Pergamon

Tetrahedron Letters, Vol. 38, No. 33, pp. 5755-5758, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01287-2

Enantioselective Diels-Alder Reactions Between Cyclopentadiene and α,β-Acetylenic Aldehydes Catalyzed by a Chiral Super Lewis Acid

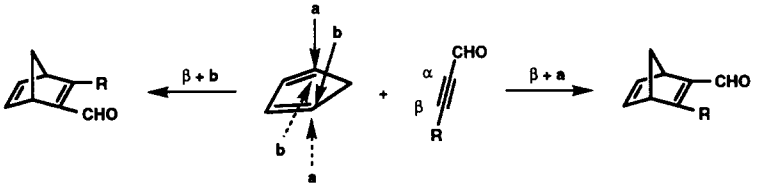
E. J. Corey* and Thomas W. Lee

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

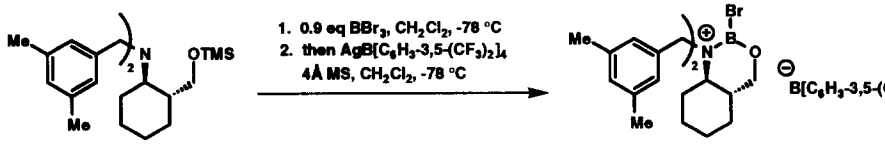
Abstract: *The first examples of catalytic enantioselective Diels-Alder reactions of cyclopentadiene and α,β-acetylenic aldehydes such as $Bu_3SnC{\equiv}CCHO$ are described.*

The normal Diels-Alder reaction of cyclopentadiene and an α,β-acetylenic aldehyde produces a racemic bicyclo[2.2.1]heptadiene carboxaldehyde since each enantiotopic face of C(1) or C(4) of the diene can couple with either the α- or β-carbon of the dienophile, as summarized in equation (1). It is not obvious from an examination of the two enantiomeric pathways shown in equation (1) that the reaction can be made enantioselective by the use of a chiral Lewis acidic catalyst. Indeed, there are no examples of this type of asymmetric catalytic Diels-Alder reaction in the literature, despite the many studies which have recently been reported in this area.[1] The first enantioselective Diels-Alder reactions according to equation (1) are described herein along with a proof of absolute stereochemistry and a rational mechanistic model. The chiral catalyst used in our work is the recently described super-reactive cationic Lewis acid **1**, prepared as shown in equation (2).[2] Catalyst **1** with the tetraarylborate counter ion was found to be more effective in this study than the precursor[2] having BBr_4^- (or Br^-) as the counterion.

Initial studies of the Diels-Alder reaction between cyclopentadiene (*ca.* 5 equiv) and 2-butyn-1-al or 2-octyn-1-al with 20 mole % of **1** as catalyst at -94 °C to -78 °C revealed only 3-5% conversion to product over a 24 h period. However, replacement of the β-alkyl substituent on the aldehyde component by R_3Si [3] or R_3Sn [4] groups resulted in much faster Diels-Alder addition. The results with these more reactive α,β-acetylenic aldehydes are summarized in Table 1. The greater yield with 3-tributylstannyl-2-propyn-1-al as compared to the 3-silyl analogs is the result of the higher reaction rate with the former. In each case good enantioselectivity (80-87% ee, 9 : 1 to 14 : 1 er) was obtained.[5] Somewhat lower enantioselectivities (71-75%) were observed with 2-



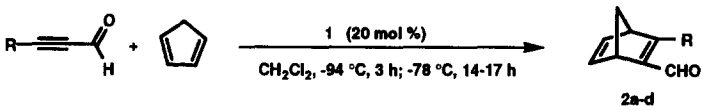
eq. (1)



eq. (2)

1

Table 1. Enantioselective alkyne-Diels-Alder reaction of cyclopentadiene with various α,β-acetylenic aldehydes in CH_2Cl_2 catalyzed by cationic Lewis acid **1**



