Preparation of New Functionalized Cyclopropylmagnesium Reagents**

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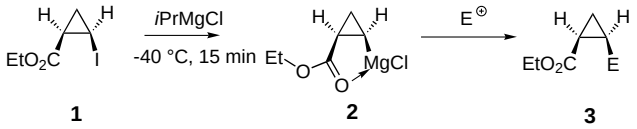
Functionalized organometallic compounds are important reagents for the preparation of complex polyfunctional molecules.[1] Recently, we have shown that polyfunctional aryl-, heteroaryl-, and alkenylmagnesium halides can be readily prepared by using an iodine–magnesium exchange reaction.[2, 3] Herein, we report the preparation of the first functionalized cyclopropylmagnesium[4] reagents bearing an ester group, as well as the stereoselective preparation of functionalized cyclopropylmagnesium carbenoids.[5] The iodine–magnesium exchange is a fast reaction with aromatic iodides bearing electron-withdrawing groups, however, it is considerably slower with alkyl iodides where competitive substitution and elimination reactions can occur. Therefore, we have directed our first investigations towards cyclopropane derivatives where substitution and elimination side reactions are difficult.[6] Thus, the readily available 2-iodocyclopropanecarboxylate[7] **1** was treated with *i*PrMgCl (1.1 equiv) in THF at −40 °C for 15 min and afforded the corresponding *cis*-cyclopropylmagnesium chloride **2** (Scheme 1). This reagent shows excellent stability as a consequence of the presence of the ester group which has stabilizing chelating and inductive effects.[8] Compound **2** can be trapped with retention of configuration by a range of electrophiles either directly (reaction with Me_3SnCl, PhSSPh, toluene-4-sulfonyl cyanide (TosCN),[9] or aldehydes) or after catalytic transmetalation to copper (reaction with allylic bromides and chlorides)[10] or palladium (reaction with functionalized aryl iodides) to give products of type **3** (Scheme 1 and Table 1).



Scheme 1. Synthesis of a functionalized cyclopropylmagnesium reagent by an iodine–magnesium exchange.

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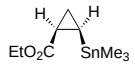
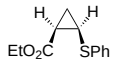
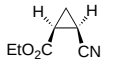
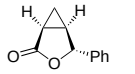
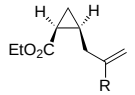
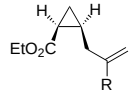
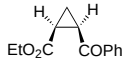
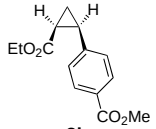
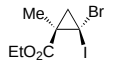
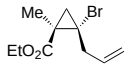
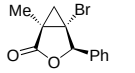
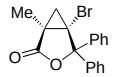
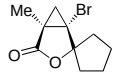
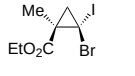
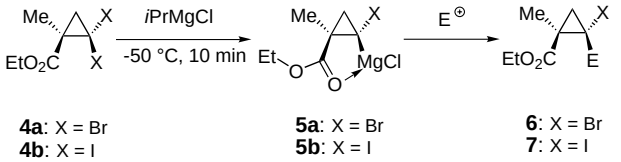
Table 1. Reactions of functionalized magnesium reagents **2**, **5a**, and **5b** with electrophiles that lead to products of type **3**, **6**, and **7**.

Entry	Grignard reagent	Electrophile	Product of type **3** or **6**	Yield [%][a]
1	**2**	Me_3SnCl	 **3a**	67
2	**2**	PhSSPh	 **3b**	52
3	**2**	TosCN	 **3c**	67
4	**2**	PhCHO	 **3d**	90[b]
5	**2**	allyl bromide	 **3e** (R = H)	75
6	**2**	ethyl (2-bromomethyl)acrylate	 **3f** (R = CO_2Et)	81
7	**2**	PhCOCl	 **3g**	73
8	**2**	4-iodobenzoic acid methyl ester	 **3h**	92
9	**5a**	I_2	 **6a**	85
10	**5a**	allyl bromide	 **6b**	64
11	**5a**	PhCHO	 **6c**	60[c]
12	**5a**	Ph_2CO	 **6d**	61
13	**5a**	C_5H_8O	 **6e**	61
14	**5b**	$(BrCl_2C)_2$	 **7a**	80

[a] Yield of analytically pure isolated product. [b] d.r. = 65:35. [c] d.r. = 92:8.

In the case of the reaction with benzaldehyde, a spontaneous lactonization occurs to give the lactone **3d** as a separable mixture of two diastereoisomers in the ratio of 65:35 (entry 4 of Table 1). In the presence of $CuCN \cdot 2\,LiCl$,[11] a smooth reaction proceeds with allyl bromide and ethyl (2-bromomethyl)acrylate[12] or benzoyl chloride (entries 5–7). A fast Negishi cross-coupling reaction[13] takes place after transmetalation to the corresponding zinc reagent with $ZnBr_2$. An efficient cross-coupling takes place in the presence of bis-dibenzylidenepalladium(0)[14] and tris-*o*-furylphosphane[15] to give the diester **3h** in 92% yield (25 °C, 6 h, entry 8). Since magnesium carbenoids are an important class of organometallic reagents,[16] we have examined the formation of carbenoids[17] bearing an ester group. The dibromocyclopropanecarboxylic acid ethyl ester **4a**[18] was treated with *i*PrMgCl (1.1 equiv) in THF which resulted in the formation of a 65:35 mixture of diastereomeric carbenoids as indicated by quenching experiments with electrophiles (Scheme 2). The major diastereoisomer was the Grignard reagent **5a**. This ratio of diastereomers did not significantly change with time. However, a completely stereoselective exchange was observed on performing the Br–Mg exchange in diethyl ether (−50 °C, 10 min). This reaction resulted in the formation of the *cis*-magnesium carbenoid **5a** (d.r. > 99:1) which can be stereoselectively trapped by several electrophiles (Scheme 2 and Table 1).



4a: X = Br
4b: X = I

5a: X = Br
5b: X = I

6: X = Br
7: X = I

Scheme 2. Synthesis of carbenoids bearing an ester group.

Thus, the reaction of the ester-substituted carbenoid **5a** with iodine furnishes stereoselectively the iodobromocyclopropane **6a** in 85% yield (entry 9). Similarly, the quenching of **6a** with allyl bromide furnishes the expected allylated product **6b** in 64% yield. The reaction of **5a** with various aldehydes or ketones proceeds readily and leads to lactones **6c–e** in 60–61% yield. The reaction with benzaldehyde was highly diastereoselective (d.r. = 92:8) to give **6c** (major isomer depicted in entry 11; its structure has been proven by X-ray analysis[19]) in 60% yield. Interestingly, the reaction of carbenoid **5b** generated by the reaction of *i*PrMgCl with the diiodocyclopropanecarboxylic acid ethyl ester **4b**[20] in diethyl ether at −50 °C is also highly diastereoselective. the isomeric iodobromocyclopropane derivative **7a** is formed in 80% yield (compare entries 9 and 14) after quenching carbenoid **5b** with 1,2-dibromotetrachloroethane.

In summary, we have reported the stereoselective preparation of functionalized cyclopropylmagnesium derivatives including carbenoids. Under our reaction conditions they are configurationally stable. Applications of these versatile cyclopropylmagnesium reagents and extensions of the preparation of other functionalized alkylmagnesium reagents are currently underway.

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