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A new synthesis of cyanocyclopropanes by the intramolecular alkylation of magnesium carbenoids as the key reaction

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ABSTRACT

Addition reaction of 1-chlorovinyl *p*-tolyl sulfoxides, derived from ketones and chloromethyl *p*-tolyl sulfoxide, with cyanomethyllithium gave adducts in quantitative yields. Treatment of the adducts with *i*-PrMgCl in THF resulted in the formation of cyanocyclopropanes via the intramolecular alkylation of the generated magnesium carbenoids. The intermediate of this reaction was proved to be a cyclopropylmagnesium chloride, and it was found to be reactive with electrophiles to give multi-substituted cyanocyclopropanes. The key reaction, intramolecular alkylation of magnesium carbenoid, is the first example for the reaction of the magnesium carbenoids with nitrile-stabilized carbanions.

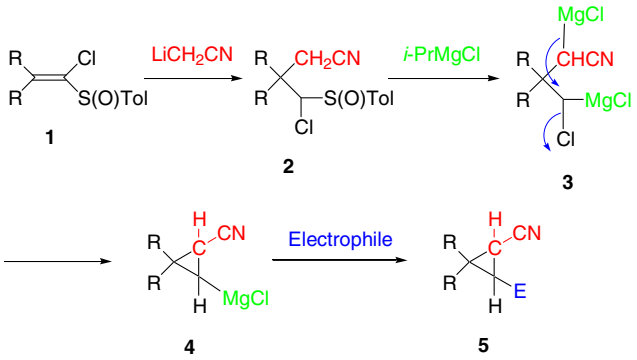
1. Introduction

Cyclopropanes are unambiguously one of the most important and fundamental compounds in organic and synthetic organic chemistry. Because of their highly strained nature, cyclopropanes are quite reactive with a variety of reagents and have long been recognized to be highly versatile and useful compounds in organic synthesis. Innumerable studies on their chemistry, synthesis, and synthetic uses have been performed; however, new methods for their synthesis are still eagerly sought.[1] We also have been interested in the synthesis of cyclopropanes based on our original methods.[2] In continuation of our investigation for the development of new synthetic methods of cyclopropanes, we recently found that the treatment of 1-chloroalkyl *p*-tolyl sulfoxides bearing a cyano group at the 3-position with *i*-PrMgCl resulted in the formation of cyanocyclopropanes in good yields (Scheme 1).[3]

Thus, 1-chlorovinyl *p*-tolyl sulfoxides **1**, prepared from ketones and chloromethyl *p*-tolyl sulfoxide,[4] were treated with cyanomethyllithium to give adducts, 1-chloroalkyl *p*-tolyl sulfoxides bearing a cyano group at 3-position **2**, in high yields.[5] Treatment of **2** with *i*-PrMgCl resulted in the formation of cyanocyclopropanes **5** (E = H) in good to high yields. This reaction was proved to proceed via the intramolecular alkylation of the generated magnesium carbenoid **3** and the intermediate of this alkylation was found to be cyclopropylmagnesium chloride **4**. The cyclopropylmagnesium intermediates **4** could be trapped with some electrophiles to give multi-substituted cyanocyclopropanes **5** (E = electrophile). Details of the procedure and the key reaction are reported.

2. Results and discussion

Recently, we reported a new method for the synthesis of bicyclo[*n*.1.0]alkanes having a *tert*-butyl carboxylate or an acetamide moiety **9** from 1-chlorovinyl *p*-tolyl sulfoxides **6**.[6] Thus, vinyl sulfoxides **6** were treated with lithium enolate of *tert*-butyl carboxylates or *N*,*N*-dimethylacetamide to afford adducts **7** in high yields. Adducts **7** were then treated with *i*-PrMgCl to result in the formation of magnesium carbenoids **8**. 1,3-CH insertion of the generated magnesium carbenoids **8** took place between the carbenoid and



Scheme 1.

