A Novel Copper(II)/Tin(II) Reagent for Regio- and Chemoselective Carbonyl Propargylation

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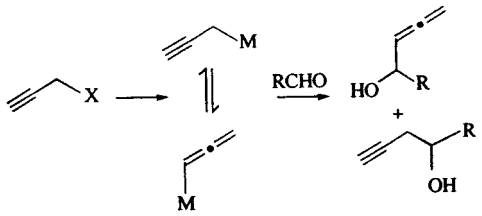
A convenient and synthetically attractive protocol for the regioselective synthesis of homopropargyl alcohols from aldehydes and 2-propynyl halides having terminal alkynes under the aegis of catalytic cupric bromide and stannous chloride in THF is described. In-situ probing by ^{1}H NMR and MIKE-CID spectrum provides evidence for the copper(I)-catalyzed formation of allenyltrihalostannane.

Introduction

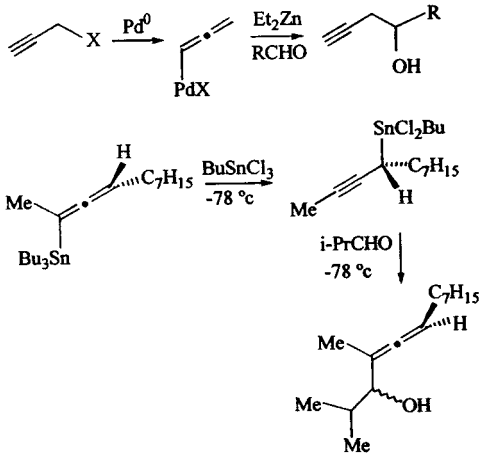
By virtue of their synthetic usefulness and mechanistic intrigue, organic reactivities of propargyl and allenyl organometallics have received considerable attention in the past two decades.[1] These reagents, like their allylic counterpart, can be generated by Grignard, as well as Barbier, methodologies.[2] The metallotropic rearrangement[3] between propargyl and allenyl organometallics often result in poor regioselection in the end organic product, for example in the case of reaction with carbonyl compounds and other electrophiles (Scheme 1). Hence, a pertinent synthetic challenge is to tune the regioselectivity toward either acetylenic or allenic species. In this context the synthesis of homopropargyl alcohols by the umpolung approach from propargylpalladium described by Tamaru et al. and the synthesis of homoallenyl alcohols from transient propargylic stannanes reported by Marshall et al. are noteworthy (Scheme 2).[4]

Our recent success in a Cu(II)/Sn(II)-promoted carbonyl allylation reaction[5] prompted us to explore the further utility of this reagent for carbonyl propargylation. To our delight, we could harness 100% regioselective syntheses of homopropargyl alcohols from 2-propynyl halides and various aldehydes (Scheme 3). Much to our surprise, we noted that the reaction is unusually chemoselective for a halide bearing a terminal alkyne in preference to an internal alkyne.

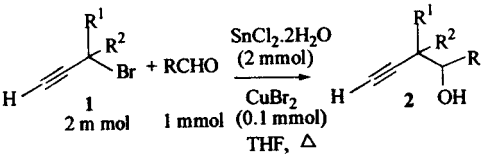
Scheme 1



Scheme 2



Scheme 3



Results and Discussion

The reaction of stannous chloride dihydrate with 2-propynyl bromide **1** in the presence of catalytic cupric bromide in refluxing THF after 4 h gave rise to the

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(1) For review see: (a) Yamamoto, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U.K., 1991; Vol. 2, pp 81−98. (b) Panek, J. S. In *Comprehensive Organic Synthesis*; Schreiber, S. L., Ed.; Pergamon: Oxford, U.K., 1991; Vol. 1, p 595 and references therein.

(2) (a) Cabezas, J. A.; Alvarez, L. X. *Tetrahedron Lett.* **1998**, *39*, 3935 and references therein. (b) Tanaka, H.; Hamatani, T.; Yamashita, S.; Torii, S. *Chem. Lett.* **1986**, 1461. (c) Dabdoub, J. M.; Totta, J. C. G. *Synlett* **1996**, 526. (d) Larock, R. C.; Chow, M.-S. *Tetrahedron Lett.* **1984**, *25*, 2727. (e) Issac, M. B.; Chan, T.-H. *J. Chem. Soc., Chem. Commun.* **1995**, 1003.

