JOC Article

Highly Selective Double Chalcogenation of Isocyanides with Disulfide−Diselenide Mixed Systems

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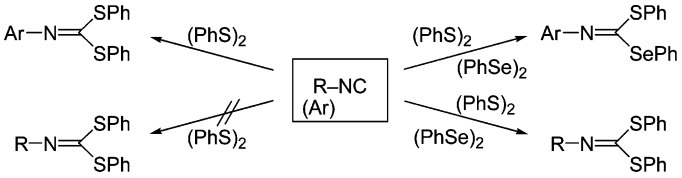
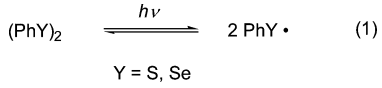


A highly selective method for introducing thio and seleno groups into a variety of isocyanides has been developed based on the elucidation of the relative reactivities of organic dichalcogenides and chalcogen-centered free radicals. When the reactions of aromatic isocyanides (ArNC) with organic disulfides (R′SSR′) and diselenides (R″SeSeR″) are conducted upon irradiation with a tungsten lamp through Pyrex ($h\nu$ > 300 nm), simultaneous introduction of both thio and seleno groups into the isocyanides takes place to provide the corresponding thioselenation products (R′S−C(=NAr)−SeR″) in good yields with excellent selectivity. In the cases of aliphatic isocyanides (RCN), a novel diselenide-assisted bisthiolation of RNC with diaryl disulfides (Ar′SSAr′) proceeds successfully to give the corresponding bisthiolation products (Ar′S−C(=NR)−SAr′), although the same photoirradiated reaction of RNC with diaryl disulfides does not occur in the absence of diselenide. These double chalcogenation reactions are assumed to proceed via the formation of imidoyl radical intermediates by the reaction of isocyanides with relatively reactive thio radicals (compared with seleno radicals). The obtained thioselenation products can be employed as useful precursors for the construction of β-lactam framework by the formal [2 + 2] cyclization with ketene equivalents.

Introduction

Organic disulfides and diselenides have their absorption maxima based on the n → σ^* transition in ultraviolet and near-UV regions, respectively (Figure 1), and therefore irradiation with these light sources causes homolytic cleavage of the chalcogen−chalcogen bonds to generate the corresponding chalcogen-centered radicals as labile species (eq 1).[1]



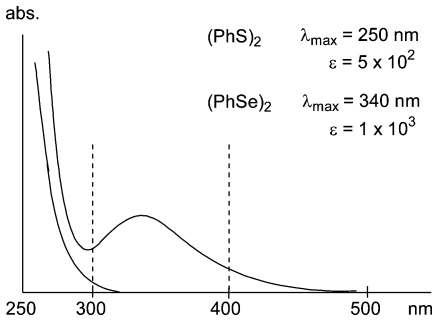


FIGURE 1. UV−visible spectra of $(PhS)_2$ and $(PhSe)_2$.

When the photolysis of dichalcogenides (PhY−YPh) is performed in the presence of carbon−carbon unsaturated compounds such as alkynes, chalcogeno radicals formed in situ

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(1) Schmidt, U.; Müller, A.; Markau, K. *Chem. Ber.* **1964**, *97*, 405.

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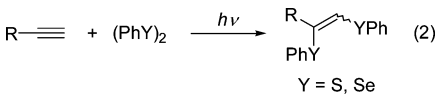
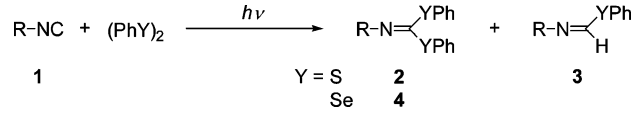
may be trapped by unsaturated compounds, affording vicinal dichalcogenation products, as exemplified in eq 2.[2−4]



Isocyanides, which bear an isoelectronic structure with carbon monoxide, are useful C1 units in organic synthesis as well as building blocks for nitrogen-containing heterocyclic compounds.[5] Isocyanides may react with carbon- or heteroatom-centered radical species (Z•) to generate the corresponding imidoyl radicals (eq 3).[6] However, the development of efficient synthetic reactions involving chalcogenoimidoyl radicals as key intermediates has remained largely unexplored.[7]

We have investigated in detail the photoirradiated reactions of isocyanides with organic dichalcogenides, and have found that a novel bischalcogenation of isocyanides with organic dichalcogenides can take place efficiently with high selectivity, based on the combination of the characteristic features of individual chalcogen-centered radicals (i.e., thio and seleno radicals) and dichalcogenides (i.e., disulfides and diselenides).

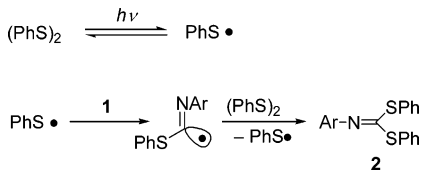
TABLE 1. Radical Addition of Dichalcogenides to Isocyanides[a]



					yield, %[b]	
entry	R	**1**	$(PhY)_2$, (equiv)	time, h	**2** (**4**)	**3**
1	2,6-xylyl	**1a**	$(PhS)_2$ (1.0)	48	17	33
2	2,6-xylyl	**1a**	$(PhS)_2$ (2.0)	48	35	24
3	2,6-xylyl	**1a**	$(PhS)_2$ (5.0)	16	58	24
4	2,6-xylyl	**1a**	$(PhS)_2$ (5.0)[c]	13	74	0
5[d]	$PhCH_2$	**1b**	$(PhS)_2$ (1.0)	10	0	0
6[d]	$^cC_6H_{11}$	**1c**	$(PhS)_2$ (1.1)	15	0	0
7[d]	2,6-xylyl	**1a**	$(PhSe)_2$ (1.0)	48	0	0
8	p-O_2N-C_6H_4	**1d**	$(PhSe)_2$ (1.2)	9	75	0
9	p-O_2N-C_6H_4	**1d**	$(PhSe)_2$ (3.0)	16	90	0

[a] Reaction conditions: isocyanide (0.25 mmol), $CDCl_3$ (0.5 mL), $h\nu$ tungsten lamp (500 W, Pyrex), 40 °C. [b] Isolated yield. [c] In the absence of solvent. [d] Isocyanide was recovered in almost quantitative yield.

SCHEME 1. A Possible Pathway for Bisthiolation of Isocyanides



Results and Discussion

Photoinduced Bisthiolation and Bisselenation of Isocyanides with Dichalcogenide−Single Systems. If the photolysis of dichalcogenides is performed in the presence of isocyanides, the formed chalcogen-centered radicals may add to the unsaturated C−N bonds, producing imidoyl radical intermediates. Thus, we examined the photoinduced reactions of diphenyl dichalcogenides with isocyanides (Table 1). When the reaction of 2,6-xylyl isocyanide (**1a**, 0.5 M) with equimolar amounts of diphenyl disulfide in $CDCl_3$ was conducted for 48 h upon irradiation with a tungsten lamp through Pyrex, 1,1-bisthiolation product (**2a**, Y = S, R = 2,6-xylyl) and 1,1-hydrothiolation product (**3a**, Y = S, R = 2,6-xylyl) were obtained in 17% and 33% yields, respectively (entry 1). The reaction may proceed via the formation of imidoyl radical intermediates by the reaction of **1a** with PhS•, and the subsequent S_H2 reaction of the imidoyl radical intermediates with $(PhS)_2$ leads to the 1,1-bisthiolation product (**2a**) (Scheme 1).

Since $(PhS)_2$ is known to convert to p-PhS-C_6H_4-SH gradually under photoirradiation conditions,[8] the formation of **3a** may be explained by the hydrogen abstraction of the imidoyl radical intermediate from p-PhS-C_6H_4-SH. With increase of the molar ratio of $(PhS)_2$/**1a**, the yields of **2a** increased (entries 1−3). In the absence of solvent (i.e., under higher concentration of the substrate), the S_H2 reaction of the imidoyl radical intermediate

(2) For a review see: Ogawa, A. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, p 813.

(3) For radical addition reactions of disulfides to alkynes, see for example: Heiba, E. I.; Dessau, R. M. *J. Org. Chem.* **1967**, *32*, 3837.

(4) For radical addition reactions of diselenides to alkynes, see for example: (a) Back, T. G.; Krishna, M. V. *J. Org. Chem.* **1988**, *53*, 2533. (b) Ogawa, A.; Yokoyama, H.; Yokoyama, K.; Masawaki, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **1991**, *56*, 5721. (c) Ogawa, A.; Takami, N.; Sekiguchi, M.; Yokoyama, H.; Kuniyasu, H.; Ryu, I.; Sonoda, N. *Chem. Lett.* **1991**, 2241.

(5) For reviews concerning radical reactions of isocyanides, see for example: (a) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (b) Nanni, D. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, p 44. (c) Tokuyama, H.; Fukuyama, T. *Chem. Rec.* **2002**, *2*, 37.

