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The first example of direct cyclopropylation of arylamines at the 2-position with magnesium cyclopropylidenes

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Abstract—Treatment of magnesium cyclopropylidenes, which were generated from 1-chlorocyclopropyl phenyl sulfoxides with isopropylmagnesium chloride in THF at −78 °C, with *N*-lithio arylamines gave arylamines cyclopropylated at the 2-position in moderate to good yields. Use of the magnesium cyclopropylidenes having at least one substituent was found to be essential to this cyclopropylation. This procedure offers a novel synthesis of arylamines having a cyclopropane ring at the 2-position directly from arylamines.

Cyclopropanes are obviously one of the most important and useful compounds in organic and synthetic organic chemistry. As the cyclopropane ring is highly strained, a variety of ring-opening reactions of cyclopropanes occur under the influence of various chemical reagents, under both acidic and basic conditions and even under neutral conditions (radical reaction), with carbon–carbon and carbon–hetero atom bond-formation. Because of these chemical properties, cyclopropanes have been recognized to be highly useful and versatile compounds in organic synthesis and innumerable studies on the preparation, chemistry, and synthetic uses have already been reported.[1]

Concerning the synthesis of cyclopropanes, cyclopropanation of olefins with carbenes or carbenoids (Simmons–Smith-type cyclopropanation) has been most widely studied.[2] However, Friedel–Crafts-type cyclopropylation of aromatic compounds does not seem to be studied. Because cyclopropyl carbocations were known to be rearranged spontaneously to their corresponding allylic cations,[1a,3] direct cyclopropylation of aromatic ring has not been reported yet.

We recently reported a new method for N-cyclopropylation of arylamines with magnesium cyclopropylidenes.[4] In continuation of our investigation for the development of new synthetic methods utilizing magnesium cyclopropylidenes, we found that the reaction of magnesium cyclopropylidenes having substituents on the cyclopropane ring (**2**), which were generated from 1-chlorocyclopropyl phenyl sulfoxides **1**, with *N*-lithio arylamines gave 2-cyclopropylated arylamines **3** in moderate to good yields (Scheme 1). This is the first example of direct cyclopropylation of arylamines on the aromatic ring. Preliminary results are reported hereinafter.

As reported previously, reaction of magnesium cyclopropylidene **2a**, generated from 1-chlorocyclopropyl phenyl sulfoxide **1a** with *i*-PrMgCl in THF at −78 °C, with *N*-lithio *N*-methyl *p*-anisidine gave N-cyclopropylated *N*-methyl *p*-anisidine **4a** in 82% yield (Table 1, entry 1).[4] To investigate the substrate scope, we generated a magnesium cyclopropylidene having a methyl group on the cyclopropane ring (**2b**) from the corresponding sulfoxide in THF at −78 °C and to this solution of the magnesium carbenoid was added a solution of *N*-lithio *N*-methyl *p*-anisidine through a cannula (Method A). Very interestingly, this reaction gave the desired N-cyclopropylated compound **4b** in 25% yield with 2-cyclopropylated compound **5b** in 16% yield (entry 2). Quite surprisingly, when the magnesium cyclopropylidene having geminal methyl groups on the cyclopropane ring (**2c**) was treated with *N*-lithio *N*-methyl *p*-anisidine,

Keywords: Magnesium cyclopropylidene; Magnesium carbenoid; Sulfoxide–magnesium exchange reaction; Cyclopropylation; 2-Cyclopropylated arylamine.
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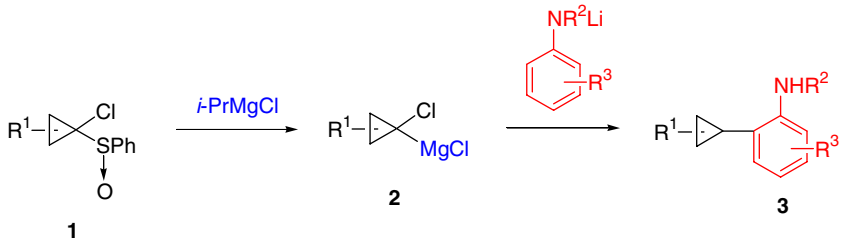
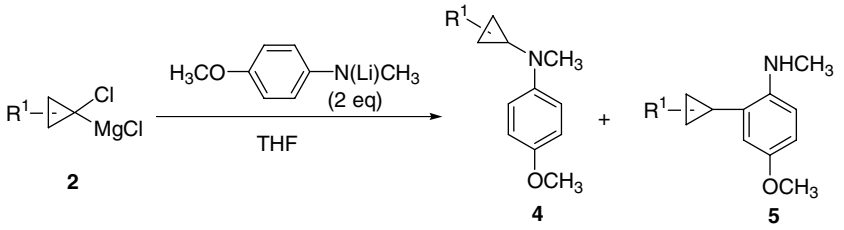
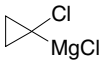
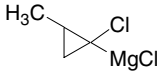
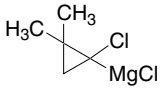


Scheme 1.

