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COORDINATIVELY INDUCED 1,4-DIASTEREOSELECTION IN THE REACTION OF ACYCLIC α,β-ENONES WITH ORGANOCOPPER REAGENTS. A NEW TYPE OF ORGANOCOPPER REAGENT

E. J. Corey,[a] Francis J. Hannon,[a] and Neil W. Boaz[a,b]

(a) Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138
(b) Corporate Research Laboratory, Eastman Kodak Company, Rochester, NY, 14650

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Abstract. A test has been made of a stereochemical prediction for conjugate addition based on the intermediacy of d,π*-complexes in the reaction of organocopper reagents with α,β-enones. The chiral α,β-enone **7** has been synthesized and subjected to reaction with various methyl cuprate reagents. Under conditions favorable to lithium chelation to the α-alkoxycarbonyl system of **7**, conjugate addition to **7** was found to proceed with high (13 : 1 to 33 : 1) 1,4-diastereoselectivity, the configuration of the major diastereomer being that predicted by the d,π*-complex model. A new and especially diastereoselective reagent has been generated by the reaction of $LiCuMe_2$ with 0.3 equivalent of water, a possible structure for which is presented.

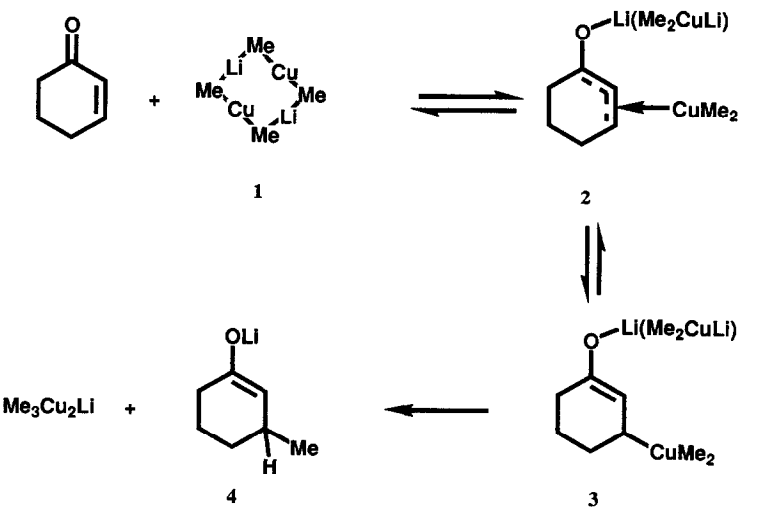
INTRODUCTION

The conjugate addition of organocopper compounds (Gilman reagents) to α,β-enones, originally observed by Kharasch,[1] is now a major tool in chemical synthesis.[2] Interest in the reaction has recently extended in the direction of stereoselectivity and the related subject of reaction mechanism. Such studies are complimentary since mechanistic hypotheses facilitate the application of organocopper reagents to stereoselective synthesis and, conversely, the observation of stereoselective effects provides helpful information with regard to reaction mechanisms. However, it must be emphasized that much of the mechanistic discussion of the enone-cuprate reaction is tentative since definitive experimental proof of mechanism is still lacking.

It is clear that the enone-cuprate conjugate addition requires initial coordination of the enone carbonyl with lithium or magnesium ion,[3-5] probably within the cuprate reagent itself.[6,7] The next step is still open to debate and may depend on the nature of the enone substrate (especially with regard to electron affinity and steric screening at the β-carbon), and the cuprate reactant. The cuprates used vary from homocuprates (Gilman reagents) of type $(R_2CuLi)_2$, to phosphine-coordinated species such as $(RCuPR'_3)_n$, to higher order species[8] such as $(R_2CuCNLi_2)_n$. Even the Gilman reagents are probably mixtures which contain small amounts of species such as R_3CuLi_2.[9] Given this range of situations, a spectrum of mechanisms is not only possible but perhaps even inevitable. Electron transfer from the organocopper reagent to the enone has often been proposed[5,10] as a crucial step in the conjugate addition, though positive identification of radical-anion or radical intermediates is lacking. Recent evidence

suggests that for sterically unhindered ketones, at least, rapid complexation of organocuprates with enones may occur directly[6,11] and lead to formation of a copper(III) β-adduct. ^{13}C and ^{1}H NMR studies suggest that such complexes involve an interaction of the cuprate with the π-system.[11] It has been proposed that the high reactivity of enones with cuprates may be due to the possibility of d,π*-complexes involving copper as a d^{10}-base with the α,β, and carbonyl carbons (π_3^*) of the enone acting as a π-acid,[12] and that this is a major pathway for copper(III) β-adduct formation. Evidence has been presented that for certain enones copper(III) β-adducts are formed reversibly.[13] In two instances enone-cuprate complexes have been isolated which may be of the d,π* type since they revert to enone upon protonation and are transformed to the trimethylsilyl enol ether of the carbon β-adduct upon treatment with chlorotrimethylsilane. Despite the absence of rigorous proof of the intermediacy of d,π*-complexes and copper(III) β–adducts, this model of the pathway is of great interest in connection with the prediction of the stereochemistry of the overall conjugate addition. An enantioselective version of the enone conjugate addition has been devised on this basis.[14] The d,π*-mechanistic pathway is summarized in *Scheme 1* for cyclohexenone as substrate and dimethylcopperlithium as reagent.[6,13] A number of different experimental results indicate that the stable geometry of the dimeric Gilman reagent $(Me_2CuLi)_2$ is rectangular with methyls at the corners and alternating lithium and copper atoms in the centers of each edge (**1**).[9,15] However, the structures of the

