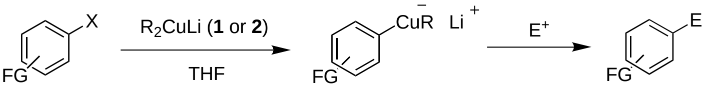
Sterically Hindered Lithium Dialkylcuprates for the Generation of Highly Functionalized Mixed Cuprates through a Halogen–Copper Exchange**

Claudia Piazza and Paul Knochel*

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 Me_2CuLi (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 ($Neopent_2CuLi$, **1**) and $(PhMe_2CCH_2)_2CuLi$, ($Neophyl_2CuLi$, **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]



3: X = Br,I **4** **5**

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 $Neopent_2CuLi$ (**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 $Neopent_2CuLi$ (**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→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 $Neophyl_2CuLi$ (**2**) allows the preparation of the corresponding cuprate **4e** in approximately 80 % yield (THF, −30→25 °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 2-iodobenzaldehyde with **1** (1.1 equiv, −40→−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 $Neopent_2CuLi$ (**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 1,4-addition 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 (**5j**): 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 $Neophyl_2CuLi$ (**2**; 1.2 mmol) and cooled to −30 °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 (**4e**). After stirring for 30 min at room temperature, the reaction mixture was quenched with saturated NH_4Cl 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 ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (pentane/diethyl ether 9:1) yielded 4-acetylbenzophenone (**5j**) as a light-yellow oil (155 mg, 77 %).

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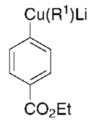
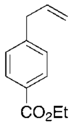
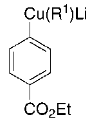
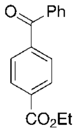
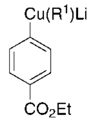
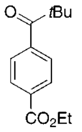
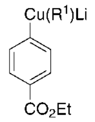
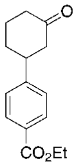
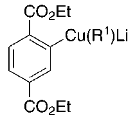
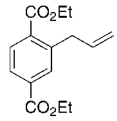
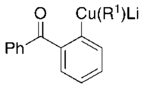
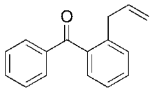
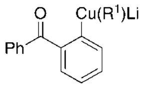
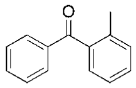
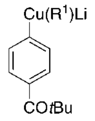
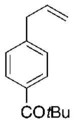
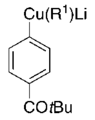
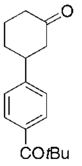
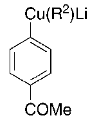
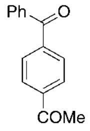
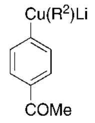
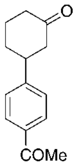
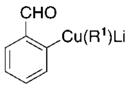
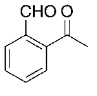
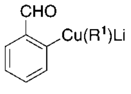
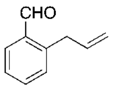
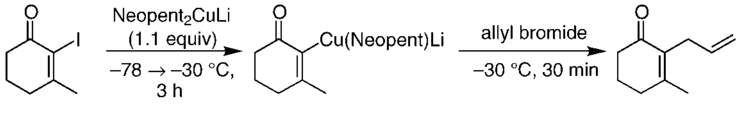
Table 1. Reaction of functionalized lithium cuprates **4** with electrophiles to give **5**.

Entry	Cuprate **4**[a]		Electrophile	Product **5**		Yield [%][b]
1		**4a**	allyl bromide		**5a**	95 90[c]
2		**4a**	PhCOCl		**5b**	87 95[c]
3		**4a**	*t*BuCOCl		**5c**	83
4		**4a**	cyclohexenone		**5d**	70
5		**4b**	allyl bromide		**5e**	76
6		**4c**	allyl bromide		**5f**	80
7		**4c**	MeI		**5g**	80
8		**4d**	allyl bromide		**5h**	93
9		**4d**	cyclohexenone		**5i**	60
10		**4e**	PhCOCl		**5j**	77[c]
11		**4e**	cyclohexenone		**5k**	68[c]
12		**4f**	CH_3COCl		**5l**	70
13		**4f**	allyl bromide		**5m**	80

[a] R^1 = neopentyl; R^2 = neophyl. [b] Yields of isolated analytically pure products. [c] Yields obtained by performing the I/Cu exchange with **2**.



