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Palladium-Catalyzed sp^2 and sp^3 C−H Bond Activation and Addition to Isatin toward 3-Hydroxy-2-oxindoles

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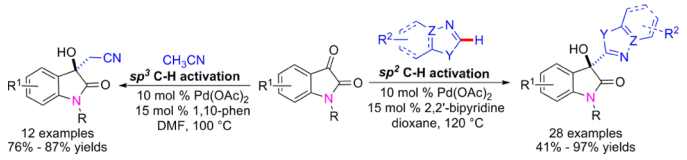
ABSTRACT



The first Pd(II)-catalyzed C−H addition to isatins by direct sp^2/sp^3 C−H bond activation for the construction of 3-substituted-3-hydroxy-2-oxindoles is reported. The bidentate nitrogen ligands were found to promote this reaction. Specifically, the preliminary bioassay indicated that 3-(5-chlorobenzoxazole)-3-hydroxy-*N*-benzyl-2-oxindole (2w) is a new inhibitor of human kidney cancer and hepatocellular carcinoma cells. Moreover, this reaction system exhibits great functional group tolerance and requires no directing group, extra base, or additives.

Very recently, nucleophilic addition to imine or carbonyl via transition-metal-catalyzed direct C−H bond activation provides a concise and highly efficient pathway to synthesize amines and alcohols.[1] Over the past several years, spectacular progress has been achieved by many groups, independently realizing direct C−H addition to aldehydes and imines with different aromatic compounds by using different transition metal catalysts such as Pd, Ir, Mn, Re, and Rh to promote C−H activation at the metal center.[2,3] Nevertheless, extending this protocol to nucleophilic addition to the carbonyl of ketones is still a formidable challenge and has been rarely reported until now.[4] Moreover, all these groundbreaking methods of C−H addition to carbonyls generally require a directing group or need to

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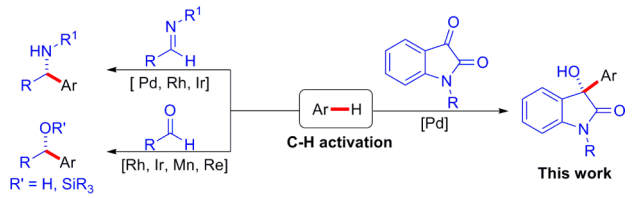
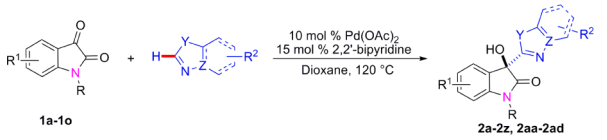
activate the aldehydes beforehand through the addition of nucleophilic reagents, and special additives are often required. Therefore, further development for a simple and convenient catalytic system is highly desired. Herein we demonstrate the first example of Pd-catalyzed intermolecular C−H addition to isatins by direct sp^2/sp^3 C−H activation for the construction of 3-substituted-3-hydroxy-2-oxindoles (Scheme 1). Thereinto, 3-azole-3-hydroxy-2-oxindoles are a kind of new structural heterocycle, which have the potential to act as maxi-K channel openers or in the modulation of human neuronal sodium channel isoform (hNa_v) 1.2 currents and hippocampal neuron action potential firing.[5] Additionally, in contrast to other C−H additions to carbonyls that have been reported, our protocol requires no directing group, extra base, or additives. The bidentate nitrogen ligands were found to significantly promote this reaction.

