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Synthetic Methods |*Hot Paper*|

# A Sequential Homologation of Alkynes and Aldehydes for Chain Elongation with Optional $^{13}$C-Labeling

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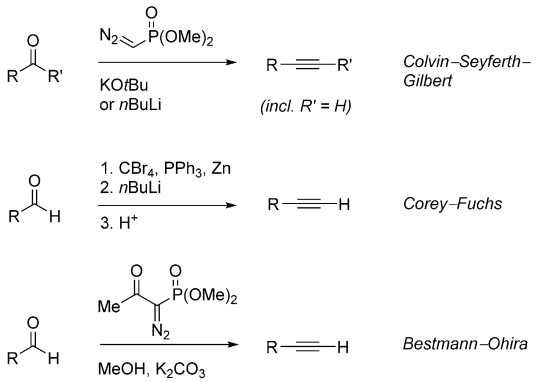
*Dedicated to Professor Antonio Togni on the occasion of his 60th birthday*

**Abstract:** Terminal alkynes (RCCH) are homologated by a sequence of ruthenium-catalyzed anti-Markovnikov hydration of alkyne to aldehyde ($RCH_2CHO$), followed by Bestmann–Ohira alkynylation of aldehyde to chain-elongated alkyne ($RCH_2CCH$). Inverting the sequence by starting from aldehyde brings about the reciprocal homologation of aldehydes instead. The use of $^{13}$C-labeled Bestmann–Ohira reagent (dimethyl ((1-$^{13}$C)-1-diazo-2-oxopropyl)phosphonate) for alkynylation provides straightforward access to singly or, through additional homologation, multiply $^{13}$C-labeled alkynes. The labeled alkynes serve as synthetic platform for accessing a multitude of specifically $^{13}$C-labeled products. Terminal alkynes with one or two $^{13}$C-labels in the alkyne unit have been submitted to alkyne–azide click reactions; the copper-catalyzed version (CuAAC) was found to display a regioselectivity of $>50\,000{:}1$ for the 1,4- over the 1,5-triazine isomer, as shown analytically by $^{13}$C NMR spectroscopy.

## Introduction

Homology is a fundamental concept in organic chemistry. The identification of homologous series (Gerhardt, 1843/44) of the formula H-$(CH_2)_n$-X (X = functional group; $n = 1, 2, 3,..$) created a basis for the development of structural theory.[1] *Homologation*, that is, the transformation of a starting material $R(CH_2)_nX$ into its next higher[2] homolog $R(CH_2)_{n+1}X$, is an important synthetic transformation that introduces flexibility in synthetic planning towards complex structures.[3] It also provides straightforward access to structural analogues of specific targets in structure–activity studies.[4,5] In the chemistry of alkynes, an important group of reactions named after Colvin–Seyferth–Gilbert,[6] Corey–Fuchs,[7] or Bestmann–Ohira[8,9] converts aldehydes RCHO into terminal alkynes RC≡CH,[9] providing a simple means of 1-carbon chain elongation (Scheme 1). Interestingly, the term homologation has been applied to some of those conversions, and apparently to any kind of carbon framework extending reactions,[10] even though they provide products with different functionality than the starting material, i.e., *heterologs*, in Gerhardt's terms. With the discovery of[11] and recent advances in catalytic anti-Markovnikov hydration of terminal alkynes to aldehydes,[12,13] terminal alkynes can now be regarded as synthetic equivalents or *masked forms* of aldehydes.[14] As a consequence, it should now be possible to realize true homologations of alkynes (in Gerhardt's sense) by applying a sequence of catalytic anti-Markovnikov hydration and either one of the aldehyde alkynylation methodologies mentioned (Scheme 1), and indeed, a single example has already been reported.[15,16]




**Scheme 1.** Important chain elongation methodology for converting aldehydes into terminal alkynes.

Here, we present a generally applicable process for the homologation of terminal alkynes that profits from very fast anti-Markovnikov hydration conditions (15–30 min). The potential of this synthetic methodology is reinforced by numerous examples of homologation and heterologation, and by its extension to a new approach of synthesizing specifically $^{13}$C-labeled building blocks. The $^{13}$C-labeled alkynes have also been used in click reactions ("$^{13}$Click"), for which it was shown that the $^{13}$C-label is a unique probe for quantitative analysis of even minor reaction products.

