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Cationic Ruthenium(II) Catalysts for Oxidative C−H/N−H Bond Functionalizations of Anilines with Removable Directing Group: Synthesis of Indoles in Water

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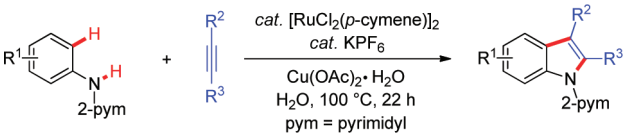
ABSTRACT



Cationic ruthenium(II) complexes enabled oxidative C−H bond functionalizations with anilines bearing removable directing groups. The C−H/N−H bond cleavages occurred most efficiently in water as a sustainable solvent and provided general access to various bioactive indoles. Mechanistic studies provided strong support for a novel reaction manifold.

Indoles are ubiquitous structural motifs in biologically active compounds and natural products.[1,2] Their central importance in medicinal chemistry and drug discovery has, thus, resulted in a continued strong demand for generally applicable, modular syntheses of this heteroaromatic moiety.[3] In this context, transition-metal-catalyzed transformations of *ortho*-halo-substituted aniline derivatives, most notably Larock's annulation,[4,5] have proven particularly useful for the selective assembly of indole derivatives.[6] Unfortunately, this approach inherently relies on the use of prefunctionalized starting materials, which reduces the overall atom and step economy. Conversely, a significantly more sustainable strategy is represented by the direct use of easily available anilines for catalytic oxidative indole syntheses.[7] As of yet, these C−H bond functionalizations[8] have predominantly been accomplished with palladium or rhodium catalysts.[9] We, in contrast, devised very recently inexpensive neutral ruthenium complexes for oxidative annulations of alkynes through C−H bond cleavages.[10] Key to success for the development of these transformations was an effective carboxylate-assisted[11] C−H bond ruthenation as the rate-limiting reaction step.[10] Hence, the chemoselectivities and site selectivities of these processes were governed by kinetic C−H bond acidity, thereby rendering

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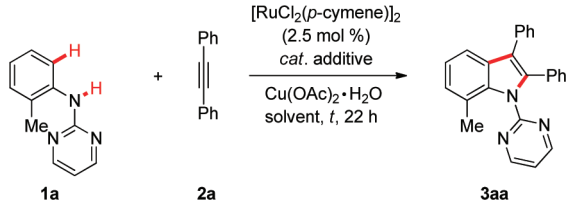
electron-deficient arenes most reactive in all studied transformations.[10] Given the prevalence of indoles in medicinal chemistry and pharmaceutical industries, we became interested in exploring the first ruthenium-catalyzed oxidative annulations with simple aniline derivatives, the development of which we report herein. Notable features of the new protocol include the unprecedented use of cationic ruthenium(II) complexes for oxidative annulations of alkynes, along with an extraordinary chemoselectivity that enabled C−H bond transformations in water[12,13] as an environmentally benign reaction medium. Importantly, mechanistic studies revealed electron-rich arenes to be converted preferentially, thus highlighting a novel reaction manifold to be operative in ruthenium-catalyzed oxidative C−H bond transformations.

Our studies were initiated by probing various solvents and cocatalytic additives for the envisioned ruthenium-catalyzed oxidative preparation of *N*-substituted indoles. Since the 2-pyrimidyl[14] group was shown to be easily removed from the indole nucleus,[15] we focused our optimization studies on the use of *N*-2-pyrimidyl-substituted anilines (Table 1). Among a set of representative solvents, water proved to be optimal (entries 1−4) and also furnished higher yields as compared to reactions performed in the absence of any solvent (entry 5). High catalytic efficacy was accomplished with a complex generated from $[RuCl_2(p\text{-cymene})]_2$ and cocatalytic amounts of KPF_6 (entries 4−7), reaction conditions previously established for the generation of cationic ruthenium(II) complexes with a weakly coordinating anion.[16−18] Transformations in the presence of the surfactant polyoxyethanyl α-tocopheryl sebacate (PTS) did not improve the yield of desired product **3aa** (entries 8 and 9), providing support for the catalytic C−H bond functionalization to take place in water.[12] Notably, the catalytic efficacy of our inexpensive cationic ruthenium complex compared favorably to the one of representative palladium or rhodium precursors (entries 3 and 4 vs 12 and 13). As to the catalytically active species, it is noteworthy that a well-defined cationic ruthenium(II) complex[16] provided a yield comparable to the one obtained with the *in situ* generated catalyst (entries 3 and 4 vs 14).

