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Catalytic Asymmetric Nucleophilic Openings of 3-Substituted Oxetanes

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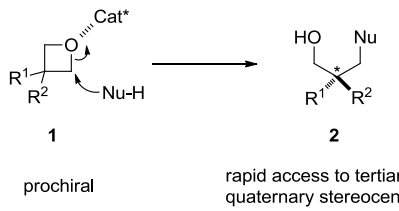
Asymmetric ring-opening of 3-substituted oxetanes provides rapid access to highly functionalized chiral building blocks. However, progress in this field is limited. Recently we developed a new catalytic system based on chiral Brønsted acids for this type of reactions and demonstrated the synthesis a range of useful molecules under mild and operationally simple conditions. In this Perspective, we describe the challenges, progress, and potential future effort on this topic.

1. Introduction

Recently, oxetanes have attracted increasing attention due to their versatility in medicinal chemistry and polymer science.[1] For example, the incorporation of this four-membered ring into potential drugs can improve their physiochemical and metabolic properties. Consequently, various methods have been developed for the efficient synthesis of oxetane-containing molecules.[1d] However, the potential utility of oxetanes as useful building blocks and synthetic intermediates in organic synthesis has not been thoroughly developed. In particular, the use of these molecules for catalytic asymmetric synthesis has met with limited success.

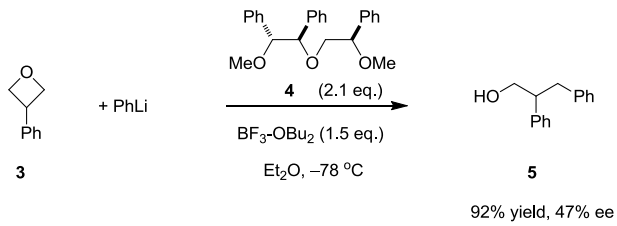
Comparing with the oxirane ring, the four-membered oxetane has slightly low ring strain, making it relatively difficult to open.[2] Nevertheless, with suitable activation by Lewis acid or Brønsted acid, oxetanes are still prone to undergo ring-opening upon nucleophilic attack. Oxetanes with substituents at the 3-position are prochiral, which could lead to chiral products upon nucleophilic ring-opening. The process could be also regarded as desymmetrization. Particularly noteworthy is the potential to rapidly generate highly functionalized three-carbon chiral building blocks bearing tertiary or quaternary stereocenters (Scheme 1). However, there are several challenges in achieving such catalytic asymmetric processes. First of all, regarding the chemical efficiency, the proper choice of both the activator and the nucleophile is critically important. Since the alcohol product is a potential competing nucleophile, the scope is theoretically limited to either internal nucleophiles or external but stronger nucleophiles. Secondly, when oxetanes are activated by a chiral Lewis or Brønsted acid catalyst, the chiral moiety of the catalyst is remote to the newly generated C(3) chiral center. Therefore, efficient chiral induction is challenging. To date, there have been few examples of such catalyst-controlled stereoselective nucleophilic openings of 3-substituted oxetanes.[3]



Scheme 1. Catalytic asymmetric nucleophilic openings of 3-substituted oxetanes.

2. Catalytic Asymmetric Nucleophilic Openings of Oxetanes

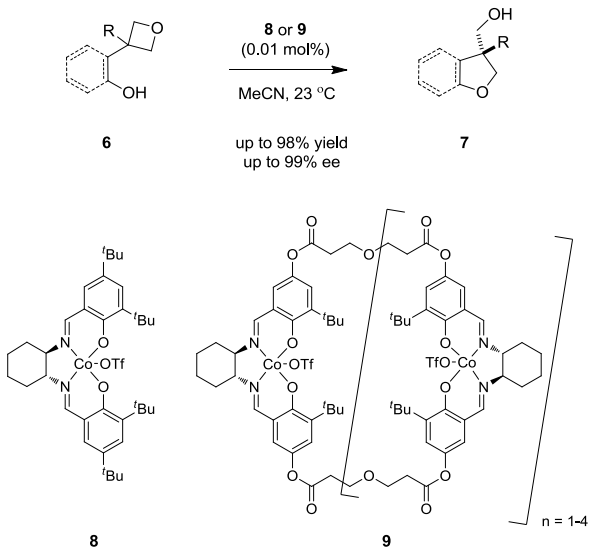
In 1996, Tomioka and co-workers reported their pioneering study of enantioselective ring-opening reactions of 3-substituted oxetanes.[4] A chiral boron reagent generated from phenyllithium, BF_3, and chiral ether **4**, reacted with 3-phenyloxetane **3** to form alcohol **5** in excellent yield but with low enantioselectivity (47% ee, Scheme 2). Although the reaction required a super-stoichiometric amount of the chiral boron reagent and proceeded with moderate stereoselectivity, it represented the first intermolecular asymmetric nucleophilic desymmetrization of 3-substituted oxetanes.



