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Pd-Catalyzed Regioselective Iminothiolation of Alkynes: A Remarkable Effect of the CF_3 Group of Iminosulfides

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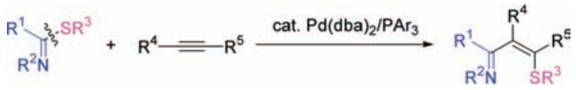
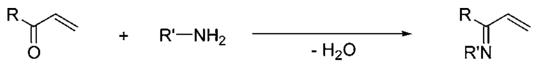
ABSTRACT

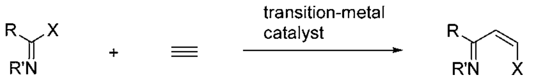


Pd-catalyzed iminothiolation of alkynes took place to afford 4-SR substituted 1-azadienes regioselectively.

1-Azadienes have been employed as versatile synthetic building blocks: electrophiles in 1,2-addition as well as Michael-type 1,4-addition, nucleophiles by a nitrogen atom, and heterodienes in hetero-Diels−Alder reactions.[1] The general method of preparation is the condensation of α,β-unsaturated ketones with primary amines (eq 1). In addition, the transition-metal-catalyzed iminocarbonvinylcarbon bond-formation reaction is a promising alternative. Although some catalytic reactions such as the Pd-catalyzed cross-coupling of imidoyl chlorides with vinyl stannanes and the Pd-catalyzed Mizoroki−Heck-type reaction of imidoyl iodides with alkenes have been reported,[2] the catalytic introduction of imino groups is still limited. In particular, to the best of our knowledge, an addition reaction to alkynes is unprecedented (eq 2).[3]



(1)



(2)

We have devoted our attention to the study of transition-metal-catalyzed carbochalcogenation of carbon−carbon unsaturated bonds.[4,5] The $Pt(PPh_3)_4$-catalyzed intermolecular decarbonylative arylthiolation of alkynes using thioesters is among them (Scheme 1, upper left).[4b,5a] Recently, CO-retained aroylthiolation (Scheme 1, lower left) and trifluoroacetylthiolation (Scheme 1, upper right) were realized by Pd/dppe and $Pt(PPh_3)_4$ catalyzes, respectively.[5e] Herein is reported a new synthetic method of 4-sulfur functionalized 1-azadienes by the iminothiolation of alkynes using iminosulfide (Scheme 1, lower right).

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(1) For a recent review, see: Groenendaal, B.; Ruijter, E.; Orru, R. V. A. *Chem. Commun.* **2008**, 5474.

(2) (a) Kobayashi, T.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* **1985**, *26*, 3463. (b) Kosugi, M.; Koshiba, M.; Atoh, A.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 677. (c) Kosugi, M.; Ogata, T.; Tamura, H.; Sano, H.; Migita, T. *Chem. Lett.* **1986**, *15*, 1197. (d) Uneyama, K.; Watanabe, H. *Tetrahedron Lett.* **1991**, *32*, 1459.

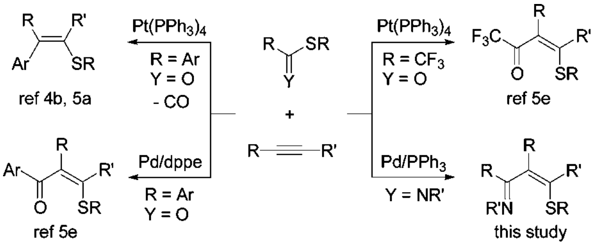
(3) The reaction of alkynes and nitriles with iodine by using a stoichiometric amount of zirconium complex to produce ((2)-β-iodoalkenyl)imines has been reported: Coperet, C.; Sugihara, T.; Wu, G.; Shimoyama, I.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 3422.

(4) For reviews, see: (a) Kuniyasu, H. In *Catalytic Heterofunctionalization*; Togni, A., Grutzmacher, H., Eds.; Wiley-VCH: Weinheim, 2001; p251. (b) Kuniyasu, H.; Kurosawa, H. *Chem.—Eur. J.* **2002**, *8*, 2660. (c) Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2006**, *35*, 1320. (d) Kuniyasu, H.; Kambe, N. *J. Synth. Org. Chem. Jpn.* **2009**, *67*, 701.