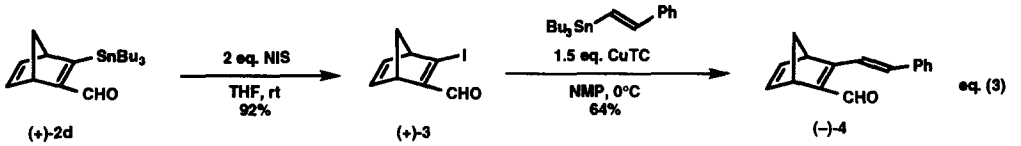
2a-d

R	Product	Yield[a] of 2 (%)	ee (%)[b] (config.)
TMS	2a	68	87 (*1R, 4S*)
TES	2b	37	85 (*1R, 4S*)
Me_2PhSi	2c	50	87 (*1R, 4S*)
Bu_3Sn	2d	83	80 (*1R, 4S*)

[a]Isolated yields of purified products. [b]Enantioselectivties were determined by reduction to the primary alcohol ($NaBH_4$ or $CeCl_3 \cdot 7H_2O$-$NaBH_4$), conversion to the (*R*)-MTPA ester and ^1H NMR (500 MHz) analysis.

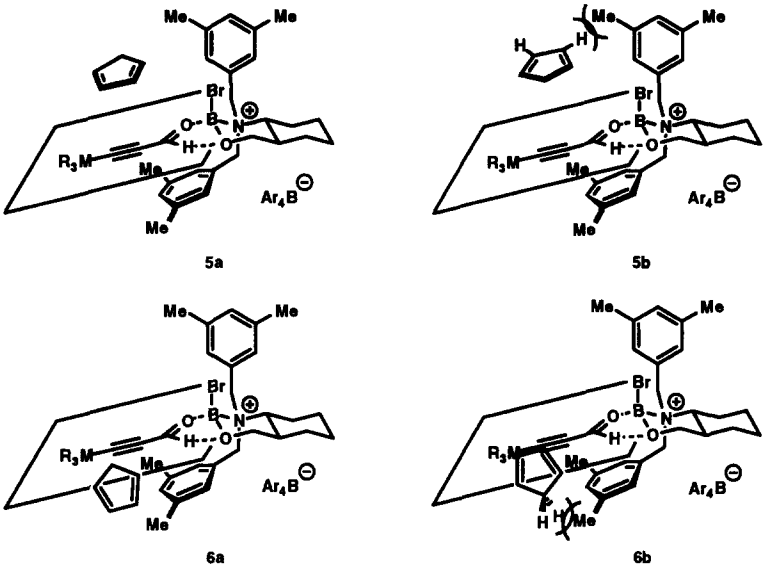
butyn-1-al or 2-octyn-1-al. The absolute configuration of the TMS adduct **2a** was determined by oxidation to the carboxylic acid, amide formation with (*S*)-α-methylbenzylamine, and X-ray crystallographic analysis.[6] In addition, adducts **2a**-**2d** were each converted by reduction and protonolysis to (–)-(1*S*,4*R*)-2-(hydroxymethyl)bicyclo[2.2.1]heptadiene.

The chiral Diels-Alder adduct **2d** (R=$SnBu_3$) is a versatile intermediate for the synthesis of many chiral bicyclo[2.2.1]heptadienes because the tri-*n*-butylstannyl group can be replaced by halogen or a wide variety of carbon appendages, the latter through the use of either copper-mediated or palladium-catalyzed cross coupling reactions. For example, as shown in equation (3), reaction of **2d** with *N*-iodosuccinimide produced the iodo aldehyde **3** in 92% yield. Coupling of **3** with (*E*)-β-styryltri-*n*-butylstannane and either 1.5 equiv of copper(I) 2-thiophenecarboxylate (CuTC) or catalytic $PdCl_2(CH_3CN)_2$ afforded the triene aldehyde **4**.[7]



(+)-2d (+)-3 (–)-4 eq. (3)

