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Communication

Epoxide Cycloadditions

Intermolecular Electrophilic Addition of Epoxides to Alkenes: [3+2] Cycloadditions Catalyzed by Lewis Acids

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Abstract: Described are the first examples of intermolecular electrophilic additions of epoxides to alkenes, which proceed through a classic cationic mechanism initiated by epoxide C–O bond cleavage. Treatment of styrene oxides and either styrenes or dienes with a variety of Lewis-acidic triflate salts generates tetrahydrofurans as products of [3+2] cycloaddition in moderate to good yields (up to 71 %). Careful choice of catalyst and reaction conditions favors the desired intermolecular reaction over epoxide degradation without requiring additional reagents or additives. The reaction proceeds diastereoselectively and provides only one regioisomer of the product. Additional highlights include inexpensive precursors, mild conditions, short reaction times, low catalyst loading, and scalability.

Introduction

Acid-promoted electrophilic additions to alkenes and acid-promoted nucleophilic additions to epoxides are both fundamental organic transformations with wide-ranging applications in synthesis. Methods that combine the two modes of reactivity, in which the epoxide acts as an electrophile in a classic addition reaction to an alkene that proceeds with epoxide C–O bond cleavage, have been described for intramolecular cases going as far back as 1962 (Figure 1).[1] The use of a Lewis acid catalyst to activate the epoxide can result in either a [3+2] cycloaddition to form a tetrahydrofuran ring or, when the substrate contains multiple C–C π-bonds, an epoxide-initiated cationic polyene cyclization.[2] In particular the latter class of transformations has been employed with considerable success for the rapid stereocontrolled assembly of complex multicyclic frameworks en route to the total synthesis of natural products.[2d] Despite this long history, to the best of our knowledge no intermolecular examples of reactions between alkenes and epoxides proceeding through this well-studied mechanistic pathway have appeared in the literature. Herein we disclose our discovery of conditions that enable this reactivity, resulting in Lewis acid catalyzed intermolecular [3+2] cycloadditions between epoxides and either styrenes or dienes.

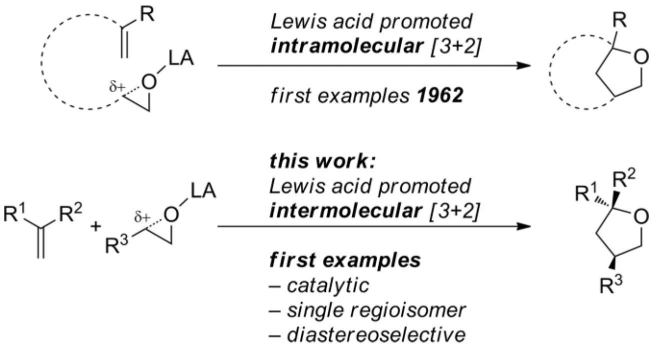

Figure 1. Cycloadditions of alkenes and epoxides proceeding with C–O bond cleavage.

Results and Discussion

There are considerable challenges to achieving an intermolecular cycloaddition, and chief among them is the instability of the formal 1,3-dipole that results from heterolytic C–O bond cleavage of the epoxide. Among the possible unwanted side reactions are a 1,2-hydride shift (also known as Meinwald rearrangement),[3] dimerization, polymerization, or elimination. Notably, the Meinwald rearrangement has been employed as a strategy to convert epoxides to aldehydes in situ prior to Lewis acid catalyzed electrophilic addition,[4] and is a substantial confounding factor even for the previously reported intramolecular cycloadditions.[2] In light of this, it was clear that careful manipulation of reaction conditions to control the relative rates of desired vs. undesired processes would be crucial to the success of an intermolecular method.

Accordingly, we envisioned that high-concentration conditions combined with slow addition of the epoxide might favor the desired bimolecular event (Table 1). This quickly led to the discovery that Lewis-acidic triflate salts proved particularly suitable for catalyzing the cycloaddition of styrene oxide and α-methylstyrene at room temperature in only 10 min, generally providing good yields of the tetrahydrofuran **6a** at 2 % loading while demonstrating selectivity over the two most commonly observed epoxide degradation products **4** and **5**. Consistent with a cationic pathway, only one regiosomer was observed,

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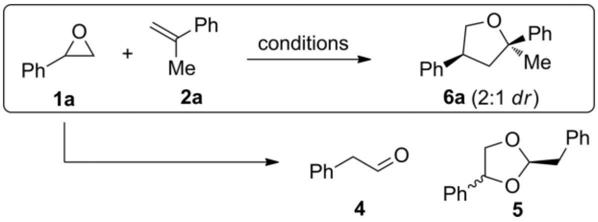
resulting presumably from nucleophilic attack of the alkene on the more substituted carbon atom of the epoxide. Additionally, the *syn* diastereomer was modestly favored. In a control experiment, the use of triflic acid as a catalyst resulted in a complex mixture containing only trace amounts of the desired product.[5] Ultimately, we elected to conduct further experiments using $Sc(OTf)_3$, which consistently provided the highest yields of the tetrahydrofuran. The use of 2 equiv. of styrene was optimal, and addition of the epoxide over periods of time longer than 10 min offered no benefit. Remarkably, on this scale the catalyst loading could be decreased to 0.25 mol-% with minimal effect on the reaction yield.

