ORGANIC LETTERS

2007
Vol. 9, No. 14
2677−2680

Formation of Benzo-Fused Carbocycles by Formal Radical Cyclization onto an Aromatic Ring

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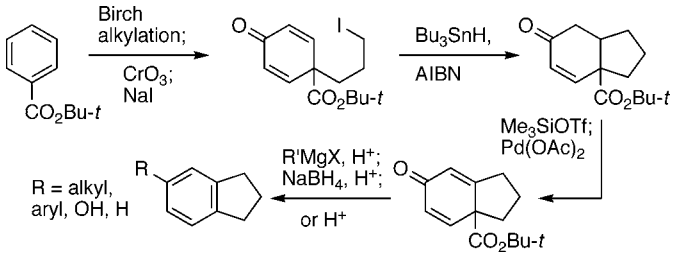
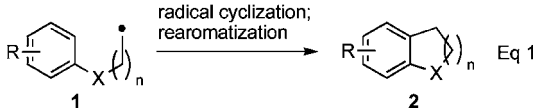
Received April 11, 2007

ABSTRACT



An indirect method for effecting radical carbocyclization onto aromatic rings is described. Cross-conjugated dienones such as 13, readily prepared by Birch reduction of aromatic *tert*-butyl esters, in situ alkylation, and oxidation (10 → 11 → 12 → 13), undergo radical cyclization; the products (14) are aromatized by silylation, Saegusa oxidation, and treatment with $BiCl_3 \cdot H_2O$. A noteworthy feature of this route is that it provides opportunities to attach an additional substituent to the original aromatic ring.

In contrast to alkyl radical cyclization onto double (and triple) bonds, related closures onto aromatic rings represent a largely undeveloped, but potentially important, area. Alkyl radical cyclization onto certain heteroaromatics is reasonably well-known,[1] but the corresponding closure onto a benzene ring (eq 1) is usually a difficult process, and its mechanism is



not fully understood.[2,3] Transformations of the type **1** → **2** can often be achieved by using xanthates as the radical precursor;[4−6] however, these powerful xanthate-based methods usually require stoichiometric amounts of peroxide as the initiator, and the reactions are sometimes done at high temperatures (refluxing chloro- or 1,2-dichlorobenzene). For situations where such conditions have to be avoided, the

(1) Typical examples of alkyl radical cyclization onto heteroaromatic rings: (a) Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47*, 4077−4088. (b) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639−2643. (c) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111−8128. (d) Marco-Contelles, J.; Rodríguez-Fernández, M. *Tetrahedron Lett.* **2000**, *41*, 381−384. (e) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 10181−10184. (f) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747−2762. (g) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2002**, *43*, 4191−4193. (h) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345−4348.

(2) (a) Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765−2770. (b) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Story, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95−98.

(3) Leading references to cyclization of aryl radicals onto aromatic rings: Clyne, M. A.; Aldaggagh, F. *Org. Biomol. Chem.* **2006**, *4*, 268−277.

(4) (a) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 1719−1722. (b) Liard, A.; Quiclet-Sire, B.; Saicic, R.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759−1762. (c) Cholleton, N.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 7295−7298. (d) Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2125−2126. (e) Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533−2536. (f) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731−733. (g) Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **2002**, 1692−1693. (h) Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **2002**, 2306−2307.

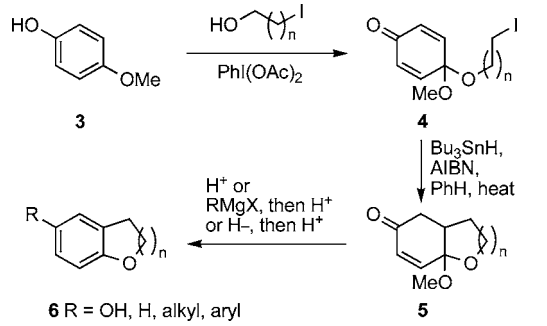
(5) For cyclizations of β-dicarbonyl compounds: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339−363.

(6) For methods that do not involve xanthates: (a) Ishibashi, H.; Nakamura, N.; Ito, K.; Kitayama, S.; Ikeda, M. *Heterocycles* **1990**, *31*, 1781−1784. (b) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377−1393. (c) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977−978.

