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A Tethering Directing Group Strategy for Ruthenium-Catalyzed Intramolecular Alkene Hydroarylation

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We report a new catalyst design for N-heterocycle synthesis that utilizes alkene-tethered amide moiety as a directing group for aromatic C-H activation. This tethering directing group strategy is demonstrated in a ruthenium-catalyzed intramolecular alkene hydroarylation with N-aryl acrylamides to form oxindole products.

Transition metal-catalyzed hydroarylation of alkenes, the formal alkene addition by an aromatic C–H bond, has evolved into a powerful strategy for atom-efficient synthesis of alkyl-substituted arenes and heteroarenes.[1,2] Recently, applications of intramolecular alkene hydroarylation for the synthesis of nitrogen- and oxygen-benzoheterocycles have drawn significant attention.[3,4] Existing reports on such cyclization processes have focused on two general approaches to transform arenes containing heteroatom-tethered alkene moieties: (1) electrophilic aromatic substitution (EAS) via alkene activation by a Lewis-acidic metal catalyst and subsequent intramolecular alkene attack by the arene nucleophile (Scheme 1a);[3,5] (2) deprotonation-based cyclometalation via chelation-assisted aromatic C–H activation with an *ortho*-directing group (DG) and subsequent intramolecular alkene insertion into the resulting metal-aryl linkage (Scheme 1b).[4,6] The resulting alkene arylmetalation intermediates in both pathways (complexes **A** and **B**) can transform into hydroarylation products via protonation[3,4] or other products via oxidative functionalization such as Heck-type olefination.[7] From a mechanistic perspective, these two catalytic cyclization strategies are inherently limited in substrate scopes regarding aromatic substituents. For the EAS approach, the reactions generally require electron-donating substituents for substrate activation and suffer significant loss of reactivity with electron-withdrawing substituents.[5] For the cyclometalation approach, the substrate structures are limited by the requirement of having carbonyl derivative-based DGs at a *meta*-position of the tethered alkene moiety.[4] In principle, incorporation of DGs into the tethered alkene moiety would eliminate the need for additional DGs and achieve broader substrate scopes (Scheme 1c). However, there are no reports on catalytic applications of such tethering DG strategy. Although several substrate classes in reported intramolecular alkene hydroarylation contain alkene-tethering amide, ester or sulfamide moieties that are potential DGs, relevant experimental results indicated that they did not provide chelation-assistance in corresponding catalytic cyclization processes.[3,4a] We hypothesize that a major challenge for the tethering DG strategy is the requirement of a balanced metal-DG coordination that not only promotes *ortho*-aromatic C–H activation (formation of intermediate **C** in Scheme 1c), but also allows facile ligand substitution on the resulting metallacycle via DG dissociation and tethered alkene coordination (**C**→**D**). Such alkene complexation is necessary for subsequent ring-closure via intramolecular alkene insertion into the metal-aryl linkage (**D**→**E**).

We herein report a demonstration of the tethering directing group strategy in Ru-catalyzed intramolecular alkene hydroarylation of N-aryl acrylamides (**1**) to form oxindoles (**2**) (Scheme 1d), which are important synthetic targets due to their biological activities.[8] Using the amide moiety as a alkene-tethered DG for aromatic C–H activation (**1**→**C1**), this catalytic cyclization process does not require additional DG assistance and tolerates a broad range of aromatic- and vinyl-substituents. With the redox-neutral nature and high atom-efficiency of alkene hydroarylation, the current method for oxindole synthesis complements existing strategies such as N-aryl acrylamide cyclizations via free radical processes and Heck-type oxidative alkene functionalizations.[7a,7b,8-10]
Current catalyst development has been guided by results from our previous study on Ru/N-heterocyclic carbene (NHC)-catalyzed [3+2] annulation between N-H aromatic ketimines and alkynes, which was promoted by [Ru(cod)(η^3-methallyl)$_2$] (**3a**) as pre-catalyst and IPr ligand (**4a**) (Scheme 2a).[11] The proposed mechanism shared key common features with the envisioned pathway for target oxindole synthesis, which included DG assistance for aromatic C-H activation (imine C=N