Scheme 2. Asymmetric opening with a lithium reagent by assistance of chiral ligand and boron reagents.

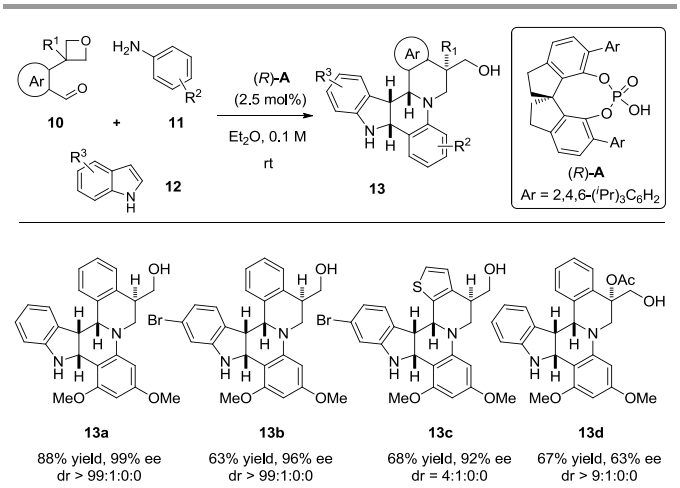
In 2009, Loy and Jacobsen reported an intramolecular desymmetrization of 3-substituted oxetanes catalyzed by

(salen)Co(III) complexes (Scheme 3).[5] With either the monomeric or oligomeric form (i.e., **8** or **9**) of the Lewis acid catalyst, oxetanes **6** underwent intramolecular opening to form a range of tetrahydrofuran products **7** with both excellent efficiency and remarkable enantioselectivity. Quaternary stereocenters could also be generated with up to 99% ee. The oligomeric complex **9** proved superior to the monomeric form **8** and the catalyst loading could be as low as 0.01 mol%. The better performance of the oligomeric catalyst, particularly in the case of tetrahydropyran synthesis, might be attributed to its capability of extending the chiral backbone for remote chiral induction. However, although the process were efficient for the synthesis of a range of highly enantioenriched tetrahydrofurans and a tetrahydropyran, it could not be extended with similar efficiency to the formation of seven-membered ring oxepanes or pyrrolidines using an internal nitrogen nucleophile. The attempt to use intermolecular nucleophiles also failed. Nevertheless, it is the first demonstration of a truly catalytic asymmetric nucleophilic opening of 3-substituted oxetanes with excellent stereocontrol.



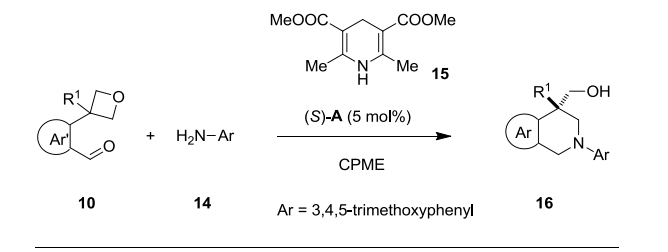
Scheme 3. (Salen)Co(III)-catalyzed intramolecular desymmetrization.

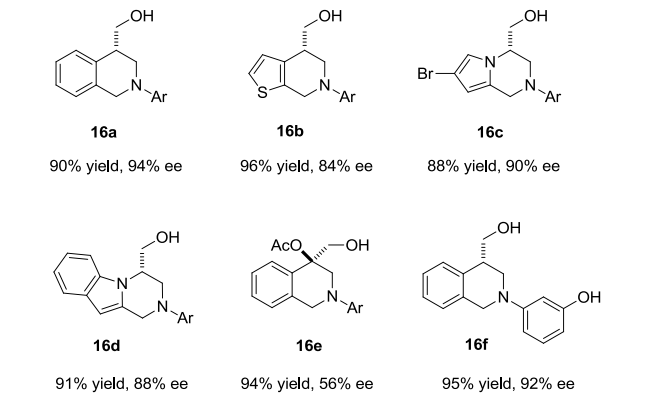
Recently, our lab has reported a series of studies of this type employing chiral Brønsted acid catalysis.[6-8] While the basicity of oxetanes is relatively higher than epoxides and normal ethers,[9] presently widely used chiral Brønsted acids, such as chiral phosphoric acids, are relatively weak in acidity. This means either strong or internal nucleophiles are necessary. We initially focused on the evaluation of internal nucleophiles. By mixing the oxetane-tethered aryl aldehydes **10**,[10] aryl amines **11**, indoles **12**, and a catalytic amount of chiral phosphoric acid **A**, we were able to observe the efficient formation of polycyclic adducts **13** (Scheme 4).[6] After simple purification by filtration or centrifugation, these heterocyclic products were isolated in good to excellent enantio- and diastereopurity. Notably, the reaction generated four new bonds (two C–C and two C–N bonds) and four new stereogenic centers in one pot from three achiral compounds. Regarding the reaction mechanism, we proposed the initial formation of the internal amine nucleophile by sequential imine formation and indole addition, followed by oxetane opening. Small positive non-linear effects were also observed, presumably suggesting a more complicated mechanism.



