Radical Reactions

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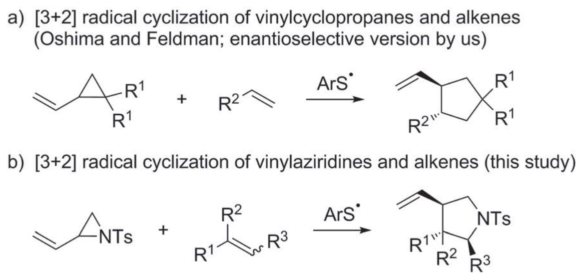
A Bulky Thiyl-Radical Catalyst for the [3+2] Cyclization of *N*-Tosyl Vinylaziridines and Alkenes

*Takuya Hashimoto, Kohei Takino, Kazuki Hato, and Keiji Maruoka**

Abstract: *Thiyl-radical-catalyzed cyclization reactions of N-tosyl vinylaziridines and alkenes were developed as a new synthetic method for the generation of substituted pyrrolidines. The key to making this process accessible to a broad range of substrates is the use of a sterically demanding thiyl radical, which prevents the undesired degradation of the catalyst.*

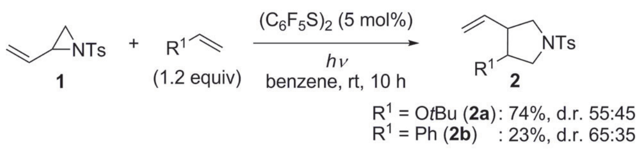
Organic thiyl radicals possess the unique ability to catalyze radical reactions.[1,2] In nature, such thiyl-radical-mediated catalytic reactions are indispensable for the biosynthesis of, for example, deoxyribonucleotides from ribonucleotides.[3] The synthetic utility of thiyl-radical catalysis also reaches into organic chemistry, and has led to the development of polarity-reversal catalysis.[4,5] Recently, interest in thiyl-radical catalysis has been rekindled, as these radicals may serve as a hydrogen-transfer cocatalyst in photoredox catalysis.[6] However, despite these remarkable examples, the number of organic reactions catalyzed by thiyl radicals still remains very limited, in sharp contrast to the rich diversity of other homogeneous catalytic reactions. In homogeneous catalysis, judicious catalyst design is crucial, as it enables the selectivity and/or reaction yield to be improved relative to that observed with the unmodified catalyst. We envisaged that the application of this fundamental strategy to thiyl-radical catalysis should greatly expand its utility in organic synthesis. In this context, we recently developed a chiral organic thiyl radical for the [3+2] cyclization of vinylcyclopropanes and electron-rich alkenes; this reaction afforded cyclopentanes with high enantioselectivity (Scheme 1 a).[7] Although conventional [3+2] cyclization reactions catalyzed by an achiral thiyl radical were introduced as early as 1988,[8] the corresponding "round-trip" thiyl-radical catalysis has not been investigated further, although it would provide access to other synthetic methodologies.[9]



Scheme 1. Thiyl-radical-catalyzed [3+2] cyclization reactions.

Herein, we report the use of this unexplored thiyl-radical catalysis for the [3+2] cyclization of *N*-tosyl vinylaziridines with a variety of alkenes as a new synthetic pathway to substituted pyrrolidines (Scheme 1 b).[10] This seemingly facile reaction is severely hampered by catalyst degradation; however, this obstacle may be circumvented by the design of a sterically demanding thiyl-radical catalyst. Although transition-metal- and Lewis acid catalyzed [3+2] cyclization reactions of vinylaziridines and alkenes have already been reported,[11,12] these reactions are restricted to electron-deficient alkenes. Owing to the polarity-reversal nature of the thiyl-radical catalysis, our method offers an electronically reversed sense of reactivity, thus favoring electron-rich alkene substrates.[13]

As the reaction proceeds through the addition of an electron-deficient *N*-tosylaminyl radical to the alkene, we initially examined the reaction of *N*-tosyl vinylaziridine (**1**) with electron-rich *tert*-butyl vinyl ether (Scheme 2; for a plausible mechanism, see Scheme 3). The catalytically active thiyl radical was generated photolytically from the corresponding aryl disulfide. After the screening of some readily available disulfides (catalyst loading: 5 mol%), we found that the use of electron-deficient pentafluorophenyl disulfide afforded **2a** in modest yield (74%). However, we soon realized that this thiyl-radical-catalyzed [3+2] cyclization suffers from poor reactivity towards less reactive alkenes. A representative example is the reaction with styrene, which gave the corresponding product **2b** in low yield (23%). Unfortunately, the yield could not be increased even by prolonging the reaction time, and higher catalyst loadings only led to a proportional increase in the yield, thus indicating deactivation of the catalyst.[14]



Scheme 2. Preliminary experiments.