(3) (a) Doherty, S.; Corrigan, J. F.; Carty, A. J.; Sappa, E. *Adv. Organomet. Chem.* **1995**, *37*, 39. (b) Wojicicki, A. *New. J. Chem.* **1994**, *18*, 61. (c) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589. (d) Ogoshi, S.; Fukunishi, Y.; Tsutsumi, K.; Kurosawa, H. *J. Chem. Soc., Chem. Commun.* **1995**, 2485. (e) Hoffmann, R. W.; Lanz, J.; Metternich, R.; Tarava, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1145.

(4) (a) Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, M.; Kimura, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 878. (b) Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550.

(5) Kundu, A.; Prabhakar, S.; Vairamani, M.; Roy, S. *Organometallics* **1997**, *16*, 4796.

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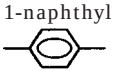
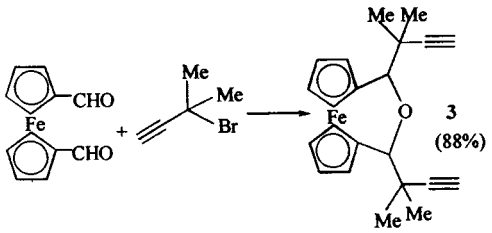
Table 1. Propargylation[a] of Aldehydes RCHO with 2-Propynyl Bromides HC≡CC(R¹R²)Br

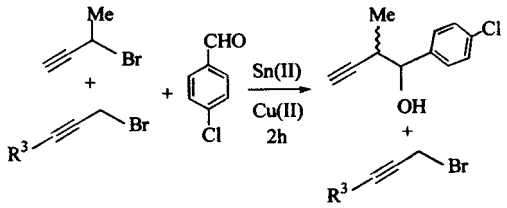
entry	R^1	R^2	R	time (h)	yield[b] (%)
1	H	H	4-chlorophenyl	4	55
2			cinnamyl	3	48
3	H	Me	1-naphthyl	2	85[c]
4				2	90[d]
5	Me	Me	4-chlorophenyl	4	90
6			benzyl	8	75
7				6	78
8			ferrocenyl	5	70
9		$-CH_2(CH_2)_3CH_2-$ [e]	piperonyl	24[f]	53
10	Me	Et	4-chlorophenyl	6	72
11			2-furyl	16[f]	48
12			ferrocenyl	5	55

[a] Unless otherwise stated all reactions were carried out in refluxing THF. [b] Isolated yields after chromatography based on aldehydes. [c] Syn:anti = 30:70. [d] Syn:anti = 45:55. [e] Chloride instead of bromide was used. [f] Reaction at room temperature.

Scheme 4



Scheme 5



(R^3 = Me, Ph)

desired homopropargyl alcohol **2** in 55% isolated yield. The reaction proceeds well with cuprous bromide also.[6] THF was found to be a better solvent in comparison to THF−H_2O, DCM, and DCM−H_2O. On the other hand, reaction without cupric bromide showed <10% conversion. This is not surprising, since propargyl bromides cannot be activated by $SnCl_2$ alone. Previous studies[7] have showed that stoichiometric excess of iodide ion can facilitate such activation; however, in most cases a mixture of homoallenyl and homopropargyl alcohols is obtained. We could extend this attractive homopropargylation reaction to a variety of 2-propynyl bromides bearing terminal alkynes and to various aldehydes (aliphatic, aromatic, vinylic, and ferrocenyl) leading to good to excellent yields of the corresponding alcohols (Table 1). Reactions could be conducted even at room temperature for reactive aldehydes (Table 1, entries 9 and 11). Interestingly, ferrocene-1,1′-bis(carboxaldehyde) gave exclusively the cyclic ether **3** from the intramolecular dehydration of the parent diol (Scheme 4).

However, reactions of 2-propynyl bromides bearing substitution at the 3-position (R^3-C≡CCH_2Br; R^3 = Me, Ph, TMS) fail.[8] In a control experiment (Scheme 5) the reaction of 4-chlorobenzaldehyde (1 mM) with a mixture of 1-methyl-2-propynyl bromide (1.5 mM) and 1-bromo-2-butyne (1.5 mM) after 2 h afforded exclusively 1-(4-chlorophenyl)-2-methyl-3-butyn-1-ol (isolated yield 0.6 mM) along with unreacted 1-bromo-2-butyne (vide GC). A similar reaction with a mixture of 1-methyl-2-propynyl bromide (1.5 mM) and 1-(3-bromo-1-propynyl)benzene (1.5 mM) after 2 h afforded exclusively 1-(4-chlorophenyl)-2-methyl-3-butyn-1-ol (isolated yield 0.65 mM) along with unreacted 1-(3-bromo-1-propynyl)benzene (isolated yield 1.2 mM). Such chemoselectivity is rather interesting and is hoped to offer innovative usage in organic synthesis. As described later, we believe that the origin of such selectivity lies in the "copper effect".

