Intramolecular Substitution Reaction of Alkylidene-Lithium Carbenoids: Regioselective Synthesis of Indenes

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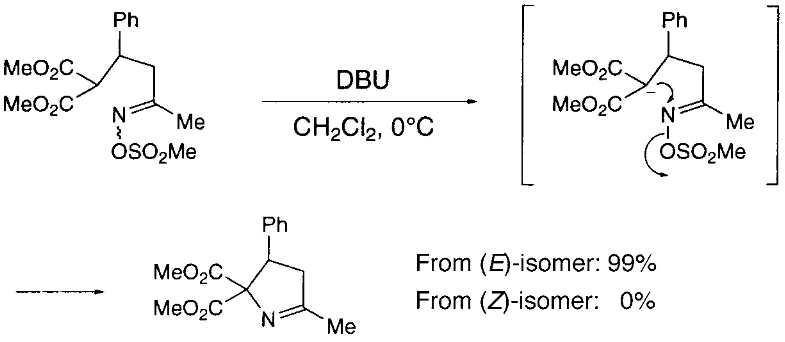
Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

Intramolecular substitution reaction of geminal dibromo alkenes proceeds to afford indenes, dihydronaphthalenes, dihydrofurans, and dihydropyran *via in situ* generated lithium alkylidene carbenoids, which have a carbon or oxygen nucleophilic moiety. This reaction provides a regioselective method for the preparation of polysubstituted indenes.

Introduction. – Recently, we reported the unusual intramolecular substitution at the sp^2-N-atom of oximes [1]. For example, *O*-methylsulfonyl oximes with an active CH group are converted to cyclic imines by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; *Scheme 1*) [1d,e]. Experimental investigation on the stereospecificity [1d,e] and a theoretical study [2] revealed that this reaction proceeds *via* an unusual S_N2-type reaction at the sp^2-N-atom of oximes, *i.e.*, backside attack at the sp^2-N-atom.

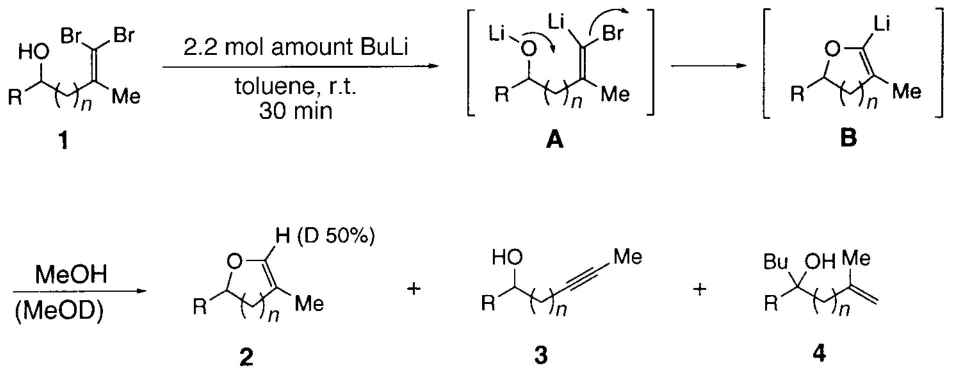
Scheme 1



It was expected that S_N2 reaction would also occur at alkylidene-metal carbenoids, due to the structural similarity between oximes and alkylidene carbenoids, both of which have an electron pair (negative charge) and a leaving group on an sp^2-atom. Actually, there are several examples of nucleophilic substitution of alkylidene-lithium carbenoids. For instance, inversion of the configuration is observed to some extent when an optically active chloroalkene is treated with *t*-BuLi [3]. Benzofurans are obtained from *o*-hydroxy-β,β-dichlorostyrenes by treatment with BuLi [4]. Although these results suggest an $S_{\mathrm{N}}2$ mechanism at the carbenoid sp^2-C-atom, other possibilities still remain. In this communication, we describe the study of intramolecular nucleophilic substitution of lithium sp^2 carbenoids and the utilization of this reaction for organic synthesis.