Scheme 4. Chiral Brønsted acid catalyzed oxetane desymmetrization with nitrogen nucleophiles.

In addition to indoles as the reaction partner, we also employed Hantzsch ester **15** for the above reaction.[7] With a similar catalytic system, the reactions of oxetanes **10** and amines **14** formed a range of tetrahydroisoquinolines **16** with excellent efficiency and good to excellent enantioselectivity (Scheme 5). Bicyclic products fused with thiophene, pyrrole, and indole, could also be generated. Oxetanes with two substituents at the 3-position could furnish the desired products with quaternary stereocenters, but unfortunately with moderate enantioselectivity.

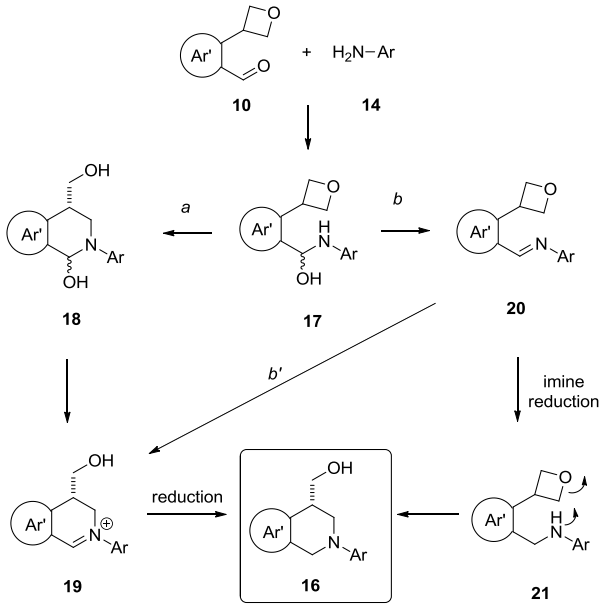




Scheme 5. Asymmetric syntheses of substituted tetrahydroisoquinolines and their analogues.

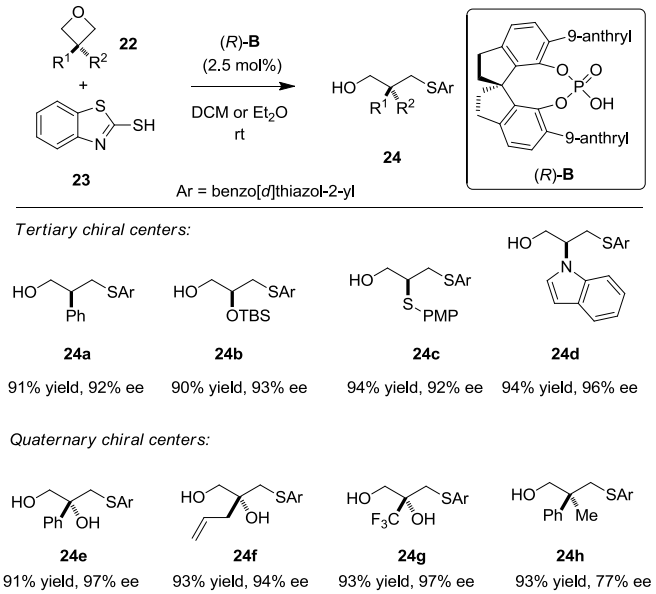
A series of control experiments were carried out to elucidate the reaction mechanism. These experiments suggested that, different pathways might be possible depending on substrates (Scheme 6). In path *a*, hemiaminal **17** was initially formed from the substrates. Rather than imine formation, the nucleophilic amine motif opens the oxetane ring, forming cyclic hemiaminal

18. Next, reduction of **18** via iminium **19** affords the observed product **16**. Alternatively, in path *b*, imine **20** is formed followed by reduction to give amine **21**. Next, enantioselective oxetane ring-opening forms the product **16**. It is also possible that the imine **20** could undergo intramolecular oxetane ring-opening to form iminium **III** (path *b'*). Control experiments indicated that all these pathways may function. One of them could be dominant depending on substrates.



