Pergamon

Tetrahedron Letters, Vol. 35, No. 40, pp. 7311-7314, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01580-5

Role of Chiral Auxiliaries in the Type 2 Intramolecular Diels-Alder Reaction. Influence on Diastereoselectivity

Kenneth J Shea* and Donald R. Gauthier, Jr.
Department of Chemistry, University of California, Irvine, CA 92717-2025

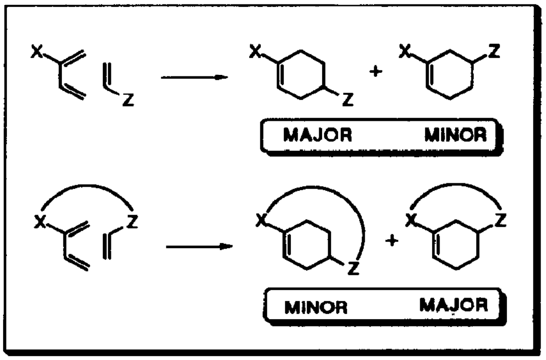
Abstract: *The incorporation of a chiral auxiliary as part of a disposable tether in the type 2 intramolecular Diels-Alder cycloaddition leads to a pair of diastereomers. Separation of the diastereomers and tether removal yields enantiomerically pure cyclohexanes and decalins.*

Considerable work is being devoted to controlling the enantiospecificity of the Diels-Alder cycloaddition. Many reports have appeared on the use of chiral Lewis acids, both catalytic and stoichiometric.[1] Chiral auxiliaries have also been used as a means of achieving asymmetry in the Diels-Alder reaction.[2]

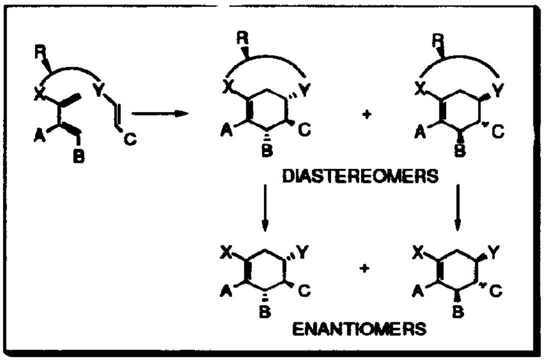
We have reported strategies for controlling both regio- and stereoselectivity in the type 2 intramolecular Diels-Alder reaction.[3,4] This methodology involves the temporary union of diene and dienophile with a "disposable" tether. The conformational constraints imposed by the tether in the type 2 reaction attains a predictable regiochemical outcome, and in some cases can reverse the normal regiochemical bias of the cycloaddition reaction (Scheme 1). For example, in situations where the normal mode for *inter*molecular cycloaddition gives preference to the "para" or 1,4-cycloadduct, the type 2 *intra*molecular reaction gives the "meta" or 1,3-cycloadduct. We have previously shown that a 5 atom tether results in complete "meta" regiochemical control while, in some cases, 6 and 7 atom tethers give mixtures of regioisomers.[4] Here we report efforts to control entantioselectivity through the incorporation of an asymmetric auxiliary on the disposable tether.

In the following examples, the introduction of asymmetry on the tether joining diene and dienophile leads to a pair of diastereomeric cycloadducts (Scheme 2). Separation of the diastereomers followed by tether/ chiral auxiliary removal leads to an ***enantiomerically pure*** cycloadduct with control of both regio- and diastereoselectivity.

