Complementary Facial Selectivity in Conjugate Additions to γ-Hydroxyenones

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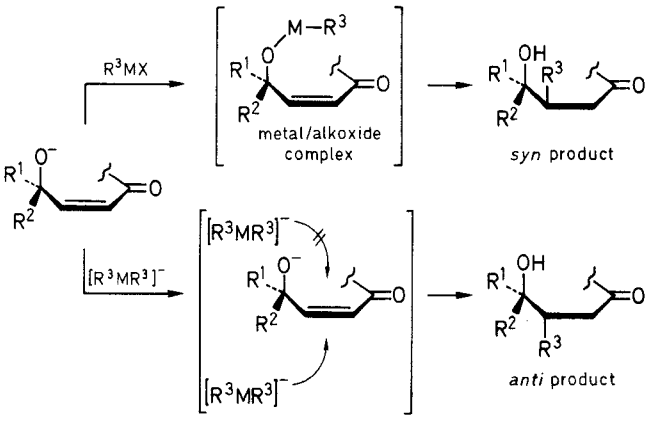
Complementary facial selectivity can be achieved in conjugate additions to γ-hydroxyenones by using either Grignard reagents or cuprates. In the case of the former, preliminary complexation of the magnesium reagent with the resident alkoxide, followed by alkyl group transfer, results in the exclusive formation of the syn product. Conversely, cuprate conjugate additions proceed in an anti fashion, presumably because, in this mode of addition, coulombic repulsions are minimized.

Alkoxides can serve as efficient groups for controlling both the regio- and stereoselectivity of nucleophilic additions. Examples of this phenomenon have been reported from a number of laboratories,[1] including our own.[2] The concept, in its simplest embodiment, involves the initial complexation of a nucleophilic reagent by an appropriately positioned alkoxide (oxido) group, followed by intramolecular delivery of the bound nucleophile to a proximate electrophilic center (vide infra).[3,4] Although the intermediates in these reactions are often more complex than is depicted by the general structure in the Scheme,[2b] the validity and utility of this complexation/delivery concept nonetheless remains intact. In this paper we report the details of a general method which utilizes the directing effects of a neighboring alkoxide group for controlling the facial selectivity of conjugate additions to γ-hydroxyenones. In particular, selective additions of alkyl substituents to either π-face of the unsaturated ketone can be efficiently achieved.



Scheme

We have previously reported that syn addition products could be obtained from reactions of Grignard reagents with a variety of quinol alkoxides.[2] In this study we extend the scope of the methodology to include Grignard reagents which possess a variety of different types of alkyl groups. In particular, as noted in entries 1, 3, 6, 8, 10 and 12 of Table 1, syn additions of Grignard reagents to **1** can be accomplished efficiently with complete diastereofacial control. In general, based on the results reported both

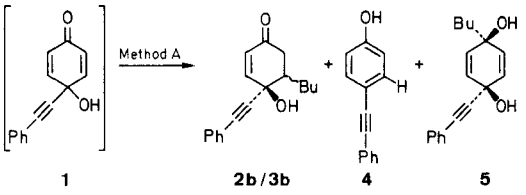
here and in our previous studies,[2] we can state state that these reactions work well with a wide variety of hydroxy-enones and Grignard reagents.

While this approach is clearly useful for the stereoselective construction of carbon–carbon bonds, its obvious limitation is that it only allows for the production of syn diastereomers. We reasoned that it might be possible to achieve the complementary anti mode of addition, if we employed metallocarbanionic reagents in which the metal in question was coordinatively saturated. Since complexation between the alkoxide and the metal is precluded under these circumstances, coulombic repulsions between the alkoxy group and the approaching nucleophile should disfavor syn attack and thereby allow for the formation of the desired anti product (*vide supra*).[5]

In attempting to evaluate the legitimacy of this concept, we sought a substrate which possesses minimal steric differences around the π-faces of the enone β-carbon, thereby permitting us to access accurately the magnitude of the effect of minimizing repulsive coulombic interactions.[6] Toward this end, we selected alkynyl quinol **1** as the substrate of choice since: (a) the alkynyl and hydroxy substituents are similar in size[7] and (b) the diastereomeric syn addition products were available to us via the previously described Grignard methodology. Regarding the coordinatively unsaturated metallocarbanionic reagents, we chose to examine the reactions of cuprates.[8] As noted in entries 2, 4,5, 7, 9, 11 and 13 of Table 1, good to excellent anti selectivities could be obtained using a variety of cuprate reagents.

