

A Practical Synthesis of α,β -Unsaturated Imides, Useful Substrates For Asymmetric Conjugate Addition Reactions

Steven N. Goodman, Eric N. Jacobsen*

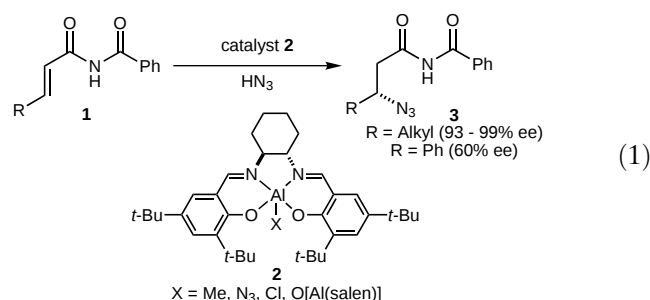
Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, MA 02138 USA
Fax: (+1)-617-496-1880, e-mail: jacobsen@chemistry.harvard.edu

Received: June 28, 2002; Accepted: July 19, 2002

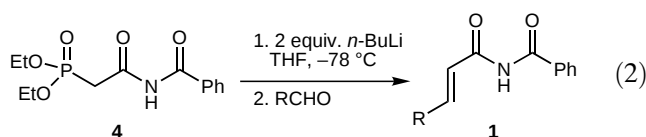
Abstract: We report an improved synthesis of α,β -unsaturated imides, a class of compounds that has been identified as broadly useful in (salen)aluminum-catalyzed asymmetric conjugate addition reactions. An efficient, scalable procedure for the synthesis of phosphonate imide reagent **4** is described, as well as a DBU-mediated Horner–Wadsworth–Emmons reaction that affords the target compounds in high yield and (*E*)-selectivity and with good functional group tolerance.

Keywords: asymmetric catalysis; Horner–Wadsworth–Emmons reactions; imides; synthetic methods; Wittig reactions

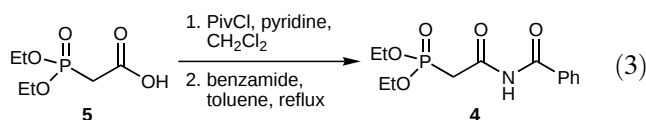
In 1999, we reported the (salen)aluminum-catalyzed asymmetric conjugate addition of azide to α,β -unsaturated imides (Eq. 1).^[1] Compounds of the general structure **1** were found to be particularly good substrates for the preparation of β -amino acid precursors (**3**) in highly enantioenriched form. Since this discovery, a variety of other nucleophiles (e.g., HCN, malononitrile, arenethiols) have been identified in effective asymmetric Al(salen)-catalyzed 1,4-additions to this class of conjugate acceptors.^[2] Given the growing importance of these α,β -unsaturated imides as substrates in asymmetric catalytic reactions, we have pursued practical and general methods for their preparation. We report here a significant advance in that regard.

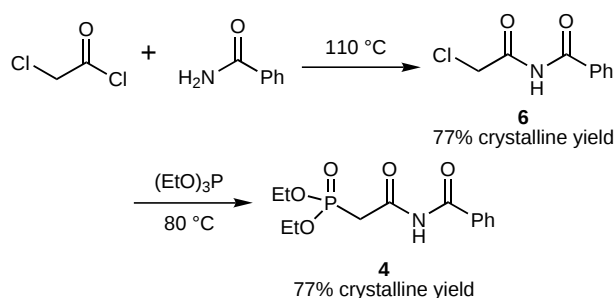


The route that we reported previously for the synthesis of **1** employed a Horner–Wadsworth–Emmons (HWE) reaction of phosphonate imide **4** and aldehydes (Eq. 2).^[1,3] The procedure involved generation of the dianion of **4** (2 equiv. *n*-BuLi, 0.2 M THF, -78°C), followed by addition of an excess of aldehyde (3 equiv.). After stirring several hours at room temperature, the product was isolated by column chromatography after work-up. While this approach effectively generated small quantities of substrates for screening purposes, many of its features made it unattractive for large-scale preparation. Problems associated with temperature control, high dilution, and use of an excess of alkyllithium base had to be resolved.



