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Seleniranium Ion-Triggered Reactions: New Aspects of Friedel−Crafts and N-Detosylative Cyclizations

Hwan Jung Lim and T. V. RajanBabu*

Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210

rajanbabu.1@osu.edu

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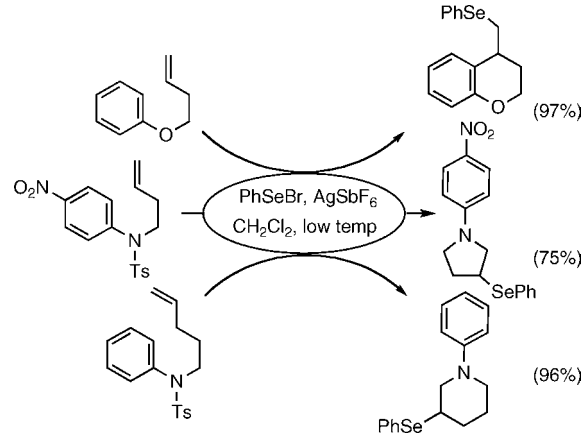
ABSTRACT



Seleniranium ions at low temperatures (−90 to −78 °C) will initiate effective Friedel−Crafts cyclization if a suitably placed arene is allowed to react even when the arene is unactivated. These intermediates generated from *N*-aryl-*N*-tosylamides undergo a novel, surprisingly efficient, detosylative cyclization to form 5- or 6-membered nitrogen heterocycles. A debenzylation route is preferred if both benzyl and tosyl groups are present in the substrate.

Electrophilic cyclizations of alkenyl carboxylic acids, alcohols, amines, amides, and functionalized dienes initiated by seleniranium ions have been broadly applied for the syntheses of diverse heterocyclic and carbocyclic compounds.[1] Intermolecular additions of carbon nucleophiles including electron-rich aromatic derivatives to seleniranium ions are also known, and these reactions have been developed to a level that it is now possible to carry out highly diastereoselective additions, using enantiopure selenium reagents.[2] Even though mechanistically related *intramolecular* additions of carbon nucleophiles to putative seleniranium ion intermediates were among the earliest examples of selenium-induced cyclizations,[3] subsequent developments in this area have been sporadic. In one such rare example, Déziel in 1998[4] reported that 4-arylbutenes (**1**) with electron-rich aryl groups undergo

(1) (a) Browne, D. M.; Wirth, T. *Curr. Org. Chem.* **2006**, *10*, 1893. (b) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273. (c) Tiecco, M. Electrophilic Selenium, Selenocyclizations. In *Topics in Current Chemistry: Organoselenium Chemistry*; Wirth, T., Ed.; Springer-Verlag: Berlin, 2000; Vol. 208, pp 7−54. (d) Wirth, T. *Angew. Chem, Int. Ed.* **2000**, *39*, 3740. (e) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986. (f) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Product Synthesis*; CIS: Philadelphia, 1984. (g) *Organoselenium Chemistry, A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999. (h) For a recent leading reference, see: Jones, A. D.; Redfern, A. L.; Knight, D. W.; Morgan, I. R.; Williams, A. C. *Tetrahedron* **2006**, *62*, 9247.

(2) (a) Toshimitsu, A. *Phosphorus, Sulfur Silicon* **2005**, *180*, 935. (b) Toshimitsu, A.; Nakano, K.; Mukai, T.; Tamao, K. *J. Am. Chem. Soc.* **1996**, *118*, 2756. (c) Okamoto, K.; Nishibayashi, Y.; Uemura, S.; Toshimitsu, A. *Tetrahedron Lett.* **2004**, *45*, 6137. (d) Okamoto, K.; Nishibayashi, Y.; Uemura, S.; Toshimitsu, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3588.

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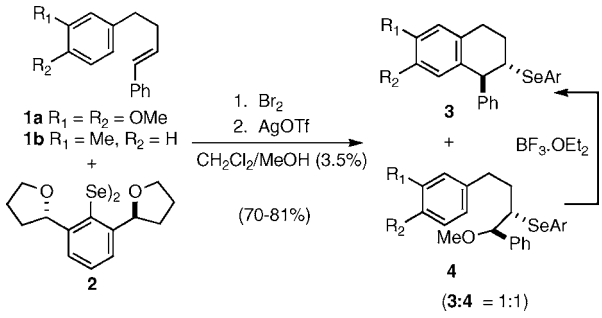
competitive carbocyclization when the reaction is conducted in a mixture of CH_2Cl_2 and methanol (Scheme 1). The major

