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The first example of 2,2-dilithiocyanocyclopropanes: generation from 2-bromo-2-sulfinylcyanocyclopropanes with *tert*-butyllithium, property, and a synthesis of fully substituted cyanocyclopropanes

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Abstract—2,2-Dilithiocyanocyclopropanes were easily generated from 2-bromo-2-(*p*-tolylsulfinyl)cyanocyclopropanes with *tert*-butyllithium in toluene at −78 °C through concomitant sulfoxide–lithium and bromine–lithium exchange reactions. The *gem*-dianions were found to be stable at −78 °C for at least 30 min. Reaction of the *gem*-dianions with electrophiles gave fully substituted cyanocyclopropanes in moderate yields.

Carbanions are obviously one of the most important reactive intermediates of carbon in synthetic organic chemistry and innumerable studies for their generation, property, and synthetic uses have been reported.[1,2] Dianions with two different carbon atoms bearing the charge have also been reported[1b,3] and extensively used in organic synthesis. However, dianions with a carbon bearing two charges, for example geminal dilithio organic compounds **1**,[4] have not been extensively studied. In addition, most of the reported geminal dilithium compounds **1** have one or two carbanion-stabilizing groups as R^1 and/or R^2 (Scheme 1).

On the other hand, the reports concerning the dianion of cyclopropanes with a carbon bearing two charges, 1,1-dilithiocyclopropane **2**, are few. Two papers for ab initio molecular orbital calculation of **2** were reported in the theoretical study of its structure, the planar tetracoordinate carbon.[5] Only one report was published for a synthesis of 1,1-dilithio-2,2,3,3-tetramethylcyclopropane **3**.[6]

Recently, we reported a synthesis of 1-bromo-2-cyanocyclopropyl *p*-tolyl sulfoxides **5**, derived from 1-chlorovinyl *p*-tolyl sulfoxides **4**, and a synthesis of fully substituted cyanoallenes.[7] In continuation of the studies for the development of new synthetic methods utilizing α-halo-α-sulfinylcyclopropanes **5**, we found that the treatment of **5** with *tert*-butyllithium in toluene at −78 °C resulted in the formation of 2,2-dilithiocyanocyclopropanes **6** in high yields. In this Letter, the generation of *gem*-dianions **6** and their property and reaction with electrophiles to give fully substituted cyanocyclopropanes **7** are reported.

The details of this study are described by using 2-bromo-2-(*p*-tolylsulfinyl)cyanocyclopropane **9** as a representative example (see Table 1). At first, 1-chlorovinyl *p*-tolyl sulfoxide **8** was synthesized from cyclopentadecanone.[8] Vinyl sulfoxide **8** was treated with α-lithiopropionitrile and the adduct was treated with *t*-BuOK to give a cyclopropyl sulfoxide, which was brominated to afford 1-bromocyclopropyl sulfoxide **9** in a good overall yield.[7] Sulfoxide **9** was obtained as a mixture of four diastereomers (one main product, over 85% yield, and three other minor diastereomers). The well crystalline main product was used in this study.

At first, bromocyclopropyl sulfoxide **9** was treated with excess *t*-BuLi in THF at −78 °C for 30 min and the reaction was quenched with water. We expected an allene as the product via the Doering–LaFlamme reaction[9] of the

