Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8051–8055

TETRAHEDRON LETTERS

Diastereoselective allylations and crotylations under phase-transfer conditions using trifluoroborate salts: an application to the total synthesis of (−)-tetrahydrolipstatin

Avinash N. Thadani and Robert A. Batey*

Department of Chemistry, 80 St. George Street, University of Toronto, Toronto, Ontario, M5S 3H6, Canada

Received 29 August 2003; accepted 8 September 2003

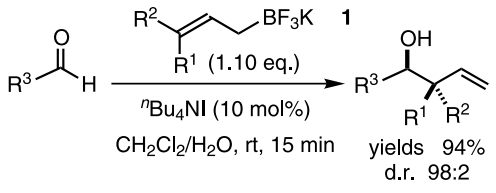
Abstract—A mild protocol for diastereoselective allylations and crotylations of α- and β-silyloxy substituted aldehydes utilizing potassium allyl/crotyltrifluoroborates is described. The reactions proceed to completion within 30 min at room temperature in biphasic or aqueous media in the presence of a phase transfer catalyst. The resulting homoallylic alcohols are obtained in high yields and moderate to excellent diastereoselectivities. The method was applied to the asymmetric total synthesis of the antiobesity agent tetrahydrolipstatin (orlistat™).

The development of new synthetic methods that are more environmentally benign has been propelled by the growing importance of green chemistry in organic synthesis.[1] One important strategy to achieve this goal are transformations that are carried out in aqueous/biphasic media, since they have the benefit of reduced use of traditional organic solvents.[2] Allylations of carbonyl compounds are among the reactions that have been successfully carried out in water or aqueous-based systems.[3] Barbier-type allylations have been promoted by a variety of metals including In,[4] Mg,[5] Sn[6] and Zn.[7] These protocols do, however, have their limitations including poor diastereoselectivities obtained for crotylations of aldehydes.

As part of an ongoing program on the use of organotrifluoroborates in organic synthesis,[8,9] we reported that potassium allyl- and crotyltrifluoroborates, a new class of allylboron reagents, undergo efficient additions to aldehydes, in the first example of Lewis-acid activated addition reactions of allylboron compounds.[8a,b,10] More, recently, we established that these reagents also undergo addition to aldehydes in both biphasic media and water to provide the corresponding homoallylic alcohols in high yields, excellent diastereoselectivity and without the necessity of any subsequent purification.[9] The presence of a phase transfer catalyst (e.g. $^{n}Bu_4NI$) was found to significantly accelerate the rate of reaction, whereas added fluoride ion retarded the reaction (Scheme 1). These observations are consistent with a mechanism involving fluoride dissociation from the trifluoroborate anion, occurring prior to the addition step.

The reaction of allyl and crotyl metal reagents with aldehydes containing adjacent stereocenters is of importance in the context of acyclic stereoselective synthesis.[11] We report in this letter the diastereoselective allylation and crotylation of α- and β-silyloxy substituted aldehydes utilizing potassium allyl and crotyltrifluoroborates **1** in biphasic media.

We first chose to examine reaction of α-*tert*-butyldimethylsiloxy substituted aldehydes **2** with **1** (Table 1). The allylation of **2** with potassium allyltrifluoroborate **1a** gave only modest diastereoselection,

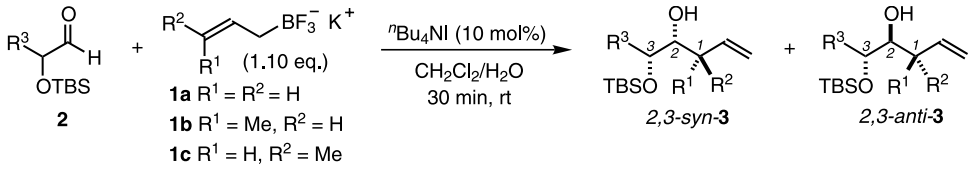


Scheme 1.

