Cyclization Reactions

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Tunable Cascade Reactions of Alkynols with Alkynes under Combined $Sc(OTf)_3$ and Rhodium Catalysis

*Deng Yuan Li, Hao Jie Chen, and Pei Nian Liu**

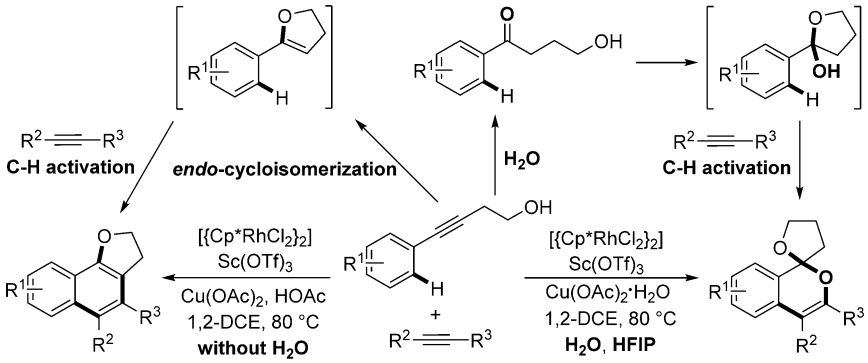
Abstract: *Two tunable cascade reactions of alkynols and alkynes have been developed by combining $Sc(OTf)_3$ and rhodium catalysis. In the absence of H_2O, an endo-cycloisomerization/C–H activation cascade reaction provided 2,3-dihydronaphtho[1,2-b]furans in good to high yields. In the presence of H_2O, the product of alkynol hydration underwent an addition/C–H activation cascade reaction with an alkyne, which led to the formation of 4,5-dihydro-3H-spiro[furan-2,1′-isochromene] derivatives in good yields under mild reaction conditions. Mechanistic studies of the cascade reactions indicated that the rate-determining step involves C–H bond cleavage and that the hydration of the alkynol plays a key role in switching between the two reaction pathways.*

Transition-metal-catalyzed cascade transformations of alkynols have attracted extensive interest because they enable the highly efficient synthesis of oxygen-containing heterocyclic compounds, including natural products and drugs.[1–9] Most of these reactions are catalyzed by tungsten,[2] gold,[3] platinum,[4] palladium,[5] and copper catalysts[6] and involve intramolecular cycloisomerization of alkynols together with diverse transformations, such as a Prins-type cyclization,[7] Diels–Alder reaction,[8] or Povarov reaction.[9] However, a cascade reaction of alkynols that involves C–H activation has not been reported.

Rhodium-catalyzed C–H activation has emerged as a powerful and promising tool for the construction of diverse heterocyclic systems in organic synthesis.[10] Activation usually requires the presence of a directing group to accelerate the reaction and ensure regioselectivity. Weakly coordinating groups, such as aliphatic hydroxy groups, have been used as directing groups in C–H activation.[11] Miura, Satoh, and co-workers reported a rhodium-catalyzed, hydroxy-group-directed C–H bond activation of benzyl and allyl alcohols for the preparation of isochromene derivatives.[12a] Nakanowatari and Ackermann developed a similar transformation catalyzed by a ruthenium complex.[12b]

As part of our research program on the construction of heterocycles from alkynols[13] and rhodium-catalyzed C–H activation,[14] we report herein the development of two tunable cascade reactions of alkynols with alkynes by merging $Sc(OTf)_3$ and rhodium catalysis. The same starting material was transformed into two different types of products: 2,3-dihydronaphtho[1,2-*b*]furans and 4,5-dihydro-3*H*-spiro-[furan-2,1′-isochromene] derivatives (Scheme 1).

