

## Michael-type addition of hydroxide to alkynylselenium salt: practical use as a ketoselenium ylide precursor

Shin-ichi Watanabe,\* Shinsuke Asaka and Tadashi Kataoka\*

Gifu Pharmaceutical University, 6-1 Mitahora-higashi 5-chome, Gifu 502-8585, Japan

Received 17 June 2004; revised 9 August 2004; accepted 9 August 2004

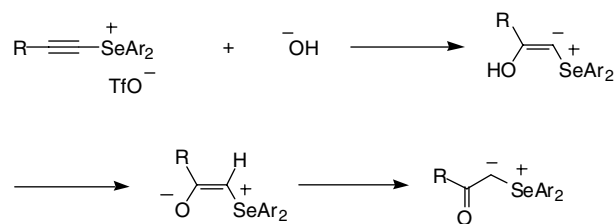
**Abstract**—A novel synthetic method of ketodiphenylselenium ylide from alkynylselenium salt is described. A reaction of alkynylselenium salt, hydroxide ion, and aldehyde in the presence of silver triflate and triethylamine gave oxiranylketones just as a *trans*-isomer in moderate to good yields, whereas benzoyl aziridine derivatives were obtained from the reaction with sodium *p*-toluenesulfonamide instead of a hydroxide ion.

© 2004 Elsevier Ltd. All rights reserved.

Selenium ylide, a versatile synthetic species in the field of organic synthesis, induces several types of C–C bond formation reactions.<sup>1</sup> While the properties of selenium and sulfonium ylides show remarkable resemblance, selenium ylides stabilized by an electron-withdrawing group are more reactive than the corresponding sulfonium ylides toward electrophiles.<sup>2</sup> Some stable selenium ylides stabilized by two electron-withdrawing substituents on the carbanionic center were generated by the reactions of the corresponding selenuranes and the active methylene compounds,<sup>3</sup> the treatment of stable selenoxides with active methylene compounds,<sup>4</sup> or electron-deficient alkynes,<sup>5</sup> and the displacement of an arylodonium group from the iodonium ylide with the selenide.<sup>6</sup> On the other hand, selenium ylides bearing an electron-withdrawing group were formed only by the deprotonation of the corresponding selenium salts.<sup>2a,7</sup> These stabilized ylides have dialkyl groups on the selenium atom, which are inconvenient for the reactions with nucleophiles because of the occurrence of a side reaction, dealkylation.<sup>8</sup> There is only one report on the synthesis of the  $\beta$ -ketodiarylselenium salt, but its reactivities are unknown.<sup>9</sup> Thus, we are interested in developing a new synthetic method of ketodiarylselenium ylide. Through our research on the reactivities of diarylalkynylselenium salts, we found

that diarylalkynylselenium salts act as a good Michael acceptor toward certain nucleophiles.<sup>10</sup> If the Michael-type addition of the hydroxide ion occurs toward an alkynylselenium salt, a ketodiarylselenium ylide would be formed after enol–keto tautomerization (Scheme 1). On the basis of this hypothesis, we investigated the reactions of the alkynylselenium salts with hydroxide to form the ketodiphenylselenium ylides and the capture of the ylide with aldehydes to produce oxiranylketones.

We first examined the reactions of phenylethyndiphenylselenium triflate **1a** and lithium hydroxide with aromatic aldehydes (Table 1). The reaction of *p*-nitrobenzaldehyde with 2 equiv of alkynylselenium salt **1a** in the presence of 3 equiv of lithium hydroxide at room temperature proceeded slowly, and *trans*-oxiranylketone **2a** and diphenyl selenoxide **3** were obtained in 17% yields (entry 1). The formation of the selenoxide probably arose from the attack of hydroxide to the selenium cation directly.<sup>11</sup> In order to activate the triple



Scheme 1. Michael addition of hydroxide to alkynylselenium salt.

**Keywords:** Michael reactions; Oxiranes; Selenium ions; Ylides; Aziridines.

\* Corresponding authors. Tel.: +81 58 237 3931; fax: +81 58 237 5979; e-mail addresses: watanabe@gifu-pu.ac.jp; kataoka@gifu-pu.ac.jp

