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Highly Diastereoselective and Stereodivergent Dihydroxylations of Acyclic Allylic Amines: Application to the Asymmetric Synthesis of 3,6-Dideoxy-3-amino-L-talose

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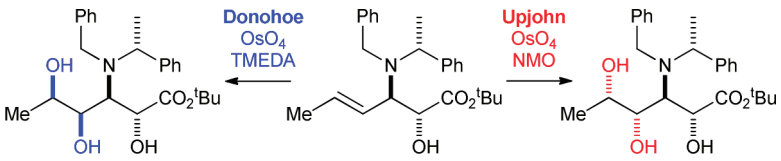
ABSTRACT



Aminohydroxylation of *tert*-butyl sorbate [*tert*-butyl (*E*,*E*)-hexa-2,4-dienoate] using enantiopure lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and (−)-camphorsulfonyloxaziridine gives *tert*-butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate in >99:1 dr. Subsequent dihydroxylation under Upjohn conditions (OsO_4/NMO) gives *tert*-butyl (2*R*,3*R*,4*S*,5*S*,α*R*)-2,4,5-trihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hexanoate (in 95:5 dr) while dihydroxylation under Donohoe conditions (OsO_4/TMEDA) proceeds with antipodal diastereofacial selectivity to give the (*R*,*R*,*R*,*R*,*R*)-diastereoisomer (in 95:5 dr). The amino triols resulting from these dihydroxylation reactions are useful for further elaboration, as demonstrated by the asymmetric synthesis of 3,6-dideoxy-3-amino-L-talose.

Carbohydrate motifs are ubiquitous in nature, and a vast range of biologically important molecules contain functionalized carbohydrates. Carbohydrate recognition events are involved in the progression of a number of diseases as the binding of many pathogens and biological toxins to host cell surfaces are carbohydrate mediated.[1] Carbohydrate mimetics therefore have the potential to become therapeutic agents, and within this area, the replacement of a hydroxyl group at any position around the ring (except the anomeric position) with an amino group has proven to be an effective way to approach carbohydrate mimetics.[1] The so-called amino sugars resulting from this formal oxygen to nitrogen transformation are also prevalent in nature, as exemplified by the occurrence of a 3,6-dideoxy-3-amino-L-talose residue as the glycosidic component of fluvirucin B_1; one member of the fluvirucin family of potent antibacterial and antiviral agents[2] (Figure 1).

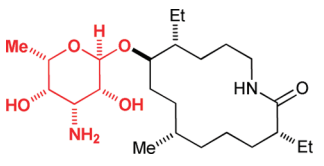


Figure 1. Structure of fluvirucin B_1 (the 3,6-dideoxy-3-amino-L-talose residue is highlighted in red).

We have instigated a research program aimed at the development of de novo asymmetric syntheses of natural

(1) Sears, P.; Wong, C. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2301.
(2) Naruse, N.; Tenmyo, O.; Kawano, K.; Tomita, K.; Ohgusa, N.; Miyaki, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 733. Naruse, N.; Tsuno, T.; Sawada, Y.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 741. Tomita, K.; Oda, N.; Hoshino, Y.; Ohkusa, N.; Chikazawa, H. *J. Antibiot.* **1991**, *44*, 940.

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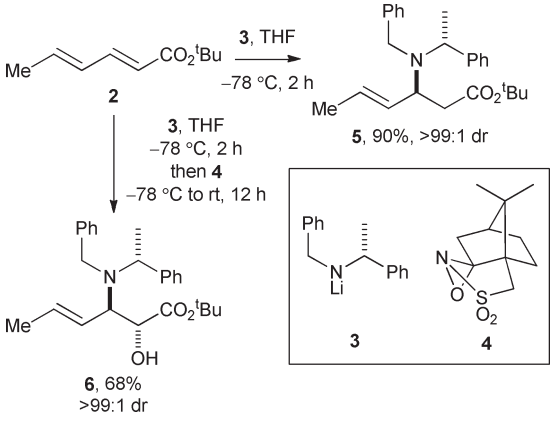
and unnatural imino[3] and amino[4] sugars. As part of our investigations, we envisaged that development of highly diastereoselective dihydroxylation protocols for *tert*-butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl) amino]hex-4-enoate would provide a synthetic route to the 3,6-dideoxy-3-aminohexose family of amino sugars and we delineate herein our initial findings within this area.