(6) For the reaction of organophosphorous compounds with isocyanides, see for example: (a) Saegusa, T.; Ito, Y.; Yasuda, N.; Hotaka, T. *J. Org. Chem.* **1970**, *35*, 4238. For the reaction of organosilicon compounds with isocyanides, see for example: (b) Chatgilialoglu, C.; Giese, B.; Kopping, B. *Tetrahedron Lett.* **1990**, *31*, 6013. For the reaction of organosulfur compounds with isocyanides, see for example: (c) Barton, D. H. R.; Ozbalik, N.; Vacher, B. *Tetrahedron* **1988**, *44*, 3501. (d) Nanni, D.; Calestani, G.; Leardini, R.; Zanardi, G. *Eur J. Org. Chem.* **2000**, 707. (e) Leardini, R.; Nanni, D.; Zanardi, G. *J. Org. Chem.* **2000**, *65*, 2763. For the reaction of organoselenium compounds with isocyanides, see for example: (f) Ogawa, A.; Doi, M.; Tsuchii, K.; Hirao, T. *Tetrahedron Lett.* **2001**, *42*, 2317. For the reaction of organotin compounds with isocyanides, see for example: (g) Saegusa, T.; Kobayashi, S.; Ito, Y.; Yasuda, N. *J. Am. Chem. Soc.* **1968**, *90*, 4182. (h) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127. (i) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863. (j) Curran, D. P.; Ko, S.-B.; Josien, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2683. (k) Curran, D. P.; Liu, H.; Josien, H.; Ko, S.-B. *Tetrahedron* **1996**, *52*, 11385. (l) Josien, H.; Curran, D. P. *Tetrahedron* **1997**, *53*, 8881. (m) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67. (n) Kobayashi, Y.; Fukuyama, T. *J. Heterocycl. Chem.* **1998**, *35*, 1043. (o) Du, W.; Curran, D. P. *Synlett* **2003**, 1299. (p) Tangirala, R.; Antony, S.; Agama, K.; Pommier, Y.; Curran, D. P. *Synlett* **2005**, 2843. For the reaction of organotellurium compounds with isocyanides, see for example: (q) Yamago, S.; Miyazoe, H.; Goto, R.; Yoshida, J. *Tetrahedron Lett.* **1999**, *40*, 2347. (r) Miyazoe, H.; Yamago, S.; Yoshida, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3669. (s) Yamago, S.; Miyazoe, H.; Sawazaki, T.; Goto, R.; Yoshida, J. *Tetrahedron Lett.* **2000**, *41*, 7517. (t) Yamago, S.; Miyazoe, H.; Goto, R.; Hashidume, M.; Sawazaki, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 3697. (u) Yamago, S.; Miyazoe, H.; Nakayama, T.; Miyoshi, M.; Yoshida, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 117. (v) Kotani, M.; Yamago, S.; Satoh, A.; Tokuyama, H.; Fukuyama, T. *Synlett* **2005**, 1893.

(7) Z = S: (a) Saegusa, T.; Kobayashi, S.; Ito, Y. *J. Org. Chem.* **1970**, *35*, 2118. (b) Bachi, M. D.; Balanov, A.; Bar-Ner, N. *J. Org. Chem.* **1994**, *59*, 7752. (c) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (d) Minozzi, M.; Nanni, D.; Walton, J. C. *Org. Lett.* **2003**, *5*, 901. Z = S, Se: (e) Minozzi, M.; Nanni, D.; Walton, J. C. *J. Org. Chem.* **2004**, *69*, 2056.

(8) Schaafsma, Y.; Bickel, A. F.; Kooyman, E. C. *Tetrahedron* **1960**, *10*, 76.

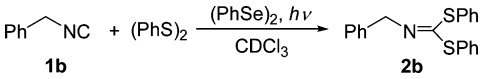
with $(PhS)_2$ proceeded to provide **2a** in a high yield selectively (entry 4). In contrast to the aromatic isocyanide, aliphatic isocyanides did not undergo similar bisthiolations at all (entries 5 and 6). This is probably due to the lack of conjugation between aromatic π-electrons and lone pairs on sulfur through C−N double bonds (observed in the case of aromatic isocyanides: $C_6H_5-N{=}C-S-Ph \leftrightarrow C_6H_5^-{=}N-C{=}S^+-Ph$). In the case of $(PhSe)_2$, the corresponding bisselenation of isocyanides (both aromatic and aliphatic ones) did not take place at all (entry 7). Owing to the weakness of the C−Se bond and the relative stability of PhSe• (compared with PhS•), the imidoyl radical bearing phenylseleno group easily undergoes reverse reaction to reform isocyanide and PhSe•. Exceptionally, isocyanide bearing a nitro group at the para position (**1d**) underwent the photoinduced bisselenation effectively to give the corresponding 1,1-bisselenated product (**4d**) in high yields (entries 8 and 9) because of the stabilization of radical intermediate by the inductive effect of the nitro group.

Diselenide-Assisted Double Thiolation of Isocyanides with Disulfides. Some kinetic data are of great importance for predicting the radical addition reactions of $(PhY)_2$ to unsaturated compounds. The reactivity of the addition of phenylseleno radical to carbon−carbon unsaturated bonds is relatively lower by the factor of about 10−50, compared with the corresponding thiyl radical.[9] On the other hand, the rate constants for the S_H2 reaction are estimated to be 7.6×10^4 M^{-1} s^{-1} for $(PhS)_2$ and 1.2×10^7 M^{-1} s^{-1} for $(PhSe)_2$ by using the free radical clock system of the 5-hexenyl radical.[10] These kinetic data indicate that $(PhSe)_2$ exhibits an excellent carbon radical capturing ability, compared with $(PhS)_2$, by the factor of approximately 160.

With these kinetic considerations in mind, we next examined the photoirradiated reactions of aliphatic isocyanides with $(PhS)_2$ in the presence of $(PhSe)_2$. When a mixture of benzyl isocyanide (**1b**), $(PhS)_2$, and $(PhSe)_2$ was irradiated with a tungsten lamp through Pyrex, surprisingly, bisthiolation product (**2b**), which could not be obtained by the reaction of aliphatic isocyanides with $(PhS)_2$ alone, was obtained in a moderate yield without formation of any selenated products (Table 2, entries 1 and 2).[11] The desired bisthiolation could take place even in the presence of catalytic amounts of $(PhSe)_2$ (entry 5).

To gain insight into the role of $(PhSe)_2$, the reaction of benzyl isocyanide (**1b**) with $(PhS)_2$ and $(PhSe)_2$ was monitored by taking the ^1H NMR spectra over a period of 50 h and the results are shown in Figure 2. As can be seen from Figure 2, thioselenation product (**5b**) was formed in the initial stage, but

TABLE 2. Bisthiolation of Benzyl Isocyanide with $(PhS)_2$ in the Presence of $(PhSe)_2$[a]



entry	$(PhSe)_2$, equiv	time, h	isolated (NMR) yield, % **2b**
1	1.0	15	53 (81)
2[b]	1.0	15	65
3[c]	1.0	15	(72)
4	0.15	22	(32)
5	0.23	15	(47)
6[d]	1.0	9	76

[a] Reaction conditions: $PhCH_2NC$ (0.25 mmol), $(PhS)_2$ (1 equiv), solvent (0.5 mL), 40 °C, $h\nu$ (>300 nm). [b] Solvent (0.1 mL). [c] $h\nu$ (>400 nm). [d] Solvent (C_6H_6).

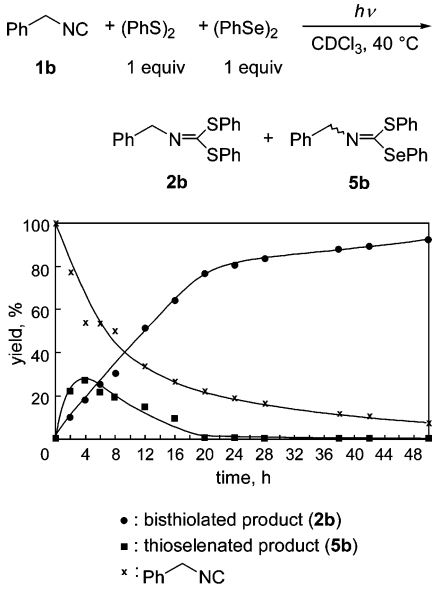


FIGURE 2. $(PhSe)_2$-assisted bisthiolation of benzyl isocyanide with $(PhS)_2$.

5b disappeared gradually, and instead, the yield of **2b** increased in the meantime.

As mentioned already, disulfide has its absorption maximum in the ultraviolet region, whereas diselenide has its absorption maximum in the near-UV region (Figure 1). Upon irradiation with a tungsten lamp through Pyrex (>300 nm), therefore, $(PhSe)_2$ undergoes homolytic cleavage of the Se−Se bond more easily compared with that of the S−S bond of $(PhS)_2$. Accordingly, thiyl radicals are probably generated by the reaction of PhSe• with $(PhS)_2$ (Scheme 2). The formed thiyl radical attacks the carbon of isocyanide to provide imidoyl radical intermediate (**6**), which is trapped by $(PhSe)_2$ to give the corresponding thioselenated product (**5**) as a kinetic product. In this reaction, **5** is probably unstable under the photoirradiation conditions. Therefore, the reverse reaction from **5** to **6** may take place, and **6** is trapped with PhSeSPh, yielding bisthiolation product (**2**) with regeneration of PhSe•. Alternatively, a thiyl radical attacks **5** to give **6** by the release of PhSSePh, and then **6** provides **2**.

