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Lewis Acid Catalyzed Carbon−Carbon Bond Cleavage of Aryl Oxiranyl Diketones: Synthesis of *cis*-2,5-Disubstituted 1,3-Dioxolanes

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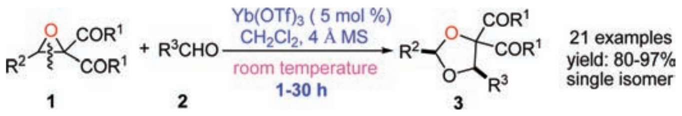
ABSTRACT



Carbonyl ylide is one of the most important intermediates which can undergo a series of 1,3-dipolar cycloaddition reactions. The C−C heterolysis of oxirane is believed to be the most atom-economic and straightforward way to generate carbonyl ylide. However, this chemistry was only achieved under photochemical and thermal conditions in past years. In this work, the one-step diastereoselective synthesis of *cis*-2,5-disubstituted 1,3-dioxolanes via [3 + 2] cycloadditions of aldehydes and carbonyl ylide, which is obtained from Lewis acid catalyzed C−C bond heterolysis of aryl oxiranyl diketones at ambient temperature, is described.

1,3-Dipolar cycloaddition reactions are known to be one of the most powerful tools for the synthesis of complex skeletons possessing five-membered heterocycles, since many 1,3-dipolar species are readily available and react with a wide range of dipolarophiles such as aldehydes, imines, electron-deficient alkenes, and alkynes.[1] The chemistry of carbonyl ylide as a reactive 1,3-dipole has been extensively reported; several methods for the generation of this dipole have been developed involving photochemical or thermal C−C bond heterolysis of oxiranes,[2] thermal decomposition of oxadiazolines,[3] 1,3-elimination reactions of trimethylsilyl substituted chloromethyl ethers,[4] SmI_2-mediated generation of nonstabilized carbonyl ylides from iodomethyl trialkylsilyl ethers,[5] thermal decomposition of organomercury compounds,[6] and a transition

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metal catalyzed diazo compound decomposition[7] in the presence of carbonyl compounds. Among these methods of generation of carbonyl ylide, it is obvious that the C−C bond heterolysis of the easily made oxiranes is the most atom-economical and straightforward one; however, the major drawback of this method is the harsh reaction conditions. On the other hand, the chemistry of oxiranes is dominated by the C−O bond heterolysis.[8] In this communication, we report a mild and efficient approach to carbonyl ylides by Lewis acid catalyzed C−C bond heterolysis of oxiranes. To the best of our knowledge, this is the first example of Lewis acid promoted C−C heterolysis of oxiranes.[9,10]

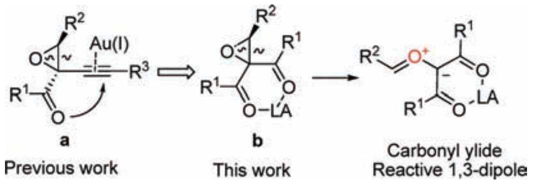
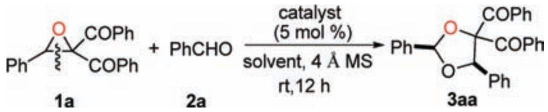


Figure 1. Novel strategies for cutting C−C bond of oxirane (a) from previous work and (b) this work.

Very recently, we developed a novel strategy to achieve the selective C−C bond cleavage of an oxirane motif by introduction of one alkyne moiety; the reaction is triggered by gold(I) activation of the alkyne moiety (Figure 1a).[11] During this study, we envisaged that the more common and easy to make substrates, oxiranyl diketones, may bind with certain Lewis acid and result in the C−C bond heterolysis.

