Cyclization by metal-catalyzed hydrogen atom transfer/radical-polar crossover

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ABSTRACT

Catalytic transformation of alkenes via the metal-hydride hydrogen atom transfer (MHAT) mechanism has notably advanced synthetic organic chemistry. This review focuses on MHAT/radical-polar crossover (MHAT/RPC) conditions, offering a novel perspective on generating electrophilic intermediates and facilitating various intramolecular reactions. Upon using cobalt hydrides, the MHAT mechanism displayed exceptional chemoselectivity and functional group tolerance, making it invaluable for the construction of complex biologically relevant molecules under mild conditions. Recent developments have enhanced regioselectivity and expanded the scope of MHAT-type reactions, enabling the formation of cyclic molecules via hydroalkoxylation, hydroacyloxylation, and hydroamination. Notably, the addition of an oxidant to traditional MHAT systems enables the synthesis of rare cationic alkylcobalt(IV) complexes, bridging radical mechanisms to ionic reaction systems. This review culminates with examples of natural product syntheses and exploration of asymmetric intramolecular hydroalkoxylation, highlighting the ongoing challenges and opportunities for future research to achieve higher enantioselectivity. This review revisits the historical evolution of the MHAT mechanism and provides the groundwork for further innovations in the synthesis of structurally diverse and complex natural products.

Introduction

Alkene transformation via metal-hydride hydrogen atom transfer (MHAT) has become an effective method in synthetic organic chemistry.[1] One of the main reasons for this is the high chemoselectivity of metal hydrides (e.g., iron and cobalt) toward alkenes (Figure 1). Markovnikov-selective formation of carbon radicals from alkenes is possible even in the presence of various functional groups on the reaction substrate. Various one-electron reactions can occur using carbon radicals. Thus, it provides excellent tolerance to a variety of functional groups that are otherwise sensitive to acids, bases, heat, and reducing and oxidizing agents, and is an essential tool for the rapid and selective construction and modification of structurally diverse compounds. The regioselectivity of MHAT-type reactions for alkenes usually exhibits the same Markovnikov selectivity as that of reactions with Brønsted acids. We began our research on molecular transformations by the MHAT mechanism approximately 10 years ago and discovered the MHAT/RPC (radical-polar crossover) reaction described below. This review discusses the history of the MHAT mechanism and recent findings during 2016 - 2024.[2]

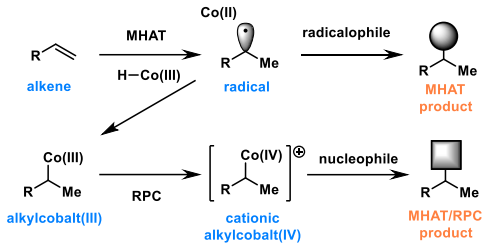


Figure 1

The MHAT mechanism was first proposed by Halpern et al. in 1975.[3] Anthracene is selectively reduced to dihydroanthracene using a cobalt carbonyl complex in a mixed gas atmosphere of hydrogen and carbon monoxide. This reaction is believed to occur via the formation of the active species, cobalt hydride, from the cobalt carbonyl complex and molecular hydrogen, leading to MHAT to anthracene. Similarly, Halpern et al. reported the MHAT-type reduction of α-methylstyrene using a manganese hydride complex.[4] More than 10 years after the report by Halpern, in 1989, Mukaiyama and Isayama reported an alkene hydration reaction using $Co(acac)_2$ and $PhSiH_3$ under an oxygen atmosphere.[5] Neither the presence of cobalt hydride nor the occurrence of the MHAT mechanism was mentioned in this paper; Nojima et al. explained the mechanism of a similar reaction by hydrometalation with cobalt hydride in 2002.[6] Although Drago also reported a similar cobalt-catalyzed reaction in 1982, before that of Mukaiyama and Isayama, the reaction conditions did not include silylhydride and the reaction was thought to occur via a reaction mechanism in which cobalt hydroperoxide was the reaction active species.[7]

Today, these cobalt-catalyzed reactions are considered to occur via the MHAT mechanism. The contributions of Shenvi[1, 8], Norton[9], Boger[10], Herzon[11], and others have been significant in organizing the reaction mechanisms. In particular, when cobalt hydride is the active species, either the MHAT or hydrometalation mechanism is considered as being possible. In this regard, Shenvi

et al. favored the MHAT mechanism for the following reasons[12]: 1) the presence of carbon radicals is supported by radical clock and radical capture experiments; 2) reactivity is not significantly affected by the steric and electronic factors of the substrate; 3) hydrometalation of alkyl-substituted double bonds is usually anti-Markovnikov selective; 4) the reaction proceeds easily at room temperature even with sterically hindered substrates to form metal-carbon bonds; and 5) the reaction proceeds without an empty coordination site near the metal-hydride ligand in a planar tetracoordinated metal complex. 6) the reaction proceeds even in the absence of a vacant coordination site near the metal-hydride bond in the square planar pyramidal complex.

Before discussing the reaction mechanism of cobalt hydrides, Carreira et al. reported various hydrofunctionalization reactions.[13] This strategy inspired the method of Isayama and Mukaiyama, in which the carbon radicals generated from cobalt hydride and alkenes react with various radical scavengers. Hydroazidation and hydrochlorination have been developed using this method. However, We included an electrophilic fluorinating agent to the reagents (cobalt salen complex, silyl hydride) and cobalt hydride was formed, which led to the discovery of MHAT/RPC.[14] The mechanism of MHAT/RPC is discussed below.

First, two molecules of cobalt(II) complex **A** react with one molecule of the oxidant to form two molecules of cationic cobalt(III) complex and a fluorine ion, which are present as dinuclear cobalt fluoride μ complex **B** (Figure 2).[15] Silylhydride then reacts to form the active species cobalt hydride **C** (this process has been accelerated by adding water, and the involvement of a cobalt aqua complex has also been reported). The hydrogen atom of the cobalt hydride is transferred to the alkene (MHAT mechanism) to form a radical pair **D** comprising a cobalt(II) complex and carbon radical; the regioselectivity of the MHAT system reaction may be attributed to the stability of this carbon radical. The radical pair comprising **A** and carbon radicals quickly collapses to generate the alkylcobalt(III) complex **E**, followed by a single-electron transfer from **E** to the residual cationic cobalt(III) complex to form a cationic alkyl cobalt(IV) complex **F**; **A** is regenerated. **F** is strongly electrophilic and can react with relatively weak nucleophiles. Cobalt(IV) complexes are particularly rare compared with cobalt(II) or cobalt(III) complexes. The displacement reactions of alkylcobalt(IV), which exhibit characteristic stereoinversion, have been discussed previously. In addition, studies on cobalt(IV) complexes using electron nuclear double resonance (ENDOR) spectroscopy and computational chemistry have been reported.[16] As described above, we succeeded in bridging the reaction system that was treated as a radical mechanism to an ionic reaction system by adding an oxidant to the MHAT reaction system. Next, examples of reactions in the MHAT/RPC system discovered since 2016 are introduced.

