Chiral α-Substituted Carbonyls and Alcohols from the S_N2' Displacement of Cuprates on Chiral Carbonates: An Alternative to the Alkylation of Chiral Enolates

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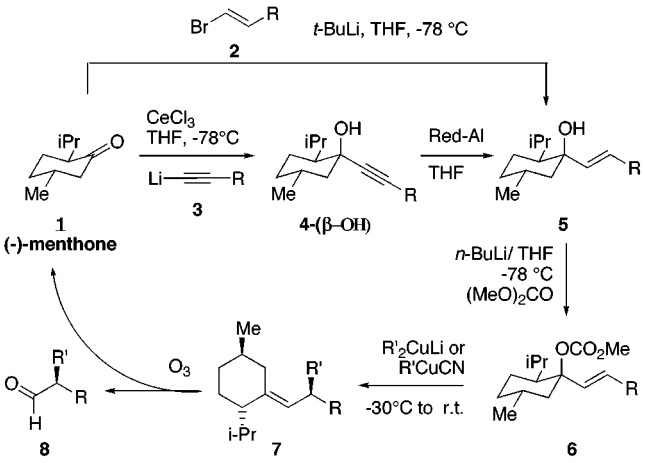
A highly stereoselective sequence of reactions, based on the *anti*-selective S_N2' addition of cuprates to allylic carbonates, transforms alkynes or alkenyl halides into carbonyls having α-chiral centers. The method, which uses menthone as a chiral auxiliary, is a useful alternative to the alkylation of chiral enolates with the added advantage of allowing for the "alkylation" of *sec*- and *tert*-alkyl and aryl groups.

Introduction

Among the most widely used methodologies to prepare compounds with chiral carbon centers sits the alkylation of chiral enolates and derivatives.[1−4] These include enolates and equivalents derived from chiral amides, esters, imines, enamines, and hydrazones and enolates possessing chirality at the metal.[1,2,4−6] The ubiquitous nature of carbonyl compounds possessing α chiral centers and the huge synthetic versatility of the carbonyl functional group are responsible for the impressive arsenal of such methodologies now available to the synthetic chemist. Each methodology has its own advantages, but they all share a common limitation: reactivity. In general, only methyl or ethyl iodide, benzyl halides, α-alkoxy halides, and similarly reactive electrophiles are adequate. Some methodologies allow for the alkylation of *β*-branched iodides,[7] but secondary, tertiary, vinyl, and aryl halides often are either unreactive or lead to secondary reactions such as elimination. The Lewis acid induced alkylation of silyl enol ethers allows reaction with S_N1-prone electrophiles but is of limited use with ester- or amide-derived *O*-silyl ketene acetals, and *sec*-alkyl electrophiles are poor electrophiles with this method.[8,9]

Scheme 1



We recently communicated our preliminary results on an alternative to the alkylation of chiral enolates involving the *anti*-selective addition of cuprate reagents onto chiral carbonates derived from menthone (Scheme 1).[10] We now report the full account of this study, disclosing the wide generality and applicability of the method to construct chiral carbon centers α to a carbonyl or hydroxymethylene unit. There are several stereochemical issues to be dealt with in this highly stereoselective sequence; the stereoselective addition of alkynyl or vinyl anions to menthone (**1** → **4** or **1** → **5**); restriction of the rotational freedom of the vinyl group in **6** during the S_N2' displacement step; the stereoselectivity of the cuprate addition process itself (**6** → **7**), and finally the configurational stability of the final carbonyl compound during the ozonolysis step (**7** → **8**). We have divided this paper in sections dealing with each issue.

Addition of Alkenyl and Alkynylmetals to Menthone. Several factors motivated our choice of menthone as the chiral auxiliary. It is inexpensive and available in both enantiomeric forms, each in high enantiomeric purity, but more importantly, we believed that the 1,2-

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Table 1. Additions of Cuprates on Chiral Carbonate 6b (R = Me).

entry	cuprate	product[a]	yield[b] (%)	% de
1	Et_2CuLi	(*R*)−**7a**	75	>99
2	EtCuCNLi	(*R*)−**7a**	67	>99
3	*n*-Bu_2CuLi	(*R*)−**7b**	70	>99
4	*n*-BuCuCNLi	(*R*)−**7b**	55	>99
5	*t*-BuCuCNLi	(*S*)−**7c**	78	>99
6	$H_2C{=}CH(CH_2)_2CuMgBr$	(*R*)−**7d**	73	>99
7	$(Cyhex)_2CuMgBr$	(*R*)−**7e**	91	>99
8	$(H_2C{=}CH)_2CuLi$	(*R*)−**7f**	20[c]	>99
9	Ph_2CuLi	(*S*)−**7g**	75	>99
10	Ph(thiophene)CuCNLi	(*S*)−**7g**	40[d]	>99
11	(*p*-MeO−Ph)$_2$CuLi	(*S*)−**7h**	44	>99
12	(*m*-MeO−Ph)$_2$CuLi	(*S*)−**7i**	64	>99
13	(4-*i*-BuPh)$_2$CuLi	(*R*)−**7j**[e]	80	>99
14	(furanyl)$_2$CuLi	(*S*)−**7k**	65	>99
15	(3-pyridinyl)$_2$CuLi	(*S*)−**7l**	17[f]	>99
16	(*n*-$Bu_3Sn)_2CuLi$	(*S*)−**7m**	>100[g]	>99

