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# Coupling of chiral 1-bromo-1,2-dienes with zinc-based cuprates: a new procedure for the regio and stereoselective synthesis of functionalized acetylenic compounds

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## Abstract

Zinc alkylcyanocuprates (Knochel reagents) are found to be active in the cross-coupling reaction with allenic bromides affording acetylenic products with a high regio and stereoselective 1,3-*anti* substitution. The coupling process, which has been successfully extended to functionalized cuprates, can also be performed with alkylzinc chlorides in the presence of catalytic amounts of cuprous salts.

*Keywords:* coupling reactions; copper; copper compounds; allenes; alkynes.

Few simple organic molecules are the object of more interest than acetylenes for molecular engineering work in organic and organometallic chemistry.[1] In particular, optically active 1-alkynes are often essential as versatile building blocks for the construction of more complex chiral molecules.[2]

In previous papers[3–6] we discussed utilization of enantioenriched 3-substituted and 3,3-disubstituted 1-bromo-1,2-dienes **1** as precursors of chiral 1-alkynes **2**, characterized by a tertiary or a quaternary stereogenic center in the α-position to the triple bond, via a cross-coupling reaction with bromocuprates $(RCuBr)MgBr{\cdot}LiBr$, obtained in THF from equimolar amounts of Grignard reagents and $LiCuBr_2$. The reaction proceeds in a highly 1,3-*anti* stereoselective fashion, but the regioselectivity appears to be sensitive to steric interactions at the reaction sites, the bulk of the *R* substituents in the copper species being the dominant factor. The acetylenic compounds **2** can be obtained in good yields (70–98%) independent of the structure of the allenic bromide only employing phenyl[3] or *n*-alkyl bromocuprates;[6] when tertiary, secondary or α-branched primary copper reagents are used, the competitive formation of allenic derivatives **3** can be favoured (Table 1).[6]

We report here new results that emphasize the dramatic improvement of our coupling methodology when cuprates based on organozinc derivatives are used.

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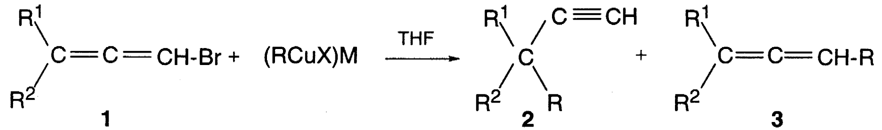
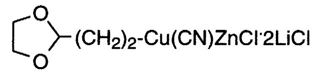
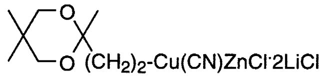
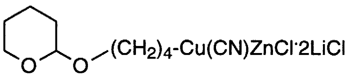
Table 1
Reaction of 1-bromo-1,2-dienes with organocuprates[a]



