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Formal [5+1] annulation reactions of dielectrophilic peroxides: facile access to functionalized dihydropyrans†

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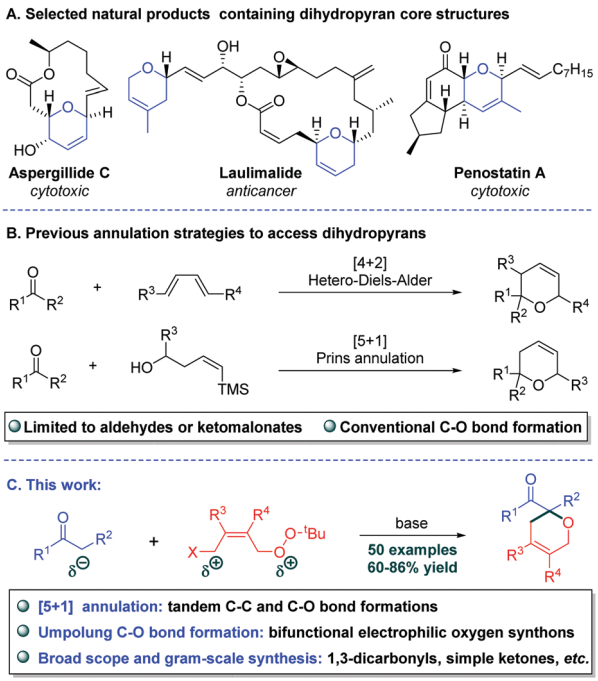
A general [5+1] annulation reaction, which utilized 4-bromo- or 4-mesyloxy-but-2-enyl peroxides as unique five-atom bielectrophilic synthons to participate in the C–C and the subsequent umpolung C–O bond-forming reactions with C1 nucleophiles, has been developed for the facile synthesis of 2,2-disubstituted dihydropyrans in high yields under mild basic conditions. The dihydropyrans, which are readily prepared on a gram scale by this new method, can be flexibly transformed into the biologically important tetrahydropyrans and pyranones in 1–2 steps.

Dihydropyrans are the core structural units of many biologically and pharmaceutically active compounds (Scheme 1A).[1] They also serve as versatile starting materials toward many other biologically important six-membered oxygenated heterocycles such as tetrahydropyrans and pyranones, since the olefin functional group provides a convenient handle for structural variations.[2] Due to the synthetic and medicinal importance of these molecules, their preparation methods have been actively pursued by the community. While many approaches have been developed for the synthesis of dihydropyrans,[3,4] highly efficient and attractive one-step annulation protocols remain limited. Currently, such annulation strategies primarily rely on the [4+2] hetero-Diels–Alder reactions[5] of carbonyl compounds with 1,3-dienes or the [5+1] Prins-type annulation reactions[6] of carbonyl compounds with 4-hydroxyl-vinylsilanes (Scheme 1B). Nonetheless, both methods generally require the use of activated aldehydes, glyoxylates or ketomalonates as substrates, which substantially restrains the scope of the reactions. In this regard, the development of a more general annulation strategy for the facile synthesis of such oxygenated heterocycles is still in high demand.

Herein, we report a highly efficient and formal [5+1] annulation approach to access a broad range of functionalized 2,2-disubstituted



Scheme 1 Background and our synthetic strategy.

3,6-dihydro-2*H*-pyrans in high yields by using 4-bromo- or 4-mesyloxy-but-2-enyl peroxides as unique five-atom bielectrophilic synthons to react with a variety of one carbon nucleophiles, such as β-keto esters, β-keto phosphonates, and simple ketones, under very mild basic conditions (Scheme 1C). Unlike previous strategies, this new annulation approach involves a tandem C–C and C–O bond-forming process, wherein the critical ring-closing C–O bond was constructed *via* an unconventional umpolung method.[7]

Previously, dialkyl peroxides have been exploited for the C–O bond-forming reactions with highly reactive carbon nucleophiles such as organolithium and Grignard reagents.[8] With this approach, ethers were generated *via* the attack of carbanion species onto the electrophilic oxygen reagents. Such an umpolung

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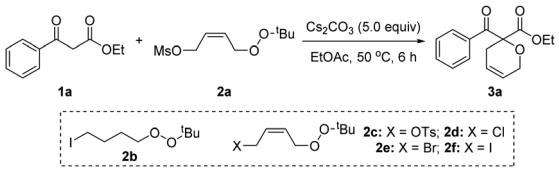
C–O bond-forming strategy, however, has long been underutilized for the synthesis of oxygen heterocycles,[9] in spite of its great potential in developing new transformations that may be difficult to access from conventional strategies. Recently, we developed a highly efficient [4+1] annulation reaction to access functionalized tetrahydrofurans under mild basic conditions.[7a] The key feature of this reaction relied on the use of peroxides as bifunctional electrophilic oxygen and carbon synthons to engage in the tandem C–C and C–O bond-forming reactions with one carbon nucleophiles. As part of our ongoing research aimed at developing new cyclization reactions from functionalized peroxides, we were particularly interested in examining whether such an annulation strategy could be applied to the synthesis of six-membered oxacycles. To the best of our knowledge, the general [5+1] annulation[10] reaction utilizing a [C1] *gem*-dianion and a [O1–C5] dielectrophile coupling strategy has not been realized to date.

