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A Mild Anionic Method for Generating *o*-Quinone Methides: Facile Preparations of *Ortho*-Functionalized Phenols

Ryan M. Jones, Ryan W. Van De Water, Christopher C. Lindsey, Christophe Hoarau,
Thay Ung, and Thomas R. R. Pettus*

*Department of Chemistry and Biochemistry, University of California,
Santa Barbara, California 93106-9510*

pettus@chem.ucsb.edu

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A low-temperature method for generating *o*-quinone methides is described which permits facile introduction of assorted R substituents onto the aryl ring system at low temperature. The method is useful for the efficient preparation of *ortho*-ring-alkylated phenols.

Introduction

Ortho-functionalized phenols are ubiquitous among natural products. Often the riposte for their synthesis has been rearrangement,[1] electrophilic substitution,[2] halogenation,[3] or a metal-mediated coupling process.[4,5] However, these methods (Figure 1) do not address all types of ring-alkylated phenols effectively. For instance, consider converting hydroquinone or resorcinol into an allylated derivative with differentiated hydroxyl residues. Devising an efficient preparation for these types of substances is not a straightforward affair. While some reactions may introduce an alkyl residue onto the electron-rich aryl ring in a regioselective manner, distinguishing between the hydroxy residues and controlling the substitution at α and γ branched sites usually requires a lengthy or inefficient synthetic sequence; in particular, consider the usual methods for preparing *ortho*-prenylated phenols such as **35**−**36** shown in Table 3.[6]

In principle, an *o*-quinone methide, such as **1**, may pose a useful solution for constructing substituted aromatic systems of these kinds. However, beyond the customary [4 + 2] cycloadditions (i),[7] (Figure 3) the traditional forceful methods for generating **1** [I, II, III, IV, V, VI, Figure 2] are incompatible with most other types of reactions.

We speculated that an anionic triggering mechanism would be compatible with several other synthetically useful reactions. For example, if **1** is generated under anionic conditions, then it should undergo a conjugate addition—significantly increasing the synthetic scope of monocyclic *o*-quinone methides. Furthermore, low-temperature generation of **1** may overcome complications that have hampered widespread use of previous methods, such as an intolerance for other functional groups and low *endo*/*exo* selectivity in [4 + 2] reactions (Figure 3).

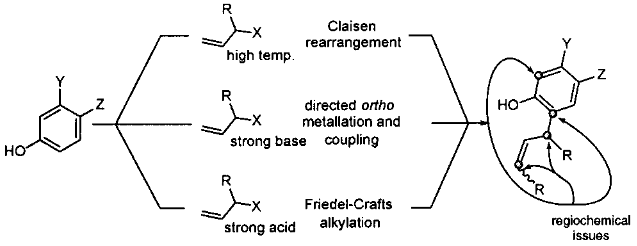

Figure 1. Traditional methods for *ortho* elaboration of phenols.

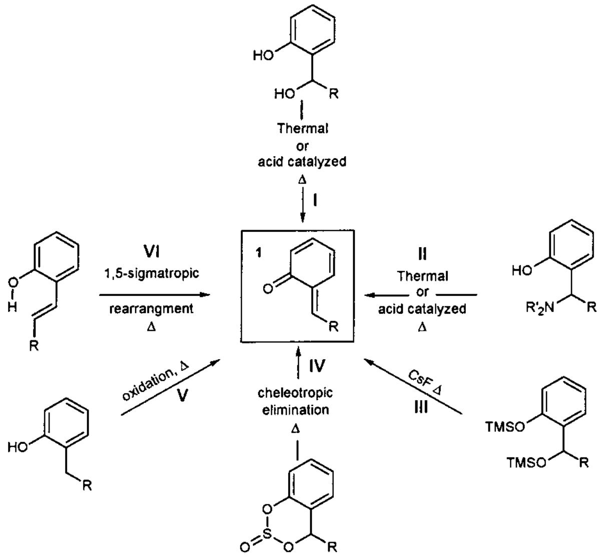

Figure 2. Prior methods for generating *o*-quinone methides **1**.

Two reports suggested to us that a mild anionic triggering mechanism for generating **1** was plausible. McLoughlin[8] and Mitchell[9] independently showed that

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[1] For work regarding Claisen rearrangement, see: Rhoads, S. J. *Organic Reactions*; John Wiley & Sons, Inc.: New York, 1974; Vol. 22, p 1. For work regarding the Fries rearrangement, see: Martin R. *Org. Prep. Proc. Int.* **1992**, *24*, 369−435.

[2] Nagata, W.; Okada, K.; Aoki, T. *Synthesis* **1979**, 365−368.

[3] Mitchell, R. H.; Lai, Y−H.; Williams, R. V. *J. Org. Chem.* **1979**, *44*, 4733−4735.

[4] Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.

[5] Oxidative insertion with electron-rich aryl halides is difficult. Knochel, P.; Majid, T. *Tetrahedron Lett.* **1990**, *31*, 4413−4416.

[6] For a fairly complete list of aryl prenylation methods, see: Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953, S4 of supporting information.

[7] A variety of targets have been constructed using monocyclic *o*-quinone methides in [4 + 2] reactions including carpanone, bruceol, cannibinol, troglitazone, pisatin, nipradilols, and tocopherol.

[8] McLoughlin, B. J. *J. Chem. Soc., Chem. Commun.* **1969**, 540−541.

10.1021/jo001752e CCC: $20.00

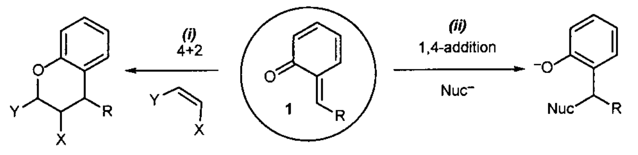


Figure 3. Reactions compatible with an anionic trigger.

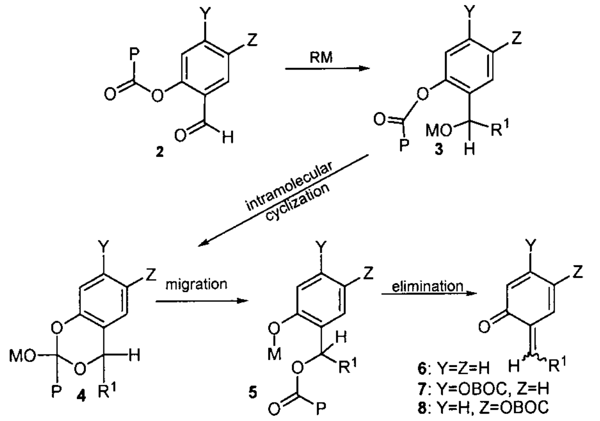


Figure 4. Mild anionic triggering mechanism.

reduction of *ortho*-O-acylated phenones results in a phenol displaying an *ortho* saturated alkyl substituent. Presumably, hydride addition results in alkoxide **3**, which proceeds to the phenoxide **5** via the *o*-ester **4**. The cascade then continues to the *o*-quinone methide **6**, which is subsequently reduced by a second hydride equivalent (Figure 4).

