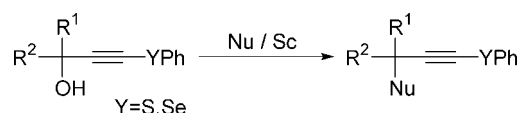


Scandium-Catalyzed Carbon–Carbon
Bond-Forming Reactions of 3-Sulfanyl-
and 3-Selanylpropargyl AlcoholsMitsuhiro Yoshimatsu,* Tokutaro Otani, Saki Matsuda, Teruhisa Yamamoto, and
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ABSTRACT



The scandium-catalyzed substitution reactions of the phenylsulfanyl and phenylselanyl propargyl alcohols 3a–i and 7a–h regioselectively proceeded to give the propargylated compounds 4 and 8 in high yields.

The acid-mediated propargylations of the corresponding alcohols have been extensively investigated using the alkyne–Co₂(CO)₆ complex, which can be regarded as a reliable tool for cationic C–C bond formations (Nicholas reaction).¹ Many chemists interested in organic synthesis use a wide variety of these complexes; however, they could never avoid the complicated addition and elimination process of the cobalt hexacarbonyl group despite the significant progress made in this area.² Recently, the transition-metal-catalyzed propargylic substitutions using Ru,³ Ir,⁴ Rh,⁵ Cu,⁶ Ti,⁷ Re,⁸ Pt,⁹ and Pd¹⁰ were also investigated as the alternative routes of the Nicholas reaction; however, the usable propargylic reagents were unfortunately strictly limited to each nucleophile.³ Al-

though the free propargylic cation could be considered as the alkynyl-substituted carbenium ions, their reactivity with nucleophiles is dependent on the kind of substituents

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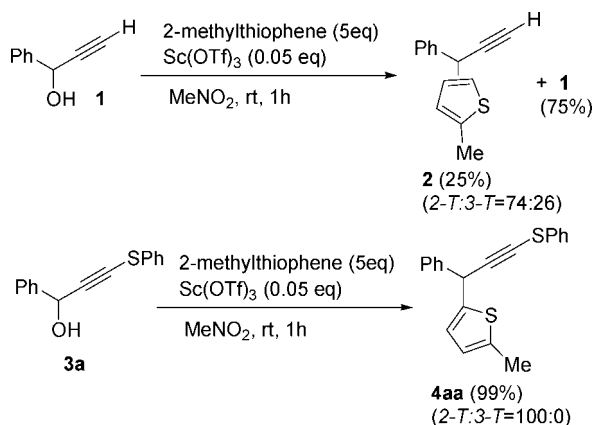
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at the α - and γ -positions.¹¹ Furthermore, the acid- or Lewis acid-mediated propargylations should involve both the β -eliminations and the Meyer–Schuster rearrangements.^{1a,12} After extensive studies of the Lewis acid catalyzed propargylation of the alcohols, we found a new versatile propargylation using alcohols bearing sulfur and selenium functional groups matched by the scandium–nitromethane catalytic system. We preliminarily exhibited the scandium-catalyzed Friedel–Crafts reactions of both propargyl alcohols **1** and **3a** with 2-methylthiophene in Scheme 1. The reaction of **1** with 2-methylthiophene in the

Scheme 1. Scandium-Catalyzed Friedel–Crafts Reactions



presence of 5 mol % of $\text{Sc}(\text{OTf})_3$ at room temperature proceeded to give a mixture of both the 2-phenylpropynylated thiophene and 3-substituted isomer **2** in 25% yield, accompanied by **1** (75%). The reaction of **3a** regioselectively provided 5-methyl-2-[1'-phenyl-3'-(phenylsulfanyl)prop-2-ynyl]thiophene (**4aa**) in quantitative yield. It was proved that the γ -sulfanyl functional group effectively played an im-

portant role in the regioselective propargylations. We now report a direct C–C bond formation of the sulfanyl- and selanyl-substituted propargyl alcohol catalyzed scandium triflate and the novel transformations using the products.

First, we chose to begin our study with the phenylsulfanyl propargyl alcohol bearing the electron-donating anisyl group **3b** and 2-methylthiophene in the presence of 5 mol % of Lewis acids (Table 1). Screening of various Lewis acids (e.g.,