We tested our hypothesis by using (3-phenyloxirane-2,2-diyl)bis(phenylmethanone) **1a** and benzaldehyde **2a** as model substrates. Initially, **1a** and **2a** were subjected to a solution of 5 mol % $\mathrm{Cu(OTf)_2}$ in $\mathrm{CH_2Cl_2}$ at room temperature. The reaction yielded the *cis*-1,3-dioxolane **3aa** in 30% yield with excellent diastereoselectivity, and 69% of starting material **1a** was recovered after running the reaction overnight (Table 1, entry 1). To improve the yield, a representative selection of Lewis acids including $\mathrm{Sn(OTf)_2}$, $\mathrm{Bi(OTf)_3}$, $\mathrm{Fe(OTf)_3}$, $\mathrm{Mg(OTf)_2}$, $\mathrm{In(OTf)_3}$, $\mathrm{Ni(ClO_4)_2 \cdot 6H_2O}$, $\mathrm{Sc(OTf)_3}$, $\mathrm{Y(OTf)_3}$, and $\mathrm{Yb(OTf)_3}$ in various solvents were tested (Table 1). Catalysts such as $\mathrm{Sn(OTf)_2}$, $\mathrm{Bi(OTf)_3}$, $\mathrm{Fe(OTf)_3}$, and $\mathrm{Mg(OTf)_2}$ result in either low efficiency or no catalytic activity (Table 1, entries 2−5). To our delight, the reaction works very well in $\mathrm{CH_2Cl_2}$, DCE, or toluene at room temperature by using 1.5 equiv of **2a** under the catalysis of 5 mol % of $\mathrm{Yb(OTf)_3}$ to give the cycloadducts **3aa** in 98% ^{1}H NMR yield as a single diastereomer (Table 1, entries 10−12).

Table 1. Screening Reaction Conditions of Benzaldehyde **2a** and Oxirane **1a**[a]



entry	catalyst	solvent	yield (%)[b]	dr
1	$\mathrm{Cu(OTf)_2}$	$\mathrm{CH_2Cl_2}$	30 (69)	100:0
2	$\mathrm{Sn(OTf)_2}$	$\mathrm{CH_2Cl_2}$	13 (81)	100:0
3	$\mathrm{Bi(OTf)_3}$	$\mathrm{CH_2Cl_2}$	9 (5)	100:0
4	$\mathrm{Fe(OTf)_3}$	$\mathrm{CH_2Cl_2}$	22	3.5:1
5	$\mathrm{Mg(OTf)_2}$	$\mathrm{CH_2Cl_2}$	0 (96)	−
6	$\mathrm{In(OTf)_3}$	$\mathrm{CH_2Cl_2}$	66	3.4:1
7	$\mathrm{Ni(ClO_4)_2 \cdot 6H_2O}$	$\mathrm{CH_2Cl_2}$	96	6.8:1
8	$\mathrm{Sc(OTf)_3}$	$\mathrm{CH_2Cl_2}$	89	16:1
9	$\mathrm{Y(OTf)_3}$	$\mathrm{CH_2Cl_2}$	97	100:0
10	$\mathrm{Yb(OTf)_3}$	$\mathrm{CH_2Cl_2}$	98	100:0
11	$\mathrm{Yb(OTf)_3}$	DCE	98	100:0
12	$\mathrm{Yb(OTf)_3}$	toluene	98	100:0

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), 5 mol % catalyst, and 60 mg of activated 4 Å MS in 3 mL of solvent at room temperature. [b] Determined by ^{1}H NMR ($\mathrm{CH_2Br_2}$ as a standard), and the number in parentheses refers to the recovered starting material **1a**.

With the optimal reaction conditions in hand, the scope of this Lewis acid catalyzed cycloaddition reaction was explored with a variety of oxiranes **1** and **2a**, and the results are summarized in Table 2. The cycloaddtion reaction of **2a** with oxiranes **1b** could give the corresponding 1,3-dioxolanes **3ba** in 88% yield (Table 2, entry 2). Donor−acceptor oxiranes bearing a 4-methoxy-phenyl substituent as the R^2 worked well to give the corresponding highly substituted 1,3-dioxolanes **3ca** in 94% yield (Table 2, entry 3). There was a significant drop in the rate of the reaction as the R^2 substituents became more electron

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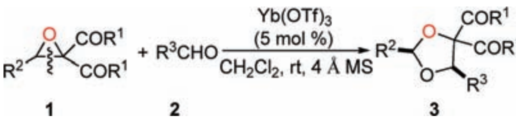
Table 2. Variation of Oxiranyl Diketone and Aldehyde Component



entry	R^1/R^2 (**1**)	R^3 (**2**)	t (h)	yield (%)[a]
1	Ph/Ph (**1a**)	Ph (**2a**)	2	**3aa** (90)
2	Ph/1-naphthyl (**1b**)	Ph (**2a**)	10	**3ba** (88)
3[b]	Ph/4-MeOC$_6$H$_4$ (**1c**)	Ph (**2a**)	10	**3ca** (94)
4[c]	Ph/4-BrC$_6$H$_4$ (**1d**)	Ph (**2a**)	26	**3da** (89)
5[d]	**1d**	4-MeOC$_6$H$_4$ (**2b**)	2	**3db** (93)
6[e]	Ph/4-MeO$_2$CC$_6$H$_4$ (**1e**)	Ph (**2a**)	30	**3ea** (89)
7	Me/Ph (**1f**)	Ph (**2a**)	2	**3fa** (87)
8[d]	**1f**	4-MeOC$_6$H$_4$ (**2b**)	1	**3fb** (88)
9	**1f**	4-MeC$_6$H$_4$ (**2c**)	2	**3fc** (96)
10	**1f**	4-BrC$_6$H$_4$ (**2d**)	1	**3fd** (82)

