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Bidirectional Metalation of Hydrobenzoin: Direct Access to New Chiral Ligands and Auxiliaries

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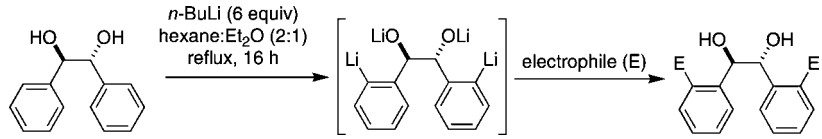
ABSTRACT



A bidirectional *ortho* metalation of the readily available chiral diol hydrobenzoin has been developed that provides direct access to new *ortho*-functionalized hydrobenzoin derivatives. This one-pot procedure should broaden the utility of hydrobenzoin as an auxiliary and ligand in asymmetric synthesis.

The discovery of new chiral auxiliaries or ligands for catalysis continues to broaden the scope of many asymmetric processes.[1] Oftentimes, however, the general utility of these auxiliaries/ligands is hampered by their cost, complexities associated with their syntheses, or their sole availability as a single enantiomer.[2] Consequently, the identification of cheap or readily accessible chiral scaffolds is an important pursuit. Both (*S*,*S*)- and (*R*,*R*)-hydrobenzoin (e.g., **1**, Figure 1) are readily available[3] and relatively inexpensive[4] and have been used as auxiliaries[5,6] and ligands[7] in a variety of asymmetric processes. For example, the boron enolate derived from oxapyrone **2** has shown useful levels of diastereoselectivity in glycolate aldol additions,[5b] and the ketene acetal **3** has been utilized in diastereoselective heterodiene cycloadditions.[5f] Notably, the diastereomeric ratio of the latter process increased from 7:3 to 9:1 with the introduction of a bromine atom in the *ortho* position on the

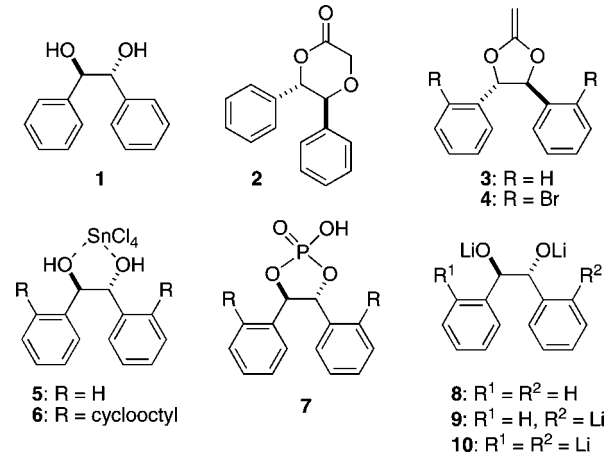


Figure 1. (*R*,*R*)-Hydrobenzoin (**1**), hydrobenzoin-containing chiral reagents and catalysts, and the novel tetraanion **10**.

(1) (a) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133. (b) Blaser, H.-U.; Pugin, B.; Spindler, F.; Thommen, M. *Acc. Chem. Res.* **2007**, *40*, 1240. (c) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278. (d) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269. (e) Desimoni, G.; Faita, G.; Jorgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

(2) Blaser, H.-U.; Studer, M. *Chirality* **1999**, *11*, 459.

(3) For a 100 g scale synthesis of (*R*, *R*)-**1** from benzoin, see: Ikariya, T.; Hashiguchi, S.; Murata, K.; Noyori, R. *Org. Synth.* **2005**, *82*, 10. For a 1 kg scale synthesis of (*R*,*R*)-**1** from *trans*-stilbene, see: Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302.

(4) Current Aldrich prices for (*R*,*R*)-**1**: $2.11(CDN)/mmol. For comparison purposes the price of (*R*)-BINOL is $16.35(CDN)/mmol.

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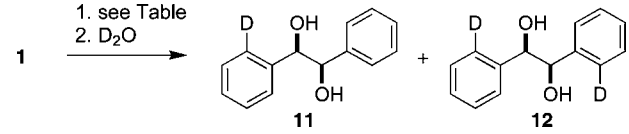
aromatic rings (i.e., **4**). Similarly, whereas the diol•$SnCl_4$ complex **5** was unable to impart significant enantioselectivity to the allylboration of hydrocinnamaldehyde (26% ee), the *ortho*-substituted derivative **6** proved to be an excellent catalyst for this reaction (93% ee).[7a] Though these *ortho*-substituted analogues of hydrobenzoin display improved stereoselectivities over **1**, their multistep preparation[8,9] and necessary enrichment to optical purity[10] realistically precludes the rapid production of congeneric libraries for ligand screening. As part of an ongoing total synthesis effort, we recently became interested in the use of Brønsted acids (e.g., **7**) as catalysts for asymmetric inverse electron-demand Diels−Alder reactions[11] and required rapid access to a variety of chiral diols for ligand screening purposes. Toward this goal, we endeavored to develop a direct synthesis of hydrobenzoin derivatives via the unprecedented tetraanion **10**. Herein we describe our efforts toward the realization of this goal, as well as the application of this reaction to the one-step synthesis of *ortho*-functionalized hydrobenzoin derivatives.

