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Palladium(0)-Catalyzed Synthesis of Medium-Sized Heterocycles by Using Bromoallenes as an Allyl Dication Equivalent

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Abstract: We have developed a highly regio- and stereoselective synthesis of medium-sized heterocycles containing one or two heteroatoms via cyclization of bromoallenes bearing an oxygen, nitrogen, or carbon nucleophilic functionality in the presence of a palladium(0) catalyst and alcohol. In this reaction, bromoallenes act as an allyl dication equivalent, and the intramolecular nucleophilic attack takes place exclusively at the central carbon atom of the allene moiety. Interestingly, bromoallenes having a carbon nucleophile with a five-atom tether afford eight-membered rings with *trans*-configuration, while those having an oxygen or a nitrogen nucleophile give the corresponding *cis*-rings selectively. This is the first example that demonstrates the synthesis of medium-sized rings via cyclization of bromoallenes, and this reaction provides a very useful method for a catalytic synthesis of seven- and eight-membered heterocycles without using high dilution conditions.

Introduction

Medium-sized heterocycles are an extremely important class of compounds, the structural units of which are commonly found within the framework of a variety of natural products.[1] In particular, seven- and eight-membered heterocycles are constituents of a number of compounds with interesting pharmacological properties.[2,3] The abundance of medium rings bearing oxygen or nitrogen atom(s) in medicinally interesting compounds continues to ensure that they are important synthetic targets for organic chemists. Synthetic routes to medium-ring heterocycles involving direct ring closure are often slow and hampered by unfavorable enthalpies (the strain in many medium rings) and entropies (probability of the chain ends meeting) of the reaction. Today, the most powerful methodology for the synthesis of medium-sized rings is the ring-closing metathesis (RCM),[4,5] that sometimes requires high dilution conditions for successful conversion and often involves generation of byproducts such as ethylene.

Currently, reactions of bromoallenes have attracted much interest due to their interesting chemical properties associated with the cumulated double bonds and a bromine atom. However, all the reactions of bromoallenes reported to date are intermolecular reactions such as organocopper-mediated substitutions,[6] palladium-catalyzed cross-coupling reactions,[7] and formation of allenylmetal reagents.[8] Recently, we reported a highly stereoselective synthetic method of 2,3-*cis*-2-ethynylaziridines via the

(1) For a recent review, see: Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131−9166.

(2) For selected examples for seven-membered heterocycles, see: (a) Duong, T.; Prager, R. H.; Tippett, J. M.; Ward, A. D.; Kerr, D. I. *Aus. J. Chem.* **1976**, *29*, 2667−2682. (b) Boros, C.; Hamilton, S. M.; Katz, B.; Kulanthaivel, P. *J. Antibiot.* **1994**, *47*, 1010−1016. (c) Ishihara, Y.; Hirai, K.; Miyamoto, M.; Goto, G. *J. Med. Chem.* **1994**, *37*, 2292−2299. (d) Morís-Varas, F.; Qian, X.-H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *33*, 7647−7652. (e) Grunewald, G. L.; Dahanukar, V. H.; Ching, P.; Criscione, K. R. *J. Med. Chem.* **1996**, *39*, 3539−3546.

(3) For selected examples for eight-membered heterocycles, see: (a) Basil, B.; Coffee, E. C. J.; Gell, D. L.; Maxwell, D. R.; Sheffield, D. J.; Wooldridge, K. R. H. *J. Med. Chem.* **1970**, *13*, 403−406. (b) Klayman, D. L.; Scovill, J. P.; Bartosevich, J. F.; Mason, C. J. *J. Med. Chem.* **1979**, *22*, 1367−1373. (c) Vedejs, E.; Galante, R. J.; Goekjian, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 3613−3622. (d) Ma, D.; Tang, G.; Kozikowski, A. P. *Org. Lett.* **2002**, *4*, 2377−2380. (e) Stærk, D.; Witt, M.; Oketch-Rabah, H. A.; Jaroszewski, J. W. *Org. Lett.* **2003**, *5*, 2793−2796 and references therein.

(4) For a recent review, see: (a) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073−2077. For selected examples, see: (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324−7325. (c) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109. (d) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291−4298. (e) Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126−8127. (f) Cook, G. R.; Shanker, P. S.; Peterson, S. L. *Org. Lett.* **1999**, *1*, 615−617. (g) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, *2*, 543−545. (h) Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811−4820. (i) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991−6997.

(5) For other recent synthesis of medium-ring heterocycles, see: (a) Evans, P. A.; Holmes, A. B.; Russel, K. *Tetrahedron: Asymmetry* **1990**, *1*, 593−596. (b) Kitano, T.; Shirai, N.; Motoi, M.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2851−2854. (c) Crombie, L.; Haigh, D.; Jones, R. C. F.; Mat-Zin, A. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2047−2054. (d) Coates, W. J.; Dhanak, D. *Heterocycles* **1993**, *36*, 1631−1639. (e) Wright, D. L.; Weekly, R. M.; Groff, R.; McMills, M. C. *Tetrahedron Lett.* **1996**, *37*, 2165−2168. (f) Bergmann, D. J.; Campi, E. M.; Jackson, W. R.; Patti, A. F.; Saylik, D. *Tetrahedron Lett.* **1999**, *40*, 5597−5600. (g) Ouyang, X.; Kiselyov, A. S. *Tetrahedron* **1999**, *55*, 8295−8302. (h) Zhang, J.; Jacobson, A.; Rusche, J. R.; Herlihy, W. *J. Org. Chem.* **1999**, *64*, 1074−1076. (i) Monovich, L. G.; Huérou. Y. L.; Rönn. M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52−57. (j) Räcker, R.; Döring, K.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 6932−6939. (k) Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413−1419. (l) Donohoe, T. J.; Raoof, A.; Linney, I. D.; Helliwell, M. *Org. Lett.* **2001**, *3*, 861−864. (m) Iradier, F.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2001**, *3*, 2957−2960. (n) Tempest, P.; Ma, V.; Kelly, M. G.; Jones, W.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4963−4968. (o) Kan, T.; Kobayashi, H.; Fukuyama, T. *Synlett* **2002**, 697−699. (p) Ma, D.; Tang, G.; Kozikowski, A. P. *Org. Lett.* **2002**, *4*, 2377−2380. See also ref 3c.

10.1021/ja048693x CCC: $27.50

Scheme 1. Aziridination of Bromoallene **1** in the Presence of a Palladium Catalyst

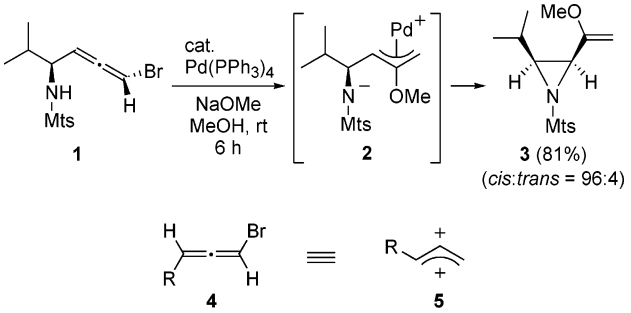
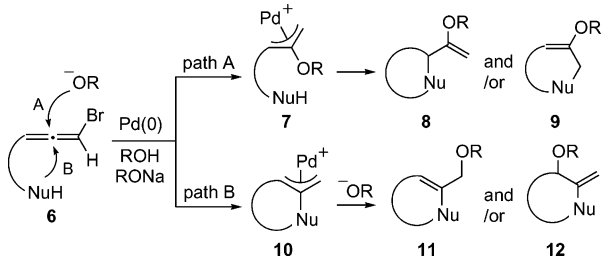


Figure 1. Bromoallenes as allyl dication equivalents.

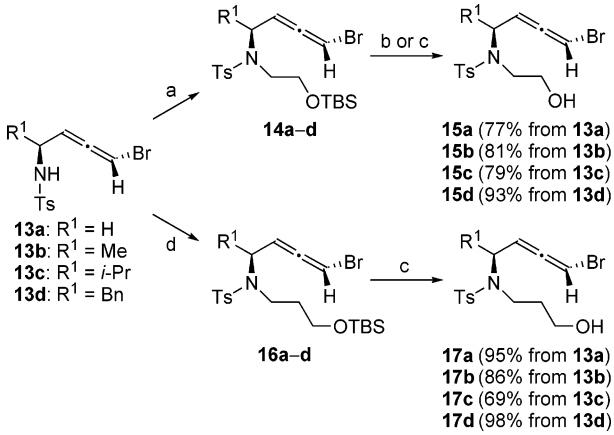
intramolecular amination of bromoallenes.[9] In the course of our examination of this aziridination reaction, we found that the reaction of bromoallene **1** with $Pd(PPh_3)_4$ and NaOMe in MeOH provided 2,3-*cis*-2-(1-methoxy)vinylaziridine **3** stereoselectively (Scheme 1). This result strongly suggests the formation of η^3-allylpalladium complex **2** bearing a methoxy group on the central carbon. Namely, bromoallene **4** can act as allyl dication equivalent **5** when treated with palladium(0) in an alcoholic solvent (Figure 1). Although similar types of reaction are often observed in propargylic carbonates with a palladium catalyst and soft nucleophiles such as active methylene, aryl alcohols or amide,[10] the reaction of allenic substrates and the synthesis of eight-membered rings are unprecedented.[11]

Utilizing this chemistry, we expected that various heterocyclic medium rings could be formed via intramolecular attack of an appropriate functionality such as an oxygen, a nitrogen, or active methylene nucleophile (Scheme 2). If the intermolecular nucleophilic attack at the central carbon atom of the allene moiety predominates over the intramolecular reaction (path A), cyclized products **8** and/or **9** would be obtained. On the other hand, if

Scheme 2. Formation of Medium Rings via Palladium(0)-Catalyzed Cyclization of Bromoallenes



Scheme 3. Synthesis of Bromoallenes Bearing an Oxygen Nucleophile[a]



[a] Reagents and conditions: (a) $HO(CH_2)_2OTBS$, DEAD, PPh_3, THF, rt; (b) TBAF, THF, 0 °C; (c) 1% HCl/EtOH, rt; (d) $HO(CH_2)_3OTBS$, DEAD, PPh_3, THF, rt. Abbreviations: TBS = *tert*-butyldimethylsilyl; DEAD = diethyl azodicarboxylate; TBAF = tetrabutylammonium fluoride.

the intramolecular nucleophilic attack takes place predominantly, cyclization at the central carbon atom of the allenic moiety would proceed to give **11** and/or **12**. In this contribution, we detail a highly regioselective synthetic method for medium-sized heterocycles **11** containing one or two heteroatoms by the palladium(0)-catalyzed cyclization of bromoallenes.[12] In all cases examined, the cyclization takes place at the central carbon regioselectively via path B to give a variety of medium-sized heterocycles.

Results and Discussion

Synthesis of Bromoallenes Bearing an Oxygen or a Nitrogen Nucleophilic Functionality. To investigate the synthesis of medium-ring heterocycles via cyclization of bromoallenes using a palladium catalyst as described in Scheme 2, the bromoallenes **15** and **17** bearing an oxygen nucleophilic functionality were prepared from bromoallenes **13**[13] as shown in Scheme 3. Diastereomerically pure (*S*,a*S*)-bromoallenes **13** were used to see the effect of the axial chirality on the cyclization reaction. Thus, the treatment of **13** with $HO(CH_2)_2$-OTBS or $HO(CH_2)_3OTBS$ under the Mitsunobu conditions gave **14** and **16** bearing the TBS group. The silyl group was then removed by TBAF or 1% HCl/EtOH to afford the desired (*S*,a*S*)-bromoallenes **15** and **17** having a hydroxyalkyl group.

