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Palladium-Catalyzed Regioselective Coupling Cyclohexenone into Indoles: Atom-Economic Synthesis of β-Indolyl Cyclohexenones and Derivatization Applications

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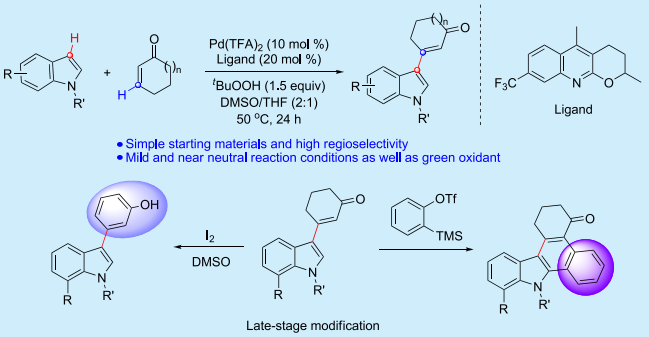
ABSTRACT: Herein, we report a palladium-catalyzed dehydrogenative cross-coupling of indoles with cyclic enones to give β-indolyl cyclic enones under mild and neutral reaction conditions. The key to the success is to explore a mild condition, which ensures the indole C−H activation and subsequent *syn* β-hydride elimination through rapid enolization isomerization of Pd(II)-enolate while suppressing other undesired side reactions. Synthetic utility has also been demonstrated in the flexible transformation of the coupling products to *meta*-phenols and benzo[a]carbazoles.



The numerous applications of functionalized indole in pharmaceuticals, agrochemicals, and functional materials have triggered long-standing and continuous efforts for the exploration of efficient and applicable approaches for the installation of these valuable compounds.[1] Transition-metal-catalyzed inert C−H bond functionalization of indole represents one of the most straightforward and efficient strategies to access structurally diversified indoles owing to its high efficiency in atom and step economy as well as sustainability (Scheme 1a).[2] Among them, palladium-catalyzed direct cross-coupling of indole with acyclic acrylate[3] has been well studied and holds a unique position in this thriving research area because of the synthetic flexibility of olefin functionality in these products, which provide opportunities for further useful transformations,[4] such as reductive additions, pericyclic additions, and so on. Thus, exploration of new coupling partners to expand this reactivity regime would constitute significant interest in direct modification of indole pharmacophores.

As a commercially available and relatively cheap reagent, cyclohexenone has been demonstrated as an excellent precursor to produce phenol.[5] In particular, dehydrogenative oxidation of β-functionalized cyclohexenones opens a new entry to access *meta*-substituted phenols,[6] which are more difficult to prepare in traditional electrophilic substitution methods owing to the intrinsic *ortho*/*para*-directing propensity of the hydroxyl group.[7] As a consequence, in order to overcome the limitations of currently used coupling reactions from prefunctionalized substrates[8] such as aryl halides and aryl boronic acids (Scheme 1b), exploring efficient synthetic approaches for β-functionalized cyclohexenones preparation through the C−H activation strategy is highly desirable. In this context, we conceived that direct cross-coupling of indole with cyclohexenone to produce β-indolyl-substituted cyclohexenone would undoubtedly expand diversified derivatization of indoles (Scheme 1c), such as unique accessibility to *meta*-indolyl phenols and benzo[a]carbazoles[9]. However, to the best of our knowledge, direct coupling of cyclohexenone to the indole moiety through C−H bond activation has not been reported owing to the substantial challenges by employing both sensitive substrates.

The challenge posed by our envisioned dehydrogenative couplings between cyclohexenone and indole is to identify a mild reaction condition which must be compatible and orderly in good delay with indole C−H activation and *syn* β-hydride elimination (Scheme 1d). First, selective palladation of the indole C−H bond and migratory insertion to cyclohexenone must be fast enough because cyclohexenone is sensitive to strong acidic/basic conditions (self-aldol condensation) as well as oxidative dehydrogenation (phenol) in palladium catalysis.[6e,10] In addition, both the substrate and product containing indole units are susceptible to decomposition under oxidative reaction conditions.[11] Thus, developing a mild and near neutral reaction conditions is highly desirable.

