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Unprecedented Noncatalyzed *anti*-Carbozincation of Diethyl Acetylenedicarboxylate through Alkylzinc Group Radical Transfer

Julien Maury, Laurence Feray,* and Michèle P. Bertrand*

Laboratoire Chimie Provence, UMR 6264, Equipe CMO, case 562,
Université Aix-Marseille, FST Saint-Jérôme, av. Escadrille Normandie Niemen,
13397 Marseille cedex 20, France

laurence.feray@univ-cezanne.fr; michele.bertrand@univ-cezanne.fr

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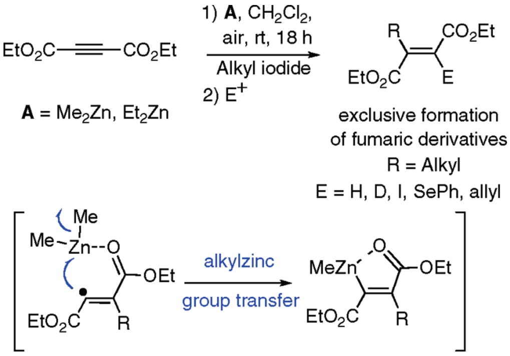
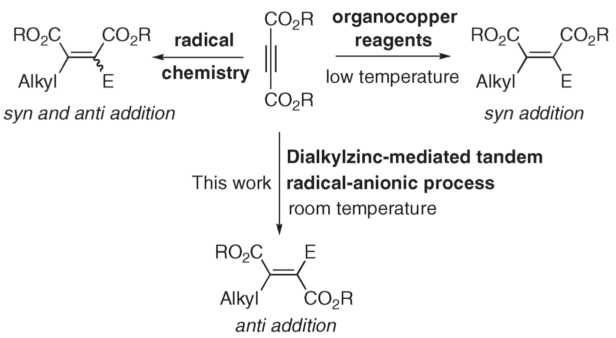
ABSTRACT



The radical carbozincation of diethyl acetylenedicarboxylate, performed at room temperature in the presence of air, leads to fumaric derivatives through a selective alkylzinc group radical transfer controlled by coordination. The total *trans* stereocontrol is unprecedented, carbocupration is well-known to give the reversal selectivity at low temperature, while classical radical addition methodologies lead to mixtures of isomers.

Stereocontrolled *anti*-carbometalation of the triple bond of dialkyl acetylenedicarboxylates remains a challenge for organic chemists.[1] To achieve the addition of organometallic reagents to these substrates, specific organocopper reagents are needed. The *syn*-carbocupration of dialkyl acetylenedicarboxylates can be realized by using organocopper−organoborane complexes ($RCu{\bullet}BR'_3$),[2] organocopper reagents derived from cuprous bromide−dimethyl sulfide complex ($RCu(Me_2S){\bullet}MgBr_2$),[3] and also mixed copper−zinc species ($RCu(CN)ZnBr$).[4] In all cases, maleic derivatives are formed at low temperature (Scheme 1). Additional functionalization has been applied to the synthesis of natural and unnatural maleic acids[5] and anhydrides.[6]

Scheme 1. Alkylation of Dialkyl Acetylenedicarboxylates



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[1] For general reviews on carbometalation and carbocupration of alkynes, see: (a) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899–5913. (b) Chemla, F.; Ferreira, F. In *Chemistry of Organocopper Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley & Sons: Hoboken, 2009; pp 527−584. (c) Basheer, A.; Marek, I. *Beilstein J. Org. Chem.* **2010**, *6* (77), 10.3762/bjoc.6.77. (d) Wipf, P.; Kendall, C. *Chem.—Eur. J.* **2002**, *8*, 1778–1784.

[2] Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Org. Chem.* **1979**, *44*, 1744–1746.

[3] Nishiyama, H.; Sasaki, M.; Itoh, K. *Chem. Lett.* **1981**, 905–908.

[4] (a) Chou, T.-S.; Knochel, P. *J. Org. Chem.* **1990**, *55*, 4791–4793. (b) Sidduri, A. R.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 7579–7581.

