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Asymmetric Diels–Alder chemistry based on a new chiral auxiliary for 1-hydroxy substituted dienes

Philip Garner,* James T. Anderson and Regis A. Turske

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-7078, USA.
E-mail: ppg@po.cwru.edu

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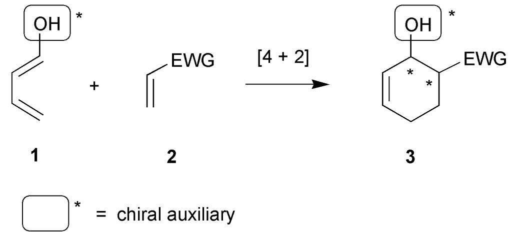
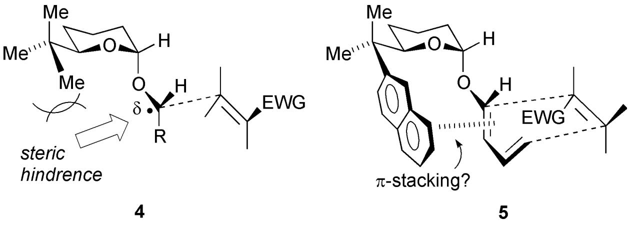
A rationally designed chiral auxiliary for hydroxylated dienes results in stereocontrolled Diels–Alder cycloadditions under purely thermal conditions.

The Diels–Alder reaction is arguably one of the most powerful synthetic transformations in the modern organic chemist's arsenal. The stereospecific creation of 2 sigma bonds and up to 4 stereocenters in a single step allows for an unsurpassed increase in the level of molecular complexity.[1] Not surprisingly, the development of asymmetric variants of the Diels–Alder reaction to yield enantiomerically-enriched products has taken center stage. Both stoichiometric (chiral auxiliaries) and catalytic (chiral Lewis acids) approaches to asymmetric Diels–Alder reactions have been investigated. The bulk of these investigations have been concerned with chiral auxiliary modified dienophiles[2] and the development of chiral (dienophile-activating) catalysts.[3] Fewer studies have dealt with chiral auxiliary modified dienes.[4] We now disclose a new THP based chiral auxiliary system for 1-hydroxylated dienes[5] that should be of general utility for a variety of thermal Diels–Alder reactions.



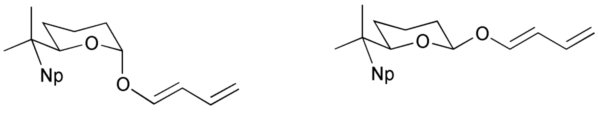
The germ for this idea came from earlier work in our laboratories which found that chiral acetaloxyalkyl radicals such as **4** were trapped preferentially on the *si*-face as a result of steric congestion by the *tert*-butyl substituent at C-6 (Fig. 1).[6] Diastereofacial bias in this TS was rationalized in terms of a radical conformation which maintained an *exo*-anomeric effect[7] and minimized steric repulsion between the acyclic side-chain and THP ring. We surmised that the same stereoelectronic control elements might be extended to the reactive *s-cis* conformation of a 1-oxygenated diene partner in a Diels–Alder reaction as well (*cf.* TS **5**). Our original design also incorporated a potential π-stacking interaction between the reactive *s-cis* diene and a properly disposed naphthalene moiety in the Diels–Alder TS. The prototype 'α-diene' **6** was synthesized along with the chromatographically separable 'β-diene' **7** from 2-naphthylisobutyraldehyde by first making the auxiliary-lactol according to ref. 6 and then incorporating it into McDougal's synthetic approach to 1-alkoxybuta-1,3-dienes.[8] α-Diene **6** was actually used as an inseparable 85:15 mixture of *E*- and *Z*-isomers, the latter being unreactive under our cycloaddition conditions.



4 **5**

Fig. 1

Chiral dienes **6** and **7** (Fig. 2) were subjected to a battery of Diels–Alder reactions with a variety of electron-deficient dienophiles (Table 1). A number of conclusions can be drawn from these collected data. First, thermal Diels–Alder reactions proceed cleanly with these chiral dienes to give good yields of cycloadducts. As expected for the 1-alkoxy-substituted diene system, higher reaction temperatures are required with the less reactive dienophiles. The observed diastereoselectivities for reactions of the α-diene with *N*-phenyl maleimide (**6** + **8** → **9**), dimethyl maleate (**6** + **11** → **12**), and methacryaldehyde (**6** + **13** → **14**) were found to be quite high (entries 1, 3, and 4) in spite of this potential limitation. Interestingly, reaction of the β-diene with *N*-phenyl maleimide (**7** + **8** → **10**) proceeded about 5 times faster than its α counterpart but with slightly lower (and opposite!)[9] facial selectivity (entry 2). Thus, complementary stereodirection is possible starting from a single antipodal form of the auxiliary. Increasing the Diels–Alder reactivity by reducing the FMO gap between the diene HOMO and dienophile LUMO had the predicted effect of enhancing the diastereoselectivity: diene **6** reacted with the reactive quinoid dienophiles **15**[10] and **17**[11] to give the respective adducts **16** and **18** almost exclusively (entries 5 and 6).[10] On the other hand, the combination of a less sterically encumbered acetylenic dienophile **19** and higher reaction temperatures resulted in a somewhat lower facial selectivity (entry 7).[12]



