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Homoallylboration and Homocrotylboration of Aldehydes

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Supporting Information

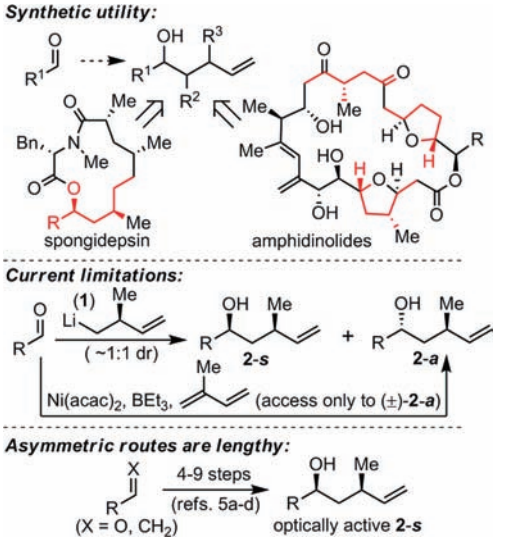
ABSTRACT: A simple method for addition of homoallylic fragments to aldehydes is described. Cyclopropanated allylboration reagents react with aldehydes in the presence of $PhBCl_2$ to give high yields of bishomoallyl alcohols. Cyclopropanated *cis*- and *trans*-crotyl reagents afford the corresponding 1,3-*anti*- and 1,3-*syn*-methyl-substituted "homocrotylated" alcohols with high selectivity, consistent with a Zimmerman–Traxler transition state. Accordingly, the optically active α-substituted reactant affords the *E*-substituted product in 97:3 er.

Allylation and crotylation of aldehydes and ketones have been studied in great detail, and numerous asymmetric methods have been developed.[1] By contrast, homoallylation reactions (Scheme 1) have been comparatively little studied, despite their utility in natural product synthesis. Substituted homoallylation reagents based on Mg and Li (such as **1**) react with aldehydes to give ~1:1 diastereomeric mixtures.[2] By contrast, reductive nickel-catalyzed homoallylation with dienes, introduced by Mori and Tamaru, is a very promising method;[3] however, regioselectivity is not high in the case of simple homoallylations with 1,3-butadiene, posing an obstacle to the development of desirable asymmetric methods. Although 1,3-*anti*-"homocrotylated" products (**2**-***a***) are accessible this way, 1,3-*syn* products (**2**-***s***) are not. The one reported asymmetric variant of this process is limited to 2,5-aryl-substituted products.[4] Other asymmetric syntheses of **2**-***s*** or **2**-***a*** from aldehydes or terminal alkenes have been accomplished in sequences of 4–9 steps.[5]

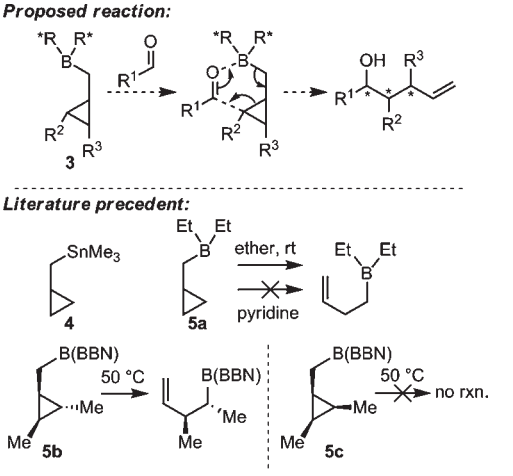
These limitations could be overcome with cyclopropanated analogues of allylboration reagents (**3**; Scheme 2). If such reagents were to react through cyclic Zimmerman–Traxler transition states,[6] they would afford bishomoallylic alcohol products with high diastereoselectivity and possibly enantioselectivity. Although stannane **4** is known, it does not homoallylate aldehydes thermally or in the presence of $BF_3 \cdot Et_2O$.[7a] In fact, its nucleophilicity was measured to be $>10^8$-fold less than that of the corresponding allylstannane. However, boranes **5a**–**c**, synthesized by Binger[7b] and Hill,[7c] were significantly less stable and rearranged to homoallylboranes at moderate temperatures. Promisingly, these rearrangements appeared to be nonradical, as they were stereospecific and could be inhibited by Lewis base.

