was purified by silica gel flash column chromatogaphy[29] (eluent, 50:50 Et_2O/petroleum ether) and purified by Kugelrohr distillation to give **25** as a mixture of diastereomers (see Table II for yields and diastereomer ratios) (bp 75–85 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) (major isomer) δ 0.85 (t, J = 6.7 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 6 H), 1.00–1.74 (m, 16 H), 1.79–2.00 (m, 2 H), 2.14 (dd, J = 6.7, 11.2 Hz, 1 H) 2.47 (dd, J = 6.4, 11.2 Hz, 1 H), 2.82 (bq, J = 2.5 Hz, 1 H), 4.91 (dd, J = 2.2, 17.0 Hz, 1 H), 4.93 (dd, J = 2.2, 10.1 Hz, 1 H), 5.47 (ddd, J = 9.8, 10.1, 17.0 Hz, 1 H); (minor isomer) δ 0.83 (t, J = 6.7 Hz, 3 H), 0.86 (d, J = 6.7 Hz, 6 H), 1.00–1.74 (m, 16 H), 1.79–2.00 (m, 2 H), 2.06 (dd, J = 6.7, 11.2 Hz, 1 H), 2.38 (dd, J = 6.4, 11.2 Hz, 1 H), 2.67 (bq, J = 2.8 Hz, 1 H), 4.94 (dd, J = 2.2, 17.0 Hz, 1 H), 4.96 (dd, J = 2.2, 10.1 Hz, 1 H), 5.53 (ddd, J = 9.8, 10.1, 17.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) (major isomer) δ 14.1, 19.9, 20.9, 21.0, 22.8, 25.4, 26.7, 28.7, 29.3, 31.1, 45.1, 46.7, 53.7, 55.9, 114.9, 143.0; (minor isomer) δ 14.0, 20.0, 20.8, 21.0, 22.8, 24.8, 26.7, 28.8, 29.4, 31.8, 45.6, 46.4, 54.1, 55.7, 114.4, 142.3; IR (neat) 3360, 3074, 2955, 2930, 2857, 1640 cm^{-1}; HRMS calcd for $C_{17}H_{33}N$ m/z 251.2613, found 251.2606.

(28) After rearrangement promoted by $(ArO)_2AlMe$ and reduction of **24**, amine **25** was treated with HCl (3 mL, 1 M in Et_2O), loaded on silica gel, and washed with 90:10 petroleum ether/Et_2O to remove the 2,6-diphenylphenol. The product was then eluted with 95:5 ether/NEt_3 to remove **25** from the column, the solvent removed, and the product distilled.

(29) Silica gel was washed with a solution of 5% NEt_3 in Et_2O prior to loading the products on the column in order to enhance resolution of the eluting compounds.

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Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of all compounds in the Experimental Section (30 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the Journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Ester Homologation Revisited: A Reliable, Higher Yielding and Better Understood Procedure

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Enolate anions **3** and **6**, prepared via enolization of α-bromo and dibromo ketones **4** and **5** were converted in high yield to ynolate anions **10** by respective addition of lithium tetramethylpiperidide (to effect deprotonation, **3** → **7**) or butyllithium (to effect metal–halogen exchange, **6** → **7**). Mixtures of such enolates were also obtainable from esters **1** on a large-scale (25 mmol) via in situ formation and addition of lithiodibromomethane (from methylene bromide and lithium tetramethylpiperidide), followed by treatment of the resulting adducts with lithium hexamethyldisilazide to ensure complete enolization. Addition of *sec*-butyllithium and *n*-butyllithium to effect ynolate anion formation, followed by quenching of the reaction mixtures into acidic ethanol, reproducibly afforded homologated esters **8** in 67–90% yield. Demonstrated for ethyl esters **1** having the carbethoxy moiety attached to primary, secondary, tertiary, aryl, and alkenyl groups, this general procedure provides a convenient, large-scale alternative to the classical Arndt–Eistert sequence.

Introduction

Previously, we published a straightforward procedure for the direct homologation of esters (i.e., **1** → **8**). Proceeding via rearrangement of carbenoid **7** to ynolate anion **10**, and quench via the ketene **9**, it occurred with retention of stereochemistry at the migrating R group.[2] Just enough attention was devoted to this novel chemistry at the time to establish a fairly general and reproducible method, but it was not thoroughly examined since our focus turned to exploration of the synthetic utility of the little studied ynolate anion species.[3] Indeed, these efforts were rewarded when subsequently it was found that ynolates **10** could be utilized in other reactions as well,[4] most significantly to prepare siloxyacetylenes **11**,[4c] which have been shown to be useful synthetic intermediates themselves.[5]

Upon repeated application of this original chemistry to prepare ynolate anions **10** for our various studies, however, two limitations became apparent. First, only moderate yields were obtained for either ester homologation or siloxyacetylene formation (i.e., about 50–75%).[2,4c] Second,

(1) SB Postdoctoral Scientist, 1990–91.

(2) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429.

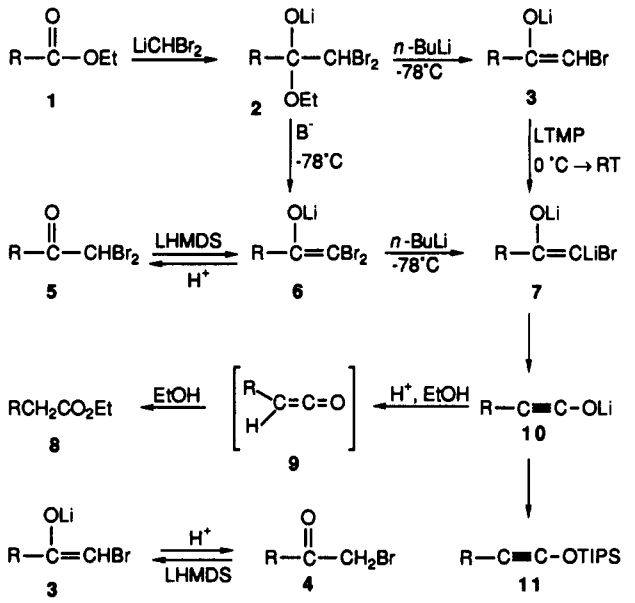
(3) (a) Hoppe, I.; Scholkopf, U. *Liebigs Ann. Chem.* **1979**, 219. (b) Woodbury, R. P.; Long, N. R.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 376.

(4) (a) Kowalski, C. J.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 1325. (b) Kowalski, C. J.; Lal, G. S. *Tetrahedron Lett.* **1987**, *28*, 2463. (c) Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127. See also: Stang, P. J.; Roberts, K. A. *J. Am. Chem. Soc.* **1986**, *108*, 7125.

(5) (a) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693. (b) Kowalski, C. J.; Sakdarat, S. *J. Org. Chem.* **1990**, *55*, 1977. (c) Danheiser, R. L.; Cha, D. D. *Tetrahedron Lett.* **1990**, *31*, 1527. (d) Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149.

0022-3263/92/1957-7194$03.00/0

Scheme I

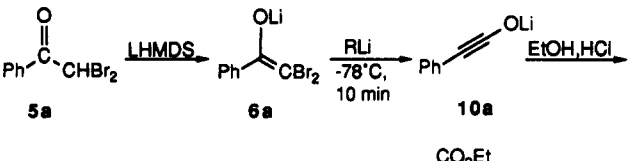


(a) R = phenyl; (b) R = cyclohexyl; for (c) – (f), see Table I

it became difficult to perform this chemistry without special cooling on scales above 2–5 mmol, since the first step involved preparation of the fairly unstable carbenoid dibromomethyllithium. Herein we report the results of a detailed reexamination of this chemistry, with consequent improvement in both the range of yields (67–90%) and our ability to reproducibly carry out the chemistry on larger scale (25 mmol).

The Original Procedure. Our original method involved preparation at −78 °C[6] of dibromomethyllithium from methylene bromide and lithium tetramethylpiperidide (LTMP), followed by addition of the ester **1** to an excess (2.2 equiv[7]) of the dibromomethyllithium solution, affording tetrahedral intermediate **2**. For bulky R groups (e.g., *tert*-butyl or cyclohexyl), significant amounts of **2** were converted to dibromo ketone enolate **6** even at −78 °C; this was evidenced by formation of ynolate anions **10** from metal–halogen exchange with *n*-butyllithium and rearrangement, both occurring *at −78 °C*, followed by formation of homologated ester **8** upon acidic ethanol quenching. This result was consistent with Normant's earlier observation that ethyl isobutyrate **1** (R = isopropyl) on treatment with dibromomethyllithium at low temperature affords **6** and on protic quench dibromo ketone **5** (R = isopropyl).[8] It is also consistent with our own observations that dibromo ketone enolates **6**, prepared from dibromo ketones by enolization with lithium hexamethyldisilazide (LHMDS), undergo metal–halogen exchange and rearrangement to ynolate anions at −78 °C (i.e., **5** → **6** → **7** → **10**).[9]

Scheme II



R-Li	**8a**	**12a**	**13a**	Total
t-BuLi	71%	5%	19%	95%
n-BuLi	77%	–	20%	97%
MeLi	75%	2%	16%	93%

For most R groups, however, tetrahedral intermediate **2** proved stable at −78 °C and could not be cleanly converted to dibromo ketone enolate **6** (e.g., by warming) without also affording monobromo ketone enolate **3** in substantial amounts (presumably from competing metal–halogen exchange by dibromomethyllithium on tetrahedral intermediate **2** upon warming). It was found that treatment of **2** with *n*-butyllithium at −78 °C resulted in metal–halogen exchange and formation of monobromo ketone enolate **3**; in fact, acidic quenching of such reactions at low temperature allowed preparative formation of monobromo ketones (i.e., **1** → **2** → **3** → **4**).[10] A critical discovery which made the homologation procedure possible was that warming of monobromo ketone enolates **3** prepared in this manner, i.e., containing LTMP (from reaction of the tetramethylpiperidine used initially and the excess *n*-butyllithium added to **2** at −78 °C), resulted in deprotonation of bromo ketone enolate anion **3** by LTMP at rt, initiating rearrangement to ynolate anion (i.e., **3** → **7** → **10**).

In light of the above two pathways, it became irrelevant whether tetrahedral intermediate **2** led to dibromo ketone enolate **6** or to the monobromo ketone enolate **3** or to mixtures of the two. Both species could be productively converted to ynolate anion **10** by the same protocol (*n*-butyllithium addition and warming). Quenching the ynolate-containing reaction mixture by adding acidic ethanol to it resulted in complex, polymer-containing mixtures, but adding the reaction mixture itself to acidic ethanol afforded the homologated ester product **8**, presumably via the ketene intermediate **9** (i.e., **10** → **9** → **8**). Although this chemistry worked for a wide variety of esters with primary, secondary, tertiary, aryl, alkenyl, and alkynyl R groups, the yields (53–75%) and scale of reactions (2–5 mmol) were only moderate.[2]

Exchange-Initiated Rearrangement. Given the complex series of reactions which constitute the process above, there were numerous areas where possible problems

(6) In some of our earlier papers (i.e., Refs 2, 4a, and 10), we reported that reactions were run with dry ice/ether-bath cooling at temperatures of about −90 °C. We note here that the −90 °C temperatures in those reports were in error, and should actually have been −78 °C instead. Two coincidental problems led to this confusion. Gorden et al. (Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972; p 451) report a table entry for a cooling bath temperature of −100 °C for diethyl ether/CO_2. This report was generally supported in our laboratories by readings from three "alcohol" thermometers. Later we found, hwoever, that those thermometers (two Fisher 15-035 and one Ertco X7048), when immersed in dry ice–acetone, read from −86 °C to −96 °C! Thus our original temperature reports were in error, and we subsequently changed to standard, −78 °C, dry ice/acetone baths to perform these chemistries. We strongly recommend calibrating any low temperature thermometer to ca. −78 °C when it is immersed in a dry ice/acetone bath and/or using digitial thermometers in place of "alcohol" thermometers.

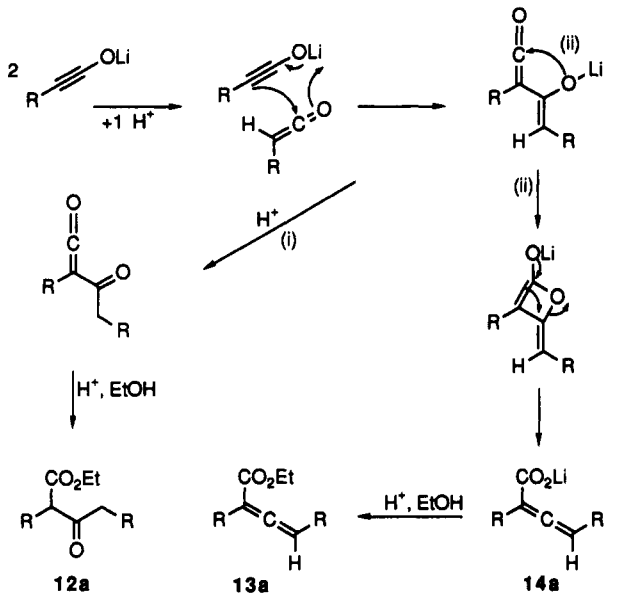
(7) Different esters require somewhat different amounts of dibromomethyllithium to effectively consume all of the starting ester, probably reflecting differing rates of addition vs decomposition of the dibromomethyllithium. The necessary amounts vary from about 1.3 to 2.2 equiv. In order to have a general procedure, not requiring separate titration experiments to determine the exact amount required for each different ester, we settled upon routine use of 2.2 equiv. In most cases, therefore, some excess of dibromomethyllithium is added and presumably is present with the tetrahedral intermediate on completion of the addition.

(8) Villieras, J.; Bacquet, C.; Normant, J.-F. *Bull. Soc. Chim. Fr.* **1975**, 1797.

(9) Kowalski, C. J.; Fields, K. W. *J. Am. Chem. Soc.* **1982**, *104*, 321.

(10) Kowalski, C. J.; Haque, M. S. *J. Org. Chem.* **1985**, *50*, 5140.

Scheme III



(a) R = phenyl; (b) R = cyclohexyl

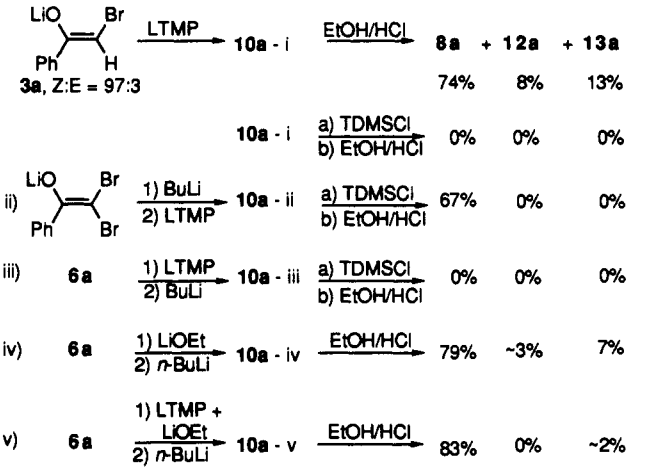
limiting yield and scale could reside. In order to improve the yields of this chemistry it was decided to examine the individual steps separately to determine the effectiveness of each. Efforts thus began with a careful reexamination of the key rearrangement step **7** → **10**. Dibromo ketone **5a** was treated with LHMDS in THF at −78 °C, and the resulting enolate **6a** was subjected to metal–halogen exchange/rearrangement at −78 °C using either *tert*-butyl-, *n*-butyl-, or methyllithium. Quenching the −78 °C solution of resulting ynolate **10a** into acidic ethanol[11] afforded the expected homologated ester **8a**, along with two dimeric products **12a** and **13a**. As indicated in Scheme II, the combined yield of these three products exceeded 90% in all three cases, showing little difference resulting from the type of alkyllithium employed.

