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Communications

Diastereoselective Diels−Alder Reactions via Cyclic Vinyloxocarbenium Ions

Tarek Sammakia* and Martin A. Berliner

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

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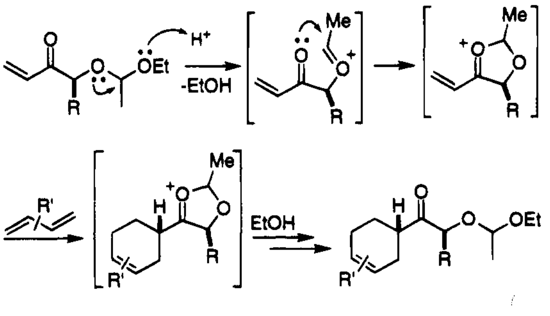
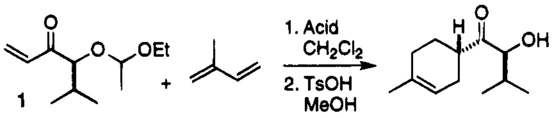
The ionic Diels−Alder reaction of α,β-unsaturated acetals developed by Gassman is a useful method for the synthesis of substituted cyclohexenes under mild conditions and in high yield.[1] We have reported a variation of this reaction using chiral acetals derived from 2,4-pentanediol which proceeds with good diastereoselection to provide enantiomerically-enriched cyclohexene carboxaldehyde derivatives upon hydrolysis of the acetal.[2] This reaction most likely proceeds by acid-catalyzed cleavage of the acetal to provide a chiral, acyclic vinyloxocarbenium ion which undergoes a diastereotopic face-selective Diels−Alder reaction. In this paper, we describe an extension of this method which proceeds by way of a cyclic oxocarbenium ion. This new method involves the generation of an acyclic oxocarbenium ion which is attacked by a proximal α,β-unsaturated carbonyl, producing a new, cyclic oxocarbenium ion bearing an activated olefin (eq 1).[3,4] We have examined this method on a series of α,β-unsaturated ketones bearing α′-hydroxy substituents that are protected as acetals, and we report herein our results which demonstrate that this is a viable strategy for effecting asymmetric Diels−Alder reactions.[5]



(1)

Our initial investigations focused on the efficacy of various acids in promoting this reaction (Table 1). We chose dienophile **1**[6] and isoprene as a typical set of reactants and examined the reaction in CH_2Cl_2[7] at the temperature and time indicated in Table 1. We found that the reaction proceeds using stoichiometric amounts of Me_2AlCl or catalytic amounts of $Sc(OTf)_3$[8] or HBF_4 (Table 1, entries 1−3). Of these, $Sc(OTf)_3$ provides lower diastereoselectivity (5:1) than Me_2AlCl (44:1) or HBF_4 (90:1). Extensive decomposition of the substrates is observed with $BF_3{\cdot}OEt_2$, and little or no reaction is observed in CH_2Cl_2 using catalytic amounts of Me_2AlCl or $Zn(OTf)_2$ or stoichiometric amounts of PPTS (Table 1, entries 4−7). The products of these reactions exist as a 1:1 mixture of diastereomers at the acetal carbon. To simplify the analysis of the products, the acetal was hydrolyzed by the addition of *p*-toluenesulfonic acid and methanol to the reaction mixture, and the corresponding alcohol was isolated.

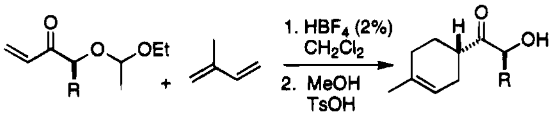
Table 1



Entry	Acid (equiv)	Temp (°C)	Time	Ratio	Yield (%)
1	$HBF_4{\cdot}OMe_2$ (0.02)	−45	10 h	90 : 1	70
2	Me_2AlCl (1.0)	−78	2 h	44 : 1	75
3	$Sc(OTf)_3$ (0.1)	−20	20 h	5.3 : 1	67
4	$BF_3{\cdot}OEt_2$ (0.10)[a]	−78	4 h	—	*b*
5	Me_2AlCl (0.25)	−78	2 h	—	0
6	PPTS (1.1)	rt	24 h	—	0[c]
7	$Zn(OTf)_2$ (0.1)	rt	24 h	—	0[c]

[a] All reactions were performed with 1 equiv of dienophile and 2 equiv of diene. (a) Reaction was conducted in toluene. (b) Extensive decomposition was observed. (c) Hydrolysis of the starting acetal was observed on workup.

