An Efficient Procedure for the Direct Nucleophilic Substitution of the Abiko–Masamune Auxiliary

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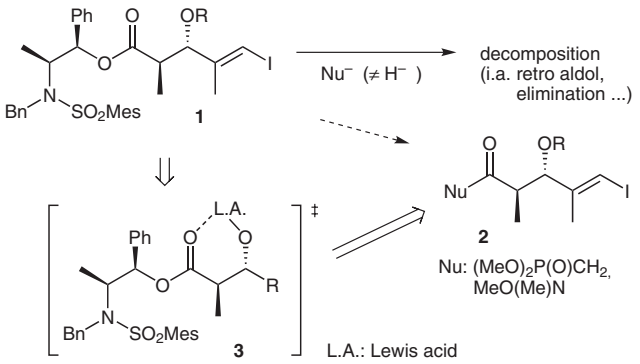
Abstract: An efficient method for the nucleophilic displacement of the Abiko–Masamune auxiliary is reported, which involves *i*-PrMgCl for intermediate ester activation.

Key words: synthetic methodology, Lewis acid, ester cleavage, aldol reaction, Abiko–Masamune auxiliary

The Abiko and Masamune aldol reaction presents one of the most widely used methods for stereoselective propionate aldol couplings.[1,2] The method allows for both *syn*- and *anti*-aldol connections with excellent diastereoselectivities and yield. Furthermore, it has demonstrated its broad substrate scope and, consequently, has been widely applied in polyketide synthesis.[3] A major drawback of the method, however, are apparent difficulties to cleave the norephedrin-derived auxiliary with nucleophiles other than hydride (e.g., phsophonates or Weinreb amides) often resulting in extensive decomposition, namely through retro-aldol or elimination pathways, which so far may only be circumvented by resorting to an alternative auxiliary.[4] As part of our synthesis of the natural product archazolid A,[3d] we encountered these problems first hand by attempting the nonreductive nucleophilic cleavage of the Abiko–Masamune aldol product **1** (Scheme 1) to access products of type **2**.

Herein, we report an efficient procedure for the direct displacement of the Abiko–Masamune auxiliary by sterically hindered nucleophiles. The method uses *i*-PrMgCl for in situ ester activation and is characterized by mild reaction conditions enabling applications also to complex and sensitive substrates.



Scheme 1

As shown in Scheme 1, our synthetic concept was based on the use of Lewis acids for ester activation, which are expected to coordinate internally to the aldol product by chelation to the β-hydroxy ester, as schematically presented in structure **3**. Consequently, this sterically congested ester should be activated and nucleophilic displacement faciliated.

To test our notion, a variety of Lews acids were studied in the nucleophilic displacement reaction of Abiko–Masamune aldol product **4** with phosphonate **5** under mild conditions (–78 to –20 °C, THF). As shown in Table 1, best results were obtained with *i*-PrMgCl among those evaluated (entries 1–6). To avoid hydrodehalogenation, choice of base for phosphonate deprotonation was critical (entries 6 and 7). After optimization of conditions,[5] the desired β-keto phosphonate **6a** was obtained with useful yields as the major product.[6,7] Notably, the chiral auxiliary may be readily recovered in 80–90% yield by column chromatography after the reaction.[5]

To further expand this concept also to Weinreb amides, the conversion of **4** to **8** was studied. As shown in Table 2, a range of Lewis acids were evaluated for this purpose (entries 1–5), under mild reaction conditions (–20 to –10 °C, THF). As before, best results were obtained with *i*-PrMgCl, giving the desired product **8** with preparatively useful yields (entry 5).[6,8] Use of BuLi mainly led to elimination along the 2,3-bond under these reaction conditions.

To evaluate the usefulness of these procedures, the conversion of **4** to phosphonate **9** and methyl ketone **11** was studied. As shown in Scheme 2, these derivatives may be readily obtained following our protocols and further conventional functional group interconversions. In contrast, the direct transformation of **10** to either **9** and **12** proceeded in only very low yields (9%, 16%), resulting mainly in elimination products.[9] Also, the likewise tested alternatives of first removing the auxiliary reductively and then introducing the required phosphonate or Weinreb amide in four-step procedures (viz. conversions of **10** to **9** or **11**) were not comparable in terms of number of steps as well as overall chemical yield with the direct method reported herein.