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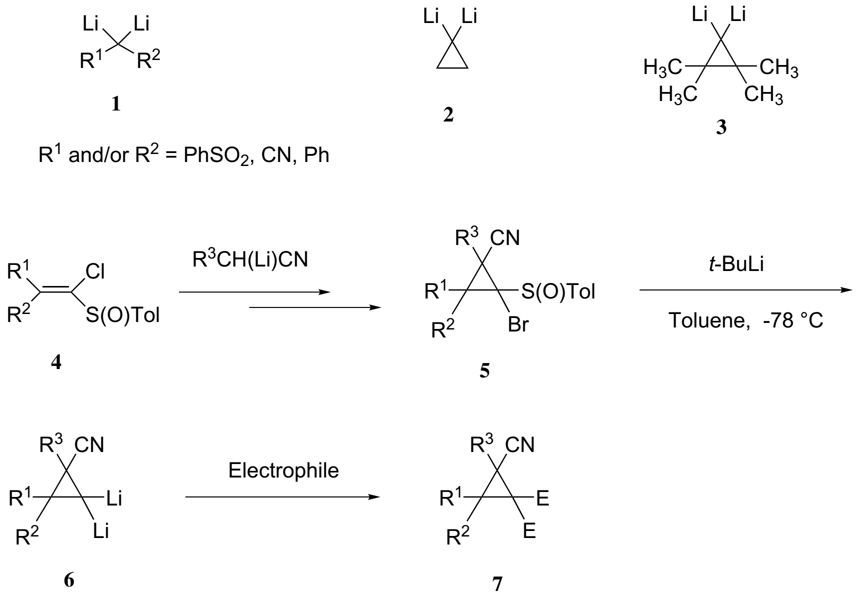
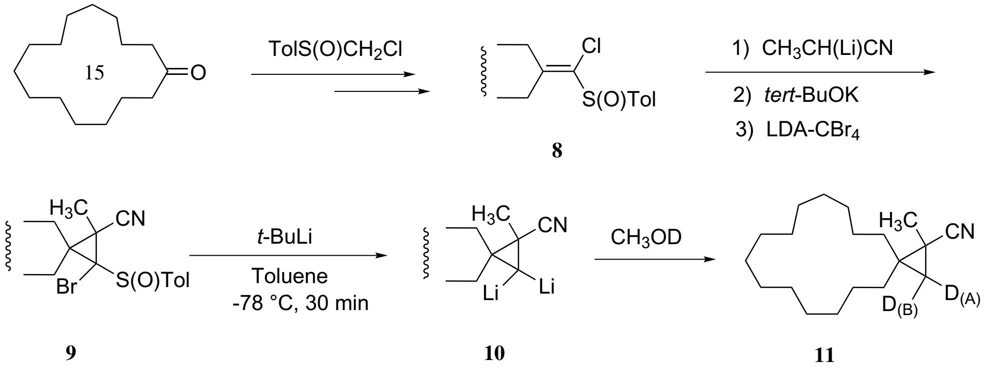


Scheme 1.

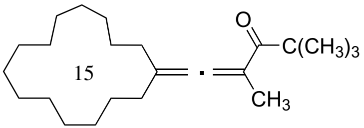
Table 1. Generation of 2,2-dilithiocyanocyclopropane **10** from 2-bromo-2-(*p*-tolylsulfinyl)cyanocyclopropane **9** and quenching of the *gem*-dianion with CH_3OD to give dideuteriocyanocyclopropane **11**



Entry	*t*-BuLi (equiv)	Conditions		Yield of **11**/% (D content/%)
		Solvent	Temperature (°C)	
1	6.0	THF	−78	74 (A: 45, B: 72)
2	6.0	THF	−50	53 (A: 36, B: 76)
3	6.0	Toluene	−78	79 (A: 95, B: 88)
4	6.0	Toluene	−50	44 (A: 85, B: 83)
5	6.0	Toluene	−30	36 (A: 74, B: 86)[a]
6	6.0	Toluene	0–rt	—[b]
7	4.5	Toluene	−78	84 (A: 93, B: 88)
8	3.0	Toluene	−78	91 (A: 95, B: 91)

[a] Allene **12** was obtained in 22% yield.

[b] Allene **12** was obtained in 67% yield.



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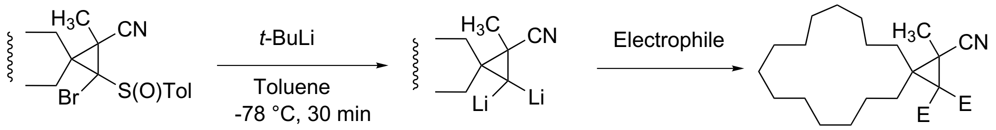
lithium cyclopropylidene intermediate which was generated by the sulfoxide–lithium exchange reaction;[10] however, somewhat surprisingly, cyclopropane **11** (hydrogen instead of deuterium) in a 74% yield was obtained as a main product. The intermediate of this interesting reaction was expected to be 2,2-dilithiocyanocyclopropane **10**.

