Mild Zinc-Promoted Horner–Wadsworth–Emmons Reactions of Diprotic Phosphonate Reagents

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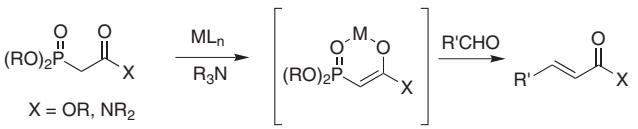
This work is dedicated to Professor Martin F. Semmelhack on the occasion of his 65th birthday

Abstract: We report the development of a mild protocol for the Horner–Wadsworth–Emmons reaction of diprotic phosphonates that makes use of a zinc triflate promoter in the presence of mild tertiary amine bases to produce α,β-unsaturated carboxylic acids and amides.

Key words: olefinations, zinc, amides, carboxylic acids, Horner–Wadsworth–Emmons reactions

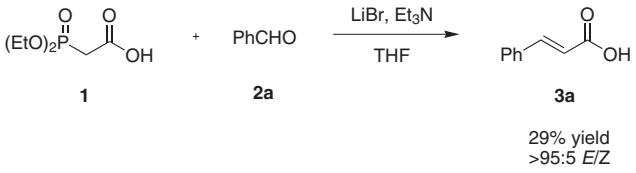
Since its discovery, the Horner–Wadsworth–Emmons (HWE) reaction has proven to be a valuable tool for the synthesis of α,β-unsaturated carbonyl compounds.[1] A number of modifications to the conditions originally reported by Wadsworth and co-workers have allowed for the synthesis of α,β-unsaturated esters, amides, carboxylic acids, ketones, and aldehydes in both *E* and *Z* configurations with excellent stereoselectivity and in high yield. One notable advance in this area has been the development of mild reaction conditions allowing for the use of tertiary amine bases in the presence of a Lewis acid as an alternative to the typical strong bases required for the HWE reaction.[2] For example, Rathke and co-workers have shown that α,β-unsaturated esters can be synthesized by the reaction of triethylphosphonoacetate with an aldehyde or ketone in the presence of triethylamine and lithium bromide.[3] A chelate model such as that illustrated in Scheme 1 has been invoked to describe the participation of the alkali metal in these reactions. Presumably, two oxygen atoms of the acyl and phosphonate group coordinate with the metal, thus enhancing the acidity of the methylene protons of the reagent.



Scheme 1 Metal-promoted HWE reactions

However, when the phosphonate reagent is diprotic, for example, when it contains a carboxylic acid moiety (i.e., X = OH), the methylene protons are expected to become considerably less acidic due to an initial deprotonation of the carboxylic acid functionality. This behavior is a potential explanation for the dearth of examples of carboxylic acid based phosphonates undergoing mild HWE reactions. As a means of supplementing and complementing the current state of the art, we report a mild protocol for the direct synthesis of α,β-unsaturated carboxylic acids via a zinc-promoted HWE reaction and the extension of this method to related diprotic secondary amides.

In our surveys of the literature, we noticed that while there is an abundance of reports describing the application of the mild Lewis acid promoted conditions to a variety of amide- and ester-based phosphonates,[4] examples of the free carboxylic acid reagent, diethylphosphonoacetic acid, undergoing reaction under such mild conditions do not exist. Conversely, there are a number of examples of such reactions being performed in the presence of very strong bases.[5] To determine whether this is a matter of non-reactivity and not simply an omission, we carried out the olefination reaction of benzaldehyde using lithium bromide as the metal promoter and triethylamine as a mild base. To our surprise, the reaction proceeded, albeit in low yield (Scheme 2), thus indicating that mild conditions are amenable to the diprotic carboxylic acid containing reagent in addition to the typical ester-containing phosphonate.



Scheme 2 LiBr-promoted HWE reaction

This result was quite encouraging and led us to explore other conditions in order to increase the reaction efficiency. A survey of several metal salts [Cu(II), Ti(IV), Zn(II)] revealed zinc triflate as an effective promoter of mild HWE reactions with diprotic substrates. With this result in hand, we then set out to optimize the yields and stereoselectivity by examining a number of variables (Table 1). Initially, we determined that two equivalents of zinc triflate were required to promote the reaction in good yields. This result indicated that under our conditions, it may be necessary for the phosphonate substrate to be bound to two zinc ions in order to affect efficient deprotonation, or

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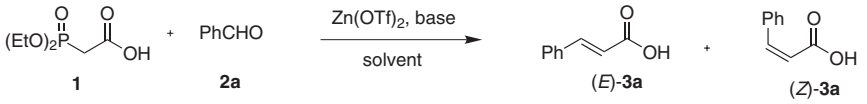
Table 1 Reaction Optimization



