Ene Reactions of 2-Phosphonoacrylates

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Trimethyl 2-phosphonoacrylate (**1a**) undergoes $EtAlCl_2$-catalyzed ene reactions in high yield at 0 °C with most classes of alkenes. The products are useful reagents for the phosphonate modification of the Wittig reaction. $EtAlCl_2$-catalyzed ene reaction of **1a** with 6-methyl-5-hepten-2-one (**18**) at −78 °C gives **19**, which undergoes an intramolecular Wittig reaction to give **21**. Ethyl α-methylene-1-cyclohexenebutanoate (**16**) undergoes a Lewis acid initiated cyclization to give the cyclopropane **30** and octalins **31** and **32**.

Introduction

The use of carbon–carbon double bonds as activating groups for the formation of new carbon–carbon bonds under mild conditions is of considerable interest in organic synthesis. The ene reaction provides a potential solution to this problem.[2] We have found that $AlCl_3$-catalyzed ene reactions of methyl acrylate occur at 25 °C[3] and that $EtAlCl_2$ is a more effective catalyst for these reactions since it can also function as a proton scavenger.[4] Lewis acid catalysis offers significant advantages over the corresponding thermal ene reactions that occur at 200–300 °C.[2a]

The Lewis acid catalyzed ene reaction of methyl acrylate is limited to 1,1-di-,[3] tri-, and tetrasubstituted alkenes at 25 °C[5] and terminal alkenes at 100 °C.[6] To increase the scope of this reaction we investigated the activation of acrylate esters by placing an electron-withdrawing group in the 2-position. We found that methyl 2-haloacrylates are roughly an order of magnitude more reactive than methyl acrylate and lead to stereoselective and regioselective ene reactions.[7] The ester group adds endo and a hydrogen is transferred selectively from the alkyl group syn to the vinylic hydrogen. On the other hand, methyl 2-cyanoacrylate is much more reactive then methyl acrylate but undergoes a Me_2AlCl-catalyzed reaction with alkenes to give a zwitterion that undergoes a variety of reactions to give a complex mixture of products.[8]

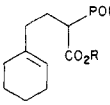
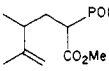
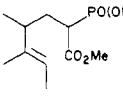
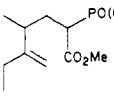
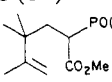
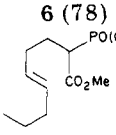
We report here studies of Lewis acid catalyzed reactions of trimethyl 2-phosphonoacrylate (**1a**) and related enophiles with alkenes. These reagents are much more reactive than methyl acrylate but, unlike the more reactive methyl 2-cyanoacrylate, give high yields of ene adducts. Furthermore these adducts are useful reagents for the synthesis of α,β-unsaturated esters via the phosphonate modification of the Wittig reaction.[9]

Results and Discussion

The results of $EtAlCl_2$-catalyzed ene reactions of trimethyl 2-phosphonoacrylate (**1a**)[10] are shown in Table I. These reactions are complete in 1 h at 0 °C, indicating that **1a** is, as expected, a very reactive electrophile. These reactions proceed even at −78 °C (vide infra). Furthermore, **1a** undergoes exclusively ene reactions. We have not isolated dihydropyrans, cyclobutanes, or 2:1 adducts that were significant products from the reactions of alkenes with methyl 2-cyanoacrylate.[8] One and a half equivalents of Lewis acid is used in all cases since the first equivalent complexes unproductively to the phosphonate oxygen. The less acidic Lewis acid Me_2AlCl is a suitable catalyst with reactive alkenes such as methylenecyclohexane, but with unreactive alkenes such as 1-hexene, conjugate addition of the methyl group to **1a** is the only reaction. This is avoided by the use of a more acidic and less nucleophilic monoalkylaluminum dichloride. No ene adduct has been obtained from **1a** and cyclohexene or *trans*-4-octene.

A hydrogen is transferred selectively from the alkyl group syn to the vinylic hydrogen in these ene reactions (Table I, entries 3, 4). The reasons for this selectivity have been discussed for other 2-substituted acrylate esters.[7] Two diastereomers of **3a** are formed in a 55:45 ratio. The

Table I. Reactions of Alkenes with Trimethyl 2-Phosphonoacrylate (1a) and $EtAlCl_2$

entry	alkene	adduct (% yield)
1		 **2a**, R = Me (71) **b**, R = Et (68)[a]
2		 **3** (69)
3		 **4** (76)
4		 **5** (53) + **4** (23)
5		 **6** (78)
6		 **7** (60)

[a] Obtained in a similar manner from triethyl 2-phosphonoacrylate (1b).

(1) Fellow of the Alfred P. Sloan Foundaton, 1979–1983. Dreyfus Teacher-Scholar, 1982–1987.
(2) (a) For a review, see: Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.
(3) Snider, B. B. *J. Org. Chem.* **1974**, *39*, 255.
(4) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927.
(5) Beckwith, A. L. J.; Moad, G. *Aust. J. Chem.* **1977**, *30*, 2733. Greuter, H.; Bellus, D. *Synth. Commun.* **1976**, *6*, 409.
(6) (a) Åkermark, B.; Ljungqvist, A. *J. Org. Chem.* **1978**, *43*, 4387. (b) Inukai, T. Y.; Nakamura, T. Y. Ger. Offen. 2063515, 1971; *Chem. Abstr.* **1971**, *75*, 109872k.
(7) Duncia, J. V.; Lansbury, P. T., Jr.; Miller, T.; Snider, B. B. *J. Am. Chem. Soc.* **1982**, *104*, 1930.
(8) Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1981**, *46*, 2563.
(9) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.
(10) McIntosh, J. M.; Sieler, R. A. *Can. J. Chem.* **1978**, *56*, 226.