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The alkylation of the triple bond of dialkyl acetylenedicarboxylates can also be achieved by using radical chemistry. Most reactions are nonstereoselective. Due to the fast isomerization of the intermediate vinylic radicals, the stereochemical outcome is mainly governed by steric effects in the atom transfer step.

The photoinduced addition of cyclic ethers,[7] alcohols,[8] 2,2-dialkyldioxolanes,[9] and cycloalkanes[10] to dimethyl acetylenedicarboxylate (DMAD), usually ends with non stereoselective hydrogen atom abstraction. The addition of adamantane to diethyl acetylenedicarboxylate catalyzed by *N*-hydroxyphtalimide and Co(II) species under O_2 atmosphere gives the *Z* and *E* adducts in a ratio close to 70:30.[11]

A radical process is also involved in the photostimulated formation of vinylmercurial from the reaction of organomercury halides with diethyl acetylenedicarboxylate. The latter can be reduced by $NaBH_4$ or cleaved by I_2 to form in each case the expected product as a mixture of *Z* and *E* isomers in a 62:38 ratio.[12]

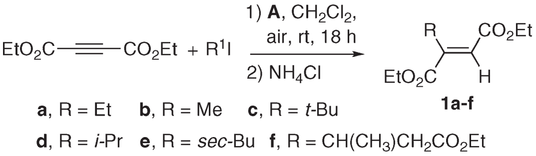
Similarly, functionalized maleic and fumaric derivatives can be obtained via Atom Transfer Radical Additions (ATRA).[13] the pioneering work in the field is due to Curran, who was the first to investigate the iodine atom transfer methodology.[13a]

However, the alkylation of dialkyl acetylenedicarboxylates leading to the exclusive formation of fumaric derivatives through either polar or radical chemistry is without precedent.

We report in this paper the highly stereoselective dialkylzinc-mediated addition of alkyl radicals to diethyl acetylenedicarboxylate at room temperature.

The addition of ethyl radical was achieved by using 2 equiv of Et_2Zn and air in dichloromethane at room temperature (entry 1, Table 1).[14] The ratio of 97:3 in favor of the *E* isomer, measured from the proton NMR spectra of the crude mixture, increased after purification and (*E*)-**1a** was isolated in 89% yield. Lower yields were obtained when diethylzinc was replaced by dimethylzinc, even in the presence of an excess (5 equiv) of the reagent (entry 2). Methyl derivative **1b** was isolated in 32% yield whereas 61% of starting material was recovered.[15] This behavior is in agreement with the poor reactivity of methyl radical regarding conjugate addition.[16]

Table 1. Dialkylzinc-Mediated Alkyl Radical Addition to Diethyl Acetylenedicarboxylate



entry	**A** (equiv)	R^1I (equiv)	**1** yield (%)	*E*:*Z*
1	Et_2Zn (2)	none	**1a** (89)	100:0[a]
2	Me_2Zn (5)	none	**1b** (32)[b]	100:0
3	Me_2Zn (3)	*t*-BuI (5)	**1c** (96)	100:0[c]
4	Me_2Zn (3)	*i*-PrI (5)	**1d** (97)	98:2
5	Me_2Zn (3)	*s*-BuI (5)	**1e** (99)	100:0
6	Me_2Zn (3)	EtI (5)	**1a** (34) **1b** (35)	100:0
7	Me_2Zn (3)	EtI (10)	**1a** (51) **1b** (33)	100:0
8[d]	Me_2Zn (3)	EtI (10)	**1a** (59) **1b** (27)	100:0
9[d]	Me_2Zn (3)	$ICH(Me)CH_2CO_2Et$ (10)	**1f** (75)	100:0

[a] Crude *E*:*Z*: 97:3. [b] Sixty-one percent of starting material was recovered. [c] Crude *E*:*Z*: 96:4. [d] Me_2Zn was added portionwise.