Scheme 1. Seleniranium-Ion Initiated Friedel−Crafts Reaction



side product, the β-methoxyselenide **4**, is readily converted into the cyclic product **3** by protic or Lewis acids. Formation of the methoxylated product **4** cannot be avoided since in the absence of methanol the reaction gave poor yields. Yet another limitation of this potentially powerful Friedel−Crafts cyclization is that nonactivated arenes (e.g., phenyl) do not participate in this reaction.[3j,4,5a]

While searching for a general route to 1-methylenetetralin and analogous heterocyclic compounds in connection with our asymmetric hydrovinylation approach to 2,3-pyrrolidinoindoles (Figure 1), we decided to revisit this area. We

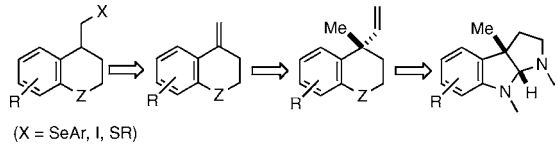


Figure 1. Alkene precursors for 2,3-pyrrolidinoindoles.

expected the alkene-forming elimination reaction to be more facile via a selenide as compared to an iodide[5] or sulfide[6] arising from alternate cyclizations, especially for the synthesis of the more sensitive N- and O-containing heterocycles. Several novel observations that were made during the course of these investigations form the basis of this paper.

(3) (a) Clive, D. L. J.; Chittatu, G.; Wong, C. K. *J. Chem. Soc., Chem. Commun.* **1978**, 441. (b) Kametani, T.; Suzuki, K.; Kurobe, H.; Nemoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 1128. (c) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704. (d) Jackson, W. P.; Ley, S. V.; Whittle, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1173. (e) Alderdice, M.; Weiler, L. *Can. J. Chem.* **1981**, *59*, 2239. (f) Jackson, W. P.; Ley, S. V.; Morton, J. A. *Tetrahedron Lett.* **1981**, *22*, 2601. (g) Kametani, T.; Suzuki, K.; Kurobe, H.; Nemoto, H. *Chem. Pharm. Bull.* **1981**, *29*, 105. (h) Ley, S. V.; Lygo, B.; Molines, H.; Morton, J. A. *J. Chem. Soc., Chem. Commun.* **1982**, 1251. (i) Toshimitsu, A.; Uemura, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1982**, 87. (j) Edstrom, E. D.; Livinghouse, T. *Tetrahedron Lett.* **1986**, *27*, 3483.

(4) Déziel, R.; Malenfant, E.; Thibault, C. *Tetrahedron Lett.* **1998**, *39*, 5493.

(5) (a) Appelbe, R.; Casey, M.; Dunne, A.; Pascarella, E. *Tetrahedron Lett.* **2003**, *44*, 7641. (b) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 3416.

(6) Edstrom, E. D.; Livinghouse, T. *J. Am. Chem. Soc.* **1986**, *108*, 1334.

Table 1. Phenylseleniranium Ion-Induced Friedel−Crafts Cyclizations

entry		reaction conditions[a]	product(s)/yield (%)
1	**5a**	−90 °C, 2 h, −80 °C, 8 h	6a (85)
2		−78 °C, 2 h	**6a** (7)
3		$AgBF_4$ (3.1 equiv) −90 °C, 2 h, −80 °C, 8 h	**6a** (75)
4		AgOTf (3.1 equiv) −90 °C, 2 h, −80 °C, 8 h	**6a** (61)
5	**7a**	−100 °C, 2 h, −80 °C, 8 h	**8a** (55), **9a** (30)
6		−90 °C, 2 h, −80 °C, 8 h	**8a** (48), **9a** (15)
7		−90 °C, 2 h, −80 °C, 8 h (no MeOH quench)	**8a** + **9a** (30%)
8		−78 °C, 2 h, rt, 8 h	**8a** + **9a** (<5%)
9		PhSeCl, $AgSbF_6$ (3.1 equiv) −90 °C, 2 h, −80 °C, 8 h	**8a** + **9a** (<5%)
10		NaBARF 1.2 (equiv), −90 °C, 2 h	**8a** (38), **9a** (15)
11	**5b**	−78 °C, 2 h	**6b** (97)
12		$AgSbF_6$ (1.05 equiv), −78 °C, 2 h	**6b** (50)
13	**10a**	−90 °C, 1 h, −70 °C, 8 h	**11a** (80)
14	**10b**	−90 °C, 1 h, −80 °C, 8 h	**11b** (52)
15	**12**	−90 °C, 2 h, −80 °C, 8 h	**13** (74)

[a] See the text and Supporting Information for details. Reactions performed in CH_2Cl_2 in the presence of 1.01 equiv of PhSeBr and 3.1 equiv of $AgSbF_6$ unless otherwise mentioned. At the end of the reaction, excess MeOH was added and the mixture stirred for 1 h before workup.