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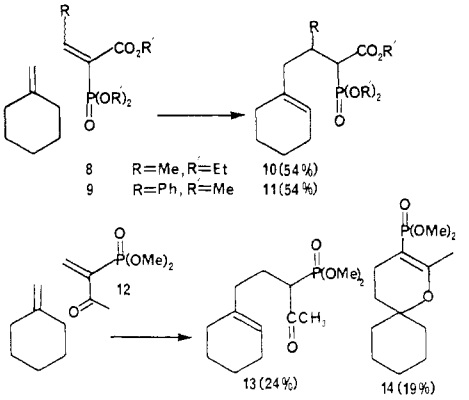
apparent lack of endo/exo selectivity may result from epimerization of the initially formed adduct. The lack of selectivity is of no consequence since the chiral center α to the ester will be lost in subsequent Wittig reactions.

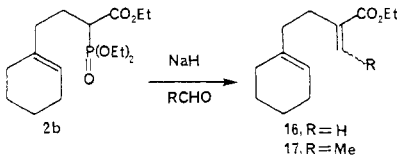
We have previously found that β-substituted acrylate esters will not react as enophiles. The high reactivity of **1a** prompted us to explore the effect of β-substituents on the reactivity of 2-phosphonoacrylate esters as enophiles. We found that triethyl 2-phosphono-2-butenoate (**8**)[11] and trimethyl α-phosphonocinnamate (**9**)[10] are still reactive in Lewis acid catalyzed ene reactions but only with the most reactive alkenes such as methylenecyclohexane. No adduct could be obained from **8** or **9** and 2-methyl-2-butene or ethylidenecyclopentane.

Dimethyl 3-phosphono-3-buten-2-one (**12**)[12] reacts with methylenecyclohexane with Me_2AlCl catalysis to give a mixture of the ene adduct **13** and inverse electron demand Diels–Alder adduct **14**. Reaction of **12** with 1-hexene gives similar results.

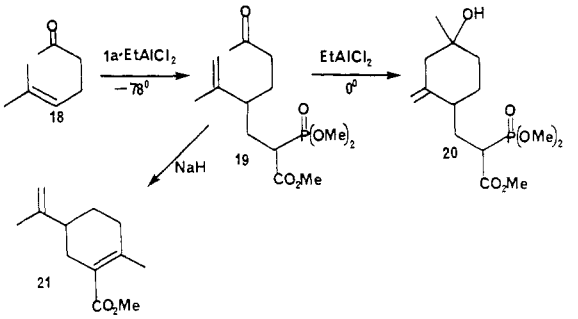


Methyl 2-(phenylsulfonyl)acrylate (**15**) could be prepared in low yield and only 50% purity.[13] Although use of crude **15** in $EtAlCl_2$-catalyzed ene reactions gives promising results, further studies must await a development of a satisfactory route to **15**.

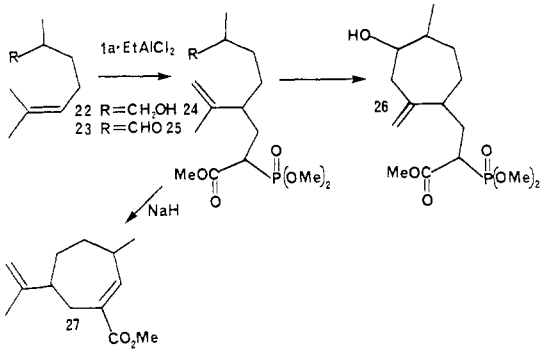
The α-phosphono esters produced in these ene reactons should be useful reagents in the phosphonate modification of the Wittig reactions.[9] Reaction of **2b** with sodium hydride and then paraformaldehyde gives a 69% yield of **16**, while reaction of **2b** with acetaldehyde gives a 49% yield of a 7:3 mixture of (*E*)- and (*Z*)-**17**. Most examples of this Wittig reaction involve phosphonoacetates or 2-phosphonopropionates. In general, somewhat lower yields of α,β-unsaturated esters are obtained from **2b** and related ene adducts, presumably due to the steric bulk of the alkyl substituent.



The reaction of **1a** with alkenes containing functional groups was investigated to prepare substrates for intramolecular Wittig reactions.[14] Reaction of 6-methyl-5-hepten-2-one (**18**) with **1a** in the presence of 1.5 equiv of $EtAlCl_2$ at −78 °C gives a 70% yield of **19**. If the reaction is carried out at 0 °C, the initially formed ene adduct **19** undergoes an intramolecular ene reaction to give **20** in 89% yield.[15] The possible intermediacy of **19** in this reaction is established by its conversion to **20** in 92% yield in the presence of $EtAlCl_2$ at 0 °C. Treatment of **19** with sodium hydride in THF gives a quantitative yield of the Wittig product **21**.



