科技报告

Plakortide 家族及相似结构的天然产物是一类重要的过氧化合物，它们通常具备强的抗癌活性，但它们天然来源的微少限制了这类分子后续生物学活性的深入研究。鉴于此，本项目拟发展新的合成方法以高效构建这类天然产物的核心骨架，并计划将新发展的方法与天然产物的合成研究结合起来，以应用于过氧天然产物及其类似物的合成。

事实上，当前催化不对称过氧化反应的研究极少。为解决手性过氧化合物合成方法稀少、合成应用受限等挑战性问题，本项目着重针对“手性 Lewis 酸或者手性 Brønsted 酸能否有效活化过氧缩酮（醛）类化合物以形成过氧碳正离子活性中间体，并诱导亲核试剂与该中间体进行不对加成反应？”这一关键科学问题开展了探索性研究。首先，我们研究了六元环的过氧缩醛底物与硅基乙烯酮缩醛亲核试剂之间的催化不对称过氧化反应。实验结果表明，过氧缩醛底物中的烷氧基团的离去能力及反应温度对反应活性有着重要影响。在手性 Lewis 酸条件下，反应未能实现立体选择性。但在手性磷酸催化的条件下，当底物中的烷氧基为离去能力较高的醋酸根时，加成反应在低温条件则可发生。更重要的是，手性磷酸催化剂对上述反应展现出了一定的不对称诱导效应。通过初步筛选催化剂结构，目前我们可以实现最好 ee 值为 56%的催化不对称过氧化反应。这些研究结果初步回答了本项目中的关键科学问题，即手性磷酸确能活化过氧缩酮化合物形成手性过氧碳正离子对中间体，并引导硅基乙烯酮缩醛类亲核试剂进行不对称过氧化反应。

随后，分别在 Lewis 酸催化和手性磷酸催化的条件下，我们合成了一定数量的 plakortide 家族天然产物类似物，首次制备了多类含有 1,2-dioxane 环的 β-过氧基羧酸酯、β-过氧基酮类化合物，以及含有 α，β 双手性中心的 β-过氧基羧酸酯类化合物。特别是 α，β 为相邻季碳手性中心的化合物，这类 1,2-dioxane 类似物结构更加刚性，合成难度高，我们研究之前还未有任何成功的合成例子。这些结构多样的 plakortide 家族 天然产物分子的类似物具有潜在的药物化学应用价值。

另外，在项目的研究过程中，我们还偶然发现过氧化合物新的合成用途。因此，我们对项目的研究内容作了适当拓展延伸。具体上，我们设计并合成了新型的双功能过氧化物试剂，使其同时具备亲电性碳和亲电性氧的反应活性。在 KOH 或 Cs_2CO_3 的简单碱性条件下，该过氧双功能合成子可与常见的亲核试剂（如，*β*–羰基酯、1,3-二羰基化合物、氰基乙酸乙酯、*β*–羰基磷酸酯、*β*–羰基亚砜等）发生串联的 C-C 和 C-O 键生成反应，即形式上的[4+1]环加成反应，实现了一步高产率构建四氢呋喃化合物的通用合成新方法。该工作发表于 Organic Letters (2019, 21, 5679)。近期，我们进一步发掘了类似试剂的合成应用价值，最新工作发表在 Asian J. Org. Chem. (2020, 9, 197)。

总而言之，本项目的考核指标是发表 SCI 研究论文 2 篇，申请发明专利 1 篇，培养高质量研究生 3 名。在本项目的资助下，我们已经发表了 2 篇 SCI 文章（1 篇一区自然指数期刊；1 篇三区文章）；申请了 1 项发明专利（申请号：2019111819616）；培养了 2 名博士，4 名硕士，完成了项目任务书的考核要求。

附件：发表 SCI 文章及申请的专利证明材料

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Letter

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General [4 + 1] Cyclization Approach To Access 2,2-Disubstituted Tetrahydrofurans Enabled by Electrophilic Bifunctional Peroxides

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Supporting Information

ABSTRACT: A general [4 + 1] cyclization reaction of carbonyl nucleophiles with 2-iodomethylallyl peroxides, which function as unique electrophilic oxygen synthons, for the synthesis of a broad range of 2,2-disubstituted tetrahydrofurans is achieved under operationally simple conditions. The unprecedented asymmetric version of such reaction is also realized via chiral auxiliary-assisted cyclization, thus providing a distinct approach to access chiral tetrahydrofurans with high diastereoselectivities. The new method can be applied to the synthesis of core structure of posaconazole drug.

