J|A|C|S COMMUNICATIONS

Published on Web 08/20/2009

# Reductive and Brominative Termination of Alkenol Cyclization in Aerobic Cobalt-Catalyzed Reactions

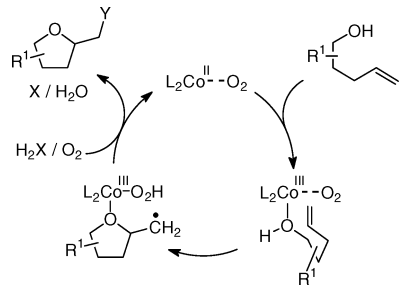
Dominik Schuch, Patrick Fries, Maike Dönges, Bárbara Menéndez Pérez, and Jens Hartung*

*Fachbereich Chemie, Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Strasse, D-67663 Kaiserslautern, Germany*

Received June 9, 2009; E-mail: hartung@chemie.uni-kl.de

Aerobic oxidations of substituted pent-4-en-1-ols (bishomoallylic alcohols) occur with notable rates and diastereoselectivity, if catalyzed with appropriate cobalt(II) chelates.[1,2] The ring closure furnishes substituted tetrahydrofuryl-2-methanols (Scheme 1, Y = OH), which constitute valuable building blocks for natural product synthesis.[3,4] In an attempt to oxidize (*E*)- and (*Z*)-configured substrates under such conditions, however, a loss of stereochemical information associated with the olefinic $\pi$-bond was observed. This finding was explained with the appearance of configurationaly labile reactive intermediates.[5] In the present report we provide evidence that these intermediates are free carbon radicals that can be converted with a variety of reagents into synthetically useful functional groups. Since oxidative catalytic methods in carbon radical chemistry so far were restricted to hydrocarbon oxyfunctionalization,[6] it was our aim in the present study to develop methods for reductive, brominative, and alkylative termination of aerobic cobalt catalyzed alkenol cyclizations.[7]

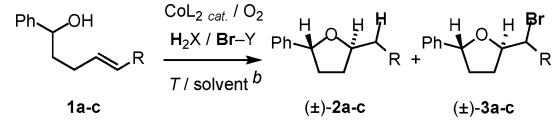
***Scheme 1.*** Proposed Catalytic Cycle for Aerobic Alkenol Oxidation[a]




[a] ($H_2X$ = coreductant, $R^1$ = e.g. alkyl or aryl; Y = OH, H; for Y = Br, and alkyl and for $CoL_2$, see text).

Reductive ring closures of chosen reporter substrates, i.e. 1-phenylpent-4-en-1-ols **1a**−**c**, required heating (60−75 °C) in solutions of cyclohexa-1,4-diene (CHD, 20 equiv) containing 1−4 mol % of {4-[3,5-bis(trifluoromethyl)-phenyl]-4-oxybut-3-en-2-one}-cobalt(II) ($CoL_2$). The reactions were run in an open flask that was connected to a reflux condenser, to allow extensive contact with air. This setup gave 2,5-*trans*-substituted tetrahydrofurans **2a**−**c** (94 ≤ de <99%) in 80−88% yields (Table 1, entries 1, 5, and 8). No substrate turnover occurred in the absence of $O_2$, CHD, and $CoL_2$ or by substituting cobalt(II) acetate or donor-substituted cobalt(II)-diketonate complexes for $CoL_2$. Tetrahydrofuryl-2-methanols (Scheme 1, Y = OH) were not formed in these runs as evident from GC analysis in combination with a highly sensitive color test, i.e. the absence of bluish staining with Ekkert's reagent of developed $SiO_2$-coated tlc sheets at $R_f$ = 0.13 [petroleum ether/acetone, 5:1 (v/v)]. Formation of suspected alcohols became evident as CHD concentrations fell below ~3 M. Replacement of CHD with its naturally occurring derivative $\gamma$-terpinene (isopropyl-4-methylcyclohexa-1,4-diene) was effective without a change in selectivity (Table 1, entries 2, 6, and 9). Such reactions provided isopropyl-4-methylbenzene and $H_2O$ as secondary products. This finding pointed to an active role of applied dihydroarenes in H-atom transfer reactions, for instance, Co(III)/Co(II) reduction for maintaining the catalytic cycle, or completion of $O_2$ conversion into $H_2O$. The stoichiometry of this redox chemistry is under current investigation.