The additions of secondary and tertiary alkyl radicals were achieved by using dimethylzinc in the presence of the

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(5) (a) Ratemi, E. S.; Dolence, J. M.; Poulter, C. D.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 6296–6301. (b) Garneau, S.; Qiao, L.; Chen, L.; Walker, S.; Vederas, J. C. *Bioorg. Med. Chem.* **2004**, *12*, 6473–6494.

(6) (a) Baldwin, J. E.; Beyeler, A.; Cox, R. J.; Keats, C.; Pritchard, G. J.; Adlington, R. M.; Watkin, D. J. *Tetrahedron* **1999**, *55*, 7363–7374. (b) Baldwin, J. E.; Adlington, R. M.; Roussi, F.; Bulger, P. G.; Marquez, R.; Mayweg, A. V. W. *Tetrahedron* **2001**, *57*, 7409–7416. (c) Adlington, R. M.; Baldwin, J. E.; Cox, R. J.; Pritchard, G. J. *Synlett* **2002**, 820–822.

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(10) The best result was obtained for the addition of cyclopentane in the presence of benzophenone as the photomediator under solar radiation. In this case the *Z* isomer was formed selectively (*Z*:*E*, 98:2), see: (a) Doohan, R. A.; Geraghty, N. W. A. *Green Chem.* **2005**, *7*, 91–96. (b) Doohan, R. A.; Hannan, J. J.; Geraghty, N. W. A. *Org. Biomol. Chem.* **2006**, *4*, 942–952.

(11) Kagayama, T.; Nakayama, M.; Oka, R.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2006**, *47*, 5459–5461.

(12) (a) Russell, G. A.; Hu, W. J. S. S.; Khanna, R. K. *J. Org. Chem.* **1986**, *51*, 5499–5501. For the addition of *t*-Bu_2Hg, see also: (b) Blaukat, U.; Neumann, W. P. *J. Organomet. Chem.* **1973**, *49*, 323–332.

(13) For examples of iodine atom transfer radical reaction involving dialkyl acetylenedicarboxylates, see: (a) Curran, D. P.; Kim, D. *Tetrahedron* **1991**, *47*, 6171–6188. (b) Araki, Y.; Endo, T.; Tanji, M.; Nagasawa, J.; Ishido, Y. *Tetrahedron Lett.* **1987**, *28*, 5853–5856. (c) Araki, Y.; Endo, T.; Tanji, M.; Nagasawa, J.; Ishido, Y. *Tetrahedron Lett.* **1988**, *29*, 351–354. (d) Harendza, M.; Lesmann, K.; Neumann, W. P. *Synlett* **1993**, 283–285. (e) Fang, X.; Yang, X.; Yang, X.; Mao, S.; Wang, Z.; Chen, G.; Wu, F. *Tetrahedron* **2007**, *63*, 10684–10692. For tellurium atom transfer addition of carbamotelluroates to DMAD, see: (f) Fujiwara, S.-I.; Shimizu, Y.; Shin-Ike, T.; Kambe, N. *Org. Lett.* **2001**, *3*, 2085–2088.

(14) A typical procedure: diethylzinc (2 equiv, 1.24 mL, 1 M in hexane) was added to a solution of diethyl acetylenedicarboxylate (100 μL, 0.62 mmol) 0.3 M in dichloromethane at room temperature. Air was introduced in the reaction mixture through a syringe pump (40 mL for 1 h). After stirring for 18 h at room temperature, the reaction was quenched with saturated NH_4Cl. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel using pentane/ethyl acetate as eluent afforded (*E*)-2-ethyl-but-2-enedioic acid diethyl ester (**1a**) in 89% yield (110 mg, >99:1 ratio for *E*:*Z* isomers). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.06 (3H, t, J = 7.5 Hz), 1.28 (3H, t, J = 7.0 Hz), 1.29 (3H, t, J = 7.0 Hz), 2.76 (2H, q, J = 7.5 Hz), 4.19 (2H, q, J = 7.0 Hz), 4.22 (2H, q, J = 7.0 Hz), 6.68 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.6 (CH_3), 14.2 (CH_3), 14.3 (CH_3), 21.5 (CH_2), 60.7 (CH_2), 61.5 (CH_2), 126.1 (=CH), 149.7 (=C), 165.8 (C=O), 166.9 (C=O). HRMS (ESI): *m*/*z*: calcd for $[MH^+]$ $C_{10}H_{17}O_4$: 201.1121; found: 201.1122.

