JOC Article

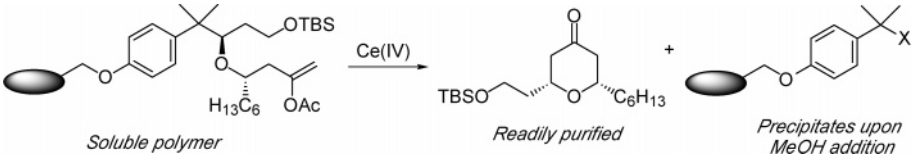
Oxidative Cyclorelease from Soluble Polymeric Supports

Hua Liu, Shuangyi Wan, and Paul E. Floreancig*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

florean@pitt.edu

Received October 27, 2004



Single electron oxidation is shown to be a viable method for effecting concomitant cyclization and cleavage (cyclorelease) of a series of polymer bound homobenzylic ethers. Soluble oligonorbornene polymers are stable toward redox chemistry and are isolable through precipitation with methanol, making them excellent supports for this process. These oxidative conditions are also shown to cleave secondary and tertiary alcohols and ethers in a new traceless approach to polymer-supported aldehyde and ketone synthesis.

Introduction

Constructing molecules on polymer supports has proven to be useful for minimizing separation-derived waste production, processing intermediates that are difficult to handle, and generally expediting chemical synthesis.[1] Although notable exceptions have been reported[2] this approach is not routinely used to prepare nonoligomeric organic molecules due to limitations in the scope of synthesis on insoluble polymers. For example, the kinetics of reactions that are performed on a solid polymeric support can be significantly different from the analogous reactions run in solution as a result of limited substrate accessiblity to reagents in certain solvents.[3] Product purification can also be difficult if all steps along a sequence do not proceed with high efficiency. The former issue has been addressed through the development of soluble polymer supports[4] that can be isolated from low molecular weight reagents and solvents by precipitation upon solvent change ("liquid-phase synthesis")[5] or by nanofiltration.[6] Alternative monomeric approaches that use a "tagging" strategy to isolate products have also been explored,[7] with fluorous tags showing particular promise in multistep syntheses.[8] Cyclorelease strategies[9] (Figure 1) have been developed to address the latter issue. Cyclorelease couples intramolecular bond formation with product cleavage from the polymer. Thus only substrates in which the requisite functional groups for the cyclization event have been successfully installed will be released from the polymer, thereby providing an editing mechanism that facilitates separation at the end of the sequence. Herein we report that substrates for electron transfer initiated cyclization (ETIC) reactions[10] can be synthesized on soluble polymeric supports, and that

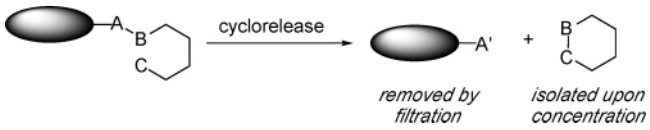


FIGURE 1. Generalized cyclorelease from a polymeric support.

(1) (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (b) Früchetel, J. S.; Jung, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 17. (c) Gold, L.; Polisky, B.; Uhlenbach, O.; Yarus, M. *Annu. Rev. Biochem.* **1995**, *64*, 763. (d) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233.

(2) For reviews, see: (a) Nicolaou, K. C.; Pfefferkorn, J. A. *Biopolymers* **2001**, *60*, 171. (b) Watson, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1903.

(3) Cilli, E. M.; Oliveira, E.; Marchetto, R.; Nakaie, C. R. *J. Org. Chem.* **1996**, *61*, 8992 and references therein.

(4) (a) Boyle, N. A.; Janda, K. D. *Curr. Opin. Chem. Biol.* **2002**, *6*, 339. (b) Wentworth, P., Jr.; Janda, K. D. *Chem. Commun*. **1999**, 1917. (c) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 469.

(5) Mutter, M.; Hagenmaier, H.; Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 811.

(6) Majumdar, D.; Zhu, T.; Boons, G.-J. *Org. Lett.* **2003**, *5*, 3591.

(7) (a) Yoshida, J.-i.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693. (b) Flynn, D. L. *Med. Res. Rev.* **1999**, *19*, 408.

(8) Curran, D. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1174.

(9) For notable examples, see: (a) Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 10061. (b) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1997**, *38*, 7143. (c) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannokakou, P.; Hamel, E. *Nature* **1997**, *387*, 268.

