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Asymmetric Synthesis of 2*H*-Azirines Derived from Phosphine Oxides Using Solid-Supported Amines. Ring Opening of Azirines with Carboxylic Acids

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A simple and efficient asymmetric synthesis of 2*H*-azirine-2-phosphine oxides **3** is described. The key step is a solid-phase bound achiral or chiral amine-mediated Neber reaction of β-ketoxime tosylates derived from phosphine oxides **1**. Reaction of 2*H*-azirines **3** and **11** with carboxylic acids **4** gives phosphorylated ketamides **5** and **12**. Ring closure of ketamides **5** and **12** with triphenylphosphine and hexachloroethane in the presence of triethylamine leads to the formation of phosphorylated oxazoles **8** and **13**.

Introduction

In the area of combinatorial chemistry and solid-phase synthesis there is a constant need for new methodologies which can be applied to the preparation of heterocycles and small molecules.[1,2] For this reason the development of new polymer-supported reagents has attracted growing interest in recent years. The highly strained 2*H*-azirine ring systems, the smallest of the nitrogen-unsaturated heterocycles, represent an important class of compounds because of their high reactivity.[3] Each of the three bonds of the azirine ring can be cleaved, depending on the experimental conditions used, and they can be used as key intermediates in organic synthesis in the preparation of acyclic functionalized amino derivatives[4a−c] and heterocycles.[4d−g] In particular, 2*H*-azirines containing a carboxylic ester group **I** are excellent reagents for the preparation of functionalized aziridines[3,5] and α-[5b,6a−d] and β-amino acid derivatives.[5b,6e−g] Furthermore, phosphorus substituents regulate many important biological functions with molecular modifications influencing the biological activity.[7] For these reasons, functionalized 2*H*-azirines containing a phosphorus substituent in the 2-position (**II**, Figure 1) are expected to play a similar role to that observed in the isosteric analogues **I**, in the enantioselective synthesis of α- and β-aminophosphorus derivatives. α-Aminophosphonates can be considered as surrogates for α-amino acids,[8a] and have been used as haptens for the generation of catalytic antibodies,[8b] as

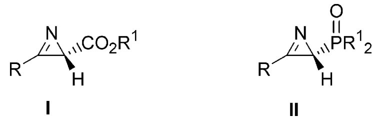

FIGURE 1.

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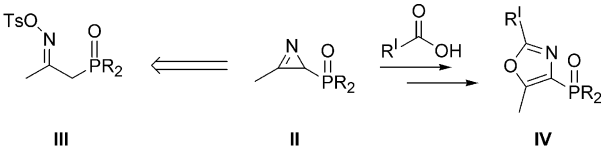
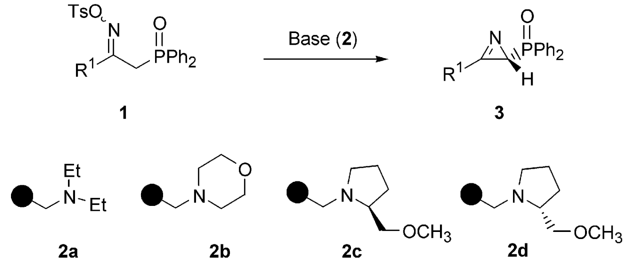
enzyme inhibitors[9a,b] and antibacterial agents,[9c] while β-aminophosphonate derivatives, some of them naturally occurring,[10a] have been used for the preparation of peptide-based enzyme inhibitors[10b,c] and as agrochemicals[10d] or pharmaceuticals.[10e,f]

Optically active 2*H*-azirines with an asymmetric center in the azirine cycle are present in some natural products,[3] and enantiomerically enriched 2-alkoxycarbonyl-2*H*-azirines **I** were previously prepared from chiral *N*-substituted aziridine 2-carboxylic esters,[11a,b] and by using the Neber reaction.[11c,d] Nevertheless, despite the potential interest of 2*H*-azirines, these three-membered heterocycles directly substituted with a phosphorus-containing functional group have received scarce attention.[12] For this reason, the development of new processes for asymmetric synthesis of substituted 2*H*-azirines can represent an important tool in organic synthesis. In this context, we have described new methods for the preparation of five-[13] and six-membered[14] phosphorus substituted nitrogen heterocycles from functionalized phosphine oxides and phosphonates and the synthetic uses of amino phosphorus derivatives as starting materials for the preparation of acyclic compounds[15] and phosphorus-containing heterocycles.[16] Recently, we disclosed the first asymmetric synthesis of 2*H*-azirines derived from phosphine oxides by the alkaloid-mediated Neber reaction of tosyloximes.[17,18] Continuing with our interest in the synthesis of new phosphorus-substituted heterocycles we here report an easy and high-yielding asymmetric synthesis of 2*H*-azirine phosphine oxides (**II**, R = Ph) from easily available tosyloximes containing a phosphine oxide (**III**, R = Ph, Scheme 1) by means of solid-supported achiral and chiral amines. The presence of the phosphorus substituent in these substrates increases the synthetic value of these compounds because they may be used as building blocks for the stereoselective construction of α- and β-aminophosphorus derivatives.[3a,c,8−10] Ring opening of 2*H*-azirines and the formation of phosphorylated oxazoles (**IV**, Scheme 1) were also explored.