Optimization of the coupling reaction would be impossible without a practical, efficient route to phosphonate reagent **4**. The published procedure, outlined in Eq. 3, begins with diethylphosphonoacetic acid (**5**). Treatment with pivaloyl chloride (PivCl) and pyridine in dichloromethane (0.3 M) affords the mixed anhydride which, after removal of the pyridinium salts by filtration, is treated with benzamide overnight in refluxing toluene (0.2 M). Column chromatography afforded pure phosphonate product.^[1] Although the sequence reliably generated **4**, the relatively high cost of reagents and the use of chromatographic purification made it difficult to execute on large scale.





Scheme 1. An improved synthesis of phosphonate **4**.

Table 1. DBU-mediated HWE reaction of various aldehydes with phosphonate imide **4**.^[a]

entry	R	Time	Product	Yield [%] ^[b]
1 ^[c]		4 h	7	90
2 ^[d,e]		1.5 h	8	91
3		45 min	9	87
4		4 h	10	82
5 ^[d]		1 h	11	92
6		30 min	12	96
7		5 min	13	90
8		10 min	14	91
9		30 min	15	94
10		15 min	16	92

[a] Unless otherwise noted, all reactions were performed using 1.0 mmol phosphonate imide **4**, 1.0 mmol aldehyde, and 1.0 mmol DBU in 1.0 mL THF at room temperature.

[b] Isolated yield after aqueous workup and purification. Yields are of the pure (*E*)-isomer.

[c] 1.1 mmol aldehyde was used.

[d] 1.05 mmol aldehyde was used.

[e] Reaction was conducted at 0 °C.

We have achieved an improved synthesis of **4**, as depicted in Scheme 1. Benzamide and chloroacetyl chloride are heated to 110 °C in the absence of solvent to produce

N-(chloroacetyl)benzamide **6** in 75–80% yield.^[4] Heating this compound to 80 °C^[5] in the presence of 2.5 equiv. triethyl phosphite (Michaelis–Arbuzov conditions^[6]) afforded the desired phosphonate imide in 77% yield after recrystallization. This two-step synthesis of **4** is experimentally straightforward, requires no chromatography, uses inexpensive reagents, circumvents the use of solvent and base, and is readily scaleable.

With an improved route to phosphonate **4** in hand, we were in a position to turn our attention to the HWE reaction. After screening a variety of bases, we were pleased to find that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) promoted the coupling of **4** with aldehydes exceptionally well, providing high yields of the desired (*E*)-olefin products.^[7] Surprisingly, lowering the amount of DBU from two equiv. to one had no appreciable effect on product formation in terms of rate or yield. Although the imide N–H is the most acidic proton of the system (pK_a ~12–13, versus pK_a ~19–20 for the α-phosphonate protons),^[8] it is apparent that its deprotonation does not lead to a productive pathway. Instead, the low concentration of the enolate that is generated apparently reacts very efficiently with the aldehyde to form the product irreversibly.

We discovered subsequently that other acidic functionalities, such as free hydroxy groups, are also tolerated in the reaction mixture. In fact, water can be employed as solvent without any deleterious effect on the reaction, obviating any need to run the reaction under inert atmosphere or dried glassware. The outcome is not altered by changing the concentration or order of addition of reagents; the base can even be added last to a mixture of phosphonate and aldehyde without aldehyde decomposition. Thus, from an experimental standpoint, this procedure appears to be very robust.

The new HWE reaction has been performed successfully on a variety of aldehydes. Table 1 lists the results obtained from a select subset of interesting examples. In almost all instances, the products were formed in > 98:2 *E:Z* selectivity as determined by ¹H NMR of the unpurified reaction mixture.^[9] Some salient features of these results merit specific comment: (1) high yields of product are obtained using equimolar amounts (or a very slight excess) of each component in very short reaction times; (2) the reactions are conducted entirely at room temperature and high concentration (1.0 M THF); (3) the HWE reaction is successful on a wide variety of aliphatic, aromatic and heteroaromatic aldehydes; (4) both electron-rich and electron-deficient aldehydes are suitable substrates, though the latter tend to undergo reaction with significantly faster rates; and (5) a variety of unprotected functional groups are compatible with this HWE reaction, including free hydroxy groups (entries 3 and 4), esters (entry 9), and ketones (entry 10).^[10] Furthermore, most of the α,β-unsaturated imide products are crystalline, allowing for simple purification without chromatography.

