Facile Access to Bicyclo[2.1.1]hexanes by Formal Cycloaddition between Silyl Enol Ethers and Bicyclo[1.1.0]butanes with Lewis acids

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KEYWORDS: cycloaddition, ketones, silyl enol ethers, carbocycles, Lewis acid.

ABSTRACT: Saturated three-dimensional carbocycles have gained increasing prominence in synthetic and medicinal chemistry. In particular, bicyclo[2.1.1]hexanes (BCHs) was identified as the molecular replacement for benzenes. Here, we present a facile access to a variety of BCHs via a stepwise two-electron formal [2+3] cycloaddition between silyl enol ethers and bicyclo[1.1.0]butanes (BCBs) under Lewis acid catalysis. The reaction features wide functional group tolerance for silyl enol ethers, allowing the efficient construction of two vicinal quaternary carbon centers and a silyl-protected tertiary alcohol unit in a streamlined fashion. Interestingly, the reaction with conjugated silyl dienol ethers could provide access to bicyclo[4.1.1]octanes (BCOs) equipped with silyl enol ethers that facilitate further transformation. The utilities of this methodology were demonstrated by the late-stage modification of natural products, transformations of tertiary alcohol units on bicyclo[2.1.1]hexane frameworks, and derivatization of silyl enol ethers on bicyclo[4.1.1]octanes, delivering novel functionalized bicycles that are traditionally inaccessible.

INTRODUCTION

The strategic replacement of benzene with conformationally rigid and stable C(sp3)-enriched polycyclic scaffolds in small molecules represents an emerging trend in medicinal chemistry. Attributed to their constrained geometries and precisely oriented pendant substituents, these saturated polycycles effectively emulate the topological characteristics of substituted benzenes, which allows for the preservation of desired interactions with biomacromolecules while enhancing the pharmacokinetics, solubility, and metabolic stability of drug candidates.[1-2] Recent studies have identified 1,2-disubstituted bicyclo[2.1.1]hexanes as potential bioisosteres for *ortho*-disubstituted benzenes with retained biological activity validated by *in vitro* experiments.[3c,3h] Hence, there is an increasing demand for development of efficient strategies for streamlined access to these bicycles.[3-8] One of most common methods to construct BCH skeleton is by an intramolecular [2+2] cycloaddition of 1,5-diene under the irradiation of light[3]. Alternatively, an intermolecular cycloaddition of bicyclo[1.1.0]butanes (BCBs) and alkenes is highly desirable since it allows the efficient construction of bicyclic ring through the fusion of two readily available starting materials. Pioneering studies were disclosed by Blanchard[5a] in 1966 and De Meijere[5b] in 1986. Subsequently, Wipf group[5c] reported an intramolecular variant of this cycloaddition under thermal condition in 2006.

More recently, by taking advantage of the ready availability and inherent ring strain of BCBs,[6b,9] the exploration of new strategies to the cycloaddition between BCBs and alkenes in the generation of various BCHs has attracted intensive attentions.[6-8] According to the reported reaction processes, most methods could be categorized into two modes: 1) radical pathway; and 2) two-electron pathway (Scheme 1b). By utilizing the photoinduced energy transfer course, Glorius[6a] and Brown[6b] groups respectively described elegant cycloaddition of BCBs and alkenes toward bicyclo[2.1.1]hexanes. The reaction was initiated by the excitation of either alkene or BCB to generate a diradical intermediate. Li[7a] and Wang[7c] groups developed a boryl-pyridine catalytic system to activate BCB as a cyclobutyl radical intermediate. Meanwhile, Procter group applied SmI_2 as a single electron reductant to achieve the insertion of electron-deficient alkene into BCB (Scheme 1b–1).[7b] Very recently, Zheng group described a Ti-catalyzed formal cycloaddition of BCB and 2-azadienes to synthesize aminobicyclo[2.1.1]hexanes.[7e] Lately, Glorius accomplished the coupling of phenol and BCB by leveraging a photoredox process.[7d] All the reactions above entailed the generation of radical species, which to some extent limited the substrate scope.