We commenced the investigation by selecting ethyl benzoylacetate **1a** as the model nucleophile and peroxides **2a–f** as possible five-atom electrophiles. Our primary concern was the competitive double intermolecular C-alkylation or O-alkylation pathways, as they would terminate the desired cyclization process. Meanwhile, we were also quite uncertain whether peroxides **2a–f** were sufficiently stable under the basic conditions, as these compounds might undergo Kornblum–DeLaMare type decomposition[11] or double bond isomerization in the presence of bases. Actually, we found that the structure of peroxides had a significant impact on the outcomes of the reaction (Table 1, entries 1–6). Peroxides **2b** and **2d** bearing alkyl iodide and allyl chloride functionalities were sufficiently stable but less reactive. Only a trace amount of the desired product was detected under various basic conditions.[12] Peroxide **2f** with an allyl iodide group was highly reactive but less stable. The double bond in this compound was readily isomerized to the *trans* geometry, which made the subsequent ring-closing C–O bond formation more difficult. Fortunately, peroxides **2a** and **2e** bearing mesyloxy and bromo groups were found to be highly reactive and sufficiently stable in the presence of the Cs_2CO_3 base. Both of them successfully provided product **3a** in 77% and 75% yields, respectively. Further optimization revealed that the base and temperature also had significant impacts on the reaction (Table 1, entries 7–13). A weaker base (K_2CO_3) or a lower temperature (25 °C) resulted in sluggish reactions, and the C-alkylation intermediate was generated as the major product. A stronger base (KOH) or a higher temperature (90 °C) led to the severe decomposition of the peroxide. Similarly, the screening of other reaction parameters such as solvents and reactant ratios also failed to improve the yield (Table 1, entries 14–16). Thus, we finally established the optimal conditions by using peroxide **2a** or **2e** as a suitable electrophile and Cs_2CO_3 (5.0 equiv.) as the base in ethyl acetate at 50 °C (Table 1, entries 1 and 5).

With the optimized reaction conditions in hand, we next evaluated the scope of the nucleophiles. As shown in Table 2, a range of aromatic β-ketoesters bearing electron-donating or electron-withdrawing groups on the phenyl ring were well tolerated and delivered dihydropyrans in 73–83% yields

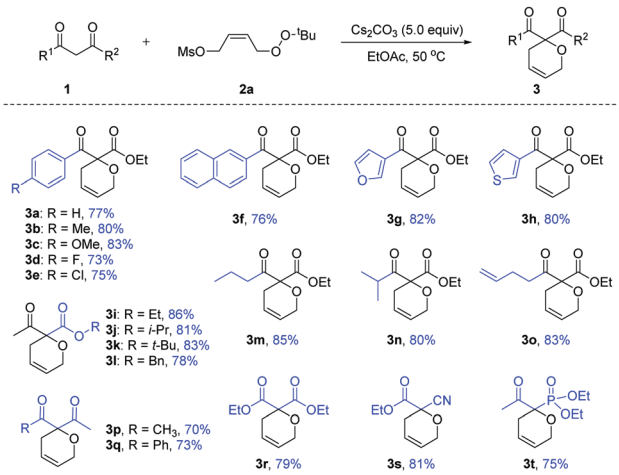
Table 1 Optimization of the reaction conditions[a]



Entry	Variation from standard conditions	Yield[b] (%)
1	None	77
2	**2b**	0
3	**2c**	50
4	**2d**	12
5	**2e**	75
6	**2f**	0[c]
7	25 °C	0[d]
8	90 °C	27
9	Cs_2CO_3 (3.0 equiv.)	35
10	Cs_2CO_3 (10.0 equiv.)	58
11	KOH (5.0 equiv.)	27
12	K_3PO_4 (5.0 equiv.)	54
13	K_2C0_3 (5.0 equiv.)	0[d]
14	DMF	0[e]
15	CH_3CN, THF, or DCM	16–46
16	**2a** (2.0 equiv.)	73

[a] Standard conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), and Cs_2CO_3 (0.50 mmol) in EtOAc, 50 °C for 6 h. [b] Isolated yield. [c] Isomerization of the double bond was observed. [d] The C-alkylation intermediate was formed. [e] Peroxide was decomposed.