In summary, we have developed a practical method for the synthesis of α,β -unsaturated imides **1**, useful substrates in a number of asymmetric catalytic conjugate addition reactions. A scaleable synthesis of the phosphonate imide **4** provides this intermediate in good yield without use of solvent or chromatography. Finally, the critical HWE reaction is a practical, highly selective DBU-mediated transformation that is tolerant of a wide range of functionality.

Experimental Section

General Remarks

All commercial reagents were used as received. DBU was purchased from Aldrich; benzamide, chloroacetyl chloride and triethyl phosphite from Alfa Aesar. Unless noted otherwise, no special precautions against water and oxygen were taken.

Synthesis of Phosphonate Imide **4**

Benzamide (12.1 g, 0.100 mol) and chloroacetyl chloride (8.20 mL, 0.103 mol) were added to a 100-mL flask equipped with a magnetic stirbar and condenser, and the mixture was heated to 110 °C under a balloon of nitrogen. Within 5 min, the mixture became homogeneous, then gradually became orange and solidified. After 30 min, the mixture was cooled and volatile by-products removed under vacuum. The solid residue was triturated with Et₂O (30 mL), and the product was collected by filtration to yield *N*-(chloroacetyl)benzamide (**6**); yield: 15.2 g (77%), which was employed in the next step without further purification.^[4,5]

Crude *N*-(chloroacetyl)benzamide (15.2 g, 0.077 mol) was placed in a 100-mL flask equipped with a stirbar and an air-cooled condenser. P(OEt)₃ (32.9 mL, 0.196 mol) was added, and the mixture was heated to 80 °C under nitrogen until the starting material was fully consumed (24–30 h, as determined by TLC analysis). After the solution was allowed to cool to room temperature, hexanes (30 mL) were added to the stirred mixture, and the clear top layer was then decanted. This process was repeated (3 × 15 mL hexanes) to remove the excess P(OEt)₃. The remaining residue was then recrystallized from *ca.* 3:1 toluene:hexanes (100–110 mL) to afford the desired phosphonate imide (**4**) as a slightly off-white solid; yield: 17.7 g (77%); mp 61–63 °C; *R*_f = 0.21 (EtOAc); IR (film): ν = 3248, 3156, 2986, 2939, 1747, 1687, 1513, 1247, 1028, 709 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ = 9.69 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.48 (m, 2H), 4.18 (m, 4H), 3.42 (d, *J* = 21.0 Hz, 2H), 1.32 (dt, *J* = 1.8 Hz, 7.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 165.2, 165.1, 133.3, 132.5, 129.0, 127.9, 63.0 (d, *J* = 6.8 Hz), 36.5 (d, *J* = 129.7 Hz), 16.3 (d, *J* = 6.1 Hz); MS (APCI): *m/z* = 300 ([M + H], 100%).

General Procedure for the Synthesis of α,β -Unsaturated Imide Substrates

A 10-mL round-bottom flask equipped with a magnetic stirbar was charged with phosphonate imide **4** (299 mg, 1.00 mmol).

THF (1.0 mL) was added, followed by DBU (0.15 mL, 1.0 mmol) and the appropriate aldehyde (1.0–1.1 mmol). [**Caution:** A slight initial exotherm can be detected after addition of aldehyde, but this can be controlled with an external water bath.] Upon completion of the reaction (as determined by TLC analysis), the reaction mixture was diluted with EtOAc (10 mL) and water (5 mL). In some cases, the product precipitated directly from the biphasic solution, and could be isolated by filtration and washing with Et₂O (Procedure A). Alternatively, the layers were separated, and the aqueous portion extracted with additional EtOAc (10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na₂SO₄, concentrated under vacuum and the material purified by column chromatography (Procedure B).

