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# Michael additions catalyzed by phosphines. An overlooked synthetic method

Carolina Gimbert, Maria Lumbierres, Caroline Marchi,† Marcial Moreno-Mañas,* Rosa M. Sebastián and Adelina Vallribera*

*Department of Chemistry, Universitat Autònoma de Barcelona, 08193 Cerdanyola, Barcelona, Spain*

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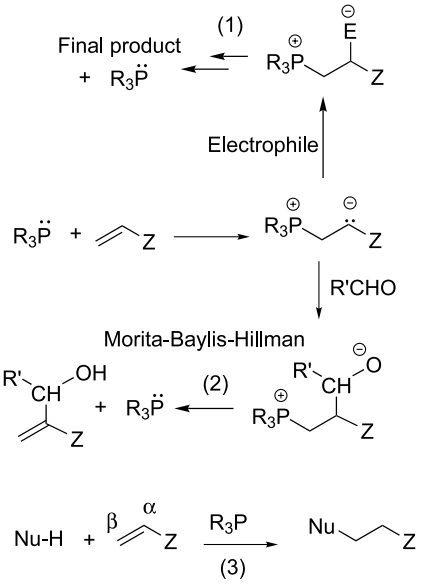
Dedicated to Professor Joaquín Plumet (Univ. Complutense de Madrid) on the occasion of his 60th birthday

**Abstract**—Triphenylphosphine and tributylphosphine are excellent catalysts for Michael additions. Many β-dicarbonyl compounds and electron-poor olefins, including sterically demanding partners, react successfully. The Michael addition catalyzed by phosphines deserves attention in its own right as a useful synthetic method.


## 1. Introduction

Organocatalysis induced by phosphines is a topic of increasing interest.[1] The most generally applied phosphine-based catalysis is also known as nucleophilic phosphine catalysis (NPC) and is initiated by the nucleophilic attack of the phosphine to the β-position of an electronically poor alkene or alkyne. The generated α-carbanion reacts as a nucleophile or as a base in many different ways. A common feature is a final step, in which phosphine is recovered thanks to its excellent leaving group properties, thus, permitting a catalytic cycle (Scheme 1, Eq. 1). The Morita–Baylis–Hillman α-hydroxyalkylation of activated olefins is perhaps the best known reaction catalyzed by nucleophilic phosphines (Eq. 2).[1e] Moreover, many different electrophiles have been used in the place of aldehydes. Thus, α,β-unsaturated ketones in intermolecular[2a] and intramolecular[2b,c] manners; π-allylpalladium complexes in intramolecular reaction;[2d] aldehydes[2e] and ketones[2f] in the intramolecular version of the Morita–Baylis–Hillman reaction; and intramolecular attack on vinylsulfones.[2g] A related reaction is the phosphine-catalyzed nucleophilic substitution of acetoxy in allylic systems.[2h] If Z=CO-R in Scheme 1 still another possibility arises: oxygen acting as nucleophile instead of carbon. At least one reaction has been described fulfilling this condition, although, in this case the phosphine was used stoichiometrically.[2i]

The stabilized α-carbanion can also react as a base. This basicity is the origin of the isomerization of acetylenic ketones into dienyl ketones under triphenylphosphine




**Scheme 1.** Nucleophilic phosphine catalysis (NPC).

*Keywords*: Organocatalysis; Phosphines; Conjugate addition; β-Dicarbonyl compounds.
* Corresponding authors. Tel./fax: +34 935811254 (M.M.-M.); tel.: +34 935813045; fax: +34 935811265 (A.V.);
e-mail addresses: marcial.moreno@uab.es; adelina.vallribera@uab.es
† Present address: Université Paul Cézanne, 13397 Marseille Cedex 20, France.

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catalysis, pioneered by Trost[3a] and reinvestigated by Lu.[3b] Moreover, basicity at C-2 or C-α has been fundamental for the, in principle, unexpected introduction of nucleophiles at C-α,[4] at C-γ,[5] or at both[6] in activated acetylenes and allenes.

This wealth of data is in sharp contrast with the attention paid to a conceptually more simple reaction, the conjugate addition to the β-position of activated alkenes or alkynes (Eq. 3). Thus, activated monosubstituted acetylenes (Z= COOR, COMe) react with thiols,[7] with alcohols,[8] and with oximes[9] to afford the products on conjugate addition at C-β. Heavily fluorinated phosphines were tested for addition of alcohols to acetylenes with the aim of recovering the catalyst in fluorous solvents.[8b,c]

Some other reactions have been recently described: the conjugate addition of water and alcohols to activated olefins under phosphine catalysis,[10] the additions of oximes to simple activated monosubstituted olefins catalyzed by triphenylphosphine,[11] and the aza-Michael addition of carbamates to unsaturated ketones, albeit in this case the presence of trimethylsilyl chloride, together with the phosphine, was essential for the outcome of the reaction.[12]