Table 1. Optimization for the Synthesis of Indole **3aa** in Water[a]



1a 2a 3aa

entry	solvent	t [°C]	additive (mol %)	**3aa** (%)
1	*t*-AmOH	100	KPF_6 (10)	44
2	DMF	100	KPF_6 (10)	19
3	H_2O	100	KPF_6 (10)	92
4	**H_2O**	**100**	**KPF_6 (20)**	**94**[b]
5	–	100	KPF_6 (10)	53
6	H_2O	100	KPF_6 (10)	–[c]
7	H_2O	100	–	6
8	H_2O	80	KPF_6 (10)	58
9	H_2O	80	KPF_6 (10)	58[d]
10	H_2O	100	KPF_6 (10)	43[e]
11	H_2O	100	KPF_6 (10), KOAc (200)	63[e]
12	H_2O	100	KPF_6 (10)	16[f]
13	H_2O	100	KPF_6 (10)	85[g]
14	**H_2O**	**100**	**$[Ru_2Cl_3(p\text{-cymene})_2][PF_6]$ (2.5)**	**96**

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $Cu(OAc)_2•H_2O$ (2.0 equiv), solvent (2.0 mL); yields of isolated product. [b] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %). [c] In the absence of $[RuCl_2(p\text{-cymene})]_2$. [d] With PTS (3 wt %). [e] $Cu(OAc)_2•H_2O$ (1.0 equiv). [f] $[Pd(PPh_3)_2Cl_2]$ (10 mol %). [g] $[RhCp^*Cl_2]_2$ (5.0 mol %).

With an optimized catalytic system in hand, we surveyed its scope in the oxidative indole synthesis in water (Scheme 1).

Anilines displaying either 2-pyrimidyl or 2-pyridyl substituents were efficiently converted to the desired indoles **3aa**−**3cb**, while the *N*-2-pyrimidyl group was easily cleaved from the indole **3aa** (Scheme 2). The cationic ruthenium(II) complex was not limited to tolane derivatives, but also allowed the efficient annulation of alkyl-substituted derivatives **2**. Unsubstituted aniline **1c** as well as derivatives **1**

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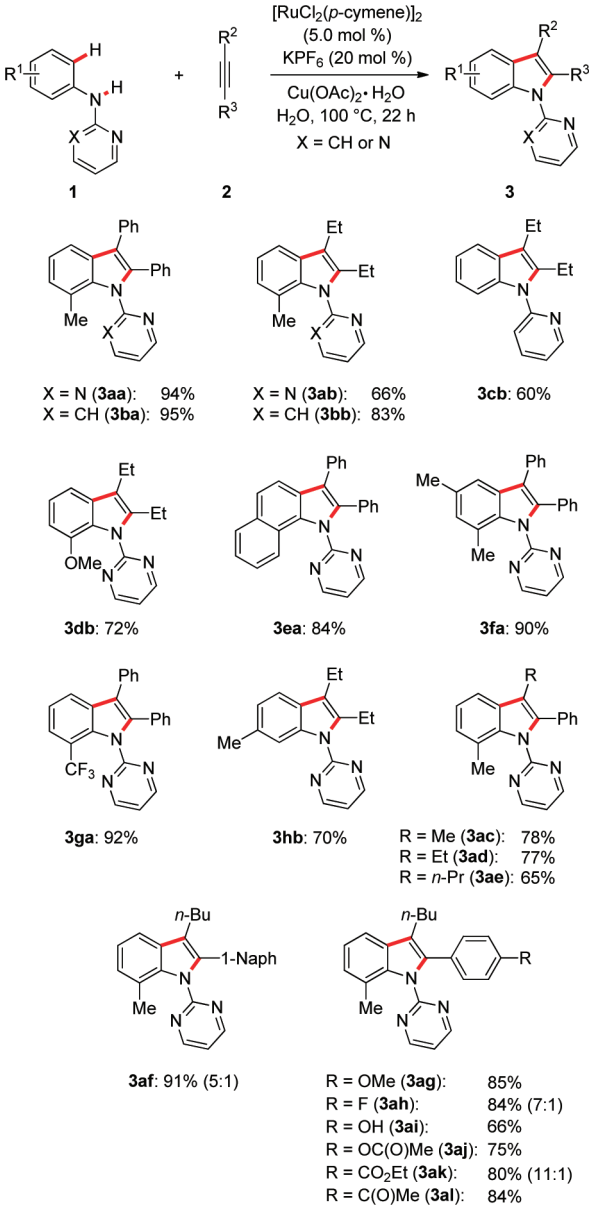
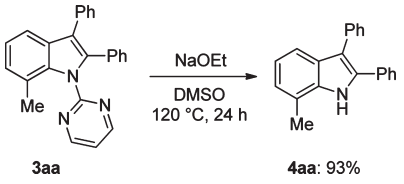
Scheme 1. Scope of Ruthenium-Catalyzed Oxidative Synthesis of Indoles **3**



