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# Cascade Reaction of Alkynols and 7-Oxabenzonorbornadienes Involving Transient Hemiketal Group Directed C−H Activation and Synergistic $Rh^{III}/Sc^{III}$ Catalysis

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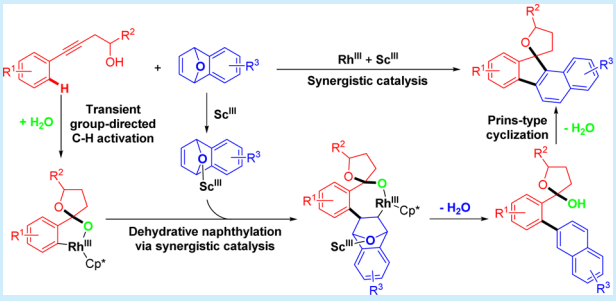
Supporting Information

**ABSTRACT:** As the first cascade C−H activation directed by a transient group, reaction of alkynols and 7-oxabenzonorbornadienes has been achieved via synergistic rhodium and scandium catalysis to afford spirocyclic dihydrobenzo[*a*]fluorenefurans. This transformation proceeds by a transient hemiketal group directed C−H activation, dehydrative naphthylation, and intramolecular Prins-type cyclization. Mechanistic studies and density functional theory calculations indicate that the rate-determining step is C−H bond cleavage and both the transient hemiketal group and synergistic $Rh^{III}/Sc^{III}$ catalysis play key roles.




Direct, transition-metal-catalyzed C−H activation has emerged as a powerful and promising tool for constructing diverse heterocyclic systems.[1] They usually require that the substrate contains a directing group that accelerates the reaction and ensures regioselectivity. Preinstallation and removal of these directing groups sometimes require tedious procedures and harsh reaction conditions incompatible with other functional groups. To avoid these problems, transient group-directed C−H activation has been developed and successfully applied in the presence of $Rh^{I}$ or $Pd^{II}$ catalyst.[2,3] Using 2-amino-3-picoline as the transient directing group, Jun reported an $Rh^{I}$-catalyzed hydroacylation of aldehyde with alkene via aldehydic C−H activation.[2a] Subsequently, Dong reported $Rh^{I}$-catalyzed *α*-alkylation and -alkenylation of ketones via vinyl C−H activation, in which an enamine intermediate with a pyridine moiety acts as the transient directing group.[2b−d] Using the reversible in situ transesterification strategy of phosphinite ligand and phenol, in which the phosphinite ligand acts as the transient directing group, Lewis reported $Rh^{I}$-catalyzed *ortho*-alkylation of phenols,[2e] while Bedford developed $Rh^{I}$-catalyzed *ortho*-arylation of phenols.[2f] More recently, Yu reported $Pd^{II}$-catalyzed arylation of aldehydes and ketones using amino acid as the transient directing group,[3a] while Dong published the $Pd^{II}$-catalyzed arylation of free primary alkylamines and anilines using 8-formylquinoline-derived imine as the transient directing group.[3b] However, the more challenging cascade C−H activation directed by a transient group has not been reported yet.

Alkynols have attracted substantial interest as important synthons because they can undergo cycloisomerization to yield *exo*- or *endo*-heterocycles with 100% atom efficiency, fulfilling the requirements of green chemistry.[4] Moreover, cascade reactions of alkynols have also been extensively reported and successfully applied for the synthesis of oxygen-containing heterocyclic compounds.[5−10] Most of these reactions proceed via cycloisomerization of alkynols, together with diverse transformations[6] such as Prins-type cyclization,[7] Diels−Alder reaction,[8] and Povarov reaction.[9] Recently, we developed a series of cascade reactions of alkynols,[10] including a cascade reaction of alkynols with alkynes involving in situ generated group-directed C−H activation.[10d]

Cascade reactions can be supported by synergistic catalysis, in which two reactants are simultaneously activated by two different catalysts in a single chemical reaction. This type of catalysis can make previously elusive or unattainable reactions possible, and it can substantially increase the efficiency as well as chemo-, regio-, and stereoselectivity of existing reactions.[11] Typical synergistic catalytic systems are organo−metal,[12] metal−metal,[13] and acid−[14a] or organo−photosensitizer.[14b,c] To our knowledge, most reports of synergistic catalysis have involved one-step reactions. Few studies have used two metals as synergistic catalysts in multistep cascade C−H activation.[13]

