

Direct preparation of copper organometallics bearing an aldehyde function *via* an iodine–copper exchange†

Xiaoyin Yang and Paul Knochel*

Received (in Cambridge, UK) 23rd March 2006, Accepted 7th April 2006

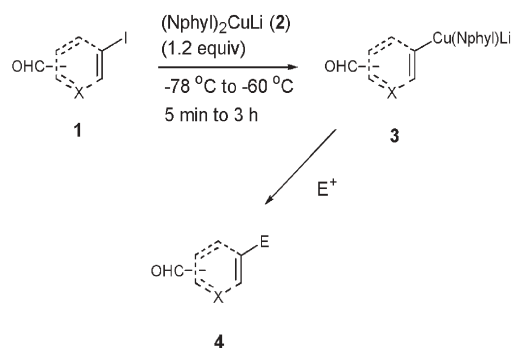
First published as an Advance Article on the web 3rd May 2006

DOI: 10.1039/b604259g

The iodine–copper exchange reaction allows the direct preparation of various aryl, heteroaryl and alkenyl cuprates bearing a formyl group, thus allowing a direct synthesis of polyfunctional aldehydes without the need of protecting groups or an additional oxidation step.

Polyfunctionalized organometallics are versatile intermediates in modern organic chemistry, since they allow the formation of multifunctional products.¹ One of the best preparation methods of these organometallic reagents is the halogen–metal exchange reaction.^{1e,2} The halogen–magnesium³ and halogen–copper⁴ exchanges have recently been extensively investigated. They allow the convenient preparation of polyfunctional aryl, heteroaryl and alkenyl organometallic reagents that bear various functional groups. The formyl group is present in numerous compounds, but has been regarded as being incompatible with most organometallic reagents.⁵ Only scarce examples of formyl-substituted aryl organometallic compounds have been reported.⁶ In most cases, tedious protection and deprotection steps or an additional oxidation step are required to introduce this sensitive function in a target molecule.⁷ Herein, we wish to report that the iodine–copper exchange reaction allows the direct preparation of polyfunctional aryl, heteroaryl and alkenyl copper reagents bearing an aldehyde group. Subsequent reactions of these formyl-substituted copper reagents with various electrophiles provide highly functionalized aldehydes in good yields. In a preliminary experiment, we have treated 4-acetoxy-3-iodo-5-methoxybenzaldehyde (**1a**) with lithium dineophylcuprate [(PhMe₂CCH₂)₂CuLi:(Nphyl)₂CuLi (**2**)] in a 5:1 mixture of THF and diethyl ether at –78 °C. Within 2 h, a complete iodine–copper exchange reaction was observed, as indicated by GC-analysis of a reaction aliquot. The resulting arylcopper reagent **3a** reacted smoothly with allyl bromide and cyclohexanecarbonyl chloride between –78 °C and rt giving the expected aldehydes **4a** and **4b** in 84% and 73% yield (Scheme 1, entries 1 and 2 of Table 1). The use of more reactive and less sterically hindered lithium dineopentylcuprate [(Me₃CCH₂)₂CuLi] led to a complex reaction mixture and the use of the lithium cuprate (**2**) is mandatory for the success of the exchange.

Interestingly, in the case of 3,5-diiodo-2-tosyloxybenzaldehyde (**1b**), the *ortho*-iodine underwent a selective I–Cu-exchange



Scheme 1

reaction with (Nphyl)₂CuLi (**2**) giving the desired aldehydes **4c** and **4d** in 80–94% yield after reactions with allyl bromide and benzoyl chloride (entries 3 and 4). Remarkably, this iodine–copper exchange reaction could also be extended to heteroaryl substrates. Thus, 5-iodo-2-thiophenecarbaldehyde (**1c**) reacted readily with (Nphyl)₂CuLi (**2**) at –78 °C within 10 min, furnishing the copper reagent **3c**, which reacted with electrophiles, such as ethyl (2-bromomethyl)acrylate, benzoyl chloride or 2-thiophene carbonyl chloride, affording the highly functionalized **4e–g** in 72–85% yield (entries 5, 6 and 7). In a similar way, the heterocyclic iodoaldehydes **1d–e** could be easily converted into the corresponding copper reagents **3d–e** under our standard reaction conditions. Subsequent reactions with various electrophiles led to highly functionalized aldehydes **4h–i** in 61–79% yield (entries 8 and 9). The presence of an adjacent heteroatom (O, N or S) decreases the reactivity of these copper heterocycles **1c–e** sufficiently so that no addition to the aldehyde occurred under the exchange reaction. Furthermore, this exchange could be applied to indoles bearing a formyl group at the 2 or 3 position. Thus, N-protected 3-iodoindole-2-carbaldehyde (**1f**) underwent a smooth I–Cu-exchange reaction with (Nphyl)₂CuLi (**2**) at –78 °C within 30 min, leading to the cuprate **3f**. The subsequent treatment with allyl bromide furnished 3-allylated indole **4j** in 83% yield (entry 10). Interestingly, even with the sterically hindered indole derivative **1g**, the exchange reaction proceeded smoothly, yielding the functionalized cuprate **3g**, which was readily allylated providing the aldehyde **4k** in 93% yield (entry 11). Finally, the functionalized pyridine **1h** reacted readily with (Nphyl)₂CuLi (**2**, 1.2 equiv.) in a 5:1 mixture of THF and ether from –78 °C to –60 °C, leading to the corresponding cuprate **3h**, which was quenched with ethyl (2-bromomethyl)acrylate or benzoyl chloride forming the trisubstituted functionalized pyridines **4l** and **4m** in 82% and 63% yields (entries 12 and 13).