Table 3 summarizes the results of a variety of aliphatic isocyanides with $(PhS)_2$ in the presence of $(PhSe)_2$. When the reaction of primary alkyl isocyanide (**1e**) with $(PhS)_2$ and $(PhSe)_2$ was conducted in the absence of solvent, the desired bisthiolated product (**2e**) was obtained in a good yield (entry

(9) (a) Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* **1979**, *101*, 1815. (b) Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* **1979**, *101*, 5732. (c) Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* **1981**, *103*, 5871. (d) Ito, O. *J. Am. Chem. Soc.* **1983**, *105*, 850. (e) Ito, O.; Matsuda, M. *J. Org. Chem.* **1984**, *49*, 17. (f) Ito, O.; Matsuda, M. *Prog. Polym. Sci.* **1992**, *17*, 827. (g) Ito, O. In *The Chemistry of Free Radicals*: *S-Centered Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, UK, 1999; Chapter 6, pp 193−224.

(10) (a) Perkins, M. J.; Turner, E. S. *J. Chem. Soc., Chem. Commun.* **1981**, 139. (b) Russell, G. A.; Tashtoush, H. *J. Am. Chem. Soc.* **1983**, *105*, 1398. (c) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H. I.; Pla-Dalmau, A.; Khanna, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 3530.

(11) For thioselenation of alkenes, see for example: (a) Ogawa, A.; Tanaka, H.; Yokoyama, H.; Obayashi, R.; Yokoyama, K.; Sonoda, N. *J. Org. Chem.* **1992**, *57*, 111. (b) Ogawa, A.; Obayashi, R.; Ine, H.; Tsuboi, Y.; Sonoda, N.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 881. (c) Ogawa, A.; Obayashi, R.; Sonoda, N.; Hirao, T. *Tetrahedron Lett.* **1998**, *39*, 1577. (d) Ogawa, A.; Obayashi, R.; Doi, M.; Sonoda, N.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 4277. (e) Ogawa, A.; Ogawa, I.; Obayashi, R.; Umezu, K.; Doi, M.; Hirao, T. *J. Org. Chem.* **1999**, *64*, 86.

SCHEME 2. Possible Pathways for Bisthiolation of Isocyanides

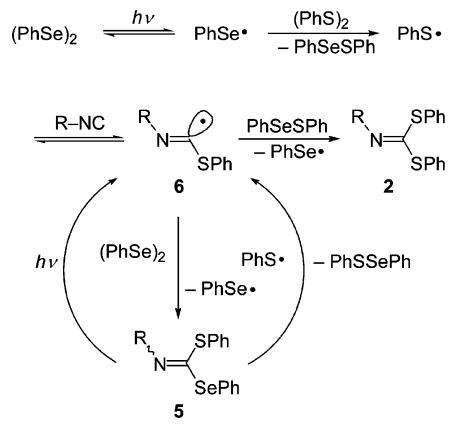
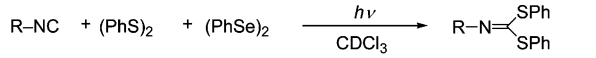
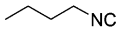
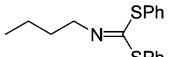
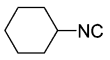
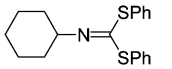
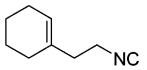
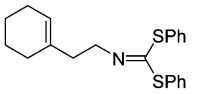
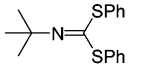


TABLE 3. Bisthiolation of Aliphatic Isocyanides with $(PhS)_2$ in the Presence of $(PhSe)_2$[a]

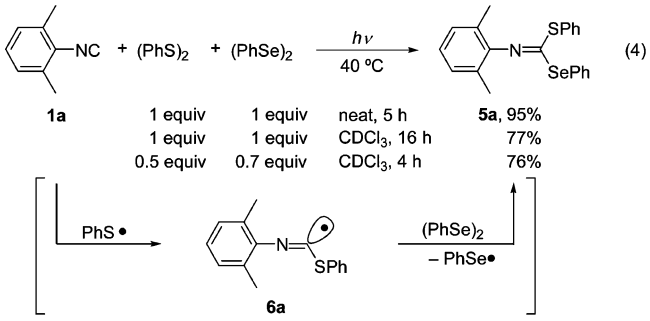


entry	isocyanide		time, h	product	yield, %[b]
1		1.0 M	46		51
2[c]	**1e**	1.0 M	46	**2e**	46
3		neat	56		78
4		0.5 M	50		39 (55)
5	**1c**	0.5 M	80	**2c**	46
6[d]		neat	23		58
	1f			**2f**	
7		neat	20		trace
	1g			**2g**	

[a] Reaction conditions: $(PhS)_2$ (1 equiv), $(PhSe)_2$ (1 equiv), 40 °C, $h\nu$ (>300 nm). [b] Isolated (NMR) yield. [c] $h\nu$ (>400 nm). [d] $(PhSe)_2$ (0.5 equiv).

3). On the other hand, in the case of isocyanides bearing a more bulky substituent (**1g**), the reaction did not proceed effectively (entry 7), probably because the imidoyl radical intermediate was unstable to decompose to *tert*-butyl radical and PhSCN.[6e]

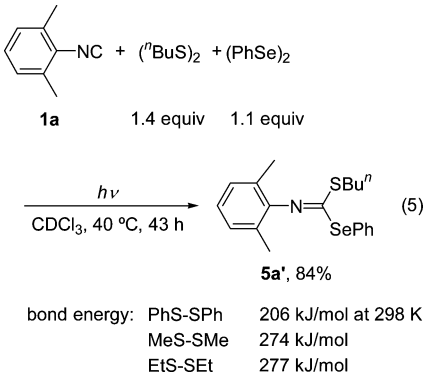
Photoinduced Thioselenation of Aromatic Isocyanides with a $(PhS)_2$−$(PhSe)_2$ Mixed System. We next examined the reaction of aromatic isocyanides by using a $(PhS)_2$−$(PhSe)_2$ mixed system. When a reaction of 2,6-xylyl isocyanide (**1a**) with $(PhS)_2$ and $(PhSe)_2$ was conducted in the absence of solvent, interestingly, the product was not the bisthiolation product but the thioselenation product (**5a**: 95%) (eq 4).[12,13] The fact that prolonged photoirradiation did not cause the conversion of the thioselenation products into the corresponding



bisthiolation products clearly indicates that the thioselenation products derived from aromatic isocyanides are stable under photoirradiation conditions. A possible reaction pathway is shown in eq 4. In situ formed thiyl radicals (from $(PhS)_2$ and PhSe•) may attack the isocyanide carbon of **1a** to give imidoyl radical intermediate (**6a**), which undergoes S_H2 reaction with $(PhSe)_2$ to provide **5a**. Even with the smaller amounts of disulfide and diselenide, effective thioselenation proceeded smoothly in $CDCl_3$ in short reaction times (**5a**: 76%).

Table 4 summarizes the results of thioselenation of various aromatic isocyanides. Similar conditions can be employed with a variety of aromatic isocyanides, and the desired thioselenated products (**5**) were obtained in excellent yields (entries 1−5).

The thioselenation of aliphatic disulfides and $(PhSe)_2$ also proceeded effectively, although the yield was slightly reduced compared with the case of aromatic disulfide (eq 5). This is partly due to the bond strength of the S−S single bond: the S−S bond of aliphatic disulfides is stronger than that of aromatic disulfides.[14]



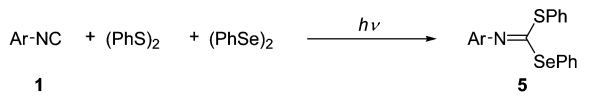
Thioselenation Products as Useful Building Blocks for the Synthesis of β-Lactam Framework. A series of thioselenated products obtained by the reaction of isocyanides with dichalcogenides are expected to convert into the β-lactam framework by formal [2+2] cyclization with ketene equivalents. When the [2+2] cyclization of the thioselenated product (**5a**) and 2 equiv of phenoxyacetyl chloride (**7a**) in the presence of triethylamine was performed, the desired β-lactam derivative (**8a**) was

(12) The syn- and anti-isomers, concerning C−N double bonds, of the products are in rapid equilibrium with each other at ambient temperature, and, as a result, the ^1H NMR spectra of the products indicate averaged signals of both isomers, see: (a) Kessler, H. *Angew. Chem.* **1970**, *82*, 237. (b) Kessler, H.; Leibfritz, D. *Tetrahedron* **1970**, *26*, 1805.