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(8) (a) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1997**, *62*, 8976−8977. (b) Ma, S.; Yu, S.; Yin, S. *J. Org. Chem.* **2003**, *68*, 8996−9002.

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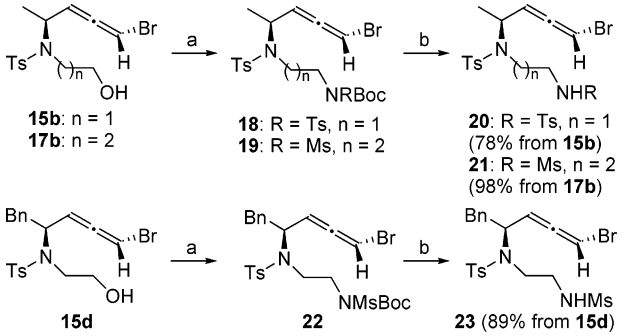
(10) (a) Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196−2198. For an excellent review, see: (b) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed.* **1995**, *34*, 2589−2612. For recent examples: (c) Monteiro, N.; Arnold, A.; Balme, G. *Synlett* **1998**, 1111−1113. (d) Yoshida, M.; Ihara, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 616−619. (e) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **2001**, *66*, 6634−6642. (f) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2001**, *42*, 4869−4873. (g) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 1499−1502. (h) Yoshida, M.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874−4881. (i) Kozawa, Y.; Mori, M. *J. Org. Chem.* **2003**, *68*, 8068−8074. (j) Yoshida, M.; Fujita, M.; Ihara, M. *Org. Lett.* **2003**, *5*, 3325−3327.

(11) For other synthesis of medium-ring heterocycles from allenes, see: (a) Shaw, R. W.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3549−3555. (b) Okawara, T.; Ehara, S.; Takenaka, A.; Hiwatashi, T.; Furukawa, M. *Heterocycles* **1995**, *41*, 1709−1714. (c) Grigg, R.; Sansano, J. M. *Tetrahedron* **1996**, *52*, 13441−13454. (d) Trost, B. M.; Michellys, P.-Y.; Gerusz, V. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 1750−1753. (e) Larock, R. C.; Tu, C.; Pace, P. *J. Org. Chem.* **1998**, *63*, 6859−6866.

(12) For preliminary communications, see: (a) Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749−1753. (b) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *Heterocycles* **2003**, *61*, 65−68.

(13) The bromoallenes **13b**−**d** were synthesized according to the reported procedure.[9] For synthesis of the bromoallene **13a**, see the Supporting Information.

Scheme 4. Synthesis of Bromoallenes Bearing a Nitrogen Nucleophile[a]

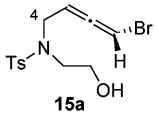
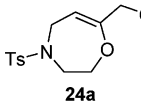
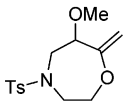
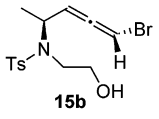
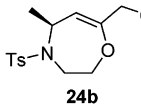
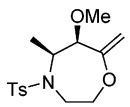
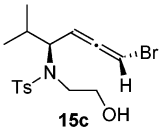
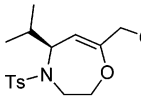
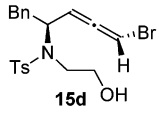
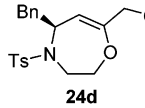
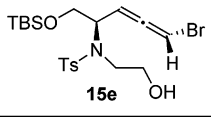
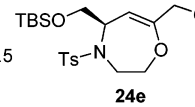


[a] Reagents and conditions: (a) TsNHBoc or MsNHBoc, DEAD, PPh_3, THF, rt; (b) 3 N HCl, EtOAc, 60 °C.

The bromoallene **20** bearing a nitrogen nucleophilic functionality was also prepared from **15b**, as shown in Scheme 4. The Mitsunobu reaction of **15b** with TsNHBoc[14] gave the *N*-Boc derivative **18**, the Boc group of which was removed with 3 N HCl to afford the desired bromoallene **20**. Similarly, **17b** and **15d** were converted into (*S*,a*S*)-bromoallenes **21** and **23**, respectively, through the reaction with MsNHBoc.[14]

Synthesis of Medium-Sized Nitrogen Heterocycles via Cyclization of Bromoallenes. According to the working hypothesis as depicted in Scheme 2, we next investigated the synthesis of medium-sized nitrogen heterocycles via cyclization of bromoallenes using a palladium catalyst. First, the bromoallene **15a** lacking a C-4 substituent was treated with NaOMe (1.5 equiv) in MeOH in the presence of $Pd(PPh_3)_4$ (10 mol %) to afford the seven-membered ring **24a** (61%) and its regioisomer **25a** (28%, Table 1, entry 1). When the bromoallene **15b** was employed, the seven-membered ring **24b**[15] (73%) and a small amount of its regioisomer **25b** were obtained (9%, entry 2). In contrast, bromoallenes **15c**−**e**[16] with a bulkier substituent at C-4 gave the seven-membered rings **24c**−**e** as the only isolable isomers (entries 3−5). These results clearly demonstrated that the regioselectivity of the second nucleophilic attack was controlled by the steric size of the substituent at C-4 of the bromoallenes. Next, the same reactions were conducted with bromoallenes **17a**−**e** bearing a five-atom tether between the allenic and hydroxyl groups (Table 2). In contrast to the seven-membered ring formation, reaction of bromoallenes **17a**−**e**[16] gave the eight-membered rings **26a**−**e** as the sole isolable isomers,[17] irrespective of the C-4 substituent of the bromoallenes. Unfortunately, the bromoallene **17c** with a bulkier substituent at C-4 gave the eight-membered ring **26c** in low yield (14%) under the identical reaction conditions. However, the reactivity of **17c** was slightly improved by using fresh NaOMe prepared in situ from NaH and MeOH (entry 3). On the other hand, in the case of bromoallene **17e** which has a bulkier substituent at C-5, the reaction proceeded smoothly to give eight-membered ring **26e** in 73% yield (entry 5).

Table 1. Synthesis of Seven-Membered Nitrogen Heterocycles via Cyclization of Bromoallenes Bearing an Oxygen Nucleophilic Functionality[a]

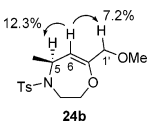
entry	substrate	$Pd(PPh_3)_4$ (mol%)	time (h)	product	yield[b]
1	 **15a**	10	6	 **24a**	61%
				 **25a**	28%
2	 **15b**	5	3	 **24b**	73%
				 **25b**	9%
3	 **15c**	5	6	 **24c**	62%
4	 **15d**	10	3.5	 **24d**	73%
5	 **15e**	10	4.5	 **24e**	74%

[a] Reactions were carried out at 25 °C in MeOH with diastereomerically pure bromoallenes, $Pd(PPh_3)_4$ (5−10 mol %), and NaOMe (1.5 equiv). [b] Isolated yields.

Next, we investigated the synthesis of seven- and eight-membered nitrogen heterocycles via cyclization of bromoallenes bearing a nitrogen functionality (Table 3). Under the identical reaction conditions, bromoallenes **20** and **23** gave the seven-membered rings **27a** and **27b**, respectively as a single isomer (entries 1 and 2). Furthermore, bromoallene **21** gave the eight-membered ring **27c** as a single isomer (entry 3). From the results shown in Tables 1−3, we found that the intramolecular nucleophilic attack takes place at the central position of the

(14) *N*-Boc sulfonamides, a useful nitrogen nucleophile in the Mitsunobu reaction, can be readily prepared by the reaction of sulfonamides with di-(*tert*-butyl) dicarbonate catalyzed by 4-(dimethylamino)pyridine: Neustadt, B. R. *Tetrahedron Lett.* **1994**, *35*, 379−380.

(15) Structure of **24b** was confirmed by NOE analysis. Irradiation of the signal of 6-H in 1,4-oxazepine **24b** led to NOE enhancement of the signal of 5-H and 1′-H (12.3% for 5-H and 7.2% for 1′-H).



(16) For synthesis of bromoallenes **15e** and **17e**, see the Supporting Information.

(17) The *cis*-configuration of the eight-membered ring **26** was determined by NOE analysis. For example, in the case of 1,5-oxazocine **26b**, NOE was observed between [6-H and 7-H (9.6%)] and [7-H and 1′-H (5.2%)].

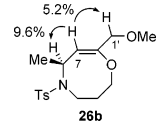
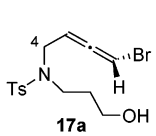
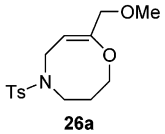
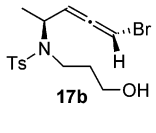
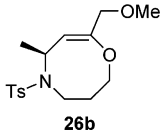
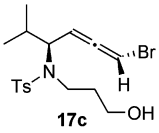
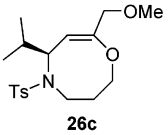
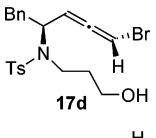
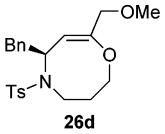
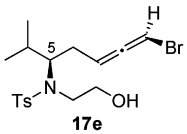
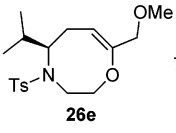
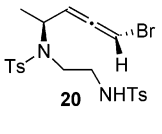
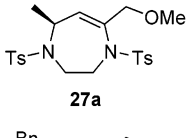
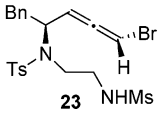
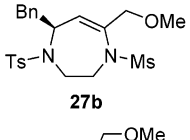
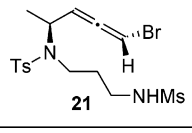
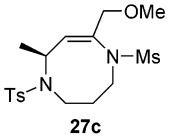


Table 2. Synthesis of Eight-Membered Nitrogen Heterocycles via Cyclization of Bromoallenes Bearing an Oxygen Nucleophilic Functionality[a]

entry	substrate	$Pd(PPh_3)_4$ (mol%)	time (h)	product	yield[d]
1	 **17a**	10	11	 **26a**	67%
2	 **17b**	5	6	 **26b**	84%
3	 **17c**	15	12[b]	 **26c**	30%
4	 **17d**	10	2.5[b]	 **26d**	57%
5	 **17e**	10	3[c]	 **26e**	73%

[a] Reactions were carried out at 25 °C in MeOH with diastereomerically pure bromoallenes, $Pd(PPh_3)_4$ (5−15 mol %), and NaOMe (1.5 equiv). [b] The reaction was conducted with NaH (1.5 equiv) and MeOH/THF (1:1) at 25 °C. [c] The reaction was conducted at 50 °C. [d] Isolated yields.

