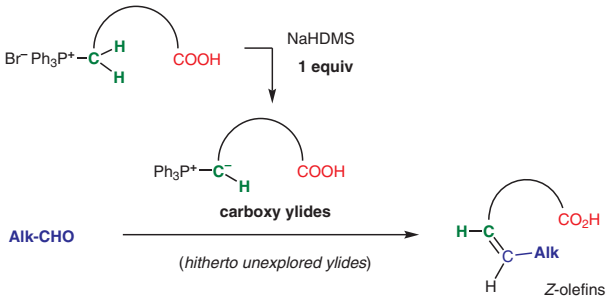
Synlett Y. Suganuma, Y. Kobayashi Letter

Formation of COOH-Ylides, and Their Reactivities and Selectivities in Wittig Reactions

Yuta Suganuma
Yuichi Kobayashi*

Department of Bioengineering, Tokyo Institute of Technology, Box B-52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan
ykobayas@bio.titech.ac.jp

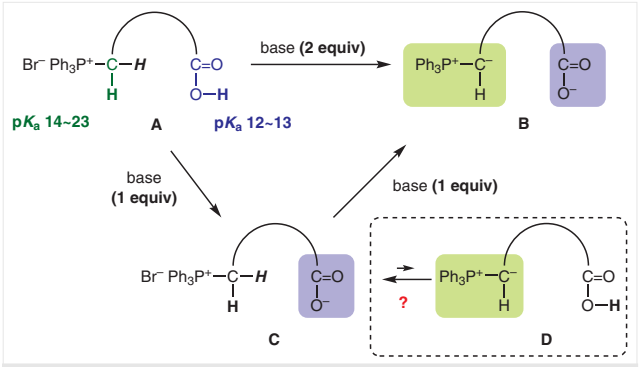


Received: 18.11.2018
Accepted: 09.12.2018
Published online: 08.01.2019
DOI: 10.1055/s-0037-1611958; Art ID: st-2018-u0752-l

Abstract Whereas two equivalents of base are typically required to prepare carboxylate (CO_2^-) ylides [$Ph_3P^+C^-$(H)-alk-CO_2^-] (alk = alkanediyl) from carboxy (CO_2H) phosphonium salts [(Ph_3PCH_2-alk-CO_2H)$^+$] X^-, we reveal, for the first time, that carboxy ylides [$Ph_3P^+C^-$(H)-alk-CO_2H] can be generated with one equivalent of NaHMDS at 0 °C, and that the Wittig reaction of simple aliphatic aldehydes (1 equiv) with these carboxy ylides (1.5–2 equiv) in THF at –95 to –90 °C for one hour, then at warming temperatures to 0 °C over two hours affords (*Z*)-alkenoic acids. Phosphonium salts containing $(CH_2)_n$ alkanediyl chains (n = 2–5) showed adequate reactivity and high *Z*-selectivity, whereas shorter or longer alkanediyl chains resulted in a low *Z*-selectivity and/or a low yield. On the basis of these results with different $(CH_2)_n$ chains and that obtained with a rigid methylene group, we propose that a rapid equilibrium between Ph_3PCH_2-alk-CO_2^- and $Ph_3P^+C^-$(H)-alk-CO_2H, through an intramolecular hydrogen exchange, accounts for the success of the Wittig reaction.

Key words Wittig reaction, carboxy phosphonium salt, carboxy ylides, carboxylate ylides, alkenoic acids

