Constructing four-membered heterocycles by cycloisomerization

Ayami Osato[1], Takashi Fujihara[2], and Hiroki Shigehisa*[, 1]

[1] Faculty of Pharmacy, Musashino University, 1-1-20 Shinmachi Nishitokyo-shi, Tokyo 202-8585, Japan

[2] Comprehensive Analysis Center for Science, Saitama University, Shimo-Okubo 255, Sakura-ku, Saitama-Shi, 338-8570, Japan

ABSTRACT: Four-membered heterocycles are highly sought after in modern drug discovery as they provide beneficial properties to the target molecules. Despite tremendous efforts by the synthetic research community, there is a need for a simple and new method to incorporate these motifs into the design molecules. Herein, we reveal a cycloisomerization strategy for the construction of oxetane and azetidine rings via metal hydride hydrogen atom transfer/radical polar crossover, which is challenging both enthalpically and entropically. This method is suitable for synthesizing polysubstituted four-membered heterocycles. This mild and functional-group tolerant reaction has a broad substrate scope, including the spiro structure, which is an important motif in drug discovery research. Various four-membered heterocyclic building blocks can be synthesized by product derivatization. We also discuss the reaction mechanism, focusing on the four membered ring formation, by deuterium experiment and DFT studies.

INTRODUCTION

Four-membered rings can generally withstand practical applications despite their stereoelectronic distortion. Recently, they have attracted particular attention in the field of drug discovery because of their conformational rigidity.[1] In particular, oxetane and azetidine are known for their polarity, which arises from the heteroatoms, i.e., oxygen and nitrogen, respectively. Bioactive molecules designed to incorporate these motifs are expected to show high selectivity for target proteins, as well as other beneficial properties such as hydrophilicity, solubility, and metabolic stability. Notably, following the milestone study by Carreira et al., who revealed that 3,3-disubstituted oxetanes are bioisosteres of carbonyl or *gem*-dimethyl groups, the construction and metabolism of the oxetane motif have been extensively explored (Figure 1A).[2] Stepan et al. reported that *gem*-dimethyloxetane shows slightly higher metabolic stability than do 3,3-disubstituted oxetanes in a γ-secretase inhibitor designed by the researchers.[3] Fish et al. reported an EC_{50} improvement by azetidine incorporation into the 5-HT_{2C} agonist.[4] The oxetane or azetidine motif can be also found in the structure of biologically active natural products and commercial drugs (e.g., paclitaxel and azelnidipine).[2b,5]

Recently, synthetic methods for four-membered heterocycles have been reinvestigated to meet the high demand for these compounds in drug discovery,[2b,5-6] and this places high priority on the three dimensionality of small molecules (Figure 1B).[7] A typical synthetic method applicable to both oxetane and azetidine is intramolecular displacement. This reaction is particularly suitable for the synthesis of 3-substituted or 3,3-disubstituted compounds, and it has been widely exploited in drug discovery. Other reactions have also been adopted to synthesize four-membered heterocycles, with varying degrees of success. Halocyclization of alkenes has not been extensively explored for synthesizing polysubstituted four-membered heterocycles.[8] Stepan et al. utilized halocyclization to synthesize their target compound, and the product was obtained in a low yield.[3] While Paternò–Büchi-type reactions are known to be suitable for polysubstituted four-membered heterocycles, structural requirements are necessary to facilitate photoactivation.[9] There are other synthetic methods to construct oxetane and/or azetidine such as ring-expansion using ylide,[10] β-lactam reduction,[11] C–H bond amination,[12] and Ti^{VI}-mediated spirocyclic azetidine synthesis.[13] Overall, the synthesis of less hindered oxetanes or azetidines is facile owing to classical intramolecular displacement reactions. However, new synthetic methods for sterically hindered and polysubstituted products are required.

The recent trends in drug discovery encouraged us to develop a simple and general synthetic method for four-membered heterocycles by harnessing the metal hydride hydrogen atom transfer (MHAT)[14]/radical polar crossover (RPC) reaction (Figure 1c). This catalytic process is realized by the combination of a cobalt catalyst, an oxidant, and a silyl hydride that generates key cobalt hydride and a highly reactive carbocationic intermediate (cationic alkylcobalt(IV) complexes) from alkenes via carbon radicals under near-neutral conditions. Following our report on cobalt-catalyzed MHAT/RPC reactions,[15] this catalytic system has been extensively utilized in cycloisomerizations,[16] deprotective cyclizations,[17] intermolecular additions,[18] rearrangements,[19] asymmetric variants,[20] and polymerizations.[21] Notably, our group,[16a,17] Pronin,[19a] and Zhu[22] have reported various cycloisomerizations to furnish numerous cyclic ethers and cyclic amines except for the synthetically challenging four-membered heterocycles. Four-membered heterocycles has not been formed by cycloisomerization, even in other catalytic reactions.[23] Two points must be considered when attempting oxetane or azetidine formation via MHAT/RPC-mediated cycloisomerization. First, the general rate of formation of saturated cyclic compounds by intramolecular displacement reactions follows the order 5 > 6 > 3 > 7 > 4 > 8–10 rings.[24]