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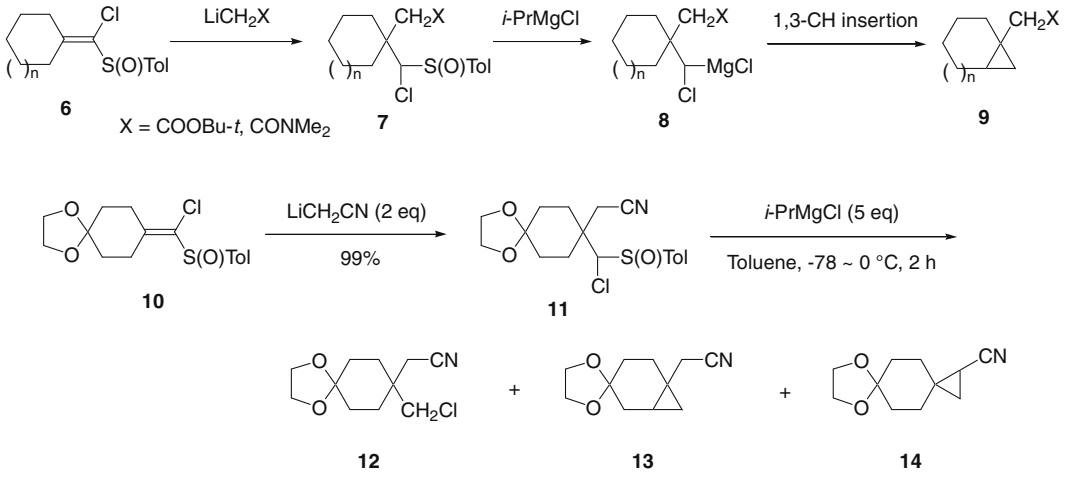


11	Yield / %		
	12	13	14
11-L	11	23	46
11-P	4	0	94

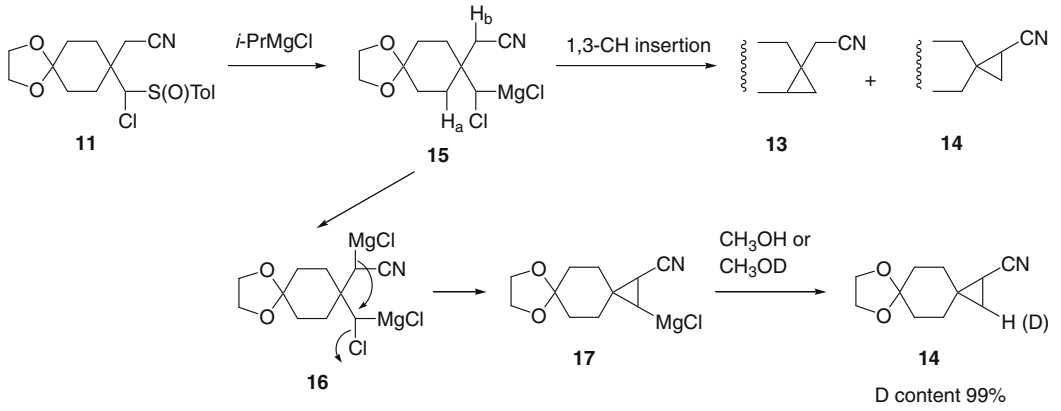
Scheme 2.

methylene carbon of the ring to give bicyclo[*n*.1.0]alkanes **9** in high yields (Scheme 2).

As we were highly interested in this reaction, the scope and limitation of the aforementioned procedure were investigated with nitriles. Thus, as shown in Scheme 2, treatment of 1-chlorovinyl *p*-tolyl sulfoxide **10**, which was derived from 1,4-cyclohexanedione mono ethylene ketal and chloromethyl *p*-tolyl sulfoxide,[4] with cyanomethyllithium gave adduct **11** in quantitative yield as a mixture of two diastereomers (we express the diastereomers as **11-L** (less polar product) and **11-P** (more polar product), **11-L**:**11-P** = 4:1). The diastereomers were easily separated by silica gel column chromatography. At first, main product **11-L** was treated with 5 equiv of *i*-PrMgCl in toluene at −78 °C and the temperature of the reaction mixture was slowly allowed to warm to 0 °C for 2 h. Three products were obtained from this reaction. One product was chloroalkane **12** (11%) and the other was the expected bicyclo[4.1.0]heptane **13** (23%). Somewhat surprisingly, the main product was proved to be 1-cyanospiro[2.5]octane derivative **14** (46%). Interestingly, the same reaction of diastereomer **11-P** gave **14** selectively in high yield and no **13** was observed (see the table in Scheme 2).