The next question to be addressed was whether one type of cuprate reagent is preferred over others. In this regard we examined the reactions of four different butylcuprate reagents with **1** (see Table 2). In the case of simple homocuprates or homocuprate/diethyl ester–boron trifluoride complex combinations, we observed good anti selectivity, but low chemical yields. The isolation of significant quantities of phenol **4** suggested that quinol reduction was competitive with conjugate addition. Since

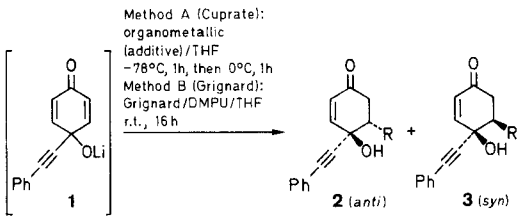
Table 2. Comparison of Various Butylcuprate Additions to **1**



1 **2b/3b** **4** **5**

Entry	Organometallic (equiv.)	Additive (equiv.)	Yield (%)		
			2a/3a (anti/syn)	**4**	**5**
1	Bu_2CuLi (2)	–	22 (95 : 5)	27	20
2	Bu_2CuLi (2)	$BF_3 \cdot OEt_2$ (1)	21 (> 95 : 5)	36	–
3	$Li_2(Bu)_2CuCN$ (1.5)	–	85 (93 : 7)	–	–
4	$Li_2(Bu)_2CuCN$ (1.5)	$BF_3 \cdot OEt_2$ (1)	61 (95 : 5)	–	–

Table 1. Comparison of Cuprate and Grignard Additions to **1**



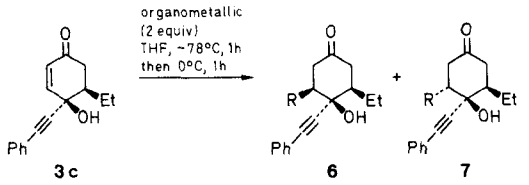
1 **2** (*anti*) **3** (*syn*)

Entry	Method	Organometallic or Grignard	Additive[d]	Product **2/3**	R	Yield[a] (%)	Ratio[b] *anti/syn*
1	A	$4\text{-}FC_6H_4MgBr$	DMPU	**a**	$4\text{-}FC_6H_4$	59	0 : 100
2	B	$(4\text{-}FC_6H_4)_2CuMgBr$	–	**a**	$4\text{-}FC_6H_4$	51	86 : 14
3	A	BuMgCl	DMPU	**b**	Bu	83	0 : 100
4	B	$Li_2(Bu)_2CuCN$	–	**b**	Bu	85	93 : 7
5	B	$Li_2(Bu)$(2-thienyl)CuCN	$BF_3 \cdot OEt_2$	**b**	Bu	61	95 : 5
6	A	EtMgBr	DMPU	**c**	Et	86	0 : 100
7	B	ClMg(Et)(2-thienyl)CuCN	$BF_3 \cdot OEt_2$	**c**	Et	52	> 98 : 2
8	A	MeMgCl	DMPU	**d**	Me	85	0 : 100
9	B	Li_2(Me)(2-thienyl)CuCN	$BF_3 \cdot OEt_2$	**d**	Me	29[c]	95 : 5
10	A	(vinyl)MgCl	DMPU	**f**	vinyl	68	0 : 100
11	B	Li_2(vinyl)(2-thienyl)CuCN	$BF_3 \cdot OEt_2$	**f**	vinyl	54	95 : 5
12	A	PhMgBr	DMPU	**e**	Ph	81	0 : 100
13	B	$LiPh_2Cu/Me_2S$		**e**	Ph	61	10 : 90