[a] Isolated yield and no any detectable other isomer. [b] The reaction was carried out at 0 °C. [c] 10 mol % Yb(OTf)$_3$ and 3.0 equiv of **2a** were used. [d] 1.5 equiv of oxirane and 1.0 equiv of **2b** were used. [e] 20 mol % Yb(OTf)$_3$ and 3.0 equiv of **2a** were used.

withdrawing as in entries 4 and 6 of Table 2. Higher catalyst loadings as well as longer reaction times were needed in these cases; however, under the optimized conditions these heterocycles could be obtained in excellent yields. When the acceptor group was switched to acetyl, the desired products **3fa**−**3fd** were also obtained in 82−96% yields regardless of the electronics of the aldehyde (Table 2, entries 7−10). The structure and the relative stereochemistry of the products were established by X-ray crystallography analysis of **3ba** and **3fb** (Figure 2).[12]

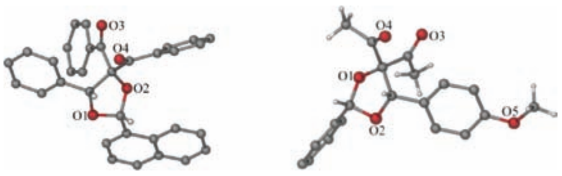
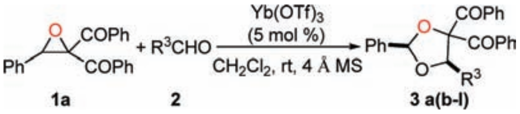


Figure 2. X-ray crystal structures of **3ba** (left) and **3fb** (right). The hydrogen atoms on the aryl ring are deleted for clarity.

Table 3. Reaction of **1a** with Various Aldehydes

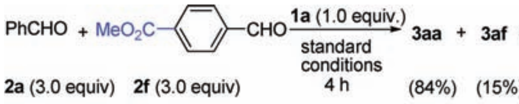


entry	R^3 (**2**)	t (h)	yield (%)[a]
1[b]	4-MeOPh (**2b**)	1	**3ab** (97)
2	4-MePh (**2c**)	2	**3ac** (90)
3	4-BrPh (**2d**)	2	**3ad** (94)
4	4-ClPh (**2e**)	2	**3ae** (91)
5	4-MeO$_2$CPh (**2f**)	16	**3af** (80)
6	3,4,5-(MeO)C$_6$H$_2$ (**2g**)	10	**3ag** (85)
7	2-furyl (**2h**)	4	**3ah** (90)
8	(*E*)-CH=CHPh (**2i**)	2	**3ai** (90)
9	Ethyl (**2j**)	10	**3aj** (91)
10	(Me)$_2$CHCH$_2$ (**2k**)	12	**3ak** (93)
11	Ph(CH$_2$)$_2$ (**2l**)	12	**3al** (96)

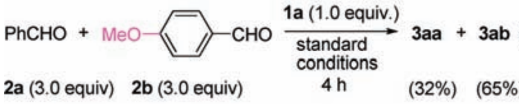
[a] Isolated yield and no other stereoismer is detectable. [b] Since the product **3ab** and aldehyde **2b** cannot be separable by TLC, 1.5 equiv of **1a** and 1.0 equiv of **2b** were used in order to achieve complete conversion of **2b**.

We next turned to study the scope of this reaction by variation of the aldehyde component (Table 3). The data in Table 3 showed that the reactions of aldehydes **2** bearing an electron-donating or electron-withdrawing group at the *para* position of the phenyl ring proceeded smoothly to provide the corresponding cycloadducts **3ab**−**3ag** in 80−97% yields (Table 3, entries 1−6). Furthermore, the furfural was also compatible with the reaction, giving the desired product **3ah** in 90% yield (Table 3, entry 7). Finally, introduction of alkenyl or alkyl substituents on the R^3 position were well tolerated, affording the corresponding cycloadducts **3ai**−**3aj** in 90−96% yields (Table 3, entries 8−11). It is also noteworthy that no other stereoisomer in all the reactions we carried out is detectable.

