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Spirodiepoxide Reaction with Cuprates

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Here we report a new approach to synthesize densely functionalized α-hydroxy ketones by way of copper-mediated spirodiepoxide (SDE) opening. Since SDEs (**2**) are unstable to Brønsted acid,[1] the prospects of transition-metal-mediated reactions and other potential applications would seem limited. Yet provided such issues are navigable, the transformation (**1** → **2** → **3**, Scheme 1) would set two stereocenters, install two oxygen atoms and one C−C bond, and thus result in the formation of a vicinal triad composed of hydroxyl, ketone, and syn-substituted carbon substituent. Moreover, the anti product (**5**) would be available as well by using R^2 as the nucleophile and R^1 as the allene substituent. This motif, and the closely related motif wherein the carbonyl is replaced with hydroxyl, is widely distributed in substances of biomedical relevance including erythromycin,[2a] cytochalasin D,[2b] and the galbonolides,[2c] oligomycins,[2d] and streptovaricins[2e] among others.

Our study focused on organocuprates, owing to the advantages of these mild reagents.[3] Dioxirane oxidation of allenes [e.g., **4** = dimethyl dioxirane (DMDO)] gave isolable SDEs, and as summarized in Table 1, a survey of methylcuprate reactions revealed that this class of reagent effects two types of SDE transformations: regioselective nucleophilic opening to give the α-hydroxy, α′-substituted ketone (**7**) and regioselective reductive opening to give the α-hydroxy ketone (**8**). The stoichiometry of cuprate reagent, solvent, and source of organic ligand significantly influence the course of the reaction. Higher order cuprates, known to be the reagents of choice for halide displacement, tosylate displacement, and epoxide opening,[4] gave lower product selectivity in ether. As with simple epoxide opening, ether is superior to THF, in that the reactions appear cleaner and faster.[5] Still, most reaction conditions favor the reduction pathway (→**8**) over addition (→**7**), except for lower order cyanocuprates. For this type of cuprate, typically used to displace activated halides and related leaving groups,[3,4,6] the more Lewis acidic Grignard-derived reagents gave the reduced product (entries 6 and 7), whereas organolithium-derived reagents gave the addition product (entries 9 and 10).

Reduction of alkyl halides[7] and epoxides[8] by Cu(I), instead of substitution, is known. When the reaction of entry 7 was quenched with D_2O, the α-hydroxy α′-deutero ketone was obtained, indicating SDE reduction to the α-hydroxy α′-ketone enolate or closely related species. One explanation consistent with these data is that the Cu(I) reagent adds to the SDE to form an α-keto-Cu(III) species. Such an intermediate could either reductively eliminate to give **7** or convert to the corresponding enolate and ultimately give **8**. According to this model, reductive elimination (→**7**) could be faster than rearrangement in the presence of the lithium counterion, whereas the more acidic magnesium counterion could induce isomerization (→**8**).[9]

We focus the remainder of the discussion on the method of carbon nucleophile delivery to SDEs. Allenes **6a**−**d** were oxidized with DMDO in chloroform[10] and then exposed to organocuprates (Table 2). The selectivity of the first oxidation, at the more substituted double bond, is excellent (r_1 = >20:1). The selectivity of the second oxidation is modest to good (r_2 = 2−8:1). In all cases, the ratio of SDEs obtained from allene oxidation matched the ratio of products obtained from cuprate addition. Crystallographic analysis of a derivative of the major product of entry 3 confirmed the syn stereochemistry of the addition product.[11] Thus, copper-mediated nucleophilic addition takes place with inversion.

Scheme 1

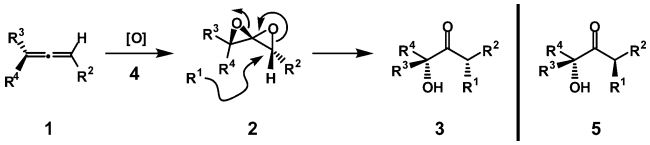
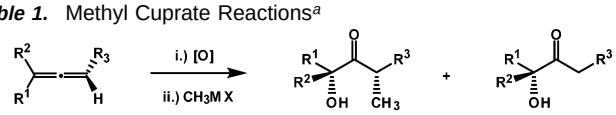