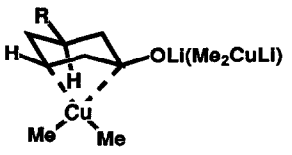
Scheme 1



reactive form of the reagent and the metallic groups in the reaction intermediates are unknown. The precise structure of the d,π*-complex **2** in terms of the distances between copper and the α,β, and carbonyl carbons is of great interest since this may play a major role in determining the

stereochemical outcome of many enone conjugate addition reactions, especially in the presence of chlorotrimethylsilane which serves to trap the d,π*-complex thereby favoring conversion to the copper(III) β-adduct over reversion to the starting enone.[13,16]

It is reasonable to use the mechanism outlined in *Scheme 1* as a working hypothesis since this appears to be most consistent with the available information on the α,β-enone-cuprate conjugate addition process, at least for unhindered ketones which are good Michael acceptors. One attractive geometrical possibility for the d,π*-complex is shown in structure **5**, R=H for the substrate 2-cyclohexenone. In this representation the carbonyl and beta carbons



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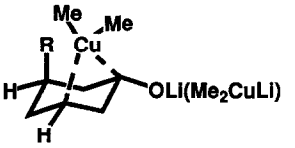

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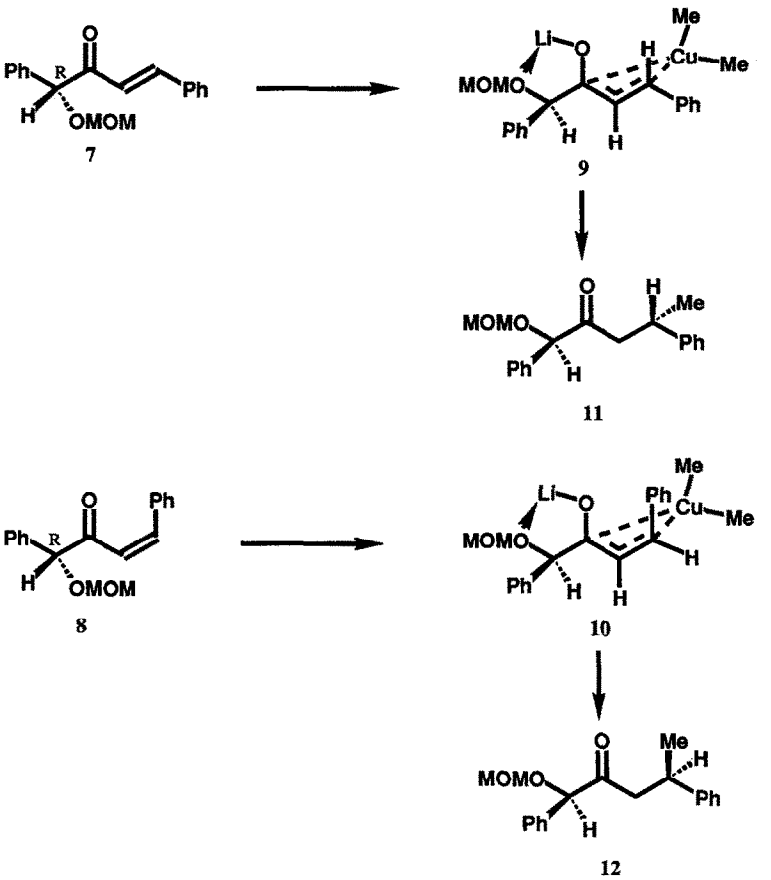
are both bonding to copper, and because of this coordination the six-membered ring is a chair-like structure with equatorial-like H and OLi substituents at the beta and carbonyl carbons, respectively. An attractive feature of this structure is that it provides a ready explanation for the known cases of high stereoselectivity involving various 2-cyclohexenones as substrates. Of special concern in this regard are the 5-alkylated-2-cyclohexenones which afford *trans*-3,5-disubstituted cyclohexanones as products in the absence or presence of chlorotrimethylsilane.[17,18] For a d,π*-complex derived from a 5-alkyl-2-cyclohexenone both *trans* and *cis* geometries, **5** and **6**, respectively are possible. Clearly **6** is expected to be less favorable because of repulsion between copper and the axial alkyl substituent. This line of thinking led to the expectation that some novel and useful stereoselective effects might be observable in the reactions of organocuprates with acyclic α,β–enones and to the study which is described herein.

RESULTS AND DISCUSSION

The focus of this investigation was the *E* and *Z* α,β-enone pair **7** and **8**. It was our expectation that these enones would be activated by bidentate coordination of the α'-alkoxycarbonyl subunit to lithium ion and that d,π*-complexation of the π-allyl type would occur selectively at one face of the π-system as a consequence of steric screening by the phenyl substituent on the chelate ring. To the extent that the copper complex involves bonding to the carbonyl as well as the beta carbon this steric bias should be increasingly important. The favored complexes from **7** and **8** are shown pictorially as **9** and **10**, respectively *(Scheme 2)*. If the major reaction products arise from the sterically more favored d,π*-complexes, the main conjugate addition pathways are predicted to be **7** → **9** → **11** and **8** → **10** → **12**.

