

# Water/MAO Acceleration of the Zirconocene-Catalyzed Asymmetric Methylalumination of $\alpha$ -Olefins

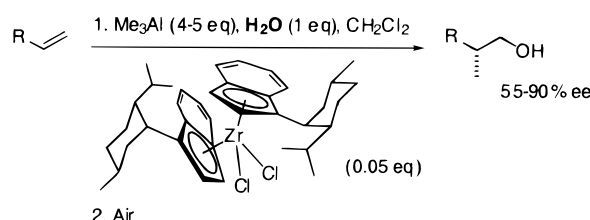
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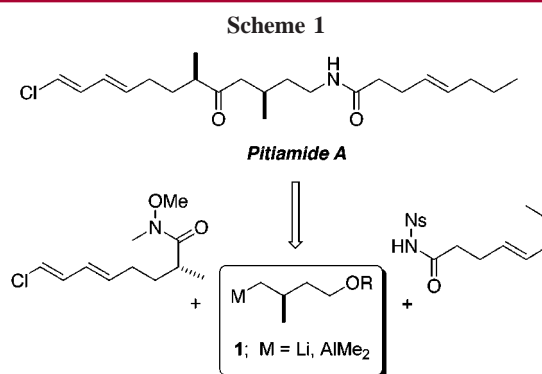
## ABSTRACT



The zirconocene-catalyzed enantioselective methylalumination of terminal alkenes is greatly accelerated in the presence of water. Terminal olefins that are inert under the standard conditions can be readily methylated in good yields and with good to high enantioselectivities. Furthermore, methylaluminoxane is also shown to accelerate the reaction, albeit at a lesser rate.

The challenging conversion of terminal alkenes into chiral branched hydrocarbons remains a frontier in the realm of asymmetric catalysis. Despite the growing interest in the Zr-catalyzed asymmetric carbomagnesiation and carboalumination of terminal alkenes, these approaches have met only limited success.<sup>1</sup> To date, the most promising results in the area of asymmetric carboalumination have been obtained by Negishi and Kondakov.<sup>2</sup> Using Erker's chiral zirconocene catalyst **2**,<sup>3</sup> (vide infra) they have shown that good to excellent yields are accompanied by synthetically useful levels of enantioselectivity for the methylalumination of terminal olefins.

Inspired by these studies, we intended to apply this asymmetric protocol toward the preparation of the key organometallic intermediate **1** in our recent synthesis of Pitiamide A (Scheme 1).<sup>4</sup> However, despite the successful use of 5-hexen-1-ol as a substrate by Negishi and Kondakov,<sup>2</sup>

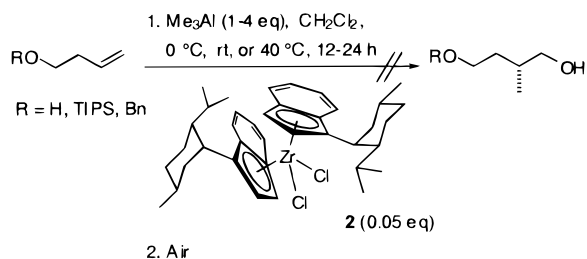


our initial attempts at the methylalumination of 3-buten-1-ol under similar conditions proved unsuccessful. Using 4–5 equiv of trimethylaluminum and 5 mol % of Erker's catalyst **2** in  $\text{CH}_2\text{Cl}_2$  at either 0 °C, room temperature, or even at 40 °C resulted only in recovered starting material after oxidative workup (Scheme 2).<sup>5</sup> Furthermore, protection of the free

(5) Quenching with  $\text{Br}_2$  gave only dibrominated product derived from the alkene.

(1) (a) Shaughnessy, K. H.; Waymouth, R. M. *Organometallics* **1998**, *17*, 5728. (b) Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 535.  
(2) (a) Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 10771. (b) Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577.  
(3) Erker, G.; Aulbach, M.; Knickmeier, M.; Wingbermhühle, D.; Krüger, C.; Nolte, M.; Werner, S. *J. Am. Chem. Soc.* **1993**, *115*, 4590.  
(4) Ribe, S.; Kondru, R. K.; Beratan, D. N.; Wipf, P. *J. Am. Chem. Soc.* **2000**, *122*, 4608.