Although the hydroxymethyl group has received limited use in directed *ortho* metalation (DoM) reactions,[12,13] we envisaged a process whereby consecutive *ortho* metalations of **1** would lead to the tetraanion **10** (Figure 1), the subsequent treatment of which with various electrophiles would provide direct access to *ortho*-substituted hydrobenzoin derivatives.[14] Toward this end we initiated a large screen of reaction conditions and were delighted to eventually find that addition of excess *n*-BuLi to a suspension of (*R*,*R*)-hydrobenzoin (**1**) in a refluxing mixture of hexane/Et_2O (4:1) resulted in the gradual dissolution of **1** and formation of a deep red solution that when treated with D_2O allowed for clean recovery of (*R*,*R*)-hydrobenzoin[15] with 75% of the expected deuterium incorporation for **12** (Table 1, entry 1).

Table 1. Bidirectional Metalation of (*R*,*R*)-Hydrobenzoin (**1**)



11 **12**

entry	alkyl lithium (equivalents)[a]	hexane: Et_2O	time	% deuterium incorporation[b,c]
1	*n*-BuLi (8)	4:1	8	75
2	*s*-BuLi (8)	4:1	8	65
3	*n*-BuLi (8)	4:1	24	82
4	*n*-BuLi (8)	3:1	8	73
5	*n*-BuLi (8)	2:1	8	83
6	*n*-BuLi (8)	1:1	8	78
7	*n*-BuLi (6)	2:1	16	92

[a] Reactions carried out on 0.5 mmol scale in refluxing solvent, [**1**] = 0.08 M. [b] Calculated from integration of ^{1}H NMR spectra of crude reaction products using the following formula (∫benzyl protons = 2): |(∫*ortho* protons)/2 − 2| × 100%. [c] **11** and **12** were indistinguishable by ^{1}H, ^{13}C, or ^{2}D NMR.

Although use of *s*-BuLi (entry 2) or addition of TMEDA[13d] failed to improve upon this result, a slight increase in deuterium incorporation was observed when the reaction time was increased to 24 h (entry 3). The optimal ratio of hexane/Et_2O was also investigated and found to be 2:1 (entries 4−6). Monitoring the formation of the tetraanion **10** by measurement of butane gas evolution indicated that rapid (20 min) deprotonation of the two alcohol functions is followed by slow (16 h) removal of two *ortho* protons. On the basis of these observations, the optimized conditions for the formation of **12** and consequently the production of the tetraanion **10** are summarized in entry 7.

The progress of the reaction of **1** with *n*-BuLi under the optimized conditions (Table 1, entry 7) was also monitored by mass spectrometry following D_2O quench. The data presented in Figure 2 suggest that a relatively slow removal of one *ortho* proton is followed by a more rapid removal of the second *ortho* proton to generate **10**. Unfortunately, ^{3}Li and ^{1}H NMR spectroscopy provided little additional insight into this process, and the nature and aggregation of the intermediate(s) involved in the production of **10** along with

(5) For example, see: (a) Broeker, J.; Knollmueller, M.; Gaertner, P. *Tetrahedron: Asymmetry* **2006**, *17*, 2413. (b) Andrus, M. B.; Sekhar, B. B. V. S.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035. (c) Kim, K. S.; Lee, Y. J.; Kim, J. H.; Sung, D. K. *Chem. Commun.* **2002**, 1116. (d) Mazé, F.; Purpura, M.; Bernaud, F.; Mangeney, P.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1957. (e) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1995**, *60*, 7230. (f) Wallace, T. W.; Wardell, I.; Li, K.-D.; Leeming, P.; Redhouse, A. D.; Challand, S. R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2293. (g) Fujioka, H.; Kitagawa, H.; Nagatomi, Y.; Kita, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2113.

(6) For examples of chiral phosphepines and thiepines that incorporate hydrobenzoin, see: (a) Wyatt, P.; Hudson, A.; Charmant, J.; Orpen, A. G.; Phetmung, H. *Org. Biomol. Chem.* **2006**, *4*, 2218. (b) Wyatt, P.; Warren, S.; McPartlin, M.; Woodroffe, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 279, and references therein.

