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Regioselective and Diastereoselective Amination of Polybenzyl Ethers Using Chlorosulfonyl Isocyanate: Total Syntheses of 1,4-Dideoxy-1,4-imino-D-arabinitol and (−)-Lentiginosine

In Su Kim, Ok Pyo Zee, and Young Hoon Jung*

College of Pharmacy, Sungkyunkwan University, Suwon 440-746, Korea

yhjung@skku.ac.kr

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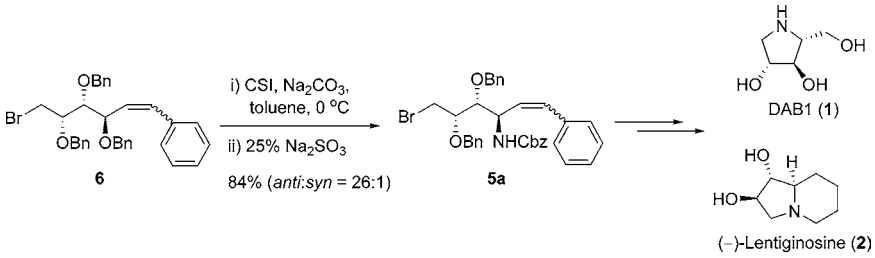
ABSTRACT



The total syntheses of DAB1 (1) and (−)-lentiginosine (2) were concisely accomplished from D-lyxose via regioselective and diastereoselective NHCbz introduction using CSI, chemoselective removal of the Cbz protection, and ring-closing metathesis as key steps.

We recently reported a novel regioselective and diastereoselective amination of *anti*-1,2-dimethyl ether with chlorosulfonyl isocyanate (CSI) and its application to the synthesis of (−)-cytoxazone.[1] As a part of our research program aimed at developing polyhydroxylated alkaloids, we extended the CSI reaction to the syntheses of pyrrolidine alkaloid 1,4-dideoxy-1,4-imino-D-arabinitol (DAB1) (**1**), isolated in 1985 from *Angylocalyx boutiqueanu*[2] and *Arachniodes standishii*,[3] and indolizidine alkaloid (−)-lentiginosine (**2**), isolated in 1990 from the leaves of *Astragalus lentiginosus*.[4] These polyhydroxylated alkaloids are receiving increasing attention as potential medical agents due to their many pharmacological properties.[5] (−)-Lentiginosine is particularly intriguing because of its potent and selective inhibition of amyloglucosidases that hydrolyze 1,4- and 1,6-α-glucosidic linkages.[4,6] Because of their potent bioactivities and relatively simple structures, numerous ways of synthesizing **1**, **2**, and their isomers have recently been reported,[7] and these studies confirmed their absolute configurations. This paper describes

(1) Kim, J. D.; Kim, I. S.; Jin, C. H.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2005**, *7*, 4025.
(2) (a) Nash, R. J.; Bell, E. A.; Williams, J. M. *Phytochemistry* **1985**, *24*, 1620. (b) Jones, D. W. C.; Nash, R. J.; Bell, E. A.; Williams, J. M. *Tetrahedron Lett.* **1985**, *26*, 3127.
(3) Furukawa, J.; Okuda, S.; Saito, K.; Hatatanaka, S.-I. *Phytochemistry* **1985**, *24*, 593.
(4) Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886.
(5) For some leading references, see: (a) Junge, B.; Matzke, M.; Stoltefuss, J. In *Handbook of Experimental Pharmacology*; Kuhlmann, J., Puls, W., Eds.; Springer-Verlag: Berlin, Heidelberg, New York, 1996; Vol. 119, pp 411−482. (b) Elbein, A. D.; Molyneux, R. J. In *Comprehensive Natural Products Chemistry*; Pinto, B. M., Ed.; Barton, D. H. R., Nakanishi, K., Meth-Cohn, O., Series Eds.; Elsevier: U.K., 1999; Chapter 7, Vol. 3. (c) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. (d) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (e) McCarter, J. D.; Withers, S. G. *Curr. Opin. Struct. Biol.* **1994**, *4*, 885. (f) Ly, H. D.; Withers, S. G. *Annu. Rev. Biochem.* **1999**, 68, 487.
(6) Brandi, A.; Cicchi, S.; Cordero, M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806.