Scheme 1



Scheme 2

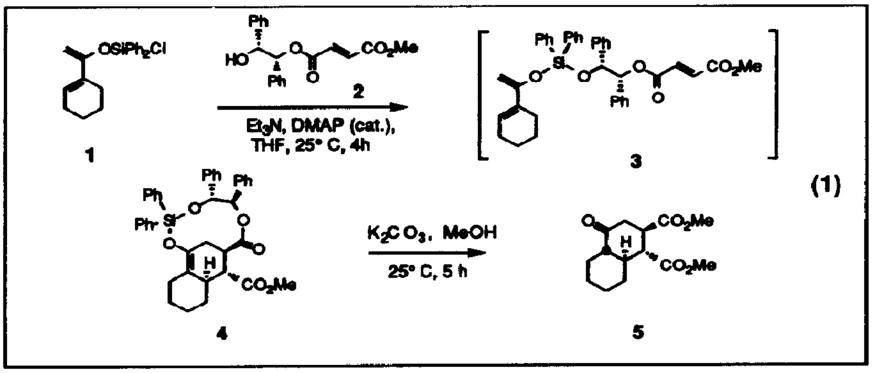


We have explored the use of both silyl acetal and silyl ether linkages in the tether. These systems contain 6 and 7 atom tethers respectively. Although complete regiochemical control was not possible in all cases using "disposable tethers" of this length, it offered the advantage of synthetic expediency since the chiral auxiliaries could readily be incorporated into the tether. In the present study, chiral diols were employed. Their availability made this approach particularly attractive.[5]

For our initial investigations, we chose a system that did not challenge the intrinsic regiochemical bias of the diene and dienophile. The silyl acetal Diels-Alder precursor (3) was prepared by coupling R,R-(+)-hydrobenzoinyl methyl fumarate (2)[6] with diphenylchlorosilyldienol ether (1) (Equation 1).[7] The Diels-Alder precursor spontaneously cyclized under the reaction conditions; DMAP (cat.), Et_3N, THF, 25 °C. NMR analysis and, in particular, integration of the tether methine signals, showed two products present in a 6:1 ratio.[8] The major isomer was isolated by radial chromatography in 62% yield. The structure of the cycloadduct and the absolute configuration of the new stereocenters were established by X-ray crystallography (Figure 1). Treatment of cycloadduct 4 with K_2CO_3 in MeOH afforded enantiomerically pure[9] ketodiester 5,[10] (-)-dimethyl-(5S, 10S)-*trans*-1-decalone-(3R,4R)-dicarboxylate in 90% yield (mp = 112 - 113 °C, $[\alpha]_D^{25} = -18.5°$, c = 1.15 in $CHCl_3$).

In a related strategy, 6 atom tethers incorporating vinyl silanes were prepared. For the preparation of the silyl ether Diels-Alder precursor (7), R,R-(+)-hydrobenzoinyl methyl fumarate (2) was coupled with 2-chlorodimethylsilyl-1,3-butadiene (6) (Equation 2).[11] Spontaneous cyclization of 7 led to a mixture of two major cycloadducts in a 3:1 ratio.[8] The major product was isolated by radial chromatography and recrystallized from hexane to give 8 in 50% yield. X-ray analysis confirmed the stereochemistry of the major diastereomer 8. Tether cleavage of cycloadduct 8 under oxidative conditions[12] gave optically pure[9] cyclohexanone 9, (-)-dimethyl-cyclohexanone-(3R, 4R)-dicarboxylate, in 60% yield ($[\alpha]_D^{25} = -22.5°$, c = 0.8 in $CHCl_3$).

In the previous examples, complete regio- and stereochemical control was achieved. Separation of the diastereomeric cycloadducts followed by removal of the tether provided enantiomerically pure products.