Bicyclo[1.1.0]butanes could be activated as an enolate nucleophile upon central σ-bond cleavage mediated by Lewis acid to attack electrophilic reagents such as aryl aldimine by Leitch group,[8a] aldehyde by Glorius group,[8c] or ketene by Studer group,[8b] followed by the intramolecular cyclization to complete the formal cycloadditions. We demonstrated that Lewis acid could activate BCBs as

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electrophiles to react with indoles as the nucleophiles to construct complex indoline polycycles (Scheme 1b–2). Notably, if a wide variety of nucleophiles could be utilized, this approach could be developed into a versatile strategy that complements existing methods involving radical or ionic intermediates to access BCHs. More recently, Feng reported the use of silver triflate to promote reactions of BCBs and indoles but with opposite regioselectivity.[8e] Despite these successful examples, there is a huge and unexplored chemical space for these bicycles, and a more general strategy to expediently construct such moieties with simple alkenes could potentially be realized. Here, we envisaged that the silyl enol ether, as the nucleophile, would be a suitable candidate in this scenario due to its importance in different cycloaddition reactions.[10] It is noteworthy that silyl enol ethers could be easily prepared by a one-step silylation of simple ketone motifs, which are presented in numerous compounds and widely used in synthetic chemistry. Although silyl enol ethers exhibit robust nucleophilicity in various synthetic contexts, such as Mukaiyama-Aldol reaction and Michael addition, their nucleophilicity towards the BCB remains unexplored. Furthermore, the subsequent intramolecular Aldol-type cyclization presents a challenge due to the formation of sterically hindered vicinal quaternary carbon centers. Despite these concerns, we aim to explore the formal [2+3] cycloaddition between silyl enol ether and BCB to realize a one-step access to a variety of BCH frameworks.

Scheme 1. Importance of bicyclo[2.1.1]hexanes and synthetic strategies by formal cycloaddition between bicyclo[1.1.0]butanes and alkenes.