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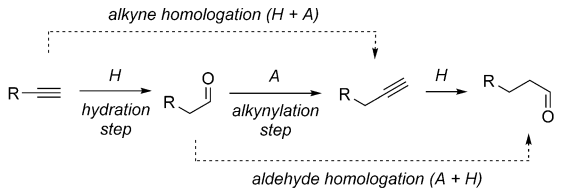
## Results and Discussion

The catalytic anti-Markovnikov hydration of a terminal alkyne yields an aldehyde. The reaction of an aldehyde with a suitable alkynylation reagent (Scheme 1) should give a product that is the next higher homolog of the original alkyne. If the homologous alkyne is again hydrated to an aldehyde, the latter is a homolog of the previous aldehyde; the methodology thus realizes *reciprocal homologation* for both alkynes and aldehydes (Scheme 2).[17]

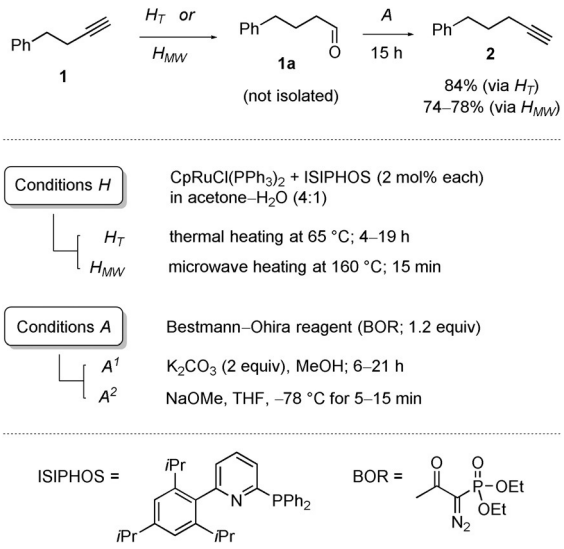
For a proof of concept, 4-phenyl-1-butyne (**1**) was hydrated by a catalyst formed in situ from $CpRuCl(PPh_3)_2$ and ISIPHOS,[18]




**Scheme 2.** Reciprocal homologation of alkynes and aldehydes by sequential anti-Markovnikov hydration of terminal alkynes and alkynylation of aldehydes.

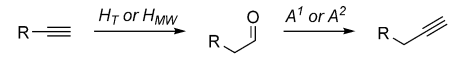
with heating either in an oil-bath ($H_T$), or by microwave irradiation ($H_{MW}$, Scheme 3).[12f] The intermediary aldehyde **1a** was alkynylated, without prior purification, by means of the Bestmann–Ohira protocol (Step A) to give homo-alkyne **2**. Microwave heating ($H_{MW}$) accelerates the hydration step considerably, rendering this two-step homologation a convenient 1 day operation.

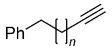
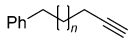
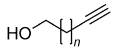
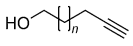
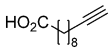
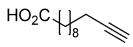
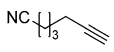
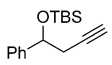
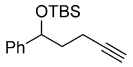
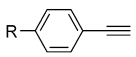
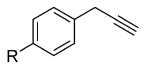
The generality of alkyne homologation by the $H_{MW}/A$-sequence was explored on a range of variably functionalized substrates, as shown in Table 1. The process is sufficiently reliable to allow for iterative sequential homologations of alkynes: thus, starting 4-phenyl-1-butyne (**1**) was extended consecutively by three $CH_2$-units to give 7-phenyl-1-heptyne (**4**) in 36% yield over six steps (entries 1–3), with some losses arising from the volatility of the materials. Another threefold iteration of alkynol **5** to **8** (entries 4–6) proceeds in 57% over six steps, with isolation of each alkynol. The homologation proceeded uneventfully with simple hydrocarbons (entries 1–3 and 7), and tolerated a range of functionality, including alcohol (entries 4–6), carboxylic acid (entry 8), nitrile (entry 9), TBS-ether (entry 10), or arene (entries 1–3, 11, and 12). Nitriles are known to reversibly inhibit the hydration catalyst,[12f] but substrate **13** could be successfully homologated in the usual short time by




