Studies on the Development of Multi-Functionalization of Acetylenes via Selective Introduction of Group 16 Heteroatoms

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Preface

This thesis deals with the studies conducted during April 2015 to March 2018 under the guidance of Professor Akiya Ogawa at the Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University.

This thesis is concerned with the development of the highly selective multiple introduction of group 16 heteroatoms and some other functional groups to acetylenes. Two important topics of this thesis are 1) the development of transition-metal-catalyzed simultaneous introduction of thio group and C1 units such as carbonyl and cyano groups; 2) the novel metal-free transformation of alkynes using a benzoyl peroxide/diphenyl diselenide binary system.

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List of Abbreviations

Functional Groups

Me	methyl	Et	ethyl
^{n}Pr	normal propyl	^{i}Pr	isopropyl
^{n}Bu	normal butyl	^{t}Bu	*tert*-butyl (tertiary butyl)
^{n}Pen	normal pentyl	^{n}Hex	normal hexyl
Ph	phenyl	Ar	aryl
Ac	acetyl	TMS	trimethylsilyl
Tf	trifluoromethanesulfonyl		

Organic Compounds

CO	carbon monoxide	BPO	benzoyl peroxide
LPO	dilauroyl peroxide	CPO	dicumyl peroxide
TBPB	*tert*-butyl perbenzoate	DTBP	di-*tert*-butyl peroxide
TBHP	*tert*-butyl hydroperoxide	TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	dppe	1,2-bis(diphenylphosphino)ethane
acac	acetylacetonate	cod	1,5-cyclooctadiene
dba	dibenzylideneacetone	pin	pinacolato
DMF	*N*,*N*-dimethylformamide	NMP	*N*-methylpyrrolidone
DCE	1,2-dichloroethane	BTF	benzotrifluoride
THF	tetrahydrofuran	DME	1,2-dimethoxyethane

Technical Terms

N.D.	not detected	N.R.	no reaction
rt	room temperature	NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect	HMBC	heteronuclear multiple bond coherence
HRMS	high resolution mass spectrometry	FAB	fast atom bombardment method
EI	electron ionization method	ESI	electrospray ionization method
IR	infrared spectroscopy	ORTEP	Oak Ridge thermal-ellipsoid plot program
PTLC	preparative tin layer chromatography	HPLC	high performance liquid chromatography
GPC	gel permeation chromatography	GC-MS	gas chromatography - mass spectrometry

Contents

Chapter 1

General Introduction

Organic synthesis creates essential chemical products for our lives from fossil and natural resources, and it is fundamental technology to realize an affluent modern society. In recent decades, with the dramatically development of functional materials, their chemical structures have become increasingly diversified. Therefore, rapid development of high efficient and selective organic reactions is required for the synthesis of a wide variety of chemical compounds. However, in many cases, these reactions, which synthesize functional materials and fine chemicals, require multi-step methods, and the resulting production of large amounts of wastes provides serious problems.[1] Therefore, the development of more direct and efficient synthetic methods for these compounds is a significant research problem in this decade.

In most of highly functional molecules, heteroatoms located at a particular position of carbon frameworks provide various functionalities. In particular, group 16 heteroatoms, such as sulfur and selenium are known to provide bioactivities and physical properties.[2] Thus, the development of highly selective and efficient methods for introduction of group 16 heteroatoms into organic molecules is of great importance. In addition, sulfur and selenium are largely produced in industry in Japan, and therefore, beneficial use of these elements is strongly desired.

Simultaneous introduction of heteroatom functional groups and other groups into organic molecules is one of the most useful tools for the direct synthesis of heteroatom containing multi-functionalized compounds.[3] In general, transition-metal-catalyzed addition and radical addition are employed for these transformations. Transition-metal-catalyzed additions of group

16 heteroatom compounds to alkynes have been developed by overcoming the nature of catalyst poison of group 16 heteroatoms.[4] Based on these researches, the series of transition-metal-catalyzed simultaneous introduction of group 16 heteroatom compounds and other compounds into unsaturated bond were also developed.[5,6] On the other hand, in recent decade, the developments of innovative photoinduced radical addition reactions of two heteroatom compounds based on characteristic features of group 16 heteroatoms were reported by Ogawa's research group and other groups.[7]

In this thesis, the author has developed highly selective multiple introduction of group 16 heteroatom substituents and other substituents to acetylenes. The first important topic of this thesis is the novel transition-metal-catalyzed simultaneous introduction of thio group, carbonyl group, and cyano group to alkyne derivatives (Chapters 2 and 3). The second topic is the development of metal-free addition reaction using a benzoyl peroxide/diphenyl diselenide binary system (Chapter 4).

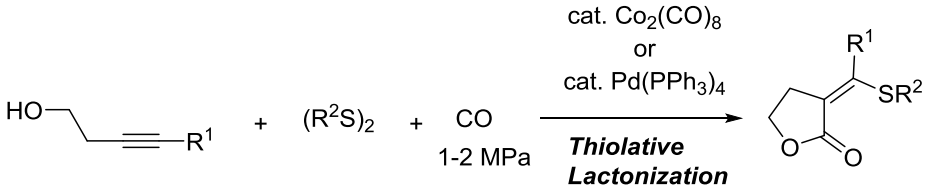
This thesis is consisted of five chapters and the outlines of each chapter are summarized as follows.

Chapter 1 describes the background, general objectives, and the contents of this thesis.

Chapter 2 describes a novel transition-metal-catalyzed thiolative lactonization of internal alkynes bearing a hydroxyl group with carbon monoxide and organic disulfides (Scheme 1-1).[8] Although many transition-metal catalysts are ineffective for the addition and carbonylative addition of organic disulfides to internal alkynes,[4,5,6] dicobalt octacarbonyl and palladium complexes such as $Pd(PPh_3)_4$ and $Pd(OAc)_2$ were found to exhibit excellent catalytic activity for the thiolative lactonization of internal alkynes bearing a hydroxyl group. In the presence of the cobalt or palladium catalyst, internal alkynes bearing a hydroxyl group, such as homopropargyl alcohol derivatives, successfully undergo thiolative carbonylation with carbon monoxide and

organic disulfides, regio- and stereoselectively to afford the corresponding thiolated lactones in good yields. In the Co-catalyzed reaction, the cobalt−alkyne complexes derived from dicobalt octacarbonyl and internal alkynes act as key species,[6] making it possible to attain thiolative lactonization of internal alkynes with a hydroxyl group (Scheme 1-1). In the Pd-catalyzed reaction, the coordination of the hydroxyl group to the palladium catalyst plays an important role for the thiolative lactonization.

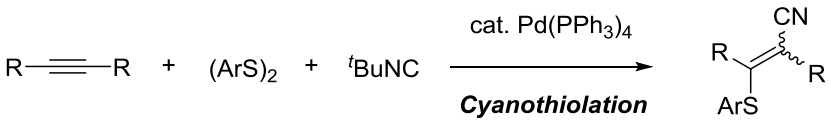
Scheme 1-1. Chapter 2



Chapter 3 describes a novel Pd-catalyzed cyanothiolation of internal alkynes with organic disulfides and *tert*-butyl isocyanide (Scheme 1-2). Simultaneous introduction of heteroatom functional groups and cyano group into carbon–carbon triple bonds is an attractive one-carbon increasing method for synthesis of heteroatom-containing alkenyl cyanides directly, because alkenyl cyanides are highly versatile and widely used in several important materials.[9] The author's group and other groups previously developed cyanothiolation of terminal alkynes or arynes with thiocyanates catalyzed by palladium or cobalt complexes.[10] These reactions proceeded to afford the corresponding sulfur-containing alkenyl cyanides or 1,2-thiobenzonitriles in one step. However, the cyanothiolation reaction of unactivated internal alkynes has been much less explored, despite the reaction provides selective synthetic method of multi-functionalized tetrasubstituted olefin. Recently, only very limited examples of cyanothiolation with other reagents such as sulfur compounds and cyano source have been reported.[11] The author focused on the use of isocyanide as a cyano source, and developed transition-metal-catalyzed cyanothiolation of internal alkynes with organic disulfides and *tert*-butyl isocyanide. This cyanation, therefore,

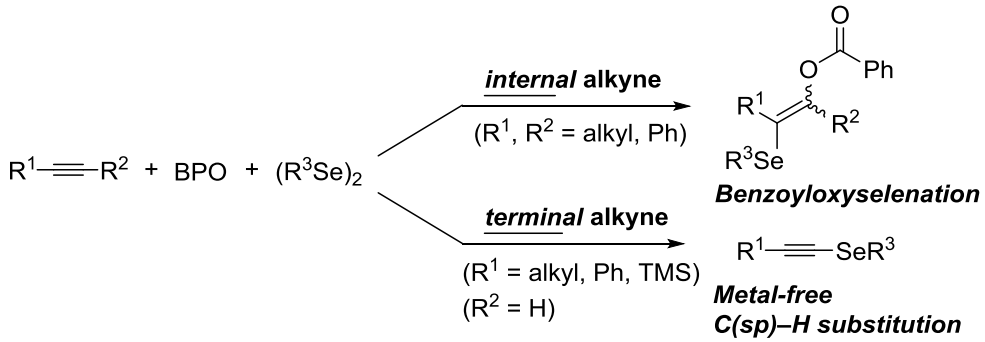
does not require the use of toxic cyanides, because *tert*-butyl isocyanide works as a safe cyano source as shown in Scheme 1-2.[12]

Scheme 1-2. Chapter 3



Chapter 4 describes a benzoyl peroxide/diphenyl diselenide binary system for selective functionalization of alkynes leading to alkenyl and alkynyl selenides (Scheme 1-3).[13] The selective radical addition of heteroatom compounds to unsaturated compounds is one of the most useful heterofunctionalization methods of unsaturated compounds in organic synthesis, because radical reactions have good tolerance to solvents and functional groups.[14] The Ogawa's research group recently developed a series of highly selective radical addition reactions of heteroatom compounds to alkynes; thereby allowing the simultaneous introduction of two heteroatom groups into alkynes at the vicinal positions.[7] Thus, to apply this methodology to oxygen-containing groups, the author developed the reaction of alkynes with benzoyl peroxide (BPO) as an oxygen functional group and diphenyl diselenide as an excellent carbon-radical-trapping reagent. Binary systems consisting of benzoyl peroxide (BPO) and diselenide are effective for the selective benzoyloxyselenation of internal alkynes to afford the corresponding *β*-(benzoyloxy)alkenyl selenides in good yields. In contrast to internal alkynes, terminal alkynes undergo a novel C(sp)–H substitution with the phenylseleno group, providing alkynyl selenides in good yields. Both selenation reactions might proceed via benzoyloxy selenide (PhC(O)O–SeAr) as a key intermediate for electrophilic addition to alkynes. The product alkenyl and alkynyl selenides are known to be useful synthetic intermediates in organic synthesis.

Scheme 1-3. Chapter 4



Chapter 5 describes the conclusion of this thesis.

This thesis describes a series of selective multiple introduction of group 16 heteroatom substituents and other substituents into unsaturated compounds. These works will open up eco-friendly refined synthesis of multi-functionalized group 16 heteroatom compounds.

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Chapter 2

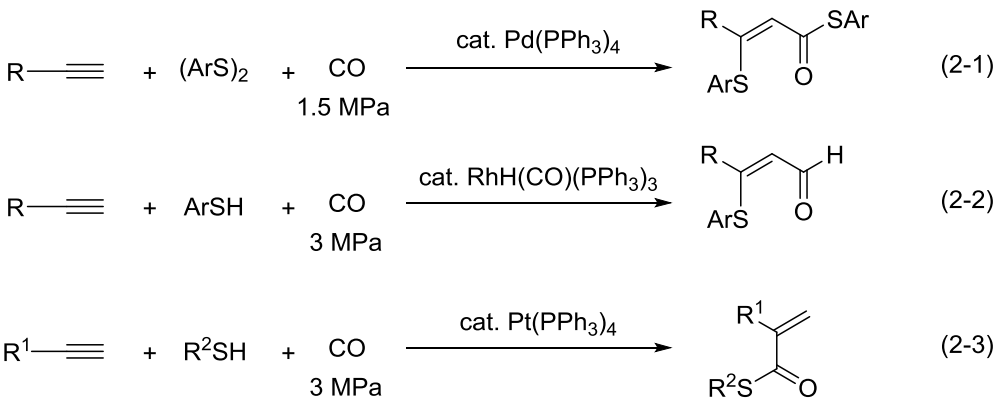
Selective Thiolative Lactonization of Internal Alkynes Bearing a Hydroxyl Group with Carbon Monoxide and Organic Disulfides Catalyzed by Transition-Metal Complexes

2-1 Introduction

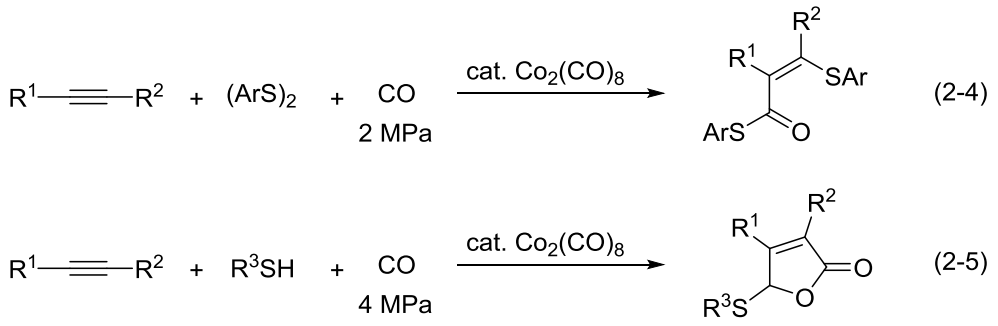
Transition-metal-catalyzed simultaneous introduction of heteroatom functional groups and carbon monoxide into organic molecules is one of the most important tools for the direct synthesis of heteroatom-functionalized carbonyl compounds.[1] Organosilicon compounds, such as hydrosilanes, are widely employed for this purpose.[2]

Organosulfur compounds are useful synthetic intermediates; however, only a very limited number of examples of transition-metal-catalyzed carbonylation with concurrent introduction of sulfur functional groups have been reported.[3,4] Recently, a series of transition-metal-catalyzed carbonylations of terminal alkynes with CO and organosulfur compounds, such as thiols and disulfides, was reported. For example, the palladium-catalyzed reaction of terminal alkynes with CO and $(ArS)_2$ affords the corresponding β-(arylthio)-α,β-unsaturated thioesters regio- and stereoselectively (Eq 2-1).[5] Rhodium complexes catalyze the regio- and stereoselective thioformylation of terminal alkynes with CO and ArSH (Eq 2-2),[6] whereas platinum complexes catalyze the hydrothioesterification of terminal alkynes with CO and R^2SH regioselectively (Eq 2-3).[7] However, these thiolative carbonylation reactions could not be applied to internal alkynes, most probably due to the increased steric

hindrance around them.

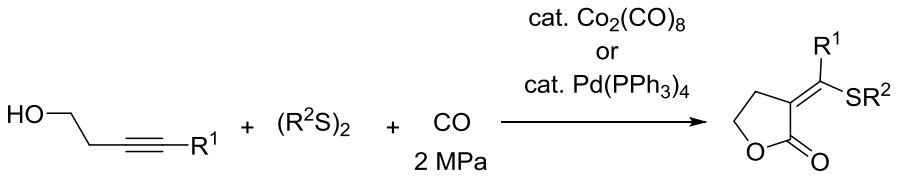


These reactions (Eqs 2-1−2-3) are assumed to proceed via the initial formation of metal−sulfide complexes, followed by their coordination by alkynes. In contrast to Pd or Rh complexes, cobalt carbonyl ($Co_2(CO)_8$) easily complexes internal alkynes to give cobalt−alkyne complexes. This coordination property of $Co_2(CO)_8$ may make it possible to attain novel thiolative carbonylation of internal alkynes. On the basis of this idea, the author has recently developed a method for the cobalt-catalyzed thiolative mono- and double carbonylation of internal alkynes with CO and disulfides or thiols. (Eqs 2-4 and 2-5).[8,9] During the course of this study, the author also found that, in the case of internal alkynes bearing a hydroxyl group, novel thiolative carbonylation took place regioselectively to afford the corresponding thiolated lactone derivatives bearing an *exo*-methylene group.



In this chapter, the author reports the cobalt-catalyzed thiolative lactonization of internal alkynes bearing a hydroxyl group with CO and disulfides. In addition, a comparison of this

thiolative lactonization to the corresponding palladium-catalyzed carbonylation is reported (Eq 2-6).



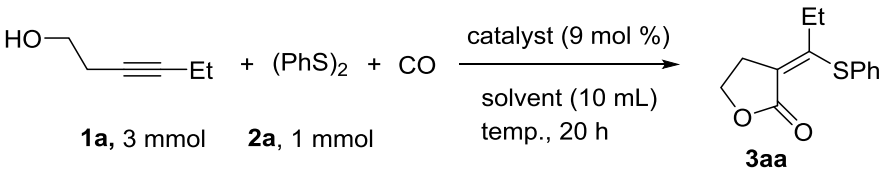
(2-6)

2-2 $Co_2(CO)_8$-Catalyzed Thiolative Lactonization of Internal Alkynes

When the reaction of 3-hexyn-1-ol **1a** (1.0 mmol) with diphenyl disulfide **2a** (1.0 mmol) under carbon monoxide (2 MPa) in toluene (10 mL) is conducted using 9 mol % of $Co_2(CO)_8$ at 140 °C for 20 h, thiolative lactonization occurs to give the corresponding *γ*-lactone derivative **3aa** bearing an *exo*-methylene group in 30% yield (Table 2-1, entry 1). The structure of **3aa** was determined unambiguously by X-ray structural analysis (Figure 2-1). As can be seen from the ORTEP representation of **3aa**, carbon monoxide is introduced regioselectively to the acetylenic carbon bonded to the hydroxyethyl group, and the thio group is located at the *cis* position of the carbonyl group. Therefore, the present thiolative carbonylation of **1a** apparently proceeds regio- and stereoselectively. The yield of **3aa** is dramatically improved with the use of excess **1a** (Table 2-1, entries 2 and 3). Higher CO pressure (3 MPa) does not increase the yield of **3aa** (Table 2-1, entry 4); however, lower CO pressure (1 MPa, 0.1 MPa) decreases the yield (Table 2-1, entries 5 and 6). With decreasing temperature, the yields of **3aa** decrease (Table 2-1, entries 7−9). Prolonging the reaction time to 40 h does not influence the yield (Table 2-1, entry 10). Decreasing the amount of the catalyst to 3 mol % results in a decrease of the yield of **3aa** (Table 2-1, entry 11). With a polar solvent (CH_3CN), the yield of **3aa** slightly decreases (Table 2-1, entry 12). Addition of 1,2-bis(diphenylphosphino)ethane (dppe) decreases the yield (Table 2-1, entry

13). Some other cobalt catalysts were investigated, and $Co(acac)_2$ also exhibited catalytic activity in this thiolative lactonization (Table 2-1, entry 14). However, with this catalyst, a regioisomeric carbonylation derivative **4aa** is also obtained. The optimum result is obtained when the thiolative carbonylation is performed under 2 MPa of CO in toluene at 140 °C for 20 h (Table 2-1, entry 3).

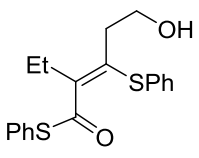
Table 2-1. $Co_2(CO)_8$-Catalyzed Thiolative Lactonization of 3-Hexyn-1-ol with $(PhS)_2$



1a, 3 mmol **2a**, 1 mmol **3aa**

entry	catalyst	CO, MPa	solvent	temp., °C	yield, %[a]
1[b]	$Co_2(CO)_8$	2	toluene	140	30
2[c]	$Co_2(CO)_8$	2	toluene	140	52
3	$Co_2(CO)_8$	2	toluene	140	82 (71)
4	$Co_2(CO)_8$	3	toluene	140	80
5	$Co_2(CO)_8$	1	toluene	140	68
6	$Co_2(CO)_8$	0.1	toluene	140	6
7	$Co_2(CO)_8$	2	toluene	120	62
8	$Co_2(CO)_8$	2	toluene	110	54
9	$Co_2(CO)_8$	2	toluene	100	30
10[d]	$Co_2(CO)_8$	2	toluene	140	80
11[e]	$Co_2(CO)_8$	2	toluene	140	78
12	$Co_2(CO)_8$	2	CH_3CN	140	60
13[f]	$Co_2(CO)_8$	2	toluene	140	50
14[g,h]	$Co(acac)_2 \cdot 2H_2O$	2	toluene	140	64
15[i]	$CoCl_2 \cdot 6H_2O$	2	toluene	140	trace
16[i]	$Co(OAc)_2 \cdot 4H_2O$	2	toluene	140	N.R.

[a] Determined by ^1H NMR (isolated). [b] 3-Hexyn-1-ol (1.0 mmol) was used. [c] 3-Hexyn-1-ol (1.5 mmol) was used. [d] Reaction time (40 h). [e] Catalyst (3 mol %).
[f] 1,2-Bis(diphenylphosphino)ethane (dppe, 18 mol %) was added. [g] Catalyst (5 mol %).
[h] Regioisomeric carbonylation byproduct **4aa** was obtained. [i] Catalyst (18 mol %).



