

The metal–halogen exchange reaction between *ortho*-substituted aryl halides and $\text{Ph}_2\text{CuLi} \cdot \text{LiCN}$: scope and applicability for coupling reactions

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Received 22 July 2003; accepted 29 September 2003

Abstract

Metal–halogen exchange between $\text{Ph}_2\text{CuLi} \cdot \text{LiCN}$ and *ortho*-substituted aryl iodides or bromides may be used to conveniently afford substituted metallated aryls which can subsequently undergo reaction with electrophiles.

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Keywords: Metal–halogen exchange; Aryl halides; Coupling; Diphenylcuprate

1. Introduction

The reactions of organometallic compounds with organic halides continues to be one of the most widely studied reactions in organic chemistry. In recent years, intensely studied strategies in this area have been the catalytic cross-coupling of main group organometallic compounds to organic halides utilizing late transition metal catalysts such as palladium [1] and the stoichiometric coupling of organocuprate reagents to organic halides [2]. Of particular interest, has been the coupling of *o*-substituted metallated aryls with organic halides [3]. However, these reactions have many associated difficulties such as the incompatibility of certain functional groups with organometallic reagents. The coupling of functionally substituted metallated aryl reagents with sterically hindered alkyl or aryl halides can also be difficult [4].

Whilst carrying out earlier work involving the coupling reactions of organocuprates with halo-substituted aryl chlorides [5] we became aware that surprisingly only very few studies have investigated the application of the

metal–halogen exchange reaction of organocuprate compounds. This of course presents a great contrast to the extensive application of lithium chemistry in this field [6]. We therefore decided to undertake a brief investigation of the reaction of aryl halides containing functional substituents in the *ortho* position with the diphenylcuprate reagent $\text{Ph}_2\text{CuLi} \cdot \text{LiCN}$ [7]. According to earlier works, in which alkyl and aryl cuprates have been reported to afford coupled products on reaction with aryl halides, it is expected that metal–halogen exchange will be the initial process [8] and by analogy with the well-known behaviour of lithium reagents, it is anticipated that the organometallic reagent containing the functional group in the *ortho* position is going to be stabilised, thus, providing a driving force for this process [5,9].

Principal advantages of using the metal–halogen exchange reaction to prepare aryl cuprate reagents are that functional groups, such as carbonyl groups, which are inert to cuprate reagents should be easily tolerated in the preparation of the reagent and that reaction conditions may be extremely mild and accessible. Furthermore, organocuprate reagents are among the most favoured reagents for coupling with organic halides. Our results here suggest that it is indeed possible to prepare such functionally substituted organocuprate reagents via metal–halogen exchange and that this

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appears to be a very suitable method employing very accessible conditions.

2. Results and discussion

We initially investigated the reactions of orthohalo-aryloxazolines (**1a–d**) with the diphenylcuprate reagent $\text{Ph}_2\text{CuLi} \cdot \text{CuCN}$ [7]. Thus, the halides were stirred at 0 °C with a fourfold excess of diphenylcuprate, in order to ensure complete consumption of starting material. After a reaction time of 30 min quenching by addition of dilute ammonium chloride solution was carried out. The desired course of this reaction was substitution of X for H to afford **3**. However, replacement of X by Ph in a coupling reaction was also observed in some cases (see Table 1).

As can be seen, of all four halo-oxazoline derivatives, the best yield of the unsubstituted product (**3**) was obtained for the bromo derivative (**1a**). Neither the chloro (**1b**) or fluoro (**1c**) derivatives gave any evidence for the formation of the desired product. However, in the case of the fluoro derivative, the phenylated product (**4**) was obtained in high yield. This could have been expected considering that this derivative is known to undergo nucleophilic substitution by organolithium reagents and lithioamides [10]. Nonetheless, the relative ease with which the reaction proceeds using such mild conditions is most noteworthy.

For the iodo derivative (**1d**), the desired product (**3**) was obtained in addition to the coupled product (**4**). As a result, in order to see whether such a mixture of products could be expected in the reactions of other

functionally substituted aryl iodides, it was decided to also carry out the reaction with the *N,N*-diethylbenzamide derivative (**1e**). In this case H incorporation was obtained in good yield without the presence of any coupled product. In Scheme 1, a tentative mechanism is given which offers an explanation for these observations.

