Direct Formation of Secondary and Tertiary Alkylzinc Bromides and Subsequent Cu(I)-Mediated Couplings

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Secondary and tertiary alkylzinc bromides can be generated from the direct oxidative addition of Rieke zinc to secondary and tertiary alkyl bromides in high yield. These organozinc reagents have been found to undergo copper-catalyzed conjugate addition, cross-coupling with acid chlorides, and carbocupration to activated alkynes.

Introduction

The first oxidative addition of zinc into a carbon−halogen bond was demonstrated in 1849 by Frankland by heating ethyl iodide and zinc metal to form diethylzinc.[1] Pursuant to this discovery, methods of metal activation were employed with zinc to increase reaction efficiency and to expand the scope of oxidative addition to more unreactive carbon−halogen bonds. These methods included washing with aqueous HCl,[2] addition of 1,2-dibromoethane[3] and/or trimethylchlorosilane,[4] Zn−Cu[5] or Zn−Cu−Ag[6] couples, sodium−zinc[7] and zinc−mercury[8] alloys, ultrasound irradiation,[9] metal−solvent cocondensation,[10] sacrificial zinc anodes,[11] pulsed sonoelectrochemical reduction of zinc salts,[12] and reduction of zinc salts on titanium dioxide.[13] The utilization of entrainment methods for zinc metal in the generation of alkylzinc halides from alkyl bromides and chlorides directly has led to limited success. The ideal alkyl halide substrates for oxidative addition, using entrainment methods, have been alkyl iodides.[14] However, activated carbon−halogen bonds have proven to be useful substrates, as in carbon−bromine bonds α to oxygen,[15] nitrogen,[15] boron,[16] or sulfur,[17] β to phosphonates,[18] and for α-halo esters, nitriles, and amides.[19] If the carbon−bromine or chlorine bond is not sufficiently activated, the oxidative addition is not effective. The zinc−copper couples display only limited effectiveness for alkyl bromides and *tert*-butyl bromides. There is evidence for the generation of dialkylzincs using this procedure.[5] However, a simple activation method was presented by Knochel in which zinc halides were reduced on titanium dioxide.[13] Using this activated zinc, secondary alkyl- and benzylzinc bromides could be prepared. There have been no synthetically useful procedures to generate tertiary alkylzinc bromides by direct oxidative addition in high yield.

In 1973, we reported a new method for the preparation of a highly reactive zinc metal which involved the reduction of zinc salts using sodium or potassium metal.[20] This reactive metal powder allowed for the first time the direct oxidative addition to primary alkyl and aryl bromides. In 1991, we published an improved method which was safer and produced an even more reactive zinc.[21] Significantly, this approach provided a direct route to highly functionalized organozinc halide reagents from alkyl bromides, aryl iodides and bromides, as well as vinyl iodides and bromides. We also reported a new more reactive zinc which will undergo oxidative addition to alkyl chlorides.[22] Recently, we reported that our highly reactive zinc could also react directly with secondary and tertiary alkyl bromides in high yield,[23] and that these reagents give the 1,4-conjugate addition product with α,β-unsaturated ketones without the use of a Cu(I) catalyst.[24]

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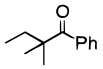
Table 1. Tertiary Alkylzinc Bromides

Entry	Bromide[a]	RCOCl equiv[b]	Product	Yield (%)
1		0.7	**1** 	75
2		0.7	**2** 	86
3		0.7	**3** 	72

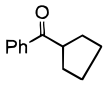
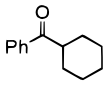
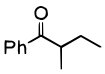
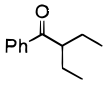
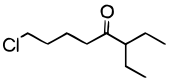
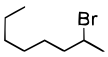
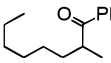
[a] Zn* 1.0−1.3 equiv, RBr 1.0 equiv, THF. [b] CuCN/LiBr 0.1 equiv, RZnBr 1.0 equiv, RCOCl 0.7 equiv, THF, −45 °C to rt.

