Doctoral Dissertation

Development of the Catalytic Reactions of Organochalcogen Compounds with Allenes and Isocyanides

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January 2015

Department of Applied Chemistry,
Graduate School of Engineering,
Osaka University

Development of the Catalytic Reactions of Organochalcogen Compounds with Allenes and Isocyanides

有機カルコゲン化合物と
アレンおよびイソシアニドとの触媒反応の開発

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Preface

The study described in this thesis has been carried out (2009-2015) under the direction of Professor Nobuaki Kambe at Department of Applied Chemistry, Graduate School of Engineering, Osaka University. The objective of this thesis is concerned with studies on the developments of catalytic reactions of organochalcogen compounds such as chalcogenocarbamates and sulfenamides with allenes and isocyanides via cleavage of carbon-chalcogen bond and nitrogen sulfur bond using palladium and Lewis acid catalysts.

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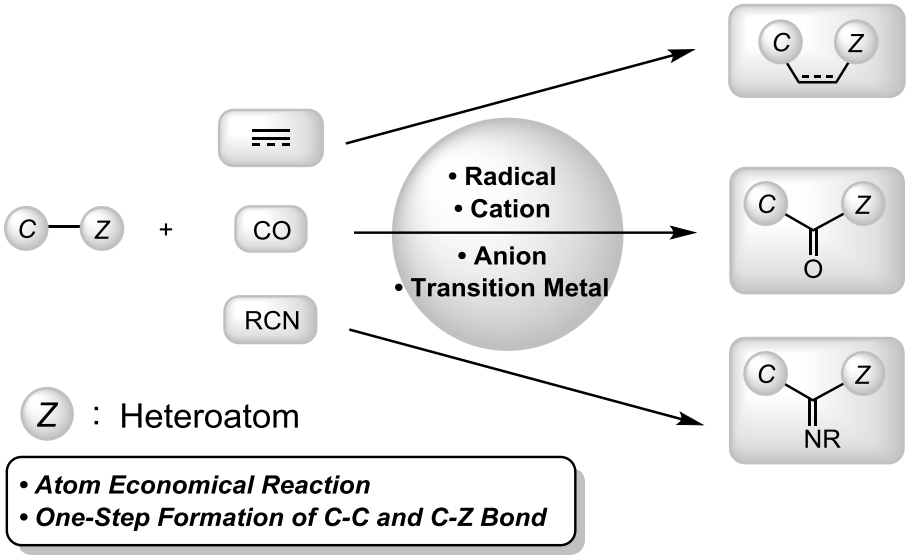
Contents

General Introduction

Insertion reaction of an unsaturated organic molecule into a carbon-heteroatom bond is synthetically very useful transformation since a new carbon-carbon bond is constructed and heteroatom functionality is introduced in one step with high atom efficacy. A number of insertion reactions have been accomplished by the use of transition metal catalysts or under radical, cationic or anionic conditions (Figure 1).

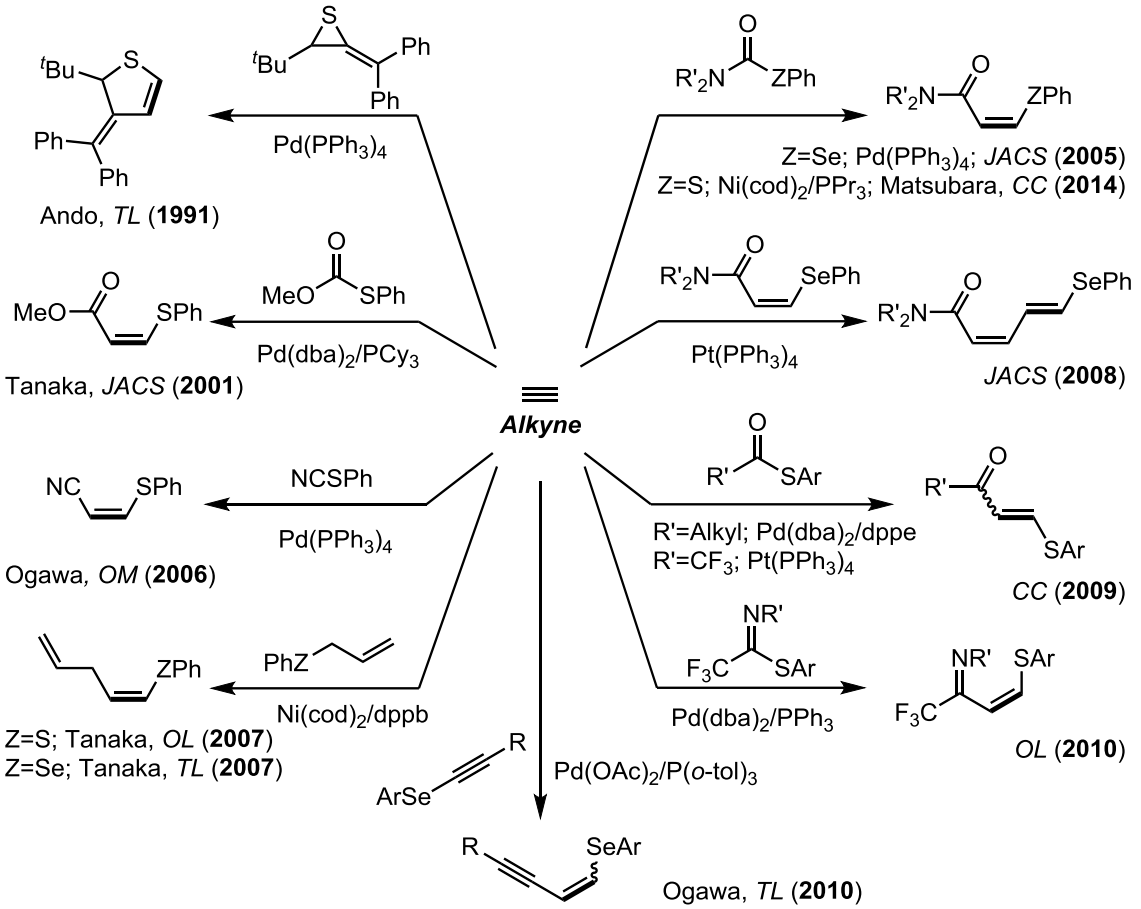
Figure 1. Insertion reactions via cleavage of carbon-heteroatom bonds.



Many research groups including our group have focused on the utilization of chalcogen atoms[1] and have developed a variety of insertion reactions of unsaturated organic molecules into carbon-chalcogen bonds of organochalcogen compounds.[2]

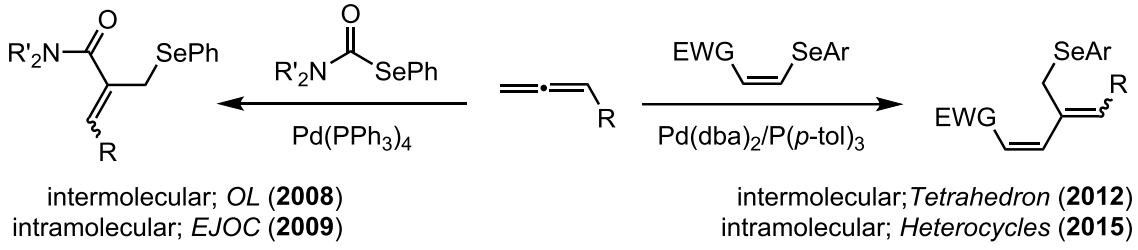
Among them, transition metal-catalyzed insertion reactions of alkynes into carbon-chalcogen bonds of organochalcogen compounds have been most energetically investigated[3] (Scheme 1). Bold lines in the corresponding products represent the parts of generating olefins derived from alkynes. Ando's group has reported the pioneering work in 1991,[3a] and many other research groups have developed several types of addition reactions. Our group has also disclosed palladium-catalyzed carbothio-[3h,3j] and selenation[3c] or platinum-catalyzed vinylselenation[3g] of alkynes with high regio- and stereoselectivity.

Scheme 1. Transition metal-catalyzed insertion of alkynes into organochalcogen compounds.



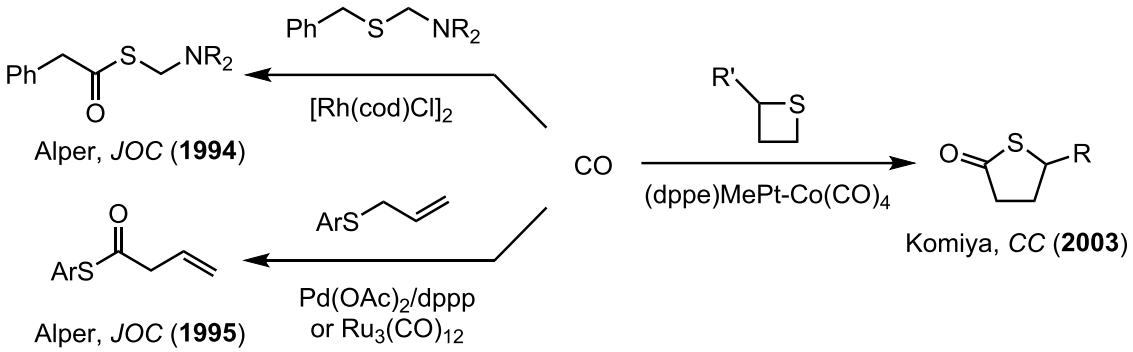
Insertion reactions of allenes into carbon-chalcogen bonds of organochalcogen compounds have also been reported; however, the numbers of reports are much fewer than those of alkynes. Recently, our group has reported inter- and intramolecular regio- and stereoselective carbo- and vinylselenation of allenes (Scheme 2).[4]

Scheme 2. Transition metal-catalyzed addition of allenes to organochalcogen compounds.



Transition metal-catalyzed insertion reactions of carbon monoxide into carbon-chalcogen bonds of organochalcogen compounds have also been reported by Alper's and Komiya's groups (Scheme 3).[5]

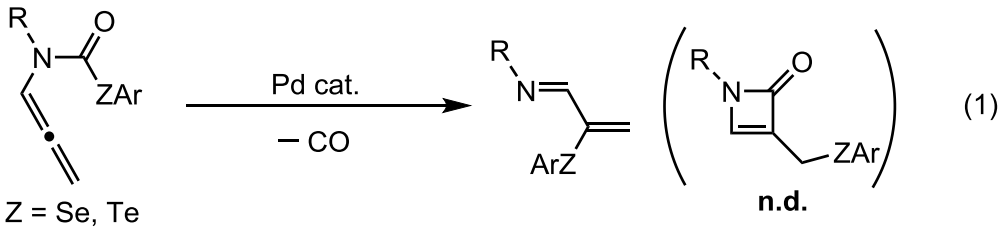
Scheme 3. Transition metal-catalyzed insertion of carbon monoxide into organochalcogen compounds.



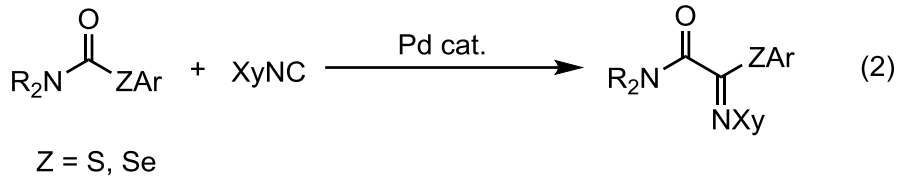
On the contrary, transition metal-catalyzed insertion reaction of isocyanides into carbon-heteroatom bonds has never been attained. Since imine derivatives, the expected products, have been employed as versatile building blocks for the syntheses of pharmacologically active compounds and natural products, the design of new catalytic insertion reactions of isocyanides will bring about productive outcomes.

Based on these backgrounds, the present study was performed aiming at development of new insertion reactions of allenes and isocyanides into carbon-chalcogen bonds and nitrogen-sulfur bonds of organochalcogen compounds. The following findings would be good representations showing great potential of organochalcogen compounds for various catalytic transformation in organic chemistry.

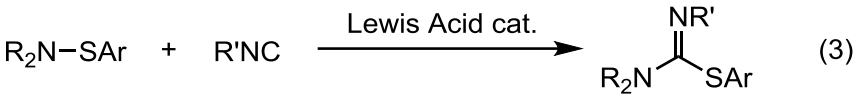
In chapter 1, palladium-catalyzed insertion of allenes into carbon-chalcogen bonds of chalcogenocarbamates was undertaken to prepare *α*,*β*-unsaturated four-membered lactams. As a result, unprecedented decarbonylative rearrangement of *N*-allenyl seleno- and tellurocarbamates proceeded giving rise to 1-azadienes (Eq. 1).



In chapter 2, palladium-catalyzed insertion reactions of isocyanides into thiocarbamates and selenocarbamates are developed (Eq. 2).



Finally, insertion reactions of isocyanides into nitrogen-sulfur bonds of sulfenamides in the presence of transition metal catalysts have been investigated. Although transition metal catalysts examined such as $Pd(PPh_3)_4$ and $Rh(PPh_3)_3Cl$ were not effective, Lewis acid catalysts exhibited high catalytic activities. Thus, in chapter 3, $AlCl_3$-catalyzed insertion of isocyanides into nitrogen-sulfur bonds of sulfenamides is described (Eq. 3).



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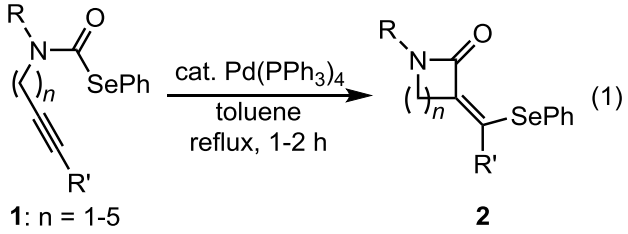
Chapter 1

Palladium-Catalyzed Decarbonylative Rearrangement of *N*-Allenyl Seleno- and Tellurocarbamates

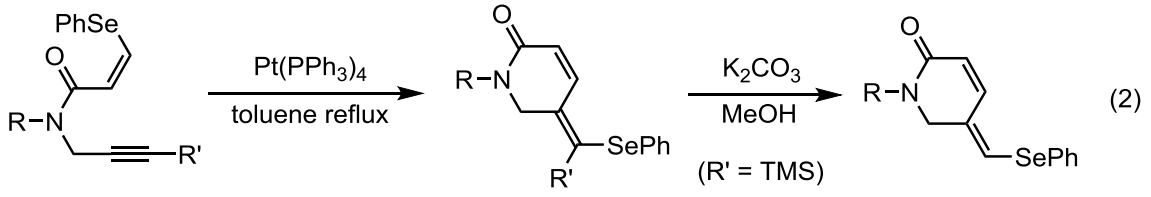
1-1 Introduction

Transition metal catalyzed addition of heteroatom-containing compounds to unsaturated hydrocarbons has been well exploited as one of the most straightforward methods for the introduction of heteroatom functionalities to organic molecules.[1] This transformation becomes more attractive and useful if carbon–carbon bonds can be created concomitantly with carbon–heteroatom bond formation. A promising approach to achieve this transformation is the insertion of an unsaturated carbon unit over a carbon–heteroatom bond. This type of transformation has been extensively explored using transition metal catalysts.[2] For example, it was reported that carbamoselenoates **1** having a terminal alkynyl moiety on the nitrogen atom underwent selenocarbamoylation of alkynes intramolecularly with high regio- and stereoselectivities to afford four- to eight-membered lactams **2** having an exocyclic double bond in high yields by the use of $Pd(PPh_3)_4$ as a catalyst (eq 1).[3]



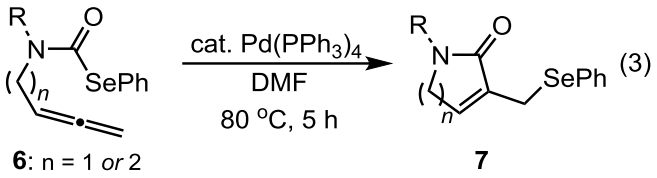
1: n = 1-5 **2**

The treatment of vinylselenides **3** having a alkynyl-methyl group on the nitrogen atom with $Pt(PPh_3)_4$ afforded six-membered lactam frameworks **4** or **5** having a dienone unit by *cis*-vinylselenation of alkynes (eq 2).[4]



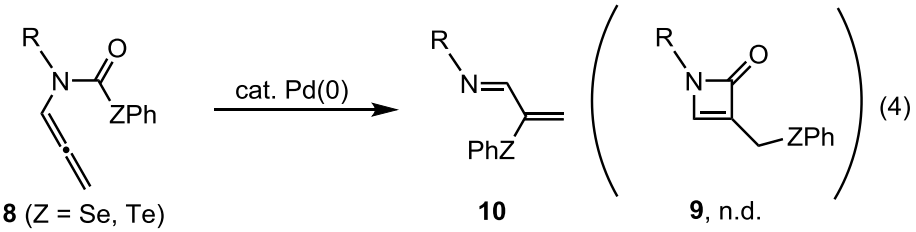
3 **4** **5**

Pd(0)-catalyzed selenocarbamoylation of allene, where carbamoselenoates **6** with a terminal allenyl group on the nitrogen atom afforded the corresponding *α,β*-unsaturated lactams **7** bearing an allylselenide moiety with perfect regioselectivity was also demonstrated (Eq. (3)).[5]



6: n = 1 *or* 2 **7**

In this chapter, the reaction of seleno- and tellurocarbamate **8** possessing an allenyl group on the nitrogen atom was examined and unexpectedly it was found that the decarbonylative rearrangement occurred, giving rise to 1-azadienes **10** without the formation of a four-membered lactam **9** (Eq. (4)).

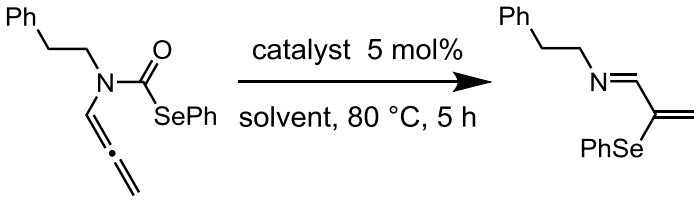


8 (Z = Se, Te) **10** **9**, n.d.

1-2 Results and Discussion

At first, the reaction of **8** was carried out under similar conditions as employed in Eq. (3). Thus, when a toluene solution containing selenocarbamate **8a** and $Pd(PPh_3)_4$ (5 mol%) was heated at 80 °C for 5 h, 1-azadiene **10a** was obtained in 36% yield (Table 1, entry 1). $Ni(cod)_2$ and $Pt(PPh_3)_4$ were also effective as a catalyst albeit in lower yields (entries 2 and 3). The use of aprotic and polar solvents such as CH_3CN, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) afforded the product in better yields. Among them, DMF gave the best yield of 58% (entries 4–8). In all entries, diphenyl diselenide and several unidentified compounds were detected as by-products.

Table 1. Reaction of **8a** with Group 10 metal complexes in various solvents.



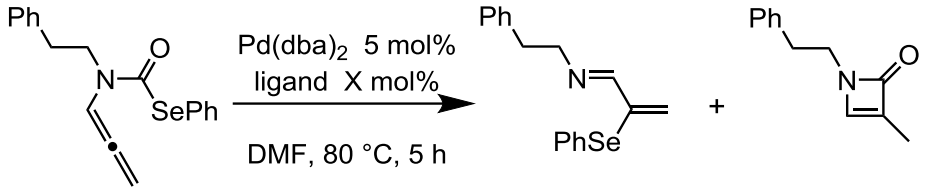
8a **10a**

entry	catalyst	solvent	conv. (%)[a]	yield (%)[a]
1	$Pd(PPh_3)_4$	toluene	77	36
2	$Ni(cod)_2$	toluene	>95	28
3	$Pt(PPh_3)_4$	toluene	17	<5
4	$Pd(PPh_3)_4$	CH_3CN	>95	53
5	$Pd(PPh_3)_4$	DMF	>95	58
6	$Pd(PPh_3)_4$	DMSO	92	52
7	$Pd(PPh_3)_4$	dioxane	63	33
8	$Pd(PPh_3)_4$	EtOH	77	20

[a] ^{1}H NMR yield.

In Table 2, results obtained using monodentate and bidentate phosphine ligands were summarized. Triarylphosphines bearing electron-donating or -withdrawing groups afforded similar results (entries 1–3). Monodentate alkyl phosphines and phosphites were not effective for the synthesis of 1-azadiene **10a** (entries 4–8). Interestingly, a four-membered lactam **11**, not incorporating selenium, was obtained as the major product when $PPhMe_2$ was employed (entry 5). To suppress decarbonylation, the reaction was performed under pressurized carbon monoxide (20 atm); however, the yield of lactam **11** was not improved (entry 6). The use of electron-rich and sterically less hindered phosphine ligands tends to favor the lactam formation. However, PCy_3 gave nearly 1:1 mixture of **10a** and **11**, indicating that selectivity of products cannot be simply explained (entry 7). Bidentate ligands such as 1,4-bis(diphenylphosphino)butane (dppb) and 1,2-bis(diphenylphosphino)ethane (dppe) afforded only azadiene **10a** like PPh_3 (entry 1) in a similar manner with lower yields, respectively (entries 1, 9, 10). Both 1,5-bis(diphenylphosphino)pentane (dppen) and 1,6-bis(diphenylphosphino)hexane (dpphex) gave mixtures of **10a** and **11** with nearly 3:1 and 2:1 ratio, respectively, as in the case of PPh_2Me probably due to the flexible tether chains (entries 4, 11, 12). On the contrary, when 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP) was employed, 3-seleno-1-azadiene **10a** was obtained in 88% yield (entry 13). Although it is unclear yet why BINAP can promote this reaction efficiently, the formation of by-products was largely suppressed. From the results in entries 9–14, the yields of azadiene **10a** do not seem to have simple correlation with bite angles of bidentate phosphines.[6]

Table 2. Pd-catalyzed rearrangement of **8a** using various ligands.