(5) For recent examples, see: (a) Yamashita, F.; Kuniyasu, H.; Terao, J.; Kambe, N. *Org. Lett.* **2008**, *10*, 101. (b) Minami, Y.; Kuniyasu, H.; Kambe, N. *Org. Lett.* **2008**, *10*, 2469. (c) Toyofuku, M.; Fujiwara, S.; Shin-ike, T.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2008**, *130*, 10504. (d) Toyofuku, M.; Murase, E.; Fujiwara, S.; Shin-ike, T.; Kuniyasu, H.; Kambe, N. *Org. Lett.* **2008**, *10*, 3957. (e) Minami, Y.; Kuniyasu, H.; Miyafuji, K.; Kambe, N. *Chem. Commun.* **2009**, 3080.

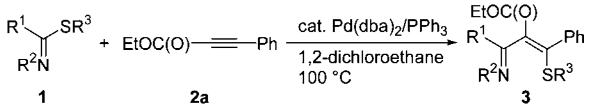
10.1021/ol101289k

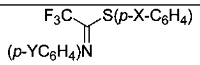
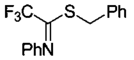
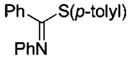
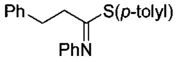
Scheme 1. A Series of Carbothiolations of Alkyne



First, the success of trifluoroacetylthiolation of alkynes by $CF_3C(O)SR$[5e] prompted scrutiny of reactions that use an iminosulfide [**1a**; $CF_3C(=NPh)S$(*p*-tolyl)]. Gratifyingly, it was found that the reaction of **1a** (0.5 mmol) with ethyl phenylpropiolate (**2a**, 1.0 mmol), which exhibited high activity for the Pt-catalyzed decarbonylative arylthiolation by thioesters,[5a,6] was catalyzed by $Pd(dba)_2$ (0.025 mmol) and PPh_3 (0.5 mmol) in 1,2-dichloroethane at 100 °C for 3 h under microwave irradiation using a sealed glass vessel. The desired adduct, *E*-$CF_3C(=NPh)C(CO_2Et)=C(Ph)[S($*p*-tolyl)] (*E*-**3a**), was isolated in 91% yield regio- and stereoselectively (entry 1, Table 1).[7] The structure of *E*-**3a** was unambiguously determined by X-ray crystallography, demonstrating that $CF_3C(=NPh)$ of **1a** was bound at the α-carbon of the EtOC(O) of **2a** and S(*p*-tolyl) of **1a** at the α-carbon of the Ph of **2a** as the *E*-isomer with *anti* conformation regarding the stereochemistry of lone pair of N (Figure 1).[8,9]

Table 1. Pd-Catalyzed Iminothiolation of **2a** Using Various Iminosulfides (**1**)[a]



entry	1		time (h)	3	(%)[b] (*E*:*Z*)
					
1	**1a**	X = Me, Y = H	3	**3a**	91 (>99:1)
2[c]	**1a**		3	**3a**	4[d] (95:5)
3[e]	**1a**		3	**3a**	n.d.
4	**1b**	X = Y = H	3	**3b**	82 (>99:1)
5	**1c**	X = Cl, Y = H	1	**3c**	71 (>99:1)
6	**1d**	X = Me, Y = OMe	1	**3d**	88 (>99:1)
7	**1e**	X = Me, Y = Cl	1	**3e**	85 (79:21)
8	**1f**		2	**3f**	91 (97:3)
9[f]	**1g**		3	**3g**	44 (81:19)
10[f]	**1h**		3	**3h**	n.d.

[a] Unless otherwise noted, **1** (0.5 mmol), **2a** (1.0 mmol), $Pd(dba)_2$ (0.025 mmol), PPh_3 (0.05 mmol), and 1,2-dichloroethane (0.25−0.5 mL) at 100 °C under microwave irradiation for 1−3 h. All reactions were performed in sealed glass vessels. [b] Isolated yield. [c] $Pd(dba)_2$ (0.025 mmol) and dppe (0.025 mmol). [d] NMR yield. [e] $Pt(PPh_3)_4$ (0.025 mmol). [f] $Pd(dba)_2$ (0.05 mmol) and P(*p*-tolyl)$_3$ (0.1 mmol). dba = dibenzylideneacetone.