Table 2[a]



Cmpd	R	Temp (°C)	Time	Ratio	Yield (%)
1	*i*-Pr	−45	10 h	90 : 1	70
2	*t*-Bu	−20	16 h	150 : 1	60
3	Me	−78	2 h	2.7 : 1	58
4	Ph	−20	16 h	3.0 : 1	70

[a] All reactions were performed with 1 equiv of dienophile and 2 equiv of diene.

We have examined a series of dienophiles in this reaction and have found that the diastereoselectivity is dependent on the size of the substituent on the α′-carbon (Table 2). Thus, while the HBF_4-catalyzed reaction of dienophiles **1** (R=*i*-Pr) and **2** (R = *t*-Bu)[9] with isoprene proceeds with high levels of asymmetric induction (90:1 and 150:1, respectively), dienophiles **3** (R = Me) and **4**

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(1) Gassmann, P. G.; Singleton, D.; Wilwerding, J. J.; Chavan, S. *J. Am. Chem. Soc.* **1987**, *109*, 2182. Gassmann, P. G.; Chavan, S. P. *J. Org. Chem.* **1988**, *53*, 2392. Gassmann, P. G.; Chavan, S. P. *Tetrahedron Lett.* **1988**, *29*, 3407. Gassmann, P. G.; Chavan, S. P. *J. Chem. Soc., Chem. Commun.* **1989**, 837.

(2) Sammakia, T.; Berliner, M. A. *J. Org. Chem.* **1994**, *23*, 6890.

(3) For a related method, see: Choy, W.; Reed, L. A.; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1137. Masamune, S.; Reed, L. A.; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441.

(4) For other examples of Diels−Alder reactions of vinyloxocarbenium ions, see: Hashimoto, Y.; Saigo, K.; Machida, S.; Hasegawa, M. *Tetrahedron Lett.* **1990**, *39*, 5625. Hashimoto, Y.; Nagashima, T.; Hasegawa, M.; Saigo, K. *Chem. Lett.* **1992**, 1353. Wipf, P.; Xu, W. *Tetrahedron* **1995**, *51*, 4551.

(5) For recent reviews on asymmetric Diels−Alder reactions, see: Oppolzer, W. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 352−379. Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

(6) This dienophile was prepared from L-valine. See supporting information for details.

(7) Comparable results were observed in toluene.

(8) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *23*, 3755.

(9) This dienophile was prepared from L-*tert*-leucine. See supporting information for details.

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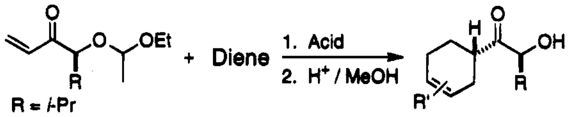
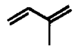
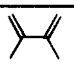
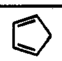
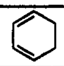
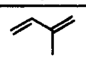
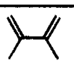
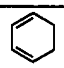
Table 3[a]



1 R = *i*-Pr
2 R = *tert*-Butyl

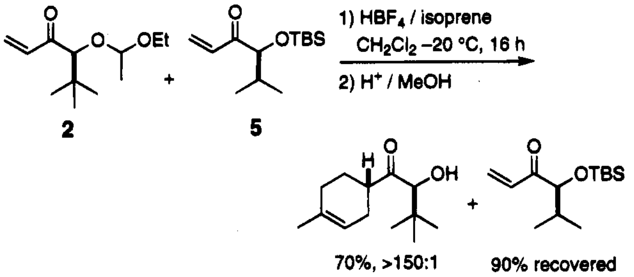
Entry	Cmpd	Diene	Solvent	Conditions	Ratio	Yield (%)
1	1		Toluene	A	98 : 1	72
2	1		CH_2Cl_2	A	90 : 1	70
3	1		Toluene	B	52 : 1	72
4	1		CH_2Cl_2	B	48 : 1	72
5	1		Toluene	C	1.4 : 1	72^e
6	1		CH_2Cl_2	D	2 : 1	70^e
7	1		Toluene	C	35 : 1	60^e
8	1		CH_2Cl_2	C	24 : 1	45^e
9	2		Toluene	B	200 : 1	72
10	2		CH_2Cl_2	B	150 : 1	60
11	2		Toluene	B	100 : 1	68
12	2		CH_2Cl_2	B	75 : 1	52
13	2		Toluene	C	50 : 1	68^e
14	2		CH_2Cl_2	C	20 : 1	58^e
15	2		CH_2Cl_2	D	5 : 1	—
16	2		Toluene	A	75 : 1	62^e
17	2		CH_2Cl_2	A	75 : 1	74^e

