Spontaneous Lossen Rearrangement of (Phosphonoformyl)hydroxamates. The Migratory Aptitude of the Phosphonyl Group

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(i-PrO)$_2$P(=O)COSEt (**1**) reacted with NH$_2$OH in pyridine at room temperature to give mainly (i-PrO)$_2$P(=O)NH$_2$ (**4**). The formation of **4** was interpreted in terms of a spontaneous Lossen rearrangement of (i-PrO)$_2$P(=O)CONHOH (**2a**) formed in the reaction. A transient ^{31}P NMR signal appearing in the reaction mixture at δ −1.8 was assigned to **2a**. Trapping of (i-PrO)$_2$P(=O)N=C=O (**5**), formed in the reaction of **1** and NH$_2$OH, by cyclohexylamine gave (i-PrO)$_2$P(=O)NHCONHC$_6$H$_{11}$ (**6**). Attempted isolation of **6** gave the hydrolyzed product *N*-cyclohexylurea (**7**). The reaction of **1** with NH$_2$OMe proceeded slower than that with NH$_2$OH and gave the expected (i-PrO)$_2$P(=O)-CONHOMe (**2b**), which was isolated and identified. **2b** converts slowly to **4** in pyridine at room temperature. In contrast, MeNHOH reacted rapidly with **1** and gave the stable crystalline (i-PrO)$_2$P(=O)CON(Me)OH (**2c**). The structure of hydroxamates **2** were assigned on the basis of ^{1}H, ^{13}C, and ^{31}P NMR spectral data. This facile Lossen rearrangement is discussed in terms of the unusually high migratory aptitude of the phosphonyl group.

Hydroxamic acid derivatives have recently attracted considerable interest because of their activity in inhibiting medically important enzymes such as metalloproteases[1] and lipoxygenase.[2] On the other hand, phosphonates have also been shown to exhibit biological activity in various areas by virtue of their analogy to naturally occurring phosphates and carboxylic acids.[3] However, to date there are only a few reports in the literature on the combination of the phosphonic and hydroxamic functions in one molecule.[4] Phosphonoacetohydroxamic acid has recently been reported to act as a powerfully binding inhibitor of enolase.[5] Phosphonoformic acid is a clinically used antiviral drug, and thus its derivatives are of continuing concern. In the context of our ongoing interest in exploring the chemical[6] and biological[7] properties of phosphorus compounds having α-carbonyl groups,[8] and their derivatives, we have undertaken the synthesis and study of (phosphonoformyl)hydroxamates. (Diisopropyl-phosphono)thiolformate **1** has been chosen as starting material, because this compound has been reported to undergo C−S cleavage, in preference over C−P cleavage, customary in acylphosphonates, and to react with ammonia to yield cleanly the corresponding phosphonoformamide.[9]

Results and Discussion

To synthesize (phosphonoformyl)hydroxamates **2a**−**c**, **1** was allowed to react with hydroxylamine and its *N*-methyl and *O*-methyl derivatives in the presence of pyridine or triethylamine. The reactions were monitored by ^{31}P NMR spectroscopy. The results from the reaction of **1** with hydroxylamine are listed in Table 1. In this table it can be seen that the reactions in the presence of Et$_3$N in MeCN led to (i-PrO)$_2$PH=O (**3**) and to diisopropyl phosphoramidate (**4**).[10] In addition, the formation of a transient product having a chemical shift of $\delta_P = -1.3$ was observed. This signal was assigned to diisopropoxyphosphinylformylhydroxamic acid (**2a**) through comparison with those of *O*-methyl[(diisopropoxyphosphinyl)-formyl]hydroxamate (**2b**) and of *N*-methyl-[(diisopropoxyphosphinyl)formyl]hydroxamic acid (**2c**) obtained from *O*-methyl- and *N*-methylhydroxylamine (*vide infra*). In contrast, reactions carried out in pyridine gave only diisopropyl phosphoramidate **4** (Scheme 1), with no P−C bond cleavage product, **3**. Compound **4** was isolated from the reaction mixture in pyridine. It was identified by elemental analysis, ^{1}H, ^{31}P, and ^{13}C NMR and IR spectroscopy, mass spectrometry, and comparison of its mp to that in the literature.[11]

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⊗ Abstract published in *Advance ACS Abstracts,* May 1, 1997.