1 2a (*E*)-**3a** (*Z*)-**3a**

Entry	$Zn(OTf)_2$ (equiv)	Base[a]	Solvent	Yield[b]	*E*:*Z*[c]
1	2.2	None	THF	0%	–
2	2.2	Et_3N (5)	THF	53%	≥95:5
3	2.2	Et_3N (20)	THF	67%	≥95:5
4	2.2	DBU (2)	THF	17%	≥95:5
5	2.2	DBU (6)	THF	72%	92:8
6	2.2	DIPEA (4)	THF	27%	≥95:5
7	1.2	DBU (4)	THF	44%	≥95:5
8	3.6	DBU (4)	THF	63%	≥95:5
9	2.2	DBU (4)	THF	84%	93:7
10	2.2	DBU (4)	CH_2Cl_2	35%	≥95:5
11	2.2	DBU (4)	$PhCH_3$	53%	94:6

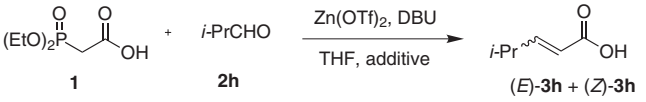
[a] Numbers in parentheses indicate the number of equivalents employed relative to phosphonate.
[b] Yields were measured by ^{1}H NMR using mesitylene as an internal standard.
[c] Ratios were measured from the ^{1}H NMR of the crude reaction material.

that the second equivalent of zinc may simply be activating the aldehyde substrate. Furthermore we found that the addition of a larger excess of zinc triflate was detrimental to the reaction (Table 1, entry 8). A survey of several bases revealed that the strong amine base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), gave optimal yields. The choice of solvent also has an impact on the reaction, as higher yields were attained using tetrahydrofuran than with any other solvent screened (Table 1, entries 9–11). All reactions in our optimization studies proceeded with excellent stereoselectivity, providing the *E* isomer exclusively under most conditions when benzaldehyde was employed as a substrate. This result was expected due to the strong precedent for such selectivity under other reported mild HWE conditions.[2,3,4a]

With these optimized conditions in hand, we then turned our attention toward aliphatic aldehydes. We were surprised when the reaction with isobutyraldehyde proceeded with only moderate *E* selectivity when the aforementioned optimized conditions were employed (Table 2, entry 1). This low selectivity was overcome by the serendipitous discovery that the addition of chelating ligands significantly enhances *E* selectivity.

A major improvement in *E* selectivity was observed upon the addition of 1.2 equivalents of (+)-*N*-methylephedrine [(+)-NME]. Interestingly, high selectivity was still observed when only 0.3 equivalent of (+)-NME was added (Table 2, entry 3). Replacing (+)-NME with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) resulted in a highly selective and more economical reaction (Table 2, entry 5). We examined the effects of using simple amines such

Table 2 Effect of Additives on *E*/*Z* Selectivity



1 2h (*E*)-**3h** + (*Z*)-**3h**

Entry	Additive[a]	Yield[b]	*E*:*Z*[c]
1	None	78%	80:20
2	(+)-NME (1.2)	95%	95:5
3	(+)-NME (0.3)	95%	94:6
4	Et_3N (1.2)	83%	67:33
5	TMEDA (1.2)	95%	95:5
6	Me_2NEt (1.2)	95%	67:33
7	DABCO (1.2)	85%	95:5

[a] Numbers in parentheses indicate the number of equivalents employed relative to phosphonate.
[b] Yields were measured by ^{1}H NMR using mesitylene as an internal standard.
[c] Ratios were measured from the ^{1}H NMR spectra of the crude reaction material.

as triethylamine and dimethylethylamine as additives, but in general, non-chelating ligands had no beneficial impact on stereoselectivity with the exception of 1,4-diazabicyclo[2.2.2]octane (DABCO; Table 2, entries 4, 6 and 7).

With optimized conditions in hand, we next set out to explore the scope of these mild HWE reactions (Table 3). In all cases, only *E* products were detected. Aromatic sub-

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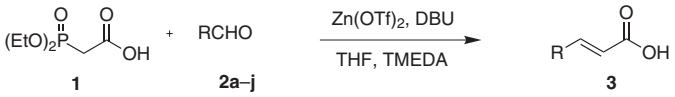
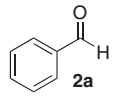
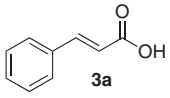
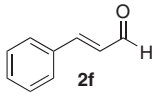
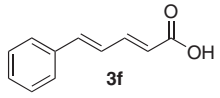
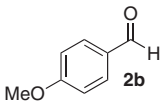
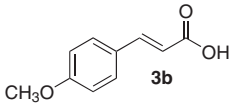
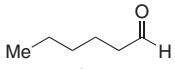
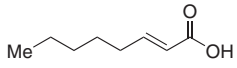
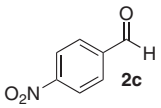
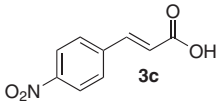
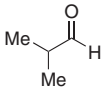
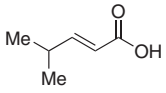
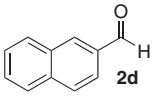
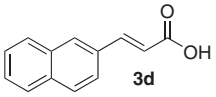
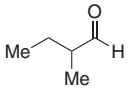
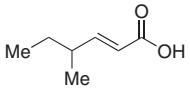
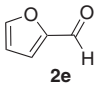
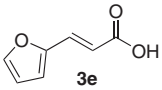
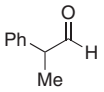
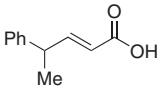
Table 3 Carboxylic Acid Reaction Scope