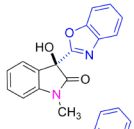
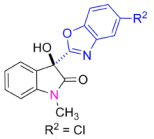
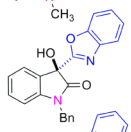
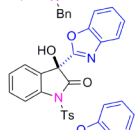
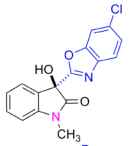
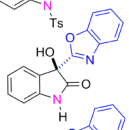
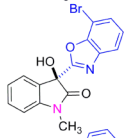
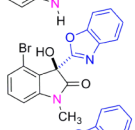
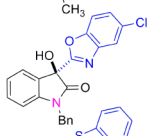
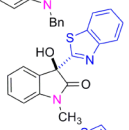
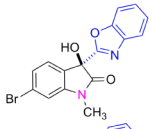
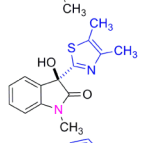
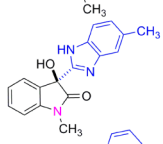
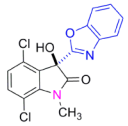
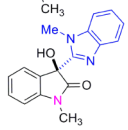
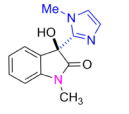
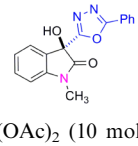
Scheme 1. Transition-Metal-Catalyzed C−H Addition to Unsaturated Compounds



We began our exploration with *N*-methylisatin **1a** and benzoxazole as model substrates to identify suitable reaction conditions because isatins are activated electrophilic species and its two carbonyls are easier to coordinate with transition metals leading to nucleophilic addition.[6] Notably various 3-substituted-3-hydroxy-2-oxindole scaffolds are well-known for their significant biological applications and wide-ranging utility as drug candidates and pharmaceuticals.[7] Furthermore, transition-metal-catalyzed direct

Table 1. Nucleopilic Addition Different Isatins and Heteroarenes[a]



entry	products	yield (%)[b]	entry	products	yield (%)[b]
2a		92%			
2b		76%	2p	R^2 = Cl	97%
			2q	R^2 = Br	84%
			2r	R^2 = CH_3	91%
			2s	R^2 = *t*-Bu	76%
			2t	R^2 = NO_2	77%
2c		0%	2u		95%
2d		41%[c]	2v		83%
2e		95%	2w		76%
2f	R^1 = F	92%	2x		52%[d]
2g	R^1 = Cl	90%			
2h	R^1 = Br	86%			
2i	R^1 = CH_3	93%			
2j	R^1 = OMe	81%			
2k	R^1 = NO_2	79%			
2l		83%	2y		71%[d]
			2z		45%[d]
2m	R^1 = Cl	92%	2aa		44%
2n	R^1 = CF_3	78%			
2o		94%	2ab		80%
2ac		76%	2ad		92%

[a] The reaction was carried out with $Pd(OAc)_2$ (10 mol %), Bipy (15 mol %), and **1a**−**1o** (0.30 mmol) in dioxane (1.0 mL) at 120 °C for 24 h under argon. [b] Isolated yield. [c] Solvent is DMF, 140 °C. [d] Heteroarenes in 10 equiv.

C−H functionalization of azoles also provided a rapid, straightforward access to different aryl-heteroaryl motifs.[8,9] Here, we wished to extend this protocol to the nucleophilic addition to the carbonyl of *N*-methylisatin **1a** and access 3-azole-3-hydroxy-2-oxindoles. From our endeavors,

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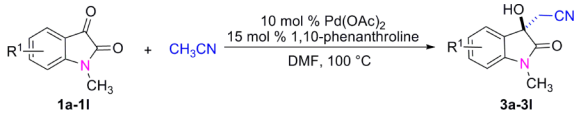
the new protocol of palladium-catalyzed intermolecular C−H addition to isatins by direct sp^2 C−H activation was built and the optimal reaction conditions were obtained by using $Pd(OAc)_2$ (10 mol %) as the catalyst, 2,2′-bipyridine (15 mol %) as the ligand in 1 mL of dioxane for 0.3 mmol of **1a**, and 4 equiv of benzoxazole at 120 °C under an argon atmosphere (for details, see Table S1 in Supporting Information (SI)).