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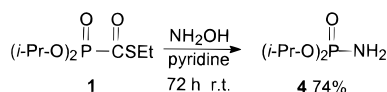
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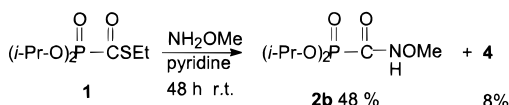**Table 1. (i-PrO)$_2$P(O)COSEt + NH$_2$OH·HCl at 25 °C**

exp	base/solvent	equiv	time, h	**1**^{a} ($\delta_P = -5.3$, %)	**2a**^{a} ($\delta_P = -1.8$, %)	**3**^{a} ($\delta_P = 4.2$, %)	**4**^{a} ($\delta_P = 9.7$, %)
1	Et$_3$N/MeCN	1	2	15	39	26	18
2	Et$_3$N/MeCN	1	72	14	7	30	48
3	Et$_3$N/MeCN	2	2	0	12	54	32
4	Pyr/MeCN	1	5	82	3	0	0
5	Pyridine	xs^b	3	37	63	0	0
6	Pyridine	xs	16	15	63	0	18
7	Pyridine	xs	22	15	51	0	31
8	Pyridine	xs	48	14	19	0	63
9	Pyridine	xs	72	11	9	0	74

^{a} The percentage figures presented are raw data obtained from the integrated ^{31}P NMR spectra and thus, possibly, are not a precise representation of the actual molar ratios of the components. ^{b} xs = excess.
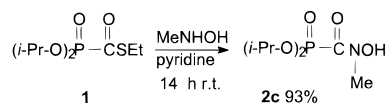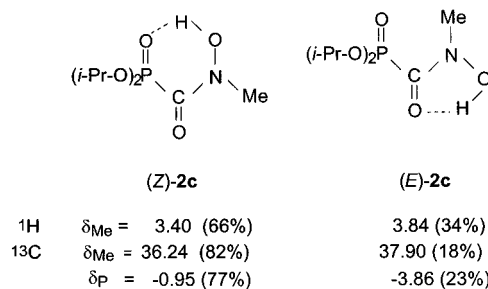
Scheme 1

Scheme 2

Scheme 3

Scheme 4

	(Z)-2c	(E)-2c
^{1}H	δ_{Me} = 3.40 (66%)	3.84 (34%)
^{13}C	δ_{Me} = 36.24 (82%)	37.90 (18%)
	δ_P = -0.95 (77%)	-3.86 (23%)

and −3.86 (23%). Similar phenomena can be seen in the ^{1}H and ^{13}C spectra of **2c** (Scheme 4). Because of hindered rotation around the amide C−N bond, hydroxamates, as amides, may exist as two rotational geometrical isomers.

Tashma has shown by NMR spectroscopy[12] that thiocarbamoylphosphonates possessing one proton on the nitrogen have a *Z* configuration.[13] Masson and coworkers prepared N,N-disubstituted thiocarbamoylphosphonates, and have shown that these exist as mixtures rotamers in solution.[14] They assigned the higher field ^{1}H and ^{13}C NMR signals for the N-substituent CH$_3$ or CH$_2$ groups *anti* to the phosphoryl group. On this basis, we can assign the structure of the major component of the *N*-methyl derivative **2c** as being the *Z* isomer. Both rotational conformers may be stabilized by intramolecular hydrogen bonds as shown in Scheme 4. Additional supporting evidence for this assignment can be derived from the $^3J_{PC}$ coupling constant of the *N*-methyl group. There are two unequal signals for this carbon in the ^{1}H-decoupled ^{13}C spectrum. The major signal (82%) at δ 36.24 ($^3J_{PC}$ = 8.8 Hz) is assigned to the *anti N*-methyl group in (*Z*)-**2c**, while the minor signal (18%) at δ 37.90 ($^3J_{PC}$ = 2.5 Hz) is assigned to the *syn N*-methyl group in (*E*)-**2c**.[15] Finally, on the basis of similarity of the ^{31}P NMR signals of **2a** and **2b** to the signals assigned to the *syn* and *anti* rotamers of **2c**, respectively, it is reasonable to speculate that **2a** has the *syn* structure, probably stabilized by a six-membered intramolecular hydrogen

Further examination of Table 1 reveals the following features:

1. Comparison of entries 1 and 3 shows the effect of the quantity of base on the reaction. In the presence of excess base the reaction is nearly complete in 2 h.

