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Lewis acid mediated diastereoselective and enantioselective cyclopropanation of Michael acceptors with sulfur ylides

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Abstract

The reaction of *N*-enoyloxazolidinones with diphenylsulfonium isoproylide in the presence of Lewis acids is explored. The diastereoselectivity of the reaction of *N*-enoyloxazolidinones **1a** and **1b** with diphenylsulfonium isopropylide could be mediated by the addition of some Lewis acids. The reaction of *N*-enoyloxazolidinone **4** with diphenylsulfonium isoproylide was also explored with chiral Lewis acids. When this reaction was run with bis(oxazoline) ligand **6** and a number of Lewis acids, product was obtained in as high as 95% ee. A loss of stereoselectivity was observed with less than stoichiometric amounts of Lewis acid. © 2000 Published by Elsevier Science Ltd.

The occurrence of the cyclopropane subunit in many natural and synthetic biologically active compounds, as well as its utility as a synthetic intermediate has prompted many strategies for its construction.[1] Among these, the vast majority of the methods developed for the synthesis of enantioenriched cyclopropanes use variants of two reactions: the Simmons–Smith cyclopropanation and the transition metal catalyzed cyclopropanation of alkenes with diazoacetates.[2,3] Interestingly, the use of sulfonium alkylidene transfer reagents for the synthesis of enantioenriched cyclopropanes has not until recently been studied even though this is well established chemistry.[4,5]

In connection with our program aimed at the development of mimics of the poly-L-proline type II (PPII) secondary structure, we sought to explore methodology for the synthesis of enantioenriched cyclopropanes.[6] Specifically we were intrigued with the possibility that Lewis acids could catalyze the diastereoselective and enantioselective cyclopropanation of Michael acceptors with sulfur ylides. The use of *N*-enoyloxazolidinones seemed an attractive starting point since high levels of diastereoselectivities and enantioselectivities have been obtained in Lewis acid catalyzed β-selective radical additions to this moiety.[7] High diastereoselectivity involves chelation control of the substrate to afford a dominant reactive rotamer in which one

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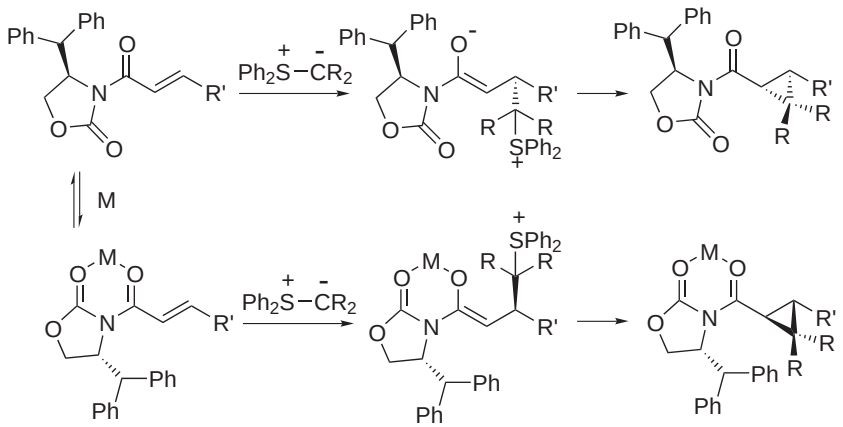
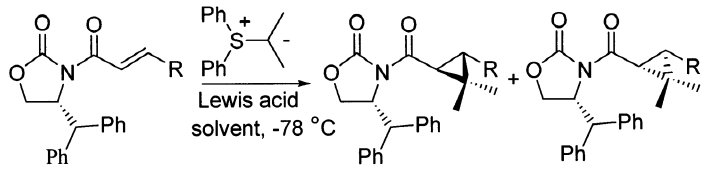
face of the β-carbon is shielded from attack. In an appropriate cyclopropanation substrate, Lewis acid mediated chelation control may not only populate a predominant rotamer it may also activate the β-carbon to attack by the sulfur ylide (Scheme 1). Activation of the β-carbon toward nucleophilic attack is expected since Lewis acid coordination of a Michael acceptor should lower the LUMO of the Michael acceptor.



Scheme 1.