Scheme 2

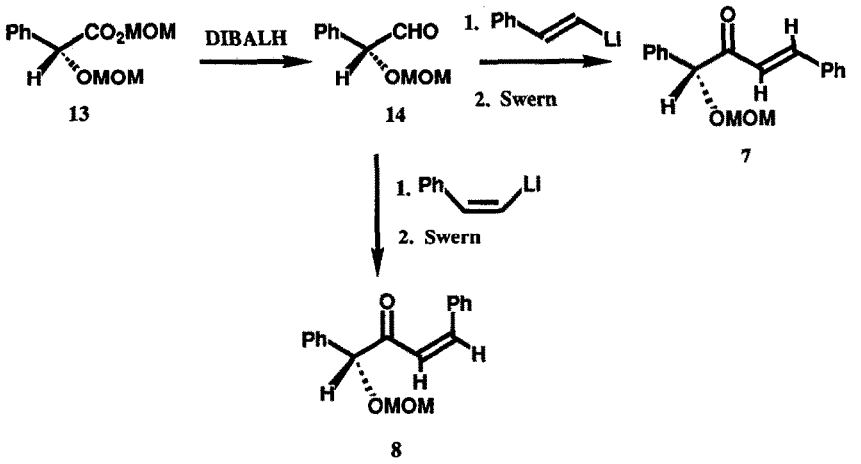


The *E*-enone **7** and the *Z* isomer **8** were synthesized as shown in *Scheme 3*. Reaction of *(R)*-(-)-mandelic acid with chloromethyl methyl ether and diisopropylethylamine produced the methoxymethyl (MOM) ester-ether **13**. Reduction of **13** with diisobutylaluminum hydride in toluene afforded the aldehyde **14** which was converted to **7** or **8** by reaction with *E*- or *Z*-β-styryllithium, respectively, followed by Swern oxidation.

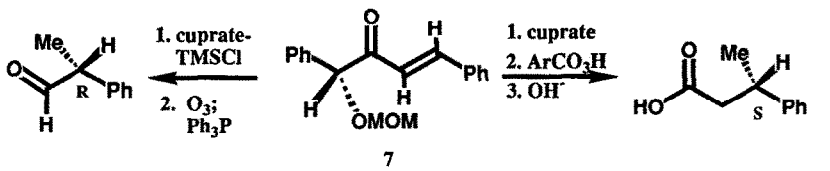
The reaction of **7** with dimethylcopperlithium was studied under various conditions with reference to the stereochemical course of conjugate addition. Under conditions which favor lithium chelate formation the addition reaction was highly stereoselective and resulted in a predominance of adduct **11**, the stereochemistry of which was established by two independent methods. Baeyer-Villiger oxidation of a 16 : 1 mixture of diastereomeric methyl cuprate adducts from **7** using *m*-chloroperbenzoic acid followed by hydrolysis afforded the known *(S)*-(+)-3-phenylbutyric acid,[19] confirming that the major diastereomer is **11**. In addition, ozonolysis of the enol ethers obtained by conjugate addition of methyl to **7** in the presence of chlorotrimethylsilane (30 : 1 mixture of diastereomeric β-methyl adducts) followed by reductive

workup with triphenylphosphine produced *(R)*-(-)-2-phenylpropanal,[20] $[\alpha]_D^{23}$ - 94.3° (c=0.61 in C_6H_6). These transformations are summarized in *Scheme 4*.

Scheme 3



Scheme 4

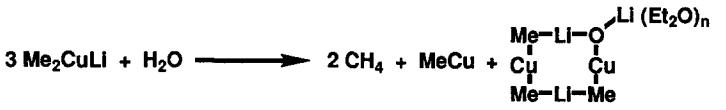


Reaction of **7** with 1.4 equiv of dimethylcopperlithium in the presence of 4 equiv of lithium iodide in ether at -45°C for 3 h afforded in 88% yield a mixture of diastereomeric adducts **11** and **12** in a ratio of 14 : 1. Without added lithium iodide in ether or in tetrahydrofuran as solvent the reaction was considerably slower, the yields were diminished, and the stereoselectivity was decreased. For example, the reaction of **7** with 1.4 equiv of dimethylcopper lithium in THF at -45°C for 16 h proceeded with only 80% conversion (20% of recovered **7**) and gave a 2.5 : 1 ratio of **11** to **12**. The yield of 1,4-addition product and the rate of reaction are both enhanced when 5 equiv of chlorotrimethylsilane is present in the reaction mixture of **7**, Me_2CuLi and THF at -78°C, but the ratio of **11** to **12** is only 2.

The slow addition of 0.3 equiv of water dissolved in ether to dimethylcopperlithium at -78°C produced a bright yellow solution (color of diazomethane) and a fine precipitate of polymeric methylcopper. The amount of water required to form the maximally yellow colored reagent (0.3 to 0.33 equiv) also leads to the most rapid and efficient conjugate addition reactions with enones **7**. The soluble reagent, methyloxidocopperlithium is highly reactive with enone **7**

and produces in 93 to 100% yield a mixture of **11** and **12** in a ratio of 16 : 1. In the presence of 5 equiv of chlorotrimethylsilane at -78°C the same reagent affords (after hydrolysis) in >90% yield **11** and **12** in a ratio of 33 : 1. The reactivity of the bright yellow reagent and the high selectivity with which **7** is converted to **11** are noteworthy.