To confirm the intermediate to be *gem*-dianion **10**, the reaction was quenched with CH_3OD (Table 1, entry 1) and indeed, dideuterated cyclopropane **11** was obtained. Interestingly, the rate of deuterium incorporation at the two positions was different (45% and 72%), although the stereochemistry is obscure at present. The yield and deuterium incorporation of **11** was diminished when the reaction was conducted at −50 °C (entry 2). The low rate of deuterium incorporation was thought to be attributable to the use of THF which may act as a proton source.

The reaction was next carried out in toluene at −78 °C (entry 3). Gratifyingly, **11** was obtained in a 79% yield and deuterium incorporation was also quite good. The reaction at −50 °C gave again a poorer result (entry 4). When this reaction was carried out at above −30 °C, allenyl ketone **12** was obtained in up to a 67% yield (entries 5 and 6). Reducing of the amount of *t*-BuLi gave a better chemical yield with better deuterium incorporation (entries 7 and 8).

As mentioned above, the *gem*-dianion having no carbanion-stabilizing group on the carbon was generally recognized to be quite difficult to generate. However, from our results described above, it was found that 2,2-dilithiocyanocyclopropane having no carbanion-stabilizing group on the carbanionic carbon could be easily prepared through concomitant sulfoxide–lithium and bromine–lithium exchange reactions. It is noteworthy that

Table 2. Generation of 2,2-dilithiocyanocyclopropane **10** from 2-bromo-2-(*p*-tolylsulfinyl)cyanocyclopropane **9** and reaction with electrophiles to afford fully substituted cyanocyclopropanes **13**

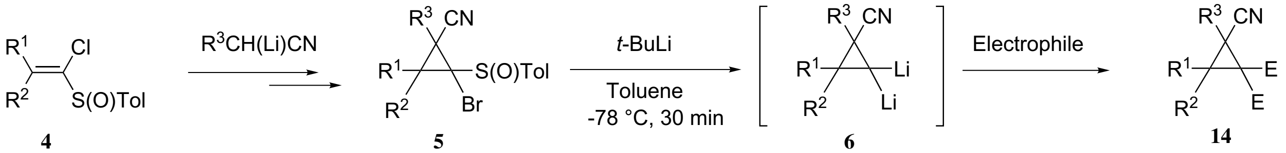


9 **10** **13**

Entry	*t*-BuLi (equiv)	Electrophile	Conditions	**13**	
				E	Yield (%)
1	6.0	CH_3I (30 equiv)	−78 to 0 °C, 2 h[a]	CH_3	5
2	4.5	CH_3OTs (15 equiv)	−78 to −50 °C, 1 h	CH_3	23
3	4.5	CH_3OTf (15 equiv)	−78 to −50 °C, 1 h	CH_3	49
4	3.0	ClCOOEt (3 equiv)	−78 °C, 1 h	COOEt	50

[a] CuI (40 mol %) was added as an additive.

Table 3. Synthesis of 2-bromo-2-(*p*-tolylsulfinyl)cyanocyclopropane **5** and treatment of **5** with *tert*-butyllithium followed by electrophiles to afford fully substituted cyanocyclopropanes **14**