(7) For example, see: (a) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. (b) Mlynarski, J.; Jankowska, J.; Rakiel, B. *Tetrahedron: Asymmetry* **2005**, *16*, 1521. (c) Mlynarski, J.; Mitura, M. *Tetrahedron Lett.* **2004**, *45*, 7549. (d) Terfort, A.; Brunner, H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1467. (e) Amurrio, D.; Khan, K.; Kündig, E. P. *J. Org. Chem.* **1996**, *61*, 2258. (f) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266.

(8) For the synthesis of *ortho*-substituted hydrobenzoin derivatives, see refs 5f, 6a, 6b, 7a, and 7d.

(9) The synthesis of *ortho*-functionalized hydrobenzoins typically involves McMurry coupling of an *ortho*-substituted benzaldehdye, followed by I_2-catalyzed isomerization of the resulting stilbene and Sharpless asymmetric dihydroxylation. For examples where Sharpless asymmetric dihydroxylation of *ortho*-functionalized *trans*-stilbenes fails to provide the desired diol, see ref 7a.

(10) For complications associated with the optical enrichment of hydrobenzoin derivatives by crystallization, see ref 7d.

(11) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070.

(12) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(13) For examples of *ortho*-metalation reactions involving a benzyl alcohol or α-methylbenzyl alcohol, see: (a) Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron: Asymmetry* **2003**, *14*, 439. (b) Hirt, U. H.; Spingler, B.; Wirth, T. *J. Org. Chem.* **1998**, *63*, 7674. (c) Panetta, C. A.; Garlick, S. M.; Durst, H. D.; Longo, F. R.; Ward, J. R. *J. Org. Chem.* **1990**, *55*, 5202. (d) Meyer, N.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 521.

(14) For a conceptually related but less direct approach to functionalized hydrobenzoins, see refs 6a and 6b.

(15) While it is unlikely that any epimerization of (*R*,*R*)-hydrobenzoin could occur during this process, the optical purity of (*R*,*R*)-hydrobenzoin recovered from the treatment of the tetraanion **10** with H_2O was confirmed by chiral GC analysis. In addition, the ^{1}H NMR spectra of the crude product contained none of the corresponding *meso*-hydrobenzoin, which can be differentiated from *dl*-hydrobenzoin by the chemical shift of the benzyl protons. ^{1}H NMR ($CDCl_3$) δ: 4.72 ppm (*dl*-hydrobenzoin); 4.80 ppm (*meso*-hydrobenzoin). Periasamy, M.; Srinivas, G.; Karunakar, G. V.; Bharathi, P. *Tetrahedron Lett.* **1999**, *40*, 7577.

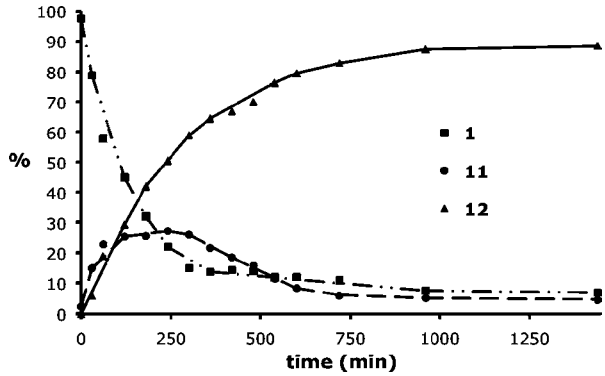
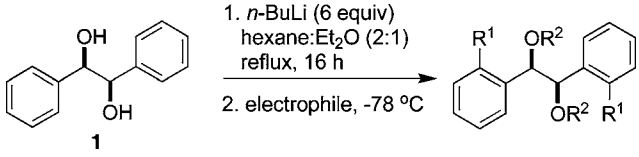


Figure 2. Percentage of hydrobenzoin (**1**), monodeuterohydrobenzoin **11**, and dideuterohydrobenzoin **12** following treatment of a refluxing solution of **1** and *n*-BuLi (6 equiv) with D_2O after various reaction times. The crude product following D_2O quench was concentrated from CH_3OH to ensure complete exchange of OH for OD. The ratio of **1**:**11**:**12** was determined by mass spectrometry (ESI).

an explanation for the relatively facile deprotonation of **9** remain the subject of an ongoing investigation.[16]

Nevertheless, with a procedure in place to generate **10** in good yield we turned our attention to exploiting this reactive intermediate in the direct synthesis of *ortho*-functionalized derivatives. As detailed in Table 2, treatment of **1** with