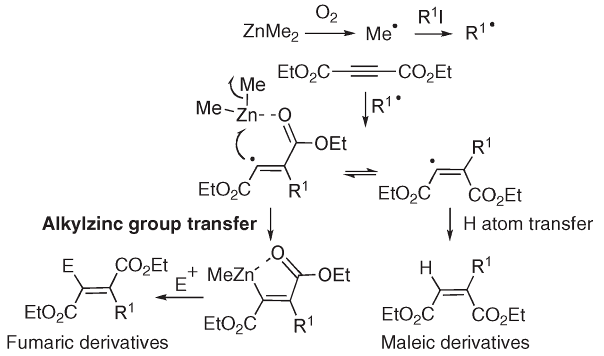
(15) When the reaction was conducted with 9 equiv of dimethylzinc in the presence of a large excess of air, **1b** was isolated in 44% yield.

(16) (a) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340–1371. (b) Gómez-Balderas, R.; Coote, M. L.; Henry, D. J.; Fischer, H.; Radom, L. *J. Phys. Chem. A* **2003**, *107*, 6082–6090. (c) Gómez-Balderas, R.; Coote, M. L.; Henry, D. J.; Radom, L. *J .Phys. Chem. A* **2004**, *108*, 2874–2883.

corresponding alkyl iodides (entries 3−5, 9). It is to be noted that the number of equivalents of alkyl iodide per mole of substrate is rather low compared to the amounts generally used in similar reactions in the literature.[17,18] High stereocontrol and yields were reached again in these cases even when a functionalized alkyl iodide was used as the radical precursor (entry 9).

Optimization was necessary to perform the addition of a primary alkyl radical from a primary alkyl iodide. Tested as a model reaction, the addition of ethyl radical mediated by the couple Me_2Zn/EtI led to a mixture of adducts **1a** and **1b** (entries 6−8). Dimethylzinc had to be added portionwise to increase the ratio of adduct **1a** which could be isolated as the major product in 59% yield (entry 8).

Scheme 2. Proposed Mechanism

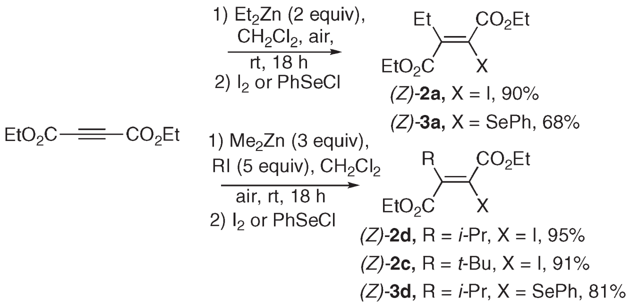


To explain the high stereochemical outcome of the reaction, we propose the mechanism depicted in Scheme 2. The reaction between the dialkylzinc and oxygen generates an alkyl radical.[18] In the presence of an alkyl iodide, the transfer of the iodine atom allows the formation of a new alkyl radical which adds to the activated triple bond to give a vinylic radical. We speculate that the reaction proceeds then through alkylzinc group transfer. The coordination of Zn(II) with the oxygen atom of the ester group explains the stereoselectivity of this transfer, which occurs in position *cis* relative to the carboxylate.[19] It is important to note that this is the first example of noncatalyzed formation of a vinylzinc from an alkyne bearing two ester groups.[20,21] The stabilized vinylzinc intermediate can then either be protonated or allowed to react with other electrophiles (the examples are not limitative) added to the reaction mixture.[22] We assume that the *Z*-isomers of products **1**, that are detected in trace amount in the crude reaction mixture, result from hydrogen atom transfer from any hydrogen atom donor present in the reaction medium and not from the protonation of the vinylzinc.[23]