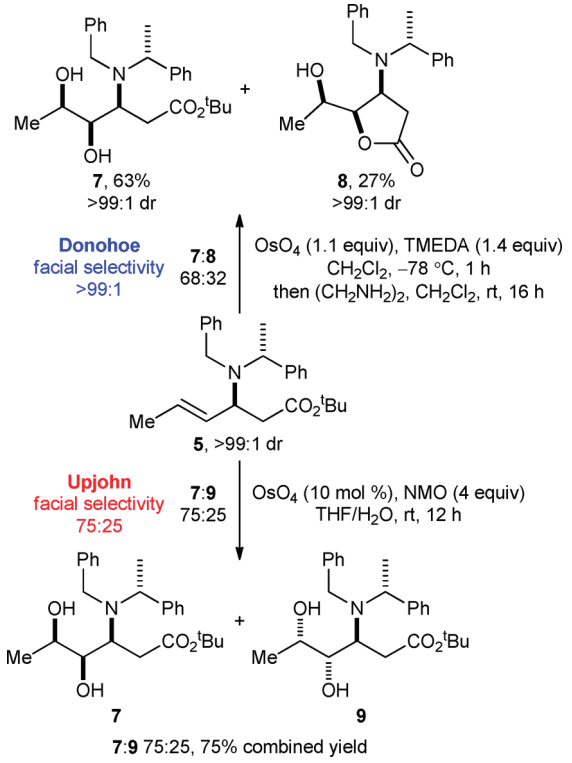
Sorbic acid [(*E*,*E*)-hexa-2,4-dienoic acid] **1** was converted to the corresponding *tert*-butyl ester **2** using isobutene and catalytic H_2SO_4 in 80% yield. Diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **3**[5] (99% ee)[6] to α,*β*-unsaturated ester **2** gave *β*-amino ester **5**[7] in 90% yield, while aminohydroxylation of **2**[8] employing conjugate addition of lithium amide **3** and in situ enolate oxidation with (−)-camphorsulfonyloxaziridine [(−)-CSO] **4**[9] gave α-hydroxy-*β*-amino ester **6**[10] as a single diastereoisomer, which was isolated in 68% yield (Scheme 1).

Scheme 1. Synthesis of *β*-Amino Ester **5** and α-Hydroxy-*β*-amino Ester **6**



Dihydroxylation of *β*-amino ester **5** was initially investigated under the conditions developed by Donohoe and co-workers (using the OsO_4/TMEDA complex)[11] and gave a 68:32 mixture of diol **7**[12] and the corresponding lactone **8**[12] (arising from in situ cyclization of diol **7**),[13] indicating complete facial selectivity for the dihydroxylation reaction. Chromatography allowed the isolation of diol **7** in 63% yield and lactone **8** in 27% yield, as a single diastereoisomer in each case (Scheme 2). The relative configuration within diol **7** was unambiguously established by single crystal X-ray diffraction analysis,[14] with the absolute (3*S*,4*R*,5*R*,α*R*)-configuration being assigned from the known configuration of the (*R*)-α-methylbenzyl stereocenter.[13] Dihydroxylation of **5** under Upjohn conditions (OsO_4/NMO)[15] resulted in the formation of a mixture of products, of which the major components (> 90%) were diols **7** and **9**, in the ratio 75:25 respectively. Chromatographic purification gave a 75:25 mixture of diols **7**:**9** in 75% yield (Scheme 2).