SCHEME 1



SCHEME 2



Results and Discussion

Solid-Phase Synthesis of Azirines 3. 2*H*-Azirines **3** ($R^1 = CH_3, C_2H_5$) have been prepared in very good yields by the modified Neber reaction of β-keto tosyloximes **1** with triethylamine or alkaloids.[17] Now, we wish to explore whether these heterocycles **3** could also be prepared by using a resin-supported amine.[19] 2*H*-Azirine-2-phosphine oxides **3a** ($R^1 = CH_3$) and **3b** ($R^1 = C_2H_5$) were generated in good yield and in a regioselective fashion by thermal treatment in benzene at 50 °C of β-ketoximes **1a**,**b** ($R^1 = CH_3, C_2H_5$) with polymer-supported amines derived from diethylamine **2a**[20] and morpholine **2b**[20] (see Scheme 2, Table 1, entries 1−4). Resin-supported amines **2a** and **2b** can be recovered after handling of the resins with triethylamine (see Experimental Section, Table 1, entry 2).

This process can also be extended to the asymmetric synthesis of 2*H*-azirines **3**, when chiral polymer-supported bases **2c** derived from (*S*)-(+)-2-(methoxymethyl)pyrrolidine and **2d** derived from (*R*)-(−)-2(methoxymethyl)pyrrolidine were used.[20] These polystyrene chiral resins **2c** and **2d** were prepared by attachment of the chiral secondary amines to solid supports with Merrifield resin. Merrifield resin was reacted with (*S*)-(+)-2-(methoxymethyl)pyrrolidine and (*R*)-(−)-2-(methoxymethyl)pyrro-

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[20] Polymer-supported amines **2a** and **2b** are commercially available. Chiral resin-bound amines **2c**,**d** were accomplished with use of Merrifield resin (see text and Experimental Section).

TABLE 1. Solid-Phase Synthesis of 2*H*-Azirine-2-phosphine Oxides 3

entry	compd	base	R^1	yield (%)	ee[c]
1	**3a**	**2a**	CH_3	70[a]	
2	**3a**	**2a**	CH_3	66[b]	
3	**3b**	**2a**	C_2H_5	88[a]	
4	**3b**	**2b**	C_2H_5	66[a]	
5	**3a**	**2c**	CH_3	74[a]	16 (*R*)
6	**3b**	**2c**	C_2H_5	65[a]	37 (*R*)
7	**3a**	**2d**	CH_3	60[a]	37 (*S*)
8	**3b**	**2d**	C_2H_5	89[a]	15 (*S*)

[a] Yield of isolated purified compounds **3**. [b] Yield of isolated purified compounds **3** from recovered amine **2a**. [c] ee was determined by ^{31}P NMR measurements, using a chiral shift reagent (Yb(tfc)$_3$).

lidine at 65 °C in DMF to afford new chiral resins **2c** and **2d**.[21] These chiral polymer-supported amines **2c** and **2d** were then used as chiral bases in the modified Neber reaction of tosyl oximes **1**, in a similar way to that reported before for achiral resin amines (**2a** and **2b**) to give enantiomerically enriched 2*H*-azirines **3** (Scheme 2, Table 1, entries 5−8). The enantiopurity of azirines derived from phosphine oxide **3** (ee 15−37%) was determined by ^{31}P NMR measurements in $CDCl_3$ by using a chiral shift reagent (Yb(tfc)$_3$). The absolute configuration of the azirines **3** was established before by reduction to aziridines and formation of the enantiopure *cis*-*N*-(*p*-toluenesulfinyl)aziridine-2-phosphine oxides.[17]

Ring-Opening of Azirines with Carboxylic Acids. Cleavage of the N−C double bond of azirines can be achieved with carboxylic acids,[4a,22] and 3-amino-2*H*-azirines have been widely used for elegant preparations of linear peptides[4a] and depsipeptides.[23] Given that, as far as we know, no ring-opening reaction of azirines containing phosphorus substituents has been reported as giving acyclic compounds,[24] we explored the reaction of azirine−phosphine oxides with carboxylic acid. This reaction can be used as a model of an acid-catalyzed ring-opening reaction of these substrates and the functionalized ketamides generated could then be used for the preparation of phosphorylated oxazoles.

