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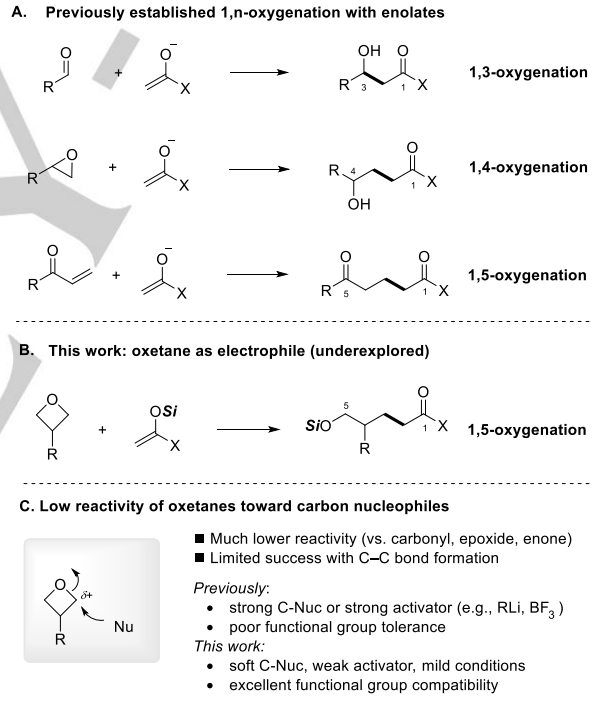
Mild C–C Bond Formation via Lewis Acid Catalyzed Oxetane Ring Opening with Soft Carbon Nucleophiles

Hai Huang, Tianyu Zhang, and Jianwei Sun*

***Abstract**: Mild oxetane opening by soft carbon nucleophiles has been developed for efficient C–C bond formation. In the presence of $LiNTf_2$ or $TBSNTf_2$ as catalyst, silyl ketene acetals were found to be effective nucleophiles to generate a wide range of highly oxygenated molecules, which are key substructure in natural products like polyketides. Furthermore, intramolecular oxetane opening by a styrene-based carbon nucleophile via a Prins-type process was also achieved with $Sc(OTf)_3$ as catalyst, leading to efficient formation of the useful 2,3-dihydrobenzo[b]oxepine skeleton.*

Carbon–carbon (C–C) bond-forming reactions are of paramount importance in organic synthesis, as they play a pivotal role in the elaboration and extension of organic molecule frameworks.[1] Among them, $C(sp^3)$–$C(sp^3)$ cross-couplings are generally more challenging than those involving $C(sp^2)$ or C(sp) atoms.[1b] Therefore, the development of efficient, selective, and mild protocols for $C(sp^3)$–$C(sp^3)$ bond formation has been a longstanding pursuit of organic chemists. Of particular note is enolate alkylation,[2] a power strategy for the access to various synthetically valuable oxygenated molecules that are key subunits of numerous natural products, such as polyketides.[3] The aldol reaction, employing simple carbonyl compounds as electrophile, represents the most versatile access to 1,3-oxygenated molecules (Scheme 1A).[4] Along this line, the use of epoxides leads to 1,4-oxygenation.[5] Furthermore, the Michael addition to enones provides 1,5-oxygenated molecules.[6] In addition to these relatively reactive electrohpiles, it is important to note that the search for additional electrophiles for mild C–C bond formation would not only enrich the enolate chemistry, but also provide complementary access to such valuable oxygenated molecules. Herein we disclose a new mild catalytic approach for the efficient synthesis of 1,5-oxygenated molecules by direct intermolecular C–C bond formation from silyl enolates and oxetanes (Scheme 1B). Oxtanes can accommodate additional functional groups in the 3-position, thus allowing more diversified functionalization/oxygenation patterns in the product framework. Further extension to the use of styrene as another type of soft carbon nucleophiles has also been achieved, providing access to the important heterocycle, 2,3-dihydrobenzo[*b*]oxepine.