**Scheme 3.** Realization of an alkyne–aldehyde–alkyne homologation. Reaction conditions for individual reaction steps, and structures of required reagents.

**Table 1.** Substrate scope of the homologation of terminal alkynes.[a,b]




| Entry | Substrate | Steps[a,b] | Product | Yield [%] |
|---|---|---|---|---|
| 1 |  **1** ($n=1$) | $H_{MW}+A^1$ |  **2** ($n=1$) | 75 |
| 2 | **2** ($n=2$) | $H_{MW}+A^1$ | **3** ($n=2$) | 69 |
| 3 | **3** ($n=3$) | $H_{MW}+A^1$ | **4** ($n=3$) | 71 |
| 4 |  **5** ($n=8$) | $H_T+A^1$ |  **6** ($n=8$) | 92 |
| 5 | **6** ($n=9$) | $H_T+A^1$ | **7** ($n=9$) | 78 |
| 6 | **7** ($n=10$) | $H_{MW}+A^1$ | **8** ($n=10$) | 80 |
| 7 |  **9** | $H_{MW}+A^1$ |  **10** | 85 |
| 8 |  **11** | $H_{MW}+A^1$ |  **12** | 76 |
| 9 |  **13** | $H_{MW}$[c]$+A^1$ |  **14** | 70 |
| 10 |  **15** | $H_{MW}$[c]$+A^1$ |  **16** | 80 |
| 11 |  **17** (R = *n*Pr) | $H_{MW}+A^2$ |  **18** (R = *n*Pr) | 65 |
| 12 | **19** (R = *t*Bu) | $H_{MW}+A^2$ | **20** (R = *t*Bu) | 72 |

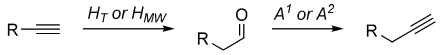
[a] Conditions for anti-Markovnikov hydration (step *H*): $CpRuCl(PPh_3)_2$ (2 mol%), ISIPHOS (2 mol%), acetone/$H_2O$ (4:1). $H_{MW}$: microwave heating, 160 °C, 15 min. $H_T$: thermal heating, 65 °C, 4–19 h. [b] Conditions for alkynylation: Method $A^1$: BOR (1.2 equiv), $K_2CO_3$ (2 equiv), MeOH, rt, overnight; Method $A^2$: BOR (1.2 equiv), NaOMe (1.2 equiv), THF, −78 °C, 20 min, addition of aldehyde, 5 min at −78 °C, 30 min at rt. [c] Catalyst loading 4 mol%.

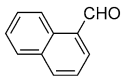
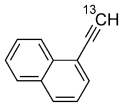
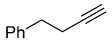
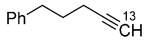
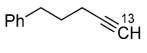
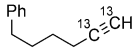
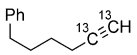
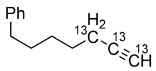
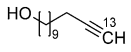
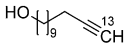
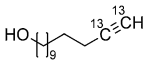
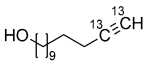
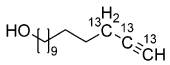
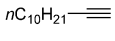
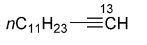
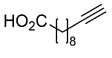
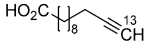
applying a slightly higher catalyst loading, and microwave heating conditions (entry 9).