Reaction of 2,6-dimethyl-5-heptenal (**23**) with **1a** and 1.5 equiv of $EtAlCl_2$ at 0 °C gives a 24% yield of **26**, which is formed by sequential ene reactions. Reaction at −78 °C gives products arising from the cyclization of **23**.[15b] Reaction of the alcohol **22** with **1a** gives the ene adduct **24** in 40% yield. Oxidaton of **24** with pyridinium dichromate gives the aldehyde **25** in 68% yield, which undergoes an intramolecular Wittig reaction to give the cycloheptenecarboxylate **27** in 25% yield.[16]

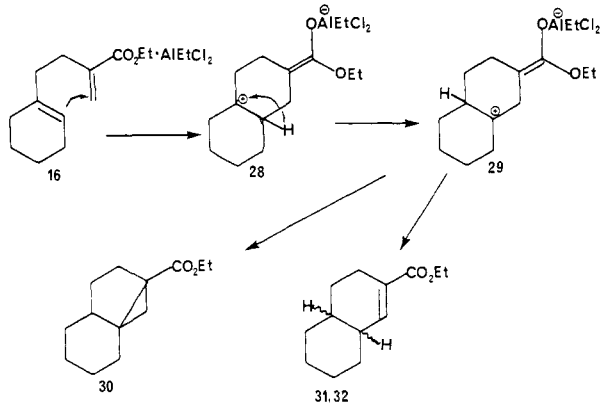


Cyclization of 16

We explored the Lewis acid catayzed cyclization of **16** in an attempt to develop new routes to bicyclic systems. Although related cyclizations of α,β-unsaturated aldehydes or ketones are now well-known,[17–19] cyclization of analogous acrylates have been reported not to proceed.[19] Treatment of **16** with 1.5 equiv of $EtAlCl_2$ for 2 days at 25 °C gives a 52% yield of a 1.4:2.7:1 mixture of **30**, **31**, and **32**. Cyclization of **16** gives **28**, which undergoes a reversible 1,2 hydride shift to give **29**. Collapse of the zwitterion gives the cyclopropane **30**, while **31** and **32** are formed by a second 1,2 hydride shift. The presence of a cyclopropane ring in **30** was established by the absorptions at δ 1.00 (d, J = 4.5 Hz) and 0.85 (d, J = 4.5 Hz) in the NMR spectrum and a weak band at 3080 cm^{-1} in the IR spectrum.[20] The

(11) Ide, J.; Endo, R.; Muramatsu, S. *Chem. Lett.* **1978**, 401.
(12) Pudovik, A. N.; Yastrebova, G. E.; Nikitina, V. I. *J. Gen. Chem. USSR* **1969**, *39*, 213.
(13) 2-Sulfonylacrylates are difficult to prepare and polymerize readily: Gipstein, E.; Willson, C. G.; Sachdev, H. S. *J. Org. Chem.* **1980**, *45*, 1486.
(14) Becker, K. B. *Tetrahedron* **1980**, *36*, 1717.
(15) For related reactions, see: (a) Snider, B. B.; Deutsch, E. A. *J. Org. Chem.* **1983**, *48*, 1822. (b) Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *Ibid.* **1982**, 47, 4538.
(16) Formation of cycloheptenes by intramolecular Wittig reactons usually proceeds in low yield.[14]
(17) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872 and references cited therein.
(18) Naegeli, P.; Wetli, M. *Tetrahedron, Suppl. 1* **1981**, *37*, 247.
(19) Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1977**, *42*, 1794.
(20) Compare to **2** in Suzuki, T.; Kikuchi, H.; Kurosawa, E. *Chem. Lett.* **1980**, 1267.

stereochemistry of **31** and **32** was not assigned. The product ratio does not change on further reaction at 25 °C or at 80 °C in 1,2-dichloroethane. The formation of α,β-unsaturated ketones analogous to **31** and **32** has been observed by Naegeli.[18] The formation of cyclopropanes is unprecedented since cyclopropyl ketones open to zwitterions in the presence of Lewis acids.[21] (*Z*)-**17** isomerizes to (*E*)-**17** on treatment with $EtAlCl_2$. No reaction occurs on treatment of (*E*)-**17** with $EtAlCl_2$.



In summary, trimethyl phosphonoacrylate (**1a**) is a very reactive enophile with Lewis acid catalysis and gives adducts that are useful Wittig reagents.

Experimental Section

NMR spectra were taken on Varian-EM390 and Bruker WH90 NMR spectrometers. IR spectra were recorded on a Perkin-Elmer 683 spectrometer. Analyses were performed by Galbraith Laboratories.

Methylene chloride was dried by distillation from calcium hydride. THF was dried by distillaton from sodium–benzophenone ketyl. $EtAlCl_2$ was purchased as a 25% solution in hexane (d = 0.75, 1.5 M) from Alfa. Me_2AlCl was purchased as a 24.9% solution in hexane (d = 0.716, 1.9 M) from Texas Alkyls, Inc.

All reactions were run in flame-dried glassware under nitrogen with magnetic stir bars. Reagents were added via dry syringes through septa.

Preparation of Starting Materials. Trimethyl 2-phosphonoacrylate (**1a**), triethyl 2-phosphonoacrylate (**1b**), and trimethyl α-phosphonocinnamate (**9**) were prepared by the literature procedure.[10] **1a** is also available from Fluka. Dimethyl 3-phosphono-3-buten-2-one (**12**) was prepared in 58% yield (bp 112 °C, 0.08 torr) by the literature procedure.[12] 2,6-Dimethyl-5-hepten-1-ol (**22**) was prepared by oxidation of the crude aldehyde **23** (Givaudan) with silver oxide to the acid followed by reduction of the base-soluble material with $LiAlH_4$ and careful chromatography.