[a] The annotation *R* or *S* designates the newly formed chiral center starting from (−)-menthone unless otherwise indicated.[b] Isolated yield for two steps from the corresponding alcohol **3**. [c] The S_N2 addition, the reduction, and the elimination products were also isolated. [d] 80% based on recovered starting material. [e] Made from (+)-menthone. [f] Alcohol **5b** was also isolated in 73% yield. [g] Contaminated with n-Bu_4Sn.

addition of organometallics to menthone would be highly selective. The experimental confirmation came as no surprise. The isopropyl group of menthone effectively directs nucleophiles to the opposite face of the carbonyl. For example, the addition of vinylmagnesium bromide prepared from **2b** (R = H) or *trans*-1-propenyllithium made from *trans*-1-bromopropene **2a** (R = Me) to menthone proceeded with complete stereoselectivity to give the axial alcohols **5a** and **5b**, respectively (Scheme 1). The addition of alkynyllithium or magnesium reagents was somewhat less stereoselective but gave good yield of the axial alcohols **4** accompanied with 5−25% of the corresponding equatorial alcohols. However, prior addition of dry cerium trichloride to the alkynyllithium reagent mixture increased significantly the selectivities which are reported in Table 2. We have also noticed that slow addition of a solution of menthone to a solution of the alkynylcerate leads to the highest selectivities. Importantly, in every instance the diastereomeric alcohols were easily separated by flash chromatography, and pure axial alcohols **4** could be isolated in good to excellent yields. The tertiary propargyl alcohols **4** could be reduced to the corresponding *trans*-allylic alcohols with Red-Al or lithium aluminum hydride in THF at room temperature or refluxing THF. No trace of the corresponding *cis*-alcohols were detected. A good yield of the allene was isolated when alkynyl silyl ether **4g** was submitted to the reducing conditions overnight at reflux. In this case, the reduction is best carried out at −10 °C for a short period of time in which case only 12% of the corresponding allene was formed vs 73% of the desired allylic alcohol. It was also possible to hydrogenate the triple bonds using Lindlar's catalyst under one atmosphere of hydrogen to obtain the *cis*-propargylic alcohols.

Alternatively, the alkynes can be hydroaluminated and quenched with iodine or NBS to give the corresponding vinyl halides. Each vinyl halide can undergo a metal−halogen exchange with *tert*-butyllithium to give the corresponding vinyllithium which add with complete stereoselectivity to menthone to give high yields of pure axial alcohols **5**. The choice between the two methods should be made based on the overall yield of pure axial alcohol **5**.

Addition of Cuprate Reagents on Chiral Carbonates. The carbonate was chosen as the leaving group because it was one of the few into which the tertiary alcohol could be derivatized. The axial tertiary alcohol in **5** is sterically congested and rather unreactive. Acetates, which are more commonly used for cuprate displacement reactions, were obtained in very low yields with much decomposition. The same was true for mesylates and carbamates. Carbonates could only be produced using dimethyl carbonate or methyl chloroformate and *n*-butyllithium in THF at −78 °C. Not surprisingly, the carbonates were unstable and had to be used immediately in the next step without further purification. Sometimes, some of the starting alcohol was recovered after the subsequent cuprate addition. We have determined that an incomplete carbonate formation or carbonate hydrolysis prior to the cuprate step was responsible for this observation. Careful and prompt handling of the carbonate compounds alleviated the problem.

The pivotal step in this sequence relied on the highly *anti*-selective addition of cuprate reagents on allylic carbonates and related systems. The first example of a cuprate reagent displacing an acetate with allylic rearrangement was published in 1969 by Crabbé and coworkers.[11] It was followed immediately by two reports from a team of Zoecon Corp. on the stereospecificity of the cuprate addition on allylic acetates.[12,13] Cuprates have since been recognized to add preferentially *anti* to acyclic or cyclic allylic, propargylic, and allenic halides, acetates, carbonates, and epoxides.[14−26] To produce a stereogenic center of high optical purity, the addition of the cuprate reagents had to occur *anti* to the carbonate on only one of the two reactive conformers **A** or **C**, respectively (Figure 1). Previous work by Crabbé[27] and ourselves[28,29] indicated that a group as small as methyl or a bromine atom adjacent to the carbonate on cyclic systems, such as **6**, was sufficient to drive the conformational equilibrium completely toward conformer **A**. Our own MMX

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Table 2. Additions of Alkenyl and Alkynyl Metals on Menthone and S_N2' Addition of Cuprates on Chiral Carbonates 6.