Table 2. Synthesis of Hydrobenzoin Derivatives

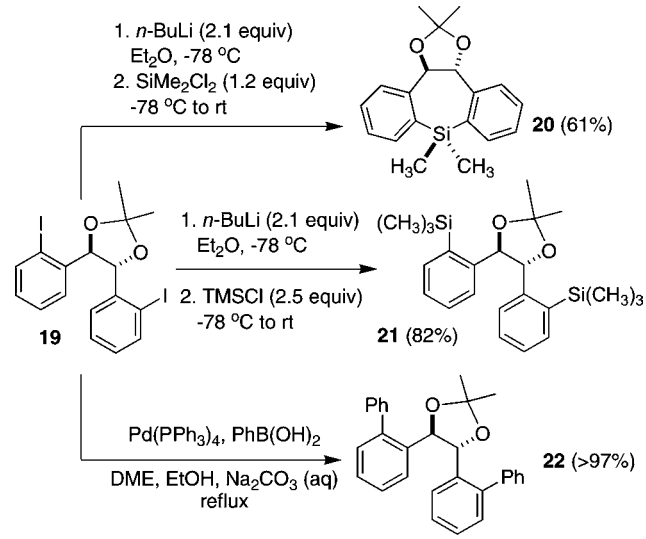


entry	electophile[a]	R^1	R^2	ratio of products[b]	product (% yield)[c]
1	CH_3I	CH_3	H	5:1:1	**13** (53)
2	I_2	I	H	6:2:1	**14** (53)
3	$(CH_2Br)_2$	Br	H	5:3:1	**15** (33)
4	CO_2	CO[d,e]		ND[f]	**16** (40)
5	$B(OCH_3)_3$[g]	B(OH)[d]		10:2:5	**17** (42)
6	$Si(CH_3)_2Cl_2$	$Si(CH_3)_2$[d]		8:2:3	**18** (36)

[a] 7 equiv of electrophile. [b] Ratio of disubstituted hydrobenzoin: monosubstituted hydrobenzoin:recovered **1** determined by analysis of ^1H NMR spectra of crude reaction mixtures. [c] Isolated yield. [d] Unambiguous assignment of a five- or six-membered ring was not possible using NMR spectroscopy. [e] IR stretch values for the carbonyl functions in **16** were consistent with those of a γ-lactone. [f] Product isolated by recrystallization. [g] $B(OCH_3)_3$ was added at 0 °C.

n-BuLi followed by CH_3I, I_2,[17] dibromoethane, CO_2, $B(OCH_3)_3$, or $Si(CH_3)_2Cl_2$ gave reasonable yields of the corresponding *ortho*-substituted hydrobenzoin derivatives, along with minor amounts of products resulting from *ortho* functionalization of only one of the aromatic rings and recovered **1**, all of which were readily purified by flash chromatography or recrystallization. Unfortunately, we were unable to translate the high level of deuterium incorporation (>90%) observed during the optimization of the DoM step (vide supra) to the reaction of **10** with a broader array of electrophiles.[18] Attempts to temper the basicity of **10** by transmetalation (e.g., $ZnCl_2$ or $MgBr_2$) also failed to improve upon these results. Despite the limited scope of electrophiles that engaged in productive reactions with **10**, the now readily available and *optically pure* aryl halide **14** proved to be a useful intermediate for the synthesis of a variety of hydrobenzoin derivatives (Scheme 1). For example, the dianion

Scheme 1. Synthesis of Hydrobenzoin Derivatives from **19**



derived from acetonide **19**[19] smoothly coupled with electrophiles (e.g., TMSCl, $SiMe_2Cl_2$), and **19** itself engages in high yielding palladium-catalyzed cross-coupling reactions,[20] providing rapid access to the *ortho*-functionalized hydrobenzoins **20**−**22**.[21]

The bis-benzoxaborol **17**[22] also proved to be a versatile intermediate for the synthesis of derivatives of **1** through

(16) For mechanistic analyses of DoM reactions, see: (a) Chadwick, S. T.; Ramirez, A.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 2259. (b) Singh, K. J.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 13753. (c) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (d) Slocum, D. W.; Dumbris, S.; Brown, S.; Jackson, G.; LaMastus, R.; Mullins, E.; Ray, J.; Shelton, P.; Walstrom, A.; Wilcox, J. M.; Holman, R. W. *Tetrahedron* **2003**, *59*, 8275. (e) Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640.

(17) Repetition of this reaction with 4 or 5 equiv of *n*-BuLi (reflux, 16 h) provided **14** in 19% or 34% isolated yield, respectively.

