ORGANIC LETTERS

2002
Vol. 4, No. 14
2357−2360

Double Diastereoselective Intramolecular Cyclopropanation to *P*-Chiral [3.1.0]-Bicyclic Phosphonates

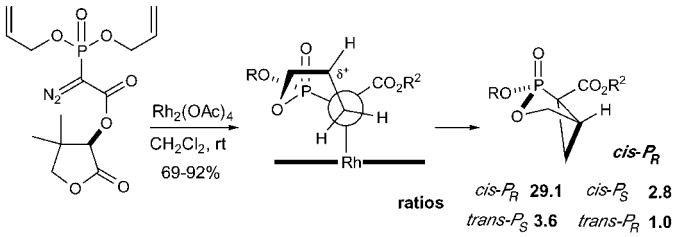
Joel D. Moore, Kevin T. Sprott, Aaron D. Wrobleski, and Paul R. Hanson*

Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045-7582

phanson@ku.edu

Received April 26, 2002

ABSTRACT



A double diastereotopic differentiation strategy on a phosphonoacetate template is described. The approach utilizes $Rh_2(OAc)_4$-catalyzed intramolecular cyclopropanation (ICP) employing the (*R*)-pantolactone auxiliary in the ester functionality of the phosphonoacetate. The olefinic diastereofacial selectivity is governed by inherent electronic and steric interactions in the reacting carbene intermediate, while the group selectivity is dictated by the chiral auxiliary. This approach is being developed as an effective method to access bicyclic *P*-chiral phosphonates.

The synthesis of new phosphorus-containing compounds has continued to gain interest due to their impressive chemical and biological profiles.[1] In particular, the utility of a number of *P*-chiral compounds has prompted new methods for their synthesis.[2] Our interest in the utilization of molecular symmetry en route to *P*-chiral compounds[3] now leads us to report a double diastereotopic differentiation/intramolecular cyclopropanation (ICP) on a diazophosphonoacetate template. This strategy utilizes the (*R*)-pantolactone ester auxiliary to derive nonracemic, *P*-chiral [3.1.0]-bicyclic phosphonates.

Intramolecular cyclopropanation (ICP) mediated by $Rh_2(OAc)_4$ continues to provide a powerful tool for the construction of constrained systems from their diazo precursors, with high levels of diastereoselectivity and enantioselectivity having been achieved in numerous instances.[4] Although α-diazophosphonoacetates have been heavily utilized in organic synthesis,[4c,5] relatively few examples exist for the ICP of α-diazophosphonoacetates.[6] Our interest in

(1) (a) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley-Interscience: New York, 2000. (b) Mader, M. M.; Bartlett, P. A. *Chem. Rev.* **1997**, *97*, 1281−1301. (c) Franz, J. E.; Mao, M. K.; Sikorski, J. A. *Glyphosate: A Unique Global Herbicide*; American Chemical Society: Washington, DC, 1997. (d) Engel, R. *Handbook of Organo-phosphorus Chemistry*; Marcel Dekker: New York, 1992. (e) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur, Silicon* **1991**, *63*, 193-215.

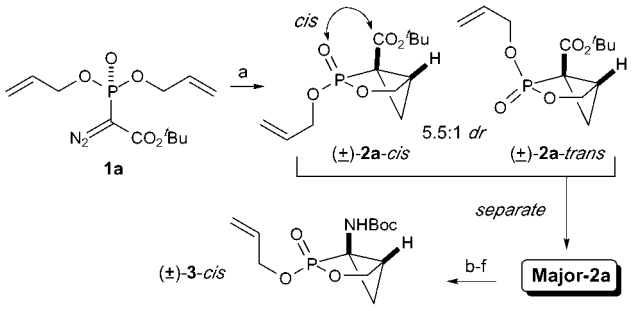
(2) For reviews on the asymmetric synthesis of phosphorus compounds, including *P*-chiral phosphorus compounds, see: (a) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279−1332. (b) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375−1411. For recent examples of the synthesis and use of *P*-chiral compounds, see: (c) Han, L.-B.; Zhao, C.-Q.; Onozawa, S.-y.; Goto, M.; Tanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 3842−3843. (d) Al-Masum, M.; Kumaraswamy, G.; Livinghouse, T. *J. Org. Chem.* **2000**, *65*, 4776−4778. (e) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982−4991. (f) Gilbertson, S. R.; Genov, D. G.; Rheingold, A. L. *Org. Lett.* **2000**, *2*, 2885−2888. (g) Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377−388. (h) Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1995**, *117*, 11879−11897.

(3) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2000**, *2*, 1769−1772.