Scheme 6. Possible mechanisms.

The above two reactions represented the first demonstration of efficient oxetane desymmetrization by nitrogen nucleophiles. Encouraged by the successful exploitation of chiral Brønsted acid catalysis, we next targeted the more challenging intermolecular opening of 3-substituted oxetanes. However, initial screening of different nucleophiles, including commonly used alcohols, amines, and thiols, resulted in no reactions in almost all cases. After considerable effort, we were pleased to find that 2-mercaptobenzothiazoles **23** could smoothly open the oxetanes **22** in the presence of catalyst **B** at room temperature, forming the desired products **24** with excellent efficiency as well as enantioselectivity. The mild conditions tolerate a wide range of functional groups. Both mono- and disubstituted oxetanes were suitable substrates, and the products bearing tertiary and quaternary stereocenters were formed efficiently. Although the nucleophiles were limited in scope, the arylthio ether moiety in the products could be easily converted to other functional groups (e.g., by Julia olefination). At present, this reaction is the only example of catalytic asymmetric intermolecular opening of 3-substituted oxetanes.



Scheme 7. Intermolecular desymmetrization of 3-substituted oxetanes.

Based on mechanistic studies using NMR experiments, we proposed two transition state models for chiral induction. In both cases, the primary activation is the hydrogen-bonding between the catalyst acidic proton and the basic oxetane moiety. For oxetanes substituted with a hydrogen-bond donor (e.g., OH) at the 3-position, this group provides secondary interaction with the phosphoryl oxygen to from the nine-membered transition state **TS1** (Figure 1). However, the orientation of those substrates without such a hydrogen-bond donor substituent is controlled by steric effect, i.e., the small substituent (R_s) is placed toward the catalyst backbone to minimize steric repulsion (Figure 1b). These models lead the nucleophiles to approach from the back face to open the ring, which is consistent with the experimental outcome.

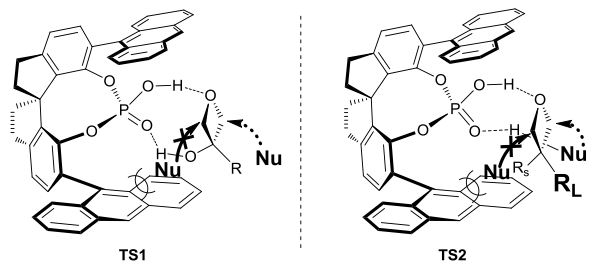


Figure 1. Plausible transition state models.

3. Conclusions

Asymmetric nucleophilic ring-opening of the prochiral 3-substituted oxetanes provides expedient access to a range of highly functionalized three-carbon chiral building blocks. Important progress has been made in the past five years. With (salen)Co(III)-based Lewis acid catalyst systems, the Jacobsen lab realized the first catalytic intramolecular process with internal alcohol nucleophile. More recently, we have successfully developed a new strategy based on chiral Brønsted acid catalysis and demonstrated highly efficient examples with

internal nitrogen nucleophiles as well as the first catalytic intermolecular example using sulphur nucleophiles. However, despite the progress, there remain significant challenges and opportunities in this field. In particular, the intermolecular ring-opening reactions are limited to a very special type of nucleophiles. Future effort should be directed at expanding the nucleophile scope to alcohols and amines as well as weak external nucleophiles, such as halogen- and carbon-based nucleophiles. However, the ring-opening alcohol product is a potential competing nucleophile, which should be taken into consideration when future new catalytic systems for weak nucleophiles are designed. Realization of these reactions with both high chemical efficiency and good stereocontrol is a daunting but highly desirable task.

Acknowledgements

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Notes and references

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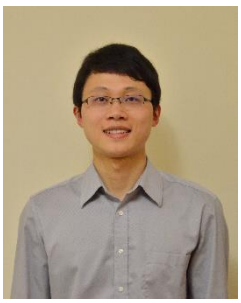

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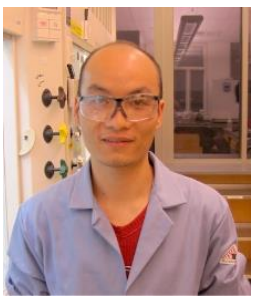

Zhilong Chen received his B.S. degree from Tongji University in 2006, and M.S. degree from Shanghai Institute of Organic Chemistry in 2009 under the supervision of Professor Chengye Yuan. After working in pharmaceutical industry for a short period, he joined Professor Jianwei Sun's group at the Hong Kong University of Science and Technology, receiving his Ph.D. degree in 2013. Currently, he is a postdoctoral fellow with Professor Qiu Wang in Duke University.

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