Table 3. Synthesis of Medium-Sized Nitrogen Heterocycles via Cyclization of Bromoallenes Bearing a Nitrogen Nucleophilic Functionality[a]

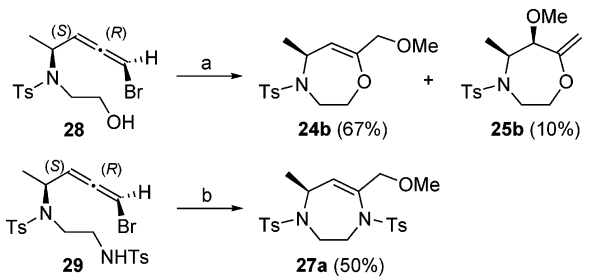
entry	substrate	time	product	yield[c]
1	 **20**	10 h	 **27a**	48%
2	 **23**	0.75 h[b]	 **27b**	53%
3	 **21**	12 h	 **27c**	63%

[a] Reactions were carried out at 25 °C in MeOH with diastereomerically pure bromoallenes, $Pd(PPh_3)_4$ (10 mol %), and NaOMe (1.5 equiv) unless otherwise stated. [b] The reaction was conducted under reflux. [c] Isolated yields.

allenic moiety (path B in Scheme 2) and, in most cases, the regioselectivity of the attack of methoxide is extremely high.

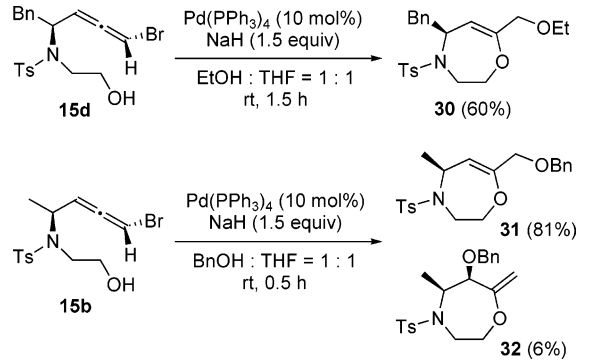
We next investigated the effect of axial chirality with (*S*,a*R*)-bromoallenes **28** and **29**[18] on the formation of medium-sized nitrogen heterocycles, as shown in Scheme 5. Thus, reaction of (*S*,a*R*)-bromoallene **28** gave 1,4-oxazepine derivatives **24b** (67%) and **25b** (10%) that is comparable to the result of (*S*,a*S*)-bromoallene **15b** (Table 1, entry 2). Similarly, (*S*,a*R*)-**29** was also cyclized into 1,4-diazepine derivative **27a** under identical reaction conditions in 50% yield (compare with Table 3, entry 1). From these results, both the (*S*,a*S*)- and (*S*,a*R*)-bromoallenes equally undergo the present transformation to give the same products, which means that a diastereomeric mixture of bromoallenes can be directly employed for preparative use.

Scheme 5. Reaction of (*S*,a*R*)-Bromoallenes



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$ (5 mol %), NaOMe (1.5 equiv), MeOH, rt, 2 h; (b) $Pd(PPh_3)_4$ (15 mol %), NaOMe (1.5 equiv), MeOH, rt, 12 h.

Scheme 6. Cyclization with Other Alcohols as the Second Nucleophile

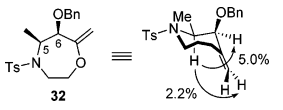


Other alcohols could be analogously used instead of MeOH for the present cyclization reaction (Scheme 6). For example, bromoallene **15d** was treated with a preformed mixture of NaH (1.5 equiv) and EtOH−THF (1:1) in the presence of $Pd(PPh_3)_4$ (10 mol %) to afford the seven-membered ring **30** having an ethoxy group (60%). Similarly, the reaction of bromoallene **15b** with BnOH gave benzyloxy derivatives **31** (81%) and **32** (6%).[19]

Next, we synthesized the bromoallene **36** with SES (2-trimethylsilylethanesulfonyl) group[20] as a nitrogen protecting group, and investigated the cyclization reaction and deprotection (Scheme 7). Compound **33** was readily prepared from L-phenylalanine following the literature.[9] The treatment of **33** with MsCl and Et_3N gave the corresponding mesylate, and the crude mesylate was then allowed to react with $CuBr\cdot SMe_2/LiBr$[21] to afford the (*S*,a*S*)-bromoallene **34**. Removal of the Boc group

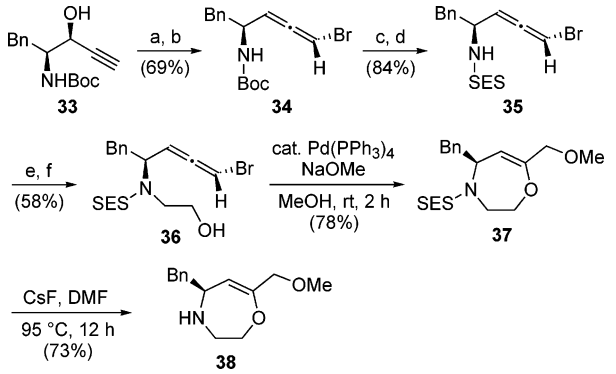
(18) The (*S*,a*R*)-bromoallenes **28** and **29** were synthesized by the identical procedure shown in Scheme 4 from known allenes.[9] For details, see the Supporting Information.

(19) Structure of **32** was confirmed by NOE analysis as shown below.



(20) Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, *27*, 2099−2102.

Scheme 7. Synthesis and Deprotection of *N*-SES-1,4-Oxazepine **37**[a]



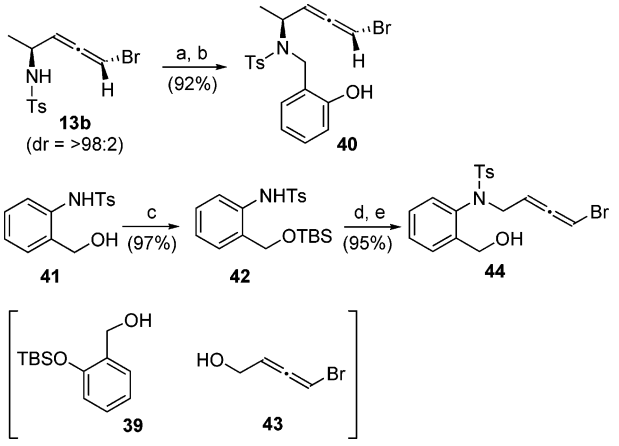
[a] Reagents and conditions: (a) MsCl, Et_3N, THF, −60 °C; (b) CuBr·DMS, LiBr, THF, rt; (c) 3 N HCl, EtOAc, 50 °C; (d) SESCl, Et_3N, DMF, 0 °C; (e) DEAD, PPh_3, $HO(CH_2)_2OTBS$, THF; (f) 1% HCl/EtOH.

gave the corresponding amine, which was then treated with SESCl to afford the SES amide **35**. The treatment of **35** with $HO(CH_2)_2OTBS$ under the Mitsunobu conditions gave the corresponding bromoallene, the silyl ether of which was then cleaved with 1% HCl/EtOH to afford **36** bearing an oxygen nucleophilic functionality. As we expected, the palladium(0)-catalyzed cyclization of the bromoallene **36** gave the seven-membered ring **37** as a single isomer. The SES group of **37** was readily removed by treatment with CsF in DMF[20] at 95 °C to give **38** in 73% yield. From these observations, the described transformation is also useful for the synthesis of 1,4-oxazepine bearing a free amino group, by using the SES group as an easily removable protecting group.

We investigated the synthesis of benzo-annulated medium-sized heterocycles, which are the basic structures of pharmacologically important compounds,[22] by cyclization of bromoallenes. The requisite bromoallenes **40** and **44** were synthesized by a similar procedure as described in Scheme 3. The treatment of **13b** with 2-(*tert*-butyldimethylsiloxy)benzyl alcohol **39**[23] under the Mitsunobu conditions followed by cleavage of the silyl ether by 1% HCl/EtOH afforded **40** having a phenolic hydroxyl group as the nucleophilic functionality (Scheme 8). The bromoallene **44** was also synthesized by the Mitsunobu reaction of an aniline derivative **42**, which was prepared from **41**[25] by protection of the primary hydroxyl group with the TBS group, with the known bromoallenol **43**.[24]

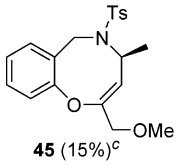
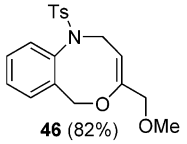
The palladium(0)-catalyzed cyclization of bromoallene **40** in MeOH gave benzo[*b*]-1,5-oxazocine **45** in low yield (15%; Table 4, entry 1). The yield was slightly improved by use of fresh NaOMe prepared from NaH and MeOH (33%; entry 2); however, a considerable amount of the starting material was recovered (24%). In contrast, when the reaction was conducted in a mixed solvent of MeOH/THF (1:1), the cyclized product

Scheme 8. Synthesis of Bromoallenes **40** and **44**[a]



[a] Reagents and conditions: (a) **39**, PPh_3, DEAD, THF, rt; (b) 1% HCl/EtOH, 75 °C; (c) TBSCl, imidazole, DMF, rt; (d) **43**, PPh_3, DEAD, THF, rt; (e) 1% HCl/EtOH, rt.

Table 4. Synthesis of Benzo-1,5-oxazocines **45** and **46**[a]

entry	substrate	base	solvent	time	product (yield)[b]
1	**40**	NaOMe	MeOH	20	 **45** (15%)[c]
2	**40**	NaH	MeOH	20	**45** (33%)[c]
3	**40**	NaH	MeOH-THF (1:1)	4	**45** (57%)
4	**44**	NaH	MeOH-THF (1:1)	5	 **46** (82%)

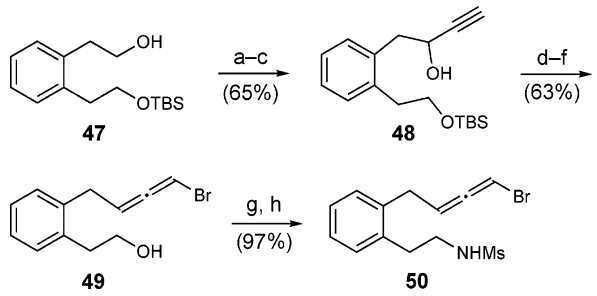
[a] Reactions were carried out at 25 °C with $Pd(PPh_3)_4$ (10 mol %) and a base (1.5 equiv). [b] Isolated yields. [c] 24% of **40** was recovered.

45 was obtained in a better yield (57%; entry 3). Similarly, the reaction of the bromoallene **44** gave benzo[*c*]-1,5-oxazocine **46** under the same reaction conditions in high yield (82%; entry 4).

