

Palladium-Catalyzed Sulfinylzincation: 1-Alkynyl Sulfoxides as a Sulfinyl Anion Equivalent

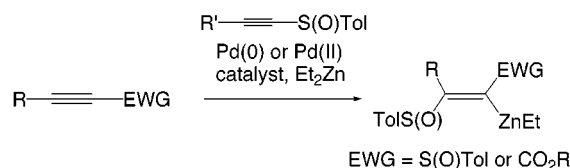
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ABSTRACT



Novel Pd-catalyzed sulfinylzincation of activated alkynes was developed, wherein 1-alkynyl sulfoxides work as a sulfinylating agent. Transfer of the sulfinyl group proceeded in a highly *syn*-selective fashion, giving a β -sulfinyl vinylzinc species. Using 3,3-dimethyl-1-butylnyl *p*-tolyl sulfoxide as a sulfinyl source, heterocoupling with propiolate derivatives was also accomplished.

Conjugate addition of sulfinylzinc (or zinc sufenate) species to activated triple bond affords a method to generate β -sulfinyl vinyl anion species, which provides versatile functionalized 1-alkenyl sulfoxides.¹ However, there are few reports on the preparation and reaction of the sulfenate anion because of instability of this species.^{2,3} In addition, the preceding methodologies required strong alkaline conditions, such as *ipso*-substitution of 2-sulfinylpyridine *N*-oxide with EtONa² or alkaline hydrolysis of the sulfenate derivatives.³ We found a conceptually new approach by an unprecedented Pd-catalyzed sulfinylzincation using 1-alkynyl sulfoxide and Et₂Zn in the presence of a Pd(II) or Pd(0) complex.⁴

This reaction proceeds under neutral and mild conditions, thereby not affecting various functional groups. Since

1-alkynyl sulfoxides can be synthesized by a reaction of acetylides with sulfinyl cation equivalents, such as menthyl sulfinate,⁵ sulfinylzincation using 1-alkynyl sulfoxides is considered to be an umpolung from the sulfinyl cation equivalent into a sulfinyl (or sulfenate) anion species.

In this paper, we describe sulfinylzincation using 1-alkynyl sulfoxides as a sulfinyl source in the presence of a Pd(0) or Pd(II) catalyst and Et₂Zn.

During the course of our study concerning the reaction of 1-alkynyl sulfoxides, we found an unusual sulfinylation of 1-hexynyl *p*-tolyl sulfoxide **1a**⁶ by the reaction with Et₂Zn in the presence of catalytic PdCl₂(dppf).⁷ The reaction gave (*E*)-bis-sulfoxide **2a**⁸ in 44% yield⁹ as a 1:1 diastereomeric mixture based on sulfur stereogenic centers along with a (*Z*)-isomer of ethylation product **3a** (19%) after protonation of

(1) (a) For reaction of vinylic sulfoxides, see: Mase, N.; Watanabe, Y.; Toru, T.; Kakumoto, T.; Hagiwara, T. *J. Org. Chem.* **2000**, *65*, 7083–7090. (b) Maezaki, N.; Izumi, M.; Yuyama, S.; Sawamoto, H.; Iwata, C.; Tanaka, T. *Tetrahedron* **2000**, *56*, 7927–7945. (c) Abe, H.; Tsuchida, D.; Kashino, S.; Takeuchi, Y.; Harayama, T. *Chem. Pharm. Bull.* **1999**, *47*, 833–837. (d) Midura, W. H.; Krysiak, J. A.; Mikolajczyk, M. *Tetrahedron* **1999**, *55*, 14791–14802. (e) Perlmutter, P. In *Conjugate Addition Reactions in Organic Synthesis*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press: Oxford, 1992; Vol. 9, pp 310–322 and references therein.

(2) Furukawa, N.; Konno, Y.; Tsuruoka, M.; Fujihara, H.; Ogawa, S. *Chem. Lett.* **1989**, 1501–1504.

(3) Hogg, D. R.; Stewart, J. J. *Chem. Soc., Perkin Trans. 2* **1974**, 43–47.