The reaction of alkynol **1a** with alkyne **2a** was initially performed in 1,2-dichloroethane (1,2-DCE) in the presence of $[\{Cp^*RhCl_2\}_2]$ (2.5 mol%) and $Cu(OAc)_2\cdot H_2O$ (2.0 equiv) at 80 °C. When $AgSbF_6$ (10 mol%) was added, the product **3a** was obtained in 33% yield along with an unexpected product **4a** in 10% yield (Table 1, entries 1 and 2). Single-crystal X-ray diffraction analysis of product **4a**[15] confirmed the structure. We then focused on optimizing the formation of product **3a**. Lower yields were observed with other rhodium catalysts, such as $[Cp^*Rh(OAc)_2]$, $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$, and $[Cp^*Rh(CH_3CN)_3](BF_4)_2$. With commonly used oxidants, such as AgOAc, $Na_2S_2O_8$, and $PhI(OAc)_2$, low yields were observed (Table 1, entries 3–5). The screening of various silver salts showed that AgOTf gave a better yield than AgOAc or $AgPF_6$ (Table 1, entries 6–8). The presence of AgOTf might promote the formation of an active cationic rhodium catalyst with trifluoromethanesulfonate anion as the counter ion. Of the Lewis acids tested, $Sc(OTf)_3$ gave the best result (Table 1, entries 9–12). The addition of AcOH (1 equiv) and the use anhydrous copper acetate increased



Scheme 1. Tunable cascade reactions of alkynols with alkynes. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl, Tf = trifluoromethanesulfonyl.

[*] Dr. D. Y. Li, H. J. Chen, Prof. Dr. P. N. Liu
Shanghai Key Laboratory of Functional Materials Chemistry
Key Lab for Advanced Materials and Institute of Fine Chemicals
East China University of Science and Technology
Meilong Road 130, Shanghai, 200237 (China)
E-mail: liupn@ecust.edu.cn

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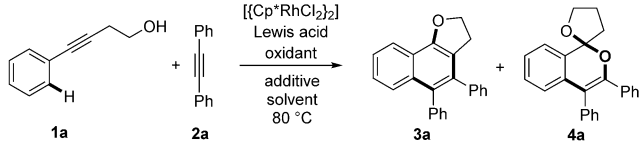
Table 1: Optimization of the cascade reactions of alkynol **1a** with alkyne **2a**.[a]