Keywords: boron; allylboration; allyltrifluoroborates; biphasic; phase transfer catalyst; tetrahydrolipstatin; total synthesis.
* Corresponding author. Tel./fax: (+1)-416-978-5059; e-mail: rbatey@chem.utoronto.ca

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.053

Table 1. Allylation and crotylation of α-(*tert*-butyldimethylsilyloxy) aldehydes by potassium allyl- and crotyltrifluoroborates **1** in biphasic media



Entry	R^1	R^2	R^3	2,3-*syn*-**3**:2,3-*anti*-**3**	Yield (%)
1	H	H	Me	30:70	95 (**3a**)
2	H	H	Ph	35:65	94 (**3b**)
3	Me	H	Me	5:95[a]	95 (**3c**)
4	H	Me	Me	75:25	95 (**3d**)
5	Me	H	Ph	10:90[b]	97 (**3e**)
6	H	Me	Ph	10:90	99 (**3f**)

[a] Trace amounts of **3d**-*syn* also present in isolated adducts.
[b] Trace amounts of **3f**-*syn* also present in isolated adducts.

although with excellent overall yields (Table 1, entries 1, 2). The desired products were cleanly obtained and chromatography was only required if separation of the two diastereomers was desired. The crotylation of **2** with potassium crotyltrifluoroborate **1b**/**c**, however, displayed greater levels of diastereoselectivity (Table 1, entries 3–6). Potassium (*Z*)-crotyltrifluoroborate **1b** displays very good 2,3-*anti* selectivity while the corresponding (*E*)-crotyl reagent **1c** shows more modest 2,3-*syn* selectivity in the reaction with 2-(*tert*-butyldimethylsilyloxy)propanal (Table 1, entries 3 and 4). These results have been rationalized by invoking Conforth-like transition states.[12] Transition states **4** and **5** have been identified by Roush and Hoffmann as the least sterically hindered ones accessible in reactions with (*Z*)- and (*E*)-crotylboron reagents, respectively (Fig. 1).[11–13] Transition state **4**, that has a Conforth-like conformation of the aldehyde, lacks any significant nonbonded interactions involving the methyl group of the (*Z*)-crotyltrifluoroborate **1b** and is presumably the lowest energy transition state structure available, leading to 1,2-*syn*-2,3-*anti*-**3** as the major product.[12] Transition state **5** experiences the fewest non-bonded (gauche pentane) interactions for the reaction of potassium (*E*)-crotyltrifluoroborate **1c**.[11,13] Transition state **6**, on the other hand, is expected to benefit from favorable stereoelectronic activation.[11] The subtle differences between **5** and **6** perhaps may rationalize the only modest 2,3-*syn* diastereoselectivity obtained for the reaction of potassium (*E*)-crotyltrifluoroborate **1c** with α-silyloxyaldehyde **2** ($R^3 = CH_3$). The reactions of both **1b**/**c** with 2-(*tert*-butyldimethylsilyloxy)-2-phenylacetaldehyde (Table 1, entries 5 and 6) displayed good 2,3-*anti* selectivity. At the present time the origin of the switch in the diastereoselectivity observed in the reaction of **1c** with this aldehyde relative to that observed with 2-(*tert*-butyldimethylsilyloxy)propanal is not clear (cf. Table 1, entries 4 and 6).

The reaction of β-(*tert*-butyldimethylsilyloxy) substituted aldehydes **7** with potassium allyl- and (*E*)- and (*Z*)-crotyltrifluoroborates **1a**–**c** results in modest diastereoselectivity in favor of the 2,4-*anti* diastereoisomer **8** (Table 2). The lower overall diastereoselection observed with β-substituted aldehydes **7** is presumably due to the more remote nature of the stereocenter.

In comparison with our earlier reported Lewis-acid catalyzed protocol,[9] the current methodology affords the resulting homoallylic alcohols in uniformly higher yields and under very mild conditions. The diastereoselectivities obtained under both protocols were identical suggesting the involvement of similar closed Zimmerman–Traxler like transition states.

The biphasic allylation methodology was applied to a short total synthesis of (−)-tetrahydrolipstatin **9** (Scheme 2). Tetrahydrolipstatin (orlistat™), the saturated form of lipstatin, was isolated in 1987 from *Spreptomyces toxytricin*[14] and functions as a triglyceride mimic. It is a potent and irreversible inhibitor of pancreatic lipase,[14b] a consequence of an irreversible