The absolute stereochemical course of the enantioselective Diels-Alder reactions summarized in Table 1 can be rationalized on the basis of the mechanistic model previously described for the reaction of α,β-enals and cyclopentadiene with **1** as catalyst in which a formyl CH--O hydrogen bond provides additional organization of the transition state.[2,8] Using that analysis there are two possibilities for approach of cyclopentadiene to the chiral Lewis-acid coordinated α,β-acetylenic aldehyde: (1) addition of the diene to the α,β-ynal π-orbital which is perpendicular to the formyl plane and (2) addition of the diene to the α,β-ynal π-orbital which is in plane with the formyl group, as represented by transition structures **5** and **6** respectively. In addition to **5a**, which is on the β+b pathway (equation (1)), there is a corresponding structure (**5b**) on the β+a pathway in which locations of the methylene and diene subunits of cyclopentadiene are switched. Stereochemical analysis of **5a** and **5b** shows that



the latter is destabilized relative to the former because of steric repulsion between carbons(2) and (3) of cyclopentadiene and the 3,5-dimethylbenzyl group which is equatorial on oxazaborinane ring. Structure **5a** which is predicted to be more stable than **5b** leads to the observed predominating enantiomer. Similar analysis of the alternative structures **6a** and **6b** leads to the prediction that **6a** should be more favorable sterically. Structure **6a** also correctly predicts the predominating stereochemical outcome. Thus, structures **5a** and **6a** are both reasonable possibilities for the preferred transition-state assemblies; a decision between them is not possible at this time, although it is clear that **5a** should be favored if (as seems likely) the reaction proceeds by an early transition state in which the β-carbon of the α,β-ynal is more strongly bonded than the α-carbon to the diene.[9]

References and Notes:

1. For example, see (a) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412. (b) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (c) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798. (d) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049. (e) Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611. (f) Corey, E. J.; Letavic, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 9616.
2. Hayashi, Y.; Rohde, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502.
3. All silylpropynals were prepared by analogy to a known two-step synthesis of 3-trimethylsilyl-2-propynal, see (a) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935. (b) Harris, N. J.; Gajewski, J. J. *J. Am. Chem. Soc.* **1994**, *116*, 6121.
4. Preparation of 3-tributylstannyl-2-propyn-1-al. To a solution of 3-tributylstannyl-2-propyn-1-ol (345 mg, 0.998 mmol) in 10 mL of CH_2Cl_2 at 0°C was added Dess-Martin periodinane (635 mg, 1.50 mmol) over the course of 1 min. After 5 min, the reaction mixture was stirred at room temperature for 30 min, quenched with $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic phases were washed with 10 mL

of half-saturated $NaHCO_3$ solution and 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated rapidly *in vacuo* to afford a colorless solid. Purification by rapid flash chromatography on silica gel (6 g) (gradient elution with 10-20% CH_2Cl_2-pentane) afforded 230 mg (67%) of (tributylstannyl)propynal as a pale yellow oil: R_f 0.21 (CH_3CN-H_2O 10:1, reverse phase Si•C_{18} TLC); FTIR (thin film) 2958, 2922, 2872, 2854, 2125, 1666; ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 1.57 (m, 6H), 1.33 (m, 6H), 1.09 (m, 6H, J_{SnH}=53 Hz), 0.90 (t, 9H, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 108.3, 106.8, 28.8 (J_{SnC}=24.2 Hz), 27.0 (J_{SnC}=60.3 Hz), 13.6, 11.4 (J_{117SnC}, J_{119SnC}=358, 374 Hz); HRMS (EF-CI) calcd for $[C_{15}H_{28}OSn]$ ($[M+NH_4]^+$): 362.1506; found 362.1503. It is crucial that an excess of silica gel not be used since this can lead to decomposition of the desired aldehyde. For this scale, c.a. 6 g of silica gel in a 1.5-cm diameter column was found to be appropriate. The progress of the chromatography was monitored by normal phase TLC (Hex-EtOAc 10:1, $KMnO_4$). The streaky higher R_f impurity can easily be distinguished from the desired product (baseline).