Results and Discussion

We have found that Rieke zinc readily yields alkylzinc bromides efficiently under mild conditions from the direct oxidative addition of Rieke zinc to secondary and tertiary alkyl bromides. This method is good for hindered and unhindered unactivated secondary and tertiary alkyl bromides. The Rieke zinc used in these experiments was generated by a two-pot procedure; to a mixture of lithium (2.1 equiv) and naphthalene (0.2 equiv) in THF was added by drop a THF solution of anhydrous zinc chloride (1.0 equiv) over 2 h. This mossy form of zinc settled rapidly and bore the same high reactivity as that of using stoichiometric lithium naphthalenide. As was previously reported,[21] a mossy form of active zinc could be prepared by allowing for a shortened reduction time. With the resulting decreased settling times, the active zinc was rapidly washed with THF to decrease the lithium chloride and naphthalene content present from reduction, which then simplified product purification. The rinsed active zinc readily reacted with alkyl bromides to cleanly produce an alkylzinc bromide. For instance, the addition of 0.9 equiv of *tert*-butyl bromide to active zinc at room temperature resulted in an exothermic reaction which was complete within 1 h. The ^{13}C NMR of the resulting *tert*-butylzinc bromide revealed a strong singlet at δ 32.3 and a weak singlet at δ 21.7. This ability to generate an alkylzinc bromide without an observable presence of a dialkylzinc, or a product resulting from reductive cleavage, is significant. In contrast, a marked difference in the ease of oxidative addition for 1-bromoadamantane was observed. At ambient temperature, the oxidative addition was slow. To effect a good conversion, an excess amount of zinc (1.2 equiv) and refluxing conditions for 3 h was necessary. The oxidative addition of magnesium (turnings) to this halide is known to result in a significant amount of reductive cleavage and homocoupling.[25] Thus, Rieke zinc was highly efficient in the oxidative addition to this difficult alkyl bromide. The bulky nature of the alkyl groups in these tertiary alkylzinc bromides was evident as the copper-mediated coupling of acid chlorides required longer reaction times than primary alkylzinc reagents. The tertiary alkylzinc bromides (Table 1) coupled slowly with benzoyl chloride using CuCN/LiBr[26] as catalyst taking 4−8 h for completion.

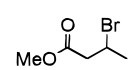
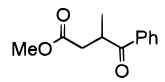
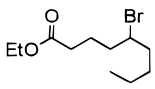
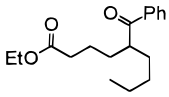
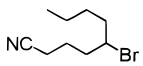
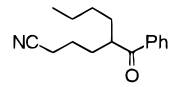
The cyclic secondary alkyl bromides (Table 2, entries 1−3) formed the alkylzinc bromide reagents in good yield.

Table 2. Secondary Alkylzinc Bromides

Entry	Bromide[a]	RCOCl equiv[b]	Product	Yield (%)
1		0.7	**4** 	75
2		0.9	**5** 	84
3		0.7	**6** 	99
4		1.0	**7** 	95
5		0.9	**8** 	87
6		0.9	**9** 	62
7		0.7	**10** 	88

[a] Zn* 1.0−1.3 equiv, RBr 1.0 equiv, THF. [b] CuCN/LiBr 0.1 equiv, RZnBr 1.0 equiv, RCOCl 0.7−1.0 equiv, THF, −45 °C to rt.

Table 3. Functionalized Secondary Alkylzinc Bromides

Entry	Bromide[a]	RCOCl equiv[b]	Product	Yield (%)
1		0.7	**11** 	75
2		0.7	**12** 	54
3		0.7	**13** 	60

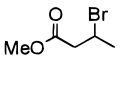
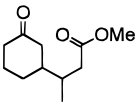
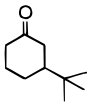
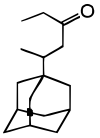
[a] Zn* 1.0−1.3 equiv, RBr 1.0 equiv, THF. [b] CuCN/LiBr 0.1 equiv, RZnBr 1.0 equiv, RCOCl 0.7 equiv, THF, −45 °C to rt.