Synthesis of Azocine, Azepine, Oxocine, and Oxepine Derivatives. From these results, we found that bromoallenes can act as allyl dication equivalents that are extremely useful for the synthesis of medium-sized nitrogen heterocycles bearing two heteroatoms. Next, we investigated a novel synthesis of seven- and eight-membered rings possessing one heteroatom, such as hexahydroazocines, tetrahydroazepines, tetrahydrooxocines, and tetrahydrooxepines. The requisite bromoallene **49** which bears an oxygen nucleophilic functionality was readily synthesized from monosilylated diol **47**[26] as shown in Scheme 9. Swern oxidation of **47**, ethynylation of the resulting aldehyde, and removal of the TMS group afforded a propargyl alcohol **48**, which was converted into the bromoallene **49** by treatment of the corresponding mesylate with $CuBr·SMe_2/LiBr$[21] followed by desilylation. Furthermore, **49** was converted into the corresponding azacycle precursor **50**, which bears an amide group as a nucleophilic functionality, by Mitsunobu condensa-

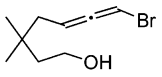
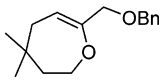
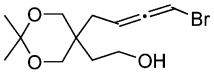
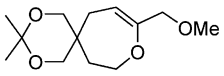
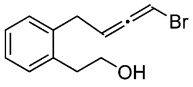
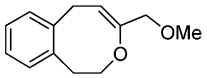
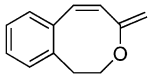
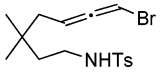
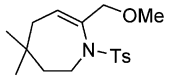
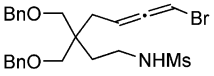
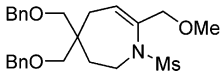
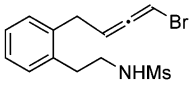
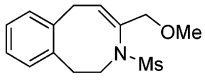
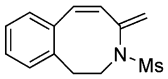
(21) (a) Montury, M.; Goré, J. *Synth. Commun.* **1980**, *10*, 873−879. (b) Elsevier, C. J.; Meijer, J.; Tadema, G.; Stehouwer, P. M.; Bos, H. J. T.; Vermeer, P. *J. Org. Chem.* **1982**, *47*, 2194−2196.
(22) See for example: (a) Kricka, L. J.; Ledwith, A. *Chem. Rev.* **1974**, *74*, 101−123. (b) Kaiser, C.; Ali, F. E.; Bondinell, W. E.; Brenner, M.; Holden, K. G.; Ku, T. W.; Oh, H.-J.; Ross, S. T.; Yim, N. C. F.; Zirkle, C. L.; Hahn, R. A.; Sarau, H. M.; Setler, P. E.; Wardell, J. R., Jr. *J. Med. Chem.* **1980**, *23*, 975−976. (c) Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914−7915. See also refs 2c and 3d.
(23) Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1994**, *35*, 7565−7568.
(24) Landor, P. D.; Landor, S. R.; Leighton, P. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1628−1632.
(25) Consonni, R.; Croce, P. D.; Ferraccioli, R.; Rosa, C. L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1809−1814.
(26) Krafft, M.; Schmidt, P. *Synth. Commun.* **2002**, *32*, 2723−2732.

Scheme 9. Synthesis of Bromoallenes **49** and **50**[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, then $(i\text{-Pr})_2NEt$; (b) TMS−acetylene, *n*-BuLi; (c) NaOMe, MeOH; (d) MsCl, Et_3N; (e) $CuBr\cdot SMe_2$, LiBr; (f) 1% HCl/EtOH; (g) MsNHBoc, PPh_3, DEAD; (h) 3 N HCl, EtOAc.

Table 5. Palladium-Catalyzed Formation Medium Rings Including One Heteroatom[a]

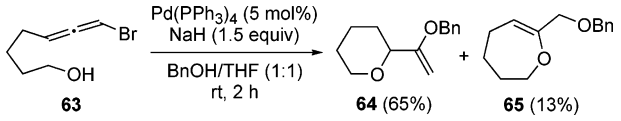
entry	bromoallene	conditions	product (yield[b])
1	 **51**	BnOH/THF (1:3) rt, 5 h	 **55** (72%)
2	 **52**	MeOH 55 °C, 2 h	 **56** (72%)
3	 **49**	MeOH/THF (1:1) rt, 4 h	 **57** (13%)  **58** (70%)
4	 **53**	MeOH 55 °C, 5 h	 **59** (76%)
5	 **54**	MeOH 55 °C, 2 h	 **60** (76%)
6	 **50**	MeOH/THF (1:1) rt, 4 h	 **61** (60%)  **62** (5%)

[a] All reactions were carried out using $Pd(PPh_3)_4$ (5 mol %) and NaH (1.5 equiv). [b] Isolated yields.

tion followed by deprotection with dilute HCl. Other requisite bromoallenes **51**, **52**, **53**, and **54** (Table 5) were also prepared by a similar procedure (see the Supporting Information).

We next investigated the cyclization reaction using the prepared bromoallenes. The results are summarized in Table 5. As we expected, treatment of the bromoallene **51** with a stirred

Scheme 10. Reaction of Bromoallene **63** Having an Unsubstituted Carbon Tether



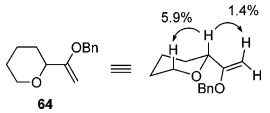
mixture of NaH, BnOH, and THF in the presence of $Pd(PPh_3)_4$ gave the tetrahydrooxepine derivative **55** in 72% yield by the first intramolecular nucleophilic addition to form an η^3-allyl palladium intermediate followed by the second nucleophilic attack by benzyloxide (entry 1). Similarly, the bromoallene **52** having a protected diol moiety was converted into **56** (entry 2). In contrast, exposure of **49** to the identical cyclization conditions afforded eight-membered heterocyclic diene **58** as a major product (entry 3), which was formed by β-hydride elimination of the η^3-allylpalladium(II) intermediate of the type **10** (Scheme 2). This is presumably due to the relatively highly acidic nature of the β-hydride at the benzylic position.[27] Medium-sized nitrogen heterocycles were also synthesized starting from the bromoallenes **53**, **54**, and **50** bearing a protected amino group (entries 4−6). Interestingly, when the amino allene **50** was used (entry 6), a methoxylated benzo[*d*]azocine derivative **61** was obtained as a major product (60% yield) along with a small amount of β-elimination product **62** (5% yield, compare with entry 3).

It should be clearly noted that, in contrast to the seven- and eight-membered ring formations possessing two heteroatoms (Table 1, entry 1 and Table 2, entry 1), bromoallene **63**[24] having an unsubstituted carbon tether afforded six-membered ring **64**[28] in 65% yield (Scheme 10) as a result of the first intermolecular nucleophilic attack by benzyloxide to form an η^3-allylpalladium intermediate of the type **7** described in Scheme 2, followed by the intramolecular nucleophilic reaction. From these results, it is apparent that the substituents or a heteroatom on the tether assists the formation of the intermediate of the type **10** described in Scheme 2.[29]

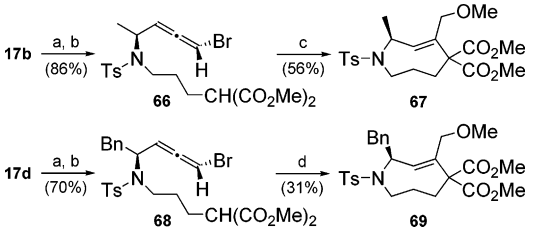
Reaction of Bromoallenes Having a Carbon Nucleophile. We next investigated the cyclization reaction of bromoallenes which have an active methylene as a nucleophile. Primary alcohols **17b** and **17d** were converted to the corresponding iodides, which were treated with NaH and dimethyl malonate to afford the requisite bromoallenes **66** and **68**, respectively, as shown in Scheme 11.

In contrast to the reaction of the bromoallenes having an oxygen or nitrogen nucleophile affording *cis*-rings exclusively, the bromoallenes **66** and **68** having an active methylene nucleophile gave eight-membered rings **67** and **69** with *trans*-configuration (56% and 31%, respectively).[30] These allenes are found to be less reactive than those having an oxygen or nitrogen nucleophile, presumably due to the steric hindrance. The observed *trans*-selectivity will be discussed later (Scheme 13).

(27) Exposure of the minor product **57** to the cyclization conditions led to complete recovery of **57**.
(28) Structure of **64** was confirmed by NOE analysis as shown below.

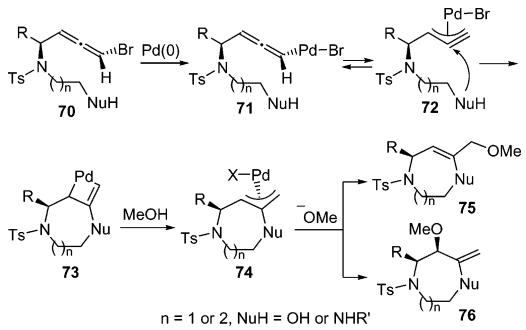


Scheme 11. Synthesis and Cyclization Reaction of Bromoallenes Having a Carbon Nucleophile[a]



[a] Reagents and conditions: (a) $(i\text{-Pr})_2NEt$, PPh_3, I_2, CH_2Cl_2, rt; (b) NaH, $CH_2(CO_2Me)_2$, DMF, rt; (c) $Pd(PPh_3)_4$ (20 mol %), NaOMe (1.5 equiv), MeOH, 50 °C, 3 h; (d) $Pd(PPh_3)_4$ (10 mol %), NaH (1.5 equiv), MeOH−THF (1:1), 50 °C, 4 h.

Scheme 12. Possible Reaction Course

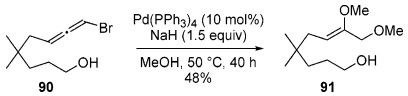


Mechanism of the Cyclization. A possible reaction course is shown in Scheme 12. Oxidative addition of bromoallene **70** to Pd(0) gives η^1-allenylpalladium complex **71**, which is in a state of equilibrium with η^3-propargylpalladium complex **72**.[31] The first intramolecular nucleophilic addition occurs to the central carbon of η^3-propargylpalladium complex **72** to produce a palladacyclobutene **73**.[32] This is followed by protonation by MeOH to generate η^3-allylpalladium complex **74**. In many cases, the methoxide attacks the terminal carbon to give **75** because of the steric repulsion with the R substituent. When the R substituent is effectively smaller (R = H or Me), a considerable amount of the adduct **76** is obtained by the attack of methoxide to the internal carbon of η^3-allylpalladium complex **74** from the backside of the palladium atom.[33,34]

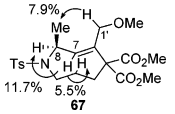
Recently, a related palladium-catalyzed cyclization of propargyl carbonates bearing a nucleophilic β-lactam moiety was reported by Mori: the reaction with a palladium catalyst in the presence of a bidentate ligand gave carbacepham derivatives which can be formed by the central attack of the lactam nitrogen onto an η^3-propargylpalladium complex, while the reaction in the presence of a monodentate ligand yielded carbapenams by a nucleophilic attack on the terminal carbon of an η^1-allenylpalladium complex.[10f,g,i] In contrast, our bromoallene cyclization proceeds in the presence of a monodentate ligand to afford medium rings by the reaction of nucleophiles onto the central carbon of the propargyl palladium complex.[35] Kurosawa, Ogoshi, and co-workers recently reported that a polar solvent shifts the equilibrium between η^1-allenyl- and η^3-propargylpalladium complexes toward the latter[31c] which is a reactive intermediate for the central attack.[36] Although the exact reason for the observed central attack in the presence of a monodentate ligand and an alcohol is unclear, the polar alcoholic solvent might promote the central attack by shifting the equilibrium toward the η^3-propargylpalladium complex **72**. An alcoholic solvent will also promote the reaction by protonation of the palladacyclobutene intermediate **73**.

As described above, bromoallenes **77** having an oxygen or nitrogen nucleophile afforded the eight-membered rings **79** with *cis*-configuration (Scheme 13), while bromoallene **66** (Scheme 11) having an active methylene nucleophile gave the corresponding *trans*-ring selectively. In the reaction of **77**, the methoxide will attack the less hindered terminal carbon of the *syn*-η^3-allylpalladium complex **78** to afford *cis*-**79**. On the other hand, the *syn*-η^3-allylpalladium complex **80**, which can be formed from **66**, will be less stable because of the steric repulsion between the axial proton and one ester group. Accordingly, the methoxide would attack the *anti*-η^3-allylpal-

(29) Although formation of benzo-annulated eight-membered ring proceeded in good yields (Table 5, entries 3 and 6), reaction of bromoallene **90** under the same reaction conditions afforded dimethoxylated product **91**. Therefore, it is apparent that a substitution which effectively assists the cyclization is essential for the eight-membered ring formation containing one heteroatom.