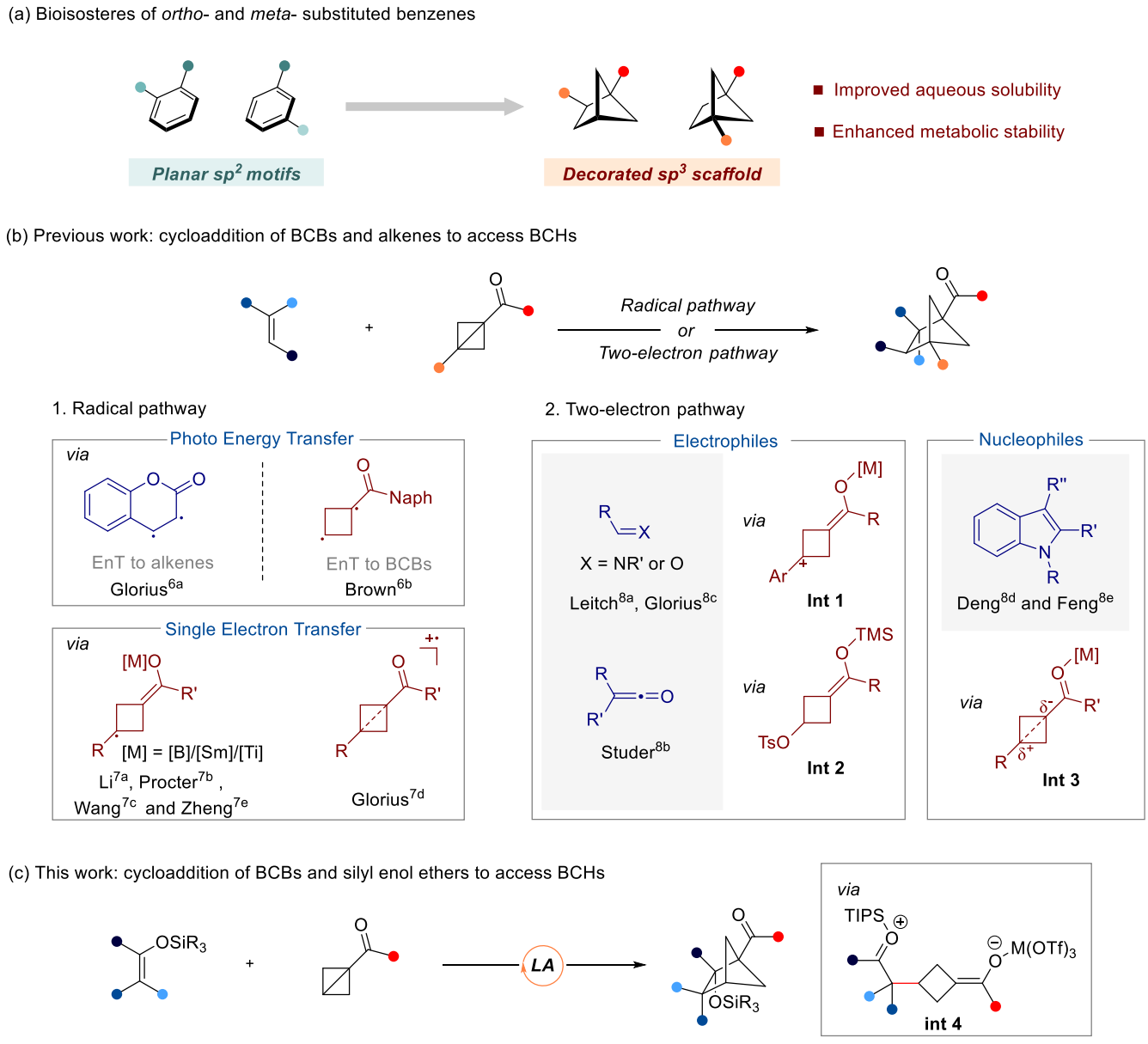

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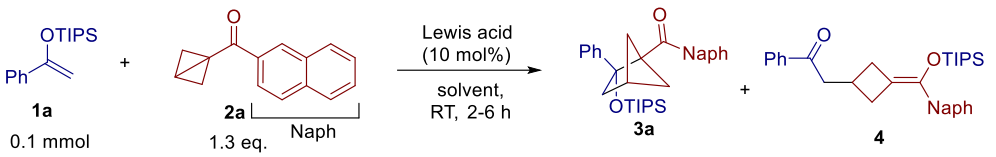
Table 1. Optimization studies of cycloaddition between silyl enol ethers and BCBs[a]



Entry	Cat.	Solvent	Results[b]
1	$Cu(OTf)_2$	DCM	**4** (45%), **3a** (5%)
2	$Zn(OTf)_2$	DCM	**4** (57%), **3a** (14%)
3	$Ni(OTf)_2$	DCM	**4** (45%), **3a** (3%)
4	AgOTf	DCM	**4** (46%), **3a** (6%)
5	$Sc(OTf)_3$	DCM	**3a** (56%)
6	$B(C_6F_5)_3$	DCM	**4** (43%)
7	$Eu(OTf)_3$	DCM	**3a** (84%)
8	$Gd(OTf)_3$	DCM	**3a** (74%)
9	$Tm(OTf)_3$	DCM	**3a** (92%)
10	$Lu(OTf)_3$	DCM	**3a** (90%)
11	$Yb(OTf)_3$	DCM	**3a** (97%)(96%)[c]
12	$YbCl_3$	DCM	n.r.
13	$Yb(OAc)_3$	DCM	n.r.
14	$Yb(OTf)_3$	toluene	**3a** (98%)(98%)[c]
15	$Yb(OTf)_3$	THF	**3a** (42%)
16	$Yb(OTf)_3$	MeCN	**3a** (63%)
17	-	DCM	n.r.

[a]Reaction conditions: unless indicated otherwise, the reaction of silyl enol ether **1** (0.1 mmol), and BCB **2** (0.13 mmol) was carried out in solvent (1 mL) in the presence of Lewis acid (0.01 mmol) at room temperature for 2-6 h. [b]Yields were determined by ^{1}H NMR analysis of the unpurified reaction mixture with 1,1,2,2-tetrachloroethane or 1,3,5-trimethoxybenzene as an internal standard. [c]The yield of the reaction with 5 mol% of $Yb(OTf)_3$. n.r., no reaction.