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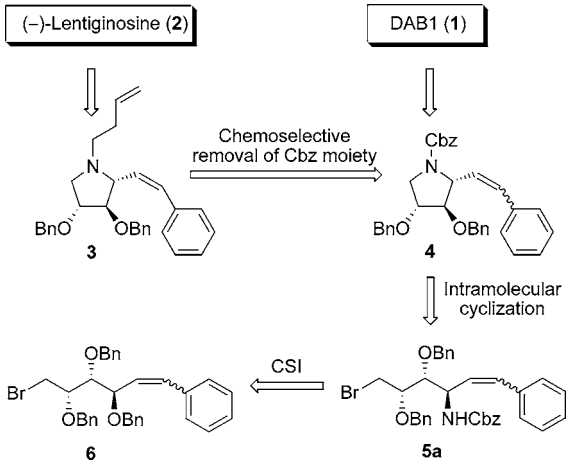
our synthetic approach to **1** and **2** utilizing the regioselective and diastereoselective CSI reaction.[8]

Our retrosynthetic analyses of **1** and **2** are outlined in Scheme 1. The common intermediate **4** would be prepared

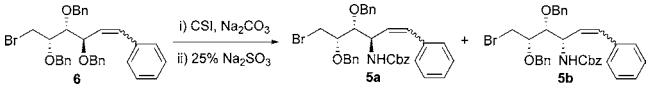
Scheme 1. Retrosynthetic Analysis of **1** and **2**



by intramolecular cyclization of bromide **5a**, which, in turn, would come from the regioselective and diastereoselective installation of an NHCbz group into cinnamyl polybenzyl ether **6** using CSI.

In initial studies, we examined the regioselectivity and diastereoselectivity of the reaction of *anti*-1,2-diether **6** with CSI. Treatment of **6** with CSI afforded the *anti*-1,2-amino alcohol **5a** as the major product. The ratio of *anti*-1,2-amino alcohol **5a** and *syn*-1,2-amino alcohol **5b** depended on solvent and temperature, as shown in Table 1.

Table 1. Diastereoselective CSI Reaction of Cinnamyl Polybenzyl Ether **6** in Various Solvents and at Different Temperatures



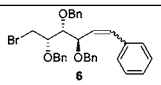
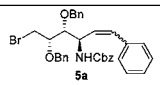
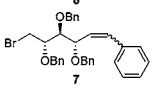
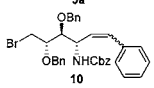
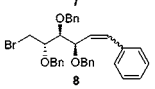
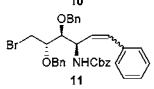
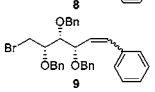
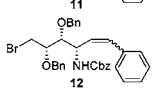
entry	solvent	T (°C)	time (h)	yield[a] (%)	ratio[b] (**5a/5b**)
1	CH_2Cl_2	0	14	80	14:1
2	$CHCl_3$	0	14	78	14:1
3	CCl_4	0	20	84	16:1
4	Et_2O	0	18	82	17:1
5	hexane	0	24	62	18:1
6	toluene	0	24	84	26:1
7		−40	72	57 (35)[c]	40:1
8		−78	168	51 (45)[c]	73:1

[a] Isolated yield of pure materials. [b] Isomer ratio determined by ^{1}H NMR spectroscopy. [c] Recovery yield of starting materials.

As solvent polarity or the reaction temperature was reduced, the diastereoselectivity increased gradually. In particular, reaction in toluene at low temperature produced the desired product **5a** in high yield (∼84%) with a remarkable increase of diastereoselectivity (26:1−73:1). This result reveals that the stereochemistry is retained more so in nonpolar solvents and at low temperature. Regioselective substitution at the cinnamylic position is expected because regioselectivity is controlled by the stability of the carbocation intermediate, i.e., the cinnamylic carbocation is more stable than the corresponding secondary carbocation. [9]

Consistent with these observations, we investigated the diastereoselectivity of the CSI reactions of the cinnamyl polybenzyl ethers **6**−**9**, which were prepared from commercially available D-sugars (D-lyxose, D-ribose, D-arabinose, and D-xylose), to afford the corresponding allylic amine products **5a** and **10**−**12** (Table 2).

Table 2. Diastereoselective CSI Reactions of Cinnamyl Polybenzyl Ethers **6**−**9**

entry	ether	product	yield (%)[a]	ratio (*syn*:*anti*)[b]
1			84	1 : 26
2			80	1 : 15
3			65	4 : 1
4			57	3 : 1

[a] Isolated yield of pure materials. [b] Isomer ratio determined by ^{1}H NMR spectroscopy.