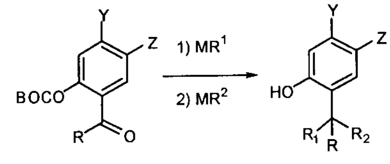
It seemed reasonable that **3** might also be accessible by combination of an aryl aldehyde, such as **2**, and an organometallic reagent. From a synthetic perspective, this combination would be of greater use. Moreover, **2** seems more readily accessible than the *o*-quinone methide precursors shown in Figure 2. However, regulation of the cascade remained as a significant obstacle. If the reaction was not carefully controlled, only products with two or more of the same substituent would be formed as in the reports of McLoughlin and Mitchell with hydride.[8,9]

Results and Discussion

Herein, we report that the cascade is controllable and access to an assortment of transient *o*-quinone methides can be achieved in a single operation resulting in a means to easily synthesize a range of *ortho*-ring-alkylated phenols.[10] The solution resides with the choice of the *O*-acyl residue [P] and other factors governing the addition, migration, and elimination, such as temperature, solvent, concentration, and the oxyphillic nature of the metal cation [M]. Three types of reactions were examined. Table 1 recounts products obtained upon addition of organometallic reagents to aldehydes, ketones, and esters **9**–**17**. Table 2 discloses products obtained from subjecting aldehydes **9**–**11** to reduction with various hydride reagents. Table 3 displays the outcome of the addition of organometallic reagents to benzyl alcohols.

Table 1. Ring-Alkylated Phenols from Aldehydes, Ketones, and Esters

aldehydes
9: R=H, Y=Z=H
10: R=H, Z=H, Y=OBOC
11: R=H, Y=H, Z=OBOC
ketones
12: R=Me, Y=Z=H
13: R=Me, Z=H, Y=OBOC
14: R=Me, Y=H, Z=OBOC
esters
15: R=OMe, Y=Z=H
16: R=OMe, Z=H, Y=OBOC
17: R=OMe, Y=H, Z=OBOC



#	SM	R^1M	R^2M	Product	%Yield
1	**9**	2.5eq. of MeMgCl	---	**18**	86
2	**10**	2.5eq. of MeMgCl	---	**19**	97
3	**11**	2.5eq. of MeMgCl	---	**20**	57
4	**11**	Inv. add. to	2.5eq. of MeMgCl	**20**	86
5	**15**	Inv. add. to	3.5eq. of MeMgCl	**21**	75
6	**16**	Inv. add. to	5eq. of MeMgCl	**22**	90
7	**17**	Inv. add. to	3.5eq. of MeMgCl	**23**	78
8	**12**	Inv. add. to	2eq. of MeMgCl	**21**	75
9	**13**	Inv. add. to	2eq. of MeMgCl	**22**	82
10	**12**	1.1eq. of MeLi	---	**24**	57
11	**13**	1.1eq. of MeLi	---	**25**	97
12	**14**	2.2eq. of MeLi	---	**26**	69
13	**10**	PhMgCl	MeMgCl	**31**	74
14	**10**	MeLi	$CH_2CHMgCl$	**28**	86
15	**10**	PhMgBr	Na-methyl malonate	**33**	73
16	**9**	PhMgBr	MeMgCl	**30**	71
17	**9**	MeLi	$CH_2CHMgBr$	**27**	56
18	**11**	PhMgBr	MeMgCl	**32**	50
19	**11**	MeLi	$CH_2CHMgBr$	**29**	65
20	**11**	PhMgBr	Na-methyl malonate	**34**	62

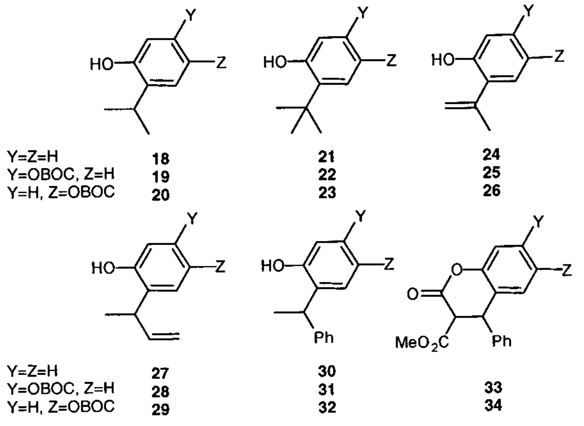


Table 1. The data (Table 1, entries 1–3) obtained by straightforward addition of MeMgCl (2.5 equiv) to aldehydes **9**–**11** at 0 °C suggested these were the highest yields that could be expected for a particular substitution pattern in subsequent reactions. For example, the isopropyl derivatives **18**–**20** are obtained in 86%, 97%, and 57%, respectively, by simply adding 2.5 equiv of MeMgCl to the respective aldehydes and stirring at 0 °C for 1 h. This trend in yield held true in subsequent reactions for the respective aldehydes (Table 1, entries 13–20). However, **20** can be prepared in 86%, averting formation of the side product **44** (Figure 5) by inverting the mode of addition (Table 1, entry 4). Inverse addition of aryl esters **15**–**17** and acetophenones **12**–**13** (0.1 M in Et_2O) to MeMgCl afforded the *tert*-butyl derivatives **21**–**23** in good yield (Table 1, entries 5–9). However, small amounts of

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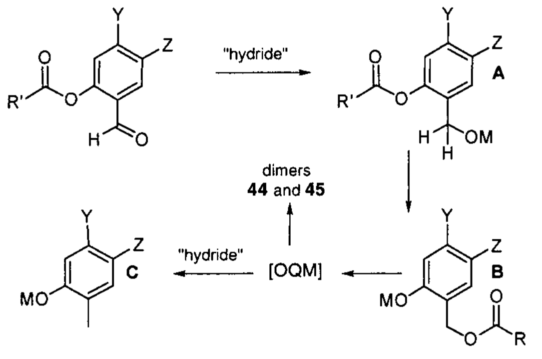
(9) Mitchell, D.; Doecke, C. W.; Hay, L. A.; Koenig, Thomas M.; Wirth, David D. *Tetrahedron Lett.* **1995**, 36, 5335–5338.

(10) For the initial communication of this work, see: Van De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*, 6502–6503.

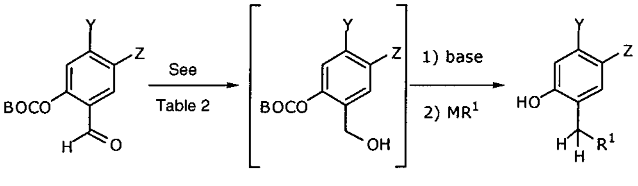
Table 2. Reduction of 9−11 with Various Hydride Sources



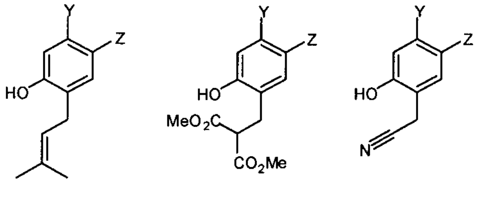
#	SM	° C	Reagent 1.05 eq.	Time min.	% of H^+ **A**	% of H^+ **B**	% of H^+ C	% of **44+45**
1	**9**	-78	L-selectride	10	--	50	--	>30
2	**10**	-78	L-selectride	15	23	77	--	--
3	**11**	-78	L-selectride	15	25	50	--	--
4	**9**	-78	$LiAl(OtBu)_3H$	15	88	--	--	--
5[a]	**11**	0	$LiAl(OtBu)_3H$	10	89	--	--	--
6	**9**	0	$NaBH_4$ THF/H_2O	5	40	--	12	>35
7[a]	**10**	0	$NaBH_4$ THF/H_2O	10	88	--	6	--
8	**11**	0	$NaBH_4$ THF/H_2O	5	76	--	24	--

[a] Optimal procedure, yield after purification by chromatography.