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, Haus F, 81377 München, Germany.

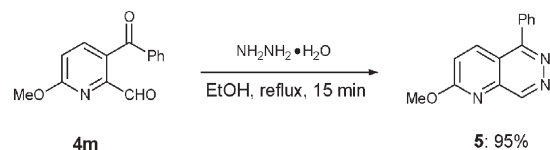
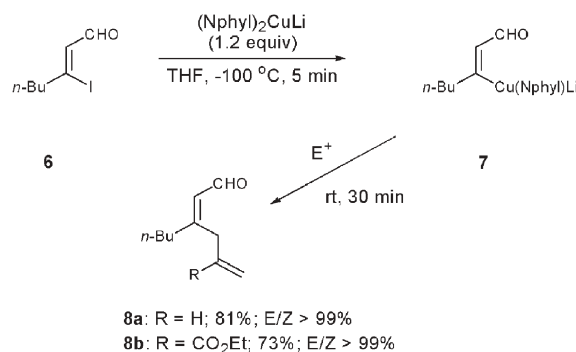
E-mail: Paul.Knochel@cup.uni-muenchen.de;

Fax: (+49)-89-2180-77680; Tel: (+49)-89-2180-77681

† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b604259g

Table 1 Aldehydes of type **4** obtained by the reaction of formyl-substituted aryl and heteroaryl copper reagents **3** with electrophiles

Entry	Copper reagent	Electrophile	Product of type 4	Yield (%) ^a
1				84
2	3a	c-HexCOCl		73 ^c
3				94
4	3b	PhCOCl		80
5				85
6	3c	PhCOCl		80
7	3c			72
8		PhCOCl		61 ^g
9				79
10				83
11				93
12				82
13	3h	PhCOCl		63

^a Isolated yields of analytically pure aldehydes.**Scheme 2****Scheme 3**

The resulting highly functionalized aldehydes of type **4** can be readily converted to polyfunctional heterocycles of potential pharmaceutical interest. The reaction of the dicarbonylated pyridine **4m** with hydrazine monohydrate in ethanol (reflux, 15 min) provided pyridopyridazine **5** in 95% yield (Scheme 2).⁸

Furthermore, this exchange reaction also allows the functionalization of β -iodo- α,β -unsaturated aldehydes. The reaction of (Z)-3-iodo-2-heptenal (**6**) with (N-phenyl)₂CuLi (**2**) in THF at $-100\text{ }^{\circ}\text{C}$ (5 min) stereoselectively furnished the alkenyl cuprate **7**. The Z configuration of the double bond (stabilized by chelation)⁹ as well as the presence of the sterically hindered butyl group disfavored an addition–elimination reaction and favored the I–Cu-exchange reaction.¹⁰ Treatment of the cuprated unsaturated aldehyde **7** with allyl bromide or ethyl (2-bromomethyl)acrylate furnished the trisubstituted α,β -unsaturated aldehydes **8a** and **8b** in 81% and 73% yields (Scheme 3).

In summary, we have shown that the iodine–copper exchange reaction allows the direct preparation of various new aryl, heteroaryl and alkenyl cuprates bearing an aldehyde group, thus expanding the applications of functionalized copper organometallic species in organic synthesis.¹¹ Further extensions of this method are currently underway in our laboratory.

Notes and references

- (a) N. Krause, *Modern Organocopper Chemistry*, Wiley-VCH, Weinheim, 2002; (b) M. d'Augustin, L. Palais and A. Alexakis, *Angew. Chem., Int. Ed.*, 2005, **44**, 1376; (c) B. L. Feringa, R. Badorrey, D. Peña, S. R. Harutyunyan and A. J. Minnaard, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5834; (d) R. Naasz, L. A. Arnold, M. Pineschi, E. Keller and B. L. Feringa, *J. Am. Chem. Soc.*, 1999, **121**, 1104; (e) P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, 2005; (f) I. Marek and J.-F. Normant, *Chem. Rev.*, 1996, **96**, 3241.
- (a) W. F. Bailey and J. J. Patricia, *J. Organomet. Chem.*, 1988, **352**, 1; (b) W. F. Bailey and E. R. Punzalan, *J. Org. Chem.*, 1990, **55**, 5404; (c) W. F. Bailey, J. D. Brubaker and K. P. Jordan, *J. Organomet. Chem.*, 2003, **681**, 210; (d) E. Negishi, D. R. Swanson and C. J. Rousset, *J. Org. Chem.*, 1990, **55**, 5406; (e) G. Boche, M. Schimeczek, J. Cioslowski and P. Piskorz, *Eur. J. Org. Chem.*, 1998, 1851; (f) H. J. Reich, M. J. Bevan,