Our studies (eqs 1 and 2; Table 1) started with cyclizations of two prototypical substrates, but-3-enyl 4-methoxyphenyl ether (**5a**) and *N*-phenyl-*N*-(but-3-enyl)-4-toluenesulfonamide (**7a**). A number of studies in the literature have suggested that counterions and additives in the reaction medium significantly affect the reactivity and selectivity of the reactions of seleniranium ions.[7] For example, in a study that is highly pertinent to the present work, it has been reported that PhSeCl in the presence of a silver salt *does not* effect the cyclization of 4-aryl-1-butenes,[5a] even though such reactions are known to proceed in moderate yields using combination of *N*-(phenylseleno)succinimide and Lewis acids[3j] as long as the arene is activated and electron-rich.

We decided to explore the effect of alternate counterions and reaction conditions on the cyclizations. Initial scouting experiments to identify the optimal reaction conditions revealed that the best yields are obtained when a combination of PhSeBr and a silver salt in anhydrous CH_2Cl_2 is employed. Thus, the but-3-enyl aryl ether **5a** gave the expected product **6a** in 85% isolated yield when the reaction was initiated at −90 °C and then stirred for 8 h at −80 °C (entry 1, Table 1). *Generation of the seleniranium ion and its subsequent reaction at low temperature* are critical for success of this reaction. Entry 2 shows a reaction that was allowed to proceed only for a shorter period, resulting in a much lower yield. Entry 8 is a related example using the substrate **7a**. Presumably, alternate modes of reactivity of the seleniranium ions have higher energies of activation and they are not competent at low temperatues where the slow cyclization ensues. Under the optimized reaction conditions, 3.1 equiv of the silver salt is used. Highly reproducible results were

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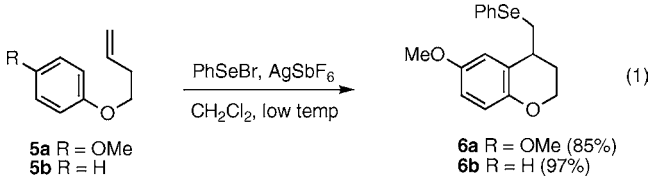
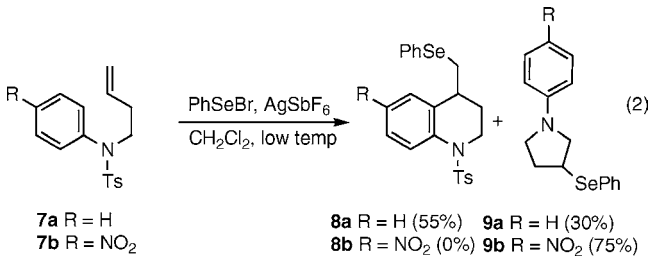
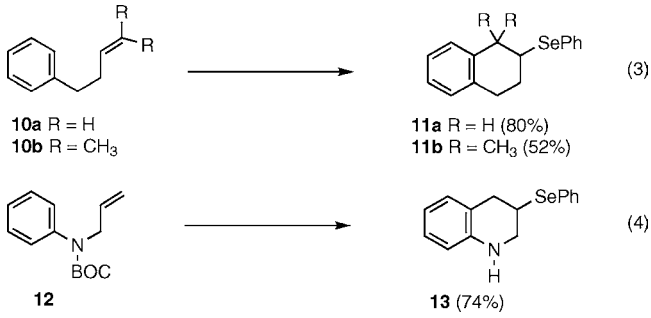
obtained when the crude reaction mixture was stirred with methanol for 60 min at the end of the reaction, presumably resulting in the decomposition of any silver complexes and/or salts that might be formed. We have noticed that skipping the methanol quench results in significant loss of material during isolation and purification by column chromatography (entry 6 vs 7). As shown in entries 3 and 4, other silver salts such as $AgBF_4$ and AgOTf also work, giving slightly lower yields of the product(s). Reactions carried out using PhSeCl and Ag salts gave lower yields (entry 9). Silver ions are known to participate in reactions of alkenes including cyclization reactions.[8] To rule out the unlikely involvement of Ag(I)−alkene intermediates in these reactions, the cyclization of **7a** was carried out using a putative seleniranium ion that was generated from PhSeBr and sodium tetrakis[3,5-di(trifluoromethyl)phenyl]borate (Na BARF).[9] The product distribution is not markedly different from the $AgSbF_6$-mediated reaction (entry 10), ruling out any special role for Ag(I) in these reactions. Note that the but-3-enyl-*N*-sulfonamide **7a** also gives varying amounts of an unexpected side product **9a**, in which the sulfonyl group has been removed concomitant with the generation of a pyrrolidine nucleus (eq 2, entries 5−10).