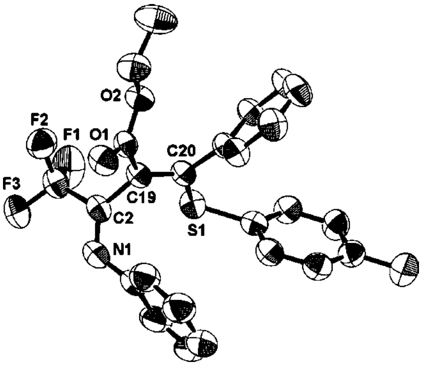


Figure 1. ORTEP diagram of *E*-**3a**.

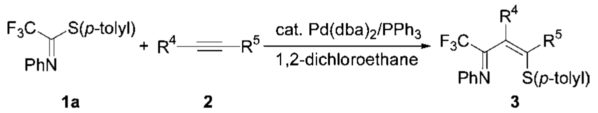
The azadiene moiety was not arranged in a planar fashion (N1−C2−C19−C20 torsion angle is 68.7°), showing that the imine and vinyl moieties are not conjugated in the solid state.

In stark contrast, Pd/dppe and $Pt(PPh_3)_4$, which work as good catalysts for aroylthiolation and trifluoroacetylthiolation, respectively (Scheme 1), hardly promoted the reaction (entries 2 and 3, Table 1).

The results of the $Pd(dba)_2/PPh_3$ catalyzed addition of various iminosulfides [**1**; $R^1C(=NR^2)SR^3$] to **2a** are summarized in Table 1. The reactions of **1b** and **1c** having SPh and S(*p*-ClC_6H_4) as S-aryl groups took place to furnish the corresponding adducts **3b** and **3c** in good yields (entries 4 and 5, Table 1). Neither electron-donating nor electron-withdrawing groups at Y interfered with the reactions (entries 6 and 7, Table 1). A similar transformation was also accomplished by using **1f** with a benzyl group as R^3 to produce **3f** in 91% yield (entry 8, Table 1). In the case of **1g** (R^1 = Ph), the desired adduct **3g** was obtained only in 44% yield even in the presence of 10 mol % of $Pd(dba)_2$/2P(*p*-tolyl)$_3$ (entry 9, Table 1). Phenethyl substituted iminosulfide (**1h**) was not effective; **3h** was not synthesized (entry 10, Table 1). These results demonstrated that CF_3 groups as R^1 of **1** is quite essential for the successful transformation.

The results of the reactions of **1a** with a variety of alkynes are summarized in Table 2. It was found that even the addition to 4-octyne (**2b**) took place at 160 °C to give **3i**, albeit in low yield (entry 1, Table 2). The treatment with 3-methoxy-1-phenylpropyne (**2c**) afforded **3j** in 51% yield (*E*:*Z* = 67:33) at 180 °C (entry 2, Table 2). On the other hand, terminal alkynes underwent the addition under much milder conditions (80 °C) than internal alkynes (entries 3−12, Table 2). Both electron-rich and electron-poor arylalkynes (**2d**−**g**) reacted with **1a** to form high yields of **3** (entries 3−6, Table 2). The product of iminothiolation was obtained in 89% yield (*E*:*Z* = 18:82) when 1-octyne was used (**2h**) (entry 7, Table 2). Cyclohexylacetylene (**2i**) was also applied

Table 2. Pd-Catalyzed Iminothiolation of Various Alkynes (**2**) Using **1a**[a]