Reaction of azirine **3a** with acetic acid **4a** ($R^2 = CH_3$) at room temperature led to the formation of α-ketamide **5aa** ($R^1 = R^2 = CH_3$) containing a phosphine oxide group in the α-position (Scheme 3, Table 2, entry 1). Spectroscopic data were in agreement with the assigned structure of compound **5aa**. Mass spectrometry of **5aa** showed the molecular ion peak (*m*/*z* 315, 2%), while in the ^{31}P NMR spectrum the phosphine oxide group resonated at δ_P 31.2 ppm. The ^{13}C NMR spectrum showed an absorption at δ_C 60.8 ppm as a doublet with coupling constant $^1J_{PC} = 65.0$ Hz for the carbon atom directly bonded to the phosphine oxide moiety, as well as a singlet at δ_C 200.8 ppm for the carbonyl group. The formation of adduct **5** could be explained by protonation of the nitrogen atom of the azirine followed by nucleophilic addition of the carboxylate to the azidinium ion to give an unstable aziridine intermediate **6**. Ring expansion of aziridine **6** promoted by intramolecular nucleophilic addition of the nitrogen pair to the carboxylic ester could give the zwitterionic oxazolone **7**, which underwent ring opening to form ketamide **5**. The scope of the reaction was not limited to alkyl carboxylic acid **4a** ($R^2 = CH_3$), given that not only benzoic acid **4b** ($R^2 = C_6H_5$) but also functionalized acids containing an ether linkage **4c** ($R^2 = CH_2OCH_3$) as well as olefinic groups **4d**,**e** ($R^2 = CH{=}CH_2$, $(CH_2)_4CH{=}CH_2$) and malonic acid **4f** ($R^2 = CH_2CO_2H$) also reacted with azirines **3** to give the corresponding substituted α-ketamides **5** (Scheme 3, Table 2, entries 2−7).

SCHEME 3

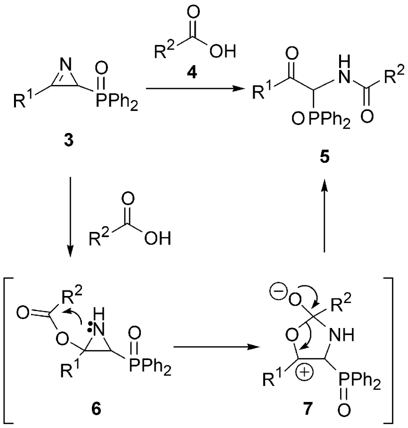

TABLE 2. α-Ketamides 5 and 12 Obtained

entry	compd	R^1	R^2	yield (%)[a]
1	**5aa**	CH_3	CH_3	75
2	**5ab**	CH_3	C_6H_5	65
3	**5ac**	CH_3	CH_3OCH_2	67
4	**5ad**	CH_3	$CH_2{=}CH$	75
5	**5ae**	CH_3	$CH_2{=}CH(CH_2)_4$	65
6	**5bb**	C_2H_5	C_6H_5	60
7	**5bf**	C_2H_5	$HO_2C{-}CH_2$	57
8	**5bg**	C_2H_5	$CH_3O_2C{-}CH_2$	67
9	**12aa**	CH_3	CH_3	75
10	**12ab**	CH_3	C_6H_5	62
11	**12bb**	C_2H_5	C_6H_5	78

[a] Yield of isolated purified compounds **5** and **12**.

Ring-Closure of α-Ketamides 5 to Phosphorus-Substituted Oxazoles 8. Oxazoles are common heterocycles in a wide variety of natural products possessing biological activity and also are widely used intermediates for functional transformations.[25,26] Given that phosphorus substituents regulate important biological functions, we thought that ketamides **5** containing a phosphine oxide substituent could be used for the preparation of oxazoles. Different reaction conditions were used for the ring-

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(21) Chiral resin-bound amines **2c**,**d** were characterized by FTIR and elemental analyses.