			addition on menthone		S_N2'Cent addition of cuprates on carbonates **6**			
entry	**3**	R	yield[a] of 4-(βOH) (%)	ratio[b] of 4-(βOH)/4-(αOH)	R′ in R'_2CuLi	Prd	yield[c] of **7** (%)	% de[d]
1	**3b**	Me	85	(5:1)[e]	see Table 1		- -	- -
2	**3c**	*n*-Bu	90	20:1	Me	(*S*)-**7b**	70	>99
3	**3d**	*i*-Pr	87	18:1	Ph	(*R*)-**7n**[f]	87	>99
4	**3d**	*i*-Pr			*p*-Cl-Ph	(*R*)-**7o**[f]	91	>99
5	**3e**	*t*-Bu	70	20:1	Me	(*R*)-**7c**	61	>99
6	**3e**	*t*-Bu			Ph	(*R*)-**7p**	72	>99
7	**3f**	$BnO-CH_2$	96	26:1	Me	(*R*)-**7q**	75	>99
8	**3g**	$TBDMSO-CH_2$	83 (56)[e]	17:1 (2:1)[e]	$PhMe_2Si$	(*R*)-**7r**	59	>99
9	**3h**	$PMBO-(CH_2)_2$	90	50:1	Me	(*R*)-**7s**[f]	82	>99
10	**3i**	Ph	80	20:1	Me	(*R*)−**7g**	61	>99
11	**3i**	Ph			*i*-Pr	(*R*)-**7t**	67	82
12	**3i**	Ph			*t*-Bu	(*S*)-**7p**	40	33
13	**3j**	*p*-MeO-Ph	86	12:1	Me	(*R*)-**7h**	58	90
14	**3j**	*p*-MeO-Ph			*i*-Pr	(*R*)-**7u**	59	33
15	**3j**	*p*-MeO-Ph			*t*-Bu	(*S*)-**7v**	49	14
16	**3k**	*m*-MeO-Ph	89	27:1	Me	(*R*)-**7i**	84	>99
17	**3l**	*p*-Cl-Ph	74	20:1	*i*-Pr	(*R*)-**7w**	63	82
18	**3m**	6-MeO-1-Npht	72	16:1	Me	(*R*)-**7x**	42[g]	>99
19	**3n**	2-furanyl	59	4:1	Me	(*R*)-**7k**	43	>99
20	**3o**	3-pyridinyl	50	16:1	Me	(*R*)-**7l**	38 (21)[h]	>99
21	**3o**	3-pyridinyl			*i*-Pr	(*R*)-**7y**	20 (48)[h]	60
22	**3o**	3-pyridinyl			*t*-Bu	(*S*)-**7z**	16 (28)[h]	60

[a] Isolated yield of pure **4** (β-OH) after separation of diastereomers starting with (−)-menthone unless otherwise stated. [b] Determined by GC or NMR on crude mixtures. [c] Isolated yield for two steps from corresponding alcohol **5**. [d] de = diastereomeric excess. [e] No $CeCl_3$ added. [f] Made from (+)-menthone. [g] Contaminated with S_N2 displacement product (see text). [h] Yield of recovered alcohol **5o** in parentheses.

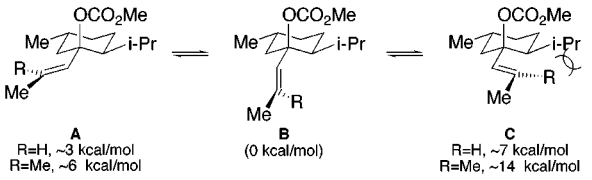
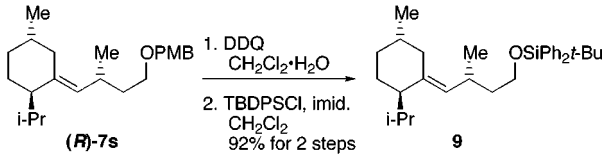


Figure 1. Energies of three conformations of **6**.

Scheme 2



calculations placed conformer **A** (R = H) at more than 4 kcal/mol lower in energy than conformer **C**.

The S_N2' displacement reactions proved highly selective indeed. The addition of various cuprate reagents to chiral carbonates **6b** (R = Me) gave essentially only one diastereomer of each adduct **7** (Table 1). We measured the ratio of diastereomers by gas chromatography (GC) against an authentic mixture of both diastereomers in most cases. Thus, by interchanging the substituents on the cuprate and alkene, we were able to prepare the diastereomers of **7b**,**c**,**g**−**i**,**k**,**l**. We then prepared equimolar mixtures of each pair of diastereomers and found that they were easily separated by GC. Injection of the pure diastereomers from the crude reaction mixture in these cases showed a single peak. This result was correlated with the proton and ^{13}C NMR spectra. The NMR spectra and GC traces of all the other adducts were found to be clean, and their diastereomeric purity was confirmed when we verified the enantiomeric purities of the corresponding alcohol compounds after ozonolysis (vide infra). The absolute stereochemistry of the adducts could be obtained from the sign of the optical rotation of some known aldehydes or acids after ozonolysis. By replacing the *p*-methoxybenzyl (PMB) group of compound (*R*)-**7s** by a TBDPS protecting group ((*R*)-**7s** → **9**, Scheme 2), we were able to grow crystals of compound **9** of sufficient quality to perform a single-crystal X-ray analysis which confirmed that the adducts possessed the stereochemistry corresponding to an *anti*-addition on conformer **A** (Figure 1). The ORTEP diagram of **9** (Supporting Information) shows the six-membered ring in a chair conformation with both the methyl and isopropyl groups in the axial position. $A^{1,3}$ strain is presumably responsible for this observation.[30] We could not confirm that this conformation was also predominant in solution.