4aa

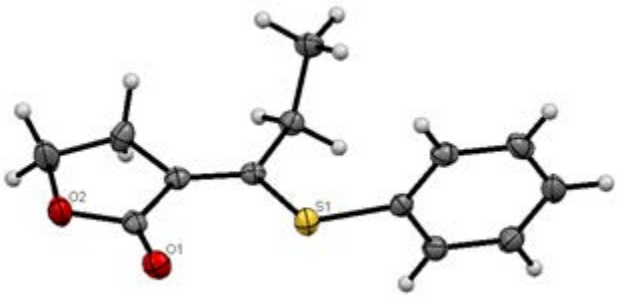
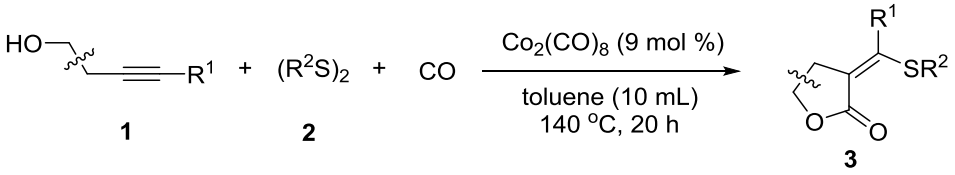


Figure 2-1. An ORTEP Drawing of **3aa** with Ellipsoids at 50% Probability

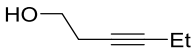
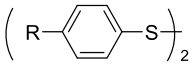
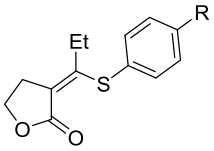
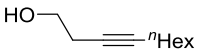
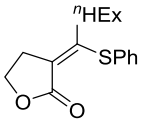
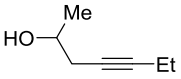
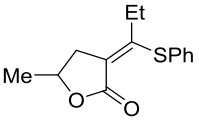
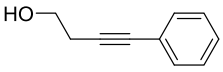
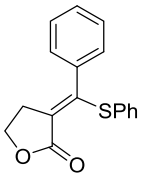
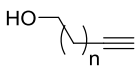
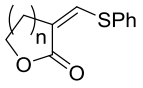
Next, the thiolative lactonization was examined using several hydroxyalkynes and diaryl disulfides under the optimized reaction conditions (Table 2-1, entry 3), and the results are shown in Table 2-2. In the cases of diaryl disulfides having an electron-donating (**2b**, **2c**) or electron-withdrawing group (**2d**), the thiolative lactonization proceeded successfully to give the corresponding γ-lactone derivatives **3ab**, **3ac**, and **3ad**, respectively, in good yields (Table 2-2, entries 2−4). Substituted hydroxyalkynes **1b** and **1c** also underwent the thiolative lactonization regio- and stereoselectively in high yields (Table 2-2, entries 5 and 6). The thiolative lactonization of **1d** took place to give thiolated lactone **3da** in 27% yield along with some byproducts (the conversion of disulfide was 78%) (Table 2-2, entry 7). The thiolative lactonization of terminal alkynes **1e** and **1f** was also attempted, and the corresponding γ- and δ-lactone derivatives **3ea** and **3fa** were obtained, respectively, although the yield of **3fa** was low (Table 2-2, entries 8 and 9). In the case of **1f**, the (*E*)-isomer of **3fa** was also obtained in 23% yield.

To gain insight into the reaction pathway for this thiolative lactonization, the same reaction was examined using a cobalt−alkyne complex as catalyst (Eq 2-7). As a result, the thiolative lactonization of **1a** proceeded successfully to give **3aa** in 81% yield. The result suggests that the cobalt−alkyne complex is a key species in this thiolative lactonization. In this $Co_2(CO)_8$-catalyzed thiolative lactonization, most of the catalyst was soluble in solution (toluene), and therefore, the reaction may proceed by homogeneous catalysis.[10] Although the precise

Table 2-2. $Co_2(CO)_8$-Catalyzed Thiolative Lactonization of Internal Alkynes with Disulfides[a]

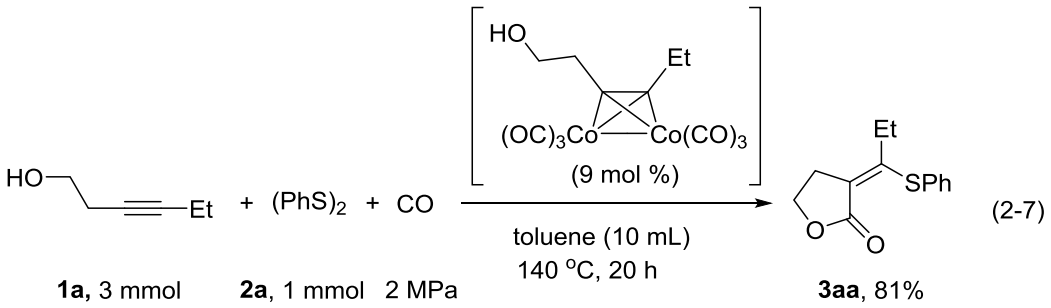


1 **2** **3**

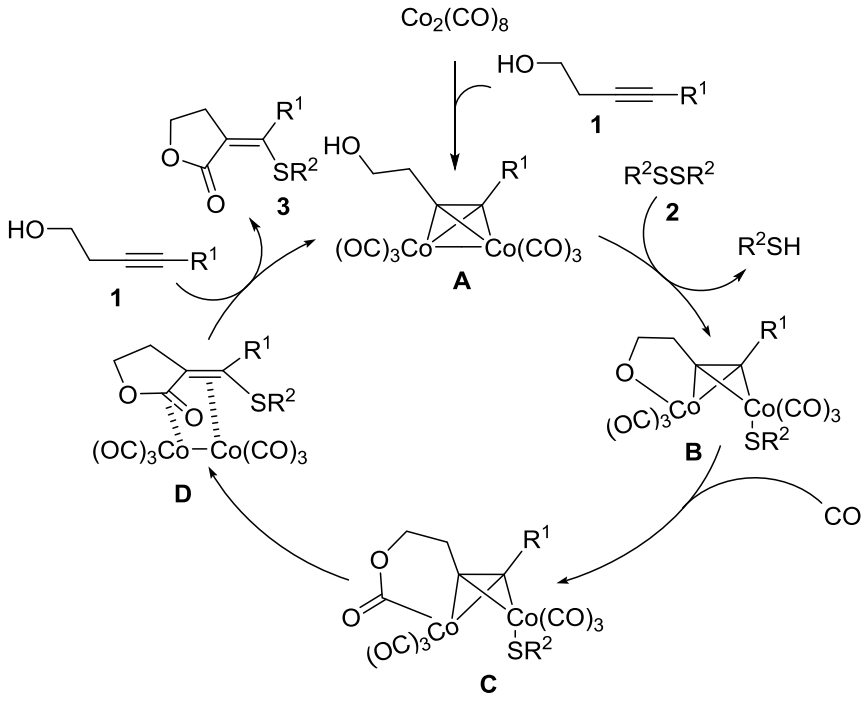
entry	alkyne **1**	disulfide **2**	yield, %[b]
			
1	**1a**	R = H (**2a**)	**3aa**, 82 (71)
2		Me (**2b**)	**3ab**, 71 (64)
3		OMe (**2c**)	**3ac**, 73 (65)
4		Cl (**2d**)	**3ad**, 81 (75)
5		$(PhS)_2$	
	1b	**2a**	**3ba**, 93
6		$(PhS)_2$	
	1c	**2a**	**3ca**, 90 (76)
7		$(PhS)_2$	
	1d	**2a**	**3da**, 27
		$(PhS)_2$	
8	n = 1 (**1e**)	**2a**	**3ea**, 82 (51)
9	2 (**1f**)		**3fa**, 39 (19)

[a] Reaction conditions: alkyne (3.0 mmol), disulfide (1.0 mmol), CO (2 MPa), toluene (10 mL), $Co_2(CO)_8$ (9 mol %), 140 °C, 20 h. [b] Determined by ^1H NMR (isolated).

mechanism for this cobalt-catalyzed thiolative lactonization requires further detailed mechanistic experiments, an outline of a possible pathway is shown in Scheme 2-1. Initially, $Co_2(CO)_8$ reacts with acetylenic alcohol **1** to form cobalt−alkyne complex **A**. Intramolecular coordination of the hydroxyl group of **1** to the cobalt atom of complex **A** and reaction with disulfide **2** leads to complex **B** with concomitant formation of the thiol. The formation of the thiol was confirmed by monitoring the reaction mixture by ^{1}H NMR. CO insertion gives complex **C**, followed by reductive elimination to form complex **D**. The subsequent ligand-exchange reaction with substrate **1** affords the desired thiolated lactone derivative **3** with regeneration of complex **A**.



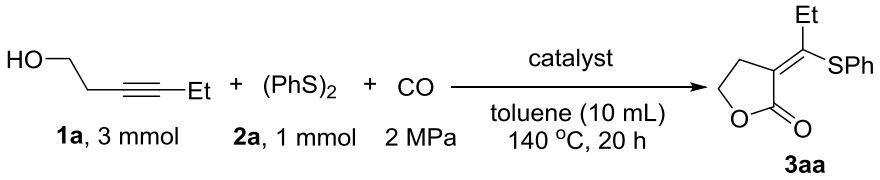
Scheme 2-1. A Possible Pathway for the $Co_2(CO)_8$-Catalyzed Thiolative Lactonization



2-3 Palladium-Catalyzed Thiolative Lactonization of Internal Alkynes

To clarify the catalyst scope of the thiolative lactonization, the author next examined the carbonylation of 3-hexyn-1-ol **1a** with CO and diphenyl disulfide **2a** by varying the catalysts, and the results are shown in Table 2-3. Among the catalysts examined, ruthenium (Table 2-3, entry 3), rhodium (Table 2-3, entry 4), nickel (Table 2-3, entries 5 and 6), and palladium (Table 2-3, entries 8−16) complexes exhibit catalytic activity in the thiolative carbonylation. Among them, $Pd(PPh_3)_4$ is the best catalyst. Interestingly, increasing the amount of the catalyst leads to

Table 2-3. Transition Metal-Catalyzed Thiolative Lactonization of 3-Hexyn-1-ol



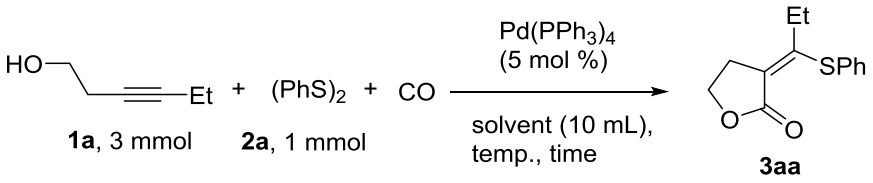
entry	catalyst		yield, %[a]
1	none		N.R.
2	$Co_2(CO)_8$	9 mol %	82
3	$RuHCl(CO)(PPh_3)_3$	5 mol %	38
4	$Rh_2Cl_2(cod)_2$	2.5 mol %	30
5	$NiCl_2$	5 mol %	24
6	$Ni(acac)_2 \cdot 2H_2O$	5 mol %	32
7	$(PPh_3)AuNTf_2$	5 mol %	N.D.
8	$PdCl_2$	5 mol %	68
9	$Pd(OAc)_2$	5 mol %	58
10	$Pd(OAc)_2$	18 mol %	76
11[b]	$PdCl_2$	5 mol %	78
12[b]	$Pd(OAc)_2$	5 mol %	82
13	$Pd_2(dba)_3 \cdot CHCl_3$	2.5 mol %	66
14	$Pd(PPh_3)_4$	5 mol %	95
15	$Pd(PPh_3)_4$	2 mol %	78
16	$Pd(PPh_3)_4$	18 mol %	98

[a] Determined by ^1H NMR. [b] PPh_3 (10 mol %) was added.

exclusive formation of the desired **3aa** (Table 2-3, entry 16). In the absence of catalyst, no reaction is observed (Table 2-3, entry 1).

Further detailed optimization of the thiolative lactonization conditions was investigated using 5 mol % of $Pd(PPh_3)_4$, and the results are shown in Table 2-4. Both lower and higher CO pressures slightly decrease the yield of **3aa** (Table 2-4, entries 1, 2, and 4). A decrease in the temperature (Table 2-4, entries 5 and 6) or the amount of **1a** (Table 2-4, entry 7) dramatically decreases the yield of **3aa**. The thiolative lactonization also proceeds in CH_3CN or PhCN as solvent (Table 2-4, entries 8 and 9). Even in 10 h, the thiolative lactonization proceeds well (Table 2-4, entry 10).

Table 2-4. Palladium-Catalyzed Thiolative Lactonization of 3-Hexyn-1-ol with $(PhS)_2$



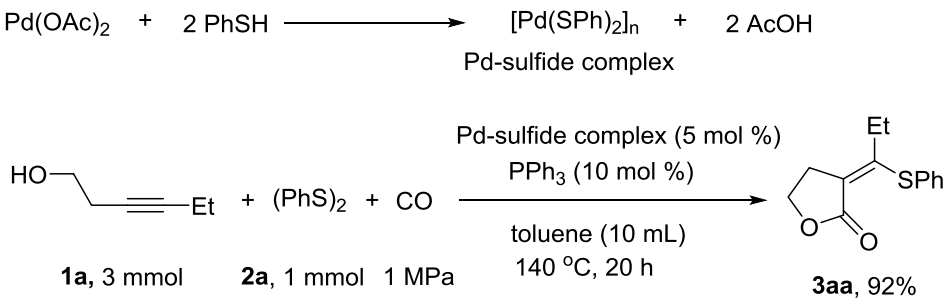
entry	CO, MPa	solvent	temp., °C	time, h	yield, %[a]
1	0.5	toluene	140	20	78
2	1	toluene	140	20	88 (83)
3	2	toluene	140	20	95
4	3	toluene	140	20	87
5	2	toluene	120	20	71
6	2	toluene	100	20	8
7[b]	2	toluene	140	20	48
8	2	CH_3CN	140	20	76
9	1	PhCN	140	20	98
10	2	toluene	140	10	91
11	2	toluene	140	40	84

[a] Determined by ^1H NMR (isolated). [b] 3-Hexyn-1-ol (1.2 mmol).

To investigate the scope and limitation of substrates, thiolative lactonization using a variety of acetylenic alcohols **1** and organic disulfides **2** in the presence of $Pd(PPh_3)_4$ catalyst was examined, and the results are shown in Table 2-5. When the reaction of hydroxyalkyne **1** (3.0 mmol) with diphenyl disulfide (1.0 mmol) was conducted in the presence of $Pd(PPh_3)_4$ (5 mol %) in toluene (10 mL) at 140 °C for 20 h, the corresponding *γ*-lactone **3** is obtained. Methoxy, chloro, and nitro groups on the *para*-position of disulfides **2c**, **2d**, and **2e** are tolerant to the thiolative lactonization (Table 2-5, entries 3−5). Similarly, both electron-donating (Table 2-5, entries 9 and 10) and electron-withdrawing (Table 2-5, entry 11) groups on the *para*-position of acetylenic alcohols **1g**, **1h**, and **1i** are also tolerant to the reaction conditions. In the case of **1d**, the conversion of disulfide was 56%, and some byproducts were obtained. A similar result was obtained from **1i**. Not only *γ*-lactones, but also *δ*-lactone **3ja**, can be synthesized by this thiolative lactonization, although the yield of **3ja** is lower compared with those of the *γ*-lactones (Table 2-5, entry 12).

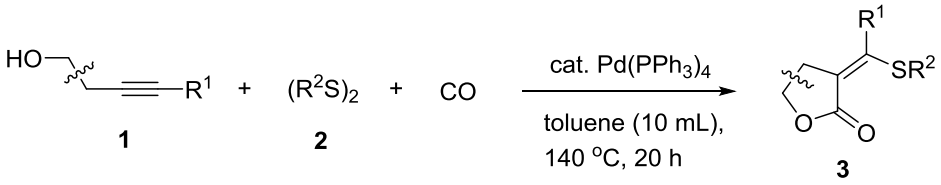
To obtain insight into the present Pd-catalyzed thiolative lactonization, the author examined the catalytic thiolative lactonization of acetylenic alcohols using a preformed Pd−sulfide complex (Scheme 2-2). Initially, the Pd−sulfide complex was prepared by reaction of $Pd(OAc)_2$ with benzenethiol according to the literature.[11] The reaction of 3-hexyn-1-ol (**1a**) with diphenyl disulfide (**2a**), triphenylphosphine, and CO in the presence of 5 mol % of Pd−sulfide

Scheme 2-2. Pd-Sulfide Complex Catalyzed Thiolative Lactonization

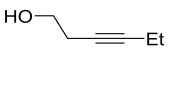
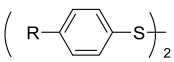
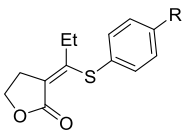
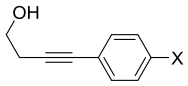
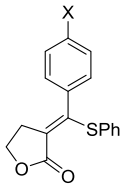
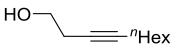
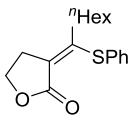
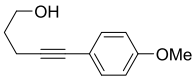
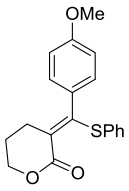
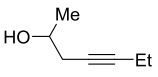
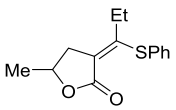


complex as a catalyst afforded the corresponding γ-lactone derivative (**3aa**) in 92% yield. This result suggests that the Pd−sulfide complex is a highly effective catalyst for the thiolative lactonization of acetylenic alcohols. In this $Pd(PPh_3)_4$-catalyzed thiolative lactonization, large amounts of a reddish brown solid (most probably Pd−sulfide cluster) were formed during the reaction. Therefore, the Pd-catalyzed reaction may proceed by heterogeneous catalysis.[12]

Table 2-5. Palladium-Catalyzed Thiolative Lactonization of Acetylenic Alcohols with Disulfides[a]

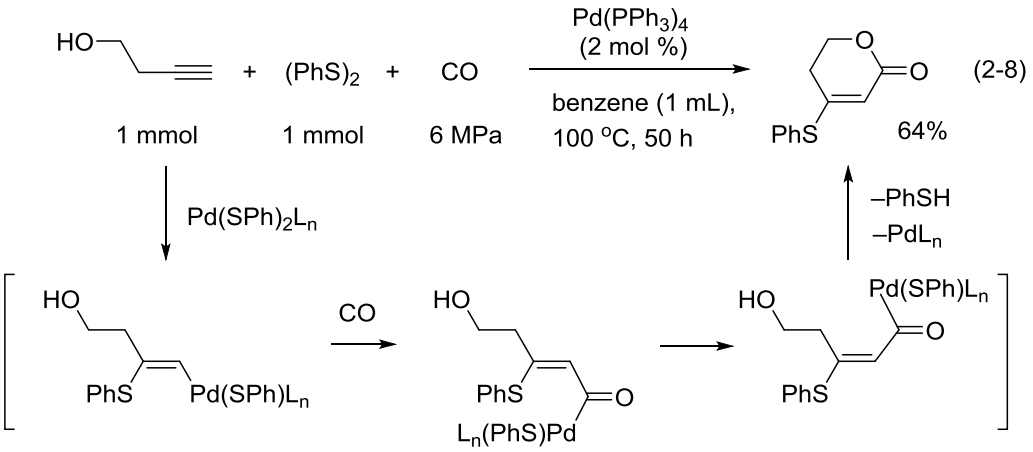


1 **2** **3**

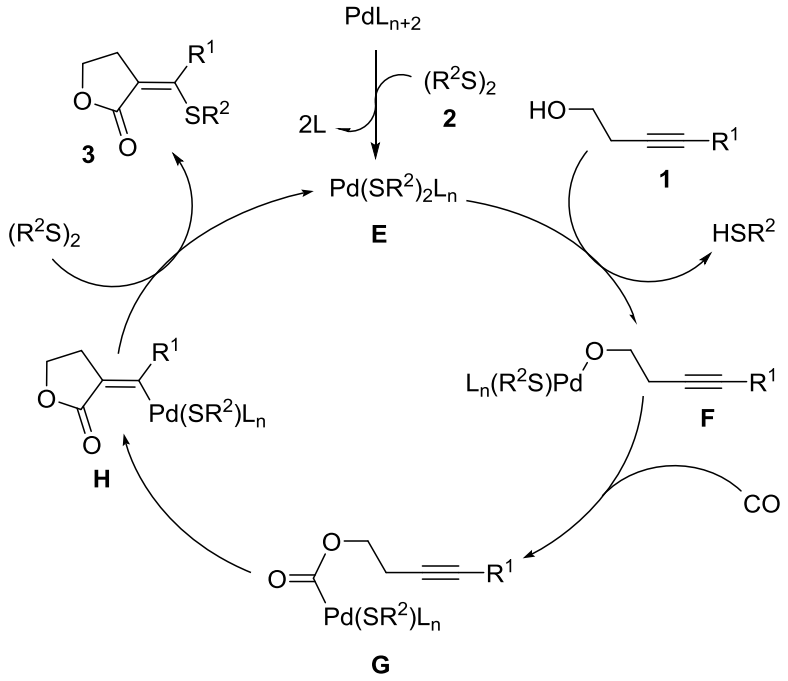
entry	alkyne	disulfide	yield, %[b]	entry	alkyne	disulfide	yield, %[b]
						$(PhS)_2$	
1	**1a**	R = H (**2a**)	**3aa**, 88 (83)	8[c]	X = H (**1d**)	**2a**	**3da**, 46 (20)
2		Me (**2b**)	**3ab**, 93 (81)	9	Me (**1g**)		**3ga**, 74 (62)
3		OMe (**2c**)	**3ac**, 90 (80)	10	OMe (**1h**)		**3ha**, 98 (83)
4		Cl (**2d**)	**3ad**, 80 (68)	11[c]	CF_3 (**1i**)		**3ia**, 40 (27)
5		NO_2 (**2e**)	**3ae**, 83 (74)				
6		$(PhS)_2$		12[c]		$(PhS)_2$	
	1b	**2a**	**3ba**, 87 (65)		**1j**	**2a**	**3ja**, 72 (55)
7		$(PhS)_2$					
	1c	**2a**	**3ca**, 71 (66)				

[a] Reaction conditions: alkyne (3.0 mmol), disulfide (1.0 mmol), CO (1 MPa), toluene (10 mL), $Pd(PPh_3)_4$ (5 mol %), 140 °C, 20 h. [b] Determined by ^1H NMR (isolated). [c] CO (2 MPa).

In 1997, Ogawa, Kuniyasu, and co-workers reported a similar thiolative lactonization of terminal alkynes having a hydroxy group using palladium catalysts such as $Pd(PPh_3)_4$ (Eq 2-8).[13] This thiolative lactonization is assumed to proceed via the oxidative addition of $(PhS)_2$ to the Pd(0) complex to generate the palladium sulfide complex, which adds regioselectively to the alkyne, followed by CO insertion, leading to the (*Z*)-isomer of the corresponding thiolative carbonylation product. Finally, *Z*-to-*E* isomerization, followed by cyclization, affords the thiolated lactone derivative. The *Z*-to-*E* isomerization gradually proceeded in situ in the presence of a hydroxyl group, and therefore, this thiolative lactonization requires a longer reaction time (50 h). The regioselectivity of this reaction is determined in the thiopalladation stage, where the more bulky palladium moiety is located at the terminal position. In the case of internal alkynes, it is reasonable to assume that a regioisomeric mixture of the thiolated lactone derivatives will be formed because of the similar bulkiness surrounding both alkyne carbons. However, the present thiolative lactonization proceeds regioselectively. This suggests that, in the thiolative lactonization of internal alkynes, coordination of the hydroxy group to the palladium catalyst plays an important role. Thus, the author proposes a possible pathway for the palladium-catalyzed thiolative lactonization of internal alkynes bearing a hydroxy group, as shown in Scheme 2-3. In contrast to $Co_2(CO)_8$, which forms the alkyne complex initially, in the palladium-catalyzed reaction, oxidative addition of disulfide **2** to the low-valence palladium complex may occur initially to form palladium sulfide complex **E**. Then, the hydroxyl group of acetylenic alcohol **1** coordinates to the palladium species **E** with release of a thiol (R^2SH), generating complex **F**. The subsequent CO insertion to give complex **G**, followed by intramolecular acylpalladation to the carbon−carbon triple bond of complex **G**, leads to complex **H**. Reductive elimination of the thiolative lactonization product **3** and oxidative addition of disulfide **2** regenerate the palladium sulfide complex **E**.