Our investigations began by exploring the Lewis acid mediated diastereoselective cyclopropanation of oxazolidinones **1a** and **1b** which incorporate the chiral auxiliary reported by Sibi.[8] The results from these studies are summarised in Table 1. Reaction of diphenylsulfonium isopropylide with substrate **1a** in THF, at −78°C without a Lewis acid afforded a 1:2 mixture of diastereomeric cyclopropanes **2a** and **3a**.[9] The stereochemical assignment is based on X-ray crystal structure analysis of diastereomer **2a**. The modest selectivity is not surprising since under non-chelation control conditions, the minimization of the net dipole moment between the carbonyls places the stereodirecting group far from the enoyl β-carbon (Scheme 1). Interestingly, when the reaction was carried out with 2 equiv. $Yb(OTf)_3$ in THF the stereoselectivity of the reaction was reversed now affording a 4:1 mixture of cyclopropanes **2a** and **3a**. Decreasing the polarity of the solvent by using a mixed THF/CH_2Cl_2 solvent system further increased the stereoselectivity of the reaction affording a 9:1 mixture of **2a**/**3a**. Further decreasing the polarity of the solvent by using a THF/CH_2Cl_2/hexanes mixture resulted in a 10:1 ratio of **2a**/**3a**. We also carried out the reaction in Et_2O as it is a less coordinating solvent than THF, however, this reaction afforded a 3:1 mixture of **2a**/**3a**. It thus appears that a simple model of solvent competition for the Lewis acid does not entirely explain the observed solvent effects. Other lanthanide triflates also reversed the stereoselectivity of the reaction with yttrium triflate affording the next best selectivity (8:1 **2a**/**3a**). It is interesting to note that potential two point binding by Lewis acids does not preclude high diastereoselectivity, as evidenced by the low selectivity in the $TiCl_4$ and MgI_2 reactions. The cyclopropanation of cinnamoyl oxazolidinone **1b** exhibited similar trends to **1a** with $Yb(OTf)_3$ and $Y(OTf)_3$ also effecting the most pronounced reversals in diastereoselectivity.[10] The origin of the lower selectivity in the cinnamoyl series is rather puzzling considering that this series afforded the better selectivity in Sibi's work. It is clear, however, that this issue is more complex than a simple chelation controlled model would suggest. We also explored the effects of Lewis acid stoichiometry. When the cyclopropanation of **1a** with diphenylsulfonium isopropylide was run with 1 and 0.5 equiv. of $Yb(OTf)_3$, **2a**/**3a**

Table 1
Stereoselectivity of Lewis acid mediated cyclopropanation of *N*-enoyl oxazolidiones



1a; R = Me
1b; R = Ph

2a; R = Me
2b; R = Ph

3a; R = Me
3b; R = Ph

Entry	Substrate	Lewis acid	Equiv.	Solvent	% Yield[a]	Ratio (**2**/**3**)[b]
1	**1a**	None		CH_2Cl_2/THF	79	1:2
2	**1a**	$Yb(OTf)_3$	2	THF	81	4:1
3	**1a**	$Yb(OTf)_3$	2	CH_2Cl_2/THF	73	9:1
4	**1a**	$Yb(OTf)_3$	2	CH_2Cl_2/Hex/THF	84	10:1
5	**1a**	$Y(OTf)_3$	2	CH_2Cl_2/Hex/THF	87	8:1
6	**1a**	$La(OTf)_3$	2	CH_2Cl_2/Hex/THF	74	4.4:1
7	**1a**	$BF_3{\cdot}OEt_2$	2	CH_2Cl_2/Hex/THF	90	1:1.1
8	**1a**	$TiCl_4$	2	CH_2Cl_2/Hex/THF	91	1:1
9	**1a**	MgI_2	2	CH_2Cl_2/Hex/THF	79	1.8:1
10	**1a**	$Yb(OTf)_3$	2	Et_2O	69	3:1
11	**1a**	$Yb(OTf)_3$	1	CH_2Cl_2/Hex/THF	78	5:1
12	**1a**	$Yb(OTf)_3$	0.5	CH_2Cl_2/Hex/THF	81	2.5:1
13	**1b**	None		CH_2Cl_2/Hex/THF	75	1:2.4
14	**1b**	$Yb(OTf)_3$	2	CH_2Cl_2/Hex/THF	75	3.3:1
15	**1b**	$Y(OTf)_3$	2	CH_2Cl_2/Hex/THF	71	2.3:1

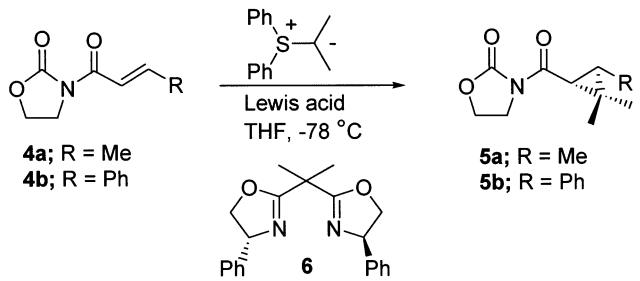
[a] Isolated yields.
[b] Diastereomer ratios were determined by integration of the NMR spectra.

were formed in 5:1 and 2.5:1 ratios, respectively. These results show that the selectivity of the reaction is dependent on the Lewis acid stoichiometry as there are notable changes in the product distribution when less than 2 equiv. $Yb(OTf)_3$ were used. However, the use of >2 equiv. $Yb(OTf)_3$ did not increase the **2a/3a** ratio.

