Ruthenium(II)-Catalyzed *Ortho*-C-H Alkylation of Naphthylamines with Diazo Compounds for Synthesis of 2,2-Disubstituted π-Extended 3-Oxindoles in Water

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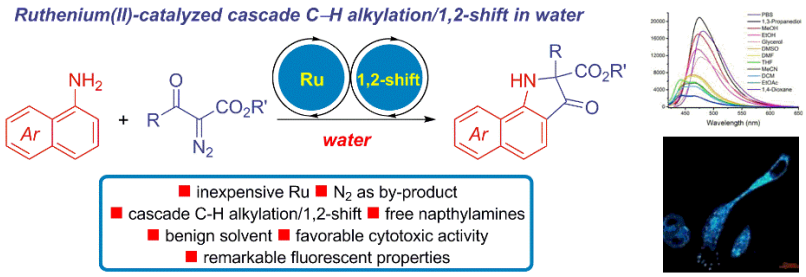
Supporting Information



ABSTRACT: Ruthenium(II)-catalyzed *ortho*-C–H alkylation of naphthylamines with diazo compounds for the synthesis of 2,2-disubstituted π-extended 3-oxindoles has been developed. The method represents the first example of C–H alkylation via carbenoid insertion in water as a sustainable solvent. The procedure exploits inexpensive ruthenium catalyst, aqueous media, and results in the release of benign N_2. The π-extended 3-oxindole products exhibit favorable antitumor properties and remarkable fluorescent properties in aqueous solution for fluorescent imaging.

π-Extended polycyclic heteroarenes play a pivotal role as versatile and important scaffolds in numerous natural products, biologically-active molecules and organic functional materials.[1] Amongst them, π-extended 3-oxindoles (3-indolinones) display favorable optoelectronic properties and have found numerous applications as dyes and pharmaceutical products.[2] In this context, transition-metal-catalyzed C–H functionalization of nitrogen-containing scaffolds is essential to organic synthesis.[3] While the ortho-position of anilides (N-acyl-anilines) can be readily functionalized through carbonyl-directed C–H activation, the direct C–H functionalization of free anilines is rare.[4] Although of significant value, C–H functionalization of π-extended naphthylamines has been much less explored than that of simple anilines.[5] More generally, direct C–H activation of 1-substituted naphthalenes can possibly lead to *peri*-C8 or *ortho*-C2 functionalization,[6] giving access to products of great synthetic value that are difficult to prepare by conventional methods.

In recent years, diazo compounds have been widely used in directed C–H functionalization/cyclization to construct useful N-heteroarenes, including indoles,[7] pyridine N-oxides,[8] isoquinolines,[9] isoquinoline N-oxides[10] and isoquinolinones.[11] However, while progress in carbenoid insertion of C(sp^2)–H bonds has been achieved using Co(III),[12] Rh(III),[13] and Ir(III)[14] catalysts, versatile and inexpensive ruthenium complexes[15–21] have rarely been explored for C–H insertion reactions using diazo compounds.[22]

Herein, we report the ruthenium(II)-catalyzed ortho-C–H alkylation of naphthylamines with diazo compounds for the synthesis of 2,2-disubstituted π-extended 3-oxindoles (Figure 1). Notable features of this protocol include (1) the first example of C–H alkylation via carbenoid insertion in water as a sustainable solvent; (2) a sustainable strategy directly using readily available naphthylamines without prefunctionalization; (3) unprecedented C–H alkylation/migration sequence allowing the synthesis of π-

extended 3-oxindoles bearing sterically-hindered quaternary center; (4) favorable antitumor properties and remarkable fluorescent properties in aqueous solution for fluorescent imaging of the C–H activation products. This method showcases a significantly opportunity for using cost-effective, operationally-simple and functional group tolerant ruthenium catalysis for direct C–H alkylation in environmentally benign reaction media.[23,24]