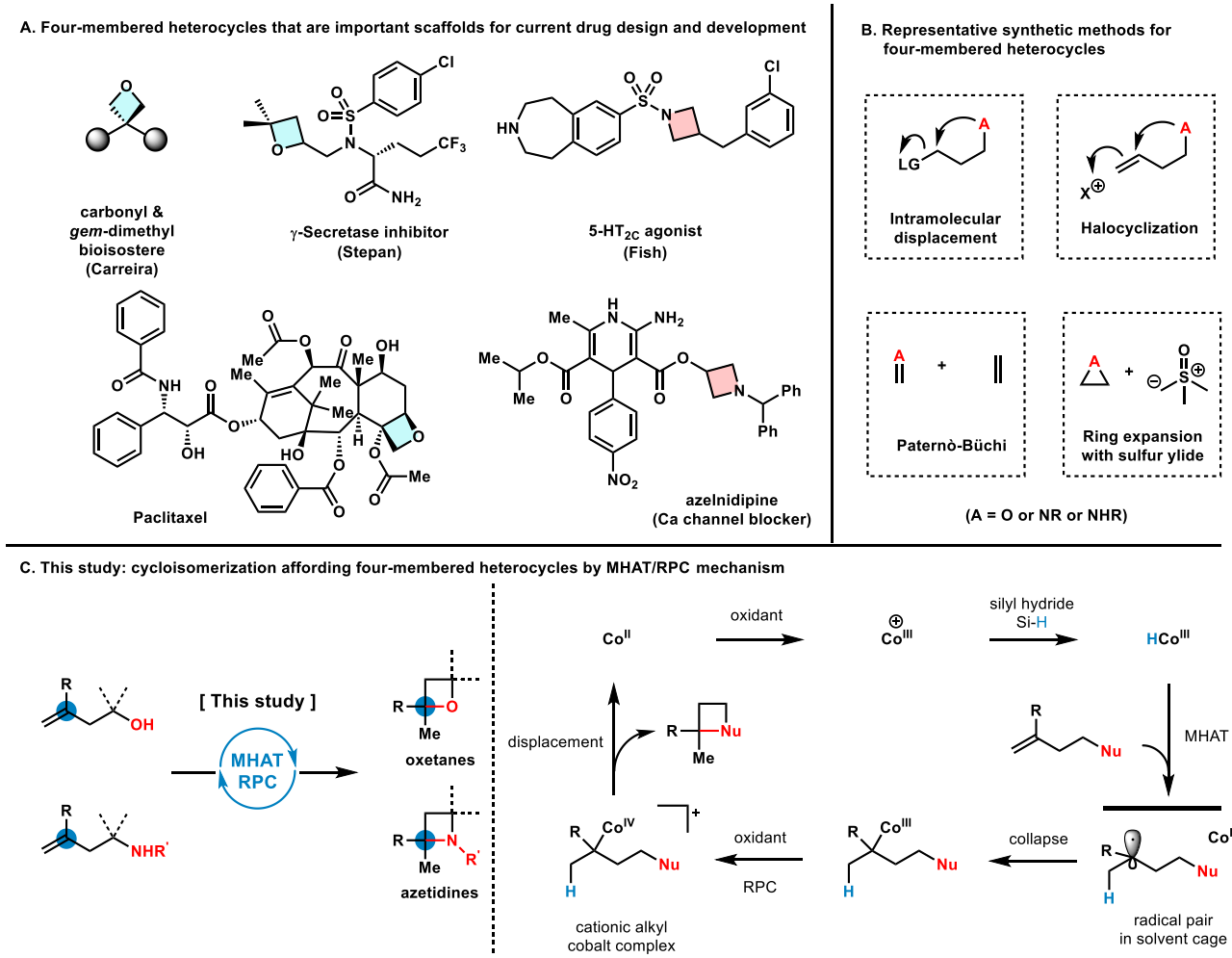


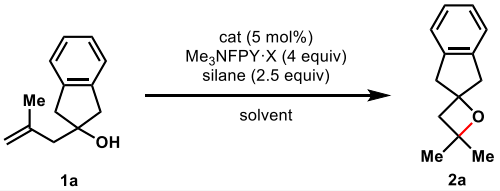
Figure 1. Background. (A) Four-membered heterocycles that are important scaffolds for current drug design and development. (B) Representative synthetic methods for four-membered heterocycles (C) This study: cycloisomerization affording four-membered heterocycles by MHAT/RPC and its mechanism

The ring-closure step in the MHAT/RPC process is an intramolecular displacement reaction (Figure 1c); therefore, there should be no significant deviation from the general order of the reaction rate. One concern with oxetane is that ring formation is more challenging than epoxide formation.[19a,20a] However, less favored eight- and nine-membered ring formation has been achieved, albeit with limited success.[17] Therefore, there was an opportunity to realize four-membered heterocycle formation via the MHAT/RPC mechanism. Second, there was a concern that the high ring strain of the product may stimulate ring opening during product formation. However, this seemed unlikely considering the remarkable functional group tolerance observed under MHAT/RPC conditions. For example, Pronin synthesized epoxides with high ring strain (114 kcal/mol), similar to those of oxetane (107 kcal/mol), under MHAT/RPC conditions.[19a,20a] Herein, we describe a method for the construction of four-membered heterocycles via the MHAT/RPC process, which is challenging both enthalpically and entropically. The substrate scope, including the spiro structure, which is important in drug discovery research, was investigated.[25] We also examined the reaction mechanism on the basis of the results of deuterium experiments and DFT calculations, focusing on the four-membered ring formation. To the best of our knowledge, this is the first example of cycloisomerization affording four-membered heterocycles despite the numerous synthetic efforts involving the intramolecular hydrofunctionalization of unactivated alkenes.

RESULTS AND DISCUSSION Cycloisomerization affording oxetane. We first investigated whether energetically challenging four-membered heterocycles could be formed via MHAT/RPC. We began by searching for a suitable homoallylic alcohol for oxetane formation. Fortunately, the screening of various homoallylic alcohols revealed that **1a** could be cycloisomerized to provide the desired oxetane **2a** in 42% yield by using a cobalt Schiff base catalyst **C1**, *N*-fluoro-2,4,6-collidinium trifluoromethanesulfonate, and 1,1,3,3-tetramethyldisiloxane (TMDSO); [Table 1, entry 1]. Screening of cobalt catalysts **C1**–**C4** revealed that a higher yield (70%) of **2a** was obtained with **C4** bearing cyclohexanediamine (entries 2–4). The yield was slightly improved upon substituting a less bulky group, the *tert*-amyl group (**C5**), for the *tert*-butyl group of the ligand (**C6** and **C7**; entries 5–7). Replacing the counteranion of the oxidant was essential for an excellent yield: hexafluorophosphate (PF_6) performed better than trifluoromethanesulfonate (OTf) and tetrafluoroborate (BF_4) (entries 8 and 9). When 2 equivalents of the oxidant were used, the yield of **2a** decreased (entry 10). Alkenyl alcohol **1a** appeared to favor intermolecular C–O bond formation. However, the yield decreased when the reaction mixture was diluted (entry 11). The

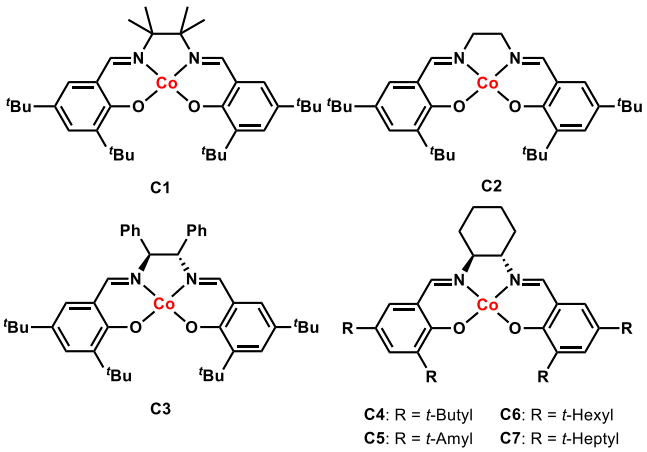
use of the common silane reagent, phenylsilane, did not afford the desired product (entry 12). Other solvents such as tetrahydrofuran, toluene, dichloromethane, and acetone also afforded the desired product, albeit in lower yields than that achieved when using 4-methyltetrahydropyran (MTHP, entries 13–16), a less commonly employed solvent.

Table 1. Optimization of oxetane formation[a]



1a 2a

entry	cat	X	silyl hydride	solvent	yield (%)[a]
1	**C1**	OTf	TMDSO	MTHP	42
2	**C2**	OTf	TMDSO	MTHP	59
3	**C3**	OTf	TMDSO	MTHP	43
4	**C4**	OTf	TMDSO	MTHP	70
5	**C5**	OTf	TMDSO	MTHP	80
6	**C6**	OTf	TMDSO	MTHP	75
7	**C7**	OTf	TMDSO	MTHP	60
8	**C5**	BF_4	TMDSO	MTHP	50
9	**C5**	PF_6	TMDSO	MTHP	90, 88[b]
10	**C5**	PF_6 (2eq)	TMDSO	MTHP	75
11	**C5**	PF_6	TMDSO	MTHP (0.05 M)	68
12	**C5**	PF_6	$PhSiH_3$	MTHP	0
13	**C5**	PF_6	TMDSO	THF	54
14	**C5**	PF_6	TMDSO	CH_3Ph	28
15	**C5**	PF_6	TMDSO	CH_2Cl_2	52
16	**C5**	PF_6	TMDSO	Acetone	20