2. Comparison of entries 1 and 4 reveals the importance of the base strength for the reaction. Although the stronger base triethylamine causes a more rapid consumption of the starting material, it also leads to byproduct **3** resulting from the C−P bond cleavage of the starting material, **1**.[10]

3. From examining the reactions in excess pyridine (entries 5−9), it is clear that there is slow conversion of the transient product **2a** to the final product of the reaction, **4**.

The reaction of *O*-methylhydroxylamine with **1** was also studied under comparable conditions. This reaction proceeded considerably slower, and in the presence of 2 equiv of Et$_3$N in MeCN after 48 h, ^{31}P NMR spectroscopy still showed the presence of 60% unreacted starting material **1**, and only **3** (10%) and **4** (30%). The same reaction carried out in pyridine without additional base also for 48 h, gave *O*-methylhydroxamic derivative **2b** (48%) along with only 8% of **4** and 44% unreacted starting material **1** (Scheme 2). *O*-Methyl[(diisopropoxyphosphinyl)formyl]hydroxamate, **2b**, was isolated by chromatography and identified by means of IR, ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy and mass spectrometry.

In contrast, the reaction of *N*-methylhydroxylamine with **1** was faster and gave in 14 h in pyridine only the expected hydroxamate, **2c** (93%, Scheme 3). In MeCN and 2 equiv of Et$_3$N the reaction was over in 2 h with the formation of **2c** (52%) and H-phosphonate **3** (30%).

NMR Spectra and Structure of (Phosphonoformyl)hydroxamates. While hydroxamates **2a** and **2b** showed one signal each (at δ −1.8 and −4.72, respectively) in the ^{31}P spectrum, the *N*-methylhydroxamate, **2c**, shows two signals of unequal intensity at δ −0.95 (77%)

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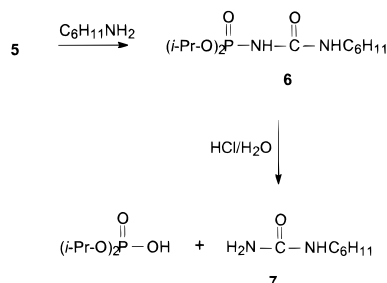(14) Bulpin, A.; Le Roy-Gourvennec, S.; Masson, S. *Phosphorus, Sulfur, Silicon* **1994,** 89, 119−32.

Scheme 5
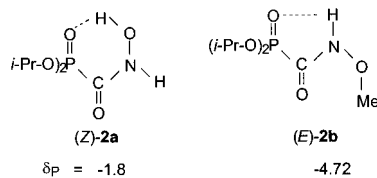
Scheme 6
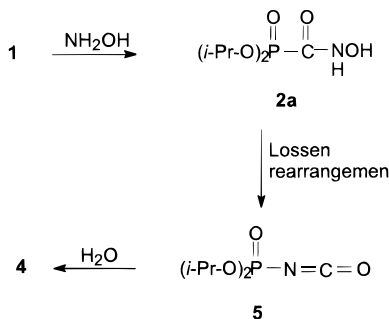
Scheme 7

bond, $-N-OH\cdots O=P-$, while **2b** in which such intramolecular H-bond is not possible has the *anti* structure having a five-membered intramolecular H-bond: $-N-H\cdots O=P-$ (Scheme 5).
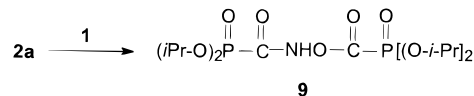
Lossen Rearrangement. The assignment of the transient signal at $\delta_P = -1.8$ appearing in the reaction of **1** with NH_2OH leading to phosphoramidate **4** as belonging to compound **2a** led us speculate that we are facing an unusually facile Lossen rearrangement, which gives the final product **4** via isocyanate **5** (Scheme 6).

In an attempt to trap the isocyanate **5** postulated in Scheme 6, **1** was allowed to react with NH_2OH in pyridine, in the presence of cyclohexylamine. Monitoring this reaction by ^{31}P NMR revealed the formation of a new product **6**, which had a chemical shift at δ 8.44. In the process of isolation of this product N-cyclohexylurea, **7** (Scheme 7), and diisopropyl hydrogen phosphate were obtained. Compound **7** was identified by comparison with an authentic sample of N-cyclohexylurea prepared by reacting cyclohexylamine with potassium isocyanate.[16] Consequently, we assign to compound **6** the structure N-(diisopropoxyphosphinyl)urea. Apparently, phosphoryl-

Scheme 8

urea **6** has undergone hydrolysis in the workup by the acid, the use of which was necessitated by the presence of the large amounts of amines present. To rule out the alternative structure $(i\text{-PrO})_2P(O)CONHC_6H_{11}$ (**8**), which also could have formed in the reaction, we have synthesized this compound by reacting cyclohexylamine with compound **1**. Compound **8** had a chemical shift at δ -2.48.

