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Acyclic Diastereocontrol and Asymmetric Transmission via Anionic Oxy-Cope Rearrangement: A Synthetic Application of Sequential [2,3]Wittig–Oxy-Cope Rearrangements

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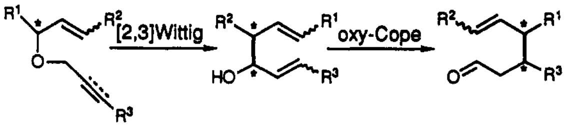
Summary: The anionic oxy-Cope rearrangements of acyclic 1,5-dien-3-ols with the 3,4-erythro configuration established by the [2,3]Wittig rearrangement are shown to provide a useful level of diastereoselection and asymmetric transmission in the context of a formal asymmetric synthesis of an insect pheromone.

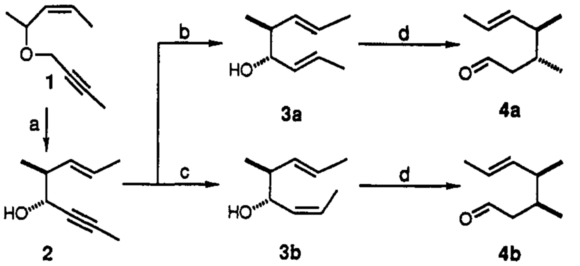
The anionic oxy-Cope rearrangement is widely utilized as a versatile class of bond reorganization in synthesis.[1] In the context of acyclic stereocontrol, however, the acyclic oxy-Cope methodology still occupies a much lower position than that of its Claisen counterpart,[2] although several oxy-Cope rearrangements of rigid, cyclic substrates have been reported to provide high levels of stereocontrol.[1,3] The key stereochemical issue inherent in the acyclic oxy-Cope process is associated with the oxyanion orientation (axial vs equatorial) in the chairlike transition states. Related studies[4] have shown that the oxyanion stereochemistry in acyclic systems cannot be effectively controlled unless other steric demand(s) such as favorable π-facial selectivity is imposed on the pericyclic array. We now disclose that the acyclic oxy-Cope rearrangement, when the proper substrate stereochemistry is generated by the [2,3]Wittig rearrangement,[5] provides a synthetically useful level of diastereoselection and asymmetric transmission (Scheme I).

At the outset, careful examination of our own transition-state model[4b] led us to postulate that if an alkyl substituent were added to the position adjacent to the hydroxyl-bearing carbon *in the erythro configuration*, the oxyanion substituent could be directed to the pseudoequatorial position in the associated transition states by virtue of the equatorial preference for the added alkyl group. To test this hypothesis, we first examined the diastereoselection in the anionic oxy-Cope process of the two geometrically isomeric erythro substrates **3a** and **3b**, which were prepared via the [2,3]Wittig rearrangement of **1**[5b] followed by trans and cis reduction of **2** (97% erythro, 99% *E*)[6] (Scheme II). We found that the standard anionic oxy-Cope rearrangement of **3a** (96% stereopurity)[6,7] and **3b** (92% stereopurity) afforded the erythro aldehyde **4a** with 94% de and 99% *E* and the threo aldehyde **4b** with 88% de and 97% *E*, respectively.[6,8] The % de's were determined by GC analysis after conversions to mixtures of the known cis and trans 3,4-dimethyloxanes.[9,10] The high levels of stereocontrol thus observed indicate that the [3,3]sigmatropy concerned proceeds almost exclusively through the chairlike transition state having both the oxyanion and the adjacent methyl group in the equatorial positions.

Scheme I

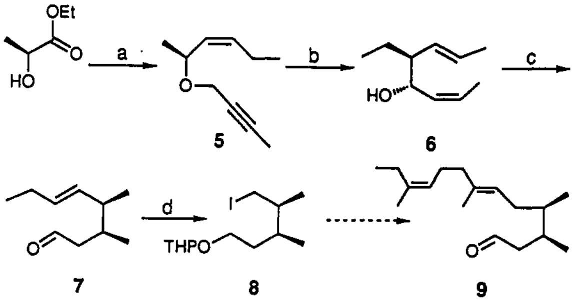


Scheme II[a]



[a] Key: (a) *n*-BuLi, –78 °C, 88%; (b) $LiAlH_4$, 91%; (c) H_2, P–2Ni, 82%; (d) KH, 18-crown-6, room temperature, 68–75%.

Scheme III[a]



[a] Key: (a) (1) $CH_3C{\equiv}CCH_2OC({=}NH)CCl_3$, H^+, 85%, (2) DIBAL, 82%, (3) *n*-$PrPPh_3Br$, *n*-BuLi, 98%; (b) (1) *n*-BuLi, –78 °C, 75%, (2) H_2, P–2Ni, 95%; (c) KH, 18-crown-6, room temperature, 75%; (d) (1) DIBAL, 93%, (2) DHP, H^+, 95%, (3) OsO_4, $NaIO_4$, then $NaBH_4$, 50%, (4) I_2, PPh_3, imidazole, 70%.

Next, we examined the sense and degree of asymmetric transmission via the anionic oxy-Cope process within the context of the asymmetric synthesis of iodo ether **8**, a key intermediate in a total synthesis of (+)-faranal (**9**), a trail pheromone of the Pharaoh's ant[11] (Scheme III).

Our synthesis of **8** began with the preparation of the optically pure [2,3]Wittig substrate **5**[12] from (*S*)-ethyl

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[6] Determined by capillary GC and ^{13}C NMR analysis.

[7] The "stereopurity" refers to the percent of the major stereoisomer among all possible isomers.