***N*-(5-Methylhex-2-enoyl)-benzamide (7):** The product was obtained as a white powder in 90% yield, using 1.1 mmol aldehyde and Procedure B; mp 84.5–85.5 °C; *R*_f = 0.33 (1:4 EtOAc:hexanes); IR (film): ν = 3295, 2959, 1725, 1679, 1640, 1481, 1255, 1167, 706 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 8.58 (s, 1H), 7.89 (m, 2H), 7.63 (tt, *J* = 1.0 Hz, 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.22 (m, 1H), 7.15 (d, *J* = 15.5 Hz, 1H), 2.23 (dt, *J* = 1.0 Hz, 7.0 Hz, 2H), 1.85 (sept, *J* = 6.5 Hz, 1H), 0.99 (d, *J* = 7.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 168.1, 166.2, 150.7, 133.0, 132.9, 128.6, 128.0, 123.8, 41.7, 27.9, 22.3; MS (APCI): *m/z* = 232 ([M + H], 100%).

***N*-(4-Benzyloxybut-2-enoyl)-benzamide (8):** The product was obtained as a white solid in 91% yield, using 1.05 mmol aldehyde and Procedure B; mp 93–94 °C; *R*_f = 0.37 (3:7 EtOAc:hexanes); IR (film): ν = 3276, 3066, 2855, 1724, 1679, 1495, 1250, 1156, 704 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 8.44 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.64 (dt, *J* = 1.0 Hz, 7.0 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.41 (m, 5H), 7.34 (m, 1H), 7.24 (dt, *J* = 4.5 Hz, 15.5 Hz, 1H), 4.64 (s, 2H), 4.30 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 166.9, 165.7, 146.5, 137.7, 133.3, 132.9, 129.0, 128.5, 127.9, 127.8, 127.8, 122.7, 72.9, 69.0; MS (APCI): *m/z* = 296 ([M + H], 100%).

***N*-[3-(5-Hydroxymethylfuran-2-yl)-acryloyl]-benzamide (9):** The product was obtained as a white solid in 87% yield, according to Procedure B; mp 158–159 °C; *R*_f = 0.14 (1:1 EtOAc:hexanes); IR (film): ν = 3278, 1719, 1621, 1486, 1253, 1148, 698 cm⁻¹; ¹H NMR (600 MHz, acetone-*d*₆): δ = 9.98 (s, 1H), 8.03 (d, *J* = 7.8 Hz, 2H), 7.63 (dt, *J* = 1.2 Hz, 7.2 Hz, 1H), 7.54 (m, 3H), 7.39 (d, *J* = 15.0 Hz, 1H), 6.81 (d, *J* = 3.6 Hz, 1H), 6.44 (d, *J* = 3.6 Hz, 1H), 4.59 (d, *J* = 6.0 Hz, 2H), 4.48 (t, *J* = 6.0 Hz, 1H); ¹³C NMR (100 MHz, acetone-*d*₆): δ = 166.9, 166.8, 159.5, 151.5, 134.4, 133.4, 131.5, 129.2, 128.9, 117.8, 117.7, 110.3, 57.2; MS (APCI): *m/z* = 272 ([M + H], 100%).

***N*-[3-(3-Hydroxyphenyl)-acryloyl]-benzamide (10):** The product was obtained as a white solid in 82% yield, using Procedure A; mp 186–187.5 °C; *R*_f = 0.33 (1:1 EtOAc:hexanes); IR (film): ν = 3264, 1725, 1625, 1480, 1256, 1153, 704 cm⁻¹; ¹H NMR (500 MHz, acetone-*d*₆): δ = 10.02 (s, 1H), 8.60 (s, 1H), 8.05 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 15.5 Hz, 1H), 7.67 (m, 2H), 7.57 (m, 2H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 2.5 Hz, 4.0 Hz, 2H), 6.94 (dd, *J* = 2.5 Hz, 7.5 Hz, 1H); ¹³C NMR (100 MHz, acetone-*d*₆): δ = 167.1, 166.9, 158.6, 144.9, 137.0, 134.4, 133.4, 130.7, 129.3, 128.9, 121.4, 120.6, 118.3, 115.0; MS (APCI): *m/z* = 268 ([M + H], 100%).