Results and Discussion. – 4,4-Dibromobut-3-en-1-ol **1a** was treated with 2.2 mol amounts of BuLi to generate alkylidene-lithium carbenoid **A**, and dihydrofuran **2a** was obtained after quenching with MeOH. After some experiments, **2a** was obtained in 81% yield when the reaction was carried out in toluene at room temperature and quenched with MeOH (*Table 1*, *Run 1*). Although both isomers of alkylidene carbenoid **A** would be generated by lithiation and only the (*E*)-isomer of **A** could participate in the $S_{\mathrm{N}}2$ mechanism, it is known that (*E*)/(*Z*)-isomerization of alkylidene-lithium carbenoids occur with co-existence of LiBr [5]. Since deuterated [D]-**2a** (D 50%) was obtained by quenching with MeOD, the cyclization definitely afforded alkenyllithium **B**. Dialkyldihydrofuran **2b** was also obtained from **1b** in 82% yield (*Run 2*). In addition to the dihydrofurans, dihydropyran **2c** was prepared from **1c** in 48% yield along with acetylene **3c**[1]) and alcohol **4c**[2]) (*Run 3*).

Table 1. *Nucleophilic Substitution at Alkylidene Carbenoids with O Nucleophiles*



Run	**1**	*n*	R	Yield/%		
				2	**3**	**4**
1	**1a**	1	Ph	81	7	0
2	**1b**	1	$PhCH_2CH_2$	82	0	0
3	**1c**	2	Ph	48	23	12

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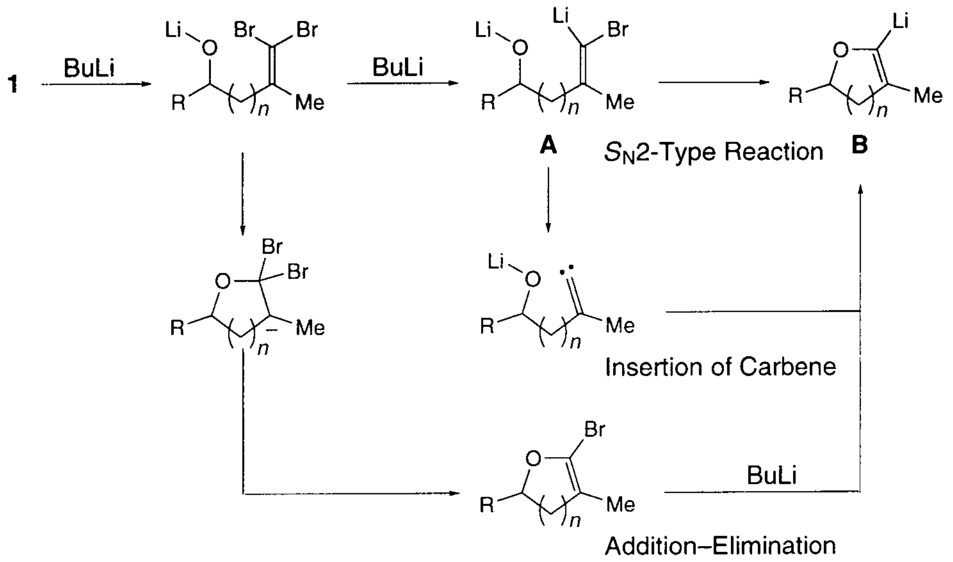
[1]) Acetylene **3** was produced as a consequence of 1,2-migration of alkylidene carbenoid **A** (*Fritsch-Buttenberg-Wiechell* rearrangement) [6].

[2]) Alcohol **4** was probably formed by the addition reaction of BuLi to ketone, which was generated *via* the intramolecular hydride attack at carbenoid **A** [7].

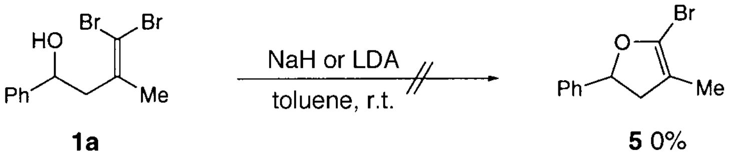
At this stage, three mechanisms were considered for this cyclization reaction, namely $S_{\mathrm{N}}2$-type substitution, insertion of a carbene intermediate, and an addition-elimination reaction (*Scheme 2*).