For example, cyclobutylzinc bromide can be prepared in quantitative yield from cyclobutyl bromide. Although, the cyclobutylzinc bromide could be generated at ambient temperature in about 12−16 h using 1.1−1.2 equiv of active zinc, the reaction time was reduced to 2 h by refluxing in THF. A surprising result was that when the oxidative addition of zinc was either performed at reflux or at ambient temperature with cyclopropyl bromide, a coupled product with benzoyl chloride using a copper catalyst could not be achieved. The secondary acyclic alkyl bromides formed the reagent in good yield with 1.1 equiv of active zinc. The oxidative addition was complete in 2.5 h under refluxing conditions. Thus, the rate of oxidative addition was faster for smaller chain lengths, but longer chain lengths required longer reaction times, up to 3 h at refluxing temperatures (cf. entry 7). This procedure was able to accommodate remote functional groups including ester and nitrile groups. The oxidative addition of Rieke zinc to methyl 3-bromobutyrate (Table 3, entry 1) was complete in 1 h at room temperature, but the ester functionality was stable to refluxing conditions even after 2.5 h. The observed trend in the ease of oxidative addition for unfunctionalized alkyl bromides

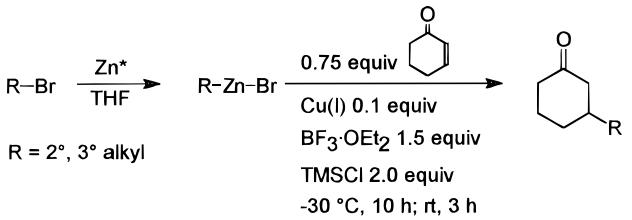
(25) Dubois, J. E.; Bauer, P.; Molle, G.; Daza, J. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1977**, *284*, 145.

(26) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

Table 4. Conjugate Addition of Secondary and Tertiary Alkylzinc Bromides Mediated by Copper Salts

Entry	Bromide	Enone	Product	Cu(X)	Yield (%)
1			**14** 	CuI	53
2			**15** 	CuCN CuI	75 96
3			**16** 	CuCN	63

Scheme 1

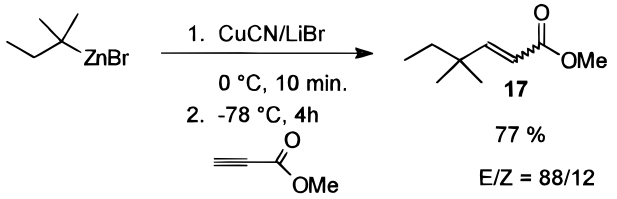


using Rieke zinc is tertiary > secondary > primary. This progression is comparable to that of primary and secondary alkyl iodides.[14]

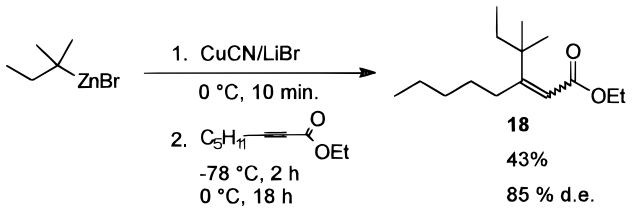
The conjugate addition of secondary and tertiary alkylzinc bromides (Table 4) mediated by copper(I) proceeds in good yield even though the reagents are bulky nucleophiles (Scheme 1). The 1,4 addition reaction was conducted as to previous literature procedure using the soluble copper cyanide/lithium bromide complex in conjunction with boron trifluoride diethyl etherate and chlorotrimethylsilane.[21] Under these conditions *tert*-butylzinc bromide reacted with 2-cyclohexenone to give **15** in 75% yield. However, using copper iodide catalytically gave the product in 96% yield. The conjugate addition involving 1-adamantylzinc bromide with 4-hexen-3-one using the previous Lewis acid combination gave a 63% isolated yield of the addition product **16**. Methyl 3-zinciobromobutyrate, a secondary alkylzinc reagent, gave the addition product **14** in moderate yield with cyclohexenone at 53% yield. The secondary and tertiary organozinc reagents required longer reaction times than primary alkylzinc reagents, usually 8−12 h for more hindered systems.

The carbocupration reaction using stoichiometric tertiary alkylzinc−copper reagents demonstrated their poor nucleophilicity toward activated alkynes. Primary and secondary organozinc reagents have been shown to be highly stereoselective in the carbocupration of activated alkynes.[16 27] We have found that the reaction of 2,2-dimethylpropylzinc bromide with the activated terminal alkyne, methyl propiolate proceeded at −78 °C in 4 h using copper cyanide/lithium bromide stoichiometrically to give good stereoselectivity (Scheme 2). The product **17** was obtained in 77% yield with the *E* isomer predominating (E/Z = 86/13). In the case of the internal alkyne ethyl 2-octynoate, the carbocupration reaction was

Scheme 2



Scheme 3



very sluggish at −78 °C, and only at 0 °C did the reaction proceed slowly. Even at the elevated reaction temperature, the diasteriomeric excess for **18** was 85% in an overall yield of 43% (Scheme 3).