The Wittig reaction is one of the most reliable methods for stereoselective construction of olefinic compounds of biological importance.[1] With respect to ylides possessing functional groups, several alkoxycarbonyl ylides (ester ylides) have been prepared from the corresponding phosphonium salts and a base in a 1:1 ratio.[2] However, the use of two equivalents of base for each equivalent of carboxyphosphonium salt **A** affords the carboxylate ylide **B** (Scheme 1); the latter gives a (*Z*)-olefin upon Wittig reaction with an aliphatic aldehyde in syntheses of prostaglandins (via the Corey lactone),[3] lipoxygenase metabolites of fatty acids,[4] or others.[5] In the search for an *E*-selective Wittig reaction of PhCHO with **B**, nonanal has been used as an additional aldehyde that showed a moderate *Z*-preference.[6] It is accepted that the ylide **B** is formed via the carboxylate phosphonium salt **C**, which, in turn, is derived from **A** through initial reaction with one equivalent of base per equivalent of **A**. The pK_a values[7] in DMSO[8] for the corresponding phosphonium salts and carboxylic acids are in accordance with these steps, and therefore, to date, **C** has been considered as simply an intermediate species. However, we noticed that a mixture of **A** and a base in a 1:1 ratio has a reddish-orange color, indicating the formation of the carboxy ylide **D** (an acid ylide), and we therefore envisioned the use of ylide **D** in a Wittig reaction. Accordingly, we present the preparation, reactivities, and *Z*-selectivities of the hitherto unexplored **D**-type ylides in Wittig reactions with aliphatic aldehydes.

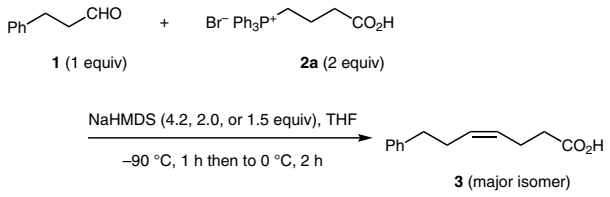


Scheme 1 Carboxylate ylides **B** and the unexplored carboxy ylides **D**

(4*Z*)-7-Phenylhept-4-enoic acid (**3**) was obtained in 63% yield upon mixing the phosphonium salt **2a** and NaHMDS in a 1:1 ratio in THF at 0 °C for one hour, followed by reaction of the resulting reddish-orange mixture with 3-phenylpropanal (**1**) at –95 to –90 °C (hereafter simplified as –90 °C) for one hour and with subsequent warming to 0 °C over two hours (Table 1, entry 1). For comparison, the carboxylate ylide, prepared from **2a** and NaHMDS in a 1:2 ratio

was subjected to the Wittig reaction with **1** under similar conditions (entry 2). The yield for entry 1 was slightly lower than that for entry 2, but the *Z*/*E* ratios, calculated from the heights or the integrations of the peaks in the ^{13}C NMR spectrum[9,10] were high, with that for entry 1 being almost same as that of entry 2. The use of fewer equivalents of NaHMDS per equivalent of **2a** was also effective (entry 3).

Table 1 Preliminary Results[a]



Entry	NaHMDS (equiv)	**2a**/NaHMDS	Yield (%)	*Z*/*E*[b]
1	2	1:1	63	90:10 (91:9)
2	4.2	1:2.1	68	91:9 (90:10)
3	1.5	1:0.75	60	90:10 (91:9)

[a] Initial temperature –95 to –90 °C (abbreviated as –90 °C).
[b] Ratios of peaks in the ^{13}C NMR by height (by integration in parentheses).

It is evident from these results that the carboxy ylide **4** (Type **D**) was indeed formed from the unreactive carboxylate species **5** (Type **C**; Figure 1). In addition, the fact that exactly one equivalent of NaHMDS is not necessarily required is a distinct operational advantage (Table 1, entries 1 and 3).

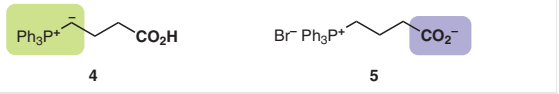


Figure 1 Carboxy ylide **4** and carboxylate anion **5**

The results that we obtained by using bases other than NaHMDS are summarized in Table 2. LiHMDS afforded **3** in a similar yield, but with a somewhat low *Z*/*E* ratio (Table 2, entry 1), whereas similarly low *Z*/*E* ratios and even lower yields were observed on using KHMDS or *t*-BuOK (entries 2 and 3). No reddish-orange color was observed when DBU, NaH, or PhONa was used; aldehyde **1** was recovered in each case (data not shown). These results are consistent with the pK_a values[7,8] of the corresponding conjugate acids. Higher temperatures of –50 °C or 0 °C resulted in lower *Z*/*E* ratios than that obtained at –90 °C (entries 4 and 5; cf. Table 1, entry 1), whereas a lower temperature resulted in a higher *Z*/*E* ratio (entry 6).