(10) (a) Kumar, V. S.; Floreancig, P. E. *J. Am. Chem. Soc.* **2001**, *123*, 3842. (b) Seiders, J. R., II; Wang, L.; Floreancig, P. E. *J. Am. Chem. Soc.* **2003**, *125*, 2406. (c) Aubele, D. L.; Rech, J. C.; Floreancig, P. E. *Adv. Synth. Catal.* **2004**, *346*, 359.

10.1021/jo0480951 CCC: $30.25
Published on Web 03/18/2005

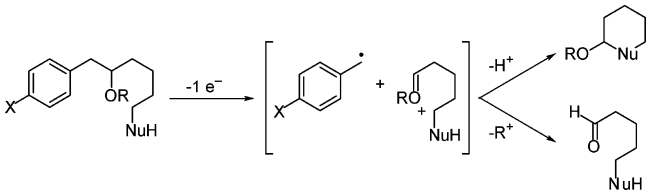


FIGURE 2. Oxidative cleavage reactions of homobenzylic ethers.

cyclorelease reactions occur efficiently upon single electron oxidation to provide products of high purity. Additionally we show that single electron oxidation is an excellent trigger for traceless liberation[11] of aldehydes and ketones from polymeric supports even in the absence of an internal nucleophile.

Upon single electron oxidation homobenzylic ethers undergo mesolytic cleavage reactions to form benzyl radicals and oxocarbenium ions.[12] This process is reversible and, in the absence of a rapid ensuing reaction, the radical cation can be regenerated and reduced by solvent with no net reaction being observed. Appending a nucleophile to the homobenzylic ether in a manner that allows for a rapid addition into the intermediate oxocarbenium ion, however, makes the oxidative cleavage irreversible and provides cyclic products. This protocol is well-suited for cyclorelease applications since rapid and irreversible carbon−carbon bond cleavage is observed only in the presence of an appropriate nucleophile. Capping the homobenzylic oxygen with an electrofugal group that will depart from the oxocarbenium ion rapidly to form an aldehyde or ketone represents an alternative method for driving the radical-ion pair toward a stable product. This approach, while not subject to the editing mechanism of cyclorelease, is a unique method for unmasking carbonyl groups during polymer supported syntheses.

The oligonorbornene scaffolding,[13] prepared from ring-opening metathesis polymerization (ROMP) of an appropriately substituted norbornene monomer, was selected as the support for this study in consideration of several desirable attributes. (1) The polymers are soluble in most organic solvents but precipitate in high yield upon methanol addition.[14] (2) Loading levels in these systems are quite high relative to other soluble polymers such as poly(ethylene glycol). (3) The polymers can be characterized by standard spectroscopic techniques throughout the course of a synthetic sequence. (4) Oxidative decomposition of the support is not expected to be a problem under cyclorelease conditions. Should the polymer prove to be susceptible to oxidation, olefin hydrogenation removes all redox active groups in the support.[15] (5) Molecular weight can be controlled rationally by adjusting metathesis catalyst loading or employing a different catalyst[16] in order to alter the solubility properties of the polymer to suit the needs of a particular class of substrate. Based on structure−reactivity studies conducted in our labs relating the effects of arene substitution to the propensity of intermediate radical cations to fragment,[10b,17] we chose to attach the polymer to the substrates through an ether linkage at the para position of the arene.

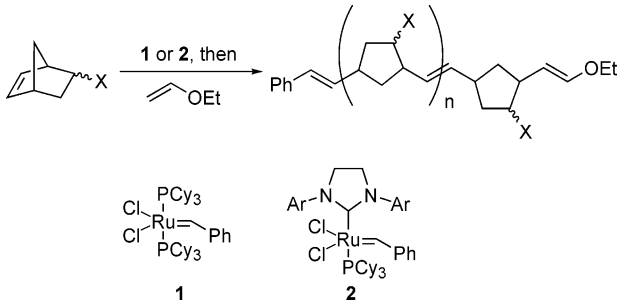


FIGURE 3. ROMP approach to oligonorbornenes.

