

Tandem Carbocupration/Oxygenation of
Terminal Alkynes

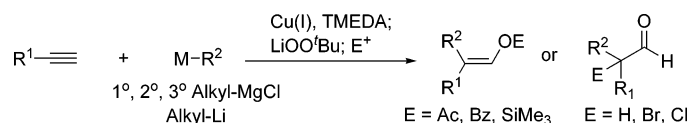
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ABSTRACT



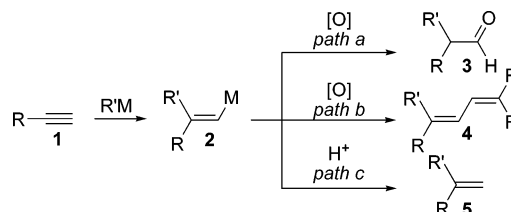
A direct and general synthesis of α -branched aldehydes and their enol derivatives is described. Carbocupration of terminal alkynes and subsequent oxygenation with lithium *tert*-butyl peroxide generates a metallo-enolate. Trapping with various electrophiles provides α -branched aldehydes or stereo-defined trisubstituted enol esters or silyl ethers. The tandem carbocupration/oxygenation tolerates alkyl and silyl ethers, esters, and tertiary amines. The reaction is effective with organocopper complexes derived from primary, secondary, and tertiary Grignard reagents and from *n*-butyllithium.

α -Branched aldehydes represent valuable synthetic intermediates but remain difficult to access. Alkylation of aldehyde enolates generally fails, so recourse has been taken to indirect methods. In a common tactic, reaction of metalated hydrazones or imines with alkyl halides leads to α -branched hydrazones or imines.¹ Hydrolysis provides the substituted aldehyde. Alternatively, alkylation of carboxylic acid derivatives and subsequent partial reduction can yield α -branched aldehyde products. In addition to requiring multiple synthetic operations, these indirect methods also suffer from limited reaction scope. Specifically, enolate or metalloenamine alkylation proceeds efficiently only with unhindered and/or electronically activated electrophiles.

Hydroformylation of terminal olefins provides an alternative to aldehyde enolate alkylation, but general strategies to control regioselectivity have proved elusive.² We report here a general and direct approach based on the addition of a carbon-based nucleophile and oxygen-based electrophile to monosubstituted acetylenes, the tandem carbocupration/oxygenation of terminal alkynes (eq 1).³

Carbometalation of terminal alkynes (**1**) generates stereo-defined vinylmetal intermediates (**2**) that can react with various electrophiles.⁴ In principle, trapping with an electrophilic oxygen donor (Scheme 1, path a) could provide an

Scheme 1



α -branched aldehyde (**3**) or its enol derivative. Among various carbometalation protocols, those based on organocopper reagents display the broadest generality.⁵ For this

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(2) Review: Clarke, M. L. *Curr. Org. Chem.* **2005**, *9*, 701–710.

(3) An elegant methylalumination/oxidation of terminal olefins has been reported: (a) Shaughnessy, K. H.; Waymouth, R. M. *J. Am. Chem. Soc.* **1995**, *117*, 5873–5874. (b) Kondakov, D. Y.; Negishi, E.-i. *J. Am. Chem. Soc.* **1995**, *117*, 10771–10772. (c) Tandem allyl zincation/thiolation: Creton, I.; Marek, I.; Normant, J. F. *Synthesis* **1996**, 1499–1508.

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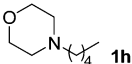
reason, we sought a method to effect oxygenation of vinyl copper species (**2**, M = Cu). However, a significant obstacle to implementing this strategy was related to the known chemistry of organocopper compounds: the oxidative dimerization of phenyl copper has been known since the early twentieth century,⁶ and more than 30 years ago Nomant described a carbocupration/oxidation sequence leading to symmetrical dienes (**4**, Scheme 1, path b).⁷

Initial efforts to effect oxygenation of vinyl copper intermediates confirmed the large body of evidence indicating that dimerization constituted the predominant reaction pathway. In particular, oxygen transfer agents such as dimethyl dioxirane and nitrosobenzene provided diene (**4**) to the exclusion of aldehyde derivatives. Other oxidants, including *N*-methyl morpholine *N*-oxide and metal salts of *m*-CPBA, were unreactive, and terminal olefin (**5**) was recovered from the reactions.