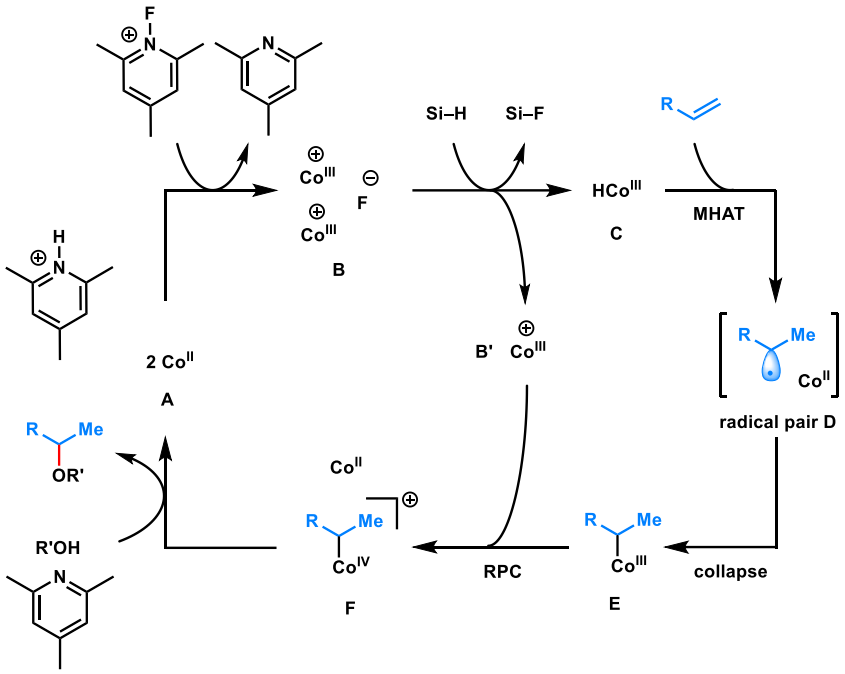


Figure 2

Intramolecular hydroalkoxylation and hydroacyloxylation reactions

Oxygen-containing heterocycles such as cyclic ethers and lactones are found in the skeletons of many biologically active natural products. Some contain five- or six-membered rings and medium-ring cyclic ethers, such as ciguatoxin, laurencin, and helianane are examples of such compounds. Many pharmaceuticals are derived from the skeletons of biologically active natural products and the activity of oxygen-containing medium rings has attracted attention in drug discovery research. However, compared with that of five- and six-membered rings, the formation of medium-membered rings is more challenging, and the development of a general synthetic method is desired. Furthermore, epoxides and oxetanes, which are three- and four-membered ring ether structures, respectively, are valuable synthetic elements characterized by ring-opening reactions derived from ring distortion. Oxetanes are also known as bioisosteres of *gem*-dimethyl and carbonyl groups in drug discovery research. Oxygen-containing heterocycles may be synthesized via intramolecular hydroalkoxylation and hydroacyloxylation, in which hydroxy or carboxy groups bond directly to the olefins. We attempted to synthesize oxygen-containing heterocycles by applying the MHAT/RPC mechanism to alkenyl alcohols and carboxylic acids.[17]

First, various cyclic ethers **2** were synthesized in high yield using the cobalt complex **C1**, *N*-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (Me_3NFPY·OTf), and 1,1,3,3-tetramethyldisiloxane [$(Me_2SiH)_2O$] in toluene at room temperature (Table 1). For example, tetrahydrofurans **2a** and **2b** were synthesized from alkenyl alcohols containing monosubstituted alkenes and **2c** from 1,1-disubstituted olefin in high yields. Starting materials containing acetals, diols, and steroid skeletons could also be used to produce **2d**, **2e**, and **2f**, respectively. When the starting material contained a phenolic hydroxyl group, complex products were formed (**2g**). Six-membered products **2h** and isochromanes **2i**–**2k** could be synthesized in high yields. Applying the same reaction conditions to alkenyl carboxylic acid **3** resulted in the formation of various five- and

six-membered ring lactones **4**. In addition to monosubstituted alkenes, 1,1-disubstituted alkenes were used to obtain **4a**–**4f** in high yields.

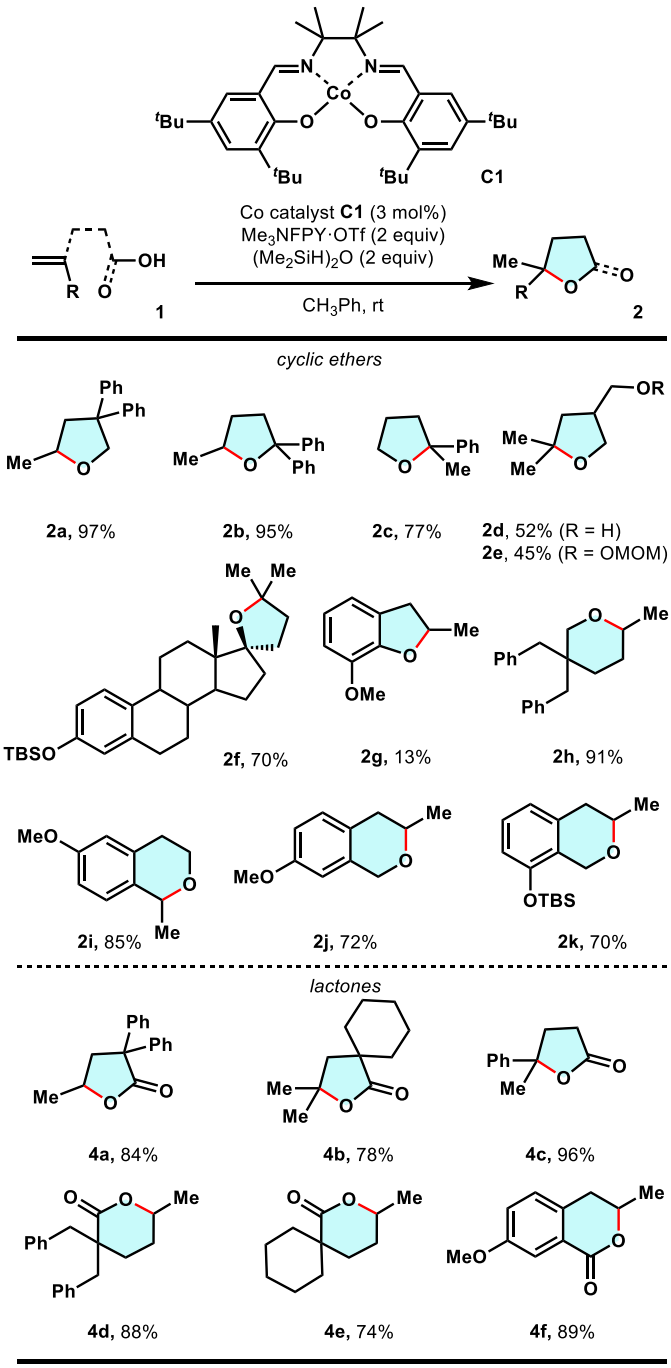
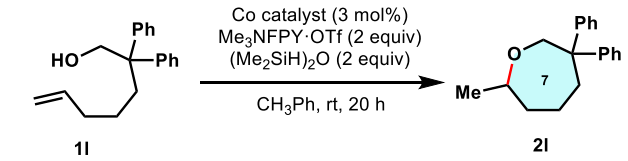
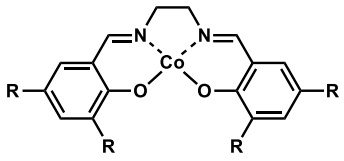