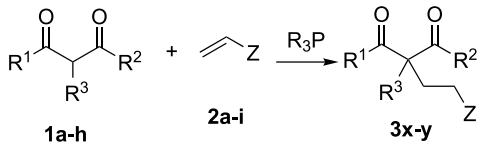
The use of phosphines as catalysts for the conventional Michael addition of compounds with active methylene groups has not been universally recognized as an interesting synthetic method. However, White and Baizer described, in a 1973 note, the reactions of sterically non-demanding nucleophiles (nitromethane, methyl malonate, acetylacetone) to simple activated olefins catalyzed by tertiary phosphines.[13] In 1982, Yoshida and Saito described the examination of the effect of several catalysts in the Michael addition of methyl (phenylsulfinyl)acetate to 1-octen-3-one.[14] Among the tested catalysts, tributylphosphine as well as triphenylphosphine gave good results.

Since then, it seems that phosphines have been forgotten in as far as Michael additions are concerned. This situation is in sharp contrast with the attention paid to transition metals and lanthanides species as catalysts for the same type of reaction[15] in spite of the inherent advantages of phosphines over metals (vide infra).

A few years ago, when examining ruthenium(II) species as possible catalysts for the Michael reaction, we rediscovered that triphenylphosphine, used as a metal stabilizing agent, was active enough to deserve attention in its own right.[16] We now want to describe a full study on the use of tertiary phosphines as excellent catalysts in the Michael addition.

## 2. Results and discussion

We have tested two phosphines, triphenylphosphine and tributylphosphine, in the Michael additions of Scheme 2. Both phosphines have nucleophilicity parameters *N* differing by slightly more than one unit: $Ph_3P$ (14.33) and $Bu_3P$ (15.49).[17] However, this apparently minimal difference is not trivial since the scale is logarithmic. Nucleophiles **1** were chosen as to embrace a broad diversity of structural types: diesters, ketoesters, diketones, ketoamides, substituted and not substituted at the intercarbonylic position, as




**Scheme 2.** Michael addition catalyzed by phosphines.

well as cyclic and open-chain compounds. Similar ideas decided the selection of electrophiles **2**: olefins activated by ketone, ester, nitrile, pyridine, phosphonate, as well as disubstituted olefins, and two azodicarboxylates. We considered a priori that if phosphines were successful in reactions combining both selections, they should be considered as general catalysts in their own right.

Indeed, this was the result (Table 1). Some general trends emerge from a perusal of the Table.

First, tributylphosphine is more active than triphenylphosphine as evidenced in entries 2 and 3 as well as in entries 8 and 9. The reactions of entries 2 and 3 failed in the presence of triphenylphosphine, whereas reaction 8 catalyzed with triphenylphosphine and gave total polymerization of the acrylate **2c**. On the contrary, tributylphosphine gave a practically quantitative yield of **3bc** (entry 9).

Second, in some cases the product was unstable, and reverted back to the starting materials on purification (entries 1, 6, and 11). Obviously, this does not imply a violation of the principle of microscopic reversibility, since some compounds **3** decompose in the absence of catalysts by a non-catalyzed process probably involving a six-membered cyclic transition state, whereas Michael addition is initiated by nucleophilic addition of the phosphine to the olefin (Scheme 3). However, the formation of unstable products **3** proves that the method works well even for intrinsically unstable Michael adducts.

Third, the reaction is quite general as is evidenced by the more than 20 different combinations of Table 1. This is in sharp contrast with the limited performances of transition metals and lanthanides in the same type of reactions.[15] In our opinion, phosphines are a better choice than metals.

Whereas some results with metals are remarkable,[15] our attempts to induce enantioselectivity failed. Thus, reaction of 1-adamantyl ester of 2-oxocyclopentanecarboxylic acid with 2-butenone catalyzed by (*R*)-Tol-BINAP gave the Michael adduct in 82% yield and 0% ee. Although negative, this result reinforces our mechanistic hypothesis since according to it (vide infra), the phosphine does not act in the key step when formation of the new chiral center occurs. Catalysis by metals can be a better alternative for induction of enantioselectivity.

Better results were produced when inducing diastereoselectivity. Thus, diastereomeric excesses (de) were sometimes moderate (entries 18, 19, and 21–23), but for product **3gb**, for which an interesting de of 86% was determined (entry 20).