This radical cyclization starts with the attack of a thiyl radical on vinylaziridine **1** to generate aminyl radical **I** (Scheme 3). In the productive catalytic cycle, this radical

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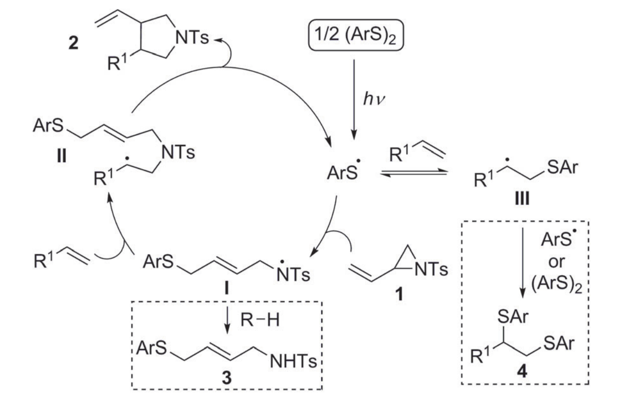
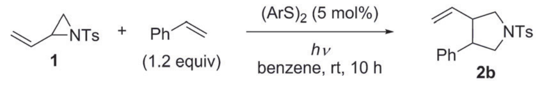


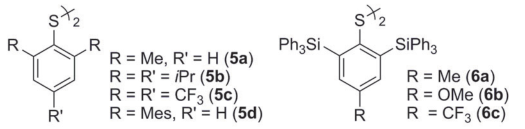
Scheme 3. Proposed catalytic cycle and catalyst-decomposition pathways.

Table 1: Optimization of the reaction conditions.[a]



Entry	$(ArS)_2$	Yield [%][b]	d.r.[c]
1	**5a**	10	67:33
2	**5b**	13	72:28
3	**5c**	48	69:31
4	**5d**	7	64:36
5	**6a**	80	72:28
6	**6b**	71	72:28
7	**6c**	88	72:28
8[d,e]	**6c**	87	72:28

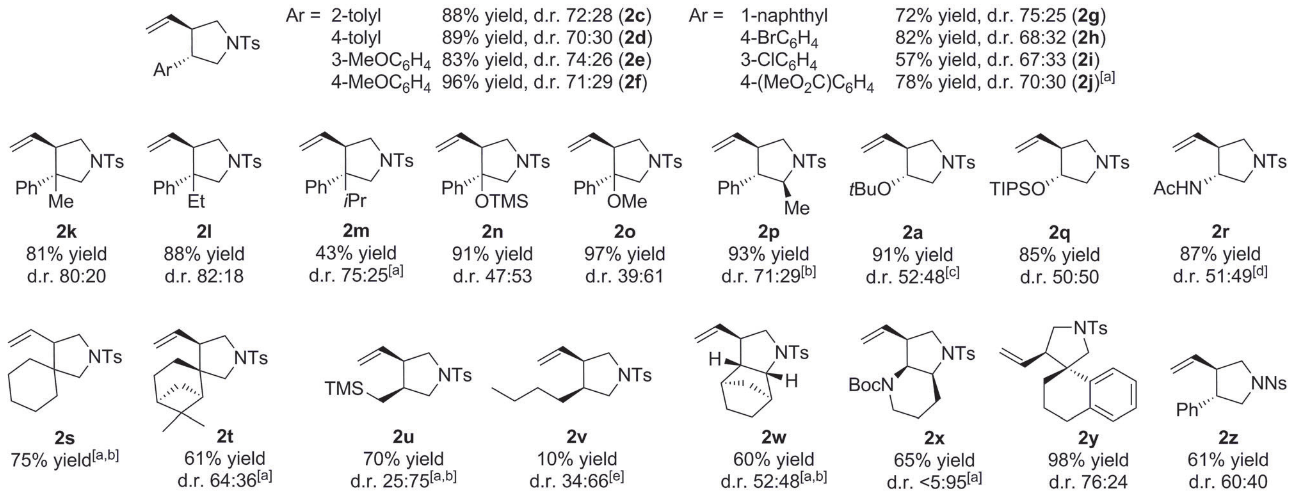
[a] Reaction conditions: *N*-tosyl vinylaziridine (**1**, 0.10 mmol), styrene (0.12 mmol), disulfide (0.005 mmol). [b] Combined yield of the diastereomers, as determined by ^{1}H NMR spectroscopy with mesitylene as an internal standard. [c] The diastereomeric ratio (*trans*/*cis*) was determined by ^{1}H NMR analysis of the crude material. [d] The reaction was carried out for 2 h with 6 mol% of the disulfide. [e] Isolated yield.