We interpreted the results of Binger and Hill as indications that more stable and easily handled allylboronates such as **7** might be useful homoallylation reagents (Table 1). TFA-accelerated Simmons–Smith cyclopropanation[8] of commercially available allylboronate **6** readily afforded **7**, which was stable at room temperature and could be isolated either by distillation or chromatography.

Scheme 1. Utility and Current Limitations of Homoallylation



Scheme 2. Homoallylboration Precedent



We then proceeded to screen thermal and acid-promoted[9] conditions for homoallylation of hydrocinnamaldehyde (**8a**). No reaction occurred when the aldehyde and boronate were heated together in several solvents up to 80 °C (entry 1). Strong Lewis acids such

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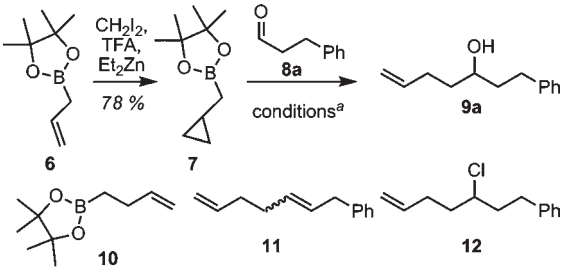
Table 1. Initial Studies with Pinacol Boronate 7



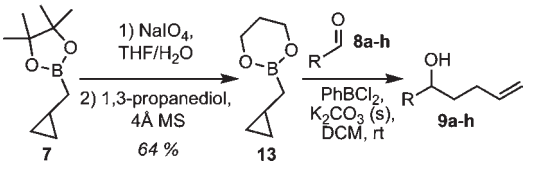
entry	temp (°C)	additives (equiv)	% yield/% conv of **8a**	side products
1	up to 80	none	0/0	none
2	rt	$Sc(OTf)_3$ (1)	0/0	none
3	50	$Sc(OTf)_3$ (1)	0/0	**10**
4	rt	$BF_3 \cdot Et_2O$ (1)	0/0	**10**
5	50	CSA (1)	0/0	none
6	rt	BCl_3 (1.1)	64/>90	**10/11/12**
7	rt	$PhBCl_2$ (1.1)	0/0[d]	none
8	rt	$PhBCl_2$ (1.1), BCl_3 (0.1)	trace/>90	**10/11/12**
9	rt	$PhBCl_2$ (1.1), AgTFA[b] (0.1)	69/>90	**10/11/12**
10[c]	rt	$PhBCl_2$ (1.1), AgTFA (0.1)	22/>90	**10**[e]

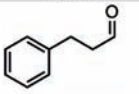
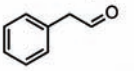
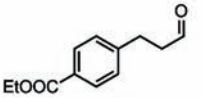
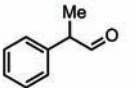
[a] Conditions: 1.5 equiv of **7** + 1.0 equiv of aldehyde; the solvent was $CDCl_3$ in all cases, except that in entry 1, THF, benzene and Et_2O were also tried. Yields are isolated yields based on aldehyde. [b] AgTFA = silver trifluoroacetate. [c] Octanal was used instead of **8a**. [d] See note 10. [e] Boronate **10**, byproducts analogous to **11**/**12**, and possible aldol adducts were observed.

as $BF_3 \cdot Et_2O$ caused rapid ring opening of the boronate (to give **10**) without consuming the aldehyde, while weaker Lewis acids and some Brønsted acids gave little or no ring opening but still no conversion of the aldehyde (entries 2−5). We were thus surprised and pleased to find that BCl_3 promoted the desired reaction to give homoallylation product **9a** in 64% yield, albeit together with side products **10** and **11** (entry 6). In search of milder conditions, we tried $PhBCl_2$, but this again resulted in no conversion (entry 7).[10] We hypothesized that the special reactivity of BCl_3 might originate from cationic boron species formed via disproportionation ($L \cdot BCl_3 + BCl_3 \rightarrow L \cdot BCl_2^+ + BCl_4^-$).[11] After screening various additives, we found that addition of catalytic silver trifluoroacetate to the $PhBCl_2$/**7** reagent mixture resulted in complete reactions, giving up to 69% yield of **9a**.[12] Unfortunately, homoallylation of other aldehydes under these conditions resulted in lower yields and inconsistent results (entry 10).