1 2a–j 3

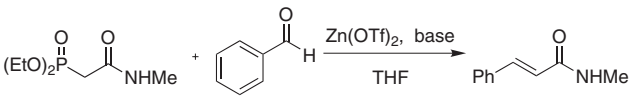
Entry	Substrate	Product	Yield[a]	Entry	Substrate	Product	Yield[a]
1	 2a	 3a	75%	6	 2f	 3f	82%
2	 2b	 3b	98%	7	 2g	 3g	100%
3	 2c	 3c	99%[b]	8	 2h	 3h	79%
4	 2d	 3d	94%	9	 2i	 3i	94%
5	 2e	 3e	72%	10	 2j	 3j	94%

[a] Isolated yields after column chromatography except where otherwise noted.
[b] Yield was calculated by ^{1}H NMR using mesitylene as an internal standard due to difficulty in isolation.

strates provided the corresponding α,β-unsaturated carboxylic acids in high yields. The reaction proved to be effective when either the electron-rich aromatic aldehyde **2b** or the electron-poor aromatic aldehyde **2c** was employed. Even the generally acid-sensitive heteroaromatic substrate, furfural (**2e**), reacted to produce 3-(2-furanyl)acrylic acid (**3e**) in good yield. We were also pleased to find that the α,β-unsaturated aldehyde cinnamaldehyde (**2f**) reacted in reasonably good yield to form conjugated diene **3f** with high *E*,*E* selectivity and with little sign of side-product formation due to Lewis acid promoted reactions of the diene product. The reaction was next tested with a variety of aliphatic aldehyde substrates including branched aliphatic aldehydes **2h**–**j**. Despite the troublesome reputation of simple aliphatic aldehydes, excellent results were seen. In accordance with literature precedent, no reaction occurred with ketones such as benzophenone and acetophenone.[3,4a]

With the reaction scope of diethylphosphonoacetic acid being thoroughly investigated under our new conditions, we then turned our attention toward the use of another type of diprotic reagent, the secondary amide containing *N*-methyl diethylphosphonoacetamide (**4**). Initially we examined the reaction of phosphonate **4** with benzaldehyde under various conditions (Table 4, entries 1–5), including those optimized for the carboxylic acid based phosphonate (Table 4, entry 5). While the reaction proceeded in high yields under the latter conditions, we were

Table 4 Optimization for Amide-Based Phosphonate **4**



4 2a 5a

Entry	$Zn(OTf)_2$ (equiv)	Base (equiv)	Yield[a]	*E*:*Z*[b]
1	0.5	DBU (2)	34%	88:12
2	1.2	DBU (2)	64%	88:12
3	1.2	None	0%	–
4	1.2	DBU (4)	68%	76:24
5	2.2	DBU (4)	98%	64:36
6[c]	2.2	DBU (4)	97%	≥95:5
7	1.2	Et_3N (4)	99%	≥95:5
8	1.2	Et_3N (1.2)	34%	≥95:5
9	1.2	Et_3N (2)	92%	≥95:5

[a] Yields were measured by ^{1}H NMR using dibenzyl ether as an internal standard.
[b] Ratios were computed from the ^{1}H NMR of the crude reaction material.
[c] TMEDA (1.2 equiv) added.

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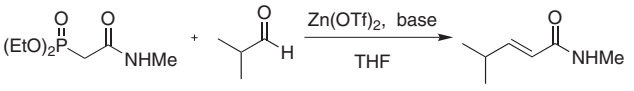
disappointed to find that the *E* selectivity was only moderate in the absence of TMEDA (Table 4, entry 5). Although the addition of TMEDA did lead to exclusive formation of the *E* product (Table 4, entry 6), we were pleased to find that the same result could be obtained by simply replacing DBU with the weaker and cheaper amine base, triethylamine (entries 7–9). Not only did triethylamine lead to enhanced *E* selectivity, but it also allowed for the employment of only 2.2 equivalents of base. Even more gratifying was the fact that under these conditions, the amount of $Zn(OTf)_2$ promoter could be reduced to just 1.2 equivalents (Table 4, entry 9). With these conditions in hand, we moved on to aliphatic aldehydes as substrates to determine whether the same decrease in *E* selectivity observed in the carboxylic acid analogues of these compounds would carry over into the amide series (Table 5). As expected, reaction of phosphonate **4** with isobutyraldehyde provided amide **5g** in high yield, but with poor stereoselectivity (Table 5, entry 1). Again, the addition of TMEDA resulted in exclusive formation of the *E* olefin (Table 5, entry 2). Interestingly, we were able to adjust the conditions such that the reaction progressed with moderate *Z* selectivity (Table 5, entries 3 and 5). Unfortunately, attempts to apply these *Z*-selective conditions to aromatic aldehydes resulted only in low *E* selectivity instead of reversal of selectivity (Table 4, entry 5).

