Annulation producing diverse heterocycles promoted by cobalt hydride

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Abstract

This study demonstrates the efficient synthesis of various heterocycles using the MHAT/RPC method, emphasizing its versatility under mild conditions with high functional group tolerance. By distinguishing between cyclization and annulation, we underscore the complexity and efficiency of this approach in constructing intricate molecular architectures. Notably, the incorporation of an acetone solvent in the formation of cyclic acetal dioxanes from homoallylic alcohols reveals a novel annulation mechanism. Extensive substrate scope analysis and DFT calculations provide insights into reaction pathways, highlighting the critical role of cationic alkylcobalt(IV) intermediates and collidine in product selectivity. This study elucidates the mechanisms of the MHAT/RPC method and showcases its potential as a robust alternative to conventional synthetic strategies.

In synthetic organic chemistry, distinguishing between cyclization and annulation is crucial for constructing complex ring systems.[1] Cyclization typically forms a single bond to create a ring, whereas annulation involves the simultaneous formation of two bonds, adding significant complexity. For instance, the Robinson annulation efficiently synthesizes cyclohexenones by integrating a Michael addition with an aldol condensation.[2] Additional prominent annulation methods, such as the Larock indole synthesis,[3] Pictet–Spengler reaction,[4] and Fischer indole synthesis,[5] exemplify the critical role of annulation in crafting complex heterocycles vital to pharmaceutical development.

Building on the foundational principles of metal hydrogen atom transfer (MHAT) introduced by Halpern,[6] subsequent research has significantly advanced the versatility and utility of this reaction mechanism.[7] The integration of the radical-polar crossover (RPC) approach has opened new avenues for the formation of electrophilic intermediates, cationic alkylcobalt(IV) complexes, that enable a broad range of intramolecular reactions (Figure 1A).[8] The MHAT/RPC method has been effectively applied to synthesize cyclic ethers,[9] lactones,[9a] and other heterocycles,[10] demonstrating its capability under milder conditions and higher functional group tolerance than that of traditional methods. These advancements not only showcase the method's adaptability but also its potential as a robust alternative to conventional synthetic strategies in organic chemistry.[11] Among the applications of the MHAT/RPC method, the work by Vanderwal et al., which demonstrated its utility in promoting annulation reactions (Figure 1B), is the most significant.[12] Their research facilitated the synthesis of intricate tetralins, highlighting the method's ability to handle complex molecular architectures. However, despite these advances, the MHAT/RPC method has not been effectively applied for heterocycle synthesis. In our previous study, we explored the synthesis of oxetanes from homoallylic alcohols **1a** under MHAT/RPC conditions and unexpectedly discovered that acetone, a solvent, was incorporated into the product, forming cyclic acetal **2a**—a clear result of annulation with the solvent (Figure 1C).[13] The versatility of cyclic acetals is showcased in their broad application scope, ranging from clinical therapeutics[14] to serving as protective groups.[15] This highlights their essential role in advancing both pharmaceutical development and synthetic organic chemistry.

To elucidate the mechanism of the formation of dioxane **2a**, the following two pathways must be discussed after alkylcobalt complex formation (Figure 1D). 1) Hemiacetal **F** formation in the acetone solvent is possible by the conjugate acid of collidine (denoted as **Py**), particularly beyond the initial stage of the reaction.

The paths leading to cationic alkylcobalt(IV) complex **F** bearing hemiacetal—a cyclization precursor—can be explained in two ways; it may proceed via cationic alkylcobalt(IV) complex **B** or alkylcobalt(III) complex **A** could undergo hemiacetalization, followed by a one-electron oxidation. 2) The oxygen atom of the acetone solvent could attack the highly electrophilic carbon atom of cationic alkylcobalt(IV) complex **B**, which is followed by the cyclization of oxonium intermediate **C** to afford dioxane **D**. The preference of intermolecular acetone incorporation **G** to intramolecular oxetane **H** formation is understandable because 4-*exo*-cyclization **I** is generally a slow process. Note that an allylic alcohol with a mono-substituted alkene was previously explored as a MHAT/RPC substrate in an acetone solvent resulted in epoxidation or semi-pinacol rearrangement; however, the solvent was not incorporated.[16]