Conclusion

In summary, we have demonstrated a method for preparing secondary and tertiary alkylzinc reagents from the stable alkyl bromides. This result is significant, in that tertiary alkylzinc bromides can be formed readily from Rieke zinc insertion in high yield. The formation of these organozinc reagents would be difficult or impossible by other methodologies which do not tolerate functionality. These organozinc reagents have been found to undergo copper-catalyzed conjugate addition, cross-coupling with acid chlorides, and carbocupration to activated alkynes.

Experimental Section

General Information. The manipulation of air-sensitive reagents was conducted in a Vacuum Atmospheres Co. drybox maintained with an argon atmosphere. Reactions were performed on a dual manifold vacuum/argon system. Linde prepurified grade argon was further purified by passing it through a 150 °C catalyst column (BASF R3−11) and then through a column of phosphorus pentoxide, followed by a column of granular potassium hydroxide. THF was distilled prior to use from NaK alloy under a blanket of argon. Anhydrous zinc chloride was purchased from Cerac, Inc., and was used as received.

Starting Materials. Functionalized alkyl bromides were prepared as described below.

Ethyl 5-Hydroxynonanoate. Prepared by literature procedure from the reduction of ethyl 5-oxononanoate[21] in methanol by $NaBH_4$.[28] The product (43% yield) was isolated from the crude reaction mixture by flash chromatography (EtOAc/hexanes, 1:4). ^{1}H NMR δ 4.12 (q, 2 H), 3.58 (m, 1 H), 2.32 (t, 2 H), 1.80−1.23 (m, 14 H), 0.91 (t, 3 H). ^{13}C NMR δ 173.7, 71.4, 60.2, 37.2, 36.7, 34.2, 27.8, 22.7, 21.0, 14.2, 14.0. IR (neat) 1720, 1739 cm^{-1}. Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.48; H, 10.76.

5-Hydroxynonanenitrile.[29] Prepared from 5-oxononanenitrile[30] as procedure above.

(27) Chou, T.-S.; Knochel, P. *J. Org. Chem.* **1990**, *55*, 4791.

(28) Mancera, O.; Ringold, H. J.; Djerassi, C.; Rosenkranz, G.; Sondheimer, F. *J. Am. Chem. Soc.* **1953**, *75*, 1286.

(29) O'Shea, M. G.; Kitching, W. *Tetrahedron* **1989**, *45*, 1177.

(30) Cohen, N.; Rosenberger, M.; Saucy, G.U.S. Patent 3898264, 1975.

Ethyl 5-Bromononanoate. The above hydroxy compounds were first converted to the mesylates[31] and the crude subjected to refluxing in a THF solution of lithium bromide.[32] The product (27% yield) was isolated from the crude reaction mixture by flash chromatography (EtOAc/hexanes, 5:95). ^{1}H δ 4.14 (q, J = 6.9, 2 H), 4.02 (m, 1 H), 2.33 (t, J = 6.9, 2 H), 1.9−1.7 (m, 6 H), 1.5−1.2 (m, 7 H), 0.90 (t, J = 7.2, 3 H). ^{13}C δ 173.2, 60.3, 57.7, 38.8, 38.3, 33.6, 29.7, 23.0, 22.1, 14.2, 13.9. Anal. Calcd for $C_{11}H_{21}BrO_2$: C, 49.82; H, 7.98. Found: C, 50.11; H, 8.00.

5-Bromononanenitrile. ^{1}H δ 4.00−3.92 (m, 1 H), 2.37−2.33 (m, 2 H), 1.97−1.71 (m, 6 H), 1.50−1.23 (m, 4 H), 0.86 (t, J = 7.2, 3 H). ^{13}C δ 119.0, 56.3, 38.6, 37.3, 29.3, 23.3, 21.8, 16.3, 13.6. IR (neat) 2244 cm^{-1}. Anal. Calcd for $C_9H_{16}BrN$: C, 49.76; H, 7.43; N, 6.45. Found: C, 49.94; H, 7.60; N, 6.57.