[8] The ^{13}C NMR (50 MHz, $CDCl_3$) peaks for the three methyls are δ 17.94, 17.44, 17.39 for **4a** and δ 18.02, 17.43, 16.41 for **4b**.

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lactate. The [2,3]Wittig process of **5** followed by cis hydrogenation gave oxy-Cope substrate **6**[12] in >96% ee (Mosher's assay) along with 100% *E* and *Z* and >99% erythro.[6] The oxy-Cope process of **6** afforded the erythro aldehyde **7**[13] essentially as a single product in 91% ee, which was then converted to **8**[10,14] as well as the known (3*S*,4*S*)-3,4-dimethyl-5-pentanolide:[10,15] $[\alpha]^{26}_{\mathrm{D}}$ −45° (*c* 1.0, MeOH); lit. $[\alpha]^{22}_{\mathrm{D}}$ −47°. The % ee of **7** was determined by HPLC analysis of the amide prepared via reaction of the preceding lactone and (*R*)-α-naphthylethylamine.[15] The most striking observation in these asymmetric oxy-Cope rearrangements is that both the absolute and relative stereochemistry of the substrate are specifically transmitted to the two new chiral centers in the product via transfer of the chiralities along the pericyclic array.

In summary, this work has convincingly demonstrated that the acyclic oxy-Cope technology, when property designed in terms of the substrate stereochemistry, provides a new, efficient method for acyclic stereocontrol. Further application of the oxy-Cope method is in progress.

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Supplementary Material Available: Experimental procedures and spectroscopic data for compounds **1–8**, for intermediates in Scheme III and for (3*R**,4*S**)-, (3*S**,4*S**)-, and (3*S*,4*S*)-3,4-dimethylpentanolides and ^{1}H and ^{13}C NMR spectra of compounds **2**, **4a**, **4b**, **5–7**, and (4*R*,5*S*,6*E*)-5-ethyl-6-octen-2-yn-4-ol (**13**) (26 pages). Ordering information is given on any current masthead page.

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[12] The spectral data are in accord with the assigned structure. The purities of **5** and **6** were determined by ^{1}H NMR, ^{13}C NMR, and capillary GC analyses (supplementary material).

[13] ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.70–9.85 (m, 1 H), 5.15–5.55 (m, 2 H), 2.30–2.60 (m, 1 H), 1.80–2.30 (m, 5 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.97 (t, J = 7.5 Hz, 3 H), 0.90 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.26, 132.66, 131.39, 48.65, 41.02, 33.05, 25.69, 17.48, 16.42, 14.03; IR (neat) 1727, 973 cm^{-1}; HRMS found *m/z* 154.1243, calcd for $C_{10}H_{18}O$ 154.1358.

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Preparation and Reactions of Zinc and Copper Organometallics Bearing Acidic Hydrogens

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Summary: Organozinc and copper reagents bearing unprotected primary or secondary amines or amides or a terminal acetylenic proton were prepared and reacted with various electrophiles in good yields.

Organometallics RM (M = Li, MgX) react rapidly with acidic hydrogens, and therefore the reaction of molecules containing primary or secondary amines, amides, thiols, or alcohols with polar organometallic compounds generally requires either the protection of these functionalities or the use of excess organometallic reagent which will first abstract the acidic hydrogen.[1] Since organozinc and organocopper compounds contain a carbon–metal bond having a low ionic character (ca. 15%),[2] it may be expected that these reagents will tolerate the presence of acidic hydrogens in the reaction media. Primary amines such as *N*-ethylamine are known to react at low temperatures with $Me_2Zn(THF)_2$ affording complexes such as $Me_2Zn(H_2N\text{–}Et)_2$.[3] These complexes decompose at higher temperatures (T >−30 °C) to give zinc amides ($(EtNH)_2Zn$). Complexes of secondary amines with $Me_2Zn(THF)_2$ were found to be substantially more stable.[3] Recently, the preparation of an alkylzinc halide bearing a NH–Boc group was reported,[4] although no information concerning the integrity of the N–H bond in this reagent was given.

Herein, we wish to report our preliminary studies showing that organozinc iodides (RZnI) can be prepared in good yields in the presence of a variety of relatively acidic hydrogens (pK_a = 18–35). Subsequent transmetalation with the THF soluble copper salt CuCN·2LiCl[5] provided the copper reagents RCu(CN)ZnI which reacted efficiently with a variety of organic electrophiles.[5,6] In order to determine the types of acidic hydrogen-bearing compounds (A–H) which are compatible with a carbon–zinc bond, a THF solution of an organic iodide (RI) and a compound (A–H) bearing an acidic hydrogen (ca. 1 M solution) was added to zinc dust, at 25 °C in the case of a primary iodide (*n*-butyl iodide) and at 5 °C in the case of a secondary iodide (cyclohexyl iodide). The reactions were performed in the presence of an internal standard (*n*-decane) and the formation of the organozinc iodide was monitored by GLC analysis of both hydrolyzed and iodolized reaction aliquots[7] (eq 1 and Table I). Primary and

$$\mathrm{R{-}I} + \mathrm{A{-}H} \xrightarrow{\mathrm{Zn,\ THF}} \mathrm{R{-}ZnI} + \mathrm{A{-}H} \tag{1}$$

secondary amines were found to be perfectly compatible with organozinc iodides and less than 5% of deprotonation was observed (entries 1–5). The presence of a primary or secondary amine (except the hindered diisopropylamine)

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[7] The yield of organozinc compounds was obtained by performing first a hydrolysis of a reaction aliquot giving the percentage of unreacted iodide and then an iodolysis giving the total percentage of iodide.

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