Tandem Reactions

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# Ru-Catalyzed Tandem Cross-Metathesis/Intramolecular-Hydroarylation Sequence**

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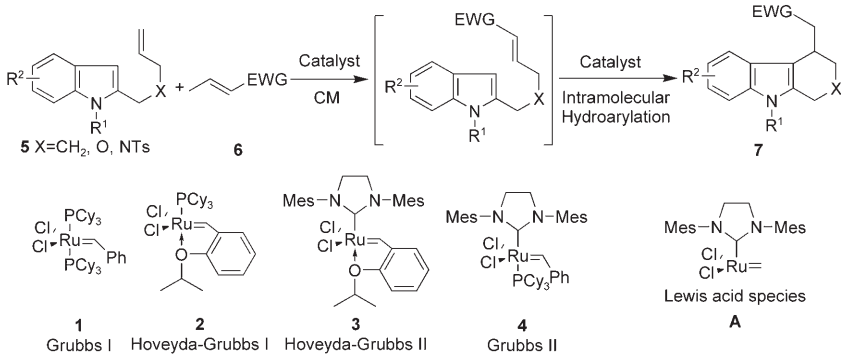
New synthetic strategies that facilitate the rapid and efficient construction of complex molecules remain a preeminent goal in the chemical sciences. Compared to stepwise syntheses, tandem transformations represent an attractive strategy for building molecular complexity because multiple-bond-cleavage and multiple-bond-forming transformations are combined in a single reaction operation.[1] The diversity of reactions catalyzed by Grubbs' ruthenium alkylidenes (**1**–**4**) suggests that potential tandem processes should be achievable by using Ru catalysts.[2] Indeed, such tandem reactions have been reported over the past few years. Elegant examples include ring-closing metathesis (RCM) with transfer dehydrogenation–hydrogenation,[3] RCM with isomerization,[4] RCM with Kharasch addition,[5] RCM with dihydroxylation,[6] enyne metathesis with Claisen rearrangement,[7] enyne metathesis with cyclopropanation,[8] ring-opening metathesis polymerization (ROMP) with hydrogenation,[9] and cross-metathesis (CM) with aza-Michael addition.[10] Critical to the success of these tandem protocols is the use of additional catalysts (such as a Lewis acid[10]) or reagents[4–9] to carry out the sequential processes. In contrast, the use of a single species to catalyze a tandem process is rare.[3]

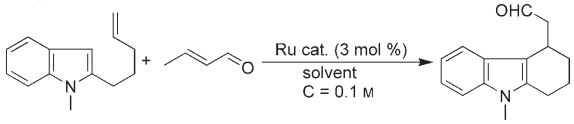



***Scheme 1.*** Concept of the Ru-catalyzed tandem CM/intramolecular-hydroarylation reaction. Ts = 4-toluenesulfonyl, EWG = electron-withdrawing group, Mes = 2,4,6-$Me_3C_6H_2$.

In our search for novel and efficient Ru-catalyzed reactions,[11] we envisaged the ruthenium alkylidene catalyzed cross-metathesis of ω-indolyl alkenes **5** with electron-deficient alkenes **6** as the first step in the tandem reaction leading to polycyclic indoles **7**. We propose that the active ruthenium species **A** (derived from the catalyst precursor) would catalyze not only the CM process, but also an intramolecular hydroarylation owing to its Lewis acidity (Scheme 1). Herein, we describe a new tandem protocol: a one-pot CM/intramolecular-hydroarylation sequence catalyzed by a single metal complex to afford diverse and structurally complex tetrahydrocarbazoles. These heterocycles are an important class of naturally occurring and biologically active molecules,[12,13] which we can now access in a concise fashion (Scheme 1).

Our tandem catalysis strategy was first examined by using compound **5a** and crotonaldehyde (**6a**) and a series of Grubbs catalysts under various reaction conditions (Table 1). Preliminary studies revealed that the proposed catalytic cascade

***Table 1:*** Optimization of conditions for the tandem CM/intramolecular-hydroarylation reaction.[a]




| Entry | Catalyst/solvent | *T* [°C] | *t* | Yield [%][b] |
|---|---|---|---|---|
| 1 | **1**/DCM | 40 | 60 min | 5 |
| 2 | **2**/DCM | 40 | 60 min | 15 |
| 3 | **3**/DCM | 40 | 60 min | 90 |
| 4 | **4**/DCM | 40 | 60 min | 79 |
| 5 | **3**/toluene | 110 | 40 min | 90 |
| 6 | **3**/DCE | 80 | 30 min | 97 |
| 7[c] | **3**/DCE | 80 | 40 min | 93 |
| 8[d] | **3**/DCE | 80 | 12 h | 63 |

[a] Conditions: **5a** (0.30 mmol), **6a** (10 equiv), Ru catalyst (3 mol%), solvent (3 mL). [b] Yield of isolated product. [c] 5 equiv **6a** was used. [d] 1 mol% of catalyst **3** was used.

