A Practical and Highly Stereoselective Umpolung Alternative to the Alkylation of Chiral Enolates

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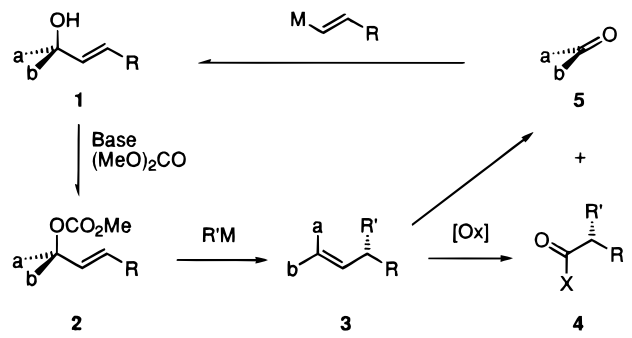
The synthetic organic chemist may nowadays select from an impressive arsenal of chiral enolates, or equivalents, to construct optically enriched carbonyls having an α-stereogenic center.[1,2] These include enolates and equivalents derived from chiral amides, esters, imines, enamines, and hydrazones and enolates possessing chirality at the metal.[1,3−6] However, reactivity imposes a serious limitation to this strategy. Many chiral enolates will alkylate only reactive electrophiles such as methyl, ethyl, and some primary alkyl iodides and benzyl or allyl halides. *s*-Alkyl, *t*-alkyl or phenyl halides are unreactive or lead to elimination products in most cases. Also, the reaction sometimes leads to self-condensation byproducts. 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 *s*-alkyl electrophiles are poor electrophiles with this method.[7,8]

In this paper, we disclose our preliminary results on a conceptually different approach to produce carbonyls with an α-chiral center of high optical purity based on the S_N2' displacement reaction of alkyl cuprates on chiral allyl carbonates. Cuprates are known to add preferentially *anti* to allylic, propargylic, and allenic halides, acetates, carbonates, and epoxides.[9,10] Thus, in principle, the displacement reaction of a chiral allyl carbonate **2** could lead to a carbonyl α to the newly created chiral center after oxidative cleavage of the newly formed double bond (cf. **4**, Scheme 1).[11] The success and practicality of such a strategy rests on several issues, the stereoselective construction of the allyl carbonate **2**, restriction of the rotational freedom of the vinyl group in **2** during the addition step, and the stereoselectivity of the addition process itself. Ideally the chiral auxiliary **5** should be inexpensive, readily available in either enantiomeric forms, and recovered after the reaction sequence. For our purposes, menthone answered all of these requirements.

The addition reaction of a series of alkynyl and alkenyl metals to (−)-menthone[12] proceeded with complete stereoselectivity to give the corresponding propargyl alcohols **8** or allylic alcohols **9** in yields of 70−99% (Scheme 2).[13] The isopropyl group effectively directed the incoming nucleophile to the opposite face of the carbonyl. The alkynyl groups were then selectively reduced in good yields (70−86%) to the (*E*)-allylic alcohols using Red-Al. Each allylic alcohol **9** was converted to its corresponding carbonate, and the crude mixture was treated with alkyl cuprates of the type R_2CuM or RCuCNLi, where M = Li or Mg (Table 1). All addition reactions gave essentially only one detectable diastereomer. The isopropyl may also assist in the *anti* selectivity

Scheme 1



Scheme 2

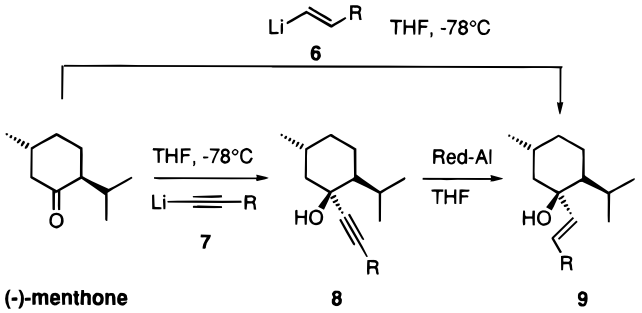
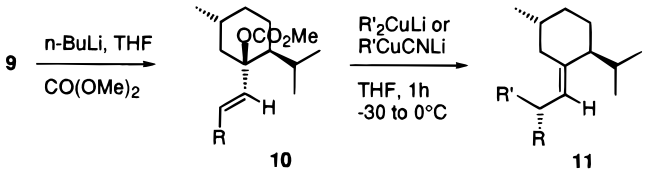


Table 1. S_N2' Displacement Reactions of Cuprates on Chiral Carbonates



					R′$_2$CuLi		R′CuCNLi	
entry	**10**	R	R′	**11**	yields[a] (%)	% de	yields[a] (%)	% de
1	**10a**	Me	Et	**11a**	75	>99	67	>99
2	**10a**	Me	*n*-Bu	**11b**	70	>99	55	>99
3	**10a**	Me	*t*-Bu	**11c**			78	>99
4	**10a**	Me	Ph	**11d**	75	>99	40[b]	>99
5	**10a**	Me	cyhex	**11e**	91[c]	>99		
6	**10b**	*n*-Bu	Me	**11f**	70	>99		
7	**10c**	*t*-Bu	Me	**11 g**	61	>99		
8	**10c**	*t*-Bu	Ph	**11h**	72[d]	>99	0	
9	**10d**	Ph	Me	**11i**	61	>99		

[a] For two steps from corresponding alcohol **9**. [b] Ph(thiophene)CuLi was used. 80% based on recovered starting material. [c] From the corresponding cyhexMgBr. [d] −30 to 25 °C for 6 h.