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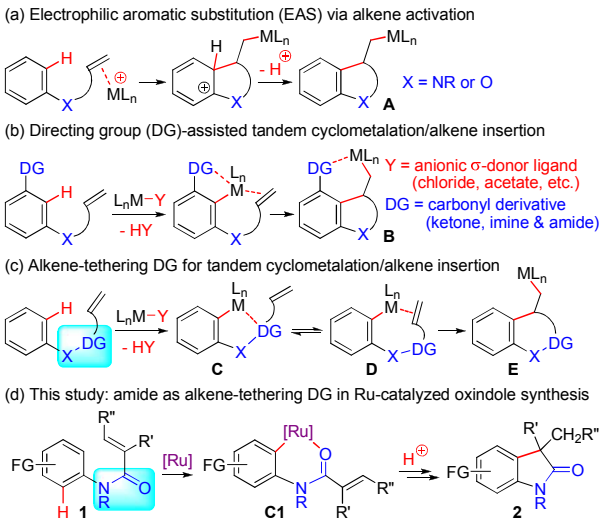
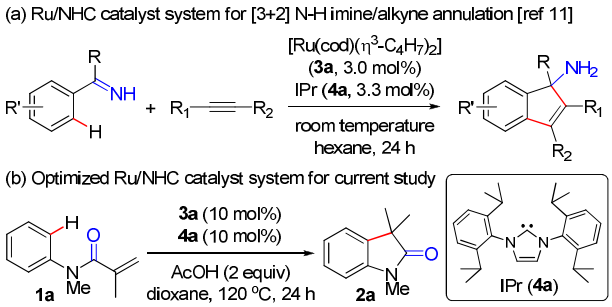
vs. amide C=O) and *5-exo-trig* ring-closure by intramolecular 1,2-insertion (imine into M-alkenyl vs. alkene into M-aryl).[12] Thus, we focused our attention on Ru(II)/NHC catalysts to evaluate conditions for a model reaction with N-methyl-N-phenyl methacrylamide (**1a**) (see Table S1 in Supplementary Information for detailed results). We found that intramolecular alkene hydroarylation with **1a** was promoted by 10 mol% [Ru(cod)(η^3-C_4H_7)$_2$]/IPr (**3a**/**4a**) and 2 equivalents of acetic acid at 120°C and in dioxane solvent. Under these conditions, the oxindole product **2a** was formed in 81% yield over 24 hours and no other by-products were detected.



Scheme 1. Transition metal-mediated intramolecular alkene arylmetalation processes via C–H activation.



Scheme 2. Ru/NHC-catalyzed cyclization processes via directed aromatic C–H activation.

With the standard reaction conditions established, various N-aryl acrylamides (**1**) were studied for Ru(II)-catalyzed intramolecular hydroarylation (Scheme 3). In general, oxindole products were formed without the detection of 2-quinolone by-products.[12] Scope of the N-aryl moiety was studied with N-aryl-N-methylmethacryl-amides to generate products **2a**-**2l'**. Good yields were acquired for substrates with *para*-electron-withdrawing groups including halogens, CF_3, NO_2, acyl, and ester moieties (products **2d**-**2j**), although *para*-iodine and –cyano functionality led to no product formation. In comparison, reduced reactivity was observed for substrates with *para*-electron-donating groups. The *p*-anisyl substrate led to product **2c** in a moderate yield of 65%, while the *p*-tolyl substrate required the use of CF_3CO_2H additive in place of acetic acid to form **2b** in 61% yield.[13] With *ortho*-fluoro substituent, harsher reaction conditions of 140 °C over 48 h was necessary to give product **2k** in 73% yield. With *meta*-fluoro substituent, mixed regioisomers **2l**/**2l'** corresponding to C–H activation *para*- vs. *ortho*-to-F were formed in 84% combined yield and 10:1 selectivity favoring *ortho*-isomer **2l'**. Replacing N-methyl with N-phenyl or N-benzyl moiety led to products **2m** and **2n** in satisfactory yields, with the latter providing a convenient handle for NH-oxindole synthesis via N-deprotection. However, N-acetyl substitution led to substrate decomposition and no detectable oxindole formation.