As shown in entries 3 and 4, the *syn*-1,2-diethers **8** and **9** in toluene at 0 °C afforded the corresponding *syn*-1,2-amino

(7) For the syntheses of 1,4-dideoxy-1,4-imino-D-arabinitol, see: (a) Fleet, G. W. J.; Smith, P. W. *Tetrahedron* **1986**, *42*, 5685. (b) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull.* **1987**, *35*, 2140. (c) Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymmetry* **1990**, *1*, 119. (d) Kim, Y. J.; Kido, M.; Bando, M.; Kitahara, T. *Tetrahedron* **1997**, *53*, 7501. (e) Hulme, A. N.; Montgomery, C. H.; Henderson, D. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1837. (f) Lombardo, M.; Fabbroni, S.; Trombini, C. *J. Org. Chem.* **2001**, *66*, 1264. For the syntheses of (−)-lentiginosine and its enantiomer, see: (g) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1455. (h) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949. (i) Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, *35*, 8871. (j) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398. (k) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706. (l) McCaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429. (m) Ha, D.-C.; Yun, C.-S.; Lee, Y.-J. *J. Org. Chem.* **2000**, *65*, 621. (n) Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 2509. (o) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438. (p) El-Nezhawy, A. O. H.; El-Diwani, H. I.; Schmidt, R. R. *Eur. J. Org. Chem.* **2002**, 4137. (q) Rabiczko, J.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1433. (r) Chandra, K. L.; Chandrasekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630. (s) Feng, Z.-X.; Zhou, W.-S. *Tetrahedron Lett.* **2003**, *44*, 497. (t) Ichikawa, Y.; Ito, T.; Nishiyama, T.; Isobe, M. *Synlett* **2003**, 1034. (u) Ayad, T.; Génisson, Y.; Baltas, M.; Gorrichon, L. *Chem. Commun.* **2003**, 582. (v) Raghavan, S.; Sreekanth, T. *Tetrahedron: Asymmetry* **2004**, *15*, 565. (w) Cardona, F.; Moreno, G.; Guarna, F.; Vogel, P.; Schuetz, C.; Merino, P.; Goti, A. *J. Org. Chem.* **2005**, *70*, 6552.

(8) (a) Kim, J. D.; Lee, M. H.; Lee, M. J.; Jung, Y. H. *Tetrahedron Lett.* **2000**, *41*, 5073. (b) Kim, J. D.; Lee, M. H.; Han, G.; Park, H.-J.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2001**, *57*, 8257. (c) Kim, J. D.; Zee, O. P.; Jung, Y. H. *J. Org. Chem.* **2003**, *68*, 3721. (d) Kim, J. D.; Kim, I. S.; Jin, C. H.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2005**, *46*, 1097.

alcohols **11** and **12** as an inseparable mixture of diastereoisomers in moderate yield with a low diastereoselectivity of 4:1 and 3:1 in favor of the *syn*-isomer. However, CSI reactions of the *anti*-1,2-diethers **6** and **7** afforded exclusively the *anti*-1,2-amino alcohols **5a** and **10** as the major products with significantly increased diastereoselectivity of 1:26 and 1:15, respectively. Table 1 shows that the stereochemistries of major products were the same as those of the starting materials, even though the CSI reaction of cinnamyl benzyl ether progresses via a carbocation intermediate.

The diastereoselectivity of these reactions can be explained by the neighboring group effect,[10] in which the NHCbz group orientation retains the original configuration in benzyl ether via a double inversion of the configuration, as shown in Figure 1. The reduced diastereoselectivities of **8** and **9** may