Herein, we initiated a detailed examination of dioxane formation using a homoallylic alcohol in an acetone solvent (Figure 1A). Building on the hypothetical reaction mechanism (Figure 1D), we further extended this MHAT/RPC-promoted annulation to the synthesis of various heterocycles beyond dioxane by altering substrate and solvent combinations. The successful synthesis of diverse heterocycles beyond cyclic acetals confirms the feasibility of the proposed method involving

an oxonium intermediate. Moreover, we examined the reaction path for dioxane formation through a powerful combination of quantum-chemical calculation with the artificial force induced reaction (AFIR) method[17] to understand the reaction mechanism in more detail.

The optimization of the reaction conditions for the formation of dioxane **2a**, as presented in our previous experiments, yielded consistent results across various catalysts and oxidants (Figure 2, see Table S1 for details). Notably, despite the influence of the catalyst structure on product selectivity, the ratio of dioxane to oxetane remained unchanged. This constancy is attributed to the strong dependence on the substrate, warranting no further investigation. Thus, catalyst **C4** and oxidant **Py1** were selected for the investigation of substrate generality.

Next, we attempted to synthesize various dioxanes **2** from homoallylic alcohol **1**, which was previously used in oxetane formation (Table 1). For example, homoallylic alcohols with nitrogen-protected heterocycles **1b** and **1c** were amenable to form dioxane **2b** and **2c**, respectively. We also succeeded in the synthesis of a mixed bis-acetal compound **2d** under the neutral reaction conditions via the MHAT/RPC method.

In addition to the dioxane bearing *spiro*-carbon (**2a**–**d**), less substituted dioxanes **2e** and **2f** were formed in acceptable yields. Note that partial oxetane formation was unavoidable even in the acetone solvent, and a small amount of oxetane was observed. Conversely, we found that bulky substrate **1g** was exceptionally biased toward oxetane formation, probably due to the high impact of the Thorpe–Ingold effect. Aryl-substituted dioxanes **2h**–**j** were also synthesized regardless of the substituent, along with small amounts of oxetane. Homoallylic alcohols **1k** and **1l** and cinnamyl alcohol **1m**, which was inefficient for oxetane formation, afforded dioxanes **2k**–**m** in acceptable yields. Instead of acetone, other ketone solvents such as cyclopentanone, 3-pentanone, and 3-methyl-2-butanone were also incorporated in the synthesis of dioxanes **2aa**, **2ab**, and **2ac**, respectively. In the case of the least reactive and bulky solvent, 3-methyl-2-butanone, the amount of oxetane **2a′** was slightly increased. The same reaction conditions can be applicable to substrate **1n**, bearing a phenyl group on an alkene moiety; however, oxetane **2n′**was unfortunately formed in a higher yield. In the case of mono-substituted alkene **1o**, the use of cobalt catalyst **C5** drastically improved the yield of **2o** or **2oa** compared to that achieved through the use of cobalt catalyst **C4**.

We next conducted the MHAT/RPC reaction using allylic alcohols bearing disubstituted alkenes and observed the diverse outcome depending on the substrates (Table 2). For example, **3a** was efficiently annulated affording dioxolane **4a** in 63% yield. In contrast, akin to **1g**, **3b** was biased to cyclization, affording epoxide **5b** as the sole product. Furthermore, the treatment of **3c** under the MHAT/RPC conditions resulted in only semi-pinacol rearrangement, exclusively producing **6c**. In comparison, we treated allylic alcohol **3d**, bearing a mono-substituted alkene, under our annulation conditions; this resulted in epoxidation (**5d**) along with semi-pinacol rearrangement (**6d**), which is consistent with the results reported by Pronin et al.[16] The yield of dioxolane from allylic alcohols **3e** was considerably low because of the unavoidable unselective epoxidation and rearrangement. Phenyl-substituted allylic alcohol **3f** was efficiently annulated, affording dioxolane **4g** in 67% yield. The synthesis of deuterated bis-acetal d_6-**4a** at the 1 mmol scale was realized using d_6-acetone as the solvent. Overall, in the case of allylic alcohols, we observed product formation via substrate control under the MHAT/RPC conditions even in acetone solvent.

