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Tandem Cyclization of Alkynylmetals Bearing a Remote Leaving Group via Cycloalkylidene Carbenes

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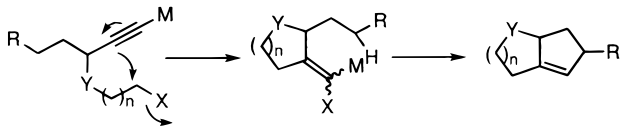
ABSTRACT

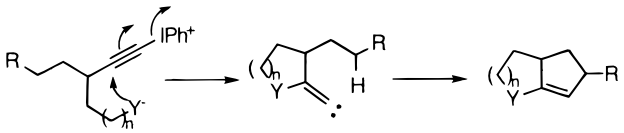


M = Li, Na, K; Y = CH_2, O; X = I, OSO_2Ar; n = 1, 2

Treatment of terminal alkynes bearing a remote leaving group with MNR_2 (M = Li, Na, K) gives bicyclo[*n*.3.0]-1-alkenes (*n* = 3, 4). The tandem cyclization proceeds through a mechanism involving *exo*-cyclization of an alkynylmetal intermediate and intramolecular C-H insertion of the resulting carbenoid.

Alkylidene carbenes undergo intramolecular C-H insertion in a regiospecific manner to give cyclopentenes.[1] The five-membered ring construction proceeds at a previously unactivated C-H site with retention of configuration at chiral centers. The reaction has been utilized as a key carbon−carbon bond-forming reaction in natural product syntheses.[1,2] Of previously reported methods for generating alkylidene carbenes (or carbenoids), the addition of nucleophiles to alkynyliodonium salts is particularly versatile and efficient.[3−5] The method not only allows the generation of functionalized carbenes but also provides a convergent strategy for the construction of polycyclic molecular frameworks as recently demonstrated by Feldman et al. (Scheme 1).[6,7] Unfortunately,

Scheme 1. Tandem Cyclization of Alkynyliodonium Salts



Y = NTs, O, n = 1-3

however, the tandem cyclization is limited to that involving certain heteroatom nucleophiles (Y = NTs, O) with an appropriate reactivity tolerated by alkynyliodonium salts.

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(2) (a) Taber, D. F.; Christos, T. E. *J. Org. Chem.* **1996**, *61*, 2081 and references therein. (b) Taber, D. F.; Yu, H.; Incarvito, C. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 13285. (c) Taber, D. F.; Christos, T. E.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1999**, *121*, 5589.

(3) For review, see: (a) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274. (b) Ochiai, M. *Reviews on Heteroatom Chemistry*, Volume 2; Oae, S., Ed.; MYU: Tokyo, 1989; p 92.

(4) (a) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281. (b) Ochiai, M.; Kunishima, M.; Fuji, K.; Nagao, Y. *J. Org. Chem.* **1988**, *53*, 6144. (c) Ochiai, M.; Ito, T.; Takaoka, Y.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 118. (d) Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3135.

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(6) (a) Schildknegt, K.; Bohnstedt, A. C.; Feldman, K. S.; Sambandam, A. *J. Am. Chem. Soc.* **1995**, *117*, 7544. (b) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440. (c) Feldman, K. S.; Bruendl, M. M. *Tetrahedron Lett.* **1998**, *39*, 2911.

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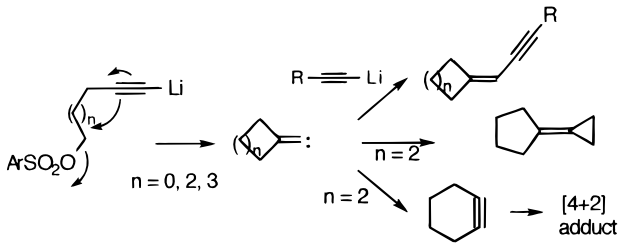
In sharp contrast to the electrophilic nature of alkynyliodonium salts in the carbene generation, we recently reported a method for alkylidene carbene generation from nucleophilic alkynylmetals.[8] We found that alkynyllithiums bearing a remote leaving group undergo facile *exo*-cyclization with carbon−carbon bond formation to give cycloalkylidene carbenes (Scheme 2). The carbene formation was demonstrated by trapping experiments with alkynyllithiums to form enynes, with alkenes to form [2 + 1] adducts, and with 1,3-diphenylisobenzofuran to form the [4 + 2] adducts of the rearranged cycloalkynes.