Table 3. Synthesis of Ring-Alkylated Phenols from Benzyladehydes

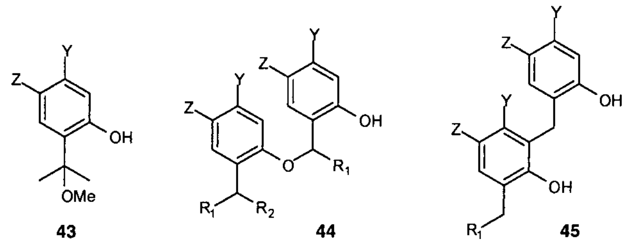


#	SM	Base	R^1M	Product	%Yield from RCHO
1	**10**	2 eq. of	$(CH_3)_2C{=}CHMgBr$	**35**	60
2	**11**	5 eq. of	$(CH_3)_2C{=}CHMgBr$	**36**	52
3	**9**	*t*-BuMgCl	Na-methyl malonate	**37**	51
4	**10**	*t*-BuMgCl	Na-methyl malonate	**38**	70
5	**11**	*t*-BuMgCl	Na-methyl malonate	**39**	68
6	**9**	*t*-BuMgCl	Bu_4NCN	**40**	62
7	**10**	*t*-BuMgCl	Bu_4NCN	**41**	76
8	**11**	*t*-BuMgCl	Bu_4NCN	**42**	60



Y=Z=H		**37**	**40**
Y=OBOC, Z=H	**35**	**38**	**41**
Y=H, Z=OBOC	**36**	**39**	**42**

several other compounds were evident in product mixtures. These include type **43** (Figure 5) methyl ethers (Table 1, entries 5−7, <5%) and styrenyl adducts corresponding to **24**−**26** (Table 1, entries 5−9, <5%). Since the undesired ether adduct is absent in reactions of acetophenones **12**−**13**, we conclude that **43** arises from the initial alkoxide proceeding through the cascade rather than collapsing to the corresponding acetophenone. The small amounts of styrenyl adduct observed most likely arise from competition between 1,5-sigmatropic shift and intermolecular 1,4-conjugate addition of the corresponding *β*-disubstituted *o*-quinone methide.



43 **44** **45**

Figure 5. Side products formed in several of these reactions.

Organolithium reagents did not lead to the anticipated adducts **18**−**23**. All attempts at multiple additions of organolithium reagents to aldehydes **9**−**11** and ester **16** failed. Quenching reactions initiated by organolithiums at low temperatures (−40 to −78 °C) resulted in isolation of the alcohol, the phenol that results from BOC migration, or mixtures of these products. However, since MeMgCl adds twice at −40 °C to **9**−**11** while MeLi does not, we concluded that the lithium species does not readily proceed to the corresponding *o*-quinone methide. The styrenyl adducts **24**−**26** further support this claim. These styrenyl adducts are formed quite rapidly when MeLi (1.0 equiv) is combined with the corresponding acetophenones **12**−**14** (0.1 M in Et_2O) at −78 °C (Table 1, entries 10−12). Although a 1,5-sigmatropic shift via a *β*-disubstituted *o*-quinone methide intermediate can explain the formation of these products, the fact that the identical intermediate generated by addition of MeMgCl (Table 1, entries 5−9) undergoes 1,4-addition suggests that *β*-disubstituted *o*-quinone methides are stable for a short period of time in solution. We therefore conclude that the styrenyl products **24**−**26** arise from intermolecular deprotonation of the corresponding cyclic carbonate, which arise from divergent collapse of intermediate **4**, facilitated by the lithium counterion.[11] This series of reactions demonstrate the importance of the identity of the counterion in controlling the course of the reaction.

In general, substitution of aldehydes **9**−**11** with two different nucleophiles to produce **27**−**34** (Table 1, entries 13−20) is accomplished by controlling the temperature of the initial nucleophilic addition, adding the less reactive nucleophile first, or initiating the cascade with an organolithium species. However, the substituents on the aryl aldehyde affect the conditions that can be employed. In regard to the addition of PhMgCl to aldehyde **9**, the resulting alkoxide **3** is evident by TLC at −78 °C, but if left untended slowly proceeds to multiple unidentified compounds. On the other hand, the type **3** alkoxides, formed from aldehydes **10** and **11**, appear stable by TLC at −40 °C for up to 9 h. Thus, we surmise that the *o*-quinone methides **7** and **8** form between −40 and 0 °C, while the *o*-quinone methide **6** forms at substantially lower temperatures. The specific temperature depends on the size of the *β*-substituent; a larger *β*-substituents requires a higher temperature.

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[11] See ref 10 for additional information.

Aldehyde **10** proved most forgiving. Several conditions led to differently branched products in similar yields. For instance, addition of methyllithium followed by the addition of PhMgCl, addition of PhMgCl followed by the addition of MeLi, and addition of PhMgCl followed by the addition of MeMgCl all afford **31** in similar yield. Compound **28** is prepared by adding MeLi (1.05 equiv) at −78 °C followed shortly thereafter by the addition of excess $CH_2{=}CHMgCl$ at −20 °C. Addition of the vinyl species as the second nucleophile prevents formation of the undesired 1,6-conjugate addition product that indeed does arise when the order of addition is reversed. Lactone **33** is produced in a manner analogous to that of compound **28**, with formation of the *o*-quinone methide initiated by addition of PhMgBr to **10**.

The window for successfully adding different nucleophiles to aldehyde **9** is narrower and likely reflects an increased electrophilicity of the carbonyl residues in the aldehyde and the carbonate. In particular, the BOC-residue *ortho* to the aldehyde is more susceptible to cleavage if the organometallic reagent used exhibits a significant amount of either LiOH or $Mg(OH)_2$. A second problem for these systems is the volatility of the phenol product. Since the *o*-quinone methide **6** forms at very low temperatures, the time between addition of the first and second reagent is kept to a minimum. Addition of freshly prepared PhMgBr, followed in 5 min by the addition of MeMgCl, affords **30** in 71%. In the case of **27**, however, MeLi is added to a solution of the aldehyde **9** (0.18 M in Et_2O), which is precooled to −78 °C. This addition is immediately followed by the addition of vinylmagnesium bromide. Warming to room temperature affords **27** in 56% along with 17% of **18**.

Substitution of **11** with two different nucleophiles proved to be challenging because of undesired formation of dimeric products of type **44** (Figure 5). However, this problem is surmountable by carefully regulating the temperature. Addition of MeLi (1.1 equiv) to **11** (0.18 M in THF at −78 °C) followed after 1 h by addition of $CH_2{=}CHMgBr$ (2 equiv) affords **29** in 65% after warming to room temperature. Similarly, addition of PhMgBr to **11** (0.1 M in toluene at −40 °C) followed in 20 min by addition of either MeMgCl or the sodium enolate of dimethyl malonate affords **32** and **34** in 50% and 62%, respectively.