At first, we presumed that the products **13** and **14** were produced by the 1,3-CH insertion reaction of the generated magnesium carbenoid intermediate **15** (Scheme 3).[6] Namely, when the 1,3-CH insertion reaction takes place between the magnesium carbenoid and the carbon bearing H_a, **13** must be produced. On the other hand, when the reaction takes place between the magnesium carbenoid and the carbon bearing H_b, **14** should be produced. However, based on our experiences, it was expected that the 1,3-CH insertion reaction between the carbenoid and the carbon bearing an electron-withdrawing group was thought to take place with difficulty.[6,7] In order to obtain some information about the mechanism of this reaction, we quenched this reaction with CH_3OD and, somewhat surprisingly, we found that the cyclopropane ring of spiro-cyclic cyanocyclopropane **14** was perfectly deuterated at 2-position.

From this result, it became apparent that the mechanism of this reaction is as follows (Scheme 3). Thus, treatment of adduct **11**



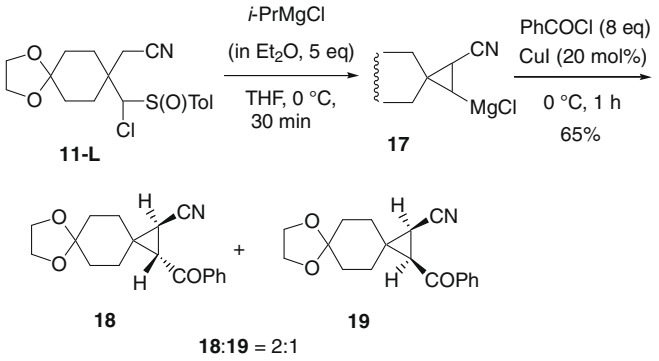
Scheme 3. Mechanism for the generation of cyanocyclopropane **14** by the treatment of **11** with *i*-PrMgCl.

with *i*-PrMgCl results in the formation of magnesium carbenoid **15** by the sulfoxide–magnesium exchange reaction. The acidic hydrogen (H_b) was eliminated with the excess *i*-PrMgCl to produce cyano-stabilized carbanion **16**. Intramolecular alkylation of the magnesium carbenoid with the cyano-stabilized carbanion occurs to give cyclopropylmagnesium chloride intermediate bearing a cyano group **17**. Quenching of **17** with deuterio methanol gives a cyanocyclopropane bearing deuterium at 2-position **14** with high deuterium incorporation. Intermolecular- or intramolecular-proton abstruction of magnesium carbenoid **15** afforded chloroalkane **12**.

Since this is an unprecedented and interesting reaction for the synthesis of cyanocyclopropanes, we investigated to find the conditions of choice for obtaining **14** from **11-L** and the results are summarized in Table 1. When this reaction was conducted in ethereal solvent, generation of bicyclic compound **13** was eliminated. Solvation of the magnesium carbenoid intermediate with Lewis basic ethereal solvent was thought to be the reason for this result. As shown in entries 1–5, this reaction can be carried out at 0 °C or at room temperature to afford the desired **14** in up to 78% yield. Especially, when this reaction was carried out with 5 equiv of *i*-PrMgCl in THF at 0 °C and the reaction was quenched with CH_3OD, spirocyanocyclopropane **14** was obtained in 78% yield with 99% deuterium content. In these conditions the yield of **12** could be reduced to 10% (entry 4).

Methylmagnesium chloride, ethylmagnesium chloride, and cyclopentylmagnesium chloride worked; however, no better result was obtained (entries 6–8). Isopropylmagnesium bromide worked well to give **14** in somewhat better yield; however, quite low deuterium incorporation was observed (entries 9 and 10). Reducing the amount of *i*-PrMgCl resulted in increasing the protonated product **12** (entries 11–13). We selected the conditions shown in entry 4 as the conditions of choice for this study.

As mentioned above, the intermediate of this reaction was proved to be cyclopropylmagnesium chloride bearing a cyano group **17**. If this intermediate can be trapped with electrophiles other than proton, the whole procedure becomes a new method for the synthesis of multi-substituted cyanocyclopropanes. We



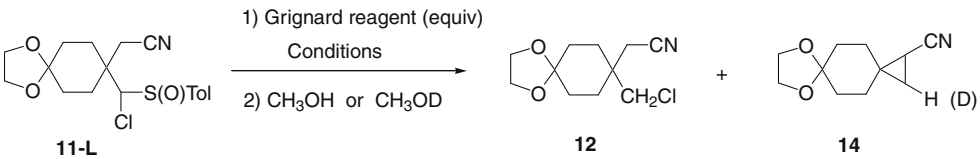
Scheme 4. Generation of cyclopropylmagnesium chloride intermediate **17** from **11-L** and trapping with benzoyl chloride.