The method described in entry 1 of Table 1 was applied to carboxy phosphonium salts containing alkanediyl groups with various numbers of methylene units. The reagent derived from **2b** (which is one carbon shorter than **2a**) and

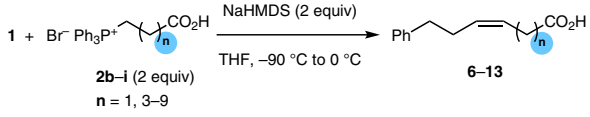
Table 2 Reactions under Various Conditions

Entry	Base	Initial temp (°C)	Yield (%)	*Z*/*E*[a]
1	LiHMDS	–90	68	84:16
2	KHMDS[b]	–90	44	83:17
3	*t*-BuOK	–90	48	87:13
4	NaHMDS	0	65	80:20
5	NaHMDS	–55	64	86:14
6	NaHMDS	–105	61	94:6

[a] Ratio of peak heights in the ^{13}C NMR.
[b] A toluene solution was used.

NaHMDS gave **6** in reasonable yield, although the *Z*-selectivity was low (Table 3, entry 1). Reagents derived from **2c–e**, which contain alkyl chains that are one, two, and three carbons longer than that in **2a**, gave good yields of **7**,[11] **8**, and **9**, respectively, with >92% *Z*-selectivity (entries 2–4). However, **2f**, which is one carbon longer than **2e**, afforded **10** in only 30% yield (entry 5); moreover, the color of the solution of **2f** and NaHMDS, before the addition of **1**, was far from reddish-orange. A creamy color appeared with compounds **2g–i**, which possess alkyl chains that are, respectively, one, two, and three carbon atoms longer than that of **2f**; consequently, the Wittig products **11–13** were obtained in quite low yields (entries 6–8). Attempts to form the ylide from **2i** by increasing the reaction time to three hours (compared with one 1 h for the other entries) or by stirring at room temperature were unsuccessful. In contrast, the use

Table 3 Reactions of Carboxy Ylides



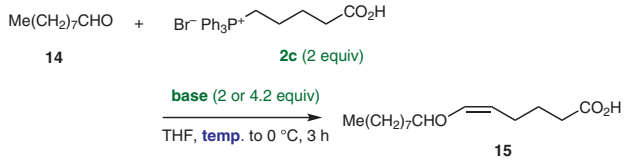
Entry	Salt	n	Product	Yield (%)	*Z*/*E*[a]
1	**2b**	1	**6**	62	61:39
2	**2c**	3	**7**	70	92:8
3	**2d**	4	**8**	73	97:3
4	**2e**	5	**9**	74	95:5
5	**2f**	6	**10**	30	>97:3
6[b]	**2g**	7	**11**	~5	ND[c]
7[b]	**2h**	8	**12**	~5	ND
8[b]	**2i**	9	**13**	~3	ND

[a] Ratios of peak heights in the ^{13}C NMR.
[b] The use of two equivalents of NaHMDS per equivalent of **2g–i** gave **11–13** in yields of 70–89% and *Z*/*E* ratios of >97:3.
[c] ND = not determined.

of two equivalents of NaHMDS per equivalent of **2g**, **2h**, or **2i** produced olefins **11**, **12**, and **13** in good yields with >97% *Z*-selectivity. The difference in reactivities between entries 1–4 and those of entries 6–8 are discussed latter, with additional results.

Previously, the Wittig olefination of nonanal (**14**) with a carboxylate ylide (type **B** ylide) derived from **2c** and LiHMDS in a 1:2 ratio at –50 °C was found to give **15** with a *Z*/*E* ratio of 73:27 (ref. 6; Table 1, entry 53; no yield given). We obtained **15** with a similar *Z*/*E* ratio and in 73% yield (Table 4, entry 4). In contrast, the carboxy ylide (a type **D** ylide) derived from **2c** and NaHMDS in a 1:1 ratio at –90 °C afforded **15** with a *Z*/*E* ratio of 97:3 and in 64% yield (entry 1). A similar reaction at –55 °C resulted in a somewhat low *Z*/*E* ratio (entry 2), whereas the carboxy ylide derived from LiHMDS gave a lower *Z*/*E* ratio (entry 3). These *Z*-selectivity ratios are in accord with the generally accepted fact that alkyl sodium ylides give higher *Z*/*E* ratios than lithium ylides.