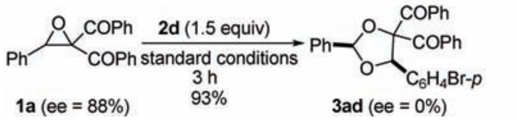
Competition experiments were performed using substituted benzaldehydes versus benzaldehyde to gain insight into this cycloaddition reaction. The treatment of oxirane **1a** with 3.0 equiv of benzaldehyde **2a** and 3.0 equiv of methyl 4-formylbenzoate **2f** under 5 mol % Yb(OTf)$_3$ gave the products **3aa** and **3af** in 84% and 15% ^{1}H NMR yield, respectively (eq 1). The control reaction of **1a** with benzaldehyde and electron-rich anisaldehyde **2b** gave a similar result (eq 2). These results indicate that the aldehyde component is involved in the rate-determining step.



(1)



(2)



(3)

According to these experimental results and previous reports for donor−acceptor cyclopropane[10] and oxiranyl ketone,[11] a plausible mechanism that accounts for these results is proposed in Scheme 1. Initially, the Lewis acid Yb(OTf)$_3$ binds to a bisketone moiety to give the

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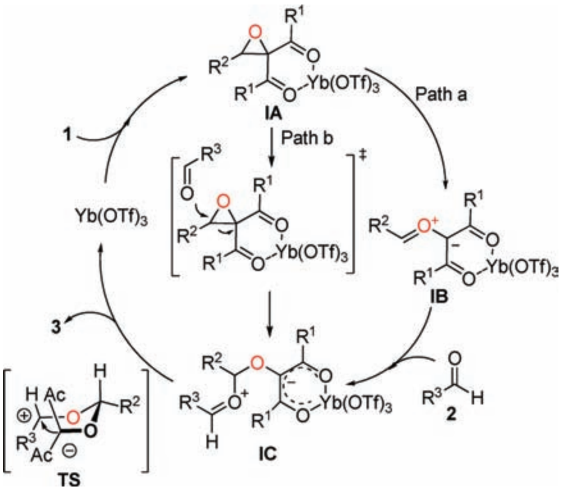
(12) The CCDC contains the supplementary crystallographic data (**3ba** and **3fb**) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

Scheme 1. Plausible Mechanism



intermediate **IA.** This binding would allow **IA** to easily undergo C−C bond cleavage via two possible reaction pathways (path **a**/**b**). The direct C−C heterolysis of **IA** would yield metal-coordinated carbonyl ylide **IB** (path **a**), which would readily react with aldehyde to give a zwitterionic intermediate **IC**. Subsquent ring closure via the favored conformation **TS** would afford the 1,3-dipolar cycloadducts and regenerate the catalyst. The alternative reaction pathway (path **b**) to generate **IC** from **IA** is via an unusual stereospecific intimate ion pair process wherein aldehyde acts as a nucleophile, causing inversion of the stereochemistry at the activated R^2 substituted carbon center of oxirane, which has been explored by Johnson in donor−acceptor cyclopropanes.[10i] Thus, the reaction of enantioenriched oxiranyl diketone would give an enantioenriched cycloadduct. In order to know which reaction pathway is the real one, enantioenriched **1a** was prepared according to Lattanzi's developed method.[13] After running for 3 h under standard conditions, the reaction afforded a racemic cycloadduct **3ad** (eq 3), indicating reaction path **a** may be the more possible reaction pathway and the rate-determining step of this reaction is the step of converting **IB** into **IC** wherein the nucleophilicity of the aldehyde plays a significant role.

In summary, we have established for the first time an efficient approach to carbonyl ylides by Lewis acid catalyzed chemoselective C−C bond heterolysis of readily available aryl oxiranyl diketones under mild conditions. Synthetically useful *cis*-1,3-disubstituted 1,3-dioxolanes with excellent diastereoselectivity can be afforded in excellent yields via the 1,3-dipolar cycloaddition of the resulting carbonyl ylides and various aldehydes. Further studies including asymmetric catalysis and expansion of the scope of dipolarophiles are ongoing in this laboratory and will be reported in due course.

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Supporting Information Available. Experimental details, characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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