| Entry | 1 | R$^1$ | R$^2$ | (RCuX)M | T (°C) | t (h) | Yield % [b] 2 | Yield % [b] 3 |
|---|---|---|---|---|---|---|---|---|
| 1[c] | 1f | Me | Bu$^t$ | ($^n$BuCuBr)MgBr·LiBr | - 70 | 0.5 | 66 | 34 |
| 2 | 1f | Me | Bu$^t$ | $^n$BuCu(CN)ZnCl·2LiCl | 20 | 3 | 98 | 2 |
| 3[c] | 1f | Me | Bu$^t$ | ($^i$BuCuBr)MgBr·LiBr | - 70 | 0.5 | - | 100 |
| 4 | 1f | Me | Bu$^t$ | $^i$BuCu(CN)ZnCl·2LiCl | 20 | 18 | 98 | 2 |
| 5[c] | 1f | Me | Bu$^t$ | ($^i$PrCuBr)MgBr·LiBr | -70 | 0.5 | 2 | 98 |
| 6 | 1f | Me | Bu$^t$ | $^i$PrCu(CN)ZnCl·2LiCl | 20 | 18 | 90 | 10 |
| 7[c] | 1a | H | Me | ($^t$BuCuBr)MgBr·LiBr | - 70 | 0.5 | 9 | 91 |
| 8 | 1a | H | Me | $^t$BuCu(CN)ZnCl·2LiCl | 20 | 1 | 94 | 6 |
| 9 | 1b | H | $^t$Bu | $^t$BuCu(CN)ZnCl·2LiCl | 20 | 15 | 4 | 96 |
| 10[d] | 1c | H | Ph | (EtCuBr)MgBr·LiBr | 20 | 0.5 | 33 | 5 |
| 11 | 1c | H | Ph | EtCu(CN)ZnCl·2LiCl | - 70 | 1 | 100(73) | - |
| 12[d] | 1d | Me | Et | (PhCuBr)MgBr·LiBr | 20 | 0.5 | 75 | 23 |
| 13 | 1d | Me | Et | PhCu(CN)ZnCl·2LiCl | 20 | 1 | 41 | 45 |
| 14 | 1f | Me | $^t$Bu |  (CH$_2$)$_2$-Cu(CN)ZnCl·2LiCl | 20 | 18 | 100(75) | - |
| 15 | 1f | Me | $^t$Bu |  (CH$_2$)$_2$-Cu(CN)ZnCl·2LiCl | 20 | 18 | 80(64) | - |
| 16 | 1f | Me | $^t$Bu |  (CH$_2$)$_4$-Cu(CN)ZnCl·2LiCl | 20 | 18 | 100(78)[e] | - |
| 17 | 1f | Me | $^t$Bu | CH$_2$=CH-(CH$_2$)$_2$-Cu(CN)ZnCl·2LiCl | 20 | 2 | 100(85) | - |
| 18 | 1f | Me | $^t$Bu | Me$_3$Si-C≡C-(CH$_2$)$_2$-Cu(CN)ZnCl·2LiCl | 20 | 18 | 100(78)[f] | - |
| 19 | 1f | Me | $^t$Bu | ClMgO-(CH$_2$)$_3$-Cu(CN)ZnCl·2LiCl | 20 | 14 | 100(88)[g] | - |
| 20 | 1f | Me | $^t$Bu | ClMgO-(CH$_2$)$_4$-Cu(CN)ZnCl·2LiCl | 20 | 3 | 100(83)[g] | - |
| 21 | 1d | Me | Et | EtOCO-(CH$_2$)$_4$-Cu(CN)ZnBr·2LiCl | 70 | 3 | (62)[h] | - |

[a] All reactions were performed by treating the starting bromoallene with 2 equiv of the organocopper reagent in THF at -70°C and by allowing the reaction mixture to warm to 20° or 70°C. Unless otherwise noted, starting alkylzinc chlorides were prepared by transmetallation of the corresponding Grignard reagents with ZnCl$_2$.

[b] Determined by GLC of the reaction mixture after work-up (Isolated yields are shown in parentheses). All new compounds were identified and characterized by FTIR, NMR ($^1$H and $^{13}$C) and elemental analysis.

[c] See ref. 6.

[d] See ref. 3.

[e] As acetylenic carbinol after deprotection of the alcoholic function *via* acid-catalyzed transetherification in MeOH (20°C, 1h).

[f] As 1,6-heptadiyne after deprotection of the silylated acetylenic moiety with 1% KOH in EtOH (20°C, 5h) [Meyer, C.; Marek, I.; Courtemanche, G.; Normant, F. *J.Org.Chem.* **1955**, *60*, 863-871].

[g] As acetylenic carbinol. The starting Grignard reagent was obtained according to Cahiez, G.; Alexakis, A.; Normant, J.F. *Tetrahedron Lett.* **1978**, 3013-3014.