Table 1

In an attempt to synthesize a medium-membered cyclic ether, applying the initial conditions to alkenyl alcohol **1l** yielded oxepane **2l** in only 30% yield due to the recovery of **1l** and alkene

isomerization (Table 2). The yield improved slightly upon changing the diamine moiety to ethylenediamine in the cobalt complex (**C2**). Changing the size of the substituents on the aromatic ring to methyl (**C3**) and isopropyl (**C4**) groups, which are smaller than *tert*-butyl groups, significantly decreased the yield of **2l**. Conversely, using a *tert*-hexyl group as a substituent successfully increased the yield to 60% (**C6**). Thus, catalyst structure optimization plays a key role in the effectiveness of the MHAT/RPC system.





C2 (R = ^{t}Bu) **C5** (R = ^{t}Am)
C3 (R = Me) **C6** (R = ^{t}Hex)
C4 (R = ^{i}Pr) **C7** (R = ^{t}Hep)

Co cat.	yield (%)
C2	43
C3	>5
C4	8
C5	57
C6	60
C7	57

Table 2

The optimized cobalt complex **C6** was then used to examine the substrate generality of the synthesis of medium-membered rings (Table 3); 1,4-Oxazepine **2m** was synthesized in a similar manner to that of **2l**. In the synthesis of the eight-membered ring ether **2n**, we again compared the cobalt complexes **C1** and **C6** and reconfirmed the superiority of **C6**. For the synthesis of nine-membered rings, **2o** was produced in low yield even when **C6** was used. In the synthesis of a medium-membered ring lactone, oxepanone **4g**, benzodioxooctanone **4h**, and benzodioxanone **4i** were furnished.

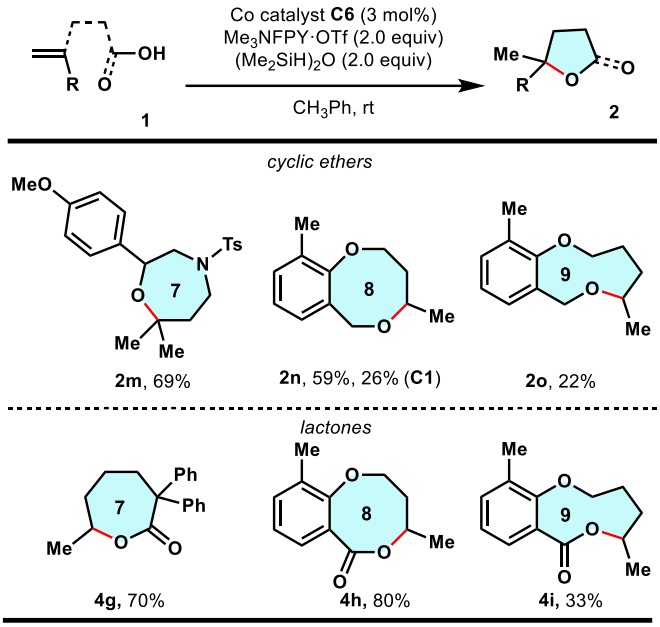
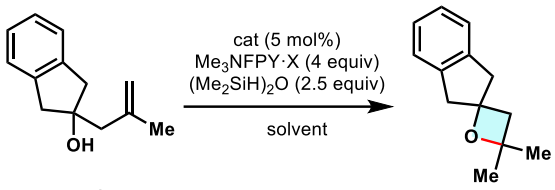


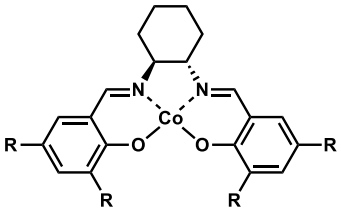
Table 3

Additionally, we attempted to construct an oxetane structure.[18] The reaction conditions were optimized using the starting material **1p**, which was synthesized in a single step from commercially available 2-indanone (Table 4). The initial conditions using **C1** produced oxetane **2p** in 42% yield (entry 1). Continued optimization of the reaction conditions revealed that **C8** improved the yield to 80% (entry 2). The type of oxidant counter anion also affected the yield, with $Me_3NFPY{\cdot}PF_6$ producing **2p** in yields of up to 90% (entries 3, 4). Using $(Me_2SiH)_2O$ proved optimal in terms of both cost and yield. 4-Methyltetrahydropyran (MTHP) was superior to a less-polar solvent such as toluene (entries 5-8).



1p 2p

entry	cat	X	solvent	yield (%)
1	**C1**	OTf	MTHP	42
2	**C8**	OTf	MTHP	80
3	**C8**	BF_4	MTHP	50
4	**C8**	PF_6	MTHP	90
5	**C8**	PF_6	THF	54
6	**C8**	PF_6	CH_2Cl_2	52
7	**C8**	PF_6	CH_3Ph	28
8	**C8**	PF_6	Acetone	20



C8: R = *t*-Amyl

Table 4

Most of the homoallylic alcohols were synthesized by treating aldehydes or ketones with zinc powder and methallyl bromide. MHAT/RPC reactions were performed on various homoallylic alcohols under optimal conditions, and various oxetane-containing compounds were successfully synthesized (Table 5). In particular, we focused on the synthesis of spiro compounds, which have attracted attention from the viewpoint of high Fsp^3 (**2q**–**2w**).[19] The problematic side reaction in this oxetane synthesis was the retro-allylation reaction, which forms ketones corresponding to the starting materials of homoallylic alcohols. The reaction is limited to that of disubstituted alkenes and is not suited to monosubstituted alkenes. In this regard, the energetic barrier for cyclization from alkyl cobalt(IV) complex was calculated and was approximately 7 kcal/mol higher for the monosubstituted alkene than that for disubstituted alkenes.