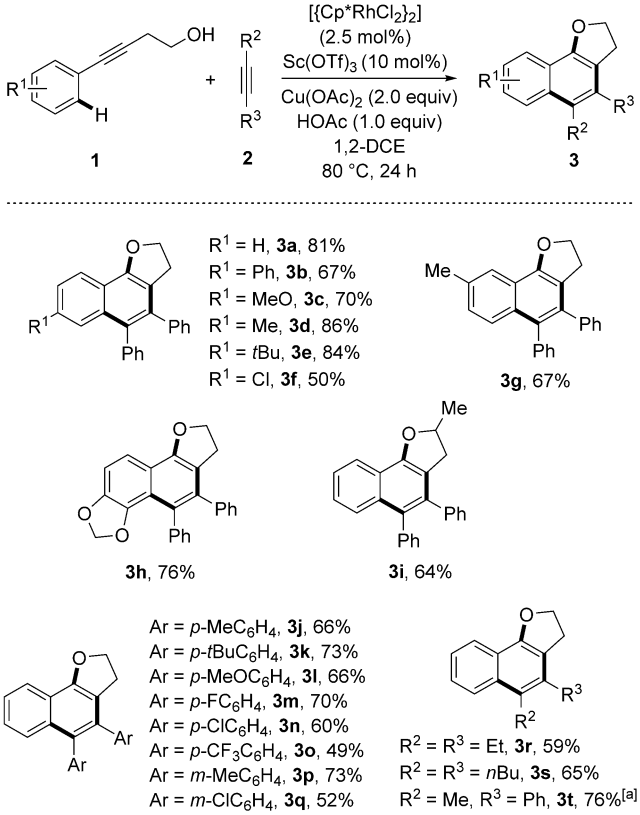


1a 2a 3a 4a

Entry	Lewis acid	Oxidant	Additive	Yield [%][b]	
				3a	**4a**
1	–	$Cu(OAc)_2{\cdot}H_2O$	–	ND	ND
2	$AgSbF_6$	$Cu(OAc)_2{\cdot}H_2O$	–	33	10
3	$AgSbF_6$	AgOAc	–	16	–
4	$AgSbF_6$	$Na_2S_2O_8$	–	trace	–
5	$AgSbF_6$	$PhI(OAc)_2$	–	ND	–
6	AgOAc	$Cu(OAc)_2{\cdot}H_2O$	–	ND	–
7	$AgBF_4$	$Cu(OAc)_2{\cdot}H_2O$	–	44	trace
8	AgOTf	$Cu(OAc)_2{\cdot}H_2O$	–	64	trace
9	$Cu(OTf)_2$	$Cu(OAc)_2{\cdot}H_2O$	–	71	trace
10	$Fe(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	–	63	trace
11	$Ce(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	–	76	trace
12	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	–	78	trace
13	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	AcOH	80	trace
14	**$Sc(OTf)_3$**	**$Cu(OAc)_2$**	**AcOH**	**81**	**–**
15[c]	$Sc(OTf)_3$	$Cu(OAc)_2$	AcOH	ND	ND
16	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	H_2O	71	trace
17	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	PivOH	55	trace
18	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	CF_3SO_3H	39	trace
19	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	HFIP	30	48
20[d]	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	HFIP + H_2O	trace	72
21[e]	**$Sc(OTf)_3$**	**$Cu(OAc)_2{\cdot}H_2O$**	**HFIP + H_2O**	**trace**	**77**
22[f]	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	HFIP + H_2O	trace	75
23[e,g]	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	HFIP + H_2O	24	36
24[e,h]	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	HFIP + H_2O	16	56
25[e,i]	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	HFIP + H_2O	11	59
26[e]	$Sc(OTf)_3$	$Cu(OAc)_2{\cdot}H_2O$	H_2O	18	55

[a] Reaction conditions: **1a** (0.45 mmol), **2a** (0.30 mmol), [{Cp*RhCl$_2$}$_2$] (0.0075 mmol), Lewis acid (0.03 mmol), oxidant (0.60 mmol), additive (0.30 mmol), 1,2-DCE (1.5 mL), 80 °C, 24 h, nitrogen atmosphere. [b] Yield of the isolated product. [c] The reaction was carried out without [{Cp*RhCl$_2$}$_2$]. [d] H_2O (1.8 mmol). [e] H_2O (2.7 mmol), 30 h. [f] H_2O (3.6 mmol), 48 h. [g] HFIP (0.60 mmol). [h] $Sc(OTf)_3$ (0.06 mmol). [i] $Cu(OAc)_2{\cdot}H_2O$ (0.36 mmol). ND = not detected, Piv = pivaloyl.

After optimizing the reaction conditions for the *endo*-cycloisomerization/C–H activation cascade reaction, we investigated the scope of the reaction by varying the substrates (Scheme 2). Alkynols with various substituents,



1 2 3

Scheme 2. Scope of the cascade reaction of alkynols **1** with alkynes **2** to give 2,3-dihydronaphtho[1,2-*b*]furans **3**. Reaction conditions: **1** (0.45 mmol), **2** (0.30 mmol), [{Cp*RhCl$_2$}$_2$] (0.0075 mmol), $Sc(OTf)_3$ (0.03 mmol), HOAc (0.30 mmol), $Cu(OAc)_2$ (0.60 mmol), 1,2-DCE (1.5 mL), 80 °C, nitrogen atmosphere. Yields are for the isolated product. [a] The product contained the non-isolable isomer **3t′** (R^2 = Ph, R^3 = Me; 3% yield).

the yield of product **3a** to 81% (Table 1, entries 13 and 14). The essential role of the rhodium catalyst was confirmed by a reaction in its absence, in which no detectable product **3a** was formed (Table 1, entry 15).