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SCHEME 4

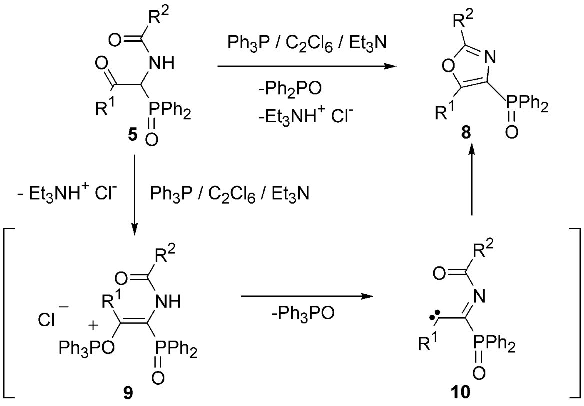


TABLE 3. Phosphorylated Oxazoles 8 and 13 Obtained

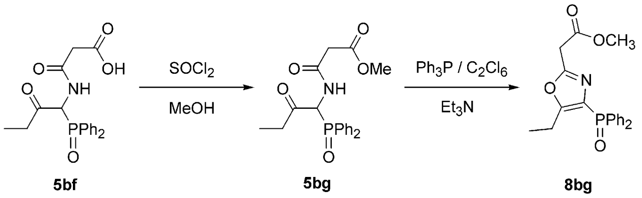
entry	compd	R^1	R^2	yield (%)[a]
1	**8aa**	CH_3	CH_3	64
2	**8ab**	CH_3	C_6H_5	79
3	**8ac**	CH_3	CH_3OCH_2	70
4	**8ad**	CH_3	$CH_2{=}CH$	59
5	**8ae**	CH_3	$CH_2{=}CH(CH_2)_4$	88
6	**8bb**	C_2H_5	C_6H_5	66
7	**8bg**	C_2H_5	$CH_3O_2C{-}CH_2$	58
8	**13aa**	CH_3	CH_3	55
9	**13ab**	CH_3	C_6H_5	58
10	**13bb**	C_2H_5	C_6H_5	62

[a] Yield of isolated purified compounds **8** and **13**.

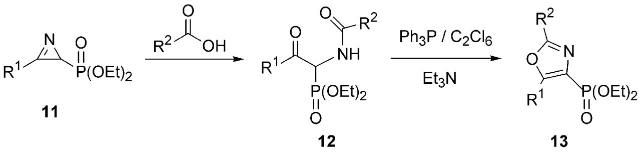
closure of ketamides **5**, such as phosphorus pentachloride, phosphorus oxychloride with sodium hydride, or phosphorus oxychloride with triethylamine, but the best results were observed when a modified Wipf method[27] was used replacing iodine for hexachloroethane. Ketamides **5** were treated with triphenylphosphine and hexachloroethane in the presence of triethylamine in THF to give oxazole phosphine oxides **8** in good yields and in a regioselective fashion (Scheme 4, Table 3, entries 1−7). Spectroscopic data were in agreement with the assigned structure of compounds **8**. Mass spectrometry of **8aa** showed the molecular ion peak (*m/z* 297, 89%), while in the ^{31}P NMR spectrum the phosphinyl group resonated at δ_P 18.8 ppm. The ^{13}C NMR spectrum of oxazole **8aa** showed doublets at δ_C 126.5 ppm ($^1J_{PC} = 145.0$ Hz) for C-4 and at δ_C 160.4 ppm ($^3J_{PC} = 19.2$ Hz) for C-2. The formation of oxazoles **8** could be explained by deprotonation of ketamides **5** by means of dichlorotriphenylphosphorane (Ph_3PCl_2), generated "in situ" from triphenylphosphine and hexachloroethane,[28] to give an intermediate enamide **9** followed by the loss of triphenylphosphine oxide and ring closure of the reactive carbene **10** formed, in a similar way to that reported for simple oxazoles.[27]