Oxetane is an important functional group in organic synthesis and medicinal chemistry.[7,8] Notably, its resemblance to a carbonyl group in dipole moments combined with the metabolic stability has enabled oxetane to serve as a unique carbonyl surrogate in medicinal chemistry.[8] On the other hand, its chemical inertness (relative to carbonyl and epoxides)[9] toward nucleophiles has resulted in a substantial paucity of transformations with broad applications in organic synthesis (Scheme 1C). Indeed, among their ring-opening reactions, the vast majority employed heteroatom-based nucleophiles.[10,11] In contrast, the use of a carbon nucleophile for C–C bond formation has been much less explored. Current success has been limited to the use of strong organometallic reagents (e.g., RLi, RMgX), typically in combination with strong Lewis acid activation (e.g, BF_3).[12] Consequently, these strong conditions led to poor functional group tolerance and limited applications in organic synthesis. In this context, a mild catalytic protocol using soft carbon nucleophiles remains highly desirable.



Scheme 1. Synthesis of 1,n-oxygenated molecules from enolates.

We began our study with **1a** as substrate. Different silyl enolates were evaluated as potential nucleophiles with $HNTf_2$ as catalyst (see the SI for details).[13,14] The preliminary results indicated that silyl ketene acetal (SKA) **2a** showed the best reactivity toward C–C bond formation. We next screened different Lewis acid catalysts (Table 1). It was found that those bearing weakly coordinating anions (e.g., $^-$OTf and $^-NTf_2$) were generally better, likely due to higher Lewis acidity than those having a stronger anion (see the SI for details).[15] $LiNTf_2$ was identified as a superior catalyst, leading to clean formation of the desired product **3a** (88% yield, entry 8). Notably, replacing either the metal ion (e.g., $NaNTf_2$, $KNTf_2$) or the counter anion (e.g., LiOTf, LiBr, LiOAc) resulted in completely no reaction.

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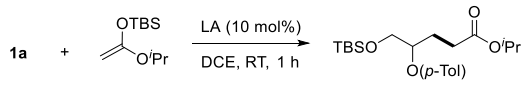
We believe that this unique combination of the most Lewis acidic alkali metal ion Li^+ and a weak anion $^-NTf_2$ is critically important. Finally, increasing the loading of SKA further improved the efficiency (entry 12).

Table 1. Screening of Lewis acid catalysts.[a]

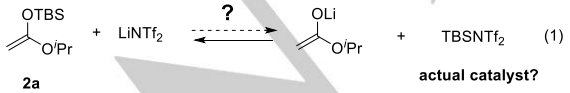


2a 3a

Entry	X	Conv. (%)	Yield[b]
1	$Sc(OTf)_3$	52	7
2	AgOTf	0	0
3	$Sn(OTf)_2$	58	23
4	$In(OTf)_3$	50	22
5	$Yb(OTf)_3$	100	66
6	$Zn(OTf)_2$	0	0
7	$AgNTf_2$	31	29
8	$LiNTf_2$	90	88
9	LiOTf	0	0
10	$NaNTf_2$	0	0
11	$KNTf_2$	0	0
12[c]	$LiNTf_2$	100	93 (80)[d]

[a] Reaction scale: **1a** (0.20 mmol), **2a** (0.3 mmol), LA (10 mol%), DCE (2.0 mL). [b] Determined by ^{1}H NMR analysis of the crude mixture using $(CH_2Br)_2$ as an internal standard. [c] 2.5 equiv of **2a**. [d] Isolated yield in parentheses.