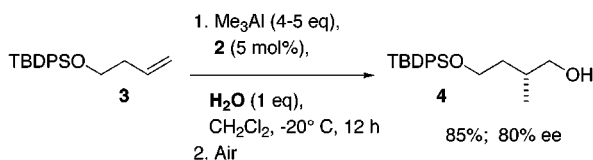
Scheme 2



hydroxy group as the TIPS ether or as the benzyl ether also resulted in unreactive substrates.

In earlier work, we have been able to demonstrate that the addition of water greatly accelerates the methylalumination of terminal alkynes.<sup>6</sup> In the hope that this modification would have a similar effect on the Negishi-Kondakov process, we treated a mixture of Me<sub>3</sub>Al and 5 mol % of Erker's catalyst **2** in CH<sub>2</sub>Cl<sub>2</sub> with 1 equiv of water. The resulting mixture proved indeed to be a vastly more reactive methylating agent. Addition of TBDPS-protected 3-buten-1-ol (**3**) to this solution at -20 °C afforded the desired methylated product **4** after 12 h (after oxidative workup) in 85% yield and in 80% ee (Scheme 3). Although this level

Scheme 3



of enantioselectivity leaves room for improvement, it compares well with the asymmetric induction reported for similar substrates by Negishi and Kondakov,<sup>2</sup> and therefore the accelerating effect of water does not seem to interfere with the transfer of chirality. Furthermore, the organoalane intermediate is not quenched by hydrolysis as long as only 1 equiv of water is used.<sup>7</sup>

Encouraged by these results, we investigated the scope of the water acceleration effect (Table 1).<sup>8</sup> The most dramatic

(6) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068.

(7) For other examples of water-accelerated processes, see (a) Chen, G.-M.; Ramachandran, P. V.; Brown, H. C. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 825. (b) Watanabe, S.; Kobayashi, Y.; Arai, T.; Sasai, H.; Bougauchi, M.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7353. (c) Miyazawa, M.; Ishibashi, N.; Ohnuma, S.; Miyashita, M. *Tetrahedron Lett.* **1997**, *38*, 3419. (d) Ward, D. E.; Gai, Y. *Tetrahedron Lett.* **1992**, *33*, 1851. (e) Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 6483. (f) Corey, E. J.; Hannon, F. J.; Boaz, N. W. *Tetrahedron* **1989**, *45*, 545.

(8) **Typical Procedure.** A solution of 0.032 g (0.048 mmol) of **2** in 4 mL of CH<sub>2</sub>Cl<sub>2</sub> was added to a mixture containing 0.306 g (4.24 mmol) of trimethylaluminum in 2 mL of CH<sub>2</sub>Cl<sub>2</sub>. The resulting yellow homogeneous reaction mixture was cooled to -50 °C, and then 18 μL (1 mmol) of water was added with vigorous stirring. (Note: the addition of water to this mixture is exothermic, and cooling below -20 °C allows for a slow and controlled reaction). The solution was warmed slowly to room temperature to effect the complete consumption of water. A color change from a light yellow to

Table 1. Water-Accelerated Methylalumination of α-Olefins<sup>8</sup>

entry	T (°C)	product, R	yield <sup>a</sup> (%)	ee (%)
1	-20	<b>5</b> , TBDPSO(CH <sub>2</sub> ) <sub>4</sub>	73	75 <sup>c</sup>
2	-20	<b>6</b> , CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	35	76 <sup>d</sup>
3	-20	<b>7</b> , HO(CH <sub>2</sub> ) <sub>4</sub>	45	86 <sup>d</sup>
4	-20	<b>8</b> , <i>c</i> -C <sub>6</sub> H <sub>11</sub>	94	55 <sup>d</sup>
5	-20	<b>9</b> , Ph	20	89 <sup>d</sup>
6	-5	<b>9</b> , Ph	73	89 <sup>d</sup>
7	0	<b>10</b> , 4-Cl-Ph	76 <sup>b</sup>	90 <sup>c</sup>

<sup>a</sup> Isolated yields. <sup>b</sup> Yield obtained after 24 h. <sup>c</sup> Determined by chiral HPLC (Chiralcel OD). <sup>d</sup> Determined by Mosher ester analysis (<sup>1</sup>H NMR).

effect was observed with styrene derivatives, as shown in entries 5–7. Negishi and Kondakov reported that styrene underwent methylation very slowly (30% yield after 22 days at room temperature).<sup>2a</sup>

In contrast, under our water-accelerated conditions, 2-phenyl-1-propanol could be obtained after 12 h at -20 °C in 20% yield (89% ee) after oxidative workup (entry 5). More importantly, performing the reaction at the slightly elevated temperature of -5 °C increased the yield of the desired product to 73% without any decrease in enantioselectivity (entry 6). Although the reaction occurred at a slower rate, 4-chlorostyrene could also be methylated in 76% yield with an ee of 90% after 24 h at 0 °C.

