New Persistent Heteroarylmethyl Radicals Resulting from the Intramolecular Addition of Aryloxymethyl Radicals onto Ketenimines. Synthesis of 2*H*-1,4-Benzoxazines

Mateo Alajarín,[a] Angel Vidal,*[a] María-Mar Ortín,[a] Delia Bautista[b]

[a] Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Campus de Espinardo, 30100, Murcia, Spain
Fax +34(968)364149; E-mail: vidal@um.es

[b] Servicio Universitario de Instrumentación Científica, Universidad de Murcia, Campus de Espinardo, 30100, Murcia, Spain

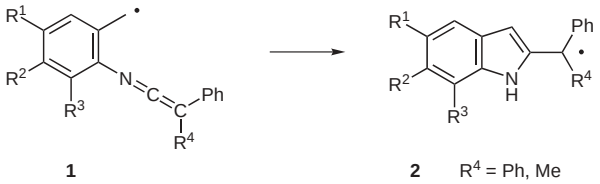
Received 16 February 2004

Abstract: A novel method for producing aryloxymethyl radicals, based on the treatment of (phenylseleno)methyl aryl ethers with tris(trimethylsilyl)silane and AIBN is disclosed, as well as the intramolecular addition of such radicals onto *C,C*-disubstituted ketenimines. The persistent α-(2*H*-1,4-benzoxazin-3-yl)benzyl radicals resulting from such cyclization processes undergo cross-coupling with the 1-cyano-1-methylethyl radical arising from the thermal decomposition of AIBN to give 2*H*-1,4-benzoxazines. These radical cyclizations are controlled by the persistent radical effect. The crystal and molecular structure of benzoxazine **10a** has been solved by X-ray analysis.

Key words: ketenimine, aryloxymethyl radical, cyclization, persistent, 1,4-benzoxazines

Radicals are called persistent if their lifetimes exceed significantly, in liquid solution and under similar conditions, those of some reactive standard radicals.[1] Carbon-centered radicals, when created under an appropriate environment, can be rendered persistent through intramolecular steric protection. Triphenylmethyl radicals, and their substituted derivatives, are the prototype of persistent carbon-centered radicals, in which the arrangement of the three phenyl groups around the trivalent carbon atom sterically slows down or inhibits their radical-radical reactions. The preparation, properties and reactivity of this type of persistent carbon-centered radicals are well known.[2] However, to the best of our knowledge, analogous triarylmethyl radicals in which the radical center is connected directly to an heteroaromatic ring are scarce. In this respect, Mangini and Zarkadis have reported respectively the formation of several thienylmethyl[3] and pyridylmethyl[4] radicals, in which the radical center is connected to three carbon atoms; and Katritzky has described the formation of diaryl(benzotriazol-1-yl)methyl radicals,[5] in which the radical center is connected to the nitrogen atom of the benzotriazolyl substituent and two carbon atoms.

As part of our research work directed towards the study of the chemical behaviour of ketenimines,[6] we have recently reported that the intramolecular addition of benzylic radicals **1** onto the central carbon atom of C,C-disubstituted ketenimine functions leads to persistent (indol-2-yl)(diphenyl)methyl **2** (R^4 = Ph) and (indol-2-yl)(methyl)(phenyl)methyl **2** (R^4 = Me) radicals (Scheme 1).[7] When the benzylic radicals **1** were generated following xanthate based chemistry the resulting (indol-2-yl)methyl radicals **2** underwent reduction or a redox process followed by other transformations of the resulting ions to give 2-substituted indoles.[7a,b] Interestingly, when the benzylic radicals **1** were produced from benzyl phenyl selenides by treatment with tris(trimethylsilyl)silane in the presence of AIBN these radical processes turned out to be controlled by the Persistent Radical Effect (PRE),[8] giving rise to 3-(1*H*-indol-2-yl)propionitriles resulting from the selective cross-coupling of the persistent radicals **2** and the transient 1-cyano-1-methylethyl radical arising from AIBN.[7c]



Scheme 1 (Indol-2-yl)methyl radicals **2**.