Tetrahydrofurans are a class of fundamentally important heterocycles widely found in numerous biologically important natural products and drug molecules (Figure 1).[1]

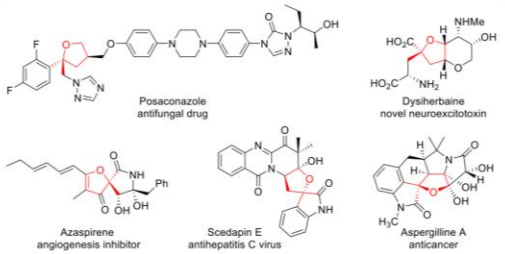
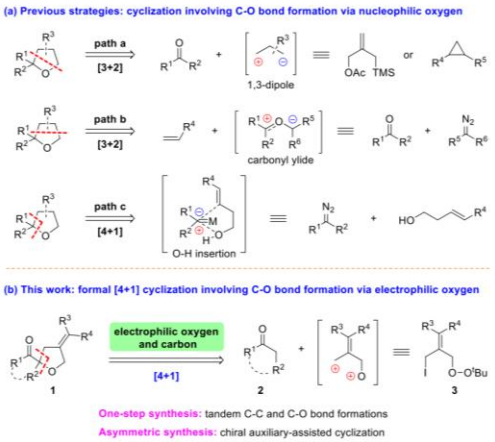


Figure 1. Representative structures of tetrahydrofuran-containing natural products and drugs.

Among those synthetic methods established,[2] cycloaddition reactions provide an attractive and powerful strategy for the one-step synthesis of these compounds.[1,2] To date, such a cyclization strategy predominantly focuses on the [3 + 2] processes,[3−5] such as the transition-metal- or Lewis-acid-catalyzed cycloaddition reactions of carbonyl ylides,[3] cyclopropanes,[4] and trimethylenemethane[5] (Scheme 1a, paths a and b). As an alternative strategy, [4 + 1] cyclization reactions, however, have been far less investigated.[6,7] Currently, a few isolated examples including transition-metal-catalyzed metallocarbene O−H insertion−Michael addition, O−H insertion−aldol, and O−H insertion−Conia-ene cascades have been reported by Hu,[6a] Moody,[6c] Hatakeyama,[6e] and Sharma,[6f,g] respectively (Scheme 1a, path c). Accordingly, the development of new [4 + 1] cyclization reactions remains an unmet challenge.

Scheme 1. Background and Our Synthetic Strategy



Herein we describe a highly efficient formal [4 + 1] cyclization reaction, a tandem C−C and C−O bond-forming process wherein the C−O bond is constructed via an unconventional electrophilic alkoxylation strategy, for the synthesis of a wide range of functionalized 2,2-disubstituted tetrahydrofurans from various carbonyl nucleophiles **2** and bifunctional 2-iodomethylallyl peroxides **3** in a single step.

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Notes

The authors declare no competing financial interest.