Plain homologation of alkynes is valuable in its own right, but we wished to extend its synthetic potential further by introducing $^{13}$C-labeled Bestmann–Ohira reagent ($^{13}$C-BOR) for the chain-elongation step, which should give straightforward access to terminally $^{13}$C-labeled alkynes.[19] The reagent $^{13}$C-BOR was prepared from $^{13}CH_3I$ through Michaelis–Arbuzov reaction,[20] Claisen-type phosphonate acylation,[21] and diazo-transfer ($p$TsN$_3$, NaH),[22] by following procedures optimized with nonlabeled reagents (Scheme 4).

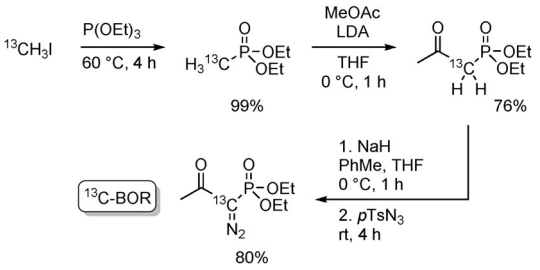
Use of $^{13}$C-BOR in the direct synthesis of a terminally $^{13}$C-labeled alkyne was first tested with a commercially available aldehyde as starting material (Table 2, entry 1). The labeling technique was next incorporated into the homologation sequence

**Table 2.** Synthesis of $^{13}$C labeled targets through homologation with $^{13}$C-BOR.[a]




| Entry | Substrate | Steps[a] | Product | Yield [%] |
|---|---|---|---|---|
| 1 |  **21** | $A^1$ |  **22** | 80 |
| 2 |  **1** | $H_{MW}+A^1$ |  (1-$^{13}$C)-**2** | 79 |
| 3 |  (1-$^{13}$C)-**2** | $H_{MW}+A^1$ |  (1,2-$^{13}C_2$)-**3** | 81 |
| 4 |  (1,2-$^{13}C_2$)-**3** | $H_{MW}+A^1$ |  (1,2,3-$^{13}C_3$)-**4** | 76 |
| 5 |  **5** | $H_{MW}+A^1$ |  (12-$^{13}$C)-**6** | 92 |
| 6 |  (12-$^{13}$C)-**6** | $H_{MW}+A^1$ |  (12,13-$^{13}C_2$)-**7** | 91 |
| 7 |  (12,13-$^{13}C_2$)-**7** | $H_{MW}+A^1$ |  (12,13,14-$^{13}C_3$)-**8** | 74 |
| 8 |  **9** | $H_{MW}+A^1$ |  (1-$^{13}$C)-**10** | 78 |
| 9 |  **11** | $H_{MW+}A^1$ |  (12-$^{13}$C)-**12** | 69 |

[a] See Table 1 for definition of the reaction conditions.




**Scheme 4.** Synthesis of (1-$^{13}$C)-diethyl (1-diazo-2-oxopropyl)phosphonate.

where it indeed provided versatile access to a variety of 1-$^{13}$C-labeled alkynes (Table 2, entries 2–9).

The iterative approach allows for inclusion of additional $^{13}$C-labels into the growing alkyl chain; this was explored for non-functionalized alkyne **1** as well as for alkynol **5**, which were both taken through a threefold iterative hydration–alkynylation–sequence to give either mono-labeled **2** or **6**, di-labeled **3** or **7**, and finally tri-labeled **4** or **8**, respectively (entries 2–4, or 5–7, respectively). A region of a $^{13}C\{^1H\}$ NMR spectrum of a triply labeled alkyne from a threefold iteration sequence with $^{13}$C-BOR, displaying characteristic ABC-coupling patterns is shown in Figure 1.

