

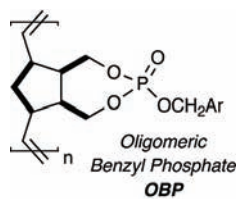
ROMP-Derived Oligomeric Phosphates
for Application in Facile BenzylolationToby R. Long,^{†,‡} Pradip K. Maity,[†] Thiwanka B. Samarakoon,[†] and
Paul R. Hanson^{*,†,‡}

Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive,
Lawrence, Kansas 66045-7582, and The Center for Chemical Methodologies and
Library Development at the University of Kansas (KU-CMLD), 2034 Becker Drive,
Del Shankel Structural Biology Center, Lawrence, Kansas 66047

phanson@ku.edu

Received March 19, 2010

ABSTRACT



The development of new ROMP-based oligomeric benzyl phosphates (OBP_n) is reported for use as soluble, stable benzylating reagents. These oligomeric reagents are readily synthesized from commercially available materials and conveniently polymerized and purified in a one-pot process, affording bench-stable, pure white, free-flowing solids on multigram scale. Utilization in benzylolation reactions with a variety of nucleophiles is reported.

The development of new immobilized reagents for the production of libraries for high-throughput screening is an important element in drug discovery. In this regard, new and improved immobilized reagents with tunable properties have emerged as critical components in facilitated synthetic protocols, particularly within the arena of combinatorial and green technologies.^{1,2} Consequently, this has driven the

development of an array of polymer-bound supports, reagents, and scavengers for streamlining synthetic methods into simple mix, filter, and evaporate protocols.^{1,2} Despite many salient attributes of current immobilized platforms, limitations in load capacity, reaction kinetics, means of delivery, and stability continue to warrant efforts in this area.³ Among these, ring-opening metathesis (ROM) polymerization of functionalized norbornenes has surfaced as a powerful tool in the generation of high-load, immobilized reagents with tunable properties.^{4–6} In this regard, we report the development of new ROMP-based

[†] University of Kansas.[‡] KU-CMLD.

(1) (a) Booth, R. J.; Hodges, J. C. *Acc. Chem. Res.* **1999**, *32*, 18–26. (b) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195. (c) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650–679. (d) Eames, J.; Watkinson, M. *Eur. J. Org. Chem.* **2001**, 1213–1224. (e) Strohmeier, G. A.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 621–624. (f) Lesch, B.; Thomson, D. W.; Lindell, S. D. *Comb. Chem. High Throughput Screening* **2008**, *11*, 31–36.

(2) For reviews concerning soluble polymers, see: (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489–509. (b) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546–554. (c) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325–3344. (d) Haag, R. *Chem.—Eur. J.* **2001**, *7*, 327–335. (e) Haag, R.; Sunder, A.; Hebel, A.; Roller, S. *J. Comb. Chem.* **2002**, *4*, 112–119. (f) Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345–3384. (g) Bergbreiter, D. E.; Tian, J.; Hongfa, C. *Chem. Rev.* **2009**, *109*, 530–582.

(3) (a) Studer, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 6681–6696. (b) Hjerten, S.; Li, Y.-M.; Liao, J. L.; Mankazato, K.; Mohammad, J.; Pettersson, G. *Nature* **1992**, *356*, 810–811. (c) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D. *Org. Biomol. Chem.* **2008**, *6*, 1577–1586.

(4) (a) Barrett, A. G. M.; Hopkins, B. T.; Kobberling, J. *Chem. Rev.* **2002**, *102*, 3301–3324. (b) Harned, A. M.; Probst, D. A.; Hanson, P. R. *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, pp 361–402. (c) Flynn, D. L.; Hanson, P. R.; Berk, S. C.; Makara, G. M. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 571–579. (d) Harned, A. M.; Zhang, M.; Vedantham, P.; Mukherjee, S.; Herpel, R. H.; Flynn, D. L.; Hanson, P. R. *Aldrichimica Acta* **2005**, *38*, 3–16.

oligomeric benzyl phosphates (OBP_n) for use as soluble, stable benzylating reagents.

The innate properties of phosphates as leaving groups have inspired the current study aimed at developing oligomeric phosphate-based reagents. While phosphates have been uniquely tailored to play vital roles in nature,⁷ only recently have they found widespread use in synthetic methodology and total synthesis.⁸ This resurgence is primarily attributed to their stability, facile assembly, and ideal monoanionic pK_a profiles.⁹ Despite these attributes, synthetic oligomeric-based phosphates and other phosphorus-containing materials have found applications primarily in the production of flame-retardant materials¹⁰ with limited use in novel therapeutic applications.¹¹ To the best of our knowledge, the literature is void of immobilized phosphate-based alkylating/benzylating agents.