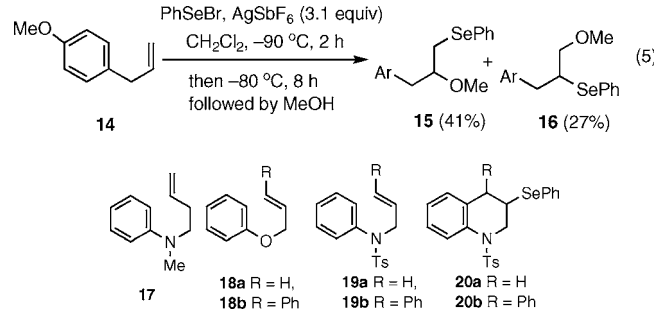




Cyclization of but-3-eneyl phenyl ether **5b** proceeds to give a nearly quantitative yield of the 6-exo-cyclization product **6b** (entry 11). As noted before, significantly higher yields are obtained when more than stoichiometric amounts of $AgSbF_6$ are used in the reaction (entry 11 vs 12).



In the most significant departure from previous studies, under these conditions, even unactivated arenes participate in the cyclization event. Thus, 4-phenylbut-1-ene **10a** and a dimethyl analogue **10b** undergo the cyclization under the standard conditions via a 6-endo-trig cyclization mode (eq 3). BOC-protected *N*-allylaniline **12** also follows a similar course giving a single product **13** in 74% yield. Loss of the BOC protecting group under these highly electrophilic conditions is no surprise.



Existence of a discrete, long-lived phenylseleniranium ion under these reaction conditions[7a] can be inferred from the reaction of 4-allylanisole **14** (eq 5), a substrate that is resistant to cyclization because of stereoelectronic considerations. Upon treatment with PhSeBr and $AgSbF_6$ under conditions similar to the cyclization (2 h at −90 °C, then 8 h at −80 °C), *followed by* addition of methanol, **14** yields the expected methoxyselenated compounds **15** and **16** in 41% and 27% yields, respectively. Similar products from allylbenzene have been observed under more standard selenoetherification conditions.[10]

N-(But-1-enyl)-*N*-methylaniline **17** failed to undergo the cyclization even though cyclization of nonaromatic homoallylamines have been reported to give either an azitidine or a pyrrolidine upon treatment with PhSeX at room temperature.[11] Allyl ethers **18a** and **18b** gave products arising from allylic-O cleavage. Allylic amine derivatives **19a** and **19b** gave low yields of the expected cyclization products **20a** and **20b** (29% and 39%, respectively).

Since cyclizations of *secondary* amine substrates carrying Tos[1h,12] and BOC[13] protecting groups on nitrogen proceed without incident, we were surprised to find the partial loss of the toluenesulfonyl group in the cyclization of **7a** to **9a** (eq 2). Even though detosylation[14] and dissociative migration of tosylates[15] have been observed under strongly electrophilic conditions, to the best of our knowledge, this detosylative cyclization represents a novel transformation. We wondered

(7) (a) Schmid, G. H.; Garratt, D. G. *Tetrahedron Lett.* **1975**, 3991. (b) Khokhar, S. S.; Wirth, T. *Eur. J. Org. Chem.* **2004**, 4567. (c) Khokhar, S. S.; Wirth, T. *Angew. Chem, Int. Ed.* **2004**, *43*, 631. (d) Denmark, S. E.; Collins, W. R. *Org. Lett.* **2007**, *9*, 3801.

(8) Weibel, J.-M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149.

(9) Use of NaBARF to generate non-coordinating counteranions in homogeneous catalysis is widely practiced. See, for example: (a) Brookhart, M.; Grant, B.; Volpe, A. F., Jr. *Organometallics* **1992**, *11*, 3920. (b) DiRenzo, G. M.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1996**, *118*, 6225. (c) Nomura, N.; Jin, J.; Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 459.

(10) Tiecco, M.; Testaferri, L.; Temperirini, A.; Bagnoli, L.; Marini, F.; Santi, C. *Synlett* **2001**, 1767.