A mechanism can be postulated (Scheme III) in which the dimeric products arise from attack of ynolate **10a** upon the initially formed ketene **9a**, followed either by (i) enolate protonation and tautomerization, with subsequent ethanol addition to afford β-ketoester **12a**; or (ii) ring closure and opening to the carboxylic acid **14a**, and esterification during removal of the acidic ethanol. Consistent with the intermediacy of **14a** is the fact that in one experiment, quenching a reaction mixture into water (actually D_2O) afforded crude carboxylate **14a**, which on treatment with the usual acidic ethanol isolation conditions did indeed convert to allenic ester **13a**. Since the orbitals do not appear properly aligned for the proposed fragmentation to **14a**, however, the actual mechanistic sequence may be more complex than suggested above.

Further support for the notion that **12a** and **13a** were derived from the ynolate anion **10a** came from an experiment designed to break up possible anion aggregates and reduce the reactivity of the ynol species present to see if dimerization could be eliminated. Indeed, when the reaction mixture containing ynolate **10a** was treated with dimethylthexylsilyl chloride to form siloxyacetylene in situ, and this mixture was then subjected to the acidic ethanol

(11) Acidic ethanol mentioned throughout this work refers to solutions prepared from acetyl chloride and absolute ethanol (1:5 ratio by vol), prepared as described in the General Procedures section of the Experimental Section.

Scheme IV



quench, a 90% yield of ester **8a** was obtained. None of the dimeric products were observed. When these same experiments were repeated on dibromo ketone **5b** (R = cyclohexyl), acidic ethanol quench afforded the ester **8b** (R = cyclohexyl) and corresponding allenic ester **13b** in 86% and 4% yields, respectively. Dimethylthexylsilyl chloride quench, followed by acidic ethanol, afforded ester **8b** in 90% yield, with no dimeric products.

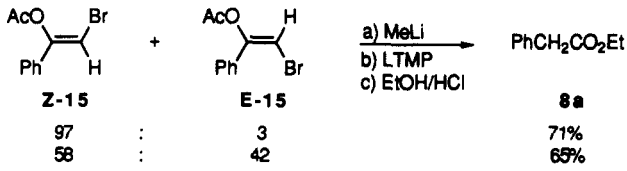
Although all the metal–halogen exchange reactions on dibromo ketone enolates **6** above were carried out at −78 °C, temperature did not appear to be critical. When enolate **6a** was treated with *n*-butyllithium at 5 °C, an 88% yield of ester **8a** was obtained after the silyl chloride quench. Thus, it appears that for both aryl and alkyl R substituents on the dibromo ketone enolates **6** metal–halogen exchange and rearrangement to the ynolate anions **10** is indeed a high-yielding process.

Base-Induced Rearrangement. Since it had been demonstrated the key rearrangement could take place in high yield (starting from dibromo ketone enolates, i.e., **6** → **7** → **10**), attention was next focused on whether the same held true for the LTMP-induced process on a monobromo ketone enolate (i.e., **3** → **7** → **10**). Enolate **3a**, prepared at −78 °C from α-bromoacetophenone and LHMDS, was treated with LTMP, allowed to warm to room temperature, and stirred for 15 min (aliquot quenches showed no conversion of enolate **3a** to ynolate **10a–i** until the reaction temperature reached nearly 20 °C). Ynolate-derived products **8a**, **12a**, and **13a** were obtained upon quenching the reaction mixture into acidic ethanol, in a combined yield of 95% (Scheme IV). The products and yield were essentially the same obtained as those obtained from the dibromo ketone enolate **6a** (Scheme II), indicating that the base-induced rearrangement of **3a** was also a good process.

It was surprising, however, that attempted quenching of ynolate **10a–i** with dimethylthexylsilyl chloride and then acidic ethanol afforded only a complex mixture of polymeric products. This procedure had worked well (90% yield) for the "same" ynolate **10a**, derived from dibromo ketone enolate **6a**, suggesting that the presence of LTMP/TMP was causing problems in the current case. To test this possibility, a solution of ynolate was prepared from dibromo ketone enolate **6a** using butyllithium as before, but a mixture of LTMP/TMP was added to the ynolate (**10a–ii**) prior to the chlorosilane quench. A much dirtier reaction occurred, but still a 67% (vs 90%) yield of product **8a** was obtained.

More startling was the result obtained when LTMP/TMP was added to enolate **6a** *prior* to butyllithium ad-

Scheme V



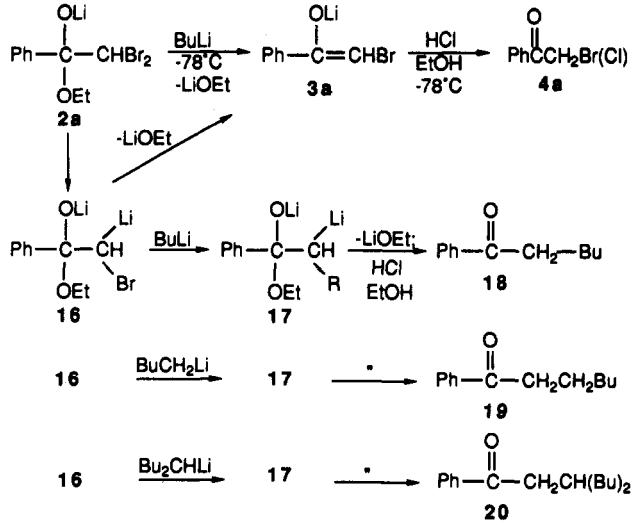
dition/ynolate formation; in this case the chlorosilane quench of ynolate **10a–iii** (clearly present based on acidic ethanol aliquot quenches) afforded no desired product **8a**, but only the same sort of complex mixture as was obtained from the monobromo ketone enolate derived ynolate **10a–i**. These results suggest that the presence of LTMP *at the time of ynolate formation* affected the reactivity of the ynolate in some way (modified aggregation state?) so as to render impossible O-silylation by dimethylthexylsilyl chloride. Indeed, our experience has been that ynolates prepared from esters via the homologation procedure (and thus containing LTMP) also fail to silylate with dimethylthexylsilyl chloride (although the reaction works quite well with triisopropylsilyl chloride[4c]).

The impressive effect upon the reactivity of ynolate **10a** due to the presence or absence of this one component led us to investigate whether the presence of LiOEt during ynolate formation might inhibit formation of the dimeric products **12a** and **13a**. When LiOEt was added to a solution of enolate **6a** just prior to butyllithium addition, and the resulting ynolate anion **10a–iv** was quenched into acidic ethanol, the amounts of **12a** and **13a** were reduced by about half, while the yield of **8a** increased to 79%. When both LiOEt and LTMP were added to **6a** prior to butyllithium addition, resulting ynolate **10a–v** afforded almost none of the dimeric products **12a** and **13a** on acidic ethanol quench, and a further increase to 83% was obtained in the yield of **8a**. Clearly LTMP and alkoxide species present at the time of ynolate formation have a significant effect on yields and products resulting from both protic and silyl chloride quenches of these species.[12]

The excellent result observed for the base-induced rearrangement of bromoenolate **3a** to ynolate anion **10a–i** above did not address the possibly significant problem of olefin geometry. When bromoenolate **3a** was again prepared in the same manner but converted into the corresponding enol acetates **15**[10] with acetic anhydride, a 97:3 mixture of the *Z* to *E* isomers was obtained. The almost exclusive *Z* geometry in the enolate **3a** thus prepared oriented the bromide leaving group trans to the migrating phenyl group, the preferred geometry for other carbenoid rearrangements.[13] This left open the possibility that bromoenolate anions of *E* geometry might not rearrange at all to ynolate anions on deprotonation by LTMP, which could result in low yields in the homologation procedure; as much as 17% of the *E* isomer of **3a** (R = Ph) had been obtained from the corresponding tetrahedral intermediate **2a** with butyllithium treatment.[10]

To test the ability of an *E* isomer to rearrange, we sought to prepare pure (*E*)-**3a**, but unfortunately our efforts were not entirely successful. As already mentioned, enolization of α-bromoacetophenone afforded almost exclusively *Z* enolate. The *Z* and *E* enol acetates **15** (a 9:1 mixture obtained from ethyl benzoate homologation as before[10]) were not readily separated preparatively. LDA-induced carbenoid rearrangement[14] of 2,2-dibromo-1-phenylethanol, followed by acetic anhydride quench, afforded exclusively the *Z*-enol acetate **15** (in poor yield). Treatment of α,α-dibromoacetophenone with *sec*-butyllithium, followed by acetic anhydride, afforded an excellent yield of **15**, but with a 96:4 *Z*:*E* ratio. Finally, photoisomerization of the enol acetate mixture thus obtained produced a 58:42 mixture of (*Z*:*E*)-**15**, which was not preparatively separable but was enriched enough in the *E*-isomer to determine if that geometry was completely resistant to ynolate formation.

Scheme VI



(n) Bu = *n*-Bu; (s) Bu = *s*-Bu; (t) Bu = *t*-Bu

As a control, a 97:3 mixture of *Z* and *E* enol acetates **15** was treated with methyllithium (to generate the enolate anions) followed by LTMP and warming as before, affording a 71% yield of ester **8a** upon acidic ethanol quench. Treatment of a 58:42 (*Z*:*E*)-**15** mixture under identical conditions afforded a 65% yield of **8a**. Although the mixture containing more of the *E*-isomer resulted in a slightly reduced yield compared to the control, one would calculate a maximum yield of 42% (based on the control) if none of the *E*-enolate had been converted to ynolate. Thus, while the experiment was less than optimal, it clearly indicated that *E*-enolate was indeed converted to ynolate (although the yield may be somewhat lower).

Discovering the Problem. None of the experiments to this point had uncovered serious problems with the rearrangement itself, which suggested that the limitation to homologation yields must have been earlier in the sequence (i.e., **1** → **2** → **3** and/or **6**). When ethyl benzoate (**1a**) was added to preformed dibromomethyllithium at −78 °C, as in the usual procedure, followed by quenching at low temperature into aqueous acid, a 20:1 mixture of α,-α-dibromo- and α-bromoacetophenone (**5a** and **4a**) was obtained in almost quantitative yield. The small amount of monobromo ketone obtained was likely due to metal–halogen exchange on tetrahedral intermediate **2a** by excess dibromomethyllithium, promoted by localized warming during the quench procedure. Thus, formation of tetrahedral intermediate **2a** was clearly not a problem, so attention was focused on the last remaining step in the sequence, conversion of tetrahedral intermediate **2a** to **3a** or **6a**.

(12) The complex nature of aggregation and its effects on reactivity of LTMP and other lithium amide bases is being examined in detailed; see: Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575 and references cited therein.

(13) Kobrich, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 41 and references cited therein.

(14) (a) Kuwajima, I.; Nakamura, E. *J. Org. Chem.* **1977**, *42*, 346. (b) Normant, H. *J. Organomet. Chem.* **1975**, *100*, 189. (c) Kobrich, G.; Grosser, J. *Tetrahedron Lett.* **1972**, 4117. (d) Villieras, J.; Bacquet, C.; Normant, *J. Organomet. Chem.* **1972**, *40*, C1.

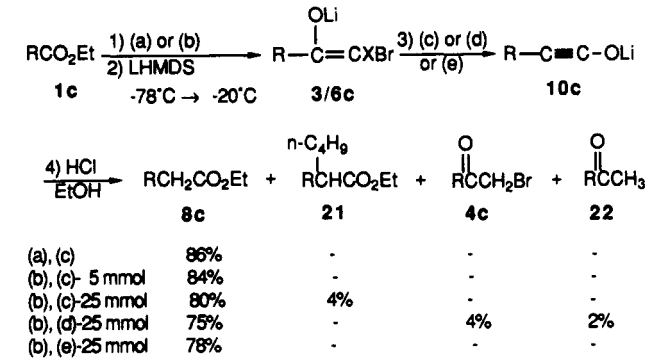
Tetrahedral intermediate **2a** was prepared at −78 °C as above and treated with *n*-butyllithium at −78 °C as in the usual procedure. When quenched into acidic ethanol *without warming* (Scheme VI), however, the expected α-bromoacetophenone **4a** was obtained in only 73% yield. In addition there were obtained in yields of 5% each hexanophenone (**18n**, Bu = *n*-Bu), heptanophenone (**19n**), and β-butylheptanophenone (**20n**), three unexpected products comprising 15% of the material!

An experiment was carried out to test whether any of these products had resulted from reaction of enolate **3a** with other materials in the homologation mixture (e.g., with *n*-butyl bromide from the metal–halogen exchange followed by halide reduction to afford **18n**). Enolate **3a** was independently prepared (from α,α-dibromoacetophenone and *n*-butyllithium), and to this solution at −78 °C were added all of the components expected to be present in the solution of enolate **3a** formed from ethyl benzoate via **2a** (i.e., dibromomethyllithium, LTMP, LiOEt, and excess *n*-butyllithium). When this −78 °C solution, a mimic of the one which had afforded the three unexpected ketones above, was quenched into acidic ethanol, α-bromoacetophenone was obtained in 89% yield with none of the previously observed byproducts being formed. Thus, bromoenolate **3a** appears stable to these reaction conditions and does not appear to be a precursor to the observed byproducts.

When tetrahedral intermediate **2a** was treated with *sec*-butyllithium or *tert*-butyllithium and then quenched without warming, ketones **18s** and **19s** (Bu = *s*-Bu) or **18t** (Bu = *t*-Bu) were similarly formed in several percent yield, respectively. Although no further mechanistic studies were done, all these data seemed consistent with an intermediate other than **3a** being formed from tetrahedral intermediate **2a** which was activated toward attack by strong nucleophiles. Attack on such dibromo tetrahedral intermediates by organocuprates has recently been reported by Barluenga to afford ketone products of addition still bearing bromine, but the mechanism was not elucidated.[15] Perhaps more relevant, carbenoids are known to undergo addition by organometallic reagents;[16] thus, one might speculate that an intermediate carbenoid such as **16** (which is the likely intermediate in formation of the major product **4a**) could couple with excess butyllithium to form **17**, the precursor to **18**. Reactions of butyllithium with the extra dibromomethyllithium used in these preparations[7] might be expected to additionally afford other alkyllithium species (i.e., $BuCH_2Li$ and Bu_2CHLi),[16] which could then result in ketone products **19** and **20** via the same pathway.

Regardless of the mechanism by which these byproducts were being formed, it was clear that reaction of tetrahedral intermediate **2a** with butyllithium resulted in significant loss of material from the desired pathway. It seemed possible, however, that by simply warming the tetrahedral intermediate **2a** to convert it into enolates **3a** and **6a** *before* adding any butyllithium, the problem might be avoided. When this was done, the desired product **8a** was obtained in essentially the same overall yield (67%) from ethyl benzoate as before. Examination of quenched aliquots as the solution of **2a** was warmed showed a progressive and eventually complete loss of the peak corresponding to the monobromo ketone (relative to dibromo ketone). This suggested that perhaps the monobromoacetophenone was not being fully enolized by the ethoxide base in the mixture and was therefore susceptible to destruction by nucleophiles in the mixture at higher temperatures.

Scheme VII[a]



(a), (c)	86%	-	-	-
(b), (c)- 5 mmol	84%	-	-	-
(b), (c)-25 mmol	80%	4%	-	-
(b), (d)-25 mmol	75%	-	4%	2%
(b), (e)-25 mmol	78%	-	-	-

[a] Key: R = $-CH_2CH_2Ph$; (a) addition of **1c** to $LiCHBr_2$; (b) addition of LTMP to **1c** + CH_2Br_2; (c) 6 equiv of *n*-BuLi, −20 °C → rt; (d) 6 equiv of *s*-BuLi, −78 °C → rt; (e) 4 equiv of *s*-BuLi, −78 °C → −20 °C; 2 equiv of *n*-BuLi, −20 °C → rt.

When a solution of tetrahedral intermediate **2a** was warmed only to −20 °C (and was shown to still contain monobromo ketone and/or enolate **4a**/**3a** by aliquot quench), treatment with butyllithium followed by the usual warming and quench again afforded only a 68% yield of ester **8a**. Finally, it was shown that if an independently prepared mixture of bromoacetophenone, LiOEt, and tetramethylpiperidine in THF was treated with butyllithium at −78 °C and warmed to rt, most of the material was destroyed and only about 25% of ester **8a** was formed. The formation and destruction of nonenolized monobromo ketone therefore appeared to preclude simple warming as a solution to the problem of utilizing tetrahedral intermediate **2a**.