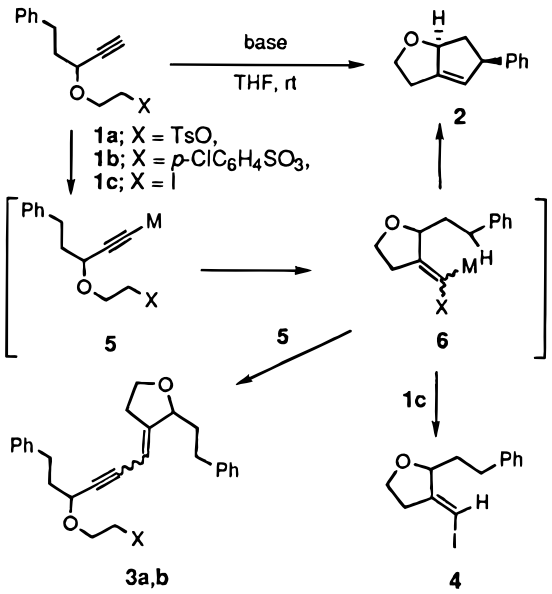
Scheme 2. *Exo*-Cyclization of Alkynyllithiums To Form Cycloalkylidene Carbenes



Herein, we wish to report the first example of tandem carbocyclization that proceeds through initial *exo*-cyclization of alkynylmetals and subsequent intramolecular C-H insertion of the resulting cycloalkylidene carbenes leading to bicyclo[3.3.0]octenes and bicyclo[4.3.0]nonenes.

(Propynyloxy)ethyl tosylate **1a** was prepared by $TiCl_4$-mediated ring cleavage of dioxolane acetal derived from 3-phenylpropanal with bis(trimethylsilyl)acetylene[9] followed by desilylation and subsequent tosylation of the resulting alcohol. Lithiation of **1a** with BuLi (1.0 equiv) in THF at −85 °C and warming of the resulting alkynyllithium **5** (M = Li) to room temperature gave tandem cyclization product **2**[10] in 32% yield with high stereoselectivity (92:8) together with enyne **3a** (X = OTs) (36%) (Scheme 3, entry 1 in Table 1). The formation of **3a** as a byproduct suggested that intermolecular reaction of carbenic species **6** with alkynyllithium **5** competed with intramolecular C-H insertion. Slow addition of BuLi to a dilute solution (0.02 M) of **1a** at room temperature retarded the undesirable pathway and improved the yield of **2** (entry 2). Further improvement was anticipated

Scheme 3. Tandem Cyclization of Propynyloxyethyl Derivatives **1a−c**



by the acceleration of the initial *exo*-cyclization of alkynylmetal **5** through the modification of a leaving group and/or a metal atom because it would reduce the lifetime of **5**. While the reaction of *p*-chlorobenzene sulfonate **1b** with BuLi gave a similar result (entry 3), that of more reactive iodide **1c** with LDA afforded **2** in 76% yield (entry 6). The tandem cyclization also proceeded through the corresponding alkynylsodium and -potassium **7** (M = Na, K) (entries 4, 5, and 7). For sulfonate **1b**, the reaction through alkynylsodium was most efficient (entry 4 vs entries 3 and 5).

Information on the nature of carbenic species generated by *exo*-cyclization was obtained in the reactions of iodide

Table 1. Tandem Cyclization of (Propynyloxy)ethyl Derivatives **1a−c**[a]

entry	substrate	base[b]	**2**		byproduct	
			yield (%)	ratio[c]		yield (%)
1[d]	**1a**	BuLi	36	92:8	**3a**	37
2		BuLi	59	93:7	**3a**	5
3	**1b**	BuLi	60	92:8	**3b**	4
4		NaHMDS	71	93:7	**3b**	9
5		KHMDS	58	92:8	**3b**	-
6	**1c**	LDA	76	94:6	**4**[e]	15
7		NaHMDS	60	93:7	**4**[e]	27

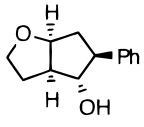
[a] Unless otherwise noted, reactions were carried out by adding a base (1.2 equiv) to a solution of **1** in THF (0.02 M) slowly over 4−5 h at room temperature. [b] NaHMDS = sodium hexamethyldisilazide; KHMDS = potassium hexamethyldisilazide.