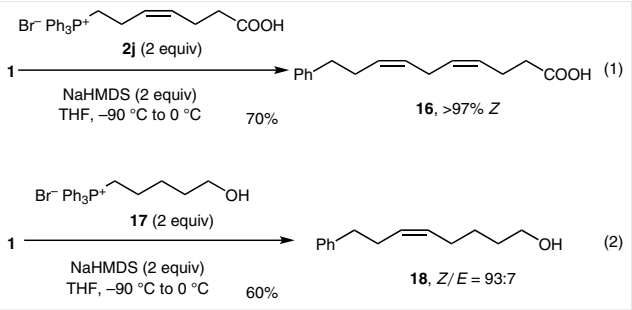
Table 4 Comparison with the Literature Conditions[a]



Entry	Base	**2c**/base	Temp (°C)	Yield (%)	*Z*/*E*[b]
1	NaHMDS	1:1	–90	64	97:3
2	NaHMDS	1:1	–55	65	90:10
3	LiHMDS	1:1	–55	60	69:31
4	LiHMDS	1:2.1	–55	73	71:29

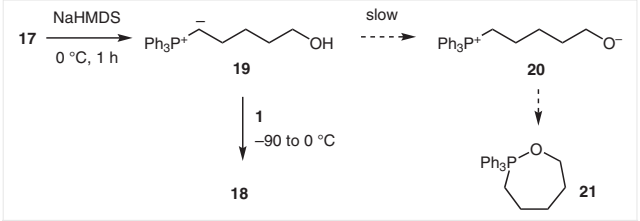
[a] Reactions at the specified temperature for 1 h, with subsequent warming to 0 °C over 2 h.
[b] Ratios of peak heights in the ^{13}C NMR.

Phosphonium salt **2j** also produced diene **16** exclusively in 70% yield (>97% *Z* by ^{13}C NMR[10]) (Scheme 2, eq. 1). The compatibility of the method with the somewhat acidic methylene between two olefin groups in the product should be useful for the synthesis of lipoxygenase metabolites of unsaturated fatty acids.



Scheme 2 Additional experiments

In view of the pK_a values of 29–30 for simple alcohols[7f] and of 14–23 for phosphonium salts,[7a,b] (ω-hydroxyalkyl)phosphonium salts should convert directly into hydroxy ylides on treatment with one equivalent of NaHMDS. In fact, the addition of **1** to a mixture of phosphonium salt **17** and NaHMDS in a 1:1 ratio afforded the alkenol **18** with 93% *Z*-purity in 60% yield (Scheme 2, eq. 2). On the basis of the high temperatures required for the preparation of 1,2-oxaphospholanes and the low reactivity of these products with aldehydes,[12] the highly reactive hydroxy ylide **19** was produced directly from **17** and remained in the solution without changing to the less reactive 1,2-oxaphospholane **21** via alkoxide **20** (Scheme 3). To the best of our knowledge, a Wittig reaction that uses hydroxy ylides has not been reported, whereas ω-alkoxy ylides have been prepared from various ω-hydroxy phosphonium salts and a base in a 1:2 ratio.[6,13]