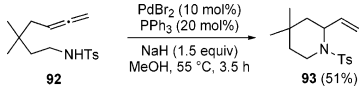
(30) The *trans*-configuration of **67** was determined by NOE analysis as shown below.



(31) (a) Ogoshi, S.; Tsutsumi, K.; Nishiguchi, S.; Kurosawa, H. *J. Organomet. Chem.* **1995**, *493*, C19−C21. (b) Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H. *J. Am. Chem. Soc.* **1998**, *120*, 1938−1939. (c) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687−2692. (d) Ogoshi, S.; Kurosawa, H. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 14−23.

(32) In the reaction of propargylic carbonates, it is proposed that the first nucleophilic addition onto the η^3-propargylpalladium produces a metallacyclobutene, protonation of which generates the η^3-allylpalladium complex: Casey, C. P.; Nash, J. R.; Yi, C. S.; Selmeczy, A. D.; Chung, S.; Powell, D. R.; Hayashi, R. K. *J. Am. Chem. Soc.* **1998**, *120*, 722−733. See also, ref 10j.

(33) As an alternative mechanism, the protonation of **71** by MeOH would lead to a terminal allene such as **92** and Pd(II), which activates the allene π-system and allows the first nucleophilic attack.[34] The second nucleophilic reaction of the resulting η^3-allylpalladium intermediate by the methoxide might lead to **59** and Pd(0). However, the cyclization reaction of the amino allene **92** with $PdBr_2$ gave the 2-vinylpiperidine **93** in 51% yield along with a trace amount of **59** (ca. 1% yield). From this result, the alternative mechanism through the terminal allene **92** cannot be the major reaction pathway.

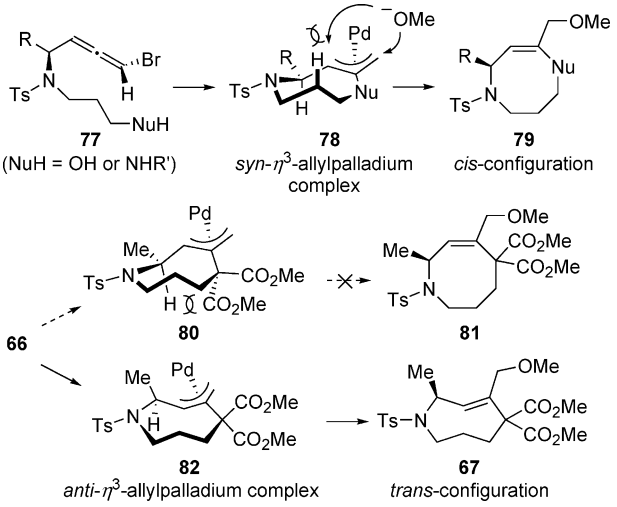


(34) A palladium(II) catalyst induces nucleophilic reaction onto allenes, see: (a) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4257−4260. (b) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1992**, *57*, 6377−6379. Hiemstra reported that the cyclization of allenic lactams takes place at the central carbon atom of allene: (c) Karstens, W. F. J.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron Lett.* **1997**, *38*, 6275−6278. (d) Karstens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Hiemstra, H. *Synlett* **1998**, 1126−1128. 2-Vinylpiperidines were synthesized from amino allenes in the presence of a catalytic amount of a palladium complex under weakly acidic conditions: (e) Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421−5424.

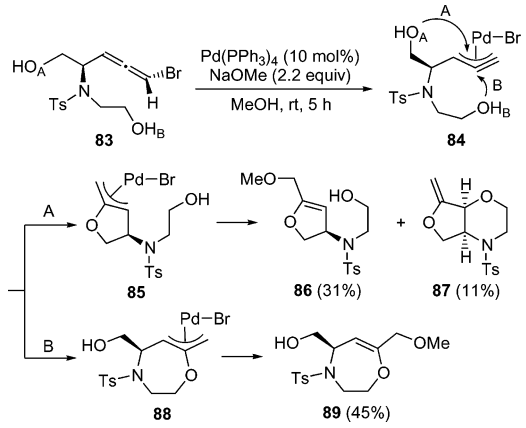
(35) It should be clearly noted that propargylic substrates are not suitable for the palladium-catalyzed medium-ring cyclization. For example, while the bromoallene **15d** yielded 1,4-oxazepine **24d** in 73% yield (Table 1), the corresponding propargylic carbonate was converted to the diol by solvolysis under identical reaction conditions. Similarly, the corresponding propargyl bromide to **17b** was found to be relatively unstable under the cyclization conditions, and only a small amount of the desired cyclized product **26b** was obtained (12% yield) by treatment with NaOMe in MeOH in the presence of $Pd(PPh_3)_4$.[12a]

(36) Baize, M. W.; Blosser, P. W.; Plantevin, V.; Schimpff, D. G.; Gallucci, J. C.; Wojcicki, A. *Organometallics* **1996**, *15*, 164−173. See also, refs 31c and 32.

Scheme 13. Possible Reaction Course



Scheme 14. Cyclization of Bromoallene **83** Bearing Two Oxygen Functionalities



ladium complex **82** to give the eight-membered ring **67** with *trans*-configuration.

Finally, we investigated the reaction of bromoallene **83**[37] bearing two oxygen functionalities, which has two reaction pathways (Scheme 14). If the hydroxyl group A (OH_A) attacks η^3-propargylpalladium(II) bromide **84** (path A), **86** and/or **87** will be produced via the intermediate **85**. In contrast, reaction of OH_B in η^3-propargylpalladium **84** (path B) leads to the seven-membered ring **89**. Interestingly, exposure of **83** to the palladium-catalyzed cyclization conditions gave **86** (31% yield), **87**[38] (11%), and **89** (45%). Although the seven-membered ring **89** has two heteroatoms, this result clearly shows that the bromoallenes cyclize into seven-membered heterocycles as easily as five-membered rings.

Conclusions

In conclusion, we have developed a novel synthesis of medium-sized heterocycles containing one or two heteroatoms via cyclization of bromoallenes bearing an oxygen, nitrogen or carbon nucleophile in the presence of a palladium(0) catalyst and alcohol. In many cases, this reaction proceeds in high regio- and stereoselectivity, and affords desired medium rings in good to high yields. In the reaction of the bromoallenes having a carbon nucleophile, the eight-membered rings with *trans*-configuration were obtained. On the other hand, the reaction of the bromoallenes having an oxygen or nitrogen nucleophile afforded the corresponding *cis*-rings exclusively. This synthetic method would provide a wide variety of heterocycles including those having an enamine or enol moiety without using high dilution conditions.

(37) For synthesis of the bromoallene **83** bearing two oxygen nucleophiles, see the Supporting Information.

Experimental Section

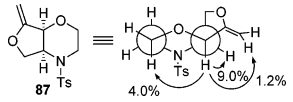
General Methods. Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported in parts per million downfield from internal Me_4Si (s = singlet, d = doublet, dd = double doublet, ddd = doublet of double doublet, t = triplet, q = quartet, m = multiplet). Optical rotations were measured in $CHCl_3$. For flash chromatography, silica gel 60 H (silica gel for thin-layer chromatography, Merck) or silica gel 60 (finer than 230 mesh, Merck) was employed.

The known compounds **1**,[9] **13b**−**d**,[9] **33**,[9] **39**,[23] **41**,[25] **43**,[24] **47**,[26] and **63**[24] were synthesized according to the literature.

(4*S*,a*S*)-1-Bromo-4-[*N*,*N*-(2-*tert*-butyldimethylsilyloxyethyl)(4-methylphenylsulfonyl)amino]penta-1,2-diene (14b). To a stirred solution of PPh_3 (551 mg, 2.1 mmol) in THF (1.5 mL) under nitrogen were added a solution of the bromoallene **13b** (190 mg, 0.60 mmol) in THF (1.5 mL), a solution of $HO(CH_2)_2OTBS$ (317 mg, 1.8 mmol) in THF (1.0 mL), and diethyl azodicarboxylate (914 mg, 2.1 mmol; 40% solution in toluene) at 0 °C, and the mixture was stirred for 2 h at room temperature. Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−ethyl acetate (10:1) to give **14b** (250 mg, 88% yield, >98% de) as a colorless oil: $[\alpha]^{26}_D$ −48.3 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 1957 (C═C═C), 1342 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 6H, $SiMe_2$), 0.90 (s, 9H, CMe_3), 1.21 (d, J = 7.0 Hz, 3H, CMe), 2.43 (s, 3H, Ph*Me*), 3.13 (ddd, J = 15.0, 8.0, 6.5 Hz, 1H, C*H*H), 3.24 (ddd, J = 15.0, 8.0, 5.5 Hz, 1H, CH*H*), 3.76 (ddd, J = 10.0, 8.0, 6.5 Hz, 1H, C*H*H), 3.85 (ddd, J = 10.0, 8.0, 5.5 Hz, 1H, CH*H*), 4.63−4.69 (m, 1H, 4-H), 5.12 (dd, J = 5.5, 5.0 Hz, 1H, 3-H), 6.05 (dd, J = 5.5, 2.5 Hz, 1H, 1-H), 7.29−7.31 (m, 2H, Ph), 7.72−7.74 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3 (2C), 18.1, 18.3, 21.5, 25.9 (3C), 45.7, 51.4, 63.0, 74.8, 101.3, 127.2 (2C), 129.8 (2C), 137.4, 143.5, 202.4; MS (FAB) *m*/*z* (%) 476 (MH^+, ^{81}Br, 27), 474 (MH^+, ^{79}Br, 28), 73 (100); HRMS (FAB) calcd for $C_{20}H_{33}BrNO_3SSi$ (MH^+, ^{79}Br), 474.1134; found, 474.1128.

(4*S*,a*S*)-1-Bromo-4-[*N*,*N*-(2-hydroxyethyl)(4-methylphenylsulfonyl)amino]penta-1,2-diene (15b). To a stirred solution of the bromoallene **14b** (230 mg, 0.485 mmol) in THF (1.5 mL) under nitrogen was added tetrabutylammonium fluoride (1.0 M solution in THF; 0.63 mL, 0.632 mmol) at 0 °C, and the mixture was stirred for 3 h at this temperature. The mixture was made acidic with 4% HCl, and the whole was extracted with Et_2O. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−ethyl acetate (2:1) to give **15b** (160 mg, 92% yield, >99% de) as a colorless oil: $[\alpha]^{21}_D$ −45.2 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 3552 (OH), 1957 (C═C═C), 1335 (NSO_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 6.6 Hz, 3H, CMe), 2.44 (s, 3H, Ph*Me*), 2.51 (dd, J = 6.0, 5.7 Hz, 1H, OH), 3.18−3.33 (m, 2H, CH_2), 3.79−3.84 (m, 2H, CH_2), 4.70−4.79 (m, 1H, 4-H), 5.14 (dd, J = 5.7, 5.1 Hz, 1H, 3-H), 6.08 (dd, J = 5.7, 2.7 Hz, 1H,

(38) The stereochemistry of the bicyclic product **87** was confirmed by NOE experiment and COSY analysis.