**Table 1.** Reactions of alkynylselenonium salt **1a** and ArCHO with LiOH

Entry	Ar	Additive	Products (yield, %)
1	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>		<b>2a</b> (17) <b>3</b> (17)
2	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	AgOTf (4equiv)	<b>2a</b> (78)
3	<i>p</i> -CNC <sub>6</sub> H <sub>4</sub>	AgOTf (4equiv)	<b>2b</b> (67)
4	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	AgOTf (4equiv)	<b>2c</b> (25)

bond toward the Michael-type addition of a nucleophile, a silver salt was added as a soft metal to the reaction mixtures. Thus, the reaction with 4equiv of silver triflate gave the product **2a** in 78% yield (entry 2). While *p*-cyanobenzaldehyde reacted with the alkynylselenonium salt and lithium hydroxide to afford the desired epoxide **2b** in good yield (entry 3), the reactivity of *p*-chlorobenzaldehyde was low to give the product **2c** only in 25% yield (entry 4). The compounds obtained from the reactions were single *trans*-isomers, and their structures were determined by comparing their <sup>1</sup>H and <sup>13</sup>C NMR data with those of authentic samples.<sup>12</sup>

Next, in order to boost the formation of ketoselenonium ylide by catalyzing the enol–keto tautomerization, the effect of amine was examined in the reaction of *p*-chlorobenzaldehyde (Table 2). The reaction of alkynylselenonium salt **1a** (2equiv) with the aldehyde and 3equiv of lithium hydroxide in the presence of 4equiv of silver triflate and 2equiv of triethylamine in a mixed solvent of CH<sub>2</sub>Cl<sub>2</sub>–MeCN was carried out at room temperature for 1 day, and the yield of the desired compound **2c** was improved up to 61% (entry 1). While the reflux condition reduced the reaction time, the yield of **2c** was decreased (entry 2). Although the increase of the amount of triethylamine to 4equiv afforded the product **2c** in 63% yield, the use of 10equiv of triethylamine decreased the yield (entries 3 and 4).

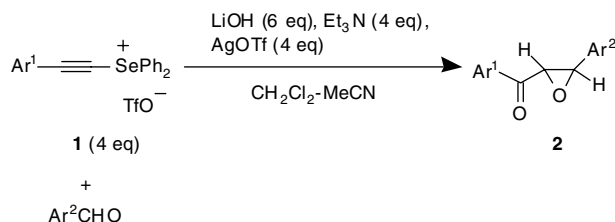
**Table 2.** The effect of triethylamine

Entry	Et <sub>3</sub> N	Conditions	<b>2c</b>
1	2equiv	rt, 1 d	61%
2	2equiv	Reflux, 8.5h	53%
3	4equiv	rt, 1.5 d	63%
4	10equiv	rt, 1.5 d	56%

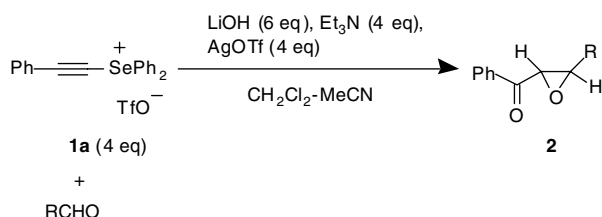
In view of the results above, the conditions for the reaction with *p*-chlorobenzaldehyde were optimized, and the best yield was obtained by the use of 4equiv of alkynylselenonium salt **1a**, silver triflate, and triethylamine and 2equiv of lithium hydroxide toward the aldehyde after 12h (Table 3, entry 1).<sup>13</sup> Under the same conditions, several aromatic aldehydes underwent the reactions, and good yields of the desired oxiranylketones were obtained. The drop in the electron density of the aromatic ring accelerated the reaction rate. Furthermore, the reactions of *p*-nitrobenzaldehyde with other alkynylselenonium salts bearing *p*-chlorophenylethynyl or *p*-methylphenylethynyl groups also afforded the corresponding oxirane derivatives in high yields.<sup>14</sup> NMR analysis showed that these oxirane compounds obtained from the above reactions were just *trans*-isomers.

Second, to broaden the scope of this reaction, we examined the reactions with a variety of aliphatic aldehydes (Table 4). The reactions with linear aliphatic aldehydes were carried out under the same reaction conditions that were used for aromatic aldehydes. While the reaction with 1-propanal gave the oxirane derivative **2l** in 18% yield, the chain lengthening of an aldehyde improved the yield of the product, and the desired compound **2n** was obtained in 54% yield from the reaction with hydrocinnamaldehyde (entries 1–3). Additionally, isobutylaldehyde as a chain-branching aldehyde, reacted with the ketoselenonium ylide to produce the oxiranyl ketone **2o** in 37% yield, and the reaction with valeraldehyde showed a better result, giving a 63% yield of oxirane **2p** (entries 4 and 5). Probably, the cause of the lower yields of oxiranyl ketones in the reactions with aliphatic aldehydes than with aromatic aldehydes is attributable to side reactions, such as the self aldol reaction. In practice, when the more sterically hindered aldehyde was used, the yields of desired products were increased by preventing the side reactions. On the other hand, isobutylaldehyde is too bulky to react with the ylide adequately. The compounds obtained from the reactions were single *trans*-isomers, and their structures were determined by comparing their <sup>1</sup>H and <sup>13</sup>C NMR data with those of authentic samples.<sup>15</sup>