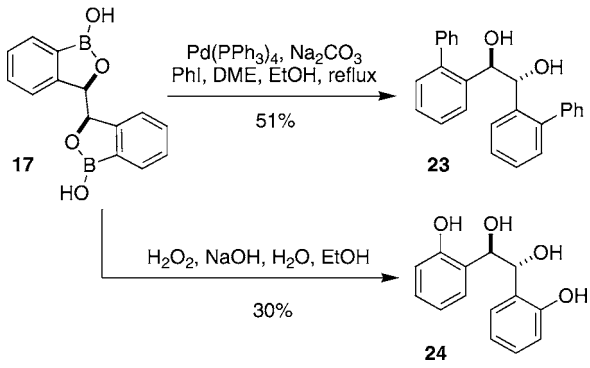
(18) Examples of electrophiles that proved incompatible with **10** and/or provided the desired product in very low yield (<10%) include benzaldehyde, acetone, acetaldehyde, diethylcarbonate, valeraldehyde, trimethylsilyl chloride, cyclohexanal, crotonaldehyde, paraformaldehyde, formaldehyde, dimethylformamide, and benzylbromide.

(19) The acetonide **19** was prepared in >97% yield by treating a solution of **14** in dimethoxypropane with a catalytic amount of HCl.

(20) Attempts to directly couple the diol **14** with aryl boronic acids resulted primarily in the formation of *cis*-4b,9b-dihydrobenzofuro[3,2-*b*]benzofuran. For an unrelated synthesis of this substance, see: Masutani, K.; Irie, R.; Katsuki, T. *Chem. Lett.* **2002**, 36.

cross-coupling reactions with aryl halides[23] or vinyl triflates.[24] This approach to functionalized hydrobenzoin derivatives complements that described above and avoids protection of the benzyl alcohol functions.[20] As indicated in Scheme 2, this process provides optically pure *ortho*-

Scheme 2. Synthesis of Hydrobenzoin Derivatives from **17**



functionalized hydrobenzoin derivatives in two steps from **1** through the intermediacy of **17**. Moreover, for the purpose of the cross-coupling, we found that purification of the bis-benzoxaborol **17** is unnecessary. For example, the *overall yield* of compound **23** from (*R*,*R*)-hydrobenzoin (**1**) was 32% when the crude bis-benzoxaborol **17** was used as compared to 21% when **17** was purified by flash chromatography. The bis-benzoxaborol **17** also proved to be a suitable precursor for the C_2-symmetric bis-phenol **24**, following hydroperoxide oxidation.[25] Notably, the acetonide of the tetraol **24** has been reported by others[26] as a potential BINOL-like ligand for asymmetric synthesis.

In summary, we have developed a one-pot process for the direct functionalization of the readily available and relatively inexpensive chiral diol hydrobenzoin. Importantly, this work provides a means to rapidly access a wide variety of new chiral ligands and auxiliaries in optically pure form. The application of chiral diols generated in this work as ligands in a variety of asymmetric processes, including Brønsted acid catalyzed inverse electron-demand Diels−Alder reactions, will be reported in due course.

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Supporting Information Available: Detailed experimental procedures and characterization data for each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Attempts to effect the cross-coupling of **19** with pyridine *N*-oxide following the procedure reported in Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020 led predominantly to the formation of the acetonide of dihydro-phenanthrenediol.

(22) The bis-benzoxaborol **17** may possess two five- or six-membered oxaborine rings. On the basis of the observation of two bands at 1346 and 1371 cm^{-1} in the IR spectrum of this compound, which are consistent with those reported at 1345 and 1365 cm^{-1} for the B−O stretching modes in 3-methyl-2,1-benzoxaborol, we have tentatively assigned the structure for **17** as shown in Scheme 2. See: Dale, W. J.; Rush, J. E. *J. Org. Chem.* **1962**, *27*, 2598.

(23) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V.; Josephy, P. D. *J. Org. Chem.* **1991**, *56*, 3763.

(24) The palladium-catalyzed cross-coupling of **17** with 1-trifluoromethanesulfonic acid cyclooct-1-enyl ester ($Pd(dppe)Cl_2$, Na_2CO_3, EtOH, DME, reflux) provided the cyclooctenyl precursor to **6** in 17% isolated yield.

(25) Simon, J.; Salzbrunn, S.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2001**, *66*, 633.

(26) The acetonide of **24** has been synthesized in 6% overall yield following a six-step sequence of reactions. See: Yamamoto, H.; Kobayashi, S.; Kanemasa, S. *Tetrahedron: Asymmetry* **1996**, *7*, 149.