(11) (a) Berthe, B.; Outurquin, F.; Paulmier, C. *Tetrahedron Lett.* **1997**, *38*, 1393. (b) Pannecoucke, X.; Outurquin, F.; Paulmier, C. *Eur. J. Org. Chem.* **2002**, 995.

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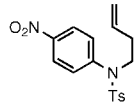
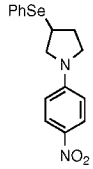
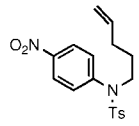
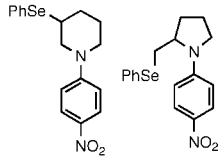
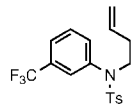
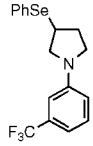
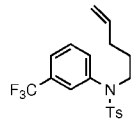
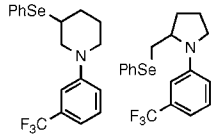
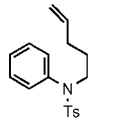
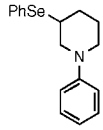
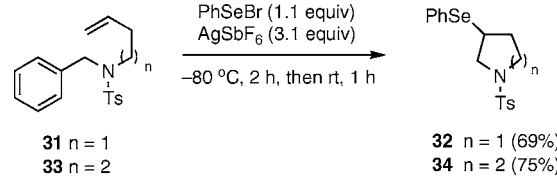
whether placing an electron-withdrawing group on the aryl ring would divert the reaction away from the Friedel−Crafts cyclization. Indeed, in substrates carrying a nitro or a trifluoromethyl group in the arene, the Friedel−Crafts pathway is completely shut down and *all cyclizations* now proceed through the detosylative pathway (eq 2, **7b** → **9b**). Other examples of this transformation are shown in Table 2. The efficiency of the detosylative cyclization depends on the length of the alkene tether and nature of other substituents on nitrogen. While the *N*-but-3-enyl derivatives (e.g., **7b** and **24**) are generally sluggish (∼8 h at −80 °C) in 5-endo-trig cyclizations, the *N*-pent-4-enyl derivatives (**21** and **26**) undergo more facile reactions giving both the 6-endo and 5-exo cyclization products (entries 2 and 4) in respectable yields. With a pent-4-enyl substituent, a deactivated aromatic nucleus is not needed for an effective the detosylative cyclization (entry 5). The expected Friedel−Crafts cyclization (compare to **7a**, eq 2) would yield a 7-membered ring by exo cyclization, and presumably this reaction is not competitive with the piperidine formation. As a result, the heterocycle **30** is formed in an astonishing 96% yield! If the substrate carries *N*-benzyl and *N*-tosyl substituents as in **31** and **33**, exclusive loss of the benzyl group is observed in the formation of the nitrogen heterocycle.[16]

Table 2. Seleniranium-Ion Initiated Detosylative Cyclizations

entry	substrate	reaction conditions[a]	products/yields
1.	 **7b**	−80 °C, 2 h, followed by −60 °C, 8 h	 **9b** (75)
2.	 **21**	−80 °C, 2 h followed by RT, 1 h	 **22** + **23** (71) 3.4:1.0
3.	 **24**	−90 °C, 2 h followed by −80 °C, 8 h	 **25** (56)
4.	 **26**	−78 °C, 2 h	 **27** (49) **28** (21)
5.	 **29**	−78 °C, 2 h	 **30** (96)

[a] See the Supporting Information for details. PhSeBr (1.1 equiv), $AgSbF_6$ (3.1 equiv) CH_2Cl_2, after reaction, mixture was stirred with MeOH for 1 h before workup.



31 n = 1
33 n = 2

32 n = 1 (69%)
34 n = 2 (75%)

In summary, here we disclose new reactions involving seleniranium ions for intramolecular cyclizations. New protocols for the Friedel−Crafts cyclizations of nonactivated arene-alkenes and novel detosylative cyclizations of tertiary *N*-*p*-toluenesulfonamides are described.

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Supporting Information Available: Full experimental details of synthesis of substrates and cyclization reactions; spectroscopic and chromatographic data for characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900961M

(12) Jones, A. D.; Knight, D. W.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett.* **1999**, *40*, 3267.
(13) Wirth, T.; Fragale, G. *Synthesis* **1998**, 162.
(14) Pelkey, E. T.; Gribble, G. W. *Can. J. Chem.* **2006**, *84*, 1338.
(15) Lee, Y. T.; Chung, Y. K. *J. Org. Chem.* **2008**, *73*, 4698.
(16) In the seleniranium-mediated cyclizations of secondary *N*-allyl-*N*-benzylamines, the benzyl group is retained in the product. See ref 11.

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