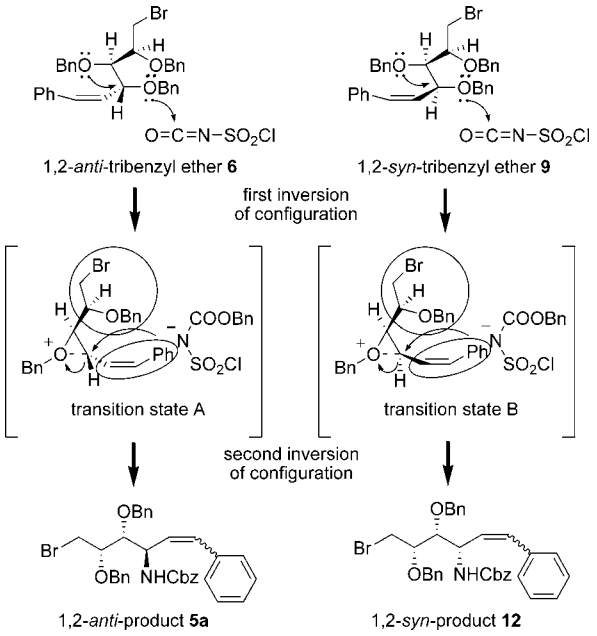


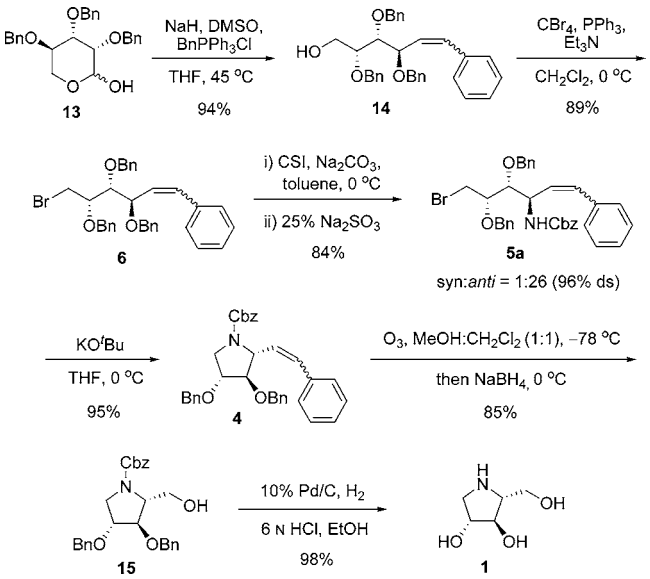
Figure 1. Proposed reaction mechanism of cinnamyl polybenzyl ethers **6** and **9** with CSI.

have been caused by the increased steric repulsion between the two bulky substituents in transition state B.

On the basis of the above results, we planned to utilize cheap and commercially available D-lyxose as the starting material for the total synthesis of DAB1 (**1**) and (−)-lentiginosine (**2**). The synthesis of **1** began with the benzyl-protected lactol **13**, prepared from D-lyxose, by the known procedure according to the literature[11] (Scheme 2).

Wittig olefination of **13** with DMSO anion[12] in THF at 45 °C afforded **14** as a ca. 3.1:1 mixture of *cis*/*trans* isomers

Scheme 2. Total Synthesis of DAB1 (**1**)



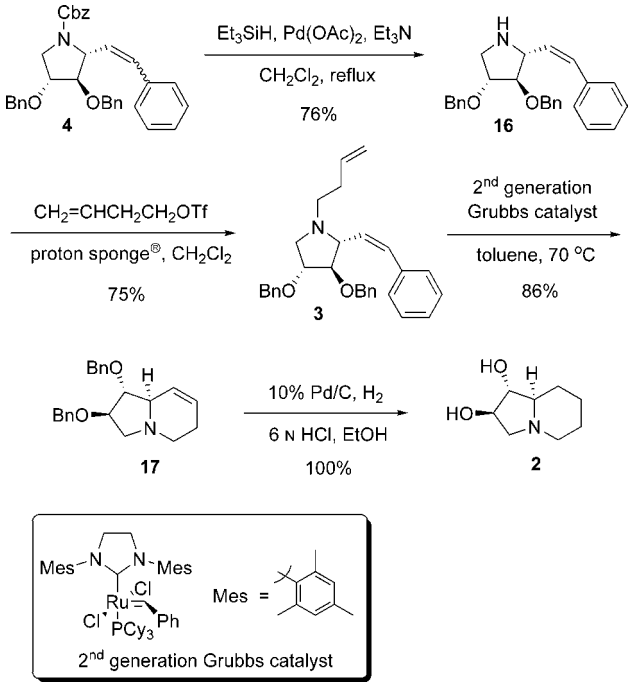
in 94% yield. The hydroxyl moiety of **14** was then converted to bromide **6** with carbon tetrabromide, triphenylphosphine, and triethylamine in 89% yield.[13]

The CSI reaction was carried out on cinnamyl tribenzyl ether **6** in toluene solution at 0 °C for 24 h, followed by desulfonylation using an aqueous solution of 25% sodium sulfite to give the allylic amine product **5a** with a high diastereoselectivity (*syn*/*anti* = 1:26, 96% ds) in 84% yield. Treatment of **5a** with potassium *tert*-butoxide provided the pyrrolidine **4**. Ozonolysis of the CH=CH bond of **4** and subsequent reduction of the resulting aldehyde gave the alcohol **15**.[7f] Finally, the benzyl and *N*-Cbz protecting groups of **15** were removed by palladium-catalyzed hydrogenolysis to give DAB1 (**1**) in 98% yield. Spectroscopic data and the specific rotation of **1** were found to be in full agreement with the reported literature values.[7a−e]

