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Unusual Highly Regioselective Direct Aldol Additions with a Moisture-Resistant and Highly Efficient Titanium Catalyst

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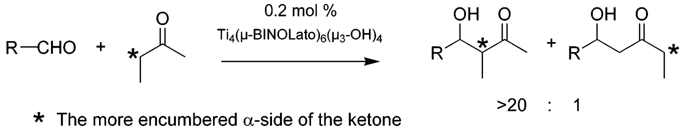
ABSTRACT



The extremely robust and water-stable tetranuclear complex $Ti_4(\mu\text{-BINOLato})_6(\mu_3\text{-OH})_4$ was found to catalyze the direct aldol addition with high regioselectivities at the more steric α-encumbered side of unsymmetrical ketones. As few as 0.2 mol % loadings with this cluster were enough to afford complete conversions. The reaction proceeds very smoothly without a significant amount of byproducts. The formation of quaternary stereocenters is described.

The aldol addition[1] is one of the most powerful methods for the formation of carbon−carbon bonds.[2] Especially since the mid-1990s, various methods for direct aldol additions have been developed.[3] Many of them are catalyzed by various kinds of metal complexes.[4] However, most of these catalysts, especially Lewis acid catalysts, are sensitive to air and/or moisture, making extended expenditures in handling necessary. On the other hand, quenching the reactions with water often causes the decomposition of the moisture-sensitive catalysts, and the decomposition products, such as BINOL, for example, make the purification of the reaction products more difficult. The recovery of the catalyst is in these cases impossible as well. Other catalysts are produced in situ, making reproducible reaction conditions difficult, as well as

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(1) (a) Kane, R. *Ann. Phys. Chem., Ser. 2* **1838**, *44*, 475. (b) Wurtz, A. *Bull. Soc. Chim. Fr.* **1872**, *17*, 436−442. Wurtz, A. *Ber. Dtsch. Chem. Ges.* **1872**, *5*, 326. Borodin, A. *Ber. Dtsch. Chem. Ges.* **1873**, *6*, 982−985.

(2) (a) Heathcock, C. H. (Chapter 1.6); Kim, B. M.; Williams, S. F.; Masamune, S. (Chapter 1.7); Rathke, M. W.; Weipert, P. (Chapter 1.8); Paterson, I. (Chapter 1.9); Gennari, C. (Chapter 2.4) In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1993; Vol. 2. (b) Braun, M. In *Houben-Weyl, Methoden der Organischen Chemie*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart 1996; Vol. E21b, pp 1603−1666. (c) Machajewski, T. D.; Wong, C. H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352−1374. (d) Mahrwald, R. *Curr. Org. Chem.* **2003**, *4*, 1713−1723. (e) Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, Germany, 2004. (f) Schetter, B.; Mahrwald, R. In *Quaternary Stereocenters-Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 51−81.

(3) (a) Mahrwald, R. *Chem. Ber.* **1995**, *128*, 919−921. (b) Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087−1089. (c) Mahrwald, R.; Costisella, B.; Gündogan, B. *Tetrahedron Lett.* **1997**, *38*, 4543−4544. (d) Mahrwald, R.; Gündogan, B. *Synthesis* **1998**, 262−264. (e) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1097−1120. (f) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178. (g) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004. (h) Mahrwald, R.; Ziemer, B. *Tetrahedron Lett.* **2002**, *43*, 4459−4461. (i) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 7386-7387. (j) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466−2467. (k) Mahrwald, R.; Ziemer, B.; Trojanov, S. *Tetrahedron Lett.* **2001**, 6843−6845. (l) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392−393. (m) Markert, M.; Mahrwald, R. *Synthesis* **2004**, 1429−1433. (n) Rohr, K.; Herre, R.; Mahrwald, R. *Org. Lett.* **2005**, *7*, 4499−4501.

(4) For an overview, see: (a) Acid catalysis: Yamamoto, H.; Futatsugi, K. *Angew. Chem.* **2005**, *117*, 1958−1977. Mikami, K.; Terada, M. In *Lewis Acids in Organic Synthesis*; Hisashi, Y., Ed.; Wiley-VCH: Weinheim, Germany 2000. (b) Titanium complexes: Mikami, K.; Matsumoto, Y.; Shiono, T. In *Science of Synthesis*; Bellus, D., Jacobsen, N. E., Ley, S. V., Noyori, R., Regitz, M., Reider, P. J., Schaumann, E., Shinkai, I., Thomas, E. J., Trost, B. M., Eds.; Thieme: Stuttgart, 2003. Product class 10: Organometallic Complexes of Titanium. (c) Applications to organic synthesis: *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002.