species reacts with an alkene to afford carbon radical **II**, which cyclizes to furnish **2** with concomitant regeneration of the thiyl radical. To elucidate the cause of catalyst deactivation, we scrutinized the residual products of the reactions described above. The isolation and identification of minor byproducts revealed that the catalyst was trapped mainly by two different pathways. One decomposition pathway for the catalyst is the abstraction of a hydrogen atom from the intermediate aminyl radical **I** to give allylic sulfide **3**. Another is the formation of bis(arylthiolated) **4**, which is formed by the addition of the thiyl radical to the alkene, followed by a reaction of the thus generated carbon radical **III** with another thiyl radical or the disulfide.[15] Whereas the former pathway (**I**→**3**) is hard to circumvent, we reasoned that the latter pathway leading to **4** could be prevented by appropriate catalyst design.

We envisaged that the use of a sterically hindered thiyl radical should prevent the second addition of a thiyl radical or disulfide (pathway **III**→**4**), thereby making the thiyl radical available for the catalytic cycle. To validate this hypothesis, we screened several aryl disulfides. For example, the 2,6-dimethylphenyl and 2,4,6-triisopropylphenyl disulfides **5a** and **5b** generated pyrrolidine **2b** merely in low yields (Table 1, entries 1 and 2), and the use of electron-deficient tris(trifluoromethyl)phenyl disulfide **5c** promoted the reaction only modestly (entry 3). No improvement in conversion was observed when 2,6-diarylphenyl disulfides, such as 2,6-dimesitylphenyl disulfide **5d**, were used (Table 1, entry 4). Consequently, we focused our attention on the introduction of sterically more demanding silyl groups at the 2,6-positions of the aryl disulfide. Even though the use of trialkylsilyl-substituted catalysts led to merely modest conversion at best (data not shown), the introduction of triphenylsilyl groups (disulfide **6a**) resulted in a dramatic improvement in the yield to 80% (Table 1, entry 5). To further improve the catalytic activity, we fine-tuned the electronic properties of the 2,6-bis(triphenylsilyl)aryl disulfide **6** by replacing the substituent at the *para* position of the catalyst (Table 1, entries 5–7). These experiments provided us with the optimal catalyst **6c**, which contains triphenylsilyl groups at the *ortho* positions and a trifluoromethyl group at the *para* position of the principal aryl moiety. To secure full consumption of vinylaziridine **1**, the catalyst loading was slightly increased to 6 mol%. Under these optimized reaction conditions, the reaction afforded the desired pyrrolidine in 87% yield within 2 h (entry 8). Although the reaction proceeds in a variety of solvents, benzene was chosen for this study because of the high solubility of the catalyst therein and the low probability of undesired hydrogen abstraction from the solvent.

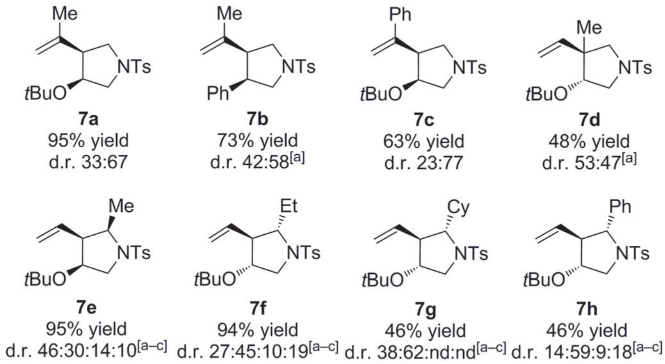
We examined the scope of the reaction by subjecting a variety of styrene derivatives to the optimized reaction conditions (Scheme 4).[16] Even though we observed that the position of the functional group on the aryl moiety did not affect the reaction yield (products **2c**,**d**), the electronic features of the styrenes were found to have a substantial effect on their reactivity. Whereas the cyclization with electron-rich styrene derivatives reached completion within 2 h (products **2e**,**f**), the reaction of electron-deficient alkenes, such as 4-bromostyrene, required longer reaction times and/or higher catalyst loadings (products **2h**–**j**). The catalytic system was applicable to α-substituted styrenes, which afforded the corresponding pyrrolidines with a quaternary center in good yield and with modest diastereoselectivity (products **2k**–**m**). The use of α-silyloxy and α-alkoxy styrenes enabled the incorporation of a protected tertiary alcohol moiety in the pyrrolidine ring (products **2n**,**o**). The reactivity of these electron-rich styrenes was found to be higher than that of α-alkyl styrenes. Notably, the reaction also proceeded with a β-substituted styrene to give the corresponding trisubstituted pyrrolidine **2p**. A *trans* configuration was ascertained for the stereochemical relationship between the methyl and phenyl group of **2p**; thus, a mixture of just two out of four possible diastereomers was obtained. The *E*/*Z* isomerization of β-methylstyrene is faster than the reaction under the previously described optimal reaction conditions, thus justifying the use of isomeric mixtures.