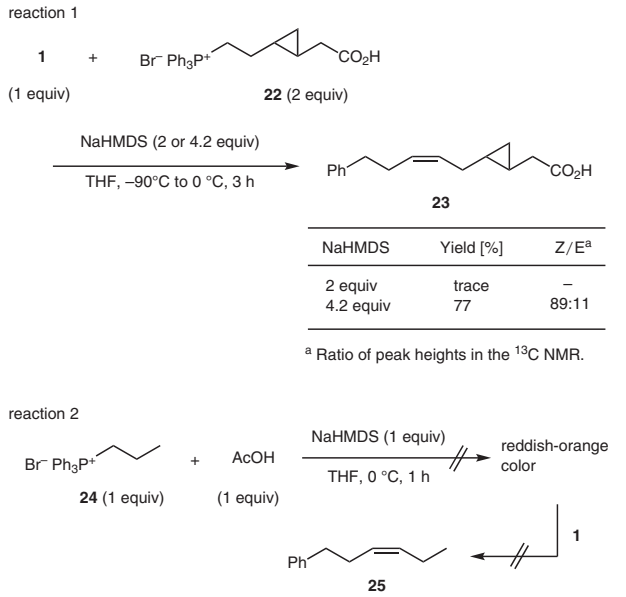


Scheme 3 Possible changes of hydroxy ylide **19**

To gain insight into the structural requirements for the formation of the carboxy ylides, we studied reactions 1 and 2 shown in Scheme 4. In reaction 1, the cyclopropylated phosphonium salt **22** was mixed with NaHMDS in a 1:1 ratio; however, the resultant mixture was faint-yellow in color, and the subsequent reaction with **1** afforded only a trace of olefin **23**.

In contrast, the use of two equivalents of NaHMDS per equivalent of **22** gave olefin **23** with 89% *Z*-selectivity in 77% yield. In reaction 2, NaHMDS was added dropwise to a 1:1 mixture of phosphonium salt **24** and AcOH. A reddish-orange color appeared shortly after each drop of the NaHMDS solution was added, but this disappeared quickly; consequently, product **25** was not obtained.

A plausible reaction pathway is summarized in Scheme 5. The equilibrium between **C** and **D** is rapidly established within one hour at 0 °C through an intramolecular hydrogen exchange via **E**. Furthermore, the equilibrium is shifted toward the product side owing to the insolubility of the NaBr co-product.[14] The production of **D** is unambiguously indicated by the reddish-orange color. The cycloaddition of **D** to aldehyde **F** takes place in a manner similar to that established for alkyl ylides,[15] and the resulting oxaphosphetane **G** releases *cis*-olefin **H** as usual. In contrast, unsuccessful formation of the carboxy ylides from phosphonium salts

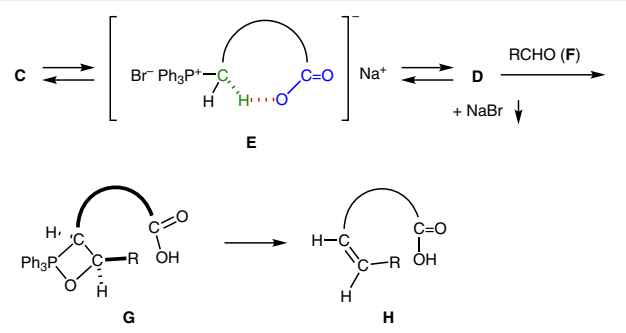


NaHMDS	Yield [%]	Z/E[a]
2 equiv	trace	–
4.2 equiv	77	89:11

[a] Ratio of peak heights in the ^{13}C NMR.

Scheme 4 Experiments related to the reaction mechanism

with longer methylene chains than **2f** or from the cyclopropane **22**[16] was evident from the faint-yellow to creamy color observed after the addition of NaHMDS, and by the recovery of unreacted aldehyde **1**. These results are consistent with the inaccessibility of **E** owing to the long chain or to structural restrictions.



Scheme 5 Plausible mechanism for the formation of carboxyl ylides **D**

In summary, carboxy ylides **D** (acid ylides) can be formed from carboxy phosphonium salts **A** and one equivalent of NaHMDS in THF (Scheme 1); these ylides can be used in Wittig reactions to produce *Z*-alkenoic acids stereoselectively.[17] The results obtained with various carboxy ylides suggest that intramolecular hydrogen exchange via **E** is responsible for the formation of carboxy ylides **D** (Scheme 4).

Funding Information

This work was supported by JSPS KAKENHI Grant Number JP15H05904.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611958.