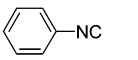
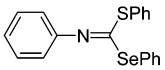
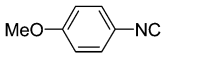
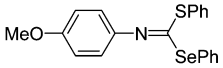
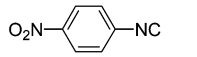
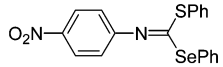
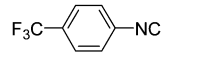
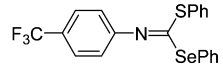
(13) When aromatic isocyanides were used in this reaction, the product (**5**) was stable relatively because of resonance stabilization between the aromatic group and the N−C double bonds. Contrary to this, in the case of aliphatic isocyanides, the product (**5**) was unstable compared to the product from aromatic isocyanides.

(14) (a) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, **17**, Suppl. No. 1. (b) Stein, S. E.; Lias, S. G.; Liebman, J. F.; Levin, R. D.; Kafafi, S. A. *NIST Standard Reference Data Base 25, NIST Structures and Properties Version 2.0*; U.S. Dept of Commerce: Gaithersburg, MD, 1994.

TABLE 4. Selective Thioselenation of Isocyanides with $(PhS)_2-(PhSe)_2$[a]

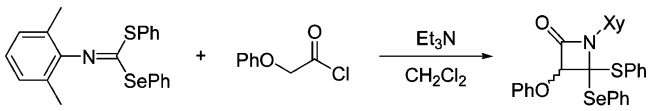


1 **5**

entry	isocyanide	time, h	product	yield, %[b]
1	 **1h**	5	 **5h**	98
2	 **1i**	5	 **5i**	63
3	 **1d**	1.5	 **5d**	90[c]
4[d]		3		92[e]
5	 **1j**	2	 **5j**	86

[a] Reaction conditions: isocyanide (0.25 mmol), $(PhS)_2$ (1 equiv), $(PhSe)_2$ (1 equiv), $CDCl_3$ (0.5 mL), *hν* tungsten lamp (500 W, Pyrex), 40 °C. [b] Isolated yield. [c] Adduct of diselenide (**4d**) was formed in 10% yield. [d] $(PhSe)_2$ (0.15 mmol). [e] Adduct of diselenide (**4d**) was formed in 2% yield.

TABLE 5. Synthesis of *β*-Lactam Bearing Thio and Seleno Groups[a]



5a **7a** **8a**

entry	**7a**, equiv	Et_3N, equiv	CH_2Cl_2, mL	yield, % isolated (NMR)	ratio of stereoisomers[b]
1	2	2	4	24	91/9
2	2	2	2	46 (54)	86/14
3[c]	2	2	4	(46)	83/17
4	5	5	2	52 (79)	89/11

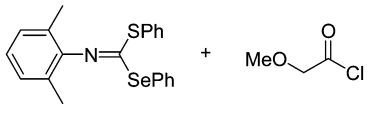
[a] Reaction conditions: **5a** (0.2 mmol), −23 °C, 1 h; then room temperature, 20 h. [b] The stereochemistry of **8a** was not determined. [c] Reflux, 16 h.

obtained successfully (Table 5, entry 1).[15] Higher concentration of a ketene precursor improved the yield of **8a** (entry 4).

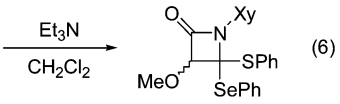
When the [2+2] cyclization reactions were attempted by using further excess amounts of methoxyacetyl chloride (**7a′**), the desired cyclization product (**8a′**) was obtained in 81% yield (eq 6). In the case of the thioselenation product (**5i**) derived from *p*-methoxyphenylisocyanide, the corresponding *β*-lactam product (**8i**) was formed in 91% yield successfully (eq 7).

Since the thus formed *β*-lactam derivatives (**8i**) have both thio and seleno groups, the chemoselective transformation with **8i** was demonstrated as follows. When the reaction of **8i** with tin hydride in the presence of AIBN was examined, the phenylseleno group of **8i** could be reduced selectively to give the *β*-lactam derivative (**9i**) in excellent yield (eq 8). Allylation

(15) Two mechanistic pathways have been reported, see: Baldwin, J. E. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon Press: Oxford, UK, 1991; Vol. 5, Chapter 2, p 63.

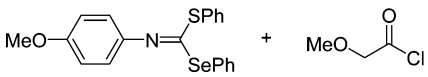


5a **7a'**, 10 equiv

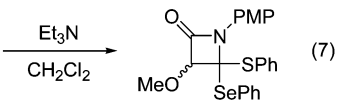


(6)

8a', 81% [81/19]



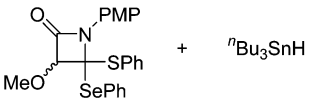
5i **7a'**, 5 equiv



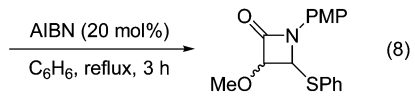
(7)

8i, 91% [52/48]

of **8i** with an allyltin compound also took place selectively at the phenylseleno group, to form *β*-lactam derivative (**10i**) in a good yield (eq 9).

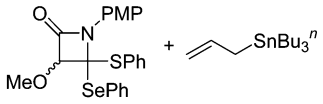


8i, 0.07 M 1.2 equiv

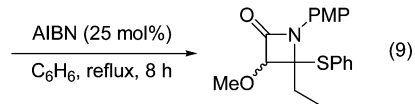


(8)

9i, 91%
[*trans*/*cis* = 64/36]



8i, 0.11 M 3 equiv



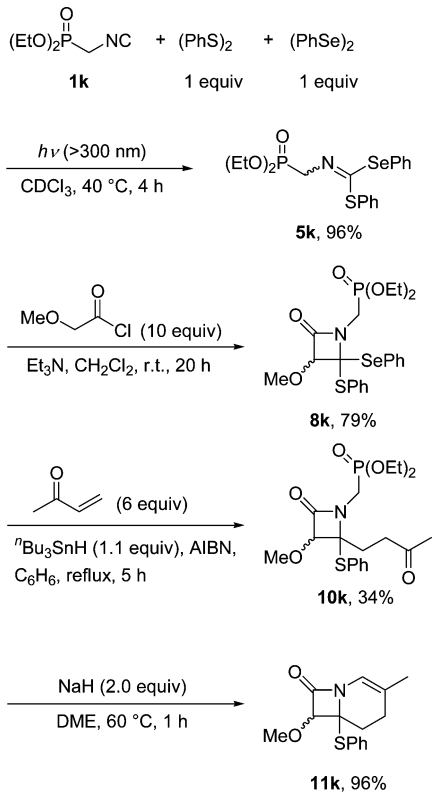
(9)

10i, 67%
[*trans*/*cis* = 64/36]

Moreover, this thioselenation and [2+2] cyclization sequence is applicable for the synthesis of carbacephems (Scheme 3).[16] When the reaction of isocyanide (**1k**) with $(PhS)_2$ and $(PhSe)_2$ was performed under the photoirradiation conditions, the corresponding thioselenated compound (**5k**) was formed in 96%

(16) Guzzo, P. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4862.

SCHEME 3. Synthesis of Carbacephem Framework



yield.[17] The thioselenation product (**5k**) reacted with methoxyacetyl chloride in the presence of triethylamine to give a β-lactam derivative (**8k**) in 79% yield. When the reaction of **8k** with 3-buten-2-one was conducted in the presence of ^{n}Bu$_3$SnH and AIBN, the seleno group of **8k** was selectively converted into the 3-butanonyl group.[18] Then, the desired carbacephem derivative (**11k**) was obtained in excellent yield by the intramolecular Horner−Emmons reaction of **10k**.[19]

Conclusion

A series of photoinduced reactions of various isocyanides with disulfide and/or diselenide were investigated in detail. The bisthiolation of aromatic isocyanides could be attained by use of excess amounts of disulfides. In contrast, aliphatic isocyanides did not undergo bisthiolation with disulfide alone. In the presence of diselenide, however, the desired bisthiolation of aliphatic isocyanides was achieved successfully. On the other hand, the reaction of aromatic isocyanides with $(PhS)_2$ and $(PhSe)_2$ afforded the corresponding thioselenation products selectively. Moreover, the synthetic utility of thioselenation products of isocyanides was demonstrated by the constraction of β-lactam flameworks.

Experimental Section

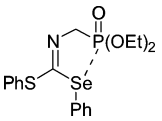
General Comments. Isocyanides,[20] aliphatic disulfides,[21] and diphenyl diselenide[22] were synthesized according to the literature. Other materials were obtained from commercial supplies and purified by distillation or recrystallization before use. Dichloromethane and triethylamine were distilled from CaH_2 and KOH, respectively. Purification of products was performed on a recycling preparative HPLC (Japan Analytical Industry Co. Ltd., Model LC-908), equipped with JAIGEL-1H and -2H columns (GPC), using $CHCl_3$ as an eluent. ^{1}H NMR spectra were recorded on a JEOL JNM-GSX-270 (270 MHz) spectrometer with $CDCl_3$ as the solvent and Me_4Si as the internal standard. ^{13}C NMR spectra were taken on a JEOL JNM-GSX-270 (68 MHz) with $CDCl_3$ as the solvent. Chemical shifts in ^{1}H NMR were measured relative to $CDCl_3$ and converted to δ (Me_4Si) values by using δ ($CDCl_3$) = 7.26 ppm. Chemical shifts in ^{13}C NMR were measured relative to $CDCl_3$ and converted to δ (Me_4Si) values by using δ ($CHCl_3$) = 77.0 ppm. IR spectra were determined on a Perkin-Elmer Model 1600 spectrometer. Melting points were determined on a Yanagimoto micro melting point apparatus. Mass spectra were obtained on a JEOL JMS-DX303 in the analytical section of Osaka University. Elemental analyses were also performed there.

