JOC The Journal of Organic Chemistry

Article

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Hetero-Diels–Alder Reaction of Phosphorylated Nitroso Alkenes with Enol Ethers on Water: A Clean Approach Toward 1,2-Oxazine Derivatives

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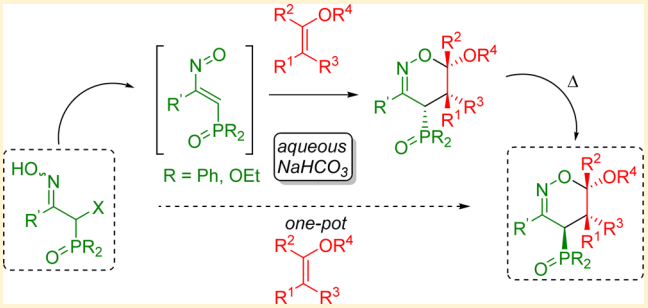
Supporting Information

ABSTRACT: A concise and eco-friendly synthesis of highly functionalized 1,2-oxazines from phosphinyl- and phosphonyl-nitroso alkenes has been developed. The key step of this process, which involves a two-step sequence of reactions on-water, is a regioselective hetero-Diels–Alder cycloaddition reaction of enol ethers to 4-phosphinyl or 4-phosphonyl nitroso alkenes mediated by water itself. The process has also been performed under solvent-free conditions and in organic solvents for comparison.



INTRODUCTION

Organic reactions are usually carried out in organic solvents. However, despite water being environmentally friendly, benign, safe, and inexpensive compared with organic solvents, the use of water as the reaction medium is very infrequent. This is in contrast to the many enzymatic processes that by necessity must occur in an aqueous environment. Since the pioneering work of Breslow and co-workers[1] who first reported how water enhances rate and selectivity in the Diels–Alder reactions (DARs), there has been increasing recognition that organic reactions performed in aqueous media may offer advantages over those occurring in organic solvents.[2] Sharpless and co-workers described "on water" conditions under which substantial rate acceleration was observed when the organic reactants were insoluble in the aqueous phase.[3] Therefore, the development of new processes "on water" is an important goal in green preparative organic chemistry.

1,2-Oxazines are compounds of biological relevance, and not only are they important structural constituents of secondary metabolite polyketides,[4a] marine-derived trichodermamides[4b] as well as many fungicides and broad spectrum bactericides,[4c] they have also been used as intermediates during the synthesis of glycosidase inhibitor analogues,[5a–c] type IV phosphodiesterase (PDE) inhibitors,[5d] or neuraminidase inhibitors,[5e] and functionalized pyrroles.[5f,g] Likewise, they have found numerous applications in the total synthesis of natural and biologically active nitrogen-containing compounds, such as alkaloids,[6] pheromones,[7a] carbohydrate mimetics,[7b] or unnatural α-amino acids.[7c]

The DAR is a highly atom-economic alternative for carbon–carbon bond construction[8] to generate molecular complexity efficiently and with industrial applications,[9] for the preparation of highly complex six-membered rings,[10] and perhaps the most striking and unexpected example of a reaction that benefits from the use of an aqueous solvent system.[1c,d] Some examples of DAR on water have also been reported,[11] including the inverse electron demand hetero-Diels–Alder reaction (HDAR) of azo alkenes[12] or nitro alkenes.[13]

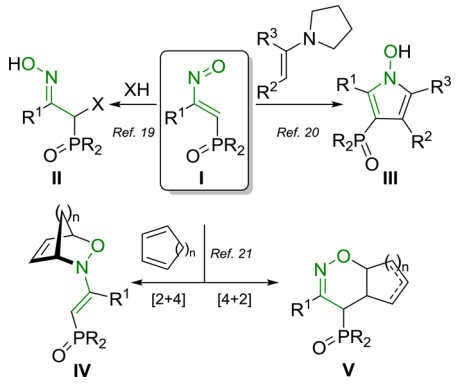
On the other hand, nitroso alkenes[14] are functionalized nitroso derivatives, which have attracted a great deal of attention owing to their usefulness as heterodienes for a [4 + 2] cycloaddition reaction. The intramolecular[15] and intermolecular HDAR of nitroso alkenes has been investigated,[16,17] and these reactions are carried out in organic solvents. However, until now no examples of nitroso alkenes as heterodienes "on water" have been described. In fact, only one example of nitroso derivative (acylnitroso), which were generated in situ using water, has been reported and in this case the nitroso moiety is involved as a heterodienophile in an intramolecular HDAR used for the preparation of (−)-pumiliotoxin C.[18]

In this context, we previously described the generation of phosphinyl **I** (R = Ph) and phosphonyl nitroso alkenes **I** (R = OEt) and the conjugate addition (1,4-addition) of some nucleophiles, such as amines and amino-esters, for the preparation of α-amino phosphonate derivatives[19] **II** (Scheme 1). Likewise, formal [3 + 2] cycloaddition processes of phosphorylated nitroso alkenes **I** have also been used for the regioselective preparation of highly functionalized *N*-hydroxy-pyrroles[20] **III**, while phosphorylated nitroso alkenes **I** react with cyclic dienes to afford HDA cycloadducts **IV** and **V**, where the nitroso alkene can participate as heterodienophile or

Received: June 16, 2014
Published: July 25, 2014

   dx.doi.org/10.1021/jo501339c | J. Org. Chem. 2014, 79, 7607–7615

Scheme 1. Reactivity Pattern of Phosphorylated Nitroso Alkenes I



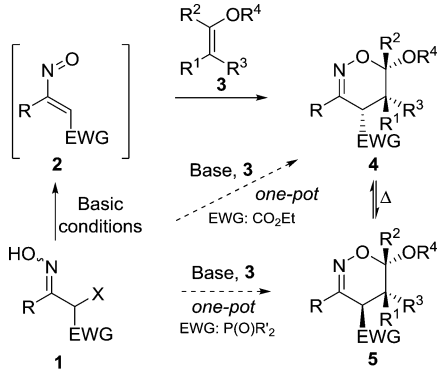
heterodiene component and the cyclic olefin acts as the 4π- or 2π-electron system, respectively (Scheme 1).[21] In this context, it is known that phosphorus substituents regulate important biological functions,[22] and the introduction of organophosphorus functionalities in simple synthons may afford the development of new strategies for the preparation of aminophosphonates[23] or phosphorylated azaheterocycles.[24] For this reason, we are interested in demonstrating the potentiality of nitroso alkenes for the preparation of nitrogen heterocycles containing a phosphine oxide or a phosphonate group, and here we wish to report the results of inverse electron demand HDAR of phosphonyl and phosphinyl nitroso alkenes **I** (R = Ph, OEt) with electron-rich dienophiles, such as enol ethers, performed under solvent-free conditions, on water and in organic solvents for comparison, for the preparation of highly functionalized 1,2-oxazines.

RESULTS AND DISCUSSION

We envisioned that base-promoted dehydrohalogenation of phosphinyl **1** (EWG = $P(O)Ph_2$), phosphonyl **1** (EWG = $P(O)(OEt)_2$) or carboxylic acid derivative halooxime **1** (EWG = CO_2Et) followed by [4 + 2] cycloaddition reaction with enol ethers would represent a practical short route to functionalized 1,2-oxazines (Scheme 2). This process might be performed in a one-pot operation that would be attractive from an atom-economic alternative for carbon–carbon and carbon–heteroatom bond construction.