We imagined that the less hindered propanediol-derived reagent **13** (Table 2) might be much more reactive than **7**, enabling reactions under milder conditions. We thus converted **7** to **13** by oxidative hydrolysis of the pinacol group and condensation of 1,3-propanediol with the resulting boronic acid.[13] **13**, which was stable to ambient moisture but not to chromatography, indeed proved to be much more reactive: it readily afforded homoallylation products in the presence of $PhBCl_2$ and no other additive. With solid K_2CO_3 added to scavenge HCl, **8a** was homoallylated in excellent yield (entry 1). Using these standard conditions, we then investigated the scope of the reaction.

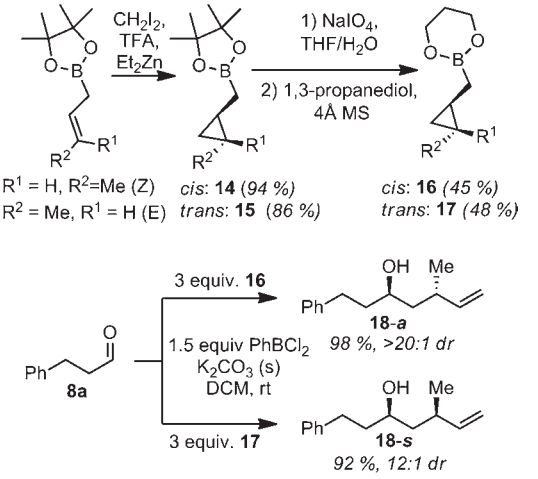
Table 2. Homoallylboration Scope with Boronate 13[a]



entry	aldehyde	time	% yield[b]
1	 (**8a**)	14 h	94
2	*n*-hept-CHO (**8b**)	2.5 h	95
3	(C_6H_{11})-CHO (**8c**)	14 h	88
4	*i*Pr-CHO (**8d**)	14 h	53 (90)[c]
5	*t*Bu-CHO (**8e**)	7 d	39 (95)[c]
6	 (**8f**)	14 h	82
7	 (**8g**)	14 h	80
8	 (**8h**)	14 h	88[d]

[a] All reactions were run with 0.2 mmol of aldehyde, 3 equiv of **13**, 1.5 equiv of $PhBCl_2$, and 6.0 equiv of K_2CO_3. [b] Isolated yields. [c] NMR yields are given in parentheses. The low isolated yields are due to product volatility. [d] dr = ~1:1.5 *anti*/*syn*.

Scheme 3. Diastereoselective Homocrotylations



Unbranched and branched aliphatic aldehydes **8a**−**e** reacted in high yield (entries 1−5). Lower isolated yields with isobutyraldehyde (**8d**; entry 4) and pivaldehyde (**8e**; entry 5) were due only to product volatility, as the NMR yields were in the same excellent range as for the other substrates. Enolization-prone phenylacetaldehyde (**8f**; entry 6) was also cleanly homoallylated under these conditions. The ester functionality of **8g** (entry 7) was also well-tolerated. Although chiral α-substituted aldehyde **8h** (entry 8) was also cleanly homoallylated, very little facial selectivity was observed.[14]

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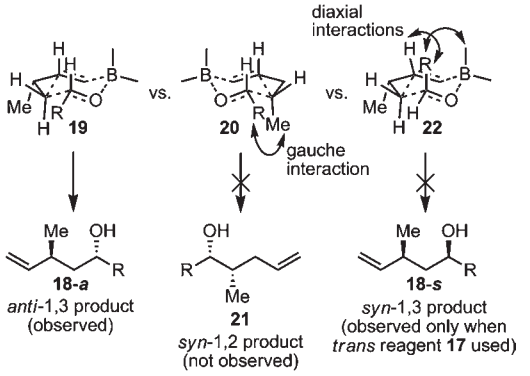
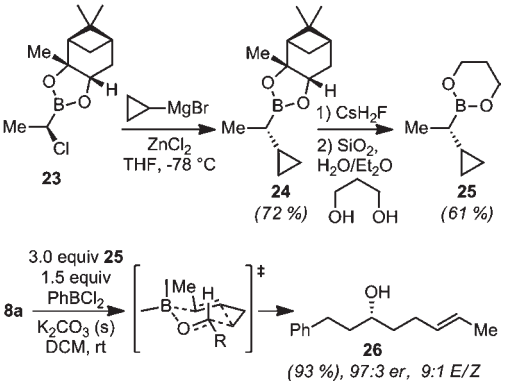
Scheme 4. Zimmerman–Traxler Models for *cis* Reagent 16