[a] Combined yield **2** + **3**.
[b] Ratio anti/syn determined by HPLC.
[c] Product was not cleanly isolated and was characterized by its ^1H NMR.
[d] DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone.

the mechanism of reduction is likely to involve single electron transfer, followed by expulsion of the undissociated hydroxy group, we speculated that this pathway could be suppressed by utilizing reagents which could rapidly deprotonate the hydroxy group and, as a consequence, dramatically reduce its ability to serve as a leaving group. As expected, the use of the more basic, higher order cuprates (either with of without diethyl ether–boron trifluoride complex) significantly improved the chemical efficiency of the addition without compromising the anti selectivity.

Table 3. Cuprate Additions to γ-Hydroxyenone **3**



Entry	Organometallic	Product 6/7	R	Yield (%)	Ratio *anti/syn*
1	$Li_2(Me)_2CuCN$	**a**	Me	65	10 : 90
2	Li_2(vinyl)(2-thienyl)Cu	**b**	vinyl	85	2 : 98

Finally, we examined cuprate conjugate additions to simple γ-hydroxyenones. Although the simple deletion of one cross-conjugated double bond appears to be a relatively innocuous change, it has profound consequences on the reactivity of these systems. Specifically, the problem is that in these systems enolate formation apparently becomes competitive with the deprotonation of the tertiary alcohol. Once an enolate is formed, conjugate addition is precluded. In an effort to circumvent this problem, we examined a variety of base/cuprate and cuprate/Lewis acid combinations. Virtually all of these proved unsuccessful. However, the simple expedient of employing two equivalents of higher order cuprates with the hydroxyenone **3c** resulted in the formations of the addition products in reasonable chemical yields and with good anti selectivity (see Table 3).

In conclusion, in this paper we have demonstrated that complementary facial selectivity can be efficiently achieved in conjugate additions to γ-hydroxyenones by using either Grignard reagents or cuprates.

THF was freshly distilled from potassium benzophenone ketyl. Et_2O was freshly distilled from sodium benzophenone ketyl. All other reagents were purchased from Aldrich and were used without further purification. Flash chromatography was performed following the method of Still.[9]