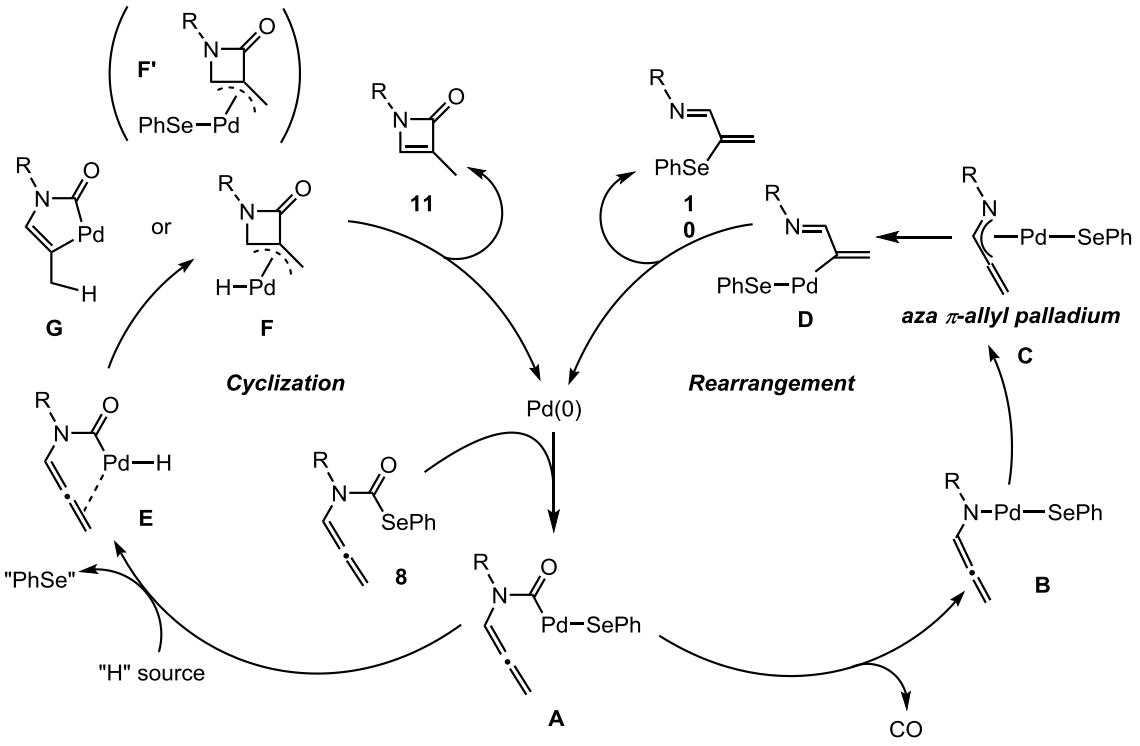
8a **10a** **11**

entry	ligand	X	**10a** (%)[a]	**11** (%)[a]	angle[b]
1	PPh_3	10	47	--	145
2	$P(C_6H_4$-*p*-$MeO)_3$	10	53	5	145
3	$P(C_6H_4$-*p*-$CF_3)_3$	10	51	--	145
4	PPh_2Me	10	23	12	136
5	$PPhMe_2$	10	<5	30	122
6[c]	$PPhMe_2$	10	6	36	122
7	PCy_3	10	17	15	170
8	$P(OEt)_3$	10	48	--	109
9	dppe	5	26	--	86
10	dppb	5	45	--	94
11	dpppen	5	51	18	
12	dpphex	5	19	12	
13	*rac*-BINAP	5	88 (79)	--	93
14	DPEphos	5	61	--	104

[a] ^{1}H NMR yield (Isolated yield). [b] Cone angles (entry 1~8) and bite angles (entry 9~14). [c] Reaction was carried out under 20 atm CO.

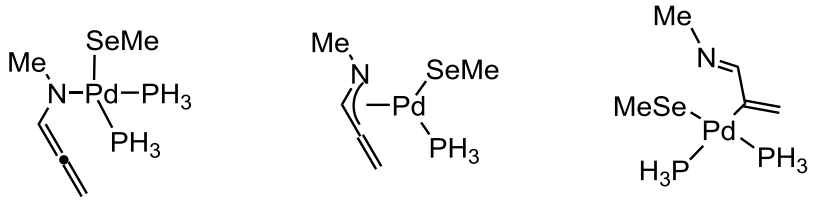
Plausible reaction pathways for the formation of 1-azadiene **10** and lactam **11** are depicted in Scheme 1. In the formation of 1-azadiene **10a** (right-hand side), the first step would be oxidative addition of the carbamoyl carbon–selenium bond of selenocarbamate **8a** to palladium to generate a NC(O)–Pd–Se unit affording intermediate **A**. Since no methylene chain exists between the nitrogen atom and the allenyl group in **A**, coordination of the terminal double bond of the allenyl group to palladium is sterically difficult. Thus decarbonylation may occur to give intermediate **B**. Azadiene **10a** may be obtained by reductive elimination of **D**, generated from **B** via aza-π-allylpalladium intermediate **C**. The formation of aza-π-allylpalladium is suggested in the literatures.[7]

Scheme 1. A Plausible Reaction Pathway.

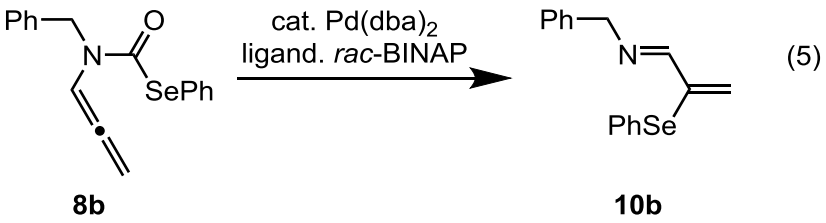


As for the formation of the lactam **11** (left-hand side), the SePh group of oxidative adduct **A** would be replaced with the hydrogen atom leading to **E**. The allene part of **E** then undergoes carbo- or hydropalladation giving **F** or **G**, and the following reductive elimination would afford lactam **11**. Although the formation of diphenyl diselenide was confirmed, all attempts to identify the hydrogen source failed unfortunately. Another possible pathway via intermediate **9** formed by intramolecular cyclization of **A** may not likely because deselenation did not proceed when the similar *α,β*-unsaturated lactams **7** bearing an allylselenide moiety were treated with $Pd(PPh_3)_4$.[5a] The formation of π-allylpalladium intermediate **F'** from **A** leading to **F** via reductive deselenation cannot be ruled out. DFT calculations[8] were performed to get information on the rearrangement pathways. These calculations were carried out using the Gaussian 09W set of programs with the B3LYP functional, the 6-31+G(d) basis set for all nonmetallic atoms (H, C, O, N, P), and the LANL2DZ basis set for Pd and Se. In Fig. 1, **B'**, **C'**, and **D'** are the model compounds for possible intermediates **B**, **C**, and **D** in Scheme 1. Although aza-π-allylpalladium complex **C'** was not optimized as a stable structure, complex **D'** was found to be 19.2 kcal/mol more stable than complex **B'**. This result may reflect the difference of bond dissociation energies between C–Pd and N–Pd bonds.[9] Although the bond dissociation energy of the N–Pd bond is unknown, the C–Pt bond is about 49 kcal/mol more stable than the N–Pt bond. From these results, it is proposed that the relative stability of **D'** over **B'** would be the driving force of decarbonylation and rearrangement, and the rearrangement from **B'** to **D'** may proceed through an aza-π-allylpalladium complex **C'**.

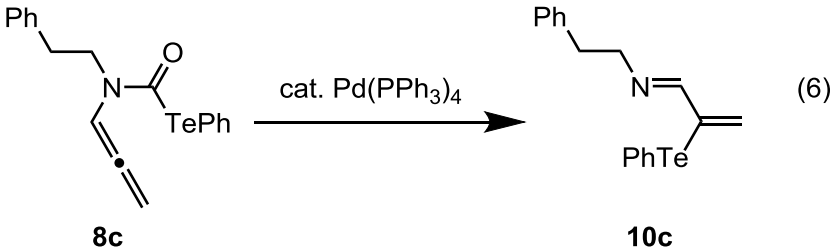
Figure 1. DFT calculations of the model compounds.



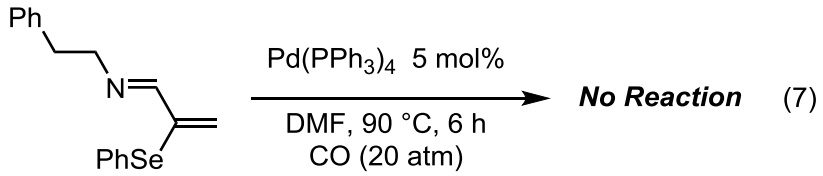
Next, carbamoselenoate **8b** bearing a benzyl group on the nitrogen was employed as a substrate. When **8b** was treated under similar reaction conditions, a decarbonylative rearrangement also proceeded giving rise to 3-seleno-1-azadiene **10b** in 47% yield (Eq. (5)). ^{1}H NMR of the crude mixture of the reaction using a selenocarbamate having a phenyl group on the nitrogen suggested that the corresponding 1-azadiene was formed in 37%; however, isolation of this product was not successful because it was hydrolyzed during purification.



In addition, this transformation also proceeded when a tellurium analogue was used (Eq. (6)). The corresponding 1-azadiene **10c** was obtained in 49% yield from tellurocarbamate **8c**.



When 1-azadiene **10a** was allowed to react with CO (20 atm) in the presence of $Pd(PPh_3)_4$, **10a** was remained unchanged (Eq. (7)). This result indicates that the reverse process does not exist in this transformation.



Decarbonylation is frequently encountered in transition metal mediated reactions of carbonyl compounds. This decarbonylation usually occurs from intermediates having a structure of R–C(O)–M, generated by oxidative addition of acid halides, aldehydes, etc.[10] Transition metal catalyzed decarbonylation of esters, thioesters, acylstannanes, and phthalimides has also reported been and is considered to proceed through oxidative adducts having the R–C(O)–M structure.[11] To the best of my knowledge, decarbonylation from the carbamoyl–metal unit (R_2N–C(O)–M) has never been reported.

1-3 Conclusions

In summary, the decarbonylative rearrangement proceeded by the treatment of an *N*-allenyl seleno- and tellurocarbamates **8** with the palladium catalyst to give a 3-seleno or 3-telluro-1-azadiene **10**, in which the use of *rac*-BINAP as a ligand afforded the highest yield. This transformation involves unusual decarbonylation from carbamoyl-Pd units. In addition, a four-membered lactam **11** incorporating no chalcogen atom was obtained as a major product in moderate yields by using $PPhMe_2$ as the ligand.

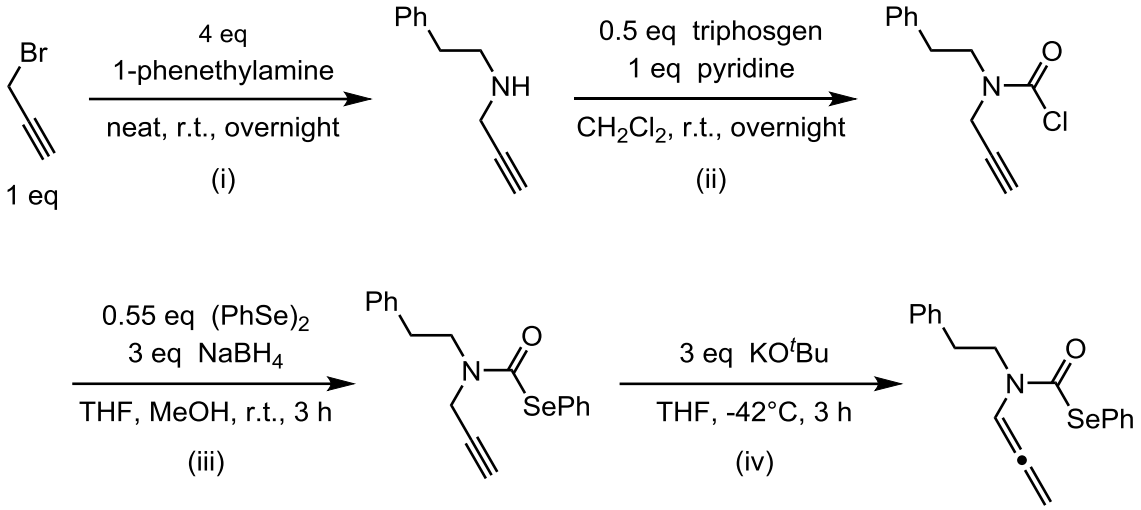
1-4 Experimental Section

General Comments

^{1}H NMR and ^{13}C NMR spectra were recorded with a JEOL JNM-Alice 400 (400 and 100 MHz, respectively) spectrometer using $CDCl_3$ as solvents and using Me_4Si as an internal standard. Chemical shifts were reported in parts per million (δ) downfield from internal tetramethylsilane. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, brs = broad singlet, m = multiplet, c = complex), coupling constant (Hz), integration. Infrared spectra (IR) were obtained on a JASCO Corporation FT/IR-4200 instrument equipped with ATR PRO450-S. Infrared spectra were recorded with a JASCO Corporation FT/IR-4200 instrument. Both conventional and high-resolution mass spectra were recorded with a JEOL JMS-DX303HF spectrometer (EI) or JEOL JMS-T100TD (DART). HPLC separations were performed on a recycling preparative HPLC (Japan Analytical; Model LC-908) equipped with JAIGEL-1H and -2H columns (GPC) using $CHCl_3$ as an eluent. 1-Phenethylamine, diphenyl diselenide (Sigma-Aldrich, Tokyo, Japan), diphenyl ditelluride, propargyl bromide, triphosgen (Tokyo Chemical, Tokyo, Japan), pyridine, sodium

borohydride (Kishida Chemical, Osaka, Japan), potassium *tert*-butoxide (Nacalai Tesque, Kyoto, Japan), and dehydrated solvents (Wako Pure Chemical, Osaka, Japan) were purchased and used as received.

Synthesis of Selenocarbamate 8a



1) A-30 mL three-necked flask with a magnetic stirrer and a 100-mL dropping funnel were dried with a heat gun at 120°C and then purged with N_2. After cooling to room temperature, 1-phenethylamine (120 mmol) was placed in the flask, 1-propargyl bromide (30 mmol) was added in the dropping funnel, and the flask was cooled in an ice bath. The solution in the funnel was added into the flask dropwise, and the reaction mixture was stirred overnight at room temperature. After the mixture was poured into NaOH (1 M) and extracted with Et_2O (30 mL × 2), the combined organic phase was dried with $MgSO_4$. The solvents were removed in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane / EtOAc = 4:3, Rf = 0.3) to afford *N*-phenethyl-*N*-propa-2-ynylamine (82%).
2) A-200 mL three-necked flask with a magnetic stirrer and a 100-mL dropping funnel were dried with the heat gun at 120°C and then purged with N_2. Into a flask, triphosgen (12.3 mmol) and CH_2Cl_2 (60 mL) were placed under N_2. After cooling in an ice bath, pyridine (24.6 mmol) was added carefully. To the solution, *N*-phenethyl-*N*-prop-2-ynylamine (24.6 mmol) was then added dropwise in CH_2Cl_2 (60 mL) from the funnel. After the mixture was warmed up to room temperature, the stirring was continued overnight. After the mixture was poured into HCl (1 M) and extracted with CH_2Cl_2 (50 mL × 2), the combined organic phase was dried with $MgSO_4$. The solvents were removed in *vacuo*, and the black product was used in the next process without purification.

   Caution: Triphosgen decomposes slightly to generate highly poisonous phosgene in air. All operation should be carried out in a well-ventilated hood.

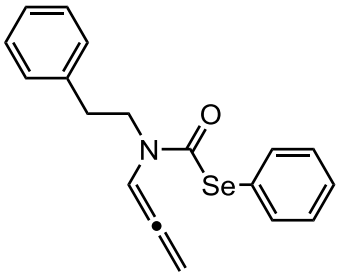
3) A-300 mL three-necked flask with a magnetic stirrer and a 50-mL dropping funnel were dried with the heat gun at 120°C and then purged with N_2. Into a 300-mL flask, diphenyl diselenide (5.5 mmol), sodium borohydride (30 mmol), and THF (50 mL) were placed under N_2 and the suspension was cooled to 0°C. After methanol (4 mL) was added slowly, vigorous bubbling was occurred. After the color changed from pale yellow to white (about 30 min), *N*-phenethyl-*N*-prop-2-ynylcarbamoyl chloride (10 mmol) in THF (60 mL) was added at the room temperature, and the mixture was stirred for 3 h. After the mixture was poured into brine (50 mL) and extracted with Et_2O (50 mL × 2), the combined organic phase was dried with $MgSO_4$. The solvents were removed in *vacuo*, and the residue was purified by silica gel column chromatography (*n*-hexane / Et_2O = 2:1, Rf = 0.5) to afford *Se*-phenyl *N*-phenethyl-*N*-propa-2-ynylcarbamoselenoate (83%).

4) A-50 mL two-necked flask with a magnetic stirrer was dried with the heat gun at 120°C and then purged with N_2. Into a 50-mL flask, *Se*-phenyl *N*-phenethyl-*N*-propa-2-ynyl carbamoselenoate (8.29 mmol) and THF (50 mL) were placed and the suspension was cooled to –42°C (CH_3CN/dry ice bath). Into the flask, potassium *tert*-butoxide (1.66 mmol) was added at the same temperature and the mixture was stirred for 3 h. After the potassium *tert*-butoxide was filtered with celite and Et_2O, the mixture was poured into brine (30 mL) and extracted with Et_2O (30 mL × 2), the combined organic phase was dried with $MgSO_4$. The solvents were removed in *vacuo*, and the residue was purified by GPC to afford ***Se*-phenyl *N*-phenethyl-*N*-propa-1,2-dien-1-yl carbamoselenoate 8a** (60%).

$Pd(dba)_2$/*rac*-BINAP-Catalyzed Decarbonylative Isomerization of 8a:

A 5-mL reaction flask equipped with a reflux condenser was dried with the heat gun at 120°C and then purged with N_2. After cooling to room temperature, $Pd(dba)_2$ (0.02 mmol), *rac*-BINAP (0.02 mmol), DMF (1.0 mL), and **8a** (0.4 mmol) were placed in the flask and added to the resulting black solution. The reaction mixture was heated in an oil bath at 80°C for 5 h. After cooling to room temperature, the volatiles were removed in *vacuo*. After the yield of 1-azadiene **10a** was determined by ^{1}H NMR spectroscopy with 3-pentanone as an internal standard, **10a** was purified with GPC (79%).

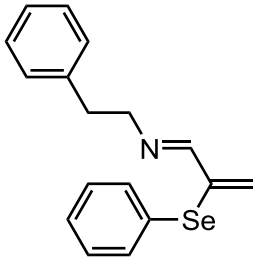
***Se*-phenyl *N*-phenethyl-*N*-propa-1,2-dien-1-yl carbamoselenoate 8a**:



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.94 (td, *J* = 7.5 Hz, 26.8 Hz, 2 H), 3.68 (td, *J* = 7.8 Hz, *J* = 14.4 Hz, 2 H), 5.47 (dd, *J* = 6.0 Hz, 12.9 Hz, 2 H), 6.65, (s, 1H), 7.19–7.59 (m, 10H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.7, 34.5, 48.8, 87.0, 87.9, 98.9, 99.7, 125.9, 128.4, 128.6, 128.8, 129.1, 136.6 (J_{Se-C} = 5.8 Hz), 137.9, 138.4, 163.1, 202.0 ppm. IR (NaCl) 3037, 2968, 2939, 2359, 1955, 1713, 1670 (C=O), 1441, 1382, 1257, 1245, 1139, 1001, 874, 732, 694, 687, 672, 607,

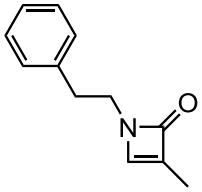
561 cm^{-1}; MS (EI) m/z (relative intensity, %) 343 (M+, 5), 315 (8), 234 (34), 224 (9), 186 (6), 157 (14), 130 (7), 105 (100); Anal. Calcd for $C_{18}H_{17}NOSe$: C, 63.16; H, 5.01; N, 4.09, Found C, 62.98; H, 4.83; N, 4.15.

(*E*)-*N*-Phenetyhyl-2-(phenylselanyl) prop-2-en-1-imine (10a):



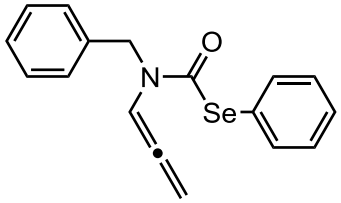
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.98 (t, *J* = 7.6 Hz, 2 H), 3.80 (t, *J* = 7.6 Hz, 2 H), 5.21 (s, 1 H), 5.89 (s, 1 H), 7.18–7.69 (m, 10 H), 7.85 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.3, 62.2, 121.8, 128.3, 128.4, 128.8, 129.0, 129.0, 129.5, 130.5, 137.2 (J_{Se-C} = 5.3 Hz), 139.7, 143.3, 161.1 ppm. IR (NaCl) 3055, 3027, 2921, 1649, 1624 (C N), 1592, 1574, 1495, 1448, 1338, 1189, 1092, 981, 885, 757, 694, 629, 556 cm–1; MS (EI) m/z (relative intensity, %) 315 (M^+, 15), 234 (100), 224 (22), 210 (11), 195 (14), 157 (33); Anal. HRMS (EI) calcd for $C_{17}H_{17}NSe$: 315.0526, Found 315.0528.

3-Methyl-1-phenethylazet-2(1*H*)-one (11):



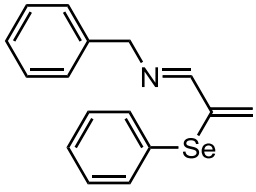
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3 H), 2.85 (t, *J* = 8.0 Hz, 2 H), 3.68 (dd, *J* = 2.7 Hz, 5.0 Hz, 2 H), 6.06 (s, 1 H), 7.15–7.65 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 34.1, 51.0, 126.1, 126.4, 126.5, 127.1, 127.6, 128.6, 128.6, 128.7, 128.7, 128.7, 128.8, 128.9, 128.9, 129.0, 129.1, 129.2, 129.5, 135.2, 136.3, 136.3, 136.7, 138.3, 139.7, 165.0 ppm.