***Table 1.*** Reagent Guided Selectivity in Cobalt-Catalyzed Alkenol Cyclizations[a]




**1a-c** (±)-**2a-c** (±)-**3a-c**

**a**: R = H; **b**: R = Me; **c**: R = $CO_2$Me

| entry | **1**−**3** | $CoL_2$[c]/ mol % | $H_2X$[d]/ equiv | **Br**−Y/ equiv | *T*/ °C | (±)-**2**[e]/ % | (±)-**3**[e]/ % |
|---|---|---|---|---|---|---|---|
| 1 | **a** | 1 | CHD/20 | − | 60 | 85 | − |
| 2 | **a** | 1.5 | $\gamma$-Ter/12 | − | 80 | 82 | − |
| 3 | **a** | 4 × 5 | CHD/30 | $BrCCl_3$/10 | 60 | −[g] | 85 |
| 4 | **a** | 2 × 5 | CHD/30 | DBM[f]/6 | 60 | 4 | 82 |
| 5 | **b** | 2 × 2 | CHD/20 | − | 75 | 80 | − |
| 6 | **b** | 2 × 2 | $\gamma$-Ter/12 | − | 80 | 70 | − |
| 7 | **b** | 4 × 10 | CHD/30 | $BrCCl_3$/10 | 75 | −[g] | 87[h] |
| 8 | **c** | 2 + 1 | CHD/20 | − | 75 | 88 | − |
| 9 | **c** | 3 + 2 | $\gamma$-Ter/12 | − | 80 | 81 | − |
| 10 | **c** | 3 × 10 | CHD/30 | $BrCCl_3$/10 | 75 | 76 | 13[h] |

[a] Quantitative conversion of **1a**−**c** (tlc). [b] Toluene for brominations; no additional solvent for reductions. [c] Portions of $CoL_2$ were added in 3 h intervals. [d] CHD = cyclohexa-1,4-diene, $\gamma$-Ter = $\gamma$-terpinene (isopropyl-4-methylcyclohexa-1,4-diene). [e] *cis*/*trans* < 1/99 for **2a**−**b**, **3a**−**c**, *cis*/*trans* = 3/97 for **2c** (GC). [f] DBM = diethyl dibromomalonate. [g] Not detected (GC−MS and $^1$H NMR). [h] Two isomers isolated (additional stereogenic center in side chain); dr = 65:35 for **3b** and 54:46 for **3c** (determined by GC).

A change in selectivity from reductive termination to bromocyclization was attainable upon addition of $BrCCl_3$ or diethyl dibromomalonate (DBM) to standard reaction mixtures (Table 1, entries 3, 4, 7).[8,9] Toluene was added as cosolvent for improving selectivity of the system. Diastereoselectivities of brominated heterocycles **3a**−**b** corresponded to values reported for tetrahydrofurans **2a**−**b** in the absence of $BrCCl_3$. Acceptor-substituted alkenol **1c** was the only substrate that resisted effective bromocyclization under such conditions (Table 1, entry 10), possibly for reasons suggested in the mechanistic discussion below. The rates of bromocyclizations were smaller than those of the reductions (i.e., formation of **2**) and required larger amounts of $CoL_2$.

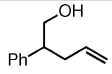
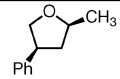
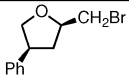
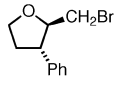
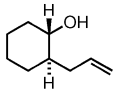
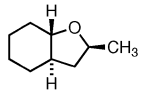
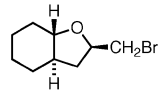
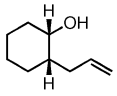
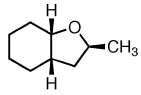
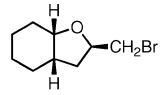
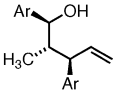
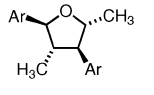
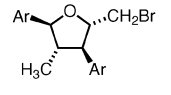
To further explore the scope of the cobalt-method, additional mono-, di-, and trisubstituted alkenols **1d**−**h** were transformed with $O_2$/$CoL_2$ in CHD into products of reductive ring closure (formation