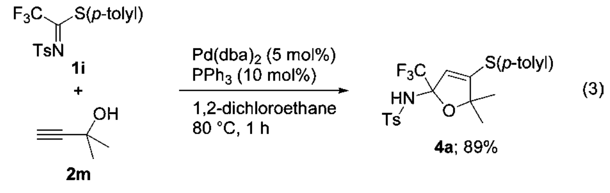


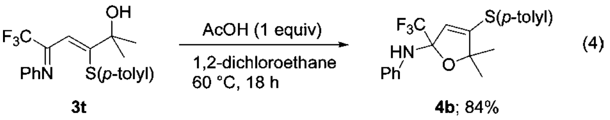
2b; $R^4 = R^5 = n$-Pr
2c; R^4 = MOM, R^5 = Ph
2d; R^4 = H, R^5 = Ph
2e; R^4 = H, R^5 = p-tolyl
2f; R^4 = H, R^5 = p-$CF_3C_6H_4$
2g; R^4 = H, R^5 = 3-thienyl
2h; R^4 = H, R^5 = n-Hex
2i; R^4 = H, R^5 = c-Hex
2j; R^4 = H, R^5 = $(CH_2)_4Cl$
2k; R^4 = H, R^5 = $(CH_2)_3CO_2Me$
2l; R^4 = H, R^5 = $(CH_2)_2O(THP)$
2m; R^4 = H, R^5 = CMe_2OH

entry	2	temp (°C)	time (h)	3	(%)[b] (E:Z)
1	**2b**	160[c]	1	**3i**	14 (5:95)
2	**2c**	180[c]	3	**3j**	51 (67:33)
3	**2d**	80	1	**3k**	92 (2:98)
4	**2e**	80	1	**3l**	95 (14:86)
5	**2f**	80	1	**3m**	74 (2:98)
6	**2g**	80	1	**3n**	83 (1:>99)
7	**2h**	80	1	**3o**	89 (18:82)
8	**2i**	80	3	**3p**	76 (14:86)
9	**2j**	80	1	**3q**	81 (13:87)
10	**2k**	80	2	**3r**	81 (14:86)
11	**2l**	80	2	**3s**	87 (13:87)
12[d]	**2m**	80	1	**3t**	89 (1:>99)

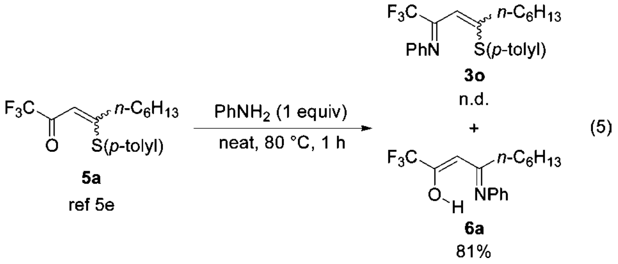
[a] Unless otherwise noted, **1a** (0.5 mmol), **2** (0.6−3.0 mmol), $Pd(dba)_2$ (0.025 mmol), PPh_3 (0.5 mmol) and 1,2-dichloroethane (0.25−0.5 mL) for 1−3 h. In the case of runs 1 and 2, reactions were performed in sealed glass vessels. [b] Isolated yield. [c] Microwave irradiation. [d] $Pd(PPh_3)_4$ (0.025 mmol). Pr = propyl, MOM = methoxymethyl, THP = 2-tetrahydro-pyranyl.

to this reaction (entry 8, Table 2). Functional groups such as chlorine (**2j**), methoxy carbonyl (**2k**), and 2-tetrahydropyranyl (**2l**) aptly furnished the corresponding adducts **3p**−**s** in high yields as *cis*-rich stereoisomers (entries 9−11, Table 2). In the case of the reaction with 2-methyl-3-butyn-2-ol (**2m**), *Z*-**3t** was selectively obtained in 89% yield (entry 12, Table 2).





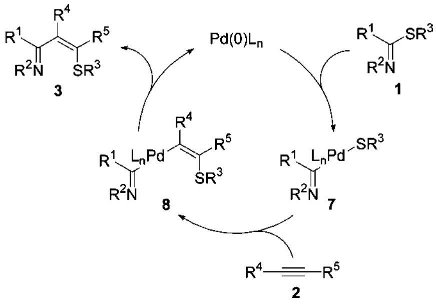
Interestingly, the reaction of **1i** containing an N-tosyl group with **2m** selectively produced furan derivative **4a** in 89% yield, indicating that the *cis*-to-*trans* isomerization of $CF_3C(=NTs)$-$C(H)=C(C(Me)_2OH)$(S-p-tolyl) (**3u**) and the following cyclization facilely occurred (eq 3).[10] A similar transformation was realized by the treatment of **3t** with AcOH to form **4b** in 84% yield (eq 4).