***Se*-Phenyl *N*-benzyl-*N*-propa-1,2-dien-1-yl carbamoselenoate (8b)**:



The corresponding analogue **8b** was prepared in a similar procedure as described for **8a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.73 (s, 2 H), 5.33 (d, *J* = 17.2 Hz, 2 H), 6.64 (s, 1 H), 7.25–7.45 (m, 8 H), 7.57–7.65 (m, 2 H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.2, 50.4, 87.2, 88.3, 99.5, 99.7, 126.7, 127.5, 128.1, 128.4, 128.6, 128.8, 129.2, 129.5, 129.9, 135.6, 136.0, 136.7 (J_{Se-C} = 5.3 Hz), 136.7, 163.9, 164.2, 202.3, 202.9 ppm. IR (NaCl) 3059, 2373, 2323, 1955, 1667 (C=O), 1578, 1496, 1475, 1439, 1378, 1295, 1251, 1173, 1098, 1073, 1022, 960, 878, 737, 688 cm^{-1}; MS (EI) m/z (relative intensity, %) 329 (M^+, 2), 301 (5), 238 (2), 220 (14), 172 (4), 157 (5), 91 (100). Anal. HRMS (EI) calcd for $C_{17}H_{15}NOSe$: 329.0319, Found. 329.0320.

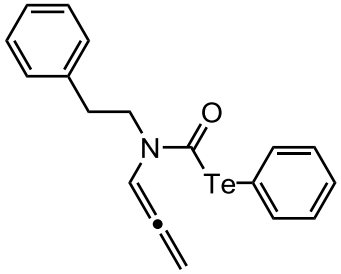
(*E*)-*N*-benzyl-2-(phenylselanyl) prop-2-en-1-imine (10b):



^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.80 (s, 2 H), 5.27 (s, 1 H), 5.97 (s, 1 H), 7.24–7.44 (m, 8 H), 7.60–7.69 (m, 2 H), 8.05 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.6, 122.2, 126.7, 127.0, 127.9, 128.5, 128.6, 128.8, 129.5, 137.2 (J_{Se-C} = 5.3 Hz), 138.7, 143.8, 161.5 ppm. IR (NaCl) 3059, 3028, 2848, 1953, 1632 (C=N), 1584, 1494, 1475, 1452, 1437, 1346, 1301,

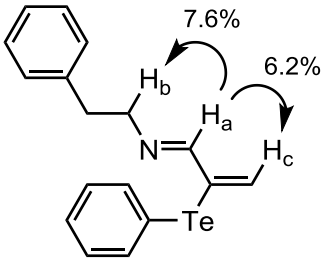
1230, 1156, 1065, 1022, 999, 960, 889, 845, 819, 736, 692 cm^{-1}; MS (EI) m/z (relative intensity, %) 301 (M^+, 21), 220 (92), 183 (4), 157 (6), 144 (14), 130 (23), 104 (18), 91 (100); Anal. HRMS (EI) calcd for $C_{16}H_{15}NSe$: 301.0370, Found. 301.0371.

***Te*-Phenyl *N*-phenethyl-*N*-propa-1,2-dien-1-yl carbamotelluroate (8c)**:



The corresponding tellurium analogue **8c** was prepared in a similar procedure as described for **8a**. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.87 (t, *J* = 7.8 Hz, 2 H), 2.99 (t, *J* = 7.8 Hz, 2 H), 3.49 (t, *J* = 7.8 Hz, 2 H), 3.74 (t, *J* = 7.8 Hz, 2 H), 5.38–5.40 (m, 2 H), 5.51–5.53 (m, 2 H), 6.24–6.27 (m, 2 H), 7.17–7.41 (m, 16 H), 7.72–7.90 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.1, 35.0, 48.9, 50.4, 86.5, 87.6, 98.0, 100.2, 114.2, 114.9, 126.4, 126.9, 128.5, 128.8, 128.9, 129.0, 129.1, 129.4, 137.8, 138.4, 140.4, 140.5, 155.6, 156.3, 202.2, 203.4 ppm. IR (NaCl) 3055, 3026, 2938, 1656 (C=O), 1435, 1376, 1246, 1141, 999, 733, 699 cm^{-1}; MS (EI) m/z (relative intensity, %) 393 (M^+, 4), 365 (13), 234 (14), 207 (15), 186 (22), 144 (27), 105 (100); Anal. Calcd for $C_{18}H_{17}NOTe$: C, 55.30; H, 4.38; N, 3.58, Found C, 55.02; H, 4.16; N, 3.54.

(*E*)-*N*-phenethyl-2-(phenyltellanyl) prop-2-en-1-imine (10c):



^1H NMR (400 MHz, $CDCl_3$): δ 2.95 (t, *J* = 7.3 Hz, 2 H), 3.78 (t, *J* = 6.8 Hz, 2 H), 5.46 (s, 1 H), 6.38 (s, 1 H), 7.18–7.41 (m, 8 H), 7.73 (s, 1 H), 7.88–7.90 (m, 2 H) ppm. Nuclear Overhauser effect experiment; irradiation at δ 7.73 (H_a) resulted in 7.6% enhancement of signal at δ 3.78 (H_b) and 6.2% enhancement of signal at δ 6.38 (H_c); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2, 61.4, 112.9, 126.1, 127.9, 128.3, 128.6, 129.1, 129.5, 133.4, 139.8, 141.7, 162.9 ppm. IR (NaCl) 3026, 2925, 2840, 1629 (C=N), 1585, 1433, 901, 735, 696 cm^{-1}; MS (EI) m/z (relative intensity, %) 365 (M^+, 31), 274 (15), 234 (44), 207 (44), 144 (100); Anal. HRMS (EI) calcd for $C_{17}H_{17}NTe$: 365.0423, Found 365.0419.

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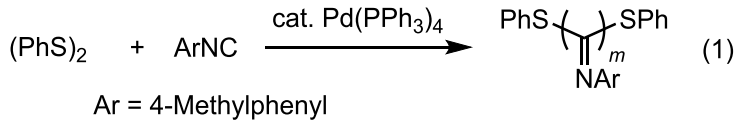
Chapter 2

Palladium-Catalyzed Insertion Reactions of Isocyanides into Thiocarbamates and Selenocarbamates

2-1 Introduction

The transition-metal-catalyzed insertion of an unsaturated organic molecule into a carbon-heteroatom bond is one of the most straightforward and atom-economical methods for the synthesis of heteroatom compounds with the concomitant extension of the carbon skeleton. However this transformation is difficult to achieve efficiently in comparison to similar insertion reactions involving heteroatom-heteroatom bonds[1] or heteroatom-hydrogen bonds.[2] This is due, in part, to fact that the cleavage of carbon-heteroatom bonds by the oxidative addition to transition metals is not as efficient as the reaction of heteroatom-heteroatom and heteroatom-hydrogen bonds. Unsaturated compounds that have been employed in such transformations include alkynes, allenes, carbon monoxide, isocyanides, etc. Among them, the insertion of alkynes into carbon-heteroatom bonds (C-Z, Z = Si, Sn, P, S, Se, etc.)[3] has been exploited extensively as a two carbon homologation reaction during the past two decades. Recently, several examples of the insertion of allenes into carbon-heteroatom bonds have been reported.[4]

Carbon monoxide has been utilized as a one-carbon homologating agent for introduction into C-O, C-N and C-S bonds giving rise to lactones, lactams, thioesters, thiolactones, etc.[5] Similarly several examples of the insertion of an isocyanide into heteroatom compounds are available,[6-9] whereas transition-metal-catalyzed reactions have been limited to the following two examples. Ito and co-workers reported on the Pd-catalyzed disilylation of isocyanides with $Me_3SiSiMe_3$.[10] Kurosawa and co-workers revealed the reaction of a disulfide with an isocyanide in the presence of a Pd catalyst to give 1:1, 1:2, and 1:3 addition products (*m* = 1-3) (eq 1).[11]



(1)

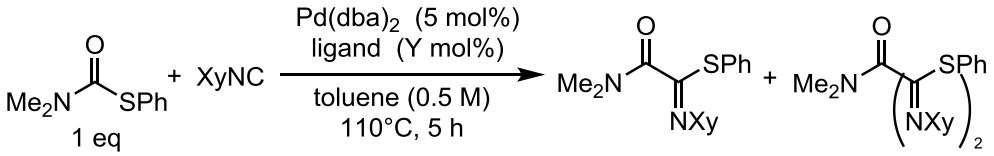
In addition, the analogous insertion of isocyanides into carbon-heteroatom bonds has never been attained. Herein, the first example of the palladium-catalyzed insertion of isocyanides **2** into carbon-sulfur and carbon-selenium bonds of thio- or selenocarbamates **1** or **5** giving rise to the 1,1-insertion products **3** or **6**, respectively, with high selectivities is described.

2-2 Results and Discussion

The reaction of a thiocarbamate (**1a**, $Me_2NC(O)SPh$) with an isocyanide **2a** was initially

examied. When a toluene solution (0.8 mL) containing 2,6-xylyl isocyanide (**2a**) (0.4 mmol), **1a** (0.4 mmol), $Pd(dba)_2$ (5 mol%) and PPh_3 (10 mol%) was heated at reflux for 5 h, the insertion product, amino 2-oxoethanimidothioate **3a**, was obtained in 32% yield (Table 1, entry 1). Unlike the reaction with a disulfide shown in eq 1, this reaction is selective and the possible 1:2 addition product **4a** was formed in only 1% yield and other multiple insertion products such as 1:3 addition products were not detected. The reaction using other monodentate and bidentate phosphine ligands was examined and the results are summarized in Table 1. The use of a triarylphosphine bearing an electron donating group, trialkylphosphine, and phosphite afforded similar results as PPh_3 (entries 1, 2, 4 and 5), however, a triarylphosphine derivative containing an electron-withdrawing CF_3 group was not a suitable ligand (entry 3). Bidentate tetraphenylbisphosphine ligands with a different tether unit afforded **3a** in similar yields (entries 7-10), but the use of an analogous tetracyclohexylbisphosphine resulted in a decreased product yield (entry 11).

Table 1. Pd-catalysed insertion of an isocyanide to **1a** using various ligands.



1a **2a** **3a** **4a**

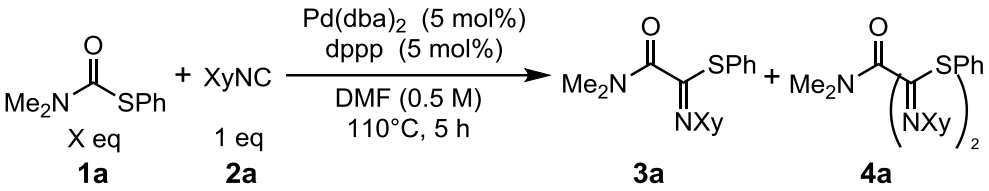
entry	ligand	Y	conv. of **1a** (%)[a]	conv. of **2a** (%)[a]	yield of **3a** (%)[a]	yield of **4a** (%)[a]
1	PPh_3	10	42	57	32	1
2	P(*p*-tolyl)$_3$	10	39	51	35	n.d.
3	P(*p*-CF_3-C_6H_4)$_3$	10	20	60	18	2
4	PCy_3	10	53	57	32	5
5	$P(OEt)_3$	10	51	70	45	n.d.
6	dppe	5	17	40	6	n.d.
7	dppp	5	66	75	60	n.d.
8	dppb	5	54	87	54	1
9	dpppen	5	63	84	55	5
10	dpphex	5	44	53	40	6
11	dcypp [b]	5	38	58	27	n.d.
12[c]	dppp	5	74	100	61	n.d.

[a] Determined by GC, and the yields are based on **2a**. [b] dppe: 1,2-bis(diphenylphosphino)ethane; dppp: 1,3-bis(diphenylphosphino)-propane; dppb: 1,4-bis(diphenylphosphino)butane; dpppen: 1,5-bis(diphenylphosphino)pentane; dpphex: 1,6-bis(diphenylphosphino)hexane; dcypp: 1,3-bis(dicyclohexylphosphino)propane.
[c] DMF was employed as a solvent.

When DMF was employed as a solvent, the isocyanide **2** was completely consumed, but the yield of **3a** was not improved (entries 7 and 12). It can be postulated that the oxidative addition of the carbon-sulfur bond of the desired product **3a** towards Pd might proceed in DMF and this further reaction resulted in the loss of the product **3a**. Thus, the reaction using excess amounts of the thiocarbamate **1a** was conducted to suppress the further reaction of **3a**

and the results are shown in Table 2. As expected, the use of an excess of **1a** improved the yields, and **3a** was obtained in 87% yield when 2.5 equiv of **1a** was employed in the reaction (entry 3). The product **3a** was isolated as a single stereoisomer by column chromatography and the *Z*-configuration with respect to C=N double bond was confirmed by X-ray analysis.

Table 2. Screening of the amount of thiocarbamate **1a**.



entry	X	conv. of **1a** (%)[a]	conv. of **2a** (%)[a]	yield of **3a** (%)[a]	yield of **4a** (%)[a]
1	1	74	100	61	n.d.
2	2	41	100	72	n.d.
3	2.5	35	100	87(83[b])	2
4	3	30	100	74	n.d.

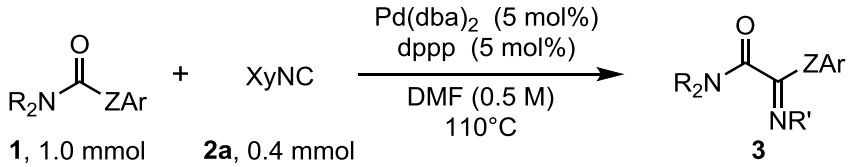
[a] Determined by GC based on **2a**. [b] Isolated yield.

This insertion reaction was carried out using several different thio- and selenocarbamates under the same conditions and the results are given in Table 3. The *N*,*N*-diethylthiocarbamate **1b** and morpholinocarbothioate **1c** also afforded the corresponding amino 2-oxoethanimidothioates **3b** and **3c** in high yields (entries 1 and 2). The thiocarbamate **1d** containing a bulkier diisopropyl amino group yielded the product in good yield (entry 3). However, the presence of a phenyl group(s) on the nitrogen led to lower yields (entries 4 and 5).

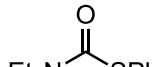
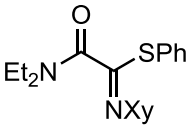
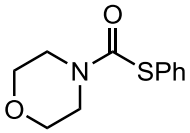
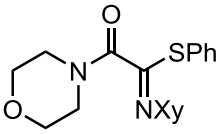
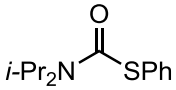
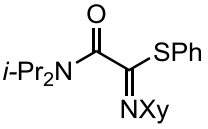
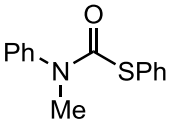
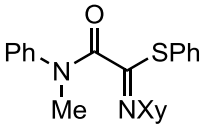
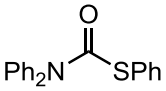
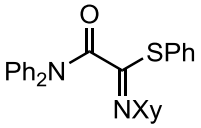
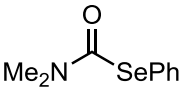
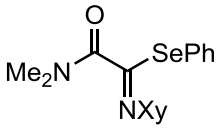
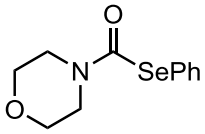
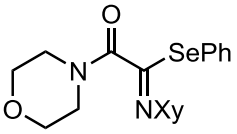
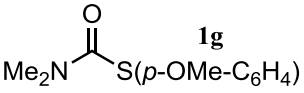
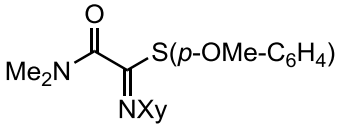
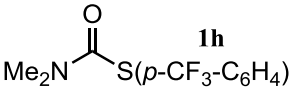
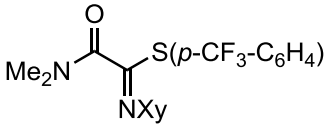
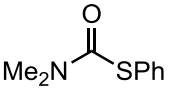
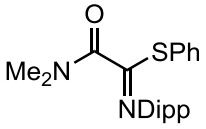
Then the influence of aryl groups on the sulfur of thiocarbamates and on the nitrogen of isocyanides was examined. The reaction of **1h** having a *p*-trifluoromethyl group on the aromatic ring afforded the expected adduct **3h** in high yield (94%), however, the presence of a *p*-methoxy group resulted in a lower yield of 60% (entries 8 and 9). Although the reaction of the 2,6-diisopropylphenyl isocyanide (**2b**) with the thiocarbamate **1a** afforded the corresponding product **3i** in 62% yield (entry 10), the desired products were not obtained from cyclohexyl, adamantyl, *p*-methoxyphenyl, *o*-tolyl, and 3,5-xylyl isocyanides. These results suggest that this reaction proceeds only with aryl isocyanides that contain substituents at both *ortho* positions.

When the selenocarbamates **5a** and **5b** were employed as substrates, the corresponding products **6a** and **6b** were obtained in moderate yields (entries 6 and 7), probably due to the partial decomposition of the products during their isolation by column chromatography.

Table 3. Syntheses of several kinds of amino 2-oxoethanimidothiotae **3**.



1, 1.0 mmol **2a**, 0.4 mmol **3**

entry	**1**	time	**3**	yield[a]
1	 **1b**	5 h		**3b**, 75%
2	 **1c**	7 h		**3c**, 81%
3	 **1d**	7 h		**3d**, 72%
4	 **1e**	5 h		**3e**, 37%
5	 **1f**	18 h		**3f**, (3%[b])
6	 **5a**	8 h		**6a**, 41%(63%[b])
7	 **5b**	24 h		**6b**, 64%(71%[b])
8	 **1g**	4 h		**3g**, 60%
9	 **1h**	7 h		**3h**, 94%
10[c]	 **1a**	7 h		**3i**, 62%

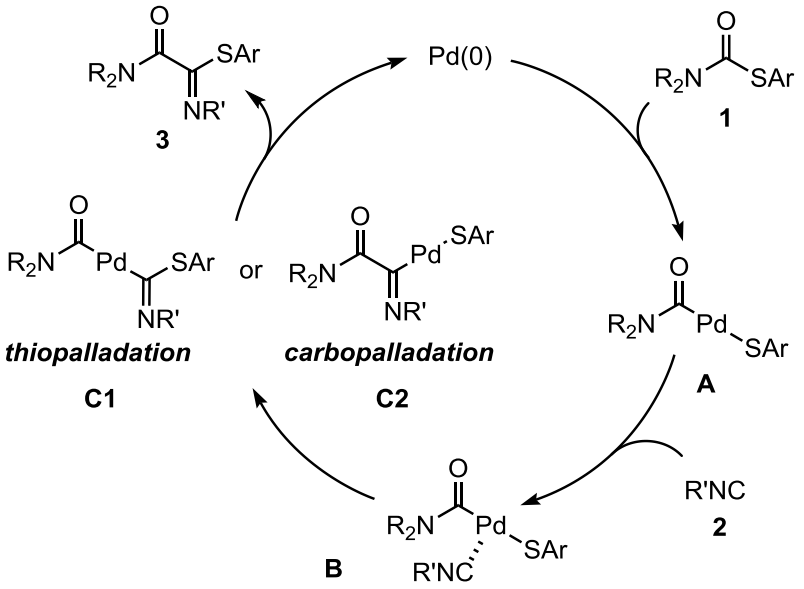
[a] Isolated yield. [b] ^{1}H NMR yield.

[c] 2,6-Diisopropylphenyl isocyanide (**2b**) was used instead of 2,6-xylyl isocyanide.

Plausible reaction pathways of thiocarbamates **1** are shown in Scheme 1. The catalytic cycle is initiated by the oxidative addition of the *carbamoyl-S* bond of **1** to Pd(0), affording the *carbamoyl-Pd-S* complex **A**. The coordination of an isocyanide to the palladium gives

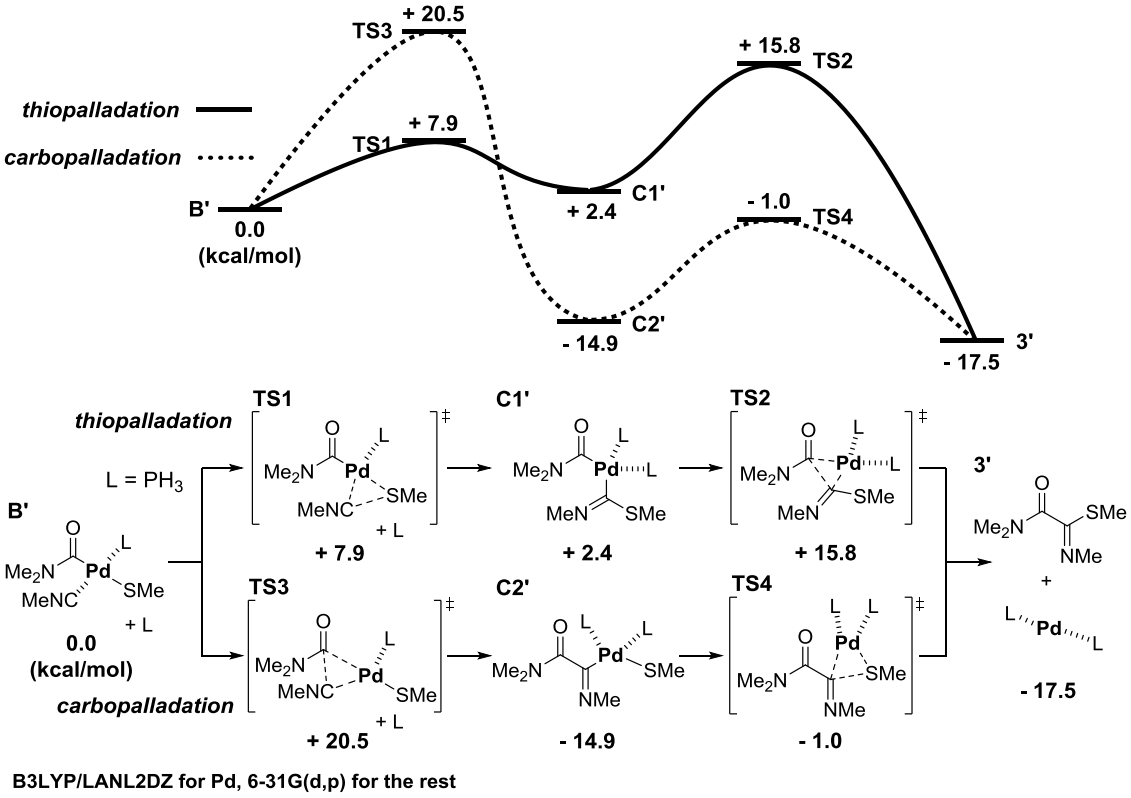
complex **B**. Insertion of the coordinated isocyanide into the *Pd-S* bond generates a *thiopalladation* intermediate **C1**, or the insertion into the *carbamoyl-Pd* bond affords a *carbopalladation* intermediate **C2**. Finally, reductive elimination from **C1** or **C2** produces the addition product **3**.