Results and Discussion

A representative synthesis of a polymer-supported substrate and the subsequent cyclorelease are shown in Scheme 1. Hydroxymethyl norbornene (**3**), which can be purchased or prepared in multigram quantities through an easy two-step sequence,[18] was converted to iodide **4** in three steps. As a demonstration of concept homobenzylic ether **5**[19] was appended to the norbornene monomer to provide **6**. Oligomerization of **6** proceeded smoothly in the presence of 5 mol % of the second generation Grubbs metathesis catalyst (**2**)[20] to yield, after capping with ethyl vinyl ether, polymer **7** with a predicted molecular weight distribution centered at appromimately 32 000 (60-mer).[21] Upon precipitation with methanol and drying the polymer was isolated in 79% yield. Subjecting the polymer-bound substrate to our standard photoinitiated aerobic ETIC conditions ($h\nu$, Pyrex filtration, 2.5 mol % of *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$), O_2, NaOAc, $Na_2S_2O_3$, 1,2-dichloroethane, toluene)[22] followed by filtering the reaction mixture over a short plug of silica gel provided the desired tetrahydrofuran **8** in 72% yield contaminated with only minor amounts of aromatic impurities. This yield is comparable to the yield observed for the oxidative cyclization of the corresponding monomeric substrate (84%).[10b]

(11) Comely, A. C.; Gibson, S. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1012.

(12) (a) Arnold, D. R.; Lamont, L. J. *Can. J. Chem.* **1989**, *67*, 2119. (b) Perrott, A. L.; Arnold, D. R. *Can. J. Chem.* **1992**, *70*, 272. (c) Arnold, D. R.; Du, X.; Chen, J. *Can. J. Chem.* **1995**, *73*, 307. (d) Perrott, A. L.; de Lisjer, H. J. P.; Arnold, D. R. *Can. J. Chem.* **1997**, *75*, 384. (e) Baciocchi, E.; Bietti, M.; Putignani, L.; Steenken, S. *J. Am. Chem. Soc.* **1996**, *118*, 5952. (f) Baciocchi, E.; Bietti, M.; Lanzalunga, O. *Acc. Chem. Res.* **2000**, 33, 243. (g) Chen, L.; Farahat, M. S.; Gan, H.; Farid, S.; Whitten, D. G. *J. Am. Chem. Soc.* **1995**, *117*, 6398. (h) Freccero, M.; Pratt, A.; Albini, A.; Long, C. *J. Am. Chem. Soc.* **1998**, *120*, 284.

(13) For initial applications of this scaffolding to multistep synthesis, see: (a) Ball, C. P.; Barrett, A. G. M.; Poitout, L. F.; Smith, M. C.; Thorn, Z. E. *Chem. Commun.* **1998**, 2453. (b) Harned, A. M.; Mukherjee, S.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2003**, *5*, 15.

(14) Barrett, A. G. M.; Hopkins, B. T.; Köbberling, J. *Chem. Rev.* **2002**, *102*, 3301.

(15) Arnauld, T.; Barrett, A. G. M.; Hopkins, B. T. *Tetrahedron Lett.* **2002**, *43*, 1081.

(16) Harned, A. M.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 1007.

(17) Wang, L.; Seiders, J. R., II; Floreancig, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 12596.

(18) Moore, J. D.; Harned, A. M.; Henle, J.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 1847.

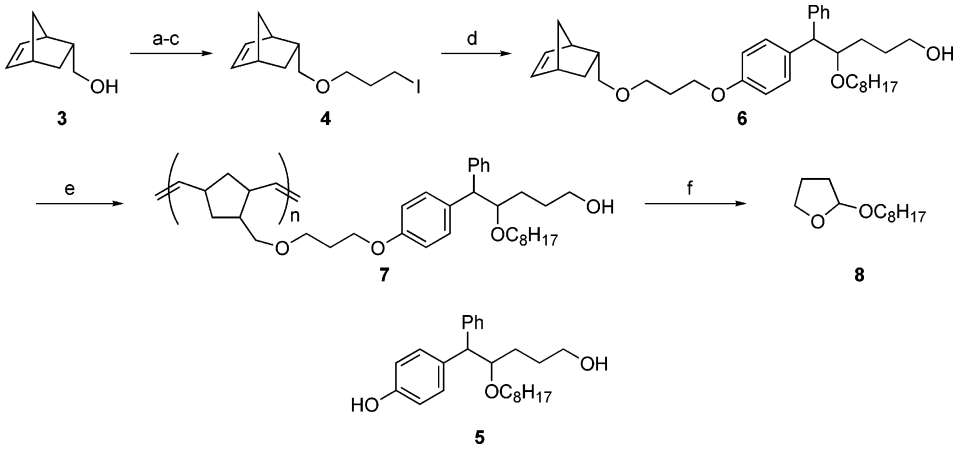
(19) The synthesis of this compound is detailed in the Supporting Information.