In the context of the generation of persistent tertiary carbon radicals bearing a nitrogenated heterocyclic ring at the carbon-center radical, and following the study of new organic processes controlled by the PRE, we present herein the intramolecular cyclization of the aryloxymethyl radicals **3** bearing N-linked ketenimine units at *ortho*-position (Figure 1). This study required the development of a new method for producing aryloxymethyl radicals like **3**, and the cyclizations that follow up the generation of such reactive species represent a novel protocol for the synthesis of 2*H*-1,4-benzoxazines.

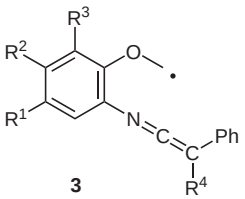


Figure 1 Aryloxymethyl radicals **3**.

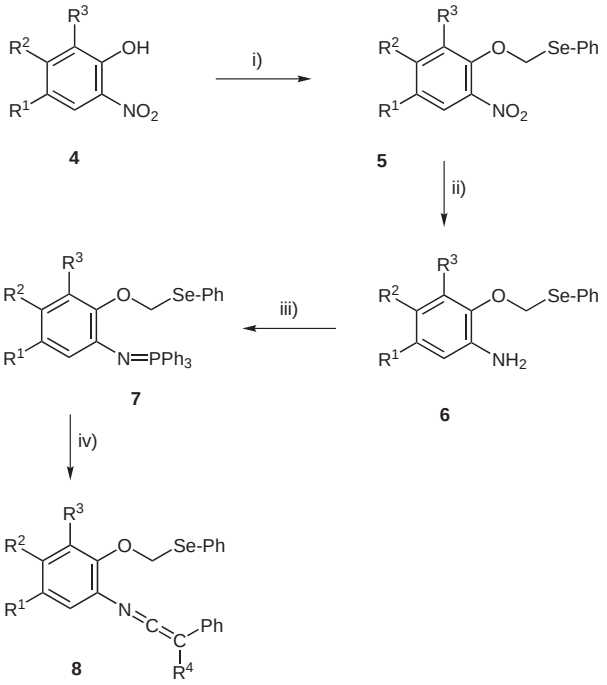
SYNLETT 2004, No. 6, pp 0991–0994
Advanced online publication: 25.03.2004
DOI: 10.1055/s-2004-822883; Art ID: G05004ST

Ketenimines **8** shown in Scheme 3 were specifically designed for generating such aryloxymethyl radicals **3** which could undergo intramolecular cyclization onto the central carbon atom of the ketenimine function. Zard generated iminyl radicals $R^1R^2C=N$ from *O*-(phenylseleno)methyl oximes $R^1R^2C=NOCH_2SePh$ by the action of tributyltin hydride/AIBN, via an intermediate $R^1R^2C=NOCH_2$ oxymethyl radical.[9] Thus, inspired by this conversion, we reasoned that the reaction of (phenylseleno)methyl aryl ethers $ArOCH_2SePh$ with tributyltin hydride/AIBN or tris(trimethylsilyl)silane/AIBN should produce aryloxymethyl radicals. Aryloxymethyl radicals have been already generated for useful purposes in organic synthesis by decarboxylation of thiohydroxamate esters,[10] either through their photolysis in the presence of 2-methylpropane-2-thiol or by treatment with tributyltin hydride/AIBN, as well as by photoinduced electron transfer reactions of α-silyl ethers[11] and α-stannyl ethers,[12] using methanol as solvent. These reported methods for the formation of aryloxymethyl radicals are not compatible with substrates **8** as all of them involve the use of a nucleophilic solvent (methanol) or additive (2-methylpropane-2-thiol) that could add to the ketenimine function.