Mechanistically, the phosphine-catalyzed Michael addition probably requires initiation and propagation steps

**Table 1**. Preparation of products **3** (Scheme 2)

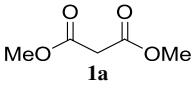
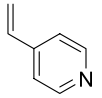
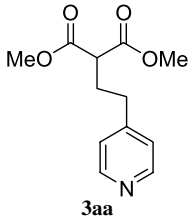
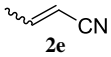
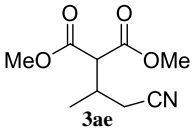
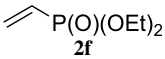
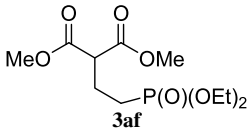
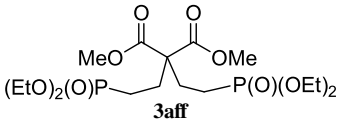
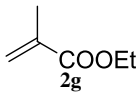
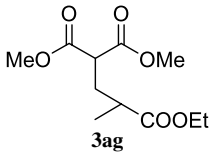
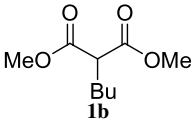
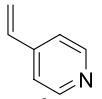
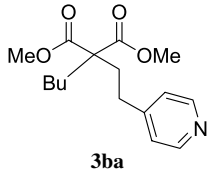
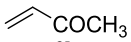
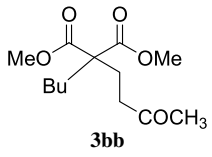
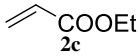
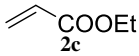
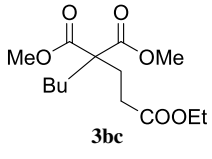
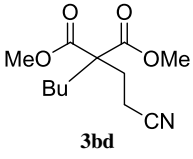
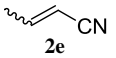
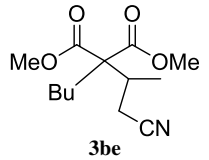
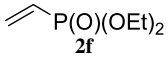
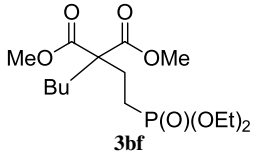
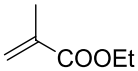
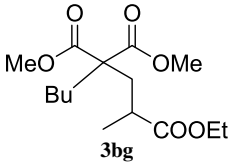
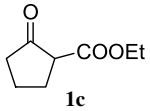
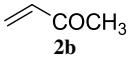
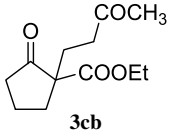
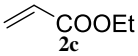
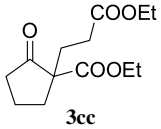
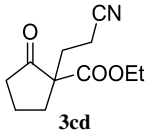
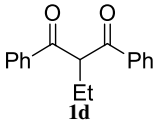
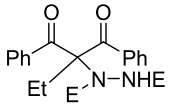
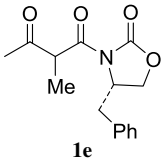
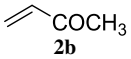
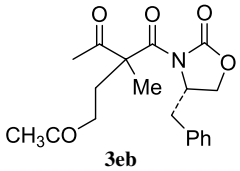
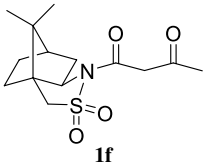
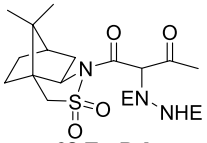
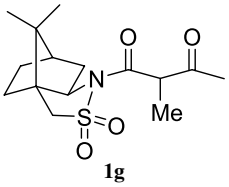
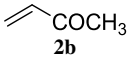
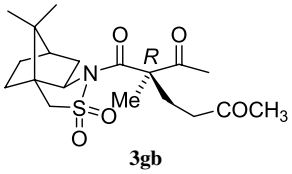
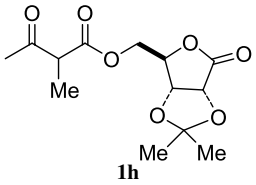
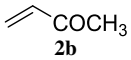
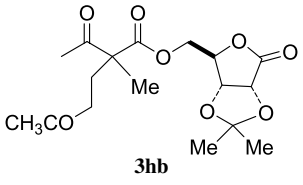
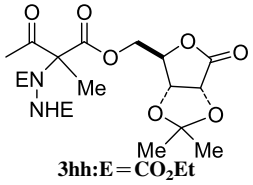
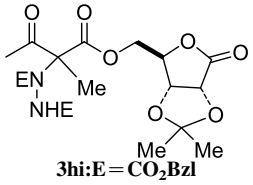
| Entry | Nucleophile | Electrophile | $R_3P$ | Product |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** | $Ph_3P$ |  **3aa** |
| 2 | **1a** |  **2e** | $Bu_3P$ |  **3ae** |
| 3 | **1a** |  **2f** | $Bu_3P$ |  **3af** |
| 4 | **1a** | **2f** | $Bu_3P$ |  **3aff** |
| 5 | **1a** |  **2g** | $Bu_3P$ |  **3ag** |
| 6 |  **1b** |  **2a** | $Ph_3P$ |  **3ba** |
| 7 | **1b** |  **2b** | $Ph_3P$ |  **3bb** |
| 8 | **1b** |  **2c** | $Ph_3P$ | Polyacrylate |
| 9 | **1b** |  **2c** | $Bu_3P$ |  **3bc** |
| 10 | **1b** |  **2d** | $Ph_3P$ |  **3bd** |

