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Birch Reductive Alkylation of Methyl *m*-(Hydroxymethyl)benzoate Derivatives and the Behavior of *o*- and *p*-(Hydroxymethyl)benzoates under Reductive Alkylation Conditions

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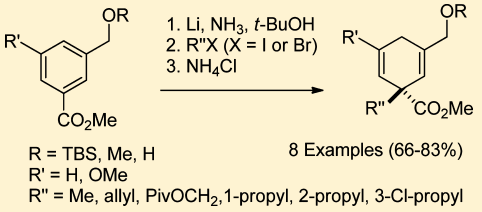
Supporting Information

ABSTRACT: Birch reductive alkylation of methyl *m*-(hydroxymethyl)benzoate derivatives, using lithium in ammonia−tetrahydrofuran in the presence of *tert*-butyl alcohol, can be achieved without significant loss of benzylic oxygen substituents. Similar treatment of *o*- and *p*-(hydroxymethyl)benzoate derivatives results largely in loss of benzylic oxygen substituents. The results are rationalized by computations describing electron density patterns in the putative radical anion intermediate involved in these reactions.



INTRODUCTION

Dissolving metal reductions are widely used in organic synthesis. Notable reductions mediated by dissolving metals include the conversion of α,β-unsaturated ketones to enolates and products derived therefrom,[1,2] reduction of σ-bonded functional groups including removal of benzylic protecting groups from alcohols,[3,4] and reduction of aromatic compounds to provide 1,4-dihydrobenzenes and derivatives thereof (Birch reduction).[5,6] In some reduction substrates, two or more of these processes can be in competition. For example, reduction of an α,β-unsaturated ketone in the presence of an electron-rich aromatic compound has been documented.[7] Reduction of an aromatic compound in the presence of a benzylic oxygen sets up a competition between the classical Birch reduction and benzylic alcohol or ether cleavage (σ-bond reduction). This has been studied in detail for substrates in which the aromatic compound is electron rich. Birch showed that *p*-hydroxymethylated anisoles (**1**) are reduced to 1,4-dihydrobenzenes, largely with retention of the benzylic oxygen, whereas *m*- and *o*-hydroxymethylated anisoles are largely reduced with loss of benzylic oxygen (**2** and **3**) (Figure 1).[8,9] The reason for this selectivity can be rationalized based on greater electron density at the *ortho* and *meta* positions in radical anion and/or dianion intermediates involved in these reactions.[10]

During the course of an approach to a family of quassinoids known as the polyandranes, we hoped to accomplish the reductive alkylation of benzoate **4** to 1,4-dihydrobenzoic acid derivative **5** (Scheme 1).[11,12]

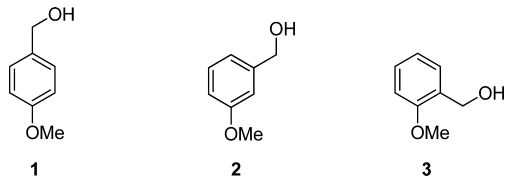
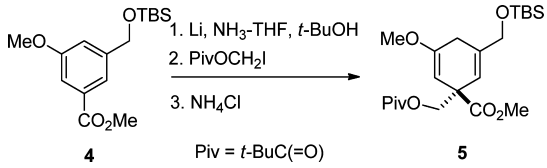


Figure 1. Electron-rich substrates studied by Birch.

Scheme 1



This substrate once again sets up a competition between Birch reduction and benzylic oxygen cleavage. In contrast with the electron-rich aromatic substrates shown in Figure 1, we could find little about such a competition with more electron-deficient substrates of type **4**.[13] This search raised the question of the fate of benzylic oxygen in Birch reductive alkylation of hydroxymethylated benzoates and derivatives thereof. Substrates **6**−**13** shown in Figure 2 were selected for study, and the results are described herein.

RESULTS AND DISCUSSION

Synthesis of Reductive Alkylation Substrates 6−13. Commercially available methyl 4-(hydroxymethyl)benzoate (**8**) was converted to the known TBS ether **6**[14] and methyl ether **7**[15] in 58% and 70% yields, respectively, using standard chemistry shown in Scheme 2. Substrates with *meta* substitution (**9**−**12**) were prepared from dimethyl isophthalate (**14**), also as described in Scheme 2. Hydrolysis of commercially available **14** gave ester−acid **15** (70%), contaminated with a small amount of isophthalic acid.[16]

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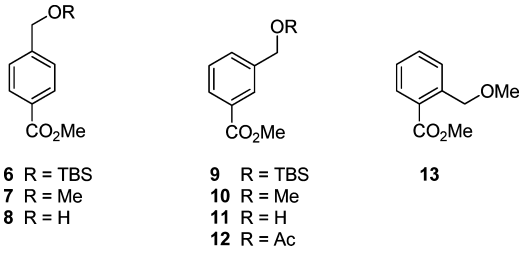
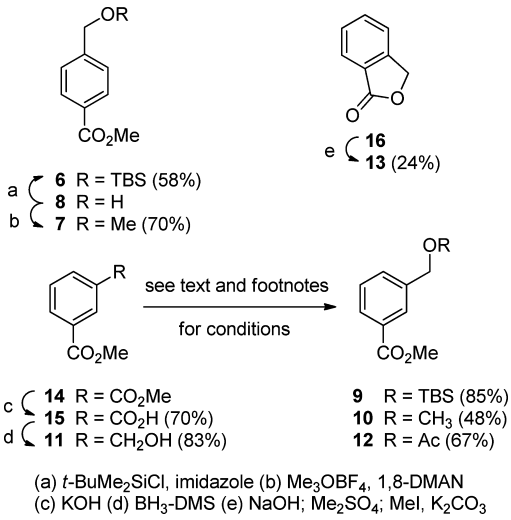


Figure 2. Electron-deficient substrates selected for reductive alkylation studies.

Scheme 2



Reduction of **15** with BH_3–DMS gave **11** (83%), easily separated from a small amount of 3-(hydroxymethyl)benzyl alcohol (5%), also formed in this reaction.[16] Alcohol **11** was converted to the known silyl ether **9** (85%),[14] methyl ether **10** (48%),[14,17] and acetate **12** (67%)[14,18] using standard chemistry. Substrate **13** was prepared from phthalide (**16**) in 24% yield using a modified literature procedure.[19]

Anticipated Reductive Alkylation Products. It was anticipated that cleavage of benzylic oxygen to provide methyl toluates **17**–**19** might be observed in Birch reductions of some of the substrates shown in Figure 2. It was also anticipated that products derived from reduction of these toluates might be observed. Thus, samples of **17**–**25** were purchased. Esters **17**–**19** were also subjected to Birch reductive alkylation (Li, *t*-BuOH, NH_3, THF, followed by MeI followed by NH_4Cl) to provide 1,4-cyclohexadienes **26**,[20] **27**[21] (as a 3:2 mixture of diastereomers), and **28**,[20,22] respectively, in accord with literature procedures (Figure 3). Armed with these potential products, we examined the reductive alkylation (with iodomethane and other alkylating agents) of substrates **6**–**13** as described below.

Reductive Alkylations. Table 1 documents reductive alkylations of *meta*-substituted substrates **9**–**12**. In each entry, the substrate and *tert*-butyl alcohol were dissolved in tetrahydrofuran (3–6 mL $mmol^{-1}$ of substrate), placed under an atmosphere of nitrogen with cooling in a dry ice acetone bath, and ammonia was added to the reaction mixture (3–6 times the volume of tetrahydrofuran) with cooling to an internal temperature of −65 °C. Lithium metal was then added in small pieces (3–6 portions) until the reaction maintained a deep blue color for 10–30 min. The alkyl halide was added,

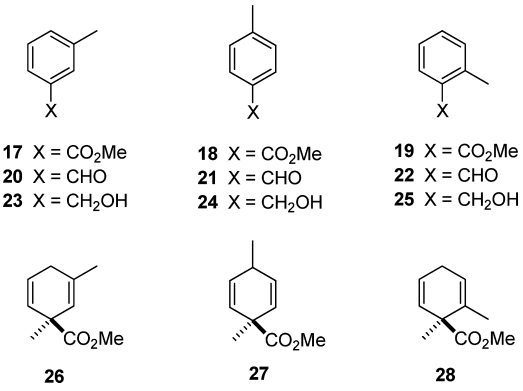
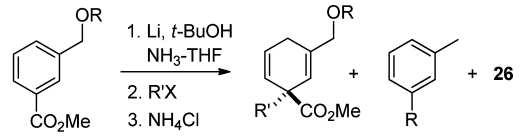


Figure 3. Products anticipated from reductive alkylation studies.