Scheme 2-3. A Possible Pathway for $Pd(PPh_3)_4$-Catalyzed Thiolative Lactonization



2-4 Conclusion

In summary, the author has developed a novel transition-metal catalyzed thiolative lactonization of internal alkynes bearing a hydroxyl group with CO and disulfides, which successfully affords γ-lactone derivatives bearing *exo*-methylene and thio groups with excellent regio- and stereoselectivities. The procedure can also be applied to δ-lactone synthesis. The

obtained thiolated lactone derivatives are promising as synthetic intermediates, as the thio group can be displaced by a variety of nucleophiles, and *exo*-methylene groups make them a possible substrate for Michael addition. The mechanistic details and scope of this thiolative carbonylation are currently under investigation.

2-5 Experimental Section

General Comment

$Co_2(CO)_8$ was obtained from commercial suppliers. $Pd(PPh_3)_4$ was synthesized according to the literature.[14] All disulfides and aliphatic alkynes (**1a**−**1c**, **1e**, and **1f**) were purchased from a commercial source and used without further purification. Aromatic alkynes (**1d** and **1g**−**1j**) were synthesized according to the literature.[15] Toluene was used as solvent after distillation using CaH_2. ^1H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were taken in $CDCl_3$ with Me_4Si as an internal standard. The use of broadband decoupling is indicated with braces. IR spectra are reported in wavenumbers (cm^{-1}). FAB mass spectra and EI mass spectra were obtained by employing double focusing mass spectrometers.

General Procedure for the Synthesis of (Z)-3-{1-(Phenylthio)propylidene}dihydrofuran-2-one (3aa).

In a 50 mL stainless steel autoclave with a magnetic stirring bar under a N_2 atmosphere were sequentially placed catalyst (0.05−0.09 mmol), distilled toluene (10 mL), alkyne (3.0 mmol), and disulfide (1.0 mmol). The vessel was purged three times with carbon monoxide and then charged with the same gas to achieve a pressure of 1−2 MPa. The reaction was conducted with magnetic stirring for 20 h at 140 °C. After removal of the unreacted carbon monoxide, the

resulting mixture was filtered through Celite with diethyl ether and concentrated in vacuo to give the crude products. Purification was performed by silica gel column chromatography (hexane:AcOEt, 2:1) followed by recrystallization or recycling preparative HPLC employing GPC columns with $CHCl_3$ as eluent.

(Z)-3-{1-(Phenylthio)propylidene}dihydrofuran-2-one (3aa). In the presence of $Co_2(CO)_8$ (30.8 mg, 0.09 mmol), compound **3aa** was obtained in 71% yield (167.6 mg) following general procedure. In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3aa** was obtained in 83% yield (195.2 mg) following general procedure. Isolated as a white solid; mp 111–113 ^oC; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.58-7.54 (m, 2H), 7.44-7.35 (m, 3H), 4.39 (t, *J* = 7.5 Hz, 2H), 2.98 (t, *J* = 7.5 Hz, 2H), 2.18 (q, *J* = 7.5 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 169.9, 156.3, 136.0, 130.4, 129.4, 129.1, 114.9, 64.9, 28.3, 27.5, 12.5; IR (KBr): 3058, 2973, 2936, 1724, 1598, 1475, 1452, 1439, 1375, 1231, 1144, 1063, 1021, 965, 931, 853, 754, 708, 695, 672, 526; HRMS (FAB) calcd for $C_{13}H_{15}O_2S$ $[M+H]^+$: 235.0787; found: 235.0784. Anal. calcd for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02. found: C, 66.52; H, 5.96.

(Z)-3-{1-(p-tolylthio)propylidene}dihydrofuran-2-one (3ab). In the presence of $Co_2(CO)_8$ (30.8 mg, 0.09 mmol), compound **3ab** was obtained in 64% yield (159.7 mg) following general procedure. In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3ab** was obtained in 81% yield (201.4 mg) following general procedure. Isolated as a white solid; mp 126–128 ^oC; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44 (d, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 4.38 (t, *J* = 7.5 Hz, 2H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.38 (s, 3H), 2.17 (q, *J* = 7.5 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 170.0, 157.0, 139.7, 136.0, 129.9, 126.7, 114.3, 64.9, 28.3, 27.4, 21.3, 12.6; IR (KBr): 2977, 2934, 2872, 1721, 1597, 1492, 1461, 1444, 1369, 1243, 1147, 1030, 1019, 970, 856, 812, 750, 679, 541, 517; HRMS (FAB) calcd for $C_{14}H_{17}O_2S$ $[M+H]^+$: 249.0944; found: 249.0933. Anal. calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49. found: C, 67.62; H, 6.48.

(Z)-3-{1-(4-methoxyphenylthio)propylidene}dihydrofuran-2-one (3ac). In the presence of $Co_2(CO)_8$ (30.8 mg, 0.09 mmol), compound **3ac** was obtained in 65% yield (171.0 mg) following general procedure. In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3ac** was obtained in 80% yield (212.3 mg) following general procedure. Isolated as a white solid; mp 139–140 ^oC; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.50–7.46 (m, 2H), 6.93–6.89 (m, 2H), 4.38 (t, *J* = 7.6 Hz, 2H), 3.84 (s, 3H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.15 (q, *J* = 7.5 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 170.0, 160.7, 157.5, 137.6, 120.6, 114.6, 113.9, 65.0, 55.3, 28.2, 27.2, 12.5; IR (KBr): 2977, 2935, 2873, 2842, 1719, 1597, 1568, 1492, 1459, 1438, 1375, 1288, 1246, 1148, 1031, 1020, 970, 855, 837, 811, 799, 748, 674, 619, 531; HRMS (FAB) calcd for $C_{14}H_{17}O_3S$ $[M+H]^+$: 265.0893; found: 265.0905. Anal. calcd for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10. found: C, 63.51; H, 6.06.

(Z)-3-{1-(4-Chlorophenylthio)propylidene}dihydrofuran-2-one (3ad). In the presence of $Co_2(CO)_8$ (30.8 mg, 0.09 mmol), compound **3ad** was obtained in 75% yield (200.8 mg) following general procedure. In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3ad** was obtained in 68% yield (182.8 mg) following general procedure. Isolated as a white solid; mp 109–110 ^oC; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.50–7.47 (m, 2H), 7.38–7.34 (m, 2H), 4.40 (t, *J* = 7.3 Hz, 2H), 2.98 (t, *J* = 7.6 Hz, 2H), 2.18 (q, *J* = 7.5 Hz, 2H), 0.91 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 169.8, 155.1, 137.0, 135.8, 129.3, 129.0, 115.6, 64.9, 28.2, 27.4, 12.4; IR (KBr): 3075, 2978, 2935, 2909, 2874, 1723, 1599, 1477, 1465, 1452, 1440, 1373, 1287, 1232, 1146, 1095, 1012, 832, 746, 515; HRMS (FAB) calcd for $C_{13}H_{14}O_2ClS$ $[M+H]^+$: 269.0398; found: 269.0382. Anal. calcd for $C_{13}H_{13}O_2ClS$: C, 58.10; H, 4.88. found: C, 57.94; H, 4.78.

(Z)-3-{1-(4-Nitrophenylthio)propylidene}dihydrofuran-2-one (3ae). In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3ae** was obtained in 74% yield (205.3 mg) following general procedure. Isolated as a yellow solid; mp 141–143 ^oC; ^1H NMR (400 MHz, $CDCl_3$, ppm):

δ 8.20–8.15 (m, 2H), 7.63–7.58 (m, 2H), 4.39 (t, *J* = 7.5 Hz, 2H), 3.02 (t, *J* = 7.4 Hz, 2H), 2.25 (q, *J* = 7.5 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 169.1, 151.2, 147.6, 140.8, 134.3, 123.9, 120.1, 64.8, 28.4, 28.1, 12.4; IR (KBr): 3091, 2980, 2935, 2917, 1873, 1715, 1598, 1576, 1441, 1379, 1344, 1301, 1279, 1257, 1235, 1225, 1175, 1148, 1065, 1033, 1011, 962, 861, 850, 747, 730, 690, 668, 572, 503; HRMS (FAB) calcd for $C_{13}H_{14}O_4NS$ $[M+H]^+$: 280.0638; found: 280.0641. Anal. calcd for $C_{13}H_{13}O_4NS$: C, 55.90; H, 4.69; N, 5.01 found: C, 55.80; H, 4.61; N, 5.08.

(Z)-3-{1-(Phenylthio)heptylidene}dihydrofuran-2-one (3ba). In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3ba** was obtained in 65% yield (188.2 mg) following general procedure. Isolated as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.56–7.53 (m, 2H), 7.44–7.35 (m, 3H), 4.38 (t, *J* = 7.6 Hz, 2H), 2.97 (t, *J* = 7.6 Hz, 2H), 2.16–2.10 (m, 2H), 1.34–1.26 (m, 2H), 1.18–1.10 (m, 2H), 1.03–0.98 (m, 4H), 0.80 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 169.8, 155.0, 135.9, 130.2, 129.2, 128.9, 115.0, 64.9, 34.0, 30.9, 28.7, 28.4, 27.7, 22.2, 13.8; IR (NaCl): 2955, 2927, 2856, 1734, 1600, 1475, 1457, 1440, 1373, 1239, 1140, 1038, 1024, 967, 831, 751, 705, 692; HRMS (EI) calcd for $C_{17}H_{22}O_2S$ $[M]^+$: 290.1341; found: 290.1350.

(Z)-5-Methyl-3-{1-(phenylthio)propylidene}dihydrofuran-2-one (3ca). In the presence of $Co_2(CO)_8$ (30.8 mg, 0.09 mmol), compound **3ca** was obtained in 76% yield (189.7 mg) following general procedure. In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3ca** was obtained in 66% yield (164.8 mg) following general procedure. Isolated as a white solid; mp 95–96 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.58–7.53 (m, 2H), 7.44–7.35 (m, 3H), 4.73–4.63 (m, 1H), 3.10 (dd, *J* = 7.8, 16.2 Hz, 1H), 2.53 (dd, *J* = 6.1, 16.2 Hz, 1H), 2.15 (q, *J* = 7.4 Hz, 2H), 1.43 (d, *J* = 6.2 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 169.5, 155.8, 135.9, 130.4, 129.3, 129.1, 116.1, 73.3, 36.0, 27.4, 22.2, 12.5; IR (KBr): 3057, 2973, 2935, 2871, 1718, 1595, 1475, 1438, 1338, 1239, 1148, 1158, 1114, 1027, 955, 934, 912, 889,

826, 753, 708, 664; HRMS (FAB) calcd for $C_{14}H_{17}O_2S$ $[M+H]^+$: 249.0944; found: 249.0956.

(Z)-3-{1-Phenyl-1-(phenylthio)methylene}dihydrofuran-2-one (3da). In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3da** was obtained in 20% yield (56.4 mg) following general procedure. Isolated as a white solid; mp 139–141 ^oC; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.20–7.16 (m, 2H), 7.14–6.95 (m, 8H), 4.33 (t, *J* = 7.4 Hz, 2H), 2.77 (t, *J* = 7.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 169.7, 153.0, 136.8, 135.3, 130.9, 128.2, 128.1, 128.0, 127.9, 117.4, 65.3, 29.9; IR (KBr): 3055, 2982, 2905,1738, 1729, 1607, 1581, 1588 1473, 1440, 1367, 1214, 1160, 1080, 1028, 967, 897, 749, 699, 684; HRMS (FAB) calcd for $C_{17}H_{15}O_2S$ $[M+H]^+$: 283.0787; found: 283.0786.

(Z)-3-{(Phenylthio)methylene}dihydrofuran-2-one (3ea). In the presence of $Co_2(CO)_8$ (30.8 mg, 0.09 mmol), compound **3ea** was obtained in 51% yield (107.3 mg) following general procedure. Isolated as a white solid; mp 125–126 ^oC; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.51–7.47 (m, 2H), 7.41–7.32 (m, 3H), 7.12 (t, *J* = 2.0 Hz, 1H), 4.42 (t, *J* = 7.5 Hz, 2H), 3.00 (td, *J* = 2.3, 7.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 170.2, 141.1, 135.5, 131.1, 129.4, 128.3, 118.2, 66.6, 28.7; IR (KBr): 2994, 2978, 2919, 1729, 1610, 1478, 1443, 1434, 1373, 1318, 1260, 1188, 1176, 1164, 1095, 1018, 963, 850, 835, 762, 745, 693, 664; HRMS (EI) calcd for $C_{11}H_{10}O_2S$ $[M]^+$: 206.0402; found: 206.0390.

(Z)-3-{(Phenylthio)methylene}tetrahydropyran-2-one (3fa). In the presence of $Co_2(CO)_8$ (30.8 mg, 0.09 mmol), compound **3fa** was obtained in 19% yield (40.9 mg) following general procedure. Isolated as a white solid; mp 148–150 ^oC; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.53–7.48 (m, 2H), 7.40–7.33 (m, 3H), 7.12 (t, *J* = 1.6 Hz, 1H), 4.37 (t, *J* = 5.5 Hz, 2H), 2.65 (dt, *J* = 1.4, 6.3 Hz, 2H), 1.98–1.91 (m, *2*H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 165.2, 148.5, 137.0, 131.2, 129.3, 128.2, 117.8, 69.3, 28.9, 23.0; IR (KBr): 2970, 2937, 2898, 1683, 1558, 1472, 1439, 1432, 1398, 1341, 1314, 1274, 1228, 1189, 1176, 1132, 1071, 980, 959, 882, 835, 828, 756,

693, 502; HRMS (FAB) calcd for $C_{12}H_{13}O_2S$ $[M+H]^+$: 221.0631; found: 221.0612.

(Z)-3-{1-(Phenylthio)-1-(p-tolyl)methylene}dihydrofuran-2-one (3ga). In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3ga** was obtained in 62% yield (185.2 mg) following general procedure. Isolated as a pale yellow solid; mp 107–109 ^oC; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.19–7.16 (m, 2H), 7.11–7.00 (m, 3H), 6.94–6.85 (m, 4H), 4.31 (t, J = 7.5 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H), 2.20 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 169.7, 153.2, 137.9, 135.1, 133.9, 131.2, 128.7, 128.2, 128.1, 128.0, 117.5, 65.2, 30.0, 21.1; IR (KBr): 3034, 2974, 2914, 1736, 1601, 1508, 1478, 1438, 1376, 1220, 1208, 1194, 1083, 1029, 968, 906, 810, 747, 691, 678, 538; HRMS (EI) calcd for $C_{18}H_{16}O_2S$ $[M]^+$: 296.0871; found: 296.0867.

(Z)-3-{1-(4-Methoxyphenyl)-1-(phenylthio)methylene}dihydrofuran-2-one (3ha). In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3ha** was obtained in 83% yield (258.3 mg) following general procedure. Isolated as a yellow solid; mp 117–119 ^oC; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.19–7.15 (m, 2H) , 7.11–7.01 (m, 3H), 6.94 (d, J = 6.8 Hz, 2H), 6.65 (d, J = 6.8 Hz, 2H), 4.31 (t, J = 7.4 Hz, 2H), 3.70 (s, 3H), 2.81 (t, J = 7.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 169.7, 159.1, 152.7, 134.8, 131.4, 129.7, 129.1, 128.2, 127.9, 117.6, 113.3, 65.1, 55.1, 30.0; IR (KBr): 3058, 2978, 2959, 2909, 2831, 1723, 1606, 1591, 1506, 1462, 1440, 1413, 1369, 1293, 1246, 1216, 1175, 1088, 1032, 972, 905, 835, 815, 744, 702, 683, 643, 590, 544, 525; HRMS (FAB) calcd for $C_{18}H_{17}O_3S$ $[M+H]^+$: 313.0893; found: 313.0884.

(Z)-3-[1-(Phenylthio)-1-{4-(trifluoromethyl)phenyl}methylene]dihydrofuran-2-one (3ia). In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3ia** was obtained in 27% yield (94.1 mg) following general procedure. Isolated as a white solid; mp 130–132 ^oC; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.41–7.36 (m, 2H), 7.19–7.15 (m, 2H), 7.13–7.08 (m, 3H), 7.07–7.01 (m, 2H), 4.35 (t, J = 7.5, 2H), 2.75 (t, J = 7.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 169.4, 151.3, 140.5, 135.5, 130.2, 130.0 (q, J_{C-F} = 32.7 Hz), 128.7, 128.6, 128.5, 125.1 (q, J_{C-F} = 3.8

Hz), 123.6 (q, J_{C-F} = 272 Hz), 118.2, 65.3, 29.8; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$, ppm): δ -62.8; IR (KBr): 3073, 3056, 2977, 2918, 1733, 1605, 1473, 1442, 1434, 1408, 1376, 1329, 1223, 1165, 1156, 1115, 1092, 1067, 1034, 1022, 977, 827, 745, 690, 664; HRMS (FAB) calcd for $C_{18}H_{14}O_2F_3S$ $[M+H]^+$: 351.0661; found: 351.0683.

(Z)-3-{1-(4-Methoxyphenyl)-1-(phenylthio)methylene}tetrahydropyran-2-one (3ja). In the presence of $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), compound **3ja** was obtained in 55% yield (178.6 mg) following general procedure. Isolated as a white solid; mp 115–117 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.17–7.13 (m, 2H), 7.10–6.98 (m, 3H), 6.79–6.74 (m, 2H), 6.63–6.58 (m, 2H), 4.32 (t, *J* = 5.2 Hz, 2H), 3.68 (s, 3H), 2.30 (t, *J* = 6.6 Hz, 2H), 1.86–1.79 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 165.8, 159.5, 158.7, 135.8, 132.6, 129.6, 129.1, 128.1, 128.0, 116.8, 113.3, 68.6, 55.1, 28.6, 23.1; IR (KBr): 2945, 2910, 2832, 1682, 1606, 1547, 1503, 1440, 1395, 1331, 1283 1267, 1245, 1174, 1129, 1110, 1073, 1032, 917, 839, 803, 742, 691, 585, 547, 539; HRMS (EI) calcd for $C_{19}H_{18}O_3S$ $[M]^+$: 326.0977; found: 326.0964.

Preparation of Cobalt Alkyne Complex

In a frask (30 mL) equipped with a magnetic stirring bar, were placed $Co_2(CO)_8$ (1.0 mmol), distilled toluene (1 mL), and 3-hexyn-1-ol (1.0 mmol). The mixture was stirred for 24 h at room temperature under N_2 atmosphere. The resulting mixture was concentrated *in vacuo*. The purification was performed by silica gel column chromatography (hexane:AcOEt, 2:1).

Investigation of Catalytic System for Cobalt-Catalyzed Thiolative Lactonization

In a 50 mL stainless steel autoclave with a magnetic stirring bar under a N_2 atmosphere were sequentially placed $Co_2(CO)_8$ (0.09 mmol), distilled toluene (10 mL), 3-hexyn-1-ol (3.0 mmol), and diphenyl disulfide (1.0 mmol). The vessel was purged three times with carbon monoxide and then charged with the same gas to achieve a pressure of 2 MPa. The reaction was

conducted with magnetic stirring for 1 h at 140 °C. After removal of the unreacted carbon monoxide, the resulting mixture was filtered through Celite with diethyl ether and diethyl ether was removed from the resulting filtrate by evapolation to give the homogeneous solution. The homogeneous solution contained the substrates, the catalyst, and lactone **3aa** (32% yield). Then, the reaction was continued using the resulting homogeneous solution under the pressure of carbon monoxide (2 MPa), affording the **3aa** in 87% yield.

2-6 References

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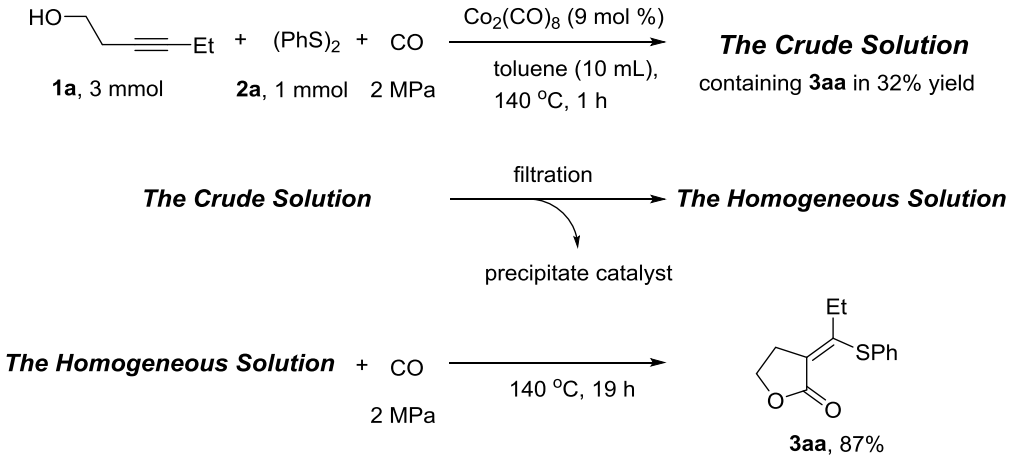
10. To gain insight into the catalytic system of cobalt for the thiolative lactonization (homogeneous or heterogeneous?), the reaction was conducted for 1 h, and small amounts of precipitate catalyst were filtered off. Then, the reaction was continued using the resulting homogeneous solution. The thiolative lactonization proceeded to afford the desired lactone **3aa** in 87% yield. As the thiolative lactonization can not proceed in the absence of catalyst, the results strongly suggest the reaction proceeds by homogeneous catalysis.