Scheme 4. Substrate scope with respect to the styrene derivative. Reaction conditions: *N*-tosyl vinylaziridine **1** (0.10 mmol), alkene (0.12 mmol), disulfide (0.06 mmol), 2–24 h. The combined yield of the diastereomeric products is given in each case. Diastereomeric ratios (*trans*/*cis*) were determined by ^{1}H NMR analysis of the crude material. The structure of the major diastereomer is shown. [a] Disulfide: 10 mol%. [b] Alkene: 5 equivalents. [c] Disulfide: 2 mol%. [d] Disulfide: 3 mol%. [e] Alkene: 20 equivalents. Boc = *N*-butoxycarbonyl, Ns = 2-nitrobenzenesulfonyl, TMS = trimethylsilyl, TIPS = triisopropylsilyl.

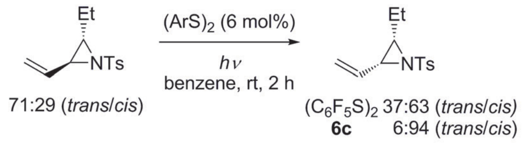
Subsequently, we focused our attention on the use of other alkenes (Scheme 4, products **2a** and **2q–x**). Monosubstituted electron-rich alkenes containing a vinyl ether, silyl enol ether, or enamide moiety reacted smoothly to afford the hetero-functionalized pyrrolidines **2a**, **2q**, and **2r**, respectively. The cyclization with a vinyl ether or a vinyl amide was possible with a catalyst loading of 2 and 3 mol%, respectively. Aliphatic 1,1-disubstituted alkenes could also be successfully converted, as demonstrated by the incorporation of exomethylenecyclohexane and β-pinene moieties to give spiropyrrolidines **2s** and **2t**. The reaction with pinene proceeded exclusively on the sterically less hindered face of the alkene. For the reaction of an allylsilane, the use of 5 equivalents of the alkene was necessary for full consumption of the vinylaziridine, and pyrrolidine **2u** was obtained with modest *cis* selectivity.[17] When an excess of 1-hexene was used, the corresponding pyrrolidine **2v** was generated in low yield. Whereas the 1,2-disubstituted alkene norbornene provided pyrrolidine **2w**, cyclohexene was absolutely unreactive. When electron-rich N-Boc-protected tetrahydropyridine was used as a reactive substrate, **2x** was obtained with exceptionally high *cis* selectivity. The reaction of 1-methylidene-1,2,3,4-tetrahydronaphthalene yielded spirocyclic **2y**, which can be used for the synthesis of a β-secretase inhibitor (see the Supporting Information),[18] in near-quantitative yield. Although the product was not formed when other N-protecting groups, such as *tert*-butoxycarbonyl and benzyl, were used on the vinylaziridine, the nosyl group was found to be applicable to this catalysis, thus enabling the synthesis of **2z** in good yield.

We further extended our method to the use of substituted vinylaziridines (Scheme 5). Substitution of the internal carbon atom of the vinyl moiety with an alkyl or aryl group did not affect the reactivity of the vinylaziridine; thus, **7a–c** were obtained in good yield. Contrary to expectation, the more congested *cis* isomer became the dominant product in