Table 1. Reductive Alkylation of *Meta*-Substituted Substrates



9 R = TBS
10 R = Me
11 R = H
12 R = Ac

29a R' = Me
29b R' = allyl
29c R' = CH_2OPiv
29d R' = *n*-Pr
29e R' = $(CH_2)_3Cl$
29f R' = $CH(CH_3)_2$

17 R = CO_2Me
20 R = CHO
23 R = CH_2OH

entry	substrate[a]	R′X[b]	products[c]	substrate/*t*-BuOH/Li[j]
1	**9**	CH_3I	**29a** (82%)[d,g]	1:1:2.4
2	**9**	allyl-Br	**29b** (71%)[e,g]	1:1:2.6
3	**9**	$PivOCH_2I$	**29c** (79%)[f,g]	1:1:4.4
4	**9**	$CH_3CH_2CH_2I$	**29d** (83%)[g]	1:1:3.8
5	**9**	$Cl(CH_2)_3I$	**29e** (83%)[g]	1:1:3.9
6	**9**	$(CH_3)_2CHI$	**29f** (68%)[g]	1:1:4.7
7	**10**	CH_3I	**29a** (78%)[h]	1:1:2.9
8	**11**	CH_3I	**29a** (66%)[i]	1:2:4.8
9	**12**	CH_3I	**26** (50%)	1:2:5.0

[a]Reactions were run with 2–10 mmol of substrate (see the Supporting Information). [b]3.0 equiv of R′X was generally used relative to substrate (see the Experimental Section and Supporting Information for details). [c]Isolated yield after purification in parentheses. [d]Product contained 6 mol % of **9**. [e]Product contained 11 mol % of **9**. [f]Product contained 8 mol % of aldehyde related to **29c** where $CO_2Me \rightarrow CHO$. [g]R = TBS. [h]R = Me. [i]R = H. [j]Molar ratio.

followed by a stirring period, followed by addition of solid ammonium chloride, warming to 15 °C, partitioning the residue between water and benzene, and purification of the product by flash chromatography (see the Supporting Information for details). Entries 1–6 indicate that silyl ether substrate **9** undergoes reductive alkylation in good yield with retention of the benzylic oxygen. On several occasions, it was noticed that up to 50% of the starting ester was recovered in spite of the reaction remaining blue for 15–30 min in the presence of excess lithium. It is suspected that use of too little tetrahydrofuran (relative to ammonia) was responsible for these results. Indeed, on these occasions the reaction became cloudy prior to addition of the lithium, presumably due to insolubility of ester **9**. The ammonia–tetrahydrofuran ratio was kept at about 3:1 for the results shown in entries 1–6. Table 1 shows that typical alkylating agents that cannot undergo β-elimination behave well (entries 1–3). Both primary and secondary alkyl

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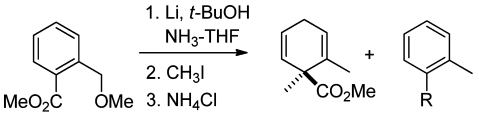
halides capable of β-elimination also behave well (entries 4–6). Entry 7 shows that methyl ether **10** also behaved well in the reductive alkylation. Trace amounts of **20** and **26** were observed in this reaction (see the Supporting Information for details). Thus, our initial fear that benzylic cleavage might compete with reductive alkylation was warranted. Entry 8 reveals that a free hydroxyl group can survive the reaction.[23] Entry 9 reveals that, given a good enough leaving group, reductive cleavage of the benzylic substituent becomes the major reaction pathway. The major product (**26**) is presumed to be formed by reductive alkylation of first-formed methyl *meta*-toluate (**17**).

Table 2 presents reductive alkylations of *ortho*-substituted substrate **13**. Entry 1 reveals a messy reaction when only 1

Table 2. Reductive Alkylation of *Ortho*-Substituted Substrate



13 **28** **19** R = CO_2Me; **22** R = CHO; **25** R = CH_2OH

entry[a]	products[b]		(substrate/*t*-BuOH/Li)[c]
1	**13** (22%)	**28** (9%)	1:1:4.6
	19 (15%)	**22** (15%)	
	25 (11%)		
2	**28** (70%)		1:2:4.7

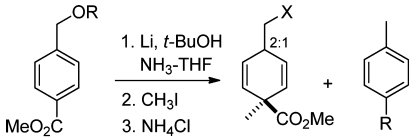
[a]Reactions were run with 2 mmol of substrate (see the Supporting Information). [b]Isolated yield after purification in parentheses. [c]Molar ratio.

equiv of *tert*-butyl alcohol is used. In addition to recovered starting material, at least four reduction products (**19**, **22**, **25**, and **28**) were observed. The benzylic methoxy group was cleaved in all reduction products.[24] Whereas **19** is a two-electron reduction product, **22** and **28** are four-electron reduction products and **25** is a six-electron reduction product. It was presumed that the messy nature of the reaction was due to a deficiency of acid (*tert*-butyl alcohol) in the reaction medium. Thus, the amount of *tert*-butyl alcohol present at the onset of the reaction was doubled (entry 2).[25] The result was dramatic. The major product became the four-electron reductive alkylation product **28**. The bottom line is that the benzylic oxygen was not retained in this substrate.[26]

Table 3 shows results with *para*-substituted substrates **6**–**8**. Two equivalents of *tert*-butyl alcohol were used due to the aforementioned over-reduction issue. Mass balance was only modest, but we are confident that the major products were identified (see the Supporting Information). TBS-ether **6** and methyl ether **7** gave only products in which the benzylic oxygen was reduced (entries 1 and 2). Alcohol substrate **8** gave over-reduction products **24** and **27**, a trace of 4-(hydroxymethyl)-benzaldehyde, and reductive alkylation product **30**. Thus, it is possible that protection of the hydroxyl group of **8** as an oxido group slows the rate of benzylic cleavage (relative to reduction of the aromatic ring) enough to allow formation of some product in which benzylic oxygen is retained.[23]

Our need to accomplish the transformation of **4** to **5** (Scheme 1) provided the stimulus for conducting this study. Studies directed toward this goal are shown in Scheme 3 and Table 4. Substrate **4** was prepared from commercially available

Table 3. Reductive Alkylation of *Para*-Substituted Substrates



6 R = TBS; **7** R = Me; **8** R = H

27 X = H; **30** X = OH

18 R = CO_2Me; **21** R = CHO; **24** R = CH_2OH

entry[a]	substrate	products[b,c]	substrate/*t*-BuOH/Li
1	**6**	**27** (45%), **21** (5%)	1:2:6.0
		24 (10%)	
2	**7**	**27** (50%), **18** (3%)	1:2:5.7
		21 (6%), **24** (8%)	
3	**8**	**27** (14%), **30** (20%)	1:2:5.5
		24 (4%)	
		4-(CH_2OH)C_6H_4CHO (trace)	

[a]Reactions were run with 2 mmol of substrate. [b]Isolated yield after purification in parentheses. [c]Compounds **27** and **30** were isolated as approximately 2:1 mixtures of diastereomers (see text and the Experimental Section for details).

Scheme 3

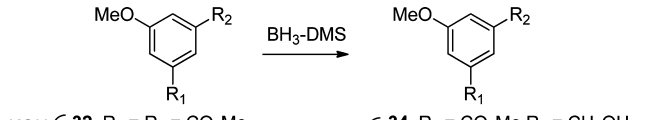
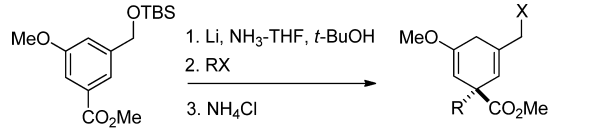


Table 4. Reductive Alkylation of *Meta*-Substituted Substrate 4



4

35 R = CH_3 X = OTBS; **36** R = CH_3 X = H; **5a** R = CH_2OPiv X = OTBS; **5b** R = CH_2OPiv X = H

entry	substrate[a]	RX[b]	products[c]	(substrate/*t*-BuOH/Li)[e]
1	**4**	CH_3I	**35** (76%)[d]	1:1:4.3
2	**4**	CH_3I	**35** (61%)[d]	1:2:4.3
3	**4**	$PivOCH_2I$	**5a** (66%)[d]	1:1:4.0

[a]Reactions were run with 2–14 mmol of substrate (see the Supporting Information). [b]3.0 equiv of CH_3I and 1.2 equiv of $PivOCH_2I$ were used, relative to substrate (see the Experimental Section for details). [c]Isolated yield after purification in parentheses. [d]See text and the Experimental Section for minor products. [e]Molar ratio.