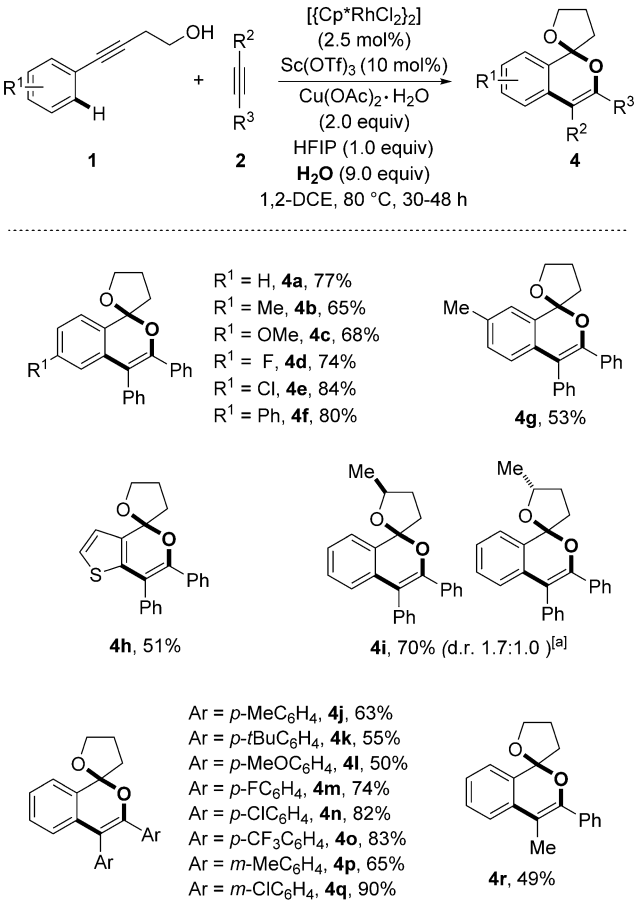
We then optimized the reaction conditions for the formation of product **4a** with $Cu(OAc)_2{\cdot}H_2O$ as the oxidant. The addition of 3,3-hexafluoro-2-propanol (HFIP) rather than H_2O, PivOH, or CF_3SO_3H increased the yield of product **4a** to 48% (Table 1, entries 16–19). The addition of more H_2O showed that 9.0 equivalents gave the best yield of product **4a** (Table 1, entries 20–22). An increase in the HFIP or $Sc(OTf)_3$ loading decreased the yield of product **4a**, as did a decrease in the $Cu(OAc)_2{\cdot}H_2O$ loading (Table 1, entries 23–25). A reaction without HFIP gave product **4a** in just 55% yield, thus illustrating the positive effect of HFIP, which might provide suitable acidic conditions for the reaction to form product **4a** (Table 1, entry 26).

such as Ph, MeO, Me, *t*Bu, or Cl, at the *para* position of the benzene ring gave the corresponding products **3b–f** in 50–86% yield. The alkynol substituted with a *m*-Me group gave the desired product **3g** selectively as a single isomer in 67% yield, but shifting the Me substituent to the *ortho* position led to no detectable product. This result demonstrates that steric hindrance at the benzene ring inhibited the reaction. Alkynols substituted with dioxol or secondary hydroxy groups gave the corresponding products **3h** (single isomer) and **3i** in 76 and 64% yield, respectively, thus indicating that the reaction is slightly influenced by steric hindrance near the hydroxy group.

Next, various aryl-substituted alkynes, featuring either electron-donating or electron-withdrawing groups, reacted efficiently with alkynol **1a** to form the desired products **3j–q** in 49–73% yield. Single-crystal X-ray diffraction analysis of product **3l**[15] confirmed the structure of the products. A cascade reaction of dialkyl-substituted alkynes with alkynol

1a produced the desired products **3r** and **3s** in moderate yields. To investigate the regioselectivity of this cascade reaction, we treated an unsymmetrical alkyne bearing one phenyl group and one methyl group with alkynol **1a**, and obtained product **3t** in 76% yield with very high regioselectivity (22:1), although the non-isolable isomer **3t′** with the positions of the R^2 and R^3 substituents reversed was also detected in 3% yield.

We tested various alkynols **1** in the reaction under the optimized conditions for the formation of product **4a** (Scheme 3). When R^1 on the phenyl group of the alkynol



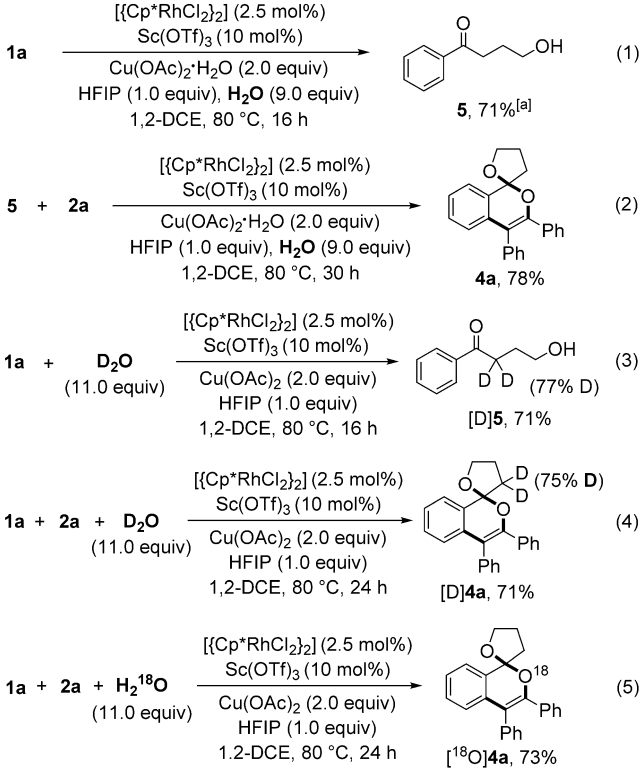
Scheme 3. Scope of the cascade reaction of alkynols **1** with alkynes **2** to give 4,5-dihydro-3*H*-spiro[furan-2,1′-isochromene] derivatives **4**. Reaction conditions: **1** (0.45 mmol), **2** (0.30 mmol), [{Cp*$RhCl_2$}$_2$] (0.0075 mmol), $Sc(OTf)_3$ (0.03 mmol), HFIP (0.30 mmol), H_2O (2.7 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.60 mmol), 1,2-DCE (1.5 mL), 80 °C, nitrogen atmosphere. Yields are for the isolated product. [a] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy.

