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Highly regioselective Lewis acid-catalyzed [3+2] cycloaddition of alkynes with donor-acceptor oxiranes by selective carbon-carbon bond cleavage of epoxides[†]

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A novel, efficient, highly regioselective $Sc(OTf)_3$ -catalyzed [3+2] cycloaddition of electron-rich alkynes with donor-acceptor oxiranes *via* highly chemoselective C–C bond cleavage under mild conditions was developed.

2,5-Dihydrofurans are widely used as building blocks in organic synthesis and frequently found as subunits in many bioactive natural products.¹ Examples include (+)-furanomycin,^{2a} salviasperanol,^{2b} diplobifuranylone B,^{2c} cryptoresinol^{2d} and griseolic acid (Fig. 1).^{2e} Thus, the development of efficient and versatile synthetic methods for these compounds has been continuously highly desirable. Marshall, Krause, Ma, and other groups have done seminal work on the synthesis of these compounds by metal-catalyzed cyclization of 1,2-allenic alcohols.³ Ring-closing metathesis of bisallyl ether provides another efficient way to 2,5-dihydrofurans.⁴

Pioneered by Huisgen, ^{5a} carbonyl ylide as an important and reactive 1,3-dipole for assembling of five member heterocycles has attracted much attention during the last few decades. ⁵⁻⁷ The transition metal catalysed [3+2] cycloaddition of carbonyl ylide,



Fig. 1 Some natural products containing a 2,5-dihydrofuran skeleton.

generated from the decomposition of diazocompound and carbonyl compounds, with the inter- or intramolecular alkynes has been extensively studied.⁷ On the other hand, the selective C-C bond cleavage of epoxides is believed to be the most straightforward, economical and hazardous diazo-compound free method to generate the reactive carbonyl ylide.⁵ However, the required harsh reaction conditions undermine their wide use in practical synthesis. For example, de March et al.^{5b} have reported a [3+2] cycloaddition reaction of oxiranyl diesters with alkynes under harsh conditions (160 °C) and only restricted to intramolecular reactions due to the generated carbonyl vlide being not reactive enough. We⁸ very recently developed a novel strategy to address this issue by introduction of electron-withdrawing group(s), which can be selectively activated by binding to a Lewis acid. For example, a highly diastereo- and chemo-selective [3+2] cycloaddition of aryl oxiranyl diketones with aldehydes under mild conditions has been demonstrated.^{8b} During the course of these studies, we envisaged that the generated metallo-carbonyl ylide will be more reactive than the corresponding carbonyl ylide without metal activation, and thus in turn will be easy to undergo the intermolecular [3+2] cycloaddition with alkynes, leading to the corresponding highly functionalized 2,5-dihydrofurans. We wish to report herein a novel, efficient Sc(OTf)₃-catalyzed inter- and intramolecular cycloaddition of alkynes with oxiranes via the selective C-C bond cleavage of epoxide under mild conditions, which provides a general, rapid, diazo-compound free access to functionalized 2,5-dihydrofurans.

We tested our hypothesis by using 3-aryloxiranyl diketone **1a** and alkyne **2a** as model substrates. Gratifyingly, after many attempts (see ESI†), the desired cycloaddition product **3a** was obtained in 98% isolated yield as a single regioisomer after running the reaction for 3 hours using 5 mol% of Sc(OTf)₃ as catalyst in DCE in the presence of 4 Å MS. Other commonly used Lewis acids such as Sn(OTf)₂, In(OTf)₃, Ni(ClO₄)₂·6H₂O, Y(OTf)₃ and Yb(OTf)₃ could also achieve the catalytic cycle, but failed to improve the yield. The reactions running in other solvents such as DCM and toluene resulted in slightly lower but reasonable yields. It is noteworthy that only a trace of the product (less than 10% yield) could be detected without Lewis acid by enhancing the temperature to more than 100 °C.