The poor yield with 1-octene as a substrate (entry 2), could be attributed to the much higher substrate turnover that the addition of water affords. After 12 h at -20 °C, 1-octene was completely consumed, but only 35% of the desired methylated product was obtained after oxidative workup.

For unsubstituted, unhindered alkenes such as 1-octene, the methylation appears not to compete successfully with accelerated side reactions. Analysis of the <sup>1</sup>H NMR spectrum of the crude reaction mixture indicated the presence of material derived from β-H elimination, hydrometalation, and oligomerization. Also worthy of comment is the low yield obtained with 5-hexen-1-ol as the substrate (entry 3). We believe this can be attributed to a slow air oxidation step due to intramolecular chelation between the resulting organoalane intermediate and the free hydroxy functionality.<sup>9</sup>

a dark orange/red color was observed. The solution was cooled to -20 °C and then treated with 120 μL (1 mmol) of 4-chlorostyrene. The reaction mixture was allowed to stir for 24 h at -20 °C before air was vigorously bubbled through the solution until all volatiles were evaporated. The resulting slurry was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with 2 N NaOH and brine, dried (MgSO<sub>4</sub>), and chromatographed on SiO<sub>2</sub> (EtOAc/hexanes, 1:4) to yield 0.123 g (0.762 mmol, 76%) of 2-(4-chloro-phenyl)propan-1-ol **9** in 90% ee as a colorless oil. The enantiomeric excess was determined by chiral HPLC on a Chiralcel OD column (1% *i*-PrOH/hexane): [α]<sub>D</sub> +13.3 (c 1.1, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.32 (d, 2 H, *J* = 8.4 Hz), 7.15 (d, 2 H, *J* = 8.4 Hz), 3.64 (d, 2 H, *J* = 6.7 Hz), 2.91 (s, 1 H, *J* = 6.9 Hz), 2.08 (bs, 1 H), 1.27 (d, 3 H, *J* = 7.0 Hz). Cook, M. J.; Khan, T. A.; Nasri, K. *Tetrahedron* **1986**, *42*, 249.

(9) Quenching this reaction mixture with 1 N HCl provided 5-methylhexan-1-ol in >85% yield.

**Table 2.** MAO-Accelerated Methylalumination of  $\alpha$ -Olefins<sup>14</sup>

entry	<i>T</i> (°C)	product, R	yield <sup>a</sup> (%)	ee (%)
1	-20	<b>4</b> , TBDPSO(CH <sub>2</sub> ) <sub>2</sub>	46	79 <sup>c</sup>
2	-20	<b>4</b> , TBDPSO(CH <sub>2</sub> ) <sub>2</sub>	88 <sup>b</sup>	80 <sup>c</sup>
3	-20	<b>5</b> , TBDPSO(CH <sub>2</sub> ) <sub>4</sub>	50	82 <sup>c</sup>
4	0	<b>5</b> , TBDPSO(CH <sub>2</sub> ) <sub>4</sub>	83	81 <sup>c</sup>
5	-20	<b>6</b> , CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	78 <sup>b</sup>	81 <sup>d</sup>
6	-20	<b>8</b> , <i>c</i> -C <sub>6</sub> H <sub>11</sub>	82 <sup>b</sup>	74 <sup>d</sup>

<sup>a</sup> Isolated yields. <sup>b</sup> Yield obtained after 24 h. <sup>c</sup> Determined by chiral HPLC (Chiralcel OD). <sup>d</sup> Determined by Mosher ester analysis (<sup>1</sup>H NMR).