As shown in Scheme 3, when I_2 was added to the reaction mixture, the vinylzinc intermediate was transformed in the corresponding vinylic iodide. Whatever the alkylgroup, primary, secondary, or tertiary, the iodides **2** were formed in good yields without any loss in selectivity.[24]

Phenylselenyl chloride was also shown to be a good trap for the vinylzinc intermediate (Scheme 3), **3a** and **3d** were isolated in satisfactory yields still with a total stereoselectivity.[25]

Scheme 3



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[17] While this work was being revised the Et_3B-mediated radical additions to activated alkynyl oxime ethers were reported, see: Ueda, M.; Matsubara, H.; Yoshida, K.-I.; Sato, A.; Naito, T.; Miyata, O. *Chem.—Eur. J.* **2011**, *17*, 1789–1792.

[18] For reviews on dialkylzincs in radical chemistry, see: (a) Bazin, S.; Feray, L.; Bertrand, M. P. *Chimia* **2006**, *60*, 260–265. (b) Akindele, T.; Yamada, K.-I.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345–355. For recent reports on the subject see also: (c) Giboulot, S.; Perez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *Tetrahedron Lett.* **2008**, *49*, 3963–3966. (d) Maury, J.; Feray, L.; Perfetti, P.; Bertrand, M. P. *Org. Lett.* **2010**, *12*, 3590–3593. (e) Akindele, T.; Mamamoto, Y.; Maekawa, M.; Umeki, H.; Yamada, K.-I.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5729–5732.

[19] For recent reports on the stereoselective formation of vinylzinc species through S_H2 process see: (a) Pérez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *Chem.—Eur. J.* **2008**, *14*, 8784–8788. (b) Feray, L.; Bertrand, M. P. *Eur. J. Org. Chem.* **2008**, 3164–3170. (c) Chen, Z.; Zhang, Y.-X.; An, Y.; Song, X.-L.; Wang, Y.-H.; Zhu, L.-L.; Guo, L. *Eur. J. Org. Chem.* **2009**, 5146–5152.

[20] Vinylzinc are usually prepared through transmetalation of differents vinylmetal. Here are selected examples: for transmetalation involving vinylnickel species, see: (a) Stüdemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299–1316. For alkene transfer from zirconium to zinc, see: (b) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761–768. For transmetalation involving vinyllithium species, see: (c) Agami, C.; Couty, F.; Evano, G. *Org. Lett.* **2000**, *2*, 2085–2088. (d) Dieter, R. K.; Guo, F. *Org. Lett.* **2006**, *8*, 4779–4782. For reactions involving vinylborane, see: (e) Wang, S.; Seto, C. T. *Org. Lett.* **2006**, *8*, 3979–3982. (f) Valenta, P.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 14179–14190 and previous refs therein.

[21] The addition of allylzinc bromide to acetylenic sulfone without any additive such as copper salt was reported, see: (a) Xie, M.; Wang, J.; Gu, X.; Sun, Y.; Wang, S. *Org. Lett.* **2006**, *8*, 431–434. Direct carbozincation reaction of trifluoromethylated acetylenic phosphonates mediated by dialkylzinc was also reported, see: (b) Konno, T.; Morigaki, A.; Ninomiya, K.; Miyabe, T.; Ishihara, T. *Synthesis* **2008**, 564–572. In these cases, a vinylzinc was formed in alpha position to an electronwithdrawing group.

[22] The formation of a zinc allenoate intermediate cannot be ruled out. We assume that the coordination of the zinc atom to the carboxylate stabilizes the vinylzinc intermediate and therefore displaces the equilibrium toward the latter. This explains the high stereoselectivity of the reaction whatever the bulk of the alkyl group is.