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Chapter 3

Palladium-Catalyzed Cyanothiolation of Internal Alkynes with Organic Disulfides and *tert*-Butyl Isocyanide

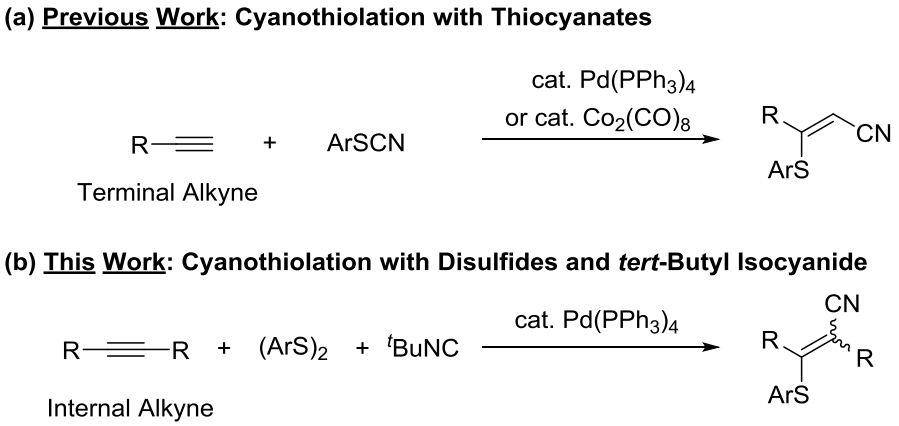
3-1 Introduction

Transition-metal-catalyzed vicinal difunctionalization of alkynes is one of the most straightforward routes to multi-functionalized alkenes.[1] In particular, heteroatom-containing alkenyl cyanides, which are highly versatile synthetic intermediates and useful monomers for polymerization, can be conveniently prepared by simultaneous introduction of heteroatom functionalities and the cyano group into carbon–carbon triple bonds.[2] In general, this transformations are commonly accomplished by addition of X–CN (X = B,[3] Si,[4] Ge,[5] Sn,[6] N,[7] O,[8] S,[9] Se,[10] Br,[11] or I[12]) to alkynes.[13,14] Among these reactions, catalytic cyanothiolation is of particular interest, since compounds containing group 16 heteroatoms (e.g., S) are known to act as catalyst poisons in transition-metal-catalyzed reactions.[15]

The cyanothiolation of terminal alkynes with thiocyanates catalyzed by Pd or Co complexes has been previously investigated (Scheme 3-1a).[10] This reaction features the cleavage of the thiocyanate C–S bond to afford the corresponding sulfur-containing alkenyl cyanides. In 2015, Werz et al. reported a one-step route to 1,2-thiobenzonitriles featuring Pd-catalyzed aryne insertion into aryl thiocyanates.[16] However, despite the availability of selective synthetic approaches to multi-functionalized tetrasubstituted olefins, the cyanothiolation of non-activated internal alkynes has been much less explored.[17] Herein, the author reports transition-

metal-catalyzed cyanothiolation of internal alkynes with organic disulfides and *tert*-butyl isocyanide, avoiding the use of toxic cyanides.[18] The developed method allows the simultaneous introduction of both thio and cyano groups into internal carbon–carbon triple bonds, which is accompanied by the release of the *tert*-butyl group (Scheme 3-1b).

Scheme 3-1. Pd-Catalyzed Cyanothiolation of Alkynes

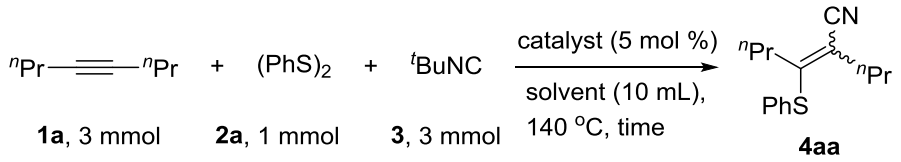


3-2 Palladium-Catalyzed Cyanothiolation of Internal Alkynes

Cyanothiolation of 4-octyne **1a** (1.0 mmol) with diphenyl disulfide **2a** (1.0 mmol) and *tert*-butyl isocyanide **3** (2.0 mmol) in toluene (10 mL) in the presence of 5 mol % $Pd(PPh_3)_4$ (140 °C, 20 h) afforded alkenyl cyanide derivative **4aa** bearing a *β*-thiol group in 48% yield (*E*/*Z* = 71/29) (Table 3-1, entry 1). Inspired by this result, the author further optimized the conditions of $Pd(PPh_3)_4$-catalyzed cyanothiolation (Table 3-1), showing that the yield of **4aa** was dramatically improved to 88% by the use of excess **1a** and **3** (Table 3-1, entry 2) despite the concomitant formation of various byproducts. Next, the author optimized the reaction temperature, reaction time, and solvent, demonstrating that the yield of **4aa** significantly decreased with decreasing temperature (Table 3-1, entry 3), whereas the reaction time did not influence the yield and selectivity (Table 3-1, entries 4 and 5). Moreover, optimal results were obtained using

1,4-dioxane as the solvent (Table 3-1, entry 6), with the utilization of polar solvents (acetonitrile, dimethylformamide (DMF), and *N*-methylpyrrolidone (NMP)) substantially decreasing the yield of **4aa** (Table 3-1, entries 7−9). In the case of benzyl isocyanide, no **4aa** was obtained, and various byproducts were observed (Table 3-1, entry 10).

Table 3-1. Optimization of Reaction Conditions for 4-Octyene Cyanothiolation[a]



entry	catalyst	solvent	time, h	yield, %[b] [*E*/*Z*][c]
1[d]	$Pd(PPh_3)_4$	toluene	20	48 [71/29]
2	$Pd(PPh_3)_4$	toluene	20	99 (88) [67/33]
3[e]	$Pd(PPh_3)_4$	toluene	20	N.D.
4	$Pd(PPh_3)_4$	toluene	72	88 [66/34]
5	$Pd(PPh_3)_4$	toluene	10	70 [70/30]
6	$Pd(PPh_3)_4$	1,4-dioxane	20	81 [61/39]
7	$Pd(PPh_3)_4$	CH_3CN	20	13 [23/77]
8	$Pd(PPh_3)_4$	DMF	20	N.D.
9	$Pd(PPh_3)_4$	NMP	20	N.D.
10[f]	$Pd(PPh_3)_4$	toluene	20	N.D.
11	$PdCl_2(PPh_3)_2$	toluene	20	95 [60/40]
12	$Pd(OAc)_2$	toluene	20	53 [57/43]
13	$RhCl(PPh_3)_3$	toluene	20	N.D.
14[g]	$Co_2(CO)_8$	toluene	20	N.D.
15	$Co(OAc)_2 \cdot 4H_2O$	toluene	20	38 [45/55]
16	none	toluene	20	trace

[a] Reaction conditions: 4-octyne **1a** (3.0 mmol), diphenyl disulfide **2a** (1.0 mmol), *tert*-butyl isocyanide **3** (3.0 mmol), catalyst (5 mol %) in solvent (10 mL), 140 °C. [b] Yield determined by ^{1}H NMR analysis (isolated yield is given in parentheses). [c] *E*/*Z* ratios were determined by ^{1}H NMR analysis of reaction mixture. [d] 4-Octyne **1a** (1.0 mmol), diphenyl disulfide **2a** (1.0 mmol), *tert*-butyl isocyanide **3** (2.0 mmol). [e] Temperature: 110 °C. [f] Benzyl isocyanide was used instead of **3**. [g] Increased catalyst loading (9 mol %) was used.

The author also examined the catalyst scope of cyanothiolation, demonstrating that the use of $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ also afforded **4aa** in good yields (Table 3-1, entries 11 and 12), whereas Rh and Co catalysts exhibited no or low catalytic activity, respectively (Table 3-1, entries 13–15), with only traces of **4aa** produced under catalyst-free conditions (Table 3-1, entry 16). Thus, optimum results were obtained when cyanothiolation was performed in toluene at 140 °C for 20 h with $Pd(PPh_3)_4$ as the catalyst (Table 3-1, entry 2).

The author next examined the scope and limitations of the developed procedure utilizing a variety of alkynes and organic disulfides (Table 3-2). Thus, aliphatic alkyne **1b** underwent cyanothiolation with moderate stereoselectivity, affording the desired product **4ba** in good yield (Table 3-2, entry 2). The reaction of dimethyl acetylenedicarboxylate **1c** afforded the desired product **4ca** in moderate yield (Table 3-2, entry 3). Notably, the use of aromatic alkynes (**1d** and **1e**) resulted in the desired alkenyl cyanides (**4da** and **4ea**, respectively) being formed with low stereoselectivity (Table 3-2, entries 4 and 5). The structures of (*E*)-**4ca** and (*Z*)-**4da** were unambiguously determined by X-ray structural analysis (Figures 3-1 and 3-2). Interestingly, although the reaction of an unsymmetrical internal alkyne bearing aryl and alkyl substituents afforded a mixture of regioisomers, **1f**, an unsymmetrical internal alkyne bearing an ester group, could be regioselectively converted into the desired alkenyl cyanide **4fa** (Table 3-2, entry 6). When a terminal alkyne such as 1-octyne was used instead of internal alkynes, the desired cyanothiolation product (3-(phenylthio)non-2-enenitrile)[10a] was obtained in only 7% yield, whereas the product obtained by 1,2-addition of diphenyl disulfide was obtained in 33% yield. Diaryl disulfides bearing electron-donating (**2b**, **2c**) or electron-withdrawing (**2d**, **2e**) groups reacted to afford the desired alkenyl cyanide derivatives (**4ab**, **4ac**, **4ad**, and **4ae**, respectively) in good yields (Table 3-2, entries 7−10). For diaryl disulfides with chloro and nitro substituents in *meta*-position(s), the corresponding alkenyl cyanides **4af** and **4ag** were obtained in moderate yields (Table 3-2, entries 11 and 12), whereas no target product was obtained when the chloro

substituent was in the *ortho*-position (Table 3-2, entry 13). Overall, cyanothiolation with the above diaryl disulfides proceeded with moderate stereoselectivity. In the case of dicyclohexyl disulfide **2i**, the desired product **4ai** was obtained in only 7% yield (Table 3-2, entry 14).

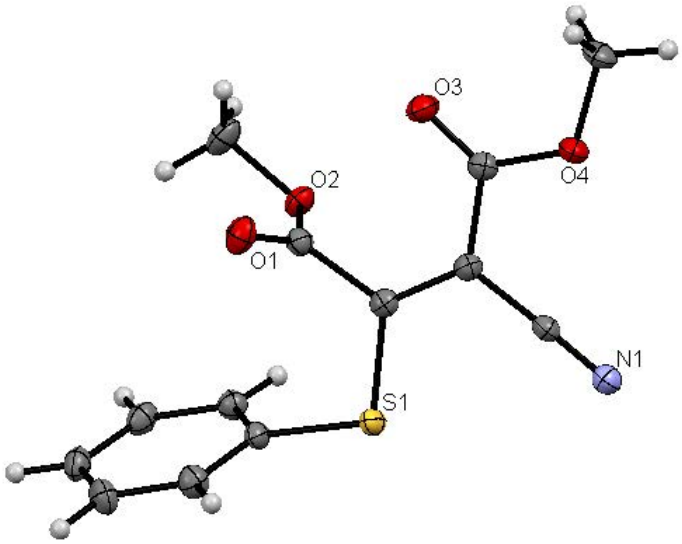


Figure 3-1. An ORTEP Drawing of (*E*)-**4ca** with Ellipsoids at 50% Probability

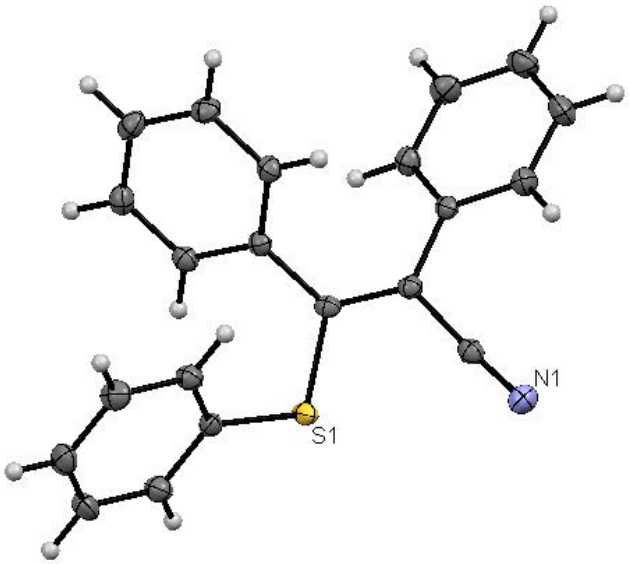
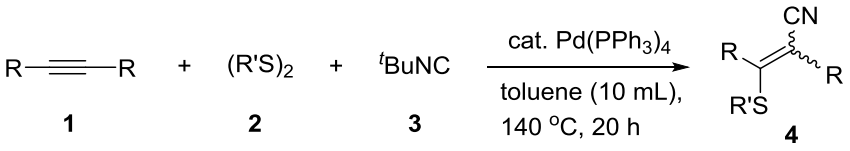
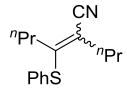
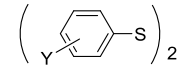
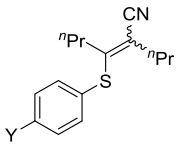
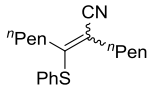
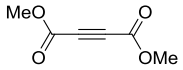
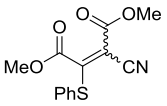
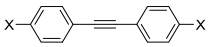
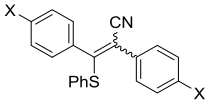
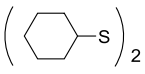
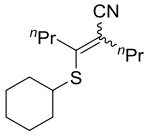
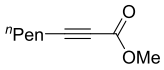
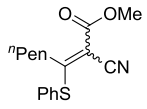


Figure 3-2. An ORTEP Drawing of (*Z*)-**4da** with Ellipsoids at 50% Probability

Table 3-2. Pd-Catalyzed Cyanothiolation: Alkyne and Disulfide Scope[a]



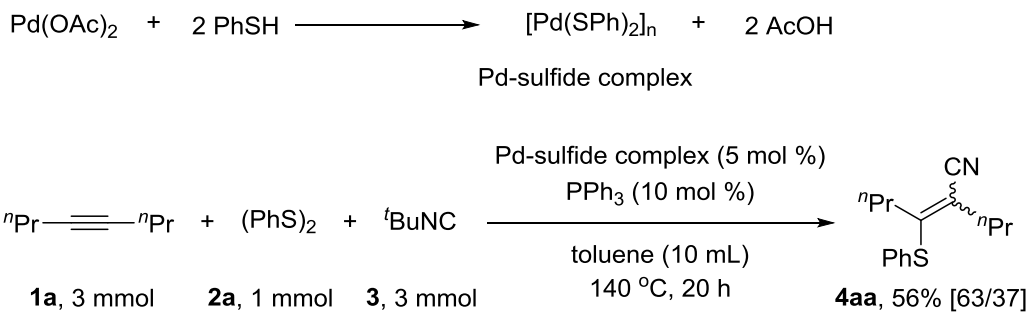
1 **2** **3** **4**

entry	alkyne **1**	disulfide **2**	yield, %[b] [E/Z][c]	entry	alkyne **1**	disulfide **2**	yield, %[b] [E/Z][c]
1		(PhS)$_2$					
	1a	**2a**	**4aa**, 88 [67/33]	7	**1a**	Y = 4–Me (**2b**)	**4ab**, 89 [63/37]
2		(PhS)$_2$		8		Y = 4–OMe (**2c**)	**4ac**, 69 [67/33][d]
				9		Y = 4–Cl (**2d**)	**4ad**, 75 [62/38]
	1b	**2a**	**4ba**, 62 [68/32][d]	10		Y = 4–NO_2 (**2e**)	**4ae**, 52 [58/42]
3		(PhS)$_2$		11		Y = 3,5–Cl_2 (**2f**)	**4af,** 52 [61/39]
				12		Y = 3–NO_2 (**2g**)	**4ag**, 50 [60/40]
	1c	**2a**	**4ca**, 45 [66/34]	13		Y = 2,6–Cl_2 (**2h**)	**4ah**, trace
		(PhS)$_2$		14			
4	X = H (**1d**)	**2a**	**4da**, 50 [41/59][d]		**1a**	**2i**	**4ai**, (7) [27/73]
5	X = OMe (**1e**)		**4ea**, 67 [41/59]				
6		(PhS)$_2$					
	1f	**2a**	**4fa**, 34 [36/64]				

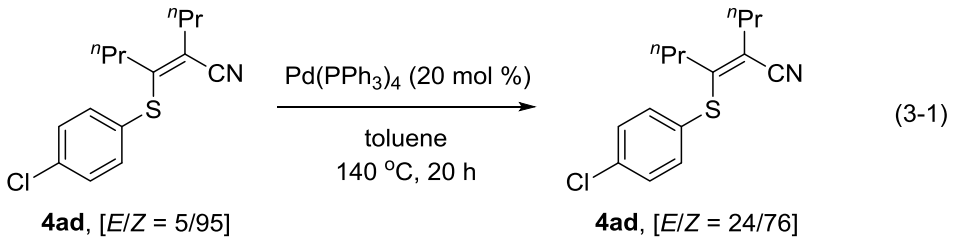
[a] Reaction conditions: alkyne **1** (3.0 mmol), disulfide **2** (1.0 mmol), *tert*-butyl isocyanide **3** (3.0 mmol), $Pd(PPh_3)_4$ (0.05 mmol) in toluene (10 mL), 140 °C, 20 h. [b] Isolated yields (yields determined by ^{1}H NMR analysis are given in parentheses). [c] *E*/*Z* ratios were determined by ^{1}H NMR analysis of reaction mixtures. [d] Determined by ^{1}H NMR analysis of the inseparable product isolated after purification.

To obtain insights into the mechanism of the developed transformation, the author examined the catalytic cyanothiolation of internal alkynes with a pre-formed Pd-sulfide complex (Scheme 3-2), which was prepared by the reaction of $Pd(OAc)_2$ with benzenethiol according to a previously described procedure.[15e] The reaction of **1a** with **2a**, **3**, and PPh_3 in the presence of the Pd-sulfide complex (5 mol %) afforded the desired **4aa** in 56% yield, which suggested that the above complex is an effective catalyst for cyanothiolation of internal alkynes.

Scheme 3-2. Cyanothiolation Catalyzed by a Pd-Sulfide Complex



To determine the origin of stereoselectivity, the author examined the isomerization of alkenyl cyanide **4ad** (*E*/*Z* = 5/95) in toluene (140 °C, 20 h) in the presence of 20 mol % of $Pd(PPh_3)_4$ (Eq 3-1), showing that the above isomerization did not effectively occur under these conditions (*E*/*Z* = 24/76), which implied that it mainly proceeded in the catalytic cycle.

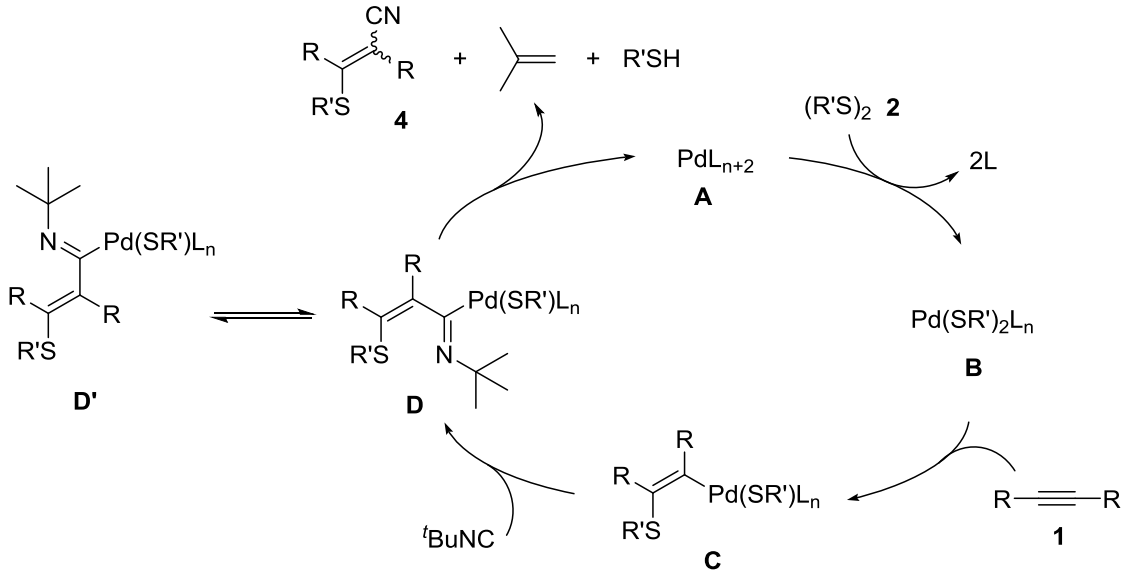


(3-1)

Based on the obtained data, the developed cyanothiolation was suggested to proceed via the initial reaction of the low-valent palladium complex **A** with disulfide **2** to form the palladium sulfide complex **B** (Scheme 3-3), which subsequently adds to internal alkyne **1**. Further *tert*-butyl

isocyanide insertion afforded complex **D**, which isomerized into **D'**, presumably via a keteneimine intermediate.[19] Finally, elimination of isobutene and thiol from **D** or **D'** afforded cyanothiolation product **4**,[18] regenerating the low-valent Pd catalyst.

Scheme 3-3. A Possible Pathway for $Pd(PPh_3)_4$-Catalyzed Cyanothiolation



3-3 Conclusion

In summary, the author has developed a novel route to alkenyl cyanide derivatives bearing a thio group at the *β*-position by Pd-catalyzed cyanothiolation of non-activated internal alkynes with organic disulfides and *tert*-butyl isocyanide. In contrast to the ineffective addition reaction between internal alkynes and thiocyanates, the developed procedure can be successfully be applied to internal alkynes, with its mechanistic details and scope being currently investigated.

