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Stereoselective Functionalization of Cyclopropane Derivatives Using Bromine/Magnesium and Sulfoxide/Magnesium Exchange Reactions

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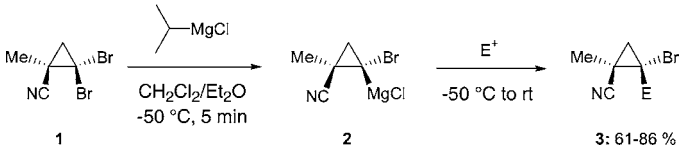
ABSTRACT



The reaction of 2,2-dibromo-1-methyl-cyclopropanecarbonitrile (1) with *i*-PrMgCl in Et_2O/CH_2Cl_2 provides the *cis*-magnesium-carbenoid (2), which reacts with high retention of configuration with various electrophiles. If E = SPh, a stereoselective generation of a quaternary center via a sequential Br/Mg- and sulfoxide/Mg-exchange can be achieved.

The functionalization of cyclopropane derivatives has been extensively investigated.[1] Since *gem*-dibromocyclopropanes are readily available,[2] we have examined the stereoselective magnesiation of the functionalized cyclopropane 2,2-dibromo-1-methyl- cyclopropanecarbonitrile (**1**).[3] Whereas the treatment of the dibromide **1** with *i*-PrMgCl in THF or Et_2O[4] at low temperature leads to products in low yields, it was found that the reaction of **1** with *i*-PrMgCl in a mixture of Et_2O and CH_2Cl_2 (1:4) at −50 °C leads within 5 min to the clean formation of the *cis*-cyclopropylmagnesium reagent **2**. The quenching of **2** with aqueous ammonium chloride affords only the *trans*-2-bromocyclopropanecarbonitrile (**3a**) in 76% yield with a diastereomeric ratio of >99:1 (entry 1 of Table 1). The high diastereoselectivity of the exchange reaction is presumably caused by the nitrile function, which can direct the exchange reaction by precoordination. The reaction of magnesium reagent **2** with iodine provides the desired iodobromocyclopropane **3b** with a diastereoselectivity of 91:9 and a yield of 77% (entry 2). The reaction of the cyclopropylmagnesium derivative **2** with $MeSSO_2Me$ and $PhSSO_2$-Ph provides the corresponding thioethers **3c** (72%; dr = 93:7) and **3d** (86%; dr = 95:5; entries 3 and 4). An X-ray analysis of the thioether **3d** confirmed the cis configuration of the cyano and thiophenyl groups (Figure 1). The reaction of **2** with *N*,*N*-diethylaminomethylbenzotriazole[5] provides the aminomethylated product **3e** in 79% yield (dr = 96:4; entry 5). Finally, the reaction of the magnesium carbenoid **2** with allyl bromide in the presence of CuCN·2LiCl[6] (0.5 mol %) furnishes the allylated cyclopropane **3f** in 78% yield (dr >

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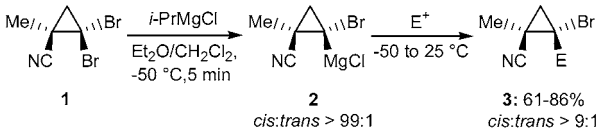
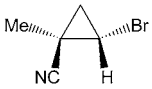
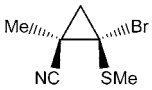
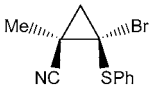
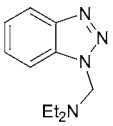
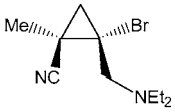
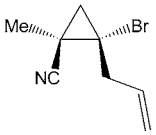
Table 1. 2-Bromocyclopropanecarbonitriles of Type **3** Obtained by the Reaction of **2** with Various Electrophiles



entry	electrophile	product of type **3**		dr[a]	yield[b]
1	H^+		**3a**	>99:1	76 %
2	I_2		**3b**	91:9	77 %[c]
3	$MeSSO_2Me$		**3c**	93:7	72 %
4	$PhSSO_2Ph$		**3d**	95:5	86 %
5			**3e**	96:4	79 %
6	allyl bromide		**3f**	>99:1	78 %[d]

[a] Diastereomeric ratio determined by GCMS analysis of the reaction mixture. [b] Isolated yields of analytically pure compounds. Yields refer to the pure main diastereoisomer. [c] Yield refers to the mixture of two diastereoisomers. [d] Reaction was conducted in the presence of CuCN·2LiCl (0.5 mol %).

99:1; entry 6). Various substituted benzaldehydes undergo the addition of reagent **2** leading to the cis configured benzylic alcoholates **4** as 1:1 mixture of diastereoisomers with respect to the newly formed carbinol centers. Interestingly, one of the diastereoisomers cyclizes to give, after workup and purification, the corresponding lactone of type **5**, whereas the other one is isolated as the alcohol of type **6** (Scheme 1). The configuration of **5a** was confirmed by X-ray analysis.