We next explored an expansion of substrate scope beyond cyclic acetals (Table 3). For example, initial attempts using MHAT/RPC conditions with allylsulfonylamide **7a** and **Py2** provided oxazolidine **8a**. Furthermore, **7b** was found to be an

exceptionally excellent substrate, affording **8b** in excellent yield. Encouraged by this result, we reduced the amount of nucleophilic ketone to 2 equivalents and replaced the solvent with dichloromethane, and successfully synthesized **8ba** (using cyclobutanone), **8bb** (co-bearing both aminal and acetal), and **8bc** (incorporating benzaldehyde). This method could be applied to the synthesis of oxazines **8c** and **8d**. To our delight, we found that allylarenes **7e** and **7f** were annulated to produce isochroman under MHAT/RPC conditions. The results of forming **8e** and **8f** clearly support the reaction mechanism (Figure 1) via an oxonium intermediate **C** formed by nucleophilic attack of acetone on the electrophilic cationic alkylcobalt(IV) complex **B**, followed by cyclization to afford the annulated products **D**. The low yield of **8f** is due to the alkene isomerization of **7f** with **Py2**. Replacing **Py2** with **Py1** resulted in undesired hydrofluorination of the alkene.[18]

We succeeded in further expanding the scope of MHAT/RPC-promoted annulation by replacing acetone with acetonitrile. Allylsulfonylamides (**7a**, **7b**, **7g**, **7h**) were converted into imidazolines. During the work-up of the reaction mixture, the use of an aqueous sodium bicarbonate solution was essential to achieve an acceptable yield and to extract the free form of the product in nitrile annulation. Various solvents such as propionitrile, isobutyronitrile, and benzonitrile could also be used, yielding the corresponding imidazolines **9ba**, **9bb**, and **9bc**. Furthermore, pyrimidine **9d** was synthesized in low yield due to undesired hydrogenation of the alkene. However, in contrast to acetone, secondary sulfonylamides could be used, yielding pyrimidines bearing phenyl (**9i**), 4-methoxyphenyl (**9j**), 4-trifluoromethylphenyl (**9k**), mesityl (**9l**), or cyclohexyl groups (**9m**). Additionally, we synthesized imidazoline bearing spiro-carbon from tertiary sulfonylamide **7n**. In acetonitrile incorporation, allylic alcohol **3f** (Table 2) and allylarene **7f** were also applicable as substrates, affording oxazoline **9o** and isoquinoline **9p**, respectively. It should be noted that **9p** could be synthesized from 1 mmol of allylarene **7f** in 64% isolated yield. These nitrile incorporations can be explained by a Ritter-type mechanism involving a nucleophilic attack of the nitrile solvent on the electrophilic cationic alkylcobalt(IV) complex, forming a nitrilium ion, followed by cyclization to achieve annulations. This mechanism is partly supported by precedented examples of MHAT/RPC-promoted Ritter reactions forming amides via nitrilium ion.[19] However, MHAT/RPC-promoted annulations with nitrile incorporation have not been reported.

Herein, we investigated the annulation of homoallylic alcohol, a common substrate in oxetane synthesis via 4-*exo*-cyclization. Based on the hypothetical mechanism of the MHAT/RPC reaction discussed in previous literature,[8b, 20] product selectivity depends on the cationic alkylcobalt(IV) intermediate. To gain further insight into the mechanism, we compared the activation barriers of possible pathways using DFT calculations (Figure 3). We investigated the reaction paths from the cationic alkylcobalt(IV) intermediate derived from both homoallylic alcohol **1a**, which prefers annulation, and **1g**, which prefers 4-*exo*-cyclization. To reduce computational costs, the catalyst structure was simplified in the calculations. For the 4-*exo*-cyclization, an acetone molecule was deliberately included to ensure an accurate energetic comparison with annulation. During the reaction pathway search for annulation, we found that collidine, derived from the oxidant, significantly lowers the activation barrier for C–O bond formation and is essential for dioxane formation via deprotonation. Therefore, the collidine molecule was explicitly included in our calculations.