10.1021/ol070849l CCC: $37.00
Published on Web 06/09/2007

development of a process that operates under the standard mild conditions for radical cyclization (Bu_3SnH, catalytic AIBN, refluxing PhH) would undoubtedly be useful. Recent publications[7,8] from this laboratory have described an indirect method for effecting such reactions, where the ring being formed contains oxygen[7] or nitrogen[8] (eq 1, X = O or NCOOPh). A key step in the approach for oxygen-containing heterocycles (Scheme 1) is oxidative conversion of the

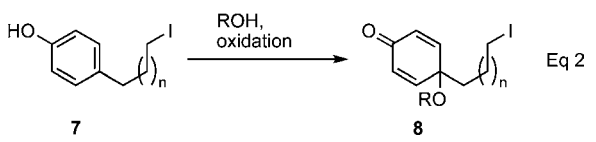
Scheme 1. Formal Cyclization onto an Aromatic Ring



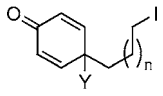
benzenoid substrate into a cross-conjugated ketone (**3** → **4**); this undergoes radical cyclization (**4** → **5**), and then acid-catalyzed rearomatization (**5** → **6**) generates the product of formal closure onto the benzene ring (cf. eq 1). The corresponding process for benzo-fused nitrogen heterocycles[8] is similar, except that a different method is used to prepare the key cross-conjugated ketone.

A useful feature of the route is that after the radical cyclization an additional substituent can be introduced (cf. **5** → **6**, R = alkyl or aryl). We have now modified our approach so that it can be applied to the case of benzo-fused carbocycles (cf. eq 1, X = carbon).

Although direct extension of Scheme 1, along the lines summarized in eq 2, would seem an obvious first step,[9] it is

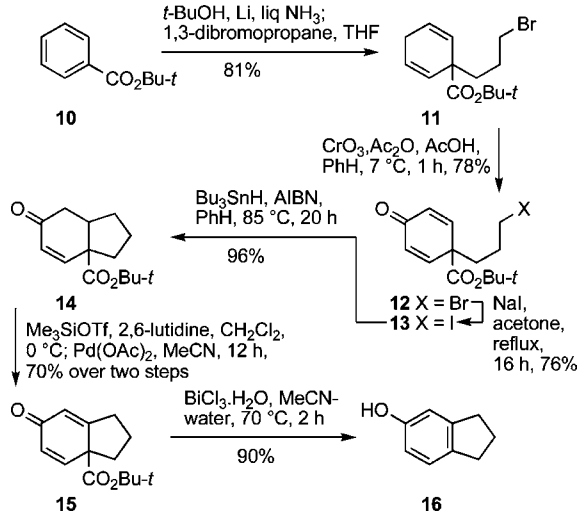


known that oxidation of *para*-alkyl phenols rarely affords good yields,[10,11] and in test experiments of our own, with several appropriately substituted *para*-alkyl phenols, we found that yields are poor (<50%) for MeOH,[12] *t*-BuOOH,[13] or water[11] as the external nucleophile.[14] Consequently, we considered alternative key intermediates that conform to the general structure **9**, where Y is a group that can be removed in the final process of rearomatization, and we eventually selected Y = CO_2Bu-*t* as a suitable candidate. This choice was guided in part by the fact that preparation of the corresponding methyl esters had already been described (Y = CO_2Me in **9**),[15] and we expected that the same procedure, using *tert*-butyl esters, would be applicable to the problem at hand.



By analogy with the methyl ester route,[15] *t*-butyl benzoate[16] was subjected to Birch reduction (Scheme 2), and the

Scheme 2. Formal Cyclization onto a Benzene Ring



intermediate anion was trapped by alkylation with 1,3-dibromopropane. Oxidation of the resulting diene, using CrO_3 in Ac_2O−AcOH,[17] served to produce the desired cross-

(7) Clive, D. L. J.; Fletcher, S. P.; Liu, D. *J. Org. Chem.* **2004**, *69*, 3282−3293.

(8) Fletcher, S. P.; Clive, D. L. J.; Peng, J.; Wingert, D. A. *Org. Lett.* **2005**, *7*, 23−26.

(9) For a related approach to cyclization onto a cross-conjugated ketone, see: Villar, F.; Kolly-Kovac, T.; Equey, O.; Renaud, P. *Chem.−Eur. J.* **2003**, *9*, 1566−1577.