Triethyl 2-Phosphono-2-butenoate (8).[11] NaH (119 mg of 60% disperson in mineral oil, 3.0 mmol) was washed twice with hexane and suspended in 2.5 mL of THF. Triethyl 2-phosphonobutanoate[22] (505 mg, 1.9 mmol) in 2.5 mL of THF was added and the resulting mixture was stirred for 1 h. Phenylselenyl chloride (481 mg, 2.5 mmol) was added and the reaction mixture was stirred for 3 h. The reaction was quenched with water and extracted with ether. The organic layer was dried (Na_2SO_4) and evaporated to give 797 mg of crude triethyl 2-phosphono-2-(phenylseleno)butanoate. This was dissolved in 12 mL of CH_2Cl_2 at 0 °C, and water (1.5 mL) and 30% hydrogen peroxide (1.5 mL) were added. The mixture was stirred for 30 min at 0 °C and 1 h at 25 °C and then pured into aqueous 5% $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4), and evaporated to give 471 mg of crude **8**. Evaporative distillation (140 °C, 0.1 torr) gave 438 mg (93%) of pure **8** as a 6:4 *Z*–*E* mixture: NMR (CCl_4) δ 7.49 (dq, 0.6 × 1, J = 45, 7 Hz, *Z*), 7.08 (dq, 0.4 × 1, J = 24, 7 Hz, *E*), 3.8–4.3 (m, 6), 2.25 (dd, 0.6 × 3, J = 3, 7 Hz, *Z*), 2.08 (dd, 0.4 × 3, J = 3, 7 Hz, *E*), 1.33 (t, 9, J = 7 Hz).

Handling of 1a, 1b, 8, 9, and 12. The yields of phosphonoacrylates were variable due to polymerization. Neat **1a** polymerized at −20 °C in 24 h although it is stable in $CHCl_3$ or CCl_4 solution at −20 °C. Neat **1b** is stable at −20 °C. All phosphonoacrylates were stored over, and distilled from, hydroquinone.

Reaction of Methylenecyclohexane and Trimethyl 2-Phosphonoacrylate (1a). $EtAlCl_2$ (2.7 mL of 1.5 M in hexane, 4.0 mmol) was added via syringe to a solution of methylenecyclohexane (260 mg, 2.7 mmol) and trimethyl 2-phosphonoacrylate (**1a**; 581 mg, 3.0 mmol) in 10 mL of CH_2Cl_2 at 0 °C in a flame-dried flask under nitrogen. The solution was stirred for 1 h and quenched by dilution with ether and slow addition of water until gas evolution ceased. The organic layer was separated. The aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give 709 mg (89%) of crude product. Evaporative distillation (126 °C, 0.1 torr) gave 569 mg (71%) of pure **2a**: NMR (CCl_4) δ 5.33 (br, 1), 3.71 (d, 3, J = 10 Hz), 3.69 (d, 3, J = 10 Hz), 3.69 (s, 3), 2.5–3.0 (br d, 1, J = 23 Hz), 1.8–2.2 (m, 8), 1.4 (m, 4); IR (neat) 3005, 2930, 1740, 1450 cm^{-1}.

Anal. Calcd for $C_{13}H_{23}O_5P$: C, 53.79; H, 7.98. Found: C, 53.92; H, 7.87.

Reaction of 2-methyl-2-butene under identical conditions gave 82% of crude product. Evaporative distillation (112 °C, 0.15 torr) gave 69% of pure **3**: NMR (CCl_4) δ 4.67 (m, 2), 3.71 (d, 3, J = 10 Hz), 3.69 (d, 3, J = 10 Hz), 3.67 (s, 3), 2.8 (br d, 1, J = 24 Hz), 1.4–2.4 (m, 3), 1.62 (br s, 3), 1.06 and 1.03 (2 d, 0.55 and 0.45 × 3, J = 6 Hz).

Anal. Calcd for $C_{11}H_{21}O_5P$: C, 50.00; H, 8.01. Found: C, 49.83; H, 8.16.

Reaction of (*E*)-3-methyl-2-pentene under identical conditions gave 95% of crude product. Evaporative distillation (110 °C, 0.04 torr) gave 76% of pure **4**: NMR (CCl_4) δ 5.20 (br q, 1, J = 6 Hz), 3.71 (d, 3, J = 10 Hz), 3.69 (d, 3, J = 10 Hz), 3.67 (s, 3), 2.4–2.9 (m, 1), 1.5–2.2 (m, 3), 1.53 (d, 3, J = 6 Hz), 1.50 (br s, 3), 0.98 (d, 3, J = 6 Hz).

Reaction of (*Z*)-3-methyl-2-pentene under identical conditions gave 87% of crude product. Evaporative distillation (110 °C, 0.22 torr) gave 76% of a 70:30 mixture of **5** and **4** as determined by NMR analysis of the olefin region. The data for **5** were determined from the mixture: NMR (CCl_4) δ 4.71 (br, 2), 3.6–3.8 (m, 9), 2.6–3.1 (m, 1), 1.7–2.3 (m, 5), 0.85–1.2 (m, 6).

Anal. Calcd for $C_{12}H_{23}O_5P$: C, 51.79; H, 8.33. Found: C, 51.48; H, 8.32.

Reaction of 2,3-dimethyl-2-butene under identical conditions gave 94% of crude product. Evaporative distillation (117 °C, 0.1 torr) gave 78% of pure **6**: NMR (CCl_4) δ 4.77 (br s, 1), 4.70 (br s, 1), 3.70 (d, 3, J = 10 Hz), 3.69 (d, 3, J = 10 Hz), 3.66 (s, 3), 2.90 (br dd, 1, J = 11, 25 Hz), 2.26 (ddd, 1, J = 3, 11, 15 Hz), 2.05 (br dd, 1, J = 15, 15 Hz), 1.69 (br s, 3), 1.06 (s, 3), 0.98 (s, 3).