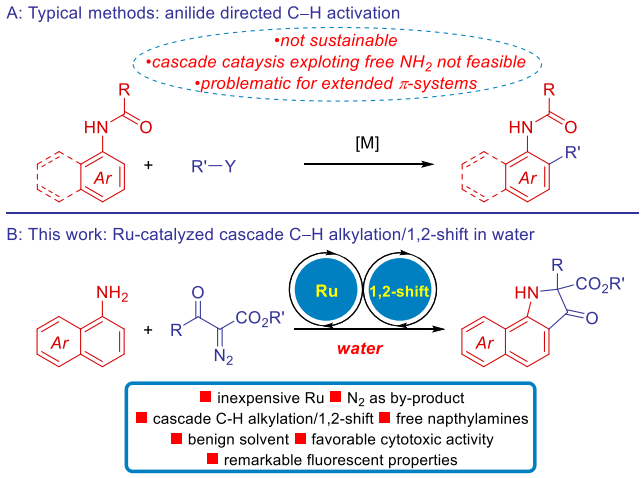
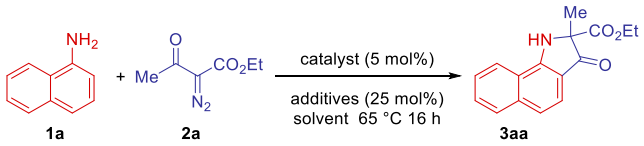


Figure 1. This work: Ru(II)-catalyzed cascade C–H alkylation/1,2-shift in water for the synthesis of 2,2-disubstituted 3-oxindoles.

Table 1. Optimization of Reaction Conditions[a]



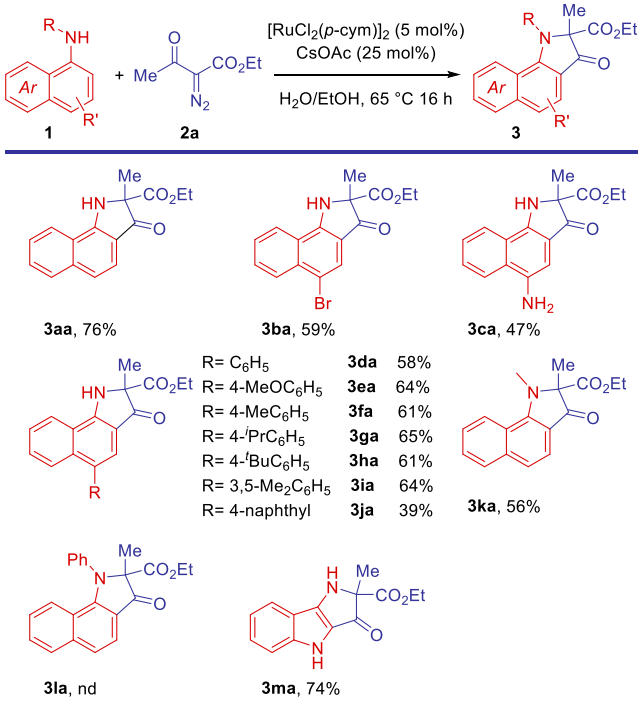
1a 2a 3aa

entry	catalyst	additive	solvent	yield (%)[b]
1	[Ru(*p*-cymene)Cl$_2$]$_2$	CsOAc	DCE	0
2	[Ru(*p*-cymene)Cl$_2$]$_2$	CsOAc	DMSO	0
3	[Ru(*p*-cymene)Cl$_2$]$_2$	CsOAc	PhCH$_3$	0
4	[Ru(*p*-cymene)Cl$_2$]$_2$	CsOAc	EtOH	<5
5	[Ru(*p*-cymene)Cl$_2$]$_2$	CsOAc	H$_2$O	38
6[c]	[Ru(*p*-cymene)Cl$_2$]$_2$	CsOAc	H$_2$O	56
7[d]	[Ru(*p*-cymene)Cl$_2$]$_2$	CsOAc	H$_2$O	76
8[d]	[Ru(*p*-cymene)Cl$_2$]$_2$	AgSbF$_6$	H$_2$O	57
9[d]	[Ru(*p*-cymene)Cl$_2$]$_2$	KOAc	H$_2$O	34
10[d]	[Ru(*p*-cymene)Cl$_2$]$_2$	Cu(OAc)$_2$	H$_2$O	26
11[d]	[Ru(*p*-cymene)Cl$_2$]$_2$	NaOAc	H$_2$O	35
12[d,e]	[Ru(*p*-cymene)Cl$_2$]$_2$	CsOAc	H$_2$O	16
13[d,f]	[Ru(*p*-cymene)Cl$_2$]$_2$	CsOAc	H$_2$O	24
14[d]	[Cp*RhCl$_2$]$_2$	CsOAc	H$_2$O	54
15[d]	[Cp*IrCl$_2$]$_2$	CsOAc	H$_2$O	17
16[d]	Pd(OAc)$_2$	CsOAc	H$_2$O	0