The highly selective homopropargylation reaction described in this work gains significance when compared to (a) the generation of allenyl-/propargyltin from propagyl halides and (b) the reactivity of such organometallic species toward carbonyl compounds. The existing literature suggests[1,2] that depending on the structure of the parent halide and the reaction condition, either allenyl- or propargyltin species can be synthesized. For example, diallenyltin dibromide is synthesized from the reaction of 2-propynyl bromide with Sn/Al, whereas under nearly similar condition 3-trimethylsilyl-2-propynyl bromide afford the corresponding dipropargyltin diiodo derivative.[9] McClusky et al. have shown similar behavior in the synthesis of either tetraallenyl- or tetrapropargyltin.[10] The allenyltin species when reacted with carbonyl compound is expected to give rise to corresponding homopropargyl alcohol via a S_E2' pathway and vice versa. However, in general[7,9−11] the reactions invariably afford a mixture of homoallenyl and homopropargyl compounds except in certain circumstances such as very low temperature, rapid addi-

(6) Imai et al. showed one example of the reaction of benzaldehyde with propargyl bromide in the presence of stannous chloride, cuprous bromide, and 30% aqueous ammonium fluoride resulting in a mixture of homopropargyl and homoallenyl alcohols (96:4, 61% isolated yield): Imai, T.; Nishida, S. *J. Chem. Soc., Chem. Commun.* **1994**, 277.

(7) (a) Houllemare, D.; Outurquin, F.; Paulmier, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1629. (b) Iyoda, M.; Kanao, Y.; Nishizaki, M.; Oda, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3380. (c) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 621. (d) Very recently Masuyama et al. have shown an interesting variation in product selectivity by varying the stannous halide, tetrabutylammonium halide, and solvent: Masuyama, Y.; Ito, A.; Fukuzawa, M.; Terada, K.; Kurusu, Y. *J. Chem. Soc., Chem. Commun.* **1998**, 2025.

(8) Extended refluxing for 48 h causes significant decomposition leading to a messy mixture of unidentified products.

(9) Nokami, J.; Tamaoka, T.; Koguchi, T.; Okawara, R. *Chem. Lett.* **1984**, 1939.

(10) McCluskey, A.; Muderawan, W.; Muntari; Young, D. J. *Synlett* **1998**, 909.

(11) Wilson, S. R.; Guazzaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087.

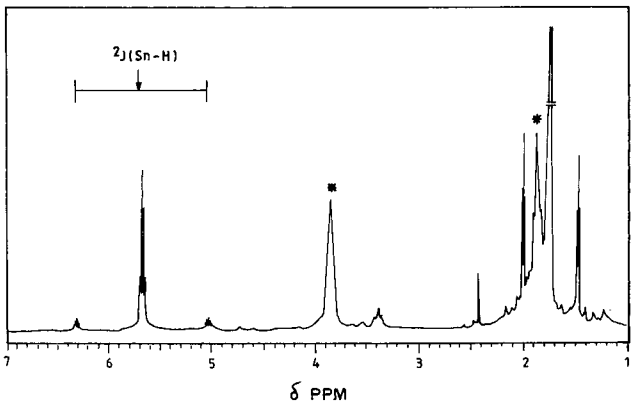


Figure 1. In-situ ^{1}H NMR spectra in $CDCl_3$ of 1,1-dimethyl-2-propynyl bromide/stannous bromide/catalytic cupric bromide. Asterisks indicate coordinated THF. For details see the text.

tion of carbonyl compounds, and TFA or $BF_3{\cdot}OEt_2$ catalyzed reactions. Taking evidence from other organometallic systems,[1,3] it may be inferred that metallotropic rearrangement between allenyl- and propargyltin may be responsible for the generally observed nonregioselectivity in carbonyl addition reactions. In light of this, we attempted to probe the organotin species in-situ by ^{1}H NMR and by mass spectroscopy.