***N*-(2,6-Dimethylphenyl)bis(phenylthio)methanimine (2a).** In a Pyrex glass tube (ϕ = 5 mm, length = 180 mm) were placed 2,6-xylyl isocyanide (**1a**, 32.8 mg, 0.25 mmol) and diphenyl disulfide (273 mg, 1.25 mmol) under an argon atmosphere. Irradiation with a tungsten lamp (500 W) was performed at 40 °C for 13 h. Purification was performed on a recycling preparative HPLC, yielding 64.7 mg (74%) of **2a** as a white solid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.10 (s, 6 H), 6.84−6.98 (m, 3 H), 7.35−7.37 (m, 6 H), 7.54−7.57 (m, 4 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 17.8, 123.6, 126.9, 127.8, 129.0, 129.2, 129.7, 136.1, 147.6, 160.1. IR (KBr): 3066, 2912, 1598, 1579, 1465, 1439, 1199, 1088, 926, 907, 766, 742, 704, 684 cm^{-1}. MS (CI): *m*/*z* 349 (M^+ + 1, 4). HRMS calcd for $C_{21}H_{19}NS_2$ 349.0959, found 349.0965.

***N*-(4-Nitropheny)bis(phenylseleno)methanimine (4d).** In a Pyrex glass tube (ϕ = 5 mm, length = 180 mm) were placed 4-nitrophenyl isocyanide (**1d**, 34.5 mg, 0.23 mmol), diphenyl diselenide (82.9 mg, 0.27 mmol), and $CDCl_3$ (0.5 mL) under an argon atmosphere. Irradiation with a tungsten lamp through Pyrex was performed at 40 °C for 9 h. Purification by preparative TLC (silica gel, pentane/Et_2O = 10/1, R_f = 0.37) and the following recrystallization from hexane provided 79.7 mg (75%) of **4d** as an orange needle crystal; mp 96.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.89 (d, J = 8.8 Hz, 2 H), 7.31−7.44 (m, 6 H), 7.64 (d, J = 6.8 Hz, 4 H), 8.13 (d, J = 9.3 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 119.9, 124.9, 127.0, 129.3 (2C), 129.7, 137.0, 144.2, 156.4. IR (KBr): 3053, 2361, 1598, 1585, 1512, 1343, 1211, 1110, 872, 858 cm^{-1}. MS (CI): *m*/*z* 463 (M^+ + 1, 92). Anal. Calcd for $C_{19}H_{14}N_2O_2Se_2$: C, 49.58; H, 3.07; N, 6.09. Found: C, 49.58; H, 3.19; N, 6.16.

***N*-Benzylbis(phenylthio)methanimine (2b) (General Procedure for the Bisthiolation of Aliphatic Isocyanides).** In a Pyrex glass tube (ϕ = 5 mm, length = 180 mm) were placed benzyl isocyanide (**1b**, 29.3 mg, 0.25 mmol), diphenyl disulfide (54.6 mg, 0.25 mmol), diphenyl diselenide (78.0 mg, 0.25 mmol), and C_6D_6 (0.5 mL) under an argon atmosphere. Irradiation with a tungsten lamp (500 W) was performed at 40 °C for 9 h. The reaction mixture

(17) The bisthiolated product was assumed to be obtained because of the reaction of aliphatic isocyanides with $(PhS)_2$ and $(PhSe)_2$. However, the thioselenated product (**5k**) was obtained as a sole product. The reason why **5k** was obtained may be explained by the coordination of a diethoxyphosphoryl group to the seleno group as shown below, which stabilizes the thioselenation products.



(18) Mesmaeker, A. De.; Hoffmann, P.; Ernst, B.; Hug, P.; Winkler, T. *Tetrahedron Lett.* **1989**, *30*, 6311.

(19) Grieco, P. A.; Pogonowski, C. S. *Synthesis* **1973**, 425.

(20) (a) Ugi, I.; Meyr, R. *Chem. Ber.* **1960**, *93*, 239. (b) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem.* **1965**, *77*, 492.

(21) Gladysz, J. A.; Wong, V. K.; Jick, B. S. *Tetrahedron* **1979**, *35*, 2329.

(22) Reich, H. J.; Renga, J. M.; Reich, I. V. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

was treated with preparative TLC on silica gel with pentane/Et_2O (50/1) as an eluent to afford 63.7 mg (76%) of **2b** as a white solid; mp 80.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.72 (s, 2 H), 7.14−7.40 (m, 13 H), 7.60 (d, J = 7.8 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 57.0, 126.5, 127.2, 128.1, 128.6, 128.7, 129.2, 129.4, 130.7, 135.0 (2 C), 135.4, 139.6, 156.8. IR (KBr): 3028, 2857, 1595, 1577, 1493, 1472, 1452, 1439, 1353, 1009, 930, 912, 757, 734, 694 cm^{-1}. MS (CI): m/z 336 ($M^+ + 1$, 39). Anal. Calcd for $C_{20}H_{17}NS_2$: C, 71.60; H, 5.11; N, 4.18. Found: C, 71.13; H, 5.21; N, 4.15.

***N*-(Butyl)bis(phenylthio)methanimine (2e):** yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.87 (t, J = 7.3 Hz, 3 H), 1.39 (sextet, J = 7.3 Hz, 2 H), 1.53 (quint, J = 7.2 Hz, 2 H), 3.50 (t, J = 6.8 Hz, 2 H), 7.25−7.26 (m, 3 H), 7.32−7.35 (m, 5 H), 7.53 (d, J = 7.3 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.8, 20.4, 32.4, 53.9, 128.3, 128.5, 128.9, 129.0, 130.0, 131.0, 134.3, 135.0, 154.1. IR (NaCl): 2930, 1598, 1580, 1475, 887, 745, 705, 689 cm^{-1}. MS (CI): m/z 302 ($M^+ + 1$, 18). HRMS calcd for $C_{17}H_{19}NS_2$ 302.1037, found 302.1044.

***N*-(Cyclohexyl)bis(phenylthio)methanimine (2c):** white solid; mp 73.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.25−1.68 (m, 10 H), 3.75−3.81 (m, 1 H), 7.24−7.35 (m, 8 H), 7.49 (br s, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.1, 25.7, 33.0, 62.5, 128.1, 128.4, 128.9 (2C), 130.5, 131.6, 134.0, 135.0, 151.8. IR (KBr): 3057, 2928, 2853, 1598, 1577, 1438, 1362, 1023, 925, 910, 871, 749, 688 cm^{-1}. MS (CI): m/z 328 ($M^+ + 1$, 35). HRMS calcd for $C_{19}H_{21}NS_2$ 328.1194, found 328.1187.

***N*-(2-(1-Cyclohexenyl)ethyl)bis(phenylthio)methanimine (2f):** yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.52−1.63 (m, 4 H), 1.87 (br s, 2 H), 1.97 (br s, 2 H), 2.18 (t, J = 7.1 Hz, 2 H), 3.60 (t, J = 7.1 Hz, 2 H), 5.37 (br s, 1 H), 7.24−7.37 (m, 8 H), 7.53−7.56 (m, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.4, 23.0, 25.3, 28.4, 38.5, 53.3, 122.5, 128.4, 128.5, 129.0, 129.1, 130.1, 131.0, 134.4, 135.0, 135.8, 154.5. IR (NaCl): 2925, 2854, 2833, 1599, 1580, 1477, 1440, 886, 744, 705, 688 cm^{-1}. MS (CI): m/z 354 ($M^+ + 1$, 24). HRMS calcd for $C_{21}H_{23}NS_2$ 354.1350, found 354.1346.

***N*-(2,6-Dimethylphenyl)(phenylseleno)(phenylthio)methanimine (5a) (General Procedure for the Thioselenation of Aromatic Isocyanide).** In a Pyrex glass tube (ϕ = 5 mm, length = 180 mm) were placed 2,6-xylyl isocyanide (**1a**, 29.3 mg, 0.22 mmol), diphenyl disulfide (55.4 mg, 0.25 mmol), and diphenyl diselenide (79.3 mg, 0.25 mmol) under an argon atmosphere. Irradiation with a tungsten lamp (500 W) was performed at 40 °C for 5 h. The reaction mixture was treated with preparative TLC (silica gel, R_f = 0.59) with pentane/Et_2O (25/1) as an eluent to afford 82.8 mg (95%) of **5a**. The product was recrystallized from hexane as a white solid; mp 72.0−73.0 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.10 (s, 6 H), 6.88−6.98 (m, 3 H), 7.32−7.35 (m, 6 H), 7.53 (br s, 2 H), 7.69 (d, J = 7.3 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 17.9, 123.8, 126.4, 126.8, 127.9, 128.9, 129.1, 129.4, 129.5, 130.0, 135.6, 137.7, 148.3, 156.2. IR (KBr): 3063, 2912, 1618, 1597, 1583, 1476, 1439, 1190, 1090, 1022, 881, 768, 738, 685 cm^{-1}. MS (CI): m/z 398 ($M^+ + 1$, 10). Anal. Calcd for $C_{21}H_{19}NSSe$: C, 63.63; H, 4.83; N, 3.53. Found: C, 63.85; H, 4.91; N, 3.77.