6 **7**

Np = 2-naphthyl

Fig. 2

Chiral dienes such as **6** offer the advantages of high and predictable facial selectivity without the need for Lewis acid activation along with the option of recovering the auxiliary while leaving the synthetically versatile cyclohexen-3-ol substructure intact. The ability to control the diastereoselectivity to the extent shown in purely thermal Diels–Alder reactions (some conducted at temperatures above 100 °C!) is quite remarkable. Although the goal of these initial studies was hypothesis validation, further optimization of the auxiliary design as well as an improved diene synthesis (*via* cross-coupling methodology as described in reference 5*g*) can certainly be envisioned. The incorporation of these chiral auxiliaries into more reactive dienes (for example, a Danishefsky-like system) is also possible. These preliminary results auger well for the further development of this asymmetric Diels–Alder variant as well as

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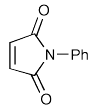
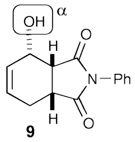
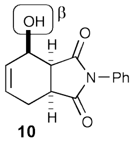
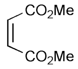
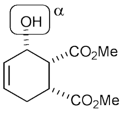
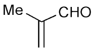
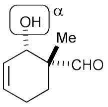
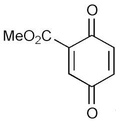
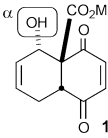
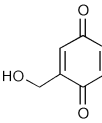
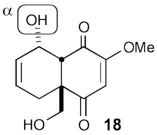
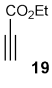
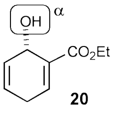
Table 1 Auxiliary-controlled Diels–Alder reactions

Entry	Diene	Dienophile (equiv.)	Reaction conditions	Major product	Yield (%)	Ds
1	**6**	 **8** (1.5)	PhH, 80 °C (sealed tube) 12 h	 **9**	76	9/1
2	**7**	**8** (1.5)	PhH, 80 °C (sealed tube) 2.5 h	 **10**	75	6/1
3	**6**	 **11** (3.0)	PhMe, 130 °C (sealed tube) 1 d	 **12**	72	9/1
4	**6**	 **13** (5.0)	PhMe, 115 °C (sealed tube) 3 d	 **14**	67	9/1
5	**6**	 **15** (0.4)	PhH, 0 °C → RT 1 h	 **16**	87	>20/1
6	**6**	 **17** (0.9)	MeOH reflux 14 h	 **18**	73	>19/1
7	**6**	 **19** (7.0)	PhH, 80 °C (sealed tube) 3 d	 **20**	86	4/1

the application of THP-based auxiliaries to other important synthetic transformations.

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Notes and references

1 For discussion of this point as well as some classic synthetic applications of the Diels–Alder reaction, see: E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, 1989.

2 G. Sarakinos and E. J. Corey, *Org. Lett.*, 1999, **1**, 1741, and references cited therein.

3 Examples of asymmetric Diels−Alder catalysis: (*a*) D. A. Evans, S. J. Miller, T. Lectka and P. von Matt, *J. Am. Chem. Soc.*, 1999, **121**, 7559; (*b*) A. K. Gosh and H. Matsuda, *Org. Lett.*, 1999, **1**, 2157.

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9 This selectivity reversal was ascertained by comparing the optical rotations of the corresponding alcohols derived from cycloadducts **9** and **10** by exposure to PPTS–MeOH. These conversions were very clean and, in both cases, the auxiliary was recovered in high yield as a mixture of anomeric methyl pyranosides. We note that the absolute sense of asymmetric induction with **7** is in accord with Stoodley's TS model for Diels–Alder additions to β-glucosylated dienes (reference 5*e*).

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11 Danishefsky and co-workers used this dienophile in a racemic approach to vernolepin: S. Danishefsky, P. Shida and K. J. Kato, *J. Org. Chem.*, 1976, **41**, 1081.

12 An analogous Diels–Alder reaction was used by Trost and co-workers in their recent synthesis of (±)-valienamine: B. M. Trost, L. S. Chupak and T. Lübbers, *J. Am. Chem. Soc.*, 1998, **120**, 1732.