A mixture of 1,1-dimethyl-2-propynyl bromide (4 mM), stannous bromide[12] (2 mM), and cupric bromide (0.1 mM) in THF (3 mL) was refluxed for 3 h giving rise to a nearly homogeneous solution. After removal of solvent, the oily residue was kept under vacuum at 0.1 Torr for 14 h, dissolved in chloroform-*d*, and subjected to NMR analysis. Barring peaks due to coordinated THF, the spectrum (Figure 1) distinctly showed the formation of an allenyltin species having signals at 5.68 ppm [$^2J(^{119}Sn-^1H) = 263$ Hz and $^2J(^{117}Sn-^1H) = 251$ Hz] due to the allenic proton and at 1.75 ppm [$J(^{119}Sn-^1H) = 107.5$ Hz and $J(^{117}Sn-^1H) = 102$ Hz] due to methyl protons.[13,14]

To ascertain the exact species, we directly injected the THF solution, prepared as above, into the mass spectrometer probe. EIMS spectrum.[15] (Figure 2) showed peaks at 67 ($C_5H_7^+$), 199 ($SnBr^+$), 278 ($SnBr_2^+$), 359 ($SnBr_3^+$), 426 ($C_5H_7SnBr_3^+$), and 438 ($SnBr_4^+$). The structure of the ion at *m/z* 426 is confirmed as $C_5H_7-SnBr_3$ on the basis of its metastable ion spectrum derived from collision-induced dissociation (CID).[16] The CID spectrum (Figure 3) of the ion at *m/z* 426 gave

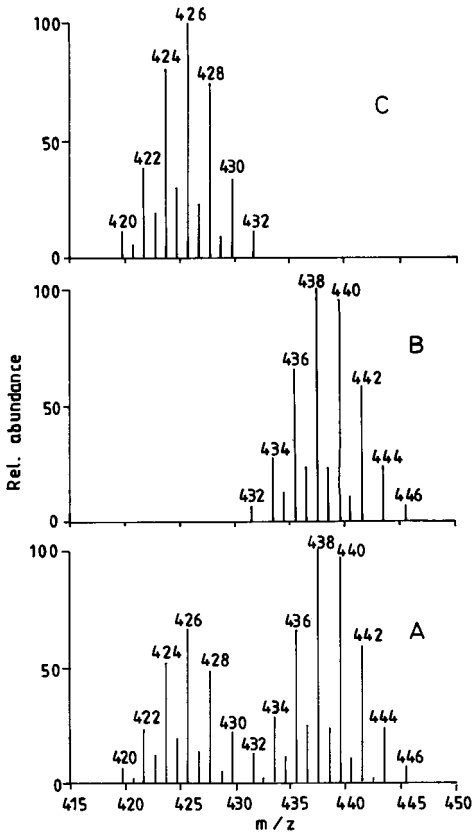


Figure 2. (A) In-situ EIMS spectra of 1,1-dimethyl-2-propynyl bromide/stannous bromide/catalytic cupric bromide in THF showing a mixture of $C_5H_7SnBr_3$ and $SnBr_4$ in 40:60 ratio. (B) Simulated spectra of $SnBr_4$. (C) Simulated spectra of $C_5H_7SnBr_3$.

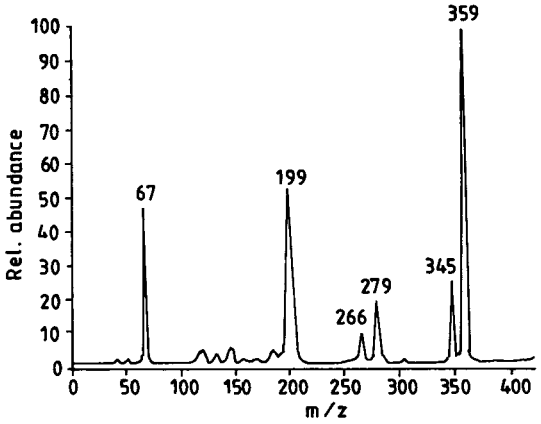


Figure 3. MIKE-CID spectrum of $C_5H_7SnBr_3$.

predominantly the ions corresponding to $SnBr_3^+$, $C_5H_7-SnBr_2^+$, $SnBr_2^+$, $C_5H_7SnBr^+$, $SnBr^+$, and $C_5H_7^+$. The NMR and MS studies, therefore, confirm the exclusive formation of allenyltrihalotin in the present reaction.

Keeping in mind the *profound catalytic effect of copper halide* in the present carbonyl propargylation reaction, the nonreactivity of 1-substituted propargyl halides, and the NMR and MS results, we propose a copper(I)-assisted[17] allenylstannation mechanism (Scheme 6). Briefly the mechanism consists of prior activation of propargyl halide by Cu(I) followed by the umpolung of the propargylcopper(I) species **II** to the allenylcopper

(12) Stannous bromide was chosen in this study to overcome the complicacy due to halo exchange as observed in earlier investigation on carbonyl allylation studies: see ref 5.

(13) For NMR of allenyl and propargyl stannanes, see refs 9 and 4b.

