Asymmetric Diels–Alder Reactions with α,β-Unsaturated Acetals

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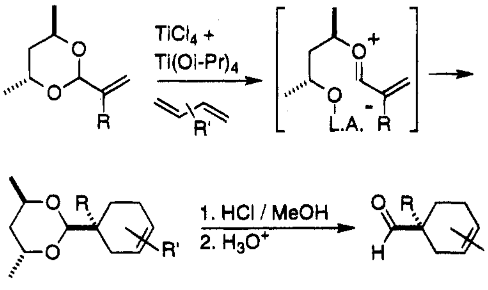
Summary: Chiral α,β–unsaturated acetals derived from 2,4–pentanediol are shown to undergo Lewis acid promoted Diels–Alder reactions with good diastereoselectivity.

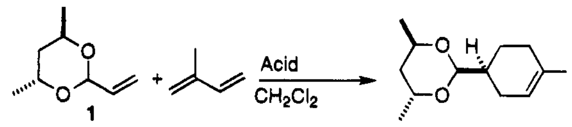
The ionic Diels–Alder reaction of α,β-unsaturated acetals developed by Gassman is a useful method for the synthesis of substituted cyclohexenes under mild conditions and in high yield.[1] We report herein a variation of this reaction using chiral acetals derived from 2,4-pentanediol which proceeds with good diastereoselection to provide enantiomerically enriched cyclohexene carboxaldehyde derivatives upon hydrolysis of the acetal (eq 1).[2]



(1)

Gassman's procedure utilizes protic acid to ionize and activate the acetal; however, we have found that this provides a 1:1 ratio of diastereomers in the reaction of isoprene and acetal **1**.[3] We therefore surveyed a variety of Lewis acids with these substrates and found that the diastereoselectivities can range from 7.5:1 to 1:1 (Table 1). In the cases where a 1:1 ratio is observed (entries 1–3), we established that the lack of selectivity is due to isomerization of the product via the corresponding ring-opened enol ether. Furthermore, in some of the cases we observe substantial amounts of byproducts which we assume to be derived from the polymerization of isoprene (entries 6, 8, and 10), while in others we observe low conversion to producs (entries 4, 9, and 11). Thus, in order to obtain optimal selectivity and yield, we require a Lewis acid of sufficient strength to promote the reaction, but not to decompose the starting materials or isomerize the products. We have found that Mukaiyama's mixed titanium Lewis acid, which consists of an equimolar mixture of TiCl$_4$ and Ti(O*i*-Pr)$_4$,[4] is superior to the others we have examined. Its advantages are due to the fact that it is very mild and that it can be used in greater than stoichiometric quantities without decomposition of the starting materials. It therefore provides products in good selectivities and yields under mild conditions.

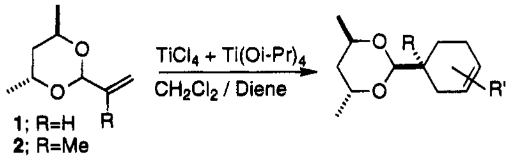
Table 1[a]



acid (equiv)	T (°C), time (h)	diastereo-selectivity
1 TfOH (0.01)	25, 12	1:1
2 TfOH (0.01)	−78, 6	1:1
3 TMSOTf (0.05)	−78 to 0, 4	1:1
4 TMSOTf (0.05)	−78, 4	6:1
5 TiCl$_4$ (0.10)	−78, 6	6.8:1
6 TiCl$_4$ (0.25)	−78, 3	6.0:1
7 TiCl$_4$(2) + Ti(O-iPr)$_4$(2)	**−78, 0.5**	**7.5:1**
8 TiCl$_3$(O-iPr) (0.1)	−78, 6	6.0:1
9 BF$_3$·OEt$_2$ (0.1)	−78, 4	5.5:1
10 EtAlCl$_2$ (0.1)	−78 to 25, 4	3:1
11 Me$_3$Al (1.0)	25, 12	(no reaction)

[a] All reactions were conducted with 1 equiv of acetal and with 2 equiv of diene.

Table 2[a]



	dienophile	
	1 de (yield, %)	**2** de (yield, %)
isoprene	7:1 (75)	15:1 (85)[b]
2,3-dimethylbutadiene	15:1 (95)	14:1 (70)[c]
cyclopentadiene	endo:exo = 8:1	endo:exo = 5:1
	de endo = 4:1	de endo = 5:1
	de exo = 3:1	de exo = 3:1
	(60%)	(54%)[d]
1,3-cyclohexadiene	endo:exo = 70:1	endo:exo = 11:1
	de endo = 6:1	de endo = 5:1
		de exo = 3:1
	(80%)	(60%)[d]

[a] Conditions: All reactions were conducted at −78 °C for 30 min with 1 equiv of acetal and 2 equiv of diene except as noted. [b] Reaction was allowed to warm to −45 °C and stir for 30 min. [c] Reaction was allowed to warm to room temperature and stir for 4 h. [d] Reaction was allowed to warm to room temperature and stir for 5 min.

We have examined the scope of this reaction and found it to display moderate to good diastereoselection in the

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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.