Table 4. Compounds **2, 3, 4, 7** Prepared

Compound	mp (°C)	Molecular Formula[a]	IR ν (cm^{-1})	MS *m/z* (%)
2a	108–109	$C_{20}H_{15}FO_2$ (306.3)	(thin film): 3400, 3070, 2910, 2240, 1675, 1511, 1074, 856, 764, 699	(EI): 306 (M^+, 2), 264 (17), 233 (6), 184 (100), 128 (62), 102 (61)
3a	160–163	$C_{20}H_{15}FO_2$ (306.3)	(thin film): 3400, 3090, 2970, 2240, 1672, 1513, 1082, 916, 760, 741, 700	(EI): 306 (M^+, 3), 288 (65), 257 (32), 183 (100), 128 (87), 102 (90)
2b	57–59	$C_{18}H_{20}O_2$ (268.4)	(thin film): 3400, 3060, 2965, 2235, 1673, 1488, 1038, 940, 758, 693	(EI): 268 (M^+, 0.2), 246 (12), 184 (100), 183 (89), 129 (28), 102 (24)
3b	oil	$C_{18}H_{20}O_2$ (268.4)	(thin film): 3400, 3070, 2970, 2940, 2239, 1675, 1495, 1052, 948, 740, 700	(EI): 268 (M^+, 3), 226 (26), 197 (32), 183 (100), 138 (42), 102 (51)
2c	84–86	$C_{16}H_{16}O_2$ (240.3)	(thin film): 3300, 3081, 2985, 2837, 2239, 1680, 1385, 1261, 931, 761	(EI): 240 (M^+, 4), 183 (100), 170 (36), 128 (54), 102 (47), 82 (21)
3c	oil	$C_{16}H_{16}O_2$ (240.3)	(thin film): 3400, 3075, 2980, 2895, 2243, 1680, 1492, 1263, 920, 761, 697	(EI): 240 (M^+, 2), 198 (18), 128 (50), 115 (11), 102 (40), 77 (14)
2d	oil	$C_{15}H_{14}O_2$ (226.3)	–	–
3d	oil	$C_{15}H_{14}O_2$ (226.3)	(thin film): 3380, 3065, 2978, 2940, 2230, 1675, 1493, 1383, 1254, 1071, 1038, 978, 937, 756, 691	(EI): 226 (M^+, 1), 198 (21), 184 (49), 183 (100), 128 (65), 102 (78), 82 (24)
2f	83–85	$C_{20}H_{16}O_2$ (288.3)	(KBr): 3430, 3050, 2930, 2220, 1670, 1480, 1361, 1250, 1060, 731, 651[b]	(EI): 288 (M^+, 2), 229 (20), 207 (39), 183 (100), 128 (47), 82 (48)
3f	106–107	$C_{20}H_{16}O_2$ (288.3)	(KBr): 3340, 3050, 2930, 2210, 1670, 1480, 1361, 1250, 1070, 740, 671[b]	(EI): 288 (M^+, 2), 270 (43), 207 (39), 183 (100), 128 (46), 82 (47)
2e	oil	$C_{16}H_{14}O_2$ (238.3)	(thin film): 3380, 3090, 2980, 2930, 2240, 1690, 1496, 1260, 950, 760, 693	(EI): 238 (M^+, 3), 183 (100), 128 (51), 102 (73), 82 (25)
3e	oil	$C_{16}H_{14}O_2$ (238.3)	(thin film): 3400, 3080, 2980, 2930, 2238, 1678, 1489, 1266, 930, 760, 693	(EI): 238 (M^+, 2), 183 (100), 128 (48), 102 (49), 82 (15)
4	123–125	$C_{14}H_{10}O_2$ (210.2)	(KBr): 3420, 3060, 2230, 1610, 1508, 1372, 1145, 1101, 829, 748, 692	(FAB): 194 (M^+)
7a	oil	$C_{17}H_{20}O_2$ (256.3)	(thin film): 3420, 3070, 2970, 2930, 2245, 1708, 1499, 1020, 750, 690	(EI): 256 (M^+, 25), 185 (71), 183 (92), 171 (100), 158 (73), 102 (95)
7b	oil	$C_{18}H_{20}O_2$ (268.4)	(thin film): 3450, 3100, 2980, 2860, 2241, 1715, 1494, 1430, 970, 760, 695	(EI): 268 (M^+, 8), 193 (25), 185 (61), 172 (42), 157 (56), 102 (100), 54 (80)

[a] Satisfactory microanalysis or HRMS obtained; C ±0.26, H ±0.25, **2d, 3d** HRMS ±0.006 amu.