Scheme 2. Dihydroxylation of *β*-Amino Ester **5**



The effect of incorporation of an α-hydroxy group into the *β*-amino ester substrate scaffold was next examined. Dihydroxylation of α-hydroxy-*β*-amino ester **6** under Donohoe conditions[11] gave triol **10** in 95:5 dr. Chromatographic purification enabled the isolation of triol **10** in 56% yield (2 steps from **6**) as a single diastereoisomer (Scheme 3). The relative configuration within **10** was unambiguously established by single crystal X-ray diffraction analysis,[16] with the absolute (*R*,*R*,*R*,*R*)-configuration being assigned from the known configuration of the (*R*)-α-methylbenzyl stereocenter; this analysis also allowed the absolute configuration within α-hydroxy-*β*-amino ester **6** to be unambiguously confirmed. Thus, the presence of the α-hydroxy group within α-hydroxy-*β*-amino ester **6** affects neither the sense nor the magnitude of the facial selectivity of the dihydroxylation reaction under Donohoe conditions previously noted for *β*-amino ester **5**. Dihydroxylation of **6** under Upjohn conditions[15] meanwhile

(3) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *Org. Lett.* **2010**, *12*, 136. Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 8133.

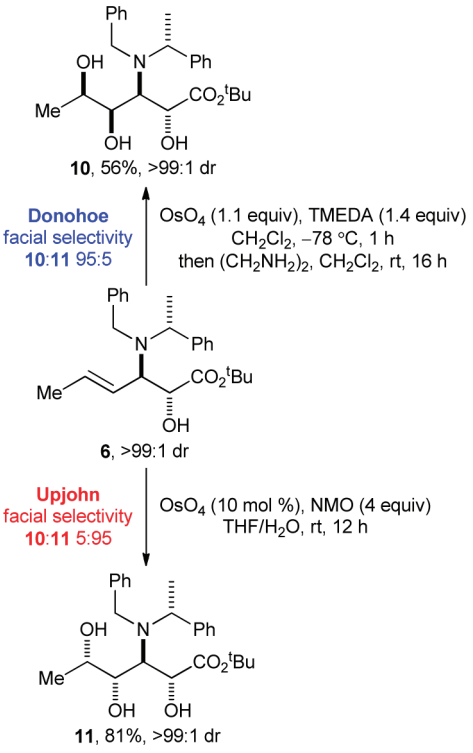
(4) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *Tetrahedron Lett.* **2011**, *52*, 2216.

(5) Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999. Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833.

(6) Enantiopure (*R*)-α-methylbenzylamine (99% ee) is commercially available. Reductive alkylation of (*R*)-α-methylbenzylamine upon treatment with benzaldehyde and $NaBH_4$ gave (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine; subsequent deprotonation with BuLi in THF generated a pink solution of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amide **3**.

(7) Davies, S. G.; Smyth, G. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2467.

Scheme 3. Dihydroxylation of α-Hydroxy-β-amino Ester **6**



proceeded with antipodal diastereofacial selectivity to give triol **11** in 95:5 dr, and in 81% isolated yield as a single diastereoisomer (> 99:1 dr) after chromatographic purification (Scheme 3). The relative configuration within **11** was unambiguously established by single crystal X-ray diffraction analysis,[17] with the absolute (2*R*,3*R*,4*S*,5*S*,α*R*)-configuration being assigned from the known configuration of the (*R*)-α-methylbenzyl stereocenter. In this case, therefore, the presence of the α-hydroxy group within α-hydroxy-β-amino ester **6** not only reverses the (modest) diastereofacial bias noted upon dihydroxylation of β-amino ester **5** but also confers excellent diastereoselectivity on the dihydroxylation process.

Antipodal diastereoselectivity has previously been noted in dihydroxylation reactions under Upjohn and Donohoe conditions in reactions of substrates that are conformationally constrained (often cyclic) and which invariably possess an allylic hydrogen-bond-donor functionality.[11,18] In these systems, the opposing diastereofacial selectivities of these dihydroxylation procedures are therefore ascribed to the ability of the OsO_4/TMEDA complex to participate as a hydrogen-bond acceptor,[11] while reaction under Upjohn conditions typically proceeds under steric or stereoelectronic control.[19] In contrast, the diastereofacial selectivities of both of these dihydroxylation procedures when applied to conformationally more labile systems are generally much lower.[20] Therefore, not only are the high levels of diastereoselectivity elicited in both the dihydroxylation reactions of α-hydroxy-β-amino ester **6** remarkable, but also the diastereodivergence, especially given that diastereoselective dihydroxylation of β-amino ester **5** and α-hydroxy-β-amino ester **6** with OsO_4/TMEDA (Donohoe conditions), demonstrates that the presence of the (homoallylic) α-hydroxyl group is not a prerequisite for determining the diastereofacial selectivity.