In the case of **1a**, the corresponding cationic alkylcobalt(IV) intermediate facilitates the formation of both dioxane and oxetane in a single step. The transition state (**TS_1**) leading to dioxane is lower by 1.4 kcal/mol, aligning well with experimental results. A more simplified substrate lacking the indane moiety also showed a preference for dioxane formation (Figure S1). Conversely, oxetane formation occurs in a single step from the cationic alkylcobalt(IV) intermediate derived from adamantane-containing

1g, whereas dioxane formation involves three steps: Co–C bond-cleavage to form a carbocation, formation of an oxonium intermediate, and cyclization along with deprotonation by collidine. The energy difference between the transition states $\mathbf{TS_4}$ and $\mathbf{TS_5}$, representing the highest energy points of each pathway, is consistent with experimental findings. The bulkiness of the adamantane resulted in the higher energy of $\mathbf{TS_5}$, making oxonium ion formation less favorable for dioxane formation. Including collidine and the cationic alkylcobalt(IV) intermediate in our calculations was essential to reflect the experimental outcomes accurately, providing valuable insights into the mechanistic pathways of the MHAT/RPC reaction.

In conclusion, we demonstrated annulation with the incorporation of acetone using the MHAT/RPC method. Our investigation underscores the versatility and robustness of this approach, particularly in synthesizing heterocycles under milder conditions with greater functional group tolerance. The successful formation of dioxanes and other heterocycles from homoallylic alcohols, allylic alcohols, and amides demonstrates the broad applicability and efficiency of the MHAT/RPC-promoted annulation. Furthermore, our DFT calculations provide valuable insights into the reaction mechanisms, confirming the role of cationic alkylcobalt(IV) intermediates and collidine in product selectivity. Future research will aim to further expand the substrate scope and develop an asymmetric variant with high enantioselectivity, potentially unlocking new synthetic pathways and applications in pharmaceutical development and beyond.

Acknowledgements

This work was supported by JSPS KAKENHI grant number 23K26661 (H. S & T. M), the Naito Foundation (H. S), Chugai Foundation for Innovative Drug Discovery Science (H. S), JST-ERATO (JPMJER1903) and . University of Tomorrow II-integrated development program of Adam Mickiewicz University in Poznań (B. S.). In this study, H. S. used AFIR method learned at the Institute for Chemical Reaction Design and Discovery (ICReDD), Hokkaido University, which was established by World Premier International Research Initiative (WPI), MEXT, Japan.