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mechanistic studies.[5] Last but not least, many catalysts are only accessible by complicated multistep reaction sequences or need rare and expensive metals as reactive centers.[6] Recent research is focused on the development of stable and storable catalysts, and the first remarkable results have been presented by Kobayashi et al.,[7] who presented stable rare-earth and zirconium catalysts for Mannich, aza-Diels−Alder, and Mukaiyama aldol reactions, and Bull et al., who described a moisture-stable titanium triflate for aza-Diels−Alder reactions.[8]

During our ongoing studies of the mechanisms of titanium(IV)-alkoxide-mediated direct aldol additions, we explored the catalytic potential of Mikami's tetranuclear titanium cluster.[9] Mikami's catalyst is crystalline and stable even against boiling 1 N HCl and 1 N LiOH in dioxane and easy to synthesize from $Ti(O^iPr)_4$, *R*-BINOL, or *S*-BINOL and water.[6] We also synthesized this cluster with *rac*-BINOL[10] and found that all six BINOL molecules which are incorporated in each cluster have the same stereochemistry. No clusters appeared in crystalline form with a mixed stereochemistry of the incorporated BINOLs. Therefore, the clusters obtained from *rac*-BINOL are identical to those produced with *R*-BINOL or *S*-BINOL (Figure 1).

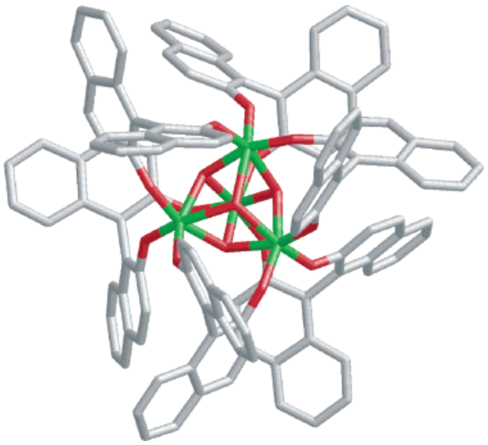
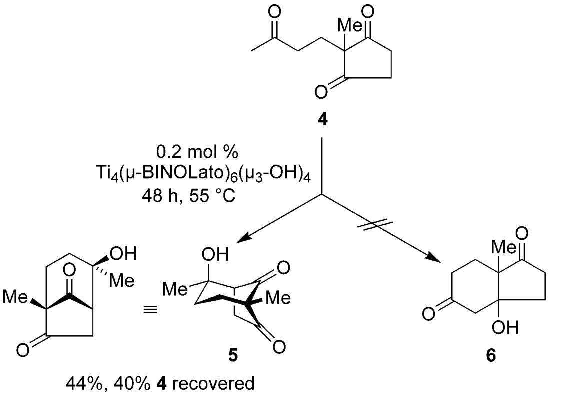


Figure 1. Crystal structure of the tetranuclear titanium complex *rac*-$Ti_4(\mu$-BINOLato$)_6(\mu_3$-OH$)_4$; hydrogen atoms are omitted for clarity.

To test the applicability of this titanium complex, we reacted several aldehydes with symmetrical and unsymmetrical ketones. In fact, the catalyst was able to promote the direct aldol addition between aldehydes **1** and ketones **2** in a remarkably clean way even with very low catalyst loadings[11] to give the aldols **3** (Table 1).[12] This reaction was found to be highly regioselective. Aldol addition is strongly preferred at the sterically more encumbered α-side of the ketone.[13] In many cases, only one regioisomer was obtained. Methyl groups of alkan-2-ones were found to be unaffected under these reaction conditions. Therefore, the Wieland−Miescher ketone **4** avoids the typically aldol cyclization to the CD bicyclic steroidal intermediate **6** (Scheme 1).[14] The bicyclic dione **5** is formed and strongly preferred with a high degree of diastereoselectivity (>95:5). Dione **5** posseses two