With respect to factors controlling the selectivity of these reactions, it is generally accepted that HWE reactions proceed via attack of the phosphonate anion on the aldehyde to give a betaine intermediate (via TS1) followed by ring closure to give an oxaphosphetane (via TS2) which can irreversibly eliminate a phosphate to give the olefin product.[6] Scheme 3 indicates how TS1 favors formation of the *Z* product, while TS2 favors formation of the *E* product. Under kinetic reaction conditions, one would expect that without equilibration between the two manifolds, the *Z* product would predominate. However, if oxaphosphetane formation is slowed by steric interactions, one can imagine a pathway by which the pro-*Z* betaine and the pro-*E* betaine can interconvert via complex **6**. This explanation is supported by our observation that higher *E* selectivity is observed in general for aromatic aldehydes than for aliphatic aldehydes in the absence of TMEDA since the aromatic substrates are better able to stabilize the charged intermediate. This idea was further explored by submitting electron-rich, -poor and -neutral aromatic aldehydes to our least selective set of reaction conditions [2.2 equiv $Zn(OTf)_2$, 4.0 equiv DBU]. For this purpose, we chose *p*-nitrobenzaldehyde, *p*-anisaldehyde, and benzaldehyde as substrates. We found that the electron-poor aldehyde, *p*-nitrobenzaldehyde, reacted with low *E* selectivity (Table 6, entry 1). This supports our belief that stereoselectivity is governed largely by electronic effects since nitrobenzaldehyde is least able to stabilize a positive charge in the benzylic position.

Table 5 Effect of Reaction Conditions on *E*/*Z* selectivity

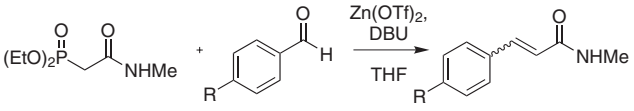


4 2h 5g

Entry	$Zn(OTf)_2$ (equiv)	Base (equiv)	Yield[a]	*E*:*Z*[b]
1	1.2	Et_3N (2.2)	98%	60:40
2[c]	1.2	Et_3N (2.2)	97%	≥95:5
3	1.2	DBU (2)	≥95%	25:75
4[c]	1.2	DBU (2)	97%	66:33
5	2.2	DBU (4)	83%	20:80
6[c]	2.2	DBU (4)	99%	66:33

[a] Yields were measured by ^{1}H NMR using dibenzyl ether as an internal standard.
[b] Ratios were measured from the ^{1}H NMR of the crude reaction material.
[c] TMEDA (1.2 equiv) was added.

Table 6 Electronic Effects on Stereoselectivity



Entry	R	Yield[a]	*E*:*Z*[b]
1	NO_2	98%	45:55
2	H	98%	69:31
3	OMe	97%	89:11

[a] Yields were measured by ^{1}H NMR using dibenzyl ether as an internal standard.
[b] Ratios were measured from the ^{1}H NMR of the crude reaction material.

Furthermore, the electron-rich anisaldehyde is quite capable of stabilizing a benzylic cation and thus facilitates entry into the manifold that produces the *E* product (Table 6, entry 3). As expected, benzaldehyde provided moderate stereoselectivity, falling between that of electron-rich and electron-poor substrates (Table 6, entry 2).

We then proceeded to examine the reaction of *N*-methyl diethylphosphonoacetamide (**4**) with several aldehydes under our optimized conditions in the presence of TMEDA (Table 7). This reaction appeared to work well for both aromatic and aliphatic aldehydes. Some difficulties were met, however, in the case of anisaldehyde to produce **5c** in low yield under these conditions (Table 7, entry 3). Aliphatic aldehydes proved to be good substrates, reacting in high yield and with excellent *E* selectivity in the presence of TMEDA. The reaction conditions appeared to be amenable to both branched and straight-chain aliphatic aldehydes (Table 7, entries 5 and 6, respectively).