3-4 Experimental Section

General Comment

$Pd(PPh_3)_4$,[20] bis(4-methoxyphenyl)acetylene **1e**,[21] and bis(2,6-dichlorophenyl) disulfide **2h**[22] were synthesized as described elsewhere. Other alkynes (**1a**–**1d**, and **1f**), disulfides (**2a**–**2g**, and **2i**) and *tert*-butyl isocyanide **3** were purchased from a commercial source and used without further purification. Toluene distilled over CaH_2 was used as a solvent. ^1H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were taken in $CDCl_3$ with Me_4Si as an internal standard. The use of broadband decoupling was indicated with braces. IR spectra are reported in wave numbers (cm^{-1}). EI mass spectra were obtained by employing double focusing mass spectrometers.

General Procedure for the Synthesis of 3-(Phenylthio)-2-propylhex-2-enenitrile (4aa)

A 50-mL stainless steel autoclave containing a magnetic stirring bar was sequentially charged with $Pd(PPh_3)_4$ (0.05 mmol), distilled toluene (10 mL), alkyne (3.0 mmol), disulfide (1.0 mmol), and *tert*-butyl isocyanide (3.0 mmol) under N_2. The vessel was closed, and the reaction was conducted upon magnetic stirring for 20 h at 140 °C. The resulting mixture was filtered through Celite, which was washed with diethyl ether, and the combined filtrate was concentrated *in vacuo* to afford crude products. Purification was performed by silica gel column chromatography (hexane:AcOEt, 10:1) followed by recycling preparative HPLC employing GPC columns with $CHCl_3$ as eluent and/or preparative thin layer chromatography on silica gel (hexane:AcOEte, 20:1).

3-(Phenylthio)-2-propylhex-2-enenitrile (4aa). Colorless oil (211.8 mg, 88%). The stereochemistry of **4aa** was confirmed by the observation of a NOE correlation between the two allylic methylenes in (*Z*)-**4aa**.

(*E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.43−7.39 (m, 2H), 7.39−7.34 (m, 3H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 1.66 (sext, *J* = 7.4 Hz, 2H), 1.46 (sext, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.3 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 157.2, 134.0, 130.6, 129.3, 128.9, 118.4, 110.9, 36.7, 33.3, 22.3, 21.4, 13.4, 13.2; IR (NaCl): 3060, 2962, 2932, 2872, 2204, 1580, 1573, 1464, 1440, 1380, 1125, 1069, 1024, 749, 704, 691; HRMS (EI) calcd for $C_{15}H_{19}NS$ $[M]^+$: 245.1238; found: 245.1238.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44−7.39 (m, 2H), 7.38−7.32 (m, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.17 (t, *J* = 7.6 Hz, 2H), 1.66 (sext, *J* = 7.5 Hz, 2H), 1.45 (sext, *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 154.7, 133.2, 131.7, 129.2, 128.5, 118.2, 114.1, 33.4, 33.1, 21.9, 21.7, 13.6, 13.5; IR (NaCl): 3059, 2963, 2932, 2872, 2204, 1582, 1576, 1476, 1465, 1440, 1379, 1108, 1086, 1024, 748, 691; HRMS (EI) calcd for $C_{15}H_{19}NS$ $[M]^+$: 245.1238; found: 245.1238.

2-Pentyl-3-(phenylthio)oct-2-enenitrile (4ba). Colorless oil (185.0 mg, 62%).

(*E*-isomer) Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.43−7.39 (m, 2H), 7.39−7.34 (m, 3H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.38 (t, *J* = 7.8 Hz, 2H), 1.66−1.56 (m, 2H), 1.47−1.33 (m, 6H), 1.22−1.07 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 157.4, 134.1, 130.6, 129.3, 128.9, 118.4, 110.8, 34.9, 31.3, 31.0, 30.9, 28.7, 27.6, 22.4, 22.1, 14.0, 13.8; IR (NaCl): 3060, 2956, 2929, 2858, 2205, 1717, 1575, 1465, 1457, 1441, 1378, 1024, 749, 691; HRMS (EI) calcd for $C_{19}H_{27}NS$ $[M]^+$: 301.1864; found: 301.1867.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44−7.39 (m, 2H), 7.38−7.33 (m, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.17 (t, *J* = 7.8 Hz, 2H), 1.66−1.55 (m, 2H), 1.45−1.29 (m, 6H), 1.24−1.07 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 154.7, 133.3, 131.7, 129.2, 128.5, 118.3, 113.9, 31.5, 31.2 (overlap), 28.2, 28.1, 22.4, 22.2, 14.0,

13.8; IR (NaCl): 3059, 2957, 2929, 2858, 2205, 1653, 1582, 1576, 1465, 1457, 1440, 1378, 1024, 748, 691; HRMS (EI) calcd for $C_{19}H_{27}NS$ $[M]^+$: 301.1864; found: 301.1867.

Dimethyl 2-Cyano-3-(phenylthio)but-2-enedioate (4ca). White solid (125.1 mg, 45%). It was difficult to separate the isomers of **4ca**.

(*E*-isomer) (*E*)-**4ca** was recrystallized by hexane and ethyl acetate. The structure of (*E*)-**4ca** was confirmed by X-ray structural analysis. White solid; mp 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.60−7.56 (m, 2H), 7.55−7.49 (m, 1H), 7.46−7.40 (m, 2H), 3.83 (s, 3H), 3.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 167.9, 161.4, 160.2, 136.4, 131.5, 129.4, 124.9, 112.8, 97.8, 53.2, 52.8; IR (KBr): 2954, 2220, 1748, 1733, 1551, 1477, 1431, 1275, 1251, 1148, 1036, 1006, 921, 787, 766, 684; HRMS (EI) calcd for $C_{13}H_{11}NO_4S$ $[M]^+$: 277.0409; found: 277.0413.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.60−7.39 (m, 5H), 3.92 (s, 3H), 3.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 169.8, 162.4, 161.5, 135.6, 131.1, 129.4, 128.2, 113.7, 97.0, 53.3, 53.2.

(*E*- and *Z*-mixture, *E*/*Z* = 34/66) White solid; mp 99–110 °C; IR (KBr): 2957, 2224, 1735, 1719, 1551, 1534, 1474, 1441, 1267, 1201, 1151, 1033, 995, 927, 764, 691; HRMS (EI) calcd for $C_{13}H_{11}NO_4S$ $[M]^+$: 277.0409; found: 277.0413.

2,3-Diphenyl-3-(phenylthio)acrylonitrile (4da). Yellow oil (157.0 mg, 50%). It was difficult to separate the isomers of **4da**.

(*E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.70−7.64 (m, 2H), 7.50−7.43 (m, 2H), 7.43−7.36 (m, 3H), 7.27−7.19 (m, 3H), 7.14−7.00 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 158.3, 136.1, 133.9, 133.7, 130.8, 129.6, 129.4, 129.2, 129.0, 128.7, 128.3, 128.1, 118.7, 110.4.

(*Z*-isomer) (*Z*)-**4da** was recrystallized by hexane. The structure of (*Z*)-**4da** was confirmed by X-ray structural analysis. Yellow solid; mp 133–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.27−7.22 (m, 2H), 7.16−7.00 (m, 13H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 155.9, 134.5, 133.9, 133.2, 130.9, 130.4, 129.2, 129.1, 128.7, 128.3, 128.2, 128.1, 118.6, 111.5; IR (KBr): 3055, 2202, 1581, 1534, 1475, 1444, 1202, 1024, 910, 767, 750, 705, 694, 664; HRMS (EI) calcd for $C_{21}H_{15}NS$ $[M]^+$: 313.0925; found: 313.0925.

(*E*- and *Z*-mixture, *E*/*Z* = 72/28) IR (NaCl): 3057, 3022, 2205, 1577, 1558, 1539, 1490, 1473, 1442, 1230, 1070, 1024, 1001, 907, 748, 696; HRMS (EI) calcd for $C_{21}H_{15}NS$ $[M]^+$: 313.0925; found: 313.0925.

2,3-Bis(4-methoxyphenyl)-3-(phenylthio)acrylonitrile (4ea). Yellow oil (231.8 mg, 67%). It was difficult to separate the isomers of **4ea**.

(*E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.57 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 9.1 Hz, 2H), 7.15−7.04 (m, 5H), 6.94 (d, *J* = 9.1 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 3.72 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 160.4, 159.8, 156.2, 132.9, 131.7, 131.3, 130.6, 128.6, 128.5, 127.9, 126.5, 119.3, 113.9, 113.5, 109.8, 55.3, 55.1.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.25−7.21 (m, 2H), 7.15−7.04 (m, 7H), 6.69 (d, *J* = 8.6 Hz, 2H), 6.57 (d, *J* = 8.6 Hz, 2H), 3.73 (s, 3H), 3.66 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 160.0, 159.2, 152.7, 132.3, 132.0, 131.8, 130.8, 128.7, 127.7, 126.8, 126.6, 119.2, 113.8, 113.6, 111.1, 55.1 (overlap).

(*E*- and *Z*-mixture, *E*/*Z* = 71/29) IR (NaCl): 3056, 3005, 2960, 2934, 2837, 2203, 1605, 1576, 1511, 1465, 1458, 1441, 1298, 1253, 1175, 1113, 1030, 831, 745, 690; HRMS (EI) calcd for $C_{23}H_{19}NO_2S$ $[M]^+$: 373.1136; found: 373.1135.

Methyl 2-Cyano-3-(phenylthio)oct-2-enoate (4fa). Reddish yellow oil (98.0 mg, 34%). It was difficult to separate the isomers of **4fa**. The regiochemistry was assigned based on HMBC experiments.

(*E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.57−7.43 (m, 5H), 3.81 (s, 3H), 2.74 (t, *J* = 8.2 Hz, 2H), 1.47−1.32 (m, 2H), 1.12−0.96 (m, 4H), 0.75 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 183.8, 161.4, 136.1, 130.9, 129.7, 127.0, 115.1, 96.9, 52.4, 32.1, 31.4, 29.4, 21.8, 13.7.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.57−7.43 (m, 5H), 3.87 (s, 3H), 2.50 (t, *J* = 8.4 Hz, 2H), 1.47−1.32 (m, 2H), 1.12−0.96 (m, 4H), 0.75 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 183.4, 163.5, 135.8, 130.7, 129.6, 128.6, 115.6, 96.6, 52.5, 36.4, 31.2, 29.5, 21.7, 13.6.

(*E*- and *Z*-mixture, *E*/Z = 18/82) IR (NaCl): 3058, 2955, 2931, 2871, 2860, 2215, 1718, 1517, 1474, 1458, 1290, 1260, 1205, 1170, 1067, 999, 775, 754, 706, 692; HRMS (EI) calcd for $C_{16}H_{19}NO_2S$ $[M]^+$: 289.1136; found: 289.1140.

2-Propyl-3-(p-tolylthio)hex-2-enenitrile (4ab). Colorless oil (234.0 mg, 89%). The stereochemistry of **4ab** was confirmed by the observation of a NOE correlation between the two allylic methylenes in (*Z*)-**4ab**.

(*E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.30 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 2.45 (t, *J* = 7.6 Hz, 2H), 2.38−2.32 (m, 5H), 1.65 (sext, *J* = 7.4 Hz, 2H), 1.45 (sext, *J* = 7.5 Hz, 2H), 1.00 (t, *J* = 7.3 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 158.0, 139.4, 134.4, 130.1, 126.7, 118.5, 109.8, 36.5, 33.1, 22.3, 21.3, 21.2, 13.4, 13.2; IR (NaCl): 3022, 2962, 2932, 2872, 2204, 1715, 1699, 1576, 1492, 1464, 1457, 1380, 1181, 1123, 1105, 1017, 811; HRMS (EI) calcd for $C_{16}H_{21}NS$ $[M]^+$: 259.1395; found: 259.1392.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.32 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 2.36 (s, 3H), 2.28 (t, *J* = 7.8 Hz, 2H), 2.14 (t, *J* = 7.6 Hz, 2H), 1.64 (sext, *J* = 7.5 Hz, 2H), 1.43 (sext, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 155.5, 139.0, 133.7, 130.0, 127.8, 118.4, 112.7, 33.1, 33.0, 21.9, 21.7, 21.2, 13.6, 13.5; IR (NaCl): 3021, 2962, 2931, 2872, 2203, 1726, 1663, 1577, 1492, 1464, 1458, 1380, 1180, 1105, 1088, 1017, 811; HRMS (EI) calcd for $C_{16}H_{21}NS$ $[M]^+$: 259.1395; found: 259.1392.

3-((4-Methoxyphenyl)thio)-2-propylhex-2-enenitrile (4ac). Colorless oil (184.2 mg, 69%). The stereochemistry of **4ac** was confirmed by the observation of a NOE correlation between the two allylic methylenes in (*Z*)-**4ac**.

(*E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.36 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 3H), 2.43 (t, *J* = 7.6 Hz, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 1.65 (sext, *J* = 7.4 Hz, 2H), 1.44 (sext, *J* = 7.5 Hz, 2H), 1.00 (t, *J* = 7.3 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 160.6, 158.7, 136.5, 120.4, 118.6, 114.8, 108.5, 55.4, 36.3, 32.9, 22.4, 21.3, 13.4, 13.2; IR (NaCl): 2962, 2933, 2872, 2203, 1592, 1571, 1494, 1463, 1288, 1250, 1173, 1105, 1031, 830, 799; HRMS (EI) calcd for $C_{16}H_{21}NOS$ $[M]^+$: 275.1344; found: 275.1342.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.39 (d, *J* = 9.1 Hz, 2H), 6.88 (d, *J* = 9.1 Hz, 2H), 3.83 (s, 3H), 2.26 (t, *J* = 7.5 Hz, 2H), 2.10 (t, *J* = 7.9 Hz, 2H), 1.63 (sext, *J* = 7.4 Hz, 2H), 1.41 (sext, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.78 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 160.4, 156.4, 136.0, 121.6, 118.4, 114.8, 111.0, 55.4, 33.0, 32.9, 21.9, 21.7, 13.6, 13.5; IR (NaCl): 2962, 2932, 2872, 2201, 1592, 1570, 1494, 1464, 1288, 1249, 1173, 1105, 1030, 830, 799; HRMS (EI) calcd for $C_{16}H_{21}NOS$ $[M]^+$: 275.1344; found: 275.1349.

3-((4-Chlorophenyl)thio)-2-propylhex-2-enenitrile (4ad). Colorless oil (206.5 mg, 75%). The stereochemistry of **4ad** was confirmed by the observation of a NOE correlation between the two allylic methylenes in (*Z*)-**4ad**.

(*E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.36−7.32 (m, 4H), 2.47 (t, *J* = 75 Hz, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 1.65 (sext, *J* = 7.5 Hz, 2H), 1.46 (sext, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 156.3, 135.3, 135.0, 129.6, 129.1, 118.1, 111.9, 36.7, 33.4, 22.2, 21.4, 13.4, 13.1; IR (NaCl): 2962, 2932, 2872, 2205, 1696, 1577, 1475, 1465, 1389, 1094, 1014, 823, 746; HRMS (EI) calcd for $C_{15}H_{18}ClNS$ $[M]^+$: 279.0848; found: 279.0847.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.36−7.30 (m, 4H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.17 (t, *J* = 7.8 Hz, 2H), 1.66 (sext, *J* = 7.4 Hz, 2H), 1.45 (sext, *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 153.8, 134.8, 134.2, 130.3, 129.5, 118.0, 115.1, 33.4, 33.1, 21.8, 21.7, 13.6, 13.5; IR (NaCl): 2963, 2932, 2872, 2205, 1577, 1559, 1475, 1465, 1390, 1093, 1013, 822, 745; HRMS (EI) calcd for $C_{15}H_{18}ClNS$ $[M]^+$: 279.0848; found: 279.0849.

3-((4-Nitrophenyl)thio)-2-propylhex-2-enenitrile (4ae). Pale yellow oil (146.9 mg, 52%).

(*E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.20 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 9.1 Hz, 2H), 2.56−2.49 (m, 4H), 1.66 (sext, *J* = 7.4 Hz, 2H), 1.54 (sext, *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 152.8, 147.0, 141.4, 131.1, 124.3, 118.1, 117.4, 37.8, 34.1, 22.2, 21.5, 13.3, 13.2; IR (NaCl): 3097, 2963, 2932, 2873, 2207, 1598, 1577, 1521, 1476, 1457, 1340, 1109, 1089, 1012, 853, 744, 685; HRMS (EI) calcd for $C_{15}H_{18}N_2O_2S$ $[M]^+$: 290.1089; found: 290.1092.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.19 (d, *J* = 9.1 Hz, 2H), 7.41 (d, *J* = 9.1 Hz, 2H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.32 (t, *J* = 7.7 Hz, 2H), 1.71 (sext, *J* = 7.4 Hz, 2H), 1.53 (sext, *J* = 7.5 Hz, 2H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 150.1, 146.7, 142.5, 130.1, 124.3, 121.7, 117.5, 34.6, 33.4, 21.9, 21.6, 13.6, 13.5; IR

(NaCl): 3097, 2963, 2932, 2873, 2209, 1597, 1577, 1517, 1476, 1458, 1340, 1109, 1088, 1012, 853, 743, 684; HRMS (EI) calcd for $C_{15}H_{18}N_2O_2S$ $[M]^+$: 290.1089; found: 290.1089.

3-((3,5-Dichlorophenyl)thio)-2-propylhex-2-enenitrile (4af). Colorless oil (164.2 mg, 52%). The stereochemistry of **4af** was confirmed by the observation of a NOE correlation between the two allylic methylenes in (*Z*)-**4af**.

(*E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.34 (t, *J* = 1.8 Hz, 1H), 7.23 (d, *J* = 1.8 Hz, 2H), 2.51−2.43 (m, 4H), 1.65 (sext, *J* = 7.4 Hz, 2H), 1.52 (sext, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 154.2, 135.6, 134.7, 130.3, 128.7, 117.7, 115.2, 37.2, 33.8, 22.2, 21.5, 13.4, 13.1; IR (NaCl): 3068, 2962, 2932, 2872, 2207, 1559, 1458, 1405, 1381, 1141, 1101, 855, 801, 668; HRMS (EI) calcd for $C_{15}H_{17}Cl_2NS$ $[M]^+$: 313.0459; found: 313.0461.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.30 (t, *J* = 1.8 Hz, 1H), 7.22 (d, *J* = 1.8 Hz, 2H), 2.35 (t, *J* = 7.7 Hz, 2H), 2.25 (t, *J* = 7.7 Hz, 2H), 1.68 (sext, *J* = 7.4 Hz, 2H), 1.50 (sext, *J* = 7.5 Hz, 2H), 1.01 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 151.4, 135.8, 135.5, 129.4, 128.2, 118.9, 117.7, 34.0, 33.3, 21.9, 21.6, 13.6, 13.5; IR (NaCl): 3069, 2963, 2932, 2872, 2208, 1718, 1557, 1465, 1405, 1380, 1140, 1100, 852, 799, 668; HRMS (EI) calcd for $C_{15}H_{17}Cl_2NS$ $[M]^+$: 313.0459; found: 313.0461.

3-((3-Nitrophenyl)thio)-2-propylhex-2-enenitrile (4ag). Pale yellow oil (145.9 mg, 50%). It was difficult to separate the isomers of **4ag**.

(*E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.23−8.18 (m, 2H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 8.2 Hz, 1H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.45 (t, *J* = 7.6 Hz, 2H), 1.67 (sext, *J* = 7.4 Hz, 2H), 1.51 (sext, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.3 Hz, 3H), 0.85 (t, *J* = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR

(100 MHz, $CDCl_3$, ppm): δ 153.9, 148.5, 138.1, 134.0, 130.2, 127.0, 123.3, 117.6, 115.4, 37.1, 33.8, 22.1, 21.5, 13.4, 13.1.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.22−8.14 (m, 2H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.26 (t, *J* = 7.6 Hz, 2H), 1.70 (sext, *J* = 7.4 Hz, 2H), 1.51 (sext, *J* = 7.6 Hz, 2H), 1.02 (t, *J* = 7.6 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 151.1, 148.5, 137.0, 135.4, 130.1, 125.7, 122.7, 119.4, 117.6, 34.1, 33.3, 21.8, 21.6, 13.6, 13.5.

(*E*- and *Z*-mixture, *E*/*Z* = 69/31) IR (NaCl): 3085, 3072, 2963, 2932, 2873, 2206, 1529, 1465, 1458, 1349, 1271, 1124, 1068, 876, 806, 749, 732, 675; HRMS (EI) calcd for $C_{15}H_{18}N_2O_2S$ $[M]^+$: 290.1089; found: 290.1094.

3-(Cyclohexylthio)-2-propylhex-2-enenitrile (4ai). Colorless oil. It was difficult to separate the isomers of **4ai**.

(*E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.09−3.00 (m, 1H), 2.61 (t, *J* = 7.3 Hz, 2H), 2.38 (t, *J* = 7.7 Hz, 2H), 1.94−1.86 (m, 2H), 1.84−1.75 (m, 2H), 1.69−1.23 (m, 10H), 1.01−0.92 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 156.9, 118.8, 111.2 43.7, 36.7, 33.9, 33.2, 25.8, 25.4, 22.8, 21.3, 13.4, 13.3.

(*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.18−3.09 (m, 1H), 2.33 (t, *J* = 7.6 Hz, 2H), 2.25 (t, *J* = 7.6 Hz, 2H), 1.94−1.86 (m, 2H), 1.84−1.75 (m, 2H), 1.69−1.23 (m, 10H), 1.01−0.92 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 154.0, 118.6, 115.1, 44.5, 34.2, 33.4, 33.0, 25.8, 25.5, 22.0, 21.7, 13.8, 13.4.

(*E*- and *Z*-mixture, *E*/*Z* = 15/85) IR (NaCl): 2961, 2931, 2872, 2855, 2203, 1577, 1458, 1449, 1380, 1340, 1262, 1201, 1121, 996, 887, 816, 741, 668; HRMS (EI) calcd for $C_{15}H_{25}NS$ $[M]^+$: 251.1708; found: 251.1709.