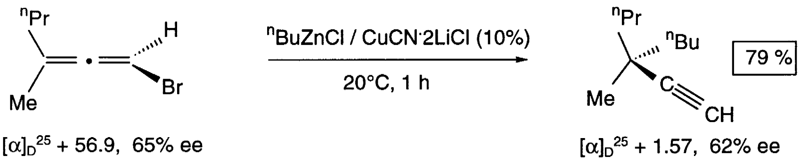
[h] The starting organozinc derivative was obtained from the corresponding bromide and highly activated zinc powder, prepared by a metal vapour technique [Klabunde, K.J.; Key, M.S.; Low, J.Y.F. *J.Am.Chem.Soc.* **1972**, *94*, 999-1000].

We have found that zinc cyanocuprates RCu(CN)ZnCl·2LiCl (Knochel reagents),[7] generated in THF at −10°C from alkylzinc chlorides and the soluble copper salt CuCN·2LiCl, react with bromoallenes **1** more slowly than the corresponding magnesium bromocuprates but afford acetylenes **2** with higher regioselectivity (Table 1). In this case, acetylenic products are obtained with a generally high yield even starting from hindered 3,3-disubstituted allenic substrates and secondary or α-branched primary copper compounds (entries 1–6); only when a tertiary group is bonded to the copper atom do the steric requirements of the substrate determine the product distribution (entries 8, 9). Interestingly, even with 3-phenyl-1-bromopropadiene, **1c**, zinc alkylcyanocuprates selectively afford 1-alkynes, while with bromocuprates substantial amounts of polymeric byproducts are obtained (entries 10, 11).[3] As an exception, it is noteworthy that the phenylbromocuprate (PhCuBr)MgBr·LiBr provides 3-phenyl-1-alkynes with a higher regioselectivity than the corresponding zinc-based cuprate (entries 12, 13).[3]

The zinc–cuprate procedure can be greatly extended to the preparation of a large variety of functionalized acetylenic systems. In fact, bromoallenes **1d** and **1f**, as hindered model substrates, have been converted in a regiospecific way into pure 1-alkynes by treatment with copper derivatives characterized by various functional groups (entries 14–21). In general, the necessary organozinc chlorides were prepared from the corresponding Grignard reagents by transmetallation with $ZnCl_2$ (entries 14–20). However, functionalized zinc derivatives can be directly obtained from organic halides with several methods[7] avoiding the use of protection–deprotection steps as well as functional group interconversions (entry 21).

Finally, the cross-coupling reaction can be done with zinc reagents using catalytic amounts of copper. Bromoallenes **1** react with alkylzinc chlorides in the presence of 5–10 mol% (relative to RZnCl) of CuCN·2LiCl, or some other cuprous salts, affording alkynes **2** with high chemo and regioselectivity (Table 2). The reaction rate is generally slow, especially increasing the steric requirements of both the reagent and the substrate, but increasing the reaction temperature can overcome this inconvenience (entries 28, 29).[8]

In all cases, carrying out the coupling process either with stoichiometric or catalytic zinc cuprates, the conversion of enantioenriched bromoallenes **1** into optically active acetylenic compounds **2** proceeds in a highly *anti* stereoselective fashion. Eq. (1) presents the stereochemical data[5] obtained in the preparation of (*S*)-3-methyl-3-propyl-1-heptyne from (*S*)-1-bromo-3-methyl-1,2-hexadiene via the copper catalyzed coupling.



(1)

In this context it is worthwhile noting that: (i) the reaction of bromoallenes with Grignard reagents in the presence of cuprous salts gives quantitatively the allenic derivatives **3** with complete inversion of the allenyl moiety;[6,9] (ii) the coupling of the same chiral substrates with organozinc chlorides promoted by nickel or palladium complexes also affords allenes but with almost complete loss of stereochemistry.[10]