Changing the type of the cuprate reagent (Gilman's, cyanocuprates, higher-order cuprates, etc.) affected the yield of the reaction but never the stereoselectivity (Table 1). Monoalkylcyano cuprates were an appealing choice in view of the fact that none of the transferable alkyl portion was wasted. It gave good yields in many cases, but we have found that dialkyl cuprates were generally superior. Higher order cuprates (not included in Table 1) also gave satisfactory yields but offered no advantage over Gilman's type cuprates. The choice of cuprate reagent should thus be made based on an optimum yield of product, taking into account the cost of the alkyl being transferred.

Table 1 lists several different alkyl and arylcuprates that reacted with **6b** (R = Me) with high stereoselectivity. (+)-Ibuprofen[31] was obtained in high enantiomeric purity from (+)-menthone (cuprate adduct (*R*)-**7j**, Table 1, entry 13) and our method seems well suited to make secondary and tertiary alkyl analogues of this important anti-

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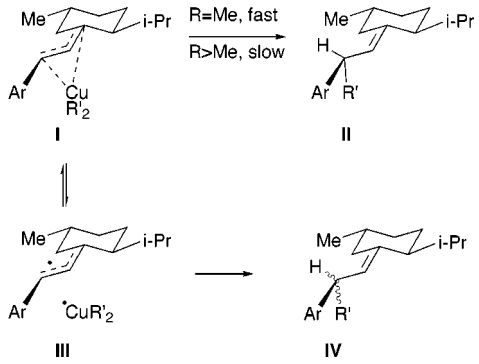
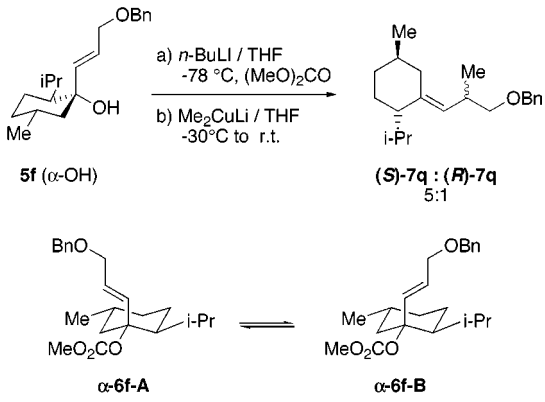
Scheme 3



Scheme 4



inflammatory drug, something not easily achieved by existing methods.[32−35] Heterosubstituted aromatic (Table 1, entries 11 and 12) and heteroaromatic cuprates (entries 14 and 15) also reacted with carbonate **6**, giving the corresponding adducts **7** with complete stereoselectivity. Finally, stannyl and silyl cuprates added highly stereoselectively as well (Table 1, entry 16, and Table 2, entry 8).

Groups of different sizes and nature were tolerated on the vinylic moiety of the carbonate molecules leading to hindered adducts with high diastereomeric purity (Table 2). For example, (*R*)-*tert*-butylphenylacetic acid was prepared in >99% ee after ozonolysis of adduct (*R*)-**7p** (Table 2, entry 6), and, as far as we are aware, this constitutes the only highly stereoselective synthesis of this compound. Metzger and co-workers prepared its ester in 32% ee using a chiral tin hydride reagent on the corresponding radical.[36,37] We also prepared (*R*)-2-(4-chlorophenyl)-3-methylbutanoic acid, a fragment of the important class of pyrethroid insecticides, from the ozonolysis of the corresponding cuprate adduct (*R*)-**7o** (Table 2, entry 4).[38] However, addition of some cuprate reagents on styryl-substituted carbonates gave substantially lower stereoselectivities (entries 11−15, 17, 21, 22). Curiously, the stereoselectivity seemed to depend on the size of the cuprate reagent. Entries 10, 13, 16, and 18−20 of Table 2 show that lithium dimethylcuprate added to styryl-substituted carbonates **6i**−**k**,**m**−**o** with high selectivity while the corresponding diisopropyl and *tert*-butyl cuprate gave products with lower % de. Larger cuprate reagents take higher temperatures and longer times to react and may produce a biradical intermediate **III** (or cationic intermediate) from a copper complex **I** in a sequence where the rate-determining step is presumably the reductive coupling (**I** → **II**) (Scheme 3). Interestingly, reactions between the small lithium dimethylcuprate and allylic carbonates **6m** and **6n** gave, along with the main S_N2' adduct, 5−25% of the S_N2 displacement products (entries 18 and 19). The S_N2 displacement product was not observed in the addition of cuprates on any other substrate we have tried. Compound **6n** started reacting with the cuprate at ca. 10 °C. Adding the cuprate at −30 °C and letting the mixture slowly warm to room temperature led to the formation of 18% of the S_N2 product. In contrast, adding the cuprate at −30 °C and warming quickly to room-temperature kept the amount of S_N2 adduct to a minimum. Since both S_N2 and S_N2' adducts were diasteromerically pure, radicals or ionic intermediates are unlikely in this case. The fact that **6j** did not give any noticeable quantity of S_N2 adduct (Table 2, entry 13) is rather difficult to interpret, and we cannot explain this discrepancy at the moment.