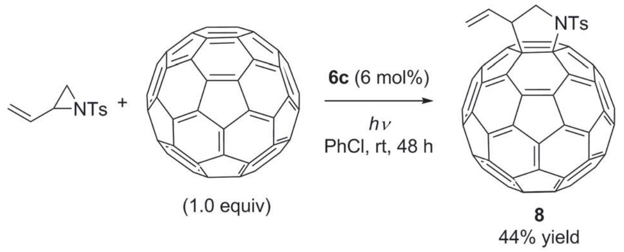


Scheme 5. Substrate scope with respect to the substituted vinylaziridine. Reaction conditions: *N*-tosyl vinylaziridine **1** (0.10 mmol), alkene (0.12 mmol), **6c** (0.06 mmol), 2–12 h. The combined yield of the diastereomeric products is given in each case. Diastereomeric ratios (*trans*/*cis*) were determined by ^{1}H NMR analysis of the crude material. The structure of the major diastereomer is shown. [a] Disulfide: 10 mol%. [b] Alkene: 10 equivalents. [c] D.r.: 2,3-*cis*, 3,4-*cis*/2,3-*trans*, 3,4-*trans*/2,3-*cis*, 3,4-*trans*/2,3-*trans*, 3,4-*cis*. Cy = cyclohexyl, nd = not detected.

these cases. Substitution of the aziridine ring with an alkyl group had a substantial effect on the reactivity. A reaction with 2-methyl-2-vinylaziridine gave the corresponding pyrrolidine **7d** in modest yield. Reactions of 2-alkyl 3-vinylaziridines were found to be slow and required an excess of *tert*-butyl vinyl ether to provide sufficient amounts of the products (**7e–h**). The diastereoselectivity of these reactions varied depending on the bulk of the alkyl group, and among the four possible diastereomers, the 2,3-*cis*/3,4-*cis*-pyrrolidine and 2,3-*trans*/3,4-*trans*-pyrrolidine were obtained as major isomers. These 2-alkyl 3-vinylaziridines were used as a mixture of diastereomers, since the bulky thiyl radical effectively facilitates the epimerization of the vinylaziridine to give the thermodynamically more stable *cis* isomer as shown in Equation (1).



One application of this catalysis is the modification of C_{60} fullerene (Scheme 6).[19,20] Disulfide **6c** was able to effectively generate functionalized fullerene **8** in modest yield (44%). Other disulfides failed to afford products in more than 1% yield, thus underlining the crucial importance of steric bulk for effective catalysis. Since the addition of an arylthiyl radical to fullerene is known to be an unfavorable process,[18] the mechanism in Scheme 3 does not explain the catalytic activity in this case. At present, our hypothesis is that the steric bulk of the catalyst prolongs the half-life of the thiyl radical, which should be generated in small amounts in the presence of the light-absorbing fullerene.[21]



Scheme 6. Thiyl-radical-catalyzed [3+2] cyclization of *N*-tosyl vinylaziridine with C_{60} fullerene.

In conclusion, we have developed a [3+2] cyclization reaction of *N*-tosyl vinylaziridines with a variety of alkenes under the catalysis of sterically hindered thiyl radicals.[22] Mechanistic analysis allowed us to identify steric bulk as the crucial feature for a successful catalyst design. Steric protection of the thiyl radicals may also offer a strategy to circumvent the irreversible formation of C–S bonds, which is a common termination pathway of thiyl-radical-mediated reactions,[1] thus potentially opening up new possibilities for thiyl-radical catalysis. Moreover, the fundamental results presented herein should enable the development of new stereoselective applications of thiyl-radical catalysts.

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Keywords: pyrrolidines · radical reactions · sulfur · thiyl radicals · vinylaziridines

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[14] We also observed the same tendency when the reactions were carried out with the chiral thiyl-radical catalyst developed in our previous study (Ref. [7]), although the enantioselectivity was promising. Product **2a** was obtained in 18% yield with d.r. 71:29 and 44/23% *ee*, and **2b** was obtained in 6% yield with d.r. 71:29 and 43/35% *ee*.
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[21] This thiyl-radical catalysis was also applicable to a vinylcyclopropane (see the Supporting Information for details).
[22] For the X-ray crystal structure of the catalyst, see the Supporting Information.

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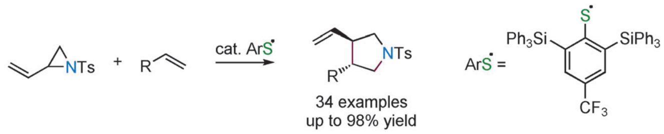
A Bulky Thiyl-Radical Catalyst for the [3+2] Cyclization of *N*-Tosyl Vinylaziridines and Alkenes



Bulk it up: A thiyl-radical-catalyzed cyclization reaction of *N*-tosyl vinylaziridines and alkenes was developed as a new synthetic method for the generation of substituted pyrrolidines (see scheme). The key to making this process accessible to a broad range of substrates is the use of a sterically demanding thiyl radical to prevent the undesired degradation of the catalyst.