1-H), 7.31−7.34 (m, 2H, Ph), 7.73−7.75 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 21.5, 45.8, 51.6, 62.7, 75.2, 100.9, 127.2 (2C), 129.9 (2C), 136.7, 143.9, 202.5; MS (FAB) *m*/*z* (%) 362 (MH^+, ^{81}Br, 29), 360 (MH^+, ^{79}Br, 30), 136 (100); HRMS (FAB) calcd for $C_{14}H_{19}BrNO_3S$ (MH^+, ^{79}Br), 360.0269; found, 360.0261.

(4*S*,a*S*)-1-Bromo-4-[*N*,*N*-(3-*tert*-butyldimethylsilyloxypropyl)(4-methylphenylsulfonyl)amino]penta-1,2-diene (16b). By a procedure similar to that described for the preparation of the bromoallene **15b** from **14b**, the bromoallene **13b** (474.3 mg, 1.5 mmol) was converted into **16b** (674 mg, 92% yield, >98% de) as a colorless oil: $[\alpha]^{24}_D$ −31.3 (*c* 0.945, $CHCl_3$); IR (KBr) cm^{-1} 1957 (C═C═C), 1342 (NSO_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H, $SiMe_2$), 0.89 (s, 9H, CMe_3), 1.22 (d, *J* = 6.6 Hz, 3H, CMe), 1.78−2.01 (m, 2H, CH_2), 2.43 (s, 3H, Ph*Me*), 3.16−3.22 (m, 2H, CH_2), 3.58−3.70 (m, 2H, CH_2), 4.68−4.77 (m, 1H, 4-H), 5.16 (dd, *J* = 5.4, 5.4 Hz, 1H, 3-H), 6.04 (dd, *J* = 5.4, 2.7 Hz, 1H, 1-H), 7.28−7.31 (m, 2H, Ph), 7.69−7.72 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.4 (2C), 17.8, 18.2, 21.5, 25.9 (3C), 34.5, 41.5, 51.4, 60.6, 74.8, 101.6, 127.1 (2C), 129.7 (2C), 137.5, 143.3, 202.2; MS (FAB) *m*/*z* (%) 490 (MH^+, ^{81}Br, 24), 488 (MH^+, ^{79}Br, 23), 73 (100); HRMS (FAB) calcd for $C_{21}H_{35}BrNO_3SSi$ (MH^+, ^{79}Br), 488.1290; found, 488.1277.

(4*S*,a*S*)-1-Bromo-4-[*N*,*N*-(3-hydroxypropyl)(4-methylphenylsulfonyl)amino]penta-1,2-diene (17b). The bromoallene **16b** (537 mg, 1.1 mmol) was dissolved in a 1% HCl solution in ethanol (6 mL), which was prepared from concentrated HCl and EtOH, and the mixture was stirred for 25 min at room temperature. Water was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−ethyl acetate (2:1) to give **17b** (386 mg, 94% yield, de = >99%) as a colorless oil: $[\alpha]^{24}_D$ −20.7 (*c* 0.77, $CHCl_3$); IR (KBr) cm^{-1} 3531 (OH), 1957 (C═C═C), 1336 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.5 Hz, 3H, CMe), 1.83−1.92 (m, 2H, CH_2), 2.19 (dd, *J* = 6.5, 4.5 Hz, 1H, OH), 2.44 (s, 3H, Ph*Me*), 3.29−3.31 (m, 2H, CH_2), 3.75−3.78 (m, 2H, CH_2), 4.68−4.74 (m, 1H, 4-H), 5.18 (dd, *J* = 5.5, 4.5 Hz, 1H, 3-H), 6.08 (dd, *J* = 5.5, 2.0 Hz, 1H, 1-H), 7.31−7.32 (m, 2H, Ph), 7.70−7.72 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 21.5, 33.8, 40.5, 51.1, 59.2, 75.2, 101.5, 127.0 (2C), 129.9 (2C), 137.2, 143.6, 202.2; MS (FAB) *m*/*z* (%) 376 (MH^+, ^{81}Br, 16), 374 (MH^+, ^{79}Br, 16), 69 (100); HRMS (FAB) calcd for $C_{15}H_{21}BrNO_3S$ (MH^+, ^{79}Br), 374.0426; found, 374.0424.

(4*S*,a*S*)-1-Bromo-4-{*N*,*N*-[2-*N*,*N*-(*tert*-butoxycarbonyl)[(4-methylphenylsulfonyl)amino]ethyl](4-methylphenylsulfonyl)amino}penta-1,2-diene (18). To a stirred mixture of PPh_3 (85.2 mg, 0.325 mmol) and TsNHBoc (88.2 mg, 0.325 mmol) in THF (1 mL) under nitrogen were added a solution of the bromoallene **15b** (90 mg, 0.25 mmol) in THF (1 mL) and diethyl azodicarboxylate (142 mg, 0.325 mmol; 40% solution in toluene) at 0 °C, and the mixture was stirred for 1 h at room temperature. Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−ethyl acetate (5:1) to give **18** (130 mg, 85% yield) as colorless crystals: mp 142 °C (*n*-hexane−ethyl acetate); $[\alpha]^{27}_D$ −68.4 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 1957 (C═C═C), 1728 (C═O), 1358 (NSO_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.9 Hz, 3H, CMe), 1.40 (s, 9H, CMe_3), 2.44 (s, 6H, 2 × Ph*Me*), 3.25 (ddd, *J* = 15.3, 10.8, 4.8 Hz, 1H, C*H*H), 3.45 (ddd, *J* = 15.3, 10.8, 5.4 Hz, 1H, CH*H*), 3.94 (ddd, *J* = 14.1, 10.8, 4.8 Hz, 1H, C*H*H), 4.20 (ddd, *J* = 14.1, 10.8, 5.4 Hz, 1H, CH*H*), 4.72−4.81 (m, 1H, 4-H), 5.06 (dd, *J* = 5.7, 5.7 Hz, 1H, 3-H), 6.05 (dd, *J* = 5.7, 2.7 Hz, 1H, 1-H), 7.29−7.34 (m, 4H, Ph), 7.77−7.83 (m, 4H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 21.5, 21.6, 27.9 (3C), 43.0, 47.6, 52.1, 74.8, 84.6, 100.6, 127.4 (2C), 128.0 (2C), 129.3 (2C), 129.9 (2C), 136.7, 136.9, 143.7, 144.3, 150.7, 202.5; MS (FAB) *m*/*z* (%) 615 (MH^+, ^{81}Br, 4.5), 613 (MH^+, ^{79}Br, 4.8), 369 (100); HRMS (FAB) calcd for $C_{26}H_{34}BrN_2O_6S_2$ (MH^+, ^{79}Br), 613.1042; found, 613.1023.

(4*S*,a*S*)-1-Bromo-4-{*N*,*N*-(4-methylphenylsulfonyl)[2-[*N*-(4-methylphenylsulfonyl)amino]ethyl]amino}penta-1,2-diene (20). To a stirred solution of the bromoallene **18** (153 mg, 0.25 mmol) in EtOAc (3 mL) was added 3 N HCl (2 mL) at room temperature. After stirring for 3 h at 60 °C, the mixture was made basic with 28% NH_4OH. The whole was extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−ethyl acetate (2:1) to give **20** (118 mg, 92% yield) as a colorless oil; $[\alpha]^{25}_D$ −22.6 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 3286 ($NHSO_2$), 1957 (C═C═C), 1331 (NSO_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.9 Hz, 3H, CMe), 2.435 (s, 3H, Ph*Me*), 2.441 (s, 3H, Ph*Me*), 3.16−3.23 (m, 4H, 2 × CH_2), 4.61−4.70 (m, 1H, 4-H), 4.95 (dd, *J* = 5.4, 5.1 Hz, 1H, 3-H), 5.17 (br s, 1H, NH), 6.05 (dd, *J* = 5.4, 2.7 Hz, 1H, 1-H), 7.29−7.35 (m, 4H, Ph), 7.65−7.68 (m, 2H, Ph), 7.78−7.80 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 21.5 (2C), 43.1, 43.8, 51.5, 75.3, 100.5, 127.18 (2C), 127.19 (2C), 129.7 (2C), 130.0 (2C), 136.3, 136.7, 143.4, 144.0, 202.4; MS (FAB) *m*/*z* (%) 515 (MH^+, ^{81}Br, 24), 513 (MH^+, ^{79}Br, 19), 369 (100); HRMS (FAB) calcd for $C_{21}H_{26}BrN_2O_4S_2$ (MH^+, ^{79}Br): 513.0517; found: 513.0535.

General Procedure for the Synthesis of Medium-Sized Heterocycles via Cyclization of Bromoallenes. Synthesis of (5*S*)-7-Methoxymethyl-5-methyl-4-(4-methylphenylsulfonyl)-2*H*,3*H*,4*H*,5*H*-1,4-oxazepine (24b) and (5*S*,6*R*)-6-Methoxy-5-methyl-7-methylene-4-(4-methylphenylsulfonyl)-1,4-oxazepine (25b) (Table 1, Entry 2). To a stirred mixture of NaOMe (12.2 mg, 0.225 mmol) and $Pd(PPh_3)_4$ (8.7 mg, 0.0075 mmol) in MeOH (1 mL) under nitrogen was added dropwise a solution of the bromoallene **15b** (54 mg, 0.15 mmol) in MeOH (1 mL) at room temperature, and the mixture was stirred for 3 h at this temperature. Concentration under reduced pressure gave an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−ethyl acetate (3:1) to give, in order of elution, **25b** (4.4 mg, 9.4% yield) and **24b** (34.1 mg, 73% yield). Compound **24b**: colorless oil; $[\alpha]^{25}_D$ +24.7 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 1674 (C═C−O), 1331 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, *J* = 7.0 Hz, 3H, CMe), 2.41 (s, 3H, Ph*Me*), 3.24 (s, 3H, OMe), 3.48 (ddd, *J* = 14.5, 6.0, 2.5 Hz, 1H, C*H*H), 3.56 (d, *J* = 12.5 Hz, 1H, MeOC*H*H), 3.60 (d, *J* = 12.5 Hz, 1H, MeOCH*H*), 3.91 (ddd, *J* = 12.5, 6.0, 3.0 Hz, 1H, C*H*H), 4.04 (ddd, *J* = 14.5, 7.0, 3.0 Hz, 1H, CH*H*), 4.14 (ddd, *J* = 12.5, 7.0, 2.5 Hz, 1H, CH*H*), 4.68 (qd, *J* = 7.0, 6.5 Hz, 1H, 5-H), 4.86 (d, *J* = 6.5 Hz, 1H, 6-H), 7.26−7.27 (m, 2H, Ph), 7.68−7.70 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 21.4, 45.0, 50.2, 58.0, 71.0, 73.0, 108.0, 127.1 (2C), 129.5 (2C), 137.7, 143.1, 154.5; MS (FAB) *m*/*z* (%) 312 (MH^+, 71), 296 (100); HRMS (FAB) calcd for $C_{15}H_{22}NO_4S$ (MH^+), 312.1270; found, 312.1274. Compound **25b**: colorless oil: $[\alpha]^{28}_D$ +46.8 (*c* 0.49, $CHCl_3$); IR (KBr) cm^{-1} 1635 (C═C), 1346 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6.5 Hz, 3H, CMe), 2.43 (s, 3H, Ph*Me*), 3.18 (ddd, *J* = 13.0, 5.0, 3.5 Hz, 1H, C*H*H), 3.46 (ddd, *J* = 13.0, 8.5, 3.0 Hz, 1H, CH*H*), 3.53 (s, 3H, OMe), 3.67 (ddd, *J* = 11.5, 5.0, 3.0 Hz, 1H, C*H*H), 3.83−3.88 (m, 2H, 5-H and 6-H), 3.90 (ddd, *J* = 11.5, 8.5, 3.5 Hz, 1H, CH*H*), 4.22 (d, *J* = 2.5 Hz, 1H, C═C*H*H), 4.40 (d, *J* = 2.5 Hz, 1H, C═CH*H*), 7.30−7.32 (m, 2H, Ph), 7.67−7.69 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6, 21.5, 42.5, 50.9, 55.0, 62.8, 79.1, 85.4, 127.4 (2C), 129.7 (2C), 136.4, 143.4, 158.6; MS (FAB) *m*/*z* (%) 312 (MH^+, 24), 136 (100); HRMS (FAB) calcd for $C_{15}H_{22}NO_4S$ (MH^+), 312.1270; found, 312.1286.