(4) (a) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 11021. (b) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897. (c) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−936. (e) Doyle, M. P. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; pp 191−228. (f) Kirkland, T. A.; Colucci, J.; Geraci, L. S.; Marx, M. A.; Schneider, M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 12432−12433. (g) Barris, M.; Perez-Prieto, J.; Stiriba, S.-E.; Lahuerta, P. *Org. Lett.* **2001**, *3*, 3317−3319.

10.1021/ol026080o CCC: $22.00
Published on Web 06/11/2002

Scheme 1[a]



[a] Reagents and conditions: (a) $Rh_2(OAc)_4$, CH_2Cl_2, reflux, 91%; *dr* = 5.5:1; (b) formic acid, neat; (c) $(COCl)_2$, CH_2Cl_2, DMF (cat.) 0 °C to rt; (d) NaN_3, CH_3CN, H_2O; (e) toluene, reflux; (f) *t*-BuOH, reflux, 50% (five steps).

the development of new strategies to *P*-chiral compounds led us to explore a double diastereotopic differentiation strategy on the unique α-diazodiallylphosphonoacetate system (Scheme 1). This system contains a prochiral phosphorus atom bearing two enantiotopic olefins, with each olefin possessing two diastereotopic faces, and thus is an ideal substrate for the study we now report.

We previously reported that the ICP of α-diazodiallylphosphonoacetate **1a** proceeds to produce a pair of racemic diastereomers (**2a**-*cis*-P_R/**2a**-*cis*-P_S and **2a**-*trans*-P_R/**2a**-*trans*-P_S).[6b] In this previous study, the level of diastereofacial selectivity was found to be dependent on the size of the ester group R^2 (Figure 1). We recently applied a Curtius rearrangement sequence (Scheme 1) that has allowed us to transform the *major*-bicyclophosphonoacetate **2a** into the crystalline carbamate **3**. X-ray crystallographic analysis of this carbamate unequivocally confirmed the *cis*-relationship between the phosphonyl oxygen and the *N*-Boc group shown in (±)-**3**-*cis* (Scheme 1).

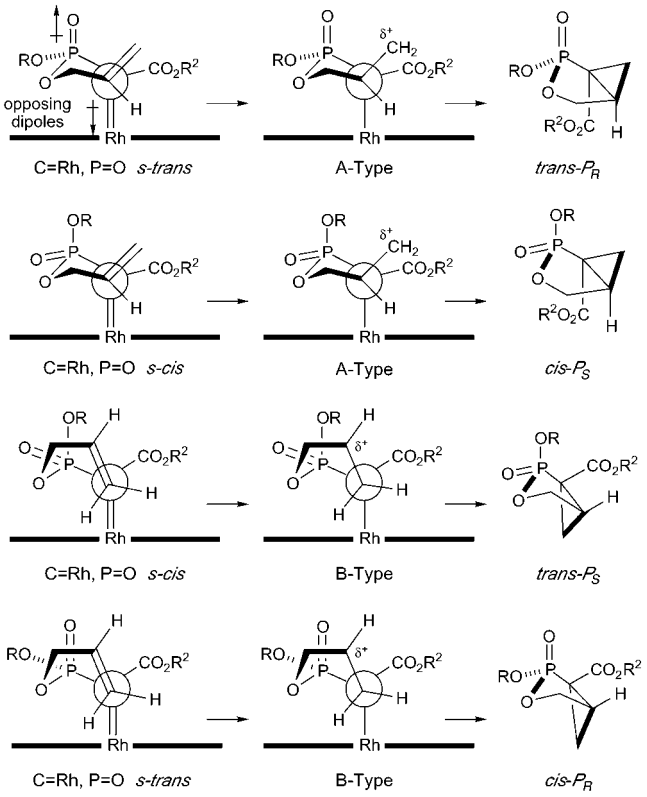


Figure 1. Conformations of reacting carbene.

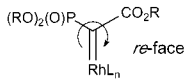
The diastereoselectivity can be rationalized by analyzing the plausible conformations shown in Figure 1 (for simplicity, we depict only those conformations involving interaction of the *re*-face[7] of the rhodium carbene). These conformations employ the widely accepted Doyle/Davies model[4,8] which invokes carbene transfer occurring on a rhodium template in a nonsynchronous manner. A number of steric and electronic factors may be operative in governing the diastereofacial selectivity obtained from these four conformations. These include (i) the facial orientation between the reacting olefin and rhodium carbene (A-type or B-type),[8] in which a B-type orientation is favored for electronic stabilization reasons, (ii) the orientation of the Rh═C and P═O π-systems (*s-trans* or *s-cis*), in which "opposing" dipole interactions between the P═O and the Rh-carbene moieties would favor the *s-trans* orientation, (iii) a possible anomeric effect in the proposed *s-cis* conformations whereby there is an axial preference for the P−OR group,[9] and (iv) a possible eclipsing interaction between the olefin terminus and the ester group thereby favoring the "B-Type" transition states. In this complex analysis, undoubtedly a combination of effects is at play.