Taking advantage of the ring-opening ability of 7-oxabenzonorbornadiene for constructing new carbon−carbon and carbon−heteratom bonds,[15] we report here a novel cascade reaction of alkynols and 7-oxabenzonorbornadienes by synergistic $Rh^{III}/Sc^{III}$ catalysis. This reaction proceeds through a transient hemiketal group directed C−H activation, followed by

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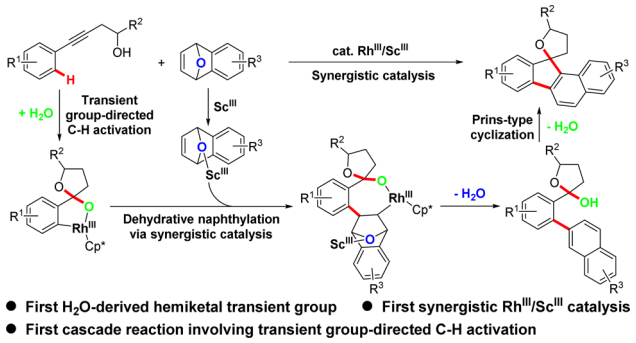
dehydrative naphthylation and intramolecular Prins-type cyclization. The process yields spirocyclic dihydrobenzo[*a*]-fluorenefurans with excellent regioselectivity and good yield (Scheme 1). Mechanistic studies and density functional theory

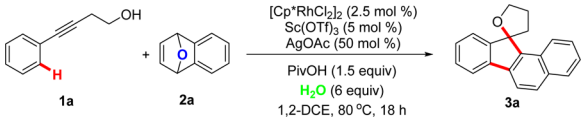
**Scheme 1. Cascade C−H Activation Directed by a Transient Hemiketal Group**




(DFT) calculations confirm that both the transient $H_2O$-derived hemiketal group and synergistic $Rh^{III}/Sc^{III}$ catalysis play key roles in the casacde reaction. To the best of our knowledge, this protocol is the first example of cascade C−H activation directed by a transient group.

We began investigations of the cascade C−H activation using **1a** and **2a** as model substrates. After screening various reaction conditions, we isolated the desired pirocyclic dihydrobenzo[*a*]-fluorenefuran **3a** in 63% yield using the catalysts $[Cp^*RhCl_2]_2$ (2.5 mol %) and $Sc(OTf)_3$ (5 mol %) and the additives AgOAc (0.5 equiv), PivOH (1.5 equiv), and $H_2O$ (6 equiv) (Table 1, entry 1). Then we clarified the role of each reactant by performing various control experiments. As expected, rhodium