5-hydroxyisophthalic acid (**31**) largely using a published procedure.[16b] Esterification of diacid **31** (H_2SO_4, MeOH) followed by *O*-methylation of the phenol (NaH, MeI, THF–DMF) gave **32** in 67% overall yield. Monohydrolysis of diester **32** gave **33** (63%) along with 16% of recovered **32**.[16b] Reduction of **33** with BH_3–DMS gave alcohol **34**, which was converted to **4** (81% from **32**) in the usual manner (Scheme 3).

Entries 1–2 of Table 4 show that the reductive alkylation tolerates the additional electron-donating group (methoxy) on the aromatic ring. The results also show that the yield of reductive alkylation product (**35**) does not vary with a change from 1 (entry 1) to 2 (entry 2) equiv of *tert*-butyl alcohol.[28] It is also notable that **35** obtained from this reaction was

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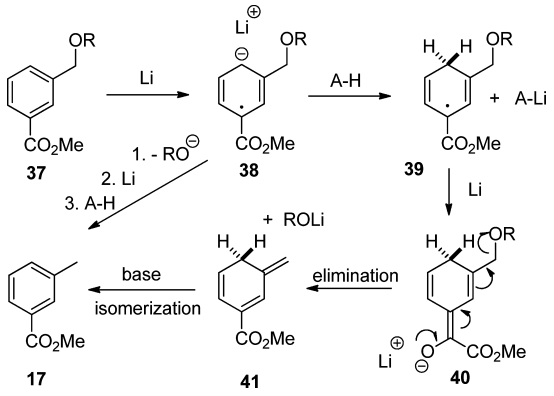
contaminated by a trace of **36** (7 mol % by ^{1}H NMR), the product of benzylic reduction prior to reductive alkylation.[27] Finally, reductive alkylation of **4** with iodomethyl pivalate [$Me_3CC(=O)OCH_2I$] provided a useful yield of the desired reductive alkylation product **5a** (entry 3). This reaction also provided a small amount of **5b** as a minor product,[11c] once again indicating that benzylic reduction can *raise its ugly head* in *meta*-substituted substrates.[29]

Discussion of Mechanism. Several mechanisms for the Birch reductive alkylation of benzoates have been discussed.[30] The mechanisms (electron transfer–protonation–electron transfer and electron transfer–electron transfer–protonation) arrive at the same place (an enolate of the 1,4-dihydrobenzoate). This discussion will be restricted to the electron-transfer–protonation–electron-transfer mechanism. This is outlined in Scheme 4 for *meta*-substituted substrates of type

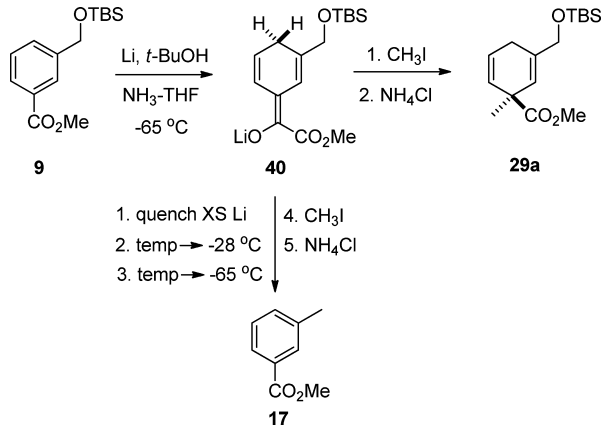
Scheme 4



37. Electron transfer to **37** provides radical anion **38**. Protonation of the anion by an acid (A–H) provides radical **39** and A–Li. The site of protonation must be *para* to the carbomethoxy group because of the nature of the products obtained from reactions. The A–Li is presumed ultimately to be lithium *tert*-butoxide, regardless of the acid (*tert*-butyl alcohol or ammonia). Transfer of an electron to **39** provides extended enolate **40**. Enolate **40** is stable to the reaction media. It is not protonated by ammonia, or apparently by any excess *tert*-butyl alcohol. Treatment of enolate **40** with an alkylating agent provides the observed reductive alkylation products (for example, see Table 1). What is the possible source of deoxygenated products? There are two possible pathways according to this mechanism. If radical anion **38** expels alkoxide, the result is the 3-carbomethoxybenzyl radical (consider resonance structures) which would be reduced to the corresponding carbanion and then protonated to provide **17**. An alternative path to **17** would involve elimination of alkoxide from enolate **40** to provide **41**, followed by base-mediated aromatization-driven isomerization to **17**. Neither of these deoxygenation paths dominates, as reductive alkylation is the major reaction pathway. The following experiment, however, indicates that the pathway from **40** to **17** can be realized (Scheme 5).

Treatment of **9** with lithium (4.3 equiv) in ammonia–THF in the presence of 1 equivalent of *tert*-butyl alcohol at −65 °C until a blue color was maintained for 20 min. The excess lithium was quenched with isoprene (1 drop) and the temperature was warmed to −28 °C over 15 min and this temperature was maintained for 20 min. The mixture was

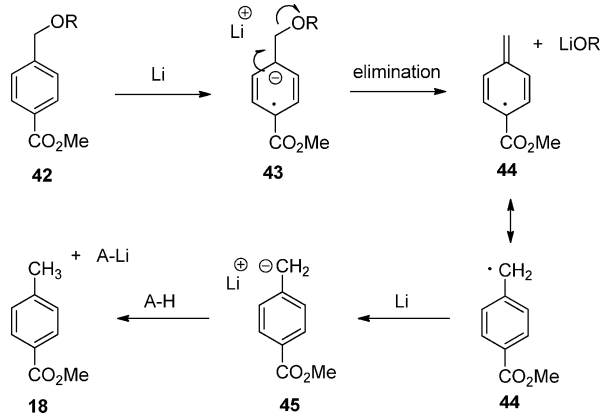
Scheme 5



cooled to −65 °C. Iodomethane was added and then the reaction was continued in the usual manner to give **17** as the major product in 25% yield. Only a trace of starting material (**9**) and the reductive alkylation product (**29a**) were observed.

A similar mechanistic treatment of substrates of type **6**–**8** is presented in Scheme 6. Electron transfer to **42** would provide

Scheme 6



radical anion **43**. Protonation of **43** *para* to the carbomethoxy group would provide an enolate that would ultimately provide **30** (X = OR) upon alkylation with iodomethane. It is notable that this enolate would not be expected to undergo elimination as observed for enolate **40**. On the other hand, elimination of alkoxide from radical anion **43** would provide benzylic radical **44**. Subsequent reduction of this radical, followed by protonation, would give **18** via benzylic anion **45**. It appears that elimination (**43** → **44**) is faster than protonation of **43** for substrates **6** and **7**. When the leaving group is hydroxide or O^{2-} (if the alcohol is converted to an oxido group in situ), elimination from **43** is slowed to the point that protonation becomes competitive.

The experimental results indicate that *ortho*-substituted substrate **13** undergoes reductive cleavage of the benzylic methoxy group faster than reductive alkylation. This could also be due to an increase in negative charge at the ortho position in the presumed radical anion intermediate (as seen for *para*-substituted substrates **6**-**8**).

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COMPUTATIONS

Using density functional theory at the B3LYP/6-31+G* level of theory and including implicit solvation with the polarizable continuum model (for tetrahydrofuran), we optimized the geometries of various precursor species, including the resulting radical anions. As shown in Tables 1 and 4, for *meta* substrates, cleavage of the benzylic methoxy group was not the preferred product, whereas for the *ortho* and *para* substrates (**13** and **10** in Tables 2 and 3), all of the reduction intermediates had the benzylic methoxy bond cleaved.