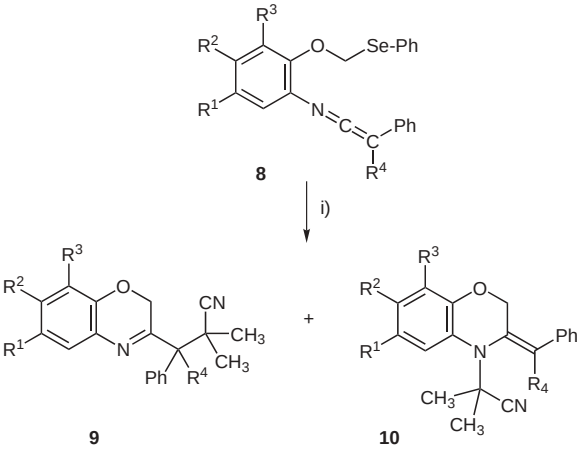
Ketenimines **8** were prepared in good overall yields (25–58%) from commercially available 2-nitrophenols **4** in four steps (Scheme 2). Alkylation of **4** with chloromethyl phenyl selenide[13] yielded the (phenylseleno)methyl aryl ethers **5**. Reduction of the nitro group in compounds **5** by the iron-acetic acid system provided amines **6**. Triphenylphosphazenes **7** were prepared by treating acetonitrile solutions of amines **6** with triphenylphosphane, carbon tetrachloride and triethylamine. Aza-Wittig reaction[14] of the triphenylphosphazenes **7** with methyl phenyl ketene[15] or diphenyl ketene[16] gave ketenimines **8**.

The radical cyclization of the C,C-disubstituted ketenimines **8** was carried out by a three-portion addition of a stoichiometric excess of tris(trimethylsilyl)silane (3 equiv) and AIBN (1.2 equiv) to a 0.015 M solution of the ketenimines in boiling benzene.[17] Pleasingly, under these conditions ketenimines **8** were totally consumed and column chromatography of the final reaction mixtures allowed the isolation of the 2*H*-1,4-benzoxazines **9** and **10**, in moderate to good combined yields (36–82%), see Scheme 3 and Table 1.

The structural characterization of the benzoxazines **9** and **10** relies on their analytical and spectroscopic data.[17] The ^1H NMR and ^{13}C NMR data of compounds **9** clearly show the presence of the propionitrile chain at the C3 position of the benzoxazine ring. The same structural fragment was also present in the 3-(1*H*-indol-2-yl)propionitriles previously prepared by us.[7c] An X-ray structure determination of benzoxazine **10a** ($R^1 = R^2 = R^3 = H$; $R^4 = C_6H_5$) was definitive for unequivocally establishing the structure of compounds **10**.[18] A NOESY spectrum of compound **10g** ($R^1 = Cl$; $R^2 = R^3 = H$; $R^4 = CH_3$) showed crosspeaks between the signals of the methyl group at the exocyclic double bond (R^4) and the two methyl groups of the *tert*-alkyl substituent at the nitrogen atom, thus proving the



Scheme 2 *Reagents and conditions*: (i) $PhSeCH_2Cl$, K_2CO_3, DMF, 80 °C, 24 h; (ii) Fe, EtOH–HOAc, reflux, 3 h; (iii) PPh_3, CCl_4, Et_3N, MeCN, r.t., 12 h; (iv) $Ph(R^4)C=C=O$, CH_2Cl_2, r.t., 30 min.



Scheme 3 *Reagents and conditions*: (i) Tris(trimethylsilyl)silane (3 equiv), AIBN (1.2 equiv), benzene, reflux, 24 h.

E-configuration of the exocyclic double bond in this compound.

A reasonable mechanistic explanation for the conversion **8** → **9** + **10** is given in Scheme 4: the in situ formed $[(CH_3)_3Si]_3Si$ radical should attack the selenium atom of ketenimines **8** to give $PhSeSi[Si(CH_3)_3]_3$ and the expected aryloxymethyl radicals **3**, which undergo cyclization to the tertiary radicals **11a** by intramolecular addition of the radical moiety onto the central carbon atom of the ketenimine function. Then (2*H*-1,4-benzoxazin-3-yl)methyl radicals **11a** undergo radical-radical cross coupling with the 1-cyano-1-methylethyl radical arising from AIBN to afford compounds **9**. The unpaired electron of radicals