10.1021/ja904577c CCC: $40.75 

of **2d**−**h**). Conversion of the given substrates using $O_2$/$CoL_2$ as oxidant in solutions of CHD, toluene, *and* $BrCCl_3$ consistently provided bromocyclized compounds **3d**−**h**. Derived tetrahydrofur-2-ylmethanols were not detected in any of these runs. Observed *cis*/*trans* ratios of products **2d**−**h**/**3d**−**h** (Table 2) agreed with stereoselectivity reported for oxidative cyclizations of the reactants in *i*PrOH in the same temperature range. The latter solvent is particularly useful for tetrahydrofurylmethanol synthesis from pent-4-en-1-ols in aerobic cobalt-catalyzed oxidations.[2]

***Table 2.*** Products of Reductive and Brominative Alkenol Cyclization in Aerobic Cobalt-Catalyzed Reactions (See the Supporting Information)

| alkenol | reductive conditions[a] | brominative conditions[b] |
|---|---|---|
|  (±)-**1d** |  (±)-**2d** (79 % / 75:25) |  (±)-**3d**(89 % / 73:27) |
|  (±)-**1e** |  (±)-**2e** (84 % / 2:98) |  (±)-**3e** (84 % / <1:99) |
|  (±)-**1f** |  (±)-**2f** (78 % / 12:88) |  (±)-**3f** (85 % / 9:91) |
|  (±)-**1g** |  (±)-**2g** (83 % / <1:99) |  (±)-**3g** (96 % / <1:99) |
|  (±)-**1h** |  (±)-**2h** (84 % / <1:99) |  (±)-**3h** (22 % / <1:99) [c] |

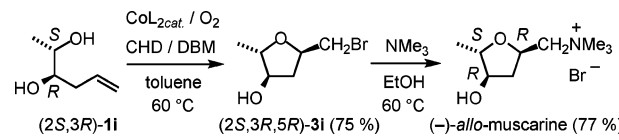
[a] 1−5 mol % $CoL_2$, 60−75 °C, 7−24 h, 20 equiv of CHD. [b] 15−40 mol % $CoL_2$, 60−75 °C, 8−22 h, 30 equiv of CHD, 10 equiv of $BrCCl_3$. [c] Additional product: ∼36% of (2,4,5-trimethoxyphenyl)prop-1-ene. Numbers in parentheses refer to yields and *cis*/*trans* ratios.

Reductive cyclization of diastereomerically pure (1*S**,2*S**,3*R**)-1,3-bis[2,4,5-(trimethoxy)phenyl]-2-methylpent-4-en-1-ol (±)-**1h**[10] provided target compound (±)-**2h**, i.e. the 5-epimer of naturally occurring antiallergic lignane magnosalicine, in 84% yield.[11] The origin of a surprisingly low yield of 22% of bromocyclization product (±)-**3h**, in combination with an unsatisfactory mass balance, even by taking formation of 36% of (2,4,5-trimethoxy)-phenylprop-1-ene into account, certainly requires future attention.

The outstanding 2,5-*trans* diastereoselectivity of cobalt-catalyzed bromocyclizations was applied in a concise synthesis of enantiomerically pure (−)-*allo*-muscarine,[12,13] one of the physiologically active constituents of the fly agaric *Amanita muscaria*[14] (Scheme 2). For practical reasons, bromocyclization of (2*S*,3*R*)-hex-5-en-2,3-diol, (2*S*,3*R*)-(**1i**), was conducted in the presence of DBM as a trapping reagent. This variation improved the yield from 65% ($BrCCl_3$) to 75%. It furthermore prevented consumption of substrate (2*S*,3*R*)-**1i** by side reactions, such as $BrCCl_3$ addition across the olefinic double bond, and thus allowed more convenient purification of product (2*S*,3*R*,5*R*)-**3i** from the reaction mixture.

