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Stereoselective Construction of Quaternary Carbons by the Reaction of Aldehydes with Allylic Chromium Reagents Prepared from 1,3-Diene Monoepoxides and $CrCl_2$

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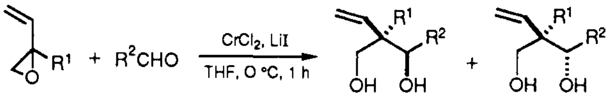
Summary: A vinyl-substituted β-hydroxy carbanion synthon is produced by reduction of 1,3-diene monoepoxide with $CrCl_2$ in the presence of LiI. The reagent reacts with aldehydes to afford R^*,R^* adducts stereoselectively.

Stereoselective formation of carbon–carbon bonds in acyclic systems has been extensively studied over the last 15 years and some remarkable progress has been made in this area.[1] One goal which has remained elusive is the stereoselective construction of quaternary carbons in acyclic chains.[2,3] One potential approach to the formation of quaternary carbons involves the reaction between a carbonyl compound and an allylic metal which is trisubstituted at one terminus of the allyl moiety.[2] Two requirements must be met in this approach. First, the allylic metal reagent should add to the carbonyl group at the more hindered trisubstituted carbon, selectively. Second, the configuration of the allylic double bonds must be fixed to one side, as this is an important factor in determining the relative stereochemistry of the carbonyl adduct when the reaction proceeds through a cyclic transition state.[4] Allylic chromium compounds satisfy the first requirement.[5] Recently, several reactions with allylic chromium reagents have been reported, wherein internal coordination of oxygen must play an important role in fixing the configuration of the allylic double bond.[6] Thus, we chose γ-metaloxymethyl-substituted allylic chromium reagents to use in this approach, since the configuration of the double bond could be fixed by the coordination of oxygen to chromium. The umpolung nature of chromium(II) made it possible to use 1,3-diene monoepoxides[7] as precursors to the γ-metaloxymethyl-substituted allylic chromium reagents. We disclose herein the diastereoselective construction of a quaternary carbon through the use of this reagent.

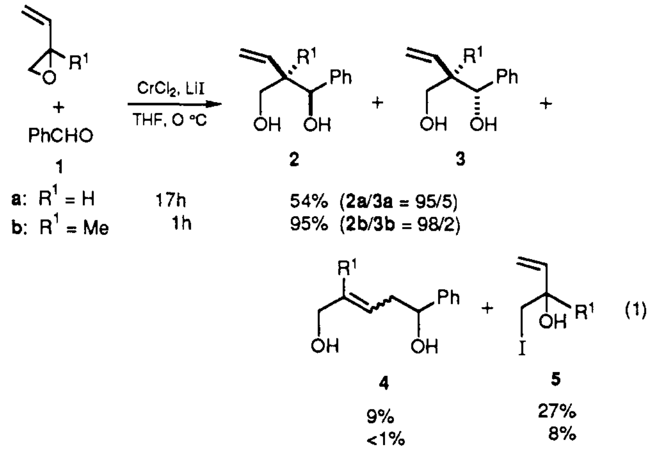
Table I. Reaction between 1,3-Diene Monoepoxides and Aldehydes by Means of $CrCl_2$ and LiI[a]



run	R^1	R^2	time, h	yield,[b] %	$(R^*,R^*)/(R^*,S^*)$[c]
1	Me	Ph	1	95	98/2
2		$PhCH_2CH_2$	1	97	96/4
3		$n-C_8H_{17}$	1	96	96/4
4		$c-C_6H_{11}$	1	98	97/3
5		PhCH=CH	1	95	90/10
6	$n-C_{11}H_{23}$	Ph	1	99	94/6
7		$n-C_8H_{17}$	1	93	92/8
8	H	Ph	17	54[d]	95/5[e]

[a] An aldehyde (1.0 equiv) was treated at 0 °C with a reagent prepared from 1,3-diene monoepoxide (2.0), $CrCl_2$ (4.0), and LiI (2.0). [b] Isolated yields. [c] The stereoisomers were identified by the transformation described in ref 14 or ^{13}C NMR analysis. The $(R^*,R^*)/(R^*,S^*)$ ratios were determined by ^1H NMR analysis. [d] See the text. [e] The major product is (R^*,S^*) because of the change in priority of the substituents.