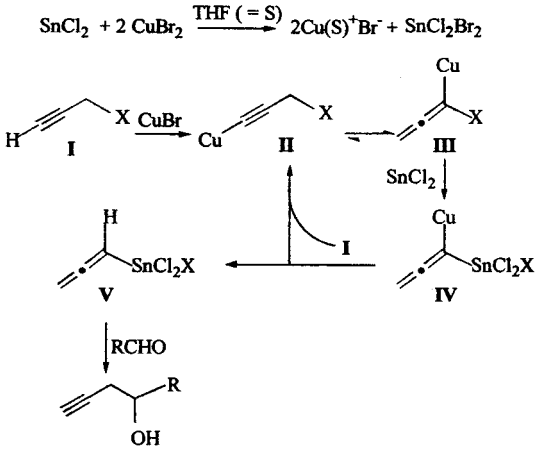
(14) Curiously, a similar experiment but in the absence of stannous halide after 24 h showed the formation of allenyl bromide. This is in accordance with earlier observation: Jacobs, T. L.; Petty, W. L. *J. Org. Chem.* **1963**, *28*, 1360.

(15) For organostannanes, EIMS is a more effective probe than FABMS: Harrison, P. G. *Chemistry of Tin*; Blackie: London, 1989; p 105.

(16) Metastable ion spectra can be used for structure elucidation. In this technique, the ion under study is selected and collided with a neutral gas, usually helium, to induce the decomposition of the ion. This leads to fragment ions formed exclusively from the selected ion. The resulting spectrum is called "mass-analyzed ion kinetic energy—collision-induced dissociation" or MIKE-CID spectrum: Chapman, J. R. *Practical Organic Mass Spectrometry*, 2nd ed.; John Wiley: New York, 1995; p 235.

(17) Cu(II) salts are easily reduced by Sn(II) halides: Nunes, T. L. *Inorg. Chem.* **1970**, *9*, 1325.

Scheme 6



intermediate **III**. Such umpolung route gains partial support from earlier proposals.[18]

Since stannous halide alone cannot mediate the present homopropargylation reaction, we, therefore, assume that intermediate **III** triggers the insertion of $SnCl_2$ into the activated carbon−halogen bond, resulting in the formation of a transient bimetallic intermediate **IV**. The catalytic cycle can be envisioned by the regeneration of intermediate **II** from **IV** with concomitant formation of allenyltrihalostannane **V**. To prove this conjecture, attempts are underway to trap intermediate of the type **IV** using a discrete copper(I) complex instead of a simple copper salt.

Summary

In this paper we have described a mild and efficient protocol for 100% regioselective carbonyl propargylation using readily available reagents. The chemoselectivity of the reaction toward 2-propynyl halides bearing a terminal alkyne adds a novel feature to this new reagent. Further examination using in-situ NMR, EIMS, and MIKE-CID probes suggest the exclusive formation of allenyltrihalostannane. While complete elaboration of the mechanism is being pursued, a rationalization based on umpolung of propargylcopper(I) to its allenyl counterpart and subsequent activation by stannous halide is proposed toward the formation of allenyltrihalostannane.

(18) Landor, P. D. In *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic Press: New York, 1982; Vol. 1, p 86.

Experimental Section

The general information regarding instruments and techniques is the same as mentioned in our earlier paper.[5] Substituted 2-propynyl bromides were prepared from the corresponding alcohols (Lancaster) using standard protocol. Stannous chloride dihydrate (Ranbaxy) and cupric bromide (Lancaster) were used as received. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use.

Typical Procedure for the Propargylation of Aldehydes. A mixture of 4-chlorobenzaldehyde (140 mg, 1 mM) and 2-propynyl bromide (238 mg, 2 mM) in dry tetrahydrofuran (2 mL) was slowly added to a stirred solution containing stannous chloride dihydrate (451 mg, 2 mM) and cupric bromide (22 mg, 0.1 mM) in THF (2 mL) and under nitrogen. The solution was refluxed for 4 h (TLC monitoring on silica gel; eluent, 1:9 v/v ethyl acetate/hexane) and then cooled to room temperature. Following addition of 15% aqueous ammonium fluoride solution (10 mL), the solution was extracted with diethyl ether (3 × 15 mL), washed with water (2 × 10 mL) and brine (2 × 10 mL), dried over magnesium sulfate, and concentrated under reduced pressure. Column chromatography (silica gel 60−120 mesh, Acme; eluent, 5:95 v/v ethyl acetate/hexane) afforded pure 1-(4-chlorophenyl)-3-butyn-1-ol as a light yellow oil (100 mg, 55% with respect to aldehyde).

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Supporting Information Available: A listing of NMR and mass spectral data of homopropargylic alcohols, along with figures showing in-situ NMR spectra, EIMS, and MIKE-CID mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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