If compared to other electrophile-induced ring closures, it is worth noting that polar bromocyclizations of substrate (2*S*,3*R*)-**1i** (nucleophilic oxygen), e.g., with $Br_2$, affords a 40/60 mixture (20 °C) of (2*S*,3*R*,5*R*)-**3i** versus the undesired (2*S*,3*R*,5*S*)-isomer.[15] The (2*R*,3*S*)-3-hydroxy-hex-5-en-2-oxyl radical in turn (electrophilic

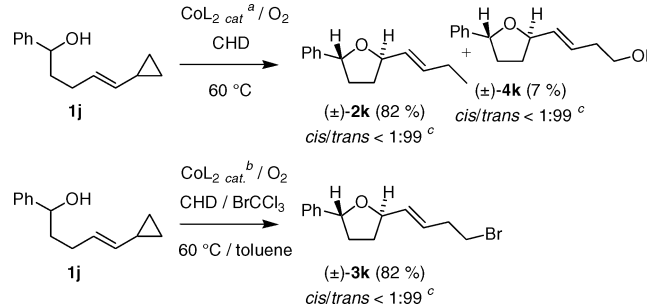
***Scheme 2.*** Synthesis of (−)-*allo*-Muscarine




oxygen, not shown) requires an adequate hydroxyl protecting group[13] to undergo 5-*exo*-trig cyclization and not a very effective $\beta$-fragmentation. No 3-hydroxyl-protecting group was necessary in the case of the cobalt-catalyzed bromocyclization.

The chemical nature of the reactive intermediate relevant for explaining selectivity in the terminating step was scrutinized in aerobic cobalt-catalyzed oxidations of cyclopropyl-substituted phenylpentenol **1j**. If conducted in CHD, the reaction furnished exclusively butenyl-substituted, diastereomerically pure tetrahydrofurans **2k** and **4k** but no cyclopropyl-substituted derivatives ($^1$H NMR and GC-MS; Scheme 3). Formation of alcohol (±)-**4k** under such conditions was unexpected in view of the observations summarized above (Tables 1−2). This product was not found in reaction mixtures obtained from aerobic oxidations of **1j** in the presence of $BrCCl_3$ (Scheme 3).

***Scheme 3.*** Formation of Butenyl-Substituted Tetrahydrofurans



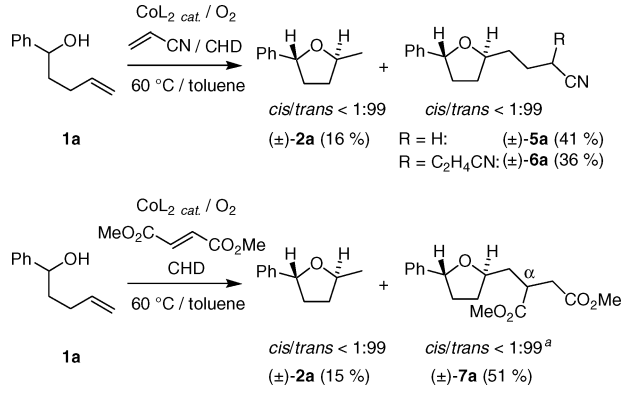

[a] 10 mol % of $CoL_2$ [b] 4 × 5 mol % of $CoL_2$. [c] GC and $^1$H NMR.

The third objective, i.e., alkylative trapping of cyclized alkenols, was feasible starting from substrate **1a** in solutions of toluene (60 °C) that contained a 3−5 M concentration of CHD and 2−4 M levels of preferentially an electron-deficient alkene. The use of acrylonitrile provided 41% of 1,1-adduct (±)-**5a**, 36% of 1,2-addition product (±)-**6a**, and 16% of reduction product **2a** (Scheme 4 and Supporting Information). Equimolar $BrCCl_3$/acrylonitrile mixtures afforded under otherwise identical conditions exclusively bromocyclization product **3a** (GC−MS; not shown). The use of dimethyl fumarate and CHD gave 51% of 1,1-adduct (±)-**7a** and 15% of *trans*-5-methyl-2-phenyltetrahydrofuran **2a** (Scheme 4). Formation of 1,2-addition products from alkenol **1a** and dimethyl fumarate was not observed.