Reaction of 1-hexene under identical conditions gave a 78% yield of crude product. Evaporative distillation (106 °C, 0.25 torr) gave 61% of pure **7**: NMR (CCl_4) δ 5.3–5.5 (m, 2), 3.70 (d, 3, J = 10 Hz), 3.68 (d, 3, J = 10 Hz), 3.68 (s, 3), 2.6–3.1 (m, 1), 1.7–2.2 (m, 6), 1.1–1.6 (m, 2), 0.90 (t, 3, J = Hz).

Anal. Calcd for $C_{12}H_{23}O_5P$: C, 51.79; H, 8.33. Found: C, 51.59; H, 8.72.

Reaction of methylenecyclohexane (60 mg, 0.6 mmol), **triethyl 2-phosphono-2-butenoate** (**8**; *E*, *Z* mixture, 168 mg, 0.6 mmol), and $EtAlCl_2$ (0.6 mL of 1.5 M in hexane, 0.9 mmol) in 2 mL of CH_2Cl_2 at 0 °C for 1 h gave 167 mg (82%) of crude product. Medium-pressure chromatograhy on silica gel (ether) gave 106 mg (52%) of pure **10**: NMR (CCl_4) δ 5.30 (br, 1), 3.8–4.2 (m, 6), 2.0–2.8 (m, 2), 1.7–2.1 (m, 6), 1.3–1.6 (m, 4), 1.33 (t, 6, J = 7 Hz), 1.30 (t, 3, J = 7 Hz), 0.99 and 0.93 (2 d, 0.5 and 0.5 × 3, J = 7 Hz).

Anal. Calcd for $C_{17}H_{31}O_5P$: C, 58.94; H, 9.02. Found: C, 57.63; H, 8.94.

Reaction of methylenecyclohexane (280 mg, 2.9 mmol), **trimethyl α-phosphonocinnamate** (**9**; *E* and *Z*, 360 mg, 3.2 mmol), and $EtAlCl_2$ (2.9 mL of 1.5 M in hexane, 4.4 mmol) in 9

(21) (a) Corey, E. J.; Balanson, R. D. *Tetrahedron Lett.* **1973**, 3153. (b) Stork, G.; Marx, M. *J. Am. Chem. Soc.* **1969**, *91*, 2371.
(22) Berry, J. P.; Isbell, A. F.; Hunt, G. E. *J. Org. Chem.* **1972**, *37*, 4396.

mL of CH_2Cl_2 for 13 h gave 951 mg (89%) of crude product. Chromatography on silica gel (1:1 hexane–ether and then ethyl acetate) gave 573 mg (54%) of pure **11** as a 3:1 mixture of diastereomers as determined by NMR analysis: NMR (CCl_4) δ 7.1 (m, 5), 5.07 (br, 1), 3.75 (d, 0.75 × 3, J = 11 Hz), 3.72 (d, 0.75 × 3, J = 11 Hz), 3.71 (s, 0.25 × 3), 3.41 (d, 0.25 × 3, J = 11 Hz), 3.31 (s, 0.75 × 3), 3.18 (d, 0.25 × 3, J = 11 Hz), 2.4–3.2 (m, 1), 2.2 (m, 1), 1.6–2.1 (m, 6), 1.2–1.6 (m, 4).

Anal. Calcd for $C_{19}H_{27}O_5P$: C, 62.28; H, 7.43. Found: C, 62.06; H, 7.30.

Reaction of methylenecyclohexane (40 mg, 0.4 mmol), **dimethyl 3-phosphono-3-buten-2-one (12**; 85 mg, 0.5 mmol), and Me_2AlCl (0.58 mL of 1.9 M in hexane, 1.1 mmol) in 2 mL of CH_2Cl_2 at 0 °C for 1 h gave 78 mg (68%) of crude product. Medium-pressure chromatography on silica gel (ethyl acetate) gave 28 mg (24%) of ene adduct **13** and 22 mg (19%) of Diels–Alder adduct **14**.

The data for **13** follow: NMR (CCl_4) δ 5.3 (br, 1), 3.70 (d, 6, J = 11 Hz), 2.7–3.2 (m, 1), 2.23 (s, 3), 1.9–2.3 (m, 2), 1.6–2.1 (m, 6), 1.3–1.6 (m, 4); IR (neat) 3040, 1715 cm^{-1}.

The data for **14** follow: NMR (CCl_4) δ 3.52 (d, 6, J = 11 Hz), 2.02 (br s, 3), 1.2–2.2 (m, 14); IR (neat) 3040, 1620 cm^{-1}.

Ethyl α-Methylene-1-cyclohexenebutanoate (16). Hexane-washed NaH (51 mg, 60% in mineral oil, 1.3 mmol) was suspended in 1 mL of THF. Phosphonate **2b** (321 mg, 0.96 mmol) in 1 mL of THF was added. The solution was stirred for 1 h and treated with paraformaldehyde (49 mg, 1.6 mmol). The solution was stirred for 2 h, diluted with pentane, and quenched with water. The organic layer was dried ($MgSO_4$) and evaporated to give 170 mg (85%) of crude **16**. Evaporative distillation (93 °C, 2.2 torr) gave 138 mg (69%) of pure **16**: NMR (CCl_4) δ 6.02 (d, 1, J = 2 Hz), 5.42 (br d, 1, J = 2 Hz), 5.34 (br, 1), 4.16 (q, 2, J = 7 Hz), 2.2–2.5 (m, 2), 1.7–2.1 (m, 6), 1.4–1.7 (m, 4), 1.31 (t, 3, J = 7 Hz); IR (neat) 3060, 3040, 1720, 1635, 1450, 1315, 1195, 1040, 950 cm^{-1}.