Fortunately, the desired aryl-substituted adducts **7** can be prepared with high stereoselectivity if the aromatic nucleus is part of the cuprate reagent. In those cases, high stereoselectivity was observed even when the allylic carbonate contained a bulky substituent such as isopropyl or *tert*-butyl (Table 2, entries 3, 4, and 6). Presumably, radical or ionic intermediates are not stable enough in these cases, and reductive coupling occurs without competition from homolytic or heterolytic cleavage. While most Ar_2CuLi reagents gave satisfactory results, addition of lithium divinylcuprate to allylic carbonate **6b** gave only 20% of the desired adduct (*R*)-**7f** and, in addition to some S_N2 adduct, much reduction and elimination products were isolated. Although vinyl cuprates have been extensively used in Michael-type additions, examples of a successful S_N2' or S_N2 addition of a vinyl cuprate on allylic systems are scarce. Ibuka reported the addition of vinyl copper species, prepared by transmetalation from divinyl zinc, onto allylic mesylate. He also reported reduction products from the addition of vinyl cuprates on allylic mesylates, perhaps via the in situ formation of copper hydride species.[14,39,40]

We have investigated the addition of lithium dimethylcuprate on the carbonate prepared from the minor equatorial alcohol **5f** (α-OH) (Scheme 4) obtained from the addition of 3-benzyloxypropynyllithium on **3f** on menthone followed by Red-Al reduction. The major cuprate adduct (*S*)-**7q** corresponded to an anti addition of the cuprate on conformation α-**6f-A** as expected, but the 5:1 selectivity observed was much lower than the near-complete selectivity obtained from the carbonate of **5f** (*β*-OH) under the same reaction conditions. We attribute this variance to a lower energy difference between

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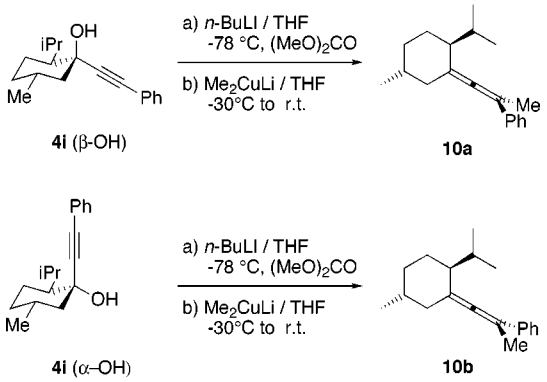
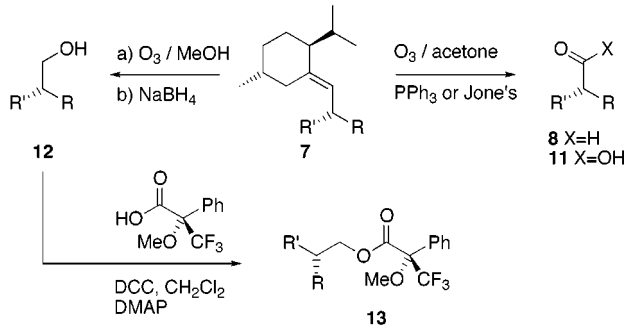
Scheme 5



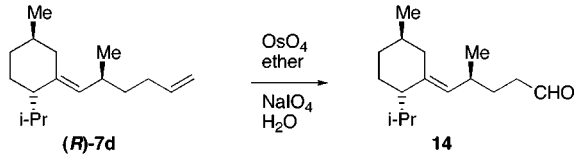
Scheme 6



the two reactive conformations α-**6f-A** and α-**6f-B** (Scheme 4). Calculations gave 2.2 kcal/mol energy difference between these two conformations while the energy difference between the two reactive conformations having the equatorial vinyl group (cf. **A** and **C** in Figure 1) was over 4 kcal/mol. We cannot exclude a syn addition of the cuprate on conformation α-**6f-A** as a source of the minor diastereomer. Interestingly, the cuprate addition on the carbonate of propargyl alcohols **4i** (*β*-OH) or **4i** (α-OH) proceeded with high stereoselectivity in both cases to give the corresponding chiral tetrasubstituted allenes **10a** and **10b** in 86 and 80% yield, respectively (Scheme 5). We did not get confirmation yet that both additions proceeded anti to the carbonate, but a highly selective syn addition is unlikely. We are currently investigating the chemistry of such chiral allenes.

Oxidative Cleavage of the Auxiliary. Oxidative cleavage of the trisubstituted double bond was best achieved with ozone in an appropriate solvent. Initially, we found that the lipophilic nature of some of our adducts led to a sluggish ozonolysis due to incomplete solubility in normal solvents such as dichloromethane and methanol at −78 °C. Addition of hexanes to the solution sometimes solved the problem, but eventually acetone was found to be a better solvent. Most ozonolyses were slow at −78 °C and required monitoring of the reaction by thin-layer chromatography since the usual blue color of excess ozone was not a reliable indication that cleavage was complete. Nonetheless, ozonolysis of all adducts gave high yields of aldehydes, alcohols, or acids depending on the workup conditions. Ozonolysis and treatment of the ozonide with sodium borohydride in methanol furnished enantiomerically pure alcohols **12** which were derivatized to their corresponding Mosher's esters **13** (Scheme 6). Each ester was checked for enantiomeric purity by proton and fluorine NMR or by GC to confirm the earlier GC analysis of the adducts **7**. Some of the α-aryl aldehydes

Scheme 7



are susceptible to racemization upon chromatography. When the crude aldehydes were reduced to the corresponding alcohols prior to purification, the Mosher esters of the latter indicated no racemization had taken place. Earlier, we reported modest yields of carboxylic acids **11** using H_2O_2 as workup conditions for the ozonolysis.[10] We have solved this problem by utilizing Jones reagent instead of hydrogen peroxide. Acids can now be obtained in reproducible 60−80% yields.