Table 2 Substrate scope for nucleophiles[a]



[a] Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), and Cs_2CO_3 (1.0 mmol) in EtOAc (2 mL) at 50 °C for 6–12 h.

(Table 2, **3a–e**). Similarly, bicyclic naphthalene as well as heteroaromatic furan and thiophene substrates were also tolerated under the current conditions, affording the products in 76–82% yields (Table 2, **3f–h**). In addition, a range of aliphatic β-keto esters were also examined for the annulation reactions. Substrates **1i–o** consistently provided the dihydropyrans in about 80% yields, regardless of the structural variation on both ester and carbonyl side groups (Table 2, **3i–o**). Meanwhile, other active methylene compounds, such as 1,3-dicarbonyl, diethyl malonate, ethyl cyanoacetate, and β-keto phosphonate

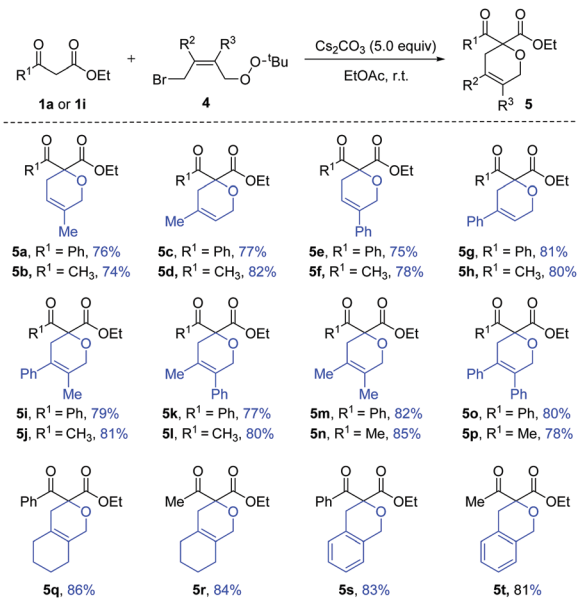
compounds, were also good substrates for this annulation. All of them smoothly furnished the products in 70–81% yields (Table 2, **3p–t**). Notably, product **3t** bearing a rare phosphonate-containing dihydropyran framework, has not been prepared previously.

To further expand the reaction scope, we next examined the structural tolerance of peroxides. As shown in Table 3, a range of 2- and 3-substituted as well as 2,3-disubstituted peroxides **4** smoothly cyclized with ethyl benzoylacetate **1a** and acetoacetate **1i** under standard conditions. A series of 2,2,4-/2,2,5-trisubstituted or 2,2,4,5-tetrasubstituted dihydropyrans, including the structurally complicated bicyclic compounds **5q–t**, were conveniently prepared in high yields (Table 3, **5a–t**). It should be noted that 4-bromo-but-2-enyl peroxides were used in these cases because they provided slightly better yields compared to 4-mesyloxy-but-2-enyl peroxides.

In addition to active methylene compounds, other common nucleophiles such as phenyl ester, cyanide, cyclic and acyclic ketones were also tested for the reaction (Table 4). Bearing less acidic α-protons, these nucleophiles were more challenging substrates for the [5+1] annulation, as peroxides may be incompatible with the stronger basic conditions required for the deprotonation step. Fortunately, after careful screening, we found that dihydropyrans **7a–j**, including those spirocyclic products **7d–g**, were successfully generated in good yields by using KO^{t}Bu as the base at a lower temperature. These results indicated that the current annulation strategy was quite general in terms of both nucleophiles and peroxides.

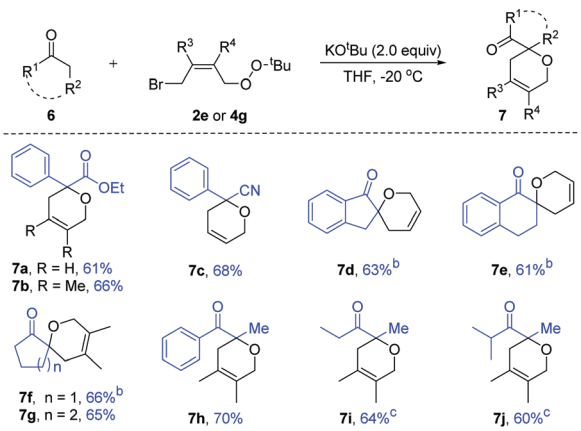
To explore the practicality of this new transformation, the gram-scale synthesis of dihydropyrans was carried out under the standard conditions. As shown in Scheme 2, [5+1] annulation reactions still proceeded well on a 5 or 9 mmol scale of peroxides and smoothly afforded products **3a**, **3i**, and **7g** in 63–78% yields.