(10) For example: (a) Camps, P.; González, A.; Muñoz-Torrero, D.; Simon, M.; Zúñiga, A.; Martins, M. A.; Font-Bardia, M.; Solan, X. *Tetrahedron* **2000**, *56*, 8141−8151. (b) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552−2553. (c) Oxidation of trimethylsilyl ethers of *para*-aryl phenols is more efficient and gives yields in the range 66−82%: Felpin, F.-X. *Tetrahedron Lett.* **2007**, *48*, 409−412. In our hands, the triisopropyl ether of *para*-propylphenol (cf. ref 11) did not react with $PhI(OAc)_2$.

(11) Cf.: McKillop, A.; McLaren, L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2047−2048.

(12) Cf.: Pelter, A.; Ward, R. S.; Abd-El-Ghani, A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2249−2251.

(13) We examined *t*-BuOOH because a few examples of phenol oxidation in acceptable yield had been reported: (a) Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Noda, S. *J. Am. Chem. Soc.* **1996**, *118*, 2509−2510. (b) Ochiai, M.; Nakanishi, A.; Yamada, A. *Tetrahedron Lett.* **1997**, *38*, 3927−2930.

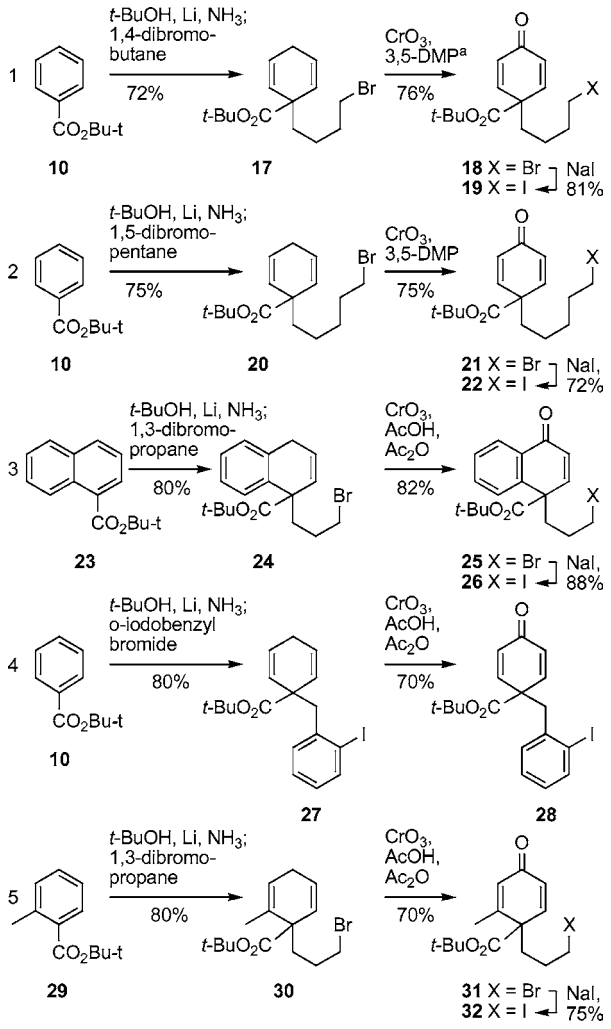
(14) We did not try the recently reported use of oxone (it does not appear to give high yields in cases where the alkyl group on the phenol is larger than methyl): Carreño, M. C.; González-López, M.; Urbano, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 2737−2741.

(15) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893−5901.

(16) Wright, S. W.; Hageman, D. L.; Wright, A. S.; McClure, L. *Tetrahedron Lett.* **1997**, *38*, 7345−7348.

(17) Schultz, A. G.; Lavieri, F. P.; Macielag, M.; Plummer, M. *J. Am. Chem. Soc.* **1987**, *109*, 3991−4000.