***N*-Phenyl(phenylseleno)(phenylthio)methanimine (5h):** white solid; mp 130.0−131.0 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.84 (d, J = 7.3 Hz, 2 H), 7.07 (t, J = 7.6 Hz, 1 H), 7.23−7.39 (m, 8 H), 7.52 (br s, 2 H), 7.69 (d, J = 6.8 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 119.9 (2 C), 124.3, 128.9 (2 C), 129.0, 129.1 (2 C), 129.3, 135.0, 137.5 (2 C), 150.4. IR (KBr): 3048, 1587, 1484, 1474, 1210, 916, 904, 867, 754, 748, 735, 692 cm^{-1}. MS (CI): m/z 370 ($M^+ + 1$, 8). Anal. Calcd for $C_{19}H_{15}NSSe$: C, 61.95; H, 4.10; N, 3.80. Found: C, 61.68; H, 4.15; N, 3.81.

***N*-(4-Methoxyphenyl)(phenylseleno)(phenylthio)methanimine (5i):** white solid; mp 133.0 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.76 (s, 3 H), 6.82 (s, 4 H), 7.28−7.42 (m, 6 H), 7.51 (br s, 2 H), 7.68 (br s, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 55.4, 114.1 (2C), 121.2 (2 C), 128.9 (2 C), 129.1 (2 C), 129.3, 134.9, 137.4, 143.6, 156.7. IR (KBr): 2998, 1604, 1587, 1574, 1504, 1458, 1439, 1290, 1245, 1030, 893, 738, 689 cm^{-1}. MS (CI): m/z 399 ($M^+ + 1$, 1). Anal. Calcd for $C_{20}H_{17}NOSSe$: C, 60.30; H, 4.30; N, 3.52. Found: C, 60.11; H, 4.40; N, 3.53.

***N*-(4-Nitrophenyl)(phenylseleno)(phenylthio)methanimine (5d):** yellow solid; mp 98.0−98.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.89 (d, J = 8.8 Hz, 2 H), 7.33−7.41 (m, 6 H), 7.51−7.54 (m, 2 H), 7.64 (d, J = 6.8 Hz, 2 H), 8.11 (d, J = 8.8 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 120.3, 124.8, 124.9, 126.0, 129.1, 129.3, 129.7, 129.9, 135.2, 137.2, 144.1, 155.9, 160.2. IR (KBr): 3066, 2363, 1597, 1559, 1510, 1475, 1342, 1111, 900, 740, 688 cm^{-1}. MS (CI): m/z 415 ($M^+ + 1$, 68). HRMS calcd for $C_{19}H_{14}N_2O_2SSe$ 415.0019, found 415.0047.

***N*-(4-Trifluoromethylphenyl)(phenylseleno)(phenylthio)-methanimine (5j):** yellow solid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.89 (d, J = 8.3 Hz, 2 H), 7.29−7.42 (m, 6 H), 7.48−7.53 (m, 4 H), 7.65 (d, J = 6.8 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 119.7, 120.1, 126.1 (J_{C-F} = 3.4 Hz), 126.1 (J_{C-F} = 32.5 Hz), 126.3 (J_{C-F} = 272.2 Hz), 129.1, 129.2, 129.5, 129.7, 135.1, 137.0, 137.3, 153.2, 158.7. IR (KBr): 1622, 1603, 1509, 1475, 1322, 1156, 1123, 1103, 1064, 878, 740, 688 cm^{-1}. MS (CI): m/z 438 ($M^+ + 1$, 13). HRMS calcd for $C_{20}H_{14}F_3NSSe$ 438.0042, found 438.0034.

***N*-(2,6-Dimethylphenyl)(butylthio)(phenylseleno)-methanimine (5a′).** The photoirradiated reaction of 2,6-xylyl isocyanide (**1a**, 26.0 mg, 0.22 mmol) with dibutyl disulfide (54.3 mg, 0.30 mmol) and diphenyl diselenide (76.1 mg, 0.24 mmol) in $CDCl_3$ (0.5 mL) at 40 °C for 43 h was performed similarly as the general procedure for the thioselenation of aromatic isocyanides. Purification by preparative TLC (silica gel, pentane/Et_2O = 50/1, R_f = 0.44) provided 66.7 mg (84%) of **5a′** as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (t, J = 7.3 Hz, 3 H), 1.37 (sextet, J = 7.3 Hz, 2 H), 1.65 (quint, J = 7.3 Hz, 2 H), 2.17 (s, 6 H), 3.05 (t, J = 7.3 Hz, 2 H), 6.96−7.05 (m, 3 H), 7.29−7.41 (m, 3 H), 7.66 (d, J = 7.3 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.7, 18.0, 22.1, 31.3, 32.6, 123.9, 125.8, 127.4, 128.1, 129.0, 129.5, 138.1, 148.5, 157.0. IR (NaCl): 2959, 2930, 1598, 1574, 1474, 1438, 916, 890, 740, 689 cm^{-1}. MS (EI): m/z 377 (M^+, 1). HRMS calcd for $C_{19}H_{23}NSSe$ 377.0716, found 377.0718.

***N*-(2,6-Dimethylphenyl)-3-phenoxy-4-(phenylseleno)-4-(phenylthio)azetidin-2-one (8a) (General Procedure for the Synthesis of β-Lactam Framework).** In a two-necked flask (20 mL) equipped with a dropping funnel and a magnetic stirring bar were placed *N*-(2,6-dimethylphenyl)(phenylseleno)(phenylthio)methanimine (**5a**, 78.9 g, 0.20 mmol) and dichloromethane (4 mL) under an argon atmosphere, and the solution was cooled at −23 °C. After the addition of phenoxyacetyl chloride (**7a**, 171 mg, 1.0 mmol) to the solution in one portion, triethylamine (139 μL, 101 mg, 1.0 mmol) was added slowly. During the addition of Et_3N, the white salt was precipitated. The suspended solution was stirred for 1 h at −23 °C and then for 20 h at ambient temperature (the solution had a color varying from initially pale yellow to brown at the end). The resulting solution was washed with water, dried over $MgSO_4$, and concentrated in vacuo. Purification of **8a** was performed by a recycling preparative HPLC and then by preparative TLC (silica gel, pentane/Et_2O = 25/1, developed two times, R_f = 0.09), affording 55.3 mg (52%, 89/11) of **8a**: yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): major isomer δ 2.50 (s, 3 H), 2.60 (s, 3 H), 5.67 (s, 1 H), 6.95−7.34 (m, 18 H); minor isomer δ 2.55 (s, 3 H), 2.57 (s, 3 H), 5.79 (s, 1 H), 6.95−7.34 (m, 18 H). ^{13}C NMR (68 MHz, $CDCl_3$): major isomer δ 20.7, 83.1, 90.4, 117.0, 123.1, 127.5, 128.1, 128.2, 128.4, 128.7, 129.0, 129.3, 129.5, 129.6, 132.3, 133.8, 135.2, 136.2, 138.1, 138.8, 157.6, 163.6; minor isomer δ 20.5, 81.9, 91.1, 117.1, 123.1, 127.9, 128.3, 129.6, 132.5, 133.9, 135.2, 137.8, 139.1, 158.2, 164.0. IR (NaCl): 3060, 1778, 1591, 1494, 1225, 1022, 738, 689 cm^{-1}. MS (CI): m/z 532 ($M^+ + 1$, 8). HRMS calcd for $C_{29}H_{25}NO_2SSe$ 532.0850, found 532.0854.