Experiments with LiOO^tBu (**6**) proved more rewarding. Boche and co-workers oxidized phenyl cuprates to phenol with this reagent.⁸ We have discovered that LiOO^tBu in conjunction with carbocupration enables the preparation of α -branched aldehydes and their derivatives from organometallic reagents and terminal alkynes. For example, carbocupration of 1-dodecyne (**1a**) with ethylcopper was followed by oxidation with LiOO^tBu. After addition of acetic anhydride to the reaction mixture, we isolated the trisubstituted enol acetate (**7**) in moderate yield. Increases in yield and reproducibility accompanied the addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) to the vinyl copper intermediate prior to oxidation (Table 1, entry 1). Other amine ligands showed no discernible effect, while phosphorus-based ligands totally suppressed oxygenation.

To expand the scope of the carbo-oxygenation, three carbocupration protocols were developed or appropriated to accommodate primary, secondary, and tertiary Grignard and primary alkyllithium reagents (Table 1). In all cases, the vinyl copper intermediate (**2**, M = Cu) was oxidized with LiOO^tBu at -78°C ; addition of Ac₂O to the crude reaction mixture led to trisubstituted enol acetates, **7**. Carbometallation with primary Grignard reagents is optimal using CuBr·Me₂S and a 1:1.5 Cu/Mg ratio (conditions A), as has been previously reported.⁹ In contrast, terminal alkynes were inert to organocopper reagents derived from secondary and tertiary alkylmagnesium halides. Diorganocuprates displayed improved reactivity, but these reactions were initially plagued by incomplete consumption of the alkyne and formation of multiple products. The low yields stemmed not from recalcitrance of the alkyne; rather, the cuprate intermediates decomposed under the reaction conditions.¹⁰ For instance,

Table 1. Tandem Carbocupration/Oxygenation of Terminal Alkynes

$\text{R}^1\text{—}\text{C}\equiv\text{C} + \text{M—R}^2 \xrightarrow[\text{conditions}]{\text{Cu(I), TMEDA; LiOO}^t\text{Bu (6); Ac}_2\text{O}} \text{R}^2\text{—C(R}^1\text{)=C(OAc)} \quad (1)$				
entry	R ¹	M—R ²	conditions ^a	yield (%) ^b
1	<i>n</i> -C ₁₀ H ₂₁ (1a)	C ₂ H ₅ MgBr	A	71
2	1a	<i>n</i> -C ₄ H ₉ MgCl	A	67
3	1a	<i>i</i> -PrMgCl	B	60
4	1a	<i>o</i> -C ₆ H ₁₁ MgCl	B	62
5	1a	<i>n</i> -C ₄ H ₉ Li	C	69
6 ^c	1a	<i>t</i> -C ₄ H ₉ MgCl	B	50
7	BnO(CH ₂) ₄ (1b)	C ₂ H ₅ MgBr	A	61
8	1b	<i>o</i> -C ₆ H ₁₁ MgCl	B	62
9	1b	<i>n</i> -C ₄ H ₉ Li	C	62
10	TBSO(CH ₂) ₄ (1c)	C ₂ H ₅ MgBr	A	59
11	1c	<i>o</i> -C ₆ H ₁₁ MgCl	B	66
12	1c	<i>n</i> -C ₄ H ₉ Li	C	61
13	BzO(CH ₂) ₄ (1d)	<i>o</i> -C ₆ H ₁₁ MgCl	B	62
14	1d	<i>n</i> -C ₄ H ₉ Li	C	55
15	Ph (1e)	<i>o</i> -C ₆ H ₁₁ MgCl	B	63
16	Bn ₂ N(CH ₂) ₄ (1f)	C ₂ H ₅ MgBr	A	52
17	1f	<i>o</i> -C ₆ H ₁₁ MgCl	B	58
18	1f	<i>n</i> -C ₄ H ₉ Li	C	51
19	PhCH ₂ (1g)	C ₂ H ₅ MgBr	A	58
20	1g	<i>o</i> -C ₆ H ₁₁ MgCl	B	66
21	1g	<i>n</i> -C ₄ H ₉ Li	C	64
22	 (1h)	<i>o</i> -C ₆ H ₁₁ MgCl	B	63