Scheme 1. Plausible reaction pathway for the formation of **3**.



To shed light on the mechanism of the insertion process from intermediate **B**, DFT calculations were performed with methyl isocyanide and $Me_2NC(O)SMe$ as substrates and PH_3 as the ligand for the palladium. Complex **B'** shown in Scheme 2 is an optimized model for the isocyanide coordinated intermediate. The intermediate **B'** undergoes *thiopalladation* or *carbopalladation* to give **C1'** or **C2'**, respectively. The relative energies of **C1'**, **C2'** and the transition states **TS1**-**TS4** shown in Scheme 2 suggest that C-S bond forming steps are more facile than C-C bond forming steps in either pathways and overall the *thiopalladation* pathway would be more likely.[12]

Scheme 2. Computational calculations for isocyanide insertion and reductive elimination.



2-3 Conclusions

In summary, the first example of the transition metal catalyzed insertion of isocyanides into carbon-sulfur bonds is revealed. This protocol could also be applied to the insertion of isocyanides into carbon-selenium bonds. DFT calculations indicate that the reaction proceeds via a *thiopalladation* pathway and not a *carbopalladation* pathway.

2-4 Experimental Section

General Comments

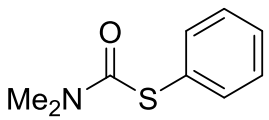
^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded with JEOL JNM-Alice 400 (400, 100 and 376 MHz, respectively) spectrometers using $CDCl_3$ as the solvent and Me_4Si as an internal standard in 5 mm NMR tubes. Chemical shifts are reported in parts per million (d) downfield from internal tetramethylsilane. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, brs = broad singlet, m = multiplet), coupling constant (Hz), integration. Infrared spectra (IR) were obtained on a JASCO Corporation FT/IR-4200 instrument equipped with ATR PRO450-S. Both conventional and high-resolution mass spectra were recorded using a JEOL JMS-DX303HF spectrometer (EI) or a JEOL JMS-T100TD (DART). Elemental analyses were performed at Instrumental Analysis Center, Faculty of Engineering, Osaka University. HPLC separations were performed on a recycling preparative HPLC (Japan Analytical; Model LC-908) equipped with JAIGEL-1H and -2H columns or Shodex K2001 and 2002 columns (GPC) using $CHCl_3$ as

the eluent. GC analyses were performed on a Shimadzu GC-2014 instrument equipped with a GL Sciences InertCap 5 capillary column (I.D. 0.25 mm, Length 30 m, df 0.25 μm). GC yields were determined using a hydrocarbon as an internal standard. GC Mass analyses (EI) were recorded with a JEOL JMS-mate operating in the electron impact mode (70 eV) equipped with InertCap 5MS/NP column (I.D. 0.25 mm, Length 30 m, df 0.25 μm). X-ray crystallographic analyses were carried out using a Rigaku R-AXIS RAPID diffractometer (Cu-Kα) (compound **3a**). The structures of **3a** was solved by direct methods (SHELX-97[13]). The structure was refined on F^2 by full-matrix least-squares method using SHELXL-97.[14] The crystal was mounted on the CryoLoop (Hampton Research Corp.) with a layer of light mineral oil and placed in a nitrogen stream at 123(2) K. Non-hydrogen atoms were anisotropically refined. Hydrogen atoms were included in the refinement on calculated positions riding on their carrier atoms. DFT calculations were executed using Gaussian 09.[15] 2,6-Xylyl isocyanide **2a**[8b] and 2,6-diisopropylphenyl isocyanide **2b**[16] were synthesized according to the literature procedure. $Pd(dba)_2$ (Tokyo Chemical Industry, Tokyo, Japan), 1,3-diphenylphosphinopropane (Sigma-Aldrich, Tokyo, Japan) and dehydrated solvents (Wako Pure chemical, Osaka, Japan) were purchased and used as received.

Syntheses of Thio- and Selenocarbamates

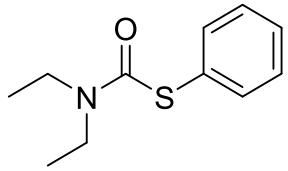
Thiocarbamates **1a-g** were obtained by the reaction of benzenethiol with the corresponding carbamoyl chlorides in THF in the presence of 5 equiv of pyridine. Thiocarbamates **1h** and **1i** were also produced by the reaction of the corresponding thiols with dimethylcarbamoyl chloride. Selenocarbamates **5a** and **5b** were prepared according to previously reported procedures.[17]

***S*-Phenyl *N,N*-dimethylcarbamothioate (1a)**:[18]



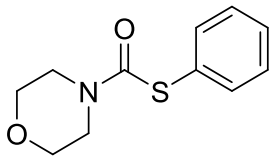
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (brs, 3 H), 3.08 (brs, 3 H), 7.35-7.39 (m, 3 H), 7.48-7.51 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 128.7, 128.8, 129.1, 135.6, 166.8 ppm. IR (neat) 2924, 1663, 1474, 1436, 1401, 1360, 1254, 1084, 1020, 906, 755, 681 cm^{-1}; MS (EI) m/z (relative intensity, %) 181 (M^+, 13), 109 (7), 72 (100), 65 (4); Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73; S, 17.69. Found C, 59.52; H, 6.04; N, 7.70; S, 17.49. Anal. HRMS (EI) calcd for $C_9H_{11}NOS$: 181.0561, Found 181.0560.

***S*-Phenyl *N,N*-diethylcarbamothioate (1b)**:[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (brs, 3 H), 1.27 (brs, 3 H), 3.43 (q, J = 6.8 Hz, 20.4 Hz, 4 H), 7.37-7.38 (m, 3 H), 7.49-7.52 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 13.7, 42.3, 77.2, 128.7, 128.8, 128.9, 135.7, 165.6 ppm. IR (neat) 2976, 1658, 1440, 1402, 1307, 1246, 1217, 1114, 1090, 1024, 941,



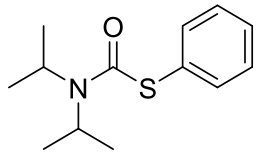
851, 746, 688, 660 cm^{-1}; MS (EI) m/z (relative intensity, %) 209 (M^+, 6), 149 (3), 109 (11), 100 (100), 72 (39), 44 (8); Anal. HRMS (EI) calcd for $C_{11}H_{15}NOS$: 209.0874, Found. 209.0874.

_S_-Phenyl morpholine-4-carbothioate (1c):[18]



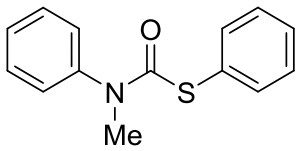
^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (t, J = 4.6 Hz, 4 H), 3.72 (t, J = 4.6 Hz, 4 H), 7.38-7.40 (m, 3 H), 7.49-7.51 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.3, 66.5, 127.9, 129.0, 129.3, 135.8, 166.3 ppm. IR (neat) 2975, 2908, 2857, 1651, 1440, 1401, 1269, 1208, 1108, 1066, 1013, 936, 878, 836, 756, 689, 682 cm^{-1}; MS (EI) m/z (relative intensity, %) 223 (M^+, 21), 114 (100), 109 (13), 70 (43); Anal. HRMS (EI) calcd for $C_{11}H_{13}NO_2S$: 223.0667, Found 223.0668.

_S_-Phenyl _N,N_-diisopropylcarbamothioate (1d):[20]



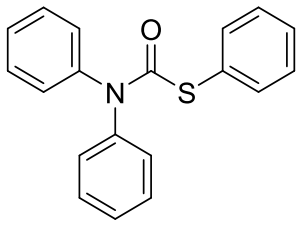
^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (brs, 12 H), 3.50 (brs, 1 H), 4.20 (brs, 1 H), 7.37-7.39 (m, 3 H), 7.49-7.51 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 47.5, 49.6, 128.8, 128.9, 129.2, 135.9, 163.8 ppm. IR (neat) 2973, 1658, 1418, 1371, 1278, 1205, 1150, 1036, 813, 748, 688, 663 cm^{-1}; MS (EI) m/z (relative intensity, %) 237 (M^+, 1), 194 (1), 152 (1), 128 (100), 110 (41), 86 (77), 43 (48); Anal. HRMS (EI) calcd for $C_{13}H_{19}NOS$: 237.1187, Found. 237.1186.

_S_-Phenyl _N_-methyl-_N_-phenylcarbamothioate (1e):[21]



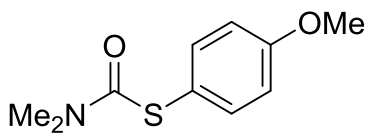
^1H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 3 H), 7.34-7.49 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.5, 128.4, 128.6, 128.8, 129.0, 129.4, 129.6, 135.4, 141.8, 167.4 ppm. IR (neat) 2926, 1665, 1593, 1340, 1170, 1108, 1022, 996, 917, 859, 749, 692 cm^{-1}; MS (EI) m/z (relative intensity, %) 243 (M^+, 14), 134 (100), 106 (21), 77 (18), 51 (4); Anal. HRMS (EI) calcd for $C_{14}H_{13}NOS$: 243.0718, Found. 243.0720.

_S_-Phenyl _N,N_-diphenylcarbamothioate (1f):



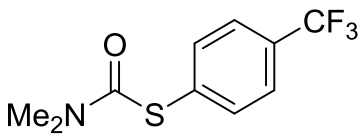
^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.32 (m, 2 H), 7.36-7.42 (m, 11 H), 7.47-7.50 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.5, 128.9, 129.1, 129.2, 129.4, 135.4, 141.3, 141.4, 167.8 ppm. IR (neat) 3061, 1677, 1590, 1489, 1441, 1259, 1142, 1068, 1023, 1001, 955, 924, 903, 826, 765, 755, 746, 690 cm^{-1}; MS (EI) m/z (relative intensity, %) 305 (M^+, 14), 196 (100), 168 (32), 109 (4), 77 (10); Anal. HRMS (EI) calcd for $C_{19}H_{15}NOS$: 305.0874, Found. 305.0875.

***S*-(4-Methoxyphenyl) *N,N*-dimethylcarbamothioate (1g)**:[18]



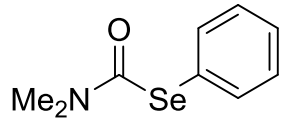
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (brs, 3 H), 3.08 (brs, 3 H), 3.82 (s, 3 H), 6.90-6.93 (m, 2 H), 7.38-7.42 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9, 55.3, 114.6, 119.4, 137.3, 160.5, 167.7 ppm. IR (neat) 2926, 1666, 1650, 1592, 1496, 1442, 1363, 1289, 1246, 1175, 1106, 1092, 1022, 908, 819, 686, 658 cm^{-1}; MS (EI) m/z (relative intensity, %) 211 (M^+, 35), 139 (11), 124 (2), 96 (3), 72 (100); Anal. HRMS (EI) calcd for $C_{10}H_{13}NO_2S$: 211.0667, Found. 211.0668.

***S*-(4-(Trifluoromethyl)phenyl) *N,N*-dimethylcarbamothioate (1h)**:[22]



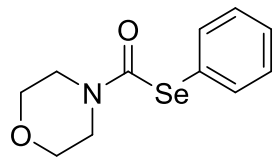
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (brs, 3 H), 3.10 (brs, 3 H), 7.62 (s, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9, 122.5, 125.2, 125.6 (q, $J_{C\text{-}F}^1$ = 2.9 Hz, 10.6 Hz), 130.8, 131.0 (q, $J_{C\text{-}F}^2$ = 32.5 Hz, 97.3 Hz), 133.6, 135.6, 165.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 ppm. IR (neat) 2930, 1657, 1607, 1480, 1401, 1634, 1322, 1258, 1158, 1120, 1105, 1088, 1059, 1015, 906, 838, 735, 686, 656 cm^{-1}; MS (EI) m/z (relative intensity, %) 249 (M^+, 4), 177 (7), 157 (3), 108 (3), 72 (100); Anal. HRMS (EI) calcd for $C_{10}H_{10}F_3NOS$: 249.0435, Found. 249.0434.

***Se*-Phenyl *N,N*-dimethylcarbamoselenoate (5a)**:[17]



^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (brs, 6 H), 7.32-7.40 (m, 3 H), 7.58-7.61 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 37.3, 126.7, 128.8, 129.0, 136.6 (t, $J_{C\text{-}Se}$ = 4.8 Hz), 164.5 ppm. IR (neat) 2878, 1668, 1476, 1438, 1356, 1253, 1205, 1070, 1021, 889, 738, 688, 669 cm^{-1}; MS (EI) m/z (relative intensity, %) 229 (M^+, 8), 157 (8), 77 (5), 72 (100); Anal. HRMS (EI) calcd for $C_9H_{11}NOSe$: 229.0006, Found 229.0007.

***Se*-Phenyl morpholine-4-carboselenoate (5b)**:[23]



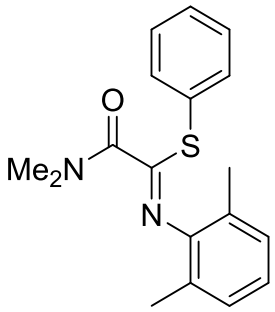
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (brs, 2 H), 3.62 (brs, 2 H), 3.72 (s, 4 H), 7.34-7.42 (m, 3 H), 7.58-7.61 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.8, 46.8, 66.5, 126.0, 129.0, 129.1, 136.7 (q, $J_{C\text{-}Se}^1$ = 4.7 Hz, $J_{C\text{-}Se}^2$ = 28.6 Hz), 163.8 ppm. IR (neat) 2971, 2908, 2858, 1658, 1439, 1391, 1269, 1204, 1108, 1011, 936, 869, 830, 749, 691, 670 cm^{-1}; MS (EI) m/z (relative intensity, %) 271 (M^+, 5), 157 (6), 114 (100), 77 (4), 70 (40), 42 (6); Anal. HRMS (EI) calcd for $C_{11}H_{13}NO_2Se$: 271.0112, Found. 271.0108.

Typical Procedure for Palladium-Catalyzed Insertion of Isocyanides into Thio- and Selenocarabamates:

A 5-mL reaction flask equipped with a reflux condenser was dried with the heat gun at

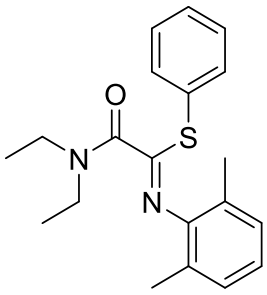
120°C and then purged with N_2. After cooling to room temperature, thiocarbamate **1a** (1.0 mmol), $Pd(dba)_2$ (0.02 mmol), dppp (0.02 mmol) and DMF (0.8 mL) were placed in the flask. After the reaction mixture was heated in an oil bath at 110°C for 5 minutes, isocyanide **2** (0.4 mmol) was added to the mixture, and the heating was continued until **2** was completely consumed (monitored by TLC). After cooling to room temperature, the residue was removed by Celite filtration with chloroform, and the volatiles were removed in vacuo. The crude compound was purified with flash column chromatography (silica gel, *n*-hexane / EtOAc = 2:1) to obtain **3a** in 83% yield as a faint yellow solid.

***N*,*N*-Dimethyl-2-(2,6-dimethylphenyl)imino-2-(phenylthio) acetamide (3a):**



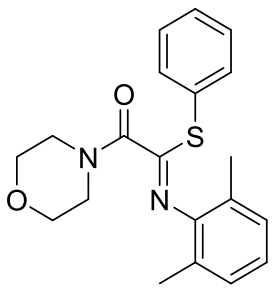
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 6 H), 2.56 (s, 3 H), 3.03 (s, 3 H), 6.99-7.03 (m, 1 H), 7.08-7.10 (m, 2 H), 7.32-7.41 (m, 3 H), 7.54-7.57 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 33.7, 37.5, 124.5, 126.6, 127.6, 128.2, 128.9, 129.9, 135.7, 146.2, 162.1, 163.1 ppm. IR (neat) 2919, 1652, 1631, 1591, 1470, 1439, 1411, 1399, 1267, 1201, 1170, 1087, 1015, 924, 887, 822, 767, 751, 690, 674 cm^{-1}; MS (EI) m/z (relative intensity, %) 312 (M^+, 3), 240 (3), 203 (40), 130 (4), 109 (3), 72 (100); m.p.: 384 K. Anal. Calcd for $C_{18}H_{20}N_2OS$: C, 69.20; H, 6.45; N, 8.97; S, 10.26. Found C, 69.25; H, 6.48; N, 8.92; S, 10.31. Anal. HRMS (EI) calcd for $C_{18}H_{20}N_2OS$: 312.1296, Found 312.1295.

***N*,*N*-Diethyl-2-(2,6-dimethylphenyl)imino-2-(phenylthio) acetamide (3b)**:



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.45 (t, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 6.8 Hz, 3 H), 2.26 (s, 6 H), 3.09 (q, *J* = 7.2 Hz, 21.6 Hz, 2 H), 3.35 (q, *J* = 6.8 Hz, 20.8 Hz, 2 H), 6.98-7.01 (m, 1 H), 7.07-7.09 (m, 2 H), 7.29-7.38 (m, 3 H), 7.55-7.57 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 13.9, 17.7, 38.0, 42.2, 124.5, 126.6, 127.5, 128.3, 129.0, 129.9, 136.3, 146.4, 161.7, 162.9 ppm. IR (neat) 2961, 2926, 1677, 1636, 1596, 1482, 1446, 1401, 1357, 1305, 1254, 1179, 1092, 1022, 891, 840, 789, 782, 741, 687 cm^{-1}; MS (EI) m/z (relative intensity, %) 340 (M^+, 3), 240 (6), 231 (39), 130 (4), 100 (100), 72 (17); Anal. HRMS (EI) calcd for $C_{20}H_{24}N_2OS$: 340.1609, Found. 340.1611.

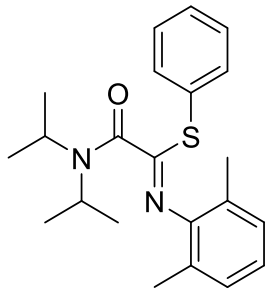
Morpholino-2-(2,6-dimethylphenyl)imino-2-(phenylthio) acetamide (3c):



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 6 H), 3.33 (dt, *J* = 4.8 Hz, 36.8 Hz, 4 H), 3.48-3.54 (m, 4 H), 7.02 (dd, *J* = 6.4 Hz, 8.4 Hz, 1 H), 7.09 (m, 2 H), 7.35-7.44 (m, 3 H), 7.57 (dt, 1.6 Hz, 6.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 41.2, 46.3, 66.1, 66.2, 124.7,

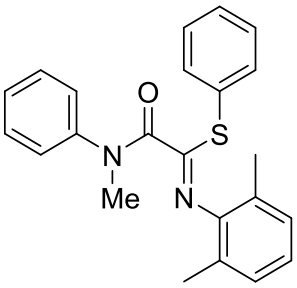
126.4, 127.5, 128.3, 129.2, 130.1, 135.9, 146.0, 161.0, 162.4 ppm. IR (neat) 2975, 2964, 1643, 1625, 1590, 1469, 1439, 1275, 1257, 1192, 1115, 1071, 1017, 995, 936, 875, 852, 808, 765, 748, 690 cm^{-1}; MS (EI) m/z (relative intensity, %) 354 (M^+, 3), 245 (42), 240 (4), 130 (5), 114 (100), 70 (30), 42 (6); Anal. HRMS (EI) calcd for $C_{20}H_{22}N_2O_2S$: 354.1402, Found 354.1399.

***N,N*-Diisopropyl-2-(2,6-dimethylphenyl)imino-2-(phenylthio) acetamide (3d)**:



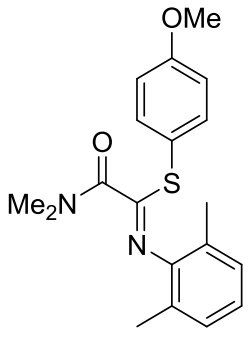
^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.8 Hz, 12 H), 2.25 (s, 6 H), 3.19 (sept, *J* = 6.8 Hz, 1 H), 4.22 (sept, *J* = 6.8 Hz, 1 H), 6.97-7.08 (m, 3 H), 7.29-7.38 (m, 3 H), 7.59-7.62 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 19.8, 20.6, 30.9, 45.5, 50.4, 124.4, 126.7, 127.6, 128.3, 128.9, 129.8, 136.6, 146.3, 161.6, 162.9 ppm. IR (neat) 2974, 2922, 1643, 1626, 1466, 1441, 1367, 1334, 1211, 1163, 1144, 1050, 1011, 899, 843, 793, 765, 756, 692, 678 cm^{-1}; MS (CI) m/z (relative intensity, %) 369 (M^+, 100), 293 (9), 259 (18), 128 (32); Anal. HRMS (CI) calcd for $C_{22}H_{28}N_2OS$: 368.1922, Found. 368.1918.

***N*-Methyl-*N*-phenyl-2-(2,6-dimethylphenyl)imino-2-(phenylthio) acetamide (3e)**



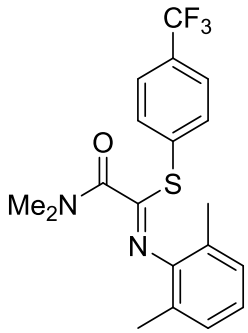
(s-*cis*/*trans* mixture): ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (s, 6 H, *major*), 2.31 (s, 6 H, *minor*), 3.02 (s, 3 H, *major*), 3.45 (s, 3 H, *minor*), 6.65-7.68 (m, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5 (*major*), 18.0 (*minor*), 37.1 (*major*), 38.9 (*minor*), 124.3, 124.6, 125.4, 126.4, 126.6, 127.0, 127.6, 127.7, 127.9, 128.0, 128.2, 128.3, 128.8, 128.9, 129.3, 129.4, 129.7, 130.2, 135.7 (*major*), 136.3 (*minor*), 141.1 (*minor*), 141.7 (*major*), 146.1 (*minor*), 146.3 (*major*), 161.7, 161.7, 161.9, 162.9. IR (neat) 2922, 1651, 1608, 1590, 1496, 1464, 1386, 1299, 1281, 1189, 1077, 1023, 969, 858, 808, 771, 753, 690 cm^{-1}; MS (EI) m/z (relative intensity, %) 374 (M^+, 1), 265 (49), 240 (3), 134 (100), 106 (12), 77 (11); Anal. HRMS (EI) calcd for $C_{23}H_{22}N_2OS$: 374.1453, Found. 374.1452.