The mechanistic role of water in the Zr-catalyzed methylalumination remains unclear. The results shown in Table 1 were obtained by the addition of 1 equiv of water to a solution containing **2** and trimethylaluminum, but we found that the order of addition is not crucial and that adding **2** to a premixed solution of water and trimethylaluminum leads to similar results.<sup>10</sup> An obvious candidate for the rate acceleration of cationic processes is MAO (methylaluminoxane).<sup>11</sup> The role that MAO plays in the activation of Cp<sub>2</sub>-ZrCl<sub>2</sub> in Ziegler–Natta-type polymerizations has been well established,<sup>12</sup> and it seems quite reasonable that the addition of water to a solution of trimethylaluminum could lead to the in situ formation of MAO. Although we ruled out the formation of MAO in our original report concerning the water-accelerated carboalumination of terminal alkynes,<sup>6</sup> we reinvestigated the use of MAO as a potential substitute for water in the present reaction. Under otherwise identical reaction conditions, the addition of 1.2 equiv of commercially available MAO<sup>13</sup> also resulted in a significant rate enhancement of the methylalumination of **3**, providing the desired chiral alcohol **4** in 46% yield and 79% ee (Table 2, entry 1).<sup>14</sup>

(10) Alkene **3** was methylated under otherwise identical conditions (-20 °C, 12 h) in 79% yield and in 80% ee.

(11) (a) Sinn, H.; Kaminsky, W. *Adv. Organomet. Chem.* **1980**, *18*, 99. (b) Pasynkiewicz, S. *Polyhedron* **1990**, *9*, 429.

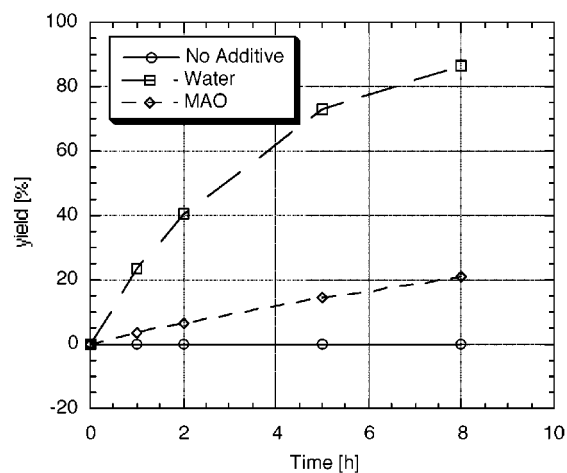
(12) Brintzinger, H. H.; Fischer, D.; Mülhaupt, R.; Rieger, B.; Waymouth, R. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1143.

(13) Obtained from Aldrich as a 10% solution in toluene. Toluene was evaporated in vacuo before use and replaced with CH<sub>2</sub>Cl<sub>2</sub>.

(14) **Typical Procedure.** A solution of 0.036 g (0.054 mmol) of **2** in 4 mL of CH<sub>2</sub>Cl<sub>2</sub> was added to a solution containing 0.324 g (4.49 mmol) of trimethylaluminum in 1 mL of CH<sub>2</sub>Cl<sub>2</sub>, followed by the addition of 1.2 mL of a 10% (by weight) solution of MAO in CH<sub>2</sub>Cl<sub>2</sub>. The resulting dark purple homogeneous solution was cooled to 0 °C, and then 0.350 g (1.04 mmol) of 1-(*tert*-butyl-diphenylsilyloxy)-5-hexene was added neat. The reaction mixture was kept at 0 °C for 12 h before air was vigorously bubbled through the reaction mixture until all volatiles were evaporated. The slurry was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with a 2 N NaOH solution and brine, dried (MgSO<sub>4</sub>), filtered, and chromatographed on SiO<sub>2</sub> (EtOAc/hexanes, 1:4) to yield 0.318 g (0.859 mmol, 83%) of (2*R*)-6-(*tert*-butyl-diphenylsilyloxy)-2-methyl-hexan-1-ol (**5**) in 81% ee as a colorless oil. The enantiomeric excess was determined by chiral HPLC on a Chiralcel OD column (1% *i*-PrOH/hexane): [α]<sub>D</sub> +3.7 (*c* 1.4, CHCl<sub>3</sub>); IR (neat) 3345, 3071, 3049, 2931, 2858, 1472, 1462, 1428, 1389, 1111, 1044, 701 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.70–7.67 (m, 4 H), 7.44–7.37 (m, 6 H),

A qualitative assessment of the accelerating ability of MAO vs water can be gained from the lower yields of the methylated products obtained after 12 h at -20 °C (Table 2, entries 1 and 3 vs Scheme 3 and Table 1, entry 1). These shortcomings could be addressed by increasing the reaction time to 24 h (entry 2) or by raising the temperature to 0 °C (entry 4). Furthermore, subjecting 1-octene to the MAO-accelerated carboalumination conditions cleanly led to the desired product in a yield of 78% after 24 h at -20 °C, with little or none of the undesired side products that were observed in the water-accelerated reaction (entry 5). Although the methylalumination proceeds at a slower rate, there are two main advantages in using MAO vs water: slightly higher ee's appear to be achievable for alkyl-substituted alkenes under the MAO-accelerated conditions, and the addition of MAO to trimethylaluminum is not exothermic and poses less of a safety hazard upon scale-up.