Typical Preparation of Rieke Zinc. To a flask charged with finely cut (ca. 0.75 × 1.0 × 5.0 mm) Li (0.11 g, 16 mmol), naphthalene (0.20 g, 1.6 mmol), and THF (10 mL) under argon was transferred via cannula a solution of zinc chloride (1.09 g, 8.00 mmol) in THF (15 mL) dropwise so addition was complete in 1.5 h. The mixture was then vigorously stirred for an additional 0.5 h until the lithium metal was consumed. The stirring was then stopped and the zinc settled in ca. 10 min. The supernatant was removed via cannula. The Rieke zinc was then washed with two consecutive portions of dry THF (15 mL). A final portion of THF was added and the Rieke zinc was ready for use.

Preparation of *tert*-Butylzinc Bromide. To a slurry of Rieke zinc (1.03 g) in THF (10.0 mL) under argon was added via disposable syringe, 1.969 g of *tert*-butyl bromide. The exothermic reaction was complete in 1 h. The zinc was allowed to settle, and 0.5 mL of the supernatant was cannulated to an NMR tube capped with a septum. A sealed capillary tube containing $CDCl_3$ inside the NMR tube was used to gain NMR lock. ^{13}C NMR (THF; δ 25.3) δ 32.3, 21.7.

Typical Procedure for Copper-Mediated Coupling of Alkylzinc Bromide Reagents with Acid Chlorides. To a slurry of Rieke zinc (7.98 mmol) in THF (25 mL) under a blanket of argon was added 2-bromobutane (7.95 mmol), and the mixture was refluxed for 2.5 h. The resulting light brown solution was cooled to rt and was transferred via cannula to a solution of CuCN (1.5 mmol) and LiBr (1.5 mmol) in THF (10 mL) at −45 °C. Benzoyl chloride (7.95 mmol) was added neat, and the mixture was warmed slowly to rt over 4 h. The reaction mixture was quenched with 3 M HCl (20 mL) and extracted with ether (3×20 mL), and the combined layers were washed with water (20 mL), dried over $MgSO_4$, and concentrated. 2-Methyl-1-phenylbutanone **7**[33] (7.52 mmol, 95%) was isolated from the crude reaction mixture by flash chromatography (EtOAc/hexanes, 5:95).

2,2-Dimethyl-1-phenyl-1-propanone (1). Reference 34.

2,2-Dimethyl-1-phenylbutanone (2). Reference 35.

Adamantyl phenyl ketone (3).[36] The product was isolated from the crude reaction mixture by flash chromatography (gradient elution: EtOAc/hexanes, 0:100, 2:98, 5:95, 8:92). ^{1}H NMR δ 7.54−7.51 (m, 2 H), 7.42−7.36 (m, 3 H), 2.06−1.99 (m, 9 H), 1.73−1.72 (m, 6 H). ^{13}C NMR δ 210.0, 139.6, 130.0, 127.8, 127.0, 46.8, 39.0, 36.4, 28.0. IR (neat)1670 cm^{-1}.

Cyclobutyl Phenyl Ketone (4). Reference 37.

Cyclopentyl Phenyl Ketone (5). Reference 38.

Cyclohexyl Phenyl Ketone (6). Reference 39.

2-Ethyl-1-Phenyl-1-Butanone (8). Reference 40.

3-Ethyl-8-chloro-4-octanone (9). The product was isolated from the crude reaction mixture by flash chromatography (EtOAc/hexanes, 5:95). ^{1}H NMR δ 3.56−3.50 (m, 2 H), 2.47−2.41 (m, 2 H), 2.33−2.30 (m, 1 H), 1.80−1.41 (m, 8 H), 0.87−0.78 (m, 6 H). ^{13}H NMR δ 214.7, 56.1, 45.3, 42.0, 41.9, 32.7, 24.9, 21.5, 21.5. IR (neat) 1709 cm^{-1}. Anal. Calcd for $C_{10}H_{19}ClO$: C, 62.98; H, 10.04. Found: C, 62.81; H, 9.89.

2-Methyl-1-phenyl-1-octanone (10). Reference 41.