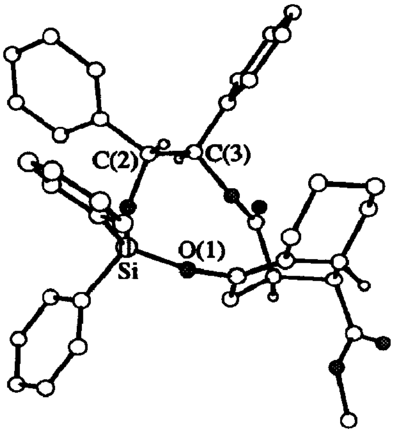
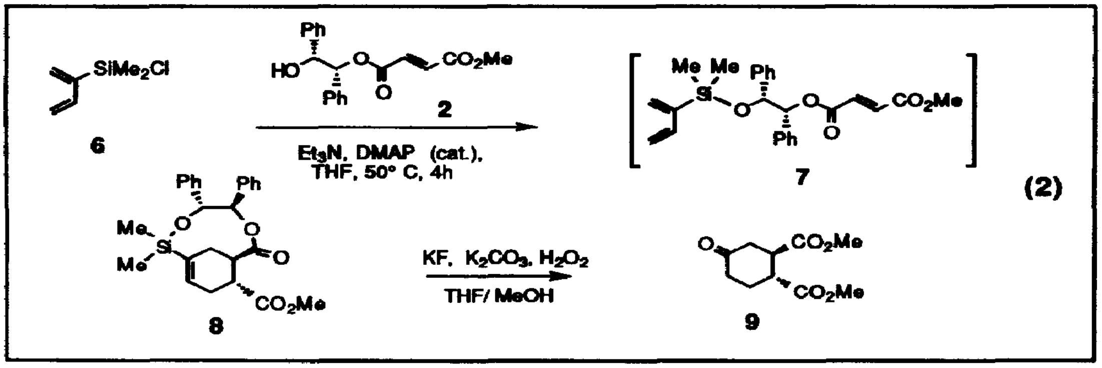
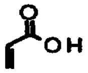
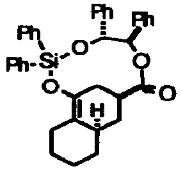
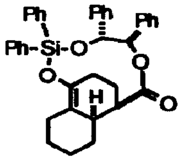
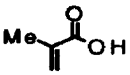
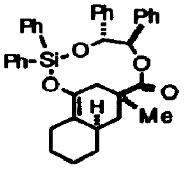
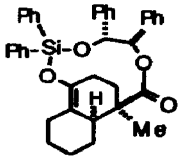
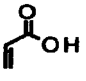
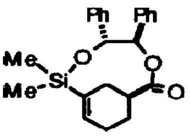
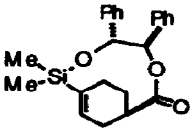
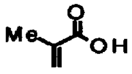
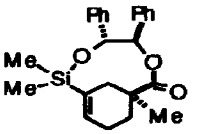
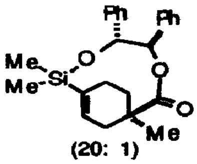


Figure 1. X-ray Structure of 4



(2)

Table 1

Dienophile	Cycloaddition Conditions[a]	Cycloadducts (diastereomeric ratios[b])		
(1) 	195° C, 9 h	 (7: 1)	+ 1: 1.5	 (7: 1)
(2) 	195° C, 7 h	 (20: 1)	+ 1: 1.6	 (20: 1)
(3) 	195° C, 9 h	 (10: 1)	+ 4: 1	 (10: 1)
(4) 	195° C, 7 h	 (20: 1)	+ 4.6: 1	 (20: 1)

[a] Cycloadditions were run in 0.1 M toluene solution at the indicated time and temperature.
[b] Only the major diastereomer of each regioisomer is drawn in each case.

We have also examined other dienophile substitution patterns which, as a result of tether size, were expected to give mixtures of regioisomers.[4] The cycloaddition reactions proceed smoothly at elevated temperatures in toluene. A summary of the results and conditions is given in Table 1. In all cases, cycloaddition led to the formation of four products. Although chromatographic separations were not successful, the diastereoselectivities, as determined by NMR, were as high as 20:1.[13] These findings suggest that a high degree of diastereoselectivity can be achieved in the type 2 intramolecular Diels-Alder cycloaddition by incorporation of a chiral auxiliary in the disposable tether. This methodology will enable synthesis of enantiomerically pure cyclohexane derivatives from readily available building blocks.

Acknowledgment: We are grateful to the National Institutes of Health for financial support of this work and to Dr. Joseph Ziller for assistance with the X-ray crystallographic work.