We speculate that the yellow cuprate reagent methyloxidocopperlithium may be formed by *equation (1)* and may possess the planar mixed cuprate structure **15**. The exocyclic lithium

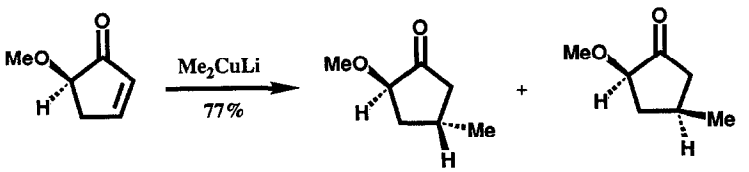


15

component of structure **15** may be quite accessible and especially suited for chelate formation with the α'-alkoxy-α,β-enone **7**.

The high selectivity observed in the reaction of **7** with Me_2CuLi/LiI and $Me_2CuLi/MeCuOLi_2$ reagents (16 : 1 to 33 : 1 in favor of diastereomeric adduct **11**) accords with the prediction outlined in *Scheme 2*. Such high stereoselectivity appears to depend on the availability of ample Lewis acidic Li^+, which also is consistent with the mechanistic and stereochemical interpretation outlined in *Scheme 2*, in particular with the postulates of (1) chelated lithium and (2) a bridged, π-allyl-like d,π*-complex of copper with the enone substrate. The lack of stereoselectivity observed in the reactions of **7** with cuprate reagents in THF may be due to the reduction of lithium chelation to **7** by this relatively basic solvent.

A similar interpretation may be used to explain the recently observed selectivity in the reaction of organocuprate reagents with 5-methoxy-2-cyclopentenone,[21] a favorable case for lithium chelation between the α'-methoxy group and the enone carbonyl.



ca. **50** : **1**

Studies involving the *Z*-enone **8** as substrate were complicated by the very rapid isomerization of **8** to **7** under conditions of the conjugate addition reaction. Thus, the reaction of **8** with Me_2CuLi/LiI and with $Me_2CuLi/MeCuOLi_2$ gave exactly the same products as were isolated from the corresponding reactions of **7**. Even at very short reaction times **8** had been converted to **7** under these conditions, and even in the presence of chlorotrimethylsilane[16] (5 to 20 equiv). However, in the presence of trimethylsilyl triflate, the *Z*-enone **8** was converted predominantly to diastereomer **12** (4.8 : 1 ratio of **12** to **11**), evidently because the $Z \rightarrow E$

isomerization was no longer so fast compared to conjugate addition. Although the pathway of the $Z \rightarrow E$ isomerization is unclear, it is an exceedingly facile process. The isomerization of **8** to **7** was found to occur rapidly in the presence of dry lithium iodide in ether at -78°C, so it is possibly totally independent of the conjugate addition reaction.

We have previously proposed that the acceleration of the conjugate addition of cuprates to α,β-enones by chlorotrimethylsilane is due to silylation of the d,π*-complex to generate the enol silyl ether of a copper(III) β-adduct rather than electrophilic activation of the enone by the chlorosilane. The present results are consistent with that view. It also might be mentioned that the 500 MHz ^{1}H NMR spectrum of benzalacetone and chlorotrimethylsilane in $CDCl_3$ show no change in chemical shift or line shape for the enone with increasing concentration of chlorotrimethylsilane. Further, it is noted that chlorotrimethylsilane does not accelerate the (very slow) reaction of dimethylcopperlithium with a non-conjugated ketone such as 4-*t*-butylcyclohexanone.

EXPERIMENTAL SECTION

General. Ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl, and methylene chloride and toluene were distilled from calcium hydride, immediately prior to use. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Dimethyl sulfoxide was distilled from calcium hydride. Chlorotrimethylsilane was distilled from calcium hydride and stored over several pieces of +4 mesh calcium hydride. Copper(I) iodide was precipitated from a solution of aqueous KI and dried *in vacuo* over P_2O_5. Lithium iodide was dried *in vacuo* over P_2O_5. All reactions involving organometallic agents or other moisture sensitive reagents were executed under an atmosphere of dry nitrogen or argon using flame-dried glassware. Ratios of diastereomers were determined using a Hewlett-Packard 5890 gas chromatograph equipped with a DB1-30W capillary column and a Hewlett-Packard 3392A integrator. FT-IR spectra were determined as neat films or as solutions in $CHCl_3$ using a Nicolet 5ZDX FT-IR spectrometer. The ^{1}H spectra were determined as solutions in $CDCl_3$ on a Bruker AM-500 (500 MHz), AM-300 (300 MHz), or AM-250 (250 MHz) spectrometer as indicated. Chemical shifts are expressed in parts per million (δ units) downfield from internal tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quadruplet; m, mutiplet; b, broad. Coupling constants are given in hertz (Hz). Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Low resolution mass spectra were obtained on a Kratos MS-50 instrument operating either in chemical ionization (CI) mode with ammonia as reagent gas, or fast atom bombardment (FAB) mode in a 3-nitrobenzyl alcohol matrix.

(*R*)-(-)-Mandelic acid methoxymethyl ether methoxymethyl ester (13). To a suspension of 10 g (66 mmole) of (*R*)-(-)-mandelic acid in CH_2Cl_2 (125 mL) was added 12.5 mL (165 mmole) of chloromethyl methyl ether and 28.8 mL (165 mmole) of diisopropylethylamine. The resulting solution came to a gentle reflux and was stirred for 24 h. The reaction mixture was washed with H_2O (3 x 50 mL), dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was eluted through a short column of SiO_2 with 4 : 1 hexanes/EtOAc to yield 13.45 g (65%) of **13**, $[\alpha]_D^{23}$ -97.9° (*c*=1.07, $CHCl_3$). ^{1}H NMR (250 MHz) δ 7.47 (m, 2 H), 7.36 (m, 3 H), 5.28 (d, J=5.98 Hz, 1 H), 5.22 (d, J=5.90 Hz, 1 H), 5.20 (s,

1 H), 4.78 (d, J=6.83 Hz, 1 H), 4.71 (d, J=6.88 Hz, 1 H), 3.40 (s, 3 H), 3.29 (s, 3 H); FT-IR (film) 2960, 1773, 1140, 1042 cm^{-1}.