The trisubstituted double bond exocyclic to the menthone nucleus is in fact quite unreactive. Treatment of (*R*)-**7b** with osmium tetraoxide for days led to recovery of that double bond intact. We could selectively cleave the monosubstituted alkene in (*R*)-**7d** with the Lemieux conditions (OsO_4/$NaIO_4$) with no concomitant cleavage of the auxiliary (Scheme 7). Unlike the amide or ester auxiliaries used in alkylation reactions, our auxiliary is virtually insensitive to strongly basic and acidic conditions. For example, compound (*S*)-**7g** was recovered intact from treatment with *n*-BuLi in ether at room temperature or 1 N sulfuric acid in methanol, each for a 12 h period. The chiral auxiliary can therefore be left on as a protecting group for the carbonyl until later in a synthesis. Of course, the final target should not contain a functionality somewhere else in the molecule that can react with ozone because it is probable that it will be cleaved along with the menthone auxiliary. For example, the adducts with a pyridine or a furan ring or the tributyltin adduct gave several products upon ozonolysis. This constitutes a limitation to the present methodology which we are addressing in the next generation chiral auxiliary. One possibility involves a chiral auxiliary bearing a functional group adequately positioned for the selective cleavage of the desired double bond.

In conclusion, we have demonstrated the utility of our sequence to produce α-chiral carbonyls or hydroxymethylenes of high enantiomeric purity. Our method is complementary to the classical approach of alkylating a chiral enolate, both from an electronic point of view (an alkylating agent is electrophilic whereas the cuprate reagent involved here is nucleophilic) and from the point of view of the nature of the "alkylating" agent (our methods allow tertiary and secondary alkyl as well as aryl groups to be introduced in a highly stereoselective manner). Finally, the very high enantiomeric purity of the final compounds obtained via our strategy compares favorably to those obtained by the alkylation of chiral enolates. Further developments are under way in our laboratory.

Experimental Section

General. Reactions were performed under a nitrogen or argon atmosphere with oven-dried glassware unless otherwise stated. Diethyl ether, hexanes, and tetrahydrofuran were distilled over sodium−benzophenone. Dichloromethane and triethylamine were distilled over calcium hydride. Flash chromatography was done using Merck Kieselgel silica gel 60 (230−400 Mesh A.S.T.M). Concentration of organic solutions implies evaporation on a rotary evaporator followed by pumping under reduce pressure (0.5 mmHg).

Melting points were determined on a Reichert 7905 melting point apparatus integrated into an Omega Engineering Model 199 Chromel-alumel thermocouple. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 spectrometer, and only the major bands are reported. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-300 instrument. The following abbreviations were used: s, singlet; d, doublet; dd, doublet of doublet; q, quadruplet; m, multiplet. Chemical shifts are reported in δ relative to chloroform or acetone. Proton decoupled carbon NMR spectra used chloroform (77.0 ppm) and methanol (49.0 ppm) as internal standards. Mass spectra (MS) were obtained on a VG Micromass ZAB-2F instrument.

General Procedure for the Addition of Alkynyl or Alkenylmetals to Menthone. The appropriate alkyne or vinyl bromide (1.2 equiv) was dissolved in dry cold (−78 °C) THF (0.7M) and *n*-BuLi (1.2 equiv) or *t*-BuLi (2.4 equiv) respectively was slowly added. Dry cerium trichloride (1.0 equiv) was added and after stirring for 60 min, (−)-menthone (1.0 equiv) was added over 5 min. The reaction mixture was stirred at −78 °C for 1 h after which time saturated sodium chloride was poured into the cold solution. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography on silica gel (hexanes−EtOAc 9:1) to give exclusively the axial alcohol compound.

(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-{2-phenyl-1-ethyn-1-yl}cyclohexan-1-ol (4i). Yield: 80%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44−7.39 (m, 2H), 7.31−7.28 (m, 3H), 2,53−2.44 (m, 1H), 2.06 (dt, 1H, J = 13.7, 2.7 Hz), 1.85−1.73 (m, 2H), 1.71−1.65 (m, 1H), 1.58−1.41 (m, 5H), 1.01 (d, 3H, J = 9.9 Hz), 0.98 (d, 3H, J = 9.9 Hz), 0.90 (d, 3H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 2 × 131.6 (s), 3 × 128.2 (s), 123.0 (s), 94.0 (s), 83.5 (s), 72.1 (s), 50.6 (d), 50.1 (t), 34.8 (t), 28.5 (d), 27.3 (d), 23.9 (q), 21.9 (q), 20.7 (t), 18.8 (q); IR (neat, cm^{-1}): 3474, 3015, 2943, 2863, 1491, 1451; LRMS (*m*/*z* (relative intensity)): 256 (M^+, 10), 241 (15), 213 (20), 171 (100); Exact mass calcd for $C_{18}H_{24}O$: 256.1827. Found: 256.1825. $[\alpha]^{20}_D$: +11.5 (*c* 0.88, $CHCl_3$).