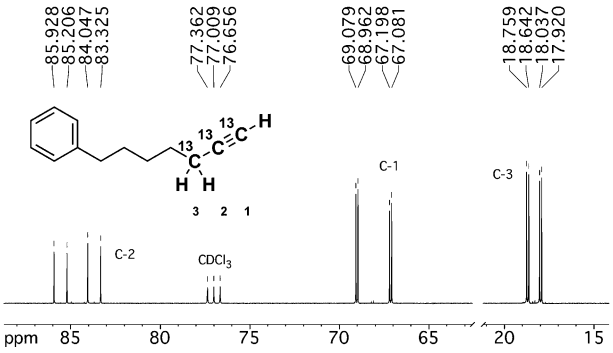
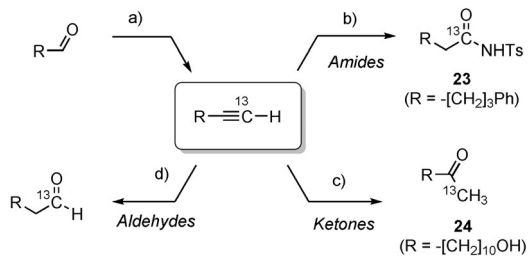
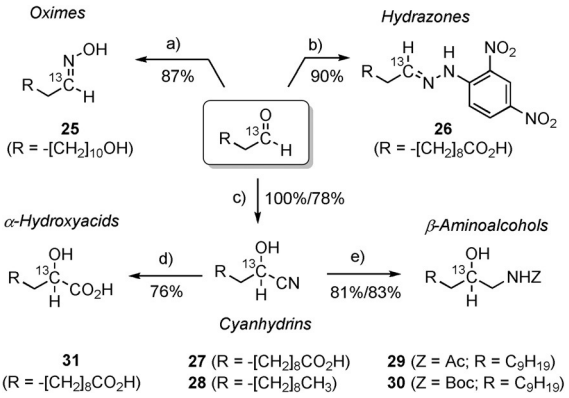



**Figure 1.** Two regions from the $^{13}C\{^1H\}$ NMR spectrum ($CDCl_3$, 91 MHz) of (1,2,3-$^{13}C_3$)-**4**.

With the straightforward and general access to $^{13}$C-labeled alkynes, a versatile synthetic platform for obtaining specifically labeled products of variable functionality can be established, as exemplified by the selected catalytic follow-up functionalization reactions of labeled alkynes presented in Scheme 5:




**Scheme 5.** Labeled alkynes as synthetic platforms: a) Table 2; b) $TsN_3$, CuI (cat.), $NEt_3$, $H_2O$, $CHCl_3$;[23] c) $NaAuCl_4$ (cat.), MeOH/$H_2O$ (10:1);[24] d) Table 2.

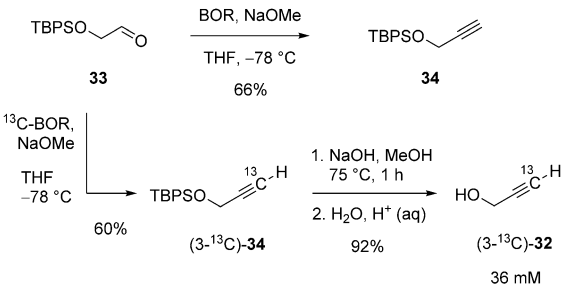



**Scheme 6.** Use of 1-$^{13}$C-labeled aldehydes as synthetic platform. a) $NH_2OH{\cdot}HCl$, NaOAc, $EtOH/H_2O$. b) 2,4-Dinitrophenylhydrazine, *p*TsOH, $CH_2Cl_2$. c) KCN, AcOH, MeOH. d) HCl conc. aq, 5 h, 115 °C. e) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, $Ac_2O$ or $Boc_2O$.[25] Boc = *t*BuOCO.

Among the products, $^{13}$C-labeled aldehydes (Scheme 5, d) can serve as starting materials in a whole array of follow-up reactions. Examples of variously functionalized labeled products, which have thus been obtained, are presented in Scheme 6.

The starting aldehydes in Scheme 6 were derived from microwave catalytic anti-Markovnikov hydration ($H_{MW}$) of the corresponding alkyne in less than 30 min and used in the next steps without purification. This procedure considerably extends the range of products available from the synthetic platform based on labeled or nonlabeled alkynes.