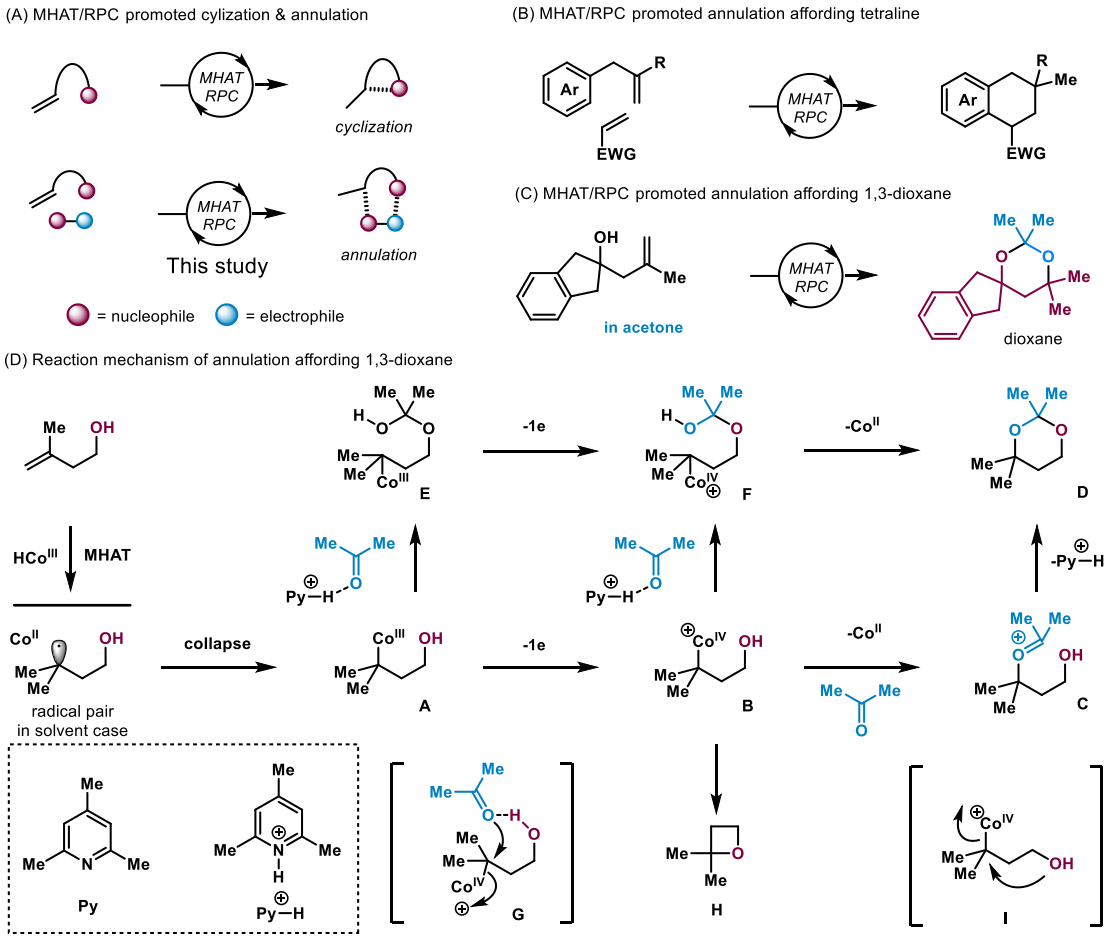


Figure 1. Background. (A) MHAT/RPC-promoted cyclization and annulation. (B) MHAT/RPC-promoted annulation yielding tetraline, as reported by Vanderwal. (C) MHAT/RPC-promoted annulation yielding 1,3-dioxane. (D) Possible reaction mechanism of annulation yielding 1,3-dioxane (collidine is denoted as Py).

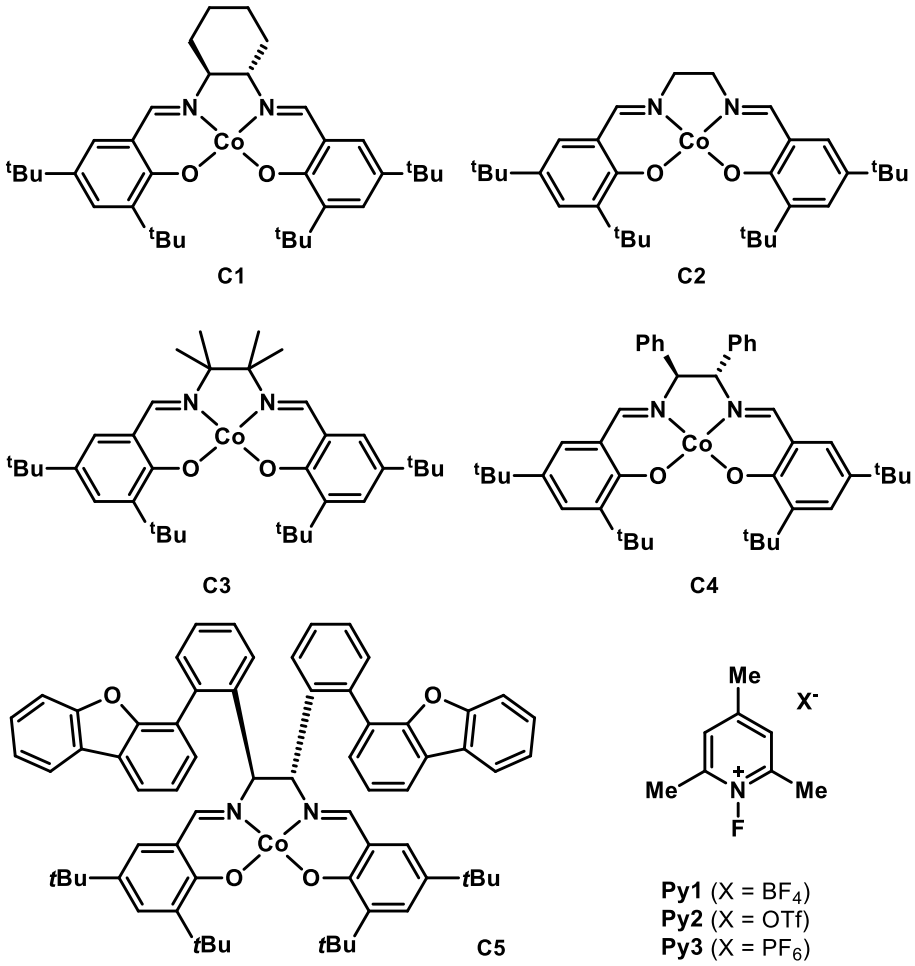
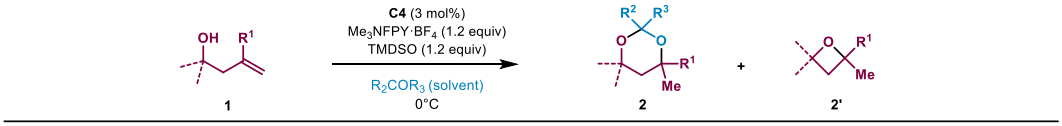
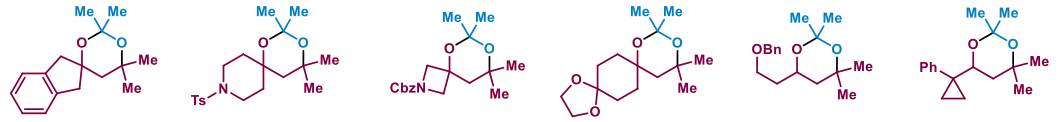