Scope of the alkene moiety was studied by modification of α- and β-vinyl substituents in N-aryl-N-methyl substrates to form products **2o**-**2v**. Replacing α-methyl with ethyl and acetoxymethyl groups in methacrylamide backbone did not cause major loss of reactivity and gave products **2o** and **2p** in 71% and 74% yield respectively. In contrast, the *cis*-2,3-dimethylacrylamide analog was much less reactive and required the use of CF_3CO_2H additive, 20 mol% Ru/NHC catalyst loading, as well as 155 °C over 72 h to give **2o** in 59% yield. Such harsher conditions were also required for the α-CF_3 analog of **1a** to form product **2q** in 61% yield, giving a rare example of synthesizing 3-CF_3-substituted oxindoles that were not accessible via established methods such as free radical cyclization.[9] The scope of α-substituents was further explored with N-4-nitrophenyl-N-methyl acrylamides to afford products **2r**-**2t** in 69-82% yields containing 3-butyl, -methoxymethyl, and -benzyl groups. Considering the high values of spiro-oxindoles in drug development,[8] we attempted the synthesis of product **2u** with a 1-cyclopentenecarboxylic amide substrate. However, only trace amount of **2u** was formed under standard conditions. A modified catalyst-ligand combination of 10 mol% [Ru(*p*-cymene)Cl_2] (**3b**) and 20 mol% 1,10-phenanthroline ligand allowed **2u** to be synthesized in 38% yield over 48 h of heating at 140 °C. Lastly, removing α-methyl from substrate **1a** led to total loss of reactivity and failure to form corresponding oxindole product **2v**.[14]

Current results on structure-reactivity correlations provide important mechanistic insight as follows: (1) The generally higher reactivity for electron-poor arene substrates than electron-rich arenes (products **2a**-**j**) strongly argues against a hydroarylation pathway via electrophilic aromatic substitution. Thus, we propose an amide-directed C–H activation that occurs by a proton abstraction pathway such as concerted metalation-deprotonation (CMD),[15] and is either the rate-limiting step or a pre-rate-limiting equilibrium. This hypothesis resonates with the proposed C–H activation mechanism in our prior report on Ru/NHC-catalyzed imine/alkyne [3+2] annulation.[11] (2) The significantly lower reactivity for substrates with *ortho*-F or relatively large vinyl substituents (products **2k**, **2o**, **2q** and **2u**) suggests that the cyclization step by intramolecular alkene arylmetalation is sterically inhibited by bulky alkene or arene moieties. (3) The exclusive formation of 5-membered oxindoles over 6-membered 2-quinolones

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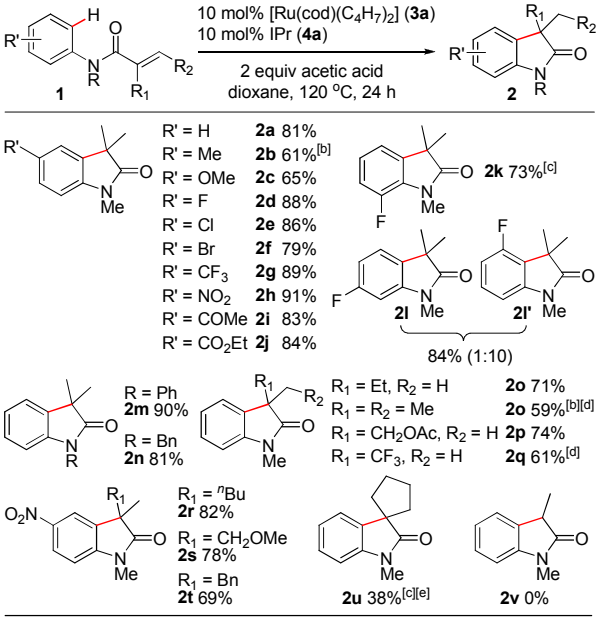
further supports a pronounced steric effect on the cyclization process, with the former favored by formation of a less crowded alkyl C–Ru bond and the later favored by electronic stabilization of the resulting enolate C–Ru bond.[16]