The benzylation of amines and alcohols continues to serve as one of the most utilized protecting group strategies in organic synthesis due to its ease of incorporation and removal.^{12,13,7b} In addition, benzylation has emerged as a key diversification reaction in medicinal/combinatorial chemistry approaches as well as diversity-oriented synthesis.¹⁴ This continued use has spurred development of a number of alternative approaches to benzylation.^{15,16} Among these, two ROMP-derived benzylating agents were recently developed in our laboratory.^{5c,16b}

(5) (a) Rolfe, A.; Probst, D.; Volp, K.; Omar, I.; Flynn, D.; Hanson, P. R. *J. Org. Chem.* **2008**, *73*, 8785–8790. (b) Stoianova, D. S.; Yao, L.; Rolfe, A.; Samarakoon, T.; Hanson, P. R. *Tetrahedron Lett.* **2008**, *49*, 4553–4555. (c) Zhang, M.; Flynn, D. L.; Hanson, P. R. *J. Org. Chem.* **2007**, *72*, 3194–3198. (d) Roberts, R. S. *J. Comb. Chem.* **2005**, *7*, 21–32. (e) Harned, A. M.; Sherrill, W. M.; Flynn, D. L.; Hanson, P. R. *Tetrahedron* **2005**, *61*, 12093–12099. (f) Arstad, E.; Barrett, A. G. M.; Tedeschi, L. *Tetrahedron Lett.* **2003**, *44*, 2703–2707. (g) Barrett, A. G. M.; Hopkins, B. T.; Love, A. C.; Tedeschi, L. *Org. Lett.* **2004**, *6*, 835–837.

(6) Vedantham, P.; Zhang, M.; Gor, P. J.; Huang, M.; Georg, G. I.; Lushington, G. H.; Mitscher, L. A.; Ye, Q.-Z.; Hanson, P. R. *J. Comb. Chem.* **2008**, *10*, 195–203.

(7) (a) Westheimer, F. H. *Science* **1987**, *235*, 1173–1178. (b) Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*, 1st ed.; John Wiley and Sons: New York, 1995; pp 316–318.

(8) (a) Yanagisawa, A.; Nomura, N.; Noritake, Y.; Yamamoto, H. *Synthesis* **1991**, *12*, 1130–1136. (b) Torneiro, M.; Fall, Y.; Castedo, L.; Mourino, A. *J. Org. Chem.* **1997**, *62*, 6344–6352. (c) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690–4691. (d) Williams, D. R.; Heidebrecht, R. W., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 1843–1850. (e) Fuwa, H.; Sasaki, M. *Heterocycles* **2008**, *76*, 521–539. (f) Thomas, C. D.; McParland, J. P.; Hanson, P. R. *Eur. J. Org. Chem.* **2009**, 5487–5500. (g) Smith, A. G.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 1784–1787.

(9) (a) Nicolaou, K. C.; Shi, G. Q.; Gunzner, J. L.; Gaertner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467–5468. (b) La Cruz, T. E.; Rychnovsky, S. D. *J. Org. Chem.* **2007**, *72*, 2602–2611. (c) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160–4163.

(10) (a) Morgan, A. B.; Tour, J. M. *J. Appl. Polym. Sci.* **1999**, *73*, 707–718. (b) Wang, J.; Mao, H.-Q.; Leong, K. W. *J. Am. Chem. Soc.* **2001**, *123*, 9480–9481. (c) Iliescu, S.; Manovicu, I.; Ilia, G.; Dehelean, G. *Room. Chem. Q. Rev.* **1997**, *5*, 267–277. (d) Kobayashi, S.; Tokunoh, M.; Saegusa, T. *Macro. Mol.* **1986**, *19*, 466–469. (e) Alcock, H. R.; de Denu, C. R.; Prange, R.; Laredo, W. R. *Macromolecules* **2001**, *34*, 2757–2765. (f) Seeberger, P. H. *Chem. Soc. Rev.* **2008**, *37*, 19–28.

(11) Kane, R. R.; Lee, C. S.; Drechsel, K.; Hawthorne, M. F. *J. Org. Chem.* **1993**, *58*, 3227–3228.

(12) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1991.

(13) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 4th ed.; John Wiley and Sons: New York, 2007; pp 102–148.

