The Copper(I)-catalysed Coupling of Grignard Reagents with 5-Lithio-2,3-dihydrofuran and 6-Lithio-3,4-dihydro-2*H*-pyran

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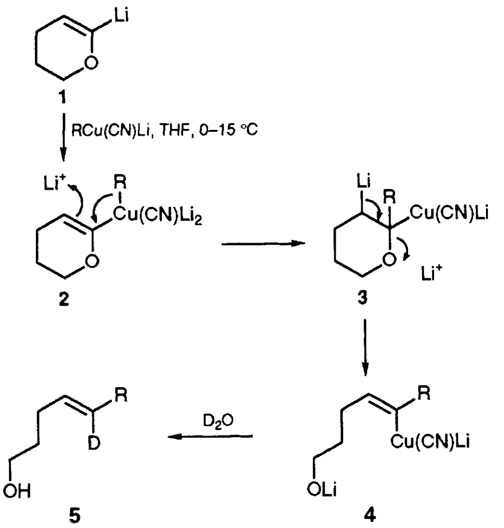
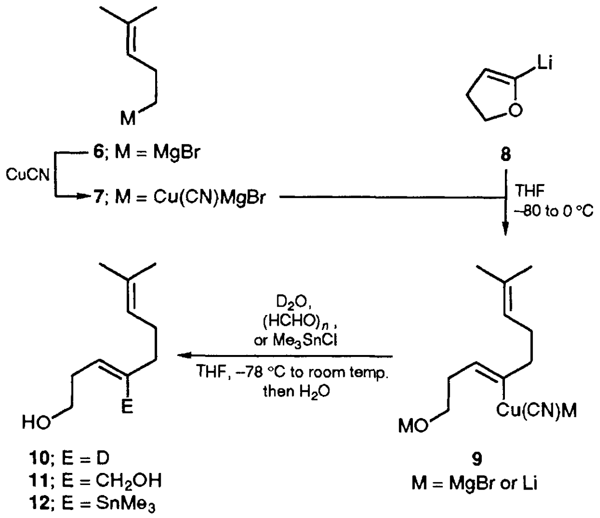
The organocuprates derived from reaction of Grignard reagents with CuBr·Me_2S react with 5-lithio-2,3-dihydrofuran and 6-lithio-3,4-dihydro-2*H*-pyran *via* a 1,2-metallate rearrangement to generate an alkenylmagnesium cuprate.

We recently reported a novel connective synthesis of alkenyllithiums and alkenylcuprates by the reaction of cyanocuprates with 6-lithio-3,4-dihydro-2*H*-pyran **1** as illustrated in Scheme 1.[1] The reaction is catalytic in Cu^I and remarkably broad in scope [R = Me, Ph, alkenyl, allyl, alkyl (primary, secondary, tertiary), cyclopropyl, $PhMe_2Si$ and Me_3Sn]. Subsequent studies on the application of the reaction to the synthesis of natural products uncovered three limitations. Firstly, four equivalents of cyanocuprate were required for optimum yields leading to conspicuous waste in the case of expensive ligands.



Scheme 1

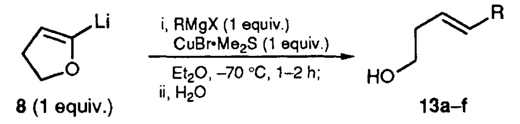


Scheme 2

Secondly, homoallylic cuprates failed to undergo the coupling owing to competing β-elimination of CuH. Finally, the requisite 1,2-metallate rearrangement of the higher order cyanocuprate **2** occasionally required temperatures at or above room temperature in which case competing destruction of the intermediate was observed leading to low yields and messy reactions. We now report that in certain cases all three limitations can be surmounted by the use of a variant which employs Grignard reagents in place of organolithium reagents in the preparation of the organocuprate precursor.