Butadiene monoepoxide **1a** gave the desired 1,3-diol **2a** as the main product (eq 1), but the reaction rate was slower and the yield was lower than those run with isoprene monoepoxide **1b**. In the case of **1a**, the regioisomer **4a** was produced in 9% yield, in sharp contrast to the reaction of **1b**. The steric factor of the substituent R^1 controls the regiochemistry, and also suppresses the formation of the undesired byproduct, iodohydrin. 1-Iodo-3-buten-2-ol (**5a**) was produced in 27% yield in the case of butadiene monoepoxide (based on the starting monoepoxide **1a**), while **5b** was formed in only 8% yield starting from **1b**.



The reaction was accelerated by addition of LiI. Iodide anion adds to 1,3-diene monoepoxides to generate primarily γ-metaloxymethyl-substituted allylic iodides, which are smoothly reduced with chromium(II).[8] Significant

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[1] For reviews, see: (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (b) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press; Orlando, 1984; Vol. 3, p 111. (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

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[3] For recent works concerning construction of a quaternary carbon, see: (a) Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146. (b) Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663. (c) Zweifel, G.; Shoup, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 5578. (d) Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *Ibid.* **1989**, *111*, 3091. (e) Faunce, J. A.; Friebe, T. L.; Grisso, B. A.; Losey, E. N.; Sabat, M.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1989**, *111*, 4508.

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[5] (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1979**, *99*, 3179. (b) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. (c) Hiyama, T.; Kimura, K.; Nozaki, H. *Ibid.* **1981**, *22*, 1037.

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[8] The reaction was incomplete at 25 °C in the absence of LiI. Addition of LiI and NaI gave nearly the same yields and selectivities. Other additives such as MgI_2, Me_3SiI, Me_3SiCl, and $EtAlCl_2$ gave less satisfactory results.

0022-3263/90/1955-1705$02.50/0

increases in yields were observed when the period of hydrolytic workup with aqueous NaCl solution was prolonged.[9]

The results in Table I show excellent yields and high diastereoselectivities for the reaction.[10,11] In the case of an α,β-unsaturated aldehyde, the 1,2-addition product was produced, as with other organochromium reagents (run 5).[5,18] γ-Metaloxymethyl-substituted allylic chromium reagents can act as vinyl-substituted β-hydroxy carbanion synthons. Organometallic reagents bearing a metaloxy group vicinal to the metal are reported to undergo elimination smoothly to give olefins.[19] Indeed, 2-undecyl-1,3-butadiene was obtained in 19% and 15% yields (based on the epoxide) as a byproduct in the case of runs 6 and 7, respectively.

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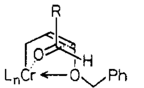
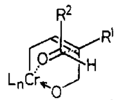
(9) The yield of the reaction between isoprene monoepoxide and benzaldehyde was 95% after hydrolysis at 25 °C for 14 h, while the following yields were obtained after shorter hydrolysis periods: 64% (15 min); 66% (1 h); 81% (7 h). These results suggest that hydrolytic fission of the O–CrL$_n$–O bond does not proceed smoothly under the reaction conditions.