References and Notes

1. For recent reviews of Catalytic Asymmetric Diels-Alder Reactions see: (a) Kagan, H.B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007, (b) Mikami, K.; Motoyama, Y.; and Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812, and (c) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763.
2. For recent examples on the use of chiral auxiliaries in the asymmetric Diels-Alder reaction, and leading references, see: (a) Alsonso, I.; Carretero, J.C.; Garcia Ruano, J.L. *J. Org. Chem.* **1994**, *59*, 1499 (b) Oppolzer, W.; Seletsky, B.M.; Bernardinelli, G. *Tetrahedron Lett.* **1994**, *35*, 3509; (c) Gosselin, P.; Bonfand, E.; Hayes P.; Retoux, R. ; Maignan, C. *Tetrahedron Asymmetry* **1994**, *5*, 781; (d) Beaudegnies, R., Ghosez, L.*Tetrahedron Asymmetry* **1994**, *5*, 557; (e) Aversa, M.C.; Bonaccorsi, P.; Giannetto, P.; Jones, D.N.*Tetrahedron Asymmetry* **1994**, *5*, 805. For a review see: Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876. For an example of an asymmetric type 1 intramolecular D-A, see Craig, D.; Geach, N.J. *Tetrahedron Asymmetry* **1991**, *2*, 1177.
3. Shea, K.J.; Zandi, K.S.; Staab, A.J.; and Carr, R. *Tetrahedron Lett.* **1990**, *31*, 5885.
4. Shea, K.J.; Zandi, K.S.; and Staab, A.J. *Tetrahedron Lett.* **1991**, *32*, 2715.
5. Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K; Wang, Z.; Xu, D.; and Zhang, X. *J. Org. Chem.* **1992**, *57*, 2768.
6. R, R-(+)-Hydrobenzoinyl methyl fumarate (mp = 143 -144 °C, $[\alpha]_D^{25}$ = + 32.6°, c = 1.49 in $CHCl_3$) is prepared in 70 % yield by treatment of 1.2 equivalents of R, R-(+)-hydrobenzoin (>99.5 % ee[5]) in CH_2Cl_2 with fumaryl chloride and triethylamine.
7. Diphenylchlorosilyldienol ether is prepared by treatment of acylcyclohexenone with LDA at -78 °C followed by trapment of the enolate with diphenyldichlorosilane.
8. The tether methine peaks, a pair of doublets, show as the only signals in the 6.0 - 4.0 ppm NMR (500 MHz) region and allow for easy integration.
9. The optical purities are >99.5 % ee as determined by chiral column GC analysis (J and W Scientific, Cyclodex-B, 30 m x 0.251 mm). Retention times (170 °C, isothermal) for (+)-**3** and (-)-**3** are 63.7 and 65.7 min., respectively. Retention times (150 °C, isothermal) for (+)-**6** and (-)-**6** are 32.6 and 33.4 min., respectively.
10. Ketodiester **5**, isolated as a 20: 1 mixture of diastereomers favoring the trans decalone, was purified by recrystallization from CH_2Cl_2/ hexane. NMR analysis of the ester methyl signals at 3.8 - 3.6 ppm allowed for easy integration.
11. 2-Chlorodimethylsilylbutadiene is prepared by reaction of the Grignard reagent derived from chloroprene with dichlorodimethylsilane.
12. For related oxidative cleavage of vinyl silanes, see (a) Tamao, K.; Akita, M.; Kumada, M. *J. Organomet. Chem.* **1983**, *254*, 631. (b) Tamao, K.; Kumada, M.; Meada, K. *Tetrahedron Lett.* **1984**, *25*, 321. (c) Tamao, K.; Meada, K.; Yamaguchi, T.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4984.
13. All new compounds gave spectroscopic and analytical data consistent with their assigned structures. Regiochemical assignment of the cycloadduct was aided by correlation with product mixtures obtained from the corresponding bimolecular reactions.

(*Received in USA* 15 *June* 1994; *revised* 4 *August* 1994; *accepted* 8 *August* 1994)