***N*-(2,6-Dimethylphenyl)-3-methoxy-4-(phenylseleno)-4-(phenylthio)azetidin-2-one (8a′).** The reaction of *N*-(2,6-dimethylphen-

yl)(phenylseleno)(phenylthio)methanimine (**5a**, 78.9 g, 0.20 mmol) with methoxyacetyl chloride (**7a′**, 217 mg, 2.0 mmol) in the presence of Et_3N (279 μL, 202 mg, 2.0 mmol) in CH_2Cl_2 (2 mL) was conducted according to the above general procedure. Isolation was performed on a recycling preparative HPLC, yielding 76.2 mg (81%, 81/19) of **8a′** as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): major isomer δ 2.48 (s, 3 H), 2.56 (s, 3 H), 3.49 (s, 3 H), 4.97 (s, 1 H), 6.92−7.34 (m, 13 H); minor isomer δ 2.50 (s, 3 H), 2.51 (s, 3 H), 3.38 (s, 3 H), 5.16 (s, 1 H), 6.92−7.34 (m, 13 H). ^{13}C NMR (68 MHz, $CDCl_3$): major isomer δ 20.6, 20.7, 60.0, 84.7, 93.3, 127.4, 127.9, 128.5, 128.7, 128.8, 128.9, 129.3, 129.4, 132.3, 132.6, 133.7, 135.6, 138.0, 138.8, 164.1; minor isomer δ 20.3, 20.6, 60.1, 82.9, 94.3, 128.0, 128.4, 129.1, 129.5, 132.7, 133.0, 133.1, 136.3, 137.6, 139.1, 164.3. IR (NaCl): 2930, 1770, 1472, 1339, 1022, 738, 690 cm^{-1}. MS (EI): *m*/*z* 470 (M^+, 1). HRMS calcd for $C_{24}H_{23}NO_2SSe$ 470.0693, found 470.0693.

3-Methoxy-*N*-(4-methoxyphenyl)-4-(phenylseleno)-4-(phenylthio)azetidin-2-one (8i). The reaction of *N*-(4-methoyphenyl)-(phenylseleno)(phenylthio)methanimine (**5i**, 0.20 mmol, 79.7 g) with methoxyacetyl chloride (**7a′**, 217 mg, 2.0 mmol) in the presence of Et_3N (279 μL, 202 mg, 2.0 mmol) in CH_2Cl_2 (2 mL) and the following purification on a recycling preparative HPLC provide 85.6 mg (91%, 52/48) of **8i** as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): major isomer δ 3.56 (s, 3 H), 3.81 (s, 3 H), 4.24 (s, 1 H), 6.85 (d, J = 9.3 Hz, 2 H), 7.09 (t, J = 8.1 Hz, 2 H), 7.20−7.38 (m, 5 H), 7.50−7.57 (m, 3 H), 7.79 (d, J = 8.8 Hz, 2 H); minor isomer δ 3.44 (s, 3 H), 3.81 (s, 3 H), 4.46 (s, 1 H), 6.87 (d, J = 8.8 Hz, 2 H), 7.12 (t, J = 8.5 Hz, 2 H), 7.20−7.38 (m, 5 H), 7.47−7.53 (m, 3 H), 7.79 (d, J = 9.3 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): major isomer δ 55.4, 59.0, 76.7, 90.9, 114.1, 120.2, 126.5, 128.5, 129.4, 129.6, 130.0, 136.2, 137.5, 156.8, 161.5; minor isomer δ 55.4, 59.1, 75.3, 89.0, 114.0, 120.2, 125.8, 128.5, 129.4, 129.6, 130.2, 136.1, 137.9, 156.8, 161.3. MS (EI): *m*/*z* 471 (M^+, 1). HRMS calcd for $C_{23}H_{21}NO_3SSe$ 471.0407, found 471.0436.

3-Methoxy-*N*-(4-methoxyphenyl)-4-(phenylthio)azetidin-2-one (9i). In a two-necked flask equipped with a condenser and a magnetic stirring bar were placed 3-methoxy-*N*-(4-methoxyphenyl)-4-(phenylseleno)-4-(phenylthio)azetidin-2-one (**8i**, 93.9 mg, 0.20 mmol), 2,2′-azobisisobutyronitrile (AIBN, 6.60 mg, 0.04 mmol), and benzene (3 mL) at ambient temperature under a nitrogen atmosphere. After the addition of tributyltin hydride (75.3 mg, 0.26 mmol) to the mixture at ambient temperature, the reaction was conducted under reflux for 3 h. The resulting solution was condensed under reduced pressure, and the residual mixture was treated with preparative TLC on silica gel (pentane/Et_2O = 10/1, three times), yielding 36.6 mg (58%, R_f = 0.14) of *trans*-**9i** and 20.8 mg (33%, R_f = 0.06) of *cic*-**9i** as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): *trans*-**10i** δ 3.51 (s, 3 H), 3.82 (s, 3 H), 4.38 (d, J = 1.5 Hz, 1 H), 5.07 (d, J = 1.5 Hz, 1 H), 6.92 (d, J = 9.3 Hz, 2 H), 7.30−7.37 (m, 5 H), 7.48 (d, J = 9.3 Hz, 2 H); *cis*-**9i** δ 3.70 (s, 3 H), 3.78 (s, 3 H), 4.82 (d, J = 4.4 Hz, 1 H), 5.47 (d, J = 4.4 Hz, 1 H), 6.80 (d, J = 8.8 Hz, 2 H), 7.23−7.31 (m, 5 H), 7.46 (d, J = 7.3 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): *trans*-**9i** δ 55.4, 58.2, 64.6, 88.5, 114.5, 119.8, 128.6, 129.3, 129.4, 135.3, 156.9, 162.1; *cis*-**9i** δ 55.4, 59.2, 68.4, 84.6, 114.2, 119.8, 128.5, 129.1, 129.4, 131.9, 134.0, 156.7, 162.7. IR (NaCl): 2933, 2836, 1760, 1514, 1385, 1249, 1130, 693 cm^{-1}. MS (EI): *m*/*z* 315 (M^+, 10). HRMS calcd for $C_{17}H_{17}NO_3S$ 315.0929, found 315.0927.

4-Allyl-3-methoxy-*N*-(4-methoxyphenyl)-4-(phenylthio)azetidin-2-one (10i). In a two-necked flask equipped with a condenser and a magnetic stirring bar were placed 3-methoxy-*N*-(4-methoxyphenyl)-4-(phenylseleno)-4-(phenylthio)azetidin-2-one (**8i**, 107 mg, 0.23 mmol), AIBN (9.9 mg, 0.06 mmol), and benzene (2 mL) at room temperature under a nitrogen atmosphere. After the addition of allyltributyltin (223 mg, 0.67 mmol) to the mixture at room temperature, the reaction was conducted under reflux for 8 h. The resulting solution was condensed under reduced pressure, and the residual mixture was treated with preparative TLC on silica gel (pentane/Et_2O = 5/1, two times), yielding 36.6 mg (43%, R_f = 0.35) of *trans*-**10i** and 20.8 mg (24%, R_f = 0.17) of *cis*-**10i** as a yellow oil. *trans*-**10i**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.03 (dd, J = 7.8, 8.3 Hz, 2 H), 3.54 (s, 3 H), 3.83 (s, 3 H), 4.21 (s, 1 H), 5.10 (dd, J = 9.7, 17.0 Hz, 2 H), 5.94 (m, 1 H), 6.92 (d, J = 8.8 Hz, 2 H), 7.24−7.39 (m, 5 H), 7.77 (d, J = 9.3 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 38.5, 55.4, 59.9, 75.1, 88.5, 114.3, 119.6, 120.0, 128.8, 129.3, 129.8, 130.2, 131.6, 136.6, 156.6, 162.9. IR (NaCl): 2935, 1756, 1513, 1378, 1298, 1247, 1133, 1021, 832 cm^{-1}. MS (EI): *m*/*z* 355 (M^+, 6). HRMS calcd for $C_{20}H_{21}NO_3S$ 355.1243, found 355.1245. *cis*-**10i**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.97 (dd, J = 6.8, 7.3 Hz, 2 H), 3.60 (s, 3 H), 3.80 (s, 3 H), 4.52 (s, 1 H), 5.23 (dd, J = 11.7, 14.7 Hz, 2 H), 5.77 (m, 1 H), 6.86 (d, J = 9.3 Hz, 2 H), 7.12−7.27 (m, 3 H), 7.45 (d, J = 8.3 Hz, 2 H), 7.59 (d, J = 9.3 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 40.9, 55.4, 59.0, 78.2, 88.3, 114.3, 120.3, 120.9, 128.4, 129.1, 129.2, 129.7, 130.8, 136.6, 156.8, 162.9. IR (NaCl): 2932, 1760, 1514, 1378, 1137, 750 cm^{-1}. MS (EI): *m*/*z* 355 (M^+, 5). HRMS calcd for $C_{20}H_{21}NO_3S$ 355.1243, found 355.1261.

***N*-((Diethoxyphosphoryl)methyl)(phenylseleno)(phenylthio)-methanimine (5k).** According to the general procedure for thioselenation of isocyanides, the photoinduced reaction of (diethoxyphosphoryl)methyl isocyanide (**1k**, 34.9 mg, 0.20 mmol) with diphenyl disulfide (44.3 mg, 0.20 mmol) and diphenyl diselenide (65.2 mg, 0.21 mmol) in $CDCl_3$ (0.5 mL) at 40 °C for 4 h was conducted. Purification on a recycling preparative HPLC provided 84.9 mg (96%) of **5k** as a pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 6 H), 3.83−4.03 (m, 6 H), 7.25−7.48 (m, 8 H), 7.64−7.72 (m, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): major isomer δ 16.2, 53.8 (J_{C-P} = 162.1 Hz), 62.4, 126.5, 128.6, 128.8, 129.0, 129.4, 130.8, 134.7, 136.1, 157.0 (J_{C-P} = 23.9 Hz); minor isomer δ 16.3, 51.7 (J_{C-P} = 162.2 Hz), 62.5, 128.5, 128.7, 129.1, 130.2, 136.2, 136.4, 159.1 (J_{C-P} = 23.9 Hz). IR (NaCl): 3118, 2989, 2854, 1576, 1476, 1440, 1391, 1237, 1162, 1062, 976, 901, 844, 801, 748, 690 cm^{-1}. MS (CI): *m*/*z* 444 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{22}NO_3PSSe$: C, 48.87; H, 5.01; N, 3.17. Found: C, 49.03; H, 5.11; N, 3.32.