Figure 2. Cobalt catalysts and oxidants.

Table 1. Substrate scope of 1,3-dioxane formation.





2a, 63% (68%)
2a', 23%

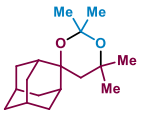
2b, 52% (61%)
2b', 13%

2c, 59% (62%)
2c', 4%

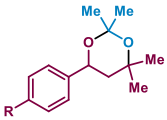
2d, 53% (61%)
2d', 21%

2e, 61% (67%)
2e', 16%

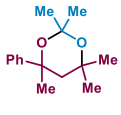
2f, 55% (63%)
2f', 23%



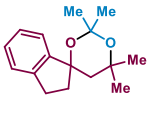
2g, 15% (35%)
2g', 57%



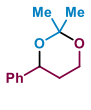
2h, 57% (59%, R = OMe)
2i, 46% (52%, R = H)
2j, 51% (58%, R = Cl)



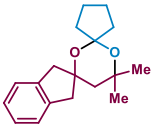
2k, 49% (52%)



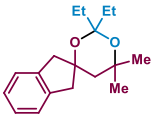
2l, 12% (15%)



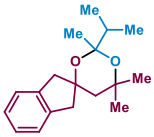
2m, 43%



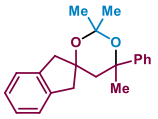
2aa, 59%[a]
2aa', 14%



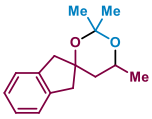
2ab, 25% (37%)[b]
2ab', 19%



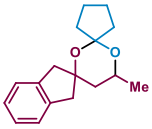
2ac, 44% (50%)[c]