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



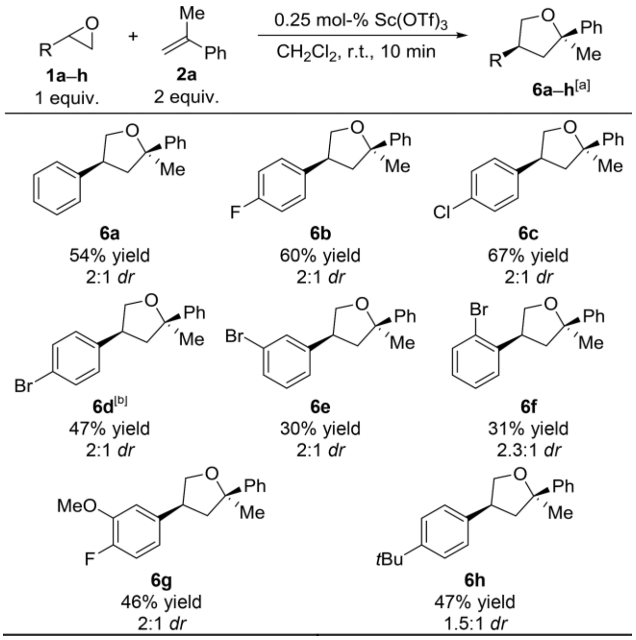
Entry	Cat. (mol-%)	**4** [%][b]	**5** [%][b]	**6a** [%][b]
1	$AgBF_4$ (2)	20	trace	2[c]
2	$AgPF_6$ (2)	26	trace	trace[c]
3	AgOTf (2)	23	3	16[c]
4	$Cu(OTf)_2$ (2)	19	14	62
5	$In(OTf)_3$ (2)	13	19	60
6	$Yb(OTf)_3$ (2)	26	13	57
7	**$Sc(OTf)_3$ (2)**	**8**	**16**	**69**
8	HOTf (2)	13	28	trace[d]
9	**$Sc(OTf)_3$ (0.25)**	**19**	**18**	**60**

[a] Reaction conditions: styrene **2a** (4 mmol) and catalyst were dissolved in anhydrous CH_2Cl_2 (0.5 mL) under N_2. Epoxide **1a** (2 mmol) was added dropwise at room temperature over 10 min. [b] Corrected GC yield using dodecane as an internal standard unless otherwise noted. Yields for **5** are based on 2 equiv. of **1a**. [c] Incomplete consumption of epoxide. [d] Full consumption of styrene and epoxide.

With optimized conditions in hand, we initially explored the scope of the method with respect to the epoxide (Table 2). In general, both electron-withdrawing and -donating substituents were tolerated. In the case of the bromo-substituted series, the decreasing trend in yield seen for *para*-, *meta*-, and *ortho*-substituted epoxides reflected the presumed influence of both sterics and inductive destabilization of a partial or full positive charge at the benzylic carbon atom on product distribution. Nevertheless, halogen substitution at the *para* position was preferred in certain cases, with the F- and Cl-substituted styrene oxides giving the highest yields of the tetrahydrofuran product (60 % and 67 % yield, respectively).

A variety of substituted styrenes were evaluated to ascertain the effect of aryl substitution of the alkene on the reaction yield (Table 3). A *para*-cyclohexyl-substituted styrene gave the highest yield observed for any epoxide/alkene combination, providing 71 % of tetrahydrofuran **7a**. Halogen substitution led to reduced reaction yields, consistent with inductive withdrawing effects reducing the nucleophilicity of the styrene. In each case the *syn* diastereomer was favored, but the magnitude of diastereoselectivity was modest. Sterically hindered alkenes (e.g. 2-methylstyrene) are tolerated and provide a small increase in diastereoselecivity (3.2:1 *dr* for example **7h**). To demonstrate the potential utility of this method in synthesis, cycloaddition