Table 1. Discovering Reaction Conditions for Scandium-Catalyzed 2-Methylthienylation^{a,b}

run	condition	% yields	
		4ba	3b
1	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (10 mol %), MeNO_2 , 0 °C, 10 min	68	0
2	TMSOTf (10 mol %), MeNO_2 , 0 °C, 10 min	65	33
3	TiCl_4 (5 mol %), MeNO_2 , rt, 0.5 h	34	20
4	$\text{Yb}(\text{OTf})_3$ (5 mol %), MeNO_2 , rt, 1.5 h	50	42
5	$\text{Hf}(\text{OTf})_4$ (5 mol %), MeNO_2 , 0 °C, 10 min	80	0
6	$\text{La}(\text{OTf})_3$ (5 mol %), MeNO_2 , rt, 1 h	30	63
7	SnCl_4 (8 mol %), MeNO_2 , 0 °C, 10 min	61	35
8	$\text{Sc}(\text{OTf})_3$ (5 mol %), MeNO_2 , 0 °C, 10 min	91	0
9	$\text{Sc}(\text{OTf})_3$ (5 mol %), CH_2Cl_2 , rt, 1 h	66	0
10	$\text{Sc}(\text{OTf})_3$ (5 mol %), THF, rt, 4 h	32	65
11	$\text{Sc}(\text{OTf})_3$ (5 mol %), DMF, rt, 72 h	100	

^a All reactions of **3b** (0.18 mmol) with 2-methylthiophene (0.54 mmol) were carried out in the presence of scandium triflate (0.009 mmol) in MeNO_2 (0.50 mL). ^b Isolated yield of **4ba**.

$\text{Yb}(\text{OTf})_3$, $\text{La}(\text{OTf})_3$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$) as well as the solvent (e.g., dichloromethane, 1,2-dichloroethane, DMF, and THF) found the best combination of both the Lewis acids and the solvents to be scandium triflate–nitromethane. Furthermore, the product **4ba** was surprisingly obtained as a single regioisomer, 5-methyl-2-[1-(*p*-anisyl)-3-(phenylsulfanyl)prop-2-ynyl]thiophene, in 91% yield (entry 8). The substitution pattern of **4ba** was determined as the 2,5-substituted product based on the coupling constant of the ^1H NMR spectrum, shown at δ 6.54 ($J = 3.6$ Hz) and 6.73 ($J = 3.6$ Hz) due to the 3- and 4-thienyl hydrogens.

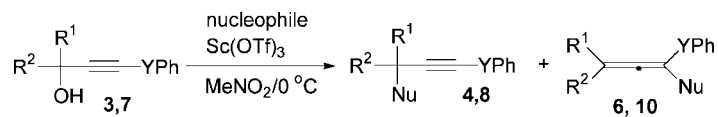
The scope of this reaction is shown in Table 2. The reaction of **3b** with *N*-methylpyrrole also gave **4bb** with complete regioselectivity (entry 1). The reaction with the silyl enol ether exclusively provided the alkyne **4bc** (entry 2). The reactions with phenylsulfanyltrimethylsilane exclusively gave the 1,3-bis(phenylsulfanyl)prop-1-yne **4bd** in quantitative yield without further addition of the phenylsulfanyl moiety (entry 3). The *p*-chlorophenyl derivative also provided the allylated **4ca** and thiophene **4cb** despite the electron-poor substituent on the aromatic ring (entries 4 and 5). The alkyl-substituted propargyl alcohols **3d,e** could be used in the reactions with nucleophiles (entries 6 and 7). Most of the previous propargylations catalyzed by the metals are

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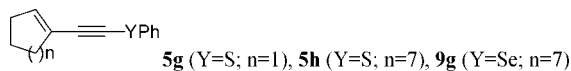
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Table 2. Regioselective Propargylation of Nucleophiles in Scandium–Nitromethane Catalytic System



run	alcohol	nucleophile	product ^a	(% yields)	run	alcohol	nucleophile	product ^a	(% yields)
1	3b (R ¹ = <i>p</i> -MeO-C ₆ H ₄ /R ² =H)			4bb (69)	15	7b (R ¹ = <i>p</i> -MeO-C ₆ H ₄ /R ² =H)	PhSSiMe ₃		8ba (94)
2	3b			4bc (quant)	16	7b			8bb (87)
3	3b	PhSSiMe ₃		4bd (quant)	17	7b			8bc (quant)
4	3c (R ¹ = <i>p</i> -Cl-C ₆ H ₄ /R ² =H)			4ca (90)	18	7c (R ¹ = <i>p</i> -Cl-C ₆ H ₄ /R ² =H)			8c (71)
5	3c			4cb (99)	19	7d (R ¹ = <i>n</i> -Bu/R ² =H)			8d (66)
6	3d (R ¹ = <i>n</i> -Bu/R ² =H)			4d (91)	20	7e (R ¹ = <i>t</i> -Bu/R ² =H)			8e (62)
7	3e (R ¹ = <i>t</i> -Bu/R ² =H)			4e (65)	21	7f (R ¹ -R ² =-(CH ₂) ₅)			8f (78)
8	3f (R ¹ -R ² =-(CH ₂) ₅)			4f (91)	22	7g (R ¹ -R ² =-(CH ₂) ₁₁)			9g (43) ^b
9	3g (R ¹ -R ² =-(CH ₂) ₄)			4ga (5%)					10 (51)
				5g (92%) ^b	23	7h (R ¹ =2-thienyl/R ² =H)			8ha (71)
10	3g			4gb (59)					8hb (70)
				5g (7) ^b	24	7h			8hb (70)
11	3h (R ¹ -R ² =-(CH ₂) ₁₁)			6 (41)	25	7i (R ¹ =2-furyl/R ² =H)			8i (68)
				5h (24)					8i (68)
12	3i (R ¹ =2-thienyl/R ² =H)			4i (74)					
13	7a (R ¹ =Ph/R ² =H)			8aa (73)					
14	7a			8ab (84)					