Initial experiments to assess the reactivity of nitroso alkenes toward enol ethers by using phosphorylated α-halooximes **1** and several base/enol ether combinations were explored. The results of cycloaddition reactions of **2** with enol ethers, in a one-pot reaction from α-halooxime **1** in the presence of a base, and using organic solvents, water, or solvent-free conditions are reported. Thus, as outlined in Scheme 2, the addition of ethyl vinyl ether **3a** ($R^1 = R^2 = R^3 = H$, $R^4 = Et$) to the reactive 4-phosphinyl **2a** (R = Me, EWG = $P(O)Ph_2$) or 4-phosphonyl nitroso alkene **2b** (R = Me, EWG = $P(O)(OEt)_2$), generated *in situ* through basic treatment (Et_3N) of α-bromooximes **1a** or **1b**, respectively,[19] under solvent-free conditions at room temperature was performed (Method A, Table 1). The highly colored 1,2-oxazabuta-1,3-dienes **2** disappeared very rapidly, and the crude reaction ^1H NMR spectra revealed the presence of a mixture of diastereoisomers epimeric at C-4 (1:1 mixture for **4aa** and **5aa**, and 3:1 mixture for **4ba** and **5ba**) (Table 1, entries 1 and 2). Oxazines **4** in refluxing chloroform suffered an imine–enamine tautomeric process to afford the thermodynamically more stable 1,2-oxazines **5** with the bulky phosphorus substituent in the *syn* position with respect to H-5 and H-6, as confirmed by the NOE experiments. The isolation of thermodynamically more stable oxazines **5** toward **4** is in agreement with the calculated free energy differences, which show that oxazines **5** are approximately between 1.2 and 5.5 kcal/mol more stable than the corresponding oxazines **4**.

Scheme 2. Inverse Electron Demand Hetero-Diels–Alder Reaction of Phosphorylated Nitroso Alkenes 2 with Enol Ethers 3



EWG: CO_2Et, $P(O)Ph_2$, $P(O)(OEt)_2$; X: Cl, Br
R: Me, Et, Ph, CO_2Me
Base: Et_3N, anhydrous Na_2CO_3, aqueous $NaHCO_3$

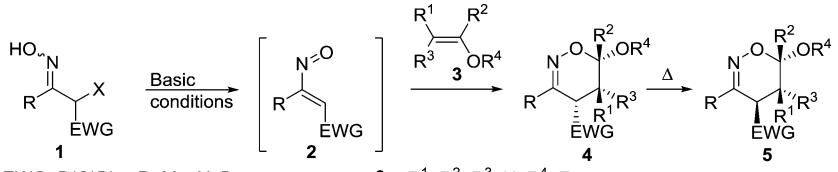
The regio- and stereochemistry of 1,2-oxazines **5** was based upon the NOE, ^1H, ^{13}C, and ^1H–^1H COSY NMR spectral data. In fact, regiochemistry seems to be governed by the ether function, giving only products with this group at 6-position as determined by ^1H NMR spectroscopy.[16] Consequently, the regio- and stereochemistry of **5aa** was assigned on the basis of NOE experiments. The 4,5-*cis* relationship of H-4 and H-5′ in the ring of 1,2-oxazine **5aa** was evident since a NOE was observed between H-4 and H-5′ (3.7%) (*cis* relative stereochemistry) after saturation of H-4 proton (Figure 1). Conversely, after the saturation of H-6 proton, a very small NOE was observed between H-6 and H-5′ (1.7%) suggesting a *trans* relationship between both protons, and a NOE (2.6%) was observed between H-6 and H-5 (*cis* relative stereochemistry). These results clearly suggest a *trans* relative stereochemisty for both the ether group and the bulky phosphorus substituent as indicated in Figure 1. Comparable values were observed when selective irradiations were performed with oxazine **5ba**.

This procedure represents a practical short regio- and diastereoselective one-pot route to functionalized 4-phosphorylated 1,2-oxazines through base-promoted dehydrohalogenation of the starting α-haolooxime **1**.

The process was extended to the [4 + 2] cycloaddition reaction of 1,2-oxazabuta-1,3-diene-4-carboxylic acid derivative **2c** (R = Me, EWG = CO_2Et) toward ethyl vinyl ether **3a** under solvent-free conditions. The hetero-Diels–Alder cycloadduct **4ca** was obtained in good chemical yield (Table 1, entry 3) with the opposite stereochemistry at C-4 as confirmed by the NOE experiments. As a rule,[17b] the *pseudo*-equatorial location of H-4 predetermines smaller coupling constants J_{4-5} and $J_{4-5'}$ ($J \approx$ 7.5, 1.8 Hz for oxazine **4ca**) compared to the corresponding values when pseudoaxial orientation of H-4 takes place ($J \approx$ 10.2, 8.4 Hz for oxazine **5ba**). Therefore, the CO_2Et group is pseudoaxial in the exclusive obtained stereoisomer for **4ca**.

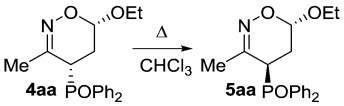
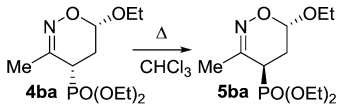
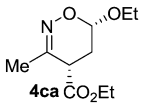
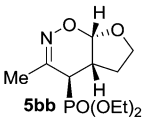
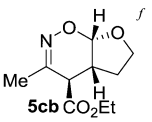
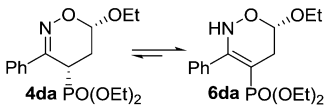
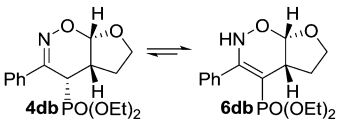
dx.doi.org/10.1021/jo501339c | J. Org. Chem. 2014, 79, 7607–7615

Table 1. 1,2-Oxazines from [4 + 2] Cycloaddition Reaction of Nitroso Alkenes 2 and Enol Ethers 3[a]



1a: EWG=P(O)Ph$_2$, R=Me, X=Br
1b: EWG=P(O)(OEt)$_2$, R=Me, X=Br
1c: EWG=CO$_2$Et, R=Me, X=Br
1d: EWG=P(O)(OEt)$_2$, R=Ph, X=Cl
1e: EWG=P(O)Ph$_2$, R=Et, X=Br
1f: EWG=P(O)Ph$_2$, R=CO$_2$Me, X=Br

3a: R^1=R^2=R^3=H, R^4=Et
3b: R^1=R^2=H, R^{3}R^4=–(CH$_2$)$_2$–
3c: R^1=R^2=H, R^{3}R^4=–(CH$_2$)$_3$–
3d: R^1=R^3=H, R^2=R^4=Me
3e: R^{1}R^2=–(CH$_2$)$_3$–, R^3=H, R^4=SiMe$_3$
3f: R^1=^{i}Pr, R^2=R^3=H, R^4=SiMe$_3$

Entry	2	3	Basic conditions[b]	Time [h]	Yield [%][c]	4:5 Ratio[d]	Compound[e]
1	**2a**	**3a**	A	0.5	94	50:50	 **4aa** **5aa**
2	**2b**	**3a**	A	0.5	92	75:25	 **4ba** **5ba**
3	**2c**	**3a**	A	0.5	79	100:0	 **4ca**
4	**2b**	**3b**	B	12	66	0:100	 **5bb**
5	**2c**	**3b**	B	12	61	10:90	 **5cb**[f]
6	**2d**	**3a**	A	0.5	82	-	 **4da** **6da**
7	**2d**	**3b**	B	12	57	-	 **4db** **6db**

[a]*Reaction Conditions:* one-pot reaction from α-halooxime **1** in the presence of a base under solvent-free conditions. [b]Method A: Et$_3$N, solvent-free; Method B: Na$_2$CO$_3$, solvent-free. [c]Isolated yield. [d]**4**:**5** Ratio was determined on ^{1}H NMR of the crude reaction mixture. [e]Compound directly obtained or obtained after heating a mixture of oxazines **4** and **5**. [f]No conversion to the thermodynamically more stable oxazine **5cb** was observed after heating the mixture of diastereoisomers **4cb**/**5cb** in refluxing chloroform.