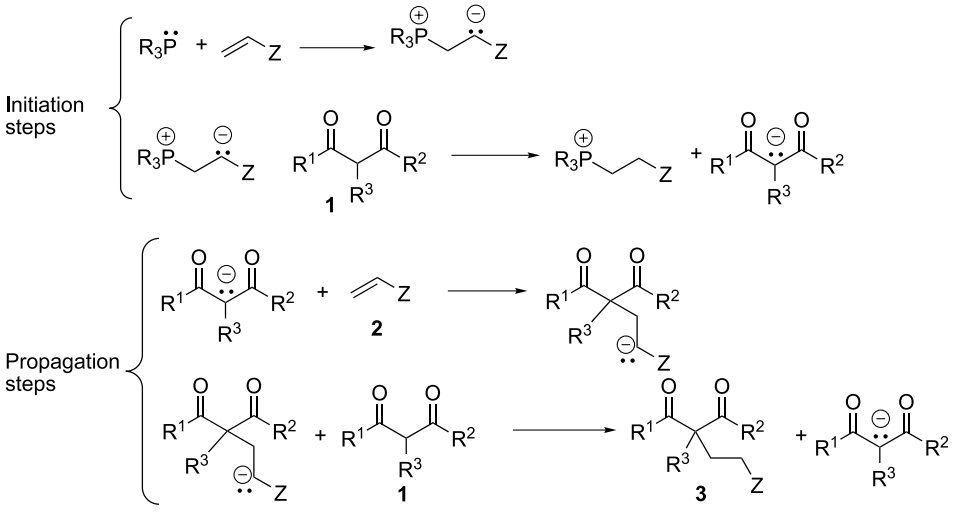
Table 1 (*continued*)

| Entry | Nucleophile | Electrophile | $R_3P$ | Product |
|---|---|---|---|---|
| 11 | **1b** |  **2e** | $Ph_3P$ |  **3be** |
| 12 | **1b** |  **2f** | $Bu_3P$ |  **3bf** |
| 13 | **1b** |  **2g** | $Bu_3P$ |  **3bg** |
| 14 |  **1c** |  **2b** | $Ph_3P$ |  **3cb** |
| 15 | **1c** |  **2c** | $Ph_3P$ |  **3cc** |
| 16 | **1c** |  **2d** | $Ph_3P$ |  **3cd** |
| 17 |  **1d** | E−N=N−E **2h:E=$CO_2$Et** | $Ph_3P$ |  **3dh:E=$CO_2$Et** |
| 18 |  **1e** |  **2b** | $Ph_3P$ |  **3eb** |
| 19 |  **1f** | E−N=N−E **2i:E=Bzl** | $Ph_3P$ |  **3fi:E=Bzl** |
| 20 |  **1g** |  **2b** | $Ph_3P$ |  **3gb** |

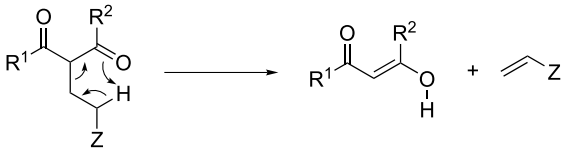
| Entry | Nucleophile | Electrophile | $R_3P$ | Product |
|---|---|---|---|---|
| 21 |  **1h** |  **2b** | $Ph_3P$ |  **3hb** |
| 22 | **1h** | E−N=N−E **2h:E = $CO_2Et$** | $Ph_3P$ |  **3hh:E = $CO_2Et$** |
| 23 | **1h** | E−N=N−E **2i:E = Bzl** | $Ph_3P$ |  **3hi:E = $CO_2Bzl$** |

(Scheme 3). Initial attack of the phosphine on the olefin generates a phosphonium β-ylid that deprotonates a molecule of the active dicarbonyl compound. The conjugate base of the dicarbonyl triggers the propagation steps as indicated. Another possibility can be envisaged; thus, the β-ylid can be converted into the α-ylid (Wittig reagent, not represented), that can give rise to side reactions. No attempts have been made to obtain more mechanistic information.

Retro-Michael reaction is probably a non-catalyzed process, particularly favorable in some cases as with




Probable mechanism for the catalyzed Michael Addition



Probable mechanism for the non-catalyzed retro-Michael Addition

**Scheme 3.** Possible mechanisms for the Michael addition catalyzed by phosphines and for the non-catalyzed retro-Michael reaction.