Having established optimal reaction conditions (Table S1, entry 18), we further investigated the scope of isatins and heteroarenes. As shown in Table 1, an investigation into different *N*-protection groups revealed that methyl and benzyl were appropriate for the reaction (**2a**−**2b**), but tosyl failed (**2c**). When the solvent was changed to DMF, the N-free isatin has been converted into the desired product **2d** in 41% yield. Various substituted *N*-methylisatins worked very well, and the corresponding products were obtained in good to excellent yields regardless of the steric hindrance and electronic properties of the substituents (**2e**−**2o**). To our delight, different substituted benzoxazoles also underwent nucleophilic addition smoothly and readily converted to the products in 76−97% yields (**2p**−**2v**). Moreover, the *N*-benzyl protected isatin reacted with 5-Cl-benzoxazole to afford the product **2w** in 76% yield. The reaction conditions displayed noteworthy tolerance to the nitro group such that the desired products **2k** and **2t** were afforded in 79% and 77% yields. Yet, other azoles such as imidazole, benzothiazole, 2-phenyl-1,3,4-oxadiazole, and their derivatives were also compatible with this transformation, and the corresponding products were obtained in moderate to excellent yields (**2x**−**2ad**). It should be noted that the product **2z** was only afforded in a 45% yield, presumably because the methyl group played a negative role in C−H bond activation.

As new structural heterocycles, these acquired 3-azole-3-hydroxy-2-oxindoles may possess antitumor potential on the cellular level. The results of the preliminary biological activity assay indicate that some of products do in fact possess antitumor activity. Encouraged by this result, we further evaluated the antitumor activity by using the kidney cancer cell of A498 and human hepatocellular carcinoma cell line SMMC-7721 (Figure S1 in SI).[10] The results showed that the *N*-protection groups of benzyl and the substituent group on the benzoxazole were the key to the improvement of antitumor activity, and **2w** yielded the lowest IC_{50} value of 42 and 45 μM. Thus, from a diverse array of structural modification and deprotection assays, we were convinced that the activity of **2w** would improve and that we would locate the antihuman kidney cancer and hepatocellular carcinoma target.

During the screening of solvents, we found that acetonitrile was activated instead of benzoxazole under initial reaction conditions. Moreover, acetonitrile provided nucleophilic addition to isatin toward the product of **3a** in 67% yield. Further optimization indicated that the best reaction condition is 10 mol % $Pd(OAc)_2$ and 15 mol % 1,10-phenanthroline in the mixture of DMF and CH_3CN (1:1) at 100 °C. Use of these conditions improved the yield of **3a** to 87%. A survey of recent literature indicates that activation of the sp^3 C−H bond of acetonitrile has attracted much attention, among some examples also involved in nucleophilic addition to carbonyl by using Ru and Cu complex catalysts in the presence of base or/and special additives.[11] Our protocol involves very different activation patterns, and its success requires neither an extra base nor an additive. Therefore, we decided to investigate the scope of different substituted *N*-methylisatins within our catalytic system. Indeed, our system displayed excellent functional group tolerance, and the corresponding products were obtained in good to excellent yields (Table 2, entries 1−12). Furthermore, using our product of **3a** as starting material, we can easily synthesize (±)-CPC-1 in 85% yield by reductive cyclization and methylation with

Table 2. Nucleopilic Addition Different Isatins with CH_3CN[a,b]



entry	substrate	R^1	product	yield (%)	entry	substrate	R^1	product	yield (%)
1	**1a**	H	**3a**	87%	7	**1g**	5-CH_3	**3g**	76%
2	**1b**	4-Br	**3b**	87%	8	**1h**	5-CH_3O	**3h**	84%
3	**1c**	5-F	**3c**	77%	9	**1i**	6-Br	**3i**	80%
4	**1d**	5-Cl	**3d**	86%	10	**1j**	7-Cl	**3j**	84%
5	**1e**	5-Br	**3e**	83%	11	**1k**	7-CF_3	**3k**	84%
6	**1f**	5-NO_2	**3f**	80%	12	**1l**	4,7-Cl	**3l**	82%

[a] The reaction was carried out with $Pd(OAc)_2$ (10 mol %), Phen (15 mol %), **1a** (0.30 mmol), and acetonitrile (1.5 mL) with DMF (1.5 mL) at 100 °C for 24 h under argon. [b] Yield of isolated product.

