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Scandium-Catalyzed Carbon−Carbon Bond-Forming Reactions of 3-Sulfanyl- and 3-Selanylpropargyl Alcohols

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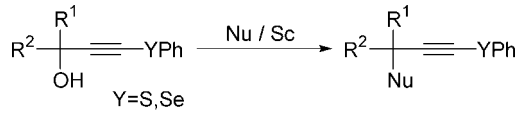
ABSTRACT



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−$Co_2(CO)_6$ 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 Pd[10] were also investigated as the alternative routes of the Nicholas reaction; however, the usable propargylic reagents were unfortunately strictly limited to each nucleophile.[3] Although the free propargylic cation could be considered as the alkynyl-substituted carbenium ions, their reactivity with nucleophiles is dependent on the kind of substituents

(1) (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207, and references therein. (b) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Pergamon: New York, 1995; *12*, Chapter 7.1. (c) Caffyn, A. J. M.; Nicholas, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 6438.

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(3) Ru: (a) Nishibayashi, Y.; Inada, Y.; Yoshikawa, M.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1495. (b) Nishibayashi, Y; Wakiji, I.; Hidai, M. *J. Am. Chem. Soc.* **2000**, *122*, 11019. (c) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846. (d) Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 15172. (e) Nishibayashi, Y.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 7900. (f) Nishibayashi, Y.; Wakiji, I.; Ishii, Y.; Uemura, S.; Hidai, M. *J. Am. Chem. Soc.* **2001**, *123*, 3393. (g) Touchard, D.; Haquette, P.; Daridor, A.; Toupet, L.; Dixneuf, P. H. *J. Am. Chem. Soc.* **1994**, *116*, 11157. (h) Nishibayashi, Y.; Milton, M. D.; Inada, Y.; Yoshikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem. Eur. J.* **2005**, *11*, 1433. (i) Inada, M.; Yoshikawa, M. D.; Milton, M. D.; Nishibayashi, Y.; Uemura, S. *Eur. J. Org. Chem.* **2006**, 881. (i) Chen, C.-T. *Coord. Chem. Rev.* **1999**, 190.

(4) Ir: Matsuda, I.; Komori, K.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 9072.

(5) Rh: (a) Werner, H. *Chem. Commun.* **1997**, 903. (b) Evans, P. A.; Lawler, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4970.

(6) Cu: (a) Yadav, J. S.; Reddy, B. V. S.; Rao, T. S.; Rao, K. V. R. *Tetrahedron Lett.* **2008**, *49*, 614. (b) Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3777. (c) Hattori, G.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3781.

(7) Ti: (a) Karunakar, G. V.; Perisamy, M. *Tetrahedron Lett.* **2006**, *47*, 3549. (b) Mahrwald, R.; Quint, S. *Tetrahedron* **2000**, *56*, 7463.

(8) Re: Kuninobu, Y.; Ishii, E.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3296. (a) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760.

(9) Pt: Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, 1169.

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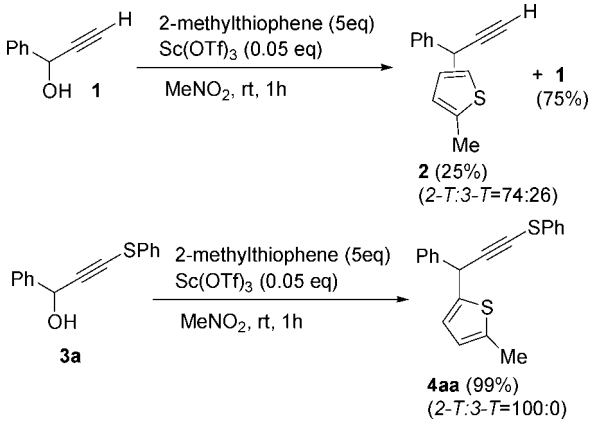
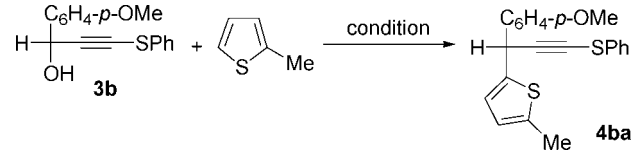
at the α- and γ-positions.[11] Furthermore, the acid- or Lewis acid-mediated propargylations should involve both the β-eliminations and the Meyer−Schuster rearrangements.[1a,12] After extensive studies of the Lewis acid catalyzed propargylation of the alcohols, we found a new versatile propargylation 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 presence of 5 mol % of $Sc(OTf)_3$ 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 important 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.

Scheme 1. Scandium-Catalyzed Friedel−Crafts Reactions



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., $Yb(OTf)_3$, $La(OTf)_3$, $BF_3{\cdot}Et_2O$) 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.