5. General procedure for the chiral super-Lewis acid **1** catalyzed alkyne Diels-Alder reaction. Preparation of Diels-Alder adduct **2d.** Chiral amino alcohol TMS ether (eq. 2) (43.1 mg, 0.096 mmol), was dried azeotropically with two 1-mL portions of benzene at 1 mmHg. It was then dissolved in 1.5 mL of CH_2Cl_2, cooled to -94 °C (hexane–liq. N_2 bath) and treated with a solution of BBr_3 (0.427 M in CH_2Cl_2, 201 μL, 0.086 mmol) (added slowly dropwise over 1 min). After 5 min, the resulting mixture was stirred at -78 °C (dry ice-acetone bath) for 1 h, and then added to a freshly prepared solution of $AgB[C_6H_3$-3,5-$(CF_3)_2]_4$ (83.5 mg, 0.086 mmol) in 1 mL of CH_2Cl_2 at -78 °C (followed by rinsing with three 0.5-mL portions of CH_2Cl_2 to ensure complete transfer of the crude catalyst). After 1 h at -78 °C, the catalyst solution was again cooled to -94 °C and 3-tributylstannyl-2-propyn-1-al[4] (0.362 M in CH_2Cl_2, 1.17 mL, 145 mg, 0.432 mmol) was added. A solution of cyclopentadiene (218 μL, 172 mg, 2.59 mmol) in 250 μL of CH_2Cl_2 was then added slowly dropwise down the side of the reaction vessel over 10 min and the reaction mixture was maintained at -94 °C for 3 h, warmed to -78 °C for 14 h, and then quenched with 200 μL of triethylamine. After warming to room temperature and removal of inorganic salts by filtration, the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient elution with 1-2% Et_2O-pentane) to give 143 mg (83%) of **2d** as a colorless oil of 80% ee: $[\alpha]_D^{23}$ +57.2 (*c* 2.45, $CHCl_3$); R_f 0.65 (Hex-EtOAc 10:1), 0.09 (CH_3CN-H_2O 10:1, reverse phase Si•C_{18} TLC); FTIR (thin film) 2957, 2929, 2871, 2853, 1665; ^1H NMR (500 MHz, $CDCl_3$) δ 9.61 (s, 1H), 6.79 (dd, 1H, *J*=3.2, 5.0 Hz), 6.56 (dd, 1H, *J*=3.2, 5.0 Hz), 4.07 (br s, 1H), 4.00 (br s, 1H), 2.04 (d, 1H, *J*=6.7 Hz), 1.93 (d, 1H, *J*=6.7 Hz), 1.47 (m, 6H), 1.29 (m, 6H), 1.05 (m, 6H, J_{SnH}=52 Hz), 0.87 (t, 9H, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 188.4, 168.4, 143.4, 140.8, 71.9 (J_{SnC}=14.1 Hz), 58.6 (J_{SnC}=23.9 Hz), 48.6 (J_{SnC}=27.2 Hz), 29.0 (J_{SnC}=21.2 Hz), 27.2 (J_{SnC}=57.4 Hz), 13.6, 10.6 (J_{117SnC}, J_{119SnC}=334, 349 Hz); HRMS (EF-CI) calcd for $[C_{20}H_{34}OSn]$ ($[M+H]^+$): 411.1710; found 411.1714.
6. The X-ray crystallographic analysis was carried out by Mr. Michael Grogan of this laboratory. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
7. (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (b) (–)-**5** can also be obtained by Pd-catalysis in 47% yield with 10 mol % $PdCl_2(CH_3CN)_2$ in DMF at room temperature.
8. See also Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Letters* **1997**, *38*, 1699.
9. This research was supported by grants from the National Science Foundation and the National Institutes of Health. T.W.L. is a Graduate Fellow of the National Science Foundation.

(*Received in USA* 22 *May* 1997; *revised* 16 *June* 1997; *accepted* 19 *June* 1997)