[a]Conditions: **1a** (1.0 equiv), **2a** (2.0 equiv), catalyst (5 mol%), additive (25 mol%), solvent (0.05 M), 65 °C, 16 h. [b]Isolated yields. [c]With 30 equiv of DMSO. [d]With 30 equiv of EtOH. [e]With 1 equiv of AcOH. [f]With 1 equiv of PivOH. See ESI for details.

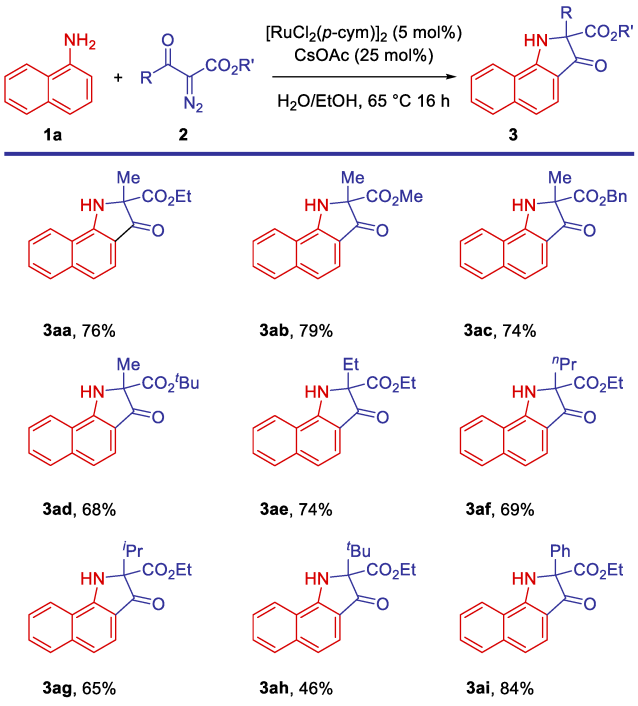
Within our program on Ru-catalyzed C–H functionalization,[16] we sought to develop an alkylation reaction of π-extended systems that is currently unavailable using other catalysts. We initiated our study by examining reaction conditions for alkylation of 1-naphthylamine (**1a**) with diazo ester (**2a**) as model substrates (Table 1). Although no reaction was observed using DCE, DMSO, toluene or EtOH in the presence of [RuCl$_2$(*p*-cym)]$_2$ (entries 1-4), we were delighted to find the formation of a π-extended 2,2-disubstituted 3-oxindole (**3aa**) using water as the reaction solvent (entry 5). The structure of a C2-Ph derivative (**3ai**) was confirmed by x-ray analysis (*vide infra*). The products resulting from non-selective *peri*-C8 functionalization were not detected (*vide infra*), thus establishing an unprecedented C2-selective C–H functionalization/migration sequence that furnishes challenging to prepare π-extended 3-oxindoles bearing sterically-hindered quaternary center. Further optimization established that adding a small amount of a co-solvent, such as DMSO or EtOH to promote solubility of the substrate, significantly improved the yield (entries 6-7). Examination of different additives, including AgSbF$_6$, KOAc, Cu(OAc)$_2$, NaOAc and CsOAc, revealed that CsOAc was optimal (entries 7-11). Furthermore, addition of Brønsted acids, such as AcOH or PivOH to promote migration, resulted in lower yields (entries 12-13). Finally, examination of other metal catalysts, including [Cp*RhCl$_2$]$_2$, [Cp*IrCl$_2$]$_2$ and Pd(OAc)$_2$ (entries 14-16), revealed that Ru is a superior promoter for this reaction.

