HETEROCYCLES, Vol. 78, No. 2, 2009, pp. 369 - 387. © The Japan Institute of Heterocyclic Chemistry
Received, 29th July, 2008, Accepted, 19th September, 2008, Published online, 25th September, 2008.
DOI: 10.3987/COM-08-11508

STUDIES ON THE AMINO-HECK REACTIONS OF UNSATURATED KETONES *O*-PHOSPHINYLOXIMES FOR THE PREPARATION OF SUBSTITUTED PYRIDINES

Jia-Liang Zhu,[a,*] Yi-Lin Su,[a] Yu-Hui Chan,[a] I-Chia Chen,[b] and Chuan-Chen Liao[a]

a) Department of Chemistry, National Dong-Hwa University, Hualien 974, Taiwan, R.O.C.; b) Department of Chemistry, National Tsing Hua University, Hsinchu 300013, Taiwan, R.O.C.
E-mail: jlzhu@mail.ndhu.edu.tw

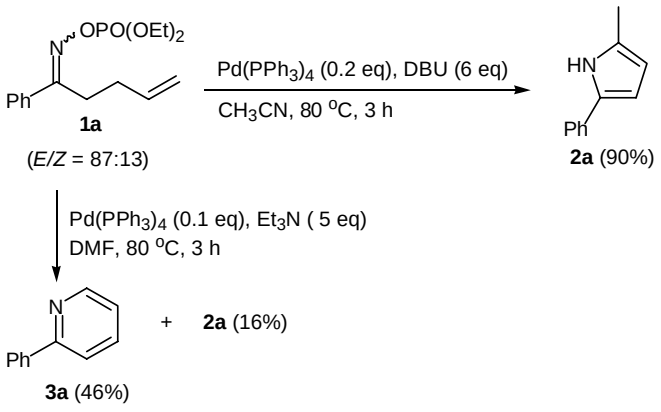
Abstract – The amino-Heck cyclization process has been applied into a range of γ,δ-unsaturated ketone *O*-diethylphosphinyloximes **1** and δ,ε-unsaturated ketone *O*-diethylphosphinyloximes **7**. Under the specific catalytic conditions developed by us, these substrates were found to preferentially undergo the 6-*endo* cyclization to give the formation of 2-substituted pyridines **3** and substituted methylpyridines **8**, respectively, in moderate to good yields. Besides, several interesting aspects on the effects of phosphinyl groups, solvents, bases and molecular sieves on the regioselectivity of the cyclization of **1** have also been realized.

INTRODUCTION

The palladium-catalyzed intramolecular Heck-type cyclization of unsaturated ketone oxime derivatives provides a conceptually powerful means for the preparation of aza-heterocycles.[1] According to literatures, a great variety of heterocyclic compounds such as pyrroles,[2-5] pyridines,[6] isoquinolines,[6b] azaazulenes,[7] and imidazoles,[8] has been achieved via this approach. For instance, there are several types oxime derivatives including γ,δ-unsaturated ketone *O*-pentafluorobenzoyloximes[1,2] and *O*-methylsulfonyloximes,[2] 3-butynyl 4-(methoxycarbonyl)-3-butynyl phenyl ketone *O*-pentafluorobenzoyloximes[5] and 3,3-difluoroallyl ketone *O*-pentafluorobenzoyloximes[3] were reported to undergo the cyclization under the catalysis of Pd(0) complexes to afford substituted pyrroles. As a complement to these existing methods, we have recently developed a novel amino-Heck protocol for the synthesis of substituted pyrroles by utilizing the readily prepared γ,δ-unsaturated ketone *O*-diethylphosphinyloximes **1** as the substrates.[9] In addition to their pronounced stability and the

efficiency for the cyclization, these precursors also exhibited the interesting regioselective tendency. For example, during the initial model studies with phenyl-4-penten-1-one *O*-diethylphosphinyloxime (**1a**), we discovered that under the reaction conditions of $Pd(PPh_3)_4/Et_3N/DMF$, which were commonly employed for other types oxime derivatives,[1,2,8] the reaction occurred preferentially in a 6-*endo* fashion to give the formation of 2-phenylpyridine (**3a**) in 46% yield. The desired product **2a** arising from the 5-*exo* cyclization was only formed in 16% yield (Scheme 1). After screening several reaction conditions, we found that **2a** could be achieved in almost quantitative yield (90%) by treating **1a** with $Pd(PPh_3)_4$ and 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU) in CH_3CN. These results suggest that with this type of oxime derivatives, the control of the regioselectivity of the cyclization can be attended to some extent with the adjustment of the catalytic conditions. We then applied the reaction conditions favouring the 5-*exo* cyclization [$Pd(PPh_3)_4$/DBU/CH_3CN] into a number of γ,δ-unsaturated *O*-diethylphosphinyloxime, to allow the generation of a series of 2-substituted 5-methylpyrroles and several indoles in good to high yields with no trace of by-products resulting from Beckmann rearrangement, a competing side process being frequently encountered by other types oxime derivatives.[1a]