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Scheme 1. Overview and Context of This Work

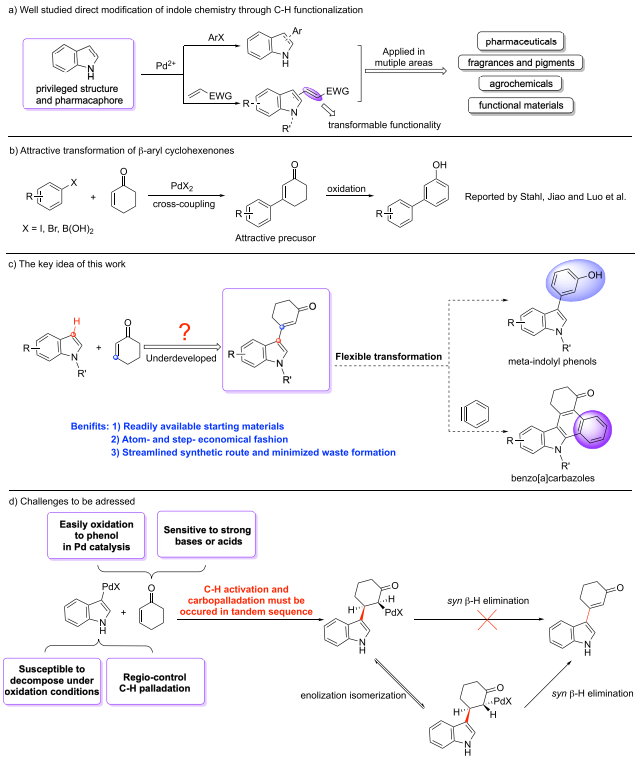
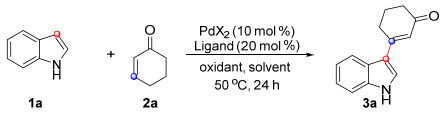
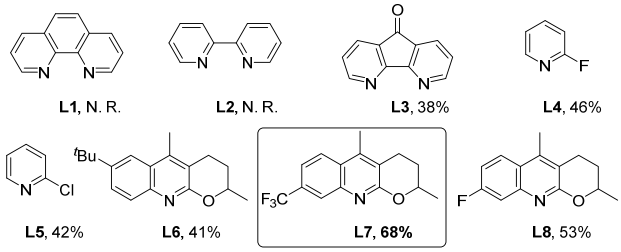


Table 1. Identification of Reaction Conditions[a,b]



entry	catalyst	ligand	oxidant	solvent	yield
1	$Pd(OAc)_2$	-	^{t}BuOOH	DMSO	trace
2	$PdCl_2$	-	^{t}BuOOH	DMSO	N.R.
3	$Pd(TFA)_2$	-	^{t}BuOOH	DMSO	20%
4	$Pd(TFA)_2$	-	Ag_2CO_3	DMSO	trace
5	$Pd(TFA)_2$	-	$Cu(OAc)_2$	DMSO	trace
6	$Pd(TFA)_2$	-	BQ	DMSO	trace
7	$Pd(TFA)_2$	-	$K_2S_2O_8$	DMSO	trace
8	$Pd(TFA)_2$	-	^{t}BuOOH	DMSO/THF (2:1)	32%
9	-	L7	^{t}BuOOH	DMSO/THF (2:1)	N.R.

Evaluation of ligands[a,b]



[a]Conditions: The reaction was conducted with **1a** (0.25 mmol), **2a** (1 mmol, 4 equiv), $Pd(TFA)_2$ (0.025 mmol, 10 mol %), ligand (0.05 mmol, 20 mol %), oxidant (0.375 mmol, 1.5 equiv) in solvent (1.2 mL) at 50 °C stirred for 24 h. [b]Isolated yield.