**Table 1. Optimized Reaction Conditions**



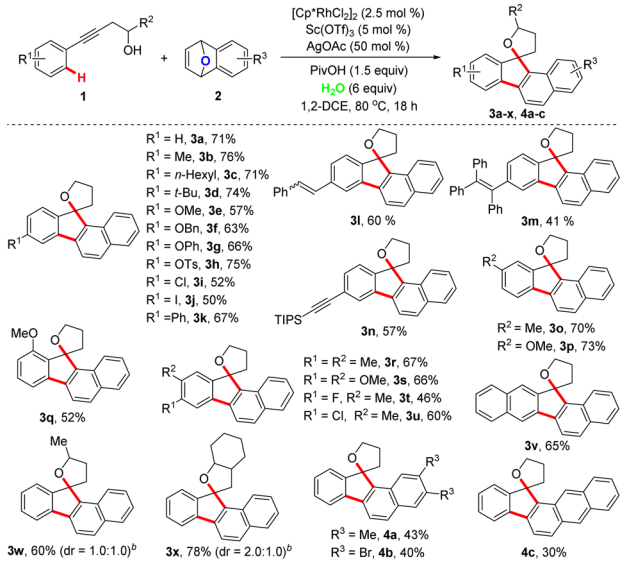

| entry | variations from reaction conditions[a] | yield[b] (%) |
|---|---|---|
| 1 | | 63 |
| 2 | without $[Cp^*RhCl_2]_2$ or $Sc(OTf)_3$ | nd |
| 3 | 5 mol % instead of 2.5 mol % $[Cp^*RhCl_2]_2$ | 62 |
| 4 | 10 mol % instead of 5 mol % $Sc(OTf)_3$ | 18 |
| 5 | $Cp^*CoI_2(CO)$ or $[RuCl_2(p\text{-Cymene})]_2$ instead of $[Cp^*RhCl_2]_2$ | nd |
| 6 | $ScCl_3$ or $Sc(OAc)_3$ used instead of $Sc(OTf)_3$ | nd |
| 7 | CsOAc, NaOAc, or NaOPiv instead of AgOAc | nd |
| 8 | 100 mol % instead of 50 mol % AgOAc | 60 |
| 9 | without PivOH | 22 |
| 10 | HOTf instead of PivOH | nd |
| 11 | HFIP instead of PivOH | 18 |
| 12 | without $H_2O$ | 7 |
| 13 | 3 equiv instead of 6 equiv of $H_2O$ | 61 |
| 14 | 12 equiv instead of 6 equiv of $H_2O$ | 60 |
| **15** | **1,2-DCE (3 mL) used** | **71** |

[a]Reaction conditions: **1a** (0.45 mmol), **2a** (0.30 mmol), $[Cp^*RhCl_2]_2$ (0.0075 mmol), $Sc(OTf)_3$ (0.015 mmol), AgOAc (0.15 mmol), PivOH (0.45 mmol), $H_2O$ (1.8 mmol), 1,2-DCE (1.5 mL), 80 °C, 18 h, under $N_2$. [b]Yields of isolated products are given. nd = not detected.

and scandium played pivotal roles in the reaction (entry 2). While 2.5 mol % of $[Cp^*RhCl_2]_2$ and 5 mol % of $Sc(OTf)_3$ proved to be optimal, the yield dropped only marginally with 5 mol % equivalents of $[Cp^*RhCl_2]_2$ (entries 3 and 4). Other common catalysts such as $Cp^*CoI_2(CO)$ or $[RuCl_2(p\text{-Cymene})]_2$ were less effective, as were other scandium catalysts such as $ScCl_3$ or $Sc(OAc)_3$ (entries 5 and 6). Testing various additives showed that AgOAc (50 mol %) facilitates cascade C−H activation (entries 7 and 8). Omitting PivOH led to low yields of product **3a** (entries 9−11), suggesting that the additive creates suitably acidic conditions for the reaction. Omitting $H_2O$ led to very low yields of **3a**, confirming its essential role (entry 12). Increasing or decreasing $H_2O$ loading did not improve the yield (entries 13 and 14). Interestingly, enhancing 1,2-DCE from 1.5 to 3 mL increased the yield to 71% (entry 15), suggesting that the amount of solvent provides a suitable concentration of reactants to promote the formation of desired product.

With the optimized reaction conditions in hand, we explored the scope of this cascade reaction (Scheme 2). Alkynols with

**Scheme 2. Substrate Scope[a]**




[a]Reaction conditions: **1** (0.45 mmol), **2** (0.30 mmol), $[Cp^*RhCl_2]_2$ (0.0075 mmol), $Sc(OTf)_3$ (0.015 mmol), AgOAc (0.15 mmol), PivOH (0.45 mmol), $H_2O$ (1.8 mmol), 1,2-DCE (3 mL), 80 °C, 18 h, under $N_2$. Yields of isolated products are given. [b]The diastereomeric ratio was determined using $^1H$ NMR spectroscopy.

functional groups such as Me, *n*-hexyl, *t*-Bu, MeO, BnO, PhO, TsO, Cl, or I at the *para* position of the aryl ring were tolerated, giving the desired products **3b−j** in good yields. Single-crystal X-ray diffraction analysis of **3e** confirmed the structure of products (see the Supporting Information). However, alkynols bearing strongly electron-withdrawing groups ($CF_3$ or CN) did not react. Alkynols substituted with phenyl, alkenyl, or ethynyl at the *para* position of the aryl ring were also tolerated, giving the products **3k−n** in good yields.

Alkynols substituted with *m*-Me or -MeO reacted well with **2a**, selectively producing **3o** and **3p** as single isomers in 70% and 73% yields, respectively. Alkynols substituted with *o*-MeO also gave the desired product **3q** in slightly lower yield of 52%. Moreover, the reaction tolerated multi-substitutions at both the *meta* and *para* positions, affording products **3r−u** as single isomers in 46−67% yields. The substrate 4-(naphthalen-2-