## Acknowledgements

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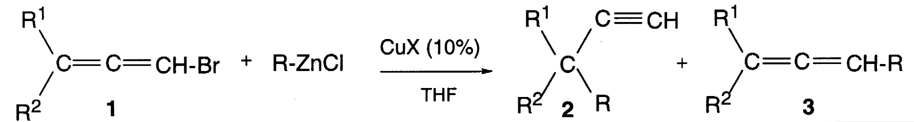
Table 2
Reaction of 1-bromo-1,2-dienes with organozinc compounds in the presence of cuprous salts[a]



| Entry | 1 | $R^1$ | $R^2$ | R | CuX | T (°C) | t (h) | Conv.[b] % | Yield %[b] 2 | 3 |
|---|---|---|---|---|---|---|---|---|---|---|
| 22 | **1e** | Me | $^n$Pr | $^n$Bu | $CuBr\cdot Me_2S$ | 20 | 1 | 89 | 96 | 4 |
| 23 | **1e** | Me | $^n$Pr | $^n$Bu | $LiCuBr_2$ | 20 | 1 | 92 | 97 | 3 |
| 24 | **1e** | Me | $^n$Pr | $^n$Bu | CuCN·2LiCl | 20 | 1 | 95 | 100 | - |
| 25 | **1e** | Me | $^n$Pr | $^i$Bu | CuCN·2LiCl | 20 | 15 | 100 | 98 | 2 |
| 26 | **1e** | Me | $^n$Pr | $^i$Pr | CuCN·2LiCl | 20 | 20 | 92 | 96 | 4 |
| 27 | **1b** | H | $^t$Bu | $^n$Bu | CuCN·2LiCl | 20 | 15 | 100 | 97 | 3 |
| 28 | **1f** | Me | $^t$Bu | $^n$Bu | CuCN·2LiCl | 20 | 15 | 77 | 95 | 5 |
| 29 | **1f** | Me | $^t$Bu | $^n$Bu | CuCN·2LiCl | 70 | 7 | 100 | 91 | 9 |
| 30 | **1d** | Me | Et | $ClMgO\text{-}(CH_2)_3$ | CuCN·2LiCl | 20 | 18 | 100 | 100(98) | - |
| 31 | **1c** | H | Ph | $ClMgO\text{-}(CH_2)_3$ | CuCN·2LiCl | 20 | 3 | 100 | 100(80) | - |
| 32 | **1d** | Me | Et | $ClMgO\text{-}(CH_2)_4$ | CuCN·2LiCl | 20 | 18 | 100 | 100(95) | - |
| 33 | **1c** | H | Ph | $CH_2{=}CH\text{-}(CH_2)_2$ | CuCN·2LiCl | 20 | 1 | 100 | 100(82) | - |

[a] All reactions were performed by treating the starting bromoallene with 2 equiv of the organozinc reagent in the presence of 10 mol% of cuprous salt (relative to RZnCl) in THF at -70°C and by allowing the reaction mixture to warm to 20° or 70°C.

[b] Determined by GLC of the reaction mixture after work-up (Isolated yields are shown in parentheses). All new compounds were identified and characterized by FTIR, NMR ($^1$H and $^{13}$C) and elemental analysis.

## References

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8. The following procedure for the preparation of 3-phenyl-6-hepten-1-yne is representative (Table 2, entry 33): 3-butenyl magnesium bromide 1.08N in THF (18 mmol) was added, at 0°C, to a stirred solution of $ZnCl_2$ (18 mmol) in THF (5 ml). The mixture was stirred for 30 min at room temperature, then treated, at −10°C, with a solution of 1.8 mmol of CuCN·2LiCl, prepared in THF (5 ml). Stirring was continued at 0°C during 30 min, then the reaction mixture was cooled at −70°C and 1-bromo-3-phenylpropadiene **1c** (1.80 g, 9 mmol) was added over a period of 5 min. The cooling bath was removed and the mixture was allowed to warm to 20°C and monitored for completion by GLC. Upon completion (1 h), the reaction was quenched with saturated ammonium chloride. Standard ethereal work-up and bulb-to-bulb distillation ($10^{-2}$ mmHg) provided the pure ene–yne (1.20 g, 82%) characterized by spectral and analytical data.
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