Second, *syn*-β-hydride elimination is inaccessible owing to the restricted bond rotation of the six-membered ring conformation for β-indolyl Pd(II)-enolate, which request its rapid enolization isomerization to align the metal for *syn* elimination.[6d] Within our ongoing efforts in the development of coupling diversifications by using challenging cyclic enones as coupling partners,[12] we have achieved the first palladium-catalyzed dehydrogenative cross-coupling of cyclic enones with indoles, which we report herein. Notable features such as excellent regioselectivity, broad functional group tolerance, as well as clean oxidant made our method more practical and appealing in synthetic chemistry. In addition, the successful transformation of coupling products to valuable *meta*-phenols and benzo[a]carbazoles is also demonstrated.

We commenced our study by investigating reaction conditions (Table 1) for dehydrogenative coupling of commercially available indole (**1a**) with cyclohexenone (**2a**). The reaction was initially performed in DMSO by using $Pd(OAc)_2$ as catalyst and *tert*-butylhydroperoxide as oxidant at 50 °C for 24 h. Preliminary catalyst examination (entry 1−3) proved that more electrophilic $Pd(TFA)_2$[13] could promote the desired product formation in 20% yield. Extensive screening of the oxidants revealed that employment of ^{t}BuOOH is the optimal oxidant to furnish the reaction at mild conditions (entries 4−7); other commonly used oxidants such as Ag_2CO_3, $Cu(OAc)_2$, and BQ proved to be ineffective (for more details, please see the Supporting Information). The yield of **3a** was enhanced slightly when mixed solvents DMSO/THF (2:1) were used (entry 8). To further improve the yield, we tested the ligand effect by using nitrogen ligands to tune the electronic property and stability of the Pd center (Table 1, evaluation of ligands).[14] To our delight, use of **L7** as ligand dramatically improved the yield of **3a** up to 68%. Finally, control experiment indicated that the palladium catalyst was essential to this reaction (entry 9). Thus, the efficient method for the facile synthesis of β-indolyl cyclohexenone has been established, starting from commercially available indole and cyclohexenone.

With the optimized reaction conditions, we then examined the generality of this dehydrogenative cross-coupling reaction. As illustrated in Scheme 2, indoles bearing various functional groups reacted efficiently with cyclic enones to give desired coupling products in good yields. Remarkably, reactions proceeded exclusively at the C3 position of indole moiety in all cases. Regardless of the substitutes, the positions of indole substrates except for C3 are all tolerated in this reaction protocol and afforded the desired products in synthetic useful yields. In addition, a wide range of functional groups, including alkyl (**3b**, **3c**), methoxyl (**3d**, **3e**, **3f**), hydroxyl (**3g**), ester (**3h**), fluoro (**3i**, **3j**, **3k**), and chloro (**3l**, **3m**), and even susceptible bromo (**3n**, **3o**, **3p**, **3q**), cyano (**3r**), aldehyde (**3s**), and nitro (**3t**), are all compatible under reaction conditions. Notably, substitutes at the C2 position of indoles, which could potentially increase steric hindrance of the coupling reaction, also afforded the corresponding products in good yields (**3u**, **3w**). Furthermore, substitutions on the nitrogen atom of indole also furnished the reaction to provide the corresponding products in good yields (**3x**, **3z**). Besides monosubstituted indoles, disubstituted indoles (**3v**, **3y**) also proved to be suitable substrates in this reaction. Other cyclic enones such as cyclopentenone and cycloheptenone can also couple with indole to give the desired coupling products (**3ab**, **3ac**), respectively. Such high chemoselectivity and broad functional