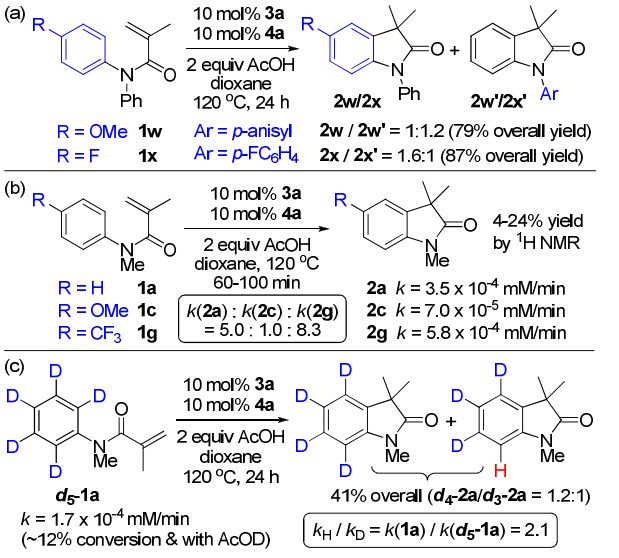
With a major focus on new method development for C–H functionalization, we carried out the following kinetic experiments to explore details of the proposed deprotonation pathway for C–H activation (Scheme 4). Firstly, intramolecular competition with unsymmetrical N,N-diaryl substrates **1w** and **1x** under standard catalytic conditions showed slightly higher C–H alkylation reactivity for more electron-deficient aryls based on yield comparison (1.2:1 for phenyl vs. *p*-anisyl, and 1.6:1 for 4-fluorophenyl vs. phenyl) (Scheme 4a). Such small differences in reactivity may be caused by intramolecular electronic effects imposed by the un-transformed aryl on reacted aryl groups. Secondly, initial-rate ^{1}H NMR kinetics with electronically differentiated substrates **1a**, **1c** and **1g** showed a clear reactivity disparity that favored more electron-deficient aryls, with 8:5:1 relative rate for 4-trifluoromethylphenyl vs. phenyl vs. *p*-anisyl moiety (Scheme 4b). Thirdly, reaction rate comparison between **1a** and its C_6D_5-analog (***d*$_5$-1a**) led to the determination of a normal isotope effect (k_H/k_D=2.1) (Scheme 4c). The reaction with ***d*$_5$-1a** under standard catalytic conditions led to a 1.2:1 product mixture of ***d*$_4$-2a** and ***d*$_3$-2a** in 41% overall yield. Compared to ***d*$_4$-2a**, ***d*$_3$-2a** contained one less aromatic deuterium, which can be attributed to *ortho*-H/D exchange of ***d*$_5$-1a** via equilibrium between Ru-mediated cyclometalation and protonation of Ru-aryl linkage (likely by acetic acid). Based on ^{1}H NMR integration analysis, deuterium incorporation at 3,3-dimethyl substituents was estimated to be 10% and >90% for reactions with ***d*$_5$-1a** using regular and deuterated acetic acid reagents (AcOH and AcOD) respectively. This result supports the involvement of acetic acid additive as an external proton source in the proposed hydroarylation pathway.[13,17] Overall, results from these studies are consistent with a reversible, amide-directed aromatic C–H activation via proton abstraction, which precedes the rate-limiting alkene arylmetalation via insertion into the Ru-aryl linkage.[16,18]

To explore the current method for practical synthetic applications, we first studied hydroarylation of **1a** under scale-up conditions (Scheme 5a). Gratifyingly, solvent volume reduction enabled scale-up reactions to proceed smoothly at reduced catalyst loadings. Thus, gram-scale synthesis of **2a** was successfully carried out with 0.70 mM substrate concentration and 2.5 or 5 mol% catalyst loading to achieve 80% and 92% isolated yield respectively. Next, we incorporated the hydroarylation method into a new synthetic route for an oxindole-based progesterone receptor antagonist (**5**) (Scheme 5b).[19] The synthesis started with turning ethylmalonic acid into 2-ethylacryloyl chloride via an established procedure.[20] The crude product was subjected to Et_3N-mediated amidation with 4-bromo-N-methylaniline to afford N-4-bromophenyl-N-methyl-2-ethylacrylamide (**1y**) in 79% yield over two steps. Intramolecular hydroarylation with **1y** was carried out using 10 mol% Ru/NHC catalyst (**3a**/**4a**) to form oxindole product **2y** in 71% yield. Lastly, Pd-catalyzed Suzuki coupling between **2y** and 4-fluorophenylboronic acid gave desired product **5** in 78% yield. Although **5** was obtained as a racemic mixture, the current method can be potentially developed towards enantioselective catalysis based on the proposed catalyst control in construction of a quaternary chiral center at the oxindole 3-position via intramolecular alkene arylmetalation.