(7) For a different approach, see ref 5d.

(8) Harada, T.; Iwazaki, K.; Otani, T. Oku, A. *J. Org. Chem.* **1998**, *63*, 9007.

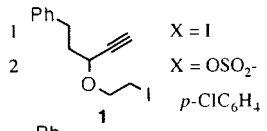
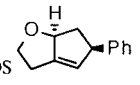
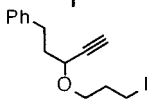
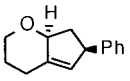
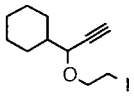
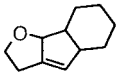
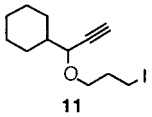
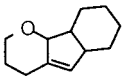
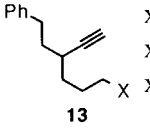
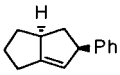
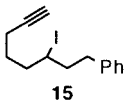
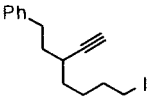
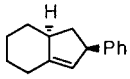
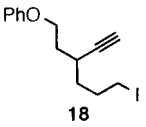
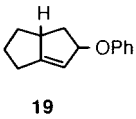
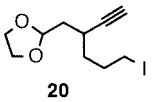
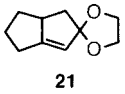
(9) Johnson, W. S.; Elliott, R.; Elliot, D. J. *J. Am. Chem. Soc.* **1983**, *105*, 2904.

(10) The stereochemistry of the major isomer was established by an NOE experiment after converting **2** into alcohol **i** ($(CH_3)_2CHC(CH_3)_2BH_2$, THF, then NaOOH; 41%).



i

Table 2. Tandem Cyclization of Alkynylmetals with Remote Leaving Grouds[a]

entry	substrate	base	product	yield [b]	ratio [c]
1	 X = I	LDA	 **2**	76	94:6
2	X = OSO_2-p-ClC_6H_4	NaHMDS		60	93:7
3 [d]	 **7**	LDA	 **8**	76	73:27
4	 **9**	LDA	 **10**	62	58:38:4
5		NaHDMS		72	56:39:5
6 [d]	 **11**	LDA	 **12**	62	60:30:10
7	 X = I	LDA	 **14** [e]	48	91:9
8	X = I	NaHDMS		61	91:9
9	**13** X = OSO_2-p-ClC_6H_4	KHMDS		57	92:8
10	 **15**	LDA	**14**	39	91:9
11 [d]	 **16**	LDA	 **17** [e]	50	60:40
12 [d]		NaHDMS		51	67:33
13	 **18**	LDA	 **19**	59	53:47
14	 **20**	LDA	 **21**	48 [f]	-

[a] Unless otherwise noted, reactions were carried out by adding a base ((1.2 equiv) to a solution of a substrate in THF (0.2 M) slowly over 4−5 h at room temperature. [b] Isolated yield unless otherwise noted. [c] Ratio of stereoisomers determined by ^{1}H NMR analysis. [d] The reaction was carried out at 40 °C. [e] The stereochemistry was tentatively assigned by analogy with that of **2** and **8**. The yield was determined by ^{1}H NMR.

1c (entries 6 and 7). Iodoalkene (*E*)-**4**[11] was formed as a byproduct despite the complete retardation of enyne formation. The observation suggests the involvement of carbenoid **6** (X = I) which might be protonated by **1c** to give **4**. The observed increase of the byproduct in the reaction involving alkynylsodium (entry 7) can be understood in terms of the higher basicity of sodium carbenoids in comparison with lithium carbenoids. Absence of such byproducts in the reactions of sulfonates **1a**,**b** is probably due to the more dissociated character of the corresponding carbenoid.[1a]