Ethyl α-Ethylidene-1-cyclohexenebutanoate (17). Acetaldehyde (160 mg, 3.6 mmol) was added to the anion prepared from phosphonate **2b** (859 mg, 2.6 mmol) and NaH (122 mg, 60% in mineral oil) as described above. The reaction was stirred for 2 h and worked up as described above to give 476 mg (83%) of crude **17**. Evaporative distillation (110 °C, 1.1 torr) gave 282 mg (49%) of a 7:3 E–Z mixture of **17**. Medium-pressure chromatography of 246 mg on silica gel (99:1 pentane–ether) gave 49 mg (9%) of (**Z**)-**17** and 117 mg (23%) of (**E**)-**17**.

The data for (**Z**)-**17** follow: NMR (CCl_4) δ 5.87 (q, 1, J = 7 Hz), 5.31 (br, 1), 4.14 (q, 2, J = 7 Hz), 2.2–2.5 (m, 2), 1.93 (d, 3, J = 7 Hz), 1.7–2.1 (m, 6), 1.4–1.7 (m, 4), 1.30 (t, 3, J = 7 Hz); IR (neat) 3050, 1725, 1645 cm^{-1}.

The data for (**E**)-**17** follow: NMR (CCl_4) δ 6.72 (q, 1, J = 7 Hz), 5.32 (br, 1), 4.11 (q, 2, J = 7 Hz), 2.2–2.5 (m, 2), 1.7–2.1 (m, 6), 1.79 (d, 3, J = 7 Hz), 1.4–1.7 (m, 4), 1.27 (t, 3, J = 7 Hz); IR (neat) 3040, 1720, 1645 cm^{-1}.

Reaction of 6-methyl-5-hepten-2-one (18; 260 mg, 2.1 mmol), **trimethyl 2-phosphonoacrylate (1a**; 465 mg, 2.4 mmol), and $EtAlCl_2$ (5.0 mL of 1.5 M in hexane, 7.5 mmol) in 10 mL of CH_2Cl_2 at −78 °C for 1 h gave 590 mg of crude product. Flash chromatography on silica gel (1:1 hexane–ether and then ethyl acetate) gave 39 mg (14%) of recovered **18** and 475 mg (70%) of pure **19**: NMR (CCl_4) δ 4.5–4.8 (m, 2), 3.73 (br d, 6, J = 11 Hz), 3.71 (s, 3), 2.5–3.0 (m, 1), 2.30 (t, 2, J = 7 Hz), 2.05 (s, 3), 1.4–2.2 (m, 5), 1.60 (br s, 3): IR (neat) 3080, 1735, 1715, 1645, 1255, 1050, 895 cm^{-1}.

Anal. Calcd for $C_{14}H_{25}O_6P$: C, 52.50; H, 7.87. Found: C, 52.43; H, 7.64.

Reaction of 18 (250 mg, 2.0 mmol), **1a** (415 mg, 2.1 mmol), and $EtAlCl_2$ (3.2 mL of 1.5 M in hexane, 4.8 mmol) in 7 mL of CH_2Cl_2 at 0 °C for 1 h gave 662 mg of crude **20**. Evaporative distillation (140 °C, 0.07 torr) gave 450 mg (89%) of pure **20**: NMR ($CDCl_3$) δ 4.7–4.9 (m, 2), 3.81 (br d, 6, J = 10 Hz), 3.80 (s, 3), 2.5–3.0 (m, 1), 2.7 (br, 1, OH), 1.8–2.4 (m, 5), 1.3–1.8 (m, 4), 1.21 (br s, 3): IR (neat) 3430, 3080, 2960, 1730, 1645, 1440 cm^{-1}.

Treatment of ketone **19** (39 mg, 0.12 mmol) with $EtAlCl_2$ (0.12 mL of 1.5 M in hexane) in 1 mL of CH_2Cl_2 for 1 h at 0 °C gave 36 mg (92%) of **20**.

Intramolecular Wittig Reaction of 19. Phosphonate ketone **19** (46 mg, 0.14 mmol) in 1 mL of THF was added via syringe to a suspension of hexane-washed NaH (9 mg of 60%, 0.22 mmol) in 1 mL of THF under nitrogen. The reaction mixture was stirred 1 h, quenched with water, and extracted with pentane. The organic layer was dried ($MgSO_4$) and evaporated to give 27 mg (100%) of chromatographically homogeneous **21**: NMR (CCl_4) δ 4.68 (br s, 2), 3.67 (s, 3), 1.9–2.4 (m, 5), 1.99 (s, 3), 1.74 (br s, 3), 1.3–1.6 (m, 2); IR (neat) 3080, 2940, 1720, 1645, 1440, 1070, 895 cm^{-1}.