With the optimal reaction conditions in hand, we investigated the scope and limitation of this Lewis acid-catalyzed regioselective

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Table 1 Variation of the alkyne components

$\begin{array}{c cccc} & & & & & & & \\ Ph & & & & & \\ R^2 & O & & & \\ & & & R^2 & O \\ & & & & R^3 & & \\ & & & & & rt, 3 h \\ & & & & & & 3 \end{array}$			
Entry	R^{1}/R^{2} (1)	R^{3}/R^{4} (2)	Yield 3 ^c (%)
1	Me/Me (1a)	2a	3a (98)
2	1a ($4-MeOC_{6}H_{4}/n-C_{4}H_{9}$ (2b)	3b (88)
3	1a	$4-\text{MeOC}_6\text{H}_4/\text{cyclopropyl}$ (2c)	3c (92)
4	1a	2-thienyl/H (2d)	3d (90)
5	1a	$4 - MeC_6H_4/H$ (2e)	3e (68)
6	1a	$4-\text{MeOC}_6H_4/(CH_2)_3Cl$ (2f)	3f (96)
7^a	1a	$4-\text{MeOC}_6\text{H}_4/4-\text{MeOC}_6\text{H}_4$ (2g)	3g (69)
8^b	Ph/Ph (1b)	$4-\text{MeOC}_6\text{H}_4/\text{Br} (2h)$	3h (82)

^{*a*} Including 9% 2,3-dihydrofuran isomer. ^{*b*} The reaction was carried out with 5 mol% of Ni(ClO₄)₂·6H₂O instead of Sc(OTf)₃. ^{*c*} Isolated yield, no other regioisomer is detected.

[3+2] cycloaddition reaction. Firstly, we tested this transformation by variation of alkynes 2 (Table 1). Several points are noteworthy from these results: (1) alkynes 2a and 2d are more efficient than alkyne 2e to give higher yields (Table 1, entries 1, 4 vs. 5), to our surprise, the reaction of more electron rich 1,2-bis(4-methoxyphenyl) ethyne 2g gives a slightly lower yield (Table 1, entry 7); (2) not only the terminal alkynes but also internal ones are compatible to give the desired products in good to excellent yields with excellent regioselectivity (the aryl group is always located at the 3-position of 2,5-dihydrofurans), for example, the internal alkynes with one alkyl substituent such as 2b, 2c and 2f with a convertible C-Cl bond are all applicable to this transformation, affording the desired 2.5-dihydrofurans with a tetrasubstituted alkene motif in excellent yields; (3) the reactive and synthetically useful cyclopropyl group is tolerant under the reaction conditions, furnishing dihydrofuran 3b in 92% yield; (4) to our delight, the alkynyl bromide is also compatible and 2,5dihydrofuran 3h can be isolated in 82% yield, which provides an opportunity for further modification by transition metal catalyzed cross-coupling reactions (Table 1, entry 8).

We next turned to examine the scope of this reaction by variation of oxirane components under optimized conditions and the results are summarized in Table 2. In general, various electron-donating and withdrawing groups can be introduced to the aryl moiety R and [3+2] cycloadducts were obtained in excellent yields (Table 2, entries 1-5). Halogen Br can be well incorporated into the phenyl group at 2, 3, or 4-position (entries 2–4). When the acceptor groups $(\mathbf{R}^1 \text{ and } \mathbf{R}^2)$ were switched to phenyl, the desired products **3n–3q** were furnished in 90-94% yields regardless of the electronic density of the aryl moiety (Table 2, entries 6-9). It is noteworthy that one of two acceptor groups can be replaced by an ester (1k, 1l); the reactions still proceed smoothly to give the desired products in good yields with good diastereoselectivities (Table 2, entries 10 and 11), the structure of the major isomer of 3s is confirmed by X-ray crystallography analysis (see ESI[†]). When both ketone groups are changed to ester groups (1m), there is a significant drop in the yield (Table 2, entry 12).