***N,N*-Dimethyl-2-(2,6-dimethylphenyl)imino-2-(4-methoxyphenylthio) acetamide (3g)**: ^1H



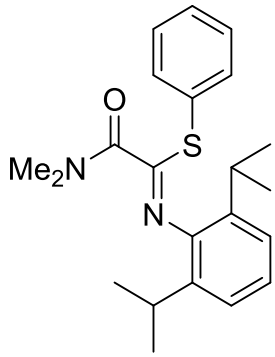
NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 6 H), 2.61 (s, 3 H), 3.05 (s, 3 H), 3.80 (s, 3 H), 6.84-6.87 (m, 2 H), 6.98 (m, 1 H), 7.07-7.09 (m, 2 H), 7.43-7.47 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 33.8, 37.5, 55.3, 114.4, 117.9, 124.4, 126.5, 128.2, 137.2, 146.2, 161.0, 162.4, 164.0 ppm. IR (neat) 2925, 1640, 1625, 1588, 1492, 1455, 1400, 1290, 1248, 1195, 1173, 1104, 1091, 1030, 1017, 885, 827, 819, 778, 678 cm^{-1}; MS (CI) m/z (relative intensity, %) 343 (M^+, 100), 203 (42), 72 (6); Anal. HRMS (CI) calcd for $C_{19}H_{22}N_2O_2S$: 342.1402, Found. 342.1402.

***N,N*-Dimethyl-2-(2,6-dimethylphenyl)imino-2-((4-trifluoromethyl)phenylthio) acetamide**



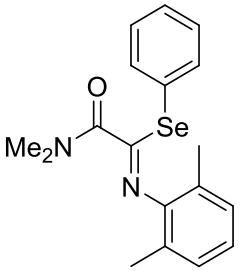
(3h): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 6 H), 2.60 (s, 3 H), 3.07 (s, 3 H), 7.00-7.10 (m, 3 H), 7.58-7.68 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 33.8, 37.5, 122.2, 124.8, 124.9, 125.6 (q, $J_{C\text{-}F}^{1}$ = 3.8 Hz, 11.5 Hz), 126.4, 128.3, 131.9 (q, $J_{C\text{-}F}^{2}$ = 32.4 Hz, 98.2 Hz), 132.6, 132.6, 145.9, 161.2, 161.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 ppm. IR (neat) 2925, 1650, 1604, 1469, 1398, 1325, 1266, 1161, 1123, 1102, 1063, 1008, 879, 837, 770, 706, 685 cm^{-1}; MS (EI) m/z (relative intensity, %) 381 (M^+, 100), 245 (4), 221 (5), 205 (58), 188 (7), 178 (7), 132 (36), 74 (10); Anal. HRMS (CI) calcd for $C_{19}H_{19}F_3N_2OS$: 380.1170, Found. 380.1165.

***N,N*-Dimethyl-2-(2,6-diisopropylphenyl)imino-2-(phenylthio) acetamide (3i)**:



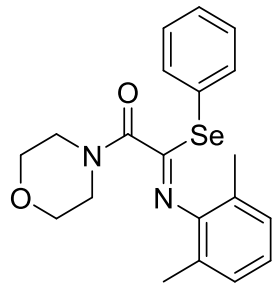
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.8 Hz, 6 H), 1.39 (d, *J* = 6.8 Hz, 6 H), 2.55 (s, 3 H), 2.99 (s, 3 H), 3.08 (sept, *J* = 6.8 Hz, 2 H), 7.16-7.22 (m, 3 H), 7.31-7.39 (m, 3 H), 7.52-7.55 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 23.6, 28.1, 33.7, 37.0, 123.4, 125.2, 127.9, 128.9, 129.9, 135.6, 137.2, 143.7, 162.1, 163.2 ppm. IR (neat) 2965, 1658, 1650, 1621, 1581, 1500, 1440, 1402, 1324, 1263, 1185, 1058, 1015, 939, 916, 884, 798, 765, 752, 706, 689 cm^{-1}; MS (EI) m/z (relative intensity, %) 368 (M^+, 4), 259 (36), 186 (93), 72 (100); Anal. HRMS (EI) calcd for $C_{22}H_{28}N_2OS$: 368.1922, Found 368.1923.

***N,N*-Dimethyl-2-(2,6-dimethylphenyl)imino-2-(phenylseleno) acetamide (6a)**:



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 6 H), 2.49 (s, 3 H), 2.98 (s, 3 H), 7.00-7.09 (m, 3 H), 7.30-7.40 (m, 3 H), 7.64-7.66 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 33.7, 37.4, 124.8, 124.9, 126.5, 128.4, 128.9, 129.5, 137.1 (t, $J_{C\text{-}Se}$ = 4.8 Hz), 147.2, 162.4, 163.1 ppm. IR (neat) 2920, 1650, 1590, 1473, 1438, 1398, 1267, 1201, 1164, 1088, 1007, 997, 922, 877, 818, 767, 743, 690, 664, 656 cm^{-1}; MS (CI) m/z (relative intensity, %) 361 (M^+, 80), 245 (4), 221 (6), 203 (100), 132 (25), 72 (9); Anal. HRMS (CI) calcd for $C_{18}H_{20}N_2OSe$: 360.0741, Found 360.0740.

Morpholino-2-(2,6-dimethylphenyl)imino-2-(phenylseleno) acetamide (6b):



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 6 H), 3.22 (t, *J* = 4.8 Hz, 2 H), 3.34 (t, *J* = 4.8 Hz, 2 H), 3.48 (m, 4 H), 7.01-7.10 (m, 3 H), 7.32-7.43 (m, 3 H), 7.65-7.68 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 41.1, 46.2, 66.1, 66.2, 124.7, 125.0, 126.3, 128.5, 129.2, 129.7,

137.2 (t, $J_{C\text{-}Se}$ = 4.8 Hz), 147.0, 161.2, 162.3 ppm. IR (neat) 2964, 2923, 2855, 1642, 1590, 1439, 1276, 1250, 1195, 1113, 1064, 1019, 986, 930, 871, 846, 804, 768, 741, 688 cm^{-1}; MS (EI) m/z (relative intensity, %) 403 (M^+, 83), 327 (16), 287 (7), 245 (100), 132 (14), 114 (15); Anal. HRMS (CI) calcd for $C_{20}H_{22}N_2O_2Se$: 402.0846, Found. 402.0848.

X-ray Crystallographic Analysis

Single crystals of **3a** suitable for X-ray crystallography were obtained by recrystallization from $CHCl_3$/hexane. M = 312.43, colorless, triclinic, *P*-1 (#2), *a* = 11.2690(2) Å, *b* = 12.2582(3) Å, *c* = 12.6321(3) Å, V = 1667.52(6) $Å^3$, *Z* = 4, D_{calcd} = 1.244 g/cm^3, T = 123(2) K, *R*1 (*wR*2) = 0.0430 (0.1161).

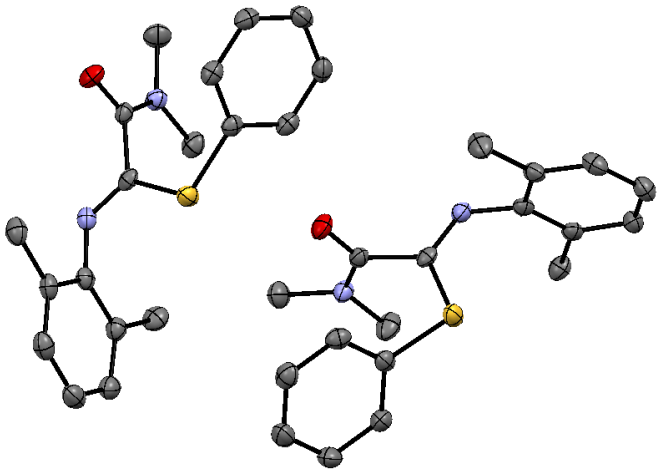


Figure S1. ORTEP drawing of both asymmetric units of **3a** with thermal ellipsoids at the 50% probability level. H atoms are omitted for clarity.

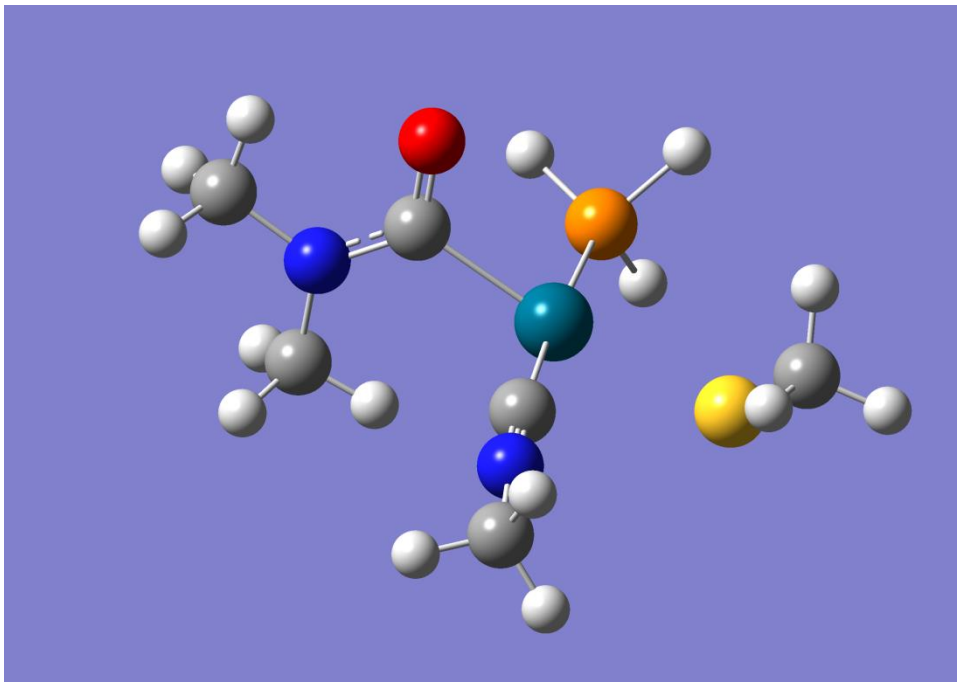
Computational Details: Energies, Cartesian Coordinates and Ball-Stick Models of Stationary Points

Table S2. Summarized energetic values of each structures.

structure	energy (HF; a.u.)
B'	-1288.701869
PH_3	-343.1450673
TS1	-1288.689351
C1'	-1631.843134
TS2	-1631.821766
TS3	-1288.669165
C2'	-1631.870753

TS4	-1631.848545
3'	-818.7847194
$Pd(PH_3)_2$	-813.0900993

Figure S2. Optimized structure of **B'**

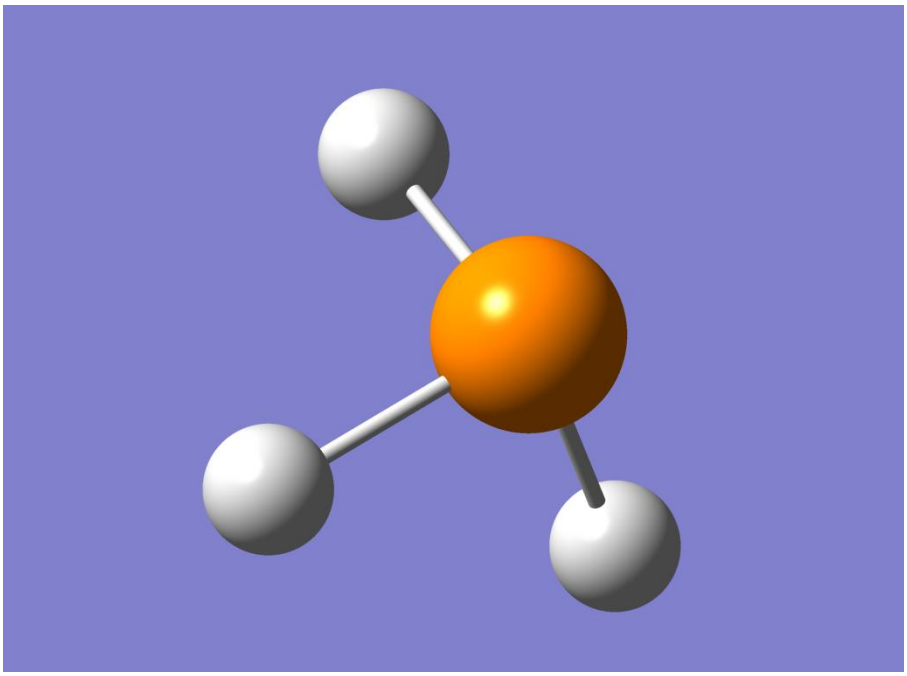


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	2.734854	0.310342	-0.196318
2	6	0	1.712124	-0.016476	0.658439
3	8	0	1.880962	-0.170764	1.861533
4	6	0	4.084268	0.492289	0.324127
5	1	0	4.779910	-0.220056	-0.138620
6	1	0	4.447036	1.507786	0.117607
7	1	0	4.056509	0.327276	1.400945
8	6	0	2.560724	0.487660	-1.622543
9	1	0	3.192586	-0.212969	-2.185847
10	1	0	1.515989	0.308348	-1.886876
11	1	0	2.832038	1.507106	-1.931041
12	46	0	-0.228979	-0.294123	-0.034413
13	6	0	-0.595364	1.661030	-0.023241
14	7	0	-0.894790	2.789867	-0.023646
15	6	0	-1.318193	4.144178	-0.040161

16	1	0	-0.496451	4.786267	-0.368089
17	1	0	-2.162291	4.256942	-0.725691
18	1	0	-1.627146	4.443451	0.964824
19	15	0	0.051982	-2.612491	-0.096467
20	1	0	-0.576868	-3.290630	0.964909
21	1	0	-0.522497	-3.292727	-1.187098
22	1	0	1.310630	-3.264160	-0.050345
23	16	0	-2.583082	-0.842786	-0.604487
24	6	0	-3.514380	-0.219285	0.856740
25	1	0	-4.573560	-0.442299	0.699241
26	1	0	-3.192188	-0.707194	1.780177
27	1	0	-3.404311	0.862742	0.975003

HF = -1288.7018689

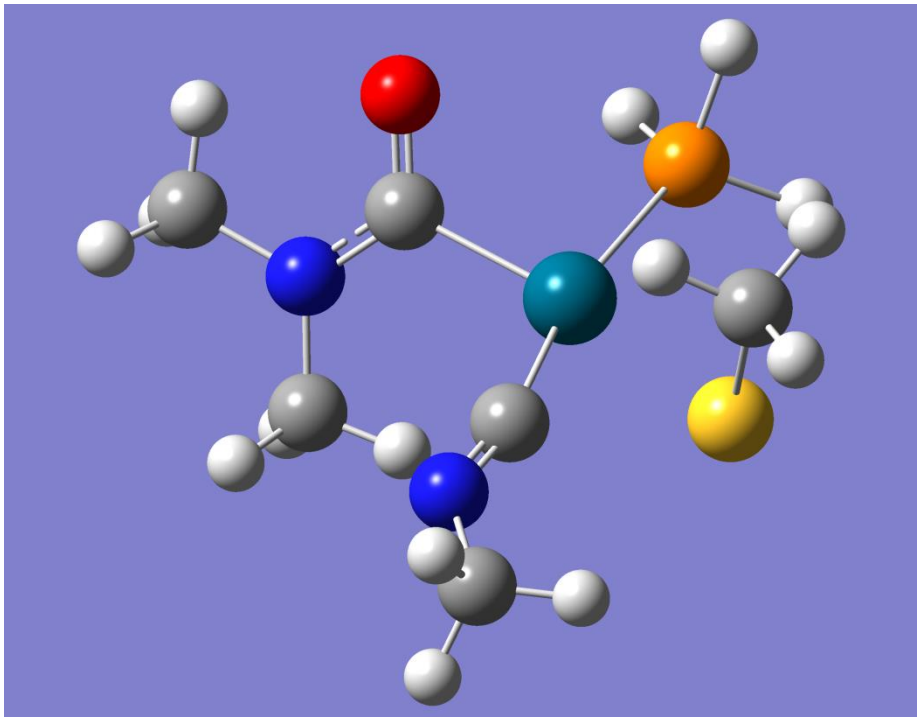
Figure S3. Optimized structure of **PH_3**



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	15	0	0.000000	0.000000	0.128400
2	1	0	0.000000	1.196594	-0.642000
3	1	0	-1.036281	-0.598297	-0.642000
4	1	0	1.036281	-0.598297	-0.642000

HF = -343.1450673

Figure S4. Optimized structure of **TS1**

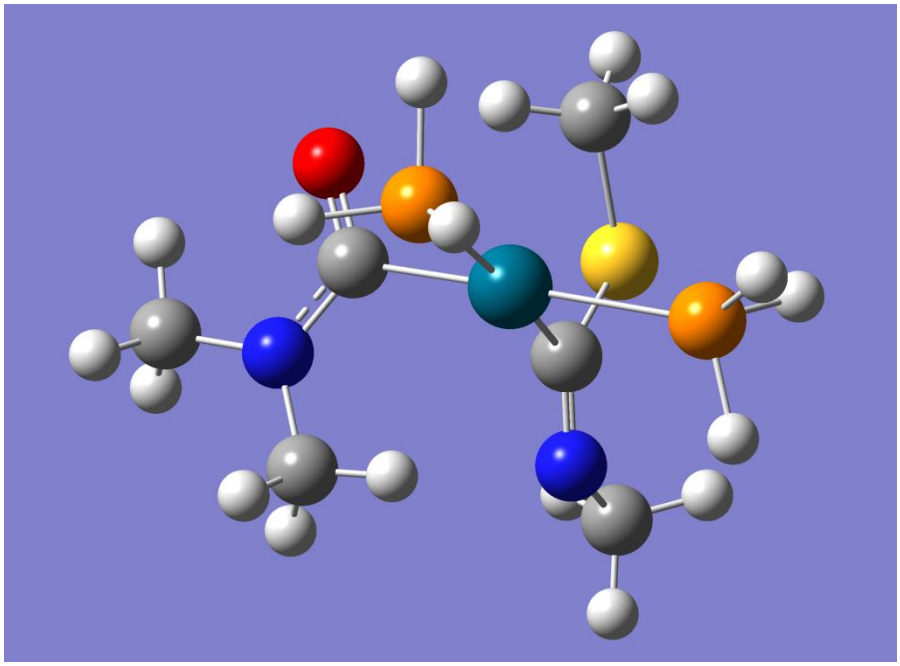


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	2.531618	1.123574	-0.060700
2	6	0	1.806647	0.135168	0.545399
3	8	0	2.204778	-0.459556	1.544763
4	6	0	3.802975	1.542899	0.518544
5	1	0	4.618447	1.416159	-0.204981
6	1	0	3.763947	2.600445	0.810094
7	1	0	3.995676	0.929849	1.398217
8	6	0	2.105616	1.830589	-1.251422
9	1	0	2.875372	1.763026	-2.031641
10	1	0	1.182058	1.388883	-1.627859
11	1	0	1.925889	2.893127	-1.039411
12	46	0	-0.048642	-0.444320	-0.116592
13	6	0	-1.119419	1.198946	0.008095
14	7	0	-1.531458	2.322880	0.136198
15	6	0	-2.806206	2.984702	0.036445
16	1	0	-3.580869	2.267899	-0.262400
17	1	0	-3.060008	3.431505	1.002056
18	1	0	-2.740142	3.790897	-0.699590
19	15	0	0.817942	-2.639581	-0.431816

20	1	0	0.696862	-3.500182	0.680702
21	1	0	0.259497	-3.491706	-1.411913
22	1	0	2.183224	-2.865299	-0.708901
23	16	0	-2.547681	-0.537798	-0.495417
24	6	0	-3.153026	-0.928446	1.201154
25	1	0	-4.217439	-0.687356	1.258189
26	1	0	-3.015156	-1.989437	1.418650
27	1	0	-2.614939	-0.342475	1.950082

HF = -1288.6893512

Figure S5. Optimized structure of **C1'**

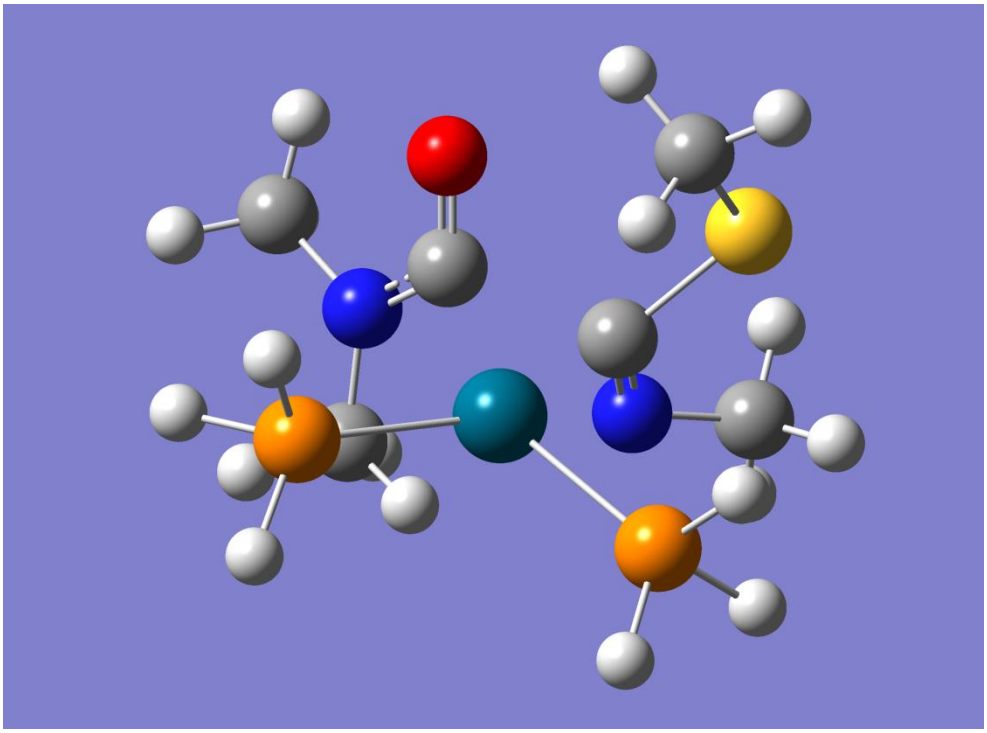


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	1.855107	-1.768124	-0.398256
2	6	0	1.352570	-0.890589	0.521161
3	8	0	1.622266	-0.966743	1.719594