***N*-(3-Pyridin-2-ylacryloyl)-benzamide (11):** The product was obtained as a white solid in 92% yield, using 1.05 mmol aldehyde and Procedure B; mp 169.5–170 °C; *R*_f = 0.61 (EtOAc); IR (film): ν = 3280, 1725, 1674, 1632, 1479, 1152,

707 cm⁻¹; ¹H NMR (400 MHz, acetone-*d*₆): δ = 10.17 (s, 1H), 8.66 (d, *J* = 4.0 Hz, 1H), 8.06 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 15.2 Hz, 1H), 7.87 (dt, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.82 (d, *J* = 15.2 Hz, 1H), 7.66 (m, 2H), 7.53 (m, 2H), 7.39 (dd, *J* = 5.2 Hz, 7.6 Hz, 1H); ¹³C NMR (100 MHz, acetone-*d*₆): δ = 166.5, 166.3, 153.4, 150.4, 143.2, 137.2, 133.9, 133.0, 128.8, 128.5, 124.9, 124.8, 124.7; MS (APCI): *m/z* = 253 ([M + H], 100%).

N-(3-Pyridin-3-ylacryloyl)-benzamide (12): The product was obtained as a white solid in 96% yield, using Procedure B: mp 151.5–152.5 °C; *R*_f = 0.40 (EtOAc); IR (film): ν = 3232, 3090, 2919, 1704, 1675, 1625, 1328, 1252, 706 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 8.82 (d, *J* = 2.0 Hz, 1H), 8.63 (dd, *J* = 1.0 Hz, 4.5 Hz, 1H), 8.55 (s, 1H), 8.00 (dt, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.92 (t, *J* = 2.5 Hz, 2H), 7.89 (dd, *J* = 1.5 Hz, 7.5 Hz, 2H), 7.65 (t, *J* = 7.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.37 (dd, *J* = 4.5 Hz, 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 151.4, 150.5, 142.8, 142.6, 134.6, 133.5, 132.8, 130.4, 129.2, 127.9, 127.7, 123.8, 121.5; MS (APCI): *m/z* = 251 ([M–H], 100%).

N-[3-(3-Nitrophenyl)-acryloyl]-benzamide (13): The product was obtained as white needles in 90% yield, using Procedure A: mp 228.5–229 °C; *R*_f = 0.45 (1:1 EtOAc:hexanes); IR (KBr): ν = 3238, 3094, 1677, 1616, 1529, 1357, 1251, 697 cm⁻¹; ¹H NMR (600 MHz, DMSO-*d*₆): δ = 11.19 (s, 1H), 8.50 (s, 1H), 8.26 (d, *J* = 9.6 Hz, 1H), 8.11 (d, *J* = 9.6 Hz, 1H), 7.95 (d, *J* = 9.6 Hz, 2H), 7.81 (d, *J* = 19.2 Hz, 1H), 7.75 (t, *J* = 10.2 Hz, 1H), 7.65 (t, *J* = 9.0 Hz, 1H), 7.54 (t, *J* = 9.0 Hz, 2H), 7.46 (d, *J* = 19.8 Hz, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 166.6, 165.4, 148.3, 140.5, 136.3, 134.4, 133.2, 132.9, 130.6, 128.5, 128.4, 124.5, 124.3, 122.1; MS (APCI): *m/z* = 297 ([M + H], 100%).