Table 5. NMR Data of Compounds **2, 3, 4, 7** Prepared

Compound	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ, J (Hz)
2a	7.38 (m, 2H), 7.31 (s, 5H), 7.09 (t, $^3J_{HF}$ = 8.6, J_{HH} = 8.6, 2H), 7.02 (d, J = 10.1, 1H), 6.11 (d, J = 10.1, 2H), 3.60 (dd, J = 13.3, 3.4, 1H), 3.20 (dd, J = 16.1, 13.3, 1H), 2.56 (dd, J = 16.1, 3.4, 1H), 2.32 (s, 1H)	199.29, 162.16 (d, J_{CF} = 247), 148.00, 133.80 (br s), 131.05, 130.58 (d, $^3J_{CF}$ = 8.0), 128.48, 127.86, 127.47, 121.46, 114.38 (d, $^2J_{CF}$ = 21), 89.59, 86.75, 66.23, 48.92, 38.33
3a	7.41 (m, 2H), 7.34 (s, 5H), 7.09 (t, $^3J_{HF}$ = 8.6, J_{HH} = 8.6, 2H), 7.01 (d, J = 10.1, 1H), 6.06 (d, J = 10.1, 2H), 3.55 (dd, J = 14.3, 3.3, 1H), 3.13 (dd, J = 16.4, 14.3, 1H), 2.71 (dd, J = 16.4, 3.3, 1H), 2.46 (s, 1H)	198.51, 162.50 (d, J_{CF} = 247), 151.16, 133.07 (br s), 131.03, 130.33 (d, $^3J_{CF}$ = 7.1), 128.63, 127.87, 126.70, 121.29, 114.55 (d, $^2J_{CF}$ = 21.7), 89.70, 85.04, 70.30, 50.90, 40.54
2b	7.39 (m, 2H), 7.31 (m, 3H), 6.90 (d, J = 10.1, 1H), 5.98 (d, J = 10.1, 1H), 2.99 (s, 1H), 2.61 (dd, J = 16.5, 4.3, 1H), 2.49 (dd, J = 16.5, 10.2, 1H), 2.30 (m, 1H), 1.96 (m, 1H), 1.4–1.3 (m, 5H), 0.89 (t, J = 7.6, 3H)	199.79, 149.27, 131.13, 128.25, 127.77, 127.29, 121.69, 90.09, 85.04, 66.94, 44.37, 38.16, 28.45, 28.24, 22.06, 13.35
3b	7.40 (m, 2H), 7.32 (m, 3H), 6.89 (d, J = 10.0, 1H), 5.95 (d, J = 10.0, 1H), 2.62 (dd, J = 16.5, 3.4, 1H), 2.60 (s, 1H), 2.36 (dd, J = 16.5, 13.2, 1H), 2.21 (m, 1H), 1.93 (m, 1H), 1.5–1.2 (m, 5H), 0.91 (t, J = 7.0, 3H)	199.59, 153.40, 131.09, 128.25, 127.72, 126.07, 121.40, 87.60, 85.20, 69.33, 45.80, 39.93, 29.08, 28.22, 22.16, 13.44
2c	7.44 (m, 2H), 7.33 (m, 3H), 6.90 (d, J = 10.1, 1H), 6.00 (d, J = 10.1, 1H), 2.65 (dd, J = 16.5, 4.1, 1H), 2.50 (dd, J = 16.5, 10.5, 1H), 2.29 (s, 1H), 2.25 (m, 1H), 2.05 (m, 1H), 1.44 (m, 1H), 1.00 (t, J = 7.5, 3H)	199.86, 149.65, 131.13, 128.22, 127.77, 127.10, 121.58, 90.03, 84.84, 66.68, 46.25, 37.62, 21.55, 11.09
3c	7.41 (m, 2H), 7.33 (m, 3H), 6.90 (d, J = 10.0, 1H), 5.94 (dd, J = 10.0, 0.9, 1H), 2.81 (s, 1H), 2.68 (ddd, J = 16.6, 3.5, 0.9, 1H), 2.36 (dd, J = 16.6, 13.2, 1H), 2.17 (m, 1H), 2.04 (m, 1H), 1.50 (m, 1H), 1.01 (t, J = 7.5, 3H)	199.36, 152.36, 152.88, 131.65, 128.87, 128.27, 127.02, 121.57, 88.18, 85.25, 69.93, 48.05, 39.91, 22.84, 11.20