^a Condition A: carbocupration carried out in Et₂O/Me₂S (1:0.3) with RMgX/CuBr·Me₂S = 1.5:1; TMEDA (1 equiv relative to Cu) added after carbocupration. Conditions B: carbocupration carried out in THF with 2:1:1 RMgX/CuBr/TMEDA. Conditions C: carbocupration carried out in Et₂O/Me₂S (1:0.8) with 1:1 RLi/CuBr·Me₂S; TMEDA and MgBr₂ (each 1 equiv relative to Cu) added after carbocupration. For all reactions, LiOO^tBu added as solution in THF at -78°C . See Supporting Information for complete experimental details. ^b Isolated yield. ^c Carbocupration carried out in Et₂O.

reactions involving (*c*-hexyl)₂CuMgBr and 1-dodecyne produced significant quantities of bicyclohexyl and 1,2-di-*cyclo*-hexyl-1-dodecene. As TMEDA appeared to minimize dimerization during oxidation, we speculated that it might also increase the stability of cyclohexyl cuprates. Indeed, the use of CuBr·TMEDA enabled the carbo-oxygenation to be performed with secondary and tertiary alkyl Grignard reagents (conditions B).

In contrast to a previous report¹¹ we observe efficient carbocupration with organocopper reagents derived from *n*-butyllithium. Unfortunately, TMEDA did not suppress diene formation during oxidation. However, the amelioratory effects of TMEDA were restored by admixture with MgBr₂ (1 equiv relative to Cu, conditions C).

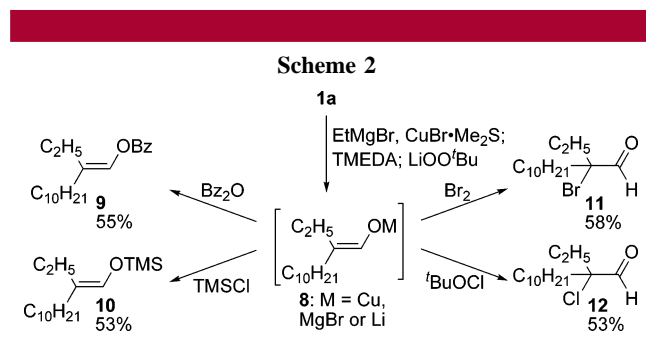
The carbo-oxygenation reaction tolerates common functionality including esters, silyl ethers, benzyl ethers and tertiary amines. In every case studied to date, the enol acetate has been isolated as a single regio- and stereoisomer.^{12,13} In

- (5) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135–631.
 (6) Krizewsky, J.; Turner, E. E. *J. Chem. Soc.* **1919**, *115*, 559–561.
 (7) Normant, J. F.; Cahiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* **1974**, *77*, 269–279.
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 (9) (a) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *3888*–3901. (b) Ashby, E. C.; Smith, R. S.; Goel, A. B. *J. Org. Chem.* **1981**, *46*, 5133–5139.
 (10) (a) Whitesides, G. M.; Casey, C. P. *J. Am. Chem. Soc.* **1966**, *88*, 4541–4542. (b) Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; Filippo, J. S., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 1426–1427.

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many instances, NOEs were observed between the olefinic proton and the formerly propargylic protons, indicating *cis* addition to the triple bond. In other cases, stereochemical assignment was made by analogy.¹⁵

Oxidation likely generates a metallo-enolate (**8**), and this intermediate can be trapped with electrophiles other than acetic anhydride. For example, quenching the reaction with benzoic anhydride or chlorotrimethylsilane yields the corresponding enol derivatives **9** and **10** (Scheme 2). Alterna-

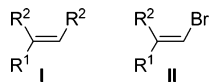


tively, α -haloaldehydes (**11**, **12**) can be isolated following addition of Br_2 or $^t\text{BuOCl}$ to the reaction mixture.