(20) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(21) Moore, J. D.; Byrne, R. J.; Vedantham, P.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2003**, *5*, 4241.

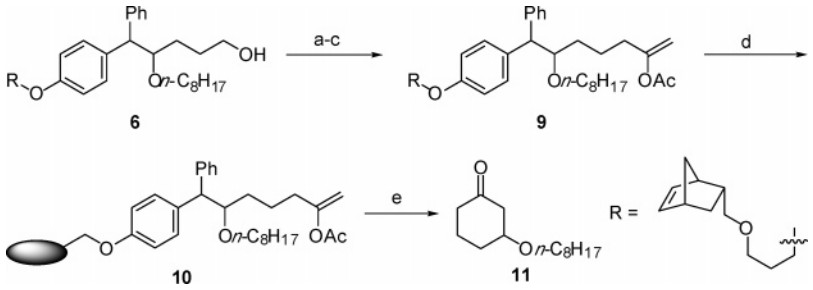
(22) Kumar, V. S.; Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2001**, *3*, 4123.

SCHEME 1. Cyclorelease through Carbon Oxygen Bond Formation[a]



[a] Reagents and conditions: (a) NaH, DMF, then allyl bromide, quant. (b) $(Sia)_2BH$, THF, −10 °C, then NaOOH, 87%. (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, then NaI, actone, 89%. (d) K_2CO_3, **5**, DMF, 76%. (e) **2** (5 mol %), CH_2Cl_2, then ethyl vinyl ether, MeOH precipitation, 79%. (f) $NMQPF_6$, *hν*, O_2, NaOAc, DCE, PhMe, 72%.

SCHEME 2. Cyclorelease through Carbon−Carbon Bond Formation[a]



[a] Reagents and conditions: (a) I_2, Ph_3P, imidazole, CH_2Cl_2, 99%. (b) Lithium acetylide, DMSO, 81%. (c) HOAc, $[Ru(p\text{-cymene})Cl_2]_2$, Fur_3P, Na_2CO_3, PhMe, 28%. (d) **1**, CH_2Cl_2, then ethyl vinyl ether, MeOH precipitation, 57%. (e) CAN, $NaHCO_3$, DCE, CH_3CN, 85%.

Having demonstrated the viability of this method to effect cyclorelease with carbon−oxygen bond formation we turned our attention toward cyclorelease through carbon−carbon bond formation. Norbornene-tagged cyclization substrate **9** was prepared in three steps from **6** (Scheme 2). To minimize the possibility of destroying the enol acetate, **9** was subjected to polymerization using the first generation Grubbs metathesis catalyst (**1**)[23,24] (2 mol %) to provide polymer **10** in 57% yield with an expected average molecular weight of 18 000 (30-mer). Cyclorelease of **10** using ceric ammonium nitrate (CAN) rather than $NMQPF_6$ provided alkoxycyclohexanone **11** in 85% yield, again in excellent purity (Figure 4) and with efficiency that rivals that of the monomeric variant of the reaction (91%).[10b]

Successful examples of carbon−carbon and carbon−oxygen bond formation and photoinitiated and ground-state oxidative cleavage reactions led us to pursue multistep protocols on the polymeric support. Alcohol **6** was again subjected to ROMP conditions, though for this sequence the polymers precipitated more readily when 4 mol % of catalyst **2** was used to give an average molecular weight of approximately 16 000 (25-mer). The three step sequence used to convert **6** to **9** was applied to polymer-supported substrate **7** (Scheme 3) to provide cyclization precursor **10** in 52% yield over four steps. This level of recovery indicates that further optimization in polymer length is still necessary for this substrate. Cyclorelease with CAN provided **11** in 79% yield. The slight drop in yield for this process relative to the cyclorelease in which the polymer was prepared directly from **9** most likely results from sub-quantitative reaction yields during the sequence.