2d	7.43 (m, 2.0H, H-8), 7.33 (m, 3.0H, H-9, 10), 6.90 (d, J = 10.0, 0.9H, H-3), 5.92 (dd, J = 10.0, 0.9, 0.9H, H-2), 2.80 (s, 1.0H, OH), 2.60 (m, 3.0H, H-12, 11), 1.15 (t, J = 7.3, 3.0H, H-12)	
3d	7.44 (m, 2.0H, H-8), 7.31 (m, 3.3H, H-9, 10), 5.99 (d, J = 10.1, 2.0H, H-3 or 2), 5.95 (d, J = 10.1, 1.9H, H-2 or 3), 2.59 (s, 1.0H, OH), 2.10 (s, 1.0H, OH), 1.37 (s, 3.0H, H-11)	199.71, 149.35, 131.12, 128.21, 127.76, 127.04, 121.56, 89.80, 84.66, 66.37, 40.80, 39.57, 14.50
2e	7.41 (m, 2H), 7.33 (m, 3H), 6.90 (d, J = 10.1, 1H), 6.10 (m, 1H), 6.02 (d, J = 10.0, 1H), 5.37 (d, J = 17.5, 1H), 5.30 (d, J = 14.0, 1H), 3.15 (q, J = 7.5, 1H), 2.69 (m, 2H) (s, 1H)	198.70, 149.51, 134.62, 131.20, 128.35, 127.81, 127.32, 121.41, 118.20, 89.20, 85.50, 65.97, 48.64, 2.49, 38.31
3e	7.44 (m, 2H), 7.32 (m, 3H), 6.92 (d, J = 10.0, 1H), 6.10 (m, 1H), 6.03 (d, J = 10.0, 1H), 5.36 (d, J = 10.5, 1H), 5.30 (d, J = 17.7, 1H), 3.16 (m, 1H), 2.76 (m, 3H), 38.66	198.47, 148.86, 134.91, 131.62, 128.81, 128.55, 127.08, 121.54, 118.97, 89.18, 85.82, 66.19, 49.07
2f	7.40–7.29 (m, 10H), 7.01 (d, J = 10.1, 1H), 6.10 (d, J = 10.1, 1H), 3.60 (dd, J = 13.2, 4.4, 1H), 3.24 (dd, J = 16.2, 13.2, 1H), 2.57 (dd, J = 16.2, 4.4, 1H), 2.46 (s, 1H)	198.42, 151.36, 136.77, 131.07, 128.87, 128.51, 127.86, 127.68, 127.54, 126.65, 121.00, 88.92, 84.84, 69.77, 51.75, 40.44
3f	7.44 (m, 2H), 7.35 (m, 5H), 7.03 (d, J = 10.1, 1H), 6.04 (d, J = 10.1, 1H), 3.54 (dd, J = 14.1, 3.3, 1H), 3.13 (dd, J = 16.5, 14.1, 1H), 2.76 (dd, J = 16.5, 3.3, 1H), 2.60 (s, 1H)	198.42, 151.36, 136.77, 131.07, 128.87, 128.51, 127.86, 127.68, 127.54, 126.65, 121.00, 88.92, 84.84, 69.77, 51.75, 40.44
4	7.52 (m, 2H), 7.42 (d, J = 7.5, 2H), 7.33 (m, 3H), 6.80 (d, J = 7.5, 2H), 5.20 (s, 1H)	155.78, 133.25, 131.42, 128.29, 127.97, 123.45, 123.45, 115.61, 115.49, 89.19, 88.06
7a	7.48 (m, 2H), 7.34 (m, 3H), 2.74 (ddd, J = 8.7, 5.4, 1.0, 1H), 2.62 (ddd, J = 14.7, 5.4, 1.0, 1H), 2.42 (m, 2H), 2.25 (m, 2H), 2.09 (m, 2H), 1.27 (m, 1H), 1.16 (d, J = 7.0, 3H), 0.96 (t, J = 7.2, 3H)	210.54, 131.65, 128.55, 128.25, 122.063, 90.09, 86.36, 73,39, 45.67, 44.32, 41.87, 40.18, 22.13, 17.02, 11.81
7b	7.43 (m, 2H), 7.31 (m, 3H), 6.02 (m, 1H), 5.22 (d, J = 10.2, 1H), 5.19 (d, J = 17.7, 1H), 2.92 (m, 2H), 2.69 (m, 2H), 2.54 (dd, J = 15.0, 7.8, 1H), 2.41 (dd, J = 15.0, 7.5, 1H), 2.09 (m, 2H), 1.25 (m, 1H), 0.93 (t, J = 7.4, 3H)	209.98, 136.74, 131.57, 128.60, 128.25, 122.02, 118.59, 89.94, 86.74, 71.96, 49.01, 45.77, 41.78, 41.65, 21.73, 11.75