(*R*)-(-)-Methoxymethoxyphenylacetaldehyde (14). To a -78°C solution of 1.5 g (6.25 mmole, 1 equiv) of **13** in toluene (30 mL) in a 100-mL three-necked flask equipped with an internal thermometer, septum and nitrogen inlet was added a solution of diisobutylaluminum hydride (5 mL of a 1.5 **M** solution in toluene, 7.5 mmole, 2 equiv). The reagent was added dropwise via syringe at a rate to keep the temperature of the solution below -55°C. The reaction mixture was stirred for two hours at -78°C, then quenched by the slow addition of 1.5 mL (20 mmole, 3.2 equiv) of propionic acid dissolved in hexanes (5 mL). The mixture was allowed to warm to room temperature, then CH_2Cl_2 (30 mL), 1.2 g (28.6 mmole, 4.6 equiv) of NaF and 0.36 mL (20 mmole, 3.2 equiv) of H_2O were added. The mixture was stirred vigorously for 30 min, then filtered through a pad of Celite. The filter pad was washed with several portions of CH_2Cl_2, and the combined filtrate and washings were concentrated at reduced pressure to yield 1.18 g (100%) of **14**, $[\alpha]_D^{23}$-112.1° (*c*=1.06, $CHCl_3$), which was used without further purification. ^1H NMR (250 MHz) δ 9.62 (d, J=1.68 Hz, 1 H), 7.39 (bs, 5 H), 5.01 (d, J=1.45 Hz, 1 H), 4.79 (d, J=6.80 Hz, 1 H), 4.75 (d, J=6.80 Hz, 1 H), 3.42 (s, 3 H); FT-IR (film) 1734 cm^{-1}; Mass spectrum (CI), *m/e* 198 (M + NH_4^+), 181 (M + H^+), 180, 151 (100%).

***E*-(*R*)-(-)-1,4-Diphenyl-4-methoxymethoxy-1-buten-3-one (7).** To a solution of 0.721 mL (5.63 mmole, 1.25 equiv) of *E*-β-bromostyrene in Et_2O (15 mL) at -78°C was added a solution of *t*-butyllithium (6.62 mL of a 1.75 **M** pentane solution, 11.25 mmole, 2.5 equiv). The resulting brown solution was stirred in the dark for 1 h at -78°C, then a solution of 810 mg (4.5 mmole, 1 equiv) of (*R*)-(-)-methoxymethoxyphenylacetaldehyde (**14**) was added dropwise via cannula. The opaque brown reaction mixture was stirred for 1 h at -78°C, then was quenched by the addition of saturated aqueous NH_4Cl (3 mL), and allowed to warm to room temperature. The mixture was poured into saturated NH_4Cl (25 mL), and extracted with Et_2O (2 x 100 mL). The extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was purified by chromatography on SiO_2 [hexanes/EtOAc (3 : 1)] to yield 679 mg (2.39 mmoles, 53%) of the allyl alcohol. This material was added as a solution in CH_2Cl_2 (5 mL) to a stirred, -78°C solution of 0.532 mL (6.65 mmole, 2.8 equiv) of dimethyl sulfoxide and 0.288 mL (3.33 mmole, 1.4 equiv) of oxalyl chloride in CH_2Cl_2 (12 mL). The reaction mixture was stirred at -78°C for 45 min, then 1.7 mL (11.85 mmole, 5 equiv) of triethylamine was added. Stirring was continued for 5 min at -78°C, then the cooling bath was removed and the mixture was allowed to warm as it was stirred for an additional 15 min. The reaction mixture was poured into H_2O (30 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic portions were washed with 1% aqueous HCl, 5% aqueous Na_2CO_3 and saturated aqueous NaCl, then dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was purified by chromatography on SiO_2 [hexanes/EtOAc (4 : 1)] to yield 468 mg (70%) of **7**, $[\alpha]_D^{23}$-92.7° (*c*=1.06, $CHCl_3$), as a viscous yellow oil. The product was further purified by bulb to bulb distillation, [215°C (oven temperature)/ 0.045 mm Hg]. ^1H NMR (500 MHz) δ 7.71 (d, J=15.94 Hz, 1 H), 7.52 (m, 2 H), 7.47 (d, J=7.15 Hz, 2 H), 7.38-7.33 (m, 6 H), 7.00 (d, J=15.92 Hz, 1 H), 5.32 (s, 1 H), 4.78 (d, J=6.76 Hz, 1 H), 4.74 (d, J=6.76 Hz, 1 H), 3.40 (s, 3 H); FT-IR (film) 2930, 1687, 1609, 1149, 1038 cm^{-1}; Mass spectrum (FAB), *m/e* 283 (M + H^+), 251, 221, 193 (100%).