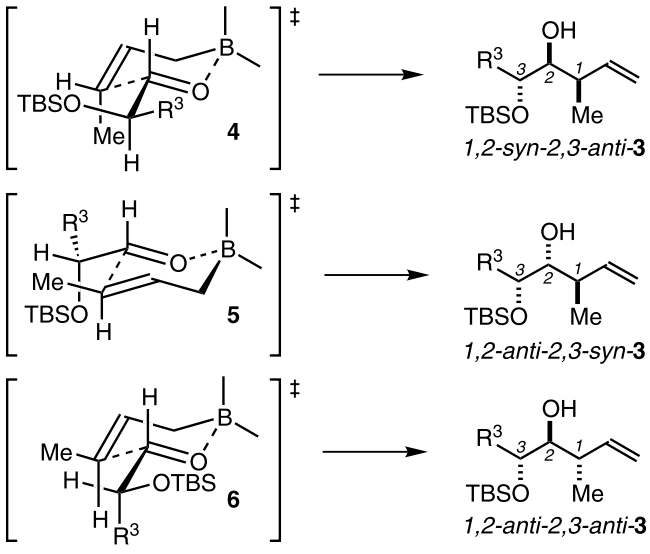
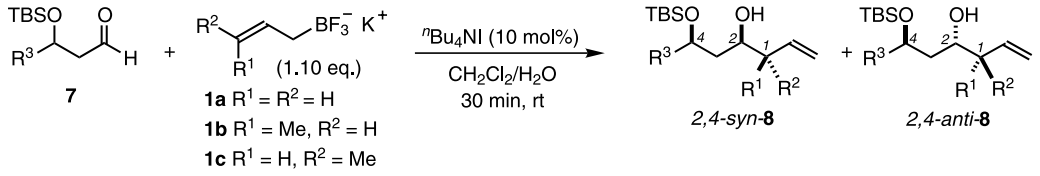
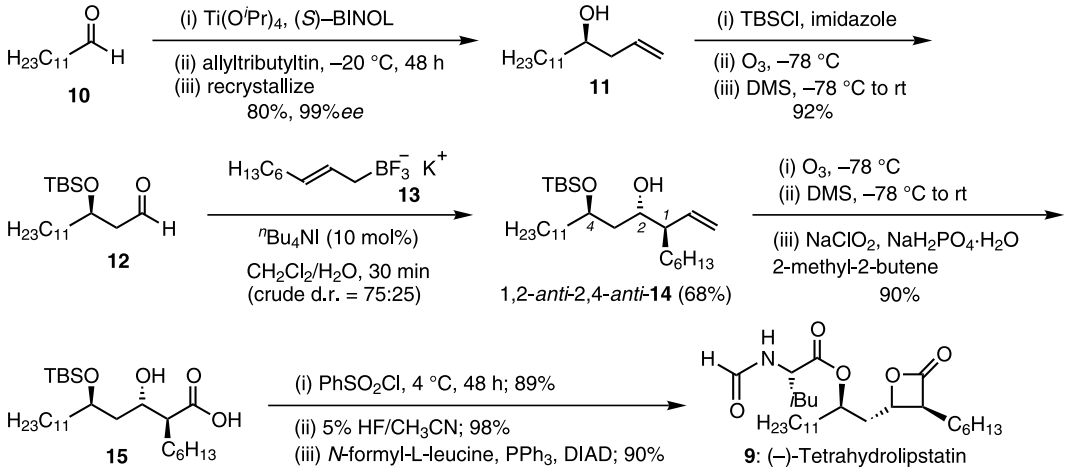


Figure 1.

Table 2. Allylation and crotylation of β-(*tert*-butyldimethylsilyloxy) aldehydes by potassium allyl- and crotyltrifluoroborates **1** in biphasic media



Entry	R^1	R^2	R^3	2,4-*syn*-**8**:2,4-*anti*-**8**	Yield (%)
1	H	H	^{i}Pr	35:65	97 (**8a**)
2	H	H	Ph	35:65	94 (**8b**)
3	Me	H	Ph	25:75	96 (**8c**)
4	H	Me	Ph	25:75	96 (**8d**)

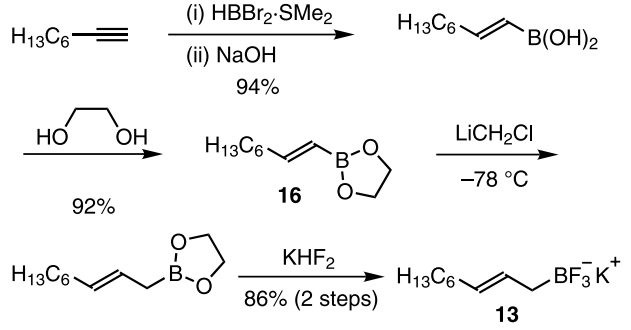


Scheme 2.

reaction of the β-lactone moiety present in **9** with an active site serine residue in the enzyme.[15] Significant synthetic studies have been directed at this target resulting in several total syntheses.[16]