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Chapter 4

A Benzoyl Peroxide/Diphenyl Diselenide Binary System for Functionalization of Alkynes Leading to Alkenyl and Alkynyl Selenides

4-1 Introduction

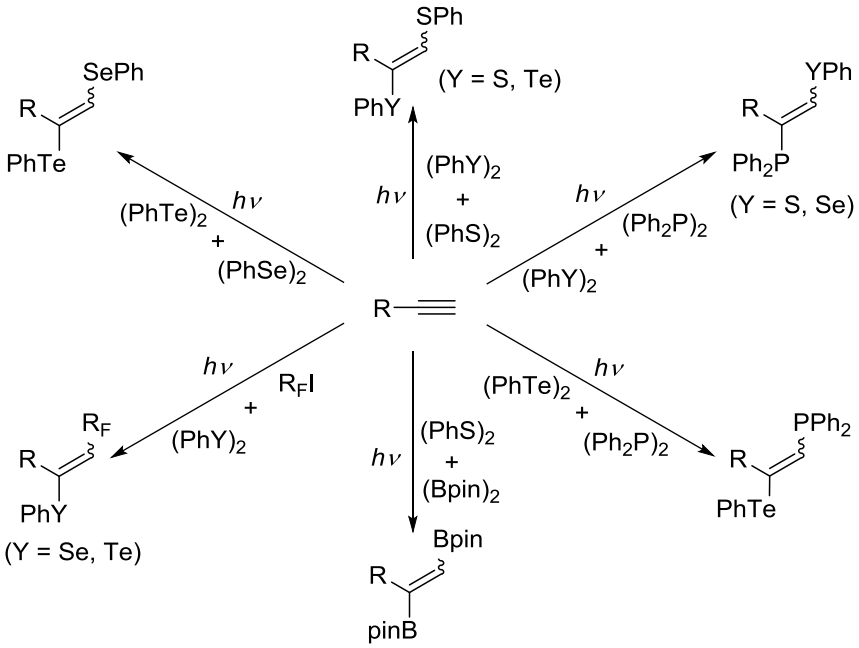
The selective addition of heteroatom compounds to unsaturated compounds is one of the most useful transformations in organic synthesis,[1] as the resulting products can often be employed as versatile synthetic intermediates due to the characteristic features of individual heteroatoms. For example, the atom-economical radical addition of heteroatom compounds to alkynes provides alkenyl heteroatoms in high selectivity.[2] Indeed, a series of highly selective radical addition reactions of two heteroatom compounds to alkynes was recently developed (Scheme 4-1).[3]

For example, the use of binary $(PhS)_2/(PhSe)_2$ systems allowed the highly regioselective thioselenation of alkynes based on kinetic control, i.e., the higher reactivity of $PhS^{\bullet}$ and the greater carbon radical capturing ability of $(PhSe)_2$.[3a] Based on this concept, thiotelluration,[3b] selenotelluration,[3b] thiophosphination,[3c] selenophosphination,[3d] phosphinotelluration,[3e] perfluoroalkyliodination,[3f] perfluoroalkylselenation,[3g] and perfluoroalkylteluration[3h] reactions have been developed in a similar manner. In addition, a combination of group 13 and 16 binary systems, i.e., $(PhS)_2/(Bpin)_2$, has recently been found to exhibit a different reactivity, whereby the photoinduced diboration rather than the thioboration of alkynes proceeds in the presence of

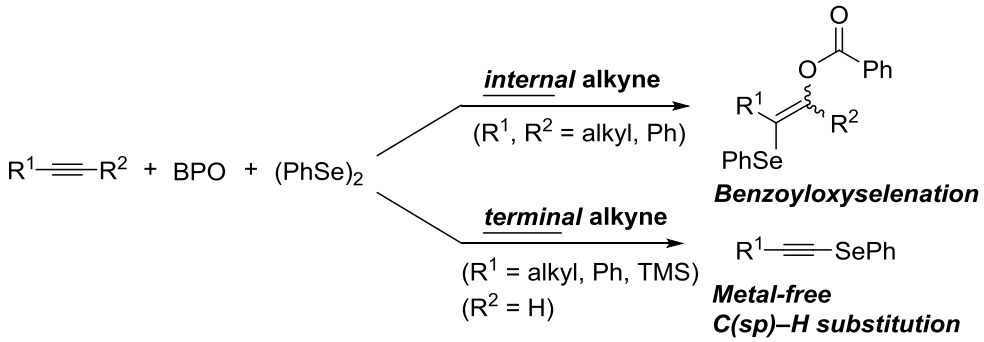
$(PhS)_2$ under photoirradiation conditions.[4]

In this chapter, to examine the application of this methodology in greater detail, the author describes the reaction of alkynes with benzoyl peroxide (BPO) (bearing an O–O bond) and diphenyl diselenide (bearing a Se–Se bond) for the benzoyloxyselenation of internal alkynes and the novel C(sp)–H substitution of terminal alkynes with the phenylseleno group (Scheme 4-2).[5]

Scheme 4-1. Simultaneous Introduction of Two Heteroatom Groups into Alkynes



Scheme 4-2. A BPO/$(PhSe)_2$ Binary System for the Selective Selenation of Alkynes

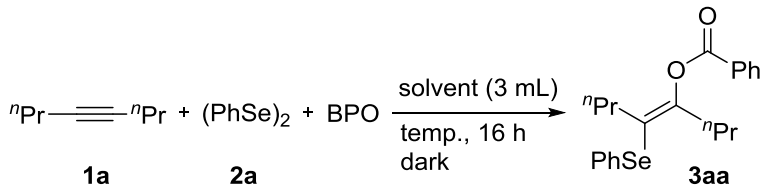


4-2 Selective Benzoyloxyselenation of Internal Alkynes

In $(PhSe)_2$-containing binary systems such as $(PhS)_2/(PhSe)_2$, $R_FI/(PhSe)_2$, and $(Ph_2P)_2/(PhSe)_2$, reaction initiation has been performed by photoirradiation. In contrast, initiation of the BPO/$(PhSe)_2$ system is possible through heating, as BPO easily undergoes homolytic cleavage upon heating ($t_{1/2}$ = *ca.* 10 h at 80 °C). As outlined in Table 4-1, upon heating an equimolar mixture of 4-octyne (**1a**), diphenyl diselenide (**2a**), and BPO in benzene at 80 °C for 16 h under air in the absence of light, benzoyloxyselenation occurred successfully, affording 4-benzoyloxy-5-phenylseleno-4-octene (**3aa**) stereoselectively in 60% yield, with only the *E*-isomer being obtained (Table 4-1, entry 1).[6,7] However, when this reaction was attempted in toluene, a poor yield of 11% was obtained (Table 4-1, entry 2). Furthermore, no trace of the desired adduct **3aa** was obtained when the reaction was carried out in diethyl ether (Et_2O) at 40 °C (Table 4-1, entry 3). However, upon increasing the temperature to 60 °C, a significant increase in yield was obtained (82% yield, Table 4-1, entry 4), although further elevating the temperature to 80 °C had a detrimental effect on the reaction (76% yield, Table 4-1, entry 5). In the case of entry 4 (i.e., reaction at 60 °C), all substrates were readily soluble in Et_2O, resulting into the formation of a homogeneous solution. Although Et_2O was gradually distilled out in the initial stages of the reaction, the majority of BPO was consumed to form to PhSeOC(O)Ph **4** upon reaction with $(PhSe)_2$. The author also examined the effect of the reaction stoichiometry at 60 °C in Et_2O, but no improvements were observed (Table 4-1, entries 6–8).[8]

Under the optimized conditions (Table 4-1, entry 4), the scope and limitations of the benzoyloxyselenation were then examined, and the results are outlined in Table 4-2. More specifically, 6-dodecyne **1b** and diphenylacetylene **1c** underwent benzoyloxyselenation successfully to afford the corresponding *β*-benzoyloxy-substituted alkenyl selenides **3ba** and **3ca**, respectively, in good yields and with excellent stereoselectivities (i.e., only the *E*-isomers were obtained). In addition, the benzoyloxyselenation of alkynes bearing a methoxy or a chloro group

Table 4-1. Benzoyloxyselenation of 4-Octyne (**1a**) with $(PhSe)_2$ and BPO



1a **2a** **3aa**

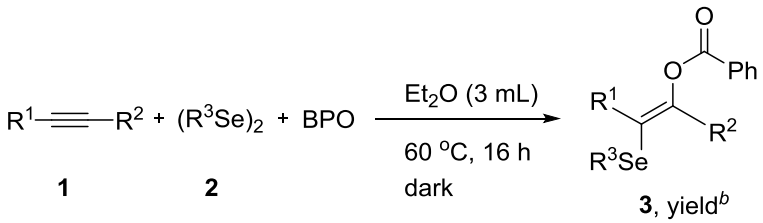
entry	**1a**/**2a**/BPO, mmol	solvent	temp., °C	yield, %[a]
1	0.2/0.2/0.2	benzene	80	60
2	0.2/0.2/0.2	toluene	80	11
3	0.2/0.2/0.2	Et_2O	40	N.D.
4[b]	0.2/0.2/0.2	Et_2O	60	82
5[b]	0.2/0.2/0.2	Et_2O	80	76
6[b]	0.2/0.2/0.4	Et_2O	60	71
7[b]	0.2/0.4/0.4	Et_2O	60	70
8[b]	0.3/0.1/0.3	Et_2O	60	53

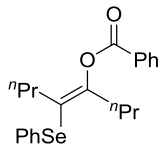
[a] Determined by ^1H NMR spectroscopy. [b] Et_2O was gradually distilled out in the initial stages of the reaction, and therefore the present reaction proceeds in neat condition.

(i.e., **1d** or **1e**) also proceeded stereoselectively, leading to **3da** and **3ea**, whereas electron-deficient acetylenedicarboxylate **1f** and propargylic alcohol **1g** failed to undergo the desired benzoyloxyselenation reaction, with being **1f** recovered mainly unchanged and **1g** affording a complex mixture.

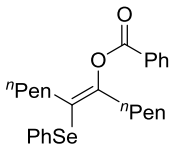
The author then examined the benzoyloxyselenation reaction using unsymmetrical alkynes. In this case, 2-octyne **1h** and 6-phenyl-2-hexyne **1i** provided the corresponding *trans*-adducts **3ha** and **3ia** (and their regioisomers), respectively. However, in the cases of 4,4-dimethyl-2-pentyne **1j** and 1-phenyl-1-pentyne **1k**, benzoyloxyselenation occurred in excellent regio- and stereoselectivities.

Table 4-2. Stereoselective Benzoyloxyselenation of Internal Alkynes with BPO/$(PhSe)_2$[a]

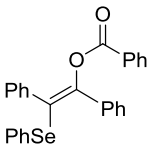




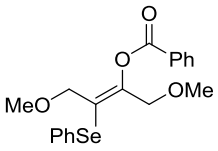
3aa, 79%



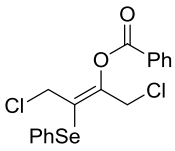
3ba, 72%



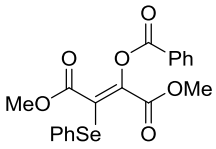
3ca, 64%



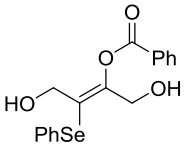
3da, 60%



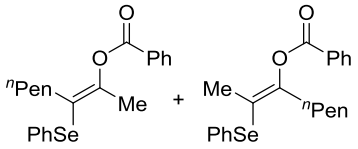
3ea, 48%



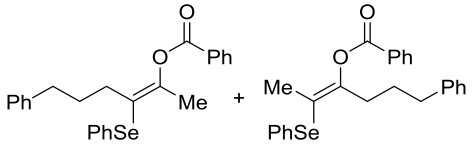
3fa, 0%



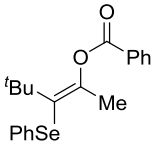
3ga, 0%



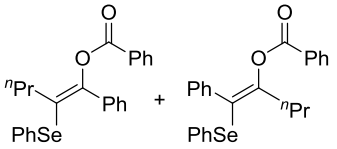
3ha + 3ha', 61% (56/44)[c]



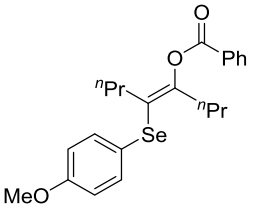
3ia + 3ia', 70% (55/45)[c]



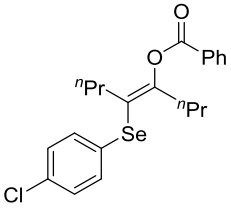
3ja, 28%



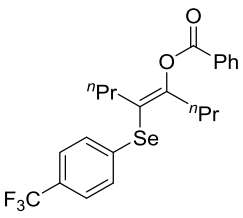
3ka + 3ka', 56% (94/6)[c]



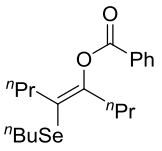
3ab, 57%



3ac, 67%



3ad, 44%



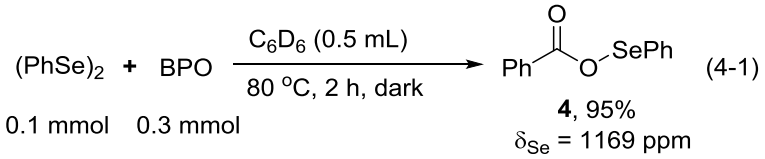
3ae, 68%

[a] Reaction conditions: alkyne (0.2 mmol), diselenide (0.2 mmol), BPO (0.2 mmol), and Et_2O (3 mL) at 60 °C for 16 h under air in the absence of light. [b] Isolated yield. [c] Isolated as a regioisomeric mixture.

Furthermore, the benzoyloxyselenation reaction was examined using a range of organic diselenide compounds. Interestingly, the presence of electron-donating (*p*-MeO) and electron-withdrawing (*p*-Cl) groups at the *para*-position of the phenylseleno moiety produced acceptable yields (57% **3ab** and 67% **3ac**), although the presence of strongly

electron-withdrawing group (p-CF_3) resulted in decreased yields of the desired adduct (i.e., **3ad**, 44%). This reaction was also applicable to aliphatic diselenide compounds, such as dibutyl diselenide, which afforded the corresponding adduct **3ae** in 68% yield.

To clarify the active species present in the benzoyloxyselenation of internal alkynes, the reaction of $(PhSe)_2$ with 3 equiv. of BPO was examined in deuterated benzene at 80 °C over 2 h, where the benzoyloxy phenyl selenide **4** was obtained in 95% yield. The formation of **4** was confirmed by ^{77}Se NMR measurements (Eq 4-1), and so this result strongly suggests that the present benzoyloxyselenation pathway involves benzoyloxy selenide **4** as a key intermediate.[9,10]

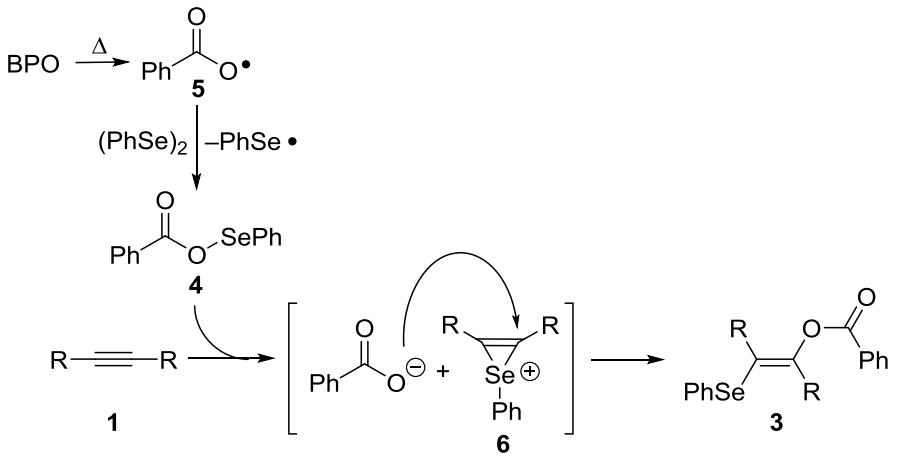


(4-1)

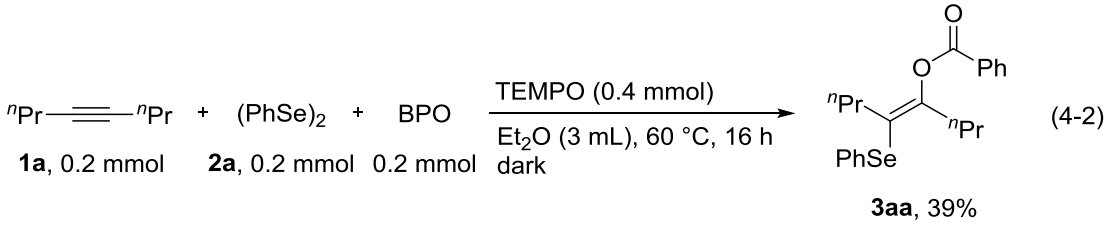
Based on the stereoselective benzoyloxyselenation of various internal alkynes in an *anti*-addition manner, the author proposed a possible pathway for this transformation, as indicated in Scheme 4-3. In this mechanistic pathway, the thermal decomposition of BPO generates benzoyloxy radical **5**, which reacts with $(PhSe)_2$ to form benzoyloxy selenide **4** as a key intermediate. The subsequent benzoyloxyselenation reaction may then proceed via an ionic mechanism, where the phenylselenenyl ion ($PhSe^+$) adds to the internal alkyne (**1**), generating the selenirenium ion (**6**), which undergoes nucleophilic attack from the benzoate anion from the opposite side to the selenium ion to give *trans*-adduct **3**.

To gain insight into the reaction pathway, the author examined the benzoyloxyselenation with 4-octyne (**1a**) (Table 4-1, entry 4) in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO). As a result, benzoyloxyselenation product **3aa** was obtained in 39% yield (Eq 4-2). In addition, the author prepared in situ benzoyloxy phenyl selenide **4** according to Eq 4-1 and

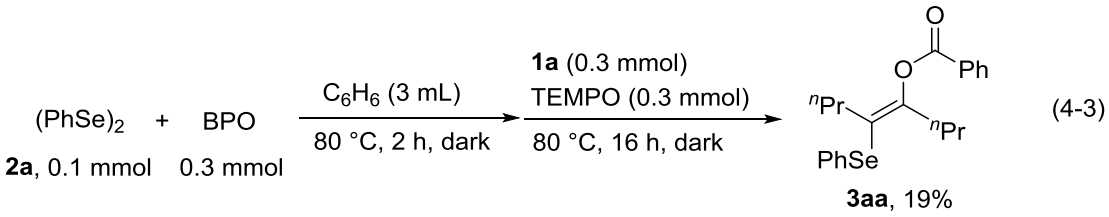
Scheme 4-3. A Plausible Pathway for the Benzoyloxyselenation of Internal Alkynes



performed the subsequent reaction of **4** with **1a** in the presence of TEMPO, which also afforded **3aa** in 19% yield (Eq 4-3). These results suggest that the present reaction proceeds via an ionic pathway rather than via a radical pathway.



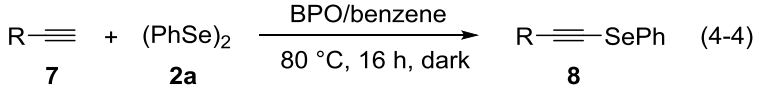
(4-2)



(4-3)

4-3 C(sp)–H Substitution of Terminal Alkynes

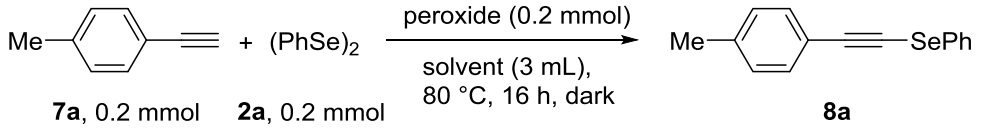
The author then examined the benzoyloxyselenation of terminal alkynes **7** in benzene at 80 °C over 16 h. However, the desired products were not observed, and surprisingly, the novel C(sp)–H substitution of alkynes with a seleno group proceeded to afford alkynyl selenides **8** (Eq 4-4).[11,12]



Based on this observation, the author investigated the reaction of 4-ethynyltoluene (**7a**) with diphenyl diselenide (**2a**) using a range of different peroxides and solvents at 80 °C over 16 h, (Table 4-3). When BPO was employed as the peroxide, alkynyl selenide **8a** was successfully obtained in 68% yield (Table 4-3, entry 1), and so the author subsequently evaluated the reaction using BPO in a range of different solvents to determine their influence on the C(sp)–H substitution reaction (Table 4-3, entries 2–8). As indicated, benzene gave the highest yield (Table 4-3, entry 1), while toluene, C_6H_5Cl, and 1,2-dichloroethane (DCE) produced only moderate yields of the desired product **8a** (Table 4-3, entries 2–4). Furthermore, the use of benzotrifluoride (BTF, $PhCF_3$) and polar solvents (CH_3CN, THF, or DME) produced particularly low yields (Table 4-3, entries 5–8).

The author then examined the influence of the peroxides employed on the reaction, but found that dilauroyl peroxide (LPO), potassium persulfate ($K_2S_2O_8$), dicumyl peroxide (CPO), *tert*-butyl perbenzoate (TBPB), di-*tert*-butyl peroxide (DTBP), and *tert*-butyl hydrogen peroxide (TBHP) produced significantly poorer results than BPO (Table 4-3, entries 9–14 versus entry 1). In addition, in the absence of peroxide, the C(sp)–H substitution reaction did not take place, thereby confirming its importance in this reaction (Table 4-3, entry 15).

Table 4-3. Optimization of Peroxides and Solvents for the C(sp)–H Substitution Reaction[a]



7a, 0.2 mmol **2a**, 0.2 mmol **8a**

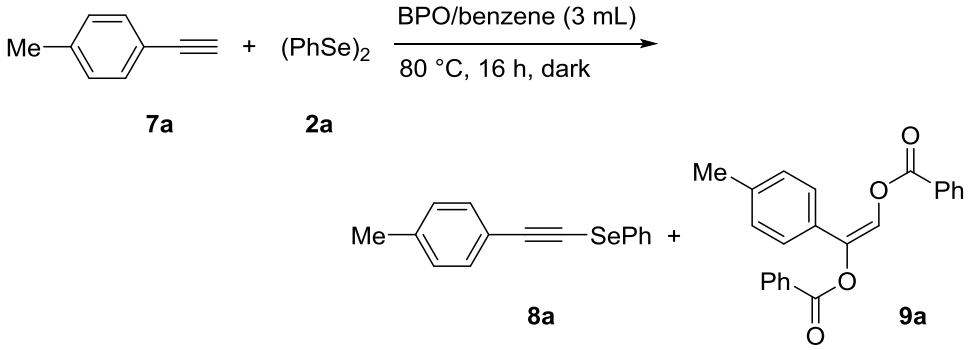
entry	peroxide	solvent	yield, %[b]
1	BPO	benzene	68
2	BPO	toluene	44
3	BPO	C_6H_5Cl	59
4	BPO	DCE	51
5	BPO	BTF	19
6	BPO	MeCN	23
7	BPO	THF	N.D.
8	BPO	DME	6
9[c]	LPO	benzene	N.D.
10	$K_2S_2O_8$	benzene	N.R.
11[d]	CPO	C_6H_5Cl	26
12[d]	TBPB	C_6H_5Cl	32
13[e]	DTBP	C_6H_5Cl	23
14[e]	TBHP	C_6H_5Cl	39
15	none	benzene	N.D.