investigated the feasibility of this plan as shown in Scheme 4. Thus, adduct **11-L** was treated with 5 equiv of *i*-PrMgCl in THF at 0 °C. After 30 min, Cu(I) iodide (20 mol %) followed by benzoyl chloride (8 equiv) were added to the reaction mixture and the whole reaction mixture was stirred at 0 °C for 1 h. This procedure gave the desired benzoylated products **18** and **19** (**18**:**19** = 2:1) in 65% yield. The stereochemistry of the products was easily determined from the coupling constant of their ^{1}H NMR (J_{H-H} of **18**, 5.2 Hz; J_{H-H} of **19**, 7.8 Hz).[8] When this reaction was conducted without Cu(I) iodide, only a complex mixture was obtained.

In order to investigate the generality of this procedure, various 1-chloroalkyl *p*-tolyl sulfoxides bearing a cyano group **2**, derived from symmetrical ketones, were treated with *i*-PrMgCl under the aforementioned conditions followed by electrophiles and the results are summarized in Table 2. As shown in entries 1–3, the reaction of **2**, derived from acetone, gave benzoylated and benzylated cyanocyclopropanes in up to 70% yield. The reaction with benzaldehyde proceeded in the presence of $EtAlCl_2$ as a Lewis acid to give adducts as a mixture of four diastereomers.

The reaction of **2** derived from benzophenone gave **5** in 42% with significant amount of rearranged product **20** as a by-product

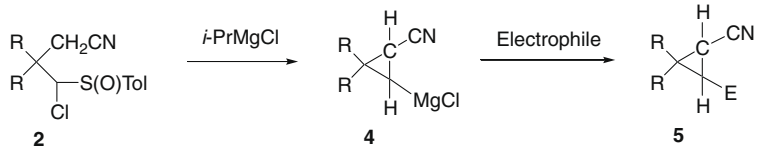
Table 1
Investigation for the best conditions for obtaining cyanocyclopropane **14** by the treatment of **11-L** with Grignard reagent

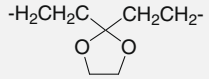
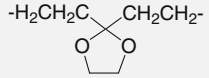
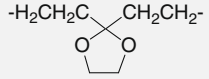
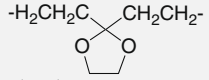


Entry	Grignard reagent (equiv)	Solvent	Temp (°C)	Time (h)	Yield/% (D content/%)	
					12	**14**
1	*i*-PrMgCl[a] (5)	Et_2O	−78 to 0	2	12	64
2	*i*-PrMgCl[a] (5)	THF	−78 to 0	2	8	69
3	*i*-PrMgCl[a] (5)	THF	−40	0.5	15	67
4	*i*-PrMgCl[a] (5)	THF	0	0.5	10	78 (99)
5	*i*-PrMgCl[a] (5)	THF	Room temperature	0.5	13	75
6	MeMgCl (5)	THF	0	0.5	43	49
7	EtMgCl (5)	THF	0	0.5	32	53
8	*c*-PentMgCl (5)	THF	0	0.5	14	77
9	*i*-PrMgBr[b] (5)	THF	0	0.5	16	74 (18)
10	*i*-PrMgBr[b] (5)	THF	Room temperature	0.5	13	86 (12)
11	*i*-PrMgCl[a] (3.5)	THF	0	0.5	18	77 (33)
12	*i*-PrMgCl[a] (3)	THF	0	0.5	28	61 (20)
13	*i*-PrMgCl[a] (2)	THF	0	0.5	47	0

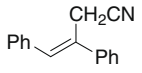
[a] Isopropylmagnesium chloride in diethyl ether was used.
[b] Isopropylmagnesium bromide in THF was used.

Table 2
Synthesis of multi-substituted cyanocyclopropanes **5** from 1-chloroalkyl *p*-tolyl sulfoxides bearing a cyano group at the 3-position **2** with *i*-PrMgCl followed by electrophiles



Entry	**2** R	Electrophile[a]	Additive	**5** Yield/% (diastereomeric ratio)
1	CH_3	PhCOCl	CuI[b]	70 (3:2)
2	CH_3	$PhCH_2Br$	CuI[b]	44 (1:0)
3	CH_3	PhCHO	$EtAlCl_2$[c]	50 (Four diastereomers)
4	Ph	CH_3OD		42[d] (Deuterium content; 95%)
5	$PhCH_2CH_2$	CH_3OD		79 (Deuterium content; 91%)
6		CH_3OD		78 (Deuterium content; 99%)
7		PhCOCl	CuI[b]	65 (2:1)
8		$PhCH_2CH_2COCl$	CuI[b]	58 (3:1)
9		$PhCH_2Br$	CuI[b]	14 (1:0)
10	$-(CH_2)_{11}-$	CH_3OD		78 (Deuterium content; 99%)
11	$-(CH_2)_{11}-$	PhCOCl	CuI[b]	64 (3:1)
12	$-(CH_2)_{14}-$	CH_3OD		73 (Deuterium content; 99%)
13	$-(CH_2)_{14}-$	PhCOCl	CuI[b]	61 (3:1)