**Table 2**. Experimental conditions for the preparation of compounds **3** in $CH_3CN$

| Entry | 3 | Molar ratio 2:1 | [1] | $R_3P$ (Molar%) | Temperature °C | Time (h)[a] | Yield% |
|---|---|---|---|---|---|---|---|
| 1 | **3aa** | 6.0 | 3.3 | $Ph_3P$ (10) | 120[b] | 44 | [c] |
| 2 | **3ae** | 5.0 | 2.9 | $Bu_3P$ (10) | Room temperature | 38 | 90 |
| 3 | **3af** | 1.1 | 2.9 | $Bu_3P$ (10) | Room temperature | 4 | 60 |
| 4 | **3aff** | 2.0 | 2.9 | $Bu_3P$ (10) | Room temperature | 46 | 78 |
| 5 | **3ag** | 1.1 | 2.9 | $Bu_3P$ (10) | Room temperature | 21 | 73 |
| 6 | **3ba** | 2.2 | 2.7 | $Ph_3P$ (20) | 100[b] | 300 | 42[c] |
| 7 | **3bb** | 4.0 | 2.5 | $Ph_3P$ (18) | Room temperature | 24 | 62 |
| 8 | **3bc** | 1.4 | 2.7 | $Ph_3P$ (10) | 100[b] | 96 | 0 |
| 9 | **3bc** | 1.5 | 2.2 | $Bu_3P$ (10) | Room temperature | 15.5 | 99 |
| 10 | **3bd** | 6.3 | 2.5 | $Ph_3P$ (18) | Room temperature | 72 | 78 |
| 11 | **3be** | 5.0 | 2.2 | $Ph_3P$ (10) | Room temperature | 165 | [c] |
| 12 | **3bf** | 1.1 | 2.2 | $Bu_3P$ (10) | Room temperature | 6.5 | 82 |
| 13 | **3bg** | 1.3 | 2.2 | $Bu_3P$ (10) | Room temperature | 12.5 | 60 |
| 14 | **3cb** | 3.0 | 3.8 | $Ph_3P$ (10) | Room temperature | 5.5 | 89 |
| 15 | **3cc** | 3.0 | 4.0 | $Ph_3P$ (10) | Reflux | 21 | 89 |
| 16 | **3cd** | 3.0 | 3.8 | $Ph_3P$ (10) | Reflux | 5.5 | 71 |
| 17 | **3dh** | 1.5 | 2.5 | $Ph_3P$ (10) | Reflux | 24 | 100 |
| 18 | **3eb** | 1.5 | 2.5 | $Ph_3P$ (10) | Room temperature | 24 | 57 de 36% |
| 19 | **3fi** | 1.2 | 0.6 | $Ph_3P$ (18) | Reflux | 24 | 86 de 22% |
| 20 | **3gb** | 2.4 | 2.0 | $Ph_3P$ (18) | Room temperature | 24 | 63 de 86%[d] |
| 21 | **3hb** | 2.4 | 2.0 | $Ph_3P$ (9–18) | Room temperature | 24 | 90–100 de 30–42% |
| 22 | **3hh** | 1.2 | 2.0 | $Ph_3P$ (9) | Room temperature | 24 | 83 de 48% |
| 23 | **3hi** | 1.2 | 2.0 | $Ph_3P$ (9) | Room temperature | 24 | 65 de 0% |

[a] Not optimized.
[b] Closed reactor.
[c] Product **3** reverted to starting materials upon purification.
[d] Diastereoisomer *R* in the new stereocenter was predominant.[16]

4-vinylpyridine, **2a**, and sterically encumbered Michael adducts.

## 3. Conclusion

Phosphine-catalyzed Michael additions are a useful and general alternative to reactions catalyzed by bases and by metals. The scope is broader than for the metal-catalyzed variant, the yields are generally good, and the process occurs in neutral media.

## 4. Experimental

### 4.1. General remarks

Melting points were determined with a Kofler apparatus and are uncorrected. IR Spectra were recorded either by transmission or by attenuated total reflectance mode (ATR). NMR Spectra were recorded with a Brucker AC250 or a Brucker AM400; $^1$H NMR chemical shifts are reported relative to tetramethylsilane at $\delta=0.00$; coupling constants are reported in Hz. $^{13}$C NMR chemical shifts are expressed relative to tetramethylsilane at $\delta=0.0$. Mass spectra (EIMS) were obtained with a Hewlett-Packard 5989A spectrometer and determined at an ionizing voltage of 70 eV; relevant data are listed as *m/z* (%). Elemental analyses were performed at 'Servei d'Anàlisi Química de la Universitat Autònoma de Barcelona'. The given data are the average of two satisfactory determinations.