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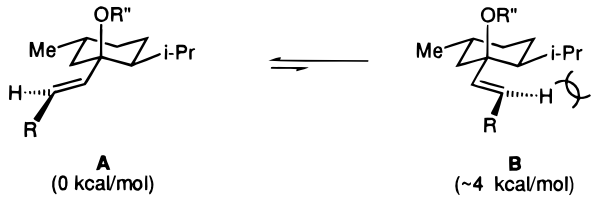
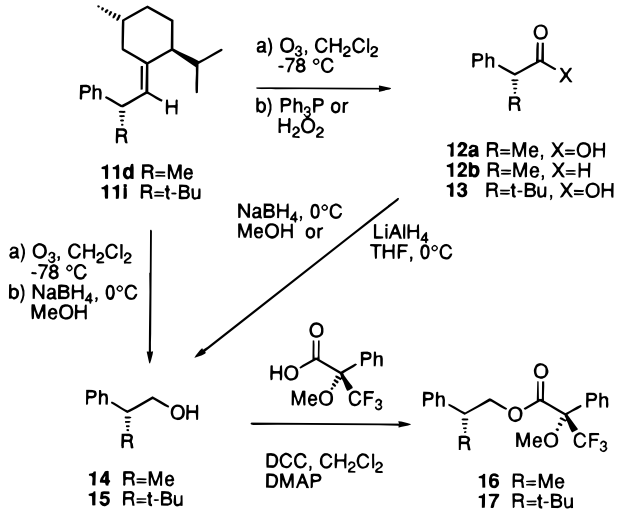


Figure 1.

of the additions. In three cases we prepared separately the other diastereomers by interchanging the substituent on the allyl moiety and on the cuprate (entries 6, 7, and 9). The diastereomeric purity of the individual adducts could then be cross-checked by injecting an equimolar mixture of the pairs in a capillary GC. The other adducts were judged to be also >99% pure from GCMS and ^{1}H and ^{13}CNMR spectra. Tertiary, secondary, and primary alkyl as well as aryl cuprates gave good yields and complete selectivities. So far, we were unsuccessful in adding vinyl cuprates. We explain this high level of selectivity from the large energy difference between the two reactive rotamers **A** and **B** of the alkenyl moiety in **10** (Figure 1).[14] This energy difference must remain at the transition state level during the *anti*-selective addition of the cuprate reagent. Note that the *Z*-isomer of **10a** did not react under those conditions, presumably because the required conformation **A** in unattainable due to steric repulsion.

The oxidative cleavage was accomplished by ozonolysis to furnish either the acid, the aldehyde, or the alcohol directly. As an example, compound **11d** was cleaved by ozonolysis to give 40%, 90%, and 75% of the corresponding acid **12a**, aldehyde **12b**, and alcohol **14**, respectively (Scheme 3). The construction of the sterically congested *tert*-butylphenyl acetic acid **13** (61%) and its alcohol **15** (70%) in >99% ee is noteworthy. Typically, (−)-menthone (or menthol) could be recovered in unoptimized yields of 60−65% after oxidative cleavage. The sense of asymmetric induction in the cuprate addition was verified by comparing the optical rotation of the alcohols with those in the literature.[15,16] It was consistent with an *anti*-selective addition of the cuprates on rotamer **A** (Figure 1). The enantiomeric purity of each isolated aldehyde or acid was established by first reducing the carbonyl to the corresponding alcohol and then converting

Scheme 3



the alcohol to its Mosher ester. Mosher esters from the racemic acid were also prepared for comparison. ^{19}F and ^{1}H NMR indicated no racemization in all cases so aldehydes and acids were obtained in >99% ee.

Our method provides a useful and practical alternative to the alkylation of chiral enolates. It is complementary since the carbonyl product is obtained, starting from an alkene or an alkyne.[17] It is also 'umpolung' since the electrophile used in the alkylation reaction becomes the nucleophile in our sequence and the auxiliary bears an electrophilic rather than nucleophilic double bond. Secondary and tertiary alkyl and aryl groups are reactive, allowing access to hindered aldehydes and acids of high optical purity. Further development and extension of this methodology is currently underway.

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Supporting Information Available: Experimental procedures, characterization data and ^{1}H NMR spectra for new compounds (41 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(14) Conformer **A** (R = Me, R″ = H) was found to be 4.1 kcal/mol lower in energy than conformer **B** using CSChem3D Software.

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