The scope of the new tandem cyclization was investigated with a variety of alkynyl iodides and sulfonates (Table 2). The reaction of a homologous substrate **7** with LDA also proceeded in an efficient manner at 40 °C to give oxabicyclononene **8**[12] stereoselectively (entry 3). Tricyclic compounds **10** and **12** were obtained in a highly convergent manner through the tandem cyclization of **9** and **11**, respectively (entries 4−6). The reaction is equally applicable to substrates bearing no oxygen atom in a main chain. For iodide **13** (X = I), the use of NaHMDS as a base gave a better result than that of LDA (entry 7 vs 8). The reactions of sulfonates **13** (X = *p*-$ClC_6H_4SO_3$) with KHMDS also gave a satisfactory result (entry 9). Intramolecular insertion into the C−H bond α to the oxygen atom also proceeded smoothly to furnish functionalized bicyclooctene **19** and **21** (entries 13 and 14). An alkynylmetal derived from secondary iodide **15** would undergo *exo*-cyclization to give the same intermediate that is generated from primary substrate **13**. Indeed, the reaction of **15** afforded bicyclooctene **14** stereoselectively albeit in lower yield (entry 10).[13]

In summary, we have shown a novel tandem carbocyclization involving *exo*-cyclization of alkynylmetals and C-H insertion of the resulting carbenes. Substrates in Table 2 were accessible in few steps either through $TiCl_4$-mediated ring cleavage of cyclic acetals or through alkylation of trilithio derivatives of ω-alkynols (LiC≡CCH(Li)$(CH_2)_n$$CH_2$-OH; n = 2, 3).[14] The reaction, therefore, serves as a useful method for the convergent synthesis of polycyclic compounds.

Acknowledgment. We thank the Ministry of Education, Science, Sports, and Culture, Japan (Grant-in-Aid for No. 11650892) for financial support.

Supporting Information Available: Preparation of starting materials **7** and **13** and characterization data for products **10**, **12**, **14**, **17**, **19**, **21**, and **i**. This material is available free for charge via the Internet at http://pubs.acs.org.

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(11) Palladium-catalyzed cross-coupling reaction of **4** (PhZnCl, $PdCl_2$-(dppf), THF) gave (*E*)-3-(phenylmethylidene)-2-(2-phenylethyl)tetrahydrofuran (87%), whose *E*-geometry was determined by an NOE experiment.

(12) The stereochemistry of the major isomer was established by NOE.

(13) **Procedure for the preparation of 8-phenyl-5-oxabicyclo[4.3.0]-nona-1(9)-ene (8) (Table 2, entry 3):** To a solution of iodide **7** (154 mg, 0.50 mmol) in THF (25 mL) at 40 °C was slowly added LDA (THF complex, 1.5 M in cyclohexane) (0.40 mL, 0.60 mmol) during 4 h by using a syringe pump. After being stirred for 1 h at 40 °C, the mixture was poured into brine and extracted twice with ether. The organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (SiO_2, 5% ethyl acetate in hexane) gave **8** (75.8 mg, 76%) as a 73:27 mixture of diastereomers. The major isomer was isolated by a recycling preparative HPLC equipped with a GPC column (JAIGEL-1H column, Japan Analytical Industry) using $CHCl_3$ as an eluent: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (1H, ddd, J = 6.5, 7.7, and 13.4 Hz), 1.76 (1H, m), 1.85 (1H, tq, J = 4.5 and 13.0 Hz), 2.32 (1H, br t, J = *ca.* 14 Hz), 2.64 (1H, br d, J = ca. 14 Hz), 2.84 (1H, td, J = 7.7 and 13.5 Hz), 3.66 (1H, dt, J = 2.1 and 11.9 Hz), 3.80 (1H, m), 4.09 (1H, br d, J = 11.5 Hz), 4.42 (1H, t, J = 6.9 Hz), 5.48 (1H, s), 7.15−7.35 (5H, m) [the minor isomer resonated at 4.60 (1H, t, J = 6.2 Hz) and 5.59 (1H, s)]; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 26.01, 27.41, 41.17, 48.17, 67.49, 83.19, 126.14, 127.11, 127.35, 128.32, 142.40, 145.72 [the minor isomer resonated at 26.20, 27.64, 40.17, 49.15, 67.62, 83.39, 125.99, 126.95, 127.16, 128.38, 142.31, 146.00]; IR (liquid film) 1600, 1080, 760, 700 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 7.99. Found: C, 83.67; H, 7.93.

(14) Brandsma, L.; Verkruijsse, H. D. *Syntheses of Acetylenes, Allenes, and Cumulenes*; Elsevier: Amsterdam, 1980; p 48.