RESULTS AND DISCUSSION

With these considerations in mind, we began our investigations with screening studies of Lewis acids on their abilities to promote the reaction of triisopropylsilyl phenyl enol ether (**1a**) from acetophenone and naphthyl BCB (**2a**). In the presence of late transition metal derived triflate salts, only trace amount of desired cycloadduct **3a** was observed by NMR analysis of the crude reaction mixture (Table 1, entry 1–4). The major product was identified to be cyclobutyl silyl enol ether **4**, presumably derived from nucleophilic addition followed by silyl migration. Additionally, $B(C_6F_5)_3$ would only give byproduct **4** (Table 1, entry 6). On the other hand, we found that with lanthanide triflates such as $Eu(OTf)_3$, $Gd(OTf)_3$, $Tm(OTf)_3$, $Lu(OTf)_3$ and $Yb(OTf)_3$ the reaction afforded the desired product **3a** in high yield (Table 1, entry 7–11). Among them, $Yb(OTf)_3$ was the optimal catalyst, allowing the reaction to proceed in 97% yield (Table 1, entry 11). Interestingly, switching the counterion from triflate to chloride or acetate is detrimental to this transformation, illustrating the acidity of Lewis acid is key for the success. (Table 1, entry 12–13). Further optimization studies identified toluene as another suitable solvent (Table 1, entry 14–16). Pleasantly, the catalyst loading could be decreased to 5 mol% without negative impact (Table 1, entry 11 and 14). Control experiments illustrated that no reaction occurred in the absence of the Lewis acid (Table 1, entry 17).

With the optimal conditions in hand, the generality of substrates in this cycloaddition was investigated as depicted in Table 2. The reactions of BCB **2a** and various silyl enol ethers **1a–d** derived from acetophenones were examined, which proceeded to completion, affording the desired products **3a–d** in 45%-93% yields. Within these substrates, those bearing more stable silyl groups resulted in higher yields.

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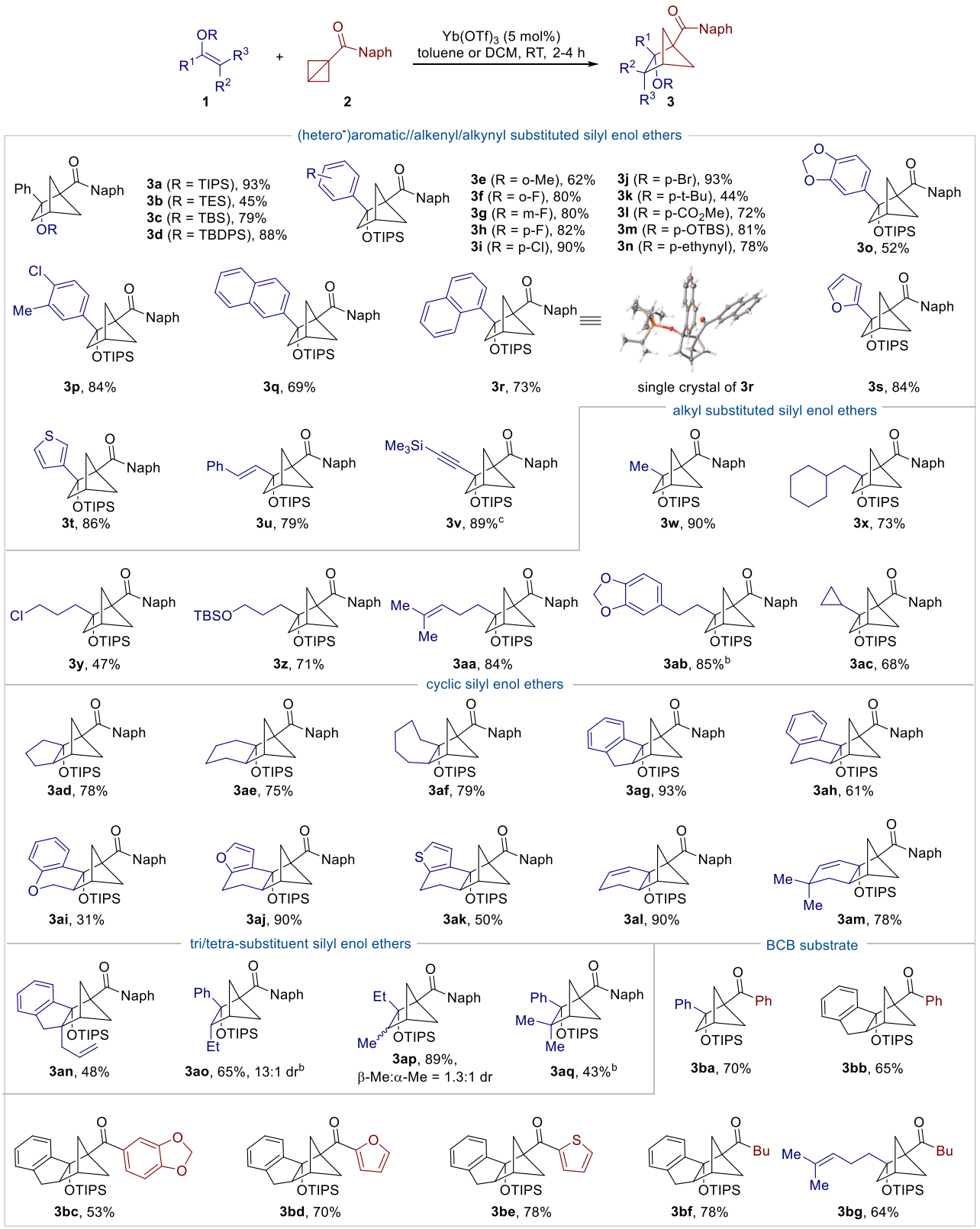
Table 2. Substate Scope of Silyl enolate and BCBs[a]