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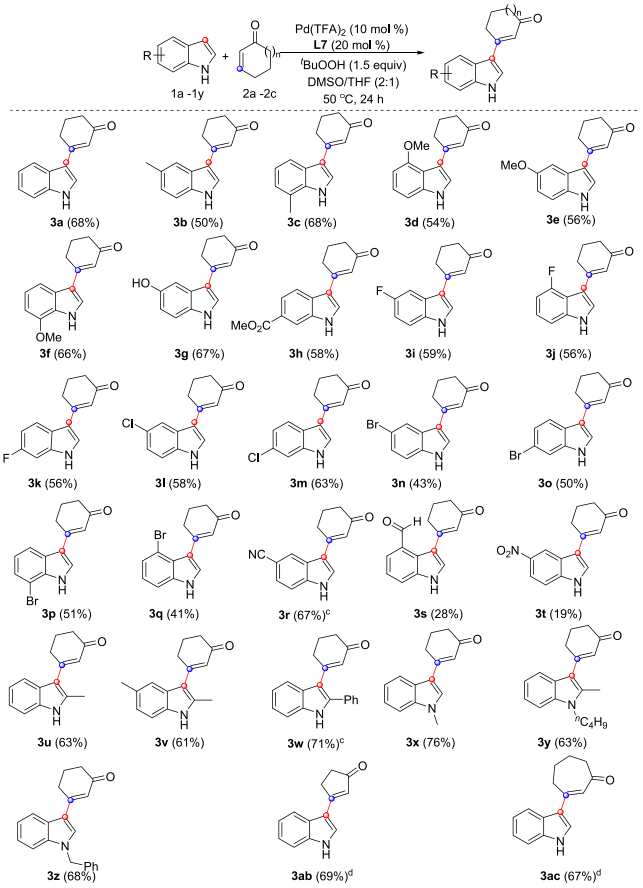
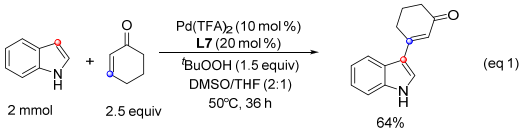
Scheme 2. Scope of Substrate[a,b]



[a]Conditions: The reaction was conducted with **1** (0.25 mmol), **2** (1 mmol, 4 equiv), $Pd(TFA)_2$ (0.025 mmol, 10 mol %), ligand (0.05 mmol, 20 mol %), ^tBuOOH (0.375 mmol, 1.5 equiv), in DMSO/THF (0.8 mL/0.4 mL) at 50 °C stirred for 24 h. [b]Isolated yield. [c]Stirred for 39 h. [d]Stirred for 48 h, yields are based on recovery of starting materials.

group compatibility are likely attributed to the mild reaction temperatures as well as avoiding use of strong acids and bases.

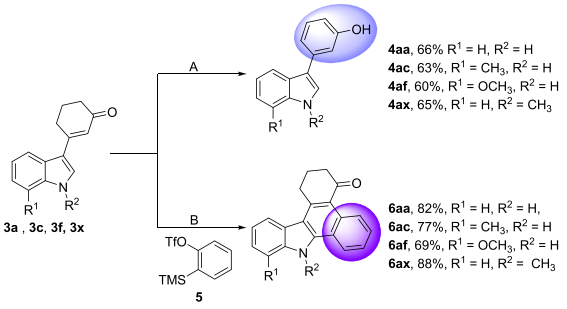
To illustrate the practicality and utility of this methodology, a scale up reaction of **1a** with **2a** was conducted and afforded the corresponding product **3a** in 64% yield (eq 1). Addition-



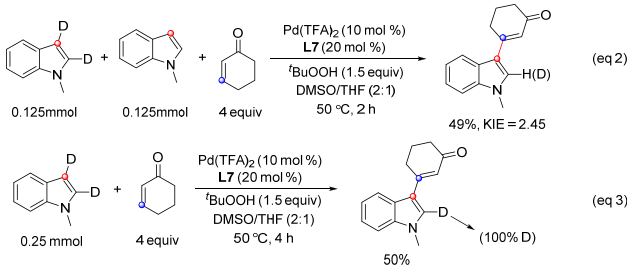
ally, in the presence of iodine catalyst, the coupling products (e.g., **3a**, **3s**, **3f**, **3x**) could be transformed to *meta*-indolyl phenols (Scheme 3) in high yields, which affords an efficient and straightforward route to access these value-added products. Furthermore, treatment of **3** with benzyne precursor at room temperature yielded valuable benzo[a]carbazoles bearing the free NH unit in good yields (Scheme 3), thus providing a more efficient and easily handled [4 + 2] annulation approach but avoiding the use of preformed α-diazo carbonyl compounds.[15]