[a] Reaction conditions: 4-ethynyltoluene (0.2 mmol), diphenyl diselenide (0.2 mmol), peroxide (0.2 mmol), and solvent (3 mL) at 80 °C for 16 h under air in the absence of light. [b] Determined by ^{1}H NMR spectroscopy using 1,3,5-trioxane as an internal standard. [c] Reaction carried out at 60 °C. [d] Reaction carried out at 115 °C. [e] Reaction carried out at 130 °C.

Subsequently, the author investigated the effect of different bases and reaction stoichiometries on the C(sp)–H substitution reaction of **7a** with $(PhSe)_2$ **2a** in the presence of BPO in benzene (Table 4-4). As benzoic acid was formed as a byproduct, the author expected that the addition of a suitable base would trap the produced benzoic acid (Table 4-4, entries 2–6). Among the various bases examined, sodium hydrogen carbonate ($NaHCO_3$) was found to be the most effective, yielding the desired product **8a** in 65% yield and suppressing the formation of the BPO adduct **9a** (Table 4-4, entry 2). A similar result was also obtained using Na_2CO_3 (Table 4-4,

entry 3). In contrast, Cs_2CO_3, NaOH, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were ineffective in the C(sp)–H substitution reaction (Table 4-4, entries 4–6). Upon variation in the reaction stoichiometry, the author found that excess BPO gave a higher product selectivity towards **8a** in the presence of $NaHCO_3$ (Table 4-4, entries 7–9). The obtained results therefore confirmed that the optimized reaction conditions for this transformation were a **7a**/**2a**/BPO molar ratio of 0.3:0.1:0.3 (mmol), $NaHCO_3$ (0.2 mmol), toluene (3 mL), and 100 ºC over 16 h, which produced alkynyl selenide **8a** in 76% yield (Table 4-4, entry 9).

Table 4-4. Optimization of the Base Employed and the Reaction Stoichiometry

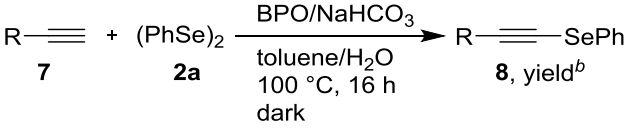


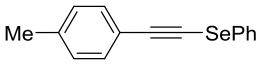
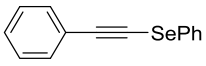
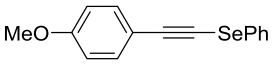
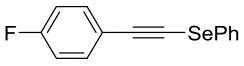
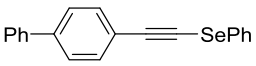
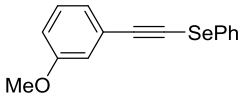
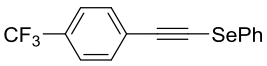
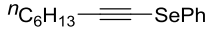
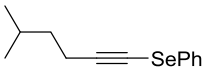
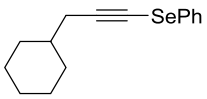
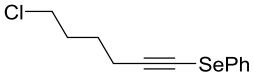
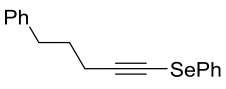
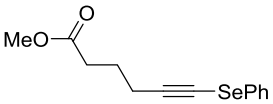
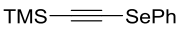
entry	**7a**/**2a**/BPO, mmol	yield of **8a**, %[a]	base	yield of **9a**, %[a]
1	0.2/0.2/0.2	68	none	11
2[b]	0.2/0.2/0.2	65	$NaHCO_3$	6
3[c]	0.2/0.2/0.2	59	Na_2CO_3	4
4[d]	0.2/0.2/0.2	N.D.	Cs_2CO_3	N.D.
5[e]	0.2/0.2/0.2	2	NaOH	trace
6[f]	0.2/0.2/0.2	10	DBU	N.D.
7[b]	0.3/0.1/0.3	64[g]	$NaHCO_3$	trace
8[b,h]	0.3/0.1/0.3	59[g]	$NaHCO_3$	trace
9[b,h,i]	0.3/0.1/0.3	76[g]	$NaHCO_3$	N.D.

[a] Determined by ^{1}H NMR spectroscopy. [b] Addition of $NaHCO_3$ (0.2 mmol) and H_2O (20 μL). [c] Addition of Na_2CO_3 (0.2 mmol) and H_2O (20 μL). [d] Addition of Cs_2CO_3 (0.2 mmol) and H_2O (20 μL). [e] Addition of NaOH (0.2 mmol) and H_2O (20 μL). [f] Addition of DBU (0.2 mmol). [g] The yield was calculated based on the starting quantity of the PhSe unit. [h] Reaction carried out at 100 °C. [i] Toluene was used as the solvent.

With the optimized conditions in hand, the author attempted the preparation of a variety of alkynyl selenides through the C(sp)–H substitution reaction, as outlined in Table 4-5. More specifically, aromatic alkynes containing electron-donating groups (i.e., **7a** and **7c**) efficiently underwent the C(sp)–H substitution reaction to afford the corresponding alkynyl selenides (**8a** and **8c**) in good yields. In contrast, the C(sp)–H substitution of electron-poor aromatic alkynes **7d**, **7e**, **7f**, and **7g** resulted in lower yields of the corresponding alkynyl selenides (**8d**, **8e**, **8f**, and **8g**). However, aliphatic alkynes **7h**–**7m** afforded the corresponding alkynyl selenides in moderate to good yields (**8h**–**8m**). These results therefore indicate that cycloalkyl, chloro, and ester groups are well tolerated in this reaction. Furthermore, trimethylsilylacetylene **7n** underwent the C(sp)–H substitution reaction, providing the desired compound (**8n**) in 34% yield.

Table 4-5. Synthesis of Alkynyl Selenides via the C(sp)–H Substitution Reaction[a]

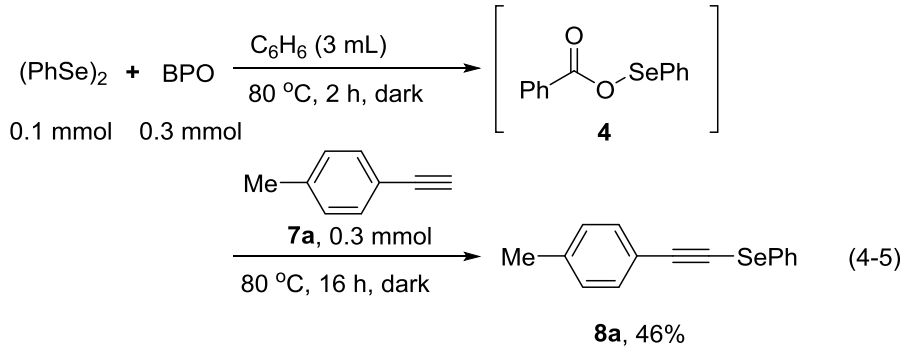


 **8a**, 71%	 **8b**, 55%	 **8c**, 80%	 **8d**, 29%
 **8e**, 40%	 **8f**, 34%	 **8g**, 16%	 **8h**, 58%
 **8i**, 63%	 **8j**, 56%	 **8k**, 48%	
 **8l**, 57%	 **8m**, 51%	 **8n**, 34%	

[a] Reaction conditions: alkyne (0.3 mmol), diphenyl diselenide (0.1 mmol), BPO (0.3 mmol), $NaHCO_3$ (1.0 mmol), H_2O (20 μL), and toluene (3 mL) at 100 °C for 16 h under air in the absence of light. [b] Isolated yield.

To gain an improved insight into the mechanism taking place during the C(sp)–H substitution reaction, Hammett plots were prepared by conducting the reaction using a mixture of aromatic alkynes **7a**, **7b**, **7c**, and **7f** and monitoring the reaction mixture by ^{1}H NMR spectroscopy after 10 min. As a result, a ρ value of −2.69 was obtained, thereby indicating that the C(sp)–H substitution reaction may involve an ionic pathway based on a cationic species as the rate-determining step. This result was supported by the fact that the reaction was significantly influenced by the solvent employed (see Table 4-3).

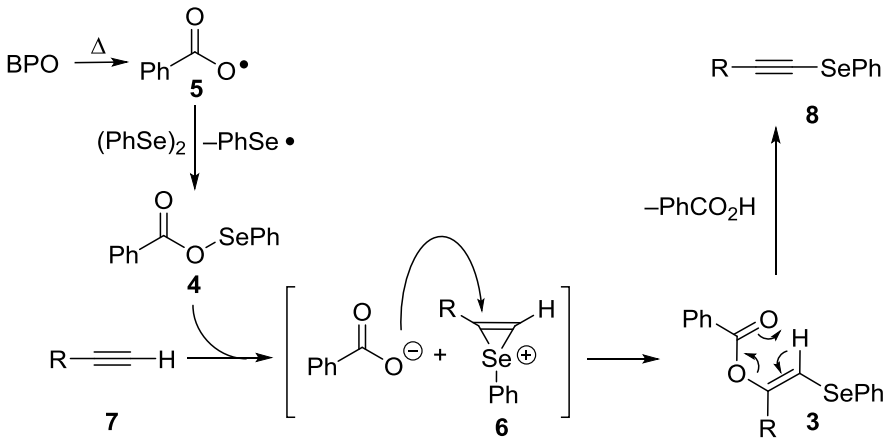
Furthermore, according to Eq 4-1, benzoyloxy phenyl selenide **4** was prepared in situ by the reaction of $(PhSe)_2$ with BPO in benzene at 80 °C over 2 h. Subsequent reaction of **4** with a terminal alkyne (**7a**) in the absence of light produced the desired alkynyl selenide **8a** in 46% yield (Eq 4-5).



(4-5)

Thus, a possible pathway for this C(sp)–H substitution process is outlined in Scheme 4-4. Initially, BPO undergoes homolysis upon heating to generate benzoyloxy radical **5**, which can be trapped by $(PhSe)_2$ to produce benzoyloxy phenyl selenide **4** as a key electrophilic intermediate. Terminal alkyne **7** can then undergo regioselective benzoyloxyselenation via the formation of selenirenium cation **6**, and a subsequent elimination of benzoic acid from **3** provides the desired alkynyl selenide **8**.

Scheme 4-4. A Possible Pathway for the C(sp)-H Substitution Reaction



4-4 Conclusion

In conclusion, a novel binary $(PhSe)_2$/BPO system has been successfully developed for the synthetic transformation of alkynes. In the case of internal alkynes, a stereoselective benzoyloxyselenation reaction afforded the corresponding *β*-(benzoyloxy)alkenyl selenides in good yields, while terminal alkynes underwent a C(sp)–H substitution reaction with $(PhSe)_2$ to produce alkynyl selenides in good yields.[13] In these reactions, the excellent radical-capturing ability of $(PhSe)_2$ contributes to a number of safe and highly selective transformations using peroxides. These results are of particular interest, as the selective addition of heteroatom compounds to unsaturated compounds is one of the most useful transformations in organic synthesis, with the resulting products often being suitable for use as versatile synthetic intermediates due to the characteristic features of individual heteroatoms.

4-5 Experimental Section

General Comment

Unless otherwise noted, all chemicals and solvents were used as received without further purification. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were taken in $CDCl_3$ with Me_4Si as an internal standard. The use of broadband decoupling is indicated with braces. IR spectra are reported in wavenumbers (cm^{-1}).

General Procedure for the Synthesis of 3.

In a 10 mL of round-bottled flask were placed BPO (48.4 mg, 0.2 mmol), $(PhSe)_2$ (62.4 mg, 0.2 mmol), alkyne (0.2 mmol), and benzene (3 mL). Then, the mixture was heated at 80 ºC for 16 h under the atmosphere in the dark. After the reaction was complete, the reaction mixture was treated with saturated aqueous sodium thiosulfate (3 mL). The product was extracted with ethyl acetate (15 mL×1), and then the organic layer combined was washed with saturated aqueous sodium bicarbonate (5 mL×3). After neutralization of the organic layer with HCl aq. (0.1 N), the combined extracts were dried with $MgSO_4$. Filtration and concentration *in vacuo* provided the crude product which was purified by GPC (eluent $CHCl_3$).

(E)-5-(Phenylselanyl)oct-4-en-4-yl Benzoate (3aa). Pale yellow liquid (57.7 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.13 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.51 (d, J = 7.6 Hz, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.31–7.19 (m, 3H), 2.79 (t, J = 7.6 Hz, 2H), 2.21 (t, J = 7.6 Hz, 2H), 1.60–1.46 (m, 4H), 0.94 (t, J = 7.6 Hz, 3H), 0.81 (t, J = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 164.4, 153.1, 133.5, 130.8, 130.7, 129.9, 129.5, 129.2, 128.6, 126.3, 120.8, 35.1, 34.3, 21.6, 20.8, 13.6, 13.5; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 343; IR (neat): 3059, 2960, 2931, 2871, 1730, 1653, 1577, 1477, 1451, 1437, 1314, 1269, 1235, 1169, 1108, 1085, 1066, 1024, 999, 917; HRMS (EI) calcd for $C_{21}H_{24}O_2Se$ $[M]^+$: 388.0941; found : 388.0911.

(E)-7-(Phenylselanyl)dodec-6-en-6-yl Benzoate (3ba). Pale yellow liquid (61.1 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.12 (d, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.30–7.20 (m, 3H), 2.80 (d, *J* = 7.6 Hz, 2H), 2.21 (d, *J* = 7.6 Hz, 2H), 1.53–1.44 (m, 4H), 1.32–1.28 (m, 4H), 1.20–1.14 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.4, 153.1, 133.4, 130.8, 130.7, 129.9, 129.5, 129.2, 128.6, 126.4, 120.8, 33.2, 32.3, 31.3, 31.1, 28.0, 27.1 22.4, 22.3, 14.0, 13.9; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 344; IR (neat): 3056, 2957, 2928, 2857, 1734, 1653, 1647, 1577, 1558, 1539, 1506, 1265, 1205, 1162,113, 1083, 1066, 1025; HRMS (EI) calcd for $C_{25}H_{32}O_2Se$ $[M]^+$: 444.1568; found: 444.1569.

(E)-1,2-Diphenyl-2-(phenylselanyl)vinyl Benzoate (3ca). Pale yellow liquid (56.8 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.40–7.31 (m, 8H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.14–7.09 (m, 5H), 7.02 (t, *J* = 7.6 Hz, 1H), ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.8, 146.7, 137.6, 136.1, 135.1, 133.3, 132.9, 129.9, 129.5, 129.2, 129.1, 129.0, 128.8, 128.3, 128.0, 127.7, 127.4, 127.1, 123.3; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 445; IR (neat): 3055, 1734, 11684, 1653, 1559, 1506, 1490, 1476, 1437, 1268, 1244, 1209, 1176, 1083, 1064, 1024; HRMS (EI) calcd for $C_{27}H_{20}O_2Se$ $[M]^+$: 456.0629; found: 456.0635.

(E)-1,4-Dimethoxy-3-(phenylselanyl)but-2-en-2-yl Benzoate (3da). Pale yellow liquid (41.5 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.13 (d, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 6.8 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.31–7.23 (m, 3H), 4.57 (s, 2H), 4.07 (s, 2H), 3.36 (s, 3H), 3.20 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.3, 150.5, 132.1, 130.2, 129.3, 128.9, 128.6, 127.3, 121.5, 70.5, 69.4, 58.5, 57.9; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 337; IR (neat): 3059, 2986, 2926, 2892, 2820, 1733, 1653, 1647, 1636, 1601, 1577, 1477, 1451, 1438, 1314, 1267, 1198, 1176, 1088, 1066, 1023, 1000, 957; HRMS (EI) calcd for $C_{19}H_{20}O_4Se$ $[M]^+$: 392.0527; found: 392.0507.

(E)-1,4-Dichloro-3-(phenylselanyl)but-2-en-2-yl Benzoate (3ea). Pale yellow liquid (36.5 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.16 (d, *J* = 7.2 Hz, 2H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.59–7.57 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.35–7.32 (m, 3H), 4.79 (s, 2H), 4.18 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.0, 149.8, 134.2, 132.8, 130.6, 130.4, 129.7 128.9, 128.8, 128.1, 128.0, 122.9, 42.5; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 364; IR (neat): 3060, 2924, 2853, 1734, 1637, 1576, 1560, 1476, 1451, 1437, 1316, 1264, 1192, 1212, 1177, 1135, 1058, 1024, 999, 973, 739, 735, 709, 691; HRMS (EI) calcd for $C_{17}H_{14}Cl_2O_2Se$ $[M]^+$: 399.9536; found: 399.9541.

(E)-3-(Phenylselanyl)oct-2-en-2-yl Benzoate (3ha); (E)-2-(Phenylselanyl)oct-2-en-3-yl Benzoate (3ha'): (**3ha**/**3ha'** = 56/44). Pale yellow liquid (46.8 mg, 61%).

(**3ha**) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.14–8.11 (m, 2H), 7.65–7.61 (m, 1H), 7.53–7.48 (m, 4H), 7.32–7.20 (m, 3H), 2.34 (s, 3H), 2.27 (t, *J* = 7.6 Hz, 2H), 1.49–1.44 (m, 2H), 1.22–1.14 (m, 4H), 0.78 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.5, 149.5, 133.4, 130.7, 130.6, 129.9, 129.5, 128.6, 126.4, 120.8, 32.5, 31.2, 28.0, 22.3, 22.0, 13.9; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 349.

(**3ha'**) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.14–8.11 (m, 2H), 7.65–7.61 (m, 1H), 7.53–7.48 (m, 4H), 7.32–7.20 (m, 3H), 2.78 (d, *J* = 7.2 Hz, 2H), 1.96 (s, 3H), 1.58–1.52 (m, 2H), 1.36–1.31 (m, 4H), 0.8 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.1, 152.2, 133.4, 131.3, 130.3, 130.0, 129.5, 129.2, 126.6, 114.8, 33.2, 31.3, 27.0, 22.4, 20.0, 19.9, 14.0; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 390; IR (neat): 3063, 3023, 2924, 2854, 1733, 1684, 1647, 1558, 1539, 1506, 1473, 1451, 1437, 1269, 1175, 1144, 1066, 1024; HRMS (EI) calcd for $C_{21}H_{24}O_2Se$ $[M]^+$: 388.0942; found: 388.0912.

(E)-6-Phenyl-3-(phenylselanyl)hex-2-en-2-yl Benzoate (3ia); (E)-6-Phenyl-2-(phenylselanyl)-hex-2-en-3-yl Benzoate (3ia'): (**3ia**/**3ia'** = 55/45). Pale yellow liquid (63.5 mg, 70%).

(**3ia**) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.04 (d, *J* = 7.6 Hz, 2H), 7.63–7.59 (m, 1H), 7.51–7.45 (m, 2H), 7.31–7.20 (m, 4H), 7.16–7.02 (m, 6H), 2.50 (t, *J* = 7.6 Hz, 2H), 2.34 (s, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 1.90–1.78 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 165.2, 150.5, 142.7, 134.2, 131.6, 131.3, 130.7, 130.0, 129.3, 129.0, 128.9, 127.3, 126.3, 121.2, 35.9, 32.8, 30.5, 20.8; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 348.

(**3ia'**) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.12 (d, *J* = 7.6 Hz, 2H), 7.63–7.59 (m, 1H), 7.51–7.45 (m, 2H), 7.31–7.20 (m, 4H), 7.16–7.02 (m, 6H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.66 (t, *J* = 8.0 Hz, 2H), 1.97 (s, 3H), 1.90–1.78 (m, 2H),^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.9, 152.3, 142.7, 134.3, 132.2, 131.0, 130.8, 130.1, 129.4, 129.1, 129.0, 127.5, 126.5, 116.2, 36.2, 33.9, 29.8, 20.7; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 391; IR (neat): 3059, 2955, 2927, 2857, 1734, 1626, 1647, 1577, 1476, 1451, 1437, 1374, 1313, 1268, 1205, 1169, 1104, 1082, 1066, 1024, 1001; HRMS (EI) calcd for $C_{25}H_{24}O_2Se$ $[M]^+$: 436.0942; found: 436.0953.

(E)-4,4-Dimethyl-3-(phenylselanyl)pent-2-en-2-yl Benzoate (3ja). Pale yellow liquid (20.3 mg, 28%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.13 (d, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.53–7.49 (m, 4H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 2.34 (s, 3H), 1.27 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.7, 150.9, 133.5, 132.9, 130.1, 129.7, 129.2, 129.0, 128.6, 128.5, 125.6, 38.7, 31.1, 23.3; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 359; IR (neat): 3056, 2963, 2910, 2865, 1730, 1684, 1576, 1558, 1506, 1473, 1457, 1437, 1268, 1147, 1088, 1068, 1022; HRMS (FAB) calcd for $C_{20}H_{23}O_2Se$ $[M+H]^+$: 375.0863; found: 375.0852.

(E)-1-Phenyl-2-(phenylselanyl)pent-1-en-1-yl Benzoate (3ka); (E)-1-Phenyl-1-(phenylselanyl)-pent-1-en-2-yl Benzoate (3ka'): (**3ka**/**3ka'** = 94/6). Pale yellow liquid (45.3 mg, 56%).

(**3ka**) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.61–7.54 (m, 3H), 7.51–7.45 (m, 4H), 7.31–7.23 (m, 6H), 2.33 (t, *J* = 7.6 Hz, 2H), 1.66–1.54 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.5, 148.2, 136.2, 133.5, 132.3, 130.3,

130.0, 129.4, 129.2, 129.1, 128.7, 128.6, 127.8, 127.0, 123.6, 34.2, 21.8, 13.7, 13.6; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 368.

(**3ka'**) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.06 (d, *J* = 7.6 Hz, 2H), 7.61–7.54 (m, 3H), 7.51–7.45 (m, 4H), 7.31–7.23 (m, 6H), 2.94 (t, *J* = 7.6 Hz, 2H), 1.66–1.54 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H); selected ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 136.2, 133.2, 131.5, 129.9, 129.8, 129.0, 128.5, 128.3, 127.6, 127.1; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 421; IR (neat): 3057, 2960, 2929, 2869, 1733, 1718, 1684, 1653, 1558, 1539, 1506, 1490, 1473, 1457, 1340, 1246, 1220, 1177, 1084, 1065, 1024; HRMS (EI) calcd for $C_{24}H_{22}O_2Se$ $[M]^+$: 422.0785; found: 422.0797.