was an electron-donating or electron-withdrawing substituent, the alkynol readily underwent the cascade reaction with alkyne **2a** to give products **4a–g** in moderate to good yields. However, alkynols bearing more strongly electron withdrawing groups, such as CF_3 or CN, did not undergo the cascade reaction. When the benzene ring of the alkynol was changed to a thiophene ring, the reaction with alkyne **2a** afforded product **4h** in moderate yield. An alkynol with a secondary hydroxy group also underwent the transformation to give the desired product **4i** in 70% yield, thus showing that the reaction is insensitive to steric hindrance near the hydroxy group.

Various alkynes **2** were also tested for their ability to react with alkynol **1a** (Scheme 3). Derivatives of 1,2-diphenylethyne with electron-donating or electron-withdrawing groups on the phenyl ring all reacted well to deliver products **4j–q** in good yields. The unsymmetrical alkyne prop-1-yn-1-ylbenzene was transformed into the single isomer **4r** in 49% yield.

To clarify the mechanism of these two cascade reactions, we determined the kinetic isotope effect (KIE) of the cascade reaction to afford product **3a**. A KIE value of 3.0 was determined from two parallel reactions and a KIE value of 2.4 was determined from a competition reaction (see the Supporting Information). The corresponding KIE values determined for the cascade reaction to afford product **4a** were 3.9 and 4.3 (see the Supporting Information). These results suggest that C–H bond cleavage is the rate-determining step in both cascade reactions.

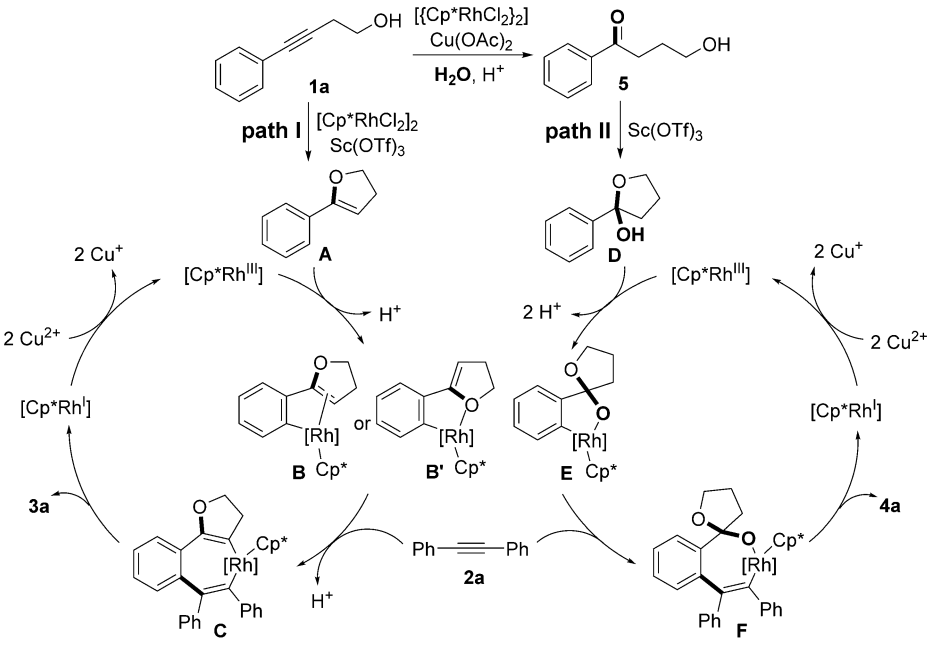
To gain a deeper understanding of the mechanism of the cascade reactions, we explored some control experiments. In the reaction of 4-([1,1′-biphenyl]-4-yl)but-3-yn-1-ol (**1b**) with [{Cp*$RhCl_2$}$_2$] (2.5 mol%) and $Sc(OTf)_3$ (10 mol%) in 1,2-DCE, the *endo*-cycloisomerization product 5-phenyl-2,3-dihydrofuran could be detected by GC–MS. In a similar reaction of **1b** with $Sc(OTf)_3$ (10 mol%) but without [{Cp*$RhCl_2$}$_2$], 5-phenyl-2,3-dihydrofuran was not detected.