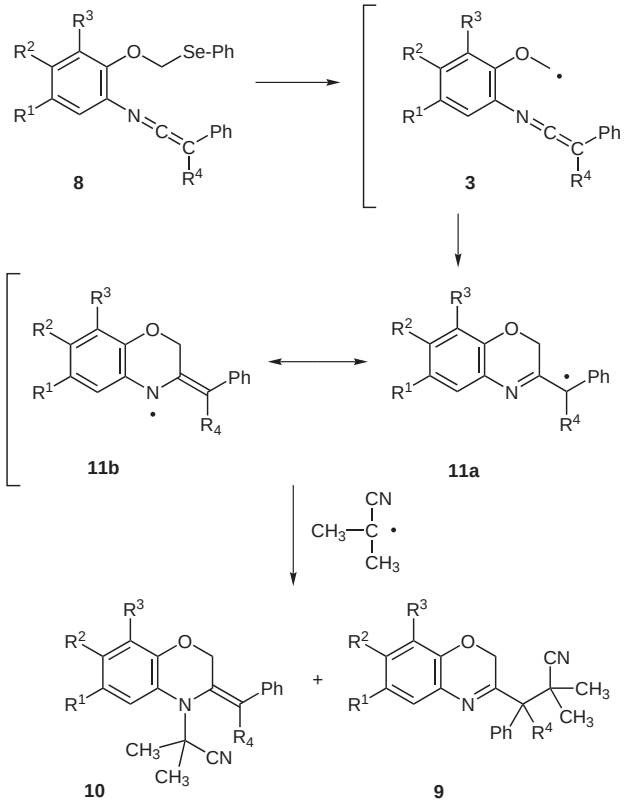
Table 1 2*H*-1,4-Benzoxazines **9** and **10**

Compounds	R^1	R^2	R^3	R^4	**9**/**10**[a]	Yield of **9** and **10** (%)[b]
9a, **10a**	H	H	H	C_6H_5	0.7:1	79
9b, **10b**	CH_3	H	H	C_6H_5	1:1	74
9c, **10c**	CH_3O	H	H	C_6H_5	1:1	36
9d, **10d**	H	C_6H_4		C_6H_5	0.7:1	73
9e, **10e**	H	CH_3	H	C_6H_5	0.7:1	66
9f, **10f**	Cl	H	H	C_6H_5	0.5:1	82
9g, **10g**	Cl	H	H	CH_3	1.8:1	78

[a] Determined in the final reaction mixture by ^{1}H NMR analysis.
[b] Combined yield after the chromatographic purification.

11a can also reside on the nitrogen atom of the 1,4-benzoxazine substituent, as indicated by the canonical form **11b**. The radical-radical coupling of **11b** with the 1-cyano-1-methylethyl radical present in the reaction medium explains the formation of compounds **10**.

To the light of these results, the (2*H*-1,4-benzoxazin-3-yl)methyl radicals **11a** seem to be persistent tertiary methyl radicals, and their canonical forms **11b** could be classified as cyclic persistent nitrogen-centered radicals.[19]



Scheme 4 Proposed mechanism for the conversion **8** → **9** + **10**.

In conclusion, in this report we have described a new method for producing aryloxymethyl radicals, and we have shown how this type of oxymethyl radicals adds intramolecularly onto ketenimines to afford new examples of persistent radicals, which in turn undergo cross-coupling with the 1-cyano-1-methylethyl radical present in the reaction medium to give finally substituted 2*H*-1,4-benzoxazines. The Persistent Radical Effect apparently controls these radical processes.

Acknowledgment

This work was supported by the MCYT and FEDER (Project BQU2001-0010), and Fundación Séneca-CARM (Project PI-1/00749/FS/01). One of us (M.-M. O.) thanks the Fundación Séneca-CARM for a fellowship.