From a mechanistic point of view, the results collected in the current study provide strong evidence for an alkenol conversion that occurs in two consecutive steps. The combination of $CoL_2$/$O_2$ thereby is assumed to serve as a one-electron oxidant for transformation of the olefin into a radical cation and subsequently into an intermediate that is for the following reasons proposed to be a free carbon radical (see also Scheme 1).[2,16]

(i) Formation of $\omega$-bromobutenyl-substituted tetrahydrofuran (±)-**3k** from $\omega$-cyclopropylphenylpentenol **1j** requires an efficient ring-opening process. Although it is not possible from the existing data to distinguish whether the cycloaliphatic ring fragments prior or after tetrahydrofuran formation, this type of reactivity restricts the set of possible intermediates to radicals, radical cations, or carbenium ions.[17]

***Scheme 4.*** Alkylative Termination of Aerobic Cobalt-Catalyzed Alkenol Ring Closure




[a] 50/50 mixture of diastereomers at $C^{\alpha}$.

(ii) 1,4-Dihydroarenes, $BrCCl_3$, and DBM are efficient radical trapping reagents[18] but typically do not react with cations.[19,20]

(iii) The notable driving force for addition to electron-deficient olefins revealed the nucleophilic behavior of cyclized intermediates. Primary, secondary, and tertiary carbon radicals are nucleophilic intermediates.[21]

Although the systematics of carbon−carbon bond formation in the aerobic cobalt catalyzed alkenol oxidation merit future attention, the observed selectivities can be rationalized on the basis of rate constants of free radical elementary reactions that typically proceed under kinetic control.[21] Addition of primary carbon radicals to acrylonitrile, for example, occurs with a rate constant of $\sim 4 \times 10^5$ $M^{-1}$ $s^{-2}$ (20 °C).[22] The rate constant for H-atom abstraction from CHD by $\bullet C_2H_5$ is $6 \times 10^4$ $M^{-1}$ $s^{-2}$ (27 °C).[23] A rate constant of $\sim 2 \times 10^8$ $M^{-1}$ $s^{-2}$ (26 °C) was determined for Br-atom transfer from $BrCCl_3$ onto primary and secondary carbon radicals using the radical clock technique.[24] By considering given reactant concentrations and product distributions obtained from such mixtures, selectivity associated with the conversion of **1a** is explicable, if the rate constant of alkylative trapping of the cyclized intermediates were 1 order of magnitude higher than that of its reaction with the reductant, i.e., CHD. The rate constant for bromination of the cyclized intermediate with $BrCCl_3$ must exceed that of the addition to acrylonitrile by at least 2 orders of magnitude. This argumentation almost perfectly matches the information obtained from the experimental data.

The proposed mechanistic scheme furthermore allows us to explain the unsatisfactory yield of acceptor-substituted bromocyclization product **3c** (Table 1, entry 10). Br-atom trapping of cyclized intermediates requires homolytic displacement of $\bullet CCl_3$ from $BrCCl_3$ by carbon radicals.[25,26] A Hammett correlation suggests that partial negative charge develops at $CCl_3$ in the transition state as the Br-atom is transferred from $BrCCl_3$ onto a positively polarized carbon radical center. The radical that is left in the course of cyclization of **1c** is expected for reasons of electron-withdrawing capabilities of the $CO_2Me$-substituent to react notably slower with $BrCCl_3$, due to a marked lowering of its SOMO energy and thus reduced ability to serve as an electron donor according to the polar transition state model. For reasons of almost equivalent group electronegativities of intermediates associated with homolytic displacement at CHD, polar effects are expected to be less relevant for explaining relative transition state energies of intermediates associated with carbon radical reductions.

The chemistry associated with the final step of cobalt-catalyzed aerobic alkenol oxidation, in conclusion, is uncontradictively explicable with the existence of free carbon radicals. If combinations of XH-acidic nucleophiles (X = e.g. O, N) and olefins other than those described in the present report were able to provide free carbon radicals, the new methodology would have the potential to supplement existing well-established tin or silicon hydride based methods for conducting carbon radical chemistry under reductive conditions, however, on the basis of a catalytic reaction.[27]

**Acknowledgment.** Financial support was provided by the Fonds der Chemischen Industrie, the state of Rheinland-Pfalz/NanoKat (scholarships for D.S.), and the DAAD (scholarship for B.M.). This paper is dedicated to Prof. Dr. Bernd Giese on the occasion of his 69th birthday.