6 **7** **8**

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

[1] A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem.* **2000**, *112*, 4584; *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.

[2] A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis* **2002**, *4*, 565.

[3] E. J. Corey, G. H. Posner, *J. Am. Chem. Soc.* **1968**, *90*, 5615.

[4] Y. Kondo, T. Matsudaira, J. Sato, N. Muraka, T. Sakamoto, *Angew. Chem.* **1996**, *108*, 818; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 736.

[5] Commercial neopentyl iodide was treated with *t*BuLi (2 equiv, Et_2O, −78 °C→RT, 1 h) to give neopentyllithium, which upon reaction with CuCN (0.5 equiv, 0 °C, 10 min) furnished the cuprate **1**. $PhMe_2CCH_2Cl$ (neophyl chloride) was converted into neophyllithium by reaction with lithium metal in dry hexane (heated overnight at reflux). The mixture was then transferred through a cannula into a 50-mL Schlenk tube, and the hexane was removed under vacuum. Dry diethyl ether was added and the mixture was centrifuged (2000 rpm, 30 min). Before use, the clear solution of neophyllithium thus obtained was titrated with menthol and *o*-phenantroline as indicator. Treatment with CuCN (0.5 equiv, room temperature, 10 min) gave the corresponding copper reagent **2**.

[6] Previously, we have shown that the neopentyl group does not readily participate in the formation of new C–C bonds: P. Jones, K. C. Reddy, P. Knochel, *Tetrahedron* **1998**, *54*, *1471*; see also: S. H. Bertz, M. Eriksson, G. Miao, J. P. Snyder, *J. Am. Chem. Soc.* **1996**, *118*, 10906.

[7] For the preparation of functionalized organocuprates by the direct insertion of activated copper, see: a) G. W. Ebert, R. D. Rieke, *J. Org. Chem.* **1984**, *49*, 5281; b) R. D. Rieke, R. H. Wehmeyer, T. C. Wu, G. W. Ebert, *Tetrahedron* **1989**, *45*, 443; c) G. W. Ebert, J. W. Cheasty, S. S. Tehrani, E. Aouad, *Organometallics* **1992**, *11*, 1560; d) G. W. Ebert, D. R. Pfennig, S. D. Suchan, T. A. Donovan, *Tetrahedron Lett.* **1993**, *34*, 2279.

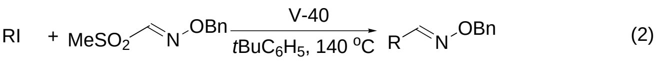
[8] a) B. H. Lipshutz, S. Sengupta, *Org. React.* **1992**, *41*, 135; b) R. J. K. Taylor, *Organocopper Reagents*, Oxford University Press, Oxford, **1994**; c) N. Krause, *Modern Organocopper Chemistry*, Wiley-VCH, Weinheim, **2002**.

[9] For a chemoselective halogen–lithium exchange, see: Y. Kondo, M. Asai, T. Uchiyama, T. Sakamoto, *Org. Lett.* **2001**, *3*, 13.

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

Sunggak Kim[*] and Chae Jo Lim

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



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 group-transfer 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–C-bond-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 precursor for radical cyanation, and our approach is outlined in Scheme 1. We envisaged that the addition of a *p*-toluenesulfonyl radical to **1** would produce an alkyl sulfonyl radical as well as *p*-tolyl allyl sulfone **4**. Although the alkyl sulfonyl

$$\underset{R=PhO(CH_2)_4}{RI} + MeSO_2CN \xrightarrow[tBuC_6H_5,\ 140\ ^{\circ}C]{V\text{-}40} \underset{21\%}{RCN} + CH_3CN \qquad (3)$$

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