- B. O. Gudmundsson and C. L. Puckett, *Angew. Chem.*, 2002, **114**, 3586, *Angew. Chem., Int. Ed.*, 2002, **41**, 3436; (g) C. E. Tucker, T. N. Majid and P. Knochel, *J. Am. Chem. Soc.*, 1992, **114**, 3983; (h) R. W. Hoffmann, P. G. Nell, R. Leo and K. Harms, *Chem.–Eur. J.*, 2000, **6**, 3359; (i) R. W. Hoffmann, B. Hölzer, O. Knopff and K. Harms, *Angew. Chem.*, 2000, **112**, 3206, *Angew. Chem., Int. Ed.*, 2000, **39**, 3072.
- 3 (a) L. Boymond, M. Rottländer, G. Cahiez and P. Knochel, *Angew. Chem.*, 1998, **110**, 1801, *Angew. Chem., Int. Ed.*, 1998, **37**, 1701; (b) A. Boudier, L. O. Bromm, M. Lotz and P. Knochel, *Angew. Chem.*, 2000, **112**, 4584, *Angew. Chem., Int. Ed.*, 2000, **39**, 4414; (c) A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu and P. Knochel, *Synthesis*, 2002, 565; (d) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis and V. A. Vu, *Angew. Chem.*, 2003, **115**, 4438, *Angew. Chem., Int. Ed.*, 2003, **42**, 4302.
- 4 (a) E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, 1968, **90**, 5615; (b) Y. Kondo, T. Matsudaira, J. Sato, N. Muraka and T. Sakamoto, *Angew. Chem.*, 1996, **108**, 818, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 736; (c) C. Piazza and P. Knochel, *Angew. Chem., Int. Ed.*, 2002, **41**, 3263; (d) X. Yang, T. Rotter, C. Piazza and P. Knochel, *Org. Lett.*, 2003, **5**, 1229; (e) X. Yang and P. Knochel, *Synlett*, 2004, 81; (f) X. Yang, A. Althammer and P. Knochel, *Org. Lett.*, 2004, **6**, 1665; (g) X. Yang and P. Knochel, *Synlett*, 2004, 2303.
- 5 (a) J. Otera, *Modern Carbonyl Chemistry*, Wiley-VCH, Weinheim, 2000; (b) J. R. Hanson, *Functional Group Chemistry*, RSC Publishing, UK, 2001.
- 6 (a) F. F. Kneisel, M. Dochnahl and P. Knochel, *Angew. Chem., Int. Ed.*, 2004, **43**, 1017; (b) F. F. Kneisel, H. Leuser and P. Knochel, *Synthesis*, 2005, 2625.
- 7 (a) A. T. Khan, E. Mondal, S. Ghosh and S. Islam, *Eur. J. Org. Chem.*, 2004, 2002; (b) R. Bernini, A. Coratti, G. Provenzano, G. Fabrizi and D. Tofani, *Tetrahedron*, 2005, **61**, 1821; (c) M. P. Groziak and L. Wei, *J. Org. Chem.*, 1991, **56**, 4296; (d) M. P. Groziak and L. Wei, *J. Org. Chem.*, 1992, **57**, 3776; (e) D. L. Comins and M. O. Killpack, *J. Org. Chem.*, 1990, **55**, 69; (f) D. L. Comins and M. O. Killpack, *J. Org. Chem.*, 1987, **52**, 104.
- 8 M. J. Haddadin, B. J. Agha and R. F. Tabri, *J. Org. Chem.*, 1979, **44**, 494.
- 9 V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.
- 10 I. Sapountzis, W. Dohle and P. Knochel, *Chem. Commun.*, 2001, 2068.
- 11 Preparation of 3-allyl-5-iodo-2-tosyloxybenzaldehyde (**4c**): a dry and argon flushed 25 mL flask, equipped with a magnetic stirring bar and a septum, was charged with CuCN (108 mg, 1.2 mmol) and dry THF (4 mL). A solution of neophyllithium (1.3 M in Et₂O, 1.8 mL, 2.4 mmol) was added at –78 °C. After stirring at rt for 10 min, the reaction mixture was cooled to –78 °C and transferred by cannula into a mixture of 3,5-diiodo-2-tosyloxybenzaldehyde (**1b**, 528 mg, 1.0 mmol) in dry THF (5 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 20 min. Allyl bromide (360 mg, 3.0 mmol) was added and the reaction mixture was stirred at rt for 30 min. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (5 mL) and poured into water (15 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL). The organic fractions were washed with brine (30 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash-chromatography to give the desired product **4c** (415 mg, 94% yield) as a colorless oil.