To compare the effect of electron transfer to **13**, we optimized neutral **13** and the corresponding radical anion $\mathbf{13}^{\bullet-}$ at the B3LYP/6-31+G* level of theory. Despite the one-electron reduction, $\mathbf{13}^{\bullet-}$ remains largely planar with significant bond-length changes. In Figure 4a, changes in the computed

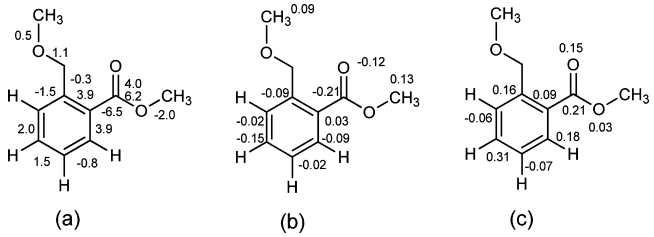

Figure 4. For **13**, significant changes in (a) the molecular geometry (in picometers) and (b) in partial atomic charges (in electrons) upon one-electron reduction of **13** to $\mathbf{13}^{\bullet-}$ and (c) calculated spin densities of $\mathbf{13}^{\bullet-}$ at the B3LYP/6-31+G* level of theory (PCM model for THF).

bond lengths, in picometers (pm), upon one-electron reduction of **13** are shown. The benzylic methoxy C−O bond length changes only by 1.1 pm, whereas more significant bond-length changes were observed in the phenyl ring as well as in the methoxycarbonyl group. This suggests that the negative charge is delocalized on the entire molecular skeleton. To support this claim, we computed the partial atomic charges using the ChelpG partitioning scheme. Figure 4b shows important changes in the partial atomic charges due to the one-electron reduction of **13**. The negative charge is primarily shared between the benzene ring and the methoxycarbonyl group, which showed the largest changes in molecular geometry. Calculated spin densities of radical anion derived from **13** (see Figure 4c) also support the assertion that the unpaired electron is localized primarily on the phenyl unit and the methoxycarbonyl group.

For additional comparison, we also computed the hypothetical thermochemistry for the "reaction" of **13** and $\mathbf{19}^{\bullet-}$ to yield $\mathbf{13}^{\bullet-}$ and **19**, which is −1.06 kcal/mol at the B3LYP/6-31+G* level of theory. This suggests that the reduction of **13** would be slightly preferred over the reduction of **19**.

To evaluate *para*-substituted substrates, we computed neutral and radical anion species of substrate **7**. Similar to the *ortho* substrates discussed above, geometrical changes suggest formation of a quinoidal structure upon one-electron reduction of **7** as shown in Figure 5a. Furthermore, the partial atomic-charge distribution indicates that the negative charge is localized at the carbon atoms *ortho* and *para* to the methoxycarbonyl group (Figure 5b). Significant negative charge is also localized at the carbonyl unit. Additionally, the spin density is localized on the phenyl unit and the carbonyl group of the methoxycarbonyl group (Figure 5c). These observations are similar to what was observed for the *ortho* substrates, which

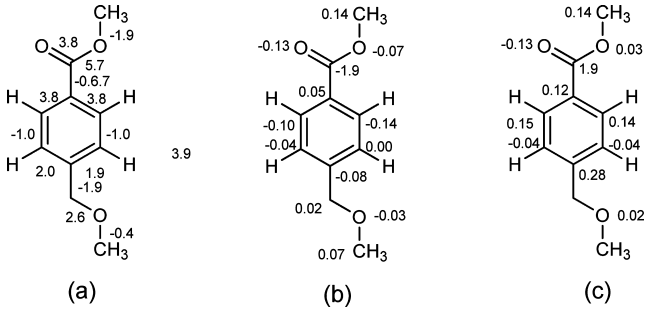

Figure 5. For **7**, significant changes in (a) the molecular geometry (in picometers) and (b) in partial atomic charges (in electrons) upon one-electron reduction of **7** to $\mathbf{7}^{\bullet-}$ and (c) calculated spin densities of $\mathbf{7}^{\bullet-}$ at the B3LYP/6-31+G* level of theory (PCM model for THF).

is in agreement with the experimental observation where both *ortho* and *para* substrates behave similarly upon reduction.

For *meta*-substituted substrates, benzylic cleavage is not a preferred pathway upon reduction (Table 1, entries 1−8, and Table 4); however, substrate **12** led to benzylic cleavage product preferentially (Table 1, entry 9). To investigate this issue, we chose substrates **10** and **12** for computational analysis. Both molecules were optimized in their neutral and radical anion forms. Differences in the optimized geometries for the substrates are shown in Figure 5a,b. The geometrical differences between the neutral and the radical anionic species are very similar between both of the substrates. However, the spin-density distribution is similar, and the additional electron is localized on the phenyl unit and the methoxycarbonyl group (Figure 6e,f). For *meta* substrate **10**, the negative charge is primarily localized on the benzene ring, whereas the negative charge is delocalized over the entire skeleton of substrate **12**. This suggests that, apart from the presence of a good leaving group in **12**, electronic structure due to substituent effects might also play a role in determining the reduction product, as substituents affect the localization of the excess electron within the molecule.

CONCLUSIONS

In summary, it has been shown that Birch reductive alkylation of *meta*- alkoxymethylated and *meta*-hydroxymethylated methyl benzoates can be accomplished in good yield. Reductive cleavage of benzylic oxygen surfaces on occasion as only a minor problem. On the other hand, *ortho*- and *para*-alkoxymethylated methyl benzoates afford only products that exhibit benzylic oxygen cleavage. A single *p*-hydroxymethylated methyl benzoate gave products involving benzylic oxygen cleavage but did afford significant amounts (20%) of reductive alkylation product retaining benzylic oxygen. These results are consistent with (and can be rationalized by) results of computations which show that, upon reduction to the corresponding radical anions, methyl benzoates show a greater increase in electron density at positions *ortho* and *para* to the methoxycarbonyl group than at the *meta* position.

EXPERIMENTAL SECTION[31]

General Information. All melting points were taken with a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra are recorded in parts per million from internal C_6D_6 or $CDCl_3$ on the δ scale and reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet), coupling constant(s) in hertz, integration]. ^{13}C NMR

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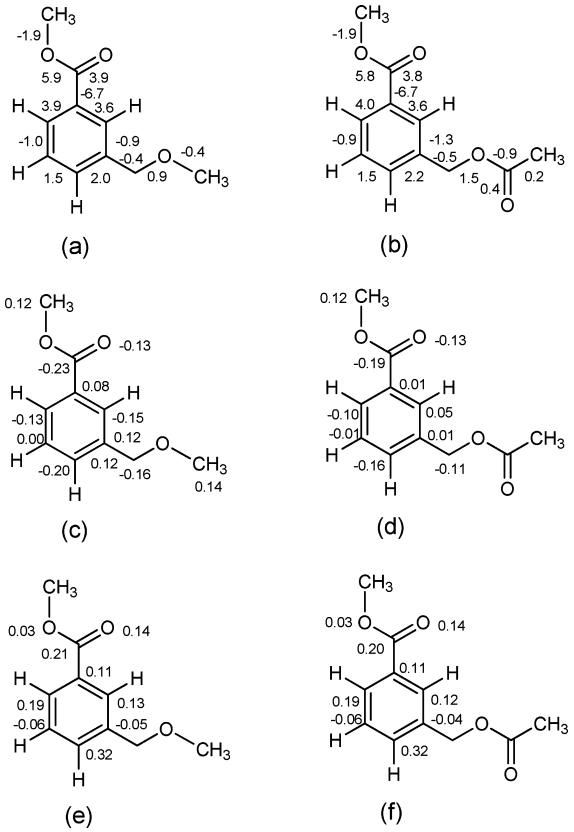

Figure 6. For **10** and **12**, respectively, (a, b) changes in the molecular geometry (in picometers) and (c, d) changes in partial atomic charges (in electrons) upon one-electron reduction and (e,f) calculated spin densities of $\mathbf{10}^{\bullet-}$ and $\mathbf{12}^{\bullet-}$ at the B3LYP/6-31+G* level of theory (PCM model for THF).

spectra are recorded in parts per million from internal C_6D_6 or $CDCl_3$ on the δ scale. Electrospray ionization and a TOF mass analyzer were used for HRMS measurements. Unless otherwise noted, all reactions were carried out under argon or nitrogen using flame or oven-dried glassware. Unless specified, commercial reagents were used without further purification. Tetrahydrofuran was distilled from sodium-benzophenone ketyl under argon. Ammonia was distilled directly from a tank into the reaction flask. Flash column chromatography was performed using 32−60 mm pore size silica gel with solvent systems indicated. Analytical thin layer chromatography was performed using 250 mm glass-backed F_{254} silica gel plates visualized by fluorescence and then by staining upon heating with phosphomolybdic acid (61 g PMA in 1 L 95% ethanol). Solvent removal was effected by rotary evaporation at temperatures no greater than 40 °C under house vacuum (25−40 Torr).