Compounds **3cb**, **3cc**, and **3cd** were prepared by ourselves under copper catalysis and fully described.[18] Compounds **3bb**, **3bd**, **3dh**, **3eb**, **3fi**, **3gb**, **3hb**, **3hh**, and **3hi** have been previously reported.[16]

**4.1.1. Dimethyl butyl-(2-diethoxyphosphoryl)ethylmalonate (3bf, entry 12); general method.** A mixture of dimethyl 2-butylmalonate (**1b**) (1.02 g, 5.4 mmol), diethyl vinylphosphonate (**2f**) (0.9 mL, 5.5 mmol), tributylphosphine (140 μL, 0.6 mmol), and anhydrous acetonitrile (2.5 mL) was magnetically stirred in a Schlenk tube under nitrogen atmosphere at room temperature for 6.5 h. The solvent was evaporated and the residue was chromatographed through silica gel with diethyl ether as eluent. Pure **3bf** (187 mg) and **3bf** contaminated with **2f** were isolated. The last fraction was distilled at 80–90 °C/1.1–1.5 mmHg (oven temperature) to afford more pure **3bf** as an oil, 1.5 g, 82%; IR (ATR): 1729, 1260, 1205, 1161, 1058, 1018, 964 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta=0.85$ (t, $J=7.2$ Hz, 3H), 1.03–1.31 (m, 4H), 1.28 (t, $J=7.0$ Hz, 6H), 1.53–1.68 (m, 2H), 1.78–1.85 (m, 2H), 2.07–2.15 (m, 2H), 3.68 (s, 6H), 4.00–4.12 (m, 4H); $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta=14.1$, 16.7 (d, $J=5.7$ Hz), 21.3 (d, $J=142.1$ Hz), 23.1, 26.1 (d, $J=3.8$ Hz), 26.4, 32.8, 52.7, 57.8 (d, $J=18.1$ Hz), 62.0 (d, $J=6.7$ Hz), 171.8; HRMS: *m/z* calcd for [M]: 352.1651 Da; found: 352.1655 Da.

All other compounds were prepared by the same general method under the specific experimental conditions of Table 2.

**4.1.2. Dimethyl(4-pyridyl)ethylmalonate (3aa, entry 1).** $^1$H NMR (250 MHz, $CDCl_3$): $\delta=2.24$ (m, 2H), 2.66 (m, 2H), 3.37 (t, $J=7$ Hz, 1H), 3.75 (s, 6H), 7.12 (dd, $J=4.5$, 1.6 Hz, 2H), 8.51 (dd, $J=4.5$, 1.6 Hz, 2H). NMR data were taken from the crude and practically pure product that reverted to starting materials upon attempted purification.

**4.1.3. Dimethyl(2-cyano-1-methyl)ethylmalonate (3ae, entry 2).**[19] Bp 60–75 °C/1.5–1.7 mmHg (oven temperature); IR (ATR): 2247, 1729 cm$^{-1}$; $^1$H NMR (250 MHz,

$CDCl_3$): $\delta$=1.15 (d, $J$=6.9 Hz, 3H), 2.44–2.65 (m, 1H), 2.56 (d, $J$=7.0 Hz, 2H), 3.40 (d, $J$=7.2 Hz, 1H), 3.73 (s, 6H); $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$=16.6, 21.4, 29.6, 51.9, 54.5, 117.1, 167.3. Anal. calcd for $C_9H_{13}O_4N$: C 54.26, H 6.58, N 7.03; found: C 54.21, H 6.72, N 7.12.

**4.1.4. Dimethyl(diethoxyphosphoryl)ethylmalonate (3af, entry 3).** Bp 150 °C (1.7 mmHg, oven temperature); IR (ATR): 2987, 2953, 1730, 1241, 1145, 1018, 959 $cm^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$=1.32 (t, $J$=7.2 Hz, 6H), 1.70–1.87 (m, 2H), 2.12–2.26 (m, 2H), 3.50 (t, $J$=7.4 Hz, 1H), 3.74 (s, 6H), 4.10 (broad dq, $J$=9.3, 7.2 Hz, 4H); $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$=16.5 (d, $J$=5.7 Hz), 22.4, 23.5 (d, $J$=147.3 Hz), 51.7 (d, $J$=16.2 Hz), 52.9, 62.0 (d, $J$=6.7 Hz), 169.4. Anal. calcd for $C_{11}H_{21}O_7P$: C 44.60, H 7.14; found: C 44.63, H 7.43.

**4.1.5. Dimethyl bis-[(diethoxyphosphoryl)ethyl]malonate (3aff, entry 4).** Oil; IR (ATR): 2984, 1730, 1243, 1164, 1017, 940 $cm^{-1}$; $^1$H NMR (250 MHz, $CD_3OD$): $\delta$=1.37 (t, $J$=7.0 Hz, 12H), 1.67–1.82 (m, 4H), 2.10–2.20 (m, 4H), 3.79 (s, 6H), 4.15 (broad dq, $J$=8.9, 7.0 Hz, 8H); $^{13}$C NMR (62.5 MHz, $CD_3OD$): $\delta$=17.6 (d, $J$=6.7 Hz), 22.0 (d, $J$=142.1 Hz), 27.6 (d, $J$=2.9 Hz), 54.2, 59.2 (apparent t, $J$=17.6 Hz), 172.8; HRMS: $m/z$ calcd for [M]: 460.1627 Da; found: 460.1639 Da.