As mentioned, for the synthesis of **3**, the conversion of $CF_3C(O)C(R^4)=C(R^5)(SR^3)$ (**5**)[5e] into **3** is conceivable. Thus, the reaction of **5a** (R^3 = p-tolyl, R^4 = H, R^5 = n-C_6H_{13}) with $PhNH_2$ was attempted (eq 5). The reaction selectively furnished $CF_3C(OH)=C(H)C(n\text{-}C_6H_{13})\text{-}(=NC_6H_5)$ (**6a**) in 81% yield, elucidating that the present Pd-catalyzed iminothiolation of **2** by **1** is complementary to the formation of **6** via **5.**

A plausible mechanism of the present reaction of iminosulfides (**1**) with alkynes (**2**) is depicted in Scheme 2. The oxidative addition of **1** to the $Pd(0)L_n$ complex triggers the reaction to afford $PdL_n[C(=NR^2)R^1](SR^3)$ (**7**).[11] Subsequent regio- and stereoselective insertion of **2** into the Pd−S bond of **7** generates *cis*-$PdL_n[C(=NR^2)R^1][Z\text{-}C(R^4)=C(R^5)(SR^3)]$ (*Z*-**8**).[12] Finally, the reductive elimination of **3** from **8** with

Scheme 2. Plausible Mechanism for the Pd-Catalyzed Iminothiolation of Alkynes (**2**) Using Iminosulfides (**1**)



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(6) The high reactivity and regioselectivity would be attributed to the oxygen atom at the propargyl moiety in alkynes; see ref 5a.

(7) When the reaction of **1a** and **2a** was performed at 100 °C in a sealed vessel without a microwave irradiation, **3a** was obtained in a *E* to *Z* ratio of 93:7 with the same yield, indicating that following isomerization of the adducts was partly prevented by the microwave irradiation.

(8) Crystal data for *E*-**3a**: space group *Pbca* (No. 61) with a = 15.2284(7) Å, b = 17.6487(8) Å, c = 17.8733(9) Å, β = 96.385(2)°, Z = 8, ρ = 1.298 g/cm^3, R = 0.0661, and Rw = 0.189. See Supporting Informaion for crystal data for *E*-**3a**.

(9) The NMR spectra of **3** showed temperature dependence due to the fluxional movement of the molecules. The ^1H NMR spectra of *E*-**3a** in toluene-d_8 solution at −40 °C appeared as a mixture of two stereoisomers by slow inversion of the N lone pair on the imino group in a ratio of 75:25 (stereochemistry undetermined).

(10) For the utility of furan derivatives, see: Eicher, T., Hauptmann, S. In *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*; Wiley-VCH: Weinheim, 2003 and references therein.

(11) (a) Bowman, W. R.; Lyon, J. E.; Pritchard, G. J. *Synlett* **2008**, 2169. (b) Takeda, H.; Ishida, T.; Takemoto, Y. *Chem. Lett.* **2009**, *38*, 772.

(12) (a) Sugoh, K.; Kuniyasu, H.; Kurosawa, H. *Chem. Lett.* **2002**, *31*, 106. (b) Kuniyasu, H.; Yamishita, F.; Terao, J.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 5929. (c) Kuniyasu, H.; Takekawa, K.; Yamashita, F.; Miyafuji, K.; Asano, S.; Takai, Y.; Ohtaka, A.; Tanaka, A.; Sugoh, K.; Kurosawa, H.; Kambe, N. *Organometallics* **2008**, *27*, 4788.

regeneration of Pd(0)L_n completes the catalytic cycle.[13] The reason that iminosulfide **1** with a CF_3 group exhibited high activity for iminothiolation is presumably due to the facile oxidative addition of a carbon−sulfur bond to the Pd(0) complex.

In conclusion, the present study substantiated the iminothiolation of alkynes with iminosulfides giving rise to the formation of 1-azadiene derivatives, where the introduction of a CF_3 group to the imino-carbon moiety is key to achieving the reaction. Furthermore, the facile syntheses of furan derivatives through 1-azadienes were also presented.

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Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] Monitoring the reaction of **1a** with **2h** at room temperature showed that the *cis*:*trans* ratio of **3o** stayed the same during the course of the reaction, implicating that *trans*-**3** was produced through isomerisation of *cis*-**8** to *trans*-**8** prior to the reductive elimination.