Preparation of Substrates. *Methyl 4-(tert-Butyldimethylsilyloxymethyl)benzoate (6).*[14] A 100-mL oven-dried round-bottom flask was equipped with a magnetic stir bar and a nitrogen line and cooled in an ice−water bath. To the flask was added, in sequence, 50 mL of reagent grade dichloromethane, 3.32 g (20 mmol) of solid alcohol **8**, 2.72 g (40 mmol) of solid imidazole, and 3.76 g (25 mmol) of *tert*-butyldimethylchlorosilane in 10 mL of dichloromethane (via pipet over 1 min). The resulting white suspension was stirred for 30 min. The cold bath was removed and stirring was continued for 2.5 h. The mixture was transferred to a separatory funnel and was washed with two 50-mL portions of water, dried (Na_2SO_4), and filtered (gravity). The filtrate was concentrated in vacuo. The residue was purified by chromatography over 100 g of flash silica gel (loaded and eluted with hexanes−ethyl acetate = 19:1; 50 mL fractions). Fractions 6−12 were pooled and concentrated to give 3.25 g (58%) of TBS-ether **6** as a water-white liquid: IR (neat) 1725 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.0 (s, 6H), 0.95 (s, 9H), 3.5 (s, 3H), 4.5 (s, 2H), 7.23 (d, J = 9 Hz, 2H), 8.12 (d, J = 9 Hz, 2H); ^{13}C NMR (C_6D_6, 100 MHz) δ −5.4, 18.4, 25.9, 51.3, 64.5, 125.9, 129.5, 129.9, 146.8, 166.5. This material was contaminated with a trace of hexanes from the chromatography.

Methyl 4-Methoxymethylbenzoate (7).[15] A 500-mL one-necked round-bottom flask was dried, placed under a nitrogen atmosphere, and charged with a stir bar and 7.47 g (45 mmol) of alcohol **8** in 180 mL of dry dichloromethane. To the stirred solution was sequentially added 9.63 g (45 mmol) of solid 1,8-bis(dimethylamino)naphthalene (proton sponge) and 7.1 g (48 mmol) of solid trimethyloxonium tetrafluoroborate (Meerwein's reagent) in single portions. The mixture was stirred at room temperature for 24 h. The solution was filtered (suction), and the filtrate was concentrated in vacuo. The residual purple solid was suspended in 30 mL of hexanes−ethyl acetate (4:1) and filtered, and the filtrate was concentrated in vacuo. The residual purple oil was subjected to chromatography over 115 g of flash silica gel (loaded and eluted with hexanes−ethyl acetate = 4:1; 50 mL fractions). Fractions 8−10 were pooled and concentrated to give 5.7 g (70%) of methyl ether **7** suitable for use in subsequent reactions: IR (neat) 1721 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 3.03 (s, 3H), 3.5 (s, 3H), 4.1 (s, 2H), 7.15 (d, J = 8 Hz, 2H), 8.13 (d, J = 8 Hz, 2H); ^{13}C NMR (C_6D_6, 100 MHz) δ 51.4, 57.8, 73.7, 127.1, 129.9, 144.1, 166.5. One aromatic carbon was obscured. The material was contaminated with a small amount of ethyl acetate and a trace of proton sponge.

Methyl 3-Hydroxymethylbenzoate (11). Compound **11** was prepared by a modification of a known procedure (see the Supporting Information for details):[16a] IR (neat) 3424, 1722 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 2.0 (br s, 1H), 3.49 (s, 3H), 4.30 (s, 2H), 7.03 (t, J = 9 Hz, 1H), 7.22 (d, J = 9 Hz, 1H), 7.97 (d, J = 9 Hz, 1H), 8.1 (s, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 51.5, 64.5, 128.0, 128.5, 128.6, 130.7, 131.1, 142.0, 167.0.

Methyl 3-(tert-Butyldimethylsilyloxymethyl)benzoate (9). Compound **9** was prepared with the same procedure that describes the preparation of **6** (see the Supporting Information for details):[14] IR (neat) 1727 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.0 (s, 6H), 0.95 (s, 9H), 3.48 (s, 3H), 4.5 (s, 2H), 7.10 (t, J = 8 Hz, 1H), 7.37 (d, J = 8 Hz, 1H), 8.0 (d, J = 8 Hz, 1H), 8.2 (s, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ −5.4, 18.4, 25.9, 51.4, 64.5, 127.5, 128.37, 128.43, 130.5, 130.8, 142.1, 166.6.

Methyl 3-Methoxymethylbenzoate (10). Compound **10** was prepared with the same procedure that describes the preparation of **7** (see the Supporting Information for details):[17] ^1H NMR (C_6D_6, 400 MHz) δ 3.13 (s, 3H), 3.5 (s, 3H), 4.1 (s, 2H), 7.05 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 1H), 8.03 (d, J = 8 Hz, 1H), 8.2 (s, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 51.4, 57.7, 73.8, 128.5, 128.73, 128.78, 130.8, 131.7, 139.4, 166.6.

Methyl 3-Acetoxymethylbenzoate (12).[14,18] To a solution of 415 mg (2.5 mmol) of alcohol **11** in 5 mL of dichloromethane (in a 25 mL one-necked RBF) was added sequentially 510 mg (5 mmol) of acetic anhydride in 1 mL of dichloromethane and 303 mg (2.5 mmol) of triethylamine in 1 mL of dichloromethane. To the solution was added 5 mg (0.04 mmol) of 4-(dimethyamino)pyridine (4-DMAP) with stirring at room temperature. An exotherm was observed upon addition of the 4-DMAP. The solution was stirred for 30 min, diluted with 15 mL of dichloromethane, washed with 5 mL of 1 N aqueous hydrochloric acid and 5 mL of saturated aqueous sodium bicarbonate, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residual liquid was subjected to chromatography over 20 g of flash silica gel (loaded and eluted with hexanes−ethyl acetate = 6:1; 10 mL fractions). Fractions 18−20 were pooled and concentrated to give 347 mg (67%) of acetate **12** as a colorless liquid: ^1H NMR (C_6D_6, 400 MHz) δ 1.6 (s, 3H), 3.48 (s, 3H), 4.84 (s, 2H), 6.98 (t, J = 8 Hz, 1H), 7.12 (d, J = 8 Hz, 1H), 8.0 (d, J = 8 Hz, 1H), 8.12 (s, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 20.1, 51.5, 63.3, 128.6, 129.3, 129.5, 131.0, 132.5, 137.1, 166.3, 169.7.

Methyl 2-Methoxymethylbenzoate (13). Compound **13** was prepared with a variation of literature procedures (see the Supporting Information for details):[19] IR (neat) 1721 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 3.30 (s, 3H), 3.46 (s, 3H), 4.92 (s, 2H), 7.0 (t, J = 8 Hz, 1H), 7.2 (t, J = 8 Hz, 1H), 7.74 (d, J = 8 Hz, 1H), 7.91 (d, J = 8 Hz, 1H);

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^{13}C NMR (C_6D_6, 100 MHz) δ 51.3, 58.2, 72.7, 126.7, 127.4, 130.5, 132.2, 141.9, 167.0. One aromatic carbon signal was obscured.

*Methyl 5-Methoxy-3-(tert-butyldimethylsilyloxymethyl)benzoate (**4**).* Compound **34** was prepared by a modification of a known procedure (see the Supporting Information for details).[16b] Compound **34** was converted to TBS-ether **4** (colorless liquid) as described for the preparation of **6** (see the Supporting Information for details): IR (neat) 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.2 (s, 6H), 0.93 (s, 9H), 3.8 (s, 2H), 3.9 (s, 2H), 4.7 (s, 2H), 7.1 (s, 1H), 7.4 (s, 1H), 7.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.1, 18.6, 26.1, 52.3, 55.7, 64.6, 112.8, 117.6, 119.75, 131.4, 143.68, 159.9, 167.2; exact mass calcd for $C_{16}H_{26}O_4Si$ (M + Na)$^+$ m/z 333.1498, found m/z 333.1496.

Preparation of Anticipated Reductive Alkylation Products. *Methyl 1,3-Dimethyl-2,5-cyclohexadiene-1-carboxylate (**26**).* This known compound was prepared for comparison by a variation of a known procedure (see the Supporting Information for details).[20] Compound **26** was obtained as a colorless oil: IR (neat) 1734 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 1.37 (s, 3H), 1.5 (s, 3H), 2.22 (d, J = 22 Hz, 1H), 2.29 (d, J = 22 Hz, 1H) 3.30 (s, 3H), 5.6 (m, 2H), 5.87 (dq, J = 10, 2 Hz, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 23.0, 27.6, 30.7, 45.3, 51.4, 124.0, 129.1, 131.5, 175.1. One vinylic carbon signal was obscured.