The potential for elaboration of the amino triols resulting from these highly diastereoselective and stereodivergent dihydroxylation reactions to the corresponding 3,6-dideoxy-3-aminohexoses was next explored. Treatment of **11** with TFA resulted in cyclization to give lactone **12** as a single diastereoisomer (> 99:1 dr) in 73% isolated yield. The relative configurations of the stereocenters around the lactone ring within **12** were assigned by ^{1}H NMR NOE analysis, with the absolute (3*R*,4*S*,5*S*,1′*S*,α*R*)-configuration of **12** being assigned from the known absolute configuration of the (*R*)-α-methylbenzyl stereocenter (and the

(8) For selected applications of our aminohydroxylation procedure, see: Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1994**, *5*, 203. Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 3708. Abraham, E.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2510. Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655. Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665. Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Savory, E. D.; Smith, A. D. *Tetrahedron: Asymmetry* **2009**, *20*, 758. Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 1594.

(9) Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Sheppard, A. C.; Kumar, A.; Davis, F. A. *Org. Synth.* **1990**, *69*, 158.

(10) Davies, S. G.; Epstein, S. W.; Garner, A. C.; Ichihara, O.; Smith, A. D. *Tetrahedron: Asymmetry* **2002**, *13*, 1555.

(11) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027. Donohoe, T. J.; Blades, K.; Moore, P. R.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *J. Org. Chem.* **1999**, *64*, 2980. Donohoe, T. J. *Synlett* **2002**, 1223. Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946.

(12) Davies, S. G.; Smyth, G. D.; Chippindale, A. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3089.

(13) Treatment of diol **7** with TFA-promoted lactonization to give **8** as the major product. The absolute configuration within lactone **8** has previously been unambiguously established by conversion to methyl D-3-*epi*-daunosaminide hydrochloride; see ref 12.

(14) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 814127.

(15) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

(16) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 805287.

(17) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 805286.

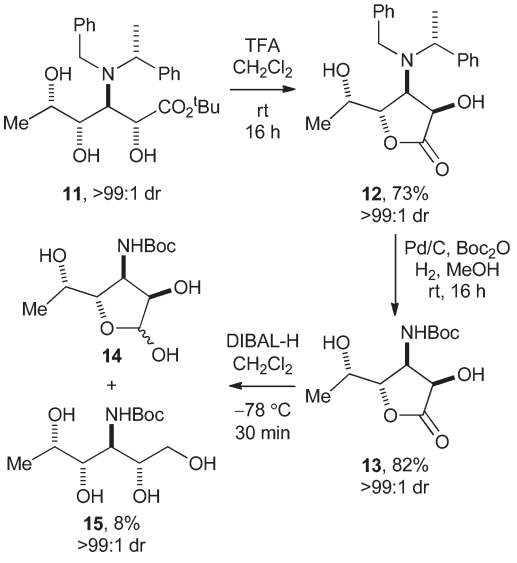
(18) A homoallylic hydroxyl group proved to be only a modest directing group for the OsO_4/TMEDA complex in a range of cyclic systems, with generally poor diastereodivergency between the two dihydroxylation protocols being noted, see: Donohoe, T. J.; Mitchell, L.; Waring, M. J.; Helliwell, M.; Bell, A.; Newcombe, N. J. *Org. Biomol. Chem.* **2003**, *1*, 2173.

(19) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947. Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. Cha, J. K.; Kin, N.-S. *Chem. Rev.* **1995**, *95*, 1761.

(20) Donohoe, T. J.; Newcombe, N. J.; Waring, M. J. *Tetrahedron Lett.* **1999**, *40*, 6881.