A range of oxetanes and SKAs smoothly participated in this process (Scheme 2). Oxetanes with various 3-substituents led to diverse γ-functionalized-δ-siloxy esters **3**. The mild conditions tolerated a broad range of functional groups. Different heterocycles and a steroid substructure were also incorporated into the products. However, oxetanes with a substituent in the 2-position did not provide a clean reaction. The low yields of **3p-q** were due to low conversion. However, in the case of **3v-y**, some unknown byproducts were observed. Increasing catalyst loading or temperature did not improve the results. An α-substituted SKA led to clean formation of the α-branched ester product **3ae**, albeit with slow conversion. A gram-scale synthesis of **3l** was also demonstrated. Notably, γ-iodo and related products **3m-o** are known intermediates in the synthesis of biologically important molecules, but their conventional synthesis typically entailed a multistep sequence.[16] Moreover, the protected γ,δ-dihydroxy carbonyl compounds are also valuable intermediates in complex molecule synthesis.[17] An enantioenriched SKA with (+)-menthol as chiral auxiliary afforded the corresponding product **3af** in 62% yield. Unfortunately, the diastereoselectivity was moderate, likely due to the remote position of the new stereogenic center relative to the chiral auxiliary.

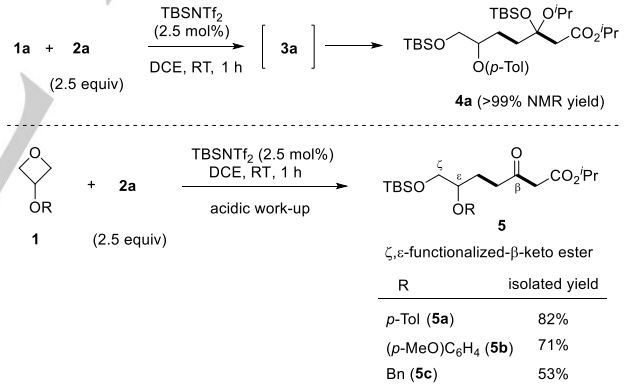


entry	sample	^{19}F NMR (δ, $CDCl_3$)
1	$LiNTf_2$	–79.0
2	$LiNTf_2$ + **2a**	–79.3
3	$TBSNTf_2$	–12.9 (Ref.19)

We were interested to know whether $LiNTf_2$ serves as a pre-catalyst of silyl triflimide, since in-situ generation of the latter has been known in the related Mukaiyama aldol reactions.[4g,14] Thus, we mixed equal amounts of substrate **2a** and $LiNTf_2$. However, no trace of $TBSNTf_2$ was observed based on ^{19}F NMR spectra (Eq. 1). Indeed, the reverse reaction between the lithium enolate and $TBSNTf_2$ should be a very facile reaction.[18]

The above results could be inconclusive. If the above equilibrium is fast and substantially favors the left side, a small amount of $TBSNTf_2$ can still be present without noticeable shift of the ^{19}F NMR signal. Next, we separately prepared $TBSNTf_2$ and examined its catalytic activity.[19] To our surprise, in the presence of 2.5 mol% of $TBSNTf_2$, the reaction between **1a** and **2a** proceeded to form product **4a** in quantitative yield (Scheme 3). This product might result from a second nucleophilic attack onto the initial product **3a** (or its analogue, *vide infra*). It is worth noting that, in the standard protocol with $LiNTf_2$ as catalyst, the formation of **4a** was essentially not observed (Scheme 3). The observation of orthogonal products is indirect evidence of involving different catalytic species in these two systems (Li^+ vs. TBS^+). Moreover, the complete incapability of $NaNTf_2$ and $KNTf_2$ for this reaction is also consistent with the key role of Li^+ for activation.

The special performance of $TBSNTf_2$ prompted us to briefly examine this cascade double C–C bond formation process. Indeed, after acidic work-up, the protected ζ,ε-dihydroxy β-ketoesters **5** could be obtained. This cascade protocol provides new access to diversely-functionalized carbonyl compounds with remarkable C–C bond-forming efficiency. Moreover, the substitution of a 3-alkoxyl group in the oxetane allowed formation of 1,2,5,7-tetraoxygenated carbon frameworks.



R	isolated yield
p-Tol (**5a**)	82%
(*p*-MeO)C_6H_4 (**5b**)	71%
Bn (**5c**)	53%

Scheme 3. Cascade bond formation with $TBSNTf_2$.