Methyl 3-Methyl-4-oxo-4-phenylbutanoate (11). The product was isolated from the crude reaction mixture by flash chromatography (EtOAc/hexanes, 15:85). ^{1}H NMR δ 7.99 (m, 2 H), 7.52 (m, 3 H), 3.95 (m, 1 H), 3.65 (s, 3 H), 2.97 (dd, J = 16.5, 4.2 Hz, 1 H), 2.47 (dd, J = 16.9, 2.9 Hz, 1 H), 1.23 (d, J = 3.06 Hz, 3 H). ^{13}C NMR δ 202.8, 172.8, 135.9, 133.1, 128.8, 128.5, 51.7, 37.2, 17.9. IR (neat) 1724, 1674 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.72; H, 6.77.

Ethyl 5-(1-Oxo-1-phenylmethyl)nonanoate (12). The product was isolated from the crude reaction mixture by flash chromatography (EtOAc/hexanes, 1:9). ^{1}H NMR δ 7.96 (m, 2 H), 7.52 (m, 3 H), 4.09 (d, J = 7.2 Hz, 2 H), 3.44 (m, 1 H), 2.27 (m, 2 H), 1.82−1.43 (m, 6 H), 1.31−1.18 (m, 7 H), 0.84 (t, J = 6.6 Hz, 3 H). ^{13}C NMR δ 204.1, 173.3, 137.5, 132.8, 128.6, 128.1, 60.22, 45.85, 34.3, 32.1, 31.5, 29.5, 22.9, 22.8, 14.1, 13.8. IR (neat) 1743, 1684 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.57; H, 9.13.

5-(1-Oxo-1-phenylmethyl)nonanenitrile (13). The product was isolated from the crude reaction mixture by flash chromatography (gradient elution: EtOAc/hexanes, 0:100, 2:98, 4:96, 6:94, 10:90). ^{1}H NMR δ 7.92−7.90 (d, 2 H), 7.45 (s, 1 H), 7.44 (s, 2 H), 3.43 (s, 1 H), 2.27 (s, 2 H), 1.88 (s, 1 H), 1.74−1.62 (m, 6 H), 1.22 (s, 4 H), 0.88 (s, 3 H). ^{13}C NMR δ 203.3, 136.9, 133.0, 128.6, 127.9, 119.2, 45.1, 32.2, 30.6, 29.2, 23.2, 22.6, 17.2, 13.7. IR (neat) 2244, 1677 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.96; H, 8.70; N, 5.76. Found: C, 79.12; H, 8.89; N, 5.67.

Typical Procedure for Copper-Mediated 1,4-Addition of Alkylzinc Bromides to α,β-Unsaturated Ketones. To a slurry of Rieke zinc (12.9 mmol) in THF (25 mL) was added methyl 3-bromobutyrate (11.6 mmol) neat via disposable syringe and the mixture stirred for 4 h at rt. The Rieke zinc was allowed to settle, the supernatant was transferred to a THF (10 mL) slurry of CuI (15.5 mmol) at rt, and the mixture was stirred for 10 min. The mixture was brought to −78 °C, and $BF_3{\cdot}Et_2O$ (12.2 mmol), TMSCl (15.8 mmol), and 2-cyclohexenone (7.54 mmol) were added neat. The reaction mixture was then brought to −30 °C and maintained for 10 h. The mixture was then warmed to rt and stirred for an additional 3 h. The reaction mixture was quenched with 3 M HCl (20 mL) and extracted with ether (3 × 20 mL), and the combined organics were washed sequentially with aqueous $Na_2S_2O_3$ (20%, 20 mL), water (3 × 20 mL), brine (20 mL) and then dried over $MgSO_4$ and concentrated. Methyl 3-(3-oxocyclohexyl)-butanoate (**14**) (4.00 mmol, 53%) was isolated from the crude as a colorless oil from silica gel (EtOAc/hexanes, 3:7). ^{1}H NMR δ 3.68 (s, 3 H), 2.42−1.15 (m, 12 H), 0.97−0.93 (m, 3 H). ^{13}C NMR δ 204.8, 173.4, 51.2, 45.6, 44.2, 43.3, 41.3, 38.8, 38.7, 34.6, 34.6, 28.9, 27.3, 25.30, 25.27, 16.3, 16.1. IR (neat) 1745, 1714 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.25; H, 8.99.

3-*tert*-Butylcyclohexanone (15). Reference 42.