***Z*-(*R*)-(-)-1,4-Diphenyl-4-methoxymethoxy-1-buten-3-one (8).** To a stirred solution of 0.667 mL (5.20 mmole, 1.22 equiv) of *Z*-β-bromostyrene in Et_2O (10 mL) at -78°C was added a solution of *t*-butyllithium (6.11 mL of a 1.7 **M** solution in pentane, 10.4 mmole, 2.4 equiv). The solution was protected from light and stirred for 1 h at -78°C. A solution of 0.780 g (4.33 mmole, 1 equiv) of **14** in Et_2O (5 mL) was added dropwise via cannula and the reaction mixture was stirred for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (3 mL), and allowed to warm to room temperature. The mixture was poured into H_2O (20 mL)

and extracted with Et_2O (2 x 100 mL). The extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was purified by chromatography on SiO_2 [hexanes/EtOAc (3 : 1)] to yield 768 mg (2.70 mmole, 62%) of the allyl alcohol. This material was added as a solution in CH_2Cl_2 (5 mL) to a stirred, -78°C solution of 0.530 mL (7.48 mmole, 2.8 equiv) of dimethyl sulfoxide and 0.325 mL (3.75 mmole, 1.4 equiv) of oxalyl chloride in CH_2Cl_2 (15 mL). The reaction mixture was stirred at -78°C for 1 h, then 1.9 mL (13.35 mmole, 5 equiv) of triethylamine was added. Stirring was continued for 5 min at -78°C, then the cooling bath was removed and the mixture was allowed to warm as it was stirred for an additional 30 min. The reaction was poured into H_2O (30 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic portions were washed with 1% aqueous HCl, 5% aqueous Na_2CO_3 and saturated aqueous NaCl, then dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was purified by chromatography on SiO_2 [hexanes/EtOAc (4 : 1)] to yield 602 mg (79%) of **8**, $[\alpha]_D^{23}$-83.1° (*c*=1.14, $CHCl_3$). The product was further purified by bulb to bulb distillation, [160°C (oven temperature)/ 0.025 mm Hg]. ^1H NMR (250 MHz) δ 7.60 (m, 2 H), 7.40-7.32 (m, 8 H), 6.83 (d, J=12.9 Hz, 1 H), 6.32 (d, J=12.9 Hz, 1 H), 5.29 (s, 1 H), 4.74 (d, J=7.33 Hz, 1 H), 4.68 (d, J=7.33 Hz, 1 H), 3.36 (s, 3 H); FT-IR (film)1696, 1608, 1150, 1029 cm^{-1}; Mass spectrum (FAB), *m/e* 283 (M + H^+), 251, 221, 193 (100%).

(*S*)-(+)-3-Phenylbutyric acid. To a solution of 30 mg (0.174 mmole, 1.7 equiv) of *m*-chloroperbenzoic acid in CH_2Cl_2 (2 mL) was added a solution of 30 mg (0.11 mmole, 1.0 equiv) of (1*R*,4*S*)-1,4-diphenyl-1-methoxymethoxypentan-2-one (16 : 1 mixture of diastereomers **11** and **12**) in CH_2Cl_2 (2 mL) and 50 mg of solid $NaHCO_3$. The mixture was stirred overnight at room temperature, then was diluted with CH_2Cl_2 (10 mL), and washed with H_2O and saturated aqueous $NaHCO_3$. The combined aqueous portions were carefully acidified with concentrated HCl and filtered through a glass frit. The filtrate was extracted with CH_2Cl_2 (2 x 25 mL), and the extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure to yield 14.3 mg of a white solid that was a mixture of *m*-chlorobenzoic acid and 3-phenylbutyric acid, $[\alpha]_D^{23}$+10.35° ($CHCl_3$). ^1H NMR (300 MHz) δ 7.4-7.2 (m, 5 H), 3.30 (dq, J=7.25, 7.00 Hz, 1 H), 2.71 (dd, J=15.6, 6.84 Hz, 1 H), 2.61 (dd, J=8.26, 15.6 Hz, 1 H), 1.34 (d, J=6.97 Hz, 3 H); FT-IR ($CHCl_3$) 3600, 3020, 1705 cm^{-1}.

(R)-(-)-2-Phenylpropanal. Ozone was bubbled through a solution of 57.6 mg (0.18 mmole, 1 equiv) of (1*R*,4*S*)-1,4-diphenyl-1-methoxymethoxy-2-trimethylsiloxy-2-pentene (30 : 1 mixture of diastereomers **11** and **12**) in CH_2Cl_2 (5 mL) at -78°C until a blue color persisted in the reaction mixture. The color was discharged by bubbling nitrogen gas through the solution, 59.8 mg (0.23 mmole, 1.27 equiv) of triphenylphosphine was added, and the reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed at reduced pressure, and the residue was chromatographed on SiO_2 [hexanes/EtOAc (9 : 1)] to yield 16.4 mg (68%) of 2-phenylpropanal, $[\alpha]_D^{23}$-88.6° (*c*=0.93, $CHCl_3$), -94.3° (*c*=0.61, C_6H_6). ^1H NMR (500 MHz) δ 9.69 (d, J=1.41 Hz, 1 H), 7.48 (t, J=1.2 Hz, 2 H), 7.32 (t, J=1.2 Hz, 1 H), 7.19 (d, J=1.2 Hz, 2 H), 3.62 (dq, J=7.0, 1.2 Hz, 1 H), 1.45 (d, J=7.1 Hz, 3 H); FT-IR (film) 3058, 2977, 1724, 1434, 668 cm^{-1}.