A drawback to the methodology described in this letter is the inability to carry out enantioselective allylation/crotylations. There are, however, several complementary methodologies that can accomplish this task. We chose the allylation protocol developed by Keck et al. to construct the first stereocenter of tetrahydrolipstatin.[17] Thus, the reaction of dodecanal **10** with allyltri-*n*-butylstannane using a titanium (*S*)-BINOL derived catalyst afforded homoallyl alcohol **11** in 80% isolated yield and 99% ee after recrystallization (Scheme 2). Protection of the free hydroxyl group of **11** as the corresponding TBS ether (quant.) and ozonolysis with reductive workup resulted in β-substituted aldehyde **12** (92%), which is poised for the pivotal diastereoselective allylation step. Reaction of **12** with potassium (2*E*)-nonenyltrifluoroborate **13** in the presence of 10 mol% ^{n}BuNI in a biphasic medium (CH_2Cl_2/H_2O) provided a 3:1 mixture of 1,2-*anti*-2,4-*anti* and 1,2-*anti*-2,4-*syn* diastereomers of **14**. Both stereoisomers of **14** had a 1,2-*anti* stereochemical relationship, consistent with reaction through a closed Zimmerman–Traxler like transition state. As anticipated from the model studies described above, the major diastereomer has a 2,4-*anti* stereochemical relationship. The major diastereomer 1,2-*anti*-2,4-*anti*-**14** was readily separated and isolated in 68% yield. A prior synthesis by Hannessian utilizing a Lewis acid catalyzed allylsilane addition for an analogous transformation, led to mixtures of 1,2-*syn* and 1,2-*anti* products.[18] Compound **14** was then subjected to ozonolysis and the intermediate aldehyde oxidized in situ to the corresponding carboxylic acid **15** (90%).[16h] Adam's protocol was used to construct the important β-lactone moiety (89%) and the silyl ether deprotected in near quantitative yield.[16a,19] Finally, installation of the *N*-formyl-L-leucine residue occurred under standard Mitsonobu conditions (90%).[16a,h] (–)-Tetrahydrolipstatin **9** was thus obtained in nine steps and 35% overall yield (based on dodecanal). The key reagent **13** employed in the synthesis was derived by hydroboration of (*E*)-octyne with $HBBr_2$, and esterification to yield the ethylene glycol derived boronate **16** (Scheme 3). Matteson homologation[20] of **16** and subsequent treatment with KHF_2 led to trifluoroborate salt **13** (Scheme 3).

In conclusion, we have demonstrated that the diastereoselective biphasic allylation and crotylation of



Scheme 3.

α- and β-substituted aldehydes utilizing potassium allyl and crotyltrifluoroborates yields the corresponding homoallylic alcohols in high yields and under very mild conditions. The utility of this methodology was demonstrated in a total synthesis of (−)-tetrahydrolipstatin, which was accomplished in nine steps from dodecanal with an overall yield of 35%. Further applications on the use of trifluoroborate salts in organic synthesis are currently underway in our laboratories and will be reported in due course.

Acknowledgements

The Natural Science and Engineering Research Council (NSERC) of Canada funded this research. R.A.B. gratefully acknowledges receipt of a Premier's Research Excellence Award. A.N.T. thanks the NSERC of Canada for postgraduate scholarships. We also thank Dr. Alex Young for mass spectral analysis.