Scheme 5. Enantioselective Homoallylation



We were then very excited to test whether substituted homoallylboration reagents would react selectively through Zimmerman–Traxler transition states to afford products such as **2-*s*** (Scheme 1), which are awkward to access by other methods.[5a,c,e] We thus synthesized homocrotylation reagents **16** and **17** by the same method used for **13** and tested their regio- and diastereoselectivity (Scheme 3). We were pleased to see that reaction of *cis* reagent **16** with **8a** under the standard conditions afforded 1,3-*anti*-methyl-substituted bishomoallylic alcohol **18-*a*** as a single diastereomer. Conversely, *trans*-cyclopropane reagent **17** afforded the *syn* diastereomer **18-*s***. Although the diastereoselectivity in this case was 12:1, this is ratio is roughly consistent with the geometric purity of the reagent, which was derived from commercial ~95% *trans*-boronate.[15,16] This is the first example of diastereoselective aldehyde alkylation to give the 1,3-*syn*-alkyl-substituted bishomoallylic alcohol directly.

The high diastereo- and regioselectivity is consistent with chair transition state models, as depicted in Scheme 4, which illustrates possible reaction pathways of *cis* reagent **16**. The preferred transition state leading to the observed product **18-*a*** is **19**; the 1,2-regioisomer **21** was not observed, presumably because of a gauche interaction in chair transition state **20**. Likewise, diastereomer **18-*s*** was avoided because of unfavorable diaxial interactions in transition state **22**. For reagent **17**, the preferred transition state analogous to **19** affords the *syn* product **18-*s***.

Importantly, the methyl stereocenter in reagent **16** retains its configuration in product **18-*a*** and essentially behaves as a chiral auxiliary.[17] Thus, a single enantiomer of reagent **16** *must* yield a single enantiomer of product **18-*a***. Development of asymmetric homocrotylation is therefore dependent only on the development of an asymmetric route to reagents **16** and **17**.

To demonstrate the utility of these reagents in enantioselective synthesis, we prepared an optically active α-chiral homoallylation reagent that is readily accessible via Matteson's chemistry[18] (Scheme 5). Cyclopropyl Grignard displacement of pinanediol chloroethyl boronate **23** afforded **24**. The unreactive pinanediol boronate was converted to the reactive propanediol boronate **25** by conversion to the cesium fluoroborate salt[19] and subsequent fluorophilic hydrolysis in the presence of silica gel and 1,3-propanediol.[20] To our delight, **25** reacted with **8a** to afford **26** in 93% yield and 97:3 er as a separable 9:1 mixture of *E* and *Z* isomers.[21]

In conclusion, we have demonstrated that it is possible to homoallylate carbonyl compounds through a stereoselective cyclic mechanism similar to that of allylboration. This chemistry provides direct access to 1,3-*syn*-homocrotylated products not previously available directly from carbonyl addition reactions. Moreover, this chemistry opens the door to the development of asymmetric homoallylations, which we have demonstrated with the synthesis of a bishomoallylic alcohol with high enantiomeric excess. Full evaluation of the reaction scope and the use of additional optically active reagents and/or chiral promoters will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures for the synthesis of reagents **13**–**17** and **23**–**25**, their use in homoallylation reactions, and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1995**, *93*, 2207. (b) Denmark, S. E.; Fu, J. P. *Chem. Rev.* **2003**, *103*, 2763. (c) Lachance, H.; Hall, D. G. *Org. React.* **2008**, *103*, 1.

(2) Li, H.; Wu, J.; Luo, J.; Dai, W. M. *Chem.—Eur. J.* **2010**, *16*, 11530.

(3) Tamaru–Mori reaction: (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (b) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033. (c) Kimura, M.; Fujimatsu, H.; Ezoe, A; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397. (d) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624. (e) Kimura, M.; Ezoe, A.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 3600. (f) Sato, Y.; Sawaki, R.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 656. (g) Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8559.

(4) Yan, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 2248.