C1 C2 C3

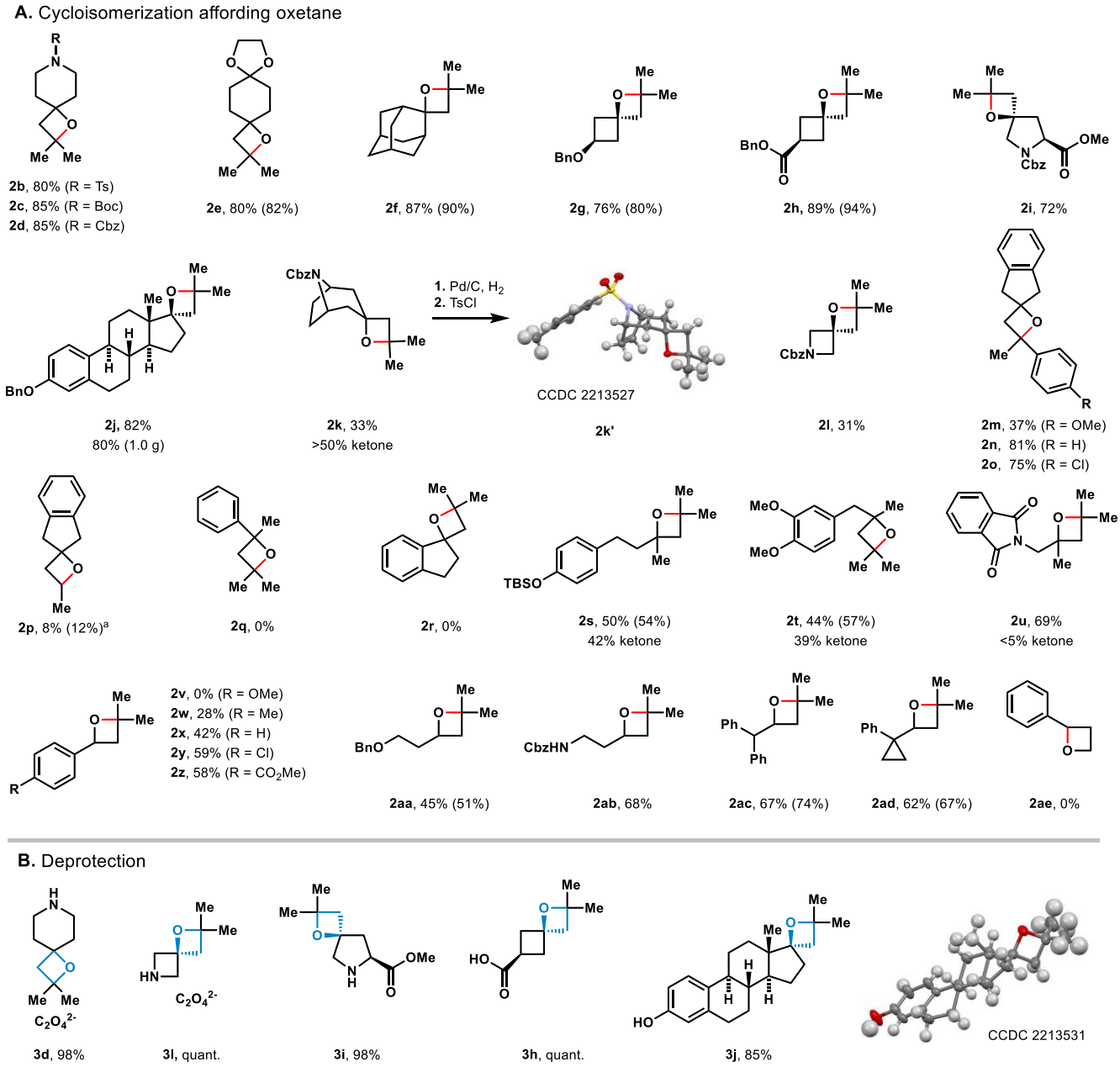
C4: R = *t*-Butyl **C6**: R = *t*-Hexyl
C5: R = *t*-Amyl **C7**: R = *t*-Heptyl

Conditions: starting material **1a** (0.2 mmol), catalyst (0.01 mmol), $Me_3NFPY·X$ (0.8 mmol), silyl hydride (0.5 mmol), solvent (1.0 mL) under argon atmosphere at 0°C for 30 min. [a]NMR yield using 1,4-bis(trifluoromethyl)benzene as an internal standard. [b]isolation yield

With the optimal conditions in hand, we next examined the substrate generality of oxetane formation (Table 2A). With regard to the scope of homomethallyl alcohol derived from various cyclic ketones, we could prepare various spiro-oxetanes, which are attractive building blocks for drug discovery. For example, substrates bearing piperidine (**1b**–**1d**) or the acid-sensitive ketal (**1e**) afforded the desired products **2b**–**2e** in excellent yields. Notably, we observed a small quantity of the corresponding ketone as a byproduct in some cases (10% from **1c** and **1d** and 18% from **1e**), probably via demethallylation (retro-carbonyl-ene reaction) from cationic alkylcobalt complexes. This undesired pathway was substrate dependent; the rigid spiro-oxetane bearing adamantane (**2f**) and cyclobutene (**2g**, **2h**), a proline derivative (**2i**), and an estrone derivative (**2j**) were synthesized in excellent yields without the formation of the corresponding ketones. Compound **2j** was synthesized from **1j** on the 1 g scale in almost the same yield. In contrast, a significant amount of ketone was formed from the nortropane derivative **1k** (>50% yield) during the formation of the oxetane product **2k** in 33% yield. The structure of **2k** was determined by X-ray analysis of its derivative **2k′**. Compound **2l** bearing an azetidine ring afforded a yield of only 31% in a complex product mixture, which did not include the ketone. We also briefly investigated the generality of the alkene moiety by replacing the methyl group of **1a** with an aryl group (**1m**–**1o**) or a hydrogen atom (**1p**). For the aryl group, we found that electron-withdrawing chorine (**1o**) and neutral hydrogen (**1n**) on the aromatic ring produced a higher yield than the electron-donating methoxy group (**1m**). When the methyl group was replaced with a hydrogen atom (**1p**), under the optimal conditions (Table 1), a trace amount of the desired product **2p** was obtained. Although the yield improved slightly when the catalyst, oxidant, and solvent were replaced, there was still room for improvement (Table S1). Remarkably, monosubstituted alkenes were not suitable despite the MHAT/RPC-mediated epoxide synthesis from a monosubstituted alkene reported by Pronin and coworkers.[19a,20a] Tertiary benzyl alcohols **1q** and **1r** were not applicable under the optimal conditions. The substrates derived from linear ketone afforded the desired oxetanes **2s**–**2u** with unavoidable demethallylation. Various homomethallyl alcohols derived from aromatic or aliphatic aldehydes were suitable substrates that afforded the corresponding products in acceptable yields. The presence of an electron-withdrawing group at the 4-position was preferable for oxetane formation. For example, the 4-methoxycarbonyl-substituted product **2z** was obtained in 58% yield. In contrast, the 4-methoxylphenyl product **2v** was not obtained. We obtained demethallylated benzaldehydes in 9%–12% yield from **1w**–**1z**. However, this demethallylation does not fully explain the origin of the electronic effect. The substrates bearing a nucleophile (**1aa**–**1ad**) potentially undergo a bifurcated competitive cyclization pathway, oxetane formation, or six-membered ring formation. Despite the challenging 4-exo cyclization process, the desired oxetanes **2aa**–**2ad** were selectively synthesized without six-membered-ring formation. Cinnamyl alcohol **1ae** was not applicable. Overall, this method is suitable for the synthesis of polysubstituted oxetane.

To demonstrate the synthetic potential of this method, a spirocyclic compound bearing an easily removable protective group was subjected to deprotection (Table 2B). The conventional palladium-catalyzed hydrogenation of **2d**, **2l**, and **2i** afforded the oxalate salt of an amine (**3d** and **3l**) or free amine (**3i**) almost quantitatively. The same reaction conditions were applicable for the synthesis of oxetane bearing carboxylic acid **3h** and an estrone derivative **3j**. Again, the structure of **3j** was unambiguously confirmed by X-ray analysis.