Scheme 2



The addition-elimination mechanism was excluded, because **1a** was recovered completely, without forming the desired bromodihydrofuran **5**, when **1a** was treated with NaH or lithium diisopropylamide (LDA) (*Scheme 3*). By the following experiment, alkylidene carbene insertion to the lithium alkoxide was also neglected as a major reaction pathway. It is known that the alkylidene carbenes, generated *via* the corresponding 1-diazo-4-(trimethylsilyloxy)but-1-ene derivatives, readily undergo intramolecular insertion to the Si–O bond to give 2,3-dihydro-5-(trimethylsilyl)furans in good yields [8]. Dihydrofuran **7**, however, was produced in only 10% yield on treatment of dibromo(trimethylsilyloxy)-alkene **6** with a slight excess of BuLi (*Scheme 4*). These results imply that the cyclization may proceed according to $S_{\mathrm{N}}2$ mechanism analogously to the substitution reaction of oximes, although the detailed reaction mechanism is still unclear[3]).

Scheme 3



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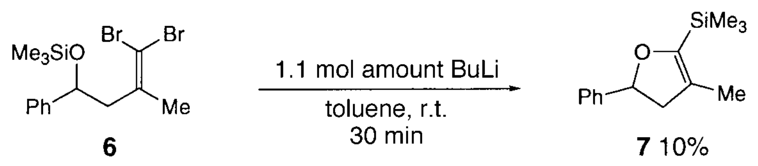
[3]) Efforts are presently underway to clarify the reaction mechanism by theoretical methods.

Scheme 4



To explore synthetic utility of this substitution reaction, preparation of indene derivatives was examined by means of 1,1-dibromo-3-(2-bromophenyl)propene derivatives **8** (*Table 2*). Because of the high nucleophilicity of carbanions **C**, the cyclization proceeded smoothly at – 90° in THF to give 1*H*-indenes **9a**–**d** in 85–86% yield (*Runs 1–4*). Furthermore, quenching with electrophiles such as PhCHO and $BrCF_2CF_2Br$ afforded polysubstituted indenes **10** and **11** regioselectively (*Runs 5–10*). Thus, the generated (1*H*-inden-3-yl)lithiums **D**4) apparently existed without isomerization of the C=C bond at – 90°, which is in contrast to the behavior of (1*H*-inden-1-yl)lithiums. Generally, the reaction of indenyllithiums having substituents with an electrophile is prone to afford a mixure of isomers as a result of isomerization5).

Although indenes are known as precursors of indenyl ligands such as *Kaminsky*-type catalysts [9], there are only few reports on regioselective synthesis of polysubstituted indenes. As a consequence, the present method offers a pathway to (1*H*-inden-3-yl)lithium to provide useful synthetic method for regioselectively polysubstituted indenes.

The construction also of six-membered rings was accomplished by this substitution reaction. Dihydronaphthalenes **13**–**15** were obtained in good yields from 1-bromo-2-(4,4-dibromo-3-mehylbut-3-enyl)benzene (**12**) (*Table 3*).

Conclusions. – Five- or six-membered rings are constructed *via* the intramolecular substitution reaction at the C-atom of alkylidene-lithium carbenoids, which are generated by the treatment of geminal dibromoalkenes with alkyllithium. Dihydrofurans and dihydropyran were obtained when alkoxides were employed as nucleophiles. In addition, 1*H*-indenes and 1,2-dihydronaphthalenes were produced when carbanions were used as nucleophiles. Furthermore, the alkenyllithium intermediates generated during cyclization react regioselectively with electrophiles to afford polysubstituted indenes and dihydronaphtalenes.

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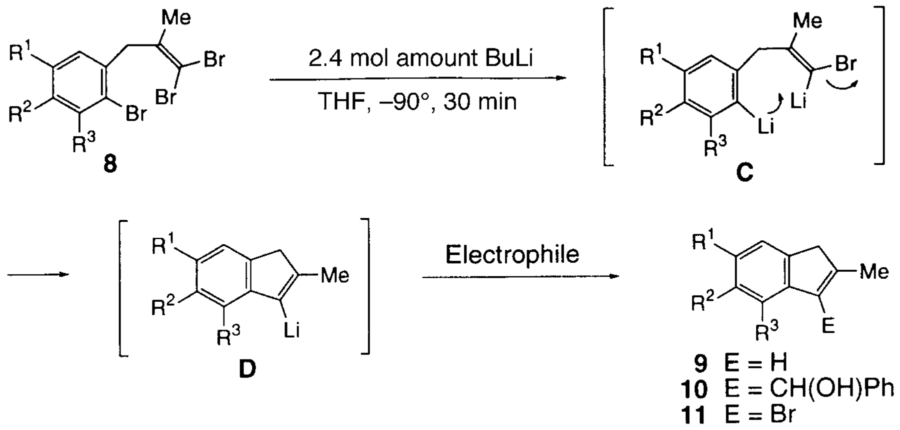
4) To the best of our knowledge, no (1*H*-inden-3-yl)lithium was reported. For the addition reaction of 1*H*-inden-3-yl anion and electrophile in the gas phase, see [11].

