimination of **II**, with the release of the acylated product. In the presence of a radical scavenger, TEMPO (2,2,6,6-tetramethyl-piperidyl-1-oxyl) up to 1.0 equiv, no acylated product was observed.[18]

In conclusion, we have developed a novel and simple Pd-catalyzed protocol for the synthesis of acylated azobenzenes from aromatic azo compounds and aldehydes via an azo-directed C−H bond activation process and with TBHP as an oxidant. The obtained acylated azobenzenes can be efficiently transformed into the corresponding indazoles through a $Zn/NH_4Cl/MeOH$ reduction at rt within 5 min in nearly quantitative yields in most cases. Further investigations into the photochromic properties, scope, and synthetic application of these azobenzene derivatives are now in progress.

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Supporting Information Available. Analytical data and spectra (^1H and ^{13}C NMR) for all the products; typical procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.