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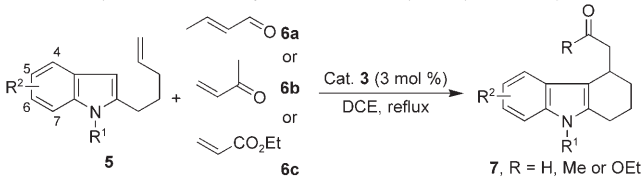
was indeed possible to afford **7a**. Significant amounts of product were formed by using ruthenium alkylidenes **1**–**4** in dichloromethane (DCM) at 40 °C (Table 1, entries 1–4). Among these complexes, ruthenium complex **3** (commonly known as Hoveyda–Grubbs second-generation catalyst) was the most efficient catalyst, providing **7a** in 90% yield (Table 1, entry 3). A brief survey of reaction media showed that 1,2-dichloroethane (DCE) was the optimal solvent for this catalytic sequence. Reducing the **6a**/**5a** reactant ratio to 5:1 (from 10:1) also afforded the product in excellent yield (Table 1, entry 7). A moderate yield was obtained with 1 mol% catalyst loading (Table 1, entry 8). The superior levels of the reaction efficiency provided by ruthenium catalyst **3** in DCE at 80 °C (Table 1, entry 7, 93% yield in 40 min, **5a**/**6a** 1:5) prompted us to select these conditions for further exploration.

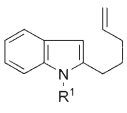
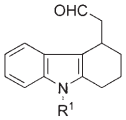
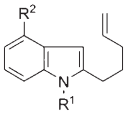
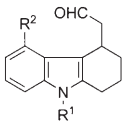
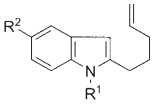
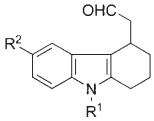
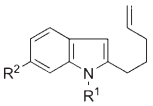
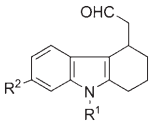
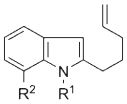
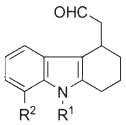
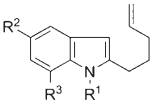
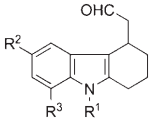
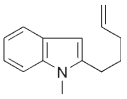
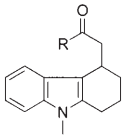
Experiments that probe the scope of substrates are summarized in Table 2. Significant structural variation in the ω-indolyl alkene component can be tolerated. The reaction displays excellent generality and functional-group tolerance. Both free *N*-H and *N*-methyl substrates could be utilized without substantial loss in yield (Table 2, entries 1 vs. 2 and 3 vs. 4). Incorporation of a methyl, ethyl, or methoxy group at positions C4–C7 of the indole ring reveals that steric modification of the indole architecture can be accomplished without compromising reaction efficiency (Table 2, entries 3, 7, 8, 10, and 12–14). Variation in the electronic contribution of the indole ring is possible. For example, methyl, methoxy, Cl, and F groups can be introduced on the indole ring at both the C4 and C5 positions without significant loss in reaction yield or efficiency (Table 2, entries 3–9). Mono-, di-, tri-, and tetrasubstituted indole derivatives can be employed to construct the tetrahydrocarbazole core, a structural motif commonly found among natural alkaloids and drug candidates.[14] As shown in entries 5, 6, 9, 11, and 15 of Table 2, we have successfully utilized halogenated indole substrates in this tandem CM/intramolecular-hydroarylation reaction. Moreover, these products should be valuable for further chemical transformations.[15]

Structural variation in the electron-deficient olefin component is also possible. For example, methyl vinyl ketone (**6b**) and ethyl acrylate (**6c**) are suitable for this protocol (Table 2, entries 16 and 17), affording **7p** and **7q** in 98 and 95% yields, respectively. Note that 10 mol% of $BF_3{\cdot}Et_2O$ is added to complete the intramolecular hydroarylation when **6c** is employed as the substrate (Table 2, entry 17).[17] To demonstrate preparative utility, the tandem reaction of **5a** (5.98 g) with **6a** was performed on a 30-mmol scale with 3 mol% Hoveyda–Grubbs catalyst **3** to afford the corresponding tetrahydrocarbazole (6.14 g) in 90% yield. More importantly, ω-indolyl alkenes **5** are easy to prepare from commercially available reagents through a two-step procedure.[18] Thus, our methodology is feasible on a preparative scale.