The success which has been achieved in conjugate additions to *N*-enoyloxazolidinones catalyzed by Lewis acid–bis(oxazoline) complexes prompted us to investigate the Lewis acid promoted asymmetric cyclopropanation of Michael acceptors with diphenylsulfonium isopropylide. The results of the cyclopropanation of **4a** with 1 equiv. of Lewis acid–ligand **6** complex are summarised in Table 2. It is apparent that a number of Lewis acids afford the desired cyclopropane in good yields and excellent levels of enantioselection with $Zn(OTf)_2$, affording as high as 95% ee. In all instances, the *R*,*R*-bis(oxazoline) ligand gave rise to the *R*,*R*-cyclopropane. Assuming two point binding of the substrate, the sense of asymmetric induction is consistent with either a square-planar or octahedral coordination in the transition state. Interestingly, the asymmetric reaction of the cinnamate **4b** proceeded in low enantiomeric excess and appears to parallel the trend observed with the chiral auxiliary. The lower selectivity observed with the cinnamate series is unclear at this juncture. We have also investigated the reaction with substoichiometric quantities of Lewis acid. When the cyclopropanation of **4b** was

run with 0.75 and 0.5 equiv. of $Zn(OTf)_2$–ligand **6**, the product was obtained in 82 and 55% ee, respectively. The course of the reaction is thus dependent on Lewis acid stoichiometry. Nevertheless, we have shown the first examples of chiral Lewis acid-mediated asymmetric cyclopropanations of a Michael acceptor with a sulfur ylide and these can proceed with excellent enantioselectivities depending on the substrate.

Table 2
Effect of Lewis acid on enantioselectivity



Entry	Substrate	Lewis acid	Equiv.	% Yield[a]	% ee[b]
1	**4a**	$Zn(OTf)_2$	1	63	95
2	**4a**	$Mg(OTf)_2$	1	57	92
3	**4a**	$ZnBr_2$	1	60	93
4	**4a**	$ZnCl_2$	1	53	92
5	**4a**	$Sn(OTf)_2$	1	60	81
6	**4a**	MgI_2	1	66	46
7	**4a**	$Zn(OTf)_2$	0.75	65	82
8	**4a**	$Zn(OTf)_2$	0.5	63	55
9	**4b**	$Zn(OTf)_2$	1	69	36
10	**4b**	MgI_2	1	70	14

[a] Isolated yield.
[b] % ee was determined by GC using a Chirasil-Val column.

The question remains as to whether Lewis acids can catalyze the cyclopropanation of Michael acceptors with sulfur ylides. It is not possible to ascertain if there is a Lewis acid-induced rate acceleration because the fast rate of the reactions with and without a Lewis acid makes such a comparison impossible. However, the dependence of both diastereoselectivity and enantioselectivity on Lewis acid stoichiometry would seem to argue against Lewis acid catalysis.

Although this effect could be due to the fast rate of the 'uncatalyzed' reaction, we explored an alternative explanation: a salt effect. $LiBF_4$, which is present in the reaction mixture from the deprotonation of diphenylisopropylsulfonium tetrafluoroborate with *t*-BuLi, could compete with the Lewis acid for the Lewis basic sites on the substrate. Since the cyclopropanation reactions can require up to 5 equiv. of sulfur ylide to proceed to completion, there can be in essence 5 equiv. of $LiBF_4$ in the reaction medium. Accordingly, the effects of $LiBF_4$ were examined on the $Yb(OTf)_3$ mediated diastereoselective cyclopropanation of **1a**. The results are notable: when extra $LiBF_4$ (5 equiv.) was added to the reaction mixture, the diastereomer ratio dropped from 10:1 to 1:1.3 (**2a**/**3a**). This result shows that $LiBF_4$ has a negative effect on the

diastereoselectivity and suggests significant competition with Lewis acid at lower Lewis acid stoichiometries. With this information in hand, we are currently exploring ways to generate salt free ylide and slow the rate of the 'uncatalyzed' reaction in order to develop reactions which are catalytic in Lewis acid.

In conclusion, we report the first examples of Lewis acid mediated diastereoselective and enantioselective cyclopropanations of Michael acceptors with sulfur ylides. These results suggest a whole new reactivity not only for sulfur ylides, but also perhaps for other ylides, which will greatly expand the synthetic utility of these species.

Acknowledgements

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