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Successive Iodine–Magnesium or –Copper Exchange Reactions for the Selective Functionalization of Polyhalogenated Aromatics

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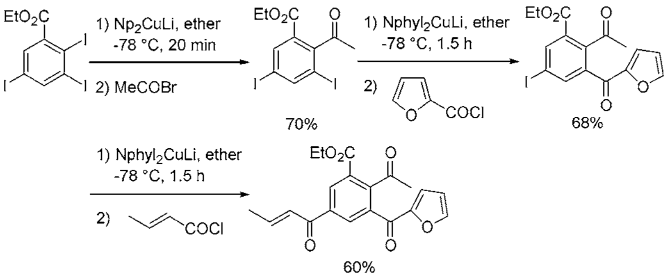
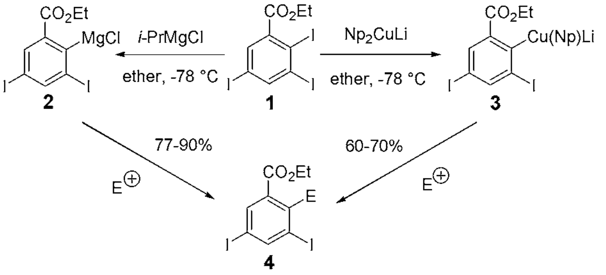
ABSTRACT



The presence of an electron-withdrawing group or chelating group was found to direct the halogen–copper and halogen–magnesium exchange with various di- or trihalogenated aromatics. Starting with a triiodobenzoate derivative, a range of tetraacylated benzenes could be prepared and used for a short synthesis of benzodiazines.

The halogen−metal exchange is a general and chemoselective method for preparing functionalized magnesium[1,2] and copper[3] reagents. It tolerates a wide range of functional groups and allows the preparation of various polyfunctional magnesium and copper organometallics. The rate of the halogen−metal exchange greatly depends on the electron-density of the aromatic or heterocyclic ring, so that an aromatic or heterocyclic dibromide or diiodide undergoes only a monoexchange.[4] Herein, we wish to report that polyhalogenated aromatics react with high regioselectivity and that up to three consecutive I/Cu exchange reactions can be performed with excellent regiocontrol leading to new polyacylated aromatics that are difficult to prepare by standard methods. Thus, readily available ethyl 2,3,5-triiodobenzoate[5] **1** was treated in diethyl ether either with *i*-PrMgCl (1.1 equiv, −78 °C, 1 h) leading to the Grignard reagent **2** or with lithium bis-neopentylcuprate (Np_2CuLi; 1.1 equiv, −78 °C, 20 min)[3a] furnishing the mixed lithium cuprate **3** (Scheme 1).

Scheme 1. Regioselective Iodine/Metal Exchange Reactions



Both organometallic species **2** and **3** reacted with various electrophiles providing products of type **4** (Scheme 1 and Table 1).

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[1] (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701. (b) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565. (c) Kneisel, F. F.; Knochel, P. *Synlett* **2002**, 1799.

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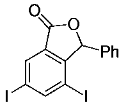
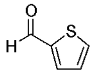
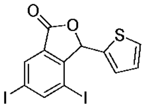
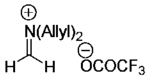
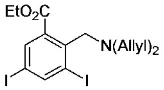
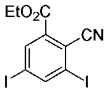
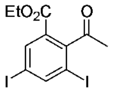
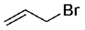
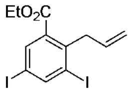
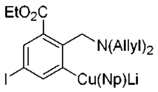
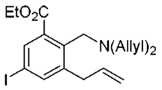
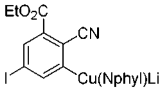
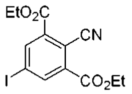
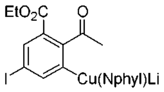
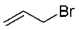
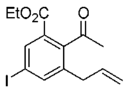
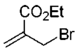
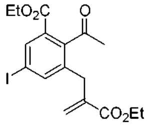
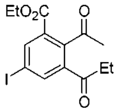
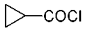
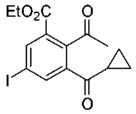
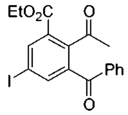
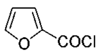
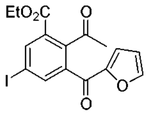
Table 1. Reactions of Polyfunctional Magnesium and Copper Organometallics of Type **2** or **3** with Various Electrophiles

entry	reagent 2 or 3	electrophile	product of type 4	yield (%)[a]
1	**2**	PhCHO	 **4a**	77
2	**2**		 **4b**	83
3	**2**		 **4c**	85
4	**2**	TosCN	 **4d**	90
5	**3**	CH_3COX^b	 **4e**	60 (70)[c]
6	**3**		 **4f**	62

[a] Yield of Analytically Pure Product. [b] X = Cl or Br. [c] Yield Obtained with AcBr.