Reaction of 2,6-dimethyl-5-hepten-1-ol (22; 281 mg, 2 mmol), trimethyl 2-phosphonoacrylate (**1a**; 428 mg, 2.2 mmol), and $EtAlCl_2$ (4.7 mL of 1.5 M solution in hexane, 7.0 mmol) in 10 mL of CH_2Cl_2 at 0 °C for 1 h gave 581 mg of crude product. Medium-pressure chromatography on silica gel (1:1 hexane–ether and then ethyl acetate) gave 73 mg (26%) of recovered **22** and 266 mg (40%) of pure **24**: NMR ($CDCl_3$) δ 4.6–4.9 (m, 2), 3.77 (br d, 6, J = 11 Hz), 3.74 (s, 3), 3.41 (br d, 2, J = 6 Hz), 2.7–3.2 (m, 2), 1.7–2.3 (m, 3), 1.58 (br s, 3), 1.2–1.7 (m, 5), 0.90 (d, 3, J = 7 Hz); IR (neat) 3450, 3080, 1740, 1645, 1050, 895 cm^{-1}.

Anal. Calcd for $C_{15}H_{29}O_6P$: C, 53.56; H, 8.69. Found: C, 53.31; H, 8.72.

Oxidation of 24. Treatment of **24** (174 mg, 0.5 mmol) in 3 mL of CH_2Cl_2 with pyridinium dichromate (313 mg, 0.83 mmol) for 1 day at 25 °C, followed by normal workup,[23] gave 118 mg (68%) of **25**, which was ca. 80% pure as determined by NMR analysis: NMR (CCl_4) δ 9.54 (br s, 1), 4.81 (br, 1), 4.63 (br, 1), 3.72 (br d, 6, J = 11 Hz), 3.70 (s, 3), 2. 5–3.1 (m, 1), 1.6–2.4 (m, 4), 1.59 (br s, 3), 1.2–1.6 (m, 4), 1.06 (d, 3, J = 7 Hz).

Intramolecular Wittig Reaction of 25. Phosphonate aldehyde **25** (115 mg, 80% pure, ca. 0.28 mmol) in 1 mL of THF was added via syringe to a suspension of hexane-washed NaH (21 mg of 60%, 0.53 mmol) in 1 mL of THF under nitrogen. The reaction mixture was stirred 1 h and worked up as described above to give 50 mg of crude product. Medium-pressure chromatography on silica gel (99:1 hexane–ether) gave 14 mg (25%) of pure **27**: NMR (CCl_4) δ 6.78 (br d, 1, J = 4 Hz), 4.64 (m, 2), 3.68 (s, 3), 1.8–3.0 (m, 4), 1.74 (br s, 3), 1.2–1.8 (m, 4), 1.15 (d, 3, J = 7 Hz); IR (neat) 3080, 1720, 1645, 895 cm^{-1}.

Reaction of 2,6-dimethyl-5-heptenal (23; 342 mg, 2.4 mmol), **trimethyl 2-phosphonoacrylate (1a**; 526 mg, 2.7 mmol), and $EtAlCl_2$ (4.2 mL of 1.5 M in hexane, 6.3 mmol) in 10 mL of CH_2Cl_2 for 1 h at 0 °C gave 729 mg of crude product. Medium-pressure chromatography on silica gel (1:1 ether–ethyl acetate) gave 97 mg of cyclization products of **23** and 197 mg (24%) of **26** as a complex mixture of diastereomers: NMR (CCl_4) δ 4.85 (br s, 1), 4.71 (br s, 1), 3.77 (br d, 6, J = 11 Hz), 3.73 (s, 3), 2.5–3.5 (m, 3), 1.1–2.3 (m, 10), 1.02 (br d, 3, J = 6 Hz); IR (neat) 3080, 1735, 1645, 1250, 1040 cm^{-1}.

Cyclization of Ethyl α-Methylene-1-cyclohexenebutanoate (16). A solution of **16** (123 mg, 0.6 mmol) in 3 mL of CH_2Cl_2 was cooled to 0 °C. $EtAlCl_2$ (0.64 mL of 1.5 M in hexane, 0.96 mmol) was added and the resulting solution was stirred 2 days at 25 °C. Normal workup gave 105 mg (85%) of a complex mixture. Medium-pressure chromatography of 98 mg on silica gel (99:1 hexane–ether) gave 10 mg of a mixture that contained some **16** (GC Carbowax 20M, 170 °C, t_R = 16, 20 (**16**), and 31 min, 3:2:1) and 64 mg (52%) of a 1.4:2.7:1 mixture of **30**, **31**, and **32** (GC Carbowax 20M, 170 °C, t_R = 18.2 (**30**), 37.6 (**31**), and 41 (**32**) min). Pure samples were obtained by preparative GC.

The data for **30** follow: NMR ($CDCl_3$) δ 4.11 (q, 2, J = 7 Hz), 1.3–2.2 (m, 13), 1.22 (t, 3, J = 7 Hz), 1.00 (d, 1, J = 4.5 Hz), 0.86 (d, 1, J = 4.5 Hz); IR (CCl_4) 3080, 1730 cm^{-1}.

The data for **31** follow: NMR ($CDCl_3$) δ 6.7 (m, 1), 4.16 (q, 2, J = 7 Hz), 2.1–2.4 (m, 2), 1.7 (m, 6), 1.1–1.5 (m, 6), 1.27 (t, 3, J = 7.0 Hz); IR (CCl_4) 3050, 1730, 1645 cm^{-1}.

The data for **32** follow: NMR ($CDCl_3$) δ 6.8 (m, 1), 4.17 (q, 2, J = 7 Hz), 2.2–2.3 (m, 2), 1.6–1.7 (m, 2), 1.4 (m, 10), 1.28 (t, 3, J = 7 Hz); IR (CCl_4) 1720, 1645 cm^{-1}.