In considering an additional group selective transformation[10] layered into this analysis, control of the reacting face of the carbene (*re* vs *si)* ultimately determines enantioselectivity (*P*-chirality) within a diastereomeric pair. We considered two possible modes of governing a group selective transformation: (i) auxiliary-based substrate control

(5) (a) Moody, C. J.; Miller, D. J. *Tetrahedron* **1998**, *54*, 2257−2268 and references therein. For the use of α-diazophosphonates as reagents in organic synthesis. see: (b) Gilbert, J. C.; Weerasooriya, U.; Giamalva, D. *Tetrahedron Lett.* **1979**, 4619−4622. For the use of α-diazophosphonates in ylide rearrangements, see: (b) Gulea, M.; Marchand, P.; Masson, S.; Saquet, M.; Collignon, N. *Synthesis* **1998**, 1635−1639. (d) Moore, J. D.; Sprott, K. T.; Hanson, P. R. *Synlett* **2001**, 605−608.

(6) For the use of α-diazophosphonates in ICP reactions, see: (a) Callant, P.; D'Haenens, L.; Vandewalle, M. *Synth. Commun.* **1984**, *14*, 155−161. (b) Hanson, P. R.; Sprott, K. T.; Wrobleski, A. D. *Tetrahedron Lett.* **1999**, *40*, 1455−1458. (c) For a review containing examples of intermolecular cyclopropanation reactions of α-diazophosphonates, see: (d) Regitz, M. *Angew. Chem.* **1975**, *87*, 259−268.

(7) Note: the corresponding four enantiomeric conformations resulting from *si*-face attack of the rhodium carbene are not shown. The *re*-face of the carbene is defined as follows:



(8) Davies, H. M. L.; Doan, B. D. *J. Org. Chem.* **1999**, *64*, 8501−8508.

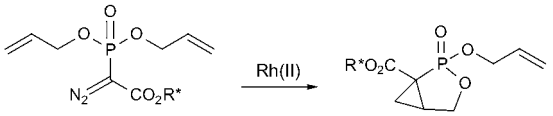
(9) Chang, J.-W. A.; Gorenstein, D. G. *Tetrahedron* **1987**, *43*, 5187−5196.

(10) For reviews of both diastereotopic and enantiotopic differentiation, see: (a) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167−2213. (b) Schreiber, S. L.; Poss, C. S. *Acc. Chem. Res.* **1994**, *27*, 9−17. See also: (c) Hoye, T. R.; Peck, D. R.; Trumper, P. K. *J. Am. Chem. Soc.* **1981**, *103*, 5618. (d) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738. (e) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303. (f) Ward, D. *Chem. Soc. Rev.* **1990**, *19*, 1−19.

resulting in double diastereotopic differentiation[11] and (ii) asymmetric reagent control,[12] which we are currently investigating.

In our substrate-controlled approach, the auxiliary is incorporated into the ester functionality of **1a**. Our initial efforts focused on the use of the menthol- and 8-phenylmenthol-based auxiliaries due to previous successes by Rein and co-workers in the desymmetrization of meso-dialdehydes using chiral phosphonates containing menthol auxiliaries.[13] We investigated the $Rh_2(OAc)_4$-catalyzed ICP of both **1b** and **1c** using various solvents (Table 1). Although modest

Table 1. Selectivities of Menthol-Based Cyclopropanations



1b, R* = menthol
1c, R* = 8-phenylmenthol

2b, R* = menthol
2c, R* = 8-phenylmenthol

entry	substrate	conditions	selectivity
1	**1b**	CH_2Cl_2, reflux	3.2:3.2:1.5:1.0
2	**1c**	CH_2Cl_2, rt	4.1:3.3:2.5:3.0
3	**1c**	Et_2O, reflux	1.5:1.3:1.1:1.0
4	**1c**	CH_2Cl_2, reflux	4.9:4.1:1.1:1.0
5	**1c**	PhH, reflux	2.2:2.0:1.2:1.0

[a] All selectivities were found using ^{1}H-decoupled ^{31}P spectroscopy. [b] The unambiguous assignment of each diastereomer was not made.

levels of diastereoselectivity were seen, these auxiliaries proved to be ineffective in differentiating the two faces of the rhodium carbene.[14] It is worth noting that temperature had a substantial effect on the diastereoselectivity (Table 1, entries 2 and 4).