5-(1-Adamantyl)hexan-3-one (16). The product was isolated from the crude by flash chromatography (gradient elution: EtOAc/hexanes, 0:100, 5:95, 10:90). ^{1}H NMR δ 2.55 (m, 1 H), 2.42 (m, 2 H), 2.05 (m, 1 H), 1.97 (s, 3 H), 1.66 (m, 7 H, 1.48 (s, 6 H), 1.05 (t, J = 7.5 Hz, 3 H), 0.78 (d, J = 7.0 Hz, 3 H). ^{13}C NMR δ 212.5, 44.0, 39.4, 38.9, 37.3, 36.4, 34.3, 28.6, 13.6, 7.9. IR (neat) 1716 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.74; H, 11.34.

Typical Procedure for the Copper Mediated Addition of Alkylzinc Bromides to Activated Alkynes. To a slurry of Rieke zinc (15.3 mmol) in THF (25 mL) was added methyl 2-bromo-2-methylbutane (15.3 mmol), neat via disposable syringe, and the mixture stirred for 2 h at rt. The Rieke zinc was allowed to settle, and the supernatant was transferred to

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a THF (20 mL) solution of CuCN (30 mmol) and lithium bromide (30 mmol) at 0 °C. The solution was stirred for 10 min, and the temperature was brought to −78 °C. Methyl propiolate was added neat, and the reaction mixture was stirred for 4 h at −78 °C. The reaction mixture was then quenched with 3 M HCl at −78 °C and was stirred for 0.5 h. The mixture was then warmed to rt over 2 h. The organics were taken up in ether (20 mL), and the aqueous layer was extracted with ether (2 × 20 mL). The combined organics were washed sequentially with water (3 × 20 mL) and brine (20 mL) and were dried over $MgSO_4$. Chromatography of the crude on silica gel (EtOAc/hexanes, 1:9) afforded methyl 4,4-dimethylhex-2-enoate (**17**) (6.08 mmol, 77%) as a mixture of isomers (*E*/*Z* = 88/12 by NMR). Major isomer (*E*): ^{1}H NMR δ 6.92 (d, J = 16 Hz, 1 H), 5.74 (d, J = 16.5 Hz, 1 H), 3.74 (s, 3 H), 1.39 (q, J = 7.5, 2 H), 1.03 (s, 6 H), 0.81, (t, J = 7.5 Hz, 3 H). ^{13}C NMR δ 167.6, 158.6, 117.5, 51.4, 36.9, 34.6, 25.8, 8.8. IR (neat) 1728, 1653 cm^{-1}. Minor isomer (*Z*): ^{1}H NMR 5.91 (d, J = 13.5 Hz, 1 H), 5.70 (d, J = 13 Hz, 1 H), 3.69 (s, 3H), 1.51 (q, J = 7.5 Hz, 2 H), 1.13 (s, 6 H), 0.84 (t, J = 7.5 Hz, 3 H). HRMS *m*/*z* for $C_{19}H_{16}O_2$ (both isomers) calcd 156.1150, found 156.1151.

Ethyl 3-(1,1-Dimethylpropyl)oct-2-enoate (**18**). The reaction was performed using the same experimental procedure as for compound **17**, except bath temperature was maintained at 0 °C for 18 h. The product was isolated (43% yield, 85% de based on NMR) from the crude reaction mixture by flash chromatography (gradient elution: EtOAc/hexanes, 0:100, 5:95). ^{1}H NMR δ 5.56 (s), 5.63 (s), 4.15 (q), 2.48 (m), 1.59−1.26 (m), 1.15 (s), 1.07 (s), 0.92−0.85 (m), 0.73 (t). ^{13}C NMR δ 170.6, 166.8, 114.5, 116.6, 60.1, 59.4, 41.6, 33.9,33.4, 32.9, 31.8, 30.4, 29.5, 29.2, 26.9, 26.36, 22.42, 14.3, 14.14, 14.05, 14.0, 9.0. IR (neat) 1720, 1627 cm^{-1}. HRMS *m*/*z* for $C_{15}H_{28}O_2$ calcd 240.2089, found 240.2088.

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Supporting Information Available: Copies of both ^{1}H and ^{13}C NMR spectra of **17** and **18** (4 pages). This material is contained in 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.

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