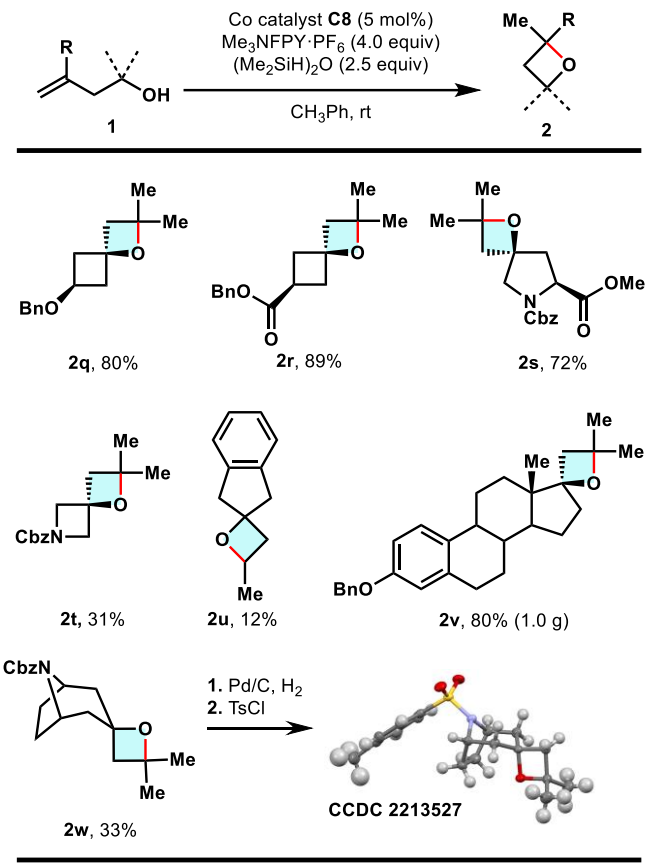


Table 5

Intramolecular hydroamination reactions

In 2014, we reported that intramolecular hydroamination proceeds via the MHAT/RPC mechanism.[20] When alkenyl sulfonylamides and other compounds are used as starting materials, various nitrogen-containing heterocycles can be constructed via nucleophilic attack of the nitrogen atom. Next, we applied the MHAT/RPC mechanism to the synthesis of cyclic guanidines commonly found in natural marine products.[21] This practical method characterized the availability of Cbz and Boc as common protective groups. The protective groups reduce the polarity of the product and facilitate purification and enable easy deprotection. Furthermore, owing to the ease of the MHAT/RPC mechanism, we synthesized novel medium-membered cyclic guanidines.

Cyclic guanidines were obtained in excellent yield using the cobalt catalyst **C6**, $Me_3NFPY{\cdot}OTf$ and $(Me_2SiH)_2O$ in toluene. (Table 6). Investigation of the electronic effects using substrates containing aniline structures produced high yields of five-membered cyclic guanidines, including electron-withdrawing, electron-donating, and unsubstituted forms (**6a**–**6c**). Benzylamine was also applied (**6d**). Moreover, alkenyl guanidines with different carbon chains were used to form six-membered ring **6e** and seven-membered ring guanidine **6f**. Next, the scope of the seven-membered ring guanidine synthesis was examined. For example, we successfully synthesized benzene-ring-fused seven-membered cyclic guanidines in good yields, for example, **6g** and **6h** by introducing

substituents on the benzene ring; **6i**, by changing the benzene ring to an alkyl group; and **6k**, by introducing a benzene ring fused to the benzene ring. The Cbz group was replaced with a Boc group, and cyclic guanidines **6l** and **6m** were obtained in good yields. Further transformations of the seven-membered cyclic guanidines enabled the formation of polycyclic compounds.

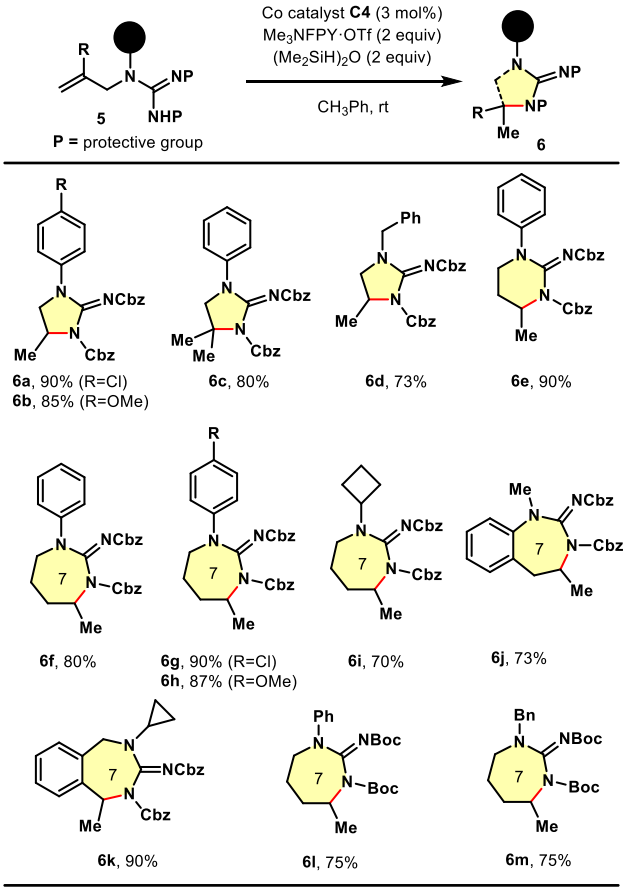


Table 6

Azetidine synthesis was also possible using homoallyl sulfonylamide as a starting material; using a tosyl group on the nitrogen is crucial in this method.[18] Dichloromethane and toluene were the optimal solvents, different from that of oxetane synthesis (4-MTHP). This method is not applicable to monosubstituted alkenes. Various reductive conditions enabled detosylation reactions for several products. For example, *bis*-azetidine **6o** is reductively deprotected by magnesium metal and the estrone derivative **6p** by lithium aluminum hydride.