We next explored the (*R*)-pantolactone auxiliary, which Davies and co-workers had previously demonstrated to be an effective auxiliary in carbenoid-mediated cyclopropanations.[15] The carbonyl moiety in this auxiliary is thought to chelate to the metallo-carbenoid center effectively "locking" the molecule in a rigid conformation and therefore blocking access to one face of the carbene. Davies has shown that an unfavorable steric interaction between the gem-dimethyl moiety and the rhodium wall in the (*R*)-pantolactone auxiliary ultimately favors *si*-face coordination and therefore *re*-face attack (Figure 2). When applied to the rhodium carbenoid

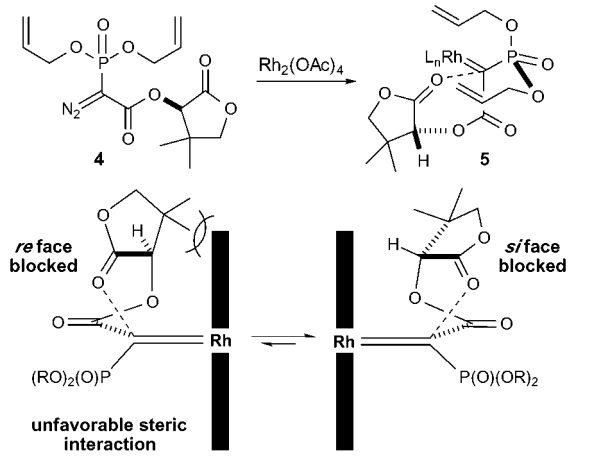
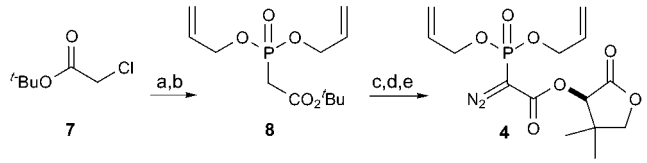


Figure 2. Steric interactions with rhodium wall.

5, utilization of the (*R*)-pantolactone auxiliary effectively blocks the *si*-face of the carbenoid carbon of **5**, thus allowing preferential access to the *re*-face from one of the four conformations depicted in Figure 1. However, the "A-type" transition states have little contribution toward the final products due to their dependence of a positive charge build-up on a primary carbon. Therefore, we believe the *trans*-P_R and *cis*-P_S diastereomers would arise from stereochemical leakage via *si*-face attack of the carbenoid carbon and the reactions proceeding through analogous "B-type" transition states.

Synthesis of **4** began with commercially available *tert*-butylchloroacetate (**7**) (Scheme 2). Conversion to the iodide

Scheme 2[a]



[a] Reagents and conditions: (a) KI, CH_3CN, >99%; (b) P(*O*-allyl)$_3$, neat, 88%; (c) HCO_2H, neat, >99%; (d) HBTU, TEA, (*R*)-pantolactone, CH_3CN, 83%; (e) NaH, TsN_3, THF, 90%.

under Finkelstein conditions (NaI, CH_3CN) followed by Arbuzov reaction with triallyl phosphite[16] yielded diallyl *tert*-butylphosphonoacetate **8** in 88% over two steps. Subsequent deprotection with formic acid, esterification with (*R*)-pantolactone utilizing HBTU coupling protocol, and final diazo transfer with NaH and TsN_3 generated the desired cyclopropanation precursor **4** in high yield.

Intramolecular cyclopropanation of **4** employing the (*R*)-pantolactone ester auxiliary produced the major diastereomer

(11) (a) Kurth, M. J.; Brown, E. G. *J. Am. Chem. Soc.* **1987**, *109*, 6844−6845. (b) McKew, J. C.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 3389. (c) See ref 10.

(12) (a) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493−4494. (b) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327−9343.

(13) (a) Norrby, P.-O.; Brandt, P.; Rein, T. *J. Org. Chem.* **1999**, *64*, 5845−5852. (b)Vares, L.; Rein, T. *Org. Lett.* **2000**, *2*, 2611−2614. (c) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284−8294.

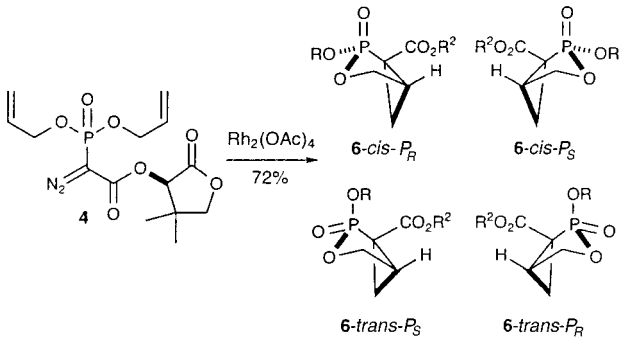
(14) Supporting material: ^{31}P analysis of the menthol-based systems.