Table 1. Reaction of magnesium cyclopropylidenes **2** with *N*-lithio *N*-methyl *p*-anisidine giving N-cyclopropylated and C-cyclopropylated *N*-methyl *p*-anisidines **4** and **5**



Entry	2	Conditions	**4**/Yield%	**5**/Yield%
1	 **2a**	−78 to −40 °C	82	0[a]
2	 **2b**	−78 to 0 °C	25	16[a]
3	 **2c**	−78 to 0 °C	0	59[a]
4		−78 to 0 °C	0	60[b]

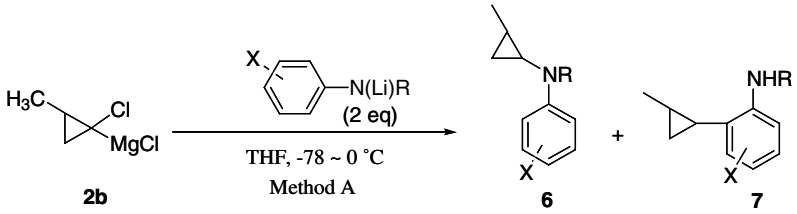
[a] Method A: A solution of *N*-lithio arylamine was added to a solution of the magnesium cyclopropylidene through a cannula.
[b] Method B: The magnesium cyclopropylidene was generated in the presence of *N*-lithio arylamine.

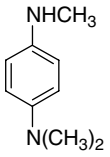
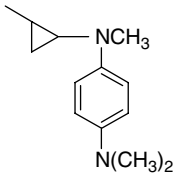
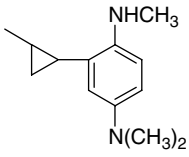
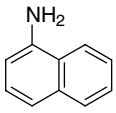
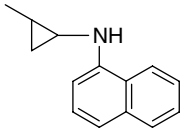
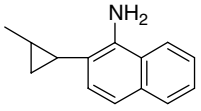
2-cyclopropylated *N*-methyl *p*-anisidine **5c** was obtained in 59% yield as a single product without any N-cyclopropylated arylamine (entry 3). Because no report was published concerning direct cyclopropylation of arylamines on the aromatic ring, as mentioned in the introduction, this is the first example of such a reaction.

We were highly interested in the generality of this reaction and, at first, conditions for this reaction were investigated. Because transfer of a solution of *N*-lithio *N*-methyl *p*-anisidine to a solution of the magnesium cyclopropylidene through a cannula (Method A) is tiresome, we sought for a concise procedure. Fortunately, as 1-chlorocyclopropyl phenyl sulfoxides **1** are found to be compatible with *N*-lithio arylamines, generation of the magnesium cyclopropylidenes in the presence of *N*-lithio arylamines could be carried out as follows (Method B). Thus, *n*-BuLi (2 equiv) was added to a solution of *N*-methyl *p*-anisidine (2 equiv) in THF at 0 °C. The reaction mixture was cooled to −78 °C and a solution of 1-chlorocyclopropyl phenyl sulfoxide **1c** (1 equiv) was added. Finally, *i*-PrMgCl (2.5 equiv) was added to the reaction mixture (generation of magnesium cyclopropylidene **2c**) and the temperature of the reaction mixture was slowly allowed to warm to 0 °C. This procedure gave *N*-methyl *p*-anisidine cyclopropylated at the 2-position **5c** in 60% yield (Table 1, entry 4).[5]

Next, we investigated the reaction of magnesium cyclopropylidene having one methyl group (**2b**) with two other arylamines under Method A and the results are summarized in Table 2. The reaction with *N*-methyl-4-(dimethylamino)aniline gave N- and C-cyclopropylated products; however, the reaction gave a rather complex mixture and the yields of the two products were low (entry 1). The reaction with 1-naphthylamine gave better yields of the products and again N-cyclopropylated 1-naphthylamine was the main product (47%) together with 2-cyclopropylated 1-naphthylamine (22%). From the results in Table 2 and in Table 1 (entry 2), the

Table 2. Reaction of magnesium cyclopropylidene **2b** with *N*-lithio arylamines giving N-cyclopropylated and C-cyclopropylated arylamines **6** ane **7**

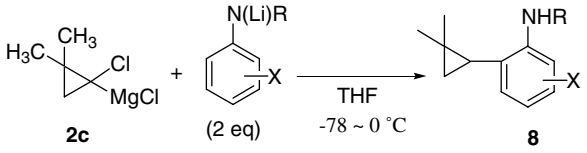


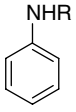
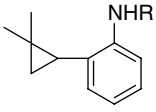
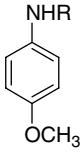
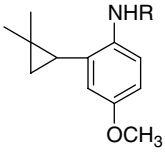
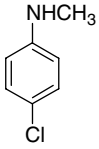
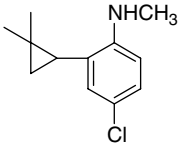
Entry	Arylamine	6	7
1		 14%	 6%
2		 47%	 22%

magnesium cyclopropylidene having one methyl group (**2b**) was proved to give both N- and C-cyclopropylated arylamines.