4	6	0	2.723470	-2.855683	0.037748
5	1	0	2.291993	-3.825251	-0.240985
6	1	0	3.713967	-2.774628	-0.429571
7	1	0	2.825754	-2.799516	1.120808
8	6	0	1.593015	-1.683868	-1.822461
9	1	0	1.200746	-2.638228	-2.194488
10	1	0	0.843249	-0.916689	-2.015838
11	1	0	2.514257	-1.453880	-2.377401
12	46	0	0.199272	0.725565	-0.096241
13	6	0	-1.351320	-0.659018	-0.234149
14	16	0	-2.322160	-1.086119	1.246713
15	7	0	-1.663512	-1.109464	-1.379600
16	6	0	-2.793943	-2.017289	-1.554919
17	1	0	-2.663058	-2.939497	-0.970923
18	1	0	-3.739679	-1.557692	-1.232150
19	1	0	-2.886400	-2.288277	-2.610153
20	6	0	-1.479327	-0.176756	2.589754
21	1	0	-1.952332	-0.512518	3.516180
22	1	0	-0.415482	-0.416737	2.608315
23	1	0	-1.626824	0.901155	2.489683
24	15	0	2.187208	2.076714	0.131385
25	1	0	3.452059	1.485604	-0.086228
26	1	0	2.443421	2.584984	1.425723
27	15	0	-1.458690	2.394208	-0.762066
28	1	0	-1.840899	2.302738	-2.118993
29	1	0	-2.748483	2.275220	-0.197269
30	1	0	2.428031	3.277759	-0.583064
31	1	0	-1.366128	3.809806	-0.698344

HF=-1631.8431337

Figure S6. Optimized structure of **TS2**

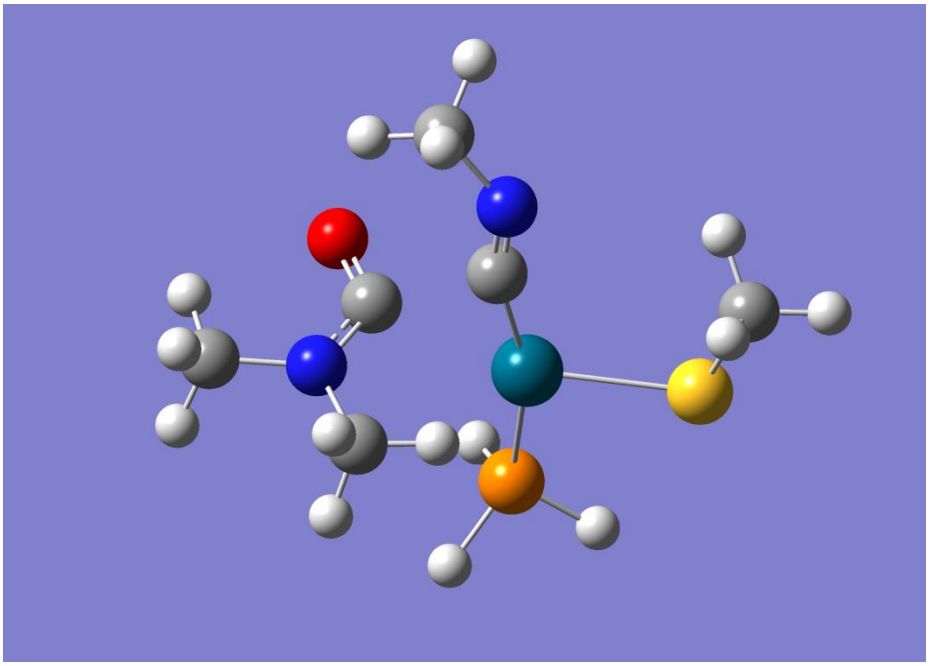


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.120516	2.459930	-0.238900
2	6	0	0.174714	1.385280	0.563039
3	8	0	0.319612	1.486280	1.776655
4	6	0	-0.126946	3.794068	0.344232
5	1	0	0.557876	4.451872	-0.206936
6	1	0	-1.131762	4.236444	0.302865
7	1	0	0.189459	3.722984	1.383688
8	6	0	-0.464726	2.378675	-1.645194
9	1	0	0.277465	2.899401	-2.262639
10	1	0	-0.503484	1.338070	-1.962279
11	1	0	-1.446718	2.843733	-1.814129
12	46	0	-0.726803	-0.515453	-0.086728
13	6	0	1.366690	0.120366	-0.229886
14	16	0	2.496720	-0.714764	0.931457
15	7	0	1.768410	0.448090	-1.394093
16	6	0	3.108772	0.123292	-1.854963
17	1	0	3.869472	0.641285	-1.252834
18	1	0	3.320592	-0.953588	-1.786805

19	1	0	3.223241	0.438022	-2.895572
20	6	0	1.495285	-1.140900	2.400342
21	1	0	2.051385	-1.926560	2.918032
22	1	0	1.358337	-0.269673	3.036298
23	1	0	0.520484	-1.528734	2.096634
24	15	0	-3.023998	-0.030386	0.321320
25	1	0	-3.513697	1.300799	0.292679
26	1	0	-3.552707	-0.350617	1.597298
27	15	0	-0.552747	-2.821208	-0.796749
28	1	0	0.445587	-3.165291	-1.741751
29	1	0	-0.241694	-3.853198	0.125785
30	1	0	-4.095889	-0.589894	-0.422897
31	1	0	-1.606224	-3.525140	-1.437541

HF = -1631.8217655

Figure S7. Optimized structure of **TS3**

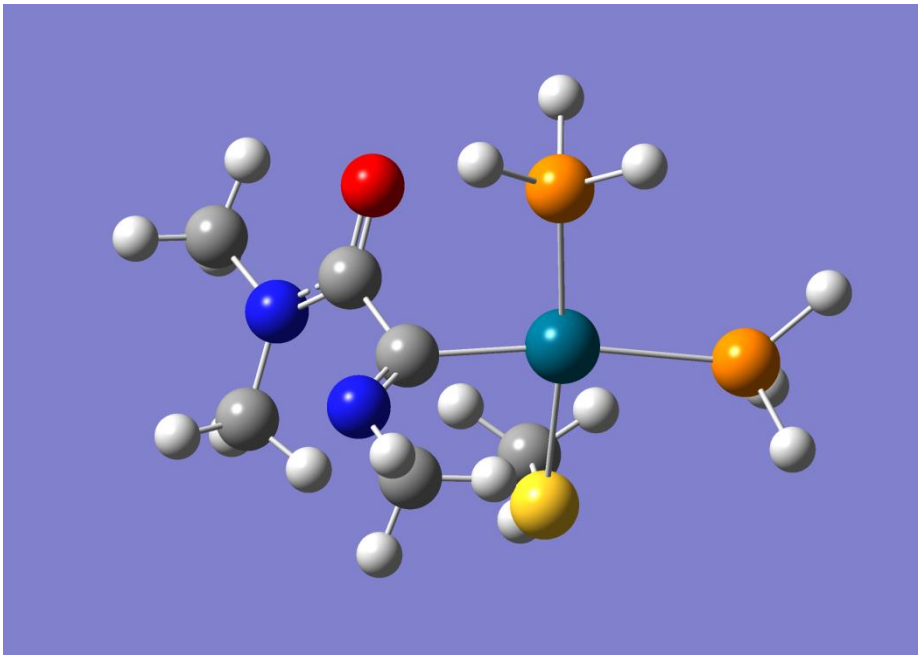


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-2.420253	-0.690053	0.583881
2	6	0	-1.699411	-0.261020	-0.493331

3	8	0	-2.065325	-0.351288	-1.653335
4	6	0	-3.712275	-1.334464	0.362030
5	1	0	-3.676852	-2.385687	0.673922
6	1	0	-4.492446	-0.828867	0.943344
7	1	0	-3.948485	-1.279763	-0.699866
8	6	0	-1.963375	-0.617216	1.962493
9	1	0	-1.875037	-1.623143	2.391450
10	1	0	-0.984851	-0.137623	2.009611
11	1	0	-2.676536	-0.046921	2.570805
12	46	0	0.653874	-0.250957	-0.104616
13	6	0	-0.578935	1.213093	-0.147616
14	7	0	-1.012679	2.338638	-0.228953
15	6	0	-2.275764	2.951600	-0.558820
16	1	0	-3.004163	2.205194	-0.898433
17	1	0	-2.663576	3.481416	0.316203
18	1	0	-2.119006	3.685962	-1.353221
19	15	0	1.597954	-2.455508	-0.360417
20	1	0	1.529602	-3.075409	-1.629657
21	1	0	2.984870	-2.602731	-0.141637
22	1	0	1.163653	-3.568062	0.400831
23	16	0	2.788627	0.667669	0.304262
24	6	0	2.566765	2.479513	0.514570
25	1	0	3.565906	2.922898	0.560182
26	1	0	2.026318	2.915881	-0.327541
27	1	0	2.036139	2.711957	1.440622

HF = -1288.6691647

Figure S8. Optimized structure of **C2'**

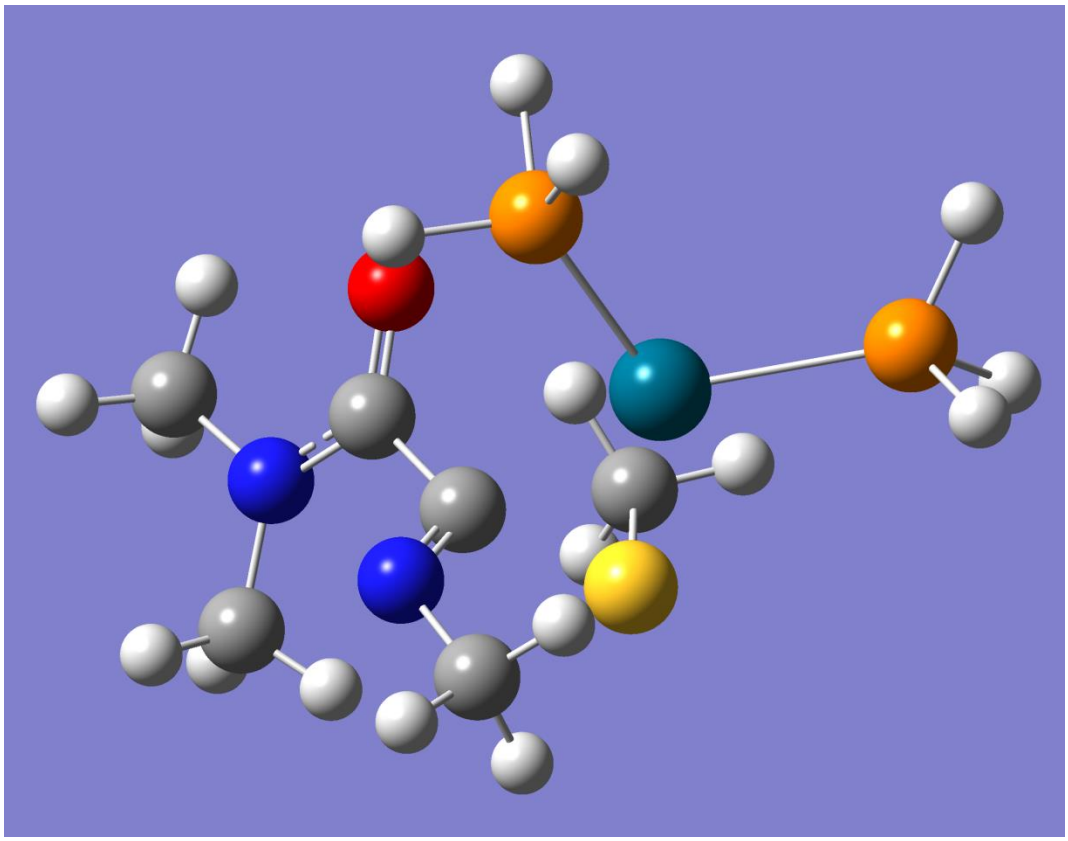


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	2.976881	0.198418	-0.545032
2	6	0	3.971277	-0.102280	-1.567061
3	1	0	3.631171	-0.962676	-2.140868
4	1	0	4.102002	0.758890	-2.232567
5	1	0	4.940484	-0.333079	-1.106498
6	6	0	3.252820	1.349095	0.309287
7	1	0	3.611036	2.172274	-0.318259
8	1	0	2.348973	1.671361	0.823669
9	1	0	4.025185	1.117769	1.053358
10	6	0	1.939573	-0.662370	-0.362034
11	8	0	1.739138	-1.645226	-1.089497
12	6	0	0.969336	-0.403273	0.774503
13	7	0	1.380322	-0.474955	1.963609
14	46	0	-0.942451	-0.196470	0.056714
15	15	0	-3.200429	0.444826	-0.705880
16	1	0	-4.003195	0.960042	0.334015
17	1	0	-3.260193	1.560451	-1.568417
18	15	0	-0.920078	-2.525250	-0.364642
19	1	0	-0.694802	-2.939094	-1.691327
20	1	0	-0.029148	-3.383907	0.304327

21	16	0	-0.695775	2.172896	0.495515
22	6	0	0.484799	-0.334453	3.097811
23	1	0	0.561737	-1.226500	3.729899
24	1	0	0.809794	0.519420	3.702389
25	1	0	-0.564286	-0.185111	2.804737
26	6	0	-0.147098	2.768439	-1.158901
27	1	0	-0.002273	3.850188	-1.085424
28	1	0	0.799283	2.309619	-1.455945
29	1	0	-0.891004	2.573279	-1.937331
30	1	0	-2.117369	-3.250539	-0.125958
31	1	0	-4.212425	-0.328151	-1.344769

HF = -1631.8707529

Figure S9. Optimized structure of **TS4**

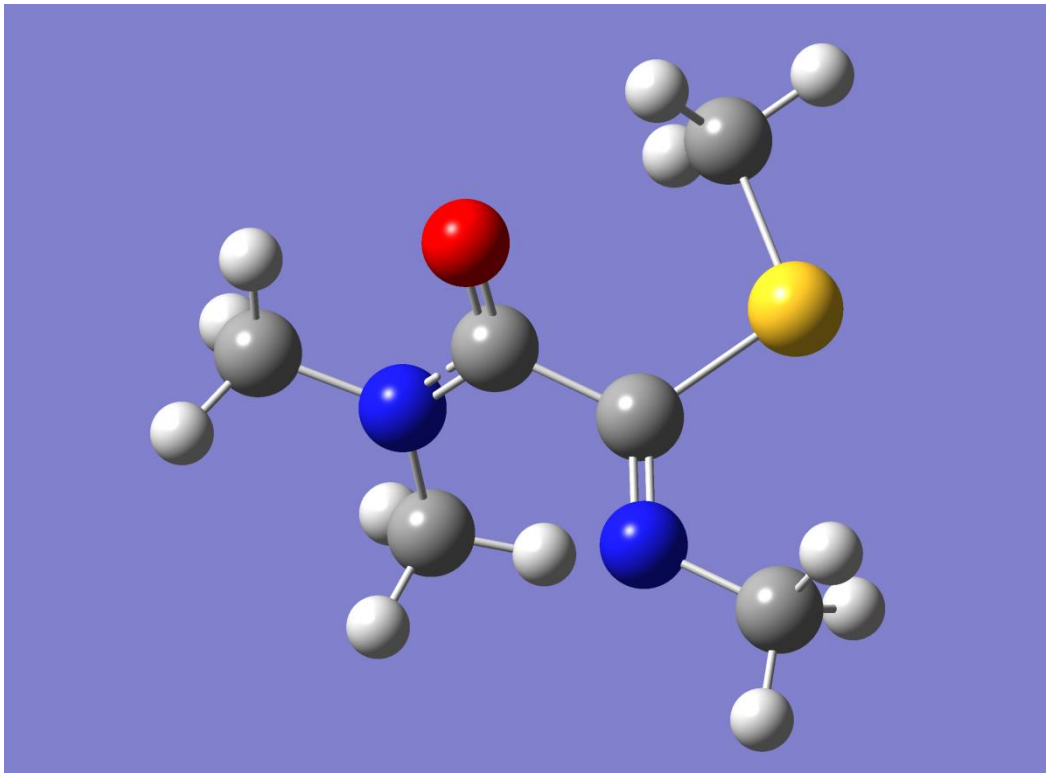


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	7	0	-3.158151	0.218985	-0.383411
2	6	0	-4.061181	0.919583	-1.288649
3	1	0	-3.473289	1.561341	-1.941950
4	1	0	-4.628470	0.199174	-1.889986
5	1	0	-4.774171	1.531800	-0.721611
6	6	0	-3.796358	-0.693317	0.557854
7	1	0	-4.537497	-1.292346	0.016283
8	1	0	-3.065954	-1.359459	1.009256
9	1	0	-4.308801	-0.145375	1.357946
10	6	0	-1.832962	0.546731	-0.394806
11	8	0	-1.355724	1.336020	-1.215326
12	6	0	-0.945842	-0.112442	0.661873
13	7	0	-1.225310	0.112373	1.889664
14	46	0	1.236732	0.075442	0.011703
15	15	0	3.491809	-0.677750	-0.552873
16	1	0	4.336700	-1.005686	0.540161
17	1	0	3.749619	-1.874244	-1.276325
18	15	0	1.217959	2.428314	0.127464
19	1	0	1.166744	3.122918	-1.103161
20	1	0	0.157036	3.114408	0.762760
21	16	0	-0.228936	-1.910722	0.051105
22	6	0	-0.484842	-0.525042	2.955380
23	1	0	0.594490	-0.318013	2.886838
24	1	0	-0.843124	-0.162982	3.923143
25	1	0	-0.612171	-1.619950	2.933416
26	6	0	-0.653820	-1.994978	-1.737613
27	1	0	-1.537850	-2.623378	-1.865872
28	1	0	-0.844171	-0.997350	-2.135659
29	1	0	0.190559	-2.432790	-2.272979
30	1	0	2.268421	3.199843	0.696599
31	1	0	4.468765	0.093966	-1.239123

HF = -1631.8485447

Figure S10. Optimized structure of **3'**

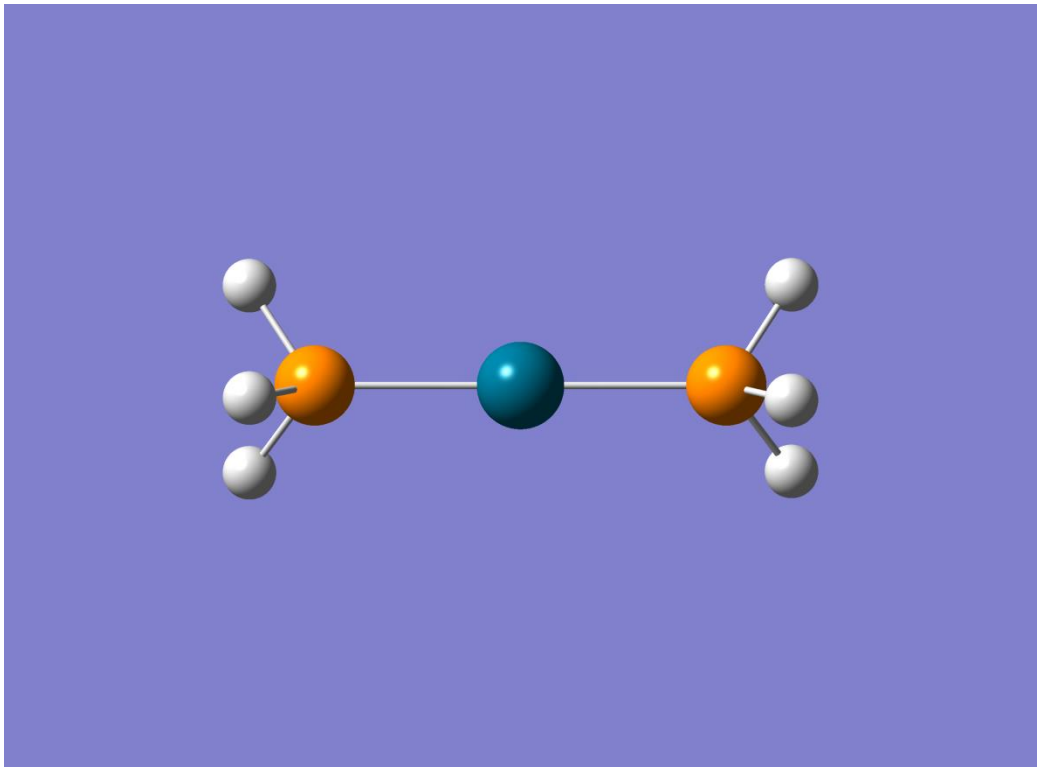


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-1.843320	0.185969	0.184423
2	6	0	-3.157677	-0.319526	-0.192832
3	1	0	-3.027223	-1.123764	-0.914412
4	1	0	-3.684567	-0.696731	0.691206
5	1	0	-3.762279	0.478621	-0.641580
6	6	0	-1.838404	1.257434	1.170843
7	1	0	-2.480396	0.970402	2.011433
8	1	0	-0.833281	1.441333	1.540498
9	1	0	-2.221877	2.191854	0.743145
10	6	0	-0.751086	-0.286462	-0.484149
11	8	0	-0.805454	-1.190339	-1.316209
12	6	0	0.597455	0.363921	-0.200579
13	7	0	0.722680	1.605896	-0.448062
14	16	0	1.963877	-0.689878	0.303419
15	6	0	1.203149	-2.332892	0.577790
16	6	0	2.030020	2.235792	-0.348006
17	1	0	1.936284	3.302089	-0.565460
18	1	0	2.462707	2.119986	0.656251

19	1	0	2.739927	1.797056	-1.062617
20	1	0	0.444928	-2.290997	1.361791
21	1	0	0.769106	-2.706956	-0.347028
22	1	0	2.022004	-2.974781	0.908815

HF = -818.7847194

Figure S11. Optimized structure of **$Pd(PPh_3)_2$**



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	46	0	-0.000002	-0.000493	0.000042
2	15	0	-2.303702	0.000691	-0.000136
3	1	0	-3.033601	1.117295	-0.482135
4	1	0	-3.032967	-0.975972	-0.725516
5	1	0	-3.032058	-0.140194	1.208704
6	15	0	2.303704	0.000752	-0.000145

7	1	0	3.034480	1.126883	-0.458039
8	1	0	3.031802	-0.166391	1.205487
9	1	0	3.032406	-0.960588	-0.746208

HF = -813.0900993

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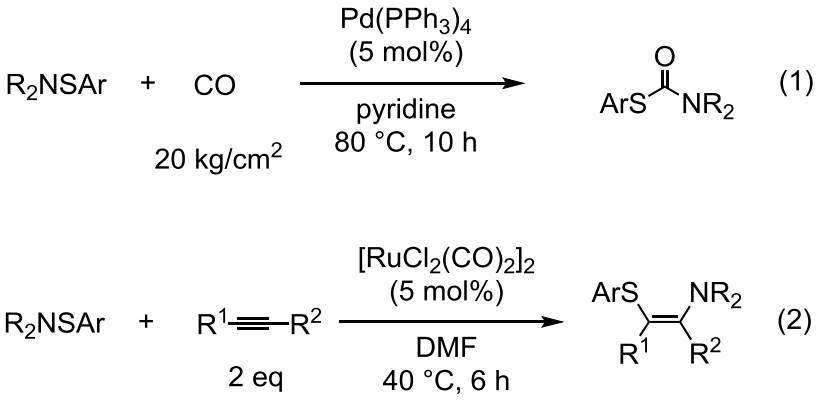
Chapter 3

$AlCl_3$-Catalyzed Insertion of Isocyanides into Nitrogen-Sulfur Bonds of Sulfenamides

3-1 Introduction

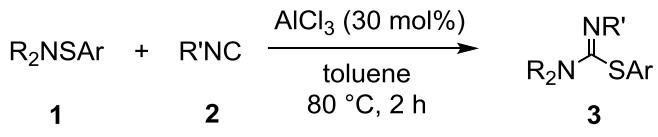
Sulfenamides, R_2NSR', are synthetically interesting and important compounds due to their wide availability[1,2] and the unique reactivity of the N-S bond.[1] Sulfenamides have been utilized as aminating reagents[3] and sulfenylating reagents[4] in addition to as aminyl radical precursors[5] and catalyst for oxidation of alcohols.[6] Furthermore, unsaturated molecules such as carbon monoxide and alkynes can be inserted into the N-S bond of sulfenamides. For example, Kurosawa and co-workers revealed for the first time in 1999 that the reaction of sulfenamides with carbon monoxide was catalyzed by $Pd(PPh_3)_4$ in pyridine to provide thiocarbamates in high yields (Scheme 1, eq 1).[7,8] Mitsudo and co-workers disclosed that the reaction of sulfenamides with alkynes was catalyzed by $[RuCl_2(CO)_2]_2$ in DMF to provide the corresponding adducts with high regio- and stereoselectivity (Scheme 1, eq 2).[9-13]

Scheme 1. Insertion of CO and alkynes into sulfenamides.