[a]Reaction conditions: unless indicated otherwise, the reaction of silyl enol ether **1** (0.2 mmol), and BCB **2** (0.26 mmol) was carried out in DCM (2 mL) or toluene (2 mL) in the presence of $Yb(OTf)_3$ (0.01 mmol) at room temperature for 2-4 h. The yield was of isolated and purified products. [b]12 h. [c]6 h.

The reactions tolerated a wide variety of aromatics with substituents on various positions and with different electronic properties (**3e**-**p**). 1-Naphthyl and 2-naphthyl substituted silyl enol ethers worked well to form the

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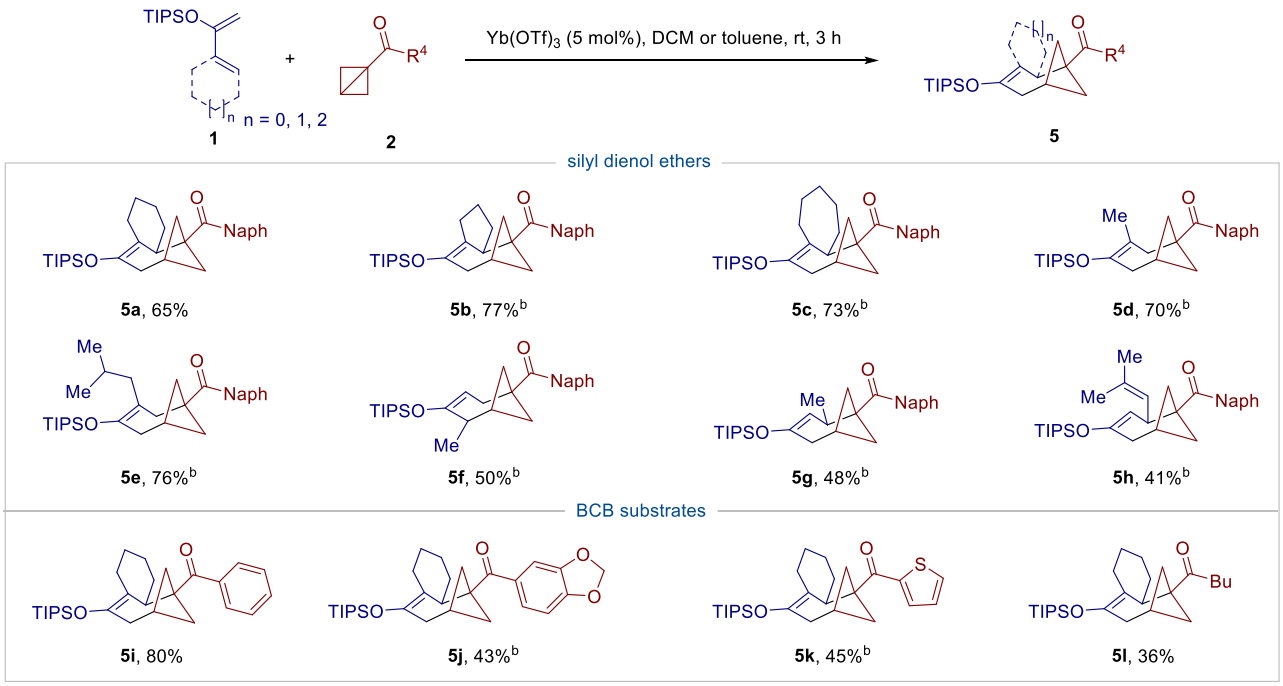
corresponding products (**3q** and **3r**). The structure of cycloadduct **3r** was unambiguously confirmed by single crystal X-ray diffraction analysis.[11] Heterocycles commonly used in medicinal chemistry such as furan and thiophene were compatible, giving their corresponding bicycles (**3s** and **3t**) in good yields. Additionally, silyl enol ethers bearing alkenyl and alkynyl groups were readily converted into the corresponding cycloadducts (**3u** and **3v**) in high yields. Importantly, the reactions with aliphatic substituted silyl enol ethers with pendant functional groups such as chloride (**3y**), silyl ether (**3z**), olefin (**3aa**), electron-rich arene (**3ab**), and cyclopropane (**3ac**) performed well to furnish the corresponding cycloadducts in 47-90% yields.