Table 2. To construct nonbranched *ortho*-substituted phenols, reliable conditions for reducing aldehydes **9**−**11** to the corresponding benzyl alcohols were needed that averted potential dimer formation or over-reduction (Table 2). In some instances, the benzylic alcohol product decomposed on chromatography so the conditions had to proceed cleanly. McLoughlin's combination of $NaBH_4$/THF/H_2O had worked well with **10**, only if the reaction was carefully monitored and stopped after 10−30 min. However, the reduction of **9** occurred so rapidly that the formation of **C** could not be prevented. Thus, we paused to investigate other methods to reduce aldehydes **9**−**11**, determining the relative percentages of **A**, **B**, and **C** for various reduction conditions by examining crude ^1H NMR spectra to which DMF [1 equiv] had been added as an internal standard. In the case of **9**, addition of 1 equiv of $NaBH_4$ (1 M THF/H_2O) to **9** in THF at 0 °C for 10 min affords 40% and 12% of **A** and **C**, respectively. Addition of L-Selectride (1 M THF) to **9** (−78 °C, 10 min) leads to **B** contaminated with a significant amount of unidentifiable products. Reduction of **9** with $LiAl(OtBu)_3H$ (1 M THF, −78 °C, 1 h), however, afforded the benzyl alcohol quite cleanly. Aldehydes **10** and **11** underwent a clean reduction over a greater range of conditions. However, in general, reduction applying $LiAl(OtBu)_3H$ required less diligent attention.

Table 3. Equipped with efficient conditions for reducing aldehydes **9**−**11** to the corresponding benzyl alcohols (Table 2, entries 4, 7, and 5, respectively), yields for subsequent addition of nucleophiles were measured. Although adducts **35**−**42** can be obtained in one pot by addition of L-Selectride followed by addition of the corresponding nucleophile or by reduction of the aldehyde and addition of excess nucleophile to the crude benzyl alcohol, the best results are achieved by reducing the corresponding aldehyde with the appropriate conditions (see Table 2) and then adding excess of the nucleophile to the desired alcohol which has been purified by chromatography. Rapid addition of the respective anion to clean benzylic alcohol (0.1 M in Et_2O) stirring at 0 °C keeps formation of dimers **44** and **45** to a minimum. For example, quick addition of $BrMgCH{=}C(CH_3)_2$ to the corresponding crystalline alcohol afforded the prenyl derivatives **35**−**36** in 68% and 58%, respectively, or 60% and 52% when measured from the starting aldehydes **10** and **11** (Table 3, entries 1−2). To the best of our knowledge, this method is among the most efficient for preparing prenylated aromatics of this type. In interesting contrast to Table 1, entries 14 and 20, addition of a sodium hydride/methyl malonate solution in THF to the unbranched benzylic alcohol (0.1 M in Et_2O) provided the opened noncyclized diesters **37**−**39** (Table 3, entries 3−5). Nitriles **40**−**42** (Table 3, entries 6−8) are produced by addition of Bu_4NCN in THF to the alcohol (0.1 M in Et_2O), followed by the addition of *t*-BuMgCl to reinitiate the cascade. However, in the case of entries 3 and 6 the corresponding crude benzyl alcohol was used.

Conclusions

A new general procedure has been developed that permits a wide range of *ortho*-ring-alkylated phenols to be constructed including branched and unbranched analogues **18**−**42**, some of which are not easily accessible by other methods. The reaction proceeds by way of a manageable monocyclic *o*-quinone methide intermediate, which is not isolated but reacted in subsequent 1,4-additions.[12] Further applications using this anionic triggering mechanism, such as for initiating successive inter- and intramolecular [4 + 2] reactions (Figure 3), will be reported shortly.

Experimental Section

General Information. These reactions required reagents of the highest quality. All the reagents were newly purchased or freshly prepared as stipulated. Starting aryl aldehydes that were not scrupulously dried often led to lower than expected yields. Sublimation of **11** was necessary to remove H_2O. Lower than expected yields generally indicated a corrupt organometallic reagent, such as one that had undergone air oxidization or contained a large amount of $Mg(OH)_2$ or LiOH in the

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(12) *o*-Quinone methides are of use in the alkylation of DNA, see: Pande, P.; Shearer, J.; Yang J.; Greenberg, W. A.; Rokita, S. E. *J. Am. Chem. Soc.* **1999**, *121*, 6773−6779. For other *o*-quinone methide chemistry, see: Taing, M.; Moore, H. *J. Org. Chem.* **1996**, *61*, 329−340 and Turnbull, K.; Dyer, R. G. *J. Org. Chem.* **1999**, *64*, 7988−7995.

reaction mixture. All column chromatography was conducted using silica gel with the indicated solvent systems.

General Procedure for Protection with BOC$_2$O (9−17). To a solution of the phenol (2.60 g, 18.8 mmol, 0.5 M in THF) at 0 °C was added the di-*tert*-butyl dicarbonate (10.29 g, 47.1 mmol) followed by sodium hydride (1.41 g, 47.1 mmol, 80% dispersion in mineral oil). The mixture was stirred at room temperature for 4 h, after which the reaction was diluted with ether. The solution was then washed with water (caution: H_2 gas evolved) and brine, dried ($MgSO_4$), and concentrated. Chromatography with silica gel (1:10 EtOAc/petroleum ether) furnished the BOC material, as a white solid for all compounds except acetophenone derivatives **9**, **12**, and **15**.

9. Isolated yield, 87%. Yellow oil. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 10.20 (s, 1H), 7.90 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 1.6$ Hz), 7.67−7.62 (m, 1H), 7.43−7.39 (m, 1H), 7.29−7.27 (m, 1H), 1.59 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 188.9, 152.2, 151.5, 135.5, 130.9, 128.5, 126.6, 123.3, 84.7, 27.8; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 2985.6, 2926.8, 2861.2, 1762.8, 1699.2, 1605.6; MS (CI) *m*/*z* 167 (40), 123 (49), 57 (100); HRMS (CI) *m*/*z* calcd for $C_{12}H_{14}O_4$ 223.0970, found 223.0970.

10. Isolated yield, 94%, mp 58−60 °C. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 10.14 (s, 1H), 7.90 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 0.4$ Hz), 7.25−7.22 (m, 2H), 1.58 (s, 9H), 1.57 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 187.8, 156.1, 153.0, 151.0, 150.5, 131.7, 125.8, 119.3, 116.3, 85.1, 84.9, 27.8 (1 unresolved); IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 2984, 1765, 1699, 1694, 1608; MS FAB *m*/*z* 227 (43), 183 (100), 139 (62); FAB MS *m*/*z* calcd for $C_{17}H_{23}O_7$ 339.1444, found 339.1458.