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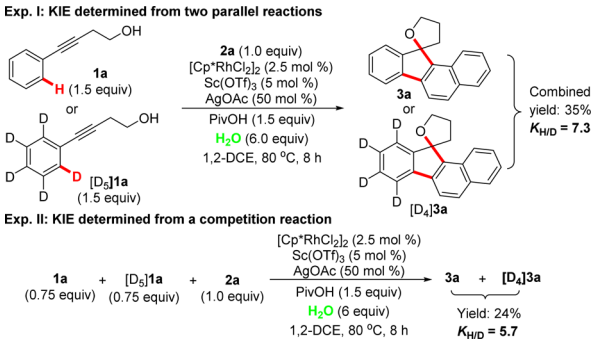
yl)but-3-yn-1-ol reacted with **2a**, giving a single isomer **3v** in 65% yield. Heteroaryl alkynols, in contrast, did not react with **2a** to form the desired products under the current conditions.

Alkynols substituted with secondary hydroxyl groups gave products **3w** and **3x** in respective yields of 60% and 78%, but those substituted with tertiary hydroxyl groups did not participate in the reaction. These results indicate that hindrance near the hydroxyl group inhibits the reaction. Not only the bicyclic olefin **2a** but also the substituted 7-oxabenzonorbornadienes reacted efficiently with **1a**, giving the products **4a**, **4b**, and **4c** in moderate yields. Note that the other alkyl- or arylalkenes such as *tert*-butyl acrylate, 1-hexene, norbornene, and styrene did not react with **1a** to give the corresponding spirocyclic products.

To shed light on the mechanism of cascade reaction, kinetic isotope effects (KIEs) were measured (Scheme 3). Two parallel

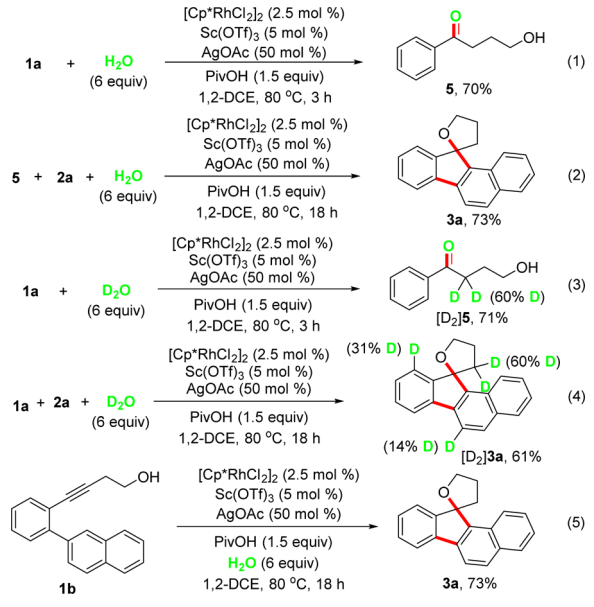
**Scheme 3. Studies of the Kinetic Isotope Effects**




reactions determined a KIE value of 7.3. A competition reaction gave a KIE value of 5.7. These results suggest that C−H bond cleavage is the rate-determining step in the cascade reaction.

To explore the mechanism of the cascade reaction in greater detail, we performed some control experiments (Scheme 4). Under standard conditions but in the absence of **2a**, **1a** reacted with $H_2O$ to form hydration product **5** in 70% isolated yield (eq 1). When **5** reacted with **2a** under the same conditions, the product **3a** was isolated in 73% yield (eq 2). Similar yields from