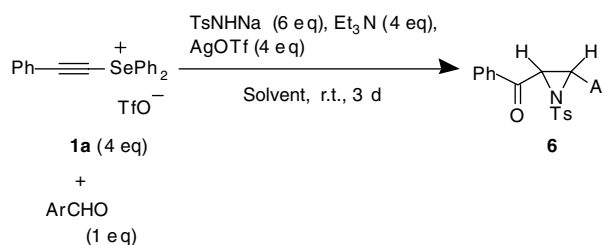
On the basis of these results, we propose a plausible mechanism for the reactions of an alkynylselenonium salt with aldehydes and a hydroxide in the presence of a silver salt and triethylamine (Scheme 2). The triple bond of the alkynylselenonium salt is activated by a silver cation, and a hydroxide ion attacks the β-carbon of the alkynylselenonium salt, similarly to the Michael-type addition, to form the vinyl ylide **4**, which is transformed to the ketodiphenylselenonium ylide by enol–keto tautomerization accelerated by triethylamine. The ylide reacts with aldehydes to give oxiranylketones together with diphenyl selenide (route A). On the other hand, diphenyl selenoxide is formed by the attack of hydroxide to a selenonium cation without activation of a triple bond by a silver ion (route B). Since these reactions were examined at room temperature, the diastereoselectivity on the betaine **5** would not be observed. The reason that only *trans*-oxiranes are formed can be explained by the assumption that an active methine

**Table 3.** Preparation of oxiranylketones

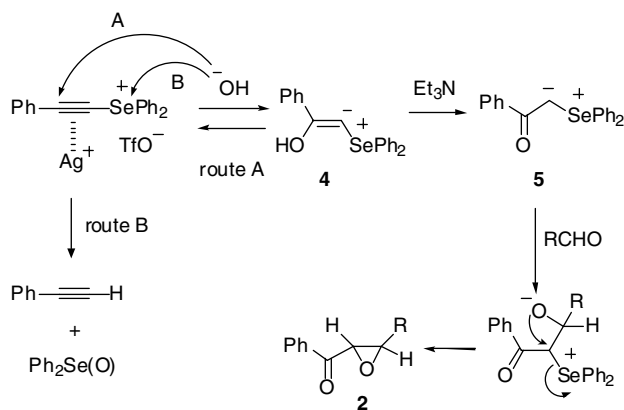
Entry	1	Ar <sup>2</sup>	Time (h)	Products (yield, %)
1	1a (Ar <sup>1</sup> = Ph)	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	12	2c (78)
2	1a	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	3.5	2a (84)
3	1a	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1.5	2d (71)
4	1a	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	2	2e (58)
5	1a	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	9	2f (55)
6	1a	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	2	2g (92)
7	1a	<i>m</i> -BrC <sub>6</sub> H <sub>4</sub>	5	2h (90)
8	1a	Ph	6.5	2i (40)
9	1b (Ar <sup>1</sup> = <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> )	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	3	2j (89)
10	1c (Ar <sup>1</sup> = <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> )	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	3	2k (71)

**Table 4.** Reactions of ketoselenonium ylide with RCHO

Entry	R	Time	Products (yield, %)
1	CH <sub>3</sub> CH <sub>2</sub>	Overnight	2l (18)
2	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub>	24 h	2m (34)
3	Ph(CH <sub>2</sub> ) <sub>2</sub>	Overnight	2n (54)
4	(CH <sub>3</sub> ) <sub>2</sub> CH	Overnight	2o (37)
5	(CH <sub>3</sub> )CHCH <sub>2</sub>	24 h	2p (63)

**Table 5.** Reactions of alkynylselenonium salt with ArCHO and TsNHNa

Entry	Ar	Solvent	Products (yield, %)
1	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub> –MeCN	6a (44)
2	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	MeCN	6b (44)
3	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	MeCN	6c (48)
4	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub> –MeCN	6d (30)

**Scheme 2.** Plausible mechanism of the reactions of an alkynylselenonium salt with an aldehyde and a hydroxide in the presence of a silver cation and triethylamine.

hydrogen in the betaine intermediate is easily deprotonated by excess bases in this system and the resulting

thermodynamically stable conformer cyclizes to produce the *trans*-epoxides 2.<sup>2a</sup>