[a] Eight equivalents of electrophile were used.
[b] 20 mol % of copper(I) iodide, based on **2** was used.
[c] Eight equivalents of $EtAlCl_2$ were added.
[d] Significant amount (25%) of rearranged product **20** was obtained.



20

(entry 4). The reaction of **2** derived from 1,5-diphenyl-3-pentanone gave **5** in 79% yield (entry 5). The results in entries 6 and 7 were mentioned before (Table 1 and Scheme 4). Alkylation of the cyclopropylmagnesium intermediate with benzyl bromide again gave the desired product in low yield (entry 9). The reaction of **2** derived from cyclododecanone and cyclopentadecanone gave moderate to good yield of the desired products (entries 10–13).

In conclusion, a method for the synthesis of multi-substituted cyanocyclopropanes was established starting from 1-chlorovinyl *p*-tolyl sulfoxides with acetonitrile and electrophiles. The key reaction of this procedure is the intramolecular alkylation of magnesium carbenoid with cyano-stabilized carbanion followed by trapping the cyclopropylmagnesium chloride intermediate with electrophiles. We believe that the results described in this Letter will contribute to a synthesis of multi-substituted cyanocyclopropanes.

Acknowledgements

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8. To a flame-dried flask was added dry THF (3 mL) followed by *i*-PrMgCl (1 mmol; 5 equiv, in ether) at 0 °C. A solution of adduct **11-L** (73.6 mg; 0.2 mmol) in THF (1 mL) was added to the solution of *i*-PrMgCl dropwise with stirring. After the reaction mixture was stirred at 0 °C for 30 min, CuI (0.04 mmol; 0.2 equiv) was added to the reaction mixture. After the reaction mixture was stirred for 5 min, benzoyl chloride (1.6 mmol; 8 equiv) was added and the whole reaction mixture was stirred for 1 h. The reaction was quenched with satd aq NH_4Cl and the whole reaction mixture was extracted with $CHCl_3$. The products were purified by silica gel column chromatography to afford 38.7 mg (65%) of a 2:1 mixture of cyanocyclopropanes **18** and **19**. Compound **18**: colorless crystals; mp 175–176 °C (hexane–AcOEt); IR (KBr) 3015, 2939, 2234 (CN), 1680 (CO), 1595, 1451, 1265, 1240, 1213, 1030, 903 cm^{-1}; ^1H NMR δ 1.40–1.51 (1H, m), 1.57–1.66 (3H, m), 1.80–2.16 (4H, m), 2.46 (1H, d, J = 5.2 Hz), 3.09 (1H, d, J = 5.2 Hz), 3.88–3.99 (4H, m), 7.47–7.55 (2H, m), 7.59–7.66 (1H, m), 7.93–7.99 (2H, m). MS m/z (%) 297 (M^+, 9), 192 (66), 105 (100), 99 (30), 86 (31), 77 (33). Calcd for $C_{18}H_{19}NO_3$: M, 297.1365. Found: m/z 297.1363. Compound **19**: colorless crystals; mp 141–142 °C (hexane–AcOEt); IR (KBr) 2925, 2949, 2864, 2238 (CN), 1668 (CO), 1594, 1557, 1448, 1412, 1220, 1129, 1098, 1040, 715 cm^{-1}; ^1H NMR δ 1.48–1.59 (1H, m), 1.64–1.85 (4H, m), 1.86–1.99 (3H, m), 1.92 (1H, d, J = 7.7 Hz), 2.89 (1H, d, J = 7.7 Hz), 3.88–4.01 (4H, m), 7.46–7.54 (2H, m), 7.57–7.65 (1H, m), 7.92–7.99 (2H, m). MS m/z (%) 297 (M^+, 10), 192 (46), 105 (100), 99 (19), 86 (30), 77 (34). Calcd for $C_{18}H_{19}NO_3$: M, 297.1365. Found: m/z 297.1366.