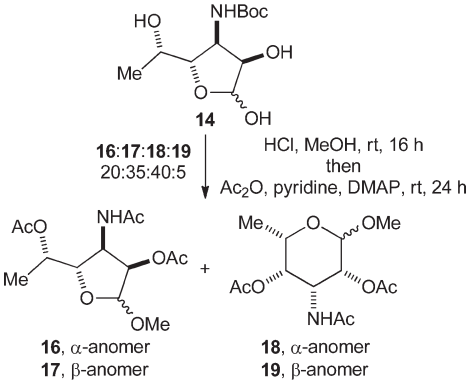
known absolute configuration within triol **11**). This study indicated that the cyclization process was not accompanied by epimerization of the α-stereocenter. Attempted reduction of lactone **12** to the corresponding lactol under a range of conditions was not efficacious and therefore an alternative strategy was pursued. Hydrogenolysis of **12** in the presence of Boc_2O gave *N*-Boc protected lactone **13** in 82% yield as a single diastereoisomer. Reduction of **13** with DIBAL-H at −78 °C for 30 min resulted in complete conversion of starting material to give lactol **14**, with only minimal over-reduction to the corresponding tetraol **15** (∼10%). Chromatographic purification gave a sample of lactol **14** in ∼90% purity[21] and tetraol **15** in 8% yield and >99:1 dr. The ^{1}H NMR spectrum of lactol **14** (in MeOH-d_4) was somewhat complex, presumably due to the presence of the anomers of both the 5- and 6-membered ring forms. Consistent with this assumption, reduction of lactone **13** with DIBAL-H and allowing the reaction mixture to warm to 0 °C gave tetraol **15** exclusively (Scheme 4).

Scheme 4. Elaboration of Triol **11**



Treatment of lactol **14** with a solution of anhydrous HCl in methanol followed by peracetylation of the crude reaction mixture gave an approximate 20:35:40:5 mixture of the α- and β-anomers of the furanose and pyranose forms of methyl *N*,*O*,*O*-triacetyl-3,6-dideoxy-3-amino-L-taloside **16**–**19**, respectively, which proved partially separable by chromatography and were isolated in 31% combined yield (in three steps from lactone **13**). Full analysis of **16**–**19** by ^{1}H and ^{13}C NMR spectroscopic analyses (including COSY, HSQC, HMBC, and NOE) allowed assignment of the structures and configurations at the anomeric centers within **16**–**19**. The ^{1}H and ^{13}C NMR spectroscopic data for our sample of methyl *N*,*O*,*O*-triacetyl-3,6-dideoxy-3-amino-α-L-talopyranoside **18** were entirely consistent with those previously reported by Hoveyda and coworkers[22] (Scheme 5).

Scheme 5. Synthesis of 3,6-Dideoxy-3-amino-L-talose



In conclusion, aminohydroxylation of *tert*-butyl sorbate [*tert*-butyl (*E*,*E*)-hexa-2,4-dienoate] using enantiopure lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and (−)-camphorsulfonyloxaziridine gives *tert*-butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate in >99:1 dr. Dihydroxylation under Upjohn conditions gives *tert*-butyl (2*R*,3*R*,4*S*,5*S*,α*R*)-2,4,5-trihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hexanoate, while dihydroxylation under Donohoe conditions proceeds with antipodal diastereofacial selectivity to give the (*R*,*R*,*R*,*R*,*R*)-diastereoisomer. The amino triols resulting from these dihydroxylation reactions are useful for further elaboration, as demonstrated by the asymmetric synthesis of 3,6-dideoxy-3-amino-L-talose. Investigations probing the origins of selectivity of these dihydroxylation reactions and further applications of these protocols to facilitate the preparation of other natural and unnatural amino sugars and polyhydroxylated amines are currently underway in our laboratory.

Acknowledgment. We thank Barbara Odell, University of Oxford, for assistance with NMR experiments.

Supporting Information Available. Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra, and crystallographic information files (for structures CCDC 805286, 805287, and 814127). This material is available free of charge via the Internet at http://pubs.acs.org.

(21) The sample of lactol **14** was contaminated with tetraol **15** alongside other unidentifiable species.

(22) Xu, Z.; Johannes, C. W.; La, D. S.; Hofilena, G. E.; Hoveyda, A. H. *Tetrahedron* **1997**, *53*, 16377. Also see: Richardson, A. C.; McLauchlan, K. A. *J. Chem. Soc.* **1962**, 2499. Čapek, K.; Jarý, J. *Coll. Czech. Chem. Commun.* **1966**, *31*, 2558. Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302.