**Supporting Information Available:** Experimental procedures, spectral and analytical data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Inoki, S.; Mukaiyama, T. *Chem. Lett.* **1990**, 67–70.
(2) Menéndez Pérez, B.; Schuch, D.; Hartung, J. *Org. Biomol. Chem.* **2008**, *6*, 3532–3541.
(3) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Tetrahedron: Asymmetry* **1999**, *10*, 667–670.
(4) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Eur. J. Org. Chem.* **2000**, 349–356.
(5) Menéndez Pérez, B.; Hartung, J. *Tetrahedron Lett.* **2009**, *50*, 960–962.
(6) Ishii, Y.; Sakaguchi, S. In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, 2004; pp 119−163.
(7) For selected reviews on stereoselective tetrahydrofuran synthesis, see: (a) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261–290. (b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321–3408.
(8) For related applications of $BrCCl_3$ in carbon radical bromination, see: Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901–3924.
(9) For use of alternative malonic acid derivatives in free radical halogenation, see: Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826–3924.
(10) Muraoka, O.; Sawada, T.; Morimoto, E.; Tanabe, G. *Chem. Pharm. Bull.* **1993**, *39*, 772–774.
(11) Tsuruga, T.; Ebizuka, Y.; Nakijima, J.; Chun, Y.-T.; Noguchi, H.; Iitaka, Y.; Sankawa, U. *Tetrahedron Lett.* **1984**, *25*, 4129–4132.
(12) Pochet, S.; Huynh-Dinh, T. *J. Org. Chem.* **1982**, *47*, 193–198.
(13) Hartung, J.; Kneuer, R. *Tetrahedron:Asymmetry* **2003**, *14*, 3019–3031.
(14) Schleusener, E.; Eugster, C. *Helv. Chim. Acta* **1970**, *53*, 130–131.
(15) Hartung, J.; Kunz, P.; Laug, S.; Schmidt, P. *Synlett* **2003**, 51–54.
(16) Tang, R. T.; Kochi, J. K. *J. Inorg. Nucl. Chem.* **1973**, *35*, 3845–3856.
(17) Newcomb, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 317−336.
(18) $C_{sp^3}$,H-BDE in CHD, 318 ± 5 kJ $mol^{-1}$: Tsang, W. *J. Phys. Chem.* **1986**, *90*, 1152–1155. C,Br-BDE in $BrCCl_3$, 231 ± 4 kJ $mol^{-1}$: Mendenhall, G. D.; Golden, D. M.; Benson, S. W. *J. Phys. Chem.* **1973**, *77*, 2707–2709.
(19) Walton, J. C.; Portela-Cubillo, F. In *Handbook of Reagents for Organic Synthesis - Reagents for Radical and Radical Ion Chemistry*; Crich., D., Ed.; Wiley: Chichester, 2008; pp 202−204.
(20) Shinokuba, H.; Oshima, K. In *Handbook of Reagents for Organic Synthesis - Reagents for Radical and Radical Ion Chemistry*; Crich., D., Ed.; Wiley: Chichester, 2008; pp 89−92.
(21) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753–764.
(22) Giese, B.; Kretzschmar, G. *Chem. Ber.* **1984**, *117*, 3160–3164.
(23) Hawari, J. A.; Engel, P. S.; Griller, D. *Int. J. Chem. Kinet.* **1985**, *17*, 1215–1219.
(24) Hartung, J.; Hertel, B.; Trach, F. *Chem. Ber.* **1993**, *126*, 1187–1191.
(25) Tanner, D. D.; Arhart, R. J.; Blackburn, E. V.; Das, N. C.; Wada, N. *J. Am. Chem. Soc.* **1974**, *96*, 829–834.
(26) Herwig, K.; Lorenz, P.; Rüchardt, C. *Chem. Ber.* **1975**, *108*, 1421–1436.
(27) Chatgilialoglou, C. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Ed.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 28−49.

JA904577C