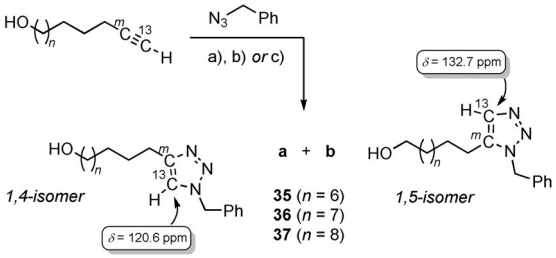
As is now established, reactions of aldehydes with $^{13}$C-BOR to give $^{13}$C-labeled terminal alkynes (cf. Table 2) render the latter readily available products. The starting aldehydes in such syntheses may come from various other sources besides anti-Markovnikov hydration of alkynes. For a specific project, in which a propargyl alcohol-derived alkyne linker was desired, we planned to access the previously unknown, specifically labeled (3-$^{13}$C)-propargyl alcohol ((3-$^{13}$C)-**32**). An evaluation of the synthetic options pointed to alkynylation of aldehyde **33**[26] as the most convenient access pathway (Scheme 7).




**Scheme 7.** Synthesis of (3-$^{13}$C)-propargyl alcohol ((3-$^{13}$C)-**32**).

Alkynylation of **33** under regular conditions (MeOH, $K_2CO_3$)[8] led to extensive desilylation of substrate and product. However, alkynylation at low temperature with stoichiometric base[19] gave the desired silyl ether **34**. Propargyl alcohol is a volatile, water-soluble compound of low molecular weight and its isolation as neat substance on millimolar scale was not attempted. Instead, precursor **34** was desilylated in hot methanolic sodium hydroxide and the solution thus obtained was neutralized with aqueous acid. After removal of silylated side-products by extraction with hexane, the concentration of product (3-$^{13}$C)-**32** was determined by $^1$H NMR spectroscopic analysis against an internal standard. The stock solution was then kept and used directly for further experiments.

Having access to $^{13}$C-labeled terminal alkynes inspired us to use them in 1,3-dipolar cycloadditions of the CuAAC[27] and RuAAC[28] type "$^{13}$Click" chemistry,[29] so to speak (Scheme 8).[30]




| Condition | *n* | $^m$C | yield | product | ratio **a** : **b** |
|---|---|---|---|---|---|
| a) thermal | 6 | $^{12}$C | 80% | **35** | 55 : 45 |
| b) CuAAC | 7 | $^{12}$C | 97% | **36** | 100 : 0 |
| c) RuAAC | 7 | $^{12}$C | 89% | **36** | 2 : 98 |
| b) CuAAC | 8 | $^{13}$C | 99% | **37** | 100 : 0 |
| c) RuAAC | 8 | $^{13}$C | 79% | **37** | 3 : 97 |

**Scheme 8.** $^{13}$Click reactions. Reaction conditions: a) toluene, 115 °C, 120 h; performed with unlabeled alkynol **5**. b) CuI (2 mol%), *i*$Pr_2$NEt (4 mol%), AcOH (4 mol%), $CH_2Cl_2$, rt, 2 d.[31] c) Cp*RuCl($PPh_3$)$_2$ (3 mol%), dioxane, 60 °C, 17 h.[28]

Thermal cycloaddition of alkynol **5** to benzyl azide proceeded slowly even upon heating, to give a mixture of regioisomers **35a**/**b** in roughly equal amounts. The reaction of alkynol (12-$^{13}$C)-**6** with benzyl azide in the presence of a copper catalyst[31] produced an almost quantitative yield of 1,4-substituted 1,2,3-triazole **36a** at room temperature, whereas ruthenium catalysis gave 1,5-substituted triazole **36b** in high, albeit imperfect regioselectivity (Scheme 8).[32] Metal-catalyzed click reactions were also performed with doubly labeled starting material (12,13-$^{13}C_2$)-**7** to give ($^{13}C_2$)-**37a** or ($^{13}C_2$)-**37b**, depending on the catalyst used. Labeled click adducts could be suitable materials for use in mass-spectrometric tagging, or as internal standards in SIM-GC-MS. The $^{13}$C-label also allows for specific and sensitive detection by NMR spectroscopy. As a first application example thereof, we analyzed the regioselectivity of click reactions quantitatively: monitoring of the minor regioisomer **36a** of the RuAAC reaction mixture next to the major component **36b** was particularly simple by $^{13}$C{$^1$H} NMR spectroscopy, for which the isomers display well-resolved, sharp signals for the labeled carbons. Even though $^1$H NMR spectroscopy is considerably more sensitive, it proved to be less suitable for analyzing product ratios in a ratio of $\geq$100:1, due to the narrow spectral range, signal splitting by homonuclear coupling, and by overlap of minor component signals with $^{13}$C satellites or impurities.