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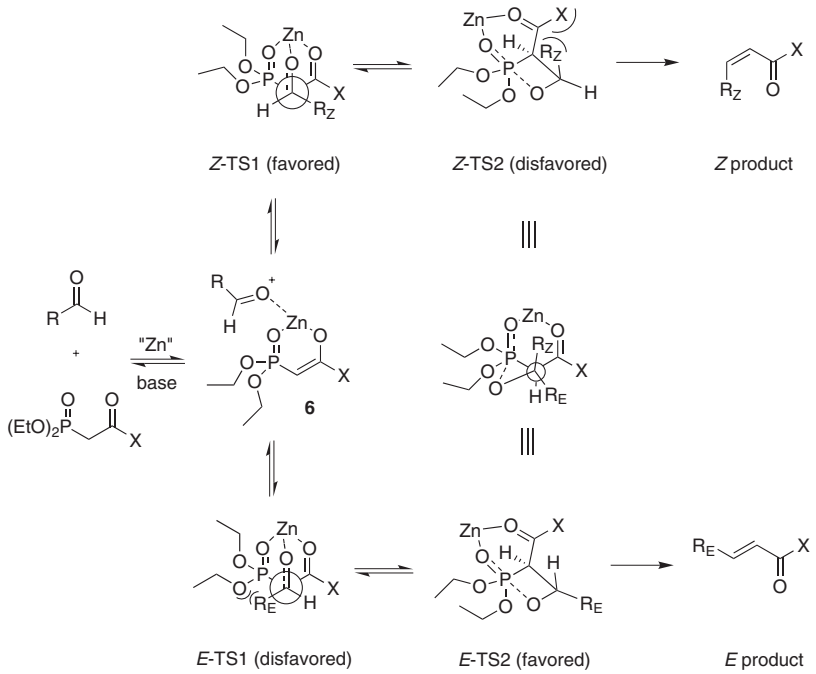
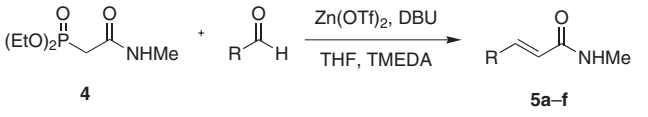


Scheme 3 Rationalization of stereoselectivity

Table 7 Scope of Amide-Based Phosphonates



4 5a–f

5a, R = Ph
5b, R = *p*-$(NO_2)C_6H_4$
5c, R = *p*-$(MeO)C_6H_4$
5d, R = 2-naphthyl
5e, R = *c*-hexyl
5f, R = *n*-hexyl

Entry	Product	Yield[a]	*E*:*Z*[b]
1	**5a**	84%	≥95:5
2	**5b**	94%	≥95:5
3	**5c**	42%	≥95:5
4	**5d**	77%	≥95:5
5	**5e**	82%	≥95:5
6	**5f**	73%	≥95:5

[a] Isolated yields after chromatography.
[b] Ratios measured from the ^{1}H NMR of the crude material.

In summary, we have reported new mild conditions for the HWE reaction of diprotic phosphonate reagents. These conditions allow for the generation of α,β-unsaturated carboxylic acids and amides, in good yields and high *E* selectivity. We have further illustrated that these reactions can be performed on a wide variety of aldehyde substrates.

All reactions were performed under an inert atmosphere with stirring. Triethylphosphonoacetate, triethylamine, methylamine, diethylphosphonoacetic acid, lithium bromide, zinc triflate, diisopropylethylamine, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from commercial sources and were used without further purification. Variation in reactivity was noted in different batches of zinc triflate obtained from different suppliers. Carbonyl substrates were washed with a saturated aqueous sodium bicarbonate solution and dried over magnesium sulfate or sodium sulfate immediately prior to use. Tetrahydrofuran and toluene were purified by passage through a solvent purification system (Innovative Technology). Dichloromethane was purified by distillation from calcium hydride. Flash chromatography was performed using Silica 60Å (230−400 mesh). ^{1}H NMR data were obtained using a 300-MHz spectrometer and referenced to $CDCl_3$ at 7.27 ppm except where otherwise noted. ^{13}C NMR data were obtained using a 500-MHz spectrometer and referenced to $CDCl_3$ at 77.23 ppm except where otherwise noted. IR spectra were measured on a Perkin Elmer Paragon 1000 FT-IR spectrometer. HRMS data were recorded on a JEOL JMS-AX505HA double sector mass spectrometer using the FAB technique. Melting points were measured on a Meltemp II apparatus.