Results of the reactions of the magnesium cyclopropylidene having geminal methyl groups (**2c**) with various *N*-lithio arylamines are summarized in Table 3. The reactions were carried out both under Methods A and B, and the better yield is listed in the table. *N*-Methylaniline and diphenylamine gave the desired 2-cyclopropylated arylamines in moderate yields (entries 1 and 2). In this case, Method B gave much better yield of the

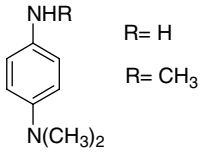
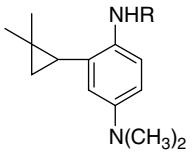
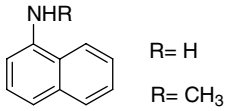
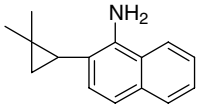
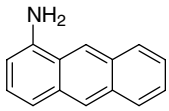
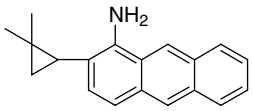
Table 3. Reaction of magnesium cyclopropylidene **2c** with *N*-lithio arylamines giving 2-cyclopropylated arylamines **8**



Entry	Arylamine		8 Yield/%
1		R= CH_3	 40[a]
2		R= Ph	50[a]
3		R= Ph	69[b]
4		R= H	 26[a]
5		R= CH_3	59[a]
6		R= Bn	22[a]
7			 9[a,c]

(*continued on next page*)

Table 3 (*continued*)

Entry	Arylamine	8	Yield/%
8	 R= H		58[b]
9	R= CH_3		64[a]
10	 R= H		69[b]
11	R= CH_3		22[a]
12			70[a]

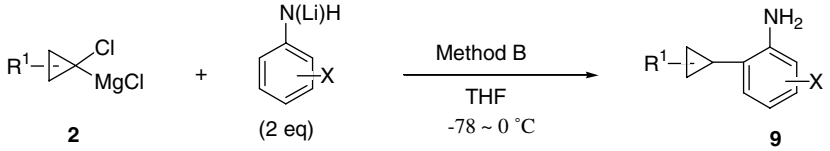
[a] The reaction was conducted under Method A.
[b] The reaction was conducted under Method B. In this experiment both the methods were applied and the better yields are shown in this table.
[c] N-Cyclopropylated product was obtained in 15% yield.

2-cyclopropylated diphenylamine (entry 3). *p*-Anisidine and its derivatives gave low to moderate yields (entries 4–6). Interestingly, *N*-methylaniline having an electron withdrawing group at *para*-position gave very low yield (9%). In this case, N-cyclopropylated product was obtained in 15% yield (see the footnote in Table 3). 4-(Dimethylamino)aniline and *N*-methyl 4-(dimethylamino)aniline both gave the desired products in up to 64% yield. Interestingly, 1-naphthylamine and 1-aminoanthracene gave 2-cyclopropylated compounds in about 70% yields (entries 10 and 12).

Table 4 shows the results of the magnesium cyclopropylidenes having geminal ethyl groups (**2d**), and having trimethyl and tetramethyl groups (**2e** and **2f**) with 4-(dimethylamino)aniline, 1-naphthylamine and 1-aminoanthracene. As shown in Table 4, the yields are about 40–65%, except in the case of 4-(dimethylamino)aniline (entry 7).

In conclusion, we found, for the first time, that the reaction of magnesium cyclopropylidenes **2**, generated from 1-chlorocyclopropyl phenyl sulfoxides **1** with *i*-PrMgCl,

Table 4. Reaction of magnesium cyclopropylidenes **2d**–**2f** with *N*-lithio arylamines under Method B giving 2-cyclopropylated arylamines **9**