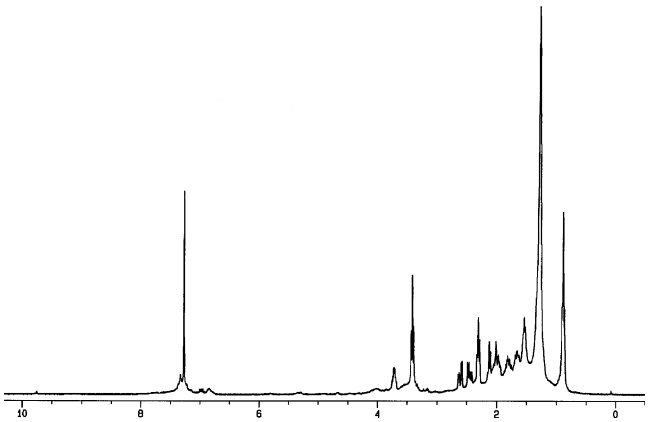
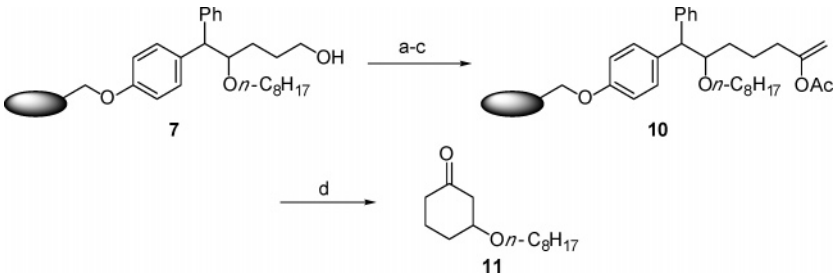


FIGURE 4. ^1H NMR spectrum of **11** following filtration.

(23) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

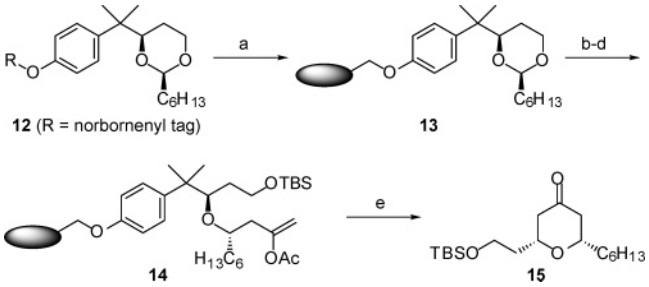
(24) For a discussion of the selectivity profiles for catalysts **1** and **2**, see: Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

SCHEME 3. Polymer Supported Substrate Synthesis and Cyclorelease[a]



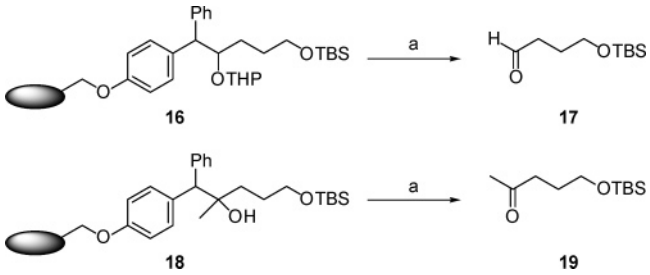
[a] Reagents and conditions: (a) I_2, Ph_3P, imidazole, CH_2Cl_2, 94%. (b) Lithium acetylide, DMSO. (c) HOAc, $[Ru(p\text{-cymene})Cl_2]_2$, Fur_3P, Na_2CO_3, PhMe, 52% from **7**. (d) CAN, $NaHCO_3$, DCE, CH_3CN, 78%.

SCHEME 4. Diastereoselective Cyclorelease[a]



[a] Reagents and conditions: (a) **1** (5 mol %), CH_2Cl_2, MeOH precipitation, 95%. (b) Tributylstannylallene, $Ti(Oi\text{-}Pr)_4/TiCl_4$, CH_2Cl_2, −78 °C, 82% recovery. (c) HOAc, $[Ru(p\text{-cymene})Cl_2]_2$, Fur_3P, Na_2CO_3, PhMe, 88% recovery. (d) TBSCl, imidazole, CH_2Cl_2, 80% recovery. (e) CAN, $NaHCO_3$, DCE, CH_3CN, 41%.

SCHEME 5. Oxidative Traceless Cleavage of Aldehydes and Ketones[a]



[a] Reagents and conditions: (a) *hν*, $NMQPF_6$, O_2, NaOAc, $Na_2S_2O_3$, DCE, PhMe, **17** (78%), **19** (89%).