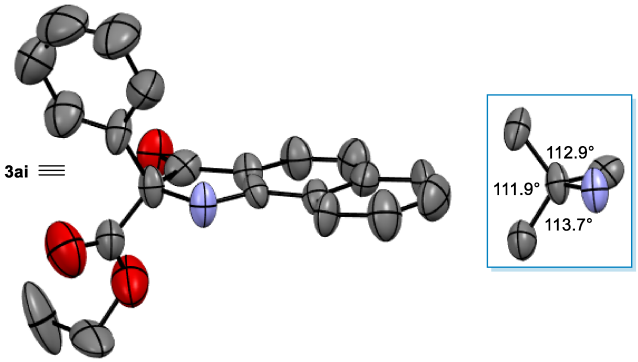
Scheme 1 Substrate Scope of Naphthylamines[a,b]



[a]Conditions: **1** (1.0 equiv), **2a** (2.0 equiv), $[RuCl_2(p\text{-cym})]_2$ (5 mol%), CsOAc (25 mol%), H_2O/EtOH (6.7/1 v/vol, 0.043 M), 65 °C, 16 h. [b]Isolated yields.

Scheme 2 Substrate Scope of Diazo Compounds[a,b]

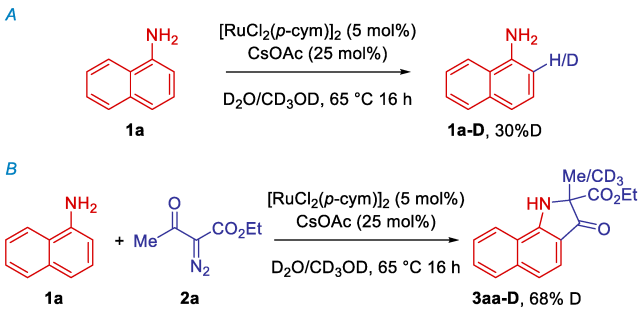




[a]Conditions: **1** (1.0 equiv), **2a** (2.0 equiv), $[RuCl_2(p\text{-cym})]_2$ (5 mol%), CsOAc (25 mol%), H_2O/EtOH (6.7/1 v/vol, 0.043 M), 65 °C, 16 h. [b]Isolated yields. X-ray structure, **3ai** (50% ellipsoids). Inset shows angles around the quaternary center. CCDC 1965995.

With the optimized conditions in hand, various readily available substituted naphthylamines were tested. As summarized in Scheme 1, the cyclization occurred very smoothly for 1-napthylamines bearing substituents at the para position. In particular, we found that the bromo substitution is well-tolerated (**3ba**). Selective mono-C–H functionalization was observed using 1,4-diaminonaphthalene (**3ca**). The use of a bromide handle permits rapid synthesis of π-extended 2-oxindole biaryls that have interesting optoelectronic properties (**3da-3ja**).[2g] Furthermore, the reaction could be extended to N-methyl naphthylamine (**3ka**), thus demonstrating that N-alkyl substitution is tolerated. However, no product was formed from the electron-deficient N-phenyl-1-naphthylamine (**3la**). Finally, we were pleased to find that these sustainable reaction conditions are also applicable to the functionalization of 4-aminoindole, thus producing the π-extended heterocyclic 3-oxindole (**3ma**) in good yield.

Scheme 3 Labelling Experiments



We next examined the generality of this C–H activation cascade with respect to the diazo compound component. As shown in Scheme 2, we found that this protocol tolerates a wide range of diazo compounds, thus enabling the selective synthesis of various C3-substituted π-extended 3-oxindoles. We were pleased that various esters, including ethyl (**3aa**), methyl (**3ab**), benzyl (**3ac**) and *tert*-butyl (**3ad**) can be installed using this new protocol. Gratifyingly, the reaction also tolerates various alkyl groups, including *n*-alkyl, such as methyl, ethyl or propyl (**3ad-3af**) as well as 2° alkyl, such as *i*-Pr (**3ag**), and 3° alkyl, such as *tert*-Bu (**3ah**), and aromatic rings, such as Ph (**3ai**). Notably, the reaction enables the synthesis of extremely hindered α-branched C2-disubstituted π-extended 3-oxindoles that are not accessible by other methods.