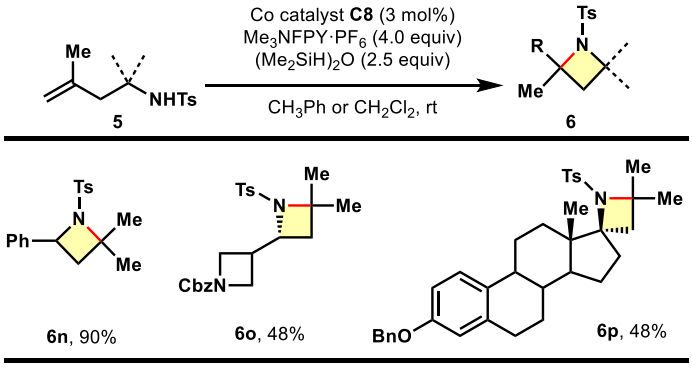
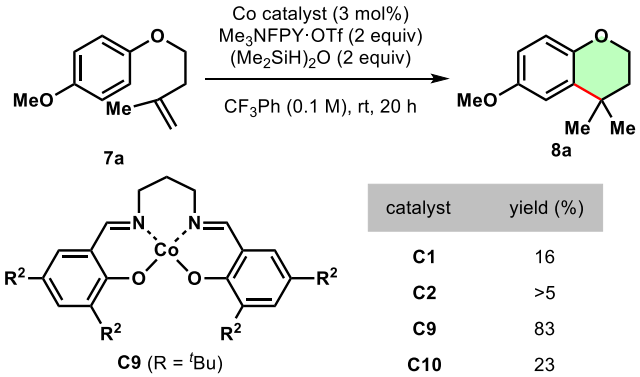


Table 7

Intramolecular hydroarylation reactions

Benzocyclic compounds are also found in important biologically active substances. In particular, the α,α-dimethyl substituent is the backbone found in synthetic analogs of retinoic acid. For example, all-*trans*-retinoic acid exhibits a wide variety of activities owing to its flexible structure and has been linked to toxicity and teratogenicity. Synthetic analogs called arotinoids (α,α-dimethyl-substituted benzocyclic compounds) have been designed including bexarotene (cutaneous T-cell lymphoma), tazarotene (acute promyelocytic leukemia), and tamivarotene (acne and psoriasis). Given this background, we examined a method for synthesizing benzocyclic compounds using the aromatic ring as the nucleophile in the MHAT/RPC mechanism.[22]

We treated alkenyl arenes **7a** with complex **C1**, $Me_3NFPY{\cdot}OTf$, and $(Me_2SiH)_2O$ in trifluorotoluene to produce chromane **8a** in low yield (Table 8); the low yield may be attributed to the formation of a trisubstituted alkene (53%) and hydrate (29%). After further optimization, when the diamine moiety of the cobalt catalyst was changed to 1,3-propanediamine (**C9**), the yield of **8a** increased to 83%. This Schiff base ligand was particularly effective for the hydroarylation of disubstituted alkenes. Further catalyst optimization revealed that bulky substituents on the aromatic ring were essential for hydroalkoxylation and hydroamination (**C9**–**C11**).



catalyst	yield (%)
C1	16
C2	>5
C9	83
C10	23
C11	51

Table 8

The substrate scope of the intramolecular hydroarylation reactions was then investigated using the cobalt complex **C9** (Table 9). Replacing the oxygen atom on the side chain with a tosylamide, methylene, or sulfur atom yielded tetrahydroquinoline **8c**, tetralin **8d**, and thiochroman **8e**. By contrast, the five-membered and seven-membered ring products were not obtained. The corresponding chromanes (**8f**, **8g**) were also obtained from each substrate comprising a MOM and TBS group, respectively. Next, we synthesized more complex molecules. For example, L-tyrosine-derived compound **7j** afforded **8j** without racemization. The effect of an olefin moiety on the reactivity was then investigated and the optimum catalyst was found to depend on alkene substitution. Complex **C1** was superior to complex **C9** for monosubstituted alkenes **8k**. However, for trans-1,2-disubstituted alkenes **8l**, the difference was more pronounced, with complex **C9** not affording a cyclized product, while complex **C1** afforded a cyclized product in excellent yield.

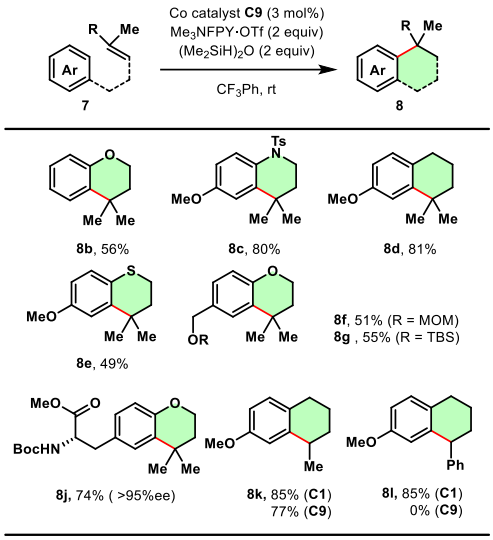


Table 9

Deprotective cyclization

Protective groups are commonly used in the synthesis of pharmaceuticals and natural products; however, more steps are required for protection and deprotection processes. However, protecting groups improve solubility, reduce polarity, or temporarily stabilize starting materials. Shigehisa found that cyclized products could be obtained directly from protected alkenyl alcohols and alkenyl carboxylic acids after deprotection under MHAT/RPC conditions.[17] For example, when protected alkenyl alcohols **9a**–**9d** were subjected to MHAT/RPC conditions, cyclic ether **10** was obtained in a high yield (Table 10). The substrate scope was investigated for three typical protective groups (TBS, MOM, and Bn), and the substrates comprising the MOM group generally afforded the product in the highest yields. Substrates with phenolic hydroxyl groups showed a

significant improvement in product yield when protective groups were used. **12** was obtained from **11** in high yield, and the MOM group, which was not involved in the cyclization, remained unchanged. Deprotective cyclization also proceeded from various alkenyl esters **13a**–**13d**, directly yielding lactone **14** in a high yield. Deprotection occurred after formation of an oxonium intermediate. Structural determination of the coproducts revealed that the MOM, Bn, and Me groups, which protected the hydroxyl and carboxyl groups, were eventually trapped by collidine.