Encouraged by our initial success in this study, we turned our attention to expanding the types of reactions that can be performed on the polymer-bound substrate and to increasing the molecular complexity of the products through conducting diastereoselective cyclorelease reactions. We prepared monomer **12** following a sequence that was developed in our recent studies[17] in stereoselective syntheses of 2,6-disubstituted tetrahydropyrones and subjected it to ROMP conditions with 5 mol % of **1** to provide polymer **13** with an expected average molecular weight of 9200 (20-mer). Exposing **13** to a three-step sequence of $TiCl_4/Ti(Oi\text{-}Pr)_4$-mediated acetal opening with allenyl tributylstannane, ruthenium catalyzed acetic acid addition, and hydroxyl silylation yielded enol acetate polymer **14** with good mass recovery at each step (Scheme 4). Cyclorelease of **14** with CAN provided **15** as a single stereoisomer in 41% yield, again demonstrating that these reactions can be used to provide products that require minimal separation following sequences that contain difficult steps that do not proceed in nearly quantitative yield.

Our demonstration of oxidative cyclorelease reactions led us to consider other modes for cleaving molecules from polymer supports by single electron oxidation. In the absence of an appended nucleophile, the alternate pathway for oxocarbenium ion decomposition of electrofuge departure to form a carbonyl group[25] creates a pathway for an oxidative, traceless release of ketones and aldehydes.[26] To test this hypothesis we prepared polymer **16** through a straightforward sequence. The THP ether was selected as the electrofugal group based on our success in using the tetrahydropyranyl cation as a proton surrogate in several cyclization reactions.[10] Subjecting **16** to our aerobic photochemical oxidation conditions indeed resulted in the formation of aldehyde **17** in 78% yield. Protection of the hydroxyl group was subsequently shown to be unnecessary, with polymeric tertiary alcohol **18** being cleaved to form ketone **19** in 89% isolated yield. The robust nature of the benzylic carbon−carbon bond in these systems, coupled with the highly selective mechanism for carbonyl release should be attractive in combinatorial synthesis and in other areas such as surface modification[17] where selective carbonyl group introduction could be quite useful.

Summary and Conclusions

We have shown that ETIC reactions are well-suited for cyclorelease chemistry. The method accommodates carbon−oxygen and carbon−carbon bond forming reactions, and can be effected by photoinitiated or ground-state electron transfer. The soluble oligonorbornene scaffolding proved to be stable toward single electron oxidation and functioned well in multistep sequences due to facile isolation by precipitation with MeOH. Cycliza-

(25) For a recent example, see: Ying, B.-P.; Trogden, B. G.; Kohlman, D. T.; Liang, S. X.; Xu, Y.-C. *Org. Lett.* **2004**, *6*, 1523.

(26) For recent reports of aldehyde and ketone cleavage from polymer supports, see: (a) Lepore, S. D.; Wiley, M. R. *Org. Lett.* **2003**, *5*, 7. (b) Lee, A.; Huang, L.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 9907. (c) Huwe, C. M.; Kunzer, H. *Tetrahedron Lett.* **1999**, *40*, 683. (d) Murphy, A. M.; Dagnino, R.; Vallar, P. L.; Trippe, A. J.; Sherman, S. L.; Lumpkin, R. H.; Tamura, S. Y.; Webb, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 3156.

(27) Redox processes have been shown to be useful for modifying surfaces for biochemical studies. Yeo, W.-S.; Yousaf, M. N.; Mrksich, M. *J. Am. Chem. Soc.* **2003**, *125*, 14994.

tion products are isolated in high purity because carbon−carbon bond cleavage is efficient only in the presence of an appropriately placed nucleophile. Substrates in which the nucleophile is not properly installed do not cleave from the support and are easily removed from solution. We have also shown that polymer-supported homobenzylic ethers and alcohols can undergo oxidative cleavage in a new method for traceless aldehyde and ketone synthesis. The high chemoselectivity demonstrated by these methods should prove to be useful for applications in combinatorial and spatially directed synthesis.

Acknowledgment. This work was supported by generous funding from the National Science Foundation and the Research Corporation (Research Innovation Award).

Supporting Information Available: Synthetic schemes for all cyclization substrates; experimental procedures and characterization for all cylorelease reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0480951