(4*R,5*S**)-5-Ethyl-4-hydroxy-4-(phenylethynyl)-2-cyclohexenone (2c) and (4*R**,5*R**)-5-Ethyl-4-hydroxy-4-(phenylethynyl)-2-cyclohexenone (3c); Typical Procedures:**

Method A (*Cuprate*): A 100 mL Schlenk flask equipped with a septum and nitrogen inlet was charged with lithium cyano(2-thienyl)copper(I) in THF (0.25 M, 60 mL, 15 mmol). The flask was cooled to −78 °C and EtMgCl in THF (3.0 M, 7.5 mL, 15 mmol) was added slowly. The Schlenk flask was allowed to warm to 0 °C for 1 min. Then the solution was recooled to −78 °C and used directly.

To a 500 mL three neck round-bottomed flask equipped with a magnetic stir bar, a thermometer inlet with thermometer and 2 septa, benzoquinone (1.08 g, 10 mmol) and anhydr. THF (100 mL) were added. The solution was cooled to −78 °C and 1 M lithium phenylacetylide in THF (11 mL, 11 mmol) was added. The blue solution was stirred for 1 h at this temperature. $BF_3 \cdot Et_2O$ (1.3 mL, 10 mmol) was added, followed quickly by the cuprate solution, which was added by cannula. The brown-red mixture was stirred for 1 h at −78 °C. Then the mixture was warmed to 0 °C and stirred for 1 h; the color of the mixture had turned brown. The reaction was quenched with ammonium buffer solution (pH 10, 40 mL), and then Et_2O (40 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 36 mL). The organic layers were combined, washed with water (2 × 50 mL) and then with brine (50 mL) and dried (anhydr. $MgSO_4$). The solvent was removed in vacuo. The residue was purified by flash column chromtography using 5:1 hexane/EtOAc which gave the product as a yellow oil (1.25 g, 52% yield).

Method B (*Grignard*): To a 500 mL three-neck round-bottomed flask equipped with a magnetic stir bar, a thermometer inlet with thermometer and 2 septa, benzoquinone (2.16 g, 20 mmol) and anhydr. THF (200 mL) were added. The solution was cooled to −78 °C and 1 M lithium phenylacetylide in THF (21 mL, 21 mmol) was added. The blue solution was stirred for 1 h at this temperature. DMPU (15.8 mL, 120 mmol) was added and stirred for 15 min. Then

3.0 M EtMgCl in THF (7.0 mL, 21 mmol) was added. The mixture was warmed to ambient temperature and stirred for 16 h. The reaction was quenched with sat. aq NH_4Cl solution (70 mL) and Et_2O (70 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 35 mL). The organic layers were combined, washed with water (90 mL) and with brine (90 mL) and dried (anhydr. $MgSO_4$). The solvent was removed in vacuo. The residue was purified by flash column chromatography using 5:1 hexane, EtOAc which gave the product as a yellow oil (4.12 g, 86 % yield).

3-Alkyl-5-ethyl-4-hydroxy-4-(phenylethynyl)cyclohexanones 6 and 7: Using the typical procedure, Method A with **3c** (200 mg, 0.83 mmol) in THF at − 78 °C and $Li_2(Me)_2CuCN$ (1.7 mmol), THF (25 mL) or Li_2(vinyl)(2-thienyl)CuCN (1.7 mmol) in THF (10 mL).

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(5) Of course, alkoxide ions are always associated with a solvated counterion and these ion pairs may exist in either monomeric or aggregated forms. Because of their size, the solvated counterion could block the syn approach of a nucleophile. Although we can not exclude this mechanism of action based on the data we have obtained, the product stereochemistry which results from either pathway should be the same.
(6) For example, 4-(*tert*-butyldimethylsiloxy)cyclohexenone has been reported to undergo preferential anti conjugate addition with lithium dimethylcuprate. However, in this case the π-face syn to the oxygen is considerably more hindered than is the corresponding anti face, so that it is difficult to separate steric and electronic effects. Note, although the anti addition product was apparently preferred, the actual anti/syn ratio which was obtained was not reported. See:
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