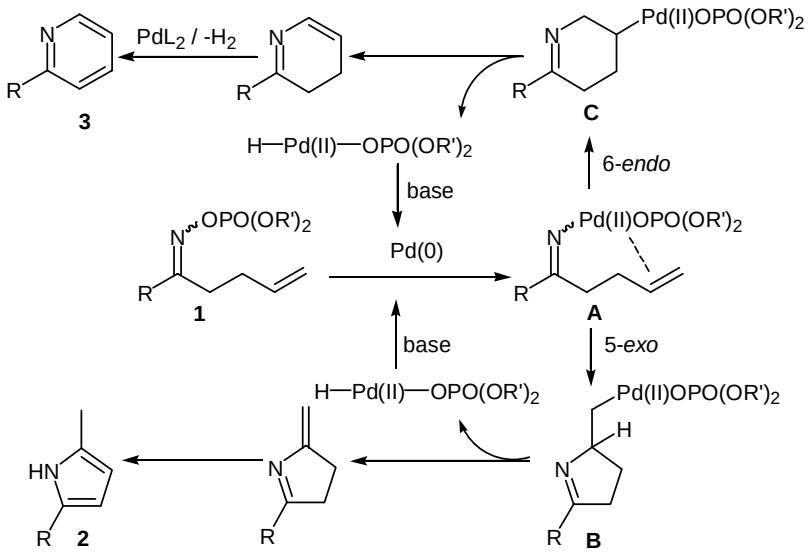
Scheme 1. Pd(0)-catalyzed cyclization of **1a** under the different reaction conditions



Similarly to other types of oxime derivatives, the cyclization of γ,δ-unsaturated ketone *O*-phosphinyloximes **1** should be initiated by the oxidative addition of **1** to Pd(0) to generate an alkylideneaminopalladium(II) intermediate **A** (Scheme 2). The subsequent 5-*exo* or 6-*endo* cyclization affords the σ-complex species **B** or **C**, respectively. From which, the substituted pyrroles **2** or pyridines **3** can be released through β-elimination followed by isomerization or oxidative dehydrogenation.[10]

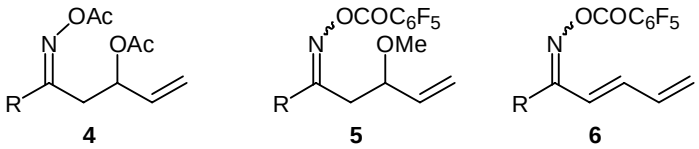
In the previous studies we did not further pursue the more favorable catalytic conditions for the 6-*endo* cyclization. Nevertheless, it should be noted that the formation of **3a** observed in our cases is quite unusual, because all of the γ,δ-unsaturated ketone oxime derivatives previously documented, differing from **1a** only by the functional groups on the nitrogen atom, were revealed to undergo the 5-*exo*

Scheme 2. Proposed mechanism of the Pd(0)-catalyzed cyclization of γ,δ-unsaturated ketone *O*-diethylphosphinyloximes



cyclization exclusively under the same reaction conditions to afford **2a** as the sole cyclization products.[1,2] On the other hand, for the substrates including *O*-pentafluorobenzoyloximes[6] and *O*-acetyloximes[10,11] used for preparing pyridines, a β- acetoxy, a β-methoxy or an α,β-unsaturated functionality was shown to be indispensable for the 6-*endo* cyclization in addition to the γ,δ-double bond. These substrates, as outlined in Figure 1 (**4**-**6**) are obviously more difficult to be accessed compared with **1**, and for some of them, the yields of the cyclization reactions are extremely low. For these reasons and due to the broad synthetic and biological utilities of the pyridinyl compounds,[12] we envisaged that it would be valuable if we could turn **1** into the useful precursors for the generation of pyridines. To this end, an extensive investigation was carried out, which eventually allowed us to find a catalytic system to further promote the 6-*endo* cyclization of **1** on the basis of what we had already accomplished in the previous studies. With its application, the synthesis of a range of 2-substituted pyridines was achieved mostly in good yields. In addition, we also applies the hitherto unexplored δ,ε-unsaturated ketone *O*-diethylphosphinyloximes to the cyclization process for the preparation of substituted methyl pyridines. Herein, we wish to report the details of these studies.