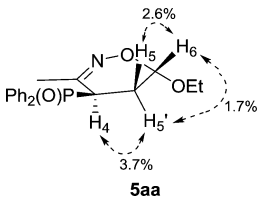
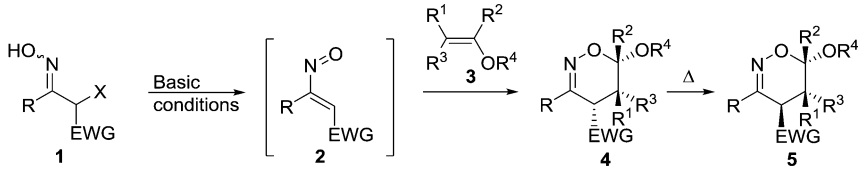


Figure 1. NOE observed for 4-phosphinyl-5,6-dihydro-4*H*-1,2-oxazine **5aa**.

Further exploration revealed that this approach is also applicable to other enol ethers. Thus, cyclic enol ethers such as 2,3-dihydrofuran **3b** (R^1 = R^2 = H, R^{3}R^4 = –(CH$_2$)$_2$–), reacted with substituted nitroso alkenes **2** to give the corresponding 1,2-oxazine derivative **5** (see Table 1, entries 4 and 5). In this case, only polymer formation has been observed with this olefin after the in situ generation of nitroso alkene **2**, through Et$_3$N-promoted dehydrohalogenation of the corresponding bromo-oxime **1**. However, changing the base to anhydrous Na$_2$CO$_3$ under solvent-free conditions and at room temperature (Method B, Table 1), significantly reduced the extent of polymerization, and 1,2-oxazines **5bb** and **5cb** were obtained in moderate yield. 1,2-Oxazine **5bb** was obtained as a sole diastereoisomer with H-4 in *pseudo*-axial location as confirmed by NOE experiments. Nevertheless, **5cb** was obtained as an (10:90) inseparable mixture of diastereoisomers. The NOE

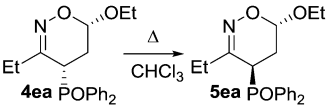
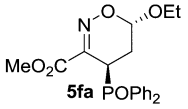
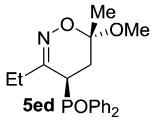
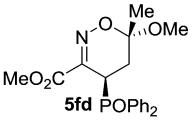
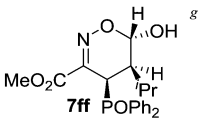
dx.doi.org/10.1021/jo501339c | J. Org. Chem. 2014, 79, 7607–7615

Table 2. 1,2-Oxazines from [4 + 2] Cycloaddition Reaction of Nitroso Alkenes 2 and Enol Ethers 3[a]



1a: EWG=P(O)Ph_2, R=Me, X=Br
1b: EWG=P(O)$(OEt)_2$, R=Me, X=Br
1c: EWG=CO_2Et, R=Me, X=Br
1d: EWG=P(O)$(OEt)_2$, R=Ph, X=Cl
1e: EWG=P(O)Ph_2, R=Et, X=Br
1f: EWG=P(O)Ph_2, R=CO_2Me, X=Br

3a: R^1=R^2=R^3=H, R^4=Et
3b: R^1=R^2=H, R^3R^4=–$(CH_2)_2$–
3c: R^1=R^2=H, R^3R^4=–$(CH_2)_3$–
3d: R^1=R^3=H, R^2=R^4=Me
3e: R^1R^2=–$(CH_2)_3$–, R^3=H, R^4=$SiMe_3$
3f: R^1=^{i}Pr, R^2=R^3=H, R^4=$SiMe_3$

Entry	2	3	Basic Conditions[b]	Time [h]	Yield [%][c]	4:5 Ratio[d]	Compound[e]
1	**2e**	**3a**	C	18	76	13:87	 **4ea** **5ea**
2	**2f**	**3a**	C	18	85	0:100	 **5fa**
3	**2e**	**3a**	D	15	95	33:67	**4ea/5ea**
4	**2f**	**3a**	D	15	90	0:100	**5fa**
5	**2a**	**3a**	D	18	94	0:100	**5aa**
6	**2b**	**3a**	D	6	62	0:100	**5ba**
7	**2a**	**3c**	D	18	-	-	-
8	**2e**	**3d**	D	16	99	n.r.[f]	 **5ed**
9	**2f**	**3d**	D	17	78	n.r.[f]	 **5fd**
10	**2f**	**3f**	D	18	98	-	 **7ff**[g]
11	**2e**	**3e**	D	24	-	-	-

[a]*Reaction Conditions:* one-pot reaction from α-halooxime **1** in the presence of a base using organic solvents or water. [b]Method C: Aqueous saturated $NaHCO_3$, CH_2Cl_2; Method D: Aqueous saturated $NaHCO_3$. [c]Isolated yield. [d]**4**:**5** Ratio was determined on ^{1}H NMR of the crude reaction mixture. [e]Compound directly obtained or obtained after heating a mixture of oxazines **4** and **5**. [f]Not reported. [g]1,2-Oxazine **7ff** was obtained after O–Si bond cleavage in 1,2-oxazine **5ef** after isolation by flash-column chromatography.

experiments of compound **5cd** are not conclusive to establish the stereochemistry of this compound. However, a small coupling constant ($^3J_{HH}$) of 3 Hz between H-4 and H-4a in **5cd** suggests a dihedral angle close to 90°, and this is consistent with a *trans* relative stereochemistry between both protons. Furthermore, calculated free energy differences indicate that compound **5cb** is about 2 kcal/mol more stable than compound **4cb**.

As illustrated in Table 1, the method is tolerant of a range of nitroso alkenes with varying substitutions at C-3 and C-4. For instance, bromooxime **1d** (R = Ph, EWG = P(O)$(OEt)_2$) reacted with Et_3N or Na_2CO_3 in the presence of ethyl vinyl ether **3a** or 2,3-dihydrofuran **3b**, respectively, under solvent-free conditions, producing 1,2-oxazines **6da** and **6db** as the enaminic tautomeric form (Table 1, entries 6 and 7). In both cases, cycloadducts **4da** and **4db** were probably initially generated followed by prototropic tautomerization to give 1,2-oxazines **6da** and **6db**. As far as we know, this strategy represents the first example for the preparation of nonfused 1,2-oxazines with a phosphorus substituent (phosphine oxide or phosphonate) in position 4.

Next, the ability of enol ethers to trap nitroso alkenes according to an inverse electron demand HDAR under both a traditional organic environment and in an aqueous medium is

dx.doi.org/10.1021/jo501339c | J. Org. Chem. 2014, 79, 7607–7615

assayed and compared. In this case, the base-mediated dehydrohalogenation was examined by using a saturated aqueous solution of $NaHCO_3$. We began our studies with the reaction between bromooxime **1e** and **1f**, ethyl vinyl ether **3a** and saturated aqueous solution of $NaHCO_3$ as base in CH_2Cl_2 (Method C, Table 2). In both cases, [4 + 2] cycloadducts **5ea** and **5fa** were produced in good yields and selectivity (Table 2, entries 1 and 2). The reactions carried out on water (Method D, Table 2) occur in the heterogeneous phase and are faster than those performed in homogeneous solution in organic solvent. Likewise, high reaction yields are obtained on water conditions (Table 2, compare entries 1 vs 3 and 2 vs 4). All the reactions are totally regioselective and highly diastereoselective. For instance, high selectivity has been observed on water conditions compared with the solvent-free conditions (compare entry 1 in Table 1 vs 5 in Table 2, and 2 in Table 1 vs 6 in Table 2).