The preparation of cyclopropanenitriles with stereochemically defined quaternary centers can be achieved by successive bromine/magnesium- and sulfoxide/magnesium-exchange.[7] Thus, the bromine/magnesium-exchange on the thioether **3d** (*i*-PrMgCl, 1.1 equiv, −50 °C, 5 min) followed by an allylation in the presence of CuCN·2LiCl with allyl

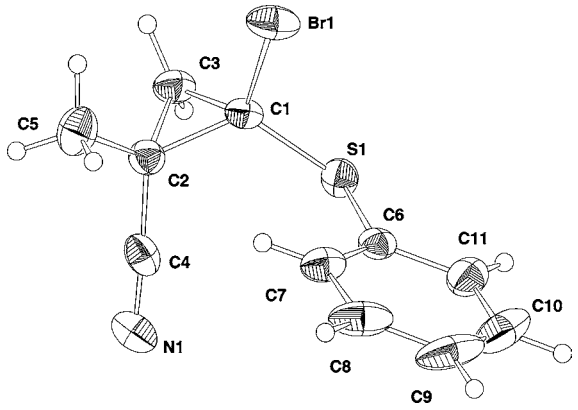
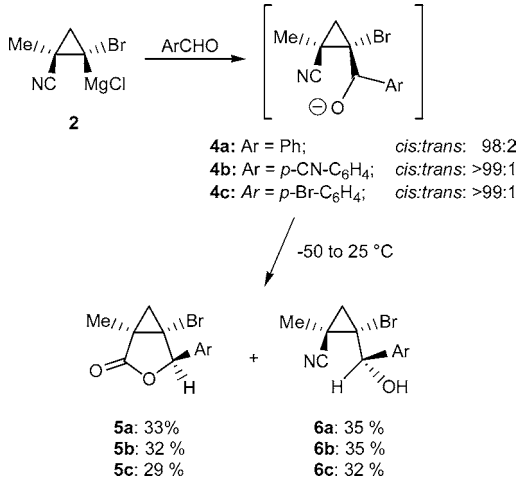


Figure 1. ORTEP drawing of **3d**.

Scheme 1



bromide or methallyl bromide, respectively, furnishes the allylated products **7a** and **7b** in 70 and 71% yield (Scheme 2). These thioethers were converted to the corresponding sulfoxides **8a**,**b** using MCPBA (1.0 equiv, CH_2Cl_2, −50 °C to room temperature, 0.5 h, 77−78%). The sulfoxide/magnesium exchange[7] was complete within 10 min at −50 °C. Treatment with either methallyl or allyl bromide in the presence of CuCN·2LiCl (0.5 mol %) provides the two diastereomeric cyclopropanenitriles **9a** (73%) and **9b** (69%) as single diastereoisomers. In summary, the bromine/magnesium exchange reaction has allowed the synthesis of various cyclopropane carbonitriles of type **3** with good diastereoselectivity. A successive bromine/magnesium and sulfoxide/magnesium exchange opens access to cyclopropanenitriles bearing a stereocontrolled quaternary center. Extensions of this reactivity pattern are currently underway in our laboratories.

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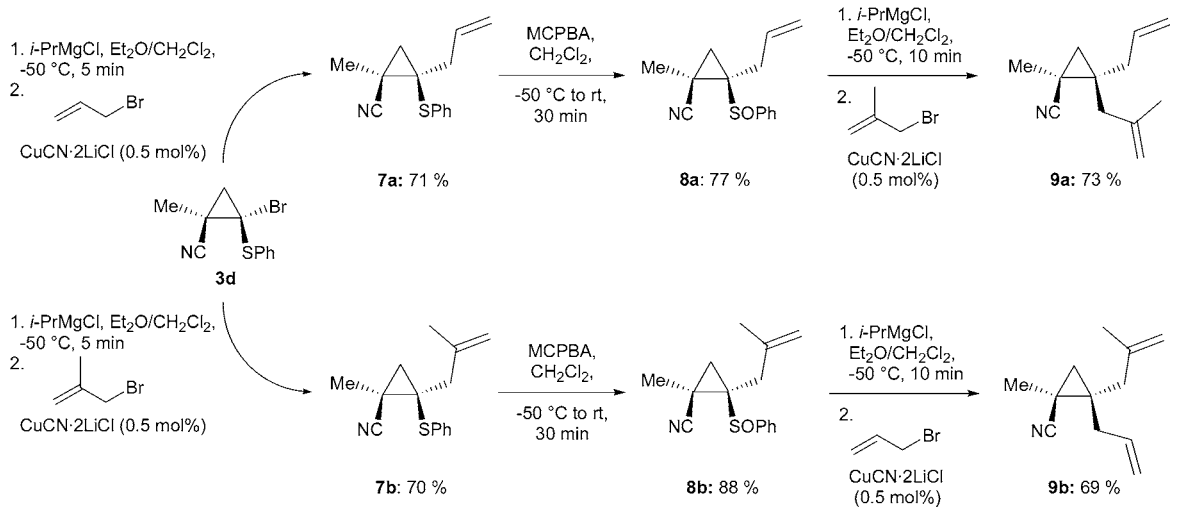
Scheme 2[a]



[a] MCPBA = 3-chloroperbenzoic acid.

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Supporting Information Available: Experimental procedure for the starting material **1**, experimental procedures and characterization of the compounds **3a**−**f**, **5a**−**c**, **6a**−**c**, **7a**,**b**, **8a**,**b**, and **9a**,**b** (^{1}H/^{13}C NMR, MS, HIRES, IR; two-dimensional NMR data of **3a**, **7a**,**b**, **8a**,**b**, **9a**,**b**), and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org. X-ray data of **3d** (CCDC275462) and **5a** (CCDC275461) have been deposited at the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033.

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