*Methyl 1,4-Dimethyl-2,5-cyclohexadiene-1-carboxylate (**27**).* This known compound was prepared for comparison by a variation of known procedures (see the Supporting Information for details).[21] Compound **27** was obtained as a colorless oil: IR (neat, mixture of diastereomers) 1732 cm^{-1}; ^{1}H NMR signals for major diastereomer (C_6D_6, 400 MHz) 0.85 (d, J = 8 Hz, 3H), 1.36 (m, 3H), 2.52 (m, 1H), 3.50 (s, 3H), 5.55 (t, J = 10 Hz, 2H), 5.85 (d, J = 10 Hz, 2H); ^{1}H NMR signals for minor diastereomer (C_6D_6, 400 MHz) 0.92 (d, J = 8 Hz, 3H), 1.35 (m, 1H), 2.48 (m, 3H), 3.48 (s, 3H), 5.55 (t, J = 10 Hz, 2H), 5.85 (d, J = 10 Hz, 2H).

*Methyl 1,2-Dimethyl-2,5-cyclohexadiene-1-carboxylate (**28**).* This known compound was prepared for comparison by a variation of known procedures (see the Supporting Information for details):[22] IR (neat) 1733 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 1.42 (s, 3H), 1.69 (q, J = 1.5 Hz, 3H), 2.40 (d, J = 22 Hz, 1H), 2.50 (d, J = 22 Hz, 1H), 3.31 (s, 3H), 5.37 (br s, 1H), 5.6 (m, 2H); ^{13}C NMR (C_6D_6, 400 MHz) δ 19.9, 24.3, 26.9, 47.7, 51.5, 121.4, 124.6, 129.9, 133.6, 174.5.

*Methyl 5-Methoxy-1,3-dimethyl-2,5-cyclohexadiene-1-carboxylate (**36**).* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. Compound **36** was obtained as a colorless oil: IR (neat) 1731 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 1.48 (s, 6H), 2.54 (d, J = 21 Hz, 1H), 2.62 (d, J = 21 Hz, 1H), 3.25 (s, 3H), 3.36 (s, 3H), 4.82 (s, 1H), 5.6 (s, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 22.4, 28.6, 33.6, 46.9, 51.4, 53.6, 96.9, 124.3, 130.6, 154.1, 175.9; exact mass calcd for $C_{11}H_{16}O_3$ (M + Na)$^+$ m/z 219.0997, found m/z 219.0990.

Reductive Alkylations: Experiments Shown in Tables 1−3. *Table 1, Entry 1: Reductive Alkylation of Methyl 3-[[(tert-Butyldimethylsilyl)oxy]methyl]benzoate (**9**) with Iodomethane.* A mixture of 2.80 g (10 mmol) of ester **9** and 0.74 g (10 mmol) of *tert*-butyl alcohol was placed in a dry 250 mL, three-necked round-bottom flask equipped with a magnetic stir bar, a coldfinger condenser topped with a nitrogen line, a low temperature thermometer, and a septum. The system was placed under a nitrogen atmosphere and dry tetrahydrofuran (25 mL) was added via syringe. The septum was replaced with a gas inlet adapter attached to an ammonia tank. The coldfinger condenser was charged with dry ice-acetone, and the reaction flask was cooled in a dry ice-acetone bath. Ammonia (approximately 100 mL) was condensed in the reaction vessel over a period of about 15 min, and then the gas inlet adapter was replaced with a glass stopper. The stirred solution was cooled to an internal temperature of −65 °C, and 167 mg (23.8 mmol) of lithium metal was added in small pieces (97 mg + 54 mg + 4 mg + 12 mg = 167 mg), through the stoppered hole of the reaction flask, over a period of 25 min. The solution maintained a deep blue color for 5 min after addition of the last piece of lithium at which point 4.26 g (30 mmol) of iodomethane was added via syringe through the stoppered hole of the reaction flask. The blue color dissipated after addition of the first few drops of iodomethane after which the remaining iodomethane was added in one portion. The mixture was stirred for 50 min at −67 °C, and 1.60 g (30 mmol) of solid ammonium chloride was added through the stoppered hole. The coldfinger condenser was quickly removed (after removing the nitrogen line), emptied, and returned to the reaction flask (without the nitrogen line), and the cold bath was removed. The stirred solution was allowed to warm to approximately −25 °C over a period of 25 min. A water bath was carefully placed under the reaction flask, and the reaction temperature increased to 22 °C over a period of 80 min. To the residual solution containing white solid was added 40 mL of water followed by 80 mL of benzene. The phases were separated, and the organic phase was dried (Na_2SO_4) and concentrated in vacuo (25−45 Torr at a temperature below 40 °C) to give 2.92 g of residue. ^{1}H NMR analysis indicated this material was mainly the desired product (**29a**) contaminated by 6 mol % of starting **9**. The residue was purified by chromatography over 100 g of flash silica gel (loaded and eluted with hexanes−ethyl acetate = 9:1) with collection of 50 mL fractions. Fractions 5−9 were pooled and concentrated in vacuo to give 2.43 g (82%) of **29a** as a colorless oil (contaminated with 6 mol % of **9** by ^{1}H NMR): IR (neat) 1735 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.0 (s, 6H), 0.90 (s, 9H), 1.35 (s, 3H), 2.43 (br s, 2H), 3.28 (s, 3H), 3.90 (s, 2H), 5.14 (m, 1H), 5.8−6.0 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz) δ −5.3, 18.4, 25.9, 26.6, 27.4, 44.9, 51.5, 66.9, 123.8, 124.0, 129.2, 134.1, 174.8; exact mass calcd for $C_{16}H_{28}O_3Si$ (M + Na)$^+$ m/z 319.1705, found m/z 319.1701. The presence of **9** (6 mol %) was apparent from ^{1}H NMR signals at δ −0.1, 3.45, and 4.45 and appropriate ^{13}C NMR signals.

*Table 1, Entry 2: Reductive Alkylation of Methyl 3-(tert-Butyldimethylsilyloxymethyl)benzoate (**9**) with Allyl Bromide.* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. Compound **29b** was obtained as a colorless oil: IR (neat) 1732 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.0 (two s, 6H), 0.91 (s, 9H), 2.40 (br s, 2H), 2.5 (d, J = 7 Hz, 2H), 3.26 (s, 3H), 3.90 (s, 2H), 4.95 (br s, 1H), 5.0 (d, J = 6 Hz, 1H), 5.65−5.95 (m, 4H); ^{13}C NMR (C_6D_6, 100 MHz) δ −5.0, 18.4, 26.0, 26.8, 44.9, 48.8, 51.4, 66.8, 118.0, 122.2, 125.2, 130.5, 133.7, 136.3, 174.0; exact mass calcd for $C_{18}H_{30}O_3Si$ (M + Na)$^+$ m/z 345.1861, found m/z 345.1853. The presence of **9** (11−12 mol %) was apparent from ^{1}H NMR signals at δ −0.1, 3.45, and 4.45 and appropriate ^{13}C NMR signals.

*Table 1, Entry 3: Reductive Alkylation of Methyl 3-(tert-Butyldimethylsilyloxymethyl)benzoate (**9**) with Iodomethyl Pivalate.* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. Compound **29c** was obtained as a colorless oil: IR (neat) 1738 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.0 (two s, 6H), 0.90 (s, 9H), 1.12 (s, 9H), 2.38 (s, 2H), 3.28 (s, 3H), 3.9 (s, 2H), 4.30 (d, J = 10 Hz, 1H), 4.37 (d, J = 10 Hz, 1H), 5.70 (dt, J = 10, 3 Hz, 1H), 5.89 (dq, J = 10, 2 Hz, 1H), 5.96 (m, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ −5.4, 18.4, 25.9, 26.8, 27.1, 38.7, 49.6, 51.6, 66.5, 69.2, 119.0, 124.6, 126.7, 138.2, 172.3, 177.1; exact mass calcd for $C_{21}H_{36}O_3Si$ (M + Na)$^+$ m/z 419.2230, found m/z 419.2223. The following peaks in NMR spectra were indicative of the aldehyde (see text): ^{1}H NMR (C_6D_6, 400 MHz) δ −0.02 (s, 6H), 0.89 (s, 9H), 1.10 (s, 9H), 2.30 (br s, 2H), 3.89 (s, 2H), 4.22 (d, J = 10 Hz, 1H), 4.30 (d, J = 10 Hz, 1H), 5.38 (dm, J = 10 Hz, 1H), 5.52 (m, 1H), 9.2 (s, 1H, CHO); ^{13}C NMR (C_6D_6, 100 MHz) δ 55.0, 65.9, 66.3, 116.1, 122.1, 128.5, 129.0, 140.5, 177.2, 196.6. The iodomethyl pivalate used in this reaction was prepared in a manner similar to that described be Knochel (see the Supporting Information for details).[32]