Synthesis of (*E*)-Cinnamic Acid[7] via a LiBr-Promoted HWE Reaction

Phosphonate (0.10 g, 0.52 mmol, 1 equiv) was added along with anhyd THF (1.5 mL) to a flask containing LiBr (2.2 equiv, 0.10 g, 1.2 mmol). DBU (0.31 mL, 4 equiv, 2.1 mmol) was added followed by the aldehyde (1.1 equiv, 0.58 mmol). The reaction mixture was stirred at 25 °C for 12 h under argon. The reaction was quenched with 1 N HCl and extracted with CH_2Cl_2 (4 × 15 mL). The organic phases were combined and dried over Na_2SO_4. Solvent was removed in vacuo to yield crude carboxylic acid. The crude product was purified via flash chromatography (silica; 30% EtOAc−hexanes). Compound **3a** was isolated (yield: 29%; 23 mg) as a white solid.

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Synthesis of α,β-Unsaturated Carboxylic Acids via a $Zn(OTf)_2$-Promoted HWE Reaction; General Procedure

Phosphonate (0.10 g, 0.52 mmol, 1 equiv) was added along with anhyd THF (1.5 mL) to a flask containing $Zn(OTf)_2$ (2.2 equiv, 0.42 g, 1.2 mmol). TMEDA (0.09 mL, 0.63 mmol) was added. DBU (0.31 mL, 4 equiv, 6.3 mmol) was added followed by aldehyde (1.1 equiv, 0.58 mmol). The reaction mixture was stirred at 25 °C for 12 h under argon. The reaction was quenched with 1 N HCl (5 mL) and extracted with CH_2Cl_2 (4 × 15 mL). The organic phases were combined and dried over Na_2SO_4. Solvent was removed in vacuo to yield crude carboxylic acid. A known quantity of mesitylene was added to the crude material. Crude yields were quantified by ^{1}H NMR via comparison of the most upfield olefinic proton signal vs. the aromatic mesitylene signal. Extended relaxation times were required in order to obtain accurate results. Products were purified by column chromatography (silica; 30% EtOAc–hexanes) except where otherwise noted.

(*E*)-Cinnamic Acid (3a)[7]

Using the procedure described above, **3a** was isolated (yield: 75%, 55 mg) as a white solid; R_f = 0.46 (hexanes–EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 16.2 Hz, 1 H), 7.58 (dd, *J* = 3.1, 6.5 Hz, 2 H), 7.38–7.48 (m, 3 H), 6.48 (d, *J* = 16.2 Hz, 1 H).

(*E*)-3-(4-Methoxyphenyl)acrylic Acid (3b)[7]

Using the procedure described above, **3b** was isolated (yield: 98%; 85 mg) as a white solid; R_f = 0.14 (hexanes–EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 16.3 Hz, 1 H), 7.52 (d, *J* = 8.6 Hz, 2 H), 6.93 (d, *J* = 8.6 Hz, 2 H), 6.33 (d, *J* = 16.3 Hz, 1 H), 3.86 (s, 3 H).

(*E*)-3-(4-Nitrophenyl)acrylic Acid (3c)[7]

Using the procedure described above, **3c** was isolated (yield: 11%; 10 mg) as a yellow solid after recrystallization from hot MeOH.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.24 (d, *J* = 8.6 Hz, 2 H), 7.99 (d, *J* = 8.6 Hz, 2 H), 7.70 (d, *J* = 16.3 Hz, 1 H), 6.75 (d, *J* = 16.3 Hz, 1 H).

(*E*)-3-(Naphthalen-2-yl)acrylic Acid (3d)[8]

Using the procedure described above, **3d** was isolated (yield: 94%; 94 mg) as a white solid; R_f = 0.10 (hexanes–EtOAc, 7:3).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.19 (s, 1 H), 7.82–8.01 (m, 4 H), 7.74 (d, *J* = 15.8 Hz, 1 H), 7.47–7.62 (m, 2 H), 6.66 (d, *J* = 15.8, 1 H).

(*E*)-3-(Furan-2-yl)acrylic Acid (3e)[9]

Using the procedure described above, **3e** was isolated (yield: 82%; 57 mg) as a white solid; R_f = 0.40 (hexanes–EtOAc, 6:4).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.58 (m, 2 H), 6.68 (m, 1 H), 6.47–6.53 (m, 1 H), 6.33 (d, *J* = 15.3 Hz, 1 H).

(2*E*,4*E*)-5-Phenylpenta-2,4-dienoic Acid (3f)[10]

Using the procedure described above, **3f** was isolated (yield: 72%; 61 mg) as a white solid; R_f = 0.42 (hexanes–EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.61 (m, 1 H), 7.46–7.52 (m, 2 H), 7.29–7.43 (m, 3 H), 6.85–7.04 (m, 2 H), 6.02 (d, *J* = 15.3 Hz, 1 H).

(*E*)-Oct-2-enoic Acid (3g)[11]

Using the procedure described above, **3g** was isolated (yield: 100%; 72 mg) as a colorless oil; R_f = 0.33 (hexanes–EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (dt, *J* = 6.7, 6.9, 15.8 Hz, 1 H), 5.83 (dt, *J* = 1.4, 1.5, 15.8 Hz, 1 H), 2.13–2.35 (m, 2 H), 1.40–1.59 (m, 2 H), 1.18–1.40 (m, 4 H), 0.90 (t, *J* = 6.0 Hz, 3 H).