(5) (a) Ghosh, A. K.; Xu, X. M. *Org. Lett.* **2004**, *6*, 2055. (b) Chen, J.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2148. (c) Ferrie, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2006**, *8*, 3441. (d) Chandrasekhar, S.; Mahipal, B.; Kavitha, M. *J. Org. Chem.* **2009**, *74*, 9531. (e) Tannert, R.; Milroy, L. G.; Ellinger, B.; Hu, T. S.; Arndt, H. D.; Waldmann, H. *J. Am. Chem. Soc.* **2010**, *132*, 3063.

(6) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(7) (a) Lucke, A. J.; Young, D. J. *J. Org. Chem.* **2005**, *70*, 3579. (b) Köster, R.; Arora, S.; Binger, P. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 205. (c) Hill, E. A.; Park, Y. W. *J. Organomet. Chem.* **1988**, *356*, 1. For reactivity of an analogous silane, see: (d) Grignon-Dubois, M.; Dunoguès, J.; Calas, E. *Can. J. Chem.* **1981**, *59*, 802.

(8) Yang, Z. Q.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621.

(9) (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (c) Lachance, H.; Lu, X. S.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160. (d) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518. (e) Gravel, M.; Lachance, H.; Lu, X. S.; Hall, D. G. *Synthesis* **2004**, 1290. (f) Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981. (g) Ramachandran, P. V.; Pratihar, D.; Biswas, D. *Org. Lett.* **2006**, *8*, 3877. (h) Rauniyar, V.; Hall, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426. (i) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (j) Elford, T. G.; Arimura, Y.; Yu, S. H.; Hall, D. G. *J. Org. Chem.* **2007**, *72*, 1276. (k) Ramachandran, P. V.; Pratihar, D. *Org. Lett.* **2007**, *9*, 2087. (l) Hall, D. G. *Synlett* **2007**, 1644. (m) Rauniyar, V.; Hall, D. G. *Synthesis* **2007**, 3421. (n) Lira, R.; Roush, W. R. *Org. Lett.* **2007**, *9*, 4315. (o) Carosi, L.; Hall, D. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 5913. (p) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398. (q) Rauniyar, V.; Zhai, H. M.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. (r) Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236. (s) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8679. (t) Chen, M.; Roush, W. R. *Org. Lett.* **2010**, *12*, 2706–2709. (u) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884.

(10) Aldehydes in fact react with $PhBCl_2$ quantitatively to form α-chloro ethers, which are hydrolyzed back to the aldehydes upon aqueous workup. Similar boron species have been observed by Lappert, and analogous silicon species have been reported by Denmark. See: (a) Frazer, M. J.; Gerrard, W.; Lappert, M. F. *J. Chem. Soc.* **1957**, 739. (b) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405.

(11) (a) Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457. (b) Evans, D. A.; Halstead, D. P.; Allison, B. D. *Tetrahedron Lett.* **1999**, *40*, 4461. (c) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840.

(12) This result does not necessarily confirm the involvement of a cationic reaction manifold, as we would expect $Ag(OCOCF_3)$ to replace chloride with the *more* strongly coordinating trifluoroacetate. By contrast, use of $Ag(SbF_6)$ as the additive results in an intractable complex mixture.

(13) Coutts, S. J.; Adams, J.; Krolikowski, D.; Snow, R. J. *Tetrahedron Lett.* **1994**, *35*, 5109.

(14) When run at −35 °C, the reaction was incomplete after days and the selectivity was not greatly improved.

(15) The minor diastereomer **18-*a*** presumably is produced from a *cis* impurity (**16**) present at a ∼5% level in the *trans* reagent **17**. Since **16** is more reactive than **17** and 3 equiv of the reagent mixture was used, the percentage of the minor diastereomer was slightly amplified in the homocrotylation product **18-*s*** relative to reagent **17**.

(16) The diastereomeric ratios for **18-*s*** and **17** were measured by integration of ^1H NMR signals.

(17) This is true under the assumption that only one bond of the cyclopropane is cleaved during the conversion of **16** to **18-*a***. Alternative mechanisms leading to **18-*a*** but involving cleavage of the other cyclopropane bonds would be very complex and are inconsistent with the high observed diastereoselectivity.

(18) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810.

(19) Matteson, D. S.; Maliakal, D.; Pharazyn, P. S.; Kim, B. J. *Synlett* **2006**, 3501.

(20) Molander, G. A.; Cavalcanti, L. N.; Canturk, B.; Pan, P.-S.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 7364.

(21) The *Z* isomer was obtained in slightly lower er (93:7) with the opposite configuration. The er was measured using chiral HPLC.