[a] General reaction conditions: **1** (0.17 mmol, 1.0 equiv), **3a** (0.10 equiv), **4a** (0.10 equiv), AcOH (2.0 equiv), dioxane (1.0 mL), 120 °C, 24h; averaged isolated yields of two runs. [b] Using CF_3CO_2H in place of AcOH. [c] Reaction at 140 °C for 48 h. [d] Using 0.20 equiv **3a** and **4a**; reaction at 155 °C for 72 h. [e] Using 10 mol % [Ru(*p*-cymene)Cl_2] (**3b**) as Ru catalyst precursor and 20 mol% 1,10-phenanthroline ligand.

Scheme 3. Scope of Ru-catalyzed intramolecular alkene hydroarylation for oxindole synthesis.[a]



Scheme 4. Results from kinetic studies and deuterium labeling experiments.

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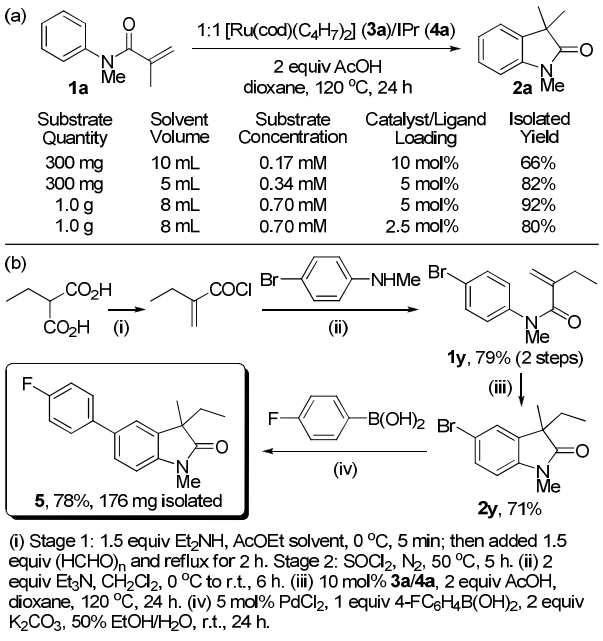

(i) Stage 1: 1.5 equiv Et_2NH, AcOEt solvent, 0 °C, 5 min; then added 1.5 equiv $(HCHO)_n$ and reflux for 2 h. Stage 2: $SOCl_2$, N_2, 50 °C, 5 h. (ii) 2 equiv Et_3N, CH_2Cl_2, 0 °C to r.t., 6 h. (iii) 10 mol% **3a**/**4a**, 2 equiv AcOH, dioxane, 120 °C, 24 h. (iv) 5 mol% $PdCl_2$, 1 equiv 4-$FC_6H_4B(OH)_2$, 2 equiv K_2CO_3, 50% EtOH/H_2O, r.t., 24 h.

Scheme 5. Studies towards practical synthetic applications of Ru-catalyzed intramolecular alkene hydroarylation.

In summary, we have demonstrated the tethering directing group strategy in a Ru-catalyzed oxindole synthesis by intramolecular alkene hydroarylation with N-aryl acrylamides. This redox-neutral, 5-exo-trig cyclization occurs via a proposed tandem sequence of chelation-assisted aromatic C–H activation and intramolecular alkene arylmetalation. By utilizing the amide moiety as an alkene-tethering directing group, the current method complements existing strategies for intramolecular alkene hydroarylation with a broadened substrate scope and does not require the assistance of additional directing groups for aromatic C-H activation. Ongoing efforts are focused on better understanding of the ligand effect on catalyst activity and ligand-based catalyst modification for broader synthetic applications.

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Conflicts of interest

There are no conflicts to declare.

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