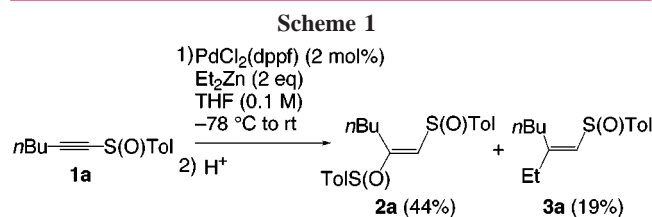
(4) Ruano reported similar sulfinylation to acetylenic *p*-tolyl sulfoxide using diethylaluminum cyanide, wherein (*Z*)-bis-sulfoxide was produced as a minor product only in 9% yield. Ruano, J. L. G.; Gamboa, A. E.; Castro, A. M. M.; Rodríguez, J. H. *J. Org. Chem.* **1998**, *63*, 3324–3332.

(5) Solladié, G.; Ruiz, P.; Colobert, F.; Carreño, M. C.; Garcia-Ruano, J. L. *Synthesis* **1991**, 1011–1012.

(6) Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078–1082.

(7) For palladium-catalyzed carbozincation using PdCl₂(dppf), see: Stadtmüller, H.; Vaupel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. *Chem. Eur. J.* **1996**, *2*, 1204–1220.

the resulting anion species. Both reactions proceeded in a highly *syn*-selective fashion (Scheme 1).



To improve the yield of the sulfinylation product **2a**, we investigated the reaction conditions (Table 1). As a result,

Table 1. Effect of Pd-Catalyst on Sulfinylzincation^a

entry	Pd-catalyst ^b	time (h)	yield (%) ^c	
			2a ^d	3a
1	none	4	56	29
2	$\text{PdCl}_2(\text{dppf})$	1	44	19
3	$\text{PdCl}_2(\text{MeCN})_2$	1	86	tr
4	$\text{PdCl}_2(\text{PPh}_3)_2$	1	82	4
5	$\text{Pd}(\text{PPh}_3)_4$	1	88	tr
6	$\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$	1	95	tr

^a All reactions were carried out using Et_2Zn (2 equiv) in THF (0.1 M) solution at -78°C to room temperature. ^b Two mole percent of catalyst was used. ^c Isolated yield. ^d The yield is based on 50% of **1a**, and the diastereomeric ratio is 1:1.

we found that the yield was remarkably increased with replacement of the ligand on palladium from dppf to MeCN or PPh_3 (entries 3 and 4). The use of $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ ($\text{Pd}(0)$ complex) improved the yield up to 95% (entry 6). In each case, only 2 mol % of catalyst is sufficient to complete the reaction. Although the reaction provided **2a** and **3a** even in the absence of a catalyst, longer reaction time was required and the yield of **2a** was reduced (entry 1).¹⁰

The plausible vinylzinc intermediate generated from **1a** could be trapped with AcOD, giving a deuterated bis-sulfoxide **4** in good yield (Scheme 2).

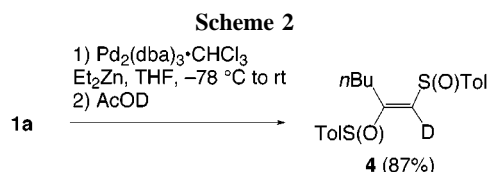


Table 2 shows the sulfinylzincation of various 1-alkynyl sulfoxides **1b–f**.⁶ Functional groups such as TBS, Ac, and

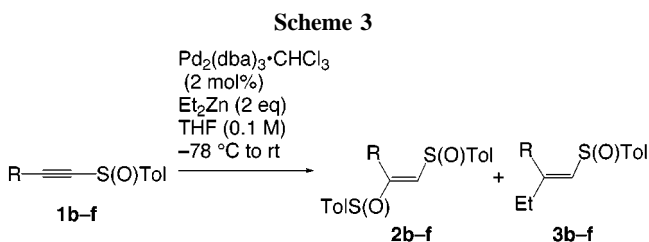
(8) Separation of the diastereomeric isomers was difficult. Their geometry was determined as follows: (1) No NOE was observed between the olefinic proton and the allylic proton in each isomer of bis-sulfoxides. (2) Oxidation of the diastereomeric mixture with *m*-CPBA led to a single (*E*)-bis-sulfone in 79% yield.