The cyclization is quite general since oxazoles **8** derived from phosphine oxides (4-position) can be prepared and substituted in the 2-position of the ring not only with alkyl substituent **8aa** ($R^2 = CH_3$) but also with aryl groups **8ab** and **8bb** ($R^2 = C_6H_5$) and ether **8ac** ($R^2 = CH_3OCH_2$) or olefine groups **8ad** ($R^2 = CH_2{=}CH$) and **8ae** ($R^2 = CH_2{=}CH(CH_2)_4$). However, the ring closure does not seem to be compatible with the presence of carboxylic acid group in ketamide **5**. Thus, oxazole **8bf** ($R^2 = CH_2CO_2H$) was not obtained by the reaction of ketamide **5bf** ($R^2 = CH_2CO_2H$), prepared by reaction of azirine **3b** and malonic acid **4f** with triphenylphosphine and hexachloroethane in the presence of triethylamine. However, the corresponding functionalized oxazole **8bg** ($R^2 = CH_2CO_2CH_3$) with the carboxylic acid protected with an ester group was isolated by the reaction, in the same conditions from the corresponding protected ketamide **5bg** ($R^2 = CH_2CO_2CH_3$), obtained by esterification of ketamide **5bf** ($R^2 = CH_2CO_2H$) with thionyl chloride and methanol (see Scheme 5).

SCHEME 5



SCHEME 6



Finally, the formation of oxazoles was extended to azirines derived from phosphonates **11**.[18a] Heating azirines **11a** (R^1 = Me) and **11b** (R^1 = Et) with acetic acid **4a** (R^2 = Me) and benzoic acid **4b** (R^2 = Ph) led to the formation of α-ketamides containing a diethoxyphosphonyl group in the α-position **12aa**−**bb** (Scheme 6, Table 2, entries 9−11).[29] The formation of adducts **12** could be explained as before (Scheme 3), by formal addition of the carboxylic acid to the reactive carbon−nitrogen azirine double bond to give an unstable aziridine intermediate, followed by ring opening of zwitterionic oxazolone. Ketamides **12** were then treated with triphenylphosphine and hexachloroethane in the presence of triethylamine and oxazole phosphonates **13** were obtained (Scheme 6, Table 3, entries 8−10). The formation of oxazoles **13** could also be explained through a similar mechanism to that reported for oxazoles **8**.

Conclusions

We have devised a simple, mild, and convenient strategy for the asymmetric synthesis of 2*H*-azirines substituted with a phosphine oxide group in the 2-position of **3** from easily available oximes **1**, using achiral or chiral polymer-bound amines **2**. These heterocycles are very useful intermediates in the formation of α-ketamides and phosphorus-substituted oxazoles. Substituted 2*H*-

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[26] For recent contributions on oxazoles see: (a) Miller, R. A.; Smith, R. M.; Karady, S.; Reamer, R. A. *Tetrahedron Lett.* **2002**, *43*, 935−938. (b) Berger, R.; Shoop, W. L.; Pivnichny, J. V.; Waarmke, L. M.; Zakson-Aiken, M.; Owens, K. A.; de Montigny, P.; Schamatz, D. M.; Wyvratt, M. J.; Fisher, M. H.; Meinke, P. T.; Coletti, S. L. *Org. Lett.* **2001**, *3*, 3715−3718. (c) Wipf, P.; Methot, J. L. *Org. Lett.* **2001**, *3*, 1261−1264.

[27] Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604−3606.

[28] Appel, R.; Schöler, H. *Chem. Ber.* **1977**, *110*, 2382−2384.

[29] A small proportion of pyrazine phosphonates (<20%) was also formed by dimerization of starting azirines **11**.[30]

azirines and oxazoles are important synthons in organic synthesis[3] and for the preparation of biologically active compounds of interest in medicinal chemistry.[3,25,26]

Experimental Section

General Methods. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use: CH_2Cl_2 (P_2O_5); *n*-hexane and diethyl ether (sodium benzophenone ketyl); ethyl acetate (K_2CO_3); $CHCl_3$ (P_2O_5); toluene (CaH_2); dioxane (Na, benzophenone). All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with silica gel 60 F_{254} plates. Visualization was accomplished by UV light and $KMnO_4$ solution. Flash chromatography was carried out with silica gel 60 (230−400 mesh). Melting points are uncorrected. ^1H (300 MHz), ^{13}C (75 MHz), and ^{31}P NMR (120 MHz) spectra were recorded with use of tetramethylsilane (TMS) (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in $CDCl_3$ or D_2O solutions for ^1H NMR spectra or chloroform (77.0 ppm) as an internal reference in $CDCl_3$ solutions for ^{13}C NMR, and phosphoric acid (85%) for ^{31}P NMR spectra. Chemical shifts (δ) are given in ppm; multiplicities are indicated by s (singlet), d (doublet), dd (double-doublet), t (triplet), q (quadruplet), or m (multiplet). Coupling constants *(J)* are reported in hertz. Low-resolution mass spectra (MS) were obtained at 50−70 eV by electron impact (EI) or chemical ionization (CI). Data are reported in the form *m*/*z* (intensity relative to base = 100). Infrared spectra (IR) were taken on a IRFT spectrometer, and were obtained as solids in KBr or as neat oils in NaCl. Peaks are reported in cm^{-1}. $[\alpha]^{20}_D$ were taken on a polarimeter with a Na/HaI lamp. Oximes **1a**,**b**,[17] morpholinomethyl polystyrene resin **2b**,[31] and 2*H*-azirine-2-phosphonates **11**[18a] were synthesized according to literature procedures.