One reaction feature of the alkynylselenonium salt is that other nucleophiles are available as Michael donor in place of hydroxide ion. In anticipation of the production of oxiranyl imines, a *p*-toluenesulfonamide was selected as a nucleophile (Table 5). The reaction of alkynylselenonium salt 1a with *p*-chlorobenzaldehyde and sodium *p*-toluenesulfonamide<sup>16</sup> in the presence of triethylamine and silver trifluoromethanesulfonate was undertaken under similar conditions to Table 3. Unexpectedly, 2-benzoyl-3-(*p*-chlorophenyl)-1-tosylaziridine 6a was obtained in 44% yield as a single *cis*-isomer after 3 days (entry 1). The structure of 6a was determined by comparing its spectral data with that of an authentic sample.<sup>17</sup> Other aldehydes also reacted to give tosylaziridine derivatives in moderate yields (entries 2–4). The coupling constants of the methine protons on the aziridine ring of 6 (7–8 Hz) indicate that these isomers are *cis* geometry.<sup>17</sup>

The initial step of the above reaction is presumed to be a formation of an *N*-sulfonylaldimine and a hydroxide ion from a *p*-toluenesulfonamide monosodium salt and an aromatic aldehyde. The subsequent reaction of the *N*-sulfonylaldimine with  $\beta$ -ketoselenonium ylide, which is generated by an alkynylselenonium salt and a hydroxide ion would lead to producing an aziridine derivative. However, the reaction of alkynylselenonium salt **1a** with *N*-tosyl-4-nitrobenzaldehyde and lithium hydroxide in the presence of triethylamine and silver trifluoromethanesulfonate at room temperature for 10h gave oxiranylketone **2a** in 42% yield and the desired aziridine derivative was not obtained. The reason for the *cis* selectivity on the aziridine formation is attributable to the stability of the *cis*-isomer.<sup>18</sup> While so far reports on the preparation of aziridines starting from ylides and imines are limited,<sup>17,19</sup> we have been able to achieve a novel type of aziridine formation reaction using alkynylselenonium salt, aldehyde, and sodium *p*-toluenesulfonamide.

In summary, we have developed a novel synthetic method of ketodiphenylselenonium ylide from alkynylselenonium salt, and the formation of the ylide was indirectly confirmed by a trap of aldehydes to afford oxiranylketones. On the other hand, by the use of sodium *p*-toluenesulfonamide as nucleophile instead of lithium hydroxide, benzoyl aziridines were obtained in moderate yields. A silver cation assists the Michael-type addition of hydroxide to an alkynylselenonium salt. Although the excess amount of starting materials toward aldehyde is a disadvantage, we found interesting reactions with alkynylselenonium salt involving the control on the addition of a hydroxide ion with a silver ion to alkynylselenonium salt. In addition, the preparation of oxiranes and aziridines was successful by only changing the hydroxide to amide. This is the first example in which an alkynylselenonium salt is used as a ylide precursor. Further applications of this methodology are currently underway in our laboratory.

### Acknowledgements

This research was partially supported by the Ministry of Education, Science, Sports, and Culture, Grant-in-Aid for the Encouragement of Young Scientists (B), 2004, 14771246.

### References and notes

1. Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986.
2. (a) Magdesieva, N. N.; Chovnikova, N. G. *Zh. Org. Khim.* **1979**, *15*, 2402–2405; (b) Johnson, A. W.; Amel, R. T. *J. Org. Chem.* **1969**, *34*, 1240–1247.
3. (a) Ernstbrunner, E.; Lloyd, D. *Liebigs Ann. Chem.* **1971**, *753*, 196–198; (b) Magdesieva, N. N.; Kyandzhetsian, R. A. *Zh. Org. Khim.* **1971**, *7*, 2228; (c) Magdesieva, N. N.; Kyandzhetsian, R. A.; Ibragimov, A. A. *J. Organomet. Chem.* **1972**, *42*, 399–404; (d) Wei, K. H.; Paul, I. C.; Chang, M. M. Y.; Musher, J. I. *J. Am. Chem. Soc.* **1974**, *96*, 4099–4102; (e) Derkach, N. Y.; Tishchenko, N. P.