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ASIAN JOURNAL OF ORGANIC CHEMISTRY Communication

A General and Practical Synthesis of Chiral 1,2-Oxazetidines

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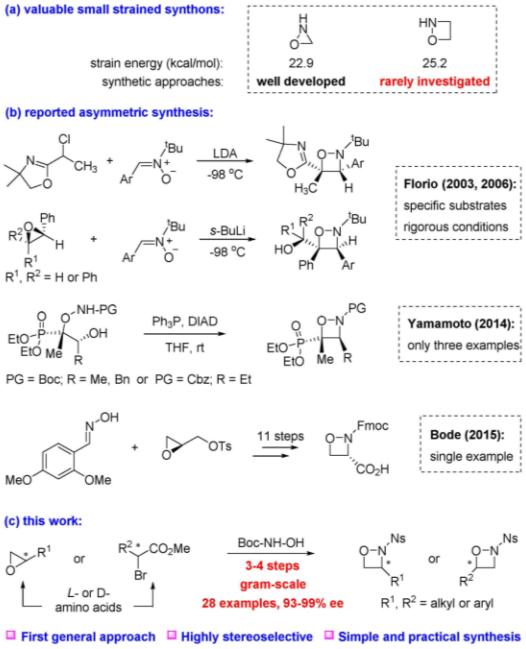
Abstract: 1,2-Oxazetidines are valuable small strained molecules that could be used to create new and conventionally difficult-to-access chemical transformations. Currently, asymmetric methods towards this class of heterocycles are very rare. Herein, we report a general and practical method to access a series of structurally diverse chiral 1,2-oxazetidines from readily available chiral epoxides and α-bromo esters in 3–4 steps by using mild Mitsunobu reactions as an efficient ring-closure approach to form the highly strained four-membered rings. The new method is operationally simple, and a range of *N*-nosyl-protected 3- and 4-substituted as well as 3,4-disubstituted chiral 1,2-oxazetidines could be conveniently prepared in gram-scale with excellent enantioselectivities (93–99% *ee*) and good overall yields for the first time.

Recently, 1,2-oxazetidines, a class of N,O-containing four-membered ring heterocycles, have attracted the attention from the synthetic community owning to their unique ring strained property[1] (25.2 kcal/mol, Scheme 1a). The intrinsic high energy stored in these small strained compounds could be harnessed to create new and conventionally difficult-to-access chemical transformations.[2] For example, Bode's group[2a] utilized the *N*-Fmoc-protected 1,2-oxazetidine amino acid as unique serine-forming ligation reagent to synthesize the complex peptides (up to 100 residues) that are inaccessible from native chemical ligation reactions of thioesters. Also, in 2015, Orentas and co-workers[2b] reported the *N*-tosyl or Boc-protected 1,2-oxazetidines could function as unusual electrophilic oxygen sources to react with aryl organometallic reagent to form ethers via distinct bond disconnections. More recently, Loh and co-workers[2c] demonstrated that *N*-tosyl-protected 1,2-oxazetidine was able to participate the cobalt-catalyzed N–O and C–C bonds cleavage reactions with heteroarenes to afford series of ortho-selective aminomethylated and hydroxymethylated products. These prominent examples reveal the synthetic values of



Scheme 1. Background and our research synopsis.

1,2-oxazetidines in chemical synthesis. However, the synthetic potentials of such heterocyclic reagents have not been fully exploited to date. One major reason is due to the limited synthetic approaches currently available towards these heterocycles.[2–4]

On the other hand, chiral 1,2-oxazetidines are synthetically more valuable, as they can be used for the construction of biologically important chiral N,O-containing scaffolds. Surprisingly, compared to the three-membered analogue oxaziridines,[5] asymmetric synthetic approaches towards chiral substituted four-membered 1,2-oxazetidines are even rare.[4] Currently, only few isolated examples for the synthesis of substituted chiral 1,2-oxazetidines have been reported. In 2003, Florio and co-workers reported the first asymmetric synthesis of chiral 1,2-oxazetidines via the addition of chiral α-lithiated 2-(1-choloroethyl)-2-oxazolines to nitrones.[4a] In 2006, the same group also accomplished the asymmetric synthesis of chiral 4-hydroxyalkyl-1,2-oxazetidines via the similar addition reactions of α-lithiated aryloxiranes with nitrones.[4b] However, both of these two reactions were limited to the preparation of the specific *N*-*tert*-butyl 1,2-oxazetidine products, and the stereoselectivities of the reactions were highly depended on the