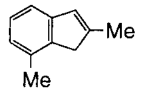
5) Inseparable isomers of adducts were obtained when 1*H*-indene **9b** was treated with *t*-BuLi to generate (1*H*-inden-1-yl)lithium, followed by addition of PhCHO at – 90°. For the isomerization of (1*H*-inden-1-yl)lithium, see [10].

Table 2. *Preparation of 1*H*-Indenes* **9**–**11**



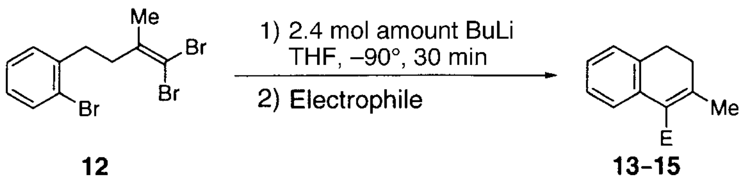
Run	R¹	R²	R³	**8**	Electrophile	E	Product	Yield/%
1	H	H	H	**8a**	MeOH	H	**9a**	85
2	MeO	H	H	**8b**	MeOH	H	**9b**	85
3	H	CF_3	H	**8c**	MeOH	H	**9c**	86
4	H	H	Me	**8d**	MeOH	H	**9d**	86[a])
5	H	H	H	**8a**	PhCHO	CH(OH)Ph	**10a**	84
6	MeO	H	H	**8b**	PhCHO	CH(OH)Ph	**10b**	87
7	H	H	Me	**8d**	PhCHO	CH(OH)Ph	**10d**	87
8	H	H	H	**8a**	$BrCF_2CF_2Br$	Br	**11a**	83
9	MeO	H	H	**8b**	$BrCF_2CF_2Br$	Br	**11b**	80
10	H	H	Me	**8d**	$BrCF_2CF_2Br$	Br	**11d**	63

[a]) A mixture of **9d** and **9d′** in a ratio of 5 : 1.



9d′

Table 3. *Preparation of 1,2-Dihydronaphthalenes* **13**–**15**



Run	Electrophile	E	Product	Yield/%
1	MeOH	H	**13**	76
2	PhCHO	CH(OH)Ph	**14**	77
3	$BrCF_2CF_2Br$	Br	**15**	77

Experimental Part

General. Toluene was distilled and dried over molecular sieves (4 Å). Anh. THF was purchased from *Kanto Chemical Co., Inc.*, and dried over molecular sieves (4 Å). BuLi (1.6M hexane soln.) was purchased from *Aldrich Co., Inc.* and used after titration. Prep. TLC: Wakogel B-5F. M.p.: uncorrected. IR Spectra: *Horiba FT 300-S* spectrophotometer. ^{1}H- (500 MHz) Spectra: *Bruker DRX-500* and *Bruker AVANCE-500* spectrometers in $CDCl_3$ with $CHCl_3$ (for ^{1}H, $\delta = 7.24$) as the internal standard. ^{13}C-NMR (125 MHz) Spectra: were recorded on *Bruker DRX-500* and *Bruker AVANCE-500* spectrometers in $CDCl_3$ with $CDCl_3$ (for ^{13}C, $\delta = 77.00$) as the internal standard. Elemental analyses were carried out at The Elemental Analysis Laboratory, Department of Chemistry, Faculty of Science, The University of Tokyo.

Typical Procedure for the Substitution Reaction with an O-Nucleophile. To a soln. of dibrom-olakenol **1a** (123 mg, 0.38 mmol) in toluene (3.8 ml) was added BuLi (1.6M in hexane, 0.52 ml, 0.81 mmol) at r.t., and the mixture was stirred for 30 min. The reaction was quenched with MeOH. The mixture was extracted with Et_2O (3×10 ml). The combined org. layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by prep. TLC to afford **2a** (50 mg, 0.32 mmol, 82% yield).