**4.1.6. Dimethyl 2-(ethoxycarbonyl)propylmalonate (3ag, entry 5).** Bp 75–90 °C/0.9–1.2 mmHg (oven temperature); IR (ATR): 1728 $cm^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$=1.18 (d, $J$=7.0 Hz, 3H), 1.24 (t, $J$=7.1 Hz, 3H), 2.01 (ddd, $J$=14.4, 8.8, 6.0 Hz, 1H), 2.23 (ddd, $J$=14.4, 8.8, 6.3 Hz, 1H), 2.46 (apparent sextet, $J$=7.1 Hz, 1H), 3.47 (dd, $J$=8.8, 6.3 Hz, 1H), 3.72 (s, 3H), 4.12 (q, $J$=7.1 Hz, 2H); $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$=14.4, 17.7, 32.5, 37.6, 49.8, 52.8, 52.9, 60.8, 169.7, 169.8, 175.7. Anal. calcd for $C_{11}H_{18}O_6$: C 53.65, H 7.37; found: C 53.47, H 7.50.

**4.1.7. Dimethyl butyl-[2-(4-pyridyl)ethyl]malonate (3ba, entry 6).** Oil; IR (ATR): 1729, 1205, 1125, 807 $cm^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$=0.90 (t, $J$=7.2 Hz, 3H), 1.12–1.38 (m, 4H), 1.91–1.98 (m, 2H), 2.14–2.21 (m, 2H), 2.47–2.54 (m, 2H), 3.74 (s, 6H), 7.10 (d, $J$=5.2 Hz, 2H), 8.49 (d, $J$=5.2 Hz, 2H); $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$=13.9, 23.0, 26.4, 30.2, 32.8, 33.5, 57.6, 123.9, 149.8, 150.4, 171.9; MS (70 eV): $m/z$ (%)=294 (M+1, 6), 262 (11), 234 (22), 202 (23), 188 (69), 146 (22), 145 (100), 128 (31); HRMS: $m/z$ calcd for [M+H]: 294.1705 Da; found: 294.1721 Da.

**4.1.8. Dimethyl butyl-(2-ethoxycarbonyl)ethylmalonate (3bc, entry 9).** Bp 120–150 °C (0.4–0.5 mmHg, oven temperature); IR (ATR): 1730 $cm^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$=0.87 (t, $J$=7.2 Hz, 3H), 1.06–1.34 (m, 4H), 1.24 (t, $J$=7.1 Hz, 3H), 1.82–1.88 (m, 2H), 2.15–2.30 (m, 4H), 3.70 (s, 6H), 4.11 (q, $J$=7.1 Hz, 2H); $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$=14.1, 14.5, 23.1, 26.5, 28.1, 29.9, 33.2, 52.6, 57.2, 60.8, 172.1, 173.0; MS (70 eV): $m/z$ (%)=288 (M, 8), 257 (51), 243 (81), 232 (94), 188 (43), 183 (66), 172 (61), 158 (34), 145 (100), 141 (39); HRMS: $m/z$ calcd for [M]: 288.1537 Da; found: 288.1614 Da.

**4.1.9. Dimethyl butyl-(2-cyano-1-methyl)ethylmalonate (3be, entry 11).** Oil; IR (ATR): 2246, 1727, 1209 $cm^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$=0.85 (t, $J$=7.2 Hz, 3H), 1.07 (d, $J$=6.9 Hz, 3H), 1.00–131 (m, 4H), 1.86 (t, $J$=8.3 Hz, 2H), 2.30 (dd, $J$=16.5, 9.3 Hz, 1H), 2.44–2.58 (m, 1H), 2.70 (dd, $J$=16.5, 3.7 Hz, 1H), 3.69 (s, 3H), 3.70 (s, 3H); $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$=13.9, 15.0, 21.9, 23.0, 26.5, 33.4, 33.6, 52.5, 52.6, 60.8, 119.1, 170.4, 171.2; MS (70 eV): $m/z$ (%)=256 (M+1, 22), 224 (61), 196 (34), 188 (40), 171 (26), 159 (100), 145 (51), 127 (53); HRMS: $m/z$ calcd for [M+H]: 256.1549 Da; found: 256.1517 Da.