All the hitherto reported Lossen rearrangements require heating and conversion of the N−OH group either to O-acylhydroxamates,[17] O-arylhydroxamates,[18] chloride or chlorosulfinate,[17] sulfate,[19] or *in situ* activation using polyphosphoric acid,[20] carbodiimide,[21] Mitsunobu[22] methodology, or silylation.[23] There is no report of a free hydroxamic acid rearranging at room temperature. As phosphonothiolformate was reported as a reactive acylating agent,[9] we needed to consider the possibility of its reaction with hydroxamate **1** to form the doubly phosphonoformylated hydroxylamine **9** (Scheme 8). However, this assumption is not consistent with the observed ^{31}P NMR spectra obtained during the progress of the reaction. An intermediate of type **9** should be accompanied by the appearance of *two* transient signals in the ^{31}P NMR spectrum. In fact, as we pointed out above, there was only one transient signal observed in the reaction mixture. Another factor relevant in this respect is the stoichiometry of the reaction. If the reaction displayed in Scheme 8 would be involved in the formation of **4**, 2 mol of **1** would be required for the formation of each mole of **4**, and thus the maximum yield of **4** based on **1** could not exceed 50% (compare Table 1, experiment 9).

The first step of the Lossen rearrangement is being visualized as the base-catalyzed removal of the NH proton. The presence of a free OH group does not obstruct this step as there is general agreement with regard to the NH proton being the most acidic in hydroxamic acids.[24] Thus, the most unusual feature of the present reaction is the spontaneous departure of the OH at room temperature. This resembles the Beckmann rearrangements we reported recently,[25,26] in which the departure of the OH group took place without the customary acid catalysis. In the present case as well as in the Beckmann rearrangements, OMe derivatives reacted much more sluggishly. Since the pK_a's of water and methanol are not very different (water, pK_a = 15.74,

(15) A Karplus-type relationship has been established for vicinal coupling ^3J(CCCP) in phosphonates: Thiem, J.; Meyer, B. *Org. Magn. Reson.* **1978**, *11*, 50−1. Adiwidjaja, G.; Meyer, B.; Thiem, J. *Z. Naturforsch.* **1979**, *34b*, 1547−51, as well as in *EZ* pairs of phosphorus-substituted alkenes: Duncan, M.; Gallagher, M. J. *Org. Magn. Reson.* **1981**, *15*, 37−42. Öhler, E.; Zbiral, E. *Monatsh. Chem.* **1984**, *115*, 493−508. Although the magnitudes of the coupling constants reported in these papers in the rigid geometrical isomers are larger ($^3J_{PC}$ values of 17−25 Hz for *E* and 4−11 Hz for *Z* isomers) than those we found for (*E*)- and (*Z*)-**2c**, still the trend is consistent. Examination of the spectral data presented by Masson (ref 13), however, reveals $^3J_{PC}$ values similar to those found by us. This paper reports $^3J_{PC}$ values of 8.1−8.7 Hz for *N*-alkyl carbons *anti* relative to phosphorus across a thioamide C−N bond.
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MeOH, pK_a = 15.5–15.7, and MeOH is also a better proton acceptor: pK_a of MeOH$_2^+$ ≃ −1.45, H$_3$O$^+$ ≃ −1.74), the better leaving group behavior of the OH is probably a reflection of its easier stabilization by solvation. The facile Lossen rearrangement of **2a** reported in this paper is viewed as an additional manifestation of the pronounced tendency of phosphoryl groups to participate in 1,2-shifts to electron deficient centers. Among the precedents that attest to this tendency are the facile migration of PO$_3$H$_2$[27] and P(O)Ph$_2$[28] groups in the Wagner–Meerwein rearrangement, in preference over phenyl migration. Examples of facile migrations to electron deficient heteroatoms include the Baeyer–Villiger oxidation of acylphosphonates[29] or the Beckmann rearrangement of α-hydroxyimino phosphinates[24] and phosphonates,[24] as well as of α-hydroxyimino phosphonamidates.[25] It seems that in spite of their electron-withdrawing effect (σ* value of 2.65 was determined for the P(O)(OMe)$_2$ group[30]), phosphoryl groups possess the capability to stabilize, possibly by hyperconjugation or by bridging,[31] an electron deficient center located on a β carbon or heteroatom and to migrate there.