*Table 1, Entry 4: Reductive Alkylation of Methyl 3-(tert-Butyldimethylsilyloxymethyl)benzoate (**9**) with 1-Iodopropane.* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. Compound **29d** was obtained as a colorless oil: IR (neat) 1734 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.0 (two s, 6H), 0.75 (t, J = 7 Hz, 3H), 0.90 (s, 9H), 1.24 (m, 2H), 1.70 (m, 2H), 2.40 (br s, 2H), 3.28 (s, 3H), 3.90 (s, 2H), 5.7 (dt, J = 10, 3 Hz, 1H), 5.85 (dq, J = 10, 2 Hz, 1H), 5.9 (br s, 1H); ^{13}C NMR (C_6D_6, 100

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MHz) δ −5.2, 14.4, 18.0, 18.4, 26.0, 26.9, 42.5, 49.1, 51.3, 67.0, 122.5, 125.0, 128.0, 136.1, 174.6; exact mass calcd for $C_{18}H_{32}O_3Si$ $(M + Na)^+$ m/z 347.2018, found m/z 347.2011.

*Table 1, Entry 5: Reductive Alkylation of Methyl 3-(tert-Butyldimethylsilyloxymethyl)benzoate (**9**) with 1-Chloro-3-iodopropane.* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. Compound **29e** was obtained as a colorless oil: IR (neat) 1733 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.0 (two s, 6H), 0.90 (s, 9H), 1.50 (m, 2H), 1.72 (m, 2H), 2.35 (d, J = 24 Hz, 1H), 2.37 (d, J = 24 Hz, 1H), 3.0 (t, J = 8 Hz, 2H), 3.25 (s, 3H), 3.88 (s, 2H), 5.65 (m, 2H), 5.78 (br s, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ −5.3, 18.4, 25.9, 26.7, 28.0, 36.9, 44.8, 48.5, 51.4, 66.7, 121.8, 125.7, 127.3, 136.9, 174.3; exact mass calcd for $C_{18}H_{31}{}^{35}ClO_3Si$ $(M + Na)^+$ m/z 381.1629, found m/z 381.1620.

*Table 1, Entry 6: Reductive alkylation of Methyl 3-(tert-Butyldimethylsilyloxymethyl)benzoate (**9**) with 2-Iodopropane.* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. Compound **29f** was obtained as a colorless oil: IR (neat) 1732 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.00 (two s, 6H), 0.84 (d, J = 7 Hz, 3H), 0.86 (d, J = 7 Hz, 3H), 0.9 (s, 9H), 2.2 (septet, J = 7 Hz, 1H), 2.4 (br s, 2H), 3.28 (s, 3H), 3.91 (s, 2H), 5.75 (dt, J = 10, 3 Hz, 1H), 5.87 (dq, J = 10, 2 Hz, 1H), 5.92 (br s, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ −5.34, −5.31, 17.52, 17.55, 18.4, 25.9, 27.2, 36.4, 51.2, 53.0, 66.9, 120.9, 125.9, 126.4, 137.0, 174.5; exact mass calcd for $C_{18}H_{32}O_3Si$ $(M + Na)^+$ m/z 347.2018, found m/z 347.2012.

*Table 1, Entry 7: Reductive Alkylation of Methyl 3-Methoxymethylbenzoate (**10**) with Iodomethane.* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. Compound **29a** (R = Me) was obtained as a colorless oil: IR (neat) 1732 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 1.37 (s, 3H), 2.46 (d, J = 23 Hz, 1H), 2.48 (d, J = 23 Hz, 1H), 3.03 (s, 3H), 3.29 (m, 3H), 3.60 (s, 2H), 5.62 (dt, J = 10, 3.5 Hz, 1H), 5.82−5.90 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz) δ 26.9, 27.5, 44.9, 51.5, 57.3, 76.1, 124.1, 126.0, 128.9, 143.9, 174.8; exact mass calcd for $C_{11}H_{16}O_3$ $(M + Na)^+$ m/z 219.0997, found m/z 219.1115.

*Table 1, Entry 8: Reductive Alkylation of Methyl 3-Hydroxymethylbenzoate (**11**) with Iodomethane.* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. Compound **29a** (R = H) was obtained as a colorless oil: IR (neat) 3434, 1731 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 1.35 (s, 3H), 2.35 (d, J = 22, 1H), 2.42 (d, J = 22 Hz, 1H), 3.30 (s, 3H), 3.73 (br s, 2H), 5.62 (dt, J = 9, 4 Hz, 1H), 5.8−5.9 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz) δ 26.5, 27.4, 44.9, 51.6, 66.3, 123.7, 124.2, 129.0, 135.8, 175.1; exact mass calcd for $C_{10}H_{14}O_3$ $(M + Na)^+$ m/z 205.0840, found m/z 205.0835.

*Table 1, Entry 9: Reductive Alkylation of Methyl 3-Acetoxymethylbenzoate (**12**) with Iodomethane.* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. Compound **26** was obtained as a colorless oil, identical (TLC, ^1H and ^{13}C NMR) to an independently prepared sample (vide supra and see the Supporting Information).

*Table 2, Entries 1 and 2: Reductive Alkylation of Methyl 2-Methoxymethylbenzoate (**13**) with Iodomethane.* When this experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS), with 2 equiv of *tert*-butyl alcohol (relative to **13**), compound **27** was obtained as a colorless oil (entry 2). TLC behavior and ^1H and ^{13}C NMR spectra of this compound were identical to those of a sample prepared by reductive alkylation of **19** (vide supra). When 1 equiv of *tert*-butyl alcohol (relative to **13**) was used, the results shown in entry 1 were obtained. The identity of alcohol **25**, aldehyde **22** and alkylation product **28** (4%) were established by comparison with ^1H NMR spectra of commercially available or independently prepared materials.

*Table 3, Entry 1: Reductive Alkylation of Methyl 4-(tert-Butyldimethylsilyloxymethyl)benzoate (**6**) with Iodomethane.* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. The identity of products (**21**, **24**, and **27**) was established by comparison with ^1H NMR spectra of commercially available or independently prepared materials.

*Table 3, Entry 2: Reductive Alkylation of Methyl 4-Methoxymethylbenzoate (**7**) with Iodomethane.* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. The identity of products (**18**, **21**, **24**, and **27**) was established by comparison with ^1H NMR spectra of commercially available or independently prepared materials.

*Table 3, Entry 3: Reductive Alkylation of Methyl 4-(Hydroxymethyl)benzoate (**8**) with Iodomethane.* This experiment was performed in a manner similar to that described for the preparation of **29a** (R = TBS). Complete details are provided in the Supporting Information. This experiment provided, among other products, a mixture of diastereomers **30** as a pale yellow oil: IR (neat of mixture) 3426, 1730 cm^{-1}; ^1H NMR signals for major diastereomer (C_6D_6, 400 MHz) 1.30 (s, 3H), 2.59 (m, 1H), 3.20 (d, J = 6 Hz, 2H), 3.27 (s, 3H), 5.58 (m, 2H), 5.90 (d, J = 11, 1.5 Hz, 2H); ^1H NMR signals for minor diastereomer (C_6D_6, 400 MHz) 1.27 (s, 3H, CH_2), 2.53 (m, 1H), 3.23 (s, 3H), 3.34 (d, J = 5 Hz, 2H), 5.58 (m, 2H), 5.77 (dd, J = 11, 1.5 Hz, 2H); ^{13}C NMR for major diastereomer (C_6D_6, 100 MHz) δ 28.0, 39.2, 44.6, 51.6, 65.9, 126.1, 130.7, 174.6; ^{13}C NMR for minor diastereomer (C_6D_6, 100 MHz) δ 26.4, 39.1, 44.9, 51.9, 65.2, 126.6, 130.8, 174.7; exact mass (mixture of diastereomers) calcd for $C_{10}H_{14}O_3$ $(M + Na)^+$ m/z 205.0840, found m/z 205.0836.