Possible mechanisms are proposed in Scheme 4. The reaction begins with oxetane activation by catalyst $MNTf_2$ (M = Li or TBS). The resulting oxonium **I** undergoes nucleophilic substitution by the silyl ketene acetal, leading to oxocarbenium **II**. With $LiNTf_2$ as catalyst, this intermediate can proceed to product **3** via two possible pathways. In path *a*, direct silyl 1,7-migration affords the observed product **3**. Alternatively, the silyl transfer can be stepwise via ester **III** by forming $TBSNTf_2$ followed by silylation on the alkoxide motif (path *b*). In contrast, with $TBSNTf_2$ as catalyst (path *c*), there is no driving force for silyl migration in intermediate **II** (M = TBS), since there is no alkoxide nucleophile in this case. This allows another molecule of silyl ketene acetal to attack the electrophilic oxocarbenium, forming the second C–C bond. The resulting intermediate **IV** finally leads to the observed product **4** and regenerates $TBSNTf_2$.

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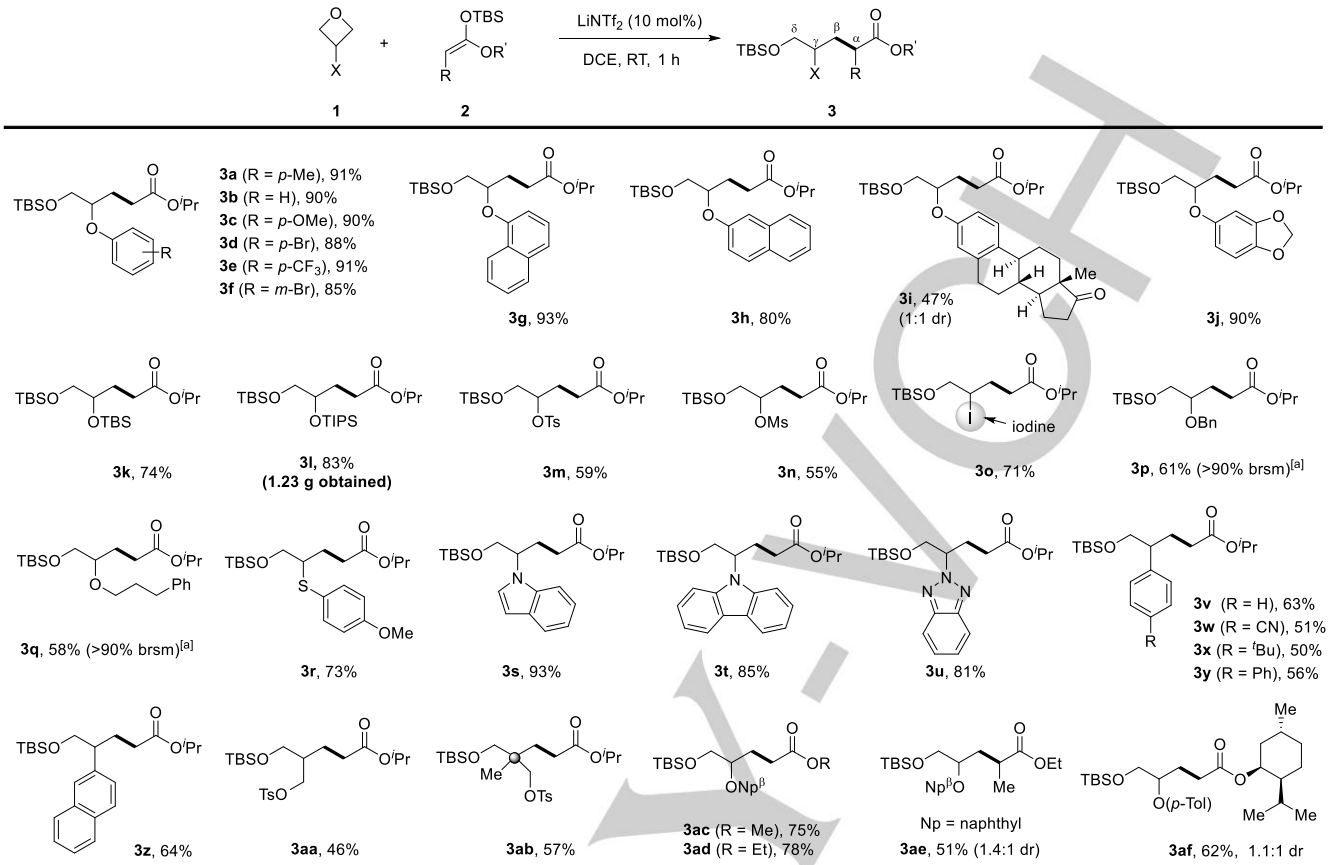
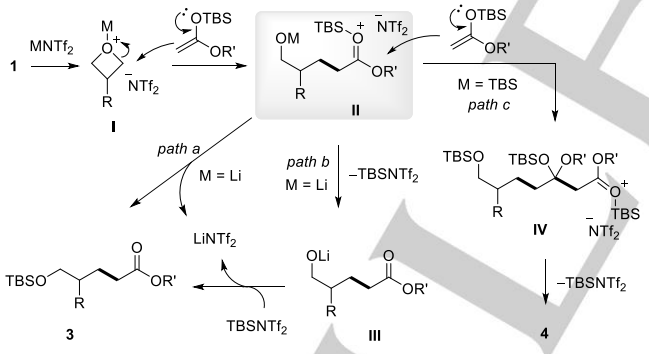