Table 2. Substrate scope of oxetane formation and deprotection



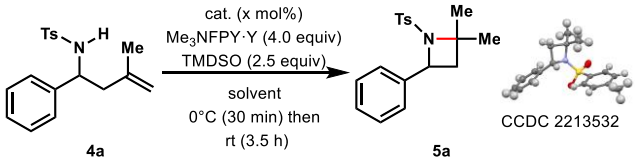
(A) Cycloisomerization affording oxetane. Conditions: starting materials **1b–1o**, **1q–1ae** (0.2 mmol), **C5** (5 mol%), *N*-fluoro-2,4,6-collidinium hexafluorophosphate (4.0 equiv), and 1,1,3,3-tetramethyldisiloxane (2.5 equiv) in 4-methyltetrahydropyran (1.0 mL) under argon atmosphere at 0°C for 30 min; isolation yield is given. Yields in parentheses are NMR yields using 1,4-bis(trifluoromethyl)benzene as an internal standard. [a]Conditions: starting material **1p** (0.5 mmol), **C3** (5 mol%), *N*-fluoro-2,4,6-collidinium hexafluorophosphate (2.0 equiv), and 1,1,3,3-tetramethyldisiloxane (2.0 equiv) in toluene (2.5 mL) under argon atmosphere at room temperature for 2 h; isolation yield is given. (B) Deprotection. Conditions: starting material and palladium on carbon in methanol under hydrogen atmosphere (details in supporting information); isolation yields are given.

Cycloisomerization affording azetidine. We next explored the azetidine formation of homomethallylamine derivative **4a** (Table 3A). First, the desired azetidine **5a** was obtained in 58% yield under the optimal oxetane formation conditions. Solvent screening revealed that toluene was optimal (89%, entries 1–3). Recently, the solvent effect on related reactions has been discussed by considering polarity and viscosity.[22a,26] In our study, the optimal solvents for four-membered heterocycles formation were MTHP for oxetane and toluene for azetidine, which reveals a clear dependency on the nucleophile. The optimal counteranion of the oxidant was found to be hexafluorophosphate (entries 3–5). Unlike in the case of oxetane formation, the yield changed slightly during catalyst screening for azetidine formation. Typically, the desired product (**5a**) was formed in excellent yields (entries 3, 6–9). When using **C4** or **C5** and upon reducing the catalyst loading to 3 mol%, we achieved excellent yields (entries 10 and 11). We finally examined the effect of chirality of substrate and ligand on yield. Compared with

the result using **C4** (entry 10), no significant difference was observed using chiral (*R*)-**4a** or ***ent*-C4** (entry 12). When using **C5** (the optimal catalyst) and chiral (*R*)-**4a**, similar results were achieved (entry 11 and 13). Therefore, the following experiments were performed using a racemic substrate, unless otherwise noted.

Table 3. Optimization of azetidine formation

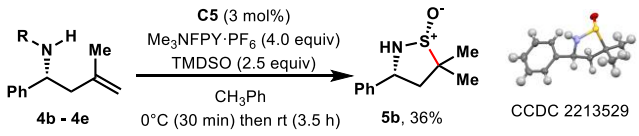
A. Optimization of reaction conditions affording azetidine



CCDC 2213532

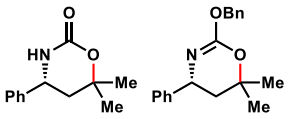
entry	cat. (x)	Y	solvent	yield (%)[a]
1	**C5** (5)	PF_6	MTHP	58
2	**C5** (5)	PF_6	acetone	43
3	**C5** (5)	PF_6	CH_3Ph	89
4	**C5** (5)	BF_4	CH_3Ph	55
5	**C5** (5)	OTf	CH_3Ph	75
6	**C1** (5)	PF_6	CH_3Ph	83
7	**C2** (5)	PF_6	CH_3Ph	87
8	**C3** (5)	PF_6	CH_3Ph	83
9	**C4** (5)	PF_6	CH_3Ph	88, 68[b]
10	**C4** (3)	PF_6	CH_3Ph	86
11	**C5** (3)	PF_6	CH_3Ph	89, 85[c]
12	**C4** (3)	PF_6	CH_3Ph	85[d], 86[d, e]
13	**C5** (3)	PF_6	CH_3Ph	90[d], 88[c]

B. Optimization of protective group



CCDC 2213529

4b (R = (*S*)-SO^{t}Bu)
4c (R = Ns)
4d (R = Boc)
4e (R = Cbz)

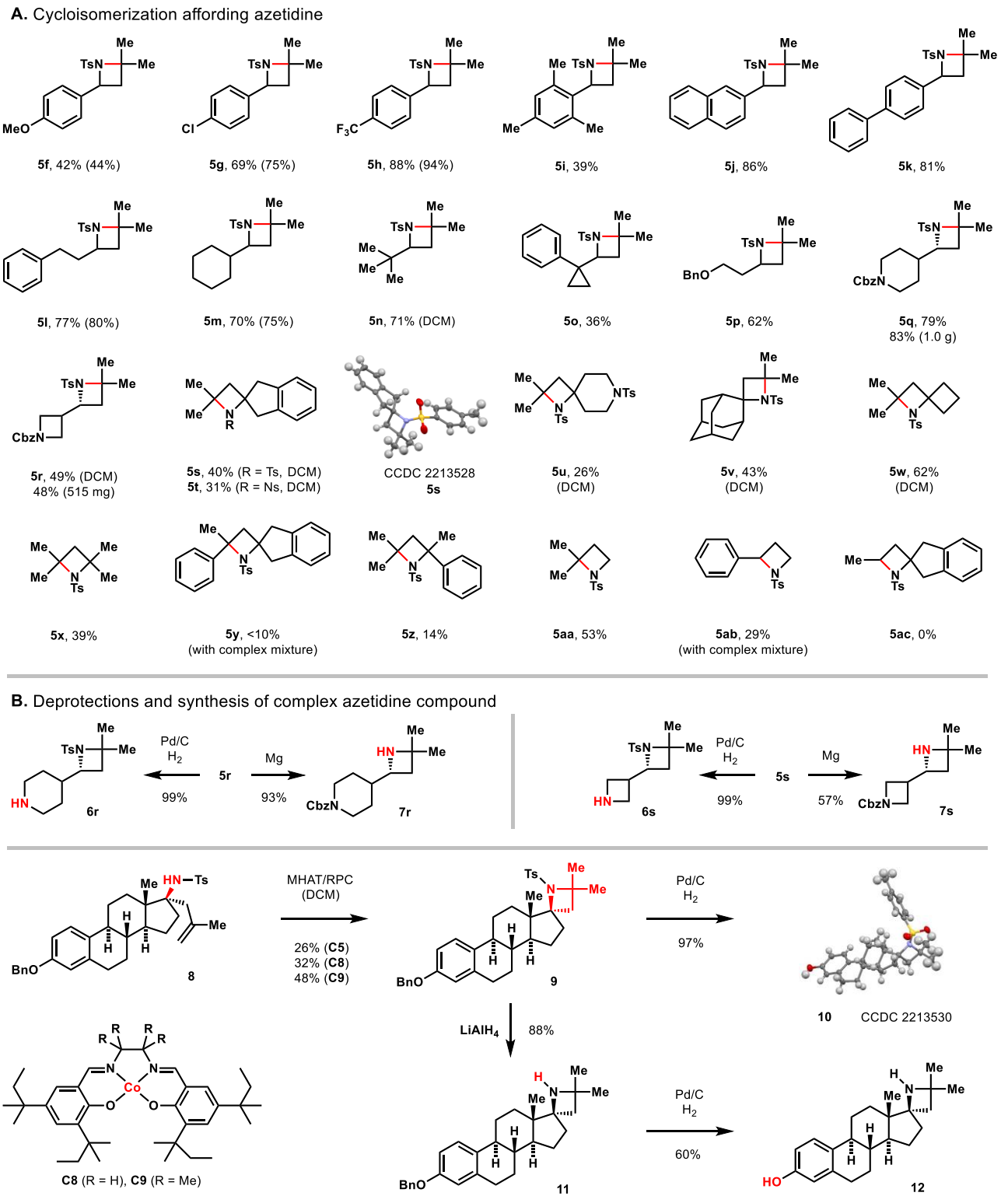


(A) Optimization of reaction conditions affording azetidine. Conditions: **4a** (0.2 mmol), catalyst (0.01 or 0.006 mmol), $Me_3NFPY{\cdot}X$ (0.8 mmol), silyl hydride (0.5 mmol), solvent (1.0 mL) under argon atmosphere at 0°C for 30 min then room temperature for 3.5 h. [a]NMR yield using 1,4-bis(trifluoromethyl)benzene as an internal standard. [b]TMDSO (1.5 equiv) [c]isolation yield [d](*R*)-starring material was used. [e]***ent*-C4** was used. (B) Optimization of protective group. Isolation yield is given.