Table 2. Pd-Catalyzed Sulfinylzincation of 1-Alkynyl *p*-Tolyl Sulfoxides **1b–f**^a

entry	substrate	R	time (h)	product	yield (%) ^b	
					2 ^c	3
1	1b	$\text{TBSO}(\text{CH}_2)_2$	1.5	b	88	0
2	1c	$\text{AcO}(\text{CH}_2)_2$	1.5	c	82	0
3	1d	$\text{I}(\text{CH}_2)_4$	1.5	d	97	0
4	1e	H	0.5	e	24 ^d	33 ^e
5	1f	<i>t</i> -Bu	12	f	complex mixture	

^a All reactions were carried out using $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (2 mol %) and Et_2Zn (2 equiv) in THF solution at -78°C to room temperature. ^b Isolated yield. ^c The yield is based on 50% of **1**. The ratio of diastereomeric isomers is ca. 1:1 unless otherwise stated. ^d Single diastereomeric isomers. ^e The ratio of (*E/Z*)-isomers is 2:1.

I are compatible in this reaction (Scheme 3). It is noteworthy that a nucleophile-sensitive acetyl group was not affected under the conditions and no iodine–zinc exchange reaction⁷ was observed.



We suggest two possible reaction mechanisms as depicted in Scheme 4. The reaction would be initiated by oxidative addition of 1-alkynyl sulfoxides to a $\text{Pd}(0)$ complex.¹¹ Then, transmetalation of the adduct with Et_2Zn would afford a zinc sulfenate intermediate,¹² which undergoes sulfinylzincation with 1-alkynyl sulfoxides, giving a bis-sulfinyl vinylzinc species (pathway a). Another possible pathway is a direct sulfinylpalladation to the 1-alkynyl sulfoxides followed by transmetalation (pathway b).

Since **1a** did not afford the adduct **2a** nor an alkynylated bis-sulfoxide (a cross-coupling product) via reductive elimi-

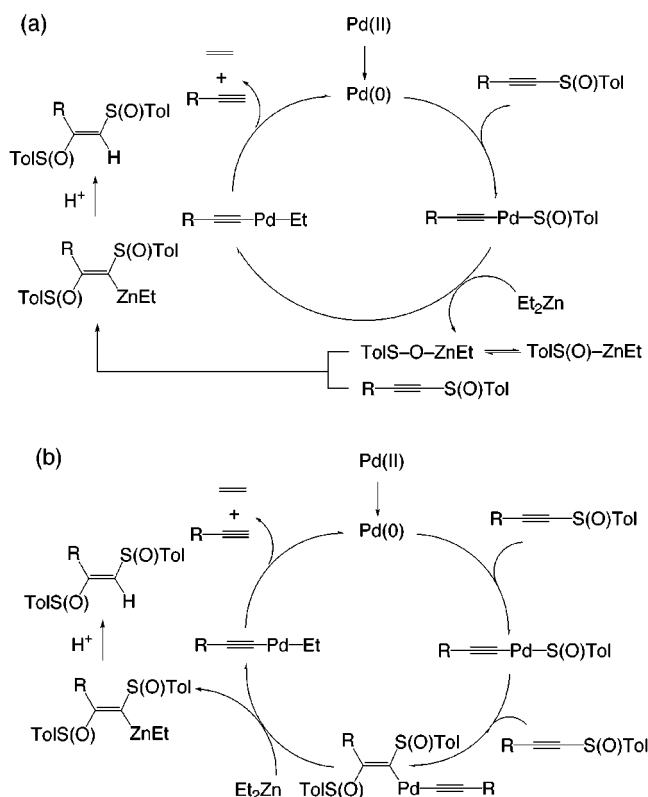
(9) Since one-half of 1-alkenyl sulfoxide is consumed as a sulfinyl source, all yields of bis-sulfoxide are based on 50% of materials.