Scheme 1. Regioselective Formation of Diketone **5**



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(5) (a) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363−2364. (b) Kitamoto, D.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1995**, *36*, 1861−1864. (c) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, 267−272. (d) Delas, C.; Szymoniak, J.; Lefranc, H.; Moïse, C. *Tetrahedron Lett.* **1999**, *40*, 1121−1122. (e) De Rosa, M.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3187−3195. (f) Davis, J. T.; Balsells, J.; Caroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 699−702. (g) Zimmer, R.; Peritz, A.; Czerwonka, R.; Schefzig, L.; Reissig, H.-U. *Eur. J. Org. Chem.* **2002**, 3419−3428. (h) Villano, R.; De Rosa, M.; Salerno, C.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1949−1952. (i) Mahrwald, R. *Org. Lett.* **2000**, *2*, 4011−4012. (j) Villano, R.; Acocella, M.; De Rosa, M.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry*, **2004**, *15*, 2422−2424;

(6) (a) Sawamura, M.; Ito, Y. In *Catalytic Asymmetric Synthesis,* 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406. Ito, Y.; Sawamura, M.; Hayashi, T. *Terahedron Lett.* **1987**, *28*, 6215−6218. (c) Sawamura, M.; Ito, Y. *Catal. Asymmetric Synth.* **1993**, 367−388.

(7) (a) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 12236−12237. (b) Kobayashi, S.; Ueno, M.; Mizuki, Y.; Ishitani, H.; Yamashita, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5476−5481.

(8) Bull, S. D.; Davidson, M. G.; Johnson, A. L.; Robinson, D. E. J. E. *Chem. Commun.* **2003**, 1750−1751.

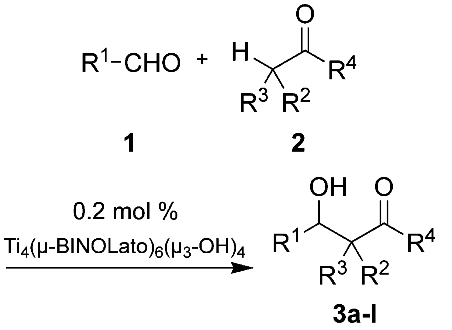
(9) Mikami, K.; Ueki, M.; Matsumoto, Y.; Terada, M. *Chirality* **2001**, *13*, 541−545.

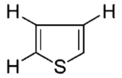
(10) The experimental procedure was the same as that given by Mikami et al. The catalyst was obtained as dark red rectangular crystals. A single-crystal structure analysis was made of a suitable crystal. The complex was found to crystallize in the cubic space group $F\bar{4}3c$. $a = b = c = 32.348$ Å; R1 = 0.049, wR2 = 0.118. Crystallographic data have been deposited at the Cambridge Crystal Data Center (CCDC 279234). This material can be obtained upon request to CCDC, 12 Union Road, Cambridge, 1EZ, U.K. (http://www.ccdc.cam.ac.uk; e-mail at deposit@ccdc.cam.ac.uk). The structure was refined with *SHELX97* (Sheldrick, G. M. *SHELX97: Program for crystal structure refinement*; Universität Göttingen: Göttingen, Germany).

(11) So far, the catalyst loadings for similar reactions range usually between 2 and 20 mol %; recently, Ding et al. presented an enantioselective carbonyl-ene reaction with comparable low catalyst loadings: Yuan, Y.; Zhang, X.; Ding, K. *Angew. Chem.* **2003**, *42*, 5478−5480.

(12) Typical experimental procedure: 1 equiv of aldehyde and 1.5 equiv of ketone were mixed at room temperature. If problems with the solubility occurred, small amounts of CH_2Cl_2 were used as solvent. A portion 0.2 mol % of the catalyst was added. The procedure of the reaction was monitored by TLC, and when the turnover was complete, the reaction mixture was diluted with diethyl ether; the reaction was then quenched with aqueous NH_4Cl. The organic layer was separated, dried ($MgSO_4$), and filtered, and the ether was removed in vacuo. CC (hexane/ethyl acetate) afforded the pure aldols. Yields have not been optimized. Large amounts of recovered aldehyde indicate the necessity of the employment of longer reaction times or higher reaction temperatures in some cases.