General Procedure for the Preparation of Polymer-Supported Amines (2c and 2d). A suspension of Merrifield resin (4 mmol, 1 mmol of Cl/g of resin, 4 g) in DMF (32 mL) was treated with (*S*)-(+)-2-(methoxymethyl)pyrrolidine or (*R*)-(−)-2-(methoxymethyl)pyrrolidine[32] (16 mmol, 2 mL). The resulting mixture was shaken at 65 °C for 18 h under N_2 atmosphere and then allowed to stand at room temperature 24 h. After the solution was cooled to room temperature, the resin was filtered and washed successively with MeOH, DMF, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, AcOEt, and pentane. The resulting polymer-supported amine was dried at 20 °C under vacuum for 12 h and stored in tightly sealed bottles.

(*S*)-(+)-2-(Methoxymethyl)pyrrolidinomethyl Polystyrene Resin (2c). IR (KBr) 2805 (OMe st), 1109 (C−O−C st) cm^{-1}. Anal. Found: C, 91.98; H, 8.93; N, 1.51.

General Procedure for the Synthesis of 2*H*-Azirine-2-phosphine Oxides (3). To a suspension of resin-supported amine **2a**−**c** (ca. 0.5 mmol, 1.1 equiv) in benzene (8.0 mL) was added tosyl oxime **1** (0.45 mmol, 1 equiv). The mixture was shaken at 50 °C for 3 to 4 days under N_2 atmosphere after which time the polymer was filtered and washed with CH_2Cl_2 (5 mL), Et_2O (5 mL), CH_2Cl_2 (5 mL), and Et_2O (5 mL). The filtrate was evaporated under vacuum. Purification of the crude product by flash chromatography (silica gel AcOEt−hexanes 4:1) afforded an oil that was precipitated with Et_2O and recrystallized from AcOEt−hexanes to yield compounds **3**. Resin-supported amines **2a**−**c** were recovered by washing successively with MeOH, TEA, CH_2Cl_2, MeOH, TEA, CH_2Cl_2, MeOH, TEA, and CH_2Cl_2.

(3-Methyl-2*H*-azirin-2-yl)phosphine Oxide (3a). (A) As described in the general procedure, 80.3 mg (70%) was obtained as a white solid from (*E*)- and (*Z*)-2-(*N*-*p*-toluenesulfonyloximino)propyldiphenylphosphine oxide **1a** and resin-supported amine **2a**. (B) As described in the general procedure, 75.7 mg (66%) was obtained as a white solid from (*E*)- and (*Z*)-2-(*N*-*p*-toluenesulfonyloximino)propyldiphenylphosphine oxide **1a** and recovered resin-supported amine **2a**: mp 97−98 °C; ^1H NMR ($CDCl_3$) δ 7.88−7.36 (m, 10H), 2.38 (s, 3H), 2.18 (d, $^2J_{PH}$ = 36.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 163.1 (d, $^2J_{PC}$ = 3.5 Hz), 133.1−128.3 (m), 27.2 (d, $^1J_{PC}$ = 111.8 Hz), 13.9 (d, $^3J_{PC}$ = 1.5 Hz) ppm; ^{31}P NMR ($CDCl_3$) δ 29.8 ppm; IR (KBr) 3062, 1736, 1442, 1192 cm^{-1}; MS (EI) *m*/*z* 255 (M^+, 63), 201 ($P(O)Ph_2^+$, 36). Anal. Calcd for $C_{15}H_{14}NOP$: C, 70.58; H, 5.53; N, 5.49. Found: C, 70.37; H, 5.52; N, 5.51.