Table 2. Selective Formation of Polyfunctional Monoiodoaryl Copper **5a**−**c** from Diiodobenzenes **4c**−**e** and Reactions with Electrophiles Leading to Products of Type **6**

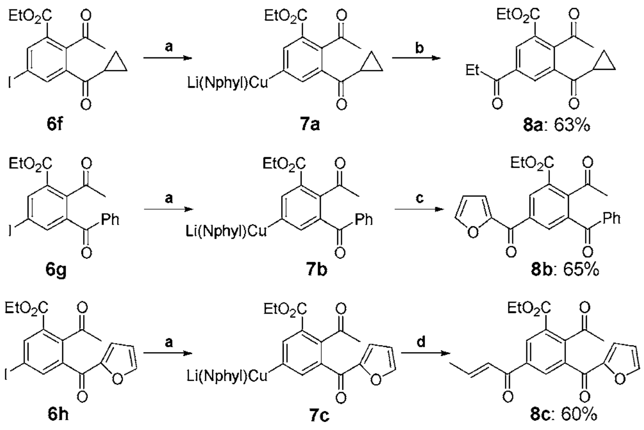
entry	reagent	electrophile	product of type 8	yield (%)[a]
1	 **5a**		 **6a**	65
2	 **5b**	NC-CO_2Et	 **6b**	70
3	 **5c**		 **6c**	75
4	**5c**		 **6d**	70
5	**5c**	EtCOCl	 **6e**	66
6	**5c**		 **6f**	64
7	**5c**	PhCOCl	 **6g**	70
8	**5c**		 **6h**	68

[a] Yield of analytically pure product.

Thus, the reaction of the functionalized arylmagnesium reagent **2** with aromatic or heterocyclic aldehydes gave the corresponding lactones **4a**,**b** in 77 and 83% yields, respectively (entries 1 and 2 of Table 1). An iminium salt like diallyl(methylene)ammonium trifluoroacetate[6] readily reacted with **2** providing the diallylamine **4c** in 85% yield (entry 3 of Table 1). Also, the reaction with tosyl cyanide[7] led to the diiodobenzonitrile derivative (**4d**) in 90% yield. The mixed lithium cuprate **3** reacted well with acyl halides and allyl bromide.[8] The acylation of cuprate **3** with acetyl chloride led to the keto ester **4e** in 60% yield. This result could be improved by using acetyl bromide that gave **4e** in 70% yield.[9] The allylation of cuprate **3** led to the expected product **4f** (entry 6). The observed selectivity of the iodine−metal exchange of the triiodobenzoate **1** was explained by a precomplexation of *i*-PrMgCl or Np_2CuLi to the ester function that favors the iodine−metal exchange in the *ortho*-position.

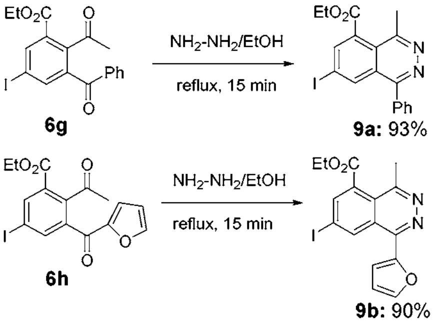
Selected products of type **4** have again been submitted to an iodine−copper exchange reaction. In the case of the diiodide **4c** (entry 3 of Table 1), which contained no sensitive functionality, the second exchange was performed with Np_2CuLi leading, after allylation, to iodoester **6a** in 65% yield (entry 1 of Table 2). In all other cases, where more sensitive functional groups were present in the starting diiodide **4**, the more selective lithium dineophylcuprate ($(Ph(Me)_2C-CH_2)_2CuLi$; $Nphyl_2CuLi$) has been used.[3a] This reagent was able to perform an I/Cu exchange in the presence of a methyl ketone.[3a] It was also readily prepared from inexpensive 2,2-dimethyl-2-phenylethyl chloride via the intermediate NphylLi obtained by the direct reaction of NphylCl with lithium powder.[3a] Thus, the reaction of the diiodobenzonitrile derivative **4d** with $Nphyl_2CuLi$ (THF, −78 °C, 2 h) only led to the formation of the mixed copper reagent **5b** (entry 2 of Table 2). Its reaction with ethyl cyanoformate (from −78 to 25 °C, 24 h) furnished the symmetrical product **6b** in 70% yield. The iodoaryl methyl ketone **4e** was selectively converted to the copper reagent **5c** (ether, −78 °C, 2 h) and

Scheme 2. Preparation of Tetraacylated Arenes via an I/Cu Exchange Reaction[a]



[a] Reagents and conditions: (a) Nphyl$_2$CuLi, THF, −78 °C, 1.5 h; (b) propionyl chloride, THF, from −78 to 0 °C, 3 h; (c) 2-furoyl chloride, THF, from −78 to 0 °C, 3 h; (**d**) *trans*-crotonyl chloride, THF, from −78 to 0 °C, 3 h.