Next, a series of cyclic silyl enol ethers derived from 5-, 6-, 7-membered cyclic ketones including those fused with aromatic- and heteroaromatic rings were assessed, producing the corresponding assortment of bridged polycycles (**3ad-an**) in synthetically useful yields. Interestingly, these reactions could convert cyclic silyl dienol ethers to tricyclic alkenes **3al** and **3am**, which are suitable for further elaborations to synthesize more complex molecular frameworks. Notably, acyclic tri- and tetra-substituted silyl enol ethers are viable substrates, allowing the rapid construction of highly substituted and compact bicycles **3ao**–**aq**. It is worth noting that the reaction with different trisubstituted silyl enol ethers resulted in distinct diastereoselectivities. In particular, **3ao** were obtained in high diastereoselectivity (13:1 dr) from corresponding silyl enol ether **1ao** (Z/E = 10:1) derived from 1-phenyl-1-butanone, while **3ap** was formed as a mixture of diastereomers (1.3:1 dr) with silyl enol ether **1ap** (Z/E = 7.4:1) derived from 3-pentanone (see the supporting information for details).

Finally, we turned our attention to the evaluation of BCB scope. BCBs with aromatic, heteroaromatic and aliphatic substituents such as benzene (**3ba**–**bb**), 1,2-methylenedioxybenzene (**3bc**), furan (**3bd**), thiophene (**3be**), and butyl (**3bf**–**bg**) are well tolerated in current conditions. The ability to tolerate variations of both silyl enol ethers and BCBs indicated the potential of this method to generate a wide range of BCHs that are not easily accessible by current methods.

Interestingly, structurally intriguing bicyclo[4.1.1]octane (BCO) architecture **5a** was formed in the reaction of cyclohexenyl silyl dienol ether and BCB **2a** under standard conditions[13]. However, regioselectivity issues between formal [4+3] and [2+3] cycloaddition might occur in this reaction. Further optimization studies identified $Sc(OTf)_3$ as an alternative efficient Lewis acid that promotes formal [4+3] cycloaddition. With both $Sc(OTf)_3$ and $Yb(OTf)_3$ catalysts, we examined the generality of formal [4+3] cycloaddition with both reaction components. The reaction conditions were compatible with silyl dienol ether containing 5 and 7-membered rings, affording tricycles **5b** and **5c** bearing bicyclo[4.1.1]octane units. Silyl dienol ethers derived from linear aliphatic vinyl ketones gave good yields (**5d**–**g**). Notably, silyl trienol ether also underwent the formal [4+3] cycloaddition selectively in synthetically useful yield (**5h**). Different substituents on BCBs such as benzene (**5i**), 1,2-methylenedioxybenzene (**5j**), thiophene (**5k**), and butyl (**5l**) groups are well tolerated, delivering desired [4+3] cycloadducts in medium to good yields. The divergent synthesis of both bicyclo[2.1.1]hexanes and bicyclo[4.1.1]octanes demonstrated the utility of silyl enol ethers and their derivatives in the construction of different bicycles.

Table 3. Substate Scope of Silyl dienol ethers and BCBs[a]



[a]Reaction conditions: unless indicated otherwise, the reaction of silyl enol ether **1** (0.2 mmol), and BCB **2** (0.26 mmol) was carried out in DCM (2 mL) or toluene (2 mL) in the presence of $Yb(OTf)_3$ (0.01 mmol) at room temperature for 3 h. [b] the reaction was run in the presence of $Sc(OTf)_3$ (0.02 mmol) at room temperature for 30 min. The yield was of isolated and purified products.