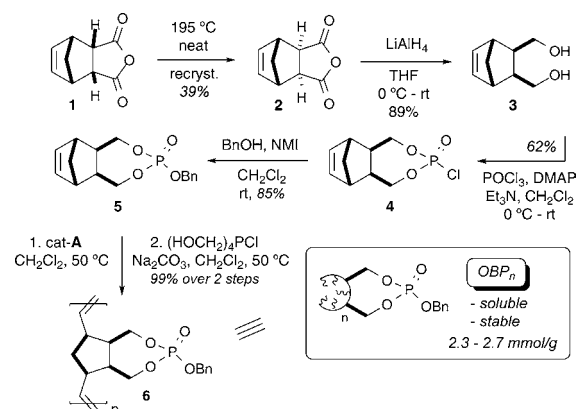
(14) (a) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2009**, *11*, 739–790. (b) Fenster, E.; Rayabarapu, D. K.; Zhang, M.; Mukherjee, S.; Hill, D.; Neuenswander, B.; Schoenen, F.; Hanson, P. R.; Aubé, J. *J. Comb. Chem.* **2008**, *10*, 230–234.

Interest in further improvements¹⁷ of such protocols has led to the study reported herein.

The synthesis of oligomeric benzyl phosphate **6** was envisioned to occur via reduction of *endo* norbornenyl anhydride **1** to the corresponding diol, followed by phosphorylation and subsequent condensation with benzyl alcohol. However, repeated attempts to polymerize the *endo* isomer of monomer **5** with a variety of metathesis catalysts resulted in incomplete conversions. Plausibly, both steric and electronic interactions of the P=O bond of the resulting *endo* isomer could interfere with catalyst/olefin activation or the subsequent propagation step.

Attention was next directed toward synthesis of the thermodynamic *exo* isomer (Scheme 1). Several thermal

Scheme 1. Synthesis of the Oligomeric Benzyl Phosphate (OBP)



isomerization reactions of the inexpensive *endo* carbic anhydride **1** were performed on large scale using classical methods.¹⁸ Sequential recrystallizations in toluene yielded *exo* product **2** with diastereomeric ratios progressively increasing and yields decreasing with each recrystallization, [i.e., dr = 15:1 and 39% yield after three recrystallizations, dr = 29:1 and 34% yield after four, up to dr = 84:1 and 20%

(15) (a) Loris, A.; Perosa, A.; Selvia, M.; Tundo, P. *J. Org. Chem.* **2004**, *69*, 3953–3956. (b) Shieh, W.-C.; Lozanov, M.; Loo, M.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2003**, *44*, 4563–4565. (c) Shieh, W.-C.; Lozanov, M.; Repic, O. *Tetrahedron Lett.* **2003**, *44*, 6943–6945. (d) Huang, W.; He, B. *Chin. J. React. Polym. (Engl.)* **1992**, *1*, 61–70. (e) Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, *118*, 9998–9999. (f) Rueter, J. K.; Nortey, S. O.; Baxter, E. W.; Leo, G. C.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 975–978. (g) Baxter, E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 979–982. (h) Takahashi, T.; Ebata, S.; Doi, T. *Tetrahedron Lett.* **1998**, *39*, 1369–1372.

(16) For recent benzylation via activation of benzyl alcohols see: (a) Poon, K. W. C.; House, S. E.; Dudley, G. B. *Synlett* **2005**, 3142–3144. (b) Zhang, M.; Moore, J. D.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2004**, *6*, 2657–2660. (c) Jha, M.; Enaohwo, O.; Marcellus, A. *Tetrahedron Lett.* **2009**, *50*, 7184–7187. (d) Martinez, R.; Ramon, D. J.; Yus, M. *Org. Biomol. Chem.* **2009**, *7*, 2176–2181. (e) Zhang, C.; Gao, X.; Zhang, J.; Peng, X. *Synlett* **2010**, 261–265.

(17) (a) The synthesis of oligomeric benzylsulfonium salts requires 5 steps and the use of benzyl bromides. These reagents were not soluble in typical organic solvents.^{5c} (b) The oligomeric sulfonate esters were used in a “catch and release” protocol whereby benzyl alcohols were reacted after polymerization.^{16b}

(18) Craig, D. J. *Am. Chem. Soc.* **1951**, *73*, 4889–4892.

yield after six]. Reduction of **2** with LiAlH₄ yielded diol **3** as a clear, viscous oil with good yield. Phosphorylation of the *exo* diol **3** was performed using distilled POCl₃ and Et₃N in the presence of catalytic DMAP to yield phosphorochloridate **4** as a white solid in moderate yields. This was conveniently stored as a solid over argon in a desiccator for use in preparing the various reagents for up to three months.