**4.1.10. Dimethyl butyl-(2-ethoxycarbonyl)propylmalonate (3bg, entry 13).** Oil; IR (ATR): 1729 $cm^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$=0.85 (t, $J$=7.2 Hz, 3H), 0.93–1.35 (m, 4H), 1.13 (d, $J$=6.9 Hz, 3H), 1.22 (t, $J$=7.1 Hz, 3H), 1.71–1.98 (m, 3H), 2.34–2.48 (m, 2H), 3.65 (s, 6H), 4.05 (q, $J$=7.1 Hz, 2H); $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$=13.9, 14.2, 19.6, 23.0, 26.4, 33.1, 35.9, 36.2, 52.3, 52.4, 57.1, 60.5, 171.9, 172.0, 176.3.

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## References and notes

1. For recent reviews see: (a) Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377–388. (b) Vedejs, E.; Daugulis, O.; MacKay, J. A.; Rozners, E. *Synlett* **2001**, 1499–1505. (c) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535–544. (d) Valentine, D. H., Jr.; Hillhouse, J. H. *Synthesis* **2003**, 317–334. (e) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891. (f) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050.
2. (a) Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901–8905. (b) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403. (c) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405. (d) Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758–7759. (e) Dinon, F.; Richards, E.; Murphy, P. J.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron Lett.* **1999**, *40*, 3279–3282. (f) Agapiou, K.; Cauble, D. F.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4528–4529. (g) Luis, A. L.; Krische, M. J. *Synthesis* **2004**, 2579–2585. (h) Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337–1339. (i) Kuroda, H.; Hanaki, E.; Izawa, H.; Kano, M.; Itahashi, H. *Tetrahedron* **2004**, *60*, 1913–1920.
3. (a) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933–7935. (b) Guo, C.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1921–1923.
4. (a) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595–7596. (b) Yavari, I.; Adib, M.; Hojabri, L. *Tetrahedron* **2002**, *58*, 6895–6899. (c) Hanédanian, M.; Loreau, O.; Taran, F.; Mioskowski, C. *Tetrahedron Lett.* **2004**, *45*, 7035–7038.
5. (a) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167–3168. (b) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**,

*116*, 10819–10820. (c) Zhang, C.; Lu, X. *Synlett* **1995**, 645–646. (d) Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670–5671. (e) Álvarez Ibarra, C.; Csákÿ, A. G.; Gómez de la Oliva, C. *Tetrahedron Lett.* **1999**, *40*, 8465–8467. (f) Lu, C.; Lu, X. *Tetrahedron* **2004**, *60*, 6575–6579.

6. (a) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906–2908. (b) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461–3466. (c) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031–5041. (d) Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. *J. Org. Chem.* **2002**, *67*, 4595–4598. (e) Lu, C.; Lu, X. *Org. Lett.* **2002**, *4*, 4677–4679.
7. Kuroka, H.; Tomita, I.; Endo, T. *Polymer* **1997**, *38*, 6049–6054.
8. (a) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241–244. (b) Wende, M.; Meier, R.; Gladysz, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 11490–11491. (c) Wende, M.; Gladysz, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5861–5872.
9. Yavari, I.; Ramazani, A. *Synth. Commun.* **1997**, *27*, 1449–1454.
10. (a) Jenner, G. *Tetrahedron* **2002**, *58*, 4311–4317. (b) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696–8697.
11. Bhuniya, D.; Mohan, S.; Narayanan, S. *Synthesis* **2003**, 1018–1024.
12. Xu, L.-W.; Xia, C.-G. *Tetrahedron Lett.* **2004**, *45*, 4507–4510.
13. White, D. A.; Baizer, M. M. *Tetrahedron Lett.* **1973**, 3597–3600.
14. Yoshida, T.; Saito, S. *Chem. Lett.* **1982**, 1587–1590.
15. For reviews see: (a) Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259–1266. (b) Comelles, J.; Moreno-Mañas, M.; Vallribera, A. *Arkivoc* **2005**, (part ix), 207–238. Available from the web page: http://www.arkat-usa.org/ark/journal/2005/I09_molina-elguero/1302/me-1302r.pdf.
16. Lumbierres, M.; Marchi, C.; Moreno-Mañas, M.; Sebastián, R. M.; Vallribera, A.; Lago, E.; Molins, E. *Eur. J. Org. Chem.* **2001**, 2321–2328.
17. Kempf, B.; Mayr, H. *Chem. Eur. J.* **2005**, *11*, 917–927.
18. Comelles, J.; Moreno-Mañas, M.; Pérez, E.; Roglans, A.; Sebastián, R. M.; Vallribera, A. *J. Org. Chem.* **2004**, *69*, 6834–6842.
19. (a) Elinson, M. N.; Feducovich, S. K.; Zakharenkov, A. A.; Ugrak, B. I.; Nikishin, G. I.; Lindeman, S. V.; Struchkov, J. T. *Tetrahedron* **1995**, *51*, 5035–5046. (b) Palombi, L.; Feroci, M.; Orsini, M.; Inesi, A. *Chem. Commun.* **2004**, 1846–1847.