Sterically Hindered Lithium Dialkylcuprates for the Generation of Highly Functionalized Mixed Cuprates through a Halogen–Copper Exchange**

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Dedicated to Professor Jean-Francois Normant

Highly functionalized organometallic compounds are key intermediates for the preparation of polyfunctionalized molecules.[1] Recently, we have shown that iodine-magnesium exchange allows the preparation of polyfunctionalized arylmagnesium reagents^[2] that bear ester, nitrile, amino, or nitro groups; however, more sensitive functionalities, for example, ketone or aldehyde groups are usually not compatible with the presence of a C-Mg bond. Herein we report a solution to this problem by using new sterically hindered organocuprates for performing an iodine-copper or bromine-copper exchange. Corey and Posner^[3] have shown that the reaction of lithium dialkylcuprates with aryl iodides leads to an iodine-copper exchange and to a competitive cross-coupling reaction. Kondo et al. have shown that the use of lithium dimethylcuprate allows an iodine-copper exchange with a functionalized aryl iodide that bears an ester group.^[4] In this case, an excess of Me₂CuLi (2 equiv) has to be used to quench the methyl iodide formed in the I/Cu-exchange reaction. In contrast, the readily prepared lithium dineopentylcuprate (Neopent₂CuLi, 1) and (PhMe2CCH2)2CuLi, (Neophyl2CuLi, 2)[5] rapidly react with various functionalized iodides of type 3 to give mixed organocuprates of type 4, which selectively transfer the aryl group^[6] to electrophiles (E⁺), thus leading to products of type **5** (Scheme 1). This approach allows a general preparation of polyfunctionalized organocuprates.^[7,8]

$$R_2$$
CuLi (1 or 2)

THF

 R_2 CuLi (1 or 2)

 R_2 CuLi (1 or 2)

 R_3 CuR Li +

 R_4 CuR Li +

 R_5 CuR Li +

FG = ester, ketone, aldehyde; $R = Me_3CCH_2$ (1) or $PhMe_2CCH_2$ (2)

Scheme 1. Preparation of highly functionalized arylcopper reagents.

The steric hindrance of **1** and **2** is essential for ensuring the chemoselectivity of the I/Cu exchange.^[9] Thus, ethyl 4-iodobenzoate (**3a**) undergoes a smooth iodine-copper exchange with Neopent₂CuLi (**1**; 1.1 equiv, -30 °C, 2 h) to

afford the desired mixed cuprate **4a**, which reacts with electrophiles such as allyl bromide, acid chlorides, or 2-cyclohexen-1-one to afford the desired products **5a-d** in yields of 70–95% (Table 1, entries 1–4). Functionalized aromatic bromides such as diethyl 2-bromoterephthalate smoothly undergo Br/Cu exchange with Neopent₂CuLi (**1**; THF, –40 °C, 30 min) to provide the lithiumcuprate **4b**, which upon allylation furnishes the diester **5e** (Table 1, entry 5).

Remarkably, ketone functions are compatible with the I/Cu-exchange reaction. Treatment of 2-iodobenzophenone with $1 (-40 \rightarrow 0$ °C, 30 min) leads to the desired mixed cuprate (4c). Allylation or methylation (methyl iodide) leads to the products **5f** and **5g**, respectively (Table 1, entries 6 and 7). Similarly, 4-iodophenyl tert-butyl ketone is converted into the cuprate 4d and subsequently allylated (Table 1, entry 8). Attempts to convert 4-iodoacetophenone into the corresponding cuprate led to extensive deprotonation. However, the use of Neophyl₂CuLi (2) allows the preparation of the corresponding cuprate 4e in approximately 80% yield (THF, $-30\rightarrow25$ °C, 1 h). This cuprate can be acylated (PhCOCl) or it can undergo a Michael addition to 2-cyclohexen-1-one, leading to the products 5j and 5k, respectively (Table 1, entries 10 and 11). Finally, even an aldehyde function is compatible with the iodine-copper exchange. Treatment of 2iodobenzaldehyde with 1 (1.1 equiv, $-40 \rightarrow -20$ °C, 4 h) provides the cuprate 4f, which is allylated to give 2-allylbenzaldehyde (5m) in 80% yield (Table 1, entry 13; see also entry 12). The bulky lithium cuprates 1 and 2 also allow the use of functionalized alkenyl iodides as substrates. The reaction of 2-iodo-3-methyl-2-cyclohexenone (6) with Neopent₂CuLi (1) furnished the corresponding alkenylcuprate 7 (Scheme 2). The presence of the methyl group at C3 in 6 as well as the bulky nature of the cuprate 1, disfavor 1,4addition and favor I/Cu exchange. After allylation, the cyclohexenone 8 is obtained in 74 % yield (Scheme 2).