Yield Improvement. Understanding that both tetrahedral intermediate **2a** (formed at low temperature) as well as bromo ketone **4a** (which formed on warming) were not fully compatible with butyllithium made clear the solution: adding a suitable base to fully enolize (and thus protect) monobromo ketone **4a** as it was produced when the tetrahedral intermediate **2a** was warmed. Initially, an attempt was made to use LTMP for this purpose, since it might have been possible to simply use a larger excess initially while forming the dibromomethyl lithium. Adding LTMP to a normal reaction mixture containing tetrahedral intermediate **2a** at −78 °C, however, produced an immediate darkening and formation of numerous byproducts (as indicated by aliquot quench) even at low temperature. Warming to 0 °C and quenching into acid afforded only a 73% yield of mono- and dibromoacetophenone, demonstrating that LTMP was not compatible with tetrahedral intermediate **2a** (in a manner reminiscent of the situation with *n*-butyllithium).

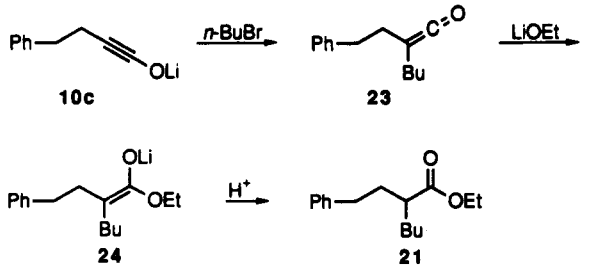
In hopes that the problem might be solved by using a base less prone to electron transfer than LTMP,[17a,b] yet known to effectively enolize α-halo ketones,[17c] a solution of tetrahedral intermediate **2a** derived from ethyl benzoate was treated with LHMDS at −78 °C and warmed to rt. Quenched aliquots showed no loss of the monobromo ketone **4a** relative to dibromo ketone **5a** on warming, suggesting that indeed the monobromo ketone was being protected as its enolate anion **3a**. Treating the solution of enolates **3a** and **6a** with *n*-butyllithium at 0 °C afforded (after warming and acidic ethanol quench) the homolo-

(15) Barluenga, J.; Llavona, L.; Yus, M.; Concellon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2890.

(16) (a) Kobrich, G.; Merkle, H. R. *Chem. Ber.* **1966**, *99*, 1782. (b) Closs, G. *J. Am. Chem. Soc.* **1962**, *84*, 809. (c) see too ref 12.

(17) (a) Creary, X. J. *J. Org. Chem.* **1980**, *45*, 2419. (b) Newcomb, M.; Reeder, R. A. *J. Org. Chem.* **1980**, *45*, 1489. (c) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601.

Scheme VIII



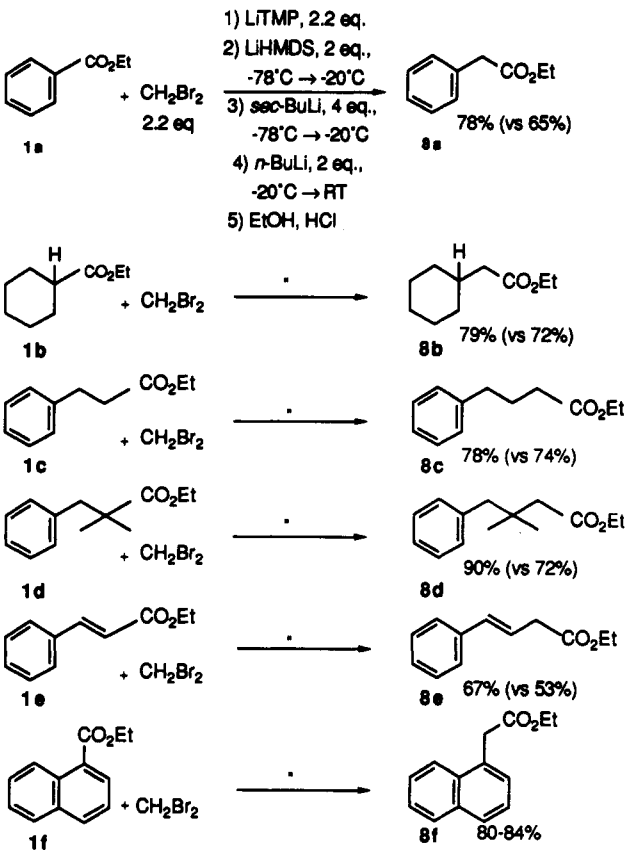
gated ester **8a** in 84% yield (nearly a 20% improvement over the original procedure). Enolization using LHMDS was indeed successful! When ethyl dihydrocinnamate **1c** was treated using this lithium hexamethyldisilazide modification (Scheme VII, a,c), homologated ester **8c** was obtained in 86% yield (a 12% improvement over the original procedure).

Larger Scale Improvement: Standard Procedure. While an improved small-scale homologation procedure appeared to be in hand, this chemistry was still subject to scale limitations since the esters were being added to solutions of preformed dibromomethyllithium. In order to eliminate the need to prepare and work with solutions of unstable carbenoids, it was decided to try using a modification of the in situ procedure of Yamamoto and Nozaki[18] for generation of dibromomethyllithium which we had employed in our very first attempt at performing ester homologation.[9] A solution of ethyl dihydrocinnamate (**1c**) and methylene bromide (2 equiv) was treated at −78 °C with LTMP to effect dibromomethyllithium formation and tetrahedral intermediate formation. Subsequent addition of LHMDS, warming to −20 °C, butyllithium addition, and final warming and quench afforded homologated product **8c** in 84% yield on a 5 mmol scale (Scheme VII, b, c, 5 mmol); thus, the in situ preparation of dibromomethyllithium worked quite well in this procedure.

When the same reaction was scaled to 25 mmol, however, the product obtained in 83% yield was contaminated with 4% of *n*-butylated product **21** (Scheme VII, b, c, 25 mmol).[19] It appeared likely that the longer addition times and increased concentrations required to carry out the chemistry on a larger scale were resulting in some alkylation of ynolate anion **10c** by the *n*-butyl bromide present from earlier metal–halogen exchange on the dibromo ketone enolate. Some of the resulting butyl ketene **23** must have undergone reaction with lithium ethoxide also present in the reaction mixture (from the starting ester) to afford enolate **24** (precursor to impurity **21**). Using a larger excess of *n*-butyllithium in this reaction (8 equiv instead of 6 equiv) to possibly destroy the *n*-butyl bromide was unsuccessful at preventing formation of **21**.

Substituting *sec*-butyllithium for *n*-butyllithium seemed likely to get around the alkylation problem, since the *sec*-butyl bromide formed would be much less prone to alkylation of the ynolate anion. Indeed, when 6 equiv of *sec*-butyllithium was substituted for 6 equiv of *n*-butyllithium in the exchange/rearrangement step, no butylation products were observed (Scheme VII, b, d, 25 mmol). Unfortunately, 4% of monobromo ketone **4c** was obtained, suggesting that the *sec*-butyllithium was undergoing other competitive reactions (e.g., with THF), such that not enough was available to generate sufficient LTMP for deprotonation of all the enolate **3c**. Adding slightly more *sec*-butyllithium might easily have solved this problem, but 2% of 4-phenyl-2-butanone (**22**) was also formed in the reaction above. This second impurity was likely being formed from metal–halogen exchange by the *sec*-butyllithium on enolate **3c** to form an α-keto dianion[20] as precursor to **22**.

Table I. Standard Procedure at a 25 mmol Scale



In order to avoid both the formation of *n*-butyl bromide in the low-temperature metal–halogen exchange step, as well as the undesired α-keto dianion formation in the higher temperature deprotonation step, a hybrid procedure was devised. Use of 4 equiv of *sec*-butyllithium at −78 °C to effect the metal–halogen exchange, followed by 2 equiv of *n*-butyllithium at −20 °C to promote formation of LTMP, afforded homologated product **8c** in 78% yield, free of undesired byproducts (Scheme VII, b, e, 25 mmol). Although the yield using this *sec*-butyllithium/*n*-butyllithium procedure on a large scale is lower than that of the best small-scale procedure using *n*-butyllithium alone (i.e., 78 vs 86%), the reproducibility and lack of byproducts of this large-scale method more than compensates for the reduction in yield.

Generality of Standard Procedure. Table I contains six examples of ester homologation carried out on a 25 mmol (ca. 5 g) scale using basically the same ("standard") procedure described above. Yields range from 67 to 90%. The first five examples (**1a–1e**) were compounds which had previously been examined using our original small-scale (2 mmol) homologation procedure.[2] The current yields were higher in every case (by as much as 18%) compared

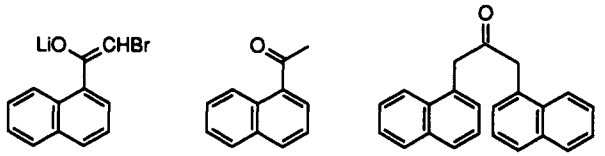
(18) Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 3010.

(19) The amount and identity of butylated compound **21** was assigned by GC and NMR based on comparison with material independently synthesized (via alkylation of the lithium enolate of ethyl 4-phenylbutyrate with *n*-butyl bromide).

(20) Kowalski, C. J.; O'Dowd, M. L.; Burke, M. C.; Fields, K. W. *J. Am. Chem. Soc.* **1980**, *102*, 5411. Subsequent to this publication we found that *s*-BuLi can be used in place of *t*-BuLi for α-keto dianion formation (unpublished results).

with those obtained *on a 2 mmol scale* from the original procedure (shown in parentheses). Thus, the new procedure not only allowed these homologations to be done on a significant scale without the problems and losses associated with scale-up of the old procedure, but it has clearly proven itself to be an improvement over the original procedure even compared to the earlier *small-scale* results.

The one new example, ethyl 1-naphthylacetate (**8f**), was selected as a target to allow comparison of this method with the classical Arndt–Eistert procedure as reported in *Organic Syntheses*;[21] in that work, ethyl 1-naphthylacetate had been obtained in 78% overall yield from 1-naphthoyl chloride via diazomethane addition followed by silver-catalyzed Wolff Rearrangement. In the present work, when ethyl 1-naphthoate (**1f**) was submitted on a 25 mmol scale to the identical procedure used for the other five esters, a 78% yield of desired ester **8f** was obtained, along with 2% of the ketone **25**. This unexpected reduction of



3f **25** **26**

the bromoenolate **3f** (R = naphthyl) to the α-keto dianion precursor of **25** did not occur as a result of the *sec*-butyllithium addition (as observed for **1b** with excess reagent above). None of the ketone **25** was present in an aliquot taken prior to addition of the *n*-butyllithium at −20 °C, indicating that for the naphthyl enolate **3f** significant metal–halogen exchange can occur even with *n*-butyllithium!

To avoid the problem of having enolate **3f** in the presence of excess *n*-butyllithium, addition of the *n*-butyllithium was tried slowly (over the course of 30 min) at 20 to 25 °C, instead of in one portion at −20 °C. Under these new conditions, the deprotonation of bromoenolate **3f** by LTMP was occurring as the butyllithium was being added, generating tetramethylpiperidine to act as a proton source to quench the butyllithium as it entered the solution (and thus providing more LTMP as well to complete deprotonation of **3f**). When this was done, an 80% yield of homologated ester products was obtained,[22] with none of the reduced product **25**.

It was interesting that in doing the chromatographic purification of the product **8f** from the naphthyl-substituted ynolate, we also isolated small amounts (2–4%) of the ketone **26**. It seemed likely this was derived from keto ester dimer analogous to that observed earlier (i.e., **12a**) from the phenyl ynolate **10a**. As already noted above, however, such dimers were not obtained from ester-derived ynolate solutions (which contained LiOEt), and thus the naphthyl ynolate seemed unusually disposed toward ynolate/ketene dimerization (perhaps as a result of π stacking in the ynolate aggregate). To see whether this dimerization process could be interfered with by the presence of even more of the desired ketene trap (i.e., LiOEt), 1 equiv of LiOEt was added along with the LHMDS in a 25 mmol experiment. In that case, virtually none of the ketone product **26** was observed, but instead a slightly improved (84%) yield of ester **8f** was obtained.

After these results were obtained, a careful look at the product **8a** from the phenyl case showed that a small amount (about 1%) of reduction (to acetophenone) had formed in that case as well. Performing the *n*-butyllithium addition at room temperature in the reaction of enolate **3a** eliminated the small amount of metal–halogen exchange previously observed there too (although without any noticeable change in yield since the initial exchange reaction had been so minor). Addition of LiOEt to homologation reactions starting from ethyl benzoate (and also from ethyl cinnamate) gave no significant improvement in yield of product **8a** (or **8e**). This was not unexpected, since dimer formation was not a problem to begin with for these starting esters. Thus while room temperature addition of the *n*-butyllithium appeared to be a useful variant to eliminate small amounts of dehalogenation when the carboethoxy group was attached to an aromatic nucleus, LiOEt addition seemed beneficial only in the naphthyl case.

Summary

An effective, reproducible protocol for large-scale homologation of esters via ynolate anions has been developed, involving sequential addition to a solution of ester and methylene bromide, of LTMP, LHMDS, *sec*-butyllithium, and *n*-butyllithium with appropriate temperature control. Demonstrated on a 25 mmol scale for ethyl esters having the carbethoxy moiety attached to primary, secondary, tertiary, aryl, and alkenyl groups, this general method provides a convenient, large-scale alternative to the classical Arndt–Eistert sequence. The procedure has been successfully applied to ethyl 1-naphthylacetate on a 100 mmol scale, as will be reported shortly in *Organic Synthesis*. In addition, work is nearly complete on a related but operationally simplified procedure for small-scale (1 g) ester homologation which will soon be reported as well. It is worth noting that while this work has focused entirely on homologation, the ynolate anions which are intermediate in this process also have other uses;[4,5] thus, the yield and scale improvements made for ynolate formation herein should be applicable to these other varied uses as well.

Experimental Section

General Procedures. IR spectra were recorded on a Nicolet 20 SXB spectrometer equipped with a DTGS detector. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) using a Bruker AM400 spectrometer. Mass spectra were obtained on a Finnigan MAT GCMS Model 4610. The GC/MS were taken on a 30-m × 0.25-mm i.d. capillary column of cross-linked methyl silicone at 80 psi of pressure for the helium carrier gas and with the column temperature raised from 100 to 300 °C at a rate of 15 °C/min. Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh), purchased from Aldrich Chemical Co. Thin-layer chromatography was performed on precoated silica gel plates (250 μm) purchased from Analtech Inc. Preparative thin-layer chromatography was performed on precoated plates (0.5 mm, silica gel 60F-254) purchased from E. Merck Industries Inc. Reactions were monitored by analyzing small aliquots, taken from the reaction mixture. All aliquots (about 0.2 mL) were withdrawn from the reaction mixture (via syringe), quenched, and diluted with ethyl acetate (about 1 mL) and water (0.5 mL). The mixture was then shaken, and most of the organic layer was transferred via pipette to a tube containing anhydrous $MgSO_4$ for drying; the solution was filtered and analyzed by GC with flame ionization detection on a 50 m × 0.32 mm i.d. capillary column of cross-linked methyl silicone at 40 psi of pressure for the helium carrier gas and a temperature raised from 100 to 300 °C at a rate of 15

(21) Lee, V.; Newman, M. S. *Organic Syntheses*; Wiley: New York, 1989; Coll. Vol. VI, p 613.

(22) In this case the homologated ester product was a mixture of the expected ethyl ester, contaminated with 2–4% of the corresponding *n*-butyl ester. An older bottle of *n*-butyllithium was used, and we had previously seen (unpublished results) that the presence of lithium butoxide in partially decomposed bottles results in formation of the corresponding *n*-butyl ester as an undesired byproduct. For all this chemistry, therefore, it is recommended that only freshly opened bottles or solutions extremely well-protected from air be used.