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Registry No. **1a**, 55168-74-6; **1b**, 20345-61-3; **2a**, 87088-30-0; **2b**, 87088-31-1; **3**, 87088-32-2; **4**, 87088-33-3; **5**, 87088-34-4; **6**, 87088-35-5; **7**, 87088-36-6; (*Z*)-**8**, 66670-44-8; (*E*)-**8**, 66670-43-7; (*Z*)-**9**, 87088-37-7; (*E*)-**9**, 87088-58-2; **10**, 87088-38-8; **11** (isomer

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1), 87088-39-9; 11 (isomer 2), 87088-59-3; 12, 87088-40-2; 13, 87088-41-3; 14, 87088-42-4; 15, 87088-43-5; 16, 87088-44-6; (Z)-17, 87088-45-7; (E)-17, 87088-46-8; 18, 110-93-0; 19, 87088-47-9; 20, 87088-48-0; 21, 87088-49-1; 22, 4234-93-9; 23, 106-72-9; 24, 87088-50-4; 25, 87088-51-5; 26, 87088-52-6; 27, 87088-53-7; 30, 87088-54-8; 31, 87088-55-9; 32, 87088-56-0; triethyl 2-phosphonobutanoate, 17145-91-4; phenylselenyl chloride, 5707-04-0; triethyl 2-phosphono-2-(phenylseleno)butanoate, 87088-57-1; methylenecyclohexane, 1192-37-6; 2-methyl-2-butene, 513-35-9; (E)-3-methyl-2-pentene, 616-12-6; (Z)-3-methyl-2-pentene, 922-62-3; 2,3-dimethyl-2-butene, 563-79-1; 1-hexene, 592-41-6; paraformaldehyde, 30525-89-4; acetaldehyde, 75-07-0.

Hydroboration Kinetics. 9.[1] Kinetics and Mechanism of the Complex Formation of 9-Borabicyclo[3.3.1]nonane Dimer with Representative Amines. Effect of Steric Hindrance on the Reaction Mechanism

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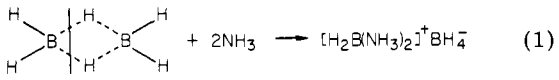
The complex formation of 9-borabicyclo[3.3.1]nonane dimer $(9\text{-BBN})_2$ with representative amines was studied. In all cases, symmetrical cleavage of the boron–hydrogen bridge bonds of $(9\text{-BBN})_2$ was observed. However, the symmetrical cleavage proceeds through a dissociation mechanism or a bimolecular direct attack mechanism, depending on the steric requirement and the nucleophilicity of the amine. With sterically unhindered amines such as pyrrolidine, piperidine, *n*-butylamine, etc., the reaction exhibits second-order kinetics, indicating that the rate-limiting step involves the direct reaction between the dimer and the amine. Sterically more hindered amines, such as *tert*-butylamine, di-*n*-butylamine, and quinuclidine, exhibit first-order kinetics, first order in $(9\text{-BBN})_2$. Obviously, in these cases the reaction proceeds by the dissociation of the dimer, followed by the reaction of the amine with the monomer. *sec*-Butylamine shows intermediate kinetic behavior. Thus, the mechanism of this reaction is strongly affected by moderate changes in the steric requirements of the amine.

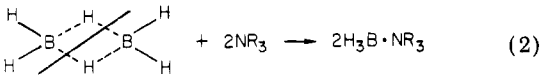
Complex formation between boron compounds and amines has been extensively studied. Studies of the thermodynamic stabilities of the borane–amine complexes have led to a quantitative understanding of steric effects as a factor in chemical behavior.[4] Synthetic applications of these addition compounds have also been investigated.[5]

The reaction mechanisms for the formation of complexes of amines with organoboranes have also been studied.[6] Two different mechanisms have been postulated for the reactions of diborane with amines. The reaction of ammonia with diborane results in the formation of the diammoniate of diborane (eq 1).[7] The reaction appears to



(1)

involve the unsymmetrical cleavage of the hydrogen bridge bonds in diborane. On the other hand, the reaction with mono-, di-, or trimethylamine produces monomeric adducts (eq 2).[8] Therefore, symmetrical cleavage of the hydrogen



(2)

R = H or CH_3

bridge bonds of diborane was postulated. The symmetrical cleavage may proceed through a unimolecular dissociation mechanism or through a bi- or termolecular direct attack mechanism.[9]

We recently investigated the kinetics and mechanism of the hydroboration of alkenes and alkynes with 9-borabicyclo[3.3.1]nonane dimer and found that the reaction proceeds through the prior dissociation of $(9\text{-BBN})_2$, followed by the reaction of the monomer with the unsaturated substrate[1a,c] (eq 3 and 4).

$$(9\text{-BBN})_2 \overset{k_1}{\rightleftharpoons} 2\ 9\text{-BBN} \quad (3)$$

$$9\text{-BBN} + \text{alkene or alkyne} \rightarrow B\text{-alkyl-9-BBN} \quad (4)$$

These results significantly differed from those on the reaction of disiamylborane dimer with alkenes, which seemed to proceed through a direct attack of the alkene on the borane dimer.[10] We thought that a systematic study of the reaction of $(9\text{-BBN})_2$ with representative nucleophiles might help in understanding the general mechanism of hydroboration by $(R_2BH)_2$. Consequently, we studied the kinetics of the reduction of aldehydes and ketones with $(9\text{-BBN})_2$ and found that the dissociation mechanism operates[1h] (eq 3 and 5). We then studied the

$$9\text{-BBN} + \text{aldehyde or ketone} \rightarrow B\text{-alkoxy-9-BBN} \quad (5)$$

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