***N*-((Diethoxyphosphoryl)methyl)-3-methoxy-4-(phenylseleno)-4-(phenylthio)azetidin-2-one (8k).** The reaction of *N*-((diethoxyphosphoryl)methyl)(phenylseleno)(phenylthio)methanimine (**5k**, 81.2 g, 0.18 mmol) with methoxyacetyl chloride (**7a′**, 2.0 mmol, 217 mg) in the presence of Et_3N (202 mg, 2.0 mmol) in CH_2Cl_2 (2 mL) was conducted according to the general procedure for the construction of the β-lactam framework. Isolation was performed on a recycling preparative HPLC, yielding 73.2 mg (79%, 64/36) of **8k** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): major isomer δ 1.32 (t, J = 7.2 Hz, 6 H), 3.20 (dd, J = 17.0, 17.0 Hz, 1 H), 3.41−3.50 (m, 1 H), 3.45 (s, 3 H), 4.11−4.23 (m, 4 H), 4.39 (s, 1 H), 7.27−7.44 (m, 6 H), 7.67 (d, J = 7.2 Hz, 2 H), 7.82 (d, J = 7.2 Hz, 2 H); minor isomer δ 1.33 (t, J = 7.2 Hz, 6 H), 3.20 (dd, J = 4.8, 16.2 Hz, 1 H), 3.41 (s, 3 H), 3.53 (dd, J = 3.4, 16.2 Hz, 1 H), 4.11−4.23 (m, 4 H), 4.38 (s, 1 H), 7.27−7.44 (m, 6 H), 7.70 (d, J = 7.2 Hz, 2 H), 7.77 (d, J = 7.6 Hz, 2 H). ^{13}C NMR (68 MHz, $CDCl_3$): major isomer δ 16.2, 36.2 (J_{C-P} = 159.0 Hz), 37.4, 58.9, 62.8, 89.2, 126.5, 129.0, 129.5, 130.1, 130.5, 136.0, 137.4, 163.7; minor isomer δ 16.3, 36.4 (J_{C-P} = 159.0 Hz), 37.6, 58.8, 62.7, 90.8, 127.2, 128.9, 129.5, 129.9, 130.2, 135.9, 137.4, 163.8. MS (CI): *m*/*z* 516 (M^+ + 1, 13.0). Anal. Calcd for $C_{21}H_{26}NO_5PSSe$: C, 49.03; H, 5.09; N, 2.72. Found: C, 48.98; H, 5.09; N, 2.68.

***N*-((Diethoxyphosphoryl)methyl)-3-methoxy-4-(phenylthio)-4-(3-oxabutyl)azetidin-2-one (10k).** In a three-necked flask equipped with a condenser, a dropping funnel, and a magnetic stirring bar were placed *N*-((diethoxyphosphoryl)methyl)-3-methoxy-4-(phenylseleno)-4-(phenylthio)azetidin-2-one (**8k**, 111 mg, 0.22 mmol), AIBN (7.7 mg, 0.05 mmol), benzene (2 mL), and 3-buten-2-one (77.1 mg, 1.10 mmol) at room temperature under a nitrogen atmosphere. The solution of tributyltin hydride (71.2 mg, 0.25 mmol) and 3-buten-2-one (15.4 mg, 0.22 mmol) in benzene (3 mL) was added dropwise to the reaction mixture over 45 min at 80 °C.

The reaction was continued at the temperature for an additional 4 h. The resulting solution was condensed under reduced pressure, and the residual mixture was treated with a recycling preparative HPLC, yielding 32.1 mg (34%, 52/48) of **10k** along with simply deselenated reduction product (55%): pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): major isomer δ 1.35 (dt, J = 3.9, 7.2 Hz, 6 H), 2.18 (s, 3 H), 2.18−2.25 (m, 1 H), 2.32−2.42 (m, 2 H), 2.79−2.85 (m, 1 H), 3.44 (s, 3 H), 3.62 (dd, J = 11.7, 16.5 Hz, 1 H), 3.81 (dd, J = 12.3, 16.5 Hz, 1 H), 4.08 (d, J = 4.5 Hz, 1 H), 4.21 (dq, J = 2.4, 7.5 Hz, 4 H), 7.27−7.44 (m, 4 H), 7.60−7.64 (m, 1 H); minor isomer δ 1.31 (dt, J = 4.9, 7.2 Hz, 6 H), 2.11−2.14 (m, 1 H), 2.19 (s, 3 H), 2.25−2.32 (m, 2 H), 2.67−2.76 (m, 1 H), 3.24 (dd, J = 11.7, 16.5 Hz, 1 H), 3.47 (dd, J = 10.9, 16.5 Hz, 1 H), 3.61 (s, 3 H), 4.18 (dq, J = 2.4, 7.2 Hz, 4 H), 4.36 (d, J = 4.3 Hz, 1 H), 7.27−7.44 (m, 4 H), 7.60−7.64 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): major isomer δ 16.4, 28.7, 30.1, 35.5 (J_{C-P} = 160.0 Hz), 38.9, 59.0, 62.9, 63.0, 79.8, 88.9, 128.4, 129.0, 129.7, 136.6, 165.1, 206.9; minor isomer δ 16.4, 30.0, 31.5, 35.6, 39.0, 59.5, 62.7, 62.8, 63.0, 77.2, 89.1, 128.7, 129.4, 130.1, 136.6, 165.6, 206.2. IR (NaCl): 2976, 1769, 1714, 1442, 1371, 1294, 1241, 1164, 1117, 1025, 972, 733, 703 cm^{-1}. MS (CI): m/z 430 ($M^+ + 1$, 36). HRMS calcd for $C_{19}H_{28}NO_6PS$ 430.1453, found 430.1440.

7-Methoxy-3-methyl-6-(phenylthio)-1-aza-bicyclo[4.2.0]oct-2-en-8-one (11k). In a two-necked flask equipped with a condenser were placed *N*-((diethoxyphosphoryl)methyl)-3-methoxy-4-(phenylthio)-4-(3-oxabutyl)azetidin-2-one (**10k**, 24.1 mg, 0.06 mmol) and dimethoxyethane (1 mL) at room temperature. After the addition of sodium hydride (2.64 mg, 0.11 mmol) to the mixture at room temperature, the mixture was stirred for 0.5 h at room temperature and then for 1 h at 60−65 °C. The resulting solution was cooled in an ice−water bath and quenched with saturated NaCl aq at 0 °C. Extraction with diethyl ether (2 × 10 mL) followed by evaporation afforded a crude product. Purification on a recycling preparative HPLC yielded 14.8 mg (96%, 53/47) of **11k** as a colorless oil (the ratio of stereoisomers is 53/47). ^{1}H NMR (300 MHz, $CDCl_3$): major isomer δ 1.74 (s, 3 H), 1.79 (dd, J = 5.4, 17.7 Hz, 1 H), 2.06 (dd, J = 7.2, 10.2 Hz, 1 H), 2.17 (dd, J = 5.4, 17.7 Hz, 1 H), 2.54−2.65 (m, 1 H), 3.64 (s, 3 H), 4.20 (s, 2 H), 6.26 (s, 1 H), 7.24−7.31 (m, 3 H), 7.51−7.54 (m, 2 H); minor isomer δ 1.77 (s, 3 H), 1.99−2.11 (m, 1 H), 2.15−2.24 (m, 2 H), 2.47−2.61 (m, 1 H), 3.43 (s, 3 H), 4.35 (s, 2 H), 6.29 (s, 1 H), 7.32−7.39 (m, 3 H), 7.45−7.49 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): major isomer δ 20.4, 25.4, 26.9, 58.7, 70.8, 91.5, 114.0, 121.6, 128.4, 128.8, 129.1, 136.6, 162.5; minor isomer δ 20.6, 24.6, 29.6, 59.3, 67.5, 90.4, 113.5, 124.2, 129.0, 129.4, 129.6, 136.3, 161.7. IR (NaCl): 3066, 2921, 1767, 1440, 1387, 1369, 1217, 1085, 1024, 815, 750, 694 cm^{-1}. MS (EI): m/z 275 (M^+, 20). HRMS calcd for $C_{15}H_{17}NO_2S$ 275.0980, found 275.0984. Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.13; H, 6.65; N, 4.52.

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Supporting Information Available: UV−vis spectra of cyclohexyl isocyanide (**1c**) and 2,6-xylyl isocyanide (**1a**). This material is available free of charge via the Internet at http://pubs.acs.org.

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