Table 1. Methyl Cuprate Reactions[a]



6a: R^1, R^3 = *n*-Bu, R^2 = H
6b: R^1, R^2 = *n*-Bu, R^3 = *i*-Bu

entry	allene	cuprate conditions	solvent	temp (°C)	yield (%) 7:8
1	**6b**	Me_2CuLi, LiI	THF	−78 to 0	23:53
2	**6b**	Me_2CuLi, LiBr	THF	−78 to 0	21:52
3	**6b**	Me_2CuLi, Me_2S, LiBr	THF	−78 to 0	33:42
4	**6b**	$Me_2Cu(CN)Li_2$	ether	−78 to 0	17:52
5	**6b**	(MeCuBr)MgBr, LiBr	THF	−78 to 0	44:15
6	**6a**	MeCu(CN)MgBr	ether	−10 to rt	<3:72
7	**6b**	MeCu(CN)MgBr	ether	−10 to rt	<3:78
8	**6b**	MeCu(CN)Li	THF	−10 to rt	51:20
9	**6a**	MeCu(CN)Li	ether	−10 to rt	74:<3
10	**6b**	MeCu(CN)Li	ether	−10 to rt	81:<3

[a] Reactions employed 3.0 equiv of DMDO in $CHCl_3$, −40 °C to rt, 2 h.

Allene oxidation/organocuprate addition gives substituted hydroxy ketones with high efficiency. Delivery of methyl generally takes place rapidly at 0 °C (entries 1−3). Consistent with known trends in cuprate addition, other alkyl ligands transfer from copper more rapidly than methyl and could be carried out at −78 °C (entries 5−15) or −40 °C (data not shown) with no variation in yield. A slight monotonic decrease in yield is notable with increased β-branching of the nucleophile (methyl → butyl → $TMSCH_2$). For trisubstituted SDEs (entries 13−15), the yield with phenyl cyanocuprate was low (10−20%). We were pleased to find that the more reactive Gilman reagent efficiently delivered phenyl. Although lower order cyanocuprates are preferred, the more reactive Gilman reagents prove useful when fast transferring ligands are of interest.[3,4,12] In each instance, the nucleophile was delivered regioselectively to the most accessible site of the SDE. No special precautions were required beyond those normally used for cuprate additions. The yields from allene to hydroxy ketone are excellent (77−92% average for oxidation and addition).

We prepared the stereotetrad of erythromycin (**10**) by using this method (Scheme 2). Known glycolic acid derivative **13**[13] was

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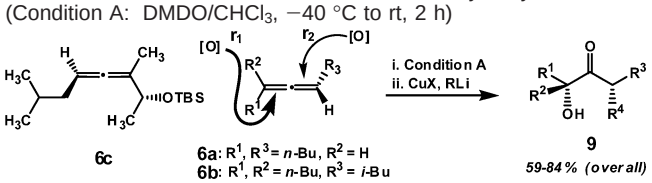
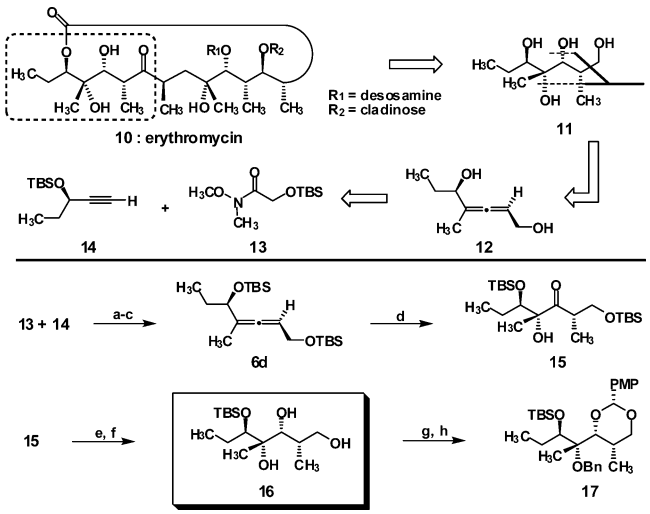
Table 2. Conversion of Allenes to Substituted Hydroxy Ketones (Condition A: DMDO/$CHCl_3$, −40 °C to rt, 2 h)