(10) **Typical Procedure** (Table I, run 1). Tetrahydrofuran (THF, 12 mL) was added at 0 °C to $CrCl_2$ (0.49 g, 4.0 mmol) under an argon atmosphere, and the pale green suspension was stirred at 0 °C for 1 h. To the suspension was added successively at 0 °C a solution of isoprene oxide (0.17 g, 2.0 mmol) in THF (2 mL), LiI (1.0 M solution of THF, 2.0 mL), and a solution of benzaldehyde (0.11 g, 1.0 mmol) in THF (2 mL). After being stirred at 0 °C for 1 h, the mixture was poured into a mixture of saturated NaCl solution, water, and ether (1:1:1, 75 mL), and the whole mixture was stirred vigorously at 25 °C for 15 h. The organic layer was separated and the remainder was extracted with ether (4 × 10 mL). The combined ethereal extracts were dried over anhydrous $MgSO_4$ and concentrated. Purification by column chromatography (ethyl acetate–hexane, 1:2) gave 1-phenyl-2-methyl-2-vinyl-1,3-propanediol in 95% yield (0.18 g, $(R^*,R^*)/(R^*,S^*)$ = 98:2): bp 130 °C (bath temp, 0.3 Torr); IR (neat) 3318, 2964, 2922, 2876, 1638, 1454, 1022, 917, 728, 700 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (s, 3 H), 3.00–3.75 (bs, 2 H), 3.41 (d, J = 12 Hz, 1 H), 3.53 (d, J = 12 Hz, 1 H), 4.57 (s, 1 H), 4.90 (dd, J = 18, 1 Hz, 1 H), 5.10 (dd, J = 11, 1 Hz, 1 H), 5.93 (dd, J = 18, 11 Hz, 1 H), 7.13–7.33 (m, 5 H). Anal. Found: C, 74.68; H, 8.63. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39.

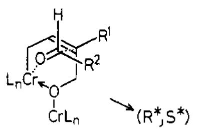
(11) We have encountered similar diastereoselectivity in the reaction of aldehydes with allylic chromium reagents derived from acrolein dialkyl acetals.[6a] In this reaction, internal coordination of the acetal oxygen to chromium should be important, and thus the boat-form six-membered transition state A was postulated. We are tempted to explain the high diastereoselectivity of the current reaction by a transition state analogous to that of A. That is, the boat-form six-membered transition state wherein internal coordination of oxygen to chromium creates another six-membered ring as shown in B and C. Because Lewis acids coordinate to the lone pair of the aldehyde oxygen at the less hindered side,[12] (i.e., the same side as hydrogen), transition state B leading to an R^*,R^* adduct is more favorable than C.



A

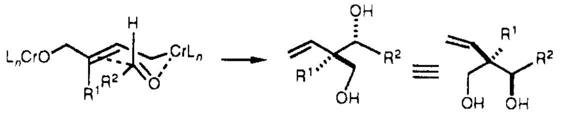


B



C

A referee has proposed the chair-like transition state D of nonchelated allylic chromium reagents to account for the observed diastereoselectivity.



D

(R^*, R^*)

Although it is difficult to ascertain the transition state, we are tempted to assume the chelated boat-form transition state because the coordination of heteroatoms frequently fixes the stereochemistry of allylic metals.[6,13]

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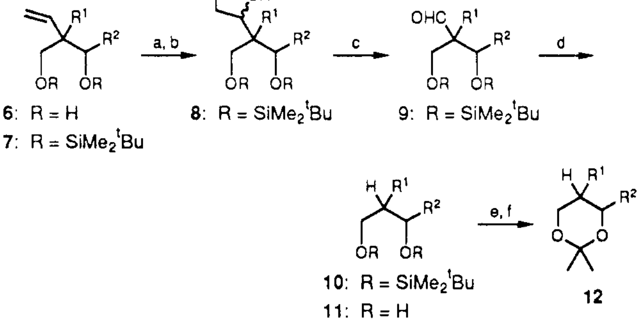
(14) The stereochemistry of the quaternary carbons was confirmed by ^{1}H NMR analyses of the degradation products **11**, which were obtained as shown below.



(a) (**6** → **7**): ^{t}BuMe$_2$SiCl, imidazole/DMF, 35 °C, 5–11 days (70–98%, 25% (R^1 = Me, R^2 = c-C_6H_{11})) or ^{t}BuMe$_2$SiOTf, 2,6-lutidine/CH_2Cl_2, 25 °C, 1 h (85%, R^1 = n-$C_{11}H_{23}$, R^2 = Ph);[15] (b) (**7** → **8**): OsO_4, $Me_3N^+O^-$, pyridine (57–90%);[16] (c) $NaIO_4$/THF, H_2O (79–96%); (d) RhCl(PPh_3)$_3$/PhCN, reflux (25–49%);[17] (e) (**10** → **11**): Bu$_4$NF/THF (88–93%); (f) (**11** → **12**): Me$_2$CO, cat. p-TsOH/PhH (83–93%).

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