Table 1. Discovering Reaction Conditions for Scandium-Catalyzed 2-Methylthienylation[a,b]



run	condition	% yields 4ba	% yields 3b
1	$BF_3{\cdot}Et_2O$ (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	$Yb(OTf)_3$ (5 mol %), $MeNO_2$, rt, 1.5 h	50	42
5	$Hf(OTf)_4$ (5 mol %), $MeNO_2$, 0 °C, 10 min	80	0
6	$La(OTf)_3$ (5 mol %), $MeNO_2$, rt, 1 h	30	63
7	$SnCl_4$ (8 mol %), $MeNO_2$, 0 °C, 10 min	61	35
8	$Sc(OTf)_3$ (5 mol %), $MeNO_2$, 0 °C, 10 min	91	0
9	$Sc(OTf)_3$ (5 mol %), CH_2Cl_2, rt, 1 h	66	0
10	$Sc(OTf)_3$ (5 mol %), THF, rt, 4 h	32	65
11	$Sc(OTf)_3$ (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**.

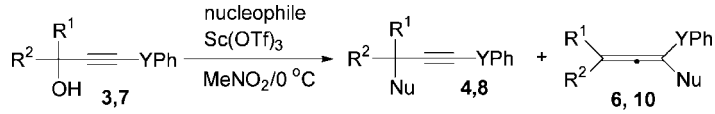
The scope of this reaction is shown in Table 2. The reaction of **3b** with *N*-methylpyrrole also gave **4bb** with complete regioselectivity (entry 1). The reaction with the silyl enol ether exclusively provided the alkyne **4bc** (entry 2). The reactions with phenylsulfanyltrimethylsilane exclusively 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

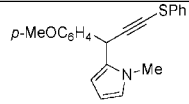
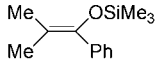
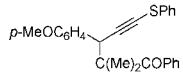
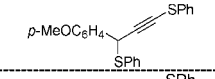
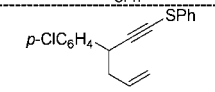
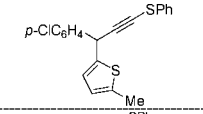
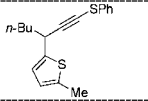
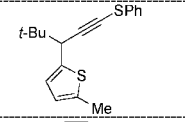
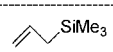
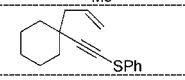
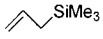
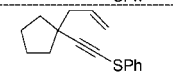
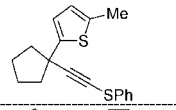
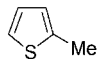
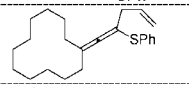
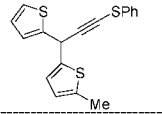
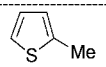
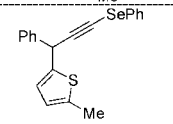
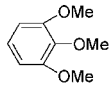
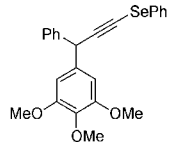
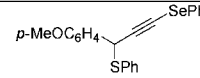
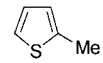
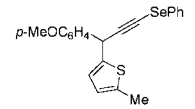
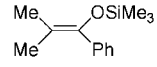
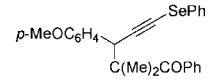
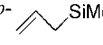
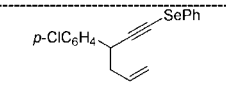
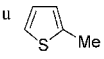
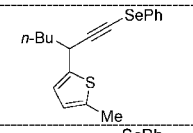
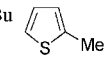
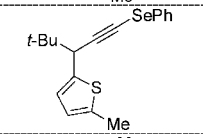
(10) Pd: (a) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874. (b) Yoshida, M.; Ohsawa, Y.; Ihara, M. *J. Org. Chem.* **2004**, *69*, 1590. Bi: (c) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180. Bi: (d) Kabalka, G. W.; Yao, M.-L.; Borella, S. *J. Am. Chem. Soc.* **2006**, *128*, 11320. (e) Zhan, Z.-P.; Yang, W.-W.; Yang, R.-F.; Yu, J.-L.; Li, J.-P.; Liu, H.-J. *Chem. Commun.* **2006**, 3352. (f) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409. (g) Srihari, P.; Bhunia, D. C.; Sreedhar, B. P.; Mandal, S. S.; Reddy, J. S. S.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 8120. Yb: (h) Huang, W.; Wang, J.; Shen, Q.; Zhou, X. *Tetrahedron* **2007**, *63*, 11636. B: (i) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z. *Org. Lett.* **2005**, *7*, 2865. (j) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2004**, *6*, 3929. (k) Kabalka, G. W.; Yao, M.-L.; Borella, S. *Org. Lett.* **2006**, *8*, 879. Fe: (l) Zhan, Z.-P.; Yu, J.-L.; Liu, H.-J.; Cui, Y.-Y.; Yang, R.-F.; Yang, W.-Z.; Li, Jun.-P. *J. Org. Chem.* **2006**, *71*, 8298.