Table 1



entry	R^1	R^2	R^3	R^4	reaction time	product	regioselectivity (ratio **3**:other aldol products)	yield (%) of **3**	*syn/anti* ratio of **3**
1	Ph	*n*-Bu	H	Me	7 d	**3a**	97:3	68	18:82
2	Ph	Me	H	Me	7 d	**3b**	95:5	74	53:47
2a	Ph	Me	H	Me	48 h, 55°C	**3b**	92:8	75	48:52
2b	Ph	Me	H	Me	12 h, 63°C	**3b**	90:10	60	50:50
3	Ph	Me	H	Et	7 d	**3c**	-	85	50:50
4	Ph	Ph	H	Me	7 d	**3d**	>95:5[a]	78	>5:95
5	3-MeO−C_6H_4	Me	H	Et	7 d	**3e**	-	64	50:50
6	4-Cl− C_6H_4	Me	H	Et	7 d	**3f**	-	54	57:43
7	4-EtO−C_6H_4	Me	H	Me	7 d	**3g**	95:5	55	50:50
8	4-EtO−C_6H_4	*n*-Bu	H	Me	7 d	**3h**	>95:5[a]	71	90:10
9	PhC≡C	Me	H	Me	7 d	**3i**	>95:5[a]	88	67:33
10		Me	H	Me	7 d	**3j**	>95:5[a]	24[b]	38:62
11	Ph	Me	Me	Me	14 d	**3k**	68:32	22[c]	-
12	PhC≡C	Me	Me	Me	7 d	**3l**	60:40	56[d]	-

[a] Regioselectivity was generally below the detection limit of 300 MHz ^{1}H NMR (>95:5). [b] 70% of the thiophenecarbaldehyde was recovered. [c] 75% of the benzaldehyde was recovered. [d] 40% of the phenylpropargylaldehyde was recovered.

quaternary stereocenters with defined relative configurations (*endo*-CH_3 and *exo*-OH, Figure 2).[15]

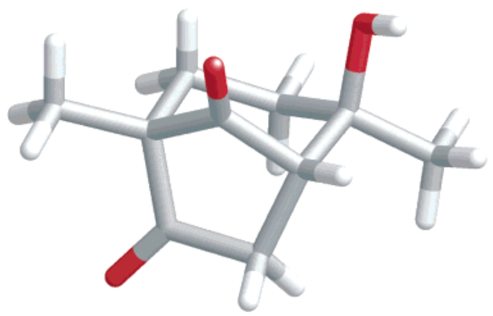


Figure 2. Crystal structure of the bicyclic dione **5**.

Other quaternary carbon atoms were also synthesized with α-methylcyclopentanone **7a** and α-methylcyclohexanone **7b** (Table 2). Surprisingly, the regioselectivity depends strongly upon the nature of the cyclic ketone in these reactions.

Because Mikami's catalyst is highly resistant against air, moisture, and acids, neither drying of the reagents and the solvents nor the application of protection gas techniques was necessary. Although the reaction stopped after adding 1 equiv of water, the aldol reaction proceeded after water removal (molsieve A3 after separation of the aqueous layer), indicating that the catalyst remained stable and active. It was even possible to recover unchanged catalyst from the reaction mixture.

Optimization of the reaction conditions indicated that reaction temperatures of 55 °C reduce the reaction times to 48 h (entry 2a, Table 1). If the reaction was carried out at 63 °C, satisfactory yields were obtained after 12 h (entry 2b, Table 1). Higher amounts of the aldehyde and higher catalyst loadings also resulted in a reduction of reaction time.

In contrast to the $TiCl_4$-mediated aldol addition,[13] this reaction is even applicable to higher functionalized ene compounds. Hydroxyacetone **10** reacts with aldehydes to give the protected aldols **11** and **12** (Table 3) with a high degree

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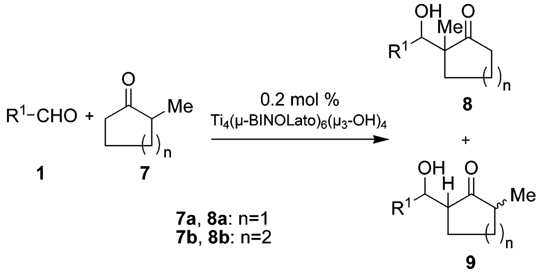
(13) Mahrwald, R.; Gündogan, B. *J. Am. Chem. Soc.* **1998**, *120*, 413−414.

(14) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621.

(15) The relative stereochemistry was unambiguously determined by single-crystal structure analysis. Substance **5** crystallizes in the orthorhombic space group $Pna2_1$. a = 12.024 Å, b = 10.6931 Å, c = 7.1249 Å; R1 = 0.025, wR2 = 0.061. Crystallographic data have been deposited at the Cambridge Crystal Data Center (CCDC 279235). This material can be obtained upon request to CCDC, 12 Union Road, Cambridge, 1EZ, U.K. (http://www.ccdc.cam.ac.uk; e-mail at deposit@ccdc.cam.ac.uk).