Scheme 4. Mechanistic studies of the cascade reactions of alkynols with alkynes. [a] The same yield was observed for the reactions with and without $Sc(OTf)_3$.

These results demonstrate that the rhodium complex is the real catalyst for the *endo*-cycloisomerization step of the alkynol, whereas $Sc(OTf)_3$ might just stabilize and reactivate the cationic rhodium complexes in the *endo*-cycloisomerization process.[16]

Under the standard conditions to form product **4a**, but in the absence of alkyne **2a**, alkynol **1a** reacted with H_2O to form product **5**, which was isolated in 71% yield with or without $Sc(OTf)_3$ [Scheme 4, Eq. (1)]. When the hydration product **5** reacted with **2a** under the same conditions, the corresponding product **4a** was obtained in 78% yield [Scheme 4, Eq. (2)]. These results indicated that the hydration product **5** was the key intermediate in the process to form product **4a**.



Scheme 5. Proposed mechanism for the cascade reactions of alkynols with alkynes.

To further evaluate the role of H_2O in the formation of product **4a**, we carried out the reaction of alkynol **1a** in the absence or presence of alkyne **2a** with D_2O (11.0 equiv). The products [D]**5** (77% deuteration ratio) and [D]**4a** (75% deuteration ratio) were obtained from the two reactions, both in 71% yield [Scheme 4, Eq. (3) and (4)]. When we repeated the reaction of **1a** and **2a** in the presence of $H_2{}^{18}O$ (95% ^{18}O), we isolated the corresponding product [^{18}O]**4a** in 73% isolated yield, with 85% ^{18}O incorporation at the position indicated [Scheme 4, Eq. (5)]. The above results demonstrate that the formation of product **4a** involves the addition of the hydroxy group to the carbonyl group of hydration intermediate **5**.

On the basis of our mechanistic studies and previous relevant reports,[11d,12a,17] we propose the following mechanism for the cascade reactions of alkynols with alkynes through combined $Sc(OTf)_3$ and rhodium catalysis (Scheme 5). In the absence of H_2O, *endo*-cycloisomerization of alkynol **1a** occurs to generate intermediate **A** in the presence of the active rhodium catalyst [Cp*Rh^{III}] generated from [{Cp*RhCl$_2$}$_2$]/$Sc(OTf)_3$ (path I). Intermediate **A** may undergo C–H activation to first generate the arene–rhodium intermediate **B** or **B′**, which undergoes alkyne insertion with alkyne **2a** and a second C–H cleavage step to form the seven-membered rhodacycle **C**. Upon subsequent reductive elimination, the product **3a** is generated, and the resulting [Cp*Rh^{I}] species may be oxidized by a copper(II) salt to regenerate the active rhodium catalyst [Cp*Rh^{III}]. In the presence of H_2O, the addition of H_2O to alkynol **1a** gives intermediate **5**, which undergoes intramolecular addition of the hydroxy group to the carbonyl group to form the hemiketal **D** (path II). After the subsequent hydroxy-directed C–H activation catalyzed by [Cp*Rh^{III}], the product **4a** is generated after similar processes to those described for path I.

In summary, we have developed tunable cascade reactions of alkynols and alkynes through the combination of $Sc(OTf)_3$ and rhodium catalysis. The reactions provide two different kinds of products in good yields. Mechanistic studies demonstrate that C–H bond cleavage is the rate-determining step and that the hydration of the C≡C bond of alkynols plays an important role in switching between the two reaction pathways. This approach appears to be the first cascade reaction of alkynols involving cycloisomerization and C–H activation, and may provide a concise synthetic strategy for the construction of drugs and natural products.

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[15] CCDC 1404923 (**3l**) and 1404924 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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