11. Isolated yield, 98%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 10.16 (s, 1H), 7.71 (d, 1H, $J = 2.9$ Hz), 7.44 (dd, 1H, $J_1 = 8.9$ Hz $J_2 = 2.9$ Hz), 7.30 (d, 1H, $J = 8.9$ Hz), 1.58 (s, 9H), 1.57 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 187.75, 151.47, 151.3, 149.55, 149.00, 129.00, 128.29, 124.39, 122.74, 84.97, 84.54, 27.86, 27.83; IR [CH_2Cl_2, ν_{max} cm^{-1}] 2984.6, 1762.8, 1698.2; MS (CI) *m*/*z* 283 (100), 227 (86), 57 (38); HRMS (CI) *m*/*z* calcd for $C_{17}H_{22}O_7$ 339.1444, found 339.1444.

12. Isolated yield, 88%. Yellow oil. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.82 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.7$ Hz), 7.56−7.52 (m, 1H), 7.37−7.29 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.20 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 1.1$ Hz), 2.59 (s, 3H), 1.58 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 197.8, 151.7, 149.6, 133.6, 131.2, 130.5, 126.3, 123.8, 84.3, 29.7, 27.9; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 2986, 2935, 1760, 1690, 1602; MS (EI) *m*/*z* 136 (21), 121 (31), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{13}H_{16}O_4$ 237.1127, found 237.1121.

13. Isolated yield, 95%, mp = 72−73 °C (sharp). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.82 (d, 1H, $J = 8.6$ Hz), 7.16 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 2.2$ Hz), 7.11 (d, 1H, $J = 2.2$ Hz), 2.55 (s, 3H), 1.55 (s, 9H), 1.54 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 196.4, 154.5, 151.1, 150.7, 150.5, 131.4, 128.3, 118.8, 116.7, 84.5, 84.4, 29.7, 27.8, 27.7; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 2985, 1763, 1689, 1607; MS FAB *m*/*z* 219 (85), 153 (83); FAB MS *m*/*z* ($M^+ + Na$) calcd for $C_{18}H_{24}O_7Na$ 375.1420, found 375.1409.

14. Isolated yield, 82%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.62 (d, 1H, $J = 2.9$ Hz), 7.36 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 2.9$ Hz), 7.21 (d, 1H, $J = 8.8$ Hz), 2.57 (s, 3H), 1.57 (s, 18H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 196.7, 151.6, 151.5, 148.6, 146.9, 131.8, 126.4, 124.8, 123.1, 84.5, 84.4, 29.7, 27.9; IR [CH_2Cl_2, ν_{max}cm^{-1}] 1761.17, 1691.75; MS (CI) *m*/*z* 297 (43), 241 (43) 57 (100); HRMS (CI) *m*/*z* calcd for $C_{18}H_{24}O_8$ 353.1600, found 353.1590.

15. Isolated yield, 88%. Yellow oil. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 8.01 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.7$ Hz), 7.58−7.54 (m, 1H), 7.34−7.30 (m, 1H), 7.18 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 1.1$ Hz), 3.89 (s, 3H), 1.58 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 165.3, 151.8, 150.8, 134.0, 132.0, 126.3, 123.8, 94.6, 83.9, 52.5, 27.9; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 2986, 2957, 1760, 1726, 1610; MS FAB *m*/*z* 197 (100), 165 (92), 121 (40); HRMS (CI) *m*/*z* calcd for $C_{13}H_{16}O_5$ 253.1076, found 253.1070.

16. Isolated yield, 94%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 8.03 (d, 1H, $J = 8.6$ Hz), 7.17 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 2.4$ Hz), 7.11 (d, 1H, $J = 2.2$ Hz), 3.88 (s, 3H), 1.56 (s, 18 H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 164.7, 154.9, 151.7, 151.4, 150.7, 132.9, 120.9, 118.9, 116.8, 84.6, 84.2, 52.5, 27.9, 27.8; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 2986, 1764, 1727, 1611; MS (CI) *m*/*z* 257 (35), 213 (71), 57 (100); HRMS (CI) *m*/*z* calcd for $C_{18}H_{24}O_7$ 369.1549, found 369.1560.

17. Isolated yield, 93%. ^{1}H NMR [$CDCl_3$, 200 MHz] δ 7.83 (d, 1H, $J = 2.9$ Hz), 7.37 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 2.9$ Hz), 7.19 (d, 1H, $J = 8.8$ Hz), 3.89 (s, 3H), 1.58 (s, 18H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 164.40, 151.64, 151.55, 148.54, 148.19, 128.55, 126.85, 124.76, 124.65, 84.38, 84.16, 52.68, 27.87; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 1762.14, 1731.76; MS (CI) *m*/*z* 313 (53), 168 (66), 57 (100); HRMS (CI) *m*/*z* calcd for $C_{18}H_{24}O_7$ 369.1549, found 369.1540.

General Procedure for the Addition of MeMgCl to Aldehydes 9−11, Ketones 12−14, and Esters 15−17. To a stirring solution of the *ortho*-Boc aldehyde, phenone, or ester (1 equiv) in Et_2O (0.2 M) at 0 °C was added the Grignard (equivalents shown in Table 1) in a dropwise fashion. The reaction was stirred at 0 °C until complete consumption of starting material was observed by TLC. HCl (0.5 N) was added while the reaction was still cold. After warming to room temperature, the mixture was extracted with Et_2O, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography with silica gel (1:9 EtOAc/petroleum ether) yielded the title compounds.

18. Isolated yield, 86%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.22 (dd, 1H, $J_1 = 8.4$ Hz), 7.08 (td, 1H, $J_1 = 7.7$ Hz, $J_2 = 1.7$ Hz), 6.93 (td, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.1$ Hz), 6.76 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz), 4.79 (s, 1H, OH), 3.23 (septet, 1H, $J = 6.96$), 1.27 (d, 6H, $J = 6.8$ Hz); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 152.9, 134.6, 126.9, 126.6, 121.2, 115.4, 27.2, 22.8; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 3586 (OH), 2965, 2933, 2869, 1671, 1606; MS (EI) *m*/*z* 121 (100), 103 (20), 77 (18); LRMS (EI) calcd for $C_9H_{12}O$ 136.0888, found 135.9025.

19. Isolated yield, 97%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.16 (d, 1H, $J = 8.4$ Hz), 6.71 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz), 6.59 (d, 1H, $J = 2.4$ Hz), 5.05 (s, 1H, OH), 3.15 (septet, 1H, $J = 7.0$ Hz), 1.57 (s, 9H), 1.22 (d, 6H, $J = 7.0$ Hz); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 153.5, 152.4, 149.5, 132.4, 127.0, 113.5, 108.8, 83.8, 27.9, 26.9, 22.7; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 3586 (OH), 2966, 2932, 2873, 1757; MS (EI) *m*/*z* 152 (37), 137 (81), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{14}H_{20}O_4$ 252.1363, found 252.1362.

20. Isolated yield, 86%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 6.96 (d,1H, $J = 2.9$ Hz), 6.86 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 2.9$ Hz), 6.67 (d, 1H, $J = 8.6$), 4.85 (s, 1H), 3.18 (septet, 1H, 6.8 Hz), 1.56 (s, 9H), 1.23(d, 6H, $J = 7.0$ Hz); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 152.76, 150.66, 144.97, 135.82, 119.34, 119.25, 115.83, 83.55, 27.95, 27.33, 22.55; IR [CH_2Cl_2, ν_{max}cm^{-1}] 3592.73 (OH), 1755.87; MS (EI) *m*/*z* 152 (82), 137 (82), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{14}H_{20}O_4$ 252.1362, found 252.1362.