In summary, we have shown that sterically hindered cuprates **1** and **2** allow a highly chemoselective I/Cu exchange. With this method, new functionalized cuprates that bear ester, ketone, or even aldehyde functions can be prepared and used in synthesis. Further investigations for the preparation of new polyfunctionalized alkenyl and heterocyclic copper reagents are underway.

Experimental Section

Typical procedure ($5\mathbf{j}$): A dry and argon-flushed 10-mL flask, equipped with a magnetic stirrer and a septum, was charged with 4-iodoacetophenone (240 mg, 1.0 mmol). Dry THF (2 mL) was added and the solution was added slowly into a dry, argon-flushed 25-mL flask that contained previously prepared Neophyl₂CuLi (2; 1.2 mmol) and cooled to $-30\,^{\circ}$ C. The mixture was warmed quickly to room temperature. The I/Cu exchange was complete within 1 h (checked by GC analysis of reaction aliquots), and benzoyl chloride (0.1 mL, 0.9 mmol) was added to the mixed organocuprate ($4\mathbf{e}$). After stirring for 30 min at room temperature, the reaction mixture was quenched with saturated NH₄Cl solution (2 mL) and poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3×30 mL). The organic fractions were washed with brine (30 mL), dried (MgSO₄), and concentrated in vacuo. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded 4-acetylbenzophenone ($5\mathbf{j}$) as a lightyellow oil (155 mg, $77\,^{\circ}$).

Received: April 25, 2002 [Z19175]

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^[**] We thank the Deutsche Forschungsgemeinschaft (Leibniz program) for financial support. We thank BASF AG (Ludwigshafen), Chemetall GmbH (Frankfurt), and Degussa AG (Hanau) for the generous gift of chemicals

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Table 1. Reaction of functionalized lithium cuprates ${\bf 4}$ with electrophiles to give ${\bf 5}$.

Entry Cuprate 4 ^[a]		Electrophile	Product 5		Yield [%] ^[b]	
1	Cu(R¹)Li ↓	4a	allyl bromide		5a	95 90 ^[c]
						900
	Ţ CO₂Et			Ϋ́ CO₂Et		
2	Cu(R ¹)Li	4a	PhCOCl	OPh	5 b	87 95 ^[c]
						93.7
	CO₂Et			CO₂Et		
	Çu(R ¹)Li			O tBu		
3		4a	tBuCOCl		5 c	83
	CO₂Et			CO₂Et		
				0022		
	Cu(R ¹)Li					
4		4a	cyclohexenone		5 d	70
	CO ₂ Et			CO ₂ Et		
	CO₂Et Cu(R¹)Li			CO₂Et		
5	Cu(N)LI	4 b	allyl bromide		5 e	76
	Υ CO₂Et			CO₂Et		
	O Cu(R¹)Li ↓ ↓					
	Ph	4 c	allyl bromide		5 f	80
	O Cu(R¹)Li			0		
7	Ph	4 c	MeI		5 g	80
	Çu(R ¹)Li					
8		4 d	allyl bromide		5h	93
	CO <i>t</i> Bu		,	CO/Bu		
				0		
	Cu(R ¹)Li					
9		4 d	cyclohexenone		5i	60
	ĊO <i>t</i> Bu			COfBu		
	Cu(R ²)Li			Ph		
10		4 e	PhCOCl		5 j	77 ^[c]
	COMe			COMe		
	Çu(R²)Li			0		
11	Cu(11)EI					501.1
		4 e	cyclohexenone		5k	68 ^[c]
	COMe			COMe		
	CHO Cu(R¹)Li			CHO O ↓ ↓		
12	53()2.	4 f	CH₃COCl		51	70
	CHO			CHO		
13	Cu(R ¹)Li	4 f	allyl bromide		5 m	80
	<u> </u>			<u> </u>		

[a] R¹ = neopentyl; R² = neophyl. [b] Yields of isolated analytically pure products. [c] Yields obtained by performing the I/Cu exchange with 2.