(5*S*)-5-Benzyl-7-ethoxymethyl-4-(4-methylphenylsulfonyl)-2*H*,3*H*,4*H*,5*H*-1,4-oxazepine (30). To NaH (6 mg, 0.15 mmol) was added EtOH (0.5 mL) at 0 °C under nitrogen, and the solution was stirred for 15 min at room temperature. To the stirred mixture were added $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol) and a solution of the bromoallene **15d** (43.6 mg, 0.10 mmol) in THF (0.5 mL) at room temperature. After stirring for 1.5 h at this temperature, the mixture was poured into ice−water (1 mL) saturated with NH_4Cl. The whole was extracted with Et_2O, and the extract was washed with water and brine and dried over

$MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−ethyl acetate (7:2) to give **30** (24 mg, 60% yield) as a colorless oil: $[\alpha]^{28}_D$ +51.3 (*c* 0.82, $CHCl_3$); IR (KBr) cm^{-1} 1684 (C═C−O), 1331 (NSO_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J = 7.0 Hz, 3H, CMe), 2.38 (s, 3H, Ph*Me*), 2.95 (dd, J = 13.0, 7.0 Hz, 1H, PhC*H*H), 2.98 (dd, J = 13.0, 8.0 Hz, 1H, PhCH*H*), 3.35 (q, J = 7.0 Hz, 2H, OCH_2Me), 3.53 (ddd, J = 15.5, 7.0, 3.0 Hz, 1H, C*H*H), 3.61 (d, J = 13.5 Hz, 1H, EtOC*H*H), 3.69 (d, J = 13.5 Hz, 1H, EtOCH*H*), 3.92 (ddd, J = 13.0, 7.0, 3.0 Hz, 1H, C*H*H), 3.97 (ddd, J = 15.5, 8.5, 3.0 Hz, 1H, CH*H*), 4.19 (ddd, J = 13.0, 8.5, 3.0 Hz, 1H, CH*H*), 4.77−4.83 (m, 1H, 5-H), 4.83 (d, J = 6.5 Hz, 1H, 6-H), 7.13−7.28 (m, 7H, Ph), 7.49−7.51 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 21.5, 40.8, 45.7, 56.0, 65.6, 70.9, 71.1, 106.7, 126.6, 127.2 (2C), 128.5 (2C), 129.2 (2C), 129.4 (2C), 137.4, 137.6, 143.0, 155.6; MS (FAB) *m*/*z* (%) 402 (MH^+, 24), 310 (100); HRMS (FAB) calcd for $C_{22}H_{28}NO_4S$ (MH^+), 402.1739; found, 402.1748.

(4*S*,a*S*)-1-Bromo-4-[*N*-(*tert*-butoxycarbonyl)amino]-5-phenylpenta-1,2-diene (34). To a stirred mixture of the propargylic alcohol **33** (1.24 g, 4.5 mmol) and Et_3N (3.1 mL, 22.5 mmol) in THF (10 mL) was added MsCl (0.69 mL, 9.0 mmol) at −78 °C, and the mixture was stirred for 0.5 h with warming to −60 °C. The mixture was made acidic with 4% HCl at −60 °C, and the whole was extracted with Et_2O. The extract was washed with water, saturated $NaHCO_3$, water, and brine and was dried over $MgSO_4$. Concentration of the filtrate under reduced pressure followed by rapid filtration through a short pad of SiO_2 with Et_2O gave a crude mesylate, which was used without further purification. A mixture of CuBr·DMS (1.8 g, 9.0 mmol) and LiBr (782 mg, 9.0 mmol) were dissolved in THF (6 mL) at room temperature under nitrogen. After stirring for 2 min, a solution of the above crude mesylate in THF (10 mL) was added to this reagent at room temperature. The mixture was stirred for 6 h at this temperature and quenched with saturated NH_4Cl (5 mL) and 28% NH_4OH (5 mL). The whole was extracted with Et_2O. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−ethyl acetate (7:1) to give **34** (1.05 g, 69% yield). Recrystallization from *n*-hexane−ethanol gave essentially pure **34** as colorless needles: mp 73 °C; $[\alpha]^{26}_D$ +140 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 3348 ($NHCO_2$), 1959 (C═C═C), 1693 (C═O); ^1H NMR (300 MHz, $CDCl_3$, 333 K) δ 1.42 (s, 9H, CMe_3), 2.83−2.96 (m, 2H, 5-CH_2), 4.47−4.59 (m, 2H, NH and 4-H), 5.42 (dd, J = 5.4, 5.4 Hz, 1H, 3-H), 6.04 (dd, J = 5.4, 2.1 Hz, 1H, 1-H), 7.17−7.31 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, 333 K) δ 28.4 (3C), 41.2, 50.0, 74.9, 79.9, 102.3, 126.8, 128.5 (2C), 129.5 (2C), 136.9, 154.9, 201.1. Anal. Calcd for $C_{16}H_{20}BrNO_2$: C, 56.82; H, 5.96; N, 4.14. Found: C, 56.81; H, 5.95; N, 4.09.

(4*S*,a*S*)-1-Bromo-4-{*N*-[2-(trimethylsilyl)ethanesulfonyl]amino}-5-phenylpenta-1,2-diene (35). To a stirred solution of the bromoallene **34** (778 mg, 2.3 mmol) in EtOAc (6 mL) was added 3 N HCl (6 mL) at room temperature. After stirring for 1 h at 50 °C, the mixture was made basic with 28% NH_4OH. The whole was extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue. To a stirred solution of the residue in DMF (4 mL) was added Et_3N (1.6 mL, 11.5 mmol) and SESCl (831 mg, 4.14 mmol) at 0 °C. The mixture was stirred for 1 h at this temperature and poured into water and extracted with Et_2O. The extract was washed with water and brine and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure followed by flash column chromatography over silica gel with *n*-hexane−ethyl acetate (6:1) gave **35** (780 mg, 84% yield) as colorless needles: mp 80 °C (*n*-hexane−Et_2O); $[\alpha]^{27}_D$ +105 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 3265 ($NHSO_2$), 1959 (C═C═C), 1325 ($NHSO_2$); ^1H NMR (500 MHz, $CDCl_3$) δ −0.02 (s, 9H, $SiMe_3$), 0.80−0.91 (m, 2H, TMSCH_2), 2.66−2.70 (m, 2H, SO_2CH_2), 2.91 (dd, J = 13.0, 6.5 Hz, 1H, 5-C*H*H), 3.00 (dd, J = 13.0, 6.0 Hz, 1H, 5-CH*H*), 4.30−4.39 (m, 2H, 4-H and NH), 5.51 (dd, J = 5.5, 5.5 Hz, 1H, 3-H), 6.12 (dd, J = 5.5, 2.5 Hz, 1H, 1-H), 7.22−7.34 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.0 (3C), 10.2, 42.4, 50.2, 53.1, 75.7, 102.3, 127.2, 128.7 (2C), 129.7 (2C), 136.2, 200.9. Anal. Calcd for $C_{16}H_{24}BrNO_2SSi$: C, 47.75; H, 6.01; N, 3.48. Found: C, 47.53; H, 5.87; N, 3.39.

(5*S*,a*S*)-1-Bromo-4-{*N*,*N*-(2-hydroxyethyl)[2-(trimethylsilyl)ethanesulfonyl]amino}-5-phenylpenta-1,2-diene (36). By a procedure similar to that described for the preparation of the bromoallene **17b** from **13b**, the bromoallene **35** (205 mg, 0.50 mmol) was converted into **36** (130 mg, 58% yield) as colorless crystals: mp 63−65 °C; $[\alpha]^{28}_D$ +42.3 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 3527 (OH), 1957 (C═C═C), 1325 (NSO_2); ^1H NMR (300 MHz, $CDCl_3$) δ −0.04 (s, 9H, $SiMe_3$), 0.82−0.88 (m, 2H, TMSCH_2), 2.09 (br s, 1H, OH), 2.31−2.42 (m, 1H, SO_2CHH), 2.51−2.61 (m, 1H, SO_2CH*H*), 2.99 (dd, J = 14.1, 8.4 Hz, 1H, 5-C*H*H), 3.06 (dd, J = 14.1, 6.9 Hz, 1H, 5-CH*H*), 3.35−3.53 (m, 2H, CH_2), 3.75−3.87 (m, 2H, CH_2), 4.77−4.85 (m, 1H, 4-H), 5.55 (dd, J = 5.7, 5.7 Hz, 1H, 3-H), 6.17 (dd, J = 5.7, 2.4 Hz, 1H, 1-H), 7.22−7.35 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.0 (3C), 10.0, 38.5, 46.6, 48.9, 57.9, 62.3, 75.5, 100.7, 127.2, 128.8 (2C), 129.2 (2C), 137.4, 202.1. Anal. Calcd for $C_{18}H_{28}BrNO_3SSi$: C, 48.42; H, 6.32; N, 3.14. Found: C, 48.59; H, 6.27; N, 3.09.

(5*S*)-5-Benzyl-7-methoxymethyl-4-[2-(trimethylsilyl)ethanesulfonyl]-2*H*,3*H*,4*H*,5*H*-1,4-oxazepine (37). By a procedure identical to that described for the preparation of the 1,4-oxazepines **24b** and **25b** from **15b**, the bromoallene **36** (49 mg, 0.11 mmol) was converted into **37** (34 mg, 78% yield) as a colorless oil: $[\alpha]^{28}_D$ +3.17 (*c* 1.02, $CHCl_3$); IR (KBr) cm^{-1} 1674 (C═C−O), 1327 (NSO_2); ^1H NMR (300 MHz, $CDCl_3$) δ −0.06 (s, 9H, $SiMe_3$), 0.71−0.88 (m, 2H, TMSCH_2), 2.28−2.38 (m, 1H, SO_2CHH), 2.41−2.52 (m, 1H, SO_2CH*H*), 2.98 (dd, J = 13.8, 6.9 Hz, 1H, BnC*H*H), 3.06 (dd, J = 13.8, 8.7 Hz, 1H, BnCH*H*), 3.34 (s, 3H, OMe), 3.57 (ddd, J = 15.3, 6.9, 2.4 Hz, 1H, C*H*H), 3.75 (d, J = 12.6 Hz, 1H, MeOC*H*H), 3.80 (d, J = 12.6 Hz, 1H, MeOCH*H*), 3.94 (ddd, J = 15.3, 6.0, 3.0 Hz, 1H, CH*H*), 4.05 (ddd, J = 12.6, 6.9, 3.0 Hz, 1H, C*H*H), 4.30 (ddd, J = 12.6, 6.0, 2.4 Hz, 1H, CH*H*), 4.61−4.69 (m, 1H, 5-H), 5.05 (d, J = 6.9 Hz, 1H, 6-H), 7.21−7.31 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.1 (3C), 10.0, 40.5, 45.9, 48.9, 56.7, 58.2, 72.3, 73.3, 108.6, 127.0, 128.6 (2C), 129.2 (2C), 137.9, 155.5; MS (FAB) *m*/*z* (%) 398 (MH^+, 6), 73 (100); HRMS (FAB) calcd for $C_{19}H_{32}NO_4SSi$ (MH^+), 398.1821; found, 398.1838.