entry	allene	R^4	temp (°C)	time (h)	Selectivity r_1	Selectivity r_2	yield (%)
1[a]	**6a**	CH_3	0	0.5	>20:1	2:1	74
2[a]	**6b**	CH_3	0	0.5	>20:1	na	81
3[a]	**6c**	CH_3	0	0.5	>20:1	6:1	84
4[b,e]	**6d**	CH_3	−78 to rt	5.5	>20:1	8:1	80
5[a]	**6a**	*n*-Bu	−78 to rt	2	>20:1	na	67
6[a]	**6b**	*n*-Bu	−78 to rt	2	>20:1	na	72
7[a]	**6c**	*n*-Bu	−78 to rt	2	>20:1	6:1	76
8[b,e]	**6d**	*n*-Bu	−78 to rt	7	>20:1	8:1	66
9[a]	**6a**	$TMS-CH_2$	−78 to rt	2	>20:1	2:1	66
10[a]	**6b**	$TMS-CH_2$	−78 to rt	2	>20:1	na	65
11[a]	**6c**	$TMS-CH_2$	−78 to rt	2	>20:1	6:1	68
12[a]	**6a**	Ph	−78 to rt	2	>20:1	2:1	59
13[c]	**6b**	Ph	−78 to rt	2	>20:1	na	71
14[c]	**6c**	Ph	−78 to rt	2	>20:1	6:1	65
15[d,e]	**6d**	Ph	−78 to rt	5	>20:1	8:1	62

[a] 2.5 equiv of CuCN, 2.5 equiv of RLi, ether. [b] 5 equiv of CuCN, 5 equiv of *n*-BuLi, ether. [c] 3 equiv of CuI, 6 equiv of PhLi, ether. [d] 6 equiv of CuI, 12 equiv of PhLi, ether. [e] See Scheme 1 for the structure of **6d**.

Scheme 2 [a]



[a] Conditions: (a) *n*-BuLi, ether, −78 °C to rt, then **13**, −20 °C; (b) {[1*S*,2*S*)-TsDPEN]RuCl(η^6-*p*-cymene)} (5 mol %), *i*PrOH, rt, 87% (2 steps), >95:5 dr; (c) i. MsCl, Et_3N, CH_2Cl_2, −78 °C to rt; ii. MeLi, CuCN, ether, −78 °C to rt, 98%, >95:5 dr; (d) i. DMDO/$CHCl_3$, −40 °C to rt; ii. MeLi, CuCN, ether, −78 °C to rt, 80%, 8:1 dr; (e) AcOH, H_2O, THF, rt, 85%; (f) $(CH_3)_4NHB(OAc)_3$, CH_3CN, AcOH, −40 °C to rt, 90%, 6:1 dr; (g) $MeOC_6H_4CH(OMe)_2$, PPTS, rt, 91%; (h) BnBr, NaH, $(n\text{-Bu})_4NI$, DMF, HMPA, rt, 76%.

alkynylated with **14**[14] and then reduced[15] by enantioselective Noyori hydrogenation to the propargyl alcohol (87% (two steps), >95:5 dr). This was exposed to mesyl chloride, and the crude mesylate was converted to allene **6d** (99%). Subjection of **6d** to oxidation/organocuprate addition gave the desired syn-α-hydroxy, α′-methyl ketone (**15**). The diastereomers were readily separated by silica gel chromatography after removal of the primary silyl group. Reduction,[16] directed by the primary alcohol, gave **16** (see box in Scheme 2). Proof of stereochemical assignment was established by preparing **17**. Selective conversion of **16** to the *p*-methoxy benzylidine followed by formation of the benzyl ether gave the known protected tetrol.[17] Thus, this oxygenated polypropionate stereotetrad was prepared in a short, efficient, and selective route.

In summary, we have disclosed the first example of a transition-metal-mediated transformation of SDEs and the first general method for addition of carbon nucleophiles to spirodiepoxide, an emergent functional group with considerable potential in synthetic applications. The method constitutes a concise approach to densely functionalized branched oxygenated motifs.

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Supporting Information Available: Synthetic methods and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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