(*E*)-4-Methylpent-2-enoic Acid (3h)[10]

Using the procedure described above, **3h** was isolated (yield: 79%; 45 mg) as a colorless oil; R_f = 0.48 (hexanes–EtOAc, 6:4).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (dd, *J* = 6.7, 15.8 Hz, 1 H), 5.79 (dd, *J* = 1.4, 15.8 Hz, 1 H), 2.41–2.59 (m, 1 H), 1.09 (d, *J* = 6.7 Hz, 6 H).

(*E*)-4-Methylhex-2-enoic Acid (3i)[12]

Using the procedure described above, **3i** was isolated (yield: 94%; 59 mg) as a colorless oil; R_f = 0.31 (hexanes–EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (dd, *J* = 7.6, 15.6 Hz, 1 H), 5.80 (dd, *J* = 1.2, 15.6 Hz, 1 H), 2.12–2.44 (m, 1 H), 1.34–1.52 (m, 2 H), 1.07 (d, *J* = 6.7 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 3 H).

(*E*)-4-Phenylpent-2-enoic Acid (3j)[13]

Using the procedure described above, **3j** was isolated (yield: 94%; 83 mg) as a colorless oil; R_f = 0.25 (hexanes–EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.43 (m, 6 H), 5.83 (d, *J* = 15.8 Hz, 1 H), 3.53–3.74 (m, 1 H), 1.46 (d, *J* = 7.2 Hz, 3 H).

Synthesis of Diethyl (Methylcarbamoyl)methylphosphonate (4)[14]

A 33% solution of methylamine (12.5 mL) in EtOH was added to a flame-dried 100-mL round-bottom flask equipped with a stir bar and rubber septum. The flask was cooled to –78 °C. Triethylphosphonoacetate (8.85 mL) was added dropwise and the reaction was stirred at 25 °C for 24 h. Solvent was removed by rotary evaporation to give the crude product. Pure product was obtained by vacuum distillation in 83% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.77 (br s, 1 H), 4.14 (quin, *J* = 6.7 Hz, 4 H), 2.83 (d, *J* = 20.33 Hz, 2 H), 2.83 (d, *J* = 4.8 Hz, 3 H), 1.34 (t, *J* = 7.2 Hz, 6 H).

$Zn(OTf)_2$-Promoted HWE Reactions of Amide-Based Phosphonates; General Procedure

Phosphonate (0.11 g, 0.52 mmol, 1 equiv) was added along with anhyd THF (1.5 mL) to a flask containing $Zn(OTf)_2$ (2.2 equiv, 0.22 g, 0.60 mmol). TMEDA (0.09 mL, 0.63 mmol) was added. Et_3N (0.16 mL, 2.2 equiv, 1.2 mmol) was added followed by the aldehyde (1.1 equiv, 0.58 mmol). The reaction mixture was stirred at 25 °C for 12 h under argon. The reaction was quenched with 1 N HCl (5 mL) and extracted with CH_2Cl_2 (4 × 15 mL). The organic phases were combined and dried over Na_2SO_4. Solvent was removed in vacuo to yield crude carboxylic acid. A known quantity of dibenzyl ether was added to the crude material. Yields were measured by ^{1}H NMR via comparison of the most upfield olefinic proton signal vs. the benzylic signal. Extended relaxation times were required in order to obtain accurate results. Products were purified by column chromatography (silica; solvent gradient: 100% hexanes → 30% EtOAc in hexanes.)

(*E*)-*N*-Methyl-3-phenyl-2-propenamide (5a)[15]

Using the procedure described above, **5a** was isolated (yield: 84%; 71 mg) as a white crystalline solid; R_f = 0.50 (hexanes–EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 15.6 Hz, 1 H), 7.51 (m, 2 H), 7.38 (m, 3 H), 6.39 (d, *J* = 15.6 Hz, 1 H), 5.61 (br s, 1 H), 2.96 (d, *J* = 4.8 Hz, 3 H).

(*E*)-*N*-Methyl-3-(4-nitrophenyl)acrylamide (5b)[16]

Using the procedure described above, **5b** was isolated (yield: 94%; 102 mg) as a yellow crystalline solid; R_f = 0.04 (hexanes–EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 9.0 Hz, 2 H), 7.69 (d, *J* = 15.3 Hz, 1 H), 7.65 (d, *J* = 9.0 Hz, 2 H), 6.51 (d, *J* = 15.6 Hz, 1 H), 5.69 (br s, 1 H), 2.99 (d, *J* = 4.8 Hz, 3 H).