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In conclusion, We have succesfully developed two general synthetic routes for the facile synthesis of a series of chiral substituted 1,2-oxazetidines from readily available chiral epoxides and α-bromo esters, both of which in turn could be readily prepared from the inexpensive chiral amino acids. Relying on the Mitsunobu reactions as a mild and powerful cyclization approach to form the strained four-membered rings, a range of structurally diverse *N*-nosyl-protected 3-substituted, 4-substituted, and 3,4-disubstituted chiral 1,2-oxazetidines could be efficiently synthesized in gram-scale with high enantioselectivities (93–99% ee) and satisfactory overall yields in 3–4 steps for the first time. The new method addresses the long-standing synthetic issues of chiral 1,2-oxazetidines and will thus facilliate their synthtic potentials in chemical synthesis. Utilization of such small strained heterocycles as unique synthons for the discovery of new chemical reactions is currently undergoing in our lab and the relevant investigation results will be reported in due course.

Experimental Section

Experimental details could be found in Supporting Information.

Acknowledgements

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Keywords: 1,2-oxazetidine · strained molecules · asymmetric synthesis · Mitsunobu reaction · heterocycles

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发文日：

2019年11月27日

申请号或专利号：201911181961.6　　发文序号：2019112702017490

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申请日：2019年11月27日
申请人：重庆大学
发明创造名称：一种制备1,2-氨氧杂环丁烷化合物的不对称合成方法

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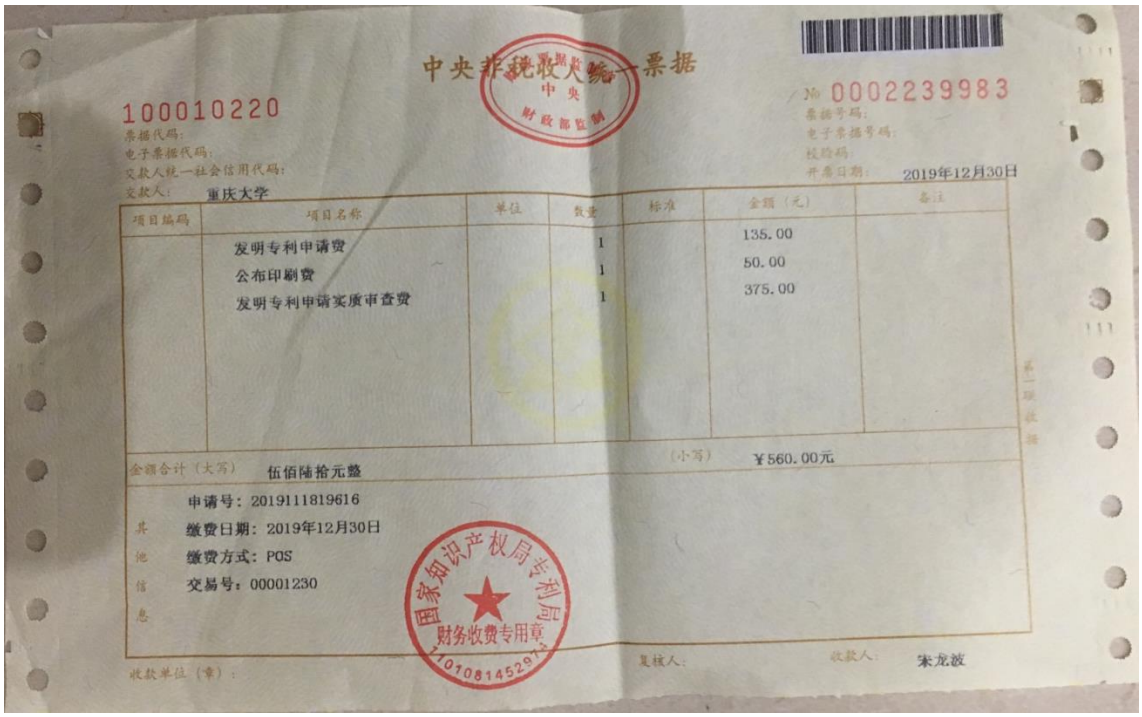

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