Addition of Dimethylcopperlithium-Lithium Iodide to 7. To a suspension of 24.0 mg (0.126 mmole, 1 equiv) of CuI in Et_2O (1.5 mL) at -78°C was added methyllithium (0.174 mL of a 1.45 **M** solution in Et_2O, 0.252 mmole, 2 equiv). The resulting mixture was stirred for 25 min at -78°C to form a clear, colorless solution. A saturated solution of lithium iodide (0.28 mL of a *ca.* 0.4 **M** solution in Et_2O, 0.112 mmole) was added until the solution was bright yellow. A solution of 21.0 mg (0.074 mmole, 0.58 equiv) of **7** in Et_2O (1.4 mL) was added dropwise via cannula. The yellow reaction mixture was stirred at -78°C for 45 min, then warmed to -45°C and stirred for 4.5 h. The reaction was quenched at -78°C by the addition of 3 mL of a 1 : 1 mixture of saturated aqueous NH_4Cl and 10% aqueous NH_4OH and allowed to warm to 23°C.

The mixture was poured into NH_4Cl-NH_4OH (12 mL) and extracted with Et_2O (2 x 20 mL). The extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure to yield 24.1 mg (colorless oil) of a 13 : 1 mixture of the diastereomeric β-methyl adducts **11** and **12** and 11% of residual **7**.

Major diastereomer **11**. ^1H NMR (500 MHz) δ 7.55-7.30 (m, 10 H), 5.04 (s, 1 H), 4.95 (s, 2 H), 3.31 (s over m, 4 H), 2.80 (dd, J=6.36, 17.2 Hz, 1 H), 2.68 (dd, J=7.94, 17.1 Hz, 1 H), 1.12 (d, J=6.95 Hz, 3 H); FT-IR (film) 2957, 1722, 1494, 1452, 1026; GC (200°C oven temperature) 10.71 min.

Minor diastereomer **12**. ^1H NMR (500 MHz) δ 7.40-7.08 (m, 10 H), 4.94 (s, 1 H), 4.59 (s, 2 H), 3.29 (s, 3 H), 2.74 (dd, J=6.57, 16.7 Hz, 1 H), 2.66 (dd, J=7.90, 16.7 Hz, 1 H), 1.14 (d, J=7.00 Hz, 3 H); FT-IR (film) 2960, 1722, 1452, 1028; GC (200°C oven temperature) 10.91 min.

Addition of Methyloxidocopperlithium to 7. To a suspension of 32.5 mg (0.171 mmole, 1 equiv) of CuI in Et_2O (2 mL) at -78°C was added a solution of methyllithium (0.235 mL of a 1.45 **M** solution in Et_2O, 0.341 mmole, 2 equiv). The mixture was stirred at -78°C for 0.5 h, and a solution of H_2O (1.84 mL of a 27.8 mM solution in Et_2O, 0.051 mmole, 0.3 equiv) was added dropwise. A solution of 34.0 mg (0.122 mmole, 0.713 equiv) of **7** in Et_2O (1.2 mL) was added via cannula to the resulting bright yellow solution. The reaction mixture was stirred for 0.5 h at -78°C, then warmed to -45°C and stirred for an additional 2 h. The reaction was quenched by the addition of a 1 : 1 mixture of saturated aqueous NH_4Cl and 10% aqueous NH_4OH (3 mL) and warmed to room temperature. The mixture was poured into NH_4Cl-NH_4OH (7 mL) and extracted with Et_2O (2 x 25 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure to yield 33.8 mg (98%) of a colorless oil that was comprised of a 13 : 1 mixture of the diastereomeric β-methyl adducts **11** and **12**.

Addition of Methyloxidocopperlithium-Chlorotrimethylsilane to 7. To a suspension of 67.5 mg (0.35 mmole, 1 equiv) of CuI in Et_2O (4 mL) at -78°C was added a solution of methyllithium (0.48 mL of a 1.45 **M** solution in Et_2O, 0.70 mmole, 2 equiv). The reaction mixture was stirred for 30 min, and a solution of H_2O (3.8 mL of a 27.8 mM solution in Et_2O, 0.105 mmole, 0.3 equiv) was added. The resulting bright yellow solution was treated with 135 μL (1.06 mmole, 3 equiv) of chlorotrimethylsilane, and a solution of 52.3 mg (0.185 mmole, 0.53 equiv) of **7** in Et_2O (1.2 mL) was added dropwise via cannula. The reaction mixture was stirred for 4 h at -78°C, and quenched by the addition of 0.5 mL of triethylamine and a 1 : 1 mixture of saturated aqueous NH_4Cl and 10% aqueous NH_4OH (3 mL). The mixture was allowed to warm to room temperature, poured into NH_4Cl-NH_4OH (20 mL), and extracted with Et_2O (2 x 50 mL). The extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure to yield 61.0 mg (89%) of a pale yellow oil. A portion (*ca.* 4 mg) was hydrolized with 0.1 **M** aqueous HCl in THF and was found to contain a 30 : 1 mixture of diastereomeric β-methyl adducts **11** and **12**.