Finally, the applicability of this procedure to an even more challenging aldol product was demonstrated, as part of

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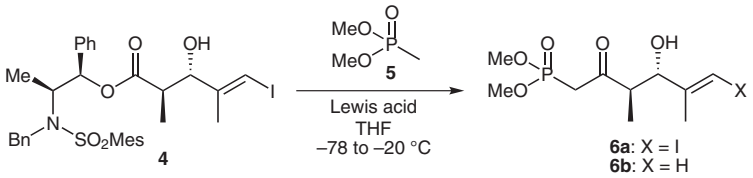
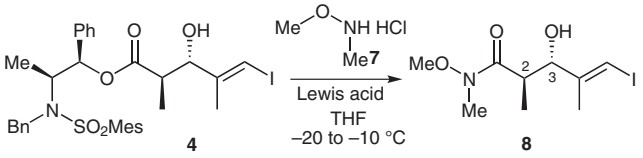
Table 1 Direct Displacement by Phosphonate



Entry	Lewis acid	Nucleophile[a]	Yield (%)
1	–	**5**, BuLi	–[b]
2	BuLi	**5**, BuLi	–[b]
3	Me_3Al	**5**, BuLi	–[c]
4	MeMgBr	**5**, BuLi	–[c]
5	EtMgBr	**5**, BuLi	–[b]
6	*i*-PrMgCl	**5**, BuLi	**6b** 86
7	*i*-PrMgCl	**5**, KHMDS	**6a** 80

[a] Deprotonation of phosphonate **5** prior to addition to **4**, see experimental procedure.[5,]
[b] Decomposition.
[c] No conversion.

Table 2 Direct Displacement by Weinreb Amide



Entry	Lewis acid	Nucleophile[a]	Yield (%)
1	Me_3Al	**7**, *i*-PrMgCl	–[b]
2	Me_2AlCl	**7**, *i*-PrMgCl	–[b]
3	DIBAL-H	**7**, *i*-PrMgCl	–[b]
4	BuLi	**7**, *i*-PrMgCl	–[c]
5	*i*-PrMgCl	**7**, *i*-PrMgCl	72

[a] Compound **7** was treated with *i*-PrMgCl prior to addition to **4**: see experimental procedure.[8,]
[b] Mainly decomposition.
[c] Mainly, elimination along the 2,3-bond was observed giving the corresponding diene.

our studies directed towards the total synthesis of etnangien,[10] as shown in Scheme 3. Substrate **16** contains a diene moiety, in combination with an additional δ-substitutent and a labile primary allylic TBS-ether, rendering it even more prone to elimination or alternative decomposition pathways. Nevertheless, the direct conversion of diene **16** into **17** proceeded smoothly using our protocol, giving the desired Weinreb amide in good yields.[6] This demonstrates the usefulness of our procedure also to particularly labile and hindered substrates. Adduct **16** was readily available by Abiko–Masamune propionate aldol reaction with aldehyde **13**, which in turn was accessible from **15**. Notably, this involved an optimized procedure for the Wittig reaction of **15** to **14**,[11] which implied use of CH_2Cl_2 as solvent and running the reaction at room temperature.[12]

In summary, we have developed an efficient procedure for the displacement of Abiko–Masamune aldol products. The procedure uses *i*-PrMgCl for intermediate activation, presumably by chelation of the β-hydroxy ester, facilitating the nucleophilic attack. It is expected that this method will be useful in further expanding the scope and applications of Abiko–Masamune aldol reactions.