[a] All reactions were performed with 1 equiv of dienophile and 2 equiv of diene. Conditions: (A) $HBF_4 \cdot OMe_2$ (0.02 equiv), −45 °C, 10 h; (B) $HBF_4 \cdot OMe_2$ (0.02 equiv), −20 °C, 16 h; (C) Me_2AlCl (1.0 equiv), −78 °C, 2 h; (D) $HBF_4 \cdot OMe_2$ (0.02 equiv), −78 °C, 2 h. (E) Endo/exo ratio > 70:1.

(R = Ph) provide significantly lower levels (2.7:1 and 3:1, respectively). We have examined the use of other Lewis acids[10] with dienophiles **3** and **4** but have not been able to improve these ratios.

We have examined the reaction of dienophiles **1** and **2** with a representative series of dienes in CH_2Cl_2 or toluene (Table 3). In most cases, HBF_4 is the acid of choice, typically providing diastereomeric ratios ranging from 50:1 to 200:1. However, for reactive diene/dienophile combinations, lower selectivity is observed. This is most likely due to protonation of the carbonyl and reaction by a simple acid-catalyzed mechanism which does not involve the desired cyclic oxocarbenium ion. In these cases, better results are obtained with Me_2AlCl (Table 3, entries 7, 8, 13, and 14), although we were unable to obtain good levels of selectivity with cyclopentadiene and dienophile **1** under any conditions (Table 3, entries 5 and 6). Consequently, during the course of optimizing this reaction for a particular set of reactants, both solvent and Lewis acid combinations should be examined.

We speculate that the mechanism of the reaction is as shown in eq 1. This mechanism is supported by the observation that the acetal-protected dienophiles are much more reactive than the corresponding silyl-protected dienophiles. This is illustrated by the following competition experiment. When an equimolar mixture of dienophile **2** and dienophile **5**, in which the hydroxyl group is protected as a TBS ether, is treated with 2 equiv of isoprene under our standard reaction conditions, a 70% yield of the Diels−Alder adduct derived from **2** is isolated, while 90% of **5** is recovered unchanged (eq 2). Under



these conditions, we cannot detect any products derived from **5** in the crude reaction mixture. The stereochemistry of the products is as shown in eq 1,[11] consistent with approach of the diene from the less hindered face of the s-cis dienophile. We are uncertain of the origin of the lack of selectivity observed with dienophiles **3** and **4**. We suspect that it is due to a decrease in the face selectivity of the olefin; however, it could also be due to a decrease in the preference for the s-cis conformation.

In summary, we have developed a mild method for performing asymmetric Diels−Alder reactions which proceeds by way of a five-membered cyclic oxocarbenium ion. This method is related to that of Masamune in which an α,β-unsaturated ketone is constrained by hydrogen bonding or by Lewis acid complexation to an α' hydroxyl group.[3] The potential advantages of our method lie in the fact that the protecting group for the hydroxyl serves as the activating group and that cyclic vinyl oxocarbenium ions larger than five-membered rings should in principle be accessible, affording opportunities for remote asymmetric induction in the Diels−Alder reaction. We are currently pursuing studies along these lines.

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Supporting Information Available: Experimental details for preparation of dienophiles **1** and **2** and characterization of the Diels−Alder adducts (9 pages).

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[10] In addition to the acids mentioned in Table 1, we also examined the use of TMSOTf and various mixtures of $TiCl_4$ + $Ti(O\text{-}i\text{-}Pr)_4$. In these cases lower yields were observed with no improvement in selectivity.

[11] The stereochemistry was ascertained by correlation with authentic material prepared by the method of Evans (Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.). See supporting information for details.