On water [4 + 2] HDAR of nitroso alkenes with enol ethers was also extended to other enol ethers, such as a 1,1-disubstituted olefin as 2-methoxypropene **3d** ($R^1 = R^3 = H$, $R^2 = R^4 = Me$), or a 1,2-disubstituted silyl enol ether **3f** ($R^1 = {}^iPr$, $R^2 = R^3 = H$, $R^4 = SiMe_3$) with two groups of moderate size on the olefin, affording cycloadducts in very good yield (Table 2, entries 8−10). However, when silyl enol ether **3f** was used, the labile O−$SiMe_3$ bond was hydrolyzed, and cycloadduct **7ff** was obtained (Table 2, entry 10). The use of cyclic silyl enol ethers **3c** and **3e** under a variety of conditions produced complex mixtures (due to self-addition of nitroso alkene) in which 1,2-oxazines adducts could not be detected (Table 2, entries 7 and 11). Furthermore, all attempts to produce 1,2-oxazines with a carboxylic acid derivative at C-4, using the corresponding bromooxime **1c** as starting material, on water conditions were unsuccessful, giving complex mixtures of products. As far as we know, this process describes the first reaction of nitroso alkene derivatives as heterodienes on water as well as the first synthesis of simple 1,2-oxazines on water.

CONCLUSIONS

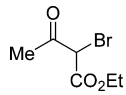
In conclusion, we describe a highly practical short and efficient route that allows for the direct construction of functionalized nitrogen- and oxygen-containing heterocycles, 5,6-dihydro-4*H*-1,2-oxazines. The first HDAR has been reported, where nitroso alkenes as heterodienes, generated *in situ* from dehydrohalogenation of phosphinyl **1** (R = Ph) or phosphonyl halooxime **1** (R = OEt), and enol ethers are coupled on water at room temperature. The direct comparison between the on water [4 + 2] cycloaddition procedure, the solvent-free conditions, and the organic counterpart carried out using organic solvents, established the superior role of water in terms of chemical efficiency, selectivity, and general applicability.

This process might be realized in a one-pot approach that would be attractive from an atom-economic strategy for carbon−carbon and carbon−heteroatom bond construction, and the resulting products would broaden the pool of available 1,2-oxazines as synthetic intermediates for the preparation of biologically active compounds of interest to medicinal chemistry.[4−7]

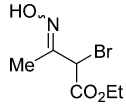
EXPERIMENTAL SECTION

General Methods. Et_3N was distilled and then dried over molecular sieves 70 Å. Anhydrous Na_2CO_3 was dried using a glass oven connected to a vacuum system. CH_2Cl_2, $CHCl_3$, EtOH, and CCl_4 were freshly distilled and dried over molecular sieves 70 Å. All other solvents and reagents were obtained from commercial sources and used without further purification. All reactions were performed under an atmosphere of dry nitrogen. Melting points are uncorrected. IR-FT spectra were obtained as solids as neat oils in NaCl. Mass spectra (MS) were made by electron impact (EI) at an ionizing voltage of 70 eV or by chemical ionization (CI), and high resolution mass spectra (HRMS) was measured by EI or CI method using a mass spectrometer Q-TOF. ^1H (300, 400 MHz), ^{13}C (75, 100 MHz) and ^{31}P NMR (120, 160 MHz) spectra were recorded on a 300 or 400 MHz spectrometer, respectively, in $CDCl_3$. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. All coupling constants (J) values are given in Hz. Chemical shifts (δ_C) are reported in parts per million (ppm), relative to $CDCl_3$, as internal standard in a broad band decoupled mode. Flash-column chromatography was performed using commercial grades of silica gel finer than 230 mesh. Analytical thin layer chromatography was performed on precoated Merck silica gel 60 F_{254} plates, and spot visualization was accomplished by UV light (254 nm) or $KMnO_4$ solution. The starting materials such as phosphorylated α-bromooximes **1a** or **1b**[19] and (*E*)-trimethyl((3-methylbut-1-en-1-yl)oxy)silane **3f**[25] were prepared according to the literature procedures.

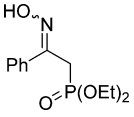
General Procedures and Spectral Data of Functionalized α-Halooximes. *Ethyl 2-Bromoacetoacetate.* To a stirred solution of sodium ethoxide (360 mg, 5 mmol) in ethanol (25 mL) was added ethyl acetoacetate (632 μL, 5.0 mmol). Then bromine (256 μL, 5.0 mmol) was added with a syringe pump (2 mL/h). The reaction mixture was allowed stir at room temperature for 1 h. The crude product was washed with water and extracted twice with dichloromethane (10 mL). The organic layers were dried over $MgSO_4$ and filtered, and the crude product was purified by flash-column chromatography (SiO_2, AcOEt/pentane 10:90) to afford the title compound as colorless oil, whose data are in agreement with those reported previously.[26]



*Ethyl (Z)- and (E)-2-Bromo-3-(hydroxyimino)butanoate (**1c**).* Hydroxylamine hydrochloride (139 mg, 2.0 mmol) and NaOH (80 mg, 2 mmol) was added to a stirred 0 °C solution of ethyl 2-bromoacetoacetate (416 mg, 2 mmol) in MeOH/H_2O (50:50) (10 mL). The reaction mixture was allowed to reach room temperature and stirred for 30 min. The MeOH layer was removed by rotary evaporation (bath temperature under 20 °C), and the aqueous layer was extracted twice with dichloromethane (20 mL). The organic layers were dried over anhydrous $MgSO_4$, filtered, and kept under nitrogen atmosphere at −20 °C. The title compound **1c** was very unstable and used without further purification steps.



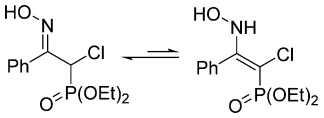
Diethyl (Z)- and (E)-(2-(Hydroxyimino)-2-phenylethyl)-phosphonate. This compound, prepared by a known procedure,[27] was shown to exhibit spectral data consistent with those reported.



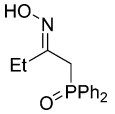
*Diethyl (E) (1-Chloro-2-(hydroxyimino)-2-phenylethyl)-phosphonate (**1d**) and Diethyl (1-Chloro-2-(hydroxyamino)-2-phenylvinyl)phosphonate (**1′d**).* NCS (267 mg, 2 mmol) was added to a stirred solution of diethyl (*Z*)- and (*E*)-(2-(hydroxyimino)-2-phenylethyl)phosphonate[27] (542 mg, 2 mmol) in dry CCl_4 (10 mL). The reaction mixture was heated in refluxing CCl_4 for 18 h. The crude product was washed with water and extracted twice with

dx.doi.org/10.1021/jo501339c | J. Org. Chem. 2014, 79, 7607−7615

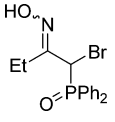
dichloromethane (30 mL). The organic layers were dried over anhydrous $MgSO_4$ and filtered, and the crude product was purified by flash-column chromatography (SiO_2, AcOEt) to afford the title compound as a mixture of oxime/enehydroxylamine tautomers in a ratio of 1:4, respectively, as colorless oil (427 mg, 70%). IR (NaCl) ν_{max} 3195, 3058, 2978, 1442, 1237, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.14 (bs, 1H)$_{major}$, 10.46 (bs, 1H)$_{minor}$, 7.67−7.32 (m, 5H), 4.85 (d, $^2J_{PH}$ = 14.1 Hz, 1H)$_{minor}$, 4.49−4.34 (m, 4H)$_{major}$, 4.25−4.07 (m, 4H)$_{minor}$, 1.39−1.36 (m, 6H)$_{major}$, 1.29−1.24 (m, 6H)$_{minor}$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1 (d, $^2J_{PC}$ = 1.5 Hz)$_{major}$, 150.6 (d, $^2J_{PC}$ = 3.0 Hz)$_{minor}$, 131.1, 131.0, 129.8, 129.4, 129.3, 129.1, 129.0, 128.4, 128.2, 127.9, 127.7, 80.4 (d, $^1J_{PC}$ = 177.3 Hz)$_{major}$, 66.3 (d, $^2J_{PC}$ = 7.0 Hz)$_{major}$, 64.4 (d, $^2J_{PC}$ = 6.5 Hz)$_{minor}$, 52.4 (d, $^1J_{PC}$ = 160.8 Hz)$_{minor}$, 16.4 (d, $^3J_{PC}$ = 5.4 Hz)$_{major}$, 16.2 (d, $^3J_{PC}$ = 6.0 Hz)$_{minor}$; ^{31}P NMR (120 MHz, $CDCl_3$) δ 16.4$_{minor}$, 10.4$_{major}$; ESI-HRMS m/z calcd for $C_{12}H_{17}ClNO_4P$ (EI) ($[M]^+$) 305.0584, found 305.0552.