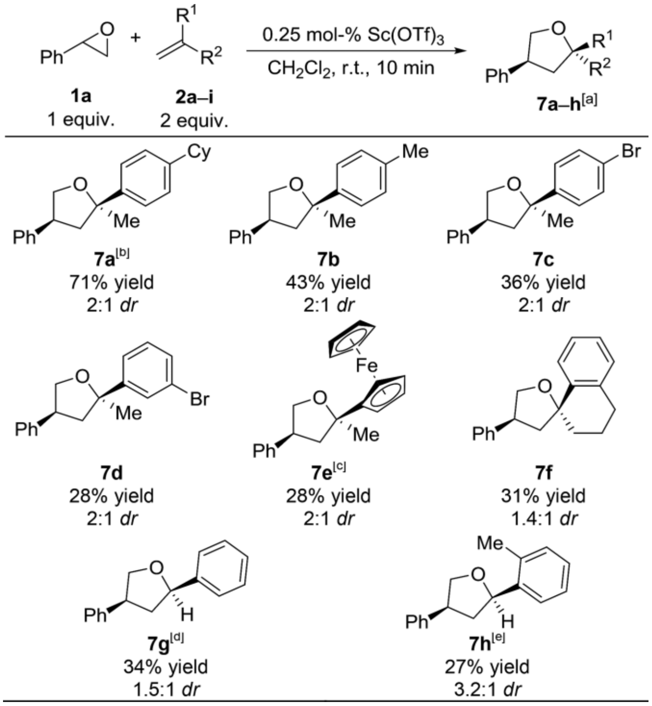
Table 2. Scope with regard to the epoxide component.



6a 54% yield 2:1 *dr*
6b 60% yield 2:1 *dr*
6c 67% yield 2:1 *dr*
6d[b] 47% yield 2:1 *dr*
6e 30% yield 2:1 *dr*
6f 31% yield 2.3:1 *dr*
6g 46% yield 2:1 *dr*
6h 47% yield 1.5:1 *dr*

[a] Isolated yield. Diastereomeric ratios are based on ^1H NMR spectroscopy of the crude reaction mixture. [b] Reaction performed using 1.0 mol-% $Sc(OTf)_3$.

Table 3. Scope with regard to the alkene component.

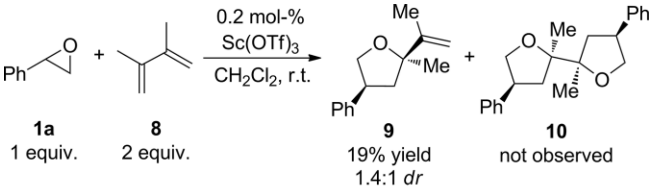


7a[b] 71% yield 2:1 *dr*
7b 43% yield 2:1 *dr*
7c 36% yield 2:1 *dr*
7d 28% yield 2:1 *dr*
7e[c] 28% yield 2:1 *dr*
7f 31% yield 1.4:1 *dr*
7g[d] 34% yield 1.5:1 *dr*
7h[e] 27% yield 3.2:1 *dr*

[a] Isolated yield. Diastereomeric ratios are based on ^1H NMR spectroscopy of the crude reaction mixture. [b] Average of two experiments. [c] Reaction performed using 1.0 mol-% $Sc(OTf)_3$. [d] Reaction performed using 0.5 mol-% $Sc(OTf)_3$. [e] Reaction performed using 0.35 mol-% $Sc(OTf)_3$.

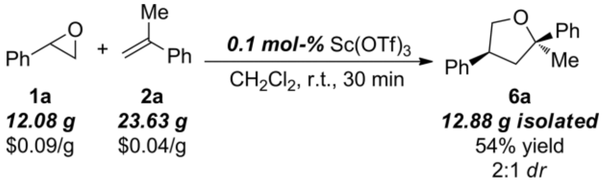
between styrene and styrene oxide provided a mixture of the diastereomeric natural products Calyxolanes A (**7g**, *anti* diastereomer) and B (**7g**, *syn* diastereomer) in a single step.[6] As evidence of the mild reaction conditions, a ferrocene-substituted alkene survived the reaction unscathed and provided the corresponding tetrahydrofuran **7e**. In all cases the only major side products observed were epoxide degradation products **4** and **5**. Unreacted alkene can be readily recovered from the reaction mixture.

In order to further probe the scope with regards to alkenes, we attempted a cycloaddition between styrene oxide and 2,3-dimethylbuta-1,3-diene (**8**; Scheme 1). Notably, this diene substrate provided only tetrahydrofuran **9** and none of the double cycloaddition product **10**, suggesting a high degree of selectivity for conjugated over non-conjugated alkenes.[7] Additionally, no [4+3] product was observed.



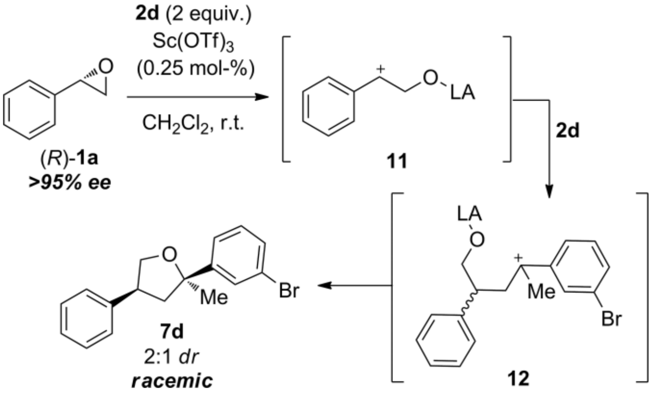
Scheme 1. Diene–epoxide [3+2] cycloaddition.