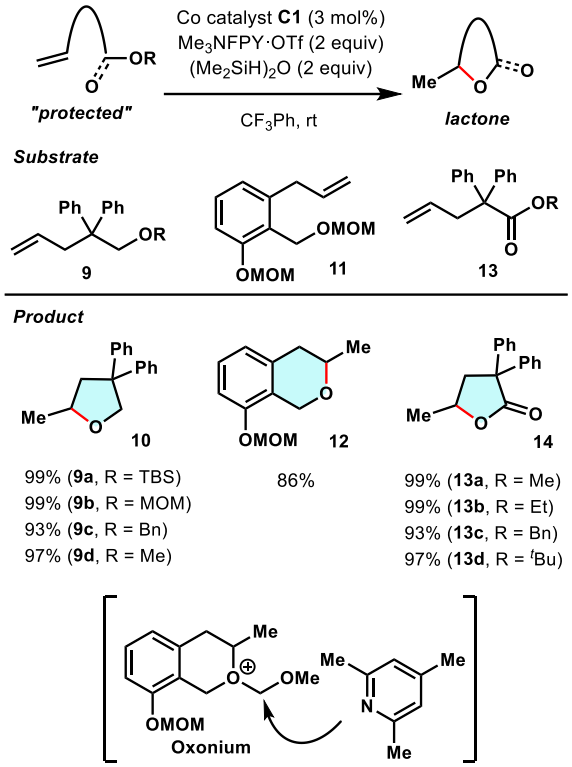


Table 10

Dealkylative cyclization can be used in the synthesis of cyclic carbamates and ureas (Table 11).[23] Various cyclic carbamates (**16a**–**16c**) comprising different ring sizes, up to seven-membered ring **16b,** could be synthesized from alkenyl carbamates with different carbon chains **15**, in acceptable yields. Compared with **C1**, the yield was found to improve when using the cobalt complex **C6**.

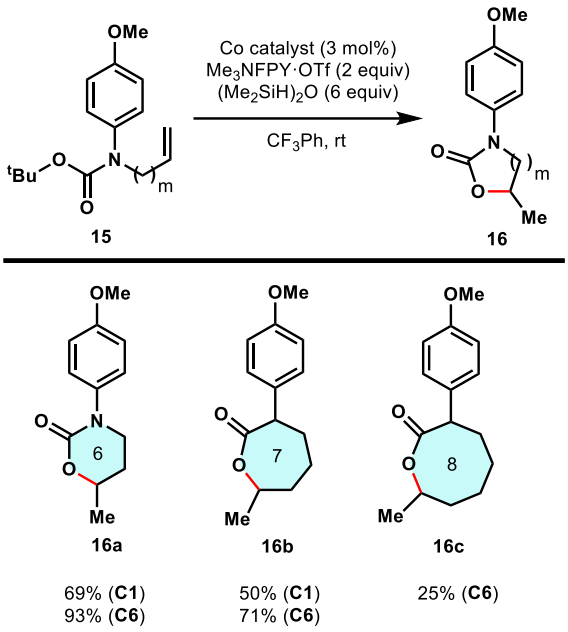


Table 11

Cyclic ureas were successfully synthesized from alkenyl isoureas comprising a tosyl group (Table 12).[23] For example, when cobalt complex **C1** was used, the 6-membered ring **18a** formed. Although the synthesis of the 7-membered ring **18b** with **C1** resulted in a low yield, the yield improved to 79% by changing the catalyst to cobalt catalyst **C6**. The 8-membered ring **18c** was not obtained when cobalt catalyst **C6** was used. Note that the Ns and TFA groups are superior to the Ts group if a deprotection step is required. As a comparison, we discovered that unusual cyclic isoureas can be selectively obtained when using alkenyl urea as a starting material. Alkenyl ureas were synthesized from alkenyl amine and cyclized immediately without purification owing to the instability of the intermediate during silica gel purification.[24]

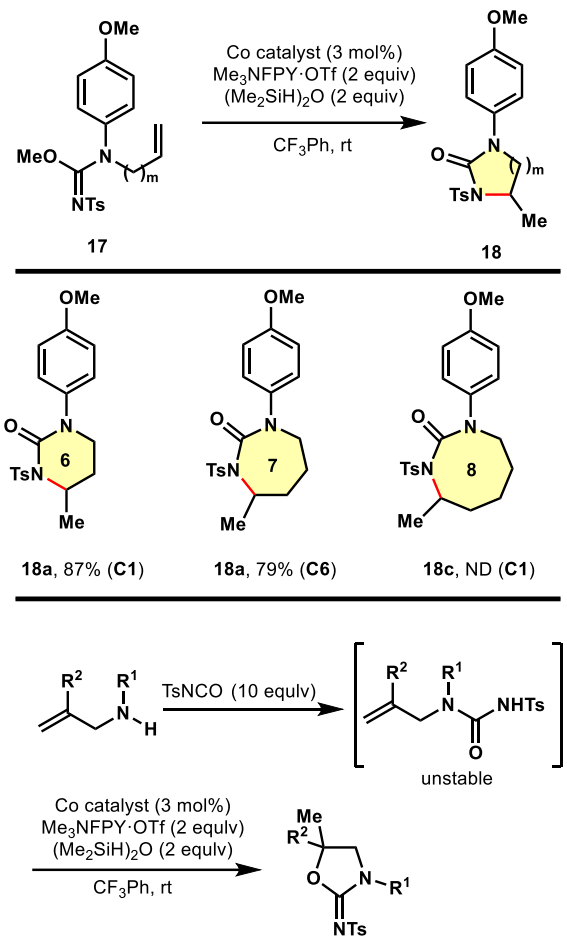


Table 12

S-containing heterocycles are found in biologically active compounds such as biotin and other pharmaceuticals. The concept of deprotective cyclization to develop an intramolecular hydrothiolation affording *S*-containing heterocycles was next applied.[25] Compared with hydroamination (C–N bond formation) and hydroalkoxylation (C–O bond formation), hydrothiolation has been reported in only three cases. No results on substrate generality can be found. Alkenyl thiols are unstable compounds owing to non-selective cyclization (five- and six-membered rings) and spontaneous oxidation to disulfides. This potential instability of alkenyl thiols could be a reason why the development of intramolecular reactions has been hindered. Therefore, several starting materials with protected thiol groups were synthesized and MHAT/RPC-promoted cyclization was attempted by We group. Using benzoyl thioesters resulted in an acceptable yield, and the *p*-methoxybenzoyl group showed no significant decrease in reactivity when the quantity of catalyst was reduced in the transformation from **19a** to **20a** (Table 13). Substrate generality was investigated using the optimized protective group, and various *S*-containing heterocycles (**20b**–**20d**) were also successfully synthesized.