with electron-donating or -withdrawing substituents furnished the desired indoles **3** in synthetically useful isolated yields. Intramolecular competition experiments with *meta*-substituted aniline **1h** led to the site-selective functionalization at the less sterically encumbered C−H bond, thereby delivering indole **3hb** as the sole product. Moreover, unsymmetrically substituted alkynes **2c**−**2l** were converted with high regioselectivity,[19] placing the aliphatic substituents distal to the nitrogen. Generally, the optimized catalytic system proved to be widely applicable, as illustrated by valuable functional groups, such as an unprotected alcohol, esters, or an enolizable ketone, being well tolerated by the cationic ruthenium(II) complex.

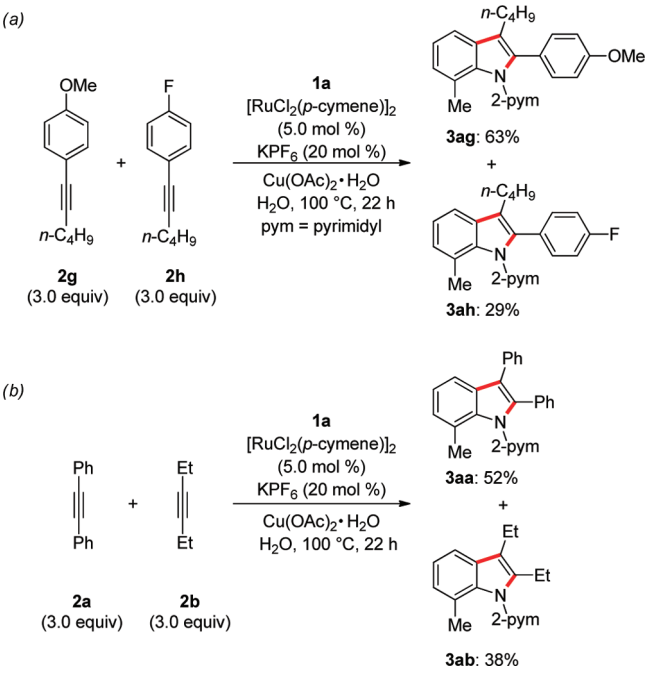
(19) For detailed information see the Supporting Information.

Scheme 2. Removal of Directing Group



Given the remarkable chemoselectivity of the ruthenium catalysis in water, we became interested in probing its mode of action. To this end, intermolecular competition experiments with differently substituted alkynes **2** revealed aryl-substituted derivatives to be converted preferentially (Scheme 3).

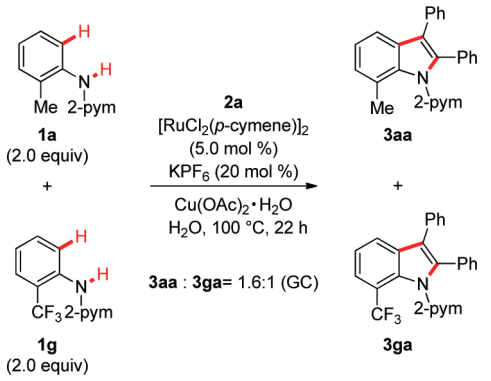
Scheme 3. Competition Experiments with Alkynes **2**



Interestingly, intermolecular competition experiments between anilines **1** highlighted arene **1a** to be converted preferentially (Scheme 4). This selectivity pattern contrasts all previously observed chemoselectivities of ruthenium-catalyzed oxidative annulations of alkynes,[10] thus being suggestive of a novel mode of activation to be operative.