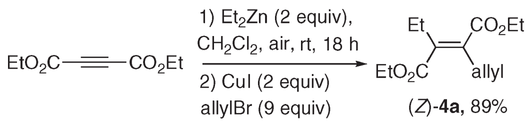
[23] This was supported by treating the reaction with ND_4Cl instead of NH_4Cl. Whatever the conditions (with or without the alkyliodide) the *E*-isomer was deuterated up to 95% whereas the traces of *Z*-isomer remained non deuterated.

[24] Note that in the presence of $(Bu_3)_2Sn_2$ under sunlamp irradiation, the addition of *t*-BuI and *i*-PrI to DMAD led to the formation of fumaric and maleic adducts in 76:24 and 16:84 relative ratios, respectively, see ref 13a.

[25] Attempts to trap the vinylzinc intermediate with reactive aldehydes such as benzaldehyde or methyl glyoxylate failed even after transmetalation with CuI.

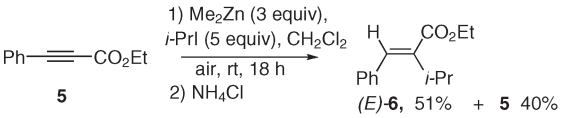
In addition, transmetalation with CuI enabled an indirect *anti*-carbocupration to be achieved at room temperature. Subsequent trapping with allylbromide led to the corresponding diene **4a** in 89% yield (Scheme 4).

Scheme 4



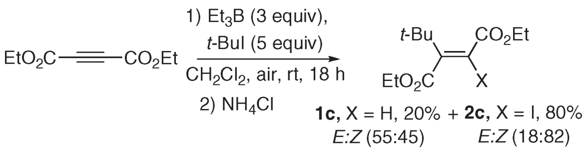
Additional experiments performed on substrate **5** confirmed that the transfer of the alkylzinc group is controlled by coordination (Scheme 5). The alkyl radical adds regioselectively to the triple bond. The resulting vinyl radical stereoselectively transfers the alkylzinc group at the expense of any iodine atom transfer.

Scheme 5



Finally, we decided to perform the reaction in the presence of triethylborane as the initiator. The addition of *t*-butyliodide led to a mixture of **1c** and **2c** in quantitative overall yield (Scheme 6). Compound **1c**, isolated as a 1:1 mixture of isomers, became the minor product of the reaction. In all likelihood, it resulted from hydrogen atom abstraction, possibly from boron derivatives. Contrary to zinc, the boron atom was not transferred to the intermediate vinylic radical.[26] The latter abstracted the iodine atom from *t*-butyliodide leading to vinyl iodide **2c** isolated in 80% yield.[27] Homolytic substitution at zinc by a vinylic radical can thus be claimed as a distinctive property of dialkylzincs that are often compared to alkylboron derivatives as mediators of radical reactions.

Scheme 6



In conclusion, we have shown that direct *anti*carbozincation of diethyl acetylenedicarboxylate can be performed through dialkylzinc-mediated alkyl radical addition. This process led to the highly stereoselective formation of diethylfumarate derivatives in good yields at room temperature. The key step relies on the ability of dialkylzincs to undergo homolytic substitution by vinylic radicals. The high selectivity observed in the transfer of the alkylzinc group is controlled by the coordination of Zn(II) to the ester group. The formation of a vinylzinc intermediate enabled further functionalization. The trapping of the latter with various electrophiles led to the corresponding fumaric derivatives in good yields without any loss in the stereoselectivity.

Acknowledgment. We gratefully acknowledge the ANR (D2R2; ANR-09-JCJC-0081) for financial support.

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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(26) When DMAD was reacted with selenoborane, the authors concluded that the intermediate formed was not a vinylborane but a vinyl radical, see: Kataoka, T.; Yoshimatsu, M.; Shimizu, H.; Hori, M. *Tetrahedron Lett.* **1990**, *31*, 5927–5930.

(27) The *E*/*Z* ratio was more or less the same as the one reported by Curran under standard iodine atom transfer radical addition of *t*-butyl iodide to DMAD, see ref 13a.