4 **5** **6** **14**

Entry	**5**				*t*-BuLi (equiv)	Electrophile	Conditions	**14**	
	R^1	R^2	R^3	Yield[a] (%)				E	Yield (%)
1	$-(CH_2)_{14}-$		$CH_3(CH_2)_3$	84	4.5	CH_3OD	−78 °C	D	73[b]
2	$-(CH_2)_{14}-$		$CH_3(CH_2)_3$		4.5	CH_3OTf	−78 to −50 °C	CH_3	34
3	$-(CH_2)_{14}-$		$CH_3(CH_2)_3$		3.0	ClCOOEt	−78 °C, 1 h	COOEt	40
4	$-(CH_2)_5-$		$CH_3(CH_2)_3$	83	4.5	CH_3OD	−78 °C	D	84[c]
5	$-(CH_2)_5-$		$CH_3(CH_2)_3$		4.5	CH_3OTf	−78 to −50 °C	CH_3	39
6	$-(CH_2)_5-$		$CH_3(CH_2)_3$		3.0	ClCOOEt	−78 °C, 1 h	COOEt	42
7	$CH_3(CH_2)_{10}$	CH_3	CH_3	74[d]	4.5	CH_3OD	−78 °C	D	99[e]
8	$CH_3(CH_2)_{10}$	CH_3	CH_3		4.5	CH_3OTf	−78 to −50 °C	CH_3	58
9	$CH_3(CH_2)_{10}$	CH_3	CH_3		3.0	ClCOOEt	−78 °C, 1 h	COOEt	52
10	$PhCH_2CH_2$	$PhCH_2CH_2$	$CH_3(CH_2)_3$	65	4.5	CH_3OD	−78 °C	D	94[f]
11	$PhCH_2CH_2$	$PhCH_2CH_2$	$CH_3(CH_2)_3$		4.5	CH_3OTf	−78 to −50 °C	CH_3	36
12	$PhCH_2CH_2$	$PhCH_2CH_2$	$CH_3(CH_2)_3$		3.0	ClCOOEt	−78 °C, 1 h	COOEt	41

[a] Three-step overall yield from 1-chlorovinyl *p*-tolyl sulfoxide **4**.

[b] D-content; 91–93%.

[c] D-content; 94–96%.

[d] One of the diastereomers that was obtained by recrystallization was used in this study.

[e] D-content; 96%.

[f] D-content; 88–92%.

this is the first example for the generation of 2,2-dilithiocyanocyclopropane.

From the viewpoint of synthetic organic chemistry, trapping of *gem*-dianion **10** with electrophiles is quite interesting. Thus, at first, **9** was treated with 6 equiv of *t*-BuLi in toluene at −78 °C for 30 min, and to this reaction mixture was added excess iodomethane; however, only 5% yield of the desired methylated cyclopropane was obtained (Table 2, entry 1). The use of methyl *p*-toluenesulfonate as the electrophile gave the desired *gem*-dimethylcyclopropane **13** in a 23% yield (entry 2). Finally, the desired dimethylcyclopropane was obtained in a 49% yield with methyl trifluoromethanesulfonate (entry 3). On the other hand, the reaction of the generated 2,2-dilithiocyanocyclopropane **10** with ethyl chloroformate gave the desired ethoxycarbonylated cyclopropane in a 50% yield. From the investigation described above, geminal dianion **10** was found to have relatively low nucleophilic property.

Finally, generality of these reactions was investigated using some 2-bromo-2-(*p*-tolylsulfinyl)cyanocyclopropanes and the results are summarized in Table 3. First, four kinds of 2-bromo-2-(*p*-tolylsulfinyl)cyanocyclopropanes **5** were synthesized from cyclopentadecanone, cyclohexanone, 2-tridecanone, and 1,5-diphenyl-3-pentanone, with acetonitrile, and hexanenitrile, and the yields from the corresponding 1-chlorovinyl *p*-tolyl sulfoxides **4** are summarized in the table. As shown in Table 3, all four 2-bromocyanocyclopropanes **5** gave 2,2-dilithiocyanocyclopropane **6** in a high yield, which was confirmed by the quenching of the reaction with deuterio methanol to give 73–99% yield of dideuterated cyanocyclopropanes **14** with a high deuterium incorporation (entries 1, 4, 7, and 10).

Dimethylation of dianions **6** with methyl trifluoromethanesulfonate gave dimethylcyclopropanes **14** in up to a 58% yield (entries 2, 5, 8, and 11). The yields for diesters **14** (E = COOEt) were found to be from 40% to 52%.

In conclusion, we have found that 2,2-dilithiocyanocyclopropanes **6** were unexpectedly easily generated from 2-bromo-2-(*p*-tolylsulfinyl)cyanocyclopropanes with *t*-BuLi in toluene at −78 °C. The *gem*-dianions were found to be stable in toluene at −78 °C for at least 30 min. The nucleophilic property was found to be rather low; however, the dianions react with methyl trifluoromethanesulfonate and ethyl chloroformate to afford the fully substituted cyanocyclopropanes in moderate yields. This method contributes to a synthesis of highly substituted cyclopropanes.

Acknowledgments

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