°C/min. Acidic ethanol as mentioned throughout these experiments was prepared by adding acetyl chloride slowly to ice-cooled absolute ethanol (1:5 ratio/vol) at 0 °C and stirring at rt for 30 min prior to the use. Reaction temperatures were measured by using thermometers (Catalog No. Z11, 011-6) purchased from Aldrich Chemical Co. or digital thermometers (7000), -200 °C to +800 °C purchased from Testoterm Inc. Unless otherwise noted, solutions were dried over $MgSO_4$ following reaction workups and solvents were removed using a rotary evaporator prior to purification. THF was freshly distilled under N_2 from a purple solution of sodium and benzophenone. All other commercially obtained solvents and reagents were used without further purification. Solutions of butyllithium were purchased from Aldrich Chemical Co. and were generally freshly opened or well protected from oxygen if stored before use.[22] 1,1,1,3,3,3-Hexamethyldisilazane and 2,2,6,6-tetramethylpiperidine are abbreviated HMDS and TMP, respectively, below. Although spectral data is only reported once for each compound, purified products were routinely checked for identity and purity by ^1H NMR and GC.

Ethyl Phenylacetate (8a) from α,α-Dibromoacetophenone (5a). (a) Using *t*-BuLi. A solution of *n*-BuLi in hexanes (0.78 mL, 1.96 mmol) was added to a stirred, 0 °C solution of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (0.45 mL, 0.345, g, 2.14 mmol) in THF (15 mL) with ice-bath cooling. After 15 min the LHMDS was cooled to -78 °C with a dry ice/acetone bath, and α,α-dibromoacetophenone (**5a**)[23] (0.5 g, 1.79 mmol) in THF (5 mL) was added. After 10 min a solution of *t*-BuLi in pentane (3.4 mL, 5.7 mmol) was added at -78 °C. The reaction mixture was stirred for 10 min at -78 °C and then added over a 15-min period to a stirred solution of acidic ethanol[11] (30 mL) at 0 °C. The mixture was diluted with ether (200 mL) and washed with 10% aqueous HCl (20 mL). The aqueous layer was reextracted with ether (2 × 35 mL), and the combined etheral layers were washed with brine and dried. The crude product (0.316 g) was purified by silica gel column chromatography (4% ethyl acetate in hexane and then slowly increased to 15% ethyl acetate in hexane) to afford 0.207 g (71%) of **8a**: ^1H NMR ($CDCl_3$) δ 7.40–7.25 (m, 5 H), 4.15 (q, 2 H), 3.60 (s, 2 H), 1.25 (t, 3 H). Also isolated were 0.012 g (5%) of **ethyl 2,4-diphenylacetoacetate (12a)** [mp 75 °C (lit.[24] mp 78 °C); IR (neat) 3442, 2988, 1734, 1715, 1600, 1498, 1454, 1211, 729, 712, and 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.15 (s, 0.44 enolic), 7.40–7.05 (m, 10 H), 4.80 (s, 0.6 H), 4.23–4.13 (m, 2 H), 3.80–3.68 (m, 1.1 H), 3.45 (s, 0.9 H), 1.25 (t, 1.8 H), 1.15 (t, 1.2 H) (compound was present in both keto and enol forms); MS *m/z* 282 (M^+), 265, 237, 209, 164, 119, 91] and 0.047 g (19%) of **ethyl 2,4-diphenyl-2,3-butadienoate (13a)**: IR (neat) 2989, 1945, 1748, 1630, 1598, 1378, 1351, 1014, 770, 717, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (d, 2 H, *J* = 7.2 Hz), 7.39–7.24 (m, 8 H), 4.82 (s, 1 H), 4.28–4.14 (m, 2 H), 1.34 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 182.54, 175.24, 135.25, 129.27, 129.23 (two carbons), 128.59 (two carbons), 128.06, 127.54 (two carbons), 126.68 (two carbons), 122.44, 70.19, 66.13, 15.53; MS *m/z* 264 (M^+), 237, 219, 191; exact mass calcd for $C_{18}H_{16}O_2$ 264.1150, obsd 264.1148.

(b) Using *n*-BuLi. A solution of *n*-BuLi in hexanes (0.78 mL, 1.96 mmol) was added to a stirred, 0 °C solution of HMDS (0.45 mL, 0.345 g, 2.14 mmol) in THF (10 mL) with ice-bath cooling. After 20 min the LHMDS was cooled to -78 °C with a dry ice/acetone bath, and α,α-dibromoacetophenone (**5a**; 0.5 g, 1.79 mmol) in THF (5 mL) was added. After 15 min a solution of *n*-BuLi in hexanes (1.57 mL, 3.93 mmol) was added. The reaction mixture was stirred for 10 min at -78 °C and was then quenched slowly into a stirred solution of acidic ethanol[11] (30 mL) at 0 °C over a 20-min period. After the quench was over, the mixture was diluted with ether (250 mL) and washed with 10% aqueous HCl (20 mL). The aqueous layer was reextracted with a portion of ether (100 mL), and the combined etheral layers were washed with brine and dried. The crude material (0.332 g) was purified by silica gel column chromatography (4% ethyl acetate in hexane and then slowly increased to 15% ethyl acetate in hexane) to afford 0.228 g (77%) of **8a** and 0.046 g (20%) of **ethyl 2,4-diphenyl-2,3-butadienoate (13a)**.

(c) Using MeLi. A stirred solution of lithium enolate **6a**, prepared from 0.5 g (1.79 mmol) of α,α-dibromoacetophenone (**5a**) (as described in b above), was treated at -78 °C with a solution of MeLi (5.1 mL, 7.1 mmol) in ether. The reaction mixture was stirred for 10 min at -78 °C and then quenched over a 25-min period into a stirred solution of acidic ethanol[11] (30 mL) at 0 °C. The mixture was diluted with ether (250 mL) and washed with 10% aqueous HCl (25 mL). The aqueous layer was reextracted with ether (2 × 50 mL), and the combined ethereal layers were washed with brine and dried. The crude product was purified by silica gel column chromatography (using 4% ethyl acetate in hexane, then slowly increased to 15% ethyl acetate in hexane) to afford 0.219 g (75%) of **8a**, 0.004 g (2%) of **ethyl diphenylacetoacetate (12a)**, and 0.038 g (16%) of **ethyl 2,4-diphenyl-2,3-butadienoate (13a)**.

(d) Using Dimethylthexylsilyl Chloride Quench. A solution of *n*-BuLi in hexanes (0.78 mL, 1.96 mmol) was added to a stirred, 0 °C solution of HMDS (0.45 mL, 0.345 g, 2.14 mmol) in THF (10 mL) with ice-bath cooling. After 18 min, the LHMDS solution was cooled to -78 °C with a dry ice/acetone bath, and α,α-dibromoacetophenone (**5a**; 0.5 g, 1.79 mmol) in THF (4 mL) was added. After 15 min a solution of *t*-BuLi in pentane (3.4 mL, 5.7 mmol) was added at -78 °C. Dimethylthexylsilyl chloride (1.75 mL, 8.5 mmol) was added to the resulting lithium ynolate solution after 10 min, and the solution was allowed to warm from -78 °C to rt with stirring. After 14 h the reaction mixture was cooled to -78 °C and quenched into an acidic ethanol[11] solution (30 mL) at 0 °C over 30 min. When the quench was over the ice-bath was removed and stirring was continued for an additional 3 h. The mixture was diluted with ether (200 mL) and washed with 10% aqueous HCl (20 mL). The aqueous layer was reextracted with ether (150 mL), and the combined ethereal layers were washed with brine (30 mL) and dried. The crude product (1.29 g) obtained was purified by silica gel column chromatography (hexane and then slowly increased to 3% ethyl acetate in hexane) to afford 0.264 g (90%) of **8a**. Neither diester **12a** nor allenic ester **13a** was present in the crude product or after chromatography.

Esterification during Workup To Form Ethyl 2,4-Diphenyl-2,3-butadienoate (13a). A solution of *n*-BuLi in hexanes (0.78 mL, 1.96 mmol) was added to a stirred, 0 °C solution of HMDS (0.45 mL, 0.345 g, 2.14 mmol) in THF (10 mL) with ice-bath cooling. After 20 min, the LHMDS solution was cooled to -78 °C, and α,α-dibromoacetophenone (**5a**; 0.5 g, 1.79 mmol) in THF (5 mL) was added with dry ice/acetone-bath cooling. After 15 min a solution of MeLi (2.8 mL, 3.93 mmol) in ether was added and after an additional 13 min the reaction mixture was quenched into D_2O (10 mL) at about 5 °C and extracted with ether (2 × 50 mL). The D_2O layer was acidified with D_2O–H_2SO_4 to a pH of about 4.0 and extracted with chloroform. The chloroform layer was washed with D_2O and dried to give 0.206 g of a crude mixture of deuteriated phenylacetic acid and allenic acid **14a**. The crude mixture was dissolved in THF, added to acidic ethanol, and stirred for 30 min at 0 °C. The solution was diluted with ether (200 mL) and washed with 10% aqueous HCl (25 mL). The aqueous layer was reextracted with ether (80 mL), and the combined ethereal layers were washed with brine (30 mL) and dried. ^1H NMR of the 0.282 g of crude material obtained indicated a mixture of deuteriated **8a** and **13a** (i.e., $PhCD_2CO_2Et$ and $PhCH/D–C–CPhCO_2Et$).

2,2-Dibromo-1-cyclohexanyl-1-ethanone (5b).[25] Via an adaptation of an unpublished procedure of Kowalski and Sakdarat, a solution of *n*-BuLi in hexanes (28.6 mL, 72 mmol) was added to a stirred, 0 °C solution of 2,2,6,6-tetramethylpiperidine (TMP) (12.6 mL, 75 mmol) in THF (50 mL) with ice-bath cooling. In a separate flask, bromoform (5.76 mL, 16.7 g, 66 mmol) in THF (35 mL) was stirred and cooled to -98 °C with a methanol/liquid N_2 bath. The LTMP solution was added over 15 min at -98 °C and after 5 min longer a solution of cyclohexanecarbonyl chloride (4.0 mL, 4.38 g, 30.0 mmol) in THF (15 mL) was added at -98 °C. After 10 min, the mixture was quenched into water (100 mL) and extracted with ether (3 × 80 mL). The combined organic layers were washed with 10% aqueous HCl, 5% aqueous $NaHCO_3$ solution, and brine. Purification of the crude product by silica gel column chromatography afforded 4.2 g (49%) of pure **5b**.

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Ethyl 2-Cyclohexanylacetate (8b) from 2,2-Dibromo-1-cyclohexanyl-1-ethanone (5b). (a) Using Direct Ethanol Quench. A solution of *n*-BuLi in hexanes (0.78 mL, 1.96 mmol) was added to a stirred, 0 °C solution of HMDS (0.45 mL, 0.345 g 2.14 mmol) in THF (10 mL) with ice-bath cooling. After 20 min, the LHMDS solution was cooled to −78 °C, and 2,2-dibromo-1-cyclohexanyl-1-ethanone (**5b**, 0.508 g, 1.79 mmol) in THF (10 mL) was added with dry ice/acetone-bath cooling. After 10 min, a solution of *n*-BuLi in hexanes (1.57 mL, 3.93 mmol) was added at −78 °C, and after another 12 min quench was begun of the −78 °C reaction mixture into a stirred acidic ethanol solution[11] (30 mL) at 0 °C over a 35-min period. The mixture was diluted with ether (200 mL) and washed with 10% aqueous HCl (30 mL). The aqueous layer was reextracted with a portion of ether (100 mL). The combined ethereal layers were washed with brine and dried. The crude product was purified by silica gel column chromatography (3% ethyl acetate in hexane and then slowly increased to 8% ethyl acetate in hexane) to afford 0.262 g (86%) of **8b**:[2] IR (neat) 2920, 1735, 1450, 1290, 1165, 1035, and 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.13 (q, 2 H), 2.15 (d, 2 H), 1.80–1.60 (m, 7 H), 1.25 (t, 3 H), 1.20–0.88 (m, 4 H) [product contains ~2% of ethyl 2,4-dicyclohexanylacetoacetate (**12b**) as indicated by GC/MS *m/z* 294 (M^+)]. Also isolated was 0.011 g (4%) of **ethyl 2,4-dicyclohexyl-2,3-butadienoate (13b)**: R_f = 0.19 10% ethyl acetate in hexane; IR (neat) 3313, 2927, 2852, 1745, 1617, 1331, and 1018 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.33–4.23 (m, 2 H), 3.4 (d, 1 H), 1.90–1.55 (m, 14 H), 1.43 (t, 3 H), 1.35–0.83 (m, 8 H); MS *m/z* 276 (M^+), 249, 155; exact mass calcd for $C_{18}H_{28}O_2$ M + H 277.2167, obsd 277.2159.

(b) Using Dimethylthexylsilyl Chloride Quench. A solution of *n*-BuLi in hexanes (0.78 mL, 1.96 mmol) was added to a stirred, 0 °C solution of HMDS (0.45 mL, 0.345 g, 2.14 mmol) in THF (10 mL) with ice-bath cooling. After 15 min, the LHMDS solution was cooled to −78 °C, and 2,2-dibromo-1-cyclohexanyl-1-ethanone (**5b**; 0.508 g, 1.79 mmol) in THF (5 mL) was added with dry ice/acetone-bath cooling. After 15 min, a solution of *n-BuLi* in hexanes (1.57 mL, 3.93 mmol) was added at −78 °C, and after another 15 min dimethylthexylsilyl chloride (1.75 mL, 8.5 mmol) was added. The −78 °C reaction mixture was then allowed to warm to rt and stirred for 14 h. The reaction mixture was cooled to −78 °C and quenched slowly into a stirred solution of acidic ethanol[11] at 0 °C over a 25-min period. The ice bath was removed, and after 2 h the mixture was diluted with ether (250 mL) and washed with 10% aqueous HCl (25 mL). The aqueous layer was reextracted with ether (100 mL) and the combined ethereal layers were washed with brine (30 mL) and dried. The crude product (1.32 g) was purified by silica gel column chromatography (hexane, then slowly increased to 3% ethyl acetate in hexane) affording 0.273 g (90%) of **8b**. None of the diester **12b** or the allenic ester **13b** was detected in either the crude or purified material.

Exchange of α,α-Dibromoacetophenone Enolate (6a) by *n*-BuLi at 5 °C. A solution of *n*-BuLi in hexanes (0.78 mL, 1.96 mmol) was added to a stirred, 0 °C solution of HMDS (0.45 mL, 0.345 g, 2.14 mmol) in THF (7 mL) with ice-bath cooling. After 20 min, the LHMDS solution was cooled to −78 °C with a dry ice/acetone bath, and α,α-dibromoacetophenone (**5a**; 0.5 g, 1.79 mmol) in THF (4 mL) was added. After 10 min the −78 °C bath was replaced with an ice bath, and 5 min later a solution of *n*-BuLi in hexanes (1.57 mL, 3.93 mmol) was added at 0–5 °C. After 10 min the ice bath was replaced with a dry ice/acetone bath, and dimethylthexylsilyl chloride (1.75 mL, 8.5 mmol) was added. The solution was allowed to warm from −78 °C to rt with stirring and after 9 h the reaction mixture was cooled to −78 °C and quenched into an acidic ethanol[11] solution (30 mL) at 0 °C over 30 min. When the quench was over the ice bath was removed and stirring was continued for an additional 3 h. The mixture was diluted with ether (200 mL) and washed with 10% aqueous HCl (20 mL). The aqueous layer was reextracted with ether (150 mL), and the combined ethereal layers were washed with brine (30 mL) and dried. The crude product was purified by silica gel column chromatography (hexane, then slowly increased to 3% ethyl acetate in hexane) to afford 0.262 g (88%) of **ethyl phenylacetate (8a)**.