21. Isolated yield, 75%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.29 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 1.65$ Hz), 7.11−7.07 (m, 1H), 6.91−6.87 (m, 1H), 6.68 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.3$ Hz), 4.82 (s, 1H, OH), 1.43 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 154.4, 136.3, 127.3, 127.2, 116.7, 34.7, 29.8.[13]

22. Isolated yield 90%, a white solid: mp = 95−98 °C. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.23 (d, 1H, $J = 8.4$ Hz), 6.67 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz), 6.54 (d, 1H, $J = 2.4$ Hz), 5.15 (s, 1H, OH), 1.57 (s, 9H), 1.37 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 154.9, 152.3, 149.8, 134.1, 127.7, 112.9, 109.8, 83.8, 34.5, 29.8, 27.9; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 3577 (OH), 2963, 2873, 1758; MS (EI) *m*/*z* 166 (25), 151 (100), 57 (69); HRMS (EI) *m*/*z* calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1527.

23. Isolated yield, 78%. ^{1}H NMR [$CDCl_3$, 200 MHz] δ 7.03 (d, 1H, $J = 2.7$ Hz), 6.88 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.9$ Hz), 6.61 (d, 1H, $J = 8.6$ Hz), 4.83 (s, 1H), 1.56 (s, 9H), 1.39 (s, 6H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 152.78, 152.07, 144.56, 137.45, 120.20, 119.44, 116.91, 83.50, 34.84, 29.54, 27.97; IR [CH_2Cl_2, ν_{max}cm^{-1}] 3580.68 (OH), 1757.80; MS (EI) *m*/*z* 166 (58), 151 (51), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1517.

General Procedure for the Addition of MeLi to Ketones 12−14. A solution of the acetophenone derivative

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(13) The ^{1}H and ^{13}C NMR spectra are identical to those of the commercially available 2-*tert*-butylphenol.

(0.0766 mmol) was taken up in 1 mL of THF and cooled to −78 °C. MeLi (1.1 equiv, 1.3 M in ether) was then added in a dropwise fashion to the stirring reaction. After 25 min the reaction was diluted with ether, washed with 0.5 N HCl, washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (1:9 EtOAc/petroleum ether) yielded product.

24. Isolated yield, 57%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.17−7.14 (m, 2H) 6.95−6.88 (m, 2H), 5.69 (s, 1H), 5.42 (t, 1H, J = 1.65 Hz), 5.16, (s, 1H), 2.13 (s, 3H).[14]

25. Isolated yield, 97%. a colorless oil. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.12 (d, 1H, J = 8.4 Hz), 6.77 (d, 1H, J = 2.4 Hz), 6.73 (d, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 5.78 (s, 1H, OH), 5.41 (s, 1H), 5.13 (s, 1H), 2.10 (s, 3H), 1.57 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 152.9, 152.0, 151.1, 141.8, 128.5, 126.7, 116.2, 113.3, 109.1, 83.8, 27.9, 24.5; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 3509 (OH), 2979, 1758; MS (EI) m/z 150 (61), 57 (100); HRMS (EI) m/z calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1210.

26. Isolated yield, 69%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 6.98−6.95 (m, 2H), 6.90 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.8 Hz), 5.62 (s, 1H), 5.43 (t, 1H, J = 1.5 Hz), 5.18 (s, 1H), 2.11 (s, 3H), 1.56 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 152.5, 149.8, 144.3, 141.6, 129.5, 121.5, 120.5, 116.6, 116.3, 83.6, 27.9, 24.3; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 3525 (OH), 2986, 1760; MS (EI) m/z 150 (65), 57 (100); HRMS (EI) m/z calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1212.

General Procedure for the Addition of Two Organometallic Reagents to 9. The first organometallic reagent (1.05 equiv) was added in a dropwise fashion to a stirring solution of the aldehyde **9** (1 equiv) in Et_2O (0.2 M) at −78 °C. The Grignard (2 equiv) was added immediately after addition of the first organometallic, the cold bath was removed, and the reaction stirred at room temperature until complete. The reaction was then quenched with 0.5 N HCl, extracted with Et_2O, washed with brine, dried (Na_2SO_4), and concentrated. Chromatography (95:5 petroleum ether/EtOAc) yielded the title compounds.

27. Isolated yield, 56%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.17−7.12 (m, 2H), 6.93 (td, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 6.82 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.3 Hz), 6.14−6.06 (m, 1H), 5.23−5.17 (m, 2H), 5.04 (s, 1H, OH), 3.74−3.68 (m, 1H), 1.41 (d, 3H, J = 7.1 Hz); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 153.9, 142.6, 130.5, 128.2, 127.8, 121.2, 116.35, 114.56, 37.85, 18.96.[15]

30. Isolated yield, 71%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.33−7.19 (m, 6H), 7.14 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.65 Hz), 6.96 (td, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 6.77 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.2 Hz), 4.62 (s, 1H, OH), 4.38 (q, 1H, J = 7.3 Hz), 1.64 (d, 3H, J = 7.3 Hz); MS (EI) m/z 85 (37), 71 (56), 57 (100); HRMS (EI) m/z calcd for $C_{14}H_{14}O$ 198.1045, found 198.1049.[13]

General Procedure for the Addition of Two Organometallic Reagents to 10. The first organometallic reagent (1.05 equiv) was added in a dropwise fashion to a stirring solution of the aldehyde **10**, (1 equiv) in THF (0.2 M) at −78 °C. After stirring for 25 min, the cold bath was removed. After an additional 10 min, the Grignard was added and the reaction was stirred at room temperature until complete. The reaction was then quenched with 0.5 N HCl, extracted with Et_2O, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (95:5 petroleum ether/EtOAc) yielded the title compounds.

28. Isolated yield, 86%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.11 (d, 1H, J = 8.5 Hz), 6.73 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.4 Hz), 6.65 (d, 1H, J = 2.4 Hz), 6.09−6.01 (m, 1H), 5.34 (s, 1H, OH), 5.22−5.16 (m, 2H), 3.68−3.65 (m, 1H), 1.56 (s, 9H), 1.37 (d, 3H, J = 7.2 Hz); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 154.5, 152.2, 150.4, 142.3, 128.6, 128.2, 114.8, 113.7, 109.7, 83.8, 37.5, 27.9, 18.9; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 3578 (OH), 3492, 3079, 2979, 2935, 2879, 1757, 1603, 1502; MS (EI) m/z 164 (67), 149 (100); HRMS (EI) m/z calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1359.

31. Isolated yield, 74%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.33−7.20 (m, 6H), 6.77 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.4 Hz) 6.26 (d, 1H, J = 2.39 Hz), 4.82 (s, 1H, OH), 4.32 (quartet, 1H, J = 7.18 Hz), 1.61 (d, 3H, J = 7.34 Hz) 1.56 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 154.0, 152.2, 150.3, 145.1, 129.8, 128.9, 128.5, 127.7, 126.8, 113.6, 109.5, 83.8, 38.7, 27.9, 21.2; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 3593 (OH), 2981, 2938, 2876, 1756, 1603; MS (EI) m/z 276 (65), 255 (71), 199 (100); HRMS (EI) m/z calcd for $C_{19}H_{22}O_4$ 314.1518, found 314.1509.