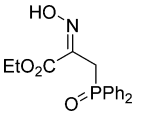
(E)-(2-(Hydroxyimino)butyl)diphenylphosphine oxide. This compound, prepared by a known procedure,[28] was shown to exhibit spectral data consistent with those reported.



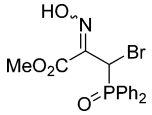
*(Z)- and (E)-(1-Bromo-2-(hydroxyimino)butyl)diphenylphosphine Oxide (**1e**).* To a stirred solution of sodium methoxide (0.65 g, 11.5 mmol) in methanol (50 mL) was added (*E*)-(2-(hydroxyimino)-butyl)diphenylphosphine oxide[28] (1.44 g, 5.0 mmol). The mixture was refluxed for 1 h and was allowed to reach 0 °C using an ice−water bath. Then bromine (256 μL, 5.0 mmol) was added with a syringe pump. The reaction mixture was stirred at room temperature for 19 h. The crude product was washed with water and extracted twice with dichloromethane (20 mL). The organic layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/*n*-hexane 50:50) to afford **1e** as a white solid (1.37 g, 73%). Mp 69−73 °C; IR (NaCl) ν_{max} 3173, 3059, 1435, 1182, 1115, 995, 729, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.53 (bs, 1H)$_{minor}$, 9.93 (bs, 1H)$_{major}$, 7.88−7.29 (m, 10H), 6.26 (s, 1H)$_{minor}$, 5.17 (s, 1H)$_{major}$, 2.79−2.64 (q, 2H)$_{minor}$, 2.56−2.35 (q, 2H)$_{major}$, 1.07−1.02 (t, 3H)$_{major}$, 0.94−0.89(t, 3H)$_{minor}$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3 (d, $^2J_{PC}$ = 2.0 Hz)$_{major}$, 153.2$_{minor}$, 132.5, 132.5, 132.3, 131.6, 131.5, 131.4, 131.3, 131.1, 131.0, 1303, 1296, 129.0, 128.6, 128.5, 46.0 (d, $^1J_{PC}$ = 68.5 Hz)$_{major}$, 34.5 (d, $^1J_{PC}$ = 67.0 Hz)$_{minor}$, 24.8$_{minor}$, 21.0$_{major}$, 10.5$_{major}$, 10.4$_{minor}$; ^{31}P NMR (120 MHz, $CDCl_3$) δ 27.6$_{major}$, 27.1$_{minor}$; ESI-HRMS (CI) m/z calcd for $C_{16}H_{18}BrNO_2P$ ($[M + H]^+$) 366.0259, found 366.0230.



Ethyl (E)-3-(Diphenylphosphoryl)-2-(hydroxyimino)propanoate. Hydroxylamine hydrochloride (264 mg, 3.8 mmol) and triethylamine (0.5 mL, 3.5 mmol) was added to a solution of ethyl 3-(diphenylphosphoryl)-2-oxopropanoate[29] (1g, 3.16 mmol) in $CHCl_3$ (40 mL) at room temperature. The reaction mixture was stirred under reflux for 23 h. The reaction was then cooled, washed with H_2O, extracted twice with CH_2Cl_2 (20 mL). The organic layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated off. Crystallization from Et_2O gave the title compound as a white solid (0.785 g, 75%). Mp 152−153 °C; IR (NaCl) ν_{max} 2990, 2765, 1705, 1476, 1435, 1163, 1100, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.83 (bs, 1H), 7.89−7.43 (m, 10H), 4.09 (q, $^3J_{HH}$ = 7 Hz, 2H), 3.95 (d, $^2J_{PH}$ = 15.0 Hz, 2H), 1.17 (t, $^3J_{HH}$ = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 142.9 (d, $^2J_{PC}$ = 10.1 Hz), 132.6, 132.0, 131.9, 131.3, 1312, 131.1, 128.5, 128.4, 61.6, 28.6 (d, $^1J_{PC}$ = 64.5 Hz), 14.0; ^{31}P NMR (120 MHz, $CDCl_3$) δ 29.1; ESI-HRMS (CI) m/z calcd for $C_{17}H_{19}NO_4P$ ($[M + H]^+$) 332.1052, found 332.1040.



*Methyl (Z)- and (E)-3-Bromo-3-(diphenylphosphoryl)-2-(hydroxyimino)propanoate (**1f**).* To a stirred solution of sodium methoxide (176 mg, 3.1 mmol) in methanol (25 mL) was added ethyl (*E*)-3-(diphenylphosphoryl)-2-(hydroxyimino)propanoate (0.41 g, 1.24 mmol). The mixture was refluxed for 1 h and was allowed to reach rt. Then bromine (127 μL, 2.48 mmol) was added with a syringe pump at rt, and the reaction mixture was stirred at for 24 h at the same temperature. Methanol was evaporated off, and the crude residue was diluted with CH_2Cl_2 and washed with water. The organic layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated. The crude product was purified by flash-column chromatography (SiO_2, AcOEt) to afford **1f** as yellow solid (0.4 g, 82%). Mp 154−155 °C; IR (NaCl) ν_{max} 2923, 1742, 1439, 1195 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.11−7.39 (m, 10H), 5.81 (d, $^2J_{PH}$ = 2.4 Hz, 1H), 3.76 (s, 3H)$_{major}$, 3.57 (s, 3H)$_{minor}$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (d, $^3J_{PC}$ = 2.1 Hz)minor, 163.3 (d, $^3J_{PC}$ = 5.8 Hz)$_{major}$, 142.7 (d, $^2J_{PC}$ = 3.6 Hz)$_{major}$, 142.1 (d, $^2J_{PC}$ = 9.9 Hz)$_{minor}$, 132.4, 132.3, 131.4, 131.3, 131.0, 130.8, 130.7, 130.6, 129.6, 129.2, 129.1, 128.6, 128.1, 128.9, 128.4, 128.3, 53.0$_{major}$, 52.7$_{minor}$, 31.9 (d, $^2J_{PC}$ = 67.0 Hz)$_{major}$, 28.2 (d, $^2J_{PC}$ = 64.8 Hz)$_{minor}$; ^{31}P NMR (120 MHz, $CDCl_3$) δ 32.0$_{minor}$, 27.1$_{major}$; ESI-HRMS (CI) m/z calcd for $C_{16}H_{16}BrNO_4P$($[M + H]^+$) 396.0000, found 395.9998.



General Procedure and Spectral Data for the Reaction of Functionalized Nitroso Alkenes 2 with Enol Ethers 3. Synthesis of Substituted 1,2-Oxazines. ***Method A***: to a stirred solution of functionalized α-halooxime **1** (1 mmol) in the corresponding enol ether **3** (10 mL) was added triethylamine (1.2 mmol) at room temperature and under a nitrogen atmosphere. The reaction was allowed to stir at room temperature for 30 min. The excess of enol ether was removed by rotary evaporation, and the residue was stirred with diethyl ether. The triethylamine hydrobromic salt was filtered through a sintered glass vacuum filtration funnel with Celite. The filtrate was concentrated to dryness in vacuum, and the crude product was purified by flash-column chromatography. ***Method B***: to a stirred solution of functionalized α-halooxime **1** (1 mmol) in the corresponding enol ether **3** (10 mL) was added anhydrous Na_2CO_3 (2 mmol) at room temperature and under a nitrogen atmosphere. The reaction was allowed to stir at room temperature for 12 h. The excess of Na_2CO_3 was filtered through a sintered glass vacuum filtration funnel with Celite. The filtrate was concentrated to dryness in vacuum, and the crude product was purified by flash-column chromatography. ***Method C***: to a stirred solution of functionalized α-halooxime **1** (1 mmol) in CH_2Cl_2 (5 mL) was added the corresponding enol ether **3** (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL) at room temperature. The reaction was allowed to stir at room temperature for 18 h. The solvent and the excess of enol ether were removed by rotary evaporation, and the residue was washed with water and extracted twice with dichloromethane (10 mL). The organic layers were dried over $MgSO_4$ and filtered, and the crude product was purified by flash-column chromatography. ***Method D***: to a stirred suspension of functionalized α-halooxime **1** (1 mmol) in the corresponding enol ether **3** (10 mL) was added a saturated aqueous

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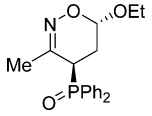
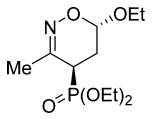
solution of $NaHCO_3$ (10 mL) at room temperature. The reaction was allowed to stir at room temperature for 6−18 h (see Table 1). The excess of enol ether was removed by rotary evaporation, and the residue was washed with water and extracted twice with dichloromethane (10 mL). The organic layers were dried over $MgSO_4$ and filtered, and the crude product was purified by flash-column chromatography.