Addition of **4** into a solution containing benzyl alcohol, NMI, and CH₂Cl₂ at room temperature cleanly afforded the benzyl phosphate **5** in good yields and purity. Polymerization of **5** and other phosphate analogues of this type in the presence of (IMesH₂)(PCy₃)₂(Cl)₂Ru=CHPh (cat. **B**)¹⁹ occurred rapidly at room temperature resulting in formation of insoluble and unusable gels. However, polymerization with RuCl₂(PCy₃)₂=CHPh (cat. **A**)²⁰ cleanly afforded the oligomeric reagent with desirable characteristics.²¹ Following polymerization, the reaction was quenched with ethyl vinyl ether (EVE) and stirred for 30 min. A basic workup involving the Pederson protocol²² was applied in the same pot until cat. **A** was visibly removed as indicated by precipitate formation and lack of coloration. The resulting solution was washed several times with water, dried over MgSO₄, and concentrated to critical viscosity.²³ Precipitation via dropwise addition into anhydrous Et₂O afforded oligomeric benzyl phosphate (OBP_{*n*}) **6** as a free-flowing white solid where *n* = relative lengths of 20-, 50-, and 100-mers, each displaying slightly different solubility profiles.²⁴

The oligomeric benzyl phosphate 20-mer (OBP₂₀) was then investigated for benzylation of various amines (Scheme 2,

Scheme 2. Benzylation of Morpholine

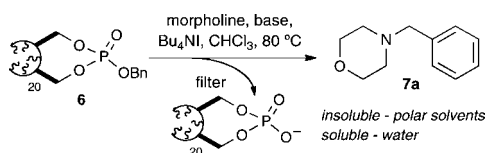


Table 1). The reagent was delivered either as a free-flowing powder or as a stock solution in anhydrous CHCl₃ alongside a catalytic amount of tetrabutylammonium iodide.²⁵ During the reaction, precipitation of the resulting oligomeric phosphate monoanion typically occurred within a 0.5–2 h period after addition of the nucleophile. The mother liquor was subsequently concentrated over silica or precipitated into

(19) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(20) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039–2041.

(21) These characteristics include homogeneity and the ability to achieve the necessary critical viscosity for precipitation.

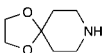
(22) Pederson, R. L.; Fellows, I. M.; Ung, T. A.; Ishihara, H.; Hajela, S. P. *Adv. Synth. Catal.* **2002**, *344*, 728–735.

(23) Critical viscosity described in these terms is the optimum viscosity to achieve a free-flowing precipitate.

(24) See Supporting Information for solubility tables of OBP_{*n*}. For information regarding Gaussian distribution of oligomers see ref 5a.

(25) We have recently formulated ROMP-tabs, whereby premeasured OBP₂₀ tablets can be conveniently added to the reaction.

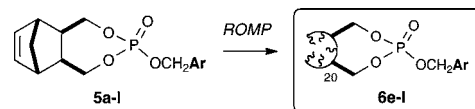
Table 1. Benzylation of *N*-, *O*-, and *S*-Nucleophiles Using OBP₂₀

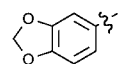
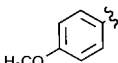

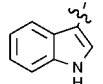
nucleophile	pdt	yield (%) ^a	purity (%) ^b
morpholine	7a	99	98
thiomorpholine	7b	93	98
<i>N</i> -phenylpiperazine	7c	98	99
piperazine	7d	95	97
pyrrolidine	7e	80	99
piperidine	7f	73	99
dihydroindole	7g	98	85
	7h	69	97
phenol	7i	80	95
lithium thiophenolate ^e	7j	98	96
Bn-NH ₂	7k/l	99 ^c	4:1 ^d
Ph-NHEt	7m	81	89

^a Isolated yields after filtration through a silica SPE. ^b Purities calculated using GC and further confirmed by ¹H NMR. ^c Percent conversion and ratio of mono- to dibenzylated amine as found by GC–MS. ^d Percent conversion and ratio of mono- to dibenzylated amine as found by GC–MS. ^e Reaction was performed with OBP₅₀.

Et₂O, filtered via silica SPE, and concentrated under vacuum to afford the corresponding benzylated analogue(s) in good to excellent yields and high purity. The resulting monoanionic oligomeric phosphate was found to be water-soluble at elevated temperatures and remained soluble on cooling to room temperature. This observation would be of particular importance in potential large-scale applications for the removal of spent oligomer without the need for precipitation.