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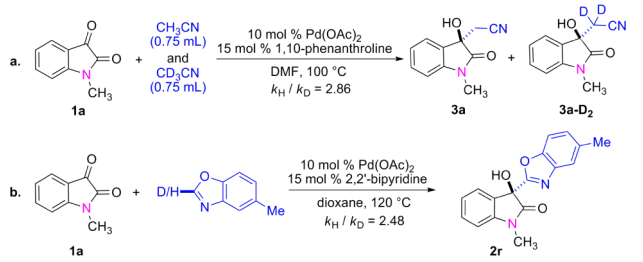
Scheme 2. Deuterium-Labeled Nucleophilic Addition to Isatin

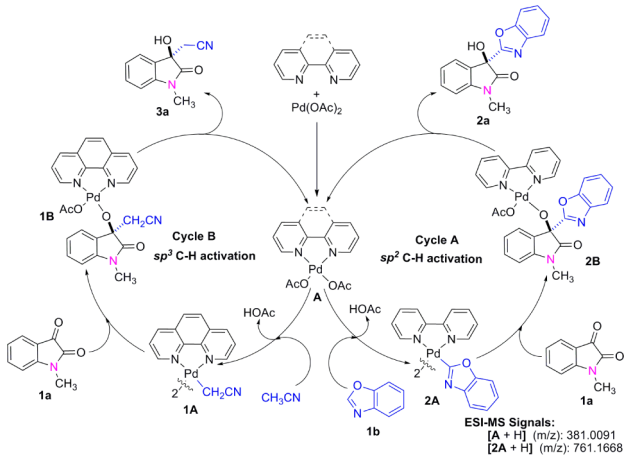


$NaCNBH_3$ and CH_3I under the basic conditions respectively (Scheme S1 in SI).

To gain insight into the reaction mechanism, we carried out kinetic isotope effect (KIE) experiments with the equal deuterium-labeled substrates acetonitrile-d_3 and acetonitrile. The kinetic isotope effects were observed with a k_H/k_D value of 2.86 (Scheme 2a). Similar results were also observed in the reaction of equal deuterium-labeled 5-methylbenzoxazole-*d* and 5-methylbenzoxazole and k_H/k_D = 2.48 (Scheme 2b).[12] These findings indicate that C−H bond cleavage may serve as the rate-determining step in this transformation.

To deepen our understanding of the catalytic cycle of the nucleophilic addition to isatin by sp^2 and sp^3 C−H activation, we performed mass spectrometry experiments on the standard catalytic reaction. We were delighted to observe both signals at *m*/*z* 381 and 761; these signals are related to the masses of intermediates **A** (the complex of 2, 2′-bipyridine and $Pd(OAc)_2$) and **2A** (Cycle A, Scheme 3). Unfortunately, mass spectrometry failed to reveal similar signals in the sp^3 C−H activation procedures. On the basis of observed experimental results in this pioneering report, we propose a plausible mechanistic pathway and outline in Scheme 3. In cycle A, $Pd(OAc)_2$ first coordinates with 2,2′-bipyridine to form the activated palladium complex **A**. Second, **A** reacts with benzoxazole by C−H bond activation to produce a dimer of **2A**. After this species

Scheme 3. Proposed Mechanisms of $Pd(OAc)_2$-Catalyzed Nucleophilic Addition to Isatin by sp^2 and sp^3 C−H Activation



coordinates with the carbonyls of isatin and leads the benzoxazole to occur, the migratory insertion to carbonyl to form the complex **2B**,[13] which then undergoes proton dissociations to afford the product **2a**, and the palladium catalyst would reinitiate the catalytic cycle synchronously. The catalytic cycle of the sp^3 C−H bond activation (Cycle B) is the same as sp^2 C−H bond activation, with the sole difference in the change of the ligand to 1,10-phenanthroline.

In conclusion, we have developed the first example of palladium-catalyzed C−H activation for a series of azoles and acetonitrile and subsequent nucleophilic addition to substituted isatins to construct 3-substituted-3-hydroxy-2-oxindoles. The bidentate nitrogen ligands play a crucial role in the transformation and significantly promote this reaction. Further bioassays and asymmetric nucleophilic additions to isatin are presently underway and will be reported in the future.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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