As can be seen in the scheme, for the fluoro derivative (**1c**), metal–halogen exchange does not occur, but instead nucleophilic substitution of the fluoro group occurs. The reaction follows a completely different path for X = Br and I. In this case, it is assumed that the first step in metal–halogen exchange is oxidative addition of Ar–X to the diarylcuprate. Assuming that oxidative addition occurs to a monomeric solvent-separated ion pair form of the cuprate [7], this process is likely to proceed to afford the square planar 16 electron Cu(III) intermediate **2a** [11]. The mechanism of this oxidative addition step may or may not involve electron transfer as has been observed for the isoelectronic d10 Ni(0) complexes with RX [12]. Reductive elimination of PhX from this intermediate could then afford the functionally substituted aryl cuprate reagent (**2b**) and subsequent reaction with water leads to formation of the unsubstituted arene (**3**).

The formation of coupled product (**4**) could also occur by a reductive elimination process from intermediate **2a**. In this case, reductive elimination of Ph–Ar would directly afford the biphenyl derivative (**4**). The observation that less coupled product is observed for the amido derivative (**1e**) than for the oxazoline derivative (**1d**) can be explained by assuming that reductive elimination of Ph–Ar is less favoured (in comparison to Ph–X) when there is an amido group present on the aryl group than when there is an oxazoline group. Using a

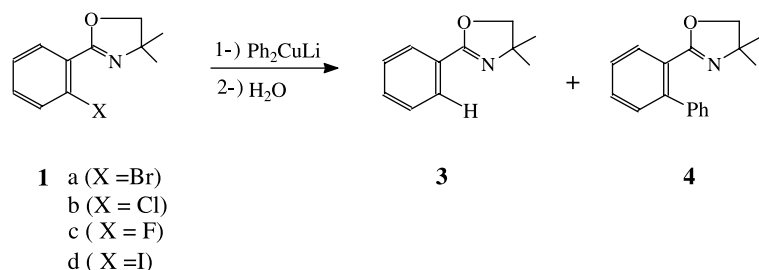
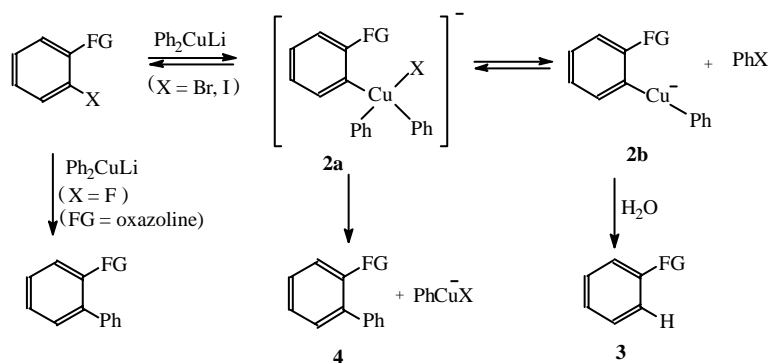


Table 1
Conditions and product yields for the reaction of *o*-substituted haloarenes with $\text{Ph}_2\text{CuLi} \cdot \text{LiCN}$ followed by aqueous quench

Entry	Aryl halide	Conditions	Yield (%)	
			Product of type 3	Product of type 4
1	1a	0 °C, 30 min	74	–
2	1b	35 °C, 60 min	–	–
3	1c	35 °C, 60 min	–	68
4	1d	0 °C, 30 min	40	50
5	<i>N,N</i> -Diethyl-2-iodobenzamide (1e)	0 °C, 30 min	86	–



similar reasoning, our observation that more unsubstituted product (**3**) was obtained for the bromo derivative (**1a**) than for the iodo derivative (**1d**) can therefore possibly be explained by assuming that PhBr is more readily eliminated than PhI from intermediate **2a**. This is consistent with the fact that C–I bonds are significantly weaker than C–Br bonds.

Having confirmed that metal–halogen exchange seems to occur in these systems, the next step was to allow the metallated arenes to react with electrophiles. The bromooxazoline derivative (**1a**), and the iodoamido derivative (**1e**) were selected for these reactions because of their earlier success in reaction to produce products of type **3** (see Table 1). Thus, **1a** and **1e** were treated first with $\text{Ph}_2\text{CuLi} \cdot \text{LiCN}$ and then subsequently with benzylbromide or benzylchloride. It was observed that there were two major products formed from these reactions, arising from incorporation of either the electrophile or hydrogen into the aryl group. The results of these reactions are given in Table 2.