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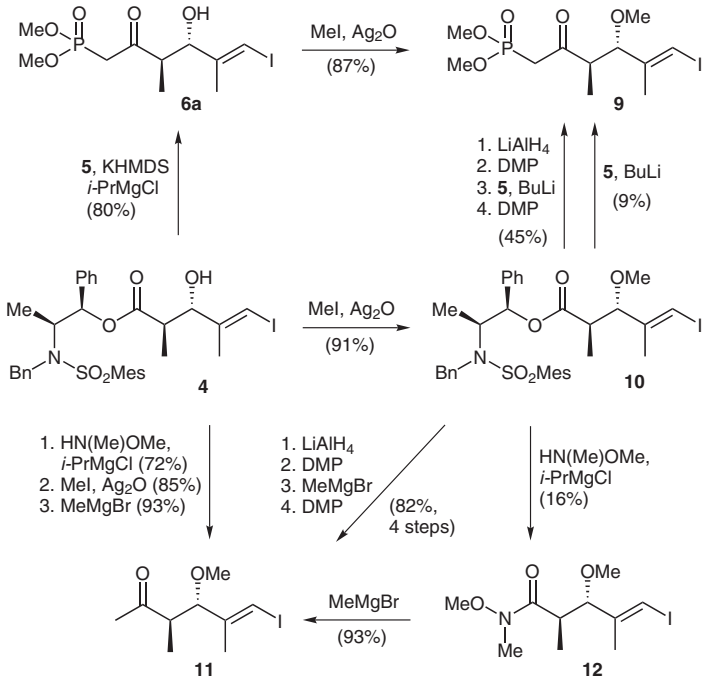
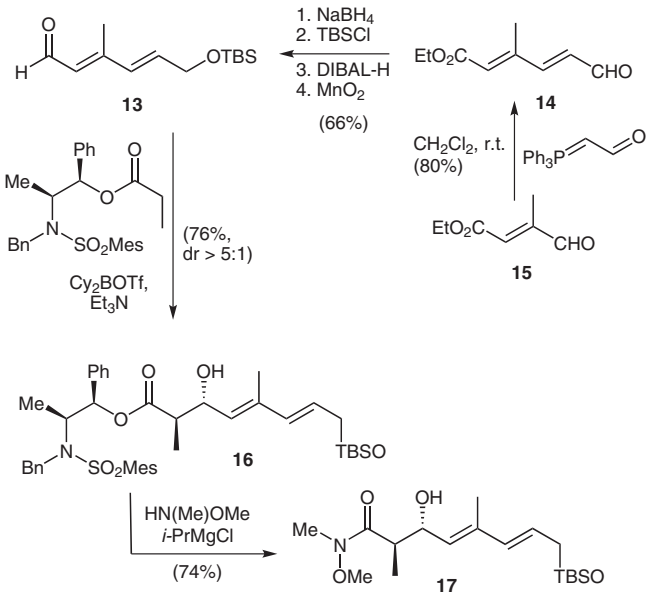
References and Notes

(1) (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586. (b) Liu, J.-F.; Abiko, A.; Pei, Z.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873. (c) Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250.
(2) For recent reviews on the aldol reaction and direct methods for polypropionate synthesis, see: (a) Brodmann, R.; Lorenz, M.; Schäckel, R.; Simsek, S.; Kalesse, M. *Synlett* **2009**, 174. (b) Li, J.; Menche, D. *Synthesis* **2009**, 2293.
(3) For selected recent examples, see: (a) Evano, G.; Schaus, J. V.; Panek, J. S. *Org. Lett.* **2004**, *6*, 525. (b) Smith, A. B. III; Simov, V. *Org. Lett.* **2006**, *8*, 3315. (c) White, J. D.; Smits, H. *Org. Lett.* **2005**, *7*, 235. (d) Menche, D.; Hassfeld, J.; Li, J.; Rudolph, S. *J. Am. Chem. Soc.* **2007**, *129*, 6100. (e) Jin, J.; Chen, Y.; Li, Y.; Wu, J.; Dai, W. *Org. Lett.* **2007**, *9*, 2585. (f) Ying, Y.; Hong, J. *Tetrahedron Lett.* **2007**, *48*, 8104.



Scheme 2



Scheme 3

(4) (a) Fanjul, S.; Hulme, A. N.; White, J. W. *Org. Lett.* **2006**, *8*, 4219. (b) Fanjul, S.; Hulme, A. N. *J. Org. Chem.* **2008**, *73*, 9788.

(5) **Experimental Procedure**
To a cold solution (–78 °C) of dimethyl methylphosphonate (156 mL, 2.93 mmol, 11 equiv) in THF (1 mL) were added KHMDS (0.5 M in toluene, 2.66 mL, 1.33 mmol, 10 equiv), and the resulting suspension was stirred at –20 °C for 2 h. To a cold solution (–78 °C) of the ester (92.1 mg, 0.136 mmol, 1.0 equiv) in THF (1 mL) was added *i*-PrMgCl (2.0 M in Et_2O, 204 μL, 0.409 mmol, 3.0 equiv). After 20 min the above mixture was added via cannula. The reaction mixture was warmed to –20 °C during 1.5 h and stirred at –20 °C for 30 min. Sat. aq NH_4Cl (6 mL) and H_2O (6 mL) were added, the organic phase separated, and the aqueous phase thoroughly extracted with EtOAc (4 × 6 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel chromatography (hexanes–EtOAc = 1:2) afforded the phosphonate **6a** (40.9 mg, 0.109 μmol, 80%) as a colorless oil and the chiral Masamune alcohol auxiliary as a white solid (50.6 mg, 0.120 mmol, 88%).

