Iodine-Zinc Exchange Reactions Mediated by *i*-Pr_2Zn. A New Preparation of Secondary Zinc Reagents

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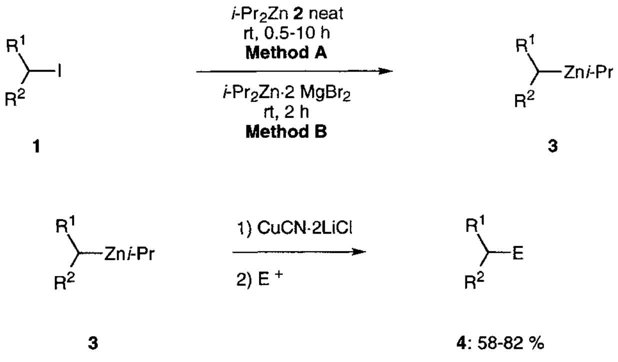
Abstract: By treatment with *i*-Pr_2Zn, functionalized secondary alkyl iodides undergo a smooth iodine-zinc exchange reaction leading to polyfunctional secondary dialkylzinc derivatives. Remarkably, *i*-Pr_2Zn generated *in situ* from *i*-PrMgBr and $ZnBr_2$ undergoes this exchange reaction almost 200 times faster than salt free *i*-Pr_2Zn and constitutes a practical source of *i*-Pr_2Zn for the performance of exchange reactions.

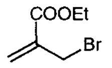
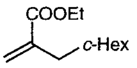
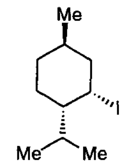
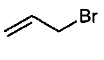
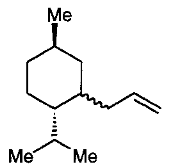
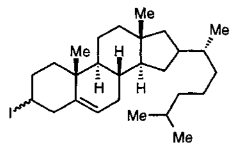
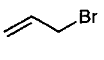
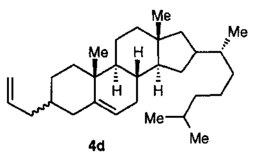
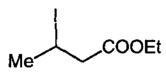
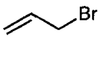
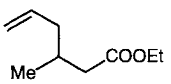
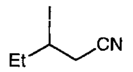
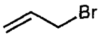
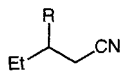
The iodine-lithium exchange reaction is an important method for the preparation of organolithiums.[1] The corresponding iodine-magnesium exchange reaction[2] has received little attention but the iodine-zinc exchange[3] has found many synthetic applications. It allows a general route to primary dialkylzincs which prove to be very useful in asymmetric synthesis.[4] Although this method gives a unique access to various zinc organometallics, it has several drawbacks: (i) it can be performed only with primary alkyl iodides; (ii) it often requires high reaction temperatures (50-60 °C) and long reaction times (6-18 h); (iii) the reaction has to be performed with Et_2Zn neat which is a pyrophoric compound.



E = allylic bromide, alkynyl bromide, acid chloride

Scheme 1

Table 1. Products of type **4** obtained by an iodine-zinc exchange from secondary alkyl iodides of type **1** followed by the reaction with an electrophile after transmetalation with CuCN•2LiCl

entry	alkyl iodide **1**	method[a]	electrophile	product **4**	yield (%)[b]
1	*c*-Hex-I	A, B		 **4a**	64 (64)[c]
2	*c*-Hex-I	A	Ph—C≡C—Br	Ph—C≡C—*c*-Hex **4b**	62
3		B		 **4c**	61
4		B		 **4d**	58
5		A, B		 **4e**	77 (70)[c]
6		A		 **4f** : R = allyl	68
7		A	Ph—C≡C—Br	**4g** : R = C≡C-Ph	65
8		A	PhCOCl	**4h** : R = COPh	82

[a] Method A: *i*-Pr_2Zn (1.5 equiv), neat, rt, 1-10 h, Method B: *i*-PrMgBr (3 equiv); $ZnBr_2$ (1.5 equiv), ether (ca. 0.3 M solution), rt, 1h.
[b] Isolated overall yield based on the alkyl iodide of analytically pure products.
[c] The yield in parantheses refers to the reaction performed accorded to method B.

Herein, we wish to report a significant extension of the iodine-zinc exchange reaction which allows to convert also *secondary* alkyl iodides into the corresponding zinc organometallics and which circumvents the manipulation of pyrophoric organozinc reagents. Thus, the treatment of a secondary alkyl iodide **1** with neat i-Pr$_2$Zn[5] **2** (1.5 equiv.; Method A) or with an etheral solution of i-Pr$_2$Zn • 2MgBr$_2$ (Method B) furnishes the desired mixed diorganozinc compound of type **3** in ca. 80 %. After transmetalation with CuCN • 2LiCl[6] and addition of an electrophile (allylic halide, acid chloride, alkynyl halide) the expected products **4** are obtained in good overall yields (Scheme 1 and Table 1).