We next examined the scope of protective groups on the nucleophilic nitrogen atom by replacing the tosyl group (Table 3B). This attempt revealed that only tosylamide enabled the formation of azetidine rings under the optimal reaction conditions. Sulfinamide **4b**, the synthetic intermediate of chiral (*R*)-**4a**, was selectively cyclized to five-membered sulfinamide **5b** (X-ray structure in Supporting Information) by the preferential nucleophilic attack of a sulfur atom with stereochemical inversion. Nosylamide **4c** was not a suitable substrate for this reaction. The use of common protective groups such as *tert*-butoxycarbonyl (Boc) or carboxybenzyl (Cbz) led to the formation of six-membered products **5d** or **5e** respectively.

Under the optimal conditions, we examined the substrate generality of azetidine formation by introducing a substituent on the aromatic ring of substrates **4a** (Table 4A). The formation of **5f** – **5h** indicates that the electronic preference is similar to that for oxetanes **2v** – **2z**. In contrast to unsuccessful **2v**, azetidine **5f** bearing *p*-methoxy phenyl could also be synthesized using this method. Encouraged by these results, we performed reactions yielding azetidines bearing sterically hindered mesityl (**5i**), 2-naphthyl (**5j**), and biphenyl (**5k**). Substrates derived from aliphatic aldimine were also applicable. For example, three azetidines **5l** – **5n** could be synthesized, regardless of steric hindrance. Dichloromethane was a better solvent than toluene for addressing the solubility issue (**5n**). Compared with the case of oxetane **3ad** (62%), azetidine **5o** was formed in only 36% yield along with tetraline **5o′** (45%; Supporting Information). In contrast, the azetidine was selectively formed, regardless of the possible deprotective cyclization (**5p**). We synthesized two chiral bicyclic compounds bearing rotatable linkers **5q** and **5r** in acceptable yields. Both compounds were synthesized on a larger scale in similar yields. Furthermore, 2,2,4,4-tetrasubstituted azetidines were synthesized by this method. Again, we confirmed the requirement of the tosyl group by using the substrate bearing an indane framework; the yield of **5s** bearing a tosyl group was higher than that of **5t** bearing a nosyl group. The substrate bearing a Cbz group afforded six-membered **5s′** (see supporting information). The yields were not satisfactory for every product **5u**, **5v**, **5w**, and **5x**; however, it should be noted that the practical synthesis of these azetidines has not yet been reported. Unfortunately, this cycloisomerization afforded **5y** or **5z** in insufficient yields. Less substituted azetidines **5aa** and **5ab** were also synthesized using this method. Homoallylamine derivative **5ac** could not be synthesized by this method. Overall, this cycloisomerization was found to be suitable for the synthesis of polysubstituted azetidines.

Table 4. Substrate scope of azetidine formation and deprotection



(A) Cycloisomerization affording azetidine. Conditions: starting material **4f-4ac** (0.2 mmol), **C5** (3 mol%), *N*-fluoro-2,4,6-collidinium hexafluorophosphate (4.0 equiv), and 1,1,3,3-tetramethyldisiloxane (2.5 equiv) in toluene (1.0 mL) under argon atmosphere at 0°C for 30 min then room temperature for 3.5 h; isolation yields are given. Yields in parentheses are NMR yields using 1,4-*bis*(trifluoromethyl)benzene as an internal standard. (B) Deprotection. Conditions of MHAT/RPC: starting material (0.1 or 1.0 mmol), catalyst (3 mol%), *N*-fluoro-2,4,6-collidinium hexafluorophosphate (4.0 equiv), and 1,1,3,3-tetramethyldisiloxane (2.5 equiv) in dichloromethane (0.5 mL) under argon atmosphere at 0°C for 30 min then room temperature for 3.5 h; isolation yields are given. Other reactions: see supporting information in detailed procedures

To confirm the synthetic utility of the azetidine products, we attempted a further transformation (Table 4B). Fortunately, either of two differentiated protective groups, the tosyl or Cbz group, could be selectively removed from bicyclic diamine **5r** by palladium-catalyzed hydrogenation (**6r**) or reduction with magnesium metal (**7r**), respectively, thereby achieving excellent yields. The same method was suitable for the synthesis of bicyclic products bearing two azetidines (**6s** and **7s**). Note that the reduction with sodium naphthalenide resulted in a complex product mixture for the purpose of detosylation of **5r** and **5s**. We finally incorporated the azetidine unit into estrone, a biologically relevant complex compound. The cycloisomerization with **C5** resulted in only 26% yield of **9**, along with the formation of several isomeric byproducts (see supporting information). However, the yield improved slightly when **C9** was used instead (48%), and the formation of the isomeric byproduct was somewhat suppressed. The structure of azetidine **9** was unambiguously determined after benzyl deprotection, followed by the X-ray analysis of **10**. Full deprotection was completed by reduction with lithium aluminum hydride and palladium-catalyzed hydrogenation. The use of magnesium metal led to the full recovery of **9** after detosylation.

Deuterium experiments. To gain insight into the mechanism, we performed a deuterium-labeling experiment with TMDSO-d_2 in the cycloisomerization of **1a** and its *homo*-analog **13** (Figure 2). The deuterium atom was incorporated into the *gem*-dimethyl moiety for **2a-D** (192%D) and **14-D** (118%D). These results indicate that the rate of the ring-closure step affected product formation and the retro-reaction. After the MHAT of alkene and the following steps, 2,4,6-collidine (derived from oxidant) probably deprotonated the alkylcobalt(IV) complex to reform the corresponding starting material (Figure SI1). We assumed that this was the main reason for the excess oxidant in this cycloisomerization. A similar phenomenon was observed during the formation of azetidine **5s-D** (214%D). Notably, the deuterium incorporation rate was 173%D in the formation of **16-D** despite rapid five-membered ring formation.

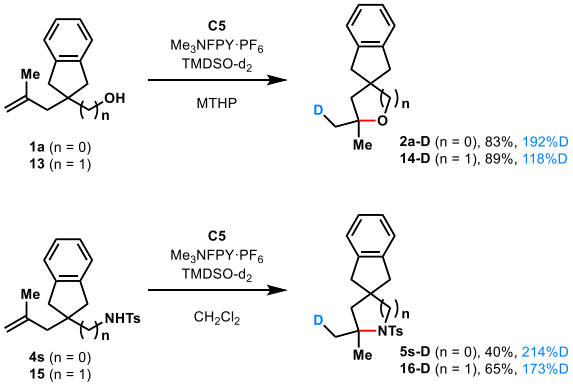


Figure 2. Deuterium experiments. Conditions A: starting materials **1a** and **13** (0.1 mmol), **C5** (5 mol%), *N*-fluoro-2,4,6-collidinium hexafluorophosphate (4.0 equiv), and 1,1,3,3-tetramethyldisiloxane-d_2 (2.5 equiv) in 4-methyltetrahydropyran (1.0 mL) under argon atmosphere at 0 °C for 30 min; isolation yield is given. Conditions B: starting materials **4s** and **15** (0.1 mmol), **C5** (3 mol%), *N*-fluoro-2,4,6-collidinium hexafluorophosphate (4.0 equiv), and 1,1,3,3-tetramethyldisiloxane-d_2 (2.5 equiv) in dichloromethane (1.0 mL) under argon atmosphere at 0 °C for 30 min, then room temperature for 3.5 h; isolation yields are given.