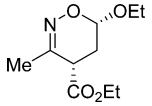
(4R,6S*)-4-(Diphenylphosphoryl)-6-ethoxy-3-methyl-5,6-dihydro-4H[1,2]oxazine (**5aa**):* (323 mg, 94%) obtained as colorless oil from bromooxime **1a** (351 mg, 1 mmol), Et_3N (168 μL, 1.2 mmol), and ethyl vinyl ether **3a** as described in ***method A***. (323 mg, 94%) obtained as colorless oil from bromooxime **1a** (351 mg, 1 mmol), saturated aqueous solution of $NaHCO_3$, and ethyl vinyl ether **3a** as described in ***method D***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/pentane 50:50). IR (NaCl) ν_{max} 3058, 2972, 1436, 1197, 1111, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86−7.46 (m, 10H), 5.06 (bt, J = 2.7 Hz, 1H), 3.79 (dq, $^2J_{HH}$ = 9.9 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 3.59−3.39 (m, 2H), 2.26−2.12 (m, 1H), 1.91 (s, 3H), 1.77−1.68 (m, 1H), 1.17 (t, $^3J_{HH}$ = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2 (d, $^2J_{PC}$ = 4.5 Hz), 132.2, 132.2, 131.7, 131.1, 131.0, 130.9, 131.9, 129.0, 128.9, 128.8, 128.7, 93.9 (d, $^3J_{PC}$ = 7.6 Hz), 63.4, 33.0 (d, $^1J_{PC}$ = 67.6 Hz), 26.5, 22.7, 14.9; ^{31}P NMR (120 MHz, $CDCl_3$) δ 30.7; ESI-HRMS (EI) m/z calcd for $C_{19}H_{22}NO_3P$ ($[M]^+$) 343.1337, found 343.1339.



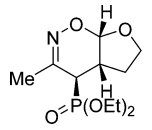
Diethyl ((4R,6S*)-6-ethoxy-3-methyl-5,6-dihydro-4H[1,2]oxazin-4-yl)phosphonate (**5ba**):* (257 mg, 92%) obtained as colorless oil from bromooxime **1b** (287 mg, 1 mmol), Et_3N (168 μL, 1.2 mmol), and ethyl vinyl ether **3a** as described in ***method A***. (173 mg, 62%) obtained as colorless oil from bromooxime **1b** (287 mg, 1 mmol), saturated aqueous solution of $NaHCO_3$, and ethyl vinyl ether **3a** as described in ***method D***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/pentane 40:60). IR (NaCl) ν_{max} 2978, 2928, 1436, 1248, 1048, 963 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (bt, J = 3.0 Hz, 1H), 4.23−4.09 (m, 4H), 3.81 (dq, $^2J_{HH}$ = 9.9 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 3.57 (dq, $^2J_{HH}$ = 9.9 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 2.87 (ddd, $^2J_{PH}$ = 27.3 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 8.4 Hz, 1H), 2.20−2.14 (m, 5H), 1.37−1.32 (m, 6H), 1.18 (t, $^3J_{HH}$ = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5 (d, $^2J_{PC}$ = 5.0 Hz), 93.8 (d, $^3J_{PC}$ = 8.5 Hz), 63.4, 62.6 (d, $^2J_{PC}$ = 6.5 Hz), 62.4 (d, $^2J_{PC}$ = 6.5 Hz), 30.5 (d, $^1J_{PC}$ = 143.7 Hz), 26.0 (d, $^2J_{PC}$ = 3.5 Hz), 21.7, 16.3 (d, $^3J_{PC}$ = 5.5 Hz), 14.9; ^{31}P NMR (120 MHz, $CDCl_3$) δ 25.1; MS (CI) m/z 280 ($[M + H]^+$, 100); ESI-HRMS (EI) m/z calcd for $C_{11}H_{22}NO_5P$ ($[M]^+$) 279.1236, found 279.1238.



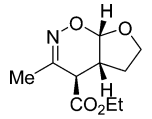
Ethyl (4S,6S*)-6-ethoxy-3-methyl-5,6-dihydro-4H[1,2]oxazine-4-carboxylate (**4ca**):* (42 mg, 79%) obtained as a yellow oil from bromooxime **1c** (50 mL from a 5 mM solution of **1c** in CH_2Cl_2, 0.25 mmol), Et_3N (43 μL, 0.3 mmol), and ethyl vinyl ether **3a** as described in ***method A***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/pentane 10:90). IR (NaCl) ν_{max} 2951, 1730, 1697, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (t, $^3J_{HH}$ = 2.7 Hz, 1H), 4.26−4.09 (m, 2H), 3.79 (dq, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 3.52 (dq, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 2.87 (dd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 1.8 Hz, 1H), 2.57 (dt, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 2.4 Hz, 1H), 2.13 (s, 3H), 2.02 (ddd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 2.7 Hz, 1H), 1.29 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.11 (t, $^3J_{HH}$ = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 152.9, 93.7, 63.0, 61.2, 36.1, 26.3, 22.5, 14.8, 14.0; MS (CI) m/z 215 ($[M]^+$, 10), 214 ($[M - H]^+$, 100); ESI-HRMS (EI) m/z calcd for $C_{10}H_{17}NO_4$ ($[M]^+$) 215.1158, found 215.1159.



Diethyl ((4R,4aS*,7aS*)-3-methyl-4a,5,6,7a-tetrahydro-4H-furo[3,2-e][1,2]oxazin-4-yl)phosphonate (**5bb**):* (183 mg, 66%) obtained as a brown oil from bromooxime **1b** (287 mg, 1 mmol), anhydrous Na_2CO_3 (212 mg, 2 mmol), and 2,3-dihydrofuran **3b** as described in ***method B***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/pentane 70:30). IR (NaCl) ν_{max} 2984, 1722, 1448, 1237, 1020, 974 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (d, $^3J_{HH}$ = 6.3 Hz, 1H), 4.23−4.11 (m, 4H), 4.05−3.98 (m, 1H), 3.88−3.80 (m, 1H), 3.19−3.06 (m, 1H), 2.75 (dd, $^2J_{PH}$ = 25.8 Hz, $^3J_{HH}$ = 1.2 Hz, 1H), 2.18 (d, $^4J_{PH}$ = 2.7 Hz, 3H), 2.04−1.95 (m, 1H), 1.69−1.56 (m, 1H), 1.43−1.26 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6 (d, $^2J_{PC}$ = 7.0 Hz), 99.4 (d, $^3J_{PC}$ = 1.5 Hz), 67.5, 63.2 (d, $^2J_{PC}$ = 6.5 Hz), 62.8 (d, $^2J_{PC}$ = 7.0 Hz), 39.0 (d, $^1J_{PC}$ = 136.7 Hz), 36.4 (d, $^2J_{PC}$ = 4.5 Hz), 30.9 (d, $^3J_{PC}$ = 14.6 Hz), 22.6 (d, $^3J_{PC}$ = 1.5 Hz), 16.3 (d, $^3J_{PC}$ = 3.0 Hz), 16.2 (d, $^3J_{PC}$ = 3.0 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 20.8; MS (CI) m/z 278 ($[M + H]^+$, 100); ESI-HRMS (EI) m/z calcd for $C_{11}H_{20}NO_5P$ ($[M]^+$) 277.1079, found 277.1099.