From the table, it can be seen that coupling of the functionally substituted aryl cuprate reagent with the electrophile to produce **5** has indeed occurred. Thus, metallation of **1e** followed by reaction with benzyl bromide gives a 23% yield of the coupled product (**5e**). Similarly, metallation of **1a**, followed by reaction with benzyl chloride afforded the coupled product (**5a**) in 35% yield. In addition to the desired product, however, significant amounts of the unsubstituted product (**3**) were also obtained. As the yields of products are quoted according to the starting aryl halide, yields of less than 50% of the desired product (**5**) are comparable with yields typically obtained for the reactions of cuprate reagents with electrophiles. This is because only one of the two anionic organic groups of a cuprate reagent are typically transferred in such reactions. However, in the reaction of **2b** with electrophiles, it would be expected that the phenyl group would first be transferred, not the functionally substituted aryl group. Although it is possible that the observed yields could be explained by as-

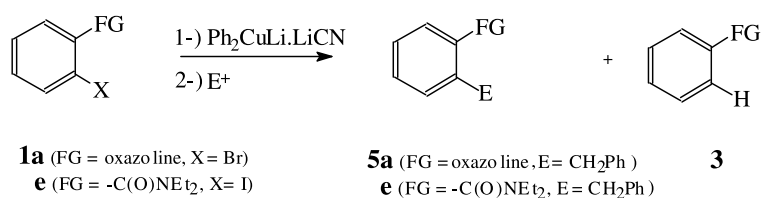


Table 2

Conditions and product yields for the reaction of o-substituted haloarenes **1a** and **1e** with $\text{Ph}_2\text{CuLi} \cdot \text{LiCN}$ followed by the addition of electrophiles

Entry	Aryl Halide	Electrophiles	Yield (%)	
			Product (5)	Product (3)
1	1a	PhCH_2Br	30	10
2	1a	PhCH_2Cl	35	10
3	1e	PhCH_2Br	23	40
4	1e	PhCH_2Cl	10	56

suming that transfer of either anionic aromatic group occurs with equal ease, or that a homocuprate reagent, $\text{Ar}_2\text{CuLi} \cdot \text{LiCN}$ has been formed by displacement of both Ph groups from Ph_2CuLi , it seems more likely that the product (**5**) is formed by transfer of an aromatic group from a secondary intermediate, presumably, $\text{Ar-Cu} \cdot \text{LiCN}$.

In summary, metal–halogen exchange does appear to occur for these functionally substituted aryl halides. In some cases, the metallated arene can subsequently be

used to combine with electrophiles to give coupled products in moderate yields. The conditions for these reactions are both mild and extremely accessible. Thus the *N,N*-diethylbenzamide derivative (**1e**) is metallated at 0 °C over 30 min. In contrast, the traditional procedure for the preparation of orthometallated benzamide derivatives would involve first orthometallation of *N,N*-diethylbenzamide at –78 °C by the use of a *sec*-BuLi–TMEDA complex [13]. This would then be followed by transmetallation reactions [13–15]. These conditions are clearly less convenient than for our procedure. Furthermore the use of the Li reagent in the initial step clearly limits the number of functional groups that can be tolerated. In contrast, our procedure only involves the use of Ph₂CuLi·LiCN and so such a problem is not inherent. Therefore, we feel strongly that this method bears further potential for the coupling of certain sensitive and functionally substituted organic compounds where both mild and convenient conditions are desirable.

3. Experimental

Oxazoline derivatives were prepared according to the literature method [16]. All reactions involving organometallic intermediates were carried out under dry nitrogen using standard Schlenk techniques. Ether was dried and distilled from sodium and benzophenone before use. The diphenylcuprate reagent was prepared from freshly prepared PhLi and CuCN in ether at 0 °C for 30 min. A weighed sample of aryl halide (0.25 eq) was subsequently added dropwise to the mixture. Optimum times and temperatures for these reactions are given in Table 1. To the reaction mixture was then added dilute NH₄Cl solution (Table 1) or electrophile (Table 2). Reactions with electrophiles were carried out by stirring at RT for 15 min (**1e**) or 1 h (**1a**). Column chromatography using Si gel and hexane/ethyl acetate (20/1) was used to purify the products. Products were analysed by IR, and ¹H NMR spectroscopy. All products have been previously prepared and comparisons of spectroscopic data with literature data were made.

(1) *2-(1,1'-biphenyl)-4,5-dihydro-4,4-dimethyloxazole* (**4**) [14]. IR (cm⁻¹) 1649, 1457; ¹H NMR (CDCl₃) δ 7.65 (1H, d, *J* = 7.7 Hz) 7.41 (1H, td, *J*_t = 7.5, *J*_d = 1.4 Hz), 7.23–7.35 (7H, m), 3.79 (2H, s), 1.20 (6H, s).