References

1. For a brief review on green chemistry, see: Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686–694.
2. For a review of diastereoselective reactions in water, including allylations, see: Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751–2772.
3. For reviews on allylations in general, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293; (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp. 1–53 and references cited therein; (c) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer-Verlag: Berlin, 1995.
4. For recent examples, see: (a) Loh, T.-P.; Yin, Z.; Song, H.-Y.; Tan, K.-L. *Tetrahedron Lett.* **2003**, *44*, 911–914; (b) Lu, W.; Chan, T. K. *J. Org. Chem.* **2001**, *66*, 3467–3473; (c) Loh, T.-P.; Zhou, J. R.; Yin, Z. *Org. Lett.* **1999**, *1*, 1855–1857; (d) Paquette, L. A.; Rothhaar, R. R. *J. Org. Chem.* **1999**, *64*, 217–224; (e) Paquette, L. A.; Mitzel, T. M. *J. Org. Chem.* **1996**, *61*, 8799–8804; (f) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228–3229.
5. Zhang, W. C.; Li, C. J. *J. Org. Chem.* **1999**, *64*, 3230–3236.
6. For recent examples, see: (a) Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* **2000**, *41*, 5261–5264; (b) Loh, T.-P.; Xu, J.; Hu, Q.-Y.; Vittal, J. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1565–1569; (c) Chan, T. H.; Yang, Y.; Li, C. J. *J. Org. Chem.* **1999**, *64*, 4452–4455; (d) Ito, A.; Kishida, M.; Kurusu, Y.; Masuyama, Y. *J. Org. Chem.* **2000**, *65*, 494–498.
7. For recent examples, see: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodríguez-Acebes, R. *J. Org. Chem.* **2001**, *66*, 5208–5216; (b) Márquez, F.; Llebaria, A.; Delgado, A. *Org. Lett.* **2000**, *2*, 547–549; (c) Marton, D.; Stivanello, D.; Tagliavini, G. *J. Org. Chem.* **1996**, *61*, 2731–2737.
8. (a) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990–998; (b) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289–4292; (c) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099–9103; (d) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683–1686; (e) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *4*, 1381–1384.
9. Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *4*, 3827–3830.
10. See also: (a) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160–10161; (b) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414–12415; (c) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586–11587.
11. (a) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422–3434; (b) Roush, W. R.; Adam, M. A.; Harris, D. J. *J. Org. Chem.* **1985**, *50*, 2000–2003.
12. (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112–127; (b) Hoffman, R. W.; Weidmann, U.; Metternich, R.; Lanz, J. In *Boron Chemistry*; Hermànek, S., Ed.; World Scientific Publishers: Singapore, 1988; pp. 337–338; (c) Roush, W. R. In *Houben-Weyl, Stereoselective Synthesis*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, Germany, 1995; Vol. E21b, pp. 1410–1486.
13. (a) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann. Chem.* **1987**, 881–887; (b) Brinkmann, H.; Hoffmann, R. W. *Chem. Ber.* **1990**, *123*, 2395–2401.
14. (a) Weibel, E. K.; Hadvary, P.; Hochuli, E.; Kupfer, E.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081–1085; (b) Hochuli, E.; Kupfer, E.; Maurer, R.; Meister, W.; Mercadel, Y.; Schmidt, K. *J. Antibiot.* **1987**, *40*, 1086–1091.
15. (a) Hadvary, P.; Sidler, W.; Meister, W.; Vetter, W.; Wolfer, H. *J. Biol. Chem.* **1991**, *266*, 2021–2027; (b) Borgstrom, B. *Biochem. Biophys. Acta* **1988**, *962*, 308–316.
16. (a) Barbier, P.; Schneider, F. *Helv. Chim. Acta* **1987**, *70*, 196–202; (b) Barbier, P.; Schneider, F.; Widmer, U. *Helv. Chim. Acta* **1987**, *70*, 1412–1418; (c) Barbier, P.; Schneider, F. *J. Org. Chem.* **1988**, *53*, 1218–1221; (d) Pons, J.-M.; Kocienski, P. J. *Tetrahedron Lett.* **1989**, *30*, 1833–1836; (e) Fleming, I.; Lawrence, N. J. *Tetrahedron Lett.* **1990**, *31*, 3645–3648; (f) Case-Green, S. C.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1991**, 781–782; (g) Chadha, N. K.; Batcho, A. D.; Tang, P. C.; Courtney, L. F.; Cook, C. M.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1991**, *56*, 4714–4718; (h) Hannessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768–7781;

(i) Pommier, A.; Pons, J.-M.; Kocienski, P. J.; Wong, L. *Synthesis* **1994**, 1294–1300; (j) Giese, B.; Roth, M. *J. Braz. Chem. Soc.* **1996**, *7*, 243–246; (k) Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2679–2686; (l) Paterson, I.; Doughty, V. A. *Tetrahedron Lett.* **1999**, *40*, 393–394; (m) Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, 1743–1744; (n) Dirat, O.; Kouklovsky, C.; Langlois, Y. *Org. Lett.* **1999**, *1*, 753–755; (o) Parsons, P. J.; Cowell, J. K. *Synlett* **2000**, 107–109; (p) Ghosh, A. K.; Fidanze, S. *Org. Lett.* **2000**, *2*, 2405–2407; (q) Bodkin, J. A.; Humphries, E. J.; McLeod, M. D. *Aust. J. Chem.* **2003**, *56*, 795–803.

17. (a) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827–7828; (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468.
18. Hanessian's approach (see Ref. 16h) generated a mixture of 1,2-*syn*-2,4-*anti*, 1,2-*anti*-2,4-*anti*, 1,2-*syn*-2,4-*syn* products in a 1: 1.5: 0.12 ratio, (the major products have an *anti*-2,4 relationship due to chelation controlled addition).
19. Adam, W.; Martinez, G.; Thompson, J. *J. Org. Chem.* **1981**, *46*, 3359–3361.
20. (a) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535–1551; (b) Matesson, D. S. *Pure Appl. Chem.* **1991**, *63*, 339–344.