The scope of this Lewis acid promoted intermolecular [3+2] cycloaddition can be well extended to the intramolecular case. For example, tricyclic 2,3-fused 2,5-dihydrofurans 7 and 8 could be achieved from the corresponding substrates 5 and 6 in moderate yields under mild conditions. Again, the

 Table 2
 Variation of the oxirane components

R	$ \begin{array}{c} $	(5 mol %) DCE R	PMP COR ¹ COR ² 3
Entry	Oxirane 1 $R/R^1/R^2$	Time/h	Yield 3^{a} (%)
1	4-MeC ₆ H ₄ /Me/Me (1c)	3	3i (97)
2	4-BrC ₆ H ₄ /Me/Me (1d)	3	3j (98)
3 ^{<i>b</i>}	2-BrC ₆ H ₄ /Me/Me (1e)	12	3k (95)
4	$3-BrC_6H_4/Me/Me$ (1f)	3	3l (85)
5	$4 - FC_6 H_4 / Me / Me (1g)$	3	3j (98)
6	Ph/Ph/Ph (1b)	2	3n (93)
7	1-Naphthyl/Ph/Ph (1h)	2	3o (90)
8	$4-MeOC_6H_4/Ph/Ph$ (1i)	2	3p (94)
9	$4-BrC_6H_4/Ph/Ph$ (1j)	2	3q (94)
10^c	Ph/Me/OEt (1k)	4	3r (93)
11^{d}	Ph/Ph/OEt (11)	4	3s (85)
12	Ph/OMe/OMe (1m)	2	3t (53)

^{*a*} Unless otherwise specified, no other stereoisomer is detected. ^{*b*} 10 mol% of catalyst was used. ^{*c*} dr = 7:1, for major isomer: Ph is *syn* with COMe ^{*d*} dr = 4:1, for major isomer: R(Ph) is *syn* with COPh. PMP = 4-MeOPh.

cycloaddition reaction with electron-donating alkyne gives higher yield (eqn (1) and (2)).



In order to gain insight into the mechanism, enantioenriched **1b** was prepared according to the procedure developed by Lattanzi and Zhao *et al.*⁹ After running for 3 hours under the standard conditions, the reaction afforded a racemic cycloadduct **3m** (eqn (3)), which indicated that in the presence of Lewis acid, the substrate first undergoes C–C bond cleavage to give the zwitterionic intermediate, which would react with an alkyne to give the product. Attempts to asymmetric catalysis have also been undertaken; the preliminary result indicates that this reaction is amendable to enantioselective catalysis albeit the e has not been acceptable so far (eqn (4)).





Scheme 1 Synthetic applications.

Synthetic applications of 2,5-dihydrofurans **3** have been showcased by the representative compound **3a** (Scheme 1). Reduction of **3a** by Pd/C hydrogenation would afford the highly substituted tetrahydrofuran **9** in 95% yield with a moderate diasteroselectivity. Trisubstituted furan **10** could be obtained in high yields by the treatment of **3a** with DDQ (2,3-dichloro-5,6dicyanobenzoquinone) or air in the presence of Cs_2CO_3 in refluxing CH₃OH. Addition of **3a** to a solution of 1.5 equivalents of KOH in methanol afforded the 2,3-dihydrofuran **11** in 90% yield. Finally, in the presence of *m*-CPBA, **3a** could be oxidized to 2,5-dihydrofuranone **12** in 38% yield.

In summary, we have established an efficient [3+2] cycloaddition reaction of alkynes with an oxirane motif by Lewis acid catalyzed selective C–C bond cleavage to build up functionalized 2,5-dihydrofurans in high yields with excellent regioselectivities. Furthermore, the resulting 2,5-dihydrofuran can be easily converted to synthetically useful furans, 2,3-dihydrofuran, tetrahydrofuran, and 2,5-dihydrofuranone, in moderate to excellent yield. Further studies including asymmetric catalysis and expansion of the scope of dipolarophiles are ongoing in our laboratory and will be reported in due course.

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