(6) All new compounds had spectroscopic data in support of the assigned structures. Sample data follow.
Compound **6a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 7.0 Hz, 3 H), 1.82 (s, 3 H), 3.06 (dq, *J* = 9.2, 7.0 Hz, 1 H), 3.17 (dd, *J* = 18.7, 13.8 Hz, 1 H), 3.25 (dd, *J* = 18.7, 13.8 Hz, 1 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 4.25 (d, *J* = 9.2 Hz, 1 H), 6.30 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 18.7, 41.2, 42.9, 50.2, 53.2, 53.3, 79.2, 80.9, 147.4, 205.4, 205.5. HRMS: *m/z* calcd for $C_{10}H_{18}IO_5PNa$ [M + Na]$^+$: 398.9834; found: 398.9836.
Compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 7.1 Hz, 3 H), 1.81 (d, *J* = 1.0 Hz, 3 H), 3.15 (m, 1 H), 3.17 (s, 3 H), 3.58 (d, *J* = 6.1 Hz, 1 H), 3.69 (s, 3 H), 4.26 (t, *J* = 6.4 Hz, 1 H), 6.30 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 20.1, 32.2, 38.2, 61.8, 79.0, 80.1, 148.1, 176.3. HRMS: *m/z* calcd for $C_9H_{16}INO_3Na$ [M + Na]$^+$: 336.0073; found: 336.0075.
Compound **17**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.90 (s, 9 H), 1.11 (d, *J* = 7.1 Hz, 3 H), 1.82 (s, 3 H), 2.94 (dq, *J* = 7.0, 7.1 Hz, 1 H), 3.04 (d, *J* = 5.6 Hz, 1 H), 3.20 (s, 3 H), 3.68 (s, 3 H), 4.24 (d, *J* = 5.1 Hz, 2 H), 4.60 (ddd, *J* = 9.2, 7.0, 5.6 Hz, 1 H), 5.43 (d, *J* = 9.2 Hz, 1 H), 5.75 (dt, *J* = 15.3, 5.1 Hz, 1 H), 6.24 (d, *J* = 15.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1, 13.2, 14.4, 18.5, 26.0, 41.5, 61.5, 63.8, 70.7, 128.7, 131.8, 133.7, 136.0, 189.2. HRMS: *m/z* calcd for $C_{18}H_{35}NO_4SiNa$ [M + Na]$^+$: 380.2233; found: 380.2232.

(7) Using metalated ethyl congener of **5**, i.e., diethyl ethylphosphonate, resulted in only low conversion under identical reaction conditions.

(8) **Experimental Procedure**
To a solution of ester 4 (231 mg, 0.342 mmol, 1.0 equiv) in THF (1 mL) was added *i*-PrMgCl (ca. 2 M in THF, 0.17 mL, 0.34 mmol, 1.0 equiv), after 10 min a suspension of magnesium chloride methoxy(methyl)amide complex, which was prepared by addition of *i*-PrMgCl (ca. 2 M in THF, 3.42 mL, 6.84 mmol, 20 equiv) to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (334 mg, 3.42 mmol, 10 equiv) in THF (3 mL) at –20 °C, was added. The reaction mixture was stirred at –20 °C for 2 h and warmed up to –10 °C (1 h). The reaction was quenched by addition of sat. aq NH_4Cl (5 mL). The product amide was extracted into EtOAc (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. After flash chromatography (hexanes–EtOAc = 2:1 to 1:1) amide **8** (77.0 mg, 0.246 mmol, 72%) was obtained as a white solid.

(9) The corresponding dienes of **9** and **12** were obtained in 38% and 6% yield, respectively.

(10) Menche, D.; Arikan, F.; Perlova, O.; Horstmann, N.; Ahlbrecht, W.; Wenzel, S. C.; Jansen, R.; Irschik, H.; Müller, R. *J. Am. Chem. Soc.* **2008**, *129*, 14234.

(11) Famer, L. J.; Marron, K. S.; Koch, S. S. C.; Hwang, C. K.; Kallel, E. A.; Zhi, L.; Nadzan, A. M.; Robertson, D. W.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2352.

(12) **Experimental Procedure**
To a flask containing $Ph_3PCHCHO$ (146 mg, 0.481 mmol, 1.0 equiv) was added a solution of **15** (207 μL, 1.52 mmol, 3.0 equiv) in dry CH_2Cl_2 (100 μL). The reaction mixture was stirred for 15 h at r.t. and purified direct by flash chromatography (hexanes–Et_2O = 6:1 to 1:1) to give aldehyde **14** (64.6 mg, 0.384 mmol, 80%) as colorless crystals.