(15) (a) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468−9479. (b) Davies, H. M. L.; Cantrell, W. R. *Tetrahedron Lett.* **1991**, *32*, 6509−6512.

(16) Triallyl phosphite was prepared from the reaction of PCl_3 and allyl alcohol in the presence of Et_3N and distilled under vacuum.

6-*cis*-P_R with good levels of olefin (10.4:1) and diastereofacial selectivity (6.9:1) (Table 2).[17] The diastereomeric ratios were conveniently determined using ^{1}H-decoupled ^{31}P NMR analysis.

Table 2. Selectivities of Pantolactone System



	selectivity[a]			
conditions	**6**-*cis*-P_R	**6**-*trans*-P_R	**6**-*cis*-P_S	**6**-*trans*-P_S
CH_2Cl_2, rt	29.1	1.0	2.8	3.6
Et_2O, reflux	14.5	1.0	2.2	2.5
CH_2Cl_2, reflux	12.0	1.0	1.8	2.6
PhH, reflux	7.4	1.0	1.4	3.0

[a] All selectivities were determined using ^{1}H-decoupled ^{31}P spectroscopy.

To associate each signal in the ^{1}H-decoupled ^{31}P NMR spectra to its corresponding diastereomer and to verify the group and facial selectivity, a correlation experiment was initially undertaken. Formic acid-mediated hydrolysis of the *racemic* mix of cyclopropanated diastereomers **2a** (~6:1, *cis*:*trans*) followed by DCC coupling with the (*R*)-pantolactone moiety produced the diastereomers **6**, preserving the 6:1 *cis*:*trans* ratio. Subsequent ^{1}H-decoupled ^{31}P NMR analysis of this racemic sample allowed for the assignments of each diastereomeric pair shown in Table 2.[18] Furthermore, both of the *cis*-diastereomers were separated using silica gel chromatography and X-ray crystallographic analysis of each, **6**-*cis*-P_R and **6**-*cis*-P_S, provided full unambiguous assignment (Figure 3). The production of **6**-*cis*-P_R as the major diastereomer is consistent with an *s-trans* orientation of the Rh═C and P═O π-systems (opposing-dipole) incorporating a B-type orientation of the reacting olefin and occurring from the *re*-face of the rhodium carbenoid (Figure 1). Although the *s-cis* conformations demonstrate the possibility of a favorable anomeric effect, it appears that the opposing dipole effect, inherent to the *s-trans* conformations, is more dominant.

(17) Although good selectivity toward the *cis*-P_R diastereomer is demonstrated, coelution with the *trans* diastereomers during flash chromatography hinders facile purification (see Supporting Information).

(18) See Supporting Information.

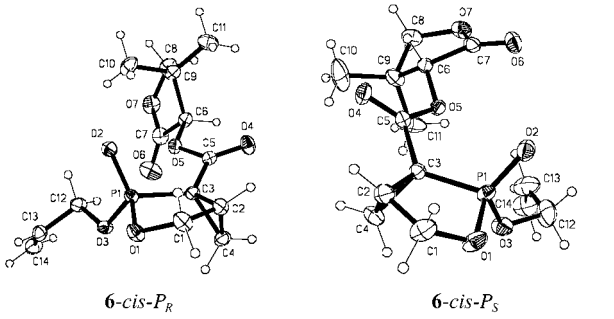


Figure 3. X-ray of major and minor *cis*-diastereomers.

In conclusion, we have demonstrated an effective double diastereotopic differentiation strategy on a phosphonoacetate template utilizing $Rh_2(OAc)_4$-catalyzed ICP employing the (*R*)-pantolactone auxiliary. This study represents part of our continuing program aimed at the synthesis of diverse *P*-heterocycles. Additional efforts probing olefinic substituent effects and utilization of chiral catalysts are underway and will be reported in due course.

Acknowledgment. This investigation was supported by funds provided by the National Institutes of Health (National Institute of General Medical Sciences, RO1-GM58103) and the Herman Frasch Foundation (442-HF97, administered by the American Chemical Society). The authors thank Huw M. L. Davies for many thoughtful discussions, Dr. David Vander Velde for assistance with NMR measurements, Dr. Todd Williams for HRMS analysis, and Dr. Douglas R. Powell for X-ray analysis.

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

OL026080O