Further experiments will be needed to explore the synthetic potential that may emerge from the *in situ* generation of dialkoxyphosphinyl isocyanates. Although phosphinyl isocyanates are not difficult to prepare,[32] they are sensitive to moisture. Therefore, an appropriate adaptation of the present method may find uses in the future in special cases.

Experimental Section[33]

Reactions of (Diisopropylphosphono)thiolformate 1 with Hydroxylamine. To a solutions of NH$_2$OH·HCl (0.695 g, 0.01 mol) in pyridine or Et$_3$N/MeCN (10 mL) was added **1** (2.54 g, 0.01 mol). The reactions were allowed to stand in an N$_2$ atmosphere at ambient temperature and monitored by ^{31}P NMR spectroscopy. The results are listed in Table 1.

[(Diisopropoxyphosphinyl)formyl]-*O*-methylhydroxamate (2b). To a solution of *O*-methylhydroxylamine hydrochloride (0.835 g, 0.01 mol) in pyridine (10 mL) at 25 °C was added dropwise **1** (2.54 g, 0.01 mol) under nitrogen. The reaction was monitored by ^{31}P NMR. After 72 h, the reaction mixture was concentrated *in vacuo*, the residue was taken up in AcOEt, filtered, and chromatographed through a silica gel column, developed by AcOEt/petroleum ether, 2:1, to give 0.908 g (38%) of *O*-methyl hydroxamate **2b** as colorless oil: ν_{max}/cm^{-1} (NaCl) 3120, 2950–2900, 1660, 1380, 1260–1210, 980; MS *m/z* found 239.28, (M$^+$) calcd for C$_8$H$_{11}$NO$_3$P 239.09; ^{1}H NMR (CDCl$_3$) δ 1.32 (12 H, m), 3.76 (3 H, s), 4.73 (2 H, m), 11.05 (1 H, b); ^{13}C NMR (CDCl$_3$) δ 23.93 (d, *J* = 4.5 Hz), 24.08 (d, *J* = 4.1 Hz), 64.30 (s), 74.34 (d, *J* = 6.5 Hz), 162.45 (d, *J* = 219 Hz); ^{31}P NMR (CDCl$_3$) δ −4.72 ppm.

[(Diisopropoxyphosphinyl)formyl]-*N*-methylhydroxamate (2c). To solution of *N*-methylhydroxylamine hydrochloride (0.835 g, 0.01 mol) in pyridine (10 mL) was added **1** (2.54 g, 0.01 mol), and the mixture was allowed to react at room temperature for 14 h under nitrogen. Monitoring of the reaction showed almost complete conversion. The reaction mixture was concentrated *in vacuo*, and the residue was taken up in AcOEt, filtered, and chromatographed through a silica gel column, and developed by AcOEt/petroleum ether, 2:1: yield 1.65 g (69%); mp 55–57 °C; ν_{max}/cm^{-1} (KBr) 3148, 2990–2931, 1649, 1390, 1238, 991; MS *m/z* 239.1 (M$^+$), calcd for C$_8$H$_{11}$NO$_3$P 239.09; ^{1}H NMR (CDCl$_3$) δ 1.52 (12 H, d, *J* = 6 Hz), 3.40 (0.66 × 3 H, s), 3.84 (0.33 × 3 H, s), 4.91 (2H, m); ^{13}C NMR (CDCl$_3$) δ 24.25 (d, *J* = 5.6 Hz), 24.33 (d, *J* = 4.90 Hz), 24.52 (d, *J* = 4.1 Hz), 24.72 (d, *J* = 3.4 Hz), 36.24 (d, *J* = 8.8 Hz), 37.90 (d, *J* = 2.5 Hz), 74.30 (d, *J* = 6 Hz), 74.56 (d, *J* = 8 Hz), 163 (d, *J* = 226 Hz); ^{31}P NMR (CDCl$_3$) δ −0.95 (77%), −3.86 (23%). Anal. Calcd for C$_8$H$_{11}$NO$_3$P: C, 40.17; H, 7.58; N, 5.86. Found: C, 40.43; H, 7.58; N, 5.79.