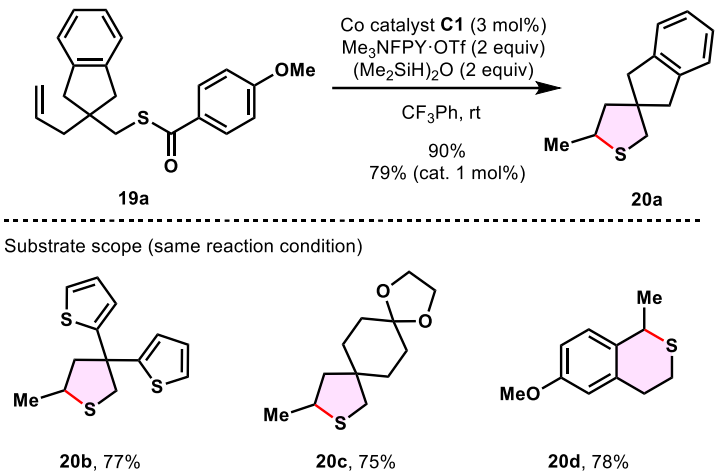


Table 13

Asymmetric intramolecular hydroalkoxylation

Remarkable progress has been made in the catalytic reactions promoted by MHAT in recent years. Notably, enantioselectivity remains a challenge because this mechanism involves highly reactive carbon radicals. Even for reactions outside the MHAT system, enantioselective reactions via carbon radicals are limited. In 2016, we reported the intramolecular hydroalkoxylation of **1a** to afford cyclic ether **2a** in 28%ee using chiral β-ketoiminato cobalt complex **C12**, $(Me_2SiH)_2O$, and *N*-fluoropyridinium salt.[17] For enantioselectivity to be observed, the chiral cobalt complex must be involved in the C–O bond forming step. Pronin reported the same concept during our investigation of the enantioselective MHAT/RPC reaction.[26] The researchers developed a catalytic asymmetric intramolecular hydroalkoxylation using an originally developed chiral cobalt complex. In this review, we discuss how our findings differ from those of Pronin et al. in several respects.[27]

After extensive optimization of the reaction conditions, we found that the chiral cobalt complex, silyl hydride, and solvent had a significant influence on both the yield and enantioselectivity. In our initial investigation, we discovered the high potential of the Katsuki ligand for the enantioselective MHAT/RPC reaction (Table 14). Further optimization based on the Katsuki ligand indicated that **C14** produced better results than those of **C12** and **C13** and the axial chirality of the biphenyl moiety played an important role in selectivity. The enantioselectivity improved by introducing a substituent in the diamine moiety (**C15**), and **2a** was successfully obtained with 93%ee using ligand **C16**, which contained cyclohexanediamine. At the beginning of the study, we speculated that silylhydride would have little effect on the enantioselectivity because it could possibly have been the hydrogen source of the cobalt hydride species. However, our extensive investigation revealed that the silylhydride has a significant impact on enantioselectivity. $(Me_2SiH)_2O$ displayed only moderate enantioselectivity (58%ee), whereas secondary silanes markedly improved the enantioselectivity, with diethylsilane providing the best result. Most noteworthy in this study is that the absolute configuration of the major product was different for tertiary and secondary silanes. This influence on the absolute configuration of the major product is surprising from the perspective of the reaction mechanism. Among the secondary silanes,

$^{i}Pr_2SiH_2$ had the same absolute configuration of the major product of the tertiary silanes (50%ee). Therefore, we examined the effect of the silyl hydride to elucidate the detailed reaction mechanism.

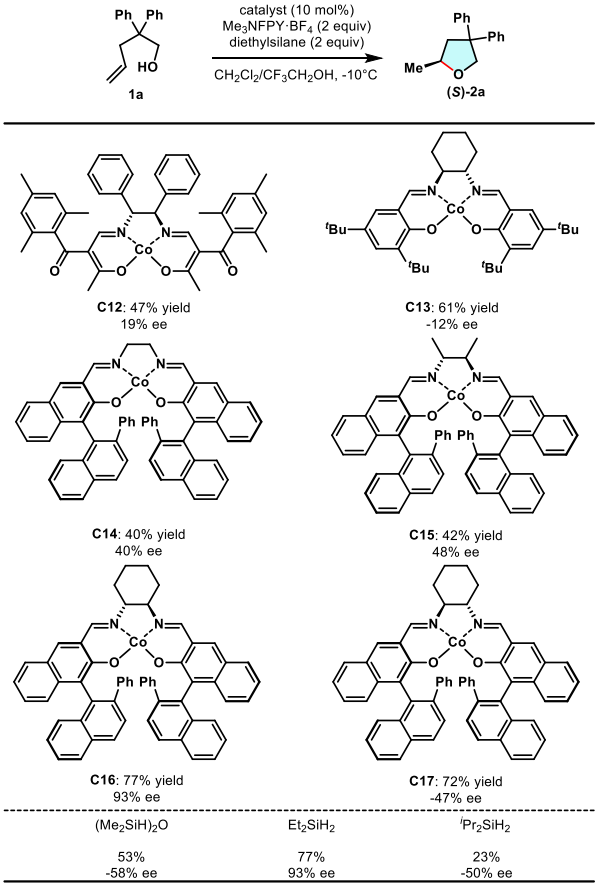


Table 14

We therefore investigated the effect of the rate of addition of silylhydride on enantioselectivity. Et_2SiH_2 was added over 2 hours, resulting in a decrease in enantioselectivity. Upon using $CyMeSiH_2$ as a different secondary silane, to the enantioselectivity decreased to 61%ee over 2 hours. Eventually, the absolute configuration of the major product was reversed over 80 hours. This result suggests that the concentration of intermediates downstream of the cobalt hydride has a significant impact on the enantioselectivity and that multiple enantioselectivity-determining steps may be in competition.

Thus, we propose a mechanism based on enantioselectivity. In Et_2SiH_2, which showed the best enantioselectivity, the steric hindrance was small and cobalt hydride formed very quickly, resulting in an increase in the concentration of the downstream intermediate. The increase in concentration facilitated radical chain reactions between the alkylcobalt(III) complex and carbon radicals that escape from the solvent cage. As a result, the alkyl cobalt (III) complex, which was initially a diastereomeric mixture (Co–C bond formation is nonselective), inclined toward the thermodynamically stable product. The stereochemistry of the alkyl cobalt (III) complex is reflected in the final product, which formed via one-electron oxidation and intramolecular

nucleophilic substitution reactions. The radical chain reaction described here is supported by two findings: 1) the enantioselectivity of the asymmetric reaction with Et_2SiH_2 was markedly reduced (from 93% to 72%ee) when degassing (trifluoroethanol) was not performed; the free carbon radicals were most probably trapped by the oxygen molecules and inhibited the radical chain reaction. 2) the free energy difference between both diastereomers of alkylcobalt(III) complexes was 1.76 kcal/mol, as determined from DFT calculations; the free energy difference is consistent with the absolute configuration of product **2a** and its enantioselectivity (93% ee) can be explained quantitatively. A CH-π interaction between the aromatic rings of each ligand and the starting material in the stable alkylcobalt(III) complex structure is very probable. However, the rate of cobalt hydride formation is lower for bulky silyl hydrides. Under these conditions, radical chain reactions are less likely to occur, and the diastereomeric alkylcobalt(III) complexes form in an almost 1:1 ratio. In this case, enantioselective kinetic resolution occurred during the intramolecular nucleophilic displacement. This explanation of the enantioselectivity is supported by the following points: 1) unlike in the case of Et_2SiH_2, the enantioselectivity with $(Me_2SiH)_2O$ was not reduced without degassing; 2) the energy difference between the two transition states in the intramolecular nucleophilic displacement was calculated to be 0.54 kcal/mol. The absolute configuration of the product was qualitatively consistent with its absolute configuration.