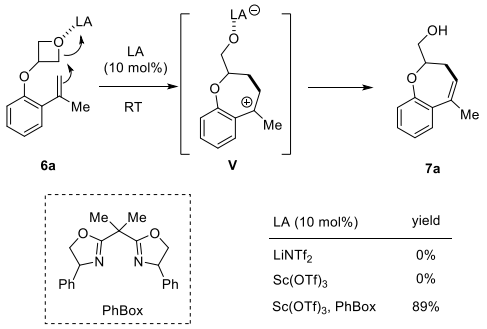
Scheme 2. Reaction scope. **1** (2.0 mmol), **2** (5.0 mmol), $LiNTf_2$ (10 mol%), DCE (20 mL); Isolated yields. [a] Yield based on recovered starting material.



Scheme 4. Proposed mechanisms.

The success with silyl enolates as nucleophile promopted us to extend the C–C bond formation to other types of soft carbon nucelophiles. Inspired by the Prins reaction,[20] which employs olefin as the nucleophile to form C–C bond with a carbonyl electrophile, we attempted an intramolecular version with styrene as the nucleophile.

The model compound **6a** was treated with catalyst $LiNTf_2$ (Scheme 5). Unfortunately, no desired C–C bond formation was observed. We next examined other Lewis acid catalysts (see the SI for details). With $Sc(OTf)_3$ alone, there was still no desired product formation. However, the use of PhBox ligand smoothly promoted the desired C–C bond formation to form the 2,3-dihydrobenzo[*b*]oxepine product **7a** in 89% yield. It was believed that the reaction initially generated the benzylic carbcation **V** followed by deprotonation.[21]



Scheme 5. Intramolecular opening by styrene. Conditions: LA (10 mol%), PhBox (20 mol%), 5Å MS, PhCl, RT.

This process is general for the synthesis of 2,3-dihydrobenzo[*b*]oxepines. The oxetane-tethered styrenes bearing various substituents on the arene or the double bond reacted with good to excellent efficiency (Scheme 6). It is worth noting that benzoxepine is a core structure of a wide range of natural products and biologically active molecules.[22]