References

(1) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1976**, *9*, 13.
(2) (a) Gomberg, M. *Chem. Rev.* **1925**, *1*, 91. (b) Ballester, M. *Pure Appl. Chem.* **1967**, *15*, 123. (c) Laukamp, H.; Nauta, W. T.; MacLean, C. *Tetrahedron Lett.* **1968**, *9*, 249. (d) Carilla, J.; Fajarí, L.; Juliá, L.; Riera, J.; Viadel, L. *Tetrahedron Lett.* **1994**, *35*, 6529. (e) Neumann, W. P.; Uzick, W.; Zarkadis, A. K. *J. Am. Chem. Soc.* **1986**, *108*, 3762. (f) Neumann, W. P.; Stapel, R. *Chem. Ber.* **1986**, *119*, 2006. (g) Sholle, V. D.; Rozantsev, E. G. *Russ. Chem. Rev.* **1973**, *42*, 1011. (h) McBride, J. M. *Tetrahedron* **1974**, *30*, 2009.
(3) (a) Mangini, A.; Pedulli, G. F.; Tiecco, M. *Tetrahedron Lett.* **1968**, *9*, 4941. (b) Mangini, A.; Pedulli, G. F.; Tiecco, M. *J. Heterocycl. Chem.* **1969**, *6*, 271.
(4) Tzerpos, N. I.; Zarkadis, A. K.; Kreher, R. P.; Repas, L.; Lehnig, M. *J. Chem. Soc., Perkin Trans. 2* **1995**, 755.
(5) Katritzky, A.; Yang, B.; Dalal, N. S. *J. Org. Chem.* **1998**, *63*, 1467.
(6) Alajarín, M.; Vidal, A.; Tovar, F. *Targets Heterocycl. Syst.* **2000**, *4*, 293; and references cited therein.
(7) (a) Alajarín, M.; Vidal, A.; Ortín, M.-M. *Tetrahedron Lett.* **2003**, *44*, 3027. (b) Alajarín, M.; Vidal, A.; Ortín, M.-M. *Org. Biomol. Chem.* **2003**, *1*, 4282. (c) Alajarín, M.; Vidal, A.; Ortín, M.-M.; Bautista, D. *New J. Chem.* in press.

(8) For a seminal paper in which the PRE was recognized see: (a) Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925. (b) For the naming of the principle of PRE see: Daikh, B. E.; Finke, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 2938. (c) For an excellent review on the PRE see: Fischer, H. *Chem. Rev.* **2001**, *101*, 3581. (d) For examples of PRE in organic synthesis see: Studer, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 1108. (e) Wetter, C.; Jantos, K.; Woithe, K.; Studer, A. *Org. Lett.* **2003**, *5*, 2899. (f) Studer, A. *Chem.–Eur. J.* **2001**, *7*, 1159. (g) Leroi, C.; Fenet, B.; Couturier, J.-L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 1079. (h) Allen, A. D.; Fenwick, M. F.; Henry-Riyad, H.; Tidwell, T. T. *J. Org. Chem.* **2001**, *66*, 5759. (i) Wetter, C.; Studer, A. *Chem. Commun.* **2004**, 174.

(9) Boivin, J.; Fouquet, E.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1769.

(10) (a) Walkington, A. J.; Whiting, D. A. *Tetrahedron Lett.* **1989**, *30*, 4731. (b) Ahmad-Junan, S. A.; Walkington, A. J.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2313.

(11) Gutenberger, G.; Steckhan, E.; Blechert, S. *Angew. Chem. Int. Ed.* **1998**, *37*, 660.

(12) Mikami, T.; Harada, M.; Narasaka, K. *Chem. Lett.* **1999**, 425.

(13) Comasseto, J. V.; Ferreira, J. T. B.; Brandt, C. A.; Petragnani, N. *J. Chem. Res., Synop.* **1982**, 212.

(14) For examples of aza-Wittig reactions between phosphazenes and ketenes see: (a) ref.[7] (b) Alajarín, M.; Vidal, A.; Tovar, F.; Ramírez de Arellano, M. C.; Cossío, F. P.; Arrieta, A.; Lecea, B. *J. Org. Chem.* **2000**, *65*, 3633. (c) Alajarín, M.; Vidal, A.; Ortín, M.-M. *Synthesis* **2002**, 2393; and references cited therein.

(15) Pracejus, H.; Wallura, G. *J. Prakt. Chem.* **1962**, *19*, 33.

(16) Taylor, E. C.; McKillop, A.; Hawks, G. H. *Org. Synth.* **1973**, *52*, 36.