Ethyl Phenylacetate (8a) from α-Bromoacetophenone (4a): (a) Using Direct Ethanol Quench. A solution of *n*-BuLi in hexanes (1.1 mL, 2.76 mmol) was added to a stirred, 0 °C solution of HMDS (0.64 mL, 3.02 mmol) in THF (10 mL) with ice-bath cooling. After 15 min, the LHMDS was cooled to −78 °C with a dry ice/acetone bath, and α-bromoacetophenone (**4a**; 0.5 g, 2.51 mmol) in THF (8 mL) was added. After 15 min a freshly prepared solution of LTMP [prepared at 0 °C in THF (15 mL) from TMP (1.7 mL, 10.04 mmol) and *n*-BuLi in hexanes (4.01 mL, 10.04 mmol)] was added at −78 °C. The reaction mixture was warmed to rt and stirred for 15 min. Analysis of a small aliquot still indicated the presence of α-bromoacetophenone, so the reaction mixture was cooled to −78 °C and a solution of *n*-BuLi in hexanes (0.75 mL, 1.87 mmol) was added to regenerate more LTMP. The mixture was warmed to rt and after stirring for 15 min it was cooled to −78 °C and added over a 25-min period to a stirred solution of acidic ethanol[11] (30 mL) at 0 °C. The mixture was diluted with ether (200 mL) and washed with 10% aqueous HCl (25 mL). The aqueous layer was reextracted with ether (80 mL), and the combined ethereal layers were washed with brine (30 mL) and dried. The crude product (0.620 g) was purified by silica gel column chromatography (4% ethyl acetate in hexane, then increased to 13% ethyl acetate in hexane) to afford 0.304 g (74%) of **8a**, 0.028 g (8%) of **ethyl diphenylacetoacetate (12a)**, and 0.045 g (13%) of **ethyl 2,4-diphenyl-2,3-butadienoate (13a)**.

(b) Using Dimethylthexylsilyl Quench. A solution of *n*-BuLi in hexanes (1.1 mL, 2.76 mmol) was added to a stirred, 0 °C solution of HMDS (0.64 mL, 0.49 g, 3.02 mmol) in THF (10 mL) with ice-bath cooling. After 12 min the LHMDS was cooled to −78 °C with a dry ice/acetone bath, and α-bromoacetophenone (**4a**; 0.5 g, 2.51 mmol) in THF (7 mL) was added. After 10 min, a freshly prepared LTMP solution [prepared at 0 °C in THF (10 mL) from TMP (1.52 mL, 1.27 g, 9.03 mmol) and *n*-BuLi in hexanes (3.51 mL, 8.79 mmol)] was added at −78 °C. The reaction mixture was allowed to warm to rt and stirred for 30 min. Analysis of a small aliquot indicated the presence of α-bromoacetophenone, so the mixture was cooled to −78 °C and a solution of *n*-BuLi in hexanes (1.0 mL, 2.5 mmol) was added to regenerate more LTMP. After warming and stirring at rt for 20 min, the mixture was cooled to −78 °C, and dimethylthexylsilyl chloride (4.2 mL, 21.3 mmol) was added. The mixture was warmed to rt, stirred for 14 h, cooled to −78 °C, and quenched into a stirred solution of acidic ethanol[11] at 0 °C over a 15-min period. After the quench was over the mixture was stirred for 2 h at rt, diluted with ether (250 mL) and washed with 10% aqueous HCl (30 mL). The ethereal layer was further washed with brine (30 mL) and dried to give the crude product (2.18 g). GC analysis did *not* show the presence of **8a** or *dimeric byproducts* **12a** and **13a**. Nevertheless, purification of the crude material by silica gel column chromatography (hexane then slowly increased to 13% ethyl acetate in hexane) was attempted and also failed to afford any of the three expected products.

Effect of Additives on Ester Yield and Formation of Dimeric Byproducts. (a) Addition of LTMP after Ynolate Formation. A solution of *n*-BuLi in hexanes (1.58 mL, 3.96 mmol) was added to a stirred, 0 °C solution of HMDS (0.9 mL, 4.32 mmol) in THF (15 mL) with ice-bath cooling. After 25 min, the LHMDS solution was cooled to −78 °C with a dry ice/acetone bath, and α,α-dibromoacetophenone (**5a**; 1.0 g, 3.60 mmol) in THF (15 mL) was added. The mixture was warmed with an ice bath for 7 min and then recooled to −78 °C. After 5 min a solution of *n*-BuLi in hexanes (3.2 mL, 7.91 mmol) was added slowly at −78 °C. An aliquot quenched into acidic ethanol was indicated by GC: 3.66 min, ethyl phenylacetate, 100%. After 30 min, a freshly prepared, −78 °C solution of tetramethylpiperidine and LTMP [initially prepared at 0 °C in THF (15 mL) from TMP (1.45 mL, 8.63 mmol) and *n*-BuLi in hexanes (1.72 mL, 4.3 mmol)] was added at −78 °C. After another 30 min, dimethylthexylsilyl chloride (3.52 mL, 17.9 mmol) was added to the reaction mixture and the solution was allowed to warm from −78 °C to rt with stirring. After 19 h the reaction mixture was cooled to −78 °C and quenched into an acidic ethanol[11] solution (60 mL) at 0 °C over 30 min. The ice bath was removed, and after 2 h the mixture was diluted with ether (200 mL) and washed with water. The aqueous layer was reextracted with ether (150 mL), and the combined ethereal layers were washed with brine (30 mL) and dried. The crude product was purified twice by silica gel column chromatography (hexane, then slowly increased to 3% ethyl

acetate in hexane to afford 1.9 g of material followed by a second column with hexane and then 4% ethyl acetate in hexane) to afford 0.890 mg of **ethyl phenylacetate (8a)** which was still only 44% pure by GC (i.e., 67% yield).

(b) Addition of LTMP before Ynolate Formation. A solution of *n*-BuLi in hexanes (1.58 mL, 3.96 mmol) was added to a stirred, 0 °C solution of HMDS (0.9 mL, 4.32 mmol) in THF (15 mL) with ice-bath cooling. After 25 min, the LHMDS solution was cooled to −78 °C with a dry ice/acetone bath, and α,α-dibromoacetophenone (**5a**; 1.0 g, 3.60 mmol) in THF (15 mL) was added. The mixture was warmed with an ice bath for 15 min and then recooled to −78 °C. After 10 min a freshly prepared, −78 °C solution of TMP and LTMP [initially prepared at 0 °C in THF (15 mL) from TMP (1.45 mL, 8.63 mmol) and *n*-BuLi in hexanes (3.2 mL, 7.9 mmol)] was added at −78 °C. An aliquot quenched into acidic ethanol was indicated by GC: 5.26 min, α,α-dibromoacetophenone, with small amounts of α-bromoacetophenone. After 20 min a solution of *n*-BuLi in hexanes (3.2 mL, 7.91 mmol) was added slowly at −78 °C. An aliquot quenched into acidic ethanol was indicated by GC: 3.66 min, ethyl phenylacetate, ~100%. After another 30 min, dimethylthexylsilyl chloride (4.3 mL, 21.5 mmol) was added to the reaction mixture, and the solution was allowed to warm from −78 °C to rt with stirring. After 15 h the reaction mixture was cooled to −78 °C and quenched into an acidic ethanol[11] solution (60 mL) at 0 °C over 30 min. The ice bath was removed, and after 3 h the mixture was diluted with ether (200 mL) and washed with water. The aqueous layer was reextracted with ether (150 mL), and the combined ethereal layers were washed with brine (30 mL) and dried. The crude product was shown by GC and NMR to be a complex mixture containing **no ethyl phenylacetate (8a)**, (GC t_R 3.66 min).

(c) Addition of LiOEt before Ynolate Formation. A solution of *n*-BuLi in hexanes (8.4 mL, 21.0 mmol) was added to a stirred, 0 °C solution of HMDS (2.5 mL, 1.91 g, 12.00 mmol) and absolute ethanol (0.58 mL, 0.455 g, 10.0 mmol) in THF (50 mL) with ice-bath cooling. After 20 min, the mixture of LHMDS and LiOEt was cooled to −78 °C with a dry ice/acetone bath, and α,α-dibromoacetophenone (**5a**; 2.78 g, 10.0 mmol) in THF (20 mL) was added. After 15 min, a solution of *n*-BuLi in hexanes (8.8 mL, 22.0 mmol) was added. After 10 min, the mixture was warmed to rt and stirred for 15 min. The mixture was cooled to −78 °C and quenched slowly into a stirred solution of acidic ethanol[11] (125 mL) at 0 °C over a 45-min period. After the quench was over, the mixture was diluted with ether (300 mL) and washed with 10% aqueous HCl (50 mL). The aqueous layer was reextracted with a portion of ether (150 mL), and the combined ethereal layers were washed with brine and dried. The crude product (1.72 g) was purified by silica gel column chromatography (3% ethyl acetate in hexane and then slowly increased to 15% ethyl acetate in hexane) to afford 1.29 g (79%) of **ethyl phenylacetate (8a)** [GC t_R 3.76, 100%], 0.056 g (3.8%) of **ethyl diphenylacetoacetate (12a)**, and 0.097 g (7.3%) of **ethyl 2,4-diphenyl-2,3-butadienoate (13a)**: GC t_R 10.23, 100%.

Addition of LiOEt/LTMP before Ynolate Formation. A solution of *n*-BuLi in hexanes (4.2 mL, 10.5 mmol) was added to a stirred, 0 °C solution of HMDS (1.58 mL, 1.21 g, 7.5 mmol) and absolute ethanol (0.29 mL, 23 g, 5.0 mmol) in THF (30 mL) with ice-bath cooling. After 20 min, the mixture of LHMDS and LiOEt was cooled to −78 °C with a dry ice/acetone bath, and α,α-dibromoacetophenone (**5a**; 1.39 g, 5.0 mmol) in THF (15 mL) was added. After 15 min, a freshly prepared, −78 °C solution of LTMP [initially prepared at 0 °C in THF (15 mL) from TMP (1.26 mL, 1.05 g, 7.5 mmol) and *n*-BuLi in hexanes (3.0 mL, 7.5 mmol)] was added. After 15 min longer, a solution of *n*-BuLi in hexanes (5.0 mL, 12.5 mmol) was added over a 10-min period, and the mixture was warmed to rt and stirred for 20 min. The mixture was cooled to −78 °C and quenched over a 75-min period into a stirred solution of acidic ethanol[11] (60 mL) at 0 °C. The mixture was diluted with ether (200 mL) and washed with 10% aqueous HCl (40 mL). The aqueous layer was reextracted once with ether (100 mL), and the combined ethereal layers were washed with brine and dried. The crude product (0.916 g) was purified by silica gel column chromatography (4% ethyl acetate in hexane, then slowly increased to 15% ethyl acetate in hexane) to afford 0.683 g (83%) of **ethyl phenylacetate (8a)** and 0.016 g (3%) of **ethyl 2,4-diphenyl-2,3-butadienoate (13a)**.

(*E*)- and (*Z*)-2-Bromo-1-phenylethenyl Acetate (15) Mixtures: (a) From α-Bromoacetophenone (4a). A solution of *n*-BuLi in hexanes (28.0 mL, 70.0 mmol) was added to a stirred, 0 °C solution of HMDS (15.8 mL, 0.49 g, 75.0 mmol) in THF (100 mL) with ice-bath cooling. After 30 min, the LHMDS was cooled to −78 °C with a dry ice/acetone bath, and a solution of α-bromoacetophenone (9.95 g, 50.0 mmol) in THF (40 mL) was added. After 25 min the −78 °C solution was quenched with acetic anhydride (47.0 mL, 0.5 mmol), allowed to warm to rt, and stirred for 90 min. The mixture was diluted with ether (500 mL), washed with cold 3% aqueous HCl (2 × 50 mL), cold 2% aqueous NaOH solution (3 × 50 mL), and brine, and dried. The crude product was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 8.91 g (74%) of **15**[10] as a 97:3 *Z*:*E* mixture: ^{1}H NMR ($CDCl_3$) δ 7.33–7.47 (m, 5 H, aromatic), 6.55 (s, 97/100, H), 6.32 (s, 3/100, H, olefinic), 2.36 (s, 97/100, *Z*, $OCOCH_3$), 2.17 (s, 3/100 H, *E*, $OCOCH_3$).

(b) From Ethyl Benzoate. A solution of *n*-BuLi in hexanes (13.2 mL, 33.0 mmol) was added to a stirred, 0 °C solution of TMP (6.06 mL, 36.0 mmol) in THF (30 mL) with ice-bath cooling and stirred for 30 min. In a separate round-bottomed flask, a mixture of ethyl benzoate (2.25 g, 15 mmol) and CH_2Br_2 (2.3 mL, 5.69 g, 33.0 mmol) in THF (20 mL) was cooled with a dry ice/acetone bath. The LTMP was added slowly to the above cooled mixture at −78 °C over a 10-min period. After 15 min, a solution of *n*-BuLi in hexanes (24.0 mL, 60.0 mmol) was added at −78 °C, and after another 20 min the reaction mixture was rapidly quenched with acetic anhydride (12.7 mL, 135.0 mmol) and was allowed to warm to rt. After 75 min, the mixture was diluted with ether (300 mL) and washed with cold 2% aqueous HCl (3 × 20 mL) and cold 2% aqueous NaOH (2 × 25 mL). The ethereal layer was washed with brine (40 mL) and dried to afford after purification by silica gel column chromatography (4% ethyl acetate in hexane) 5.8 g (81%) of **15** as a 90:10 *Z*:*E* mixture. The isomers could not be separated using silica gel chromatography to afford pure (*E*)-**15**.

(c) From Rearrangement of 2,2-Dibromo-1-phenylethanol.[14] Sodium borohydride (0.078 g, 1.79 mmol) was added to a stirred, 0 °C solution of α,α-dibromoacetophenone (**5a**; 1.0 g, 3.6 mmol) in methanol (10 mL). After 15 min, the reaction mixture was diluted with 5% acidic ethanol (4 mL) followed by water. The solvent was removed using a rotary evaporator, and the residue was extracted with ethyl acetate (2 × 75 mL). The combined organic layers were washed with brine and dried. The crude product (1.1 g) was purified by silica gel column chromatography (12% ethyl acetate in hexane) to afford 0.99 g (98%) of **2,2-dibromo-1-phenylethanol**:[26] IR (neat) 3400, 1490, 1450, 1180, 1070, and 940 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55–7.30 (m, 5 H, aromatic), 5.80 (d, 1 H, $-CHBr_2$), 5.05 (dd, 1 H, Ph C*H*OHCHBr_2), 2.98 (d, 1 H, OH); GC/MS *m*/*z* 280 (M^+).

A solution of *n*-BuLi in hexanes (0.93 mL, 2.32 mmol) was added to a stirred, 0 °C solution of diisopropylamine (0.38 mL, 2.43 mmol) in THF (13 mL) with ice-bath cooling. After 10 min this was added to a solution of 2,2-dibromo-1-phenylethanol (0.325 g, 1.16 mmol) in THF (6 mL) and cooled to −78 °C with a dry ice/acetone bath. The reaction mixture was warmed to about −55 °C using a dry ice/chloroform/carbon tetrachloride bath and stirred at this temperature for 3 h 20 min. The mixture was cooled to −78 °C, quenched with acetic anhydride (1.64 mL, 17.0 mmol), and stirred at rt for 12 h. The mixture was diluted with ether (150 mL), washed with cold 2% aqueous HCl (2 × 10 mL), 4% $NaHCO_3$ solution (2 × 15 mL), and brine, and dried to afford 0.21 g of crude (*Z*)-**15** as the only isomer, which was not purified further.

(d) From α,α-Dibromoacetophenone (5a). A solution of *s*-BuLi in cyclohexane (2.0 mL, 3.0 mmol) was added to a −78 °C solution of α,α-dibromoacetophenone (**5a**; 0.417 g, 1.5 mmol) in THF (10 mL). After being stirred for 30 min, the reaction mixture was quenched with acetic anhydride (2.1 mL, 5.25 mmol), allowed to warm to rt, and stirred for 75 h. The mixture was diluted with ether (150 mL), washed with 4% $NaHCO_3$ solution (2 × 15 mL) and brine, and dried. The crude product was purified by silica

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gel column chromatography (4% ethyl acetate in hexane) to afford 0.345 g (95%) of **15** as a 96:4 *Z*:*E* mixture.