(E)-5-((4-Methoxyphenyl)selanyl)oct-4-en-4-yl Benzoate (3ab). Pale yellow liquid (45.0 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.51–7.45 (m, 4H), 6.85 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 3H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.12 (t, *J* = 7.2 Hz, 2H), 1.58–1.43 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.5, 159.0, 151.0, 133.8, 133.4, 129.9, 129.6, 128.6, 122.0, 120.1, 114.7, 55.3, 35.0, 33.6, 21.5, 20.8, 13.7, 13.5; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 333; IR (neat): 2960, 2931, 2973, 1734, 1418, 1700, 1684, 1653, 1558, 1539, 1506, 1457, 1325, 1269, 1235, 1168, 1107, 1074, 1065, 1012; HRMS (EI) calcd for $C_{22}H_{26}O_3Se$ $[M]^+$: 418.1047; found: 418.1050.

(E)-5-((4-Chlorophenyl)selanyl)oct-4-en-4-yl Benzoate (3ac). Pale yellow liquid (37.8 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.12 (d, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.19 (t, *J* = 7.2 Hz, 2H), 1.59–1.46 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.4, 153.6, 133.6, 132.5, 131.8, 130.0, 129.3, 129.1, 128.6, 120.6, 35.2, 34.4, 21.6, 20.8, 13.6, 13.5; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 343;

IR (neat): 2961, 2930, 2870, 1734, 1684, 1653, 1558, 1539, 1506, 1476, 1457, 1340, 1269, 1234, 1169, 1089, 1065, 1010; HRMS (EI) calcd for $C_{21}H_{23}ClO_2Se$ $[M]^+$: 422.0552; found: 422.0540.

(E)-5-((4-(Trifluoromethyl)phenyl)selanyl)oct-4-en-4-yl Benzoate (3ad). Pale yellow liquid (55.6 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.14 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.66–7.45 (m, 7H), 2.76 (d, *J* = 7.2 Hz, 2H), 2.25 (d, *J* = 7.2 Hz, 2H), 1.60–1.47 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.4, 155.1, 136.8, 133.6, 130.0, 129.5, 129.3, 128.7, 128.2 (q, *J* = 32.4 Hz), 125.9 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 270.3 Hz), 119.7, 35.3, 34.9, 21.7, 20.7, 13.6, 13.5; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 353; IR (neat): 2960, 2931, 2872, 1733, 1718, 1684, 1653, 1646, 1635, 1558, 1539, 1506, 1465, 1457, 1451, 1269, 1234, 1168, 1108, 1086, 1066, 1025; HRMS (EI) calcd for $C_{22}H_{23}F_3O_2Se$ $[M]^+$: 456.0815; found: 456.0807.

(E)-5-(Butylselanyl)oct-4-en-4-yl Benzoate (3ae). Pale yellow liquid (48.1 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.09 (d, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 2H), 2.75 (d, *J* = 7.6 Hz, 2H), 2.68 (d, *J* = 7.2 Hz, 2H), 2.23 (d, *J* = 7.2 Hz, 2H), 1.68 (q, *J* = 7.6 Hz, 2H), 1.59–1.48 (m, 4H), 1.47–1.38 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 6H), 0.86 (t, *J* = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 164.4, 150.4, 133.4, 133.3, 129.9, 129.7, 128.5, 128.4, 120.0, 34.9, 33.7, 32.4, 25.7, 22.9, 21.6, 20.7, 13.6; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 217; IR (neat): 2957, 2929, 2870, 2836, 1734, 1684, 1653, 1558, 1539, 1506, 1490, 1457, 1340, 1269, 1247, 1172, 1066, 1025; HRMS (EI) calcd for $C_{19}H_{28}O_2Se$ $[M]^+$: 368.1255; found: 368.1256.

General Procedure for the Synthesis of Alkynyl Selenides 8.

In a 10 mL of round-bottled flask equipped with condenser were placed $(PhSe)_2$ (31.2 mg, 0.1 mmol), sodium bicarbonate (25.2 mg, 0.3 mmol), BPO (48.4 mg, 0.2 mmol), H_2O (20 μL), alkyne (0.3 mmol), and toluene (3 mL). Then, the mixture was heated at 100 ºC for 16 h under the atmosphere in the dark. After the reaction was complete, the reaction mixture was

treated with saturated aqueous sodium thiosulfate (3 mL). The product was extracted with ethyl acetate (15 mL × 1), and then the organic layer combined was washed with saturated aqueous sodium bicarbonate (5 mL × 3). After neutralization of the organic layer with HCl aq. (0.1 N), the combined extracts were dried with $MgSO_4$. Filtration and concentration *in vacuo* provided the crude product which was purified by GPC (eluent $CHCl_3$) or PTLC.

(p-Tolylethynyl)(phenyl)selane (8a). Pale yellow liquid (37.9 mg, 71%). **8a** is a known compound.[12g] ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.58 (d, *J* = 9.2 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.24 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 138.8, 133.0, 131.7, 129.5, 129.1, 128.9, 127.0, 120.1, 103.1, 68.1, 21.5; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 273; IR (neat): 3057, 3025, 2919, 2156, 1574, 1507, 1475, 1437, 1178, 1063; GC-MS (EI) *m/z* = 272 (M^+), 192 (M^+–Se).

(Phenylethynyl)(phenyl)selane (8b). Pale yellow liquid (27.5 mg, 55%). **8b** is a known compound.[12g] ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.51–7.49 (m, 2H), 7.35–7.26 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 131.7, 129.5, 129.0, 128.9, 128.6, 128.3, 127.1, 123.1, 102.9, 69.2; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 273; IR (neat): 3056, 2920, 2162, 1575, 1476, 1439, 1066, 1019; GC-MS (EI) *m/z* = 258 (M^+), 178 (M^+–Se).

(p-Methoxyphenylethynyl)(phenyl)selane (8c). Pale yellow liquid (45.7 mg, 80%). **8c** is a known compound.[12d] ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.58 (d, *J* = 9.2 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.24 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 160.0, 133.6, 129.5, 129.2, 128.8, 126.9, 115.2, 114.0, 103.2, 67.1, 55.3; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 272; IR (neat): 3052, 3001, 2997, 2953, 2835, 2540, 2154, 1603, 1577, 1508, 1476, 1440, 1290, 1250, 1171, 1031, 1066; GC-MS (EI) *m/z* = 288 (M^+), 208 (M^+–Se).

(p-Fluorophenylethynyl)(phenyl)selane (8d). Pale yellow liquid (15.6 mg, 29%). **8d** is a known compound.[12h] ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.58 (d, *J* = 6.8 Hz, 2H), 7.49 (d, *J* = 5.6 Hz, 2H), 7.35–7.26 (m, 3H), 7.03 (t, *J* = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 162.7 (d, *J* = 249.8 Hz), 133.8 (d, *J* = 8.6 Hz), 129.6, 129.1, 128.7, 127.2, 119.3, 115.6 (d, *J* = 21.9 Hz), 101.7, 69.0; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 273; IR (neat): 1596, 1575, 1504, 1475, 1440, 1228, 1215, 1115, 1033; HRMS (ESI) calcd for $C_{14}H_9FSe$ $[M+H]^+$: 276.9926, found: 276.9914.

(p-Biphenylethynyl)(phenyl)selane (8e). Pale yellow solid (25.5 mg, 40%). **8e** is a known compound.[12e] mp 93–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.61–7.55 (m, 4H), 7.60 (s, 4H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.38–7.32 (m, 3H), 7.29–7.25 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 141.3, 140.2, 132.2, 129.6, 129.0, 128.9, 128.86, 127.7, 127.1, 127.0, 122.0, 102.8, 69.9; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 274; IR (KBr): 3059, 3040, 3035, 2924, 2160, 1577, 1488, 1475, 1438, 1404, 1067, 1019, 1007; GC-MS (EI) *m/z* = 334 (M^+), 254 (M^+–Se).

(m-Methoxyphenylethynyl)(phenyl)selane (8f). Pale yellow liquid (19.3 mg, 34%). **8f** is a known compound.[12i] ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.59 (d, *J* = 5.6 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.29–7.21 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.02 (brs, 1H), 6.90 (dd, *J* = 8.0 Hz, 1H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 159.3, 129.6, 129.4, 129.0, 128.8, 127.1, 124.3, 124.1, 116.5, 115.2, 102.8, 69.1, 55.3; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 273; IR (neat): 3058, 3000, 2960, 2936, 2908, 2833, 2155, 1732, 1592, 1574, 1477, 1439, 1418, 1318, 1285, 1264, 1155, 1005; HRMS (ESI) calcd for $C_{15}H_{12}OSe$ $[M+H]^+$: 289.0126, found: 289.0150.

(p-Trifluoromethylphenylethynyl)(phenyl)selane (8g). Pale yellow solid (10.4 mg, 16%). **8g** is a known compound.[12h] mp 59–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.58 (s, 4H), 7.38–7.27 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 131.6, 129.7, 129.4, 129.2, 128.2, 127.5, 125.3 (q, *J* = 3.8 Hz), 101.4, 73.0 [note: The signals for CF_3 and its

ipso-carbon were too weak to be firmly assigned due to $^{13}C–^{19}F$ coupling and the low intensity of quaternary carbon atoms.]; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 277; IR (KBr): 3072, 2924, 2161, 1610, 1578, 1476, 1440, 1403, 1166, 1105, 1067, 1016; HRMS (ESI) calcd for $C_{15}H_{12}OSe$ $[M+H]^+$: 326.9894, found: 326.9855.

(Oct-1-ynyl)(phenyl)selane (8h). Pale yellow liquid (28.3 mg, 58%). **8h** is a known compound.[12d] ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.52 (d, *J* = 7.6 Hz, 2H), 7.32–7.21 (m, 3H), 2.45 (t, *J* = 7.2 Hz, 2H), 1.63–1.55 (m, 2H), 1.45–1.40 (m, 2H), 1.32–1.28 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 129.3, 128.6, 126.7, 104.8, 57.3, 31.3, 28.7, 28.6, 22.5, 20.6, 14.0; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 268; IR (neat): 3060, 2929, 2856, 2155, 1578, 1477, 1455, 1440, 1325, 1069, 1021; GC-MS (EI) *m/z* = 266 (M^+).

(5-Methylhex-1-ynyl)(phenyl)selane (8i). Pale yellow liquid (31.7 mg, 63%). **8i** is a known compound.[12a] ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.51 (d, *J* = 7.2 Hz, 2H), 7.32–7.21 (m, 3H), 2.46 (t, *J* = 7.2 Hz, 2H), 1.77–1.69 (m, 1H), 1.53–1.46 (q, 2H), 0.92 (d, *J* = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 133.0, 129.3, 128.6, 126.7, 104.7, 57.2, 37.5, 27.2, 22.1, 18.6; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 268; IR (neat): 3058, 2931, 2865, 2183, 1577, 1476, 1440, 1069, 1021; GC-MS (EI) *m/z* = 252 (M^+).

(3-Cyclohexylbut-1-ynyl)(phenyl)selane (8j). Pale yellow liquid (30.4 mg, 56%). ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.52 (d, *J* = 7.6 Hz, 2H), 7.32–7.21 (m, 3H), 2.36 (d, *J* = 6.4 Hz, 2H), 1.84 (dd, *J* = 6.4 Hz, 2.0 Hz, 2H), 1.78–1.50 (m, 4H), 1.31–0.99 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 133.0, 129.3, 128.5, 126.6, 103.7, 58.1, 37.5, 32.7, 28.4, 26.2, 26.1; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 269; IR (neat): 3058, 2922, 2850, 2160, 1578, 1476, 1439, 1324, 1069, 1021; HRMS (ESI) calcd for $C_{15}H_{18}Se$ $[M+H]^+$: 279.0646, found: 279.0642.

(6-Chlorohex-1-ynyl)(phenyl)selane (8k). Pale yellow liquid (25.3 mg, 48%). ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.32–7.22 (m, 3H), 3.58 (t, *J* = 6.4 Hz, 2H), 2.51

(t, *J* = 6.8 Hz, 2H), 1.97–1.90 (quint., 2H), 1.79–1.71 (quint., 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 129.4, 129.0, 128.7, 126.8, 103.4, 58.4, 44.5, 31.5, 25.8, 19.9; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 269; IR (neat): 3057, 2951, 2864, 2130, 1578, 1476, 1439, 1300, 1274, 1067, 1021; HRMS (ESI) calcd for $C_{12}H_{13}ClSe$ $[M+H]^+$: 272.9944, found: 272.9931.

(5-Phenylpent-1-ynyl)(phenyl)selane (8l). Pale yellow liquid (33.6 mg, 57%). **8l** is a known compound.[12f] ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.53 (d, *J* = 7.2 Hz, 2H), 7.32–7.18 (m, 8H), 2.76 (t, *J* = 7.2 Hz, 2H), 2.46 (t, *J* = 6.8 Hz, 2H), 1.94–1.87 (quint., 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 141.4, 129.4, 129.2, 128.7, 128.5, 128.4, 126.8, 125.9, 104.0, 58.2, 34.8, 30.2, 20.0; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 269; IR (neat): 3025, 2954, 2177, 1578, 1476, 1439, 1383, 1367, 1318, 1069, 1021; GC-MS (EI) *m/z* = 300 (M^+).

(5-Methoxycarbonylpent-1-ynyl)(phenyl)selane (8m). Pale yellow liquid (28.1 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.32–7.22 (m, 3H), 3.68 (s, 3H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.95–1.88 (quint., 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.5, 129.4, 129.0, 128.7, 126.8, 103.0, 58.8, 51.6, 32.8, 23.8, 20.0; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 269; IR (neat): 3057, 2949, 2842, 2150, 1736, 1578, 1477, 1439, 1369, 1315, 1248, 1219, 1158, 1066, 1021; HRMS (ESI) calcd for $C_{13}H_{14}O_2Se$ $[M+H]^+$: 283.0232, found: 283.0243.

(2-Trimetylsilylet-1-ynyl)(phenyl)selane (8n). Pale yellow liquid (17.0 mg, 34%). **8n** is a known compound.[12b] ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.51 (d, *J* = 7.2 Hz, 2H), 7.34–7.24 (m, 3H), 0.239 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 129.5, 128.8, 128.4, 127.0, 111.6, 84.2, −0.078; ^{77}Se NMR (76 MHz, $CDCl_3$, ppm): δ 287; IR (neat): 3074, 2959, 2928, 2899, 2852, 2091, 1578, 1477, 1440, 1250, 1067, 1021; GC-MS (EI) *m/z* = 254 (M^+).

4-6 References

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5. Organoselenium compounds have played an important role in many fields, including biochemistry, materials chemistry, medicinal chemistry, organic synthetic chemistry, and so forth. Selected reviews, see: (a) Mugesh, G.; Singh, H. B. *Chem. Soc. Rev.* **2000**, *29*, 347. (b) Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125. (c) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255. (d) Perin, G.; Lenardão, E. J.; Jacob, R. G.; Panatieri, R. B. *Chem. Rev.* **2009**, *109*, 1277. (e) Manjare, S. T.; Kim, Y.; Churchill, D. G. *Acc. Chem. Res.* **2014**, *47*, 2985.

6. An NOE signal was not observed between allylic protons of benzoyloxyselenation product **3aa** despite the fact that the corresponding *cis*-adduct should exhibit NOE. In addition, the addition reaction of phenyl acetylene with benzeneselenenyl trifluoroacetate ($PhSeOCOCF_3$) was reported by Kice and Zefirov *et al.*, where *trans* addition product, (*E*)-1-phenyl-2-(phenylselanyl)ethenyl trifluoroacetate, is formed as a single regio- and stereoisomer via an ionic pathway.[7] From these situations, the author consider that the *trans* addition proceeds in the present reaction system in this stage.

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8. The author confirmed the formation of $(PhSe)_2$ and no formation of byproduct containing organoselenium moiety after the reaction, although the present benzoyloxyselenation required an equimolar amount of $(PhSe)_2$

9. Although BPO should be handled carefully, BPO was almost quantitatively consumed by $(PhSe)_2$ in the initial reaction stage, which enables the safe transformation of alkynes using peroxide (BPO).

10. Benzoyloxy phenyl selenide **4** was too unstable to be isolated. Isolated benzoyloxy aryl selenide and its ^{77}Se NMR chemical shift (δ_{Se} = 1183 ppm) were reported by Fujihara and Furukawa *et al.*, see: Fujihara, H.; Tanaka, H.; Furukawa, N. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2375.

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13. The author further examined the reactions with heteroarene-substituted acetylenes (i.e., 1,2-di(pyridin-3-yl)ethyne and 3-ethynylpyridine) under the optimized reaction conditions shown in Tables 4-1 and 4-4. Unfortunately, however, a mixture including some unidentified selenium species (detected by ^{77}Se NMR) was formed and could not be separated in both cases. The author considers that further optimization of reaction conditions is necessary for the reaction with heteroarene-substituted acetylenes.

Chapter 5

Conclusion

In this research work, the development of new selective multiple introduction of group 16 heteroatom substituents and other substituents to acetylenes has been investigated.

Chapter 2 described a novel transition-metal-catalyzed thiolative lactonization of internal alkynes bearing a hydroxyl group with carbon monoxide and organic disulfides. Although many transition-metal catalysts are ineffective for the addition and carbonylative addition of organic disulfides to internal alkynes, dicobalt octacarbonyl and palladium complexes such as $Pd(PPh_3)_4$ and $Pd(OAc)_2$ were found to exhibit excellent catalytic activity for the thiolative lactonization of internal alkynes bearing a hydroxyl group. This thiolative lactonization gives γ- and δ-lactone derivatives bearing *exo*-methylene and thio groups with excellent regio- and stereoselectivities. The obtained thiolated lactone derivatives are promising as synthetic intermediates, as the thio group can be displaced by a variety of nucleophiles, and *exo*-methylene groups make them possible substrates for Michael addition.

Chapter 3 mentioned a highly selective palladium-catalyzed cyanothiolation of unactivated internal alkeynes with organic disulfides and *tert*-butyl isocyanide. The previously reported cyanothiolation with thiocyanates can be applied to terminal alkynes and arynes. By contrast, this cyanothiolation with organic disulfides and *tert*-butyl isocyanides can be applied to unactivated internal alkynes effectively. This reaction requires no toxic cyanides, because *tert*-butyl isocyanide works as a cyano source. The produced alkenyl cyanides and vinyl sulfides are known as useful synthetic intermediates, bioactive compounds, and monomers to manufacture many different types of polymers.

Chapter 4 described the functionalization of alkynes using a benzoyl peroxide

(BPO)/diphenyl diselenide binary system for the syntheses of alkenyl and alkynyl selenides. Binary systems consisting of benzoyl peroxide and organic diselenides are effective in the selective benzoyloxyselenation of internal alkynes to afford the corresponding *β*-(benzyloxy)alkenyl selenides in good yields. In contrast to internal alkynes, terminal alkynes undergo a novel C(sp)−H substitution with the phenylseleno group, providing alkynyl selenides in good yields. Both selenation reactions might proceed via benzoyloxy selenide (PhC(O)O−SeAr) as a key intermediate for electrophilic addition to alkynes. The products alkenyl and alkynyl selenides are expected to be useful synthetic intermediates in organic synthesis.

In summary, several novel simultaneous introductions of group 16 heteroatom compounds and other compounds to carbon–carbon unsaturated bonds have been developed. The author believes that these developed methods will make a great contribution to the chemistry of group 16 heteroatom compounds.

List of Publications

1. Selective Thiolative Lactonization of Internal Alkynes Bearing a Hydroxyl Group with Carbon Monoxide and Organic Disulfides Catalyzed by Transition-Metal Complexes

   Higashimae, S.; Tamai, T.; Nomoto, A.; Ogawa, A.

   J. Org. Chem. **2015**, *80*, 7126–7133.

   (Chapter 2)

2. Palladium-Catalyzed Cyanothiolation of Internal Alkynes Using Organic Disulfides and *tert*-Butyl Isocyanide

   Higashimae, S.; Kurata, D.; Kawaguchi, S-i.; Kodama, S.; Sonoda, M.; Nomoto, A.; Ogawa, A.

   J. Org. Chem. Submitted.

   (Chapter 3)

3. A Benzoyl Peroxide/Diphenyl Diselenide Binary System for Functionalization of Alkynes Leading to Alkenyl and Alkynyl Selenides

   Kodama, S.; Saeki, T.; Mihara, K.; Higashimae, S.; Kawaguchi, S-i.; Sonoda, M.; Nomoto, A.; Ogawa, A.

   J. Org. Chem. **2017**, 82, 12477–12484.

   (Chapter 4)

Other Publications

4. An Efficient and Highly Selective Carbonylative Bisthiolation of Internal Alkynes with Organic Disulfides Catalyzed by [$Co_2(CO)_8$]

   Higuchi, Y.; Higashimae, S.; Tamai, T.; Nomoto, A.; Sonoda, M.; Ogawa, A.

   Chem. Lett. **2013**, *42*, 1303–1304.

5. A Highly Selective Cobalt-Catalyzed Carbonylative Cyclization of Internal Alkynes with Carbon Monoxide and Organic Thiols

   Higuchi, Y.; Higashimae, S.; Tamai, T.; Ogawa, A.

   Tetrahedron **2013**, *69*, 11197–11202.

6. Palladium-Catalyzed Markovnikov-Selective Hydroselenation of *N*-Vinyl Lactams with Selenols Affording *N*,*Se*-Acetals

   Tamai, T.; Yoshikawa, M.; Higashimae, S.; Nomoto, A.; Ogawa, A.

   J. Org. Chem. **2016**, *81*, 324–329.

7. Gold-Catalyzed *anti*-Markovnikov Hydrothiolation of Unactivated Alkenes

   Tamai, T.; Fujiwara, K.; Higashimae, S.; Nomoto, A.; Ogawa, A.

   Org. Lett. **2016**, *18*, 2114–2117.

8. Electrochemical Investigation of Isoprenoid Quinone Productions by Shewanella oneidensis MR-1 Detected by Its Destructive Adsorption on an Indium-Tin-Oxide Electrode

   Morishita, A.; Higashimae, S.; Nomoto, A.; Shiigi, H.; Nagaoka, T.

   J. Electrochem. Soc. **2016**, *163*, G166–G172.

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