Neopent₂CuLi
$$(1.1 \text{ equiv})$$
 $-78 \rightarrow -30 \,^{\circ}\text{C}$, 3 h $-30 \,^{\circ}\text{C}$, 30 min $-30 \,^{\circ}\text{C}$, 30 min $-30 \,^{\circ}\text{C}$, 30 min

Scheme 2. Iodine-copper exchange with 2-iodo-3-methyl-2-cyclohexenone.

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Tin-Free Radical-Mediated C-C-Bond Formations with Alkyl Allyl Sulfones as Radical Precursors**

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The synthetic importance of tin-free radical reactions has been well recognized in recent years.^[1] Among several

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[**] We thank CMDS and BK21 project for financial support.

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approaches, an organosulfone-mediated approach is very effective for allylation, [2] vinylation, [3] and azidation [4] [Eq. (1), AIBN = 2,2'-azobisisobutyronitrile]. However, the reported methods did not work well with primary alkyl iodides and xanthates owing to inefficient iodine-atom transfer and xanthate-group transfer, respectively. Recently, we also reported a tin-free acylation approach

$$RX + SO_2Et \xrightarrow{AIBN} R$$
 (1)
 $X = I$, xanthate

using methanesulfonyl oxime ether, in which primary alkyl iodides and xanthates caused the same problem as a result of the small energy difference between the methyl radical and the primary alkyl radical [Eq. (2), V-40 = 1,1'-azobis(cyclohexane-1-carbonitrile)].^[5]

RI + MeSO₂
$$N^{OBn} \frac{V-40}{BuC_6H_{5, 140} \circ C} R^{OBn}$$
 (2)

As our extensive efforts to generate primary alkyl radicals from primary alkyl iodides and xanthates were unsuccessful, we have been interested in developing a new reliable method to generate primary alkyl radicals by using new types of radical precursors that do not require an atom- or a grouptransfer step. In this regard, we have studied the possibility of using an alkyl allyl sulfone as a radical precursor. Alkyl allyl sulfones have been widely used as radical acceptors to transfer an allyl group to a radical precursor. [6] Although alkyl allyl sulfones have been used once as the radical precursor in an allylation reaction, [2a] primary alkyl allyl sulfones have not been examined. To the best of our knowledge, S-alkoxycarbonyl dithiocarbonates are the only generators of primary alkyl radicals from alcohols, but they cannot be applied to C-C-bond formations owing to the rapid formation of the corresponding xanthates.[7] We have found that alkyl allyl sulfones are highly efficient and reliable radical precursors for the generation of primary alkyl radicals under tin-free conditions and can be successfully applied to various C-Cbond-formation reactions.

Initially, we focused on radical cyanation,^[8] and began our study with a primary alkyl iodide and methanesulfonyl cyanide.^[9] The reaction of 4-phenoxybutyl iodide with methanesulfonyl cyanide (2 equiv) and V-40 (0.2 equiv) in *tert*-butylbenzene at 140°C for 5 h afforded 4-phenoxybutyl cyanide in only 21% yield together with recovered 4-phenoxybutyl iodide (77%). Notably, methanesulfonyl cyanide was completely consumed, with acetonitrile as the major product [Eq. (3)].^[10] However, allyl sulfone **1** was an effective

RI + MeSO₂CN
$$\frac{V-40}{tBuC_6H_5, 140 \, ^{\circ}C}$$
 RCN + CH₃CN (3)
R=PhO(CH₂)₄

precursor for radical cyanation, and our approach is outlined in Scheme 1. We envisaged that the addition of a p-toluene-sulfonyl radical to $\mathbf{1}$ would produce an alkyl sulfonyl radical as well as p-tolyl allyl sulfone $\mathbf{4}$. Although the alkyl sulfonyl