**Scheme 4. Control Experiments**

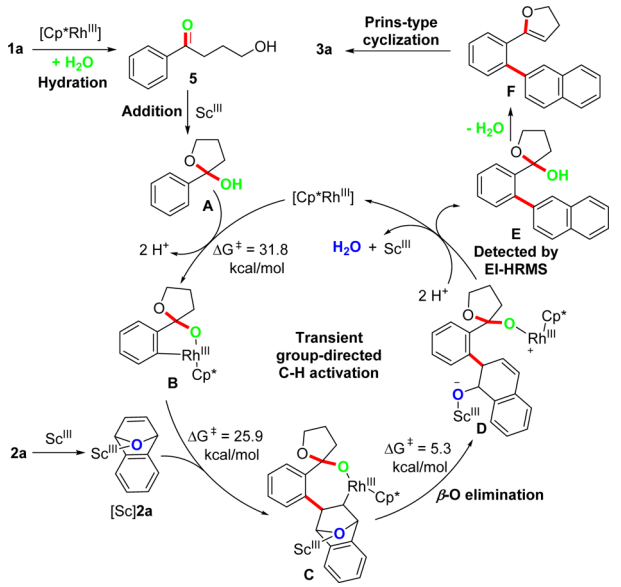



**1a** and **5** identify the hydration product **5** as the key intermediate in the cascade reaction.

Morever, the reaction was carried out with **1a** and $D_2O$ in the absence of **2a**, affording product [$D_2$]**5** (60% deuteration ratio) in 71% yield (eq 3). When the reaction was repeated in the presence of **2a**, [$D_2$]**3a** (60% deuteration ratio in tetrahydrofuran ring) was isolated in a slightly lower yield of 61%, and H/D exchange was observed from the different aryl ring of [$D_2$]**3a** with deuteration ratios of 31% and 14% (eq 4), respectively. These results further demonstrate that C−H bond cleavage is a reversible step in the cascade reaction.

Next, we performed an intramolecular reaction under standard conditions using alkynol **1b** as reactant (eq 5). Product **3a** was isolated in 73% yield, and a similar yield was obtained when the reaction was repeated in the absence of [$Cp^*RhCl_2$]$_2$, Sc(OTf)$_3$, or $H_2O$. When **1a** was allowed to react with **2a** within 6 h under standard conditions, the naphthylation intermediate **E** was detectable by EI-HRMS (calcd for $C_{20}H_{18}O_2$ [M]$^+$ 290.1307, found 290.1310, Scheme 5). These results suggest that the reaction involves a Prins-type cyclization step.

**Scheme 5. Proposed Mechanism**




To clarify the role of Sc(OTf)$_3$ in the cascade reaction, we performed DFT calculations on the direct C−H activation step involving **1a** and **2a** (see the Supporting Information for details) and established a synergistic $Rh^{III}/Sc^{III}$ catalysis pathway to be the lowest energy (Scheme 5). In the pathway, hydration/addition of alkynol **1a** and $H_2O$ forms the hemiketal **A** in the presence of Sc(OTf)$_3$ and active rhodium catalyst [$Cp^*Rh^{III}$] generated from the [$Cp^*RhCl_2$]$_2$/AgOAc. Then, **A** undergoes hydroxyl-directed C−H activation assisted by a pivalate or acetate anion via concerted metalation−deprotonation for which the calculated activation free energy is 31.8 kcal/mol.[16,17] This step reversibly generates arene rhodium intermediate **B**, which undergoes alkene insertion with [Sc]**2a** derived from **2a** and Sc(OTf)$_3$ with an activation barrier as low as 25.9 kcal/mol, generating bimetallic intermediate **C**. Subsequent *β*-oxygen elimination with a lower activation free energy of 5.3 kcal/mol generates the intermediate **D**. However, in the absence of Sc(OTf)$_3$, intermediate **C** would have to overcome a higher activation free energy of 46.6 kcal/mol to afford the *β*-oxygen



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elimination intermediate **D**. This calculated activation free energy is much higher than the free energy of C−H activation (31.8 kcal/mol), which is inconsistent with our experiments identifying C−H bond cleavage as the rate-determining step. Finally, protonolysis and dehydration regenerate the active rhodium catalyst [Cp*$Rh^{III}$] and release the detected naphthylation intermediate **E**. Dehydration in **E** occurs preferentially, forming the cyclic enol ether intermediate **F**, which undergoes intramolecular Prins-type cyclization to give the product **3a**.

In summary, we have developed a novel cascade reaction of alkynols and 7-oxabenzonorbornadienes driven by the synergistic merger of rhodium and scandium catalysts. The process provides spirocyclic dihydrobenzo[*a*]fluorenefurans with excellent regioselectivity and good yields. The process involves intramolecular addition of the hydration product of alkynols, hemiketal-directed C−H activation, dehydrative naphthylation, and Prins-type cyclization. Experimental studies and DFT calculations identify C−H bond cleavage as the rate-determining step, and they indicate that both the transient hemiketal group and the synergistic $Rh^{III}/Sc^{III}$ catalysis are key to the selective dehydrative naphthylation of C−H bonds. This appears to be the first report of the cascade C−H activation directed by a transient group, which may open a door for the development of more cascade reactions involving transient group-directed C−H activation as highly efficient strategies to construct complicated structures.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02587.

Experimental procedures, characterization data (NMR, HRMS, etc.), spectra of the products, and DFT data (PDF)

X-ray crystal structures of **3e** (CIF)

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### Notes

The authors declare no competing financial interest.

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