Table 2. Aldol Additions to α-Methylcycloalkanones



entry	ketone	R^1	regioselectivity **8**:**9**	*syn*-**8**: *anti*-**8**	*syn*-**9**: *anti*-**9**	overall yield (%)
1	**7a**	Ph	>95:5[a]	52:48		85
2	**7b**	Ph	66:34	55:45	72:28	53[d]
3	**7a**	PhC≡C	94:6	51:49		81
4	**7b**	PhC≡C	78:22	52:48	70:30	72
5	**7a**	4-EtO−C_6H_4	>95:5[a]	65:35		61[c]
6	**7b**	4-EtO−C_6H_4	no reaction			
7	**7a**	4-Cl−C_6H_4	96:4	55:45	nd[b]	68
8	**7b**	4-Cl−C_6H_4	81:19	65:35	67:33	34
9	**7a**	3-MeO−C_6H_4	96:4	67:33	nd[b]	68
10	**7b**	3-MeO−C_6H_4	75:25	63:37	65:35	12[e]

[a] Regioselectivity was generally below the detection limit of 300 MHz ^{1}H NMR (>95:5). [b] Not determined. [c] 28% of the aldehyde was recovered. [d] 38% of the aldehyde was recovered. [e] 78% of the aldehyde was recovered. [f] Relative stereochemistry determined by X-ray structure determination.

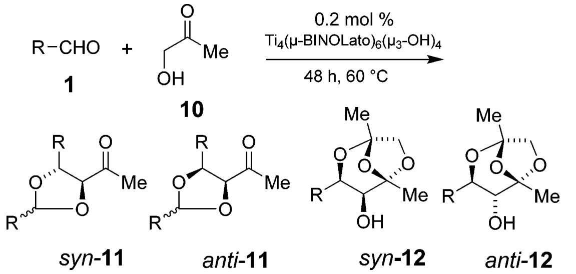
of diastereoselectivity. In these cases, only one regioisomer was detected as well.

The outcome of this reaction is tunable by the stoichiometry of the reactants. By employing equimolar amounts of aldehyde **1** and hydroxyacetone **10**, we obtained the anti-configured aldol adduct **12** (a hydroxyacetone acetal) as the main product, whereas a 5-fold excess of the aldehyde **1** resulted in the syn-configured aldol **11** (an aldehyde acetal).

Additional experiments concerning the concept of chiral amplification and chiral poisoning[16] of the racemic catalyst are ongoing. Recently, other multinuclear chiral titanium clusters (e.g., a hexanuclear cluster with a chiral reactive cave) have been synthesized in our laboratories, and the catalytic properties will be explored.

In summary, herein, we demonstrate for the first time the synthetic power of stable and storable titanium clusters for the direct aldol addition, which is promoted with extremely low catalyst loadings. The complimentary regioselectivity is remarkable compared with the proline-catalyzed direct aldol additions and the regioselective MgI_2−amine-promoted direct aldol addition.[17] With aliphatic aldehydes, aldols could be obtained as well under certain reaction conditions. Because the outcome of this reaction is sensitive to the reaction conditions and other reaction products could be obtained in high yields as well under application of other reaction conditions, these results will be reported in a separate forthcoming paper.

Table 3. Aldol Additions to Hydroxyacetone



entry	R	ratio **1**:**10**	yield **11** (%)	*syn*-**11**: *anti*-**11**	yield **12** (%)	*syn*-**12**: *anti*-**12**
1	Ph	1:1	22	86:14	63	13:87
2	Ph	5:1	88	65:35		
3	PhC≡C	1:1	trace		61	20:80

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Konrad-Adenauer-Stiftung. Enantiopure BINOL was a gift from Merck KGaA, Darmstadt, Germany. Dr. Burkhard Ziemer, Gregor Schnakenburg, and Petra Neubauer are gratefully acknowledged for the X-ray structure analysis.

Supporting Information Available: NMR data of all synthesized species and full characterization of novel compounds as well as selected X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Keck, G. E.; Tarbet, K. H.; Kenneth H. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468. (b) Faller, J. W.; Sams, D. W. I.; Liu, X. *J. Am. Chem. Soc.* **1996**, *118*, 1217−1218.

(17) Wei, H.-X.; Jasoni, R. L.; Shao, H.; Hu, J.; Paré, P. W. *Tetrahedron* **2004**, *60*, 11829−11835.