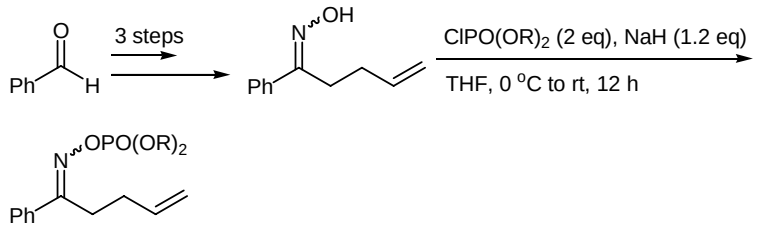
Figure 1. Oxime derivatives previously reported to undergo 6-*endo* cyclization



RESULTS AND DISCUSSION

We speculated that the unusual regioselectivity observed for **1a** under the conditions of $Pd(PPh_3)_4/Et_3N/DMF$ (Scheme 1) might be attributed to the unique coordination nature and/or the steric effect of the phosphinyl group. With true reason(s) being obscure for us, we began our investigation by surveying the substitution effect of phosphinyl groups on the regioselectivity. Accordingly, substrates **1b** and **1c**, with a bulkier diphenylphosphinyl and a smaller dimethylphosphinyl groups to replace the diethylphosphinyl moeity of **1a**, were prepared following the procedure previously developed for the preparation of **1a**.[9] As shown in Scheme 3, treatment of the *O*-hydroxyoxime intermediate derived from benzaldehyde in three synthetic steps with diphenyl chlorophosphate [$ClPO(OPh)_2$] and dimethyl chlorophosphate [$ClPO(OMe)_2$], respectively, in the presence of NaH readily led to the formation of **1b** and **1c** in high yields. Since the stereogeometry of **1a** had been proven to have no influence on the regioselectivity of the cyclization,[9] both **1b** (*E*/*Z* = 78:22) and **1c** (*E*/*Z* = 90:10) were used as the unseparated isomeric mixtures[13] for the subsequent investigation. The results of the cyclization reactions of **1a-c** under the same catalytic conditions are given in Table 1.

Scheme 3. Preparation of phenyl-4-penten-1-one *O*-phosphinylphinyloximes **1a-c**

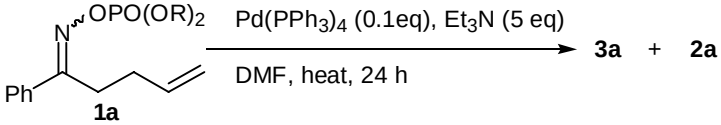


1a (R = Et, 83%, *E*/*Z* = 87:13)

1b (R = Ph, 79%, *E*/*Z* = 78:22)

1c (R = Me, 85%, *E*/*Z* = 90:10)

Table 1. Substitution effect of the phosphinyl groups on the Pd(0)-catalyzed cyclization



1a

entry[a]	substrate	yield (%)[b]		ratio of **3a**:**2a**
		3a	**2a**	
1	**1a** (R = Et)	46	16	74:26
2	**1b** (R = Ph)	30	53	36:64
3	**1c** (R = Me)	50	18	74:26

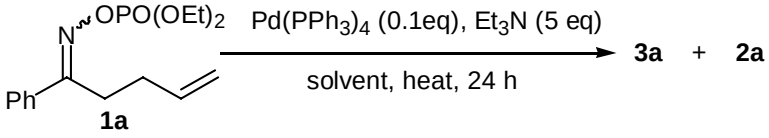
a) All reactions were performed using one equivalent of substrate in a 0.02 M DMF solution. b) Isolated yields.

Among three substrates, **1b** was shown to be mostly in favour of the 5-*exo* cyclization to give the highest ratio between **2a** and **3a** (64:36) (Table 1, entry 2). This result can presumably be rationalized in term of a

steric effect, i.e. a bulky diphenylphosphinyl group being prone to adopt the *exo* position in a cyclic transition state (Scheme 2, intermediate **B**) in order to minimize the conformational strain. However, what was not clear from these experiments was the same **3a**/**2a** ratios obtained from **1a** and **1c** (74:26) (Table 1, entries 1 and 3). The assumption that the steric difference between the diethylphosphinyl and the dimethylphosphinyl groups was not sufficiently large enough to make the difference in regioselectivity may somewhat account for this observation. Given the similar regioselectivity, reactivity and the preparative manner, the unsaturated *O*-diethylphosphinyl oximes should be more appropriate to be used as substrates than the corresponding *O*-dimethylphosphinyl oximes with regard to the much higher cost of $ClPO(OMe)_2$ than that of $ClPO(OEt)_2$. Consequently, we used *O*-diethylphosphinyl oximes as the substrates for the following experiments.