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(*E*)-3-(4-Methoxyphenyl)-*N*-methylacrylamide (5c)
Using the procedure described above, **5c** was isolated (yield; 42%; 42 mg) as a white crystalline solid; mp 118−122 °C; R_f = 0.06 (hexanes–EtOAc, 7:3).

IR (film): 3272, 3098, 2932, 1655, 1605, 1572, 1510, 1353 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 15.6 Hz, 1 H), 7.46 (d, *J* = 8.7 Hz, 2 H), 6.90 (d, *J* = 9.0 Hz, 2 H), 6.26 (d, *J* = 15.6 Hz, 1 H), 5.52 (br s, 1 H), 3.84 (s, 3 H), 2.95 (d, *J* = 4.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.3, 160.9, 140.4, 129.5, 127.7, 118.4, 114.4, 55.5, 26.7.

HRMS (FAB$^+$): *m*/*z* [M + H$^+$] calcd for $C_{11}H_{14}NO_2$: 192.1025; found: 192.1011.

(*E*)-*N*-Methyl-3-(naphthalen-6-yl)acrylamide (5d)
Using the procedure described above, **5d** was isolated (yield: 77%; 85 mg) as a white crystalline solid; mp 183–184 °C; R_f = 0.08 (hexanes–EtOAc, 7:3).

IR (KBr): 3269, 1655, 1618, 1560, 1384 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (s, 1 H), 7.73–7.63 (m, 4 H), 7.55 (dd, *J* = 1.5, 8.7 Hz, 1 H), 7.38 (m, 2 H), 6.84 (br s, 1 H), 6.54 (d, *J* = 15.9 Hz, 1 H), 2.84 (d, *J* = 4.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 139.9, 133.7, 133.3, 132.5, 129.0, 128.4, 128.3, 127.6, 126.7, 126.5, 123.5, 121.4, 26.3.

HRMS (FAB$^+$): *m*/*z* [M + H$^+$] calcd for $C_{14}H_{14}NO$: 212.1075; found: 212.1082.

(*E*)-3-Cyclohexyl-*N*-methylacrylamide (5e)
Using the procedure described above, **5e** was isolated (yield: 82%; 72 mg) as a white solid; mp 82−83 °C; R_f = 0.12 (hexanes–EtOAc, 7:3).

IR (KBr): 3442, 3295, 2918, 2845, 1668, 1638, 1563, 1384 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.78 (dd, *J* = 6.6, 15.3 Hz, 1 H), 5.70 (dd, *J* = 1.5, 15.3 Hz, 1 H), 5.48 (br s, 1 H), 2.88 (d, *J* = 4.8 Hz, 3 H), 2.10 (m, 1 H), 1.64−1.77 (m, 5 H), 1.21 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 149.9, 121.1, 40.4, 32.2, 26.5, 26.2, 26.0.

HRMS (FAB$^+$): *m*/*z* [M + H$^+$] calcd for $C_{10}H_{18}NO$: 168.1388; found: 168.1368.

(*E*)-*N*-Methyloct-2-enamide (5f)
Using the procedure described above, **5f** was isolated (yield: 73%; 59 mg) as a white crystalline solid; mp 40−42 °C; R_f = 0.17 (hexanes–EtOAc, 7:3).

IR (film): 3297, 3081, 2924, 1668, 1622, 1560 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.84 (dt, *J* = 6.9, 15.3 Hz, 1 H), 5.75 (dt, *J* = 1.5, 15.3 Hz, 1 H), 5.39 (br s, 1 H), 2.88 (d, *J* = 5.1 Hz, 3 H), 2.17 (dq, *J* = 1.8, 7.5 Hz, 2 H), 1.46 (m, 2 H), 1.30 (m, 4 H), 0.89 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 144.7, 123.4, 32.0, 31.3, 28.0, 26.3, 22.5, 14.0.

HRMS (FAB$^+$): *m*/*z* [M + H$^+$] calcd for $C_9H_{18}NO$: 156.1388; found: 156.1400.

(*E*)-*N*,4-Dimethylpent-2-enamide (5g)[16]
Using the procedure described above, **5g** was produced in 97% yield as measured by ^1H NMR using dibenzyl ether as an internal standard.

IR (KBr): 3276, 3085, 2959, 2851, 1673, 1628, 1560, 1356, 980 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.81 (dd, *J* = 7.0, 15.5 Hz, 1 H), 5.71 (dd, *J* = 1.0, 15.5 Hz, 1 H), 5.45 (br s, 1 H), 2.88 (d, *J* = 5.0 Hz, 3 H), 2.44 (m, 1 H), 1.06 (d, *J* = 6.5 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.2, 151.1, 120.8, 30.9, 26.5, 21.7.

HRMS (FAB$^+$): *m*/*z* [M + H$^+$] calcd for $C_7H_{14}NO$: 128.1075; found: 128.1085.

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