(5*S*)-5-Benzyl-7-methoxymethyl-2*H*,3*H*,4*H*,5*H*-1,4-oxazepine (38). To a stirred solution of CsF (159 mg, 10.5 mmol) in DMF (1 mL) was added 1,4-oxazepine **37** (83 mg, 0.21 mmol) in DMF (1 mL) at room temperature. After stirring for 12 h at 95 °C, MeOH (3 mL) was added, and the mixture was concentrated under reduced pressure. The residue was diluted with Et_2O (5 mL), filtered, and evaporated. The crude amine was purified by column chromatography over silica gel with *n*-hexane−ethanol−chloroform (5:1:1) to give **38** (36 mg, 73% yield) as a colorless oil: $[\alpha]^{27}_D$ +19.6 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 3323 (NH), 1672 (C═C−O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (br s, 1H, NH), 2.77−2.86 (m, 2H, PhCH_2), 2.90 (ddd, J = 13.8, 7.8, 1.8 Hz, 1H, C*H*H), 3.17 (ddd, J = 13.8, 6.0, 2.4 Hz, 1H, CH*H*), 3.34 (s, 3H, OMe), 3.66−3.86 (m, 4H, 5-H, MeOCH_2 and C*H*H), 4.24 (ddd, J = 12.3, 6.0, 1.8 Hz, 1H, CH*H*), 4.94 (d, J = 3.0 Hz, 1H, 6-H), 7.21−7.34 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.2, 50.1, 56.9, 58.1, 73.6, 73.7, 111.6, 126.5, 128.5 (2C), 129.2 (2C), 138.7, 155.0; MS (FAB) *m*/*z* (%) 234 (MH^+, 85), 142 (100); HRMS (FAB) calcd for $C_{14}H_{20}NO_2$ (MH^+), 234.1494; found, 234.1499.

1-{2-[2-(*tert*-Butyldimethylsiloxy)ethyl]phenyl}but-3-yn-2-ol (48). To a stirred solution of oxalyl chloride (2.93 mL, 33.6 mmol) in CH_2Cl_2 (30 mL) at −78 °C under nitrogen was added dropwise a solution of DMSO (7.96 mL, 112 mmol) in CH_2Cl_2 (10 mL). After 45 min, a solution of the alcohol **47** (6.28 g, 22.4 mmol) in CH_2Cl_2 (20 mL) was added to the above reagent at −78 °C, and the mixture was stirred for 1 h at this temperature. Diisopropylethylamine (27.0 mL, 157 mmol) was added to the above solution at −78 °C, and the mixture was stirred

for 30 min with warming to 0 °C. The mixture was made acidic with 4% HCl, and the whole was extracted with Et_2O. The extract was washed successively with water, saturated $NaHCO_3$, and brine and was dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a crude aldehyde as an oil. To a stirred solution of trimethylsilylacetylene (3.96 mL, 28.0 mmol) in dry THF (10 mL) under nitrogen was added *n*-BuLi (1.56 M solution in *n*-hexane; 17.2 mL, 26.9 mmol) at 0 °C, and the mixture was stirred for 20 min at this temperature. A solution of the crude aldehyde in dry THF (15 mL) was added to the above stirred reagent at −78 °C, and the mixture was stirred for 1 h with warming to −60 °C, followed by quenching with saturated NH_4Cl. The mixture was made acidic with 4% HCl, and the whole was extracted with Et_2O. The extract was washed successively with water, saturated $NaHCO_3$, and brine and was dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give the TMS derivative as an oil. To a stirred solution of this oil in MeOH (20 mL) was added dropwise NaOMe (242 mg, 4.5 mmol) in MeOH (4.5 mL) at 0 °C, and the mixture was stirred for 2 h at room temperature. The mixture was concentrated under reduced pressure, and the residue was filtered through a short pad of SiO_2 with *n*-hexane−ethyl acetate (5:2) and concentrated. The residue was purified by column chromatography over silica gel with *n*-hexane−ethyl acetate (4:1) to give **48** (4.43 g, 65% yield) as a colorless oil: IR (KBr) cm^{-1} 3298 (OH), 2116 (C≡C); ^1H NMR (300 MHz, $CDCl_3$) δ −0.02 (s, 6H, $SiMe_2$), 0.85 (s, 9H, CMe_3), 2.44 (d, J = 5.7 Hz, 1H, OH), 2.49 (d, J = 1.8 Hz, 1H, 4-H), 2.94 (t, J = 6.9 Hz, 2H, 1′-CH_2), 3.10−3.13 (m, 2H, 1-CH_2), 3.84 (t, J = 6.9 Hz, 2H, 2′-CH_2), 4.56−4.63 (m, 1H, 2-H), 7.13−7.27 (m, 4H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.48 (2C), 18.4, 25.9 (3C), 35.8, 40.6, 62.9, 64.3, 73.6, 84.3, 126.3, 127.0, 130.1, 130.8, 135.0, 137.9; MS (FAB) *m*/*z* (%) 305 (MH^+, 29), 155 (100); HRMS (FAB) calcd for $C_{18}H_{29}O_2Si$ (MH^+), 305.1937; found, 305.1931.

General Procedure for the Synthesis of Bromoallenes Bearing an Active Methylene Nucleophile. Synthesis of (4*S*,a*S*)-1-Bromo-4-{*N*,*N*-[4,4-bis(methoxycarbonyl)butyl](4-methylphenylsulfonyl)amino}penta-1,2-diene (66). To a stirred mixture of PPh_3 (157 mg, 0.60 mmol), the bromoallene **15b** (150 mg, 0.40 mmol), and diisopropylethylamine (0.104 mL, 0.60 mmol) in CH_2Cl_2 (4 mL) under nitrogen was added I_2 (152 mg, 0.60 mmol) at room temperature, and the mixture was stirred for 6 h at this temperature. Concentration under reduced pressure gave an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−ethyl acetate (5:1) to give the corresponding iodide (184 mg, 95% yield) as colorless needles. To a stirred suspension of NaH (18 mg, 0.45 mmol) in DMF (1 mL) under nitrogen was added dimethyl malonate (0.057 mL, 0.50 mmol) at 0 °C, and the mixture was stirred for 20 min at room temperature. To the stirred mixture was added a solution of the above iodide (121 mg, 0.25 mmol) in DMF (2 mL) at 0 °C, and the mixture was stirred for 2.5 h at room temperature. The mixture was poured into ice−water (1 mL) saturated with NH_4Cl, and the whole was extracted with Et_2O. The extract was washed with water and brine and was dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−ethyl acetate (3:1) to give **66** (110 mg, 90% yield; 86% yield for two steps) as a colorless oil: $[\alpha]^{27}_D$ −34.5 (*c* 1.05, $CHCl_3$); IR (KBr) cm^{-1} 1957 (C═C═C), 1751 (C═O), 1736 (C═O), 1340 (NSO_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, J = 6.9 Hz, 3H, CMe), 1.61−1.83 (m, 2H, CH_2), 1.89−1.97 (m, 2H, CH_2), 2.43 (s, 3H, Ph*Me*), 3.07−3.13 (m, 2H, CH_2), 3.40 [dd, J = 7.5, 7.5 Hz, 1H, C*H*(CO_2Me)$_2$], 3.75 (s, 6H, 2 × OMe), 4.63−4.73 (m, 1H, 4-H), 5.16 (dd, J = 5.4, 5.4 Hz, 1H, 3-H), 6.07 (dd, J = 5.4, 2.4 Hz, 1H, 1-H), 7.29−7.32 (m, 2H, Ph), 7.68−7.71 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 21.5, 26.1, 29.0, 43.4, 51.10, 51.14, 52.5 (2C), 75.1, 101.3, 127.1 (2C), 129.8 (2C), 137.4, 143.5, 169.5 (2C), 202.3; MS (FAB) *m*/*z* (%) 490 (MH^+, ^{81}Br, 54), 488 (MH^+, ^{79}Br, 54), 344 (100); HRMS (FAB) calcd for $C_{20}H_{27}BrNO_6S$ (MH^+, ^{79}Br), 488.0742; found, 488.0747.

(8*S*,6*Z*)-5,5-Bis(methoxycarbonyl)-6-methoxymethyl-8-methyl-1-(4-methylphenylsulfonyl)-1*H*,3*H*,4*H*,8*H*-tetrahydroazocine (67). By a procedure identical to that described for the preparation of the 1,4-oxazepines **24b** and **25b** from **15b**, the bromoallene **66** (48.8 mg, 0.10 mmol) was converted into **67** (24.5 mg, 56% yield) as colorless needles: mp 150−153 °C (*n*-hexane−ethyl acetate); $[\alpha]^{27}_D$ +7.88 (*c* 0.90, $CHCl_3$); IR (KBr) cm^{-1} 1747 (C═O), 1716 (C═O), 1335 (NSO_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.27−1.34 (m, 1H, 3-C*H*H), 1.41 (d, J = 7.0 Hz, 3H, CMe), 1.88−1.95 (m, 1H, 3-CH*H*), 2.32−2.37 (m, 1H, 4-C*H*H), 2.42 (s, 3H, Ph*Me*), 2.55−2.59 (m, 1H, 4-CH*H*), 2.93−2.97 (m, 1H, 2-C*H*H), 3.23 (s, 3H, OMe), 3.65−3.75 (m, 1H, 2-CH*H*), 3.67 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.92 (d, J = 11.5 Hz, 1H, MeOC*H*H), 4.29 (d, J = 11.5 Hz, 1H, MeOCH*H*), 4.93 (qd, J = 7.0, 5.0 Hz, 1H, 8-H), 5.53 (d, J = 5.0 Hz, 1H, 7-H), 7.27−7.29 (m, 2H, Ph), 7.70−7.72 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 21.4, 28.2, 41.0, 43.7, 52.6, 52.9, 56.6, 58.5, 65.7, 67.6, 126.9 (2C), 129.6 (2C), 135.8, 138.0, 139.0, 143.0, 169.4, 169.9; MS (FAB) *m*/*z* (%) 440 (MH^+, 32.0), 136 (100); HRMS (FAB) calcd for $C_{21}H_{30}NO_7S$ (MH^+), 440.1743; found, 440.1735.

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Supporting Information Available: Synthetic procedures and characterization for **3**, **13a**, **15a**, **15c**−**e**, **17a**, **17c**−**e**, **21**, **23**, **24a**, **24c**−**e**, **25a**, **26a**−**e**, **27a**−**c**, **28**, **29**, **31**, **32**, **40**, **42**, **44**−**46**, **49**−**62**, **64**, **65**, **68**, **69**, **83**, **86**, **87**, **89**−**92**, and **93**; ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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