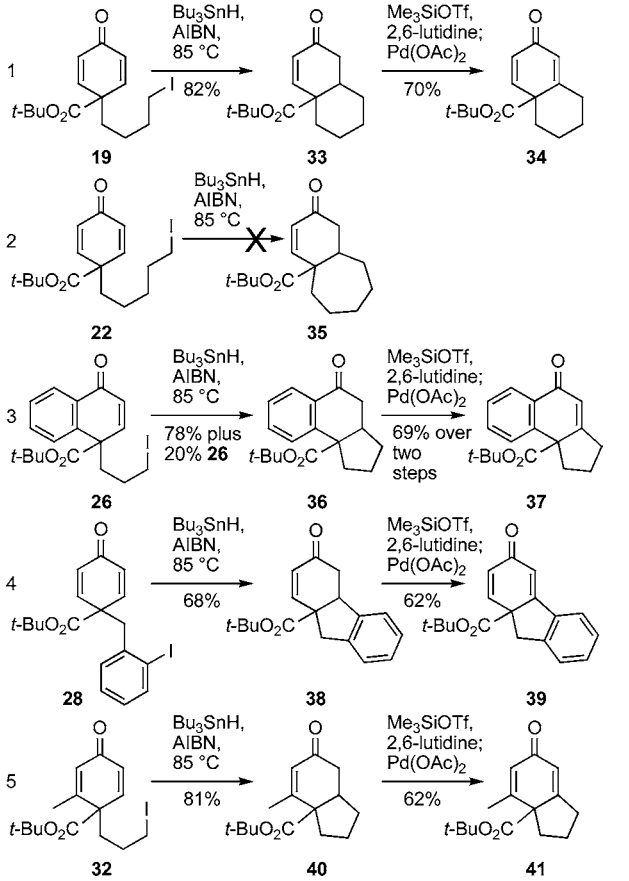
Scheme 3. Cross-Conjugated Ketones



[a] 3,5-DMP = 3,5-dimethylpyrazole.

conjugated ketone **12**, and this was transformed into the corresponding iodide **13** by Finkelstein reaction. Radical cyclization (**13** → **14**) then proceeded without incident (96%). As observed by Beckwith and Roberts,[15] we have found[18] that bromides are unsuitable for the radical step, presumably because of an unfavorable competition between dienone reduction and C−Br homolysis. With **14** in hand, we then attempted to regenerate the aromatic system. To this end, the *tert*-butyl group was removed by treatment with CF_3CO_2H (CH_2Cl_2, water, 96%), but to our surprise, attempts to convert the resulting acid (**14**, H instead of *t*-Bu) into the rearomatized product **16** by oxidation with $Pb(OAc)_4$, $PhI(OAc)_2$, or DDQ were unpromising.[19] Accordingly, we first introduced a double bond by silylation and Saegusa oxidation (**14** → **15**) and then removed the *tert*-butyl group. Treatment with CF_3CO_2H proved unsuitable for this purpose; the desired phenol **16** was formed, but only in 55% yield. However, use of $BiCl_3 \cdot H_2O$[20] in MeCN resulted in a significantly better outcome, and **16** could be isolated in 90% yield. This reagent was introduced recently for the deprotection of *N*-Boc carbamates;[20,21] we find it works well for our *tert*-butyl esters, and decarboxylation then occurs spontaneously to generate the aromatized system **16**. In some cases, a full equivalent of $BiCl_3 \cdot H_2O$ is required, but in others, less than 50 mol % is satisfactory (see later, Scheme 5). The sequence of Scheme 2 is general and can accommodate a number of variations. Scheme 3 shows the other cyclohexadienes which we have prepared and then oxidized under acidic[17] ($AcOH$, Ac_2O) or basic[15] (NaOH, 3,5-dimethylpyrazole) conditions to afford the key cross-conjugated ketones. As indicated, these steps work well for both benzenoid and naphthalenoid substrates. The initial bromides were converted into the corresponding iodides, which underwent radical cyclization (Scheme 4)

Scheme 4. Radical Cyclization and Saegusa Oxidation



under mild conditions [slow addition of Bu_3SnH to a hot (85 °C) solution of the substrate and a catalytic amount of AIBN].

Although five- and six-membered rings are easily formed, a seven-membered ring could not be generated (Scheme 4,

(18) As judged by using bromide **25** as a test case.

(19) Use of $Pb(OAc)_4$ and $Cu(OAc)_2 \cdot 5H_2O$ merely replaced the CO_2H by AcO (55%); use of DDQ in dioxane gave **16** in 33% yield. $PhI(OAc)_2$ alone afforded a complex mixture of products.

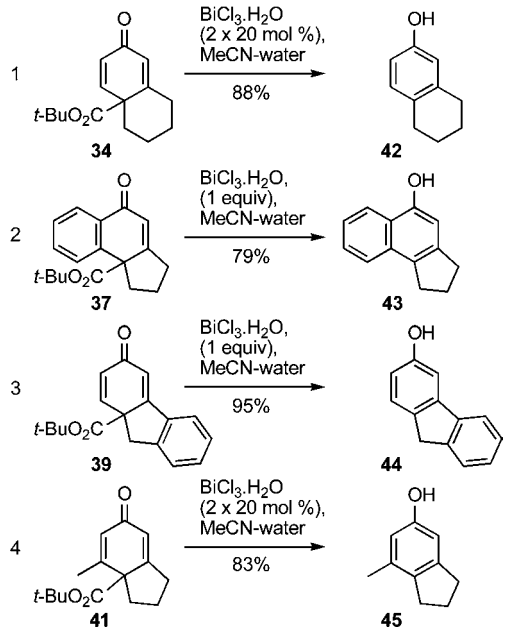
(20) Navath, R. S.; Pabbisetty, K. B.; Hu, L. *Tetrahedron Lett.* **2006**, *47*, 389−393.