DFT study. As aforementioned, a disubstituted alkene is preferable to its monosubstituted counterpart in this four-membered heterocycle formation. From a mechanistic standpoint, this preference merits discussion. For this purpose, we focused on the cyclization of a cationic alkylcobalt(IV) complex. According to the literature, a disubstituted alkene forms a sterically hindered reactive carbon, which is generally unfavorable for S_N2-type processes.[27] In classic nucleophilic substitution, this is more likely to be an S_N1-type process, i.e., dissociation of the Co–C bond, which generates a highly electrophilic tertiary carbocation intermediate, followed by ring formation. To verify our hypothesis regarding the ring-formation step, we performed DFT calculations by using a simple model with the minimum structural requirements for oxetane synthesis to reduce the computational cost (Figure 3). Activation energies were estimated for three types of cyclizations with alkene (mono- or di-) substitution and ring size (four or five). As is intuitive, when reactions with the same substituted alkene were compared, the energetic barrier for the four-membered ring formation was higher than that for the five-membered ring formation (**TS1a** and **TS1c**). More importantly, when reactions involving the same ring size were compared, the activation energies for disubstituted alkenes were clearly lower than those for monosubstituted alkenes, which was consistent with the experimental results (**TS1a** and **TS1b**). A slight vibration of the cobalt atom in the transition states of **TS1a** and **TS1c** was observed according to the frequency analysis results. Notably, **TS1a** had the longest Co–C bond distance (3.53 Å) and had a transition state most similar to an S_N1-type transition state. The orbital overlap, which is required for S_N2-type transition states, may be structurally restricted during the four-membered ring formation. Instead, the prior extension of the Co–C bond led to the formation of a more electrophilic carbon atom (closer to a tertiary carbocation), before enabling the following C–O bond formation. For the monosubstituted alkenes, the C–O bond extension was even more difficult due to the generation of the more unstable secondary carbocation, which suggested that product formation was inefficient. The DFT calculations gave similar results for azetidine formation (**TS2a–TS2c**).

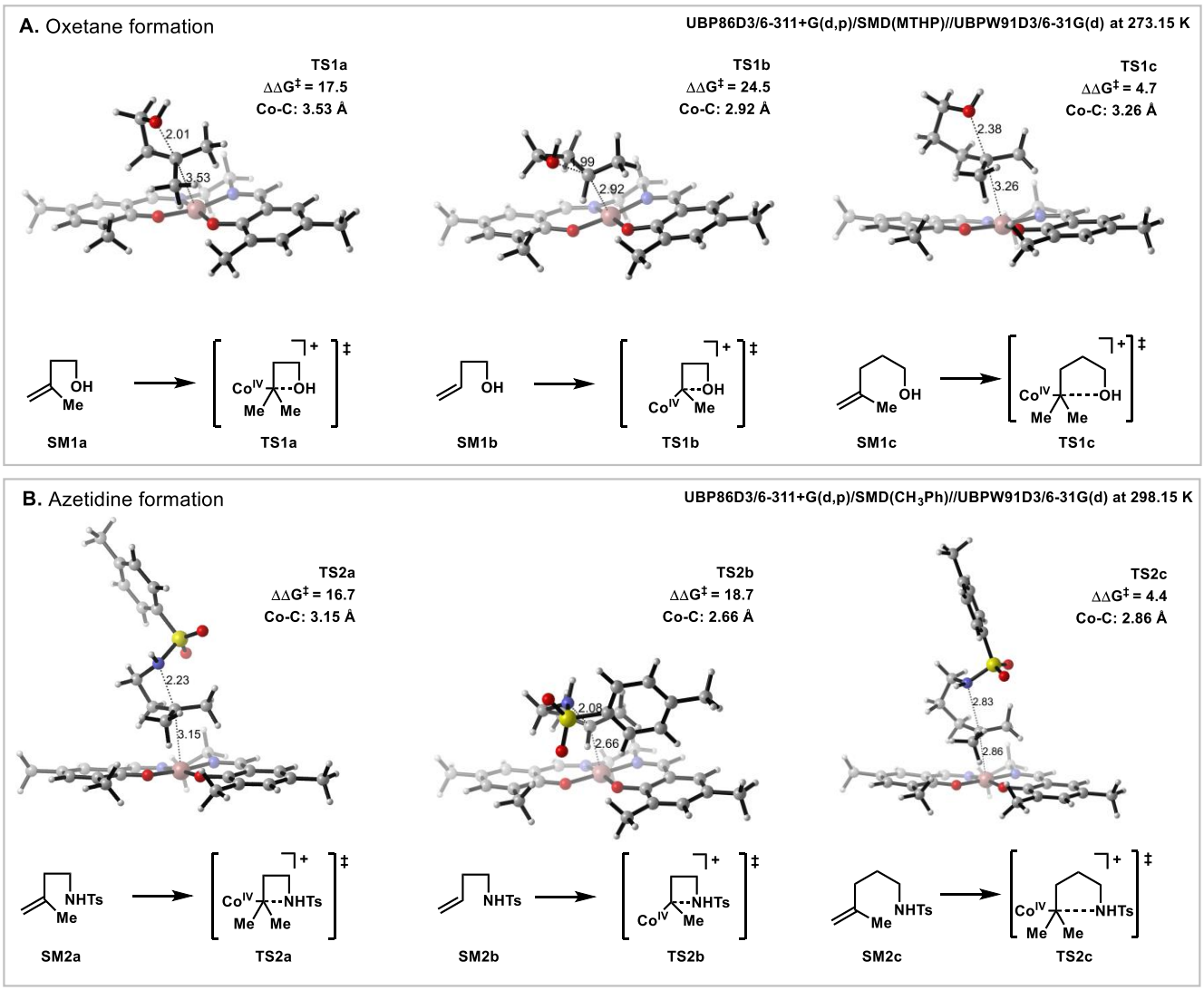


Figure 3. DFT study of ring-closure step using simplified models (A) Oxetane formation (B) Azetidine formation (kcal/mol).

In conclusion, we developed an unprecedented cycloisomerization for the synthesis of four-membered heterocycles via a cobalt-catalyzed MHAT/RPC mechanism. The reaction conditions were mild, and the starting materials (homomethallyl alcohol or homomethallyl amine derivatives) could be easily prepared by conventional methods. This synthetic method successfully generated a broad range of polysubstituted four-membered heterocycles. The products were derivatized to demonstrate the applicability of our method. DFT studies confirmed that a four-membered heterocycle could be formed via an S_N1 displacement-like reaction. In the future, we hope to expand the substrate scope to include monosubstituted alkenes by redesigning the cobalt catalyst and optimizing the reaction conditions. Further studies should focus on the design of enantioselective variants. Additionally, from the standpoint of medicinal chemistry, the physicochemical and metabolic properties of the oxetane and azetidine modules produced by this method should be evaluated systematically.

Associated Content

Supporting Information. Experimental procedures and analytical data (^{1}H and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*cgehisa@musashino-u.ac.jp.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant number 20K06976 and The Naito Foundation. We thank Chikayoshi Sebe and Koki Nogami for synthesizing some materials.