(e) Via Photoisomerization of 2-Bromo-1-phenylethynyl Acetate ((*Z*)-15). A solution of a 97:3 *Z*:*E* mixture of 2-bromo-1-phenylethynyl acetate (**15**, 1.0 g, 4.13 mmol) in hexane–toluene (160 mL, 2:1 ratio) was taken in a quartz vessel and irradiated with a Mercury vapor lamp (Hanovia, Cat. No. 679 A36, 450 W, 135 V, 3.6 A) for 48 h at gentle reflux with continuous stirring. The solvent was removed, and the crude product was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 0.82 g (82%) of **15** as a *Z*:*E* = 58:42 mixture: *Z* isomer GC t_R 7.27; *E* isomer GC t_R 6.55.

Ethyl Phenylacetate (8a): (a) From 2-Bromo-1-phenylethenyl Acetate (15; *Z*:*E* = 97:3). A solution of *n*-BuLi in hexanes (30 mL, 7.5 mmol) was added to a stirred, 0 °C solution of TMP (1.3 mL, 7.76 mmol) in THF (10 mL) with ice-bath cooling. In a separate flask 2-bromo-1-phenylethenyl acetate (**15**; *Z*:*E* = 97:3) (0.5 g, 2.07 mmol) in THF (10 mL) was cooled to −78 °C with a dry ice/acetone bath, and a solution of MeLi (3.25 mL, 4.55 mmol) in ether was added. After 10 min, the solution of LTMP prepared above was also added at −78 °C. The mixture was allowed to warm to rt and stirred for 30 min, cooled to −78 °C, and quenched into a stirred solution of acidic ethanol[11] at 0 °C over a 20-min period. After the quench was over the mixture was diluted with ether (200 mL) and washed with 10% aqueous HCl (25 mL). The aqueous layer was reextracted with portions of ether (60 mL). The combined ethereal layers were washed with brine and dried. The crude product was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 0.240 g (71%) of **8a**: GC t_R 3.71, 100%.

(b) From 2-Bromo-1-phenylethenyl Acetate (15; *Z*:*E* = 58:42). A solution of *n*-BuLi in hexanes (1.5 mL, 3.75 mmol) was added to a stirred, 0 °C solution of TMP (0.65 mL, 7.76 mmol) in THF (10 mL) with ice-bath cooling. In a separate flask 2-bromo-1-phenylethenyl acetate (**15**, *Z*:*E* = 58:42) (0.250 g, 1.04 mmol) in THF (10 mL) was cooled to −78 °C with a dry ice/acetone bath, and a solution of MeLi (1.65 mL, 4.28 mmol) in ether was added. After the resulting enolate solution was stirred for 20 min at −78 °C, the solution of LTMP was added and the mixture was allowed to warm to rt. After 25 min, the mixture was cooled to −78 °C and quenched over a 20-min period into a stirred solution of acidic ethanol[11] at 0 °C. The mixture was diluted with ether (200 mL) and washed with 10% aqueous HCl (20 mL). The aqueous layer was reextracted with 60 mL of ether, and the combined ethereal layers were washed with brine and dried. The crude product was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 0.109 g (65%) of **8a**: GC t_R 3.69, 100%.

α,α-Dibromoacetophenone (5a) from Ethyl Benzoate (1a). A solution of *n*-BuLi in hexanes (5.9 mL, 14.74 mmol) was added to a 0 °C solution of TMP (2.7 mL, 15.9 mmol) in THF (15 mL) with ice-bath cooling. In a separate flask CH_2Br_2 (2.55 g, 14.74 mmol) in THF (15 mL) was stirred and cooled to about −85 °C (internal temperature) with an acetone/liquid N_2 bath), and the LTMP solution was added. After 10 min, ethyl benzoate (**1a**, 1.0 g, 6.7 mmol) in THF (8 mL) was added at a temperature below −75 °C, and 20 min later the cold reaction mixture was quenched into 5% aqueous sulfuric acid (25 mL). The mixture was diluted with ether (200 mmol), and the aqueous layer was reextracted with 60 mL of ether. The combined ethereal layers were washed with 10% $NaHCO_3$ solution (2 × 20 mL), brine, and dried. The crude product was purified by silica gel column chromatography (5% ethyl acetate) to afford 1.79 g (97%) of a 95:5 mixture of **α,α-dibromoacetophenone (5a)** and **α-bromoacetophenone (4a)**, as determined by GC and NMR integration.

Reaction of Tetrahedral Intermediate 2a with *n*-BuLi Affording 18n, 19n, and 20n. A solution of *n*-BuLi in hexanes (5.9 mL, 14.74 mmol) was added to a 0 °C solution of TMP (2.7 mL, 15.9 mmol) in THF (15 mL) with ice-bath cooling. In a separate flask CH_2Br_2 (2.55 g, 14.74 mmol) in THF (15 mL) was cooled to −85 °C (internal solution temperature) with an acetone/liquid N_2 bath, and the solution of LTMP was added. After 10 min, a solution of ethyl benzoate (1.0 g, 6.7 mmol) in THF (10 mL) was added. After another 15 min, a solution of *n*-BuLi in hexanes (13.4 mL, 35.5 mmol) was added at −78 °C, and 18 min later the mixture was quenched into a stirred solution of acidic ethanol[11] (25 mL) at 0 °C. The mixture was diluted with ether (200 mL) and washed with 10% aqueous HCl (20 mL). The aqueous layer was reextracted with 50 mL of ether, and the combined ethereal layers were washed with brine and dried. The crude material was purified by silica gel column chromatogrpahy (3% ethyl acetate in hexane) to afford 0.961 g (73%) of **α-bromoacetophenone (4a)**, containing ~3% of α-chloroacetophenone (presumably formed from α-bromoacetophenone and chloride ion during workup). Also isolated was 0.205 g of a nonpolar mixture which was further purified by preparative TLC (3% ethyl acetate in hexane) to afford 0.114 g (10%) of a 1:1 mixture of **1-phenyl-1-hexanone (18n)** [GC t_R 4.78 1-phenyl-1-hexanone 50.8%; GC/MS *m*/*z* 176 (M^+); authentic 1-phenyl-1-hexanone (Aldrich) GC t_R 4.79] and **1-phenyl-1-heptanone (19n)** GC t_R 5.44 1-phenyl-1-heptanone 49.16%; GC/MS *m*/*z* 190 (M^+); authentic 1-phenyl-1-heptanone (Aldrich) GC t_R 5.46. Also obtained was 0.076 g (5%) of **3-butyl-1-phenyl-1-heptanone (20n)**: IR (neat) 2955, 2930, 1687, 1607, 1598, 1467, 1448, 752, and 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (d, 2 H), 7.55 (t, 1 H), 7.48 (t, 2 H), 2.88 (d, 2 H), 1.45–1.25 (m, 13 H), 0.95–0.85 (m, 6 H); MS *m*/*z* 246 (M^+), 231, 217, 187, 169, 120, 105; exact mass calcd for $C_{17}H_{26}O$ + H^+ 247.2059, obsd 247.2061.

Lack of Formation of 18n, 19n, and 20n from Bromoenolate 3a. A solution of *n*-BuLi in hexanes (1.44 mL, 3.6 mmol) was added to a −78 °C solution of α,α-dibromoacetophenone (**5a**; 1.0 g, 3.6 mmol) in THF (20 mL) cooled with a dry ice/acetone bath at −78 °C to afford lithium enolate **3a**. In a separate flask, a freshly prepared solution of LTMP solution [prepared at 0 °C from TMP (1.45 mL, 1.21 g, 8.64 mmol) and *n*-BuLi in hexanes (1.73 mL, 4.32 mmol) in THF (15 mL)] was added to a −78 °C solution of CH_2Br_2 (0.31 mL, 0.767 g, 4.32 mmol) in THF (10 mL) cooled with a dry ice/acetone bath. After 10 min the cold (−78 °C) solution of lithium enolate **3a** was then added via a double-ended needle to the stirred, −78 °C mixture of lithiodibromomethane and tetramethylpiperidine prepared above. After 20 min, a mixture of LiOEt and *n*-BuLi in hexanes [prepared at 0 °C in THF (10 mL) from absolute ethanol (0.21 mL, 0.165 g, 3.6 mmol) and *n*-BuLi in hexanes (7.2 mL, 18.0 mmol)] was added at −78 °C using a double-ended needle. After 30 min, the mixture was quenched into a stirred solution of acidic ethanol[11] (30 mL) at 0 °C, diluted with ether (300 mL), and washed with 10% aqueous HCl (35 mL). The aqueous layer was reextracted with ether (2 × 50 mL), and the combined ethereal layers were washed with brine and dried. The crude product was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 0.634 g (89%) of **α-bromoacetophenone (4a)**, containing ~5% of α-chloroacetophenone. No butylated ketones (**18n, 19n, 20n**) were obtained, nor were they present in the crude product as indicated by GC analysis.

Reaction of Tetrahedral Intermediate 2a with *s*-BuLi Affording 18s and 19s. Ethyl benzoate (1.0 g, 6.7 mmol) in THF (10 mL) was added to a stirred, −78 °C solution of lithiodibromomethane (2.2 equiv, prepared as described for the *n*-BuLi reaction above). After 15 min, a solution of *s*-BuLi in cyclohexane 21.6 mL, 28.4 mmol) was added slowly at −78 °C over a 10-min period. After 15 min, the mixture was quenched into a stirred solution of acidic ethanol[11] (30 mL) at 0 °C. The mixture was diluted with ether (250 mL) and washed with 10% aqueous HCl (30 mL). The aqueous layer was reextracted with ether (60 mL), and the combined ethereal layers were washed with brine and dried. The crude product was purified by silica gel column chromatography (5% ethyl acetate in hexanes) to afford of 0.890 g (69%) of **α-bromoacetophenone (4a)** containing ~5% of α-chloroacetophenone. Also isolated was 0.065 g (6%) of a mixture of **3-methyl-1-phenyl-1-pentanone (18s)**[27] [GC t_R 4.54; GC/MS *m*/*z* 176 (M^+)] and **4-methyl-1-phenyl-1-hexanone (19s)**.[28] GC t_R 4.62; GC/MS *m*/*z* 190 (M^+).

Reaction of Tetrahedral Intermediate 2a with *t*-BuLi Affording 18t. Ethyl benzoate (1.0 g, 6.7 mmol) in THF (15 mL) was added to a stirred, −78 °C solution of the lithiodibromomethane (2.2 equiv, prepared as described for the *n*-BuLi reaction above). After 20 min a solution of *t*-BuLi in pentane (14.0 mL,

(27) Suzuki, A.; Tabata, M.; Ueda, M. *Tetrahedron Lett.* **1975**, 2195.
(28) Yoneda, N.; Takahashi, Y.; Suzuki, A. *Chem. Lett.* **1978**, 231.

28.14 mmol) was added at −78 °C, and 20 min later the mixture was quenched into acidic ethanol[11] (30 mL) at 0 °C, diluted with ether (300 mL), and washed with 10% aqueous HCl (25 mL). The aqueous layer was reextracted with 50 mL of ether, and the combined ethereal layers were washed with brine and dried. The crude product was purified by silica gel column chromatography (5% ethyl acetate in hexane) to afford 1.101 g (84%) of **α-bromoacetophenone (4a)** (containing about 12% of α-chloroacetophenone). Also isolated was 0.058 g (5%) of **2,2-dimethyl-1-phenyl-1-butanone (18t)**:[29] GC t_R 4.11; GC/MS m/z 176 (M^+).

Ethyl Phenylacetate (8a): (a) From Ethyl Benzoate, Decomposing the Tetrahedral Intermediate at rt. A solution of *n*-BuLi (5.9 mL, 14.74 mmol) in hexanes was added to a stirred, 0 °C solution of TMP (2.7 mL, 2.26 g, 16.08 mmol) in THF (20 mL) with ice-bath cooling. A stirred solution of CH_2Br_2 (2.55 g, 14.74 mmol) in THF (20 mL) was cooled to −85 °C (internal solution temperature) using an acetone/liquid N_2 bath. After 30 min the LTMP solution was added at a temperature below −70 °C. After 10 min, ethyl benzoate (1.0 g, 6.7 mmol) in THF (10.0 mL) was added over a 10-min period at a temperature below −70 °C, and the mixture was then allowed to warm to 0 °C. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R 5.37 α,α-dibromoacetophenone 80% and t_R 4.24 α-bromoacetophenone 20%. The mixture was further warmed to rt, and an aliquot quenched into acidic ethanol and analyzed by GC showed t_R 5.36 α,α-dibromoacetophenone 100% and none of the α-bromoacetophenone. The mixture was cooled to −78 °C, and a solution of *n*-BuLi in hexanes (13.4 mL, 33.5 mmol) was added. After 20 min, the mixture was quenched into a stirred solution of acidic ethanol[11] (30 mL) at 0 °C over a 25 min period. The mixture was diluted with ether (300 mL) and washed with 10% aqueous HCl (35 mL). The aqueous layer was reextracted with ether (150 mL), and the combined ethereal layers were washed with brine and dried. The crude product was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 0.728 g (67%) of 8a.

(b) From Ethyl Benzoate, Decomposing the Tetrahedral Intermediate at −20 °C. A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (75 mL) with ice-bath cooling. In a separate flask a mixture of ethyl benzoate (3.75 g, 25.0 mmol) and CH_2Br_2 (3.83 mL, 9.49 g, 55.0 mmol) in THF (60 mL) was cooled to −78 °C with a dry ice/acetone bath. After 30 min, the LTMP solution was cooled with a dry ice/acetone bath and added to the other flask over a 25-min period at a temperature below −65 °C. After the addition was over, the mixture was allowed to warm to −20 °C and then cooled again to −78 °C. An aliquot was quenched into acidic ethanol and analyzed by GC showing t_R 5.39 α,α-dibromoacetophenone 63% and t_R 4.25 α-bromoacetophenone 37%. A solution of *s*-BuLi in cyclohexane (77.0 mL, 100.0 mmol) was added over a 20-min period at a temperature below −62 °C. After the addition was over, the mixture was warmed to 20 °C, and a solution of *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) was added slowly over a 25-min period. The mixture was stirred at rt for 30 min, cooled to −78 °C, and quenched into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C over a 100-min period. The mixture was diluted with ether (1 L) and washed with 10% aqueous HCl (150 mL). The aqueuous layer was reextracted once with ether (300 mL), and the combined ethereal layers were washed with brine and dried. The crude product (4.83 g) was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 2.77 g (68%) of 8a: GC t_R 3.72, 100%.

(c) From α-Bromoacetophenone (4a), Tetrahedral Intermediate Decomposition Product. TMP (10.1 mL, 8.45 g, 60.0 mmol), followed by a freshly prepared solution of LiOEt [prepared at 0 °C in THF (30 mL) from absolute ethanol (1.46 mL, 1.15 g, 25.0 mmol) and *n*-BuLi in hexanes (20.0 mL, 25.0 mmol)], was added to a −78 °C solution of α-bromoacetophenone (4a; 4.975 g 25.0 mmol) in THF (120 mL) with dry ice/acetone bath cooling. After 10 min, a solution of *s*-BuLi in cyclohexane (77.0 mL, 100.0 mmol) was added at a temperature below −60 °C over 25 min. The mixture was then warmed to 20 °C, and a solution of *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) was added over a 25-min period between 20 and 25 °C. The mixture was stirred at rt for 30 min, cooled to −78 °C, and slowly quenched into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C over a 90-min period. The mixture was diluted with ether (1 L) and washed with 10% aqueous HCl (150 mL). The aqueous layer was reextracted once with ether (100 mL), and the combined ethereal layers were washed with brine and dried. The crude product (5.21 g, a mixture of several compounds as indicated by GC) was purified by silica gel column chromatography (4% ethyl acetate in hexanes) to afford 1.85 g (27% based on purity) of 8a, along with other unidentified products: GC t_R 3.86, 60.13%.