References and Notes

(1) Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann.* **1997**, 1283.
(2) For example: (a) Perlmutter, P.; Selajerern, W.; Vounatsos, F. *Org. Biomol. Chem.* **2004**, *2*, 2220. (b) Han, X.; Crane, S. N.; Corey, E. J. *Org. Lett.* **2000**, *2*, 3437. (c) Nicolaou, K. C.; Prasad, C. V. C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1990**, *112*, 4988. (d) Delorme, D.; Girard, Y.; Rokach, J. *J. Org. Chem.* **1989**, *54*, 3635.
(3) For example: (a) Baars, H.; Classen, M. J.; Aggarwal, V. K. *Org. Lett.* **2017**, *19*, 6008. (b) Prévost, S.; Thai, K.; Schützenmeister, N.; Coulthard, G.; Erb, W.; Aggarwal, V. K. *Org. Lett.* **2015**, *17*, 504. (c) Quan, L. G.; Cha, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 12424. (d) Boulton, L. T.; Brick, D.; Fox, M. E.; Jackson, M.; Lennon, I. C.; McCague, R.; Parkin, N.; Rhodes, D.; Ruecroft, G. *Org. Process Res. Dev.* **2002**, *6*, 138. (e) Grieco, P. A.; Reap, J. J. *J. Org. Chem.* **1973**, *38*, 3413.
(4) For examples, see: (a) Srinivas, J.; Namito, Y.; Matsubara, R.; Hayashi, M. *J. Org. Chem.* **2017**, *82*, 5146. (b) Ishigami, K.; Kobayashi, M.; Takagi, M.; Shin-ya, K.; Watanabe, H. *Tetrahedron* **2015**, *71*, 8436. (c) Critcher, D. J.; Connolly, S.; Wills, M. *J. Org. Chem.* **1997**, *62*, 6638. (d) Wang, S. S.; Shi, X.-X.; Powell, W. S.; Tieman, T.; Feinmark, S. J.; Rokach, J. *Tetrahedron Lett.* **1995**, *36*, 513. (e) Just, G.; Wang, Z. Y. *J. Org. Chem.* **1986**, *51*, 4796.
(5) For examples, see: (a) Ortgies, S.; Rieger, R.; Rode, K.; Koszinowski, K.; Kind, J.; Thiele, C. M.; Rehbein, J.; Breder, A. *ACS Catal.* **2017**, *7*, 7578. (b) Hao, H.-D.; Trauner, D. *J. Am. Chem. Soc.* **2017**, *139*, 4117. (c) Liu, Y.-T.; Chen, J.-Q.; Li, L.-P.; Shao, X.-Y.; Xie, J.-H.; Zhou, Q.-L. *Org. Lett.* **2017**, *19*, 3231. (d) Paull, D. H.; Fang, C.; Donald, J. R.; Pansick, A. D.; Martin, S. F. *J. Am. Chem. Soc.* **2012**, *134*, 11128. (e) Poth, D.; Wollenberg, K. C.; Vences, M.; Schulz, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 2187; *Angew. Chem.* **2012**, *124*, 2229. (f) Wube, A. A.; Hüfner, A.; Thomaschitz, C.; Blunder, M.; Kollroser, M.; Bauer, R.; Bucar, F. *Bioorg. Med. Chem.* **2011**, *19*, 567. (g) Seike, H.; Ghosh, I.; Kishi, Y. *Org. Lett.* **2006**, *8*, 3865. (h) Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 3118.
(6) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217.
(7) For pK_a values in DMSO of phosphonium salts (14–23), see: (a) Ling-Chung, S.; Sales, K. D.; Utley, J. H. P. *J. Chem. Soc., Chem. Commun.* **1990**, 662. (b) Zhang, X.-M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 968. For carboxylic acids (pK_a = 12–13) see: (c) Bordwell, F. G.; Algrim, D. *J. Org. Chem.* **1976**, *41*, 2507. For HN(TMS)$_2$ (pK_a = 26), see: (d) Grimm, D. T.; Bartmess, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 1227. For HN(TMS)$_2$ in THF (pK_a = 25.8), see: (e) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232. For *t*-BuOH (pK_a = 32) and ROH (R = Me, Et) (pK_a = 29–30), see; (f) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295. For DBU·H$^+$ (pK_a = 14), see: (g) Hulla, M.; Chamam, S. M. A.; Laurenczy, G.;

Das, S.; Dyson, P. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 10559. *Angew. Chem.* **2017**, *129*, 10695. For PhOH (pK_a= 16–18), see: (h) Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem.* **1984**, *49*, 1424; and also ref. 7c.