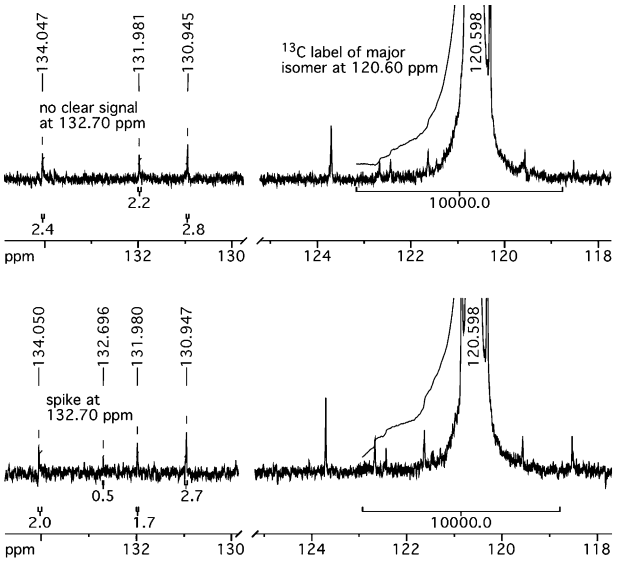



**Figure 2.** Excerpt of the $^{13}C\{^1H\}$ NMR (cryo-probe, 126 MHz, $CDCl_3$, 1024 scans, d1 = 4 sec) spectrum of a CuAAC reaction mixture (10 mg). Top: CuAAC reaction product. Peaks at $\delta = 134.05$, 131.98 and 130.95 ppm are from unidentified impurities. Bottom: same sample after spiking with 0.2 μg (1.3 μM) of 4-$^{13}$C-**36b**. The time required for each analysis was 140 min.

The CuAAC reaction is known to be highly regioselective,[27c] but we are not aware of any experimental detection of the regioisomeric ratio. Analysis of the CuAAC product **36a** (10 mg in 450 μL of $CDCl_3$) by $^{13}C\{^1H\}$ NMR analysis failed to show a peak for the labeled carbon of minor regioisomer **36b** (Figure 2, top).[33]

To define practical detection limits, the sample was spiked with minute amounts of RuAAC-product (4-$^{13}$C)-**36b**, and a clear-cut signal (*S*/*N* ratio > 4) of the latter could be seen even after addition of only 0.2 μg of material (Figure 2, bottom), placing a lower limit for the regioselectivity of the CuAAC reaction at 50,000:1. Additional spiking was performed to assure that the signal at 132.70 ppm was indeed due to **36b**.[34] Notably, 0.6 nmol of $^{13}$Click product was readily detected under the conditions of this experiment, at a concentration of 1.3 μM.

## Conclusion

The reciprocal, iterative homologation of alkynes and aldehydes has been established as a process of considerable synthetic potential. The majority of preparative examples presented have been carried out as alkyne homologations, rather than aldehyde homologations, because aldehydes typically have limited shelf-live and are not preferred intermediates for storage. Nevertheless, the process presents a complementary alternative to Levine's aldehyde homologation with $Ph_3P{=}CHOMe$,[17] which requires an enol ether hydrolysis under strongly acidic conditions.