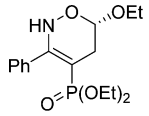


Ethyl ((4R,4aR*,7aS*)-3-methyl-4a,5,6,7a-tetrahydro-4H-furo-[3,2-e][1,2]oxazine-4-carboxylate (**5cb**):* (33 mg, 61%) obtained as colorless oil from bromooxime **1c** (50 mL from a 5 mM solution of **1c** in CH_2Cl_2, 0.25 mmol), anhydrous Na_2CO_3 (53 mg, 0.5 mmol), and 2,3-dihydrofuran **3b** as described in ***method B***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/pentane 20:80). Data for the major diastereoisomer: IR (NaCl) ν_{max} 2947, 1727, 1695, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.64 (d, $^3J_{HH}$ = 6.6 Hz, 1H), 4.21 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 4.02−3.98 (m, 1H), 3.89−3.84 (m, 1H), 3.29−3.21 (m, 1H), 3.17 (d, $^3J_{HH}$ = 3.0 Hz, 1H), 2.17 (s, 3H), 1.68−1.61 (m, 2H), 1.28 (t, $^3J_{HH}$ = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 162.8, 100.9, 67.7, 61.9, 44.7, 39.1, 29.1, 21.9, 14.0; MS (CI) m/z 214 ($[M + H]^+$, 100); ESI-HRMS (CI) m/z calcd for $C_{10}H_{16}NO_4$ ($[M + H]^+$) 214.1079, found 214.1091.

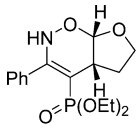


*Diethyl (6-ethoxy-3-methyl-5,6-dihydro-2H[1,2]oxazin-4-yl)-phosphonate (**6da**):* (280 mg, 82%) obtained as colorless oil from chlorooxime **1d** (305 mg, 1 mmol), Et_3N (168 μL, 1.2 mmol), and ethyl vinyl ether **3a** as described in ***method A***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/pentane 35:65). IR (NaCl) ν_{max} 3492, 2978, 2926, 1442, 1259, 1039, 894 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72−7.69 (m, 2H), 7.40−7.34 (m, 3H), 5.37 (t, $^3J_{HH}$ = 3.3 Hz, 1H), 4.16−3.85 (m, 5H), 3.64 (dq, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 2.95 (ddd, $^2J_{HH}$ = 15.3 Hz, $^3J_{PH}$ = 12.3 Hz, $^3J_{HH}$ = 3.3 Hz, 1H), 2.70 (ddd, $^2J_{HH}$ = 15.3 Hz, $^3J_{PH}$ = 6.9 Hz, $^3J_{HH}$ = 3.3 Hz, 1H), 1.28−1.21 (m, 6H), 1.14 (t, $^3J_{HH}$ = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (d, $^2J_{PC}$ = 1.4 Hz), 134.8, 130.0, 129.2, 127.5, 94.2 (d, $^3J_{PC}$ = 6.4 Hz), 65.0 (d, $^2J_{PC}$ = 7.0 Hz), 64.3, 64.2 (d, $^2J_{PC}$ = 7.5 Hz), 51.7 (d, $^1J_{PC}$ = 162.2 Hz), 36.8, 16.2 (d, $^3J_{PC}$ = 5.6 Hz), 16.0 (d, $^3J_{PC}$ = 6.0 Hz), 14.9; ^{31}P NMR (120 MHz, $CDCl_3$) δ 15.8; ESI-HRMS (EI) m/z calcd for $C_{14}H_{19}NO_4P$ ($[M - OEt]^+$) 296.1052, found 296.1079.

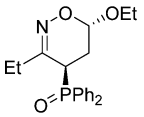
dx.doi.org/10.1021/jo501339c | J. Org. Chem. 2014, 79, 7607−7615



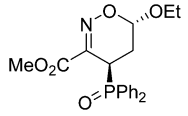
Diethyl ((4aS,7aS*)-3-phenyl 4a,5,6,7a-tetrahydro-2H-furo[3,2-e][1,2]oxazin-4-yl)phosphonate (**6db**):* (193 mg, 57%) obtained as colorless oil from chlorooxime **1d** (305 mg, 1 mmol), anhydrous Na_2CO_3 (212 mg, 2 mmol), and 2,3-dihydrofuran **3b** as described in ***method B***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/pentane 33:64). IR (NaCl) ν_{max} 3429, 2978, 1722, 1442, 1254, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80−7.77 (m, 2H), 7.42−7.37 (m, 3H), 5.98 (d, $^3J_{HH}$ = 5.4 Hz, 1H), 4.38−4.14 (m, 5H), 4.02 (q, $^3J_{HH}$ = 8.1 Hz, 1H), 3.40 (dtd, $^3J_{PH}$ = 10.2 Hz, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 5.4 Hz, 1H), 2.41−2.30 (m, 1H), 2.08−1.94 (m, 1H), 1.41 (td, $^3J_{HH}$ = 7.2 Hz, $^4J_{PH}$ = 0.6 Hz, 3H), 1.32 (td, $^3J_{HH}$ = 7.2 Hz, $^4J_{PH}$ = 0.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4 (d, $^2J_{PC}$ = 2.0 Hz), 133.7, 129.4, 129.3, 127.8, 102.0, 67.0, 65.8 (d, $^2J_{PC}$ = 7.0 Hz), 64.9 (d, $^2J_{PC}$ = 7.5 Hz), 61.9 (d, $^1J_{PC}$ = 155.8 Hz), 45.4 (d, $^2J_{PC}$ = 2.0 Hz), 28.4 (d, $^3J_{PC}$ = 9.1 Hz), 16.4 (d, $^3J_{PC}$ = 6.0 Hz), 16.2 (d, $^3J_{PC}$ = 5.5 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 14.9; ESI-HRMS (EI) *m/z* calcd for $C_{16}H_{22}NO_5P$ ($[M]^+$) 339.1236, found 339.1207.



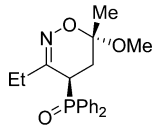
(4R,6S*)-4-(Diphenylphosphoryl)-6-ethoxy-3-ethyl-5,6-dihydro-4H[1,2]oxazine (**5ea**):* (271 mg, 76%) obtained as colorless oil from bromooxime **1e** (365 mg, 1 mmol), a saturated aqueous solution of $NaHCO_3$ (10 mL), and ethyl vinyl ether **3a** as described in ***method C***. (339 mg, 95%) obtained as colorless oil from bromooxime **1e** (365 mg, 1 mmol), a saturated aqueous solution of $NaHCO_3$ (10 mL), and ethyl vinyl ether **3a** as described in ***method D***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/*n*-hexane 34:66). IR (NaCl) ν_{max} 3430, 2977, 1438, 1191, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78−7.43 (m, 10H), 5.00 (bt, *J* = 2.3 Hz, 1H), 3.78−3.68 (m, 1H), 3.53−3.39 (m, 2H), 2.36−2.09 (m, 2H + 1H), 1.76−1.66 (m, 1H), 1.11 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 0.97 (t, $^3J_{HH}$ = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0 (d, $^2J_{PC}$ = 3.8 Hz), 132.2, 131.2 131.1, 131.0, 130.9, 129.0, 128.8, 128.7, 93.9 (d, $^3J_{PC}$ = 7.1 Hz), 63.2, 32.4 (d, $^1J_{PC}$ = 67.5 Hz), 29.2, 27.4, 14.8, 10.9; ^{31}P NMR (120 MHz, $CDCl_3$) δ 32.2; ESI-HRMS (CI) *m/z* calcd for $C_{20}H_{25}NO_3P$ ($[M + H]^+$) 358.1572, found 358.1554.