(11) (a) Olah, G. A.; Spear, R. J.; Westerman, P. W.; Denis, J.-M. *J. Am. Chem. Soc.* **1974**, *96*, 5855. (b) Prakash, G. K. S.; Krishnamurthy, V. V.; Olah, G. A.; Farnum, D. G. *J. Am. Chem. Soc.* **1985**, *107*, 3928. (c) Krishnamurthy, V. V.; Prakash, G. K. S.; Iyer, P. S.; Olah, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 1575. (d) Olah, G. A.; Krishnamurthy, V. V.; Prakash, G. K. S. *J. Org. Chem.* **1990**, *55*, 6060. (e) Mayr, H.; Bauml, E. *Tetrahedron Lett.* **1983**, *24*, 357–360. (f) Mayr, H.; Halberstadt-Kausch, I. K. *Chem. Ber.* **1982**, *115*, 3479.

(12) (a) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429. (b) Edens, M.; Boerner, D.; Chase, C. R.; Nass, D.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 3403. (c) Yoshimatsu, M.; Naito, M.; Kawahigashi, M.; Shimizu, H.; Kataoka, T. *J. Org. Chem.* **1995**, *60*, 4798. (d) Ishikawa, T.; Okano, M.; Aikawa, T.; Saito, S. *J. Org. Chem.* **2001**, *66*, 4635.

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



run	alcohol	nucleophile	product[a]	(% yields)
1	**3b** (R^1=*p*-MeO-C_6H_4/R^2=H)			**4bb** (69)
2	**3b**			**4bc** (quant)
3	**3b**	$PhSSiMe_3$		**4bd** (quant)
4	**3c** (R^1=*p*-ClC_6H_4/R^2=H)			**4ca** (90)
5	**3c**			**4cb** (99)
6	**3d** (R^1=*n*-Bu /R^2=H)			**4d** (91)
7	**3e** (R^1=*t*-Bu /R^2=H)			**4e** (65)
8	**3f** (R^1-R^2 =$(CH_2)_5$)			**4f** (91)
9	**3g** (R^1-R^2 =$(CH_2)_4$)			**4ga** (5%) **5g** (92%)[b]
10	**3g**			**4gb** (59) **5g** (7)[b]
11	**3h** (R^1-R^2 =$(CH_2)_{11}$)			**6** (41) **5h** (24)
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)
15	**7b** (R^1=*p*-$MeOC_6H_4$ /R^2=H)	$PhSSiMe_3$		**8ba** (94)
16	**7b**			**8bb** (87)
17	**7b**			**8bc** (quant)
18	**7c** (R^1=*p*-ClC_6H_4/ R^2=H)			**8c** (71)
19	**7d** (R^1=*n*-Bu /R^2=H)			**8d** (66)
20	**7e** (R^1=*t*-Bu /R^2=H)			**8e** (62)
21	**7f** (R^1-R^2 =$(CH_2)_5$)			**8f** (78)
22	**7g** (R^1-R^2 =$(CH_2)_{11}$)			**9g** (43)[b] **10** (51)
23	**7h** (R^1=2-thienyl/R^2 =H)			**8ha** (71)
24	**7h**			**8hb** (70)
25	**7i** (R^1=2-furyl/R^2 =H)			**8i** (68)

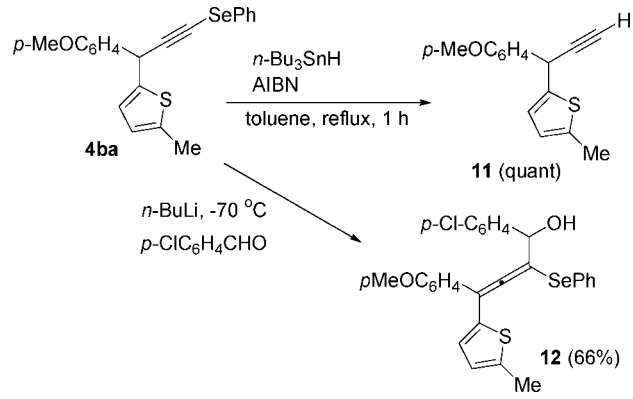
[a] All reactions of **3** and **7** (0.50−3.0 mmol) with nucleophiles were carried out in the presence of scandium triflate (0.05 equiv) in $MeNO_2$. [b] **5g** (Y=S; n=1), **5h** (Y=S; n=7), **9g** (Y=Se; n=7)

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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