Table 2. Synthesis of Various OBP Analogues



monomer	Ar	yield (%) ^a	monomer	Ar	yield (%) ^a
5a		23%	5e	<i>o</i> -CH ₃ Ph	75%
5b		21%	5f	3,5-(OCH ₃) ₂ Ph	70%
5c		<10%	5g	<i>p</i> -BrPh	79%
5d		<10%	5h	<i>p</i> -ClPh	76%
			5i	<i>p</i> -FPh	80%
			5j	<i>p</i> -NO ₂ Ph	70%
			5k	<i>m</i> -N(CH ₃) ₂ Ph	73%
			5l	<i>p</i> -CF ₃ Ph	77%

^a Yields correspond to monomeric phosphates. Quantitative conversions were obtained for oligomers **6e–l**. Monomers **5a–d** were not polymerized.

A number of cyclic and acyclic amines as well as *O*- and *S*-nucleophiles were subjected to the established benzylation protocol and were found to proceed smoothly to afford the desired benzylated products in excellent yields and purities (Table 1). A number of monomeric analogues of OBP were also prepared in good yields using several substituted benzyl alcohols. Subjection of the monomers to the established ROM polymerization protocol afforded the desired oligomeric products in excellent yields as free-flowing white solids. Interestingly, efforts toward production of monomeric phosphates **5a–d** did not afford the desired products. This is likely due to a combination of the substituent mesomeric effect and/or eliminative degradation pathways of these phosphates (Table 2). The corresponding oligomers **6e–l** were subjected to established benzylation conditions utilizing morpholine as a test substrate and conveniently afforded the desired benzylated products in moderate to good yields and purities (Table 3).

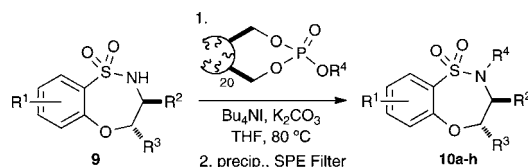
Table 3. Benzylation of Amines Using Various OBP Analogues

entry	SM	product	yield (%)	purity (%) ^a	
1	6e		8e	64	94
2	6f		8f	54	89
3	6g		8g	82	93
4	6h		8h	67	97
5	6i		8i	70	96
6	6j		8j	74	93
7	6k		8k^b	78	98
8	6k		8k'^b	93	98
9	6l		8l	68	95

^a Purities calculated using GC and further confirmed by ¹H NMR.
^b Despite their simplicity, each compound is classified as a NCE.

The 20-mer of OBP was tested on a select benzofused sultam scaffold for benzylation (Table 4). The reagent was

Table 4. Benzylation of Benzothiazepine-1,1-dioxides



SM	R ¹	R ²	R ³	R ⁴	pdt	yield (%) ^a
9a	4-Br	Ph	H	Bn	10a	99
9a	4-Br	Ph	H	3,5-diMeO-Bn	10b	72
9a	4-Br	Ph	H	4-F Bn	10c	85
9b	4-Br	^t Bu	H	4-F Bn	10d	97
9b	4-Br	^t Bu	H	2-Me Bn	10e	81
9c	3-Cl	^t Bu	H	4-Cl Bn	10f	76
9d	5-Cl	Me	Ph	2-Me Bn	10g	78
9d	3-Cl	Me	Ph	2-Me Bn	10h	83

^a Yields after filtration through a SiO₂ SPE.

added to a THF solution containing benzothiazepine-1,1-dioxide (**9a**) in the presence of K₂CO₃ and Bu₄NI and stirred at 80 °C overnight. The resulting mother liquor was precipitated from a Et₂O/EtOAc mixture. Subsequent filtration employing a silica SPE cartridge, and evaporation of solvent afforded the desired benzylated product **10a** in excellent yield and high purity. With this result in place, sultams **9a–d** were subjected to benzylation employing OBP derivatives utilizing the conditions established above to afford the desired products (**10b–h**) in good to excellent yields.

In conclusion, we have demonstrated the synthesis and utilization of ROMP-based oligomeric phosphates for facilitated benzylation of cyclic amines and have applied it toward simple diversification pathways in relevant scaffolds. These oligomeric reagents are readily synthesized from commercially available materials and are conveniently polymerized and purified in a one-pot process affording pure reagent on multigram scale. Efforts to widen the scope of this reagent, improvement in synthesis and scale-up, and its continued integration into diversity-oriented synthetic protocols is underway. The results of these endeavors will be reported in due course.

Acknowledgment. This investigation was generously supported by the National Institute of General Medical Sciences (NIH P050-GM069663 and NIH-STTR R41 GM076765) with additional funds from the State of Kansas. We would like to also thank Materia, Inc. for supplying catalyst and helpful discussions.

Supporting Information Available: Detailed experimental procedures and tabulated ¹H NMR, ¹³C NMR, ³¹P NMR, FTIR, and mass data and ¹H NMR spectra of crude products obtained by the described benzylation method. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL1006604