While verdict on the mechanism is premature at this point, Uchimaru established that Ru-catalyzed ortho-directed C–H activation of aniline is feasible.[25] To gain insight into the positional C2/C8 selectivity of the reaction, we conducted control experiments employing D_2O/CD_3OD as the solvent (Scheme 3). (1) We observed exclusive C–H/C–D exchange at the C2 position (Scheme 3A). Importantly, the scrambling occurred in the absence of the diazo compound. It should be noted that there is no H/D exchange in the absence of ruthenium. (2) Furthermore, significant C–H/C–D exchange occurred at the methyl position in (**3aa**) when the reaction was performed in the presence of the diazo compound (Scheme 3B). It should be noted that H/D exchange was not observed in the reisolated substrate. We believe that the H/D exchange in the methyl group is a result of keto/enol exchange under the reaction conditions. (3) Furthermore, control reactions with 2-napthylamine, 2-toluidine and aniline as C–H activation substrates resulted in unproductive reactions, emphasizing the key role of 1-napthylamine template. It should be noted that deuterium incorporation at the exchangeable NH position is not observed due to product isolation on silica gel. There is no productive reaction using diazo substrates from 1,3-diketones or TMS diazomethane. We believe that naphthylamines are preferred substrates due to the conjugated system stabilizing the four-membered in-

termediate. A possible mechanism could also involve activation of the diazo compound with the formation of metal carbene, followed by attack of the amino group at the electrophilic carbene center with concomitant C-H activation. Ongoing work in our laboratory is focused on mechanistic

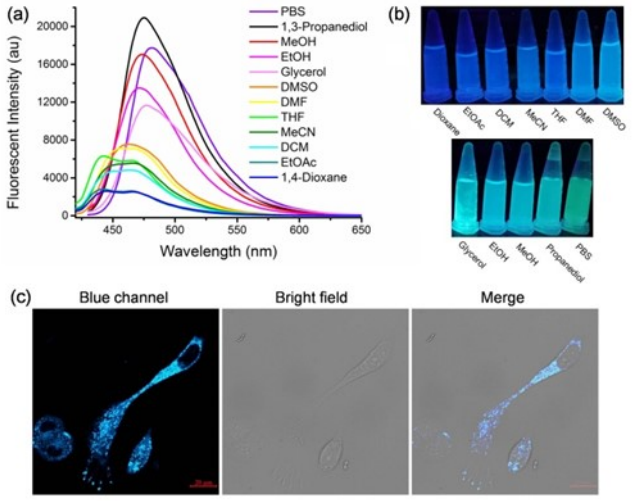


Figure 2. Fluorescent properties and fluorescent imaging of compound **3da** in living cells.

studies in Ru-catalysis, and this work will be published in due course.

Since one of the major goals of C–H activation methods is preparing novel structural motifs for pharmaceutical and biochemical research, we were interested to test the activity of these novel products as potential cytotoxic lead compounds. Thus, all of the synthesized products were tested against human prostate cancer cells (PC3), human lung cancer cells (A549), and human breast adeno-carcinoma cells (MCF-7). The results of inhibitory activity are summarized in the SI. In particular, **3ia** showed the most potent activity (IC_{50} = 22.98 mM against PC3 cells, IC_{50} = 21.06 mM against A549 cells, IC_{50} = 21.29 mM against MCF-7 cells). These results demonstrate that π-extended 3-oxoindole derivatives represent promising leads for the development of new cytotoxic agents.[26]

Even more interestingly, we observed that these C–H activation products show bright cyan fluorescence in aqueous solutions, which renders them attractive for fluorescent imaging in living cells (Figure 2a-c, Figure. S1 and Table S1, see SI for discussion).[27]

In summary, we have developed a cascade Ru(II)-catalyzed C–H alkylation of naphthylamines with diazo compounds for the synthesis of 2,2-disubstituted π-extended 3-oxindoles in water. The unprecedented C–H functionalization/migration is enabled through a rare strategy directly using readily available naphthylamines for the selective *ortho*-C–H alkylation. The C–H functionalization 2,2-disubstituted π-extended 3-oxindole products show promising cytotoxic activity and favorable fluorescence in aqueous solutions that could enable their biological applications in living cells.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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