(17) **Typical Procedure**: A solution of the corresponding ketenimine **8** (1.5 mmol) in anhyd benzene (100 mL) was heated under nitrogen at reflux temperature and tris(trimethylsilyl)silane (0.56 g, 2.25 mmol) and AIBN (0.098 g, 0.6 mmol) were added. Further additions of tris(trimethylsilyl)silane and AIBN were made as follows: 1) after 4 h since the first addition, tris(trimethylsilyl)silane (0.19 g, 0.75 mmol) and AIBN (0.098 g, 0.6 mmol) and 2) 4 h later, tris(trimethylsilyl)silane (0.37 g, 1.5 mmol) and AIBN (0.098 g, 0.6 mmol). After 16 h since the last addition the solvent was removed under reduced pressure and the crude material was chromatographed on a silica gel column, using hexanes/EtOAc (9:1) as eluent.
1,4-Benzoxazine 9f: R_f = 0.48; yield 27%; colorless prisms (Et_2O); mp 177–178 °C. IR (nujol): 2234, 1625, 1258, 1220, 1164, 1117, 1074, 1044, 964, 889, 827, 741, 707 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 3 H), 1.50 (s, 3 H), 3.39 (d, 1 H, *J* = 13.5 Hz), 4.28 (d, 1 H, *J* = 13.5 Hz), 6.79 (d, 1 H, *J* = 8.7 Hz), 7.11 (dd, 1 H, *J* = 8.7, 2.7 Hz), 7.41 (very broad s, 8 H), 7.61 (d, 1 H, *J* = 2.7 Hz), 7.91 (broad s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3, 27.6, 37.3 (s), 63.6, 64.2 (s), 116.7, 127.2 (s), 127.4, 127.7 (s), 128.3, 128.5, 128.6, 128.9, 130.0, 131.1, 133.9 (s), 136.4 (s), 137.0 (s), 145.2 (s), 164.9 (s). MS: *m/z* (relative intensity) = 402 (3) [M^+ + 2], 400 (8) [M^+], 332 (100). Anal. Calcd for $C_{25}H_{21}ClN_2O$: C, 74.90; H, 5.28; N, 6.99. Found: C, 74.77; H, 5.21; N, 7.11.
1,4-Benzoxazine 10f: R_f = 0.36; yield 55%; colorless prisms (Et_2O); mp 143–144 °C. IR (nujol): 2233, 1624, 1600, 1579, 1494, 1299, 1261, 1236, 1198, 1128, 971, 870, 819, 763, 709, 668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3 H), 1.51 (s, 3 H), 4.77 (d, 1 H, *J* = 11.7 Hz), 4.92 (d, 1 H, *J* = 11.7 Hz), 6.82 (d, 1 H, *J* = 8.7 Hz), 6.99 (dd, 1 H, *J* = 8.7, 2.4 Hz), 7.08–7.11 (m, 2 H), 7.15 (d, 1 H, *J* = 2.4 Hz), 7.16–7.19 (m, 2 H), 7.28–7.35 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8, 28.9, 56.8 (s), 65.2, 118.3, 121.8 (s), 123.4, 124.7, 125.1 (s), 128.1, 128.2, 128.4, 128.5, 129.8, 130.6, 132.4 (s), 139.5 (s), 140.2 (s), 142.8 (s), 147.5 (s). MS: *m/z* (relative intensity) = 402 (2) [M^+ + 2], 400 (5) [M^+], 332 (100). Anal. Calcd for $C_{25}H_{21}ClN_2O$: C, 74.90; H, 5.28; N, 6.99. Found: C, 74.76; H, 5.18; N, 7.08.

(18) Crystallographic data for the structure **10a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 229317. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

(19) For articles dealing with persistent nitrogen-centered radicals see: (a) Nakatsuji, M.; Miura, Y.; Teki, Y. *J. Chem. Soc., Perkin Trans. 2* **2001**, 738. (b) Miura, Y.; Momoki, M.; Fuchikami, T.; Teki, Y.; Itoh, K.; Mizutani, H. *J. Org. Chem.* **1996**, *61*, 4300. (c) Roberts, J. R.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 3228. (d) Griller, D.; Mendenhall, G. D.; van Hoof, W.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 6068.