Scheme 3. Synthesis of Benzodiazines of Type 9



treated with various allylic bromides[10] (entries 3 and 4) leading to the desired products **6c** and **6d** in 75 and 70% yields, respectively. Also a range of aliphatic, aromatic, and heterocyclic acid chlorides were treated with **5c** providing the corresponding ketones **6e−h** in 64−70% yield (entries 5−8 of Table 2). In each case, a selective I/Cu exchange has been observed. This selectivity was due to the presence of an *ortho*-substituent,[11] which by chelating or inductive effect directed the I/Cu exchange reaction.

Finally, a third I/Cu exchange was performed on diketoesters **6f−h**. Their reactions with Nphyl$_2$CuLi (THF, −78 °C, 1.5 h) produced the corresponding copper reagents **7a−c**, which reacted with various aliphatic, heterocyclic, or unsaturated acid chlorides leading to the tetraacylated benzenes **8a−c** in 60−65% yield (Scheme 2). Compounds of type **8** are very difficult to prepare by standard methods. Our synthesis offers a general approach to this new class of functionalized aromatic molecules.

These polyacylated compounds are very useful for the synthesis of heterocycles. This was demonstrated by treating dicarbonylated iodoarenes **6g** and **6h** with hydrazine in ethanol (reflux, 15 min) providing polyfunctional[12] benzodiazines **9a** and **9b** in 90−93% yield (Scheme 3).

In summary, we have shown that functionalized di- or triiodoarenes can undergo a selective I/Cu and I/Mg exchange reaction. The I/Cu exchange was found to be superior to the I/Mg exchange if sensitive functional groups such as acyl groups were present in the starting aryl polyiodides. A range of new polyacylated benzenes such as **8a−c** became available by this method.[13] Further applications to the preparation of polyfunctional heterocycles and molecules of biological interest are currently underway.

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Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) (a) Lee, J.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428. (b) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481. (c) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.

(3) (a) Piazza, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3263. (b) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615. (c) Kondo, Y.; Matsudaira, T.; Sato, J.; Muraka, N.; Sakamoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 736.

(4) (a) Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett* **2001**, *4*, 477. (b) Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449. (c) Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 351. (d) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1999**, *40*, 4339.

(5) 2,3,5-Triiodobenzoic acid is commercially available from Aldrich.

(6) Millot, N.; Piazza, C.; Avolio, S.; Knochel, P. *Synthesis* **2000**, *7*, 941.

(7) Klement, I.; Lennick, K.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 4623.

(8) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

(9) **Typical Procedure: Preparation of 4e.** A dry and argon-flushed 50 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of ethyl 2,3,5-triiodobenzoate (528 mg, 1.0 mmol) in dry diethyl ether (30 mL). Np$_2$CuLi (1.0 M/Et$_2$O, 1.1 mmol, 1.1 equiv) was added slowly at −78 °C, and the resulting mixture was stirred at this temperature for 20 min to complete the iodine−copper exchange (checked by GC-MS analysis of reaction aliquots). Then, acetyl bromide (369 mg, 3.0 mmol, 3.0 equiv) was added. The mixture was warmed to 0 °C, and the reaction was quenched after 30 min with saturated aqueous NH$_4$Cl solution; the mixture was then poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3 × 80 mL). The organic fractions were washed with brine (80 mL), dried over MgSO$_4$, and concentrated in vacuo. Purification by flash chromatography (*n*-pentane/diethyl ether = 10:1) yielded 310 mg (70% yield) of **4e** as a white solid, mp 76 °C.

(10) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.

(11) This effect has been extensively used to perform *ortho*-directed metalations: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(12) Haddadin, M. J.; Agha, B. J.; Tabri, R. F. *J. Org. Chem.* **1979**, *44*, 494.

(13) **Typical Procedure: Preparation of 6g.** A dry and argon-flushed 100 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of ethyl 2-acetyl-3,5-diiodobenzoate (444 mg, 1.0 mmol) in dry diethyl ether (50 mL). (Nphyl)$_2$CuLi (1.5 M/Et$_2$O, 1.1 mmol, 1.1 equiv) was added slowly at −78 °C. After 1 h, the iodine−copper exchange was complete (checked by GC-MS analysis of reaction aliquots). Then, benzoyl chloride (422 mg, 3.0 mmol, 3.0 equiv) was added. The mixture was warmed to 0 °C, and the reaction was quenched with saturated aqueous NH$_4$Cl solution after 3 h; the mixture was then poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3 × 80 mL). The organic fractions were washed with brine (80 mL), dried over MgSO$_4$, and concentrated in vacuo. Purification by flash chromatography (*n*-pentane/diethyl ether = 2:1) yielded 295 mg (70%) of **6g** as a colorless oil.