To further explore the synthetic utility of the CSI reaction, we envisioned that the selective removal of the Cbz protection of **4** could potentially provide the most direct approach to (−)-lentiginosine via a three-step synthesis (Scheme 3). After several failed attempts (e.g., BBr_3,[14] hydrogenations, and KOH[15]), chemoselective removal of the Cbz protection of **4** was achieved under palladium-catalyzed *N*-deprotection conditions[16] (Et_3SiH, $Pd(OAc)_2$, triethylamine, CH_2Cl_2, reflux) to give the secondary amine **16** concomitant with isomerization of the *cis*/*trans* olefin mixtures **4** to produce exclusively the *cis*-olefin.[17] Direct introduction of the 3-butenyl moiety into **16** was carried out using 3-butenyl trifluoromethanesulfonate[18] and Proton Sponge to afford **3** in 75% yield.

(9) Kim, J. D.; Han, G.; Jeong, L. S.; Park, H.-J.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2002**, *58*, 4395.
(10) (a) Allred, E. L.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 3991. (b) Allred, E. L.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 3998. (c) Roberts, D. D. *J. Org. Chem.* **1997**, *62*, 1857. (d) Krow, G. R.; Yuan, J.; Lin, G.; Sonnet, P. E. *Org. Lett.* **2002**, *4*, 1259.
(11) Nadein, O. N.; Kornienko, A. *Org. Lett.* **2004**, *6*, 831
(12) For a recent review, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
(13) (a) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4252. (b) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358. (c) Kashem, A.; Anisuzzaman, M.; Whistler, R. L. *Carbohydr. Res.* **1978**, *61*, 511.
(14) Pless, P.; Bauer, W. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 147.
(15) Angel, S. R.; Arnaiz, D. O. *Tetrahedron Lett.* **1989**, *30*, 515.
(16) (a) Sakatani, M.; Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1986**, *27*, 3753. (b) Wipf, P.; Uto, Y. *Tetrahedron Lett.* **1999**, *40*, 5165.

Scheme 3. Total Synthesis of (−)-Lentiginosine (**2**)



To obtain the indolizidine framework, several conditions were investigated. Treatment of **3** with first-generation Grubbs catalyst in methylene chloride at reflux provided **17** in low yield (~10%). The yield of **17** was improved to 56% when second-generation Grubbs catalyst in methylene chloride was employed; however, the reaction required 60 h to go to completion. The best result was realized when **3** was exposed to second-generation Grubbs catalyst in toluene, which provided the bicyclic compound **17** in high yield (86%) within 8 h.[19] The final deprotection of benzyl groups and hydrogenation of the double bond afforded (−)-lentiginosine (**2**) as a crystalline form: mp 105−106 °C ($CHCl_3$/hexane) [lit.[7l] mp 106−107 °C]; $[\alpha]^{25}_D$ −3.1 (*c* 0.8, MeOH) [lit.[7l] $[\alpha]^{25}_D$ −3.05 (*c* 1.0, MeOH)]. Moreover, **2** had spectral properties (^{1}H and ^{13}C NMR) in full agreement with the reported literature values.[7g−w]

In conclusion, we described a newly developed method for the regioselective and diastereoselective introduction of an NHCbz group into cinnamyl polybenzyl ethers using chlorosulfonyl isocyanate (CSI). Moreover, we have demonstrated the application of this methodology to the total syntheses of DAB1 and (−)-lentiginosine. We believe that this synthetic protocol will be useful for the preparation of stereodefined hydroxyl amino alcohols and hydroxyl amino acids, and for the preparation of pyrrolidine, piperidine, pyrrolizidine, and indolizidine alkaloids; important components of various glycosidase inhibitors.

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

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(17) (a) LaPointe, A. M.; Rix, F. C.; Brookhart, M. *J. Am. Chem. Soc*. **1997**, *119*, 906. (b) Chatgilialoglu, C.; Ballestr, M.; Ferreri, C.; Vecchi, D. *J. Org. Chem*. **1995**, *60*, 3826. (c) Mizra-Aghayan, M.; Boukherroub, R.; Bolourtchian, M.; Hoseini, M.; Tabar-Hydar, K. *J. Organomet. Chem*. **2003**, *678*, 1.

(18) Xu, Y.-C.; Wulff, W. D. *J. Org. Chem*. **1987**, *52*, 3263.

(19) (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc*. **1992**, *114*, 3974. (b) Grubbs, R. H.; Miller, S. J. *Acc. Chem. Res*. **1995**, *28*, 446. (c) Harned, A. M.; Mukherjee, S.; Flynn, D. L.; Hanson, P. R. *Org. Lett*. **2003**, *5*, 15.