REFERENCES

1. Bauer, M. R.; Di Fruscia, P.; Lucas, S. C. C.; Michaelides, I. N.; Nelson, J. E.; Storer, R. I.; Whitehurst, B. C., Put a ring on it: application of small aliphatic rings in medicinal chemistry. *RSC Med. Chem.* **2021**, *12*, 448-471.
2. (a) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M., Oxetanes as Versatile Elements in Drug Discovery and Synthesis. *Angew. Chem. Int. Ed.* **2010**, *49*, 9052-9067; (b) Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F., Oxetanes: Recent Advances in Synthesis, Reactivity, and Medicinal Chemistry. *Chem. Rev.* **2016**, *116*, 12150-12233; (c) Toselli, F.; Fredenwall, M.; Svensson, P.; Li, X.-Q.; Johansson, A.; Weidolf, L.; Hayes, M. A., Hip To Be Square: Oxetanes as Design Elements To Alter Metabolic Pathways. *J. Med. Chem.* **2019**, *62*, 7383-7399.
3. Stepan, A. F.; Karki, K.; McDonald, W. S.; Dorff, P. H.; Dutra, J. K.; DiRico, K. J.; Won, A.; Subramanyam, C.; Efremov, I. V.; O'Donnell, C. J.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Sneed, B.; Sun, H.; Lu, Y.; Robshaw, A. E.; Riddell, D.; O'Sullivan, T. J.; Sibley, E.; Capetta, S.; Atchison, K.; Hallgren, A. J.; Miller, E.; Wood, A.; Obach, R. S., Metabolism-Directed Design of Oxetane-Containing Arylsulfonamide Derivatives as γ-Secretase Inhibitors. *J. Med. Chem.* **2011**, *54*, 7772-7783.
4. Fish, P. V.; Brown, A. D.; Evrard, E.; Roberts, L. R., 7-Sulfonamido-3-benzazepines as potent and selective 5-HT2C receptor agonists: Hit-to-lead optimization. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1871-1875.
5. Parmar, D. R.; Soni, J. Y.; Guduru, R.; Rayani, R. H.; Kusurkar, R. V.; Vala, A. G., Azetidines of pharmacological interest. *Arch. Pharm.* **2021**, *354*, 2100062.
6. Mehra, V.; Lumb, I.; Anand, A.; Kumar, V., Recent advances in synthetic facets of immensely reactive azetidines. *RSC Adv.* **2017**, *7*, 45763-45783.
7. (a) Lovering, F., Escape from Flatland 2: complexity and promiscuity. *MedChemComm* **2013**, *4*, 515-519; (b) Lovering, F.; Bikker, J.; Humblet, C., Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752-6756.
8. (a) Galatsis, P.; Millan, S. D.; Nechala, P.; Ferguson, G., Tandem Aldol-Cyclization Sequence for the Construction of Cyclic Ethers. The Formation of Substituted Tetrahydrofurans. *J. Org. Chem.* **1994**, *59*, 6643-6651; (b) Feula, A.; Dhillon, S. S.; Byravan, R.; Sangha, M.; Ebanks, R.; Hama Salih, M. A.; Spencer, N.; Male, L.; Magyary, I.; Deng, W.-P.; Müller, F.; Fossey, J. S., Synthesis of azetidines and pyrrolidines via iodocyclisation of homoallyl amines and exploration of activity in a zebrafish embryo assay. *Org. Biomol. Chem.* **2013**, *11*, 5083-5093.
9. (a) Flores, D. M.; Schmidt, V. A., Intermolecular 2 + 2 Carbonyl–Olefin Photocycloadditions Enabled by Cu(I)–Norbornene MLCT. *J. Am. Chem. Soc.* **2019**, *141*, 8741-8745; (b) Mateos, J.; Vega-Peñaloza, A.; Franceschi, P.; Rigodanza, F.; Andreetta, P.; Companyó, X.; Pelosi, G.; Bonchio, M.; Dell'Amico, L., A visible-light Paternò–Büchi dearomatisation process towards the construction of oxeto-indolinic polycycles. *Chem. Sci.* **2020**, *11*, 6532-6538; (c) Rykaczewski, K. A.; Schindler, C. S., Visible-Light-Enabled Paternò–Büchi Reaction via Triplet Energy Transfer for the Synthesis of Oxetanes. *Org. Lett.* **2020**, *22*, 6516-6519; (d) Becker, M. R.; Richardson, A. D.; Schindler, C. S., Functionalized azetidines via visible light-enabled aza Paternò-Büchi reactions. *Nat. Commun.* **2019**, *10*, 5095; (e) Becker, M. R.; Wearing, E. R.; Schindler, C. S., Synthesis of azetidines via visible-light-mediated intermolecular [2+2] photocycloadditions. *Nat. Chem.* **2020**, *12*, 898-905; (f) Flores, D. M.; Neville, M. L.; Schmidt, V. A., Intermolecular 2+2 imine-olefin photocycloadditions enabled by Cu(I)-alkene MLCT. *Nat. Commun.* **2022**, *13*, 2764.
10. (a) Sone, T.; Lu, G.; Matsunaga, S.; Shibasaki, M., Catalytic Asymmetric Synthesis of 2,2-Disubstituted Oxetanes from Ketones by Using a One-Pot Sequential Addition of Sulfur Ylide. *Angew. Chem. Int. Ed.* **2009**, *48*, 1677-1680; (b) Garima; Srivastava, V. P.; Yadav, L. D. S., The first example of ring expansion of N-tosylaziridines to 2-aroyl-N-tosylazetidines with nitrogen ylides in an aqueous medium. *Green Chem.* **2010**, *12*, 1460-1465; (c) Malik, S.; Nadir, U. K., A Facile Synthesis of 1-Arenesulfonylazetidines through Reaction of 1-Arenesulfonylaziridines with Dimethylsulfoxonium Methylide Generated under Microwave Irradiation. *Synlett* **2008**, *2008*, 108-110.
11. Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R., Azetidines and bisazetidines. Their synthesis and use as the key intermediates to enantiomerically pure diamines, amino alcohols, and polyamines. *The Journal of Organic Chemistry* **1991**, *56*, 5263-5277.
12. Nappi, M.; He, C.; Whitehurst, W. G.; Chappell, B. G. N.; Gaunt, M. J., Selective Reductive Elimination at Alkyl Palladium(IV) by Dissociative Ligand Ionization: Catalytic C(sp3)−H Amination to Azetidines. *Angew. Chem. Int. Ed.* **2018**, *57*, 3178-3182.
13. Behnke, N. E.; Lovato, K.; Yousufuddin, M.; Kürti, L., Titanium-Mediated Synthesis of Spirocyclic NH-Azetidines from Oxime Ethers. *Angew. Chem. Int. Ed.* **2019**, *58*, 14219-14223.
14. (a) Shevick, S. L.; Wilson, C. V.; Kotesova, S.; Kim, D.; Holland, P. L.; Shenvi, R. A., Catalytic hydrogen atom transfer to alkenes: a roadmap for metal hydrides and radicals. *Chem. Sci.* **2020**; (b) Crossley, S. W.; Obradors, C.; Martinez, R. M.; Shenvi, R. A., Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116*, 8912-9000; (c) Green, S. A.; Crossley, S. W. M.; Matos, J. L. M.; Vásquez-Céspedes, S.; Shevick, S. L.; Shenvi, R. A., The High Chemofidelity of Metal-Catalyzed Hydrogen Atom Transfer. *Acc. Chem. Res.* **2018**, *51*, 2628-2640; (d) Eisenberg, D. C.; Norton, J. R., Hydrogen-Atom Transfer Reactions of Transition-Metal Hydrides. *Isr. J. Chem.* **1991**, *31*, 55-66.
15. Shigehisa, H.; Aoki, T.; Yamaguchi, S.; Shimizu, N.; Hiroya, K., Hydroalkoxylation of Unactivated Olefins with Carbon Radicals and Carbocation Species as Key Intermediates. *J. Am. Chem. Soc.* **2013**, *135*, 10306-10309.
16. (a) Shigehisa, H.; Koseki, N.; Shimizu, N.; Fujisawa, M.; Niitsu, M.; Hiroya, K., Catalytic Hydroamination of Unactivated Olefins Using a Co Catalyst for Complex Molecule Synthesis. *J. Am. Chem. Soc.* **2014**, *136*, 13534-13537; (b) Vrubliauskas, D.; Vanderwal, C. D., Cobalt-Catalyzed Hydrogen-Atom Transfer Induces Bicyclizations that Tolerate Electron-Rich and Electron-Deficient Intermediate Alkenes. *Angew. Chem. Int. Ed.* **2020**, *59*, 6115-6121.
17. Shigehisa, H.; Hayashi, M.; Ohkawa, H.; Suzuki, T.; Okayasu, H.; Mukai, M.; Yamazaki, A.; Kawai, R.; Kikuchi, H.; Satoh, Y.; Fukuyama, A.; Hiroya, K., Catalytic Synthesis of Saturated Oxygen Heterocycles by Hydrofunctionalization of Unactivated Olefins: Unprotected and Protected Strategies. *J. Am. Chem. Soc.* **2016**, *138*, 10597-10604.
18. (a) Sun, H.-L.; Yang, F.; Ye, W.-T.; Wang, J.-J.; Zhu, R., Dual Cobalt and Photoredox Catalysis Enabled Intermolecular Oxidative Hydrofunctionalization. *ACS Catal.* **2020**, 4983-4989; (b) Zhou, X. L.; Yang, F.; Sun, H. L.; Yin, Y. N.; Ye, W. T.; Zhu, R., Cobalt-Catalyzed Intermolecular Hydrofunctionalization of Alkenes: Evidence for a Bimetallic Pathway. *J. Am. Chem. Soc.* **2019**, *141*, 7250-7255; (c) Nakagawa, M.; Matsuki, Y.; Nagao, K.; Ohmiya, H., A Triple Photoredox/Cobalt/Brønsted Acid Catalysis Enabling Markovnikov Hydroalkoxylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2022**, *144*, 7953-7959; (d) Yin, Y.-N.; Ding, R.-Q.; Ouyang, D.-C.; Zhang, Q.; Zhu, R., Highly chemoselective synthesis of hindered amides via cobalt-catalyzed intermolecular oxidative hydroamidation. *Nat. Commun.* **2021**, *12*, 2552.
19. (a) Touney, E. E.; Foy, N. J.; Pronin, S. V., Catalytic Radical-Polar Crossover Reactions of Allylic Alcohols. *J. Am. Chem. Soc.* **2018**, *140*, 16982-16987; (b) Zhao, Y.; Hu, J.; Chen, R.; Xiong, F.; Xie, H.; Ding, H., Divergent Total Syntheses of (−)-Crinipellins