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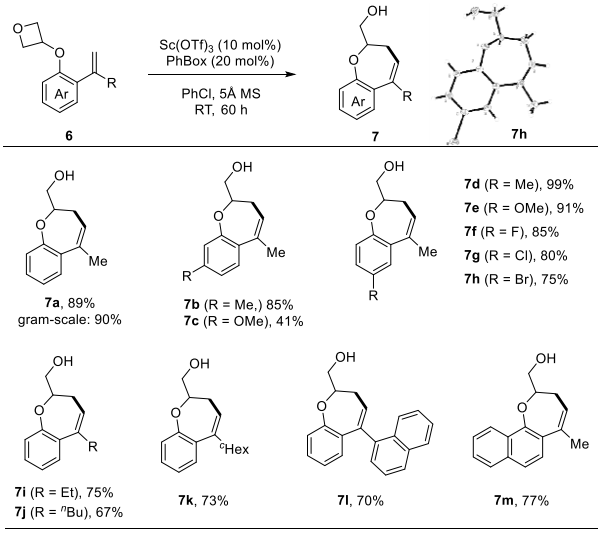
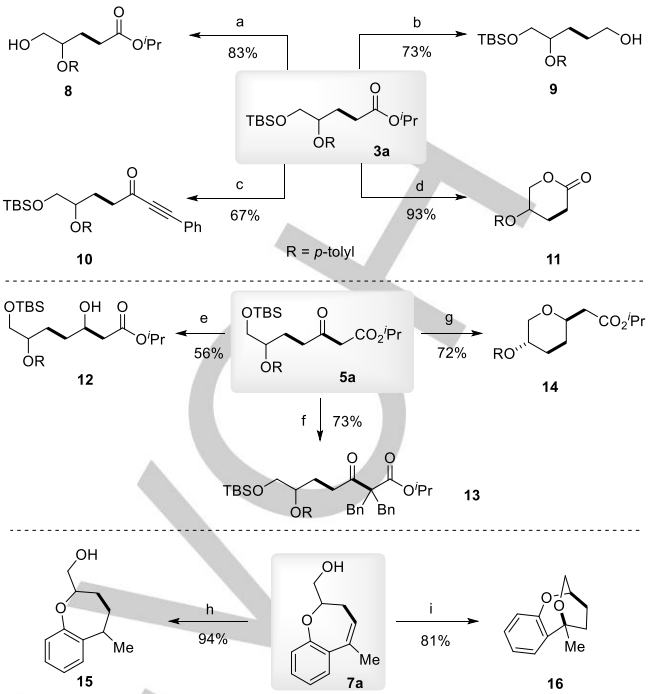


Scheme 6. Scope for the synthesis of 2,3-dihydrobenzo[*b*]oxepines. Scale: **6** (0.50 mmol), $Sc(OTf)_3$ (10 mol%), PhBox (20 mol%), 5Å MS (100 mg), PhCl (6.0 mL); Isolated yields.

The products obtained from our reaction could be precursors to other highly oxygenated molecules (Scheme 7). For example, after simple silyl deprotection of product **3a** with TBAF, free δ-hydroxy ester **8** was afforded in high yield. The ester group could also be reduced to primary alcohol **9**. Direct conversion to ynone **10** was also feasible using lithium acetylide as the nucleophile. Furthermore, under acidic conditions, the δ-silyl deprotection could be coupled with one-pot transesterification to form the δ-lactone **11** in excellent yield. Some derivatizations of the cascade product **5a** were also demonstrated. The ketoester could be selectively reduced to ζ-siloxy-ε-aryloxy-β-hydroxy ester **12**. Moreover, facile double α-alkylation of the ketoester furnished **13**. Finally, acidic deprotection of the silyl group in **5a** followed by one-pot treatment with BF_3•OEt_2 and Et_3SiH resulted in formation of tetrahydropyran **14**, likely via a cyclic oxocarbenium intermediate. These densely-oxygenated carbon frameworks are highly useful in polyketide synthesis, but their assembly by conventional approaches was not as straightforward.[23] Additionally, the 2,3-dihydrobenzo[*b*]oxepine product **7a** could undergo hydrogenation to form 2,3,4,5-tetrahydrobenzo[*b*]oxepine **15** with high efficiency. Interestingly, a catalytic amount of $B(C_6F_5)_3$ catalyzed intramolecular cyclization of **7a** to form bicyclic compound **16**.