(8) (a) pK_a Values in THF for most of compounds shown in ref. 7 are not available, except for that of $HN(TMS)_2$, which is almost the same in THF as in DMSO.[7d,e] Therefore, values of other compounds in DMSO are quoted for discussion of the relative acidity. (b) For a collection of pK_a values of compounds, see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(9) The ^{1}H NMR spectrum of **3** was superimposed with that of the (*E*)-isomer, which was synthesized by a method described in the Supplementary Information.

(10) Signal-to-noise ratios of the ^{1}H and ^{13}C NMR spectra were ~95% and ~97%, respectively.

(11) Alkenoic acid **7** was previously synthesized by using **2c** and *t*-BuOK (1:2); the ^{13}C NMR spectrum provided in the Supporting Information of ref. 5a (page S97) allowed us to calculate the *Z*-selectivity to be 90%, by using the peak heights.

(12) Hands, A. R.; Mercer, A. J. H. *J. Chem. Soc. C* **1968**, 2448.

(13) For examples, see: (a) Zeng, X.; Miao, C.; Wang, S.; Xia, C.; Sun, W. *Chem. Commun.* **2013**, *49*, 2418. (b) Meyers, A. I.; Collington, E. W. *Tetrahedron* **1971**, *27*, 5979.

(14) Phosphonium salt **2a** and NaHMDS were mixed in a ratio of 0.8:1 or 2.1:1 then quenched with D_2O (10 equiv). However, the recovered material showed complicated ^{1}H NMR spectra, which prevented calculation of the incorporation of deuterium into **2a**.

(15) (a) Byrne, P. A.; Gilheany, D. G. *Chem. Soc. Rev.* **2013**, *42*, 6670. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (c) Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R. Jr.; Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 7664.

(16) A molecular model of the (*E*)-5-carboxypent-3-en-1-ylphosphonium salt, the *trans*-olefin analogue of **22**, showed easy access to **E**.

(17) **(4*Z*)-7-Phenylhept-4-enoic acid (3; Table 1, Entry 1); Typical Procedure**

A 1.0 M solution of NaHMDS in THF (1.0 mL, 1.0 mmol, 2 equiv) was added to an ice-cold suspension of **2a** (432 mg, 1.01 mmol, 2 equiv) in THF (5 mL). The mixture was stirred at 0 °C for 1 h and then the resulting reddish-orange mixture was cooled to –95 to –90 °C in a slushy mixture of hexane and liquid N_2. A solution of aldehyde **1** (67 mg, 0.50 mmol, 1 equiv) in THF (1.5 mL) was added dropwise to the mixture. After 1 h, the mixture was warmed to 0 °C over 2 h then sat. aq NH_4Cl was added. The resulting mixture was extracted with Et_2O (×3). The extracts were combined, dried ($MgSO_4$), and concentrated to afford a residue that was purified by chromatography (silica gel, hexane–EtOAc) to give a colorless liquid; yield: 66 mg (63%, *Z*/*E* = 90:10); R_f = 0.13 (hexane–EtOAc, 4:1).

IR (neat): 2924, 1710, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.5–3.0 (br s, 1 H), 2.24–2.44 (m, 6 H), 2.66 (t, *J* = 7.5 Hz, 2 H), 5.30–5.42 (m, 1 H), 5.42–5.53 (m, 1 H), 7.14–7.32 (m, 5 H). ^{13}C-APT NMR (75 MHz, $CDCl_3$): δ = 22.5 (–), 29.2 (–), 34.0 (–), 35.8 (–), 125.9 (+), 127.9 (+), 128.3 (+), 128.5 (+), 130.5 (+), 141.9 (–), 179.8 (–). HRMS (FAB$^+$): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{16}NaO_2$: 227.1048; found. 227.1045.

Note that candy-like phosphonium salts, such as **2f**, or longer-chain methylene salts were heated to form a viscous mass that was transferred quickly to the reaction flask. After the addition of THF and a solution of NaHMDS, the mixture was sonicated at 0 °C until the candy-like phosphonium salt that caked in the flask was sufficiently dissolved to allow smooth stirring. The mixture was stirred at 0 °C for a total of 1 h after the addition of NaHMDS, then cooled to –90 °C before addition of aldehyde **1**.