General Procedure for the Addition of Two Organometallic Reagents to 11. The first organometallic reagent (1.1 equiv) was added in a dropwise fashion to a stirring solution of the aldehyde **11** (1 equiv) in THF (0.18 M) at −78 °C. After stirring for 30 min, the Grignard (2 equiv) was added, the cooling bath was removed, and the reaction was stirred at room temperature until complete. The reaction was then quenched with 0.5 N HCl, extracted with Et_2O, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (95:5 petroleum ether/EtOAc) yielded the title compounds.

29. Isolated yield, 65%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 6.94 (s, 1H), 6.92 (s, 1H), 6.78 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 6.09−6.01 (m, 1H) 5.23−5.17 (m, 2H), 5.12 (s, 1H, OH), 3.69−3.66 (m, 1H), 1.56 (s, 9H), 1.38 (d, 3H, J = 7.1 Hz); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 152.5, 151.5, 145.0, 142.0, 131.4, 120.8, 120.4, 116.8, 115.1, 83.5, 37.9, 27.9, 18.8; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 3582 (OH), 3489, 2976, 2932, 1755; MS (EI) m/z 164 (35), 149 (19), 57 (100); HRMS (EI) m/z calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1365.

32. Isolated yield, 50%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.22−7.25 (m, 5H), 7.05 (d, 1H, J = 2.7 Hz), 6.94 (dd, 1H, J_1 = 8.6 Hz, J_2 = 8.6 Hz), 6.72 (s, 1H, J = 8.6 Hz), 4.63 (s, 1H, OH), 4.32 (q, 1H, J = 7.32 Hz), 1.61 (d, 3H, J = 7.3 Hz), 1.57 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 152.48, 151.11, 145.04, 144.88, 133.022, 129.00, 127.73, 126.86, 120.830, 120.23, 116.60, 83.52, 39.11, 27.95, 21.24. IR [CH_2Cl_2, ν_{max} cm^{-1}] 3586.95 (OH), 1755.87; MS (EI) m/z 214 (100), 199 (67), 57 (83); HRMS (EI) m/z calcd for $C_{19}H_{22}O_4$ 314.1518, found 314.1509.

General Procedure for the Addition of an Organometallic to Aldehyde 10, Followed by an Enolate. The Grignard (1.05 equiv) was added dropwise to aldehyde **10** (0.1 M in Et_2O) at −78 °C. After stirring for 25 min, the cold bath was removed. After an additional 10 min, a mixture of sodium hydride (2 equiv) and methyl malonate (2 equiv) in THF (0.1 M) was added. The reaction was stirred until complete. The reaction was then quenched with 0.5 N HCl, extracted with Et_2O, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (95:5 petroleum ether/EtOAc) yielded the title compounds.

33. Isolated yield 73%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.38−7.30 (m, 3 H) 7.18−7.15 (m, 2H), 7.03 (d, 1H, J = 2.2 Hz), 6.95−6.90 (m, 2H), 4.72 (d, 1H, 8.6 Hz), 3.98 (d, 1H, J = 8.5 Hz), 3.66 (s, 3H), 1.57 (s, 9H); ^{13}C NMR [$CDCl_3$, 100.6 MHz] δ 167.3, 163.9, 151.5, 151.4, 151.3, 138.1, 129.5, 128.4, 128.2, 121.6, 118.2, 110.7, 84.4, 53.8, 53.3, 44.0, 27.8; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 3679 (OH), 3065, 2987, 2957, 2933, 1761, 1620, 1598, 1501; MS (EI) m/z 239 (47), 57 (100); HRMS (EI) m/z calcd for $C_{22}H_{22}O_7$ 398.1366, found 398.1377.

General Procedure for the Addition of an Organometallic to Aldehyde 11, Followed by an Enolate. The Grignard (1.1 equiv) was added to the aldehyde (1 equiv, 0.1 M in Et_2O) at −78 °C. In a separate flask, NaH (2 equiv) was dissolved in THF (0.1 M) and dimethyl malonate (2 equiv) was added. This enolate solution was then added to the aldehyde/Grignard mixture at −78 °C. The mixture was stirred at room temperature until complete. The reaction was then quenched with 0.5 N HCl, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. To complete closure of product **34**, the crude product was redissolved in THF and stirred in the presence of camphorsulfonic acid (5 equiv) for 8 h. Flash chromatography (95:5 petroleum ether/EtOAc) yielded the title compounds.

34. Isolated yield, 62%. ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.37−7.32 (m, 3H), 7.17 (s, 4H), 6.73 (s, 1H), 4.73 (d, 1H, J = 9.0

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[14] For previous characterization, see: Oude-Alink, B. A. M.; Chan, A. W. K.; Gutsche, C. D. *J. Org. Chem* **1973**, *38*, 1993−2001.

[15] Habich, A.; Barner, R.; Roberts, R. M.; Schmid, H. *Helv. Chim. Acta* **1962**, *45*, 1943.

Hz), 3.98 (d, 1H, $J = 9.0$ Hz), 3.66 (s, 3H), 1.52 (s, 9H); ^{13}C NMR [CDCl$_3$, 100.6 MHz] δ ; IR [CH$_2$Cl$_2$ solution, ν_{max} cm^{-1}] 2984, 2930, 1759; MS (CI) *m/z* 343 (100), 299 (43), 239 (38); HRMS (CI) *m/z* calcd for $C_{22}H_{22}O_7$ 399.1444, found 399.1429.

General Procedure for the Addition of an Organometallic to Benzylic Alcohols. The alcohol (1 equiv) was dissolved in Et$_2$O (0.1 M), and to this solution was added the Grignard (3 equiv) at 0 °C. The reaction was stirred for 1 h at 0 °C, warmed to room temperature, and stirred for an additional 10 h. The reaction was quenched with 0.5 N HCl, extracted with ether, washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. Chromatography (95:5 petroleum ether/EtOAc) yielded the title compounds.

35. Isolated yield, 60%. ^{1}H NMR [CDCl$_3$, 400 MHz] δ 7.07 (d, 1H, $J = 8.1$ Hz), 6.68 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 2.4$ Hz), 6.64 (d, 1H, $J = 2.4$ Hz), 5.33 (s, 1H, OH), 5.29 (m, 1H), 3.32 (d, 2H, $J = 6.9$ Hz), 1.77 (s, 6H), 1.56 (s, 9H); ^{13}C NMR [CDCl$_3$, 100.6 MHz] δ 155.0, 152.2, 150.4, 135.3, 130.4, 124.7, 121.7, 113.5, 109.3, 83.7, 29.5, 27.9, 26.0, 18.1; IR [CH$_2$Cl$_2$ solution, ν_{max} cm^{-1}] 3584 (OH), 3446, 2982, 2932, 1757, 1600, 1502; MS (EI) *m/z* 178 (38), 123 (53), 57 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1523.