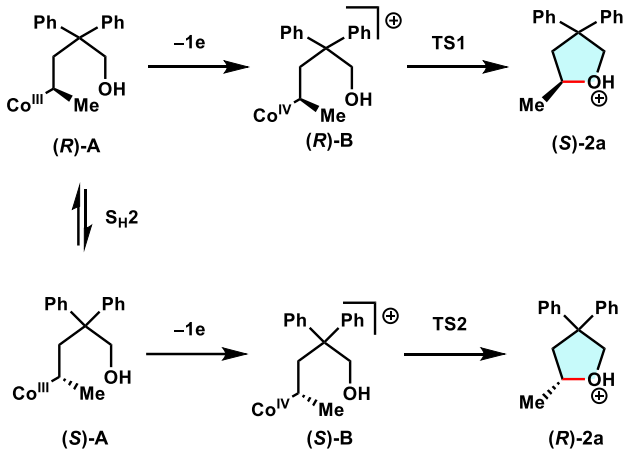


Figure 5

Since the first report on the MHAT/RPC mechanism was published in 2013, a number of groups have reported related methodologies for natural product syntheses (Figure 6). Pronin et al. used MHAT/RPC conditions with allyl alcohol as a starting material and produced both epoxide and semipinacol rearrangement products.[28] The selectivity of both products was controlled using different cobalt complexes. Zhu et al. achieved intermolecular acyloxylation reactions by MHAT/RPC reactions using hypervalent iodine reagents as the oxidant.[29] Both researchers also reported Ritter reactions by the MHAT/RPC mechanism with different oxidants.[30] Furthermore, Omiya-Nagao et al. achieved a similar conversion excluding an oxidant by cleverly utilizing a photoredox catalyst.[31] Kim et al. similarly avoided the use of oxidants by using electrochemical conditions.[32]

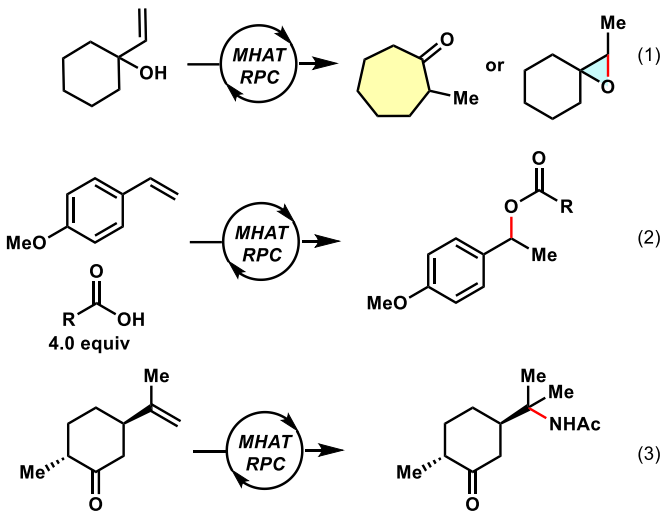


Figure 6

The excellent functional group tolerance of the MHAT/RPC reaction conditions ensures it is a powerful synthetic tool for the synthesis of complex natural products (Figure 7). The application by Newhouse-Maimone et al. to terpenoid synthesis is particularly notable; the framework of andrastin D was synthesized via MHAT/RPC-promoted rearrangement and a total synthesis was accomplished.[33] Furthermore, Vanderwal et al. synthesized plebedipene B via polycyclization under the MHAT/RPC reaction conditions.[34] Moreover, Ding et al. achieved the total synthesis of crinipellins by application of the Dowd-Beckwith rearrangement.[35]

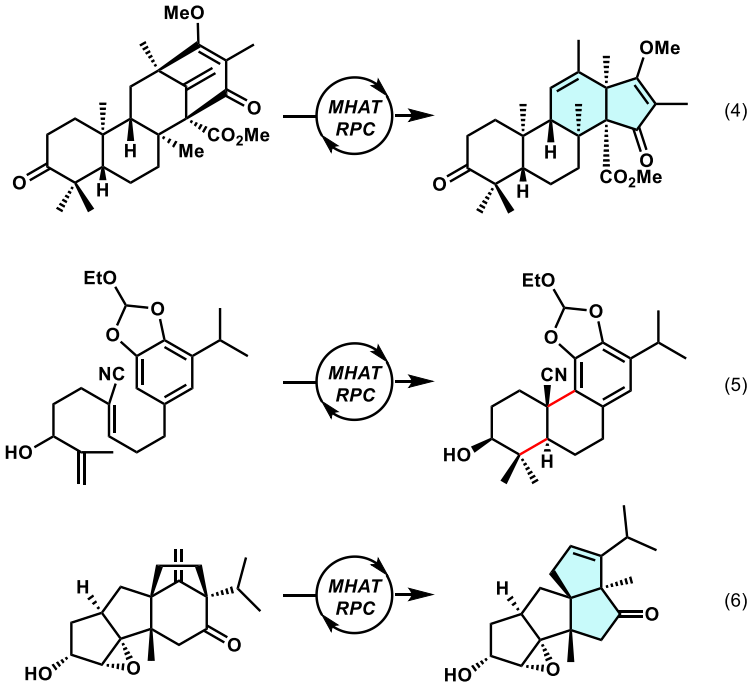


Figure 7

We have been studying alkene transformations based on the MHAT mechanism and have identified that the MHAT/RPC reaction condition can be used to generate a strong electrophilic intermediate (cationic alkylcobalt(IV) complex) by adding an oxidant. The focus was placed on intramolecular reactions affording cyclic molecules, because the cationic alkylcobalt(IV) complex is equivalent to the carbocation obtained by protonated alkenes. We also studied an asymmetric version of MHAT/RPC, which has been a challenging transformation; however, the number of highly enantioselective examples is still limited. Further developments are anticipated.

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