N-[3-(4-Nitrophenyl)-acryloyl]-benzamide (14): The product was obtained as a pale yellow solid in 91% yield, according to Procedure A: mp 220–221 °C; *R*_f = 0.46 (1:1 EtOAc:hexanes); IR (KBr): ν = 3241, 3109, 1715, 1677, 1621, 1518, 1342, 1246, 697 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 11.26 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 2H), 7.94 (t, *J* = 8.0 Hz, 4H), 7.78 (d, *J* = 16.0 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 15.5 Hz, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 166.7, 165.6, 148.0, 141.0, 140.4, 133.2, 132.9, 129.2, 128.6, 128.5, 125.6, 124.2; MS (APCI): *m/z* = 295 ([M–H], 100%).

4-(3-Benzoylamino-3-oxopropenyl)-benzoic acid methyl ester (15): The product was obtained as a white solid in 94% yield, using Procedure A: mp 201–201.5 °C; *R*_f = 0.42 (1:1 EtOAc:hexanes); IR (KBr): ν = 3277, 1711, 1670, 1611, 1344, 1283, 701 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 11.22 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.93 (dd, *J* = 1.2 Hz, 8.0 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 15.6 Hz, 1H), 7.64 (dt, *J* = 1.2 Hz, 7.2 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 15.6 Hz, 1H), 3.85 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 166.7, 165.7, 165.6, 141.6, 139.0, 133.3, 132.9, 130.7, 129.8, 128.5, 128.4, 128.3, 124.0, 52.3; MS (EI): *m/z* = 309 ([M]⁺, 100%).

N-[3-(4-Acetylphenyl)-acryloyl]-benzamide (16): The product was obtained as a white solid in 92% yield, using

Procedure A: mp 182.5–183.5 °C; *R*_f = 0.38 (1:1 EtOAc:hexanes); IR (KBr): ν = 3281, 1671, 1612, 1357, 1245, 696 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 8.60 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 2H), 7.92 (s, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.67 (dt, *J* = 1.5 Hz, 7.8 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 2H), 2.66 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 197.4, 167.2, 165.9, 144.9, 138.9, 138.3, 133.5, 132.8, 129.2, 128.9, 128.7, 127.7, 121.8, 26.8; MS (APCI): *m/z* = 294 ([M + H], 80%).

Acknowledgements

This work was supported by the NIH under GM-59316.

References and Notes

- [1] J. K. Myers, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 8959.
- [2] Q. Chen, G. M. Sammis, M. S. Taylor, E. N. Jacobsen, manuscripts in preparation.
- [3] An alternative synthesis of β-aryl-α,β-unsaturated imides has been reported, involving reaction of α,β-unsaturated acid chlorides and the sodium salt of benzamide. This procedure is convenient for readily available acid chlorides, see: Y. S. Laxmi, D. S. Iyengar, *J. Chem. Soc. Perkin Trans. 1* **1995**, 3043.
- [4] J. B. Polya, T. M. Spotsword, *Recl. Trav. Chim. Pays-Bas* **1947**, *67*, 927.
- [5] Heating to higher temperatures leads to unwanted oxazoline formation, see: R. M. Rodehorst, T. H. Koch, *J. Am. Chem. Soc.* **1975**, *97*, 7298.
- [6] a) A. K. Bhattacharya, G. Thyagarajan, *Chem. Rev.* **1981**, *81*, 415; b) B. A. Arbuzov, *Pure App. Chem.* **1964**, *9*, 307.
- [7] Na₂CO₃, K₂CO₃, Et₃N, and DABCO were not as effective as DBU. Ba(OH)₂ afforded high reactivity, but the *E/Z* selectivity was much lower than that obtained with DBU. For an early example of the use of DBU in highly *E*-selective HWE reactions, see: U. Schmidt, H. Griesser, V. Leitenberger, A. Lieberknecht, R. Mangold, R. Meyer, B. Riedl, *Synthesis* **1992**, 487.
- [8] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456.
- [9] Benzyloxyacetaldehyde (entry 2) showed a 95:5 *E:Z* selectivity.
- [10] Thus far, the only substrates we have identified to be incompatible with this protocol are tautomerizable electron-rich aromatic aldehydes (e.g., 4-hydroxybenzaldehyde or pyrrole-2-carboxaldehyde) or aliphatic aldehydes susceptible to β-elimination under basic conditions (e.g., 3-silyloxypropionaldehyde).