Thus, cyclohexyl iodide reacts with i-Pr$_2$Zn in the absence of solvent reaching an equilibrium conversion of ca. 84 % (GC yield determined by iodolysis) after a reaction time of 10 h at rt (Method A). Remarkably, i-Pr$_2$Zn generated *in situ* by the reaction of i-PrMgBr (2 equiv) with ZnBr$_2$ (1 equiv) in ether (0.3 M solution) leads to the same conversion of 84 % after a reaction time of 1 h showing a rate acceleration compared to neat i-Pr$_2$Zn of ca. 200 times. After transmetalation with CuCN • LiCl[6] and allylation with ethyl (α-bromomethyl)acrylate[7] (3 equiv, -78 °C to 25 °C, 1 h) the expected allylated product **4a** is obtained in 64 % yield (entry 1 of Table 1). An excess of electrophile was used in these reactions in order to quench also the i-Pr group of the mixed zinc reagents **3**. No attempt was made to distill off the excess i-Pr$_2$Zn before adding the electrophile. A range of other electrophiles can be treated with these secondary zinc compounds. The reaction of the copper derivative of cyclohexyl(isopropyl)zinc with 2-bromo-1-phenylacetylene[8] leads to the disubstituted alkyne **4b** in 62 % yield (see entry 2). As noticed previously organozinc derivatives catalyze the isomerization of secondary alkyl iodides.[9] Thus the treatment of menthyl iodide[10] with i-Pr$_2$Zn • 2MgBr$_2$ furnishes after allylation a mixture of epimeric allylated products **4c**. This experiment shows that the iodine-zinc exchange reaction proceeds at secondary carbon centers with racemization. More complex alkyl iodides like a steroid undergo the exchange reaction as well leading after allylation to the product **4d** in 58 % yield (entry 4 of Table 1). The iodine-zinc exchange can also be applied to polyfunctional secondary alkyl iodides and the reaction of ethyl 3-iodobutyrate is complete whithin a few minutes at rt. After allylation with allyl bromide in the presence of a catalytic amount or stoichiometric amount of CuCN • 2LiCl, the expected product **4e** is obtained in 77 % using Method A and 70 % according to Method B. Similarly, the secondary iodonitrile, 3-iodopentanenitrile, is converted within 0.5 h to the corresponding secondary zinc reagent and trapped, after transmetalation to the corresponding copper reagent, with various electrophiles leading to the polyfunctional nitriles **4f-h** in 68-82 % yield (see entries 6-8 of Table 1).

In summary we have developed a general and practical method for performing an iodine-zinc exchange reaction with secondary alkyl iodides leading to mixed secondary diorganozincs.[11] The scope and applications of this method are currently under study in our laboratory.[12]

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12. **Typical procedures:**

a) Preparation of 1-phenyl-2-cyclohexylacetylene (**4b**). (**Method A**; entry 2 of Table 1).

Diisopropylzinc (2.1 g, 13.5 mmol, 1.5 equiv) was added to cyclohexyl iodide (1.83 g, 8.7 mmol, 1 equiv) under argon at rt. The reaction mixture was stirred for 10 h and the excess of i-Pr$_2$Zn was distilled off (rt, 1 h, 1 mmHg). A mixture of CuCN (1.79 g, 20 mmol) and LiCl (1.70 g, 40 mmol) was dried at 130 ¡C (0.1 mmHg), dissolved in THF (20 mL) and added to the previously prepared solution of the zinc reagent. 2-Bromo-1-phenylacetylene (3.6 g, 20 mmol) was added at -78 °C. The reaction mixture was slowly allowed to warm to rt and was worked up as usual affording a crude oil which was purified by flash chromatography (hexanes) providing the product **4b** (1.0 g, 5.4 mmol, 62 % yield).

b) Preparation of ethyl 2-(methylcyclohexyl)acrylate (**4a**). (**Method B**; entry 1 of Table 1).

A solution of isopropylmagnesium bromide (48 mL, 29.0 mmol, 0.6 M in ether, 3 equiv) was added to zinc bromide (3.56 g, 14.5 mmol) under argon atmosphere. The reaction mixture was stirred for 0.5 h at rt leading to a clear solution. Cyclohexyl iodide (2.0 g, 9.6 mmol) was added. The reaction mixture was stirred for 1 h at rt and a THF solution of CuCN • 2LiCl (20 mmol, prepared as described above) was added at -78 °C followed by the addition of ethyl (α-bromomethyl)acrylate (5.80 g, 30 mmol). The reaction mixture was warmed up to 0 °C and was worked up as usual affording after flash chromatography (ether / hexanes) the product **4a** (1.20 g, 6.10 mmol, 64 % yield).