(2) *2-(2'-(phenylmethyl)phenyl)-4,5-dihydro-4,4-dimethyloxazole* (**5a**) [17]. IR (cm⁻¹) 1640, 1455; ¹H NMR (CDCl₃) δ 7.68 (1H, dd, *J* = 7.7, 1.3 Hz) 7.27 (1H, td, *J*_t = 7.5, *J*_d = 1.4 Hz), 7.04–7.20 (7H, m), 4.35 (2H, s), 3.85 (2H, s), 1.20 (6H, s).

(3) *N,N*-diethyl-2-(phenylmethyl)benzamide (**5e**) [13]. IR (cm⁻¹) 1634, 1428; ¹H NMR 7.10–7.40 (9H, m), 3.95 (2H, br), 3.57 (1H, br), 3.29 (1H, br), 2.76 (2H, br) 1.11 (3H, t, *J* = 7.1), 0.88 (3H, t, *J* = 7.1).

Acknowledgements

We thank the Science Faculty of Ege University and the Scientific and Technical Research Council of Turkey (TÜBİTAK) for their financial support.

References

- [1] F. Diederich, P.J. Stang (Eds.), *Metal-Catalyzed Cross-Coupling Reactions*, Wiley/VCH, Weinheim, 1998.
- [2] (a) I. Owao, *Applications of Organometallic Compounds*, Wiley, London, 1998;
(b) B.H. Lipshutz, *SynLett* (1990) 119.
- [3] (a) H. Chaumeil, S. Signorella, C. Le Drian, *Tetrahedron* 56 (2000) 9655;
(b) W. Dohle, D.M. Lindsay, P. Knochel, *Org. Lett.* 3 (2001) 2871;
(c) T. Wanatabe, N. Miyaura, A. Suzuki, *SynLett* (1992) 207.
- [4] (a) C. Griffiths, N.E. Leadbeater, *Tetrahedron Lett.* 41 (2000) 2487;
(b) A.E. Jensen, W. Dohle, P. Knochel, *Tetrahedron* 56 (2000) 4197;
(c) A. Boudier, L.O. Bromm, M. Lotz, P. Knochel, *Agnew. Chem., Int. Ed.* 39 (2000) 4414–4435.
- [5] S. Karagöz, D.K. Astley, S.T. Astley, *Appl. Organometal. Chem.* 14 (2000) 341.
- [6] M.B. Smith, J. March, *Advanced Organic Chemistry*, fifth ed., Wiley, New York, 2002, p. 803.
- [7] R.M. Gschwind, P.R. Rajamohanan, M. John, G. Boche, *Organometallics* 19 (2000) 2868.
- [8] (a) G.M. Whitesides, W.F. Fischer Jr., J. San Filippo Jr., R.W. Bashe, H.O. House, *J. Am. Chem. Soc.* 91 (1969) 4871;
(b) H.O. House, D.G. Koepsell, W.J. Campbell, *J. Org. Chem.* 37 (1972) 1003.
- [9] W.E. Parham, C.K. Bradsher, *Acc. Chem Res.* 15 (1982) 300.
- [10] A.I. Meyers, B.E. Williams, *Tetrahedron Lett.* (1978) 223.
- [11] An alternative mechanism could feasibly occur by binuclear oxidative addition to a dimeric contact ion pair form of the cuprate. The observed products could subsequently be obtained from this intermediate by binuclear reductive elimination processes. See J.P. Collman, L.S. Hegedus, J.R. Norton, R.G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill valley, 1987, p. 686.
- [12] T.T. Tsou, J.K. Kochi, *J. Am. Chem. Soc.* 101 (1979) 6319.
- [13] R. Casas, C. Cave, J. d' Angelo, *Tetrahedron Lett.* 36 (1995) 1039.
- [14] K. Koch, R.J. Chambers, M.S. Biggers, *SynLett* 5 (1994) 347.
- [15] J.F. Eaddy, *Org. Prep. Proc. Int.* 27 (1995) 367.
- [16] A.I. Meyers, D.L. Temple, D. Haidukewych, E.D. Mihelich, *J. Org. Chem.* 39 (1974) 2787.
- [17] J.M. Kane, C.R. Dalton, N.L. Velago, D. Rampe, *Biorg. Med. Chem. Lett.* 5 (1995) 873.