To acquire the mode of action of this dehydrogenative cross-coupling reaction, an intermolecular KIE reaction study (eq 2) was operated under standard reaction conditions for 2 h. The

Scheme 3. Synthetic Applications[a,b]

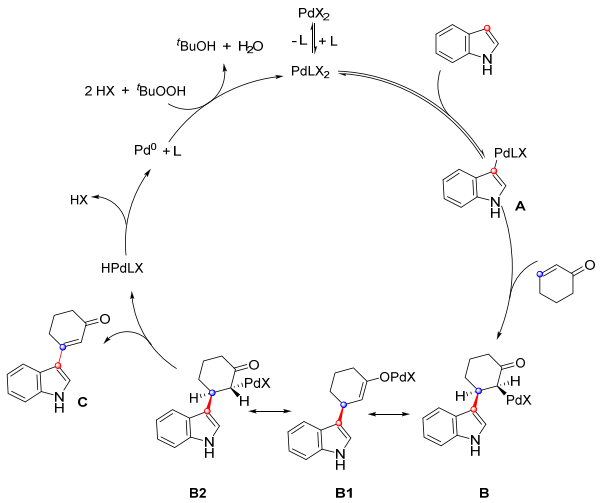


[a]Conditions: (A) The reaction was conducted with **3** (0.25 mmol), I_2 (0.075 mmol, 30 mmol %), DMSO (1 mL) at 60 °C stirred for 31 h. (B) The reaction was conducted under N_2 balloon with **3** (0.25 mmol), CsF (1.5 mmol, 6 equiv), **5** (0.75 mmol, 3 equiv), CH_3CN (2 mL) at room temperature stirred for 46 h. [b]Isolated yield.



2.45 KIE value suggested that C−H bond cleavage of indole is possibly involved in the rate-limiting step. Furthermore, the deuterium retaining 100% in the 2-position of the coupling product revealed that H/D exchange of the 2-position of the indole moiety was not involved in this dehydrogenative coupling reaction (eq 3). Thus, a plausible mechanism for the catalytic cycle was proposed in Scheme 4. Initially, with the

Scheme 4. Proposed Mechanism



C−H bond cleavage of indole with more electrophilic Pd(II), an indolyl-Pd(II) intermediate (**A**) was formed; subsequent migratory insertion to cyclohexenone would generate Pd(II)-enolate (**B**), which underwent a rapid enolization isomerization (**B**−**B1**−**B2**) to maintain the Pd and β hydrogen atom at the *cis* position for facile *syn*-β-hydride elimination to

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provide the desired product (**C**) with the concomitant generation of Pd(0), wherein DMSO is expected as a suitable base and polar solvent to facilitate enolization isomerization.[16] Finally, in the presence of *tert*-butylhydroperoxide, the active Pd(II) catalyst could be regenerated to accomplish the catalytic cycle.

In conclusion, we have developed an efficient method for the facile synthesis of β-indolyl cyclic enones, starting from the commercially available indoles and cyclic enones. Various substituted indoles with broad functional group compatibility are tolerated in this protocol to give the desired coupling products in moderate to high yields. Further transformation of the β-indolyl cyclohexenones to valuable *meta*-phenols and benzo[a]carbazoles demonstrated the utility of our methodology. We expect that this cost-efficient and easy-to-handle strategy has great prospective applications in indole modification chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01763.

Detailed experimental procedures and spectral data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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