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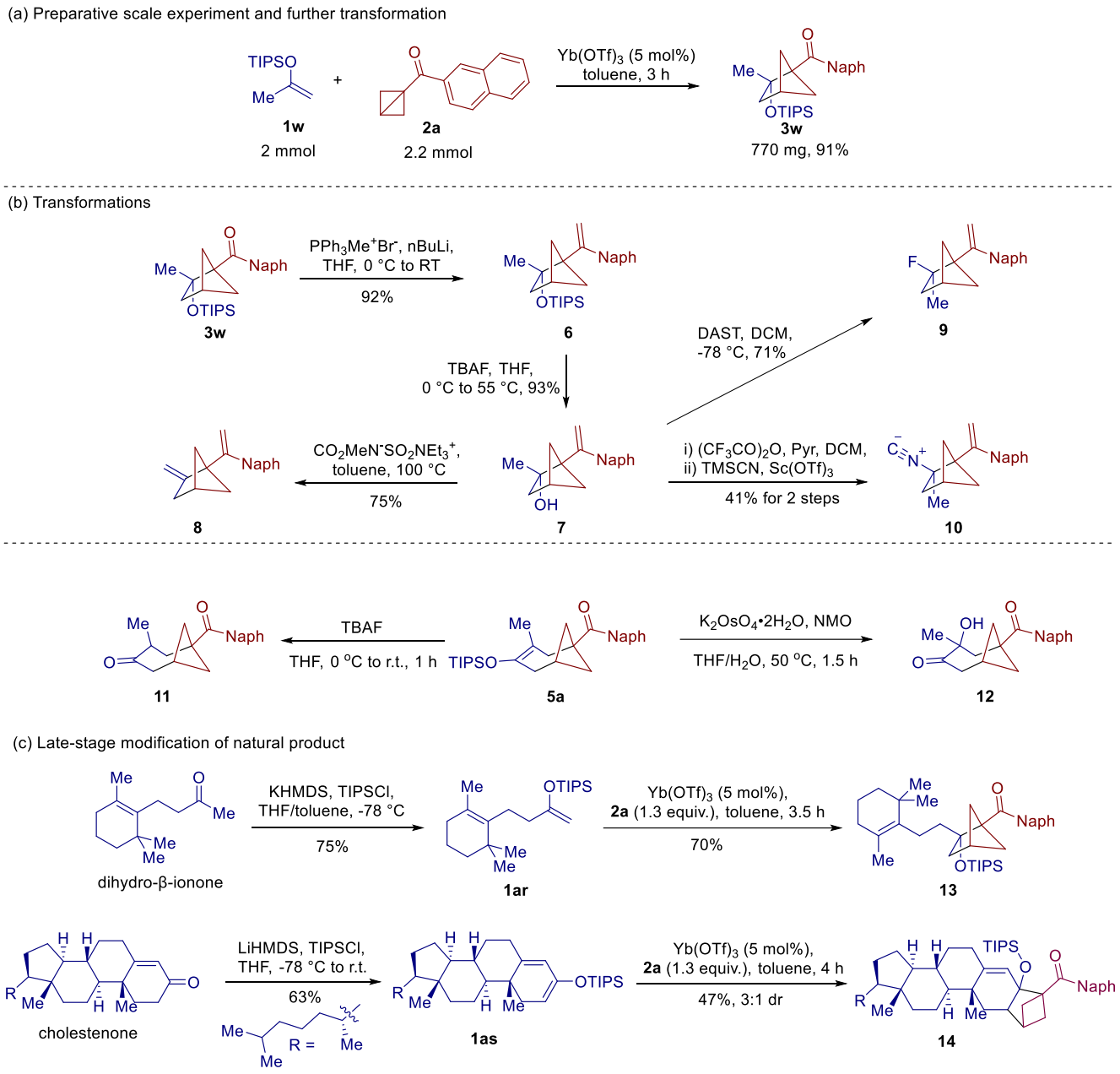
Scheme 2. Applications



To illustrate the utilities of this method, we conducted this reaction on a preparative scale with silyl enol ether **1w** and BCB **2a**, which afforded the cycloadduct **3w** in 91% yield (770 mg). Both the ketone and tertiary alcohol moieties in **3w** provided handles for further synthetic elaborations to procure a wide array of new bicyclo[2.1.1]hexanes. Specifically, subjecting bicycle **3w** to the Wittig reaction condition led to olefin **6**. After deprotection of the silyl group, the free alcohol **7** have been proved versatile for various transformations, including the dehydration to olefin **8** by treatment with Burgess reagent and fluorination to **9** in the presence of DAST reagent. Furthermore, isonitrile **10** would be readily obtained using Shenvi's methodology.[12] All of derivatizations above further extended the attainability of new bicyclo[2.1.1]hexanes using this developed manifold. Additionally, the resulting silyl enol ether unit from the [4+3] cycloadducts could be further transformed to ketone **11** via desilylation and α-hydroxyketone **12** via dihydroxylation. Importantly, owing to its generality with respect to silyl enol ethers, this method could be applied to late-stage modifications of natural products, as bridged polycycles **13** and **14** were formed in synthetically useful yield from commercially available dihydro-β-ionone and cholestenone through ketone silylation and formal cycloaddition sequence (Scheme 2).