The practical advantages of using Grignard reagents as reaction partners in the Cu^I-catalysed coupling with α-lithiated enol ethers is illustrated by the transformation shown in Scheme 2: a transformation which we tried in vain to accomplish according to our original protocol using cuprates derived from organolithiums. The homoallylic Grignard reagent **6** was added to a suspension of CuCN in tetrahydrofuran (THF). To the resultant cyanocuprate **7** was added a solution of 5-lithio-2,3-dihydrofuran **8** at −80 °C and the mixture allowed to warm to 0 °C during which time the 1,2-metallate rearrangement took place to produce the alkenylcuprate **9**. After recooling to −78 °C, the indicated electrophiles were added to give homoallylic alcohols **10–12** in 75% yield after aqueous work-up.

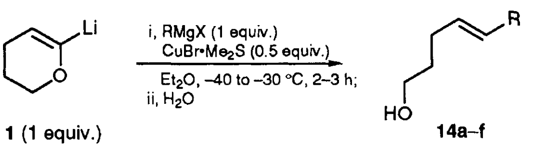
Table 1 4-Substituted but-3-en-1-ols from Cu^I-catalysed reaction of Grignard reagents with 5-lithio-2,3-dihydrofuran



Entry	R	X	Product	Yield[a] (%)
1	Bu^n	Br	**13a**	31
2	n-Hex	Br	**13b**	38
3	n-Hex	Br	**13b**	49
4	Bu^s	Cl	**13c**	33
5	c-Hex	Cl	**13d**	84
6	Bu^t	Cl	**13e**	33
7	Ph	Br	**13f**	50

[a] Yields refer to products purified by column chromatography followed by distillation. [b] Grignard reagent: **8** = 3:2.

Table 2 5-Substituted pent-4-en-1-ols from Cu^I-catalysed reaction of Grignard reagents with 6-lithio-3,4-dihydro-2*H*-pyran



Entry	R	X	Product	Yield[a] (%)
1	Me	Br	**14a**	29
2	Et	Br	**14b**	40
3	Bu^n	Br	**14c**	48
4	n-Hex	Br	**14d**	64
5	Pr^i	Cl	**14e**	60
6	Bu^s	Cl	**14f**	58
7	c-Hex	Cl	**14g**	54
8	Bu^t	Cl	**14h**	64
9	Allyl	Br	**14i**	44
10	2-Methylallyl	Cl	**14j**	45
11	Isopropenyl	Br	**14k**	32
12	Ph	Br	**14l**	46

[a] Yields refer to products purified by column chromatography followed by distillation. [b] Grignard reagent: **1** = 3:2.

In order to establish the scope and limitations of the reaction depicted in Scheme 2 we examined similar transformations with a variety of Grignard reagents and 5-lithio-2,3-dihydrofuran **8** or 6-lithio-3,4-dihydro-2*H*-pyran **1** in Et_2O using $CuBr{\cdot}Me_2S$ complex as the source of Cu^I to give the corresponding substituted (*E*)-but-3-en-1-ols **13a–f** and (*E*)-pent-4-en-1-ols **14a–l** respectively. Ever mindful of the need for economy, we optimised the reaction for 1 equivalent each of the Grignard reagent and the α-metallated enol ether even though superior yields could be obtained by using an excess of Grignard reagent (compare entries 2 and 3, Table 1 and entries 3 and 4, Table 2). The following general observations are pertinent to the results which are summarised in Tables 1 and 2.

(*i*) In every case examined, the *trans*-1,2-disubstituted alkenes **13a–f** and **14a–l** were formed with ≥97% stereoselectivity according to high-field ^1H and ^{13}C NMR spectroscopy.

(*ii*) Fewer side reactions and greater reproducibility were obtained when $CuBr{\cdot}Me_2S$ complex was used instead of CuCN probably because of the greater solubility of the former. Although as little as 10 mol% of Cu^I could be used with only a negligible loss in yield, the reactions were cleaner, and therefore product purification easier, when 0.5 equiv. was used with **1** or 1.0 equiv. with **8**.