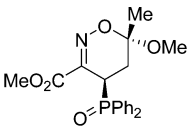
Methyl (4R,6S*)-4-(diphenylphosphoryl)-6-ethoxy-5,6-dihydro-4H[1,2]oxazine-3-carboxylate(**5fa**):* (329 mg, 85%) obtained as colorless oil from bromooxime **1f** (395 mg, 1 mmol), a saturated aqueous solution of $NaHCO_3$ (10 mL), and ethyl vinyl ether **3a** as described in ***method C***. (348 mg, 90%) obtained as colorless oil from bromooxime **1e** (395 mg, 1 mmol), a saturated aqueous solution of $NaHCO_3$ (10 mL), and ethyl vinyl ether **3a** as described in ***method D***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/*n*-hexane 50:50). IR (NaCl) ν_{max} 3452, 2930, 1733, 1438, 1191, 1118, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96−7.35 (m, 10H), 5.56 (dd, $^3J_{HH}$ = 3.2 Hz, $^3J_{HH}$ = 7.6 Hz, 1H), 4.05 (ddd, $^3J_{HH}$ = 3.7 Hz, $^3J_{HH}$ = 7.4 Hz, $^2J_{PH}$ = 12.9 Hz, 1H), 3.96 (dq, $^3J_{HH}$ = 7.0 Hz, $^2J_{HH}$ = 9.6 Hz, 1H), 3.67 (dq, $^3J_{HH}$ = 7.1 Hz, $^2J_{HH}$ = 9.6 Hz, 1H), 3.30 (s, 3H), 2.37 (tt, $^3J_{HH}$ = 3.5 Hz, $^2J_{HH}$ = 13.9 Hz, 1H), 1.86 (ddd, $^3J_{HH}$ = 7.6 Hz, $^2J_{HH}$ = 13.9 Hz, 1H), 1.17 (t, $^3J_{HH}$ = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 145.9 (d, $^2J_{PC}$ = 5.0 Hz), 132.6, 132.2, 131.6, 131.5, 131.0, 129.6, 128.9, 128.3, 98.5 (d, $^3J_{PC}$ = 1.6 Hz), 65.6, 52.8, 33.7 (d, $^1J_{PC}$ = 63.0 Hz), 24.9, 15.4; ^{31}P NMR (120 MHz, $CDCl_3$) δ 31.1; ESI-HRMS (CI) *m/z* calcd for $C_{20}H_{23}NO_5P$ ($[M + H]^+$) 388.1314, found 388.1320.



(4R,6S*)-4-(Diphenylphosphoryl)-3-ethyl-6-methoxy-6-methyl-5,6-dihydro-4H[1,2]oxazine(**5ed**):* (367 mg, 99%) obtained as a brown oil from bromooxime **1e** (365 mg, 1 mmol), a saturated aqueous solution of $NaHCO_3$ (10 mL), and 2-methoxypropene **3d** as described in ***method D***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/*n*-hexane 75:25). IR (NaCl) ν_{max} 3414, 2984, 1711, 1438, 1201, 906 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78−7.39 (m, 10H), 3.57−3.47 (m, 1H), 3.16 (s, 3H), 2.66−2.59 (m, 1H), 2.43−2.15 (m, 2H), 1.73−1.66 (m, 1H), 1.30 (s, 3H), 0.96 (t, $^3J_{HH}$ = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3 (d, $^2J_{PC}$ = 4.1 Hz), 133.0, 132.2, 131.0, 130.9, 130.8, 130.3, 128.8, 128.7, 95.9 (d, $^3J_{PC}$ =8.6 Hz), 49.2, 34.0 (d, $^1J_{PC}$ = 67.5 Hz), 32.7, 29.0, 21.3, 11.0; ^{31}P NMR (120 MHz, $CDCl_3$) δ 32.2; ESI-HRMS (CI) *m/z* calcd for $C_{20}H_{25}NO_3P$ ($[M + H]^+$) 358.1572, found 358.1567.

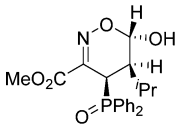


Methyl (4R,6S*)-4-(diphenylphosphoryl)-6-methoxy-6-methyl-5,6-dihydro-4H[1,2]oxazine-3-carboxylate (**5fd**):* (302 mg, 78%) obtained as a white solid from bromooxime **1f** (395 mg, 1 mmol), a saturated aqueous solution of $NaHCO_3$ (10 mL), and 2-methoxypropene **3d** as described in ***method D***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/*n*-hexane 75:25). Mp 158−159 °C; IR (NaCl) ν_{max} 2926, 1733, 1439, 1192, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85−7.43 (m, 10H), 4.06−3.96 (m, 1H), 3.35 (s, 3H), 3.15 (s, 3H), 2.42−2.31 (m, 1H), 2.16−2.09 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 151.3 (d, $^2J_{PC}$ = 4.5 Hz), 132.4, 132.2, 131.6, 131.5, 130.0, 129.9, 128.7, 128.6, 97.9 (d, $^3J_{PC}$ = 6.5 Hz), 52.5, 49.6, 32.7 (d, $^1J_{PC}$ = 63.5 Hz), 29.6, 20.8; ^{31}P NMR (120 MHz, $CDCl_3$) δ 32.0; ESI-HRMS (CI) *m/z* calcd for $C_{20}H_{23}NO_5P$ ($[M + H]^+$) 388.1314, found 388.1313.



Methyl (4R,5R*,6S*)-4-(diphenylphosphoryl)-6-hydroxy-5-isopropyl-5,6-dihydro-4H[1,2]oxazine-3-carboxylate (**7ff**):* (393 mg, 98%) obtained as a yellow oil from bromooxime **1f** (395 mg, 1 mmol), a saturated aqueous solution of $NaHCO_3$ (10 mL), and (*E*)-trimethyl((3-methylbut-1-en-1-yl)oxy)silane **3f**[25] as described in ***method D***. The crude product was purified by flash-column chromatography (SiO_2, AcOEt/*n*-hexane 34:66). IR (NaCl) ν_{max} 3062, 2927, 1726, 1438, 1191, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 8.11−7.39 (m, 10H), 5.39 (d, $^3J_{HH}$ = 9.1 Hz, 1H), 3.88 (d, $^2J_{PH}$ = 15.0 Hz, 1H), 3.31(s, 3H), 2.35 (dd, $^3J_{HH}$ = 6.4 Hz, $^3J_{HH}$ = 9.0 Hz, 1H), 1.70−1.59 (m, 1H), 0.82 (d, $^3J_{HH}$ = 6.7 Hz, 3H), 0.74 (d, $^3J_{HH}$ = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 143.7 (d, $^2J_{PC}$ = 5.5 Hz), 133.3, 132.7, 132.0, 131.9, 129.3, 128.7, 128.0, 126.3, 92.5, 52.7, 39.7 (d, $^3J_{PC}$ = 2.6 Hz), 33.7 (d, $^1J_{PC}$ = 62.9 Hz), 30.5 (d, $^2J_{PC}$ = 10.1 Hz), 20.3, 19.3; ^{31}P NMR (120 MHz, $CDCl_3$) δ 37.5; ESI-HRMS (CI) *m/z* calcd for $C_{21}H_{25}NO_5P$ ($[M + H]^+$) 402.1470, found 402.1474.

dx.doi.org/10.1021/jo501339c | J. Org. Chem. 2014, 79, 7607−7615



■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Dirección General de Investigación del Ministerio de Ciencia e Innovación (DGI, MINECO, CTQ2012-34323) as well as the Departamento de Educación, Universidades e Investigación del Gobierno Vasco and Universidad del País Vasco (GV, IT 422-10; UPV/EHU-UFI-QOSYC 11/22). We also thank UPV/EHU-SGIker technical support and Dr. G. Rubiales for computational resources, and HRMS and NMR spectra (MCINN, GV/EJ, European Social Fund).

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