ORGANIC LETTERS

2001
Vol. 3, No. 23
3627−3629

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

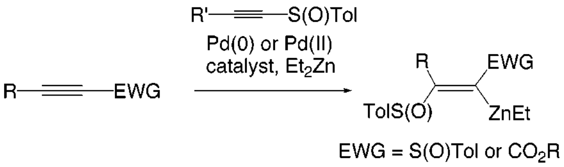
Naoyoshi Maezaki, Ryoko Yoshigami, Jun Maeda, and Tetsuaki Tanaka*

Graduate School of Pharmaceutical Sciences, Osaka University,
1-6 Yamadaoka, Suita, Osaka, 565-0871, Japan

t-tanaka@phs.osaka-u.ac.jp

Received August 9, 2001

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-butynyl *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 EtONa[2] 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 Et_2Zn 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 Et_2Zn.

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 Et_2Zn in the presence of catalytic $PdCl_2(dppf)$.[7] The reaction gave (*E*)-bis-sulfoxide **2a**[8] in 44% yield[9] as a 1:1 diastereomeric mixture based on sulfur stereogenic centers along with a (*Z*)-isomer of ethylation product **3a** (19%) after protonation of

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[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 diethylalminium 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.

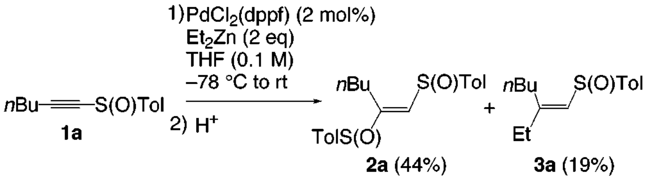
[6] Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078−1082.

[7] For palladium-catalyzed carbozincation using $PdCl_2(dppf)$, see: Stadtmüller, H.; Vaupel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. *Chem. Eur. J.* **1996**, *2*, 1204−1220.

10.1021/ol016552j CCC: $20.00 © 2001 American Chemical Society
Published on Web 10/23/2001

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

Scheme 1



To improve the yield of the sulfinylation product **2a**, we investigated the reaction conditions (Table 1). As a result, 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 $Pd_2(dba)_3{\cdot}CHCl_3$ (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]

Table 1. Effect of Pd-Catalyst on Sulfinylzincation[a]

entry	Pd-catalyst[b]	time (h)	yield (%)[c] **2a**[d]	yield (%)[c] **3a**
1	none	4	56	29
2	$PdCl_2(dppf)$	1	44	19
3	$PdCl_2(MeCN)_2$	1	86	tr
4	$PdCl_2(PPh_3)_2$	1	82	4
5	$Pd(PPh_3)_4$	1	88	tr
6	$Pd_2(dba)_3{\cdot}CHCl_3$	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.

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

Scheme 2

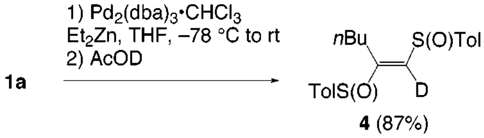


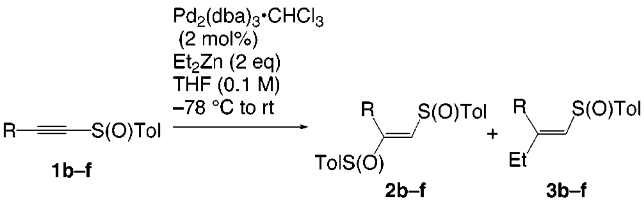
Table 2 shows the sulfinylzincation of various 1-alkynyl sulfoxides **1b**−**f**.[6] Functional groups such as TBS, Ac, and I are compatible in this reaction (Scheme 3). It is noteworthy that a nucleophile-sensitive acetyl group was not affected under the conditions and no iodine−zinc exchange reaction[7] was observed.

Table 2. Pd-Catalyzed Sulfinylzincation of 1-Alkynyl *p*-Tolyl Sulfoxides **1b**−**f**[a]

entry	substrate	R	time (h)	product	yield (%)[b] **2**[c]	yield (%)[b] **3**
1	**1b**	$TBSO(CH_2)_2$	1.5	**b**	88	0
2	**1c**	$AcO(CH_2)_2$	1.5	**c**	82	0
3	**1d**	$I(CH_2)_4$	1.5	**d**	97	0
4	**1e**	H	0.5	**e**	24[d]	33[e]
5	**1f**	*t*-Bu	12	**f**	complex mixture	

[a] All reactions were carried out using $Pd_2(dba)_3{\cdot}CHCl_3$ (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.

Scheme 3



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 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-

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(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.

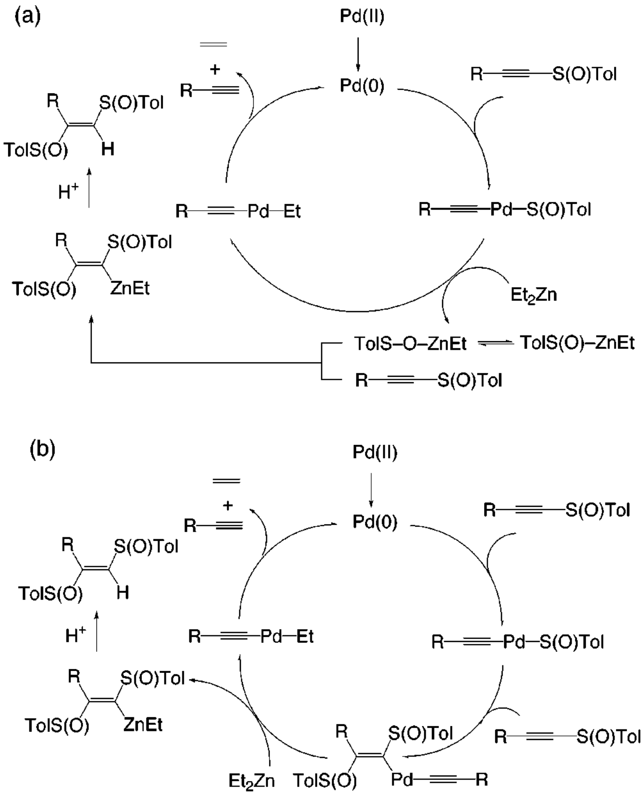
(9) Since one-half of 1-alkenyl sulfoxide is consumed as a sulfinyl source, all yields of bis-sulfoxide are based on 50% of materials.

(10) We examined the effect of Pd-catalyst on the byproducts of the sulfinylzincation. In contrast to the reaction of 4-(*tert*-butyldiphenylsilyloxy)-1-butynyl *p*-tolyl sulfoxide using Pd-catalyst, which produced 3-butyn-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 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.

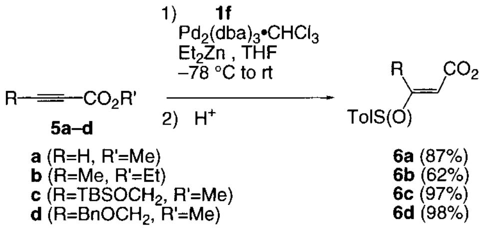
Scheme 4



nation on treatment with a stoichiometric amount of $Pd_2(dba)_3{\cdot}CHCl_3$ (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 $Pd_2(dba)_3{\cdot}CHCl_3$ (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 sulfinylzincation 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 sulfinylzincation 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.