α-Bromoacetophenone (4a) from Ethyl Benzoate Using Excess LiTMP. A solution of *n*-BuLi in hexanes (5.9 mL, 64.74 mmol) was added to a stirred, 0 °C solution of TMP (2.7 mL, 2.26 g, 16.08 mmol) in THF (20 mL) with ice-bath cooling. After 25 min, the LTMP solution was added to a stirred, −85 °C solution of CH_2Br_2 (1.03 mL, 2.55 g, 14.74 mmol) in THF (18 mL) with acetone/liquid N_2-bath cooling. After 10 min a solution of ethyl benzoate (1.0 g, 6.7 mmol) in THF (10 mL) was added at −78 °C, and the mixture was stirred for 10 min. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R 4.20 α-bromoacetophenone 42% and t_R 5.31 α,α-dibromoacetophenone 58%. A freshly prepared solution of LTMP [prepared at 0 °C in THF (20 mL) from TMP (2.3 mL, 1.93 g, 13.4 mmol) and *n*-BuLi in hexanes (5.4 mL, 13.4 mmol)] was then added at −78 °C. The reaction mixture immediately turned from light red to black in color; the cooling bath was removed, and the mixture was allowed to warm to 0 °C, was cooled to −78 °C, and was quenched into acidic ethanol[11] (30 mL) at 0 °C. The mixture was diluted with ether (300 mL) and washed with 10% aqueous HCl (30 mL). The aqueous layer was reextracted with ether (100 mL), and the combined ethereal layers were washed with brine and dried. The crude product was purified by silica gel column chromatography (5% ethyl acetate in hexane) to afford 1.1 g (73%) a mixture of **α-bromoacetophenone (4a) and α,α-dibromoacetophenone (5a)**.

Ethyl Phenylacetate (8a) from Ethyl Benzoate Using LHMDS. A solution of *n*-BuLi in hexanes (5.9 mL, 14.74 mmol) was added to a stirred, 0 °C solution of TMP (2.7 mL, 2.26 g, 15.9 mmol) in THF (20 mL) was ice-bath cooling. In a separate flask, CH_2Br_2 (2.55 g, 14.74 mmol) in THF (20 mL) was cooled to ∼−85 °C with an acetone/liquid N_2 bath. After 30 min, the solution of LTMP was added at a temperature below −78 °C. After 5 min a solution of ethyl benzoate (1.0 g, 6.7 mmol) in THF (10 mL) was added at a temperature below −78 °C, and after 10 min, a freshly prepared solution of LHMDS [prepared in THF (15 mL) at 0 °C from HMDS (2.82 mL, 2.14 g, 13.4 mmol) and *n*-BuLi in hexanes (5.3 mL, 13.4 mmol)] was added at −78 °C. The reaction was allowed to warm to 0 °C, and an aliquot quenched into acidic ethanol and analyzed by GC showed t_R 4.20 α-bromoacetophenone 84% and t_R 5.30 α,α-dibromoacetophenone 16%. The mixture was warmed to rt with a tap-water bath, and an aliquot quenched into acidic ethanol and analyzed by GC showed t_R 4.20 α-bromoacetophenone 78% and t_R 5.30 α,α-dibromoacetophenone 22%. The mixture was cooled to −78 °C, and a solution of *n*-BuLi in hexanes (13.4 mL, 33.5 mmol) was added before being warmed to rt and stirred for 30 min. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R 3.69 ethyl phenylacetate 49% and t_R 4.20 α-bromoacetophenone 51%, indicating that insufficient *n*-BuLi had been added. The mixture was therefore cooled to −78 °C, treated with a solution of *n*-BuLi in hexanes (8.04 mL, 20.1 mmol), warmed to rt, and stirred for 30 min. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R 3.68 ethyl phenylacetate 100%. The mixture was cooled to −78 °C and slowly quenched into a stirred solution of acidic ethanol[11] (30 mL) at 0 °C. The mixture was diluted with ether (250 mL) and washed with 10% aqueous HCl (25 mL). The aqueous layer was reextracted with ether (60 mL), and the combined ethereal layers were washed with brine (30 mL) and dried. The crude product was purified by silica gel column chromatography (3% ethyl acetate in hexane) to afford 0.918 g (84%) of 8a: GC t_R 3.69, 100%.

Ethyl 4-Phenylbutyrate (8c): (a) Using Preformed Dibromoethyllithium and LHMDS. A solution of *n*-BuLi in hexanes (4.9 mL, 12.36 mmol) was added to a stirred, 0 °C solution

(29) Chan, T.; H.; Paterson, I.; Pinsonnault, J. *Tetrahedron Lett.* **1977**, 4183.

of TMP (2.3 mL, 1.92 g, 13.49 mmol) in THF (20 mL) with ice-bath cooling. In a separate flask CH_2Br_2 (0.87 mL, 2.15 g, 12.30 mmol) in THF (15 mL) was stirred and cooled to −90 °C with an acetone/liquid N_2 bath. After 30 min, the LTMP solution was added over 10 min at a temperature below −78 °C, and after 10 min longer a solution of ethyl 3-phenylpropionate (1c; 1.0 g, 5.62 mmol) in THF (10 mL) was added at −78 °C and stirred for 15 min. A freshly prepared solution of LHMDS [prepared in THF (20 mL) at 0 °C from HMDS (2.4 mL, 1.84 g, 11.2 mmol) and *n*-BuLi in hexanes (4.5 mL, 11.2 mmol)] was added at −78 °C. After the addition was over the cooling bath was removed and the mixture was allowed to warm gradually to 0 °C. It was then cooled with an ice bath, and a solution of *n*-BuLi in hexanes (13.5 mL, 33.7 mmol) was added over 20 min at a temperature below 8 °C. The mixture was then warmed to rt and stirred for 30 min. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R 4.75 ethyl 4-phenylbutyrate 100%. The mixture was cooled to −78 °C and quenched into a stirred solution of acidic ethanol[11] (30 mL) at 0 °C over a 40-min period. The mixture was diluted with ether (300 mL) and washed with water (50 mL). The aqueous layer was reextracted with ethyl acetate (2 × 75 mL), and the combined organic layers were washed with brine and dried. Purification of the crude product by silica gel column chromatography (5% ethyl acetate in hexane) afforded 0.93 g (86%) of 8c: GC t_R 4.75 = 100%; IR (neat) 2950, 1740, 1610, 1200, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (m, 5 H, aromatic), 4.10 (q, 2 H, J = 7 Hz), 2.65 (t, 2 H, J = 7 Hz), 2.25 (m, 2 H), 1.95 (m, 2 H), and 1.20 (t, 3 H, J = 7 Hz).

(b) Using in Situ Preparation of Dibromomethyllithium on a 5 mmol Scale. A solution of *n*-BuLi in hexanes was added (4.9 mL, 12.36 mmol) to a stirred solution of TMP (2.3 mL, 1.92 g, 13.49 mmol) in THF (25 mL) with ice-bath cooling. In a separate flask, a stirred mixture of ethyl 3-phenylpropionate (1c; 1.0 g, 5.6 mmol) and CH_2Br_2 (0.87 mL, 2.15 g, 12.36 mmol) in THF (20 mL) was cooled to −78 °C with a dry ice/acetone bath, and the LTMP solution was then added over a 15-min period at a temperature below −65 °C. After 10 min, a freshly prepared solution of LHMDS [prepared in THF (20 mL) at 0 °C from HMDS (2.4 mL, 1.84 g, 11.2 mmol) and *n*-BuLi in hexanes (4.5 mL, 11.2 mmol)] was added over a 10-min period at −78 °C. Following the addition, the cooling bath was removed and the mixture was allowed to warm gradually to 0 °C. The mixture was cooled with an ice bath, and a solution of *n*-BuLi in hexanes (13.5 mL, 33.7 mmol) was added at a temperature below 5 °C over a 15-min period. The mixture was warmed to rt and stirred for 45 min. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R 4.74 ethyl 4-phenylbutyrate 100%. The mixture was cooled to −78 °C and quenched over a 50-min period into a stirred solution of acidic ethanol (30 mL) at 0 °C. The mixture was diluted with ether (400 mL) and washed with 10% aqueuous HCl (40 mL). The aqueous layer was reextracted with ethyl acetate (2 × 75 mL), and the combined organic layers were washed with brine and dried. The crude product was purified by silica gel column chromatography (5% ethyl acetate in hexane) to afford 0.902 g (84%) of 8c: GC t_R 4.74, 100%.

(c) Using in Situ Preparation of Dibromomethyllithium on a 25 mmol Scale. A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (60 mL) with ice-bath cooling. In a separate flask, a stirred mixture of ethyl 3-phenylpropionate (1c; 4.45 g, 25.0 mmol) and CH_2Br_2 (3.85 mL, 9.49 g, 55.0 mmol) in THF (40 mL) was cooled to −78 °C with a dry ice/acetone bath. After 30 min, the LTMP was cooled with a dry ice/acetone bath and added via a double-ended needle to the above mixture over a 35-min period at a temperature below −66 °C. After another 25 min, a freshly prepared, −78 °C solution of LHMDS [initially prepared at 0 °C in THF (25 mL) from HMDS (10.5 mL, 8.03 g, 50.0 mmol) and *n*-BuLi in hexanes (20.0 mL, 50.0 mmol)] was added over a 15-min period below −68 °C. After the addition was over, the mixture was allowed to warm gradually to −20 °C and then cooled to −78 °C. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R 5.11 1-bromo-4-phenyl-2-butanone 32%, t_R 6.24 1,1-dibromo-4-phenyl-2-butanone 68%. A solution of *n*-BuLi in hexanes (60.0 mL, 150 mmol, 6 equiv) was added over a 20-min period at a temperature below −60 °C. The mixture was warmed to rt and stirred for 30 min. The mixture was cooled to −78 °C and quenched over a 90-min period into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C. The mixture was diluted with ether (700 mL) and washed with 10% aqueous HCl (175 mL), and the aqueous layer was reextracted with ethyl acetate (2 × 125 mL). The combined organic layers were washed with brine and dried. The crude product (7.4 g) was purified by silica gel column chromatography (5% ethyl acetate in hexane) to afford 3.98 g (83%) of a mixture containing 8c [GC t_R 4.73, 96%] and **ethyl 2-(2-phenylethyl)hexanoate (21)**:[30] GC t_R 6.50, 4%; GC/MS m/z 248 (M^+), 203, 174, 91 (comparable with an authentic sample).

(d) Using 8 equiv of *n*-BuLi for Exchange on a 25 mmol Scale. The experiment described in c directly above was repeated on exactly the same scale and under the same conditions except that 8 equiv of *n*-BuLi in hexanes (80.0 mL, 200 mmol) instead of 6 equiv was added to effect metal–halogen exchange and rearrangement. After purification there was obtained 3.84 g (80%) of the same mixture of 8c [GC t_R 4.73, 96%] and **ethyl 2-(2-phenylethyl)hexanoate (21)** [GC t_R 6.50, 4%] as indicated by GC and NMR.

(e) Using *s*-BuLi for Exchange on a 25 mmol Scale. A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (60 mL) with ice-bath cooling. In a separate flask, a stirred mixture of ethyl 3-phenylpropionate (1c; 4.45 g, 25.0 mmol) and CH_2Br_2 (3.85 mL, 9.49 g, 55.0 mmol) in THF (40 mL) was cooled to −78 °C with a dry ice/acetone bath. After 25 min, the LTMP was cooled with a dry ice/acetone bath and added over a 30-min period (via a double-ended needle) to the above mixture at a temperature below −68 °C. After 17 min, a freshly prepared, −78 °C solution of LHMDS [initially prepared at 0 °C from HMDS (10.5 mL, 8.03 g, 50.0 mmol) and *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) in THF (40 mL)] was added at a temperature below −70 °C over a 12-min period. After the addition was over, the mixture was allowed to warm gradually to −20 °C and was then cooled again to −78 °C. A solution of *s*-BuLi in cyclohexane (115.0 mL, 150.0 mmol) was added at a temperature below −59 °C over a 15-min period, and the mixture was warmed to rt and stirred for 35 min. The mixture was cooled to −78 °C and quenched slowly into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C over a 90-min period. The mixture was diluted with ether (700 mL) and washed with 10% aqueous HCl (175 mL), and the aqueous layer was reextracted with ether (2 × 125 mL). The combined ethereal layers were washed with brine and dried. The crude product (6.7 g) was purified by silica gel column chromatography (5% ethyl acetate in hexane) to afford 3.61 g (75%) of 8c [GC t_R 4.75, 100%], 0.07 g (2%) of **4-phenyl-2-butanone (22)**[31] [GC t_R 3.65; GC/MS m/z 148 (m^+), 133], and 0.22 g (4%) of **1-bromo-4-phenyl-2-butanone (4b)**:[32] GC t_R 5.10; GC/MS m/z 226 and 227 (M^+), 147, 133.

(f) Using the Standard Procedure on a 25 mmol Scale. A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (60 mL) with ice-bath cooling. In a separate flask, a stirred mixture of ethyl 3-phenylpropionate (1c; 4.45 g, 25.0 mmol) and CH_2Br_2 (3.85 mL, 9.49 g, 55.0 mmol) in THF (40 mL) was cooled to −78 °C with a dry ice/acetone bath. After 30 min, the LTMP was cooled with a dry ice/acetone bath and added to the above mixture via a double-ended needle at a temperature below −68 °C. After 5 min, a freshly prepared, −78 °C solution of LHMDS [initially prepared at 0 °C in THF (40 mL) from HMDS (10.5 mL, 8.03 g, 50.0 mmol) and *n*-BuLi in hexanes (20.0 mL, 50.0 mmol)] was added at a temperature below −69 °C over a 15-min period. Following the addition, the mixture was allowed to warm to −20 °C and was then cooled to −78 °C. A solution of *s*-BuLi in cyclohexane (77.0 mL, 100.0 mmol) was added over a 12 min period at a temperature below −52 °C. The mixture was then warmed to −20 °C, and a solution of *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) was added. The mixture was warmed to rt and stirred for 1 h. An aliquot quenched into acidic ethanol and analyzed

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by GC showed t_R 4.72 ethyl 4-phenylbutyrate 100%. The mixture was cooled to −78 °C and quenched over a 90-min period into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C. The mixture was diluted with ether (1.0 L) and washed with 10% aqueous HCl (175 mL). The aqueous layer was reextracted with ether (2 × 125 mL), and the combined ethereal layers were washed with brine and dried. The crude product (6.3 g) was purified by silica gel column chromatography (5% ethyl acetate in hexane) to afford 3.73 g (78%) of **8c** GC t_R 4.71, 100%.

Ethyl Phenylacetate (8a) Using the Standard Procedure. A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (60 mL) was ice-bath cooling. In a separate flask, a stirred mixture of ethyl benzoate (3.75 g, 25.0 mmol) and CH_2Br_2 (3.83 mL, 9.49 g, 55.0 mmol) in THF (50 mL) was cooled to −78 °C with a dry ice/acetone bath. After 30 min, the LTMP was cooled with a dry ice/acetone bath and added to the above mixture via a double-ended needle over a 25-min period at a temperature below −65 °C. After 5 min, a freshly prepared, −78 °C solution of LHMDS [initially prepared at 0 °C in THF (40 mL) from HMDS (10.5 mL, 8.03 g, 50.0 mmol) and *n*-BuLi in hexanes (20.0 mL, 50.0 mmol)] was added over a 15-min period at a temperature below −69 °C. Following the addition, the mixture was allowed to warm to −20 °C and then cooled to −78 °C. A solution of *s*-BuLi in cyclohexane (77.0 mL, 100.0 mmol) was added at a temperature below −60 °C over a 10-min period. The mixture was allowed to warm to −20 °C, and solution of *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) was added. The mixture was warmed to rt and stirred for 45 min. The mixture was then cooled to −78 °C and quenched over an 85-min period into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C. The mixture was diluted with ether (800 mL) and washed with 10% aqueous HCl (175 mL). The aqueous layer was reextracted with ether (2 × 100 mL), and the combined ethereal layers were washed with brine and dried. The crude products (6.52 g) was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 3.19 g (78%) of **8a**: GC t_R 3.71 (containing about 1% of **acetophenone** as estimated from NMR).