(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-{1-propen-1-yl}cyclohexan-1-ol (5b). Yield: 99%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.65 (dq, 1H, J = 15.4, 6.7 Hz), 5.45 (d, 1H, J = 15.4 Hz), 2.05−1.90 (m, 1H), 1.80−1,65 (m, 2H), 1.71 (dd, 1.71, 3H, J = 6.7, 1.7 Hz), 1.53−1.38 (m, 4H), 1.20 (s, 1H), 1.13−1.00 (m, 2H), 0.90−0.80 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.4 (d), 121.6 (d), 76.0 (s), 49.6 (t), 49.5 (d), 35.1 (t), 27.9 (d), 26.7 (d), 23.8 (q), 22.3 (q), 20.9 (t), 18.5 (q), 17.7 (q); IR (neat, cm^{-1}): 3600, 3507, 2943, 2871, 1451, 1169; LRMS (*m*/*z* (relative intensity)): 196 (M^+, 10), 181 (5), 163 (5), 111 (100), 69 (25); Exact mass calcd for $C_{13}H_{24}O$: 196.1827. Found: 196.1832. $[\alpha]^{20}_D$: −31.0 (*c* 1.30, $CHCl_3$).

General Procedure for the Reduction of the Propargyl Alcohols to the Corresponding Allyl Alcohols. The alkyne was dissolved in THF (to a concentration of ca. 0.3 mol/L), and Red-Al (1.5 equiv), dissolved in THF (at a concentration of ca. 0.6 mol/L), was added dropwise at room temperature. The reaction mixture was stirred at reflux for 14 h (except for 3,3-dimethyl-1-butyne where the reaction was done at room temperature to avoid allene formation) after which time H_2SO_4 (10%) was poured slowly into the solution precooled at 0 °C. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with sat. sodium carbonate solution, dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography on silica gel (hexanes−EtOAc 15:1) to give allyl alcohol.

2-Isopropyl-5-methyl-1-{2-phenyl-1-ethen-1-yl}cyclohexan-1-ol (5i). Yield: 86%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41−7.19 (m, 5H), 6.64 (d, 1H, J = 16.2 Hz), 6.22 (d, 1H, J = 16.2 Hz), 2.05−1.94 (m, 1H), 1,87−1.72 (m, 2H), 1.62−1.37 (m, 4H), 1.31−1.07 (m, 3H), 0.98−0.87 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.2 (d), 137.2 (s), 2 × 128.4 (d), 127.0 (d), 126.5 (d), 2 × 126.2 (d), 76.6 (s), 49.7 (d), 49.2 (t), 35.0 (t), 27.8 (d), 27.1 (d), 23.8 (q), 22.0 (q), 20.9 (t), 18.6 (q); IR (neat, cm^{-1}): 3594, 3494, 3014, 2943, 2863, 1496, 1446, 1171; LRMS (*m*/*z* (relative intensity)): 258 (M^+, 20), 223 (5), 202 (20), 173 (100); Exact mass calcd for $C_{18}H_{26}O$: 258.1984. Found: 258.1989. $[\alpha]^{20}_D$: −51.5 (*c* 3.06, $CHCl_3$)

General Procedure for the Conversion of the Alcohols to Carbonates. The appropriate alcohol was dissolved in dry cold (−78 °C) THF (to a concentration of ca. 0.1 mol/L), n-BuLi (2 equiv) was added dropwise, and the yellow solution was stirred at −78 °C for 30 min and then at 0 °C for another 30 min. Then, dimethyl carbonate (2 equiv) was added, and the reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 1.5 h, after which time sat. ammonium chloride was poured into the cold solution. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give the carbonates which were used crude in the next reaction.

Carbonate 6b. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.72 (dm, 1H, J = 16.2 Hz), 5.45 (dq, 1H, J = 16.2, 6.1 Hz), 3.71 (s, 3H), 2.71 (dm, 1H, J = 15.2 Hz), 2.23−2.13 (m, 1H), 1.83−1.72 (m, 4H), 1.70−1.05 (m, 6H), 0.97−0.83 (m, 9H).

Carbonate 6i. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40−7.28 (m, 5H), 6.48 (d, 1H, J = 16.2 Hz), 6.35 (d, 1H, J = 16.2 Hz), 3.75 (d, 3H), 2.83 (dm, 1H, J = 15.3 Hz), 2.25−2.16 (m, 1H), 1.90−1.75 (m, 2H), 1.69−1.15 (m, 5H), 0.98−0.83 (m, 9H).

General Procedure for the Addition of Cuprates to Allyl Carbonates. Procedure A: Dialkyl Cuprates. The cuprates were prepared by adding 2.4 equiv of the organolithium to a suspension of purified copper iodide (1.2 equiv) and lithium iodide (1.2 equiv) in dry THF (0.1 M) at −30 °C. After the second equivalent of organolithium was added, the solution was stirred 30 min at −30 °C, and then the crude carbonate (1 equiv) dissolved in THF was added dropwise. The reaction mixture was stirred at −30 °C for 30 min and then for 1 h at 0 °C (adduct 11 h required rt for completion) after which time a solution of sat. ammonium chloride and ammonium hydroxide (9:1) was poured into the cooled solution (0 °C). The aqueous phase was separated and extracted with pentane, and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography on silica gel (100% hexanes) to give exclusively the anti S_N2' diastereomer.