Terminal alkynes RC≡CH can be considered storable forms for aldehydes $RCH_2CHO$, because the former are readily converted into the latter in less than 30 min by following the microwave catalytic anti-Markovnikov hydration protocol.[12f]

Inclusion of $^{13}$C-labeled Bestmann–Ohira reagent (BOR) into the alkyne homologation sequence gives direct access to specifically $^{13}$C-labeled alkynes. By suitable synthetic elaboration, almost any desired $^{13}$C-labeled aliphatic chain compound should be accessible through this route. The $^{13}$C-labeled alkynes are useful in their own right as tools for mechanistic studies, or as substrates in $^{13}$Click reactions. Those click reactions may prove useful for applications involving tagging techniques in mass-spectrometric analysis.

## Experimental Section

### Synthesis

Homologation of **19** to **20** is described as an example; general procedures and complete experimental details with characterization data and NMR spectra can be found in the Supporting Information.

**Microwave-assisted anti-Markovnikov hydration of 19, and Bestmann–Ohira alkynylation to 20**: Catalytic anti-Markovnikov hydration was carried out by using the microwave heating protocol.[12f] To a 10 mL microwave reaction vessel equipped with a stirring bar, $CpRuCl(PPh_3)_2$ (7.3 mg, 0.01 mmol, 2 mol%), ISIPHOS (4.7 mg, 0.01 mmol, 2 mol%), degassed acetone (1.5 mL), degassed $H_2O$ (375 μL), and alkyne **19** (79.1 mg, 0.50 mmol) were added under argon. After capping of the vessel, the mixture was heated in the microwave reactor to 160 °C with magnetic stirring for 15 min. After cooling to RT, the reaction mixture was diluted with $Et_2O$ (30 mL) and saturated aqueous NaCl (30 mL). The phases were separated, the aqueous phase was extracted with $Et_2O$ (3 × 40 mL), and the combined organic phases were washed with saturated aqueous NaCl (40 mL). After drying ($MgSO_4$), filtration, and evaporation under reduced pressure, the crude aldehyde was dissolved in THF (4.0 mL). In a separate Schlenk flask, NaOMe (1.0 M in MeOH, 0.60 mL, 1.2 equiv) was added dropwise to a cooled (−78 °C) solution of BOR (132 mg, 0.60 mmol, 1.2 equiv) in anhydrous THF (6.0 mL) under argon. After stirring the mixture for 15 min at −78 °C, the aldehyde solution was added slowly to the Schlenk flask, and the reaction mixture was stirred and warmed from −78 °C to RT. After dilution with *t*BuOMe (10 mL) and saturated aqueous $NH_4Cl$ (10 mL), the aqueous phase was extracted with *t*BuOMe (3 × 15 mL) and the combined organic phases were washed with saturated aqueous $NH_4Cl$ (20 mL). After drying ($MgSO_4$), filtration, and evaporation under reduced pressure, the residue was purified by column chromatography ($SiO_2$; pentane) to give 1-(*tert*-butyl)-4-(2-propyn-1-yl)benzene (**20**; 62.5 mg, 0.36 mmol, 72%) as a colorless oil. Known compound, CAS 70090–67–4. $R_f = 0.47$ ($Et_2O$/pentane, 1:50); $^1$H NMR (360 MHz, $CDCl_3$): $\delta =$ 1.31 (s, 9H; *t*Bu), 2.16 (t, $^3J(H,H) = 2.7$ Hz, 1H; H-1), 3.57 (d, $^3J(H,H) =$ 2.7 Hz, 2H; H-3), 7.27–7.37 ppm (m, 4H; ArH); $^{13}$C NMR (91 MHz, $CDCl_3$): $\delta = 24.5$, 31.5, 34.6, 70.3, 82.4, 125.7, 127.7, 133.2, 149.8 ppm.

**Keywords:** alkynes · click chemistry · homogeneous catalysis · ruthenium · synthetic methods

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[33] Only extractive workup was applied to the CuAAC reaction mixture, but neither chromatography nor crystallization, which might have removed the minor isomer.

[34] See the Supporting Information for experimental details.

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