2 (2 eq) **9**

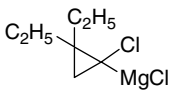
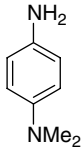
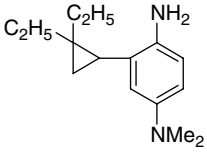
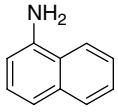
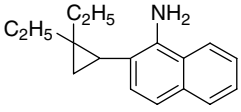
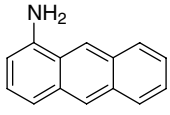
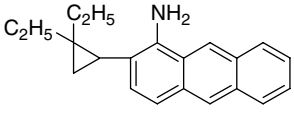
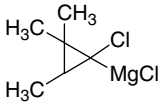
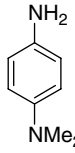
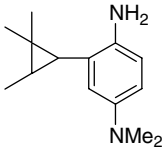
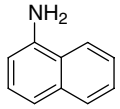
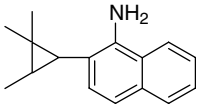
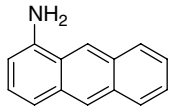
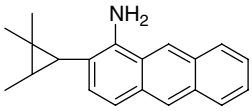
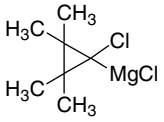
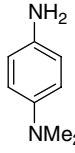
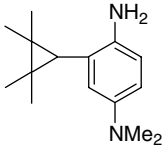
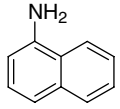
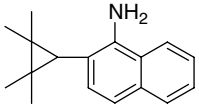
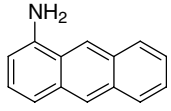
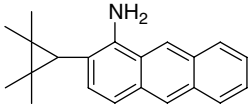
Entry	2	Arylamine	9	Yield/%
1	 **2d**			35
2				55
3				38

Table 4 (*continued*)

Entry	2	Arylamine	9	
				Yield/%
4	 **2e**			44
5				47
6				65
7	 **2f**			15
8				43
9				56

with *N*-lithio arylamines gave 2-cyclopropylated arylamines **3** in moderate to good yields. We are uncertain at present the reason why the C-cyclopropylation needs at least one substituent on the cyclopropane ring; however, the chemistry described in this Letter contributes to a new synthesis of 2-cyclopropylated arylamines and also to further development of the chemistry of magnesium cyclopropylidenes.

Acknowledgement

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References and notes

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5. *N-Methyl-2-(2,2-dimethylcyclopropyl)-4-methoxyaniline* (**5c**). *Method A*: To a solution of *i*-PrMgCl (1.0 mol/l; 0.5 mmol) in 0.5 ml of dry THF in a flame-dried flask at −78 °C under argon atmosphere was added a solution of **1c** (45.7 mg, 0.2 mmol) in 0.8 ml of dry THF dropwise with stirring and the reaction mixture was stirred for 10 min to give magnesium cyclopropylidene **2c**. In another flame-dried flask, *n*-BuLi (0.4 mmol) was added to a solution of

N-methyl-*p*-anisidine (54.8 mg, 0.4 mmol) in 0.5 ml of dry THF at −78 °C under argon atmosphere to give *N*-lithio *N*-methyl-*p*-anisidine. This solution was added to a solution of magnesium cyclopropylidene **2c** through a cannula. Temperature of the reaction mixture was gradually allowed to warm to 0 °C. The reaction was quenched by salt aq NH_4Cl and the whole was extracted with ethyl acetate. The organic layer was washed once with water and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **5c** (24.2 mg, 59%) as a colorless oil; IR (neat) 3431 (NH), 2938, 1510, 1452, 1285, 1216, 1168, 1053, 1033, 800 cm^{-1}; ^1H NMR δ 0.74 (1H, m), 0.76 (3H, s), 0.79-0.83 (1H, m), 1.30 (3H, s), 1.49 (1H, dd, $J = 8.3$, 5.8 Hz), 2.88 (3H, s), 3.61 (1H, br s), 3.74 (3H, s), 6.55 (1H, d, $J = 8.6$ Hz), 6.62 (1H, d, $J = 3.1$ Hz), 6.72 (1H, dd, J=8.6, 3.1 Hz). MS *m*/*z* (%) 205 (M^+, 100), 190 (67), 175 (18), 174 (23), 162 (28), 160 (27), 150 (32), 148 (27). Calcd for $C_{13}H_{19}NO$: *M*, 205.1465. Found: *m*/*z* 205.1452.

Method B: To a solution of *N*-methyl-*p*-anisidine (0.4 mmol) in 0.5 ml of dry THF in a flame-dried flask at 0 °C under argon atmosphere was added *n*-BuLi (0.4 mmol) dropwise with stirring. The reaction mixture was cooled to −78 °C and a solution of **1c** (45.7 mg, 0.2 mmol) in 0.8 ml of dry THF was added dropwise with stirring. After 10 min, *i*-PrMgCl (1.0 mol/l; 0.5 mmol) was added to the reaction mixture and the temperature of the reaction mixture was slowly allowed to warm to 0 °C. The reaction was quenched by salt aq NH_4Cl and the whole was extracted with AcOEt. The organic layer was washed once with water and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **5c** (24.5 mg, 60%).