- Voloshchuk, S. A. *Zh. Org. Khim.* **1978**, *14*, 958–962; (f) Shevelev, S. A.; Semenov, V. V.; Fainzil'berg, A. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, 1091–1098.
4. (a) Magdesieva, N. N.; Kyandzhetsian, R. A. *Zh. Org. Khim.* **1973**, *9*, 1755–1756; (b) Magdesieva, N. N.; Kyandzhetsian, R. A. *Zh. Org. Khim.* **1974**, *10*, 1708–1711; (c) Magdesieva, N. N.; Kyandzhetsian, R. A.; Astafurov, V. M. *Zh. Org. Khim.* **1975**, *11*, 508–511; (d) Tamagaki, S.; Akatsuka, R.; Kozuka, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 817–818.
5. (a) Magdesieva, N. N.; Kyandzhetsian, R. A.; Gordeev, M. F. *Zh. Org. Khim.* **1982**, *18*, 2514–2523; (b) Kataoka, T.; Tomimatsu, K.; Shimizu, H.; Hori, M. *Tetrahedron Lett.* **1983**, *24*, 75–78.
6. Semenov, V. V.; Mel'nikova, L. G.; Shevelev, S. A.; Fainzil'berg, A. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, 138–144.
7. Lotz, W. W.; Gosselck, J. *Tetrahedron* **1973**, *29*, 917–919.
8. Magdesieva, N. N.; Kyandzhetsian, R. A.; Chovnikova, N. G.; Emel'yanova, N. N. *Zh. Org. Khim.* **1981**, *17*, 340–342.
9. Hashimoto, T.; Kitano, H.; Fukui, K. *Nippon Kagaku Zasshi* **1968**, *89*, 784–786.
10. (a) Kataoka, T.; Banno, Y.; Watanabe, S.; Iwamura, T.; Shimizu, H. *Tetrahedron Lett.* **1997**, *38*, 1809–1812; (b) Kataoka, T.; Watanabe, S.; Yamamoto, K.; Yoshimatsu, M.; Tanabe, G.; Muraoka, O. *J. Org. Chem.* **1998**, *63*, 6382–6386; (c) Watanabe, S.; Yamamoto, K.; Itagaki, Y.; Kataoka, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2053–2055; (d) Watanabe, S.; Mori, E.; Nagai, H.; Kataoka, T. *Synlett* **2000**, 49–52; (e) Watanabe, S.; Mori, E.; Nagai, H.; Iwamura, T.; Iwama, T.; Kataoka, T. *J. Org. Chem.* **2000**, *65*, 8893–8898; (f) Watanabe, S.; Yamamoto, K.; Itagaki, Y.; Iwamura, T.; Iwama, T.; Kataoka, T.; Tanabe, G.; Muraoka, O. *J. Chem. Soc., Perkin Trans. 1* **2001**, 239–247.
11. (a) Detty, M. R. *J. Org. Chem.* **1980**, *45*, 274–279; Harirchian, B.; Magnus, P. D. *Chem. Commun.* **1977**, 522–523.
12. Shi, M.; Itoh, N.; Masaki, Y. *J. Chem. Res. (S)* **1995**, 304–305.
13. Typical procedure: Alkynylselenonium salt **1** (0.8 mmol), an aromatic aldehyde (0.2 mmol) and silver triflate (0.8 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub>–MeCN (4:1, 5 mL). Anhydrous lithium hydroxide (1.2 mmol) and then triethylamine (0.8 mmol) were added to the solution. The mixture was stirred for 1.5–12h at room temperature. The typical work-up with water, extraction with ethyl acetate, and preparative TLC purification afforded **2**.
14. Chlorophenylethynyldiphenylselenonium triflate **1c** was prepared by the adaption of published procedure.<sup>10b</sup>
15. (a) Enders, D.; Zhu, J.; Kramps, L. *Liebigs Ann. Chem.* **1997**, 1101–1113; (b) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381–1390.
16. Bottini, F.; Grazia, M. D.; Finocchiaro, P.; Fronczek F. R.; Mamo, A.; Pappalardo, S. *J. Org. Chem.* **1988**, *53*, 3521–3529.
17. Matano, Y.; Yoshimune, M.; Suzuki, H. *J. Org. Chem.* **1995**, *60*, 4663–4665.
18. (a) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999–1015; (b) Ibuka, T.; Mimura, N.; Ohno, H.; Nakai, K.; Akaji, M.; Habashita, H.; Tamamura, H.; Miwa, Y.; Taga, T.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2982–2991; (c) Ohno, H. *Yakugaku Zasshi* **2001**, *121*, 733–741.
19. (a) Wan, D.; Dai, L.; Hou, X. *Chem. Commun.* **1997**, 1231–1232; (b) Ochiai, M.; Kitagawa, Y. *Tetrahedron Lett.* **1998**, *39*, 5569–5570; (c) Ochiai, M.; Kitagawa, Y.

*J. Org. Chem.* **1999**, *64*, 3181–3189; (d) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433–1436; (e)

Aggarwal, V. K.; Ferrara, M.; O'Brien, C. J.; Thompson, A.; Jones, R. V. H.; Fieldhouse, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1635–1643.