2,3-Dihydro-4-methyl-2-phenylfuran (**2a**). Colorless oil. IR (KBr): 2964, 1728, 1454, 1022, 997, 758, 700. ^{1}H-NMR: 1.66–1.67 (*m*, Me); 2.49–2.54 (*m*, 1 H, CH_2); 2.94–3.00 (*m*, 1 H, CH_2); 5.50 (*dd*, $J = 8.3$, 10.6, PhC*H*); 6.16 (*m*, C=CH); 7.25–7.29 (*m*, 1 arom. H); 7.31–7.35 (*m*, 4 arom. H). ^{13}C-NMR: 11.1; 42.8; 82.5; 109.0; 125.5; 127.5; 128.5; 139.5; 143.5. Anal. calc. for $C_{11}H_{12}O$: C 82.46, H 7.55; found: C 82.30, H 7.63.

Typical Procedure for the Substitution Reaction with C Nucleophile. To a soln. of dibromo-alkene **8a** (184 mg, 0.50 mmol) in THF (5.0 ml) was added BuLi (1.6M in hexane, 0.74 ml, 1.2 mmol) at −90°, and the mixture was stirred for 30 min. The reaction was quenched with MeOH. The mixture was extracted with Et_2O (3×10 ml). The combined org. layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by prep. TLC to afforded **9a** (55 mg, 0.42 mmol, 85% yield).

*2-Methyl-1*H*-indene* (**9a**). Colorless oil. IR (KBr): 1616, 1464, 1392, 750, 715. ^{1}H-NMR: 2.15–2.15 (*m*, Me); 3.29 (*m*, CH_2); 6.48 (*m*, C=CH); 7.09 (*ddd*, $J = 1.3$, 7.3, 7.3, arom. H); 7.19–7.25 (*m*, 2 arom. H); 7.35–7.37 (*m*, 1 arom. H). ^{13}C-NMR: 16.7; 42.7; 119.7; 123.2; 123.4; 126.2; 127.1; 143.3; 145.9; 146.0.

REFERENCES

[1] a) H. Kusama, Y. Yamashita, K. Narasaka, *Chem. Lett.* **1995**, 5; b) H. Kusama, K. Uchiyama, Y. Yamashita, K. Narasaka, *Chem. Lett.* **1995**, 715; c) H. Kusama, Y. Yamashita, K. Uchiyama, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 965; d) K. Uchiyama, M. Yoshida, Y. Hayashi, K. Narasaka, *Chem. Lett.* **1998**, 607; e) M. Yoshida, K. Uchiyama, K. Narasaka, *Heterocycles* **2000**, *52*, 681.

[2] S. Mori, K. Uchiyama, Y. Hayashi, K. Narasaka, E. Nakamura, *Chem. Lett.* **1998**, 111.

[3] a) M. Duraisamy, H. M. Walborsky, *J. Am. Chem. Soc.* **1984**, *106*, 5035; b) M. Topolski, M. Duraisamy, J. Rachon, J. Gawronski, K. Gawronska, V. Goedken, H. M. Walborsky, *J. Org. Chem.* **1993**, *58*, 546.

[4] M. Topolski, *J. Org. Chem.* **1995**, *60*, 5588.

[5] a) G. Köbrich, F. Ansari, *Chem. Ber.* **1967**, *100*, 2011; b) G. Boche, J. C. W. Lohrenz, *Chem. Rev.* **2001**, *101*, 697.

[6] E. T. Chernick, S. Eisler, R. R. Tykwinski, *Tetrahedron Lett.* **2001**, *42,* 8575, and refs. cit. therein.

[7] A. Oku, T. Harada, K. Hattori, Y. Nozaki, Y. Yamaura, *J. Org. Chem.* **1988**, *53*, 3089.

[8] K. Miwa, T. Aoyama, T. Shioiri, *Synlett* **1994**, 461.

[9] 'Metallocenes: Synthesis Reactivity Applications' Vol. 1, 2 Eds. A. Togni, R. L. Halterman, Wiley-VCH, Weinheim, 1998.

[10] W. Spaleck, M. Antberg, J. Rohrmann, A. Winter, B. Bachmann, P. Kiprof, J. Behm, W. A. Herrmann, *Angew. Chem., Int. Ed.* **1992**, *31*, 1347.

[11] K. M. Broadus, S. Han, S. R. Kass, *J. Org. Chem.* **2001**, *66*, 99.

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