*Table 4, Entries 1 and 2: Reductive Alkylation of Methyl 5-Methoxy-3-[(trimethylsilyloxy)methyl]benzoate (**4**) with Iodomethane.* These experiments were performed in a manner similar to that described for the preparation of **29a** (R = TBS). Details are provided in the Supporting Information. Compound **35** was obtained as a colorless oil: IR (neat) 1734 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.0 (two s, 6H), 0.92 (s, 9H), 1.48 (s, 3H), 2.79 (br s, 2H), 3.22 (s, 3H), 3.33 (s, 3H), 3.92 (s, 2H), 4.81 (s, 1H), 5.90 (s, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ −5.3, 18.4, 26.0, 28.4, 29.4, 46.6, 51.5, 53.7, 66.5, 97.0, 124.0, 134.4, 154.1, 175.6; exact mass calcd for $C_{17}H_{30}O_4Si$ $(M + Na)^+$ m/z 349.1811, found m/z 349.1803. This material was contaminated with small amounts of compound **36** (7 mol %) based on ^1H NMR spectroscopy (see the Supporting Information).

*Table 4, Entry 3: Reductive Alkylation of Methyl 5-Methoxy-3-[(trimethylsilyloxy)methyl)]benzoate (**4**) with Iodomethyl Pivalate.* A mixture of 3.1 g (10 mmol) of ester **4** and 740 mg (10 mmol) of *tert*-butyl alcohol was placed in a dry 250 mL, three-necked round-bottom flask equipped with a magnetic stir bar, a coldfinger condenser topped with a nitrogen line, a low temperature thermometer, and a septum. The system was placed under a nitrogen atmosphere, and dry tetrahydrofuran (30 mL) was added via syringe. The septum was replaced with a gas inlet adapter attached to an ammonia tank. The coldfinger condenser was charged with dry ice−acetone, and the reaction flask was also cooled in a dry ice-acetone bath. Ammonia (100−120 mL) was condensed in the reaction vessel over a period of about 15 min, and then the gas inlet adapter was replaced with a glass stopper. The stirred solution was cooled to an internal temperature of −65 °C and 280 mg (40 mmol) of lithium metal was added (64 mg + 73 mg + 87 mg + 56 mg = 280 mg)) through the stoppered hole of the reaction flask over a period of 20 min. The solution maintained a deep blue color for 10 min after addition of the last piece of lithium. To the solution was added 4.84 g (20 mmol) of iodomethyl pivalate in one portion via pipet. The solution color changed from blue to yellow-orange. The mixture was stirred for 30 min at −65 °C, and 1.07 g (20 mmol) of solid ammonium chloride was added. The coldfinger condenser was quickly removed (after removing the nitrogen line), emptied, and returned to the reaction flask (without the nitrogen line), and the cold bath was removed. The stirred solution was allowed to warm to approximately −25 °C over a period of 25 min. A water bath was placed under the reaction flask and the reaction temperature

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increased to 20 °C over a period of 50 min. To the residue was added 60 mL of water followed by 150 mL of benzene. The phases were separated and the organic phase was dried (Na_2SO_4) and concentrated in vacuo (25−45 Torr at a temperature below 40 °C) to give 5.2 g of a pale yellow liquid. The residue was purified by chromatography over 120 g of flash silica gel (loaded and eluted with hexanes−ethyl acetate = 10:1) with collection of 50 mL fractions. Fractions 9−12 were pooled and concentrated in vacuo to give 2.83 g (66%) of **5a** as a colorless oil that solidified on standing: mp 54−58 °C; IR (neat) 1736, 1701, 1663 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.0 (two s, 6H), 0.95 (s, 9H), 1.20 (s, 9H), 2.7 (s, 2H), 3.2 (s, 3H), 3.37 (s, 3H), 3.9 (s, 2H), 4.34 (d, J = 10 Hz, 1H), 4.5 (d, J = 10 Hz, 1H), 4.8 (s, 1H), 6.05 (s, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ −5.4, 18.4, 25.9, 27.2, 29.6, 38.8, 51.3, 51.7, 53.8, 66.1, 70.0, 92.1, 119.3, 136.9, 156.1, 173.1, 177.1; exact mass calcd for $C_{22}H_{38}O_6Si$ $(M + Na)^+$ m/z 449.2335, found m/z 449.2329. Fraction 13 gave 207 mg of a pale yellow liquid that gave a yellow solid on standing. NMR analysis indicated this material was a 4:3 molar ratio of **5a** and **5b**. The following signals for **5b**[11c] in the ^1H NMR signals support this supposition: ^1H NMR (C_6D_6) δ 1.16 (s, 9H), 1.45 (s, 3H), 2.48 (d, J = 22 Hz, 1H), 2.52 (d, J = 22 Hz, 1H), 3.22 (s, 3H), 3.36 (s, 3H), 4.37 (d, J = 10 Hz, 1H), 4.39 (d, J = 10 Hz, 1H), 4.82 (br s, 1H), 5.64 (m, 1H). ^1H NMR spectra of the crude reaction product indicate a 7:1 molar ratio of **5a** and **5b** is produced in this reaction.

*Mechanistic Experiment in Scheme 5: Reductive Alkylation of Methyl 3-[[(tert-Butyldimethylsilyl)oxy]methyl]benzoate (**9**) with iodomethane at −28 °C.* A mixture of 560 mg (2 mmol) of ester **9** and 148 mg (2 mmol) of *tert*-butyl alcohol was placed in a dry 100 mL, three-necked round-bottom flask equipped with a magnetic stir bar, a coldfinger condenser topped with a nitrogen line, a low temperature thermometer, and a septum. The system was placed under a nitrogen atmosphere, and dry tetrahydrofuran (14 mL) was added via syringe. The septum was replaced with a gas inlet adapter attached to an ammonia tank. The coldfinger condenser was charged with dry ice−acetone and the reaction flask was also cooled in a dry ice−acetone bath. Ammonia (35−40 mL) was condensed in the reaction vessel over a period of about 10 min and then the gas inlet adapter was replaced with a glass stopper. The stirred solution was cooled to an internal temperature of −65 °C and 61 mg (8.6 mmol) of lithium metal was added in small pieces (20 mg + 18 mg + 17 mg + 4 mg + 2 mg = 61 mg), through the stoppered hole of the reaction flask, over a period of 90 min. The solution maintained a deep blue color for 17 min after addition of the last piece of lithium at which point one drop of isoprene was added and the blue color dissipated. The cold bath was removed, and the temperature was allowed to rise to −28 °C over a period of 13 min. The solution was stirred under reflux (−28 °C) for 20 min and then cooled in a dry ice−acetone bath until the temperature reached −65 °C. To the solution was added 852 mg (6 mmol) of iodomethane. The solution was stirred for 25 min, and then 321 mg (2 mmol) of solid ammonium chloride was added. The coldfinger condenser was quickly removed (after removing the nitrogen line), emptied, and returned to the reaction flask (without the nitrogen line), and the cold bath was removed. The stirred solution was allowed to warm to approximately −28 °C over a period of 10 min. A water bath was carefully placed under the reaction flask and the reaction temperature increased to 15 °C over a period of 45 min. To the residue was added 15 mL of water followed by 30 mL of benzene. The phases were separated, and the organic phase was dried (Na_2SO_4) and concentrated in vacuo (25−45 Torr at a temperature below 40 °C) to give 428 mg of residue. ^1H NMR analysis indicated the major component of the mixture was methyl *m*-toluate (**17**). The residue was purified by chromatography over 18 g of flash silica gel (eluted with hexanes−ethyl acetate = 10:1) with collection of 10 mL fractions. Fractions 5−6 were pooled and concentrated in vacuo to give 24 mg of a mixture of **9**, **17** and **29a**. Fractions 7−8 provided 74 mg (25%) of **17** whose TLC behavior and ^1H NMR spectrum were identical with those of a commercially available sample.

COMPUTATIONAL METHODOLOGY

All of the calculations were performed using Gaussian09[33] software package at the Ohio Supercomputer Center. Structures were optimized using Becke's three-parameter hybrid exchange functional[34] combined with the Lee−Yang−Parr correlation functional[35] (B3LYP) and the 6-31+G* basis set. Implicit solvation was utilized for all of the calculations using the Polarizable Continuum Model (PCM)[36] of tetrahydrofuran (THF). Stationary points were confirmed to be minima by calculating the second derivatives analytically, and each minimum was verified to have all real vibrational frequencies. Atomic charges were computed using the ChelpG[37] scheme. Spin densities were obtained from a natural population analysis[38] at the B3LYP/6-31+G* level of theory, with consideration of the PCM model for THF.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures not included in the text, details of computations, and ^1H and ^{13}C NMR spectra for all new compounds and compounds purchased or prepared for the purpose of comparison. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to the memory of Robert Ireland (1930−2012).

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