(10) We examined the effect of Pd-catalyst on the byproducts of the sulfinylzincation. In contrast to the reaction of 4-(*tert*-butyldiphenylsilyloxy)-1-butyne *p*-tolyl sulfoxide using Pd-catalyst, which produced 3-butyne-1-ol *tert*-butyldiphenylsilyl (TBDPS) ether in 68% yield via β -hydride elimination as shown in Scheme 4, the corresponding reaction without Pd-catalyst underwent replacement of the sulfinyl group into an ethyl group to give 3-hexyn-1-ol TBDPS ether in 54% yield. Similar substitution reactions of acetylenic sulfones with Grignard reagents and organolithium compounds have been reported, and a plausible mechanism involving electron transfer was suggested; see: Back, T. G. *Tetrahedron* **2001**, 57, 5263–5301 and references therein.

(11) Oxidative addition of $\text{Pd}(0)$ to the carbon–sulfur bond of the thioalkynes was recently reported; see: Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, 3, 91–93.

(12) Sulfinylzincation using optically pure 1-alkenylsulfoxide **1a** provided a 1:1 mixture of diastereomeric isomers, which was presumably produced by racemization of the introduced sulfoxide via sulfinyl–sulfenate tautomerization.

Scheme 4

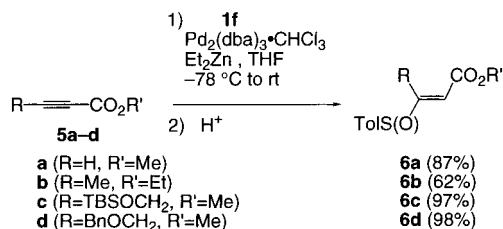


nation on treatment with a stoichiometric amount of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (0.5 equiv) without Et_2Zn , pathway a is suggested as the actual reaction mechanism.

Next, we focused on sulfinylation of another activated alkyne (Scheme 5). A substrate free from homocoupling is expected to work as a sulfinylating agent for other activated alkynes. The reaction of 1-alkynyl sulfoxide **1f** bearing a *tert*-butyl group at the β -sulfinyl position was sluggish and did not undergo homocoupling reaction presumably as a result of steric hindrance of the *tert*-butyl group. Therefore, we investigated the ability of **1f** as a sulfinylating agent. As we expected, the sulfenyl anion (or sulfinyl anion) generated

on treatment with a mixture of 1-alkynyl sulfoxide **1f** with $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (2 mol %) and Et_2Zn (2 equiv) in THF (0.1 M) was trapped with large excess of propiolate derivatives **5a–d** (10 equiv) to furnish methyl (*E*)-3-(*p*-tolylsulfinyl)-acrylate derivatives **6a–d** in good to moderate yield.¹³ The reaction also exclusively afforded the (*E*)-isomer of **6a–d**, and no geometric isomer was observed.¹⁴

Scheme 5



In conclusion, we have found a novel Pd-catalyzed sulfinylation to activated alkynes. The sulfinyl group was transferred to 1-alkynyl sulfoxides and propiolate derivatives in a *syn*-selective fashion, giving a β -sulfinyl vinylzinc species. It is noteworthy that S–C bond fission and S–C bond formation proceeded under mild conditions, wherein various functional groups are compatible. In addition, since Michael addition of thiolates to activated alkynes regularly proceeds with *anti*-selectivity,^{1e} the sulfinylation can be complementarily used in combination with a sulfinylation–oxidation procedure. Work is currently in progress in our laboratory in order to explore the scope and limitations of this reaction.

Supporting Information Available: ^1H and ^{13}C NMR spectral data for **2a–e** and **6a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* **1984**, 25, 1727–1728.

(14) Trapping of unstable sulfenic acid (RSOH) with methyl propiolate was reported; see: Mitra K.; Barnes C. L.; Gates K. S. *J. Chem. Crystallogr.* **1999**, 29, 1133–1136.