With these experimental results, a possible mechanism was proposed and illustrated in Scheme 3. The reaction presumably underwent a stepwise pathway, commencing with the nucleophilic addition of silyl enol ether with Lewis acid-activated BCB to form the zwitterionic intermediate **Int 4**. This was succeeded by an intramolecular Aldol-type

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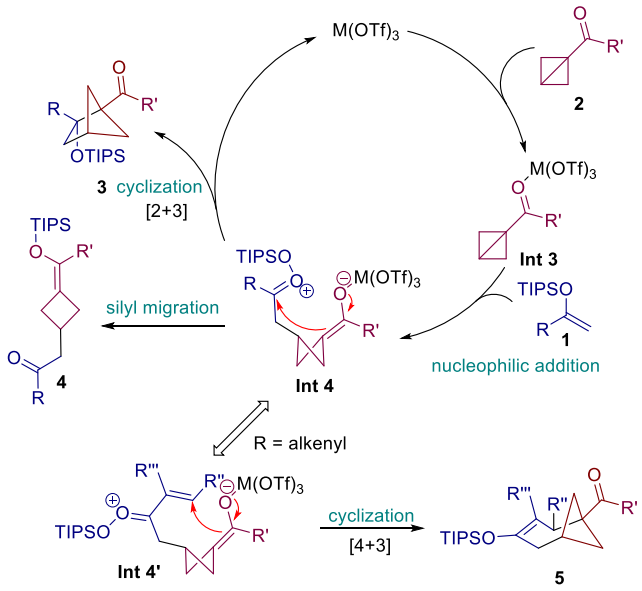
reaction, resulting in the formation of the bicycle **3**. Otherwise, silyl migration might occur after the *in situ* generation of **Int 4**, which leads to the cyclobutyl silyl enol ether byproduct **4**. Additionally, when BCB reacts with silyl dienol ether to generate **Int 4'**, the reaction could proceed through 1,4-addition, delivering bicyclo[4.1.1]octane **5**. Considering the proposed reaction process, the origin of distinction in diastereoselectivity possibly arose from the steric bulk of the attached substituent geminal to silyloxyl group on silyl enol ether in the Aldol-type cyclization step.

Scheme 3. Proposed mechanism



CONCLUSIONS

In summary, we developed a Lewis acid catalyzed formal [2+3] cycloaddition of silyl enol ethers and BCBs.[14] This reaction exhibits high efficiency along with mild condition, operative simplicity, and broad substrate scope with respect to silyl enol ethers, which are readily available from ketone precursors. Notably, ketone is one of the most widely presented functional groups in organic molecules including natural products. Moreover, this formal [2+3] cycloaddition can be further extended to a [4+3] variant with silyl dienol ether. This discovery enables the divergent syntheses of different structurally intriguing polycyclic frameworks and highlights the great potential of silyl enol ethers in polycyclic synthesis. Importantly, this method should provide a broadly useful entry into bicyclo[2.1.1]hexanes from easily accessible starting materials covering a wide range of structural complexity. Further studies for the development of new reactions involving other widely available starting materials and BCBs are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge at https://pubs.acs.org/
Experimental procedures and analysis data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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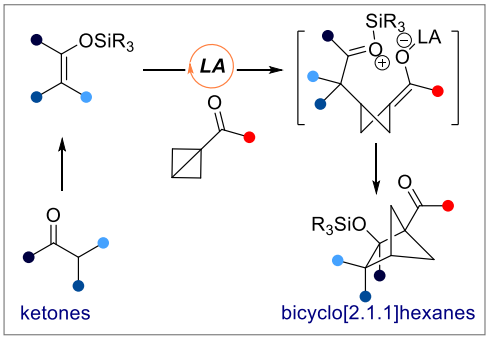

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