As illustrated in Equation (1), this Ru-catalyzed tandem CM/intramolecular-hydroarylation reaction is also general with respect to the nature of the heteroatom in the alkenyl chain of the substrate. Substrates bearing oxygen and nitrogen

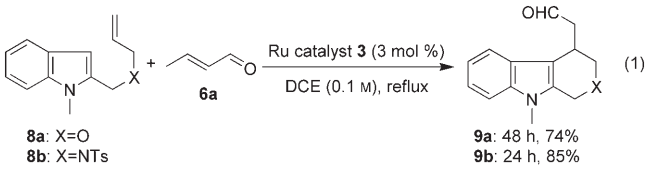
***Table 2:*** Scope of Ru-catalyzed tandem CM/intramolecular-hydroarylation sequence.[a]




| Entry | Alkenyl indole | | Product | | $R^1$, $R^2$, $R^3$ | *t* [min] | Yield [%][b] |
|---|---|---|---|---|---|---|---|
| 1 |  | **5a** |  | **7a** | $R^1$ = Me | 40 | 93 |
| 2 | | **5b** | | **7b** | $R^1$ = H | 70 | 82 |
| 3 |  | **5c** |  | **7c** | $R^1$ = Me, $R^2$ = Me | 40 | 95 |
| 4 | | **5d** | | **7d** | $R^1$ = H, $R^2$ = Me | 40 | 82 |
| 5 | | **5e** | | **7e** | $R^1$ = Me, $R^2$ = Cl | 90 | 86 |
| 6 | | **5f** | | **7f** | $R^1$ = Me, $R^2$ = F | 90 | 90 |
| 7 |  | **5g** |  | **7g** | $R^1$ = Me, $R^2$ = Me | 40 | 90 |
| 8 | | **5h** | | **7h** | $R^1$ = Me, $R^2$ = OMe | 90 | 88 |
| 9 | | **5i** | | **7i** | $R^1$ = Me, $R^2$ = F | 90 | 95 |
| 10 |  | **5j** |  | **7j** | $R^1$ = Me, $R^2$ = Me | 30 | 88 |
| 11 | | **5k** | | **7k** | $R^1$ = Me, $R^2$ = Cl | 55 | 81 |
| 12 |  | **5l** |  | **7l** | $R^1$ = Me, $R^2$ = Me | 30 | 96 |
| 13 | | **5m** | | **7m** | $R^1$ = Me, $R^2$ = Et | 60 | 80 |
| 14 |  | **5n** |  | **7n** | $R^1$ = Me, $R^2$ = Me, $R^3$ = Me | 30 | 91 |
| 15[c] | | **5o** | | **7o** | $R^1$ = Me, $R^2$ = Me, $R^3$ = Cl | 40 | 99 |
| 16[d] |  | **5a** |  | **7p** | R = Me | 30 | 98 |
| 17[e] | | **5a** | | **7q** | R = OEt | 90 | 95 |

[a] Conditions: **5** (0.30 mmol), **6** (5 equiv), **3** (3 mol%), DCE (3 mL). [b] Yield of isolated product. [c] The structure of **7o** was further confirmed by X-ray analysis; see reference [16]. [d] Methyl vinyl ketone (**6b**) was used. [e] Ethyl acrylate (**6c**) was used, and 10 mol% $BF_3{\cdot}Et_2O$ was added.

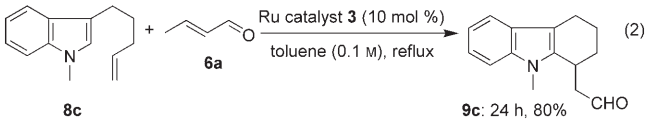



(1)

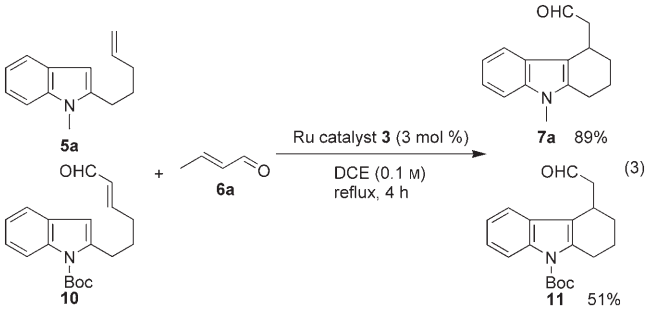
atoms in the alkenyl chain undergo tandem catalysis to form **9a** and **9b** in 74 and 85% yield, respectively.