The reported [3+2] cycloaddition has potential advantages over other cycloaddition methods that form tetrahydrofuran rings[8] in that it utilizes abundant and inexpensive or easily prepared precursors and a single reagent in catalytic amounts. The prospect of an efficient, catalyzed preparation of tetrahydrofurans from simple building blocks such as alkenes and styrene oxides led us to explore the potential advantages of the method on a gram-scale (Scheme 2). Starting with 12.08 g of styrene oxide (\$0.09/g) and 23.63 g of α-methylstyrene (\$0.04/g), catalyst loading could be reduced 2.5-fold to 0.1 mol-% without affecting the yield, providing 12.88 g of tetrahydrofuran **6a**. In comparison, other Lewis acid catalyzed cycloadditions that form tetrahydrofurans, for example those occurring between donor–acceptor cyclopropanes and aldehydes, typically employ 5–10 mol-% catalyst.[8h,8m,8n] Given that tetrahydrofurans are common motifs in pharmaceutical drugs and bioactive natural products,[9] this general approach that employs readily available substrates and only a single catalytic reagent could ultimately prove advantageous for the practical synthesis of drug leads.



Scheme 2. Multigram-scale reaction.

Mechanistically, the observation of aldehyde **4** arising from Meinwald rearrangement implicates the formation of fully ring-opened dipolar intermediate **11** (Scheme 3). To evaluate whether nucleophilic attack by the alkene occurs to any extent prior to epoxide ring opening, enantiopure (*R*)-styrene oxide was employed in a cycloaddition reaction with 3-bromo-α-methylstyrene. In this case, only racemic product was observed, suggesting that nucleophilic attack by the alkene on a fully carbocationic center is the dominant mechanistic pathway and that diastereoselectivity is set during the subsequent ring closure.[10] Previously, successful competition of intermolecular nucleophilic attack with Meinwald rearrangement under similar circumstances has only been observed with heteroatomic nucleophiles.[11]



Scheme 3. Investigation of the reaction mechanism.

Conclusions

We have developed conditions that enable for the first time intermolecular electrophilic additions of epoxides to alkenes that proceed with epoxide C–O bond cleavage. The Lewis acid catalyzed [3+2] cycloaddition results in the scalable and highly regioselective synthesis of substituted tetrahydrofurans from readily available and inexpensive starting materials using exceptionally low catalyst loadings. Ultimately, careful choice of catalyst and reaction conditions allowed for the desired intermolecular reaction to successfully compete with epoxide degradation, enabling reactivity that was previously only observed for intramolecular examples. Current efforts seek to expand the scope and stereoselectivity of the reaction and to explore related intermolecular cycloadditions with other previously unreactive π-nucleophiles.

Experimental Section

Representative Procedure for Cycloaddition: A 5 mL round-bottomed flask was charged with a magnetic stir bar, $Sc(OTf)_3$ (2.5 mg, 0.05 mmol), 1-methyl-1-phenylethene (**2a**; 0.52 mL, 4 mmol), and anhydrous dichloromethane (0.5 mL). To the resulting mixture under N_2 and at room temperature was added 1-phenyloxirane (**1a**; 0.23 mL, 2 mmol) dropwise by syringe pump over 10 min. After the addition was complete, the crude reaction mixture was loaded directly onto a silica gel column and purified by chromatography (100 % hexanes to ethyl acetate/hexanes, 5:95) to provide product **6a** (259 mg, 54 %, 1.5:1 *dr*) as a colorless oil.

Acknowledgments

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Keywords: Alkenes · Cycloaddition · Epoxides · Heterocycles · Ring expansion

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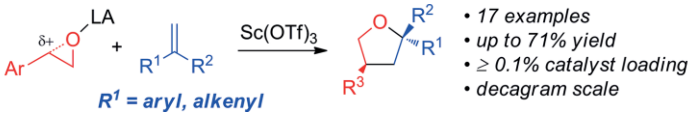
Intermolecular Electrophilic Addition of Epoxides to Alkenes: [3+2] Cycloadditions Catalyzed by Lewis Acids



An intermolecular cycloaddition between epoxides and styrenes to form tetrahydrofurans has been developed. The reaction is catalyzed by Lewis acids and proceeds through a mechanism involving cationic intermediates. The cycloaddition proceeds diastereoselectively and with complete control of regioselectivity. Advantages of scalability and minimal catalyst loading are demonstrated.

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