Procedure B: Alkyl Cyanocuprates. The cuprates were prepared by adding 1.5 equiv of the organolithium to a suspension of copper cyanide (1.5 equiv) in dry THF (0.1 M) at −78 °C. The suspension was stirred for 30 min at −78 °C after which time the crude carbonate (1 equiv) dissolved in THF was added. The reaction mixture was heated to room temperature for 4 h after which time a solution of sat. ammonium chloride and ammonium hydroxide (9:1) was poured into the reaction mixture. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography on silica gel (100% hexanes) to give exclusively the anti S_N2' diastereomer.

Adduct (*S*)-7g. Yield: 75%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32−7.17 (m, 5H), 5.24 (d, 1H, J = 9.2 Hz), 3.77−3.72 (m, 1H), 2.41 (dm, 1H, J = 8.9 Hz), 1.95 (octet, 1H, J = 6.7 Hz), 1.85−1.65 (m, 4H), 1.63−1.54 (m, 1H), 1.45−1.25 (m, 1H), 1.30 (d, 3H, J = 6.6 Hz), 1.18−1.07 (m, 1H), 0.90−0.85 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.2 (s), 138.7 (s), 128.3 (d), 2 × 127.5 (d), 126.9 (d), 2 × 125.6 (d), 51.1 (d), 37.2 (d), 35.2 (t), 32.4 (d), 31.7 (t), 26.6 (t), 26.5 (d), 22.9 (q), 22.0 (q), 20.6 (q), 19.8 (q); IR (neat, cm^{-1}): 3015, 2974, 2872, 1595, 1446; LRMS (*m*/*z* (relative intensity)): 256 (M^+, 30), 213 (100), 157 (50), 131 (65); Exact mass calcd for $C_{19}H_{28}$: 256.2191. Found: 256.2195. $[\alpha]^{20}_D$: +47.3 (*c* 1.90, $CHCl_3$)

Adduct (*R*)-7g. Yield: 61%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28−7.12 (m, 5H), 5.24 (d, 1H, J = 9.2 Hz), 3.77−3.68 (m, 1H), 2.36 (dd, 1H, J = 13.3, 4.2 Hz), 1.94 (octet, 1H, J = 7.8 Hz), 1.82−1.54 (m, 5H), 1.45−1.35 (m, 1H), 1.32 (d, 3H, J = 7.3 Hz), 1.18−1.07 (m, 1H), 0.95−0.80 (m, 9H). $[\alpha]^{20}_D$: −102.9 (*c* 0.99, $CHCl_3$)

General Procedure for the Ozonolysis of the Cuprate Adducts to Alcohols. The alkenes were dissolved in dichloromethane (0.1 M), the solution was cooled to −78 °C, and ozone was bubbled through. When the solution remained light blue, indicating excess ozone, the ozone flow was stopped and N_2 was bubbled to remove excess of ozone. Then, dichloromethane was evaporated, the ozonide was dissolved in MeOH (0.1M), and sodium borohydride was added (5 equiv) at 0 °C. The resulting slurry was stirred at room temperature for 10 h. HCl (1 N) was then slowly added to the mixture cooled at 0 °C to destroy the excess reagent. Water and ether were added, the aqueous phase was separated and extracted with ether, and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered, concentrated in vacuo. and purified by flash chromatography on silica gel (hexanes−EtOAc 4:1) to give the desired alcohol.

(*R*)-2-Phenylpropanol (12g). Yield: 75%. $[\alpha]^{20}_D$: +14.3 (*c* 1.65, $CHCl_3$), lit. $[\alpha]^{20}_D$: +15.8 (neat).[41]

General Procedure for the Ozonolysis of the Cuprate Adducts to Aldehydes. Same procedure as above. After bubbing N_2, triphenylphosphine was added (1 equiv) at −78 °C, and the resulting solution was stirred at room temperature for 2 h. Dichloromethane was evaporated, and the residue was purified by flash chromatography on silica gel (hexanes−EtOAc 15:1) to give the desired aldehyde

(*R*)-2-Phenylpropanaldehyde (8g). Yield: 86%. $[\alpha]^{20}_D$: product racemizes upon flash chromatography on silica gel. However, the $[\alpha]^{20}_D$ of the alcohol **12g** obtained from the reduction of the crude aldehyde was identical with that of the alcohol **12g** obtained by direct $NaBH_4$ reduction of the ozonide.

General Procedure for the Ozonolysis of the Cuprate Adducts to Acids. Same procedure as above. After bubbing N_2, the solvent was evaporated and the ozonide was dissolved in a mixture of EtOAc, H_2O_2 (30%) and water (2.5:1:1 respectively) (0.1 M) and heated at 60 °C for 16 h. Then the solution was cooled to room temperature, and NaOH (2 N) was added followed by addition of ether. The organic and aqueous phase were separated, and the aqueous was washed with ether and acidified with HCl (12 N) to pH = 1. The aqueous phase was extracted with ether, and the combined organic phases were dried over magnesium sulfate, filtered, and concentrated in vacuo to give the desired acids.

(*R*)-2-Phenylpropanoic Acid (11g). Yield: 70%. $[\alpha]^{20}_D$: −71.8 (*c* 1.57, $CHCl_3$), lit. $[\alpha]^{20}_D$: −76.5 (neat).[42]

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for new compounds and X-ray data and ORTEP for **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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