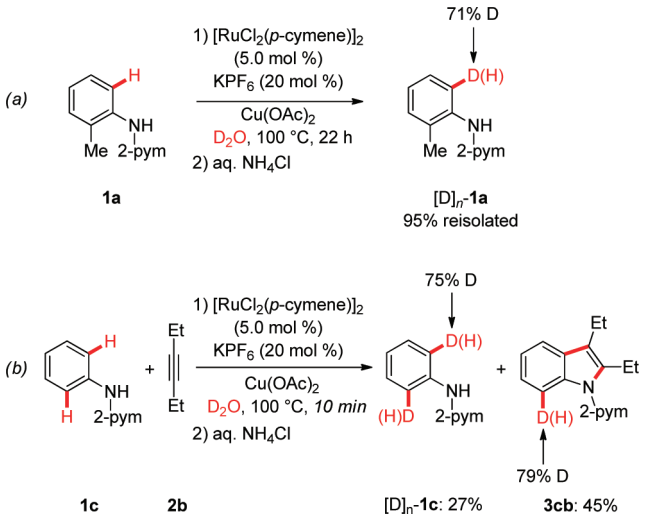
Additionally, we observed an H/D exchange when employing D_2O as the solvent (Scheme 5). This scrambling occurred exclusively in the *ortho*-position of substrates **1a** and **1c**. More importantly, deuterium incorporation took place both in the absence (*a*) and in the presence of alkynes

Scheme 4. Competition Experiment with Anilines **1**



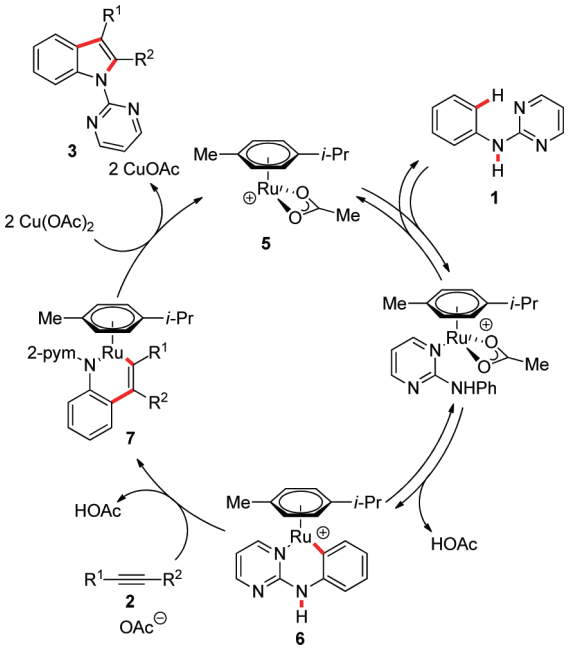
2 (*b*), a significant difference from a rhodium-catalyzed oxidative synthesis of *N*-acetyl indoles.[9a,b]

Scheme 5. Reversible C−H bond Functionalizations in D_2O



Based on these experimental findings we propose a catalytic cycle relying on initial reversible cyclometalation with cationic ruthenium(II) complex **5** (Scheme 6). Thereby, six-membered ruthenacycle **6** is formed as a key intermediate. Note that all ruthenium-catalyzed oxidative annulations of alkynes[10] were thus far limited to substrates that form five-membered ruthenacycles. Subsequently, complex **6** is proposed to undergo coordination and migratory insertion with alkyne **2** to furnish ruthenacycle **7**. Finally, reductive elimination delivers desired product **3**, and reoxidation regenerates the catalytically active cationic complex **5**.

Scheme 6. Proposed Catalytic Cycle



In summary, we have reported on the first ruthenium-catalyzed oxidative annulation of alkynes by aniline derivatives. The most efficient catalysis was accomplished with a cationic ruthenium(II) complex in water as a sustainable solvent, thereby setting the stage for an expedient synthesis of bioactive indoles with ample scope. Mechanistic studies indicated a novel reaction manifold through the reversible formation of six-membered ruthenacycles as key intermediates.

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Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.