To expand the scope of this tandem reaction, **8c**, which can be readily prepared from commercially available indole and 5-bromo-1-pentene by a known procedure,[19] was examined under our standard conditions. To our delight, the reaction worked well with the use of catalyst **3** in anhydrous toluene at 110 °C, affording **9c** in 80% yield of isolated product [Eq. (2)].

Experiments to classify the Lewis acidic nature of the ruthenium species **A** were performed by using N-protected **10**[18,20] as the substrate. It was found that refluxing **10** alone or together with 3 mol% **3** in DCE for 4 h did not give any hydroarylation product **11**. However, the experiment with a mixture of **10** (0.3 mmol), **5a** (0.3 mmol), and **6a** (1.5 mmol) under the optimized conditions does give **11** in 51% yield, along with **7a** in 89% yield [Eq. (3); Boc = *tert*-




(2)

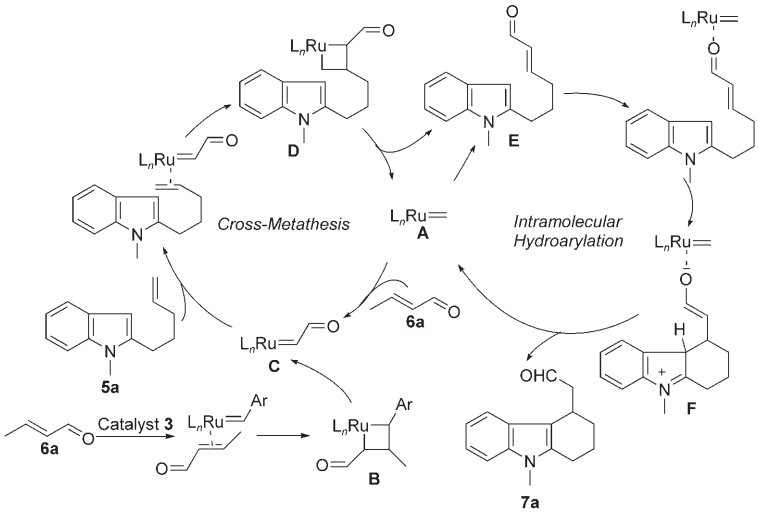



(3)

butoxycarbonyl]. These results show that the active ruthenium methylene **A** is generated after the catalytic cycle of the CM reaction between **5a** and crotonaldehyde. This Ru species acts as a Lewis acid to catalyze the intramolecular hydroarylation of **10** and afford the cyclization product **11**.

Using the reaction of alkenyl indole **5a** and crotonaldehyde as a model, a possible mechanism for the ruthenium-catalyzed tandem CM/intramolecular-hydroarylation reaction is outlined in Scheme 2. In the presence of ruthenium catalyst **3**, cross-metathesis of **5a** and **6a** occurs.[3,21] After a single turnover, the CM reaction generates intermediate **E** and methylidene complex **A**. We envisioned that the ruthenium complex **A** (which can accept electrons owing to its empty d orbital) acts as a Lewis acid and activates **E**. Subsequent intramolecular cyclization forms indolium **F**, which undergoes aromatization by loss of a proton to afford **7a** and regenerate catalyst **A** for the next catalytic cycle.

In summary, a new process combining a cross-metathesis step and an intramolecular hydroarylation has been devel-




***Scheme 2.*** Proposed mechanism for the ruthenium alkylidene catalyzed tandem CM/intramolecular-hydroarylation sequence.

oped for the efficient synthesis of complex multiring heterocyclic compounds. The combination of two mechanistically distinct transformations relying on a single catalyst precursor makes this tandem reaction particularly useful. Further studies to develop an asymmetric version[22] of this reaction are in progress.

## Experimental Section

Representative procedure: Ru catalyst **3** (0.009 mmol, 3 mol% based on **5a**) was added to a mixture of alkenyl indole **5a** (0.30 mmol), crotonaldehyde (**6a**; 1.5 mmol), and DCE (3 mL). The reaction mixture was then stirred in boiling DCE. After completion of the reaction (as determined by TLC), the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate 10:1) to give pure **7a**.

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**Keywords:** cross-metathesis · homogeneous catalysis · hydroarylation · ruthenium · tandem reactions

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