Addition of Methyloxidocopperlithium-Chlorotrimethylsilane to 8. To a suspension of 22.8 mg (0.12 mmole, 1 equiv) of CuI in Et_2O (2 mL) at -78°C was added a solution of methyllithium (0.165 mL of a 1.45 **M** solution in Et_2O, 0.24 mmole, 2 equiv). The mixture was stirred at -78°C for 20 min, and a solution of H_2O (1.4 mL of a 27.8 mM solution in Et_2O, 0.036 mmole, 0.3 equiv) was added. The resulting bright yellow solution was treated with 55 μL (0.433 mmole, 3.6 equiv) of chlorotrimethylsilane, and a solution of 21.7 mg (0.077 mmole, 0.71 equiv) of **8** in Et_2O (1.2 mL) was added via cannula. The resulting orange-yellow solution was stirred at -78°C for 4 h, and quenched with 3 mL of a 1 : 1 mixture of saturated aqueous NH_4Cl and 10% aqueous NH_4OH. The mixture was warmed to room temperature, poured into NH_4Cl-NH_4OH (15 mL), and extracted with Et_2O (2 x 25 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was dissolved in 4 mL of THF and stirred with 0.5 mL of 0.1 **M** aqueous HCl for 15 min. The THF was

removed at reduced pressure and the residue was taken up in pH 7 buffer (4 mL) and extracted with Et_2O (2 x 15 mL). The extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure to yield 22.1 mg (77%) of a pale yellow oil, which was comprised of a 33 : 1 mixture of diastereomeric β-methyl adducts **11** and **12**.

Addition of Methyloxidocopperlithium-Trimethylsilyl trifluoromethanesulfonate to 8. To a stirred suspension of 23.5 mg (0.123 mmole) of CuI in Et_2O (1.5 mL) at -78°C was added a solution of methyllithium (0.169 mL of a 1.45 **M** solution in Et_2O, 0.245 mmole). The mixture was stirred for 30 min at -78°C and treated with a solution of H_2O (1.2 mL of a 27.8 mM solution in Et_2O, 0.036 mmole). The resulting bright yellow solution was stirred for 5 min, cooled to -98°C, and 0.135 mL (0.7 mmole) of trimethylsilyl triflate was added. A solution of 20 mg (0.071 mmole) of **8** in Et_2O (1.2 mL) was added dropwise via cannula. The clear yellow solution was stirred for 15 min at -98°C, and an aliquot (approximately 100 μl) was removed and quenched at -78°C with a 10% solution of propionic acid in THF (approximately 100 μL). The quenched aliqout was partitioned between NH_4Cl-NH_4OH and Et_2O, and GC analysis of the organic portion showed a 1 : 4.8 ratio of diastereomeric β-methyl adducts **11** and **12** (35%) and a 1.3 : 1 ratio of **7** and **8** (65%). The reaction was stirred for a total of 90 min, and quenched by the addition of a 1 : 1 mixture of saturated aqueous NH_4Cl and 10% aqueous NH_4OH (3 mL). The mixture was warmed to room temperature, poured into NH_4Cl-NH_4OH (15 mL), and extracted with Et_2O (2 x 25 mL). The extracts were dried ($MgSO_4$) and the solvent was removed at reduced pressure to yield 21 mg of a pale yellow oil which was shown to consist of a 1 : 3 mixture of diastereomeric β-methyl adducts **11** and **12** (56%) and residual **7** and **8** in a ratio of 4 : 1 (44%).

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REFERENCES AND NOTES

1. M. S. Kharasch and P. O. Tawney, *J. Am. Chem. Soc.*, **1941**, *63*, 2308.
2. See G. H. Posner, *An Introduction to Synthesis Using Organocopper Reagents*, Wiley-Interscience, New York, 1980.
3. C. Ouannes, G. Dessaire, and Y. Langlois, *Tetrahedron Letters*, **1977**, 815.
4. G. Hallnemo and C. Ullenius, *Tetrahedron*, **1983**, *39*, 1621.
5. H. O. House and J. M. Wilkins, *J. Org. Chem.*, **1978**, *43*, 2443.
6. S. R. Krauss and S. G. Smith, *J. Am. Chem. Soc.*, **1981**, *103*, 141.
7. G. Hallnemo and C. Ullenius, *Tetrahedron Letters*, **1986**, *27*, 395.
8. B. H. Lipschutz, R. S. Wilhelm, and J. A. Kozlowski, *Tetrahedron*, **1984**, *40*, 5005.
9. B. H. Lipschutz, J. A. Kozlowski, and C. M. Breneman, *J. Am. Chem. Soc.*, **1985**, *107*, 3197.
10. H. O. House, *Acc. Chem. Res.*, **1976**, *9*, 59.
11. G. Hallnemo, T. Olsson, and T. Ullenius, *J. Organomet. Chem.*, **1985**, *282*, 133.
12. E. J. Corey and N. W. Boaz, *Tetrahedron Letters*, **1984**, *25*, 3063.
13. E. J. Corey and N. W. Boaz, *Tetrahedron Letters*, **1985**, *26*, 6015.
14. E. J. Corey, R. Naef, and F. J. Hannon, *J. Am. Chem. Soc.*, **1986**, *108*, 7114.
15. R. G. Pearson and C. D. Gregory, *J. Am. Chem. Soc.*, **1976**, *98*, 4098.
16. E. J. Corey and N. W. Boaz, *Tetrahedron Letters*, **1985**, *26*, 6019.
17. H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **1968**, *33*, 949.
18. The chlorotrimethylsilane results were obtained by the present authors.
19. D. J. Cram, *J. Am. Chem. Soc.*, **1952**, *74*, 2137.
20. H. Matsushita, Y. Tsugimo, M. Noguchi, and S. Yoshikawa, *Bull. Chem. Soc. Jap.*, **1978**, *51*, 201.
21. A. B. Smith III, N. K. Dunlap, and G. A. Sulikowski, *Tetrahedron Letters*, **1988**, *29*, 439.