Scheme 7. Product transformations. (a) TBAF, THF, RT, 1 h. (b) $LiAlH_4$, THF, 60 °C, 1 h. (c) PhC≡CLi, BF_3•OEt_2, THF, RT, 5 h. (d) HCl (conc.), DCM, RT, 48 h. (e) $NaBH_4$, THF, RT, 2 h, 1:1 dr. (f) NaH, BnBr, THF, RT, 6 h. (g) HCl (conc.), DCM, RT, 48 h; BF_3•OEt_2, $HSi(Et)_3$, CH_3CN, >20:1 dr. (h) Pd/C, H_2, MeOH, 12 h. (i) $B(C_6F_5)_3$ (5 mol%), DCM, RT, 12 h.

In conclusion, we have demonstrated that oxetane can serve as a useful electrophile for the mild efficient C–C bond formation with soft carbon nucleophiles, despite the low reactivity of both reaction partners. With silyl ketene acetals, the process provided expedient access to a wide range of 1,5-oxygenated molecules, an attractive complement to the Michael addition of enolates. The uniquely effective catalyst $LiNTf_2$ enabled this reaction to proceed under extremely mild conditions, thus compatible with a diverse range of functional groups. With $TBSNTf_2$ as catalyst, this process was further extended to cascade C–C bond formation leading to 1,3,7-oxygenated products. These highly oxygenated organic frameworks are substructures of useful complex molecules including polyketides. Mechanistically, the orthogonal catalytic activity of $LiNTf_2$ and $TBSNTf_2$ is evident to rule out the possibility of in-situ generation of the latter as true catalyst in the former case. Furthermore, intramolecular C–C bond formation by styrene was also achieve with $Sc(OTf)_3$ as catalyst, which provided mild access to 2,3-dihydrobenzo[*b*]oxepines.

Acknowledgements

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Keywords: strained molecules • C–C bond formation • Lewis acids • oxetane • ring opening

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[18] Silyl ketene acetals are typically prepared irreversibly from the corresponding lithium enolates and a silyl chloride or triflate. The corresponding silyl triflimide should be even more reactive.

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[21] (a) The presence of the ether bridge is believed to stabilize this cation and thus reduce the barrier for this reaction. In the absence of this ether bridge, the reaction is less effective. (b) With enantiopure PhBox as ligand, preliminary study showed that **3a** was obtained in 65% ee.

[22] For examples of useful molecules containing the benzoxepin core: a) B. W. T. Gruijters, A. Van Veldhuizen, C. A. G. Weijers, J. B. P. A. Wijnberg, *J. Nat. Prod.* **2002**, *65*, 558−561; b) D. G. Lloyd, R. B. Hughes, D. M. Zisterer, D. C. Williams, C. Fattorusso, B. Catalanotti, G. Campiani, M. J. Meegan, *J. Med. Chem.* **2004**, *47*, 4512−5615; c) C.-L. Gao, G.G. Hou, J. Liu, T. Ru, Y.-Z. Xu, S.-Y. Zhao, H. Ye, L.-Y. Zhang, K.-X. Chen, Y. W. Guo, T. Pang, X.-W. Li, *Angew. Chem., Int. Ed.* **2020**, *59*, 2429−2439.

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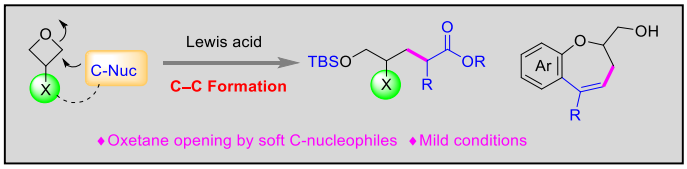

Herein we describe mild C–C bond formation processes via ring-opening of oxetanes by soft carbon nucleophiles to access the useful 1,n-oxygenated molecules and heterocycles.