Surprisingly, attempts to quench the enolate **8** with proton sources led not to the expected aldehyde **14** but to ketone **13** (Scheme 3). Ultimately, we determined that addition of ethylenediamine prior to the addition of water allowed the isolation of the α -branched aldehyde in good yield. Other Lewis bases (Et_3N , Bu_3P) were similarly effective, although simple reductive aqueous workup (e.g., $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$) led to lower yields of **14**. Ketone **13** is likely the product of a Baeyer–Villiger oxidation of aldehydes **11** and/or **15** promoted by excess *tert*-butyl peroxide. Aldehydes **11** and **15** may arise in situ from α -oxidation of **8** or **14**.¹⁴ Consistent with this interpretation, aldehydes **11** and **15** both convert to ketone **13** under the reaction conditions.^{15,16}

(12) Carbocupration of 1-decyne with $(^t\text{Bu})_2\text{CuMgBr}$ proceeds with 4.7:1 regioselectivity favoring the 2,2-disubstituted product. However, no products derived from oxidation of the minor regioisomer were detected in the crude carbo-oxygenation reaction mixture. All other carbocuprations occurred with >50:1 selectivity.

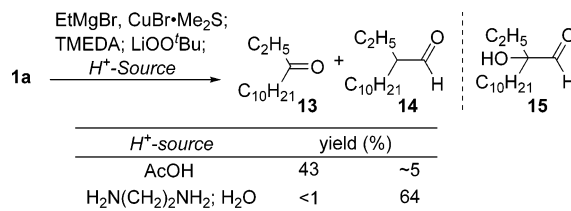
(13) Identifiable side products include trisubstituted olefin **I** (ca. 5%), vinyl bromide **II** (ca. 5%), and dimer **4** (ca. 10%). See also ref 14.



(14) Bromoaldehyde **11** was observed as a minor product (< 5%) in reactions leading to **9**, **10**, and **12**, as well as in the reaction described in Table 1, entry 1. *tert*-Butyl hypobromite is likely formed from oxidation of Br^- present in the reaction mixture.

(15) See Supporting Information for details.

Scheme 3



Oxidation of the vinyl copper intermediate could occur by direct addition to lithium *tert*-butyl peroxide. Alternatively, peroxide coordination to copper could precede an alkyl migration from Cu to O. Such a process would resemble the oxidation of alkyl boron and silicon compounds. The stereospecificity of the oxygenation undermines mechanistic proposals involving free radicals. Future efforts will aim to clarify the reaction mechanism with the anticipation that this understanding will aid efforts to expand the utility of the carbocupration/oxygenation method. Irrespective of mechanism, this transformation currently enables the direct synthesis of α -branched aldehydes and stereodefined enol derivatives. The latter hold promise as valuable reagents for asymmetric reductions, oxidations, and umpolung reactions.¹⁷

Acknowledgment. We acknowledge financial support from the NIGMS (GM074822) and UT Southwestern (J.M.R. is a Southwestern Medical Foundation Scholar in Biomedical Research). This investigation was conducted in a facility constructed with support from the Research Facilities Improvement Program Grant Number C06 RR-15437.

Supporting Information Available: Experimental procedures for carbo-oxygenation reactions. Spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) **Representative Procedure.** EtMgBr (0.48 mmol) was added dropwise to a suspension of $\text{CuBr}\cdot\text{Me}_2\text{S}$ (68 mg, 0.33 mmol) in ether (1 mL) and Me_2S (0.3 mL) at -45°C . The resulting yellow mixture was stirred at this temperature for 1 h, and then dodecyne (0.3 mmol) was added by syringe. The reaction flask was rinsed with ether (0.5 mL). After stirring at -25°C for 2.5 h, the resulting dark green solution was cooled to -78°C , and TMEDA (0.05 mL, 0.33 mmol) was added by syringe. After 1 h freshly prepared¹⁵ $^t\text{BuOOLi}$ (1.0 mmol in 2.0 mL THF) was added slowly along the wall of the reaction flask. Stirring was continued for 3 h at -78°C after which Ac_2O (0.3 mL, 3.0 mmol) was added. The reaction mixture was stirred at -78°C for 5 min and then allowed to warm to room temperature over 20 min. The suspension was diluted with ether and washed with saturated aqueous NaHCO_3 . The aqueous phase was extracted with ether. The combined organic phases were dried over Na_2SO_4 , concentrated, and purified by flash chromatography.