Ethyl 2-Cyclohexanylacetate (8b) Using the Standard Procedure. A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (60 mL) with ice-bath cooling. In a separate flask, a stirred mixture of ethyl cyclohexanylcarboxylate (**1b**; 3.9 g, 25.0 mmol) and CH_2Br_2 (3.83 mL, 9.49 g, 55.0 mmol) in THF (50 mL) was cooled to −78 °C with a dry ice/acetone bath. After 30 min, the LTMP was cooled with a dry ice/acetone bath and added over a 30-min period via a double ended needle to the above mixture at a temperature below −68 °C. After 14 min, a freshly prepared, −78 °C solution of LHMDS [initially prepared at 0 °C from HMDS (10.5 mL, 8.03 g, 50.0 mmol) and *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) in THF (40 mL)] was added over a 10-min period at a temperature below −70 °C. The mixture was allowed to warm to −20 °C and then cooled to −78 °C. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R 4.00 2-bromo-1-cyclohexanyl-1-ethanone 5.9%, t_R 4.90 2,2-dibromo-1-cyclohexanyl-1-ethanone 94.1%. A solution of *s*-BuLi in cyclohexane (77.0 mL, 100.0 mmol) was added over a 17-min period at a temperature below −52 °C. The mixture was allowed to warm to −20 °C, and a solution of *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) was added. The mixture was warmed to rt and stirred for 35 min. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R ethyl 2-cyclohexanylacetate 100%. The mixture was cooled to −78 °C and quenched over an 85-min period into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C. The mixture was diluted with ether (900 mL) and washed with 10% aqueous HCl (150 mL). The aqueous layer was reextracted with ether (2 × 150 mL), and the combined ethereal layers were washed with brine and dried. The crude product (5.95 g) was purified by silica gel column chromatography (5% ethyl acetate in hexane) to afford 3.67 g (79%) of **8b**: GC t_R 3.66, 100%; IR (neat) 2920, 1735, 1450, 1290, 1165, 1035, and 790 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.13 (q, 2 H), 2.15 (d, 2 H), 1.80–1.60 (m, 7 H), 1.25 (t, 3 H), 1.20–0.88 (m, 4 H).

Ethyl 3,3-Dimethyl-4-phenylbutyrate (8d) Using the Standard Procedure. A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (60 mL) with ice-bath cooling. In a separate flask, a stirred mixture of ethyl 2,2-dimethyl-3-phenylpropionate (**1d**)[2] (5.15 g, 25.0 mmol) and CH_2Br_2 (3.83 mL, 9.49 g, 55.0 mmol) in THF (50 mL) was cooled to −78 °C with a dry ice/acetone bath. After 30 min, the LTMP was cooled with a dry ice/acetone bath and added via a double-ended needle over a 25-min period to the above mixture at a temperature below −71 °C. After 10 min, a freshly prepared, −78 °C solution of LHMDS [initially prepared at 0 °C in THF (40 mL) from HMDS (10.5 mL, 8.03 g, 50.0 mmol) and *n*-BuLi in hexanes (20.0 mL, 50.0 mmol)] was added over a 14-min period at a temperature below −74 °C. The mixture was allowed to warm to −20 °C and was then cooled to −78 °C. A solution of *s*-BuLi in cyclohexane (77.0 mL, 100.0 mmol) was added over a 20-min period at a temperature below −59 °C. The mixture was allowed to warm to −20 °C, and a solution of *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) was added. The mixture was warmed to rt and stirred for 55 min. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R 5.35 ethyl 3,3-dimethyl-4-phenylbutyrate 100%. The mixture was cooled to −78 °C and quenched over a 75-min period into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C. The mixture was diluted with ether (900 mL) and washed with 10% aqueous HCl (150 mL). The aqueous layer was reextracted with ether (2 × 125 mL), and the combined ethereal layers were washed with brine and dried. The crude product (7.98 g) was purified by silica gel column chromatography (5% ethyl acetate in hexane) to afford 4.96 g (90%) of **8d**:[2] GC t_R 5.43, 100%; IR (neat) 2920, 1730, 1605, 1470, 1370, 1215, and 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30–7.15 (m, 5 H, aromatic), 4.15 (q, 2 H, J = 7.0 Hz), 2.68 (s, 2 H), 2.20 (s, 2 H), 1.28 (t, 3 H, J = 7.0 Hz), 1.00 (s, 6 H); GC/MS m/z 220 (M^+).

(*E*)-Ethyl 4-Phenyl-3-butenoate (8e). A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (60 mL) with ice-bath cooling. In a separate flask, a mixture of ethyl cinnamate (**1e**; 4.4 g, 25.0 mmol) and CH_2Br_2 (3.83 mL, 9.49 g, 55.0 mmol) in THF (50 mL) was cooled to −78 °C with a dry ice/acetone bath. After 35 min, the LTMP was cooled with a dry ice/acetone bath and added over a 32-min period via a double-ended needle to the above mixture at a temperature below −68 °C. After 10 min, a freshly prepared, −78 °C solution of LHMDS [initially prepared at 0 °C in THF (40 mL) from HMDS (10.5 mL, 8.03 g, 50.0 mmol) and *n*-BuLi in hexanes (20.0 mL, 50.0 mmol)] was added over a 15-min period at a temperature below −70 °C. The mixture was allowed to warm to −20 °C and then cooled to −78 °C. A solution of *s*-BuLi in cyclohexane (77.0 mL, 100.0 mmol) was added over a 25-min period at a temperature below −58 °C. The mixture was allowed to warm to −20 °C, and a solution of *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) was added. The mixture was warmed to rt, and stirred for 55 min. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R 5.29 (*E*)-ethyl-4-phenyl-3-butenoate 100%. The mixture was cooled to −78 °C and quenched over an 80-min period into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C. The mixture was diluted with ether (900 mL) and washed with 10% aqueous HCl (150 mL). The aqueous layer was reextracted with ether (2 × 150 mL), and the combined ethereal layers were washed with brine and dried. The crude product (6.68 g) was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 3.17 g (67%) of **8e**:[2] GC t_R 5.37, 100%; IR (neat) 2960, 1735, 1600, 1495, 1450, 1370, 1250, 1160, 970, 790, and 765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35–7.20 (m, 5 H, aromatic), 6.50 (d, 1 H), 6.35 (t, $^1/_2$ H), 6.30 (t, $^1/_2$ H), 4.15 (q, 2 H), 3.25 (d, 2 H), 1.28 (t, 3 H); GC/MS m/z 190 (M^+).

Ethyl 1-Naphthylacetate (8f). (a) Using the Standard Procedure. A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (60 mL) with ice-bath cooling. In a separate flask, a mixture of ethyl 1-naphthoate (**1f**; 5.0 g, 25.0 mmol) and CH_2Br_2 (3.83 mL, 9.49 g, 55.0 mmol) in THF (50 mL) was cooled to −78 °C with a dry ice/acetone bath. After 35 min, the LTMP was cooled with a dry ice/acetone bath and added over a 32-min period, via a double-ended needle, to the above mixture at a temperature below −64 °C. After 10 min, a freshly prepared, −78 °C solution of LHMDS [initially prepared at 0 °C in THF (40 mL) from HMDS (10.5 mL, 8.03 g, 50.0 mmol) and *n*-BuLi in

hexanes (20.0 mL, 50.0 mmol)] was added over a 15-min period at a temperature below −66 °C. Following the addition, the mixture was allowed to warm to −20 °C and then cooled to −78 °C. An aliquot quenched into acidic ethanol and analyzed by GC showed t_R 7.05 2-chloro-1-naphthyl-ethanone 12.5%, t_R 7.67 2-bromo-1-naphthylethanone 42.5%, and t_R 8.95 2,2-dibromo-1-naphthylethanone 45.0%. A solution of *s*-BuLi in cyclohexane (77.0 mL, 100.0 mmol) was added at a temperature below −57 °C over a 25-min period. Following the addition, the mixture was allowed to warm to −20 °C, and a solution of *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) was added. The mixture was warmed to rt, stirred for 1 h, and then cooled to −78 °C and quenched over an 80-min period into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C. The mixture was diluted with ether (700 mL) and washed with 10% aqueous HCl (150 mL). The aqueous layer was reextracted with ether (2 × 150 mL), and the combined ethereal layers were washed with brine and dried. The crude product (7.35 g) was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 4.31 g (80%) of a mixture containing **8f** [GC t_R 6.79, 94%] **butyl 1-naphthylacetate**[22,33] [GC t_R 8.03, 4%; GC/MS *m/z* 242 (M^+)] and **1-acetonaphthone (25)**: GC t_R 5.64, (2%; GC/MS *m/z* 170 (M^+), 155, 127 (comparable with 1-acetonaphthone purchased from Aldrich Co.). Isolated separately was 0.089 g (2.3%) of **1,3-bis(1-naphthyl)propan-2-one (26)**: mp 107–108 °C (lit.[34] mp 109–110); GC t_R 13.27; R_f 0.41 (10% ethyl acetate in hexane); IR (KBr) 1711, 1598, 1511, 1418, 1332, 1077, 1053, 788, and 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.85 (d, 2 H, *J* = 8.1 Hz), 7.79 (d, 2 H, *J* = 8.2 Hz), 7.69 (d, 2 H, *J* = 8.4 Hz), 7.49–7.38 (m, 6 H), 7.28 (d, 2 H, *J* = 6.9 Hz), 4.15 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 206.38, 133.87, 132.18, 130.78, 128.73, 128.47, 128.09, 126.41, 125.86, 125.48, 123.86, 47.09; MS *m/z* 311 $(M + H)^+$, 293, 169, 141.

(b) Using the Standard Procedure with Addition of *n*-BuLi at 20 °C. A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (60 mL) with ice-bath cooling. In a separate flask, a stirred mixture of ethyl 1-naphthoate (**1f**; 5.0 g, 25.0 mmol) and CH_2Br_2 (3.83 mL, 9.49 g, 55.0 mmol) in THF (50 mL) was cooled to −78 °C with a dry ice/acetone bath. After 35 min, the LTMP was cooled with a dry ice/acetone bath and added via a double-ended needle to the above mixture over a 30-min period at a temperature below −71 °C. After 13 min, a freshly prepared, −78 °C solution of LHMDS [initially prepared at 0 °C in THF (40 mL) from HMDS (10.5 mL, 8.03 g, 50.0 mmol) and *n*-BuLi in hexanes (20.0 mL, 50.0 mmol)] was added over 15 min at a temperature below −72 °C. Following addition, the mixture was allowed to warm to −20 °C and then cooled to −78 °C. An aliquot quenched into acidic ethanol and analyzed by GC indicated t_R 7.09 2-chloro-1-naphthylethanone 18.04%, t_R 7.70 2-bromo-1-naphthylethanone 38.32%, and t_R 9.00 2,2-dibromo-1-naphthylethanone 43.64%. A solution of *s*-BuLi in cyclohexane (77.0 mL, 100.0 mmol) was added over a 16-min period at a temperature below −60 °C. The mixture was allowed to warm to 20 °C, and a solution of *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) was added over a 30-min period while the temperature was maintained between 20 and 25 °C with a cold water bath. After being stirred at rt for 30 min, the mixture was cooled to −78 °C and quenched over a 100-min period into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C. The mixture was diluted with ether (900 mL) and washed with 10% aqueous HCl (175 mL). The aqueous layer was reextracted with ether (2 × 150 mL), and the combined ethereal layers were washed with brine and dried. The crude product (6.93 g) was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 4.42 g (80%) of a mixture of **8f** [GC t_R 6.79, 98%)] and **butyl 1-naphthylacetate**[22] [GC t_R 7.98, 2%] as well as 0.082 g (2.1%) of **1,3-bis(1-naphthyl)propan-2-one (26)**: GC t_R 13.27.

(c) Using Same Procedure as b but with 1.0 equiv of LiOEt. A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (60 mL) with ice-bath cooling. In a separate flask, a stirred mixture of ethyl 1-naphthoate (**1f**; 5.0 g, 25.0 mmol) and CH_2Br_2 (3.83 mL, 9.49 g, 55.0 mmol) in THF (50 mL) was cooled to −78 °C with a dry ice/acetone bath. After 30 min, the LTMP was cooled with a dry ice/acetone bath and added over 30-min period (via a double-ended needle) to the above mixture at a temperature below −71 °C. After 10 min, a freshly prepared, −78 °C mixture of LHMDS and LiOEt [initially prepared at 0 °C in THF (40 mL) from HMDS (10.5 mL, 8.03 g, 50.0 mmol), absolute ethanol (1.46 mL, 25.0 mmol), and *n*-BuLi in hexanes (30.0 mL, 75.0 mmol)] was added over 15 min at a temperature below −72 °C. The mixture was allowed to warm to −20 °C and then cooled to −78 °C. An aliquot quenched into acidic ethanol and analyzed by GC indicated t_R 7.08 2-chloro-1-naphthylethanone 10.86%, t_R 7.72 2-bromo-1-naphthylethanone 44.73%, and t_R 9.00 2,2-dibromo-1-naphthylethanone 44.41%. A solution of *s*-BuLi in cyclohexane (77.0 mL, 100.0 mmol) was added over a 22-min period at a temperature below −60 °C. The mixture was warmed to 20 °C, and a solution of *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) was added over a 35-min period while the temperature was maintained between 20 and 25 °C with a cold-water bath. The cooling bath was removed, and the mixture was stirred at rt for 30 min. The mixture was cooled to −78 °C and quenched over an 85-min period into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C. The mixture was diluted with ether (1.0 L) and washed with 10% aqueous HCl (175 mL). The aqueous layer was reextracted with ether (2 × 125 mL), and the combined ethereal layers were washed with brine and dried. The crude product (7.05 g) was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 4.51 g (84%) of **8f**: GC t_R 6.79; IR (neat) 2981, 1734, 1598, 1512, 1445, 1174, 792, and 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (d, 1 H, *J* = 8.3 Hz), 7.84 (d, 1 H, *J* = 7.9 Hz), 7.76 (dd, 1 H, *J* = 2.4, 7.1 Hz), 7.51–7.39 (m, 4 H), 4.13 (q, 2 H, *J* = 7.1 Hz), 4.04 (s, 2 H), 1.19 (t, 3 H, *J* = 7.0 Hz); MS *m/z* 215 $(M + H)^+$, 181, 169, 141, 129; exact mass calcd for $C_{14}H_{14}O_2$ 214.0993, obsd 214.0994.

Ethyl Phenylacetate (8a) Using the Standard Procedure, but with Final Addition of *n*-BuLi at 20 °C. A solution of *n*-BuLi in hexanes (22.0 mL, 55.0 mmol) was added to a stirred, 0 °C solution of TMP (10.1 mL, 8.45 g, 60.0 mmol) in THF (60 mL) with ice-bath cooling. In a separate flask, a stirred mixture of ethyl benzoate (3.75 g, 25.0 mmol) and CH_2Br_2 (3.83 mL, 9.49 g, 55.0 mmol) in THF (50 mL) was cooled to −78 °C with a dry ice/acetone bath. After 30 min, the LTMP was cooled with a dry ice/acetone bath, and added via a double-ended needle over a 30-min period to the above mixture while the temperature was maintained below −70 °C. After 9 min, a freshly prepared, −78 °C solution of LHMDS [initially prepared at 0 °C in THF (40 mL) from HMDS (10.5 mL, 8.03 g, 50.0 mmol) and *n*-BuLi in hexanes (20.0 mL, 50.0 mmol)] was added over 10 min. The mixture was allowed to warm to −20 °C and was then cooled to −78 °C. An aliquot quenched into acidic ethanol and analyzed by GC indicated t_R 4.28 α-bromoacetophenone 80.9%, t_R 5.35 α,α-dibromoacetophenone 19.1%. A solution of *s*-BuLi in cyclohexane (77.0 mL, 100.0 mmol) was added over a 14-min period at a temperature below −62 °C. The mixture was allowed to warm to 20 °C, and solution of *n*-BuLi in hexanes (20.0 mL, 50.0 mmol) was added over a 32-min period while the temperature was maintained between 20 and 25 °C with a cold-water bath. After being stirred at rt for 50 min, the mixture was cooled to −78 °C and quenched over a 75-min period into a stirred solution of acidic ethanol[11] (150 mL) at 0 °C. The mixture was diluted with ether (800 mL) and washed with 10% aqueous HCl (160 mL). The aqueous layer was reextracted with ether (2 × 150 mL), and the combined ethereal layers were washed with brine and dried. The crude product (5.44 g) was purified by silica gel column chromatography (4% ethyl acetate in hexane) to afford 3.214 g (78%) of **8a**: GC t_R 3.79, 100%, containing no acetophenone as indicated by NMR.

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