2n, 29% (30%)
2n', 67%



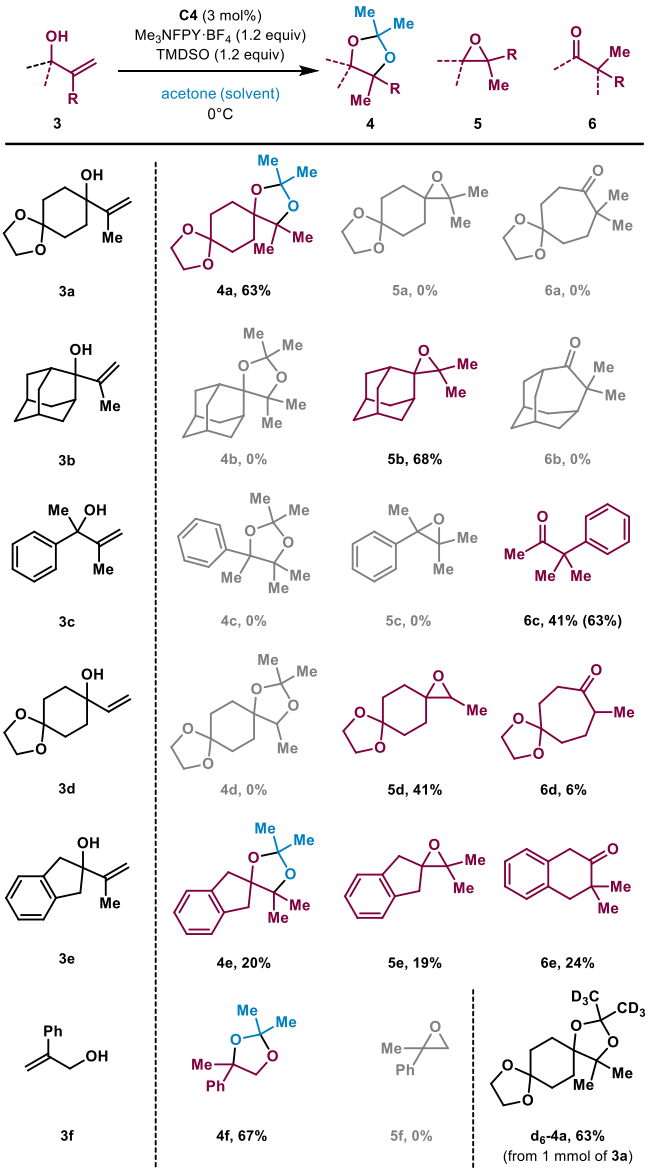
2o, 60%, 3% ee[d]



2oa, 72%[a,d]

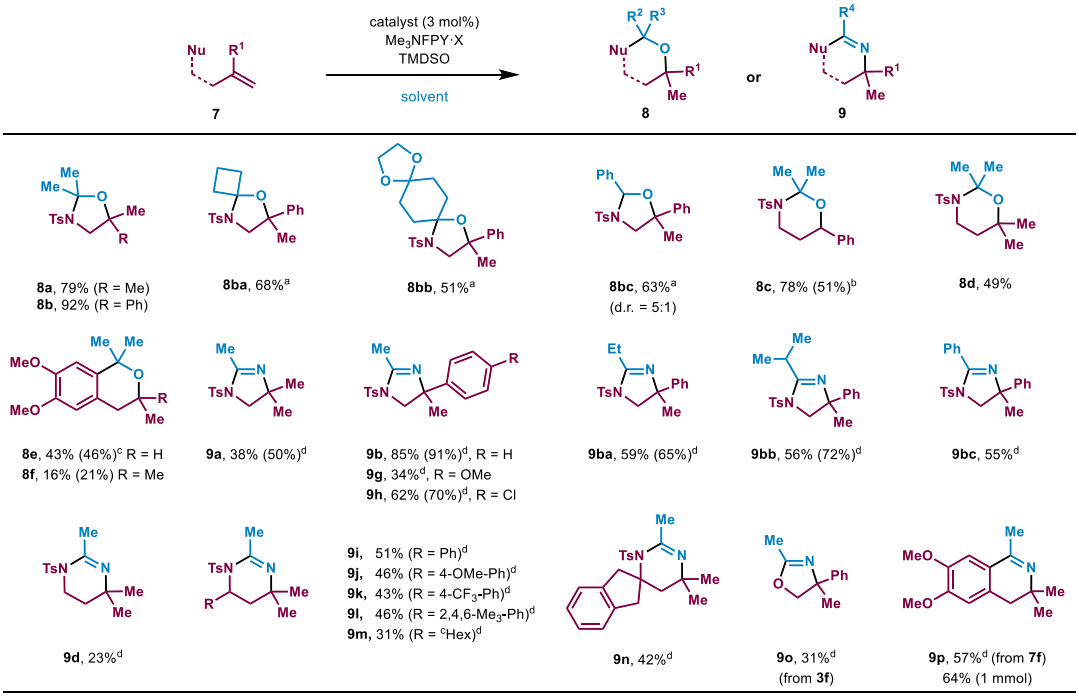
Conditions: Starting material (0.2 mmol), **C4** (3 mol%), *N*-fluoro-2,4,6-collidinium tetrafluoroborate (1.2 equiv), and 1,1,3,3-tetramethyldisiloxane (1.2 equiv) in acetone (2.0 mL) under argon atmosphere at 0 °C for 3 h; isolation yield is provided. Yields in parentheses are NMR yields using 1,4-bis(trifluoromethyl)benzene as an internal standard. [a]in cyclopentanone (2.0 mL) [b]in pentanone (2.0 mL) [c]in 3-methyl-2-butanone (2.0 mL) [d]**C5** (3 mol%) at 0 °C for 12 h.