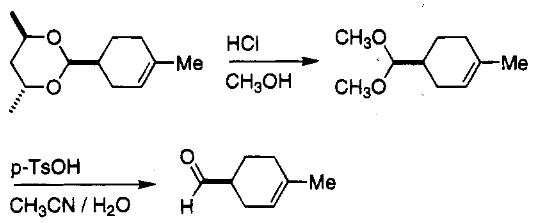
(2) There is an extensive literature on asymmetric Diels–Alder reactions. For leading references, see: Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991, Vol. 5, pp 352–379. Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. Pindur, U.;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

(3) Alexakis has reported a similar reaction catalyzed by triflic acid which proceeds with low de. See: Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.

(4) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817. Johnson and Denmark have found that a similar reagent, which consists of a 6:5 mixture of TiCl$_4$ and Ti(O-*i*-Pr)$_4$, is the Lewis acid of choice in alkylation reactions of chiral acetals. See: Johnson, W. S.; Crackett, P. H.; Elliot, J. D.; Jagodzinski, J. J.; Lindel, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951. Denmark, S. E.; Almstead, N. *J. Org. Chem.* **1991**, *56*, 6485.

0022-3263/94/1959-6890$04.50/0

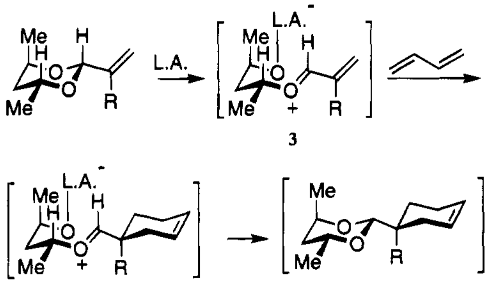
cases we have examined (Table 2). Reactions are run in CH_2Cl_2 by treatment of a mixture of acetal (1 equiv) and diene (2 equiv) with the Lewis acid at the temperature indicated in the table. Acyclic dienes display higher diastereoselectivites than cyclic dienes with the selectivities being between 3:1 and 15:1. Unfortunately, we have not been able to use Danishefsky's diene in this reaction.[5] Complex reaction mixtures with little or no desired product result. Hydrolysis of the dioxane acetal to the aldehyde proved difficult to effect in a single step without racemization, but is easily accomplished in two steps. Thus, conversion of the dioxane to the dimethyl acetal by treatment with anhydrous HCl in methanol (generated from $SOCl_2$ in methanol) followed by hydrolysis of the dimethyl acetal to the aldehyde in aqueous acidic acetonitrile[6] provides the desired aldehyde in good yields with no detectable racemization (eq 2). The stereochemistry of the products was determined by correlation with material prepared by the method of Evans.[7]



(2)

The mechanism of this reaction almost certainly involves an oxocarbenium ion generated from the acetal, which activates the olefin of the dienophile much as a Lewis acid complex of an α,β−unsaturated aldehyde (Scheme 1). The sense of asymmetric induction observed is consistent with compound **3** shown in Scheme 1 and is very similar to that proposed for the addition of nucleophiles to chiral acetals.[8] The relevant features of this structure are that the sp^3 carbon bound to the oxonium ion is cis to the smaller group (hydrogen), rather than the larger alkyl group, reminiscent of the preferred structure of Lewis acid complexes of aldehydes.[9] Also, the C−H bond of the carbon bound to the oxonium ion is eclipsed with C−O bond.[10] Finally, electrostatic attraction between the partial positive charge of the oxocarbenium oxygen and the negatively charged TiX_4 alkoxide holds the alkoxide in proximity to the C=O π-bond as a tight ion pair and effectively blocks one face of the molecule. Diels−Alder reaction from the s-trans conformation then provides the observed stereochemical outcome. We note that this reaction is an example of 1,4-asymmetric induction.

Scheme 1



In summary, we have discovered a useful variant of the ionic Diels−Alder reaction which proceeds in moderate to good diastereoselectivity under mild conditions. The reaction most likely occurs via an acyclic oxocarbenium ion intermediate. Further studies which utilize oxocarbenium ions in the Diels−Alder reaction are currently in progress.

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Supplementary Material Available: Experimental data (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(5) We have not examined any other oxygenated dienes.

(6) McGill, J. M. *Synthesis* **1993**, 1089.

(7) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(8) For recent mechanistic studies on chiral acetal addition reactions, see: Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089. Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458. Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998. Sammakia, T.; Smith, R. S. *J. Org. Chem.* **1992**, *57*, 2997. For an interesting study which probes the mechanism of acetal cleavage reactions in the absence of nucleophiles, see: Rychnovsky, S. D.; Kim. J. *Tetrahedron Lett.* **1991**, *32*, 7223.

(9) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew, Chem., Int. Ed. Engl.* **1990**, *29*, 256.

(10) Typically, the preferred conformation of sp^3−sp^2 bonds contains one of the ligands of the sp^3 atom eclipsing the π-bond. Recent calculations by Houk and co-workers indicate that this conformation is also an energy minimum in oxocarbenium ions. According to these calculations, the preference for the eclipsed conformation in oxocarbenium ions is on the order of about 1−2 kcal/mol depending on the substrate. See: Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006.