Here it is disclosed that $AlCl_3$ catalyzes insertion of isocyanides **2** into N-S bonds of sulfenamides **1** giving rise to the formation of isothioureas **3** (Scheme 2).

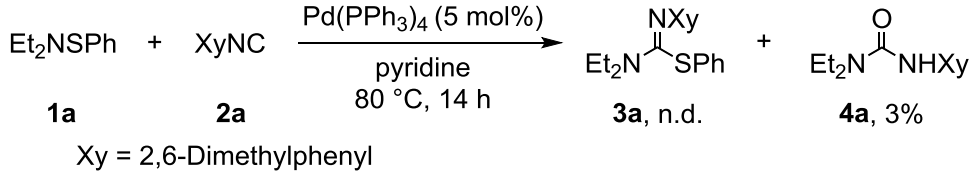
Scheme 2. $AlCl_3$-catalyzed syntheses of isothioureas from isocyanides and sulfenamides.



3-2 Results and Discussions

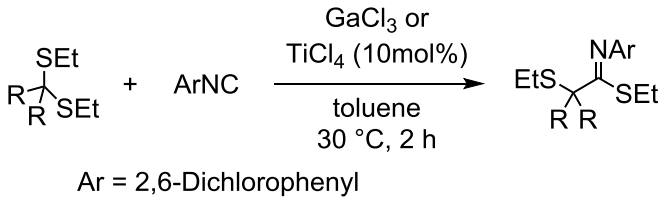
It was reported that thiophthalimides reacted with isocyanides without a catalyst in refluxing acetonitrile to give insertion products.[14] However, when a mixture of *S*-phenyl-*N*,*N*-diethylsulfenamide **1a** and 2,6-xylyl isocyanide **2a** in acetonitrile was heated under similar conditions, insertion reaction did not proceed at all. Then the palladium catalyzed system developed for azathiolation of carbon monoxide shown in Scheme 1 was examined. When a pyridine (0.4 mL) solution of sulfenamide **1a** (0.4 mmol), isocyanide **2a** (0.4 mmol), and $Pd(PPh_3)_4$ (5 mol%) was heated at 80 °C for 14 h, desired isothiourea **3a** was not formed and the corresponding urea **4a**, a hydrolyzed product of **3a**, was obtained in 3% yield (Scheme 3). Even after several trials by the use of other metal catalysts such as $Rh(PPh_3)_3Cl$ the yields of **3a** and **4a** were not improved so much.

Scheme 3. Reaction of a sulfenamide with an isocyanide in the presence of $Pd(PPh_3)_4$.



Recently, Chatani and co-workers disclosed that isocyanides reacted with dithioacetals to give insertion products in the presence of Lewis acids such as $GaCl_3$ and $TiCl_4$ (Scheme 4).[15]

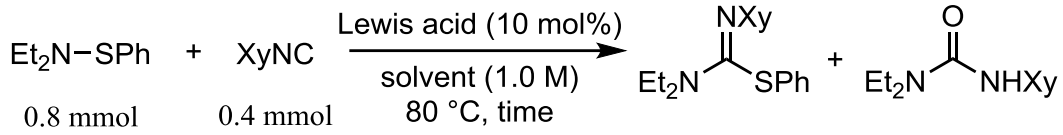
Scheme 4. Lewis acid-catalyzed insertion of isocyanides into a C-S bond of dithioacetals.



Then the reaction of sulfenamide **1a** with isocyanide **2a** was conducted in the presence of Lewis acids and the results are given in Table 1. When 2,6-xylyl isocyanide **2a** (0.4 mmol) was allowed to react with sulfenamide **1a** (2 equiv) in the presence of $GaCl_3$ (10 mol%) in DMF at 80 °C for 24 h, isothiourea **3a** was formed in 72% yield (entry 1). In this reaction, 8% of urea **4a** was also obtained; however, multiple insertion products incorporating more than one isocyanide molecules were not detected. In the case of $TiCl_4$, urea **4a** became the major product (entry 2). $InCl_3$, $ZrCl_4$ and BPh_3 exhibited similar activities as $GaCl_3$, and use of $AlCl_3$ gave the best selectivity (entries 3-9). Interestingly, when 1 equiv of acetic acid was employed as an additive, urea **4a** was formed in 79% yield (entry 10). Since 13% of isocyanide **2a** remained unreacted in run 4, we used 30 mol% of $AlCl_3$ but the yield of **3a** was improved only slightly (entries 4 and 11). Use of toluene as the solvent retarded the formation

of urea **4a** (entry 12). Isothiourea **3a** was obtained in good yield when the amount of sulfenamide **1a** was reduced to 1 equiv and the reaction time was shortened to 2 h (entry 13).[16]

Table 1. Screening of Lewis acids.



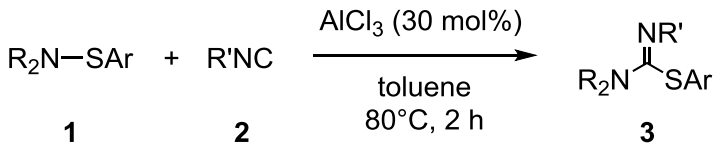
0.8 mmol **1a**, 2 equiv — 0.4 mmol **2a** — **3a** — **4a**

entry	Lewis acid	solvent	time (h)	yield **3a** (%)[a,b]	yield **4a** (%)[a,b]
1	$GaCl_3$	DMF	24	72	8
2	$TiCl_4$	DMF	24	32	50
3	$InCl_4$	DMF	24	72	9
4	$AlCl_3$	DMF	24	72	2
5	$ZrCl_4$	DMF	24	70	14
6	BBu_3	DMF	24	58	9
7	BPh_3	DMF	24	72	4
8	$B(C_6F_5)_3$	DMF	24	66	14
9	BF_3•OEt_2	DMF	24	72	10
10[c]	CH_3COOH	DMF	24	6	79(78)
11[d]	$AlCl_3$	DMF	24	75	3
12[d]	$AlCl_3$	toulene	24	81	n.d.
13[d,e]	$AlCl_3$	toluene	2	80(77)	n.d.

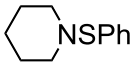
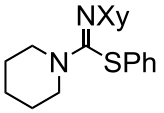
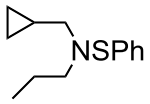
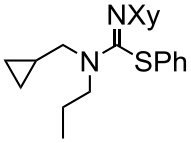
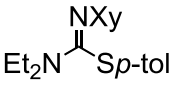
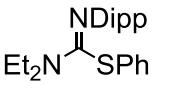
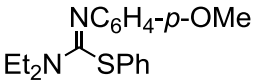
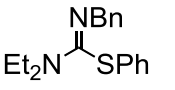
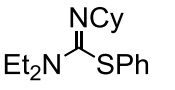
Conditions: **15a** (0.4 mmol), **14a** (2 equiv), Lewis acid (10 mol%), solvent (0.4 mL).
[a] NMR yields. [b] Isolated yield are in parentehses. [c] CH_3COOH (1 equiv).
[d] $AlCl_3$ (30 mol%). [e] **15a** (1 equiv).

Table 2 summarizes the results obtained using several sulfenamides **1** and isocyanides **2** under the optimized reaction conditions (entry 13 in Table 1). 2,6-Xylyl isocyanide **2a** was also inserted into sulfenamides **1b**, **1c** and **1d** affording the corresponding isothioureas **3b**, **3c** and **3d** in 79%, 69% and 70% yields, respectively (entries 1-3). The reaction of sterically hindered 2,6-diisopropylphenyl isocyanide **2b** gave isothiourea **3e** in 78% yield (entry4). Insertion of *p*-methoxyphenyl isocyanide **2c** was inefficient and **3f** was formed in 47% yield even when the reaction was run using 2 equiv of **2c** for prolonged reaction time (5 h) (entry 5). Aliphatic isocyanides could also be employed as suitable reagents. For example, the reaction of benzyl isocyanide **2d** with sulfenamide **1a** afforded the corresponding product **3g** in 93% yield (entry 6). However, the desired product **3h** was obtained in a low yield (35%) when cyclohexyl isocyanide **2e** was employed (entry 7). These isothioureas **3g** and **3h**, obtained from aliphatic isocyanides, were labile and easily hydrolyzed to ureas during purification by preparative TLC. So the isolation was performed by recycling preparative HPLC.

Table 2. $AlCl_3$-catalyzed reaction of isocyanides with sulfenamides leading to isothioureas.



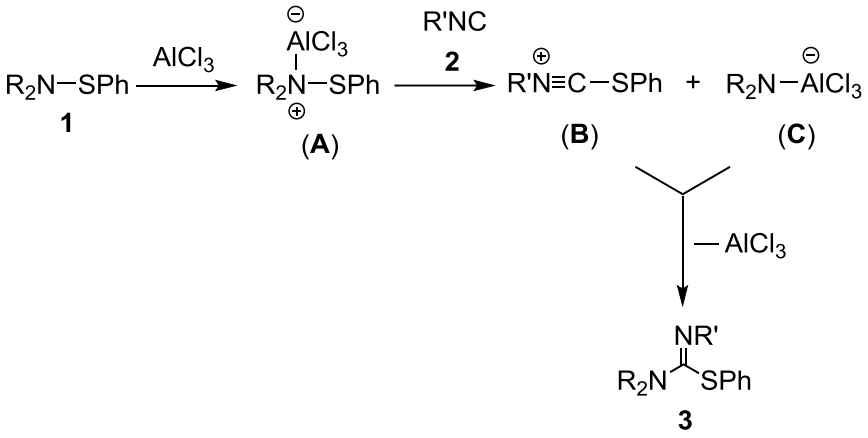
1 **2** **3**

entry	sulfenamide	isocyanide	isothiourea	yield[a]
1	 **1b**	XyNC **2a**	 **3b**	79%
2	 **1c**	**2a**	 **3c**	69%
3	Et_2NSp-tol **1d**	**2a**	 **3d**	70%
4[b]	Et_2NSPh **1a**	DippNC **2b**	 **3e**	78%
5[c]	**1a**	p-$MeOC_6H_4NC$ **2c**	 **3f**	47%
6	**1a**	BnNC **2d**	 **3g**	93%
7	**1a**	CyNC **2e**	 **3h**	35%

Conditions: sulfenamide **1** (0.4 mmol), isocyanide **2** (0.4 mmol), $AlCl_3$ (30 mol%), toluene (0.4 mL), 80°C, 2 h. [a] Isolated yield. [b] DippNC = 2,6-Diisopropylphenyl isocyanide. [c] p-$MeOC_6H_4NC$ (2 equiv), 5 h.

The reaction pathway for the present $AlCl_3$-catalyzed insertion of isocyanides into sulfenamides is not clear yet but a possible pathway was depicted in Scheme 5. The N-S bond in sulfenamide **1** is activated by the coordination of $AlCl_3$ to the nitrogen atom generating **A**. Then isocyanide **2** attacks the sulfur atom of the intermediate **A** to generate an ion pair **B** and **C** which then react with each other to afford an isothiourea **3**.

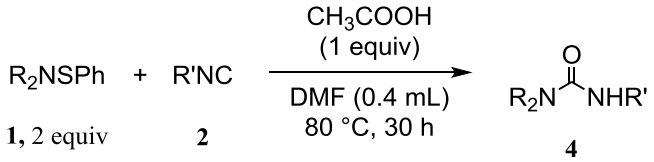
Scheme 5. A possible reaction pathway.

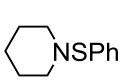
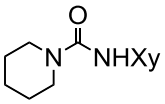
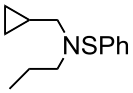
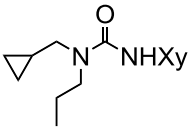
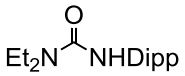
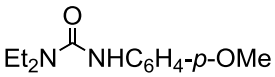


Isothioureas are useful and interesting compounds as inhibitors of nitric oxide synthases (NOS)[17] and Lewis base organocatalysts.[18] As for the synthesis of isothioureas, they have been usually prepared by the alkylation of isolated or *in situ* generated thioureas.[19] The present method described here is synthetically useful since various isothioureas are obtained by a convenient one-pot procedure from easily available substrates.

Finally, a one-pot synthesis of unsymmetrical ureas **4** was undertaken under the reaction conditions employed in run 10 in Table 2, and the results are summarized in Table 3. In all entries unsymmetrical ureas **4** were obtained in moderate to high yields.[20]

Table 3. Acetic acid-assisted preparation of unsymmetrical ureas from isocyanides and sulfenamides.



entry	sulfenamide	isocyanide	urea	yield[a]
1		XyNC		77%
	1b	**2a**	**4b**	
2		**2a**		81%
	1c		**4c**	
3	Et_2NSPh	DippNC		72%
	1a	**2b**	**4d**	
4	**1a**	*p*-$MeOC_6H_4NC$		50%
		2c	**4e**	

Conditions: sulfenamide **1** (0.8 mmol), isocyanide **2** (0.4 mmol), CH_3COOH (0.4 mmol), DMF (0.4 mL), 80 °C, 30 h. [a] Isolated yield. [b] DippNC = 2,6-Diisopropylphenyl isocyanide.

3-3 Conclusions

A simple and convenient reaction for the synthesis of isothioureas by Lewis acid-catalyzed insertion of isocyanides into the N-S bond of sulfenamides has been developed. Since only a few classical preparative methods of isothioureas are available, the present new approach would attract considerable attention as a practical supplemental method for isothiourea synthesis.

3-4 Experimental Section

General

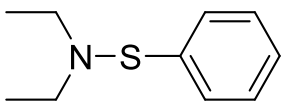
^{1}H NMR and ^{13}C NMR spectra were recorded with JEOL JNM-Alice 400 (400 and 100 MHz, respectively) spectrometers using $CDCl_3$ as the solvent and Me_4Si as an internal standard in 5 mm NMR tubes. Chemical shifts are reported in parts per million (d) downfield from internal tetramethylsilane. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet), coupling constant (Hz), integration. Infrared spectra (IR) were obtained on a JASCO Corporation FT/IR-4200 instrument equipped with ATR PRO450-S. Both conventional and high-resolution mass spectra were recorded using a JEOL JMS-DX303HF spectrometer (EI) or a JEOL JMS-T100TD (DART). Elemental analyses were performed at Instrumental Analysis Center, Faculty of Engineering, Osaka University. HPLC separations were performed on a recycling preparative HPLC (Japan Analytical; Model LC-908) equipped with JAIGEL-1H and -2H columns or Shodex K2001 and 2002 columns (GPC) using $CHCl_3$ as the eluent.

2,6-Xylyl isocyanide **2a**[21] and 2,6-diisopropylphenyl isocyanide **2b**[22] were synthesized according to the literature procedure. $AlCl_3$, *p*-methoxyphenyl isocyanide (Sigma-Aldrich, Tokyo, Japan), benzyl isocyanide, cyclohexyl isocyanide (Tokyo Chemical Industry, Tokyo, Japan), and dehydrated solvents (Wako Pure chemical, Osaka, Japan) were purchased and used as received.

Syntheses of sulfenamides 1a-d

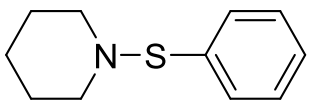
Sulfenamides **1a-d** were obtained by the reaction of diaryl disulfides with the corresponding amines in methanol in the presence of 1 equiv of $AgNO_3$.[23]

***S*-Phenyl-*N*,*N*-diethylsulfenamide (1a)**:



^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.0 Hz, 6 H), 2.99 (q, *J* = 7.2 Hz, 21.2 Hz, 4 H), 7.10-7.14 (m, 1 H), 7.24-7.33 (m, 4 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.7, 52.1, 125.0, 125.4, 128.5, 141.1 ppm. IR (neat) 2973, 2921, 1582, 1475, 1439, 1380, 1290, 1236, 1177, 1090, 1023, 892, 737, 691 cm^{-1}; MS (EI) m/z (relative intensity, %) 181 (M^+, 100), 166 (90), 123 (3), 109 (20), 56 (7); Anal. HRMS (EI) calcd for $C_{10}H_{15}NS$: 181.0925, Found 181.0924.

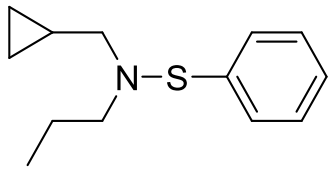
***N*-(Phenylthio)piperidine (1b)**:



^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.33-1.39 (m, 2 H), 1.61-1.66 (m, 4 H), 2.94 (t, *J* = 5.4 Hz, 4 H), 7.21-7.51 (m, 5 H) ppm.

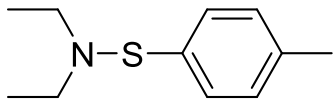
^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.1, 27.3, 57.6, 127.1, 127.2, 127.4, 128.5, 129.1, 129.6, 136.1, 137.0 ppm. IR (neat) 2934, 2817, 1739, 1582, 1474, 1439, 1367, 1217, 1149, 1101, 1024, 917, 857, 735, 689 cm^{-1}; MS (EI) m/z (relative intensity, %) 193 (M^+, 100), 110 (6), 84 (30); Anal. HRMS (EI) calcd for $C_{11}H_{15}NS$: 193.0925, Found 193.0924.

***N*-(Cyclopropylmethyl)-*S*-phenyl-*N*-propylsulfenamide (1c)**:



^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.17 (q, *J* = 6.0 Hz, 15.2 Hz, 2 H), 0.47-0.51 (m, 2 H), 0.89 (t, *J* = 7.4 Hz, 3 H), 1.03-1.08 (m, 1 H), 1.60-1.69 (m, 2 H), 2.89 (d, *J* = 6.8 Hz, 2 H), 2.98-3.01 (m, 2 H), 7.09-7.13 (m, 1 H), 7.26-7.33 (m, 4 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 3.8, 10.5, 11.5, 21.7, 59.7, 63.9, 124.3, 125.1, 128.5, 142.0 ppm. IR (neat) 3074, 3003, 2959, 2931, 2872, 2837, 1582, 1475, 1439, 1381, 1329, 1167, 1081, 1044, 1019, 828, 736, 689 cm^{-1}; MS (EI) m/z (relative intensity, %) 221 (M^+, 91), 192 (100), 180 (8), 164 (13), 150 (5), 138 (7), 123 (6), 109 (7), 72 (4), 55 (18); Anal. HRMS (EI) calcd for $C_{13}H_{19}NS$: 221.1238, Found 221.1239.

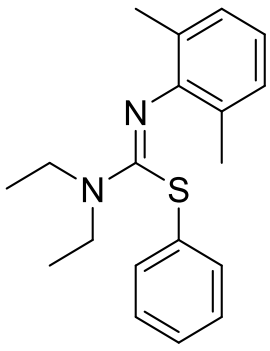
***N*,*N*-Diethyl-*S*-(4-methylphenyl)sulfenamide (1d)**:



^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.2 Hz, 6 H), 2.29 (s, 3 H), 2.90 (q, *J* = 6.8 Hz, 21.6 Hz, 6 H), 7.07-7.09 (m, 2 H), 7.23-7.25 (m, 2 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.6, 20.9, 51.8, 127.2, 129.2, 135.6, 135.6, 135.8 ppm. IR (neat) 2971, 2930, 2846, 1597, 1490, 1445, 1375, 1177, 1135, 1112, 1080, 1058, 1032, 1015, 965, 803, 678 cm^{-1}; MS (EI) m/z (relative intensity, %) 195 (M^+, 81), 180 (73), 165 (4), 139 (4), 123 (100), 91 (7), 79 (7), 56 (7); Anal. HRMS (EI) calcd for $C_{11}H_{17}NS$: 195.1082, Found 195.1081.