^a All reactions of **3** and **7** (0.50–3.0 mmol) with nucleophiles were carried out in the presence of scandium triflate (0.05 equiv) in MeNO₂. ^b

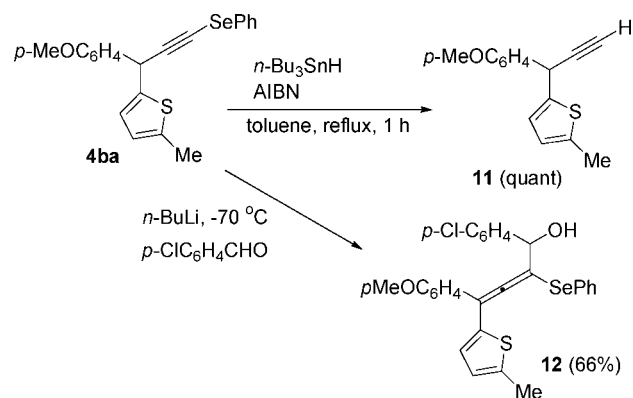


performed using 1,3-bis(aryl)- and 1,3-bis(hetaryl)propargyl alcohols. Our method proved to be applicable to the alkyl-substituted propargyl alcohols. It was worth noting that in the Friedel–Crafts reactions of the cycloalkanols **3f–h**, the cyclohexanol **3f** predominantly produced 2-(1-(phenylsulfanylethynyl)cyclohexyl-5-methylthiophene (**4f**) in 91% yield for the scandium-catalyzed reactions without β -elimination (entry 8); however, the allylation of the cyclopentanol **3g** provided 1-phenylsulfanylethynylcyclopent-1-ene (**5g**) in 92% yield, accompanied by a small amount of the allylated product **4ga** (entry 9), while the Friedel–Crafts reaction of **3g** provided 5-methyl-2-[(1'-phenylsulfanylethynyl)cyclopentyl]thiophene (**4gb**) in satisfactory yield (entry 10). Surprisingly, the cyclododecanol **3h** gave the allenic compound, 2-(phenylsulfanyl)pent-1,4-dienylidenecyclododecane **6**, in 41% yield (entry 11). The different regioselectivity of both cyclododecanol **3h** might be attributed to the steric effect; however, the details of this reaction are still unclear. The thienyl-substituted propargyl alcohol **3i** was also effective for the regioselective Friedel–Crafts propargylation (entry 12).

We then investigated and determined the scandium-catalyzed propargylations from the alcohols bearing the γ -phenylselanyl group as shown in Table 2 (entries 13–25). The propargyl alcohols **7a–c** reacted with very similar nucleophiles as that performed using the sulfur analogues to give the corresponding adducts **8aa–8c** in high to excellent yields (entries 14–19). It was noteworthy that a complete regioselectivity occurred for all of the Friedel–Crafts products **8aa**, **8bb**, **8d**, **8e**, **8f**, **8ha,b**, **8i** (entries 13, 14, 19–21, 23–25).

Next, we extended the further transformations of the products. Typical results are shown in Scheme 2. The Friedel–Crafts product **4ba** easily underwent C–Se bond cleavage on the alkynyl carbon to form the terminal acetylene **11**. This result shows that the propargylated products bearing

Scheme 2. Transformations of the Friedel–Crafts Product



selenium functional group would easily transform to a wide variety of alkynyl compounds by the alkylations of the corresponding acetylides. The treatment of the thiophene **4ba** with *n*-butyllithium and *p*-chlorobenzaldehyde gave the allenyl alcohol **12** via the allenyllithium intermediate.

In summary, these results proved that the sulfur and selenium functional groups of the propargyl alcohols would provide two kinds of excellent regioselectivities using a novel catalytic system; one is the regioselectivity on both the propargyl and allenyl cation, while the other is that of the Friedel–Crafts substitutions. Now we are investigating further transformations of the propargyl alcohols in detail. These results will be reported elsewhere.

Supporting Information Available: Experimental procedures, spectral data, and copies of all of the new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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