(21) Review on applications of Bi(III) compounds: Leonard, N. M.; Wieland, l. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373−8397.

example 2), even though simple 7-*exo* trigonal closures are known.[22] We tried a number of different conditions, including the use of Et_3B-Bu_3SnH at low temperature, but still obtained mainly the reduced product (Scheme 4, H instead of I in **22**).

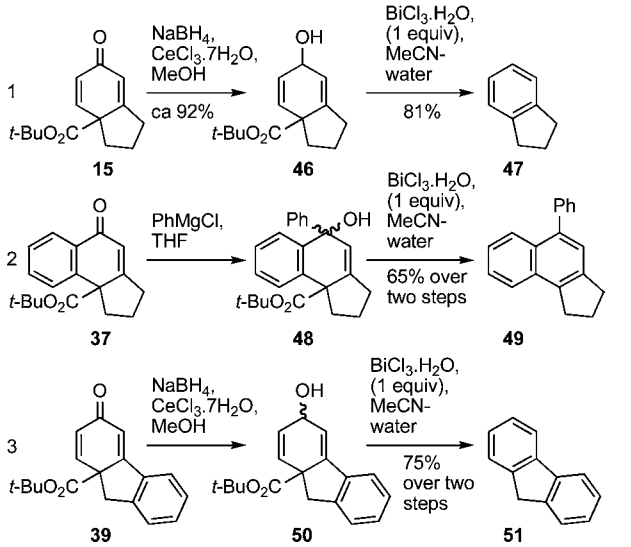
The radical cyclization products were silylated and oxidized under Saegusa conditions to provide the dienones listed in Scheme 4.[23] These dienones were then processed in a number of ways (Schemes 5 and 6). Treatment with $BiCl_3 \cdot H_2O$ in MeCN at 65−70 °C caused loss of the *tert*-butyl group and decarboxylation (Scheme 5). We did not establish if the intermediate loss of CO_2 was facilitated by the presence of $BiCl_3 \cdot H_2O$.

Scheme 5. Rearomatization of Cyclization Products



Although the usual products of the rearomatization are phenols, the intermediate dienones can easily be diverted to nonphenolic compounds. In the case of dienones **15** and **39**, the ketone carbonyl was reduced under Luche conditions (Scheme 6, entries 1 and 3) so that aromatization, which now required a stoichiometric amount of $BiCl_3 \cdot H_2O$, afforded a hydrocarbon rather than a phenol. Similarly, reaction of enone **37** with PhMgCl affords the hydrocarbon **49** after treatment with $BiCl_3 \cdot H_2O$.

Scheme 6. Transformations of the Intermediate Ketones



In summary, we have developed a method for achieving the same result as would arise from the otherwise difficult sequence of alkyl radical cyclization onto an aromatic ring, followed by rearomatization. This route to aryl-fused carbocycles is general; it illustrates the effectiveness of $BiCl_3 \cdot H_2O$ for deprotection of *tert*-butyl esters and has the especially useful feature of allowing the introduction of an additional substituent on the original aromatic ring.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

Supporting Information Available: Experimental procedures and spectral data, as well as copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Examples of 7-*exo* trigonal cyclization: (a) Moody, C. J.; Norton, C. L. *Tetrahedron Lett.* **1995**, *36*, 9051−9052. (b) Yuasa, Y.; Sato, W.; Shibuya, S. *Synth. Commun.* **1997**, *27*, 573−585. (c) Marco-Contelles, J.; de Opazo, E. *Tetrahedron Lett.* **2000**, *41*, 5341−5345. (d) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2002**, *67*, 3705−3717. (e) Evans, P. A.; Manangan, T. *Tetrahedron Lett.* **1997**, *38*, 8165−8168. (f) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472−473.

(23) Barrett, A. G. M.; Blaney, F.; Campbell, A. D.; Hamprecht, D.; Meyer, T.; White, A. J. P.; Witty, D.; Williams, D. J. *J. Org. Chem.* **2002**, *67*, 2735−2750.