Facilitated by a HAT-Initiated Dowd–Beckwith Rearrangement. *J. Am. Chem. Soc.* **2022**, *144*, 2495-2500; (c) Xu, G.; Elkin, M.; Tantillo, D. J.; Newhouse, T. R.; Maimone, T. J., Traversing Biosynthetic Carbocation Landscapes in the Total Synthesis of Andrastin and Terretonin Meroterpenes. *Angew. Chem. Int. Ed.* **2017**, *56*, 12498-12502.
20. (a) Discolo, C. A.; Touney, E. E.; Pronin, S. V., Catalytic Asymmetric Radical–Polar Crossover Hydroalkoxylation. *J. Am. Chem. Soc.* **2019**, 17527-17532; (b) Ebisawa, K.; Izumi, K.; Ooka, Y.; Kato, H.; Kanazawa, S.; Komatsu, S.; Nishi, E.; Shigehisa, H., Catalyst- and Silane-Controlled Enantioselective Hydrofunctionalization of Alkenes by Cobalt-Catalyzed Hydrogen Atom Transfer and Radical-Polar Crossover. *J. Am. Chem. Soc.* **2020**, *142*, 13481-13490; (c) Qin, T.; Lv, G.; Meng, Q.; Zhang, G.; Xiong, T.; Zhang, Q., Cobalt-Catalyzed Radical Hydroamination of Alkenes with N-Fluorobenzenesulfonimides. *Angew. Chem. Int. Ed.* **2021**, *60*, 25949-25957; (d) Qin, T.; Lv, G.; Miao, H.; Guan, M.; Xu, C.; Zhang, G.; Xiong, T.; Zhang, Q., Cobalt-Catalyzed Asymmetric Alkylation of (Hetero)Arenes with Styrenes. *Angew. Chem. Int. Ed.* **2022**, *61*, e202201967; (e) Miao, H.; Guan, M.; Xiong, T.; Zhang, G.; Zhang, Q., Cobalt-Catalyzed Enantioselective Hydroamination of Arylalkenes with Secondary Amines. *Angew. Chem. Int. Ed. n/a*, e202213913.
21. Dadashi-Silab, S.; Stache, E. E., A Hydrometalation Initiation Mechanism via a Discrete Cobalt-Hydride for a Rapid and Controlled Radical Polymerization. *J. Am. Chem. Soc.* **2022**, *144*, 13311-13318.
22. (a) Ye, W.-T.; Zhu, R., Dioxygen-promoted cobalt-catalyzed oxidative hydroamination using unactivated alkenes and free amines. *Chem Catalysis* **2022**, *2*, 345-357; (b) Yang, F.; Nie, Y.-C.; Liu, H.-Y.; Zhang, L.; Mo, F.; Zhu, R., Electrocatalytic Oxidative Hydrofunctionalization Reactions of Alkenes via Co(II/III/IV) Cycle. *ACS Catal.* **2022**, *12*, 2132-2137.
23. (a) Zhou, Y.; Xu, X.; Sun, H.; Tao, G.; Chang, X.-Y.; Xing, X.; Chen, B.; Xu, C., Development of highly efficient platinum catalysts for hydroalkoxylation and hydroamination of unactivated alkenes. *Nat. Commun.* **2021**, *12*, 1953; (b) Trowbridge, A.; Walton, S. M.; Gaunt, M. J., New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. *Chem. Rev.* **2020**, *120*, 2613-2692; (c) Schlüter, J.; Blazejak, M.; Boeck, F.; Hintermann, L., Asymmetric Hydroalkoxylation of Non-Activated Alkenes: Titanium-Catalyzed Cycloisomerization of Allylphenols at High Temperatures. *Angew. Chem. Int. Ed.* **2015**, *54*, 4014-4017.
24. Di Martino, A.; Galli, C.; Gargano, P.; Mandolini, L., Ring-closure reactions. Part 23. Kinetics of formation of three- to seven-membered-ring N-tosylazacycloalkanes. The role of ring strain in small- and common-sized-ring formation. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1345-1349.
25. Carreira, E. M.; Fessard, T. C., Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114*, 8257-8322.
26. Fischer, D. M.; Balkenhohl, M.; Carreira, E. M., Cobalt-Catalyzed Cyclization of Unsaturated N-Acyl Sulfonamides: a Diverted Mukaiyama Hydration Reaction. *JACS Au* **2022**, *2*, 1071-1077.
27. (a) Anderson, S. N.; Ballard, D. H.; Chrzastowski, J. Z.; Dodd, D.; Johnson, M. D., Inversion of Configuration in the Nucleophilic Displacement of Cobalt from Alkylcobalt(IV) Complexes and Its Relevance to the Halogenation of the Corresponding Alkylcobalt(III) Complexes. *J. Chem. Soc., Chem. Commun.* **1972**, 685-686; (b) Vol'pin, M. E.; Levitin, I. Y.; Sigan, A. L.; Halpern, J.; Tom, G. M., Reactivity of Organocobalt(IV) Chelate Complexes Toward Nucleophiles: Diversity of Mechanisms. *Inorg. Chim. Acta* **1980**, *41*, 271-277; (c) Wilson, C. V.; Kim, D.; Sharma, A.; Hooper, R. X.; Poli, R.; Hoffman, B. M.; Holland, P. L., Cobalt–Carbon Bonding in a Salen-Supported Cobalt(IV) Alkyl Complex Postulated in Oxidative MHAT Catalysis. *J. Am. Chem. Soc.* **2022**, *144*, 10361-10367.