Table 3 Substrate scope for peroxides[a]



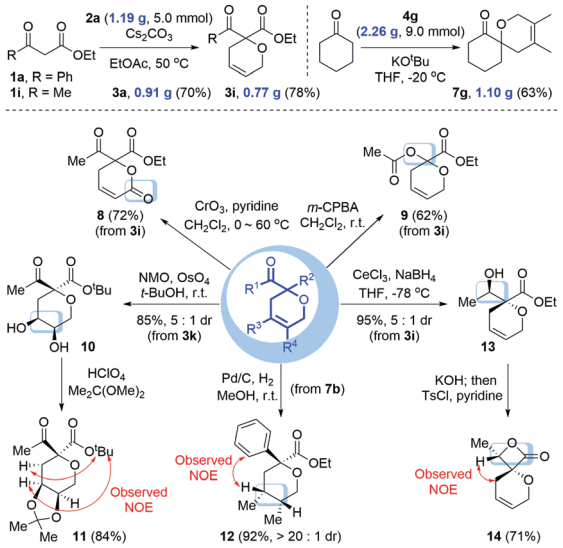
[a] Reaction conditions: **1a** or **1i** (0.24 mmol), **4** (0.2 mmol), and Cs_2CO_3 (1.0 mmol) in EtOAc (2 mL), r.t. for 6–12 h.

Table 4 Substrate scope for other common nucleophiles[a]

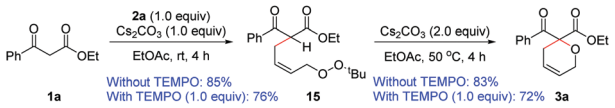


[a] Reaction conditions: **6** (0.24 mmol), **2a** or **4g** (0.2 mmol), and KO^{t}Bu (0.4 mmol) in THF (2 mL), −20 °C for 10 min. [b] The reaction was carried out at −40 °C. [c] 3.0 equiv. of **6** and KO^{t}Bu were used.

Bearing the versatile olefin and carbonyl functionalities, the dihydropyrans prepared using the current method are highly valuable building blocks for the synthesis of other six-membered oxygenated heterocycles. As shown in Scheme 2, compound **3i** was readily converted into dihydropyranone **8** in 72% yield after a single step of chemoselective oxidation with CrO_3–pyridine reagents. Similarly, the treatment of **3i** with *m*-CPBA selectively produced the active ketal compound **9** in 62% yield *via* Baeyer–Villiger oxidation. Also, the treatment of dihydropyran **3k** with OsO_4 (5 mol%) and NMO afforded diol **10** in 85% yield and 5 : 1 dr. Impressively, tetrahydropyran **12** could be obtained in 92% yield and with excellent diastereoselectivity (>20 : 1 dr) *via* the hydrogenation of compound **7b**. Moreover, the carbonyl functionalities in dihydropyran molecules could also be utilized for further transformation. For example, compound **3i** was smoothly transformed into β-lactone **14** in 67%



Scheme 2 Gram-scale synthesis and synthetic applications.



Scheme 3 Control experiments.

overall yield and 5 : 1 dr after two steps of reduction and cyclization operations. Again, this rigid spirocyclic compound is structurally new, and was prepared for the first time. The relative configurations of the above products were unequivocally assigned by the nuclear Overhauser effect analysis.[12]

Finally, to gain insights into this annulation process, we conducted the following control experiments (Scheme 3). When carrying out the reaction of **1a** and **2a** at room temperature, we isolated the C-alkylation intermediate **15** in 85% yield. After resubmitting this intermediate to the standard conditions, the final product **3a** was obtained in 83% yield. Furthermore, adding a stoichiometric amount of TEMPO to the above conditions did not significantly affect the reaction yields. These results indicated that the tandem process probably proceeded *via* a C–C → C–O bond-forming sequence, wherein both bonds were more likely formed *via* a nucleophilic substitution mechanism instead of a radical pathway.[8,9]

In conclusion, we have developed a highly efficient and general [5+1] annulation reaction of 4-bromo- or 4-mesyloxy-but-2-enyl peroxides with various carbon nucleophiles for the facile synthesis of a wide range of 2,2-disubstituted dihydropyrans in high yields. Unlike previous strategies, this new approach utilized the peroxides as unique five-atom bielectrophilic synthons to participate in the C–C and subsequent umpolung C–O bond-forming reactions with C1 nucleophiles, thus providing a distinct strategy to access the target dihydropyrans under operationally simple conditions. We also demonstrated that these dihydropyran products were readily synthesized on a gram-scale and could be flexibly transformed into other biologically important six-membered oxacycles such as tetrahydropyran, pyranone, structurally novel spirocyclic β-lactone, and active ketal products in 1–2 steps.

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Conflicts of interest

There are no conflicts of interest to declare.

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