(*iii*) The efficiency and rate of the 1,2-metallate rearrangements depended on the structure of metallated enol ether as well as the structure of the structure of the organometallic ligand. Fastest rates, cleanest reactions, and best yields were obtained with tertiary and secondary alkyl Grignard reagents. In contrast to the lithiocuprates reported previously, the magnesiocuprates gave better yields with the dihydropyran **1** than the dihydrofuran **8**.

(*iv*) The higher order cuprates derived from organolithiums, lithiated enol ethers **1** or **8**, and CuBr·Me_2S rearranged at appreciable rates at 0–35 °C whereas the corresponding reactions with organomagnesium reagents occurred at −70 °C in the case of **8** or *ca.* −30 °C in the case of **1**. The significance of the metal cation in the course of the rearrangement was demonstrable. Thus, the reaction of **1** with $Bu^n{}_2CuLi{\cdot}Me_2S$ occurred normally at *ca.* −5 °C and the rate was unaffected by addition of $MgBr_2$–Et_2O. However, addition of 1 equivalent of LiCl to the reaction mixture derived from $Bu^s{}_2CuMgBr$ and **1** appreciably depressed the rate: the reaction now required a temperature of −5 °C instead of −30 °C, the temperature required for reaction in the absence of LiCl. Speculation on the origin of this marked effect is premature.

The following procedure is representative (Table 2, entry 8). To a solution of freshly distilled 3,4-dihydro-2*H*-pyran (150 mg, 1.8 mmol) in THF (5 ml) at −30 °C was added Bu^tLi (1.7 mol l^{-1} in pentanes; 1.1 ml, 1.9 mmol). The resultant yellow solution was stirred for 30 min, whereupon the solvent was removed *in vacuo* (oil pump). The residual 6-lithio-3,4-dihydro-2*H*-pyran **1** was dissolved in Et_2O (5 ml). In a separate vessel, $Bu^t{}_2CuMgCl$ was prepared by the addition of Bu^tMgCl (2.0 mol l^{-1} in Et_2O; 1.0 ml, 2.0 mmol) to a stirred slurry of CuBr·Me_2S (171 mg, 0.83 mmol) in Et_2O (10 ml) at −78 °C. The resultant solution was stirred for 30 min at −78 °C before addition of the solution of **1**. The solution was allowed to warm slowly to −30 °C and stirred at this temperature for 2.5 h before the reaction mixture was quenched by addition of 10% ammonium hydroxide solution in saturated ammonium chloride (15 ml). After vigorous stirring for 10 min, the product was recovered by standard extractive work-up and column chromatography on silica gel (Et_2O–light petroleum, 1 : 5) to give alkenol **14h** (163 mg, 1.15 mmol, 64%) after kugelrohr distillation.

In previous publications, we have demonstrated the synthetic utility of 1,2-metallate rearrangements for the stereoselective synthesis of polyketide chains[2–4] and the scope and economy of the reaction has now been further enhanced by our discovery that Grignard reagents, which are usually more readily available and cheaper than the corresponding organolithium reagents, readily participate in the reaction to give moderate to good yields of alkenols. The principal limitation to the deployment of the Grignard variant we have noted to date is the sluggish rate at which the intermediate alkenylmetals (*e.g.* **9** in Scheme 2) undergo alkylation even with electrophiles such as MeI.

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References

1 P. Kocieński, S. Wadman and K. Cooper, *J. Am. Chem. Soc.*, 1989, **111**, 2363.

2 M. Stocks, P. Kocieński and D. Donald, *Tetrahedron Lett.*, 1990, **31**, 1637.

3 A. Takle and P. Kocieński, *Tetrahedron*, 1990, **46**, 4503.

4 P. Kocieński and C. Barber, *Pure Appl. Chem.*, 1990, **62**, 1933.