36. Isolated yield, 52%. ^{1}H NMR [CDCl$_3$, 400 MHz] δ 6.92−6.89 (m, 2H), 6.78−6.76 (m, 1H), 5.32−5.30 (m, 1H), 5.08 (s, 1H, OH), 3.33 (d, 1H, $J = 7.3$ Hz), 1.78−1.77 (m, 6H), 1.56 (s, 9H); ^{13}C NMR [CDCl$_3$, 100.6 MHz] δ 152.1, 144.7, 135.6, 128.0, 122.6, 121.3, 120.2, 116.3, 94.6, 83.5, 27.9, 26.0, 18.1; IR [CH$_2$Cl$_2$ solution, ν_{max} cm^{-1}] 3577, 2985, 2929, 2854, 1755, 1496, 1371, 1276, 1251, 1143; MS (EI) *m/z* 232 (33), 178 (50), 57 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1528.

General Procedure for the Addition of an Enolate to the Benzylic Alcohols. The in situ generated sodium enolate of dimethyl malonate (2 equiv, 0.1 M in THF) was added to a stirring solution of the alcohol (1 equiv, 0.1 M in Et$_2$O) at 0 °C. After addition of the enolate, *t*-BuMgCl (1.1 equiv, 2 M in THF) was added and the cold bath was removed, allowing the reaction to proceed at room temperature until complete. The reaction was then quenched with 0.5 N HCl, extracted with Et$_2$O, washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Chromatography (95:5 petroleum ether/EtOAc) yielded the title compounds.

37. Isolated yield, 51%. ^{1}H NMR [CDCl$_3$, 400 MHz] δ 7.16−7.10 (m, 2H) 6.89−6.85 (m, 2H), 6.61 (s, 1H, OH), 3.81 (t, 1H, $J = 7.14$ Hz), 3.74 (s, 6H), 3.2 (d, 2H, $J = 7.14$ Hz); ^{13}C NMR [CDCl$_3$, 100.6 MHz] δ 170.5, 154.4, 131.3, 128.8, 124.4, 121.2, 117.4, 53.2, 53.0, 29.4; IR [CH$_2$Cl$_2$ solution, ν_{max} cm^{-1}] 3569, 3387, 2949, 1737; MS (EI) *m/z* 147 (100), 107 (35); HRMS (EI) *m/z* calcd for $C_{12}H_{14}O_5$ 238.0841, found 238.0847.

38. Isolated yield, 70%. ^{1}H NMR [CDCl$_3$, 400 MHz] δ 7.10−7.08 (m, 1H), 7.02 (s, 1H), 6.71−6.68 (m, 2H), 3.77−3.74 (m, 7H), 3.15 (d, 2H, $J = 7.2$ Hz), 1.55 (s, 9H); ^{13}C NMR [CDCl$_3$, 100.6 MHz] δ 170.4, 155.3, 152.0, 151.1, 131.6, 122.1, 114.0, 110.7, 83.8, 53.2, 53.0, 28.9, 27.9; IR [CH$_2$Cl$_2$ solution, ν_{max} cm^{-1}] 3577, 3343, 2957, 2985, 2931, 1756, 1609, 1502; MS (EI) *m/z* 254 (83), 163 (68), 57 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{22}O_8$ 354.1315, found 354.1312.

39. Isolated yield, 68%. ^{1}H NMR [CDCl$_3$, 400 MHz] δ 6.94−6.91 (m, 2H), 6.83−6.79 (m, 2H), 3.79 (t, 1H, $J = 7.3$ Hz), 3.74 (s, 6H), 3.16 (d, 1H, $J = 7.1$ Hz), 1.55 (s, 9H); ^{13}C NMR [CDCl$_3$, 100.6 MHz] δ 170.3, 152.6, 152.2, 144.7, 125.2, 123.6, 121.5, 117.9, 83.6, 53.2, 52.7, 29.4, 27.9; IR [CH$_2$Cl$_2$ solution, ν_{max} cm^{-1}] 3584, 3387, 2986, 2957, 1753; MS (EI) *m/z* 254 (74), 190 (38), 57 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{22}O_8$ 354.1315, found 354.1315.

General Procedure for the Addition of a Cyano Group to the Benzylic Alcohols. Tetrabutylammonium cyanide (2 equiv) was dissolved in THF (0.5 M) and added to a stirring solution of the alcohol in Et$_2$O (0.1 M) at 0 °C. Next, *t*-BuMgCl (1.1 equiv, 2 M in THF) was added, and the reaction was stirred at room temperature until complete. The reaction was then quenched with 0.5 N HCl, extracted with Et$_2$O, washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. Chromatography (95:5 petroleum ether/EtOAc) yielded the title compounds.

40. Isolated yield, 62%. ^{1}H NMR [CDCl$_3$, 400 MHz] δ 7.36−7.34 (m, 1H), 7.24−7.19 (m, 1H), 6.98−6.94 (m, 1H), 6.8 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.0$ Hz), 5.47 (s, 1H, OH), 3.74, (s, 2H); ^{13}C NMR [CDCl$_3$, 100.6 MHz] δ 153.3, 129.8, 129.7, 121.5, 118.2, 117.1, 115.5, 18.7; IR [CH$_2$Cl$_2$ solution, ν_{max} cm^{-1}] 3577, 3380, 2928, 2256, 1602, 1503; MS (EI) *m/z* 106 (49), 78 (84); HRMS (EI) *m/z* calcd for C_8H_7NO 133.0528, found 133.0526.

41. Isolated yield, 76%. ^{1}H NMR [CDCl$_3$, 400 MHz] δ 7.32 (d, 1H, $J = 8.3$ Hz), 6.76 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 2.2$ Hz), 6.62 (d, 1H, $J = 2.2$ Hz), 5.95 (s, 1H, OH), 3.64 (s, 2H), 1.58 (s, 9H); ^{13}C NMR [CDCl$_3$, 100.6 MHz] δ 154.0, 152.3, 151.5, 130.3, 117.9, 115.1, 114.0, 109.1, 84.6, 27.9, 18.3; IR [CH$_2$Cl$_2$ solution, ν_{max} cm^{-1}] 3577, 3372, 2986, 2935, 2861, 2256, 1759, 1726, 1613, 1515; MS FAB *m/z* 191 (37), 154 (100), 136 (70); HRMS (CI) *m/z* calcd for $C_{13}H_{15}NO_4$ 250.1079, found 250.1084.

42. Isolated yield, 60%. ^{1}H NMR [CDCl$_3$, 400 MHz] δ 7.14 (s, 1H), 6.95 (d, 1H, $J = 8.6$ Hz), 6.66 (d, 1H, $J = 8.6$ Hz), 3.66 (s, 2H), 1.57 (s, 9H), OH unresolved; ^{13}C NMR [CDCl$_3$, 100.6 MHz] δ 152.9, 151.3, 144.6, 122.5, 122.3, 118.2, 117.7, 116.2, 84.3, 27.9, 18.7; IR [CH$_2$Cl$_2$ solution, ν_{max} cm^{-1}] 3577, 3387(OH), 2978, 2927, 2256, 1757, 1713, 1510; MS (CI) *m/z* 194 (22), 149 (26), 57 (45); HRMS (CI) *m/z* calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.1006.

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Supporting Information Available: ^{1}H NMR spectra for compounds **9**−**42**. This material is available free of charge via the Internet at http://pubs.acs.org.

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