Typical procedure of $AlCl_3$-catalyzed insertion of isocyanides into nitrogen-sulfur bonds of sulfenamides:

Into a 5-mL flask equipped with a reflux condenser were placed 2,6-xylyl isocyanide **2a** (0.4 mmol), sulfenamide **1a** (0.4 mmol), toluene (0.4 mL), and $AlCl_3$ (0.12 mmol) at room temperature under N_2. The mixture was heated at 80 ºC for 2 h, then filtered through the celite pad with EtOAc, and volatiles were removed in vacuo. After the yield was determined by ^{1}H NMR (80%), the crude product was purified by preparative TLC (silica gel, *n*-hexane / Et_2O = 10:1, Rf = 0.60) to obtain phenyl *N'*-(2,6-dimethylphenyl)-*N*,*N*-diethylcarbamimidothioate **3a** in 77% yield as a colorless oil.

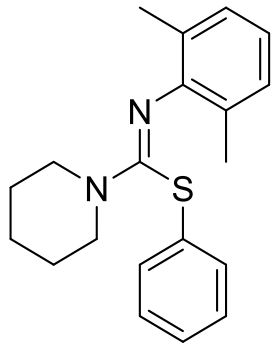


Phenyl-*N'*-(2,6-dimethylphenyl)-*N*,*N*-diethylcarbamimidothioate (3a)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.15 (t, *J* = 6.8 Hz, 6 H), 2.04 (s, 6 H),

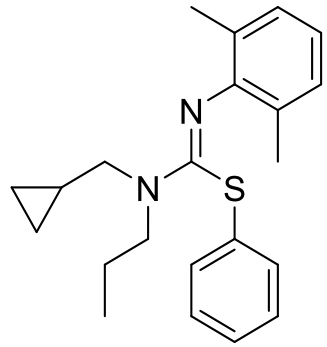
3.53 (q, *J* = 7.2 Hz, 21.2 Hz, 3 H), 6.77-6.81 (m, 1 H), 6.88-6.90 (m, 2 H), 7.12-7.20 (m, 5 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.3, 18.6, 44.1, 122.1, 127.0, 127.4, 128.7, 128.8, 131.1, 133.1, 147.8, 150.8 ppm. IR (neat) 2970, 2930, 2866, 1604, 1580, 1471, 1440, 1375, 1359, 1246, 1222, 1181, 1110, 1081, 871, 761, 743, 702, 687 cm^{-1}; MS (EI) m/z (relative intensity, %) 312 (M^+, 6), 203 (100), 159 (3), 145 (6), 132 (7), 105 (4), 72 (22); Anal. HRMS (EI) calcd for $C_{19}H_{24}N_2S$: 312.1660, Found 312.1662.

Phenyl-*N*-(2,6-dimethylphenyl)piperidine-1-carbimidothioate (3b)



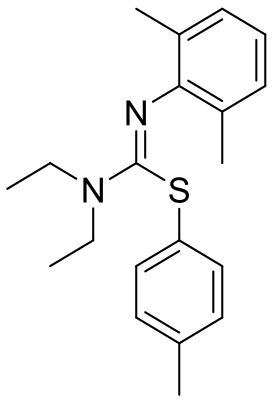
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.37-1.42 (m, 4 H), 1.52-1.58 (m, 2 H), 2.11 (s, 6 H), 3.47 (t, *J* = 5.4 Hz, 4 H), 6.83-6.87 (m, 1 H), 6.96-6.98 (m, 2 H), 7.16-7.28 (m, 5 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.5, 24.9, 25.4, 49.5, 122.5, 127.1, 127.5, 128.5, 128.8, 131.5, 133.4, 147.7, 154.2 ppm. IR (neat) 2934, 2852, 1605, 1581, 1472, 1440, 1371, 1224, 1173, 1120, 1087, 1023, 1008, 882, 849, 761, 741, 702, 687 cm^{-1}; MS (EI) m/z (relative intensity, %) 324 (M^+, 7), 215 (100), 130 (10), 105 (6), 84 (65), 41 (6); Anal. HRMS (EI) calcd for $C_{20}H_{24}N_2S$: 324.1660, Found 324.1658.

Phenyl-*N*-(cyclopropylmethyl)-*N'*-(2,6-dimethylphenyl)-*N*-propylcarbamimidothioate (3c)



^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.24 (q, *J* = 5.2 Hz, 15.2 Hz, 2 H), 0.50-0.55 (m, 2 H), 0.89 (t, *J* = 7.2 Hz, 3 H), 1.03-1.10 (m, 1 H), 1.60-1.69 (m, 2 H), 2.04 (s, 6 H), 3.38 (d, *J* = 6.8 Hz, 2 H), 3.50 (t, *J* = 7.6 Hz, 3 H), 6.78-6.81 (m, 1 H), 6.89-6.91 (m, 2 H), 7.15-7.19 (m, 5 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 3.7, 9.8, 11.5, 18.6, 21.2, 51.3, 54.1, 122.1, 126.9, 127.4, 128.7, 128.8, 131.0, 133.3, 147.9, 151.7 ppm. IR (neat) 2964, 2873, 1595, 1459, 1353, 1307, 1207, 1136, 1101, 1048, 932, 864, 826, 795, 722, 657 cm^{-1}; MS (EI) m/z (relative intensity, %) 352 (M^+, 6), 243 (100), 201 (18), 189 (7), 159 (7), 130 (7), 55 (26); Anal. HRMS (EI) calcd for $C_{22}H_{28}N_2S$: 352.1973, Found 352.1976.

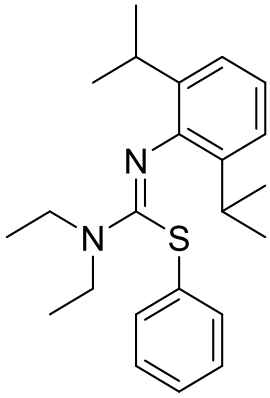
***p*-Tolyl-*N'*-(2,6-dimethylphenyl)-*N*,*N*-diethylcarbamimidothioate (3d)**:



^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 6.8 Hz, 6 H), 2.04 (s, 6 H), 2.27 (s, 3 H), 3.51 (q, *J* = 6.8 Hz, 21.2 Hz, 4 H), 6.77-6.81 (m, 1 H), 6.88-6.90 (m, 2 H), 6.95-6.97 (m, 2 H), 7.04-7.06 (m, 2 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.3, 18.6, 21.1, 44.0, 122.0, 127.4, 128.8, 129.4, 129.4, 131.3, 137.1, 147.9, 151.4 ppm. IR (neat) 2988, 2939, 1739, 1605, 1582, 1464, 1435, 1369, 1219, 1113, 1086, 1017,

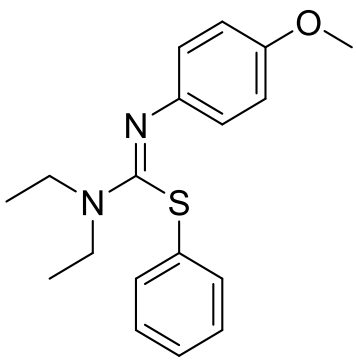
872, 805, 759, 704 cm^{-1}; MS (EI) m/z (relative intensity, %) 326 (M^+, 4), 203 (100), 145 (5), 132 (5), 105 (3), 72 (13); Anal. HRMS (EI) calcd for $C_{20}H_{26}N_2S$: 326.1817, Found 326.1814.

Phenyl-*N'*-(2,6-diisopropylphenyl)-*N,N*-diethylcarbamimidothioate (3e):



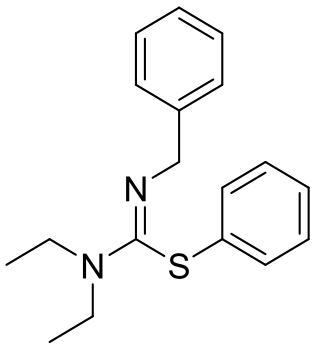
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.09 (t, *J* = 7.0 Hz, 6 H), 1.16 (q, *J* = 4.0 Hz, 18.0 Hz, 12 H), 2.97 (sept, *J* = 6.8 Hz, 13.6 Hz, 20.4 Hz, 2 H), 3.44 (q, *J* = 6.8 Hz, 20.8 Hz, 4 H), 6.98-7.06 (m, 3 H), 7.13-7.25 (m, 5 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.0, 22.9, 23.7, 28.2, 43.8, 122.5, 122.7, 126.7, 128.8, 130.4, 134.1, 138.6, 145.4, 150.8 ppm. IR (neat) 2959, 2866, 1599, 1359, 1324, 1256, 1231, 1173, 1095, 1065, 1041, 1003, 936, 872, 798, 780, 755, 692 cm^{-1}; MS (EI) m/z (relative intensity, %) 368 (M^+, 7), 259 (100), 186 (81), 171 (8), 144 (7), 109 (4), 72 (4); Anal. HRMS (EI) calcd for $C_{23}H_{32}N_2S$: 368.2286, Found 368.2288.

Phenyl-*N,N*-diethyl-*N'*-(4-methoxyphenyl)carbamimidothioate (3f):



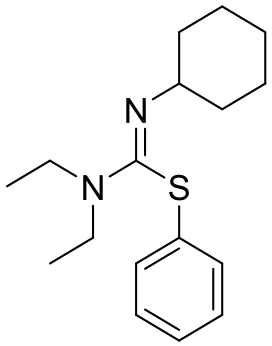
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.14 (t, *J* = 6.8 Hz, 6 H), 3.55 (q, *J* = 6.8 Hz, 20.8 Hz, 4 H), 3.73 (s, 3 H), 6.58-6.68 (m, 4 H), 7.09-7.18 (m, 5 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.4, 44.1, 55.4, 113.6, 122.8, 126.4, 128.7, 130.2, 133.8, 144.3, 151.0, 154.9 ppm. IR (neat) 2992, 2931, 2905, 2831, 1590, 1571, 1503, 1400, 1283, 1237, 1225, 1185, 1111, 1037, 877, 827, 741, 687 cm^{-1}; MS (EI) m/z (relative intensity, %) 314 (M^+, 8), 205 (100), 176 (17), 161 (4), 133 (10), 100 (4); Anal. HRMS (EI) calcd for $C_{18}H_{22}N_2OS$: 314.1453, Found 314.1454.

Phenyl-*N'*-benzyl-*N,N*-diethylcarbamimidothioate (3g):



^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.09 (t, *J* = 6.8 Hz, 6 H), 3.51 (q, *J* = 6.8, 21.2 Hz, 4 H), 4.69 (s, 2 H), 7.13-7.19 (m, 2 H), 7.22-7.28 (m, 8 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.6, 43.8, 56.3, 125.9, 126.0, 127.2, 128.0, 128.3, 129.1, 134.5, 142.1, 149.8 ppm. IR (neat) 2973, 2875, 2820, 1579, 1494, 1424, 1396, 1342, 1296, 1252, 1214, 1120, 1022, 846, 819, 730, 696 cm^{-1}; MS (EI) m/z (relative intensity, %) 299 (M^+, 100), 226 (7), 207 (5), 189 (57), 111 (6), 91 (5); Anal. HRMS (CI) calcd for $C_{18}H_{22}N_2S$: 298.1504, Found 298.1506.

Phenyl-*N'*-cyclohexyl-*N*,*N*-diethylcarbamimidothioate (3h):

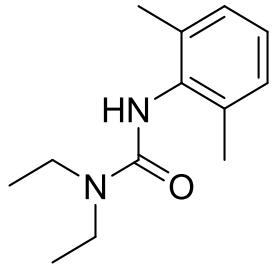


^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.98 (t, *J* = 6.8 Hz, 6 H), 1.10-1.42 (m, 5 H), 1.55-1.58 (m, 3 H), 1.69-1.73 (m, 2 H), 3.36 (q, *J* = 6.8 Hz, 21.2 Hz, 4 H), 3.57-3.64 (m, 1 H), 7.13-7.19 (m, 1 H), 7.24-7.26 (m, 4 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ13.1, 24.9, 25.9, 35.1, 43.5, 61.0, 125.8, 128.9, 128.9, 135.5, 146.8 ppm. IR (neat) 2925, 2851, 1739, 1599, 1478, 1446, 1375, 1357, 1345, 1305, 1248, 1213, 1147, 1065, 1024, 970, 894, 852, 737, 687 cm^{-1}; MS (EI) m/z (relative intensity, %) 291 (M^+, 63), 218 (19), 199 (6), 181 (100), 111 (7), 99 (8); Anal. HRMS (CI) calcd for $C_{17}H_{26}N_2S$: 290.1817, Found 290.1819.

Typical procedure of acetic acid- assisted preparation of unsymmetrical ureas from isocyanides and sulfenamides:

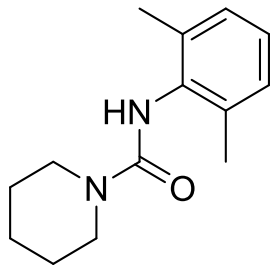
Into a 5-mL flask equipped with a reflux condenser were placed 2,6-xylyl isocyanide **2a** (0.4 mmol), sulfenamide **1a** (0.8 mmol), DMF (0.4 mL), and acetic acid (0.4 mmol) at room temperature under N_2. The mixture was heated at 80 ºC for 30 h, then filtered through the celite pad with AcOEt, and volatiles were removed in vacuo. After the yield was determined by ^{1}H NMR (79%), the crude product was purified by preparative TLC (silica gel, *n*-hexane / Et_2O = 10:1, Rf = 0.10) to obtain 3-(2,6-dimethylphenyl)-1,1-diethylurea **4a** in 78% yield as a white needle.

3-(2,6-Dimethylphenyl)-1,1-diethylurea (4a):



^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7.2 Hz, 6 H), 2.23 (s, 6 H), 3.36 (q, *J* = 7.2 Hz, 21.6 Hz, 4 H), 5.75 (s, 1 H), 7.01-7.07 (m, 3 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.1, 18.5, 41.6, 126.2, 128.0, 135.6, 155.1 ppm. IR (neat) 3266, 2970, 2926, 1626, 1590, 1511, 1449, 1396, 1377, 1279, 1224, 1172, 1094, 1077, 1048, 972, 826, 788, 727, 700 cm^{-1}; MS (EI) m/z (relative intensity, %) 220 (M^+, 46), 205 (4), 147 (7), 120 (5), 100 (100), 72 (41), 58 (7), 44 (6); Anal. HRMS (EI) calcd for $C_{13}H_{20}N_2O$: 220.1576, Found 220.1575. mp; 178-179°C

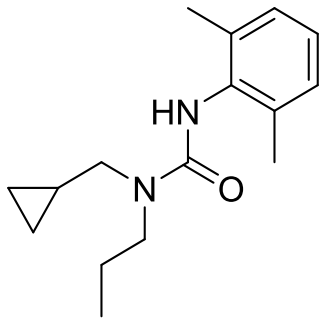
***N*-(2,6-Dimethylphenyl)piperidine-1-carboxamide (4b)**:



^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.56-1.68 (m, 6 H), 2.22 (s, 6 H), 3.42 (t, *J* = 5.2 Hz, 4 H), 5.85 (s, 1 H), 7.00-7.08 (m, 3 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.4, 24.5, 25.8, 45.5, 126.2, 128.0, 135.3, 135.5, 155.7 ppm. IR (neat) 3311, 3037, 2938, 2850, 1632, 1522, 1505, 1467, 1441, 1387, 1356,1267, 1253, 1235, 1129, 1086, 1023, 981, 898, 851, 766, 730, 701 cm^{-1}; MS (EI) m/z (relative intensity, %) 232 (M^+, 54), 217 (15), 147 (51), 132 (15), 119 (20), 112 (100), 84 (30), 69 (50),

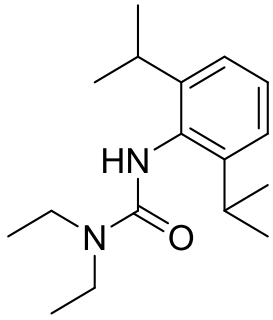
41 (15); Anal. HRMS (EI) calcd for $C_{14}H_{20}N_2O$: 232.1576, Found 232.1573.

1-(Cyclopropylmethyl)-3-(2,6-dimethylphenyl)-1-propylurea (4c):



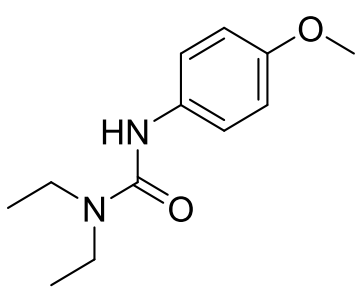
^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.27 (q, *J* = 6.0 Hz, 15.2 Hz, 2 H), 0.55-0.60 (m, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H), 0.96-1.08 (m, 1 H), 1.19-1.23 (m, 2 H), 1.66-1.73 (m, 2 H), 2.23 (s, 6 H), 3.25 (d, *J* = 6.4 Hz, 2 H), 3.34 (t, *J* = 7.6 Hz, 2 H), 5.89 (s, 1 H), 7.01-7.07 (m, 3 H) ppm.^{13}C-NMR (100 MHz, $CDCl_3$): δ 3.8, 3.9, 10.6, 11.4, 14.1, 14.1, 18.5, 21.9, 28.7, 41.5, 41.7, 49.5, 51.6, 123.2, 123.2, 126.2, 127.4, 128.1, 132.8, 135.5, 135.6, 146.5, 155.7 ppm. IR (neat) 3270, 2965, 2872, 1743, 1618, 1588, 1518, 1490, 1378, 1333, 1306, 1260, 1244, 1213, 1171, 1117, 1060, 1015, 935, 827, 780, 742 cm^{-1}; MS (EI) m/z (relative intensity, %) 260 (M^+, 40), 231 (5), 203 (8), 176 (5), 147 (11), 140 (25), 134 (18), 121 (12), 100 (14), 84 (19), 72 (10), 55 (100); Anal. HRMS (EI) calcd for $C_{16}H_{24}N_2O$: 260.1889, Found 260.1887.

3-(2,6-Diisopropylphenyl)-1,1-diethylurea (4d):



^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.20-1.25 (m, 18 H), 3.12 (quint, *J* = 6.8 Hz, 13.6 Hz, 2 H), 3.39 (q, *J* = 7.6 Hz, 21.2 Hz, 4 H), 5.65 (s, 1 H), 7.14-7.26 (m, 3 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.1, 23.6, 28.7, 41.7, 123.2, 127.4, 132.8, 146.5, 155.9 ppm. IR (neat) 3301, 2860, 2868, 1739, 1628, 1599, 1559, 1504, 1450, 1400, 1361, 1275, 1208, 1077, 972, 863, 807, 792, 741 cm^{-1}; MS (EI) m/z (relative intensity, %) 276 (M^+, 17), 233 (26), 203 (96), 188 (100), 176 (28), 160 (21), 146 (34), 100 (75), 72 (35), 58 (22); Anal. HRMS (EI) calcd for $C_{17}H_{28}N_2O$: 276.2202, Found 276.2203.

1,1-Diethyl-3-(4-methoxyphenyl)urea (4e):



^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 6 H), 3.37 (q, *J* = 7.6 Hz, 21.6 Hz, 4 H), 3.78 (s, 3 H), 6.12 (s, 1 H), 6.82-6.86 (m, 2 H), 7.26-7.30 (m, 2 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.9, 41.6, 55.5, 114.1, 122.1, 132.3, 155.0, 155.7 ppm. IR (neat) 3330, 2975, 2930, 1639, 1513, 1420, 1297, 1266, 1243, 1165, 1037, 826, 756 cm^{-1}; MS (EI) m/z (relative intensity, %) 222 (M^+, 49), 149 (100), 134 (49), 106 (22), 100 (65), 72 (38), 58 (24); Anal. HRMS (EI) calcd for $C_{12}H_{18}N_2O_2$: 222.1368, Found 222.1367.

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Summary

In this thesis, the studies on palladium or Lewis acid catalyzed cleavage of carbon-chalcogen bonds or nitrogen-sulfur bond and the subsequent decarbonylative rearrangement reaction of allenes or insertion of isocyanides were described. These aspects would be good representations showing great potential of organochalcogen compounds for various catalytic transformations in organic chemistry.

In chapter 1, palladium-catalyzed decarbonylative rearrangement of *N*-allenyl seleno- and tellurocarbamates was described. In this system, decarbonylative rearrangement proceeded by the treatment of *N*-allenyl seleno- and tellurocarbamates with the palladium catalyst to give 3-seleno or 3-telluro-1-azadienes with the use of *rac*-BINAP as a ligand. This transformation involves unusual decarbonylation from carbamoyl-Pd units. In addition, a four-membered lactam incorporating no chalcogen atom was obtained as a major product in moderate yields by using $PPhMe_2$ as the ligand.

In chapter 2, the first example of the transition metal catalyzed insertion reactions of isocyanides into thiocarbamates and selenocarbamates were described. This protocol could also be applied to the insertion of isocyanides into carbon-selenium bonds. DFT calculations indicate that the reaction proceeds via a *thiopalladation* pathway and not a *carbopalladation* pathway.

In chapter 3, a simple and convenient reaction for the synthesis of isothioureas by $AlCl_3$-catalyzed insertion of isocyanides into the N-S bond of sulfonamides was disclosed. Since only a few classical preparative methods of isothioureas are available, the present new approach would attract considerable attention as a practical supplemental method for isothiourea synthesis. Acetic acid-assisted, one-pot preparation of unsymmetrical ureas from isocyanides and sulfenamides was also described.

These new aspects revealed through this study show a great benefit in transition metal- and Lewis acid-catalyzed unique transformation using organochalcogen compounds with allenes and isocyanides. Any further developments of these reactions are expected to be based on the works in this thesis.

List of Publications

(1) "Palladium-Catalyzed Decarbonylative Rearrangement of *N*-Allenyl Seleno- and Tellurocarbamates"
Shiro, D.; Nagai, H.; Fujiwara, S.; Tsuda, S.; Iwasaki, T.; Kuniyasu, H.; Kambe, N. *Heteroatom Chem.* **2014**, *25*, 518.

(2) "Palladium-Catalyzed Insertion Reactions of Isocyanides into Thiocarbamates and Selenocarbamates"
Shiro, D.; Fujiwara, S.; Tsuda, S.; Iwasaki, T.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2015**, *accepted* (doi: 10.1246/cl.141141).

(3) "$AlCl_3$-Catalyzed Insertion of Isocyanides into Nitrogen-Sulfur Bonds of Sulfenamides"
Shiro, D.; Fujiwara, S.; Tsuda, S.; Iwasaki, T.; Kuniyasu, H.; Kambe, N. *Tetrahedron Lett.* **2015**, *accepted* (doi:10.1016/j.tetlet.2015.01.096).

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