(−)-(*R*)−(3-Methyl-2*H*-azirin-2-yl)phosphine Oxide (3a). As described in the general procedure, 84.9 mg (74%) was obtained as a white solid from (*E*)- and (*Z*)-2-(*N*-*p*-toluenesulfonyloximino)propyldiphenylphosphine oxide **1a** and resin-supported amine **2c**, ee 16%; $[\alpha]^{20}_D$ −8.0. For spectroscopic data see above.

General Procedure for the Synthesis of α-Ketamides Derived from Phosphines Oxides (5). Method A: To a −80 °C solution of 2*H*-azirine **3** (5 mmol) in THF (5 mL) was added a solution of carboxylic acid **4** (15 mmol) in THF (5 mL) under nitrogen atmosphere. Then, the mixture was allowed to warm to room temperature and was stirred for 1 to 4 days. The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography (silica gel AcOEt). Method B: The carboxilic acid **4** (5.5 mmol) was added under nitrogen atmosphere and at room temperature to 2*H*-azirine **3** (5 mmol) without solvent. The mixture was stirred for 12−20 h and then the crude residue was crystallized from diethyl ether to yield products **5** as white solids.

***N*-[1-(Diphenylphosphinoyl)-2-oxopropyl]acetamide (5aa). 5aa** (1.18 g, 75%) was obtained as a white solid from 2*H*-azirine **3a** (1.28 g, 5 mmol) and acetic acid glacial **4a** (0.32 g, 5 mmol) as described in the general procedure Method B: mp 193−194 °C; ^1H NMR ($CDCl_3$) δ 7.97−7.46 (m, 10H), 7.13 (d, $^3J_{HH}$ = 9.0 Hz, 1H), 5.85 (dd, $^2J_{PH}$ = 11.4 Hz, $^3J_{HH}$ = 9.0 Hz, 1H), 2.15 (s, 3H), 1.86 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 200.8, 169.3, 133.2−128.1 (m), 60.8 (d, $^1J_{PC}$ = 65.0 Hz), 29.9, 22.7 ppm; ^{31}P NMR ($CDCl_3$) δ 31.2 ppm; IR (KBr) 3190, 3032, 3022, 1720, 1680 cm^{-1}; MS (EI) *m*/*z* 315 (M^+ + 2), 201 (P(O)-Ph_2^+, 40). Anal. Calcd for $C_{17}H_{18}NO_3P$: C, 64.76; H, 5.75; N, 4.44. Found: C, 64.58; H, 5.74; N, 4.47.

General Procedure for the Preparation of Oxazoles (8). To a room temperature solution of triphenyl phosphine (1.70 g, 6.5 mmol) and hexachloroethane (1.54 g, 6.5 mmol) in THF (20 mL) was added a solution of α-ketamide **5** (5 mmol) in THF (5 mL) under nitrogen atmosphere. The mixture was stirred at room temperature for 5 min. After that, triethylamine (2.10 mL, 15 mmol) was dropped for 10 min. The mixture was heated at THF reflux for 20 h. The solvent was evaporated under vacuum and the residue was diluted with water and extracted with CH_2Cl_2. The organic layers where dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The crude residue was purified by flash chromatography (silica gel AcOEt).

4-(Diphenylphosphinoyl)-2,5-dimethyloxazole (8aa). 8aa (0.95 g, 64%) was obtained as a white solid from α-ketamide **5aa** (1.58 g, 5 mmol) as described in the general procedure: mp 117−118 °C; ^1H NMR ($CDCl_3$) δ 7.88−7.41 (m, 10H), 2.59 (d, $^4J_{PH}$ = 1.8 Hz, 3H), 2.42 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 160.4 (d, $^3J_{PC}$ = 19.2 Hz,), 158.9 (d, $^2J_{PC}$ = 26.1 Hz), 133.2−128.3 (m), 126.5 (d, $^1J_{PC}$ = 145.0 Hz), 13.8, 11.6 ppm; ^{31}P NMR ($CDCl_3$) δ 18.8 ppm; IR (KBr) 3070,1590, 1195 cm^{-1}; MS (EI) *m*/*z* 297 (M^+, 89). Anal. Calcd for $C_{17}H_{16}NO_2P$: C, 68.68; H, 5.42; N, 4.71. Found: C, 68.88; H, 5.40; N, 4.72.