A more quantitative assessment of the rate difference between water and MAO was obtained for the methylalumination of styrene at 0 °C. Monitoring the appearance of 2-phenyl-propane (obtained after quenching the reaction mixture with 1 N HCl) by GC revealed that under the water-accelerated conditions the reaction was 85% complete after 8 h (Figure 1). Under the MAO-accelerated conditions,



**Figure 1.** Kinetic analysis of the Zr-catalyzed methylalumination of styrene using no additive, 1.2 equiv of MAO, and 1.0 equiv of water, respectively. Reactions were performed at 0 °C using 4–5 equiv of Me<sub>3</sub>Al and 5 mol % of **2**, and data were obtained by GC analysis of quenched samples with dodecane as internal standard. The concentration of styrene was kept constant at 0.17 M.

however, only about 20% of the methylated product was detected after this time. In contrast to the use of water or MAO as an additive, no product could be detected in the absence of either of these additives (i.e., the original

3.68 (t, 2 H, *J* = 6.3 Hz), 3.50 (dd, 1 H, *J* = 10.5, 5.8 Hz), 3.41 (dd, 1 H, *J* = 10.4, 6.5 Hz), 1.60–1.55 (m, 3 H), 1.45–1.35 (m, 4 H), 1.08–1.03 (m, 10 H), 0.92 (d, 3 H, *J* = 6.6 Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 135.8, 134.3, 129.7, 127.8, 68.6, 64.0, 35.9, 33.0 (2×), 27.1, 23.3, 19.4, 16.7; HRMS (EI) calcd for C<sub>19</sub>H<sub>25</sub>O<sub>2</sub>Si (M - C<sub>4</sub>H<sub>9</sub>) 313.1624, found 313.1626.

Negishi–Kondakov conditions), even after 12 h at 0 °C. This kinetic analysis confirmed that the use of water does indeed greatly accelerate the methylalumination of styrene at low temperatures. In addition, MAO also exhibited a substantial rate-enhancing effect.<sup>15,16</sup> While this study adds further support to the hypothesis that an agent more reactive than commercially available MAO is generated upon the addition of water to trimethylaluminum, further mechanistic analysis will be necessary to clarify the exact source of the water acceleration.

In conclusion, we have demonstrated that the zirconocene-catalyzed asymmetric methylalumination of monosubstituted

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(15) When the ratio of MAO to Zr was further increased, an additional rate increase in the methylalumination of styrene resulted. With 2 and 3 equiv of MAO, a ca. 29% and 57% conversion, respectively, of styrene was detected after 5 h at 0 °C, whereas 1.0 equiv of MAO and 1.0 equiv of H<sub>2</sub>O led to 14% and 72%, respectively.

(16) For other examples of MAO-accelerated processes, see (a) Yamanoi, S.; Ohrui, H.; Seki, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1999**, *40*, 8407. (b) Yamanoi, S.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1999**, *40*, 2793. (c) Yamanoi, S.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1998**, *39*, 9727. (d) Chen, E. Y.-X.; Marks, T. J. *Chem. Rev.* **2000**, *100*, 1391, and references therein.

alkenes is greatly accelerated by the action of water and, to a lesser extent, commercially available MAO, without compromising enantioselectivities or product yields. This modification appears to be general for  $\alpha$ -olefins and extends the reaction scope considerably to otherwise unreactive functionalized alkenes.<sup>17</sup> MAO can be a superior additive for alkenes prone to side reactions under the most reactive conditions. Further investigations of the water/MAO-accelerated carboalumination will be reported in due course.

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(17) Strongly Lewis basic functional groups such as benzyl ethers remain prohibitively rate-inhibiting even under our modified reaction conditions. Studies that address catalyst turnover in the presence of ether and carbonyl functionalities are in progress.