Table 2. Substrate scope from allylic alcohol.



Conditions: Starting material (0.2 mmol), **C4** (3 mol%), *N*-fluoro-2,4,6-collidinium tetrafluoroborate (1.2 equiv), and 1,1,3,3-tetramethyldisiloxane (1.2 equiv) in acetone (2.0 mL) under argon atmosphere at 0 °C for 3 h; isolation yield is provided. Yields in parentheses are NMR yields using 1,4-bis(trifluoromethyl)benzene as an internal standard.

Table 3. Further Substrate Scope of MHAT/RPC-promoted annulation.



Conditions: Starting material (0.1–0.2 mmol), **C4** (3 mol%), *N*-fluoro-2,4,6-collidinium trifluoromethanesulfonate (2.0 equiv), and 1,1,3,3-tetramethyldisiloxane (2.0 equiv) in acetone (1.0 mL) under argon atmosphere at 0 °C for 30 minutes; isolation yield is provided. Yields in parentheses are NMR yields using 1,4-bis(trifluoromethyl)benzene as an internal standard. [a]ketone or aldehyde (2.0 equiv) in DCM (2.0 mL) [b]condition in Table 1 [c]**C1** (3 mol%) [d]acetonitrile (1.0 mL) at 25 °C for 2 h.

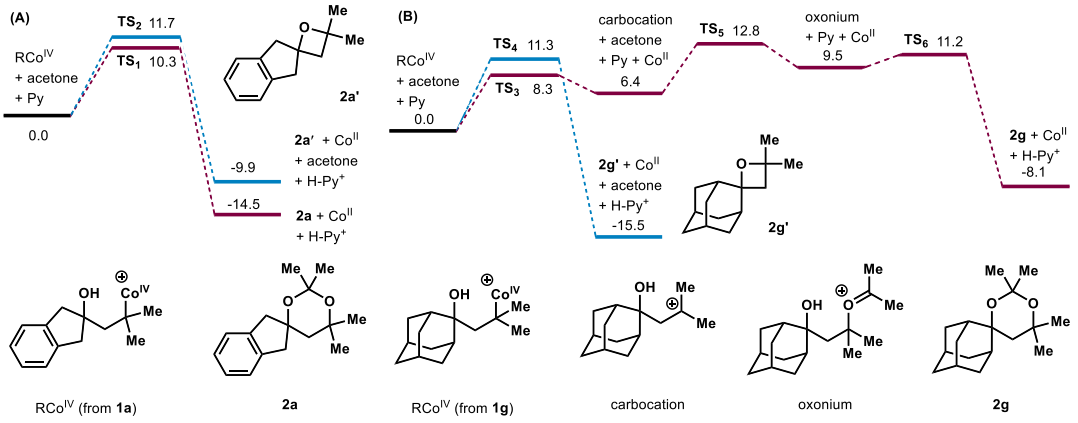


Figure 3. DFT study of RCo^{IV} intermediate. (A) Reaction path derived from **1a.** (B) Reaction path derived from **1g**, UBP86-D3/6-311+G(d,p)/SMD(acetone)/UBP86-D3/6-31G(d) at 273.15 K (kcal/mol).

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