General Procedure for Synthesis of α-Ketamides Derived from Phosphonates (12). The carboxylic acid **4** (7.5 mmol) was added to 2*H*-azirinephosphonate **11** (5 mmol)

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without solvent, under nitrogen atmosphere, at room temperature, and with continuous stirring. The mixture was heated at 70 °C for 2 h. Then, the crude residue was purified by flash chromatography (silica gel AcOEt/hexanes) affording α-ketamides **12** and a small proportion (15−20%) of pyrazine phosphonates.[30]

Diethyl (1-Acetylamino-2-oxopropyl)phosphonate (12aa). **12aa** (0.94 g, 75%) was obtained as an oil from 2*H*-azirinephosphonate **11a** (0.96 g, 5 mmol) and acetic acid **4a** (0.45 g, 7.5 mmol) as described in the general procedure: R_f 0.51 (AcOEt); ^{1}H NMR (CDCl$_3$) δ 6.48 (d, ${}^3J_{HH} = 8.4$ Hz, 1H), 5.25 (dd, ${}^2J_{PH} = 23.3$ Hz, ${}^3J_{HH} = 8.4$ Hz, 1H), 4.11 (m, 4H), 2.36 (s, 3H), 2.01 (s, 3H), 1.28 (m, 6H) ppm; ^{13}C NMR (CDCl$_3$) δ 199.9, 169.4 (d, ${}^3J_{PC} = 5.0$ Hz), 63.5 (d, ${}^2J_{PC} = 6.1$ Hz), 57.9 (d, ${}^1J_{PC} = 141.0$ Hz), 29.0, 22.8, 16.2 ppm; ^{31}P NMR (CDCl$_3$) δ 16.2 ppm; IR (NaCl) 3262, 3040, 1731, 1678 cm^{-1}; MS (EI) m/z 252 (M$^+$ + 1, 4). Anal. Calcd for $C_9H_{18}NO_5P$: C, 43.03; H, 7.22; N, 5.58. Found: C, 43.14; H, 7.20; N, 5.60.

General Procedure for the Preparation of Diethyl (2,4-Dialkyloxazol-4-yl)phosphonates (13). To a room temperature solution of triphenylphosphine (1.70 g, 6.5 mmol) and hexachloroethane (1.54 g, 6.5 mmol) in toluene (20 mL) was added a solution of α-ketamide **12** (5 mmol) in toluene (5 mL) under nitrogen atmosphere. The mixture was stirred at that temperature for 5 min. After that, triethylamine (2.10 mL, 15 mmol) was dropped for 10 min. The subsequent mixture was heated at toluene reflux for 20 h. The solvent was evaporated under vacuum and the residue was purified by precipitation in cold ethyl ether. The organic layers were concentrated under vacuum and the subsequent residue was ground with cold water and filtered. The aqueous layer was concentrated, affording compounds **13** as colorless oils.

Diethyl (2,5-Dimethyloxazol-4-yl)phosphonate (13aa). **13aa** (0.64 g, 55%) was obtained as a colorless oil from α-ketamide **12aa** (1.26 g, 5 mmol) as described in the general method: R_f 0.34 (AcOEt); ^{1}H NMR (CDCl$_3$) δ 4.16 (m, 4H), 2.54 (d, ${}^4J_{PH} = 2.3$ Hz, 3H), 2.44 (s, 3H), 1.35 (t, ${}^3J_{HH} = 7.1$ Hz, 6H); ^{13}C NMR (CDCl$_3$) δ 160.9 (d, ${}^3J_{PC} = 22.2$ Hz), 158.5 (d, ${}^2J_{PC} = 39.8$ Hz), 127 (d, ${}^1J_{PC} = 243.7$), 62.5 (d, ${}^2J_{PC} = 5.5$ Hz), 16.4 (d, ${}^3J_{PC} = 6.6$ Hz), 11.5; ^{31}P NMR (CDCl$_3$) δ 10.0 ppm; IR (NaCl) 2985, 2919, 1730, 1600,1440, 1029, 970 cm^{-1}; MS (EI) m/z 233 (M$^+$, 28). Anal. Calcd for $C_9H_{16}NO_4P$: C, 46.35; H, 6.92; N, 6.01. Found: C, 46.20; H, 6.89; N, 5.99.

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Supporting Information Available: Experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR, and MS) for all new compounds (−)-**2d**, **3b**, (−)-**3b**, (+)-**3a**, (+)-**3b**, **5ab**, **5ac**, **5ad**, **5ae**, **5bb**, **5bf**, **5bg**, **8ab**, **8ac**, **8ad**, **8ae**, **8bb**, **8bg**, **12ab**, **12bb**, **13ab**, and **13bb**. This material is available free of charge via the Internet at http://pubs.acs.org.

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