Diisopropyl Phosphoramidate (4). Diisopropyl phosphoramidate was obtained from the reaction of **1** with hydroxylamine hydrochloride under the conditions specified in experiment 9, Table 1. The reaction mixture was concentrated *in vacuo*, and the residue was taken up in AcOEt, filtered and chromatographed through a silica gel column, and developed by AcOEt: yield 0.977 g (54%); mp 53–54 °C (lit.[10] mp 56–57 °C); IR (KBr) ν_{max}/cm^{-1} 3362, 2975, 1573, 1385, 1224, 983; MS *m/z* found 181.8, calcd 181.17; ^{1}H NMR (CDCl$_3$) δ 1.31 (12 H, d, *J* = 6 Hz), 2.79 (2 H, s), 4.64 (2 H, m); ^{13}C NMR (CDCl$_3$) δ 24.43 (d, *J* = 4.8 Hz), 71.52 (d, *J* = 5.4 Hz); ^{31}P NMR (CDCl$_3$) δ 8.30. Anal. Calcd for C$_6$H$_{16}$NO$_3$P: C, 39.77; H, 8.83; N, 7.73. Found: C, 39.82.43; H, 8.58; N, 7.68.

Reaction of 1 with Hydroxylamine in the Presence of Cyclohexylamine. To a solution of hydroxylamine hydrochloride (0.695 g, 0.01 mol) in pyridine (10 mL) at 25 °C was added dropwise **1** (2.54 g, 0.01 mol) under nitrogen. After 0.5 h, cyclohexylamine (4.96 g, 0.05 mol) was added dropwise. The reaction progress was monitored by ^{31}P NMR, and after 3 h signals were observed at δ 10.40 (**4**, 1%), 8.46 (**6**, 55%), 4.30 (**3**, 30%), −0.49 (**2a**, 11%). The reaction mixture was concentrated *in vacuo*, and the residue was taken up in AcOEt and extracted with 1 N HCl and H$_2$O. ^{31}P NMR examination of the aqueous phase showed a new signal at δ −4.09 ppm (diisopropyl hydrogen phosphate). This fraction was evaporated *in vacuo*, the residue was digested with water four times, and the crude residue was recrystallized from methanol to give **7** (0.625 g, 44%): mp 191–2 °C, mixed mp with authentic sample prepared in the next experiment 191 °C; MS *m/z* found 142, calcd for C$_7$H$_{14}$N$_2$O 142.2; ^{1}H NMR (D$_2$O) δ 1.18–1.26 (5 H, m), 1.50–1.55 (1 H, m), 1.68 (2 H, m), 1.86 (2 H, m), 3.02 (1H, m).

Cyclohexylurea (7). To a solution of cyclohexylamine (0.854 g, 8.63 mmol) and potassium isocyanate (0.70 g, 8.63 mmol) in water (10 mL) was added acetic acid (0.517 g, 8.63 mmol) at 0 °C. After 5 h, the solvent was evaporated *in vacuo*, the crude residue was digested five times with water and decanted, and the residue was recrystallized from methanol to yield 1.02 g (83%): mp 192–3 °C (lit.[15] mp 195–6 °C); ^{1}H NMR spectrum identical with the product obtained in the previous experiment.

***N*-Cyclohexyl(diisopropoxyphosphinyl)formamide (8).** To a mixture of cyclohexylamine (0.81 g, 0.0082 mol) and Et$_3$N (1.66 g, 0.016 mol) in MeCN (10 mL) was added **1** (2.1 g, 0.0082 mol) under nitrogen. The reaction progress was monitored by ^{31}P NMR. After 8 h the reaction mixture was concentrated *in vacuo*, and the residue was taken up in AcOEt, filtered, and washed successively with 1 N HCl, H$_2$O, 10% NaHCO$_3$, and brine. The organic phase was dried over MgSO$_4$, filtered, and concentrated *in vacuo* to give a white solid: yield 1.85 g (78%); mp 78–80 °C; ^{1}H NMR (CDCl$_3$) δ 1.17–1.30 (4 H, m), 1.35 (16 H, t), 1.74 (1 H, m), 1.90 (1 H, m), 3.85 (1H, m), 4.76 (2 H, m), 6.92 (1 H, m); ^{31}P NMR (CDCl$_3$) δ −2.48. Anal. Calcd for C$_{13}$H$_{26}$NO$_4$P: C, 53.58; H, 9.00; N, 4.81. Found: C, 53.41; H, 9.00; N, 4.98.

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