After the aforementioned investigation, we then turned our attention to identifying reaction conditions that would enhance the desired 6-*endo* cyclization. The previous experiments had already demonstrated that when accompanied with $Pd(PPh_3)_4$ and Et_3N, DMF was superior to CH_3CN as a solvent in respect of offering higher yield of **3a**.[9] On the basis of these results, several other solvent systems including tetrahydrofurane (THF), 1,4-dioxane, dimethyl sulfoxide (DMSO) and *N*,*N*-dimethyl acetamide (DMA) were investigated with **1a**. As shown in Table 2, the reactions carried out with THF and 1,4-dioxane proceeded sluggishly to afford only trace amounts of **3a** (5% and 6%) and **2a** (8%), along with recovered **1a** in 40% and 52% yields even after prolonged reaction times (Table 2, entries 1 and 2). Moreover, the use of DMSO also turned out to be unsuccessful in giving no detectable formation of **3a** and **2a**, and 80% of intact **1a** (entry 3). The reaction in DMA gave a comparable **3a**/**2a** ratio (70:30) with that obtained from DMF (Table 1, entry 1), but a much lower yield of **3a** (Table 2, entry 4). These disappointing results led us to look for other variants to modify reaction conditions.

Table 2. Effect of solvents on the palladium(0)-catalyzed cyclization of **1a**



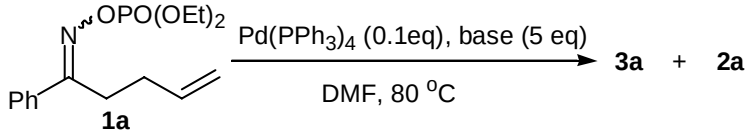
1a

entry[a]	solvent	yield (%)[d]		ratio of **3a**:**2a**
		3a	**2a**	
1[b]	THF	5	8	38:62
2[c]	1,4-dioxane	6	8	43:57
3[c]	DMSO	-	-	-
4[c]	DMA	28	12	70:30

a) All reactions were performed using 1 equiv of **1a** in a 0.02 M solution. b) The reaction was performed in refluxing THF. c) The reactions were carried out at 80 ^{o}C. d) Isolated yields.

Having proved DMF to be not displaceable for the 6-*endo* cyclization, we next evaluated a range of bases by using **1a** as the substrate and $Pd(PPh_3)_4$ as the catalyst. As illustrated in Table 3, when potassium carbonate and acetate were employed, the reactions displayed some preference for the 6-*endo* cyclization to give **3a** and **2a** in the ratios of 55:45 and 64:36, respectively, but the yields of **3a** were only modest (Table 3, entries 1, 2). Furthermore, we observed that the reaction performed with potassium *t*-butoxide only afforded a trace amount of **3a** (5%) as the only detectable cyclization product (entry 3), and the starting material easily decomposed within a short period of time (＜10 min) to yield a complex mixture under such strong basic conditions. The use of DBU produced only 9% of **3a** as the minor regioisomeric product together with 27% of **2a** (entry 4). In the case of 1,4-diazabicylo[2,2,2]octane (Dabco) (entry 5), the desired **3a** was also formed in low yield (19%) but as the major cyclization product (**3a**:**2a** 59:41). The use of pyridine resulted in the relative higher **3a**/**2a** ratio in comparison with that given in entry 5, but the yield of **3a** was still only moderate (29%) (entry 6). Finally, we were gratified to discover that with the employment of diisopropylethyl amine (DIPEA) as the base, the yield of **3a** could be significantly improved to 71% (entry 7), higher than those obtained from the other types of oxime derivatives.[6,11] Meanwhile, the competing 5-*exo* cyclization was also suppressed to a large extend as reflected by the ratio between **3a** and **2a** (83:17). Thus, the results given in entry 7 represented the best ones obtained from **1a** in terms of both yield of **3a** and **3a**/**2a** ratio.

Table 3. Effect of bases on the Pd(0)-catalyzed cyclization of **1a**



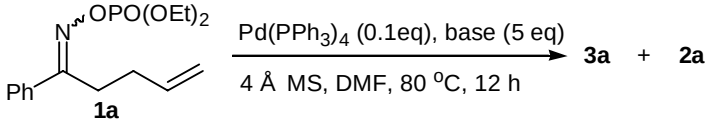
entry[a]	base	time (h)	yield (%)[b]		ratio of **3a**:**2a**
			3a	**2a**	
1	K_2CO_3	12	27	22	55:45
2	KOAc	12	27	15	64:36
3	*t*-BuO^-K^+	3	5	-	100:0
4	DBU	12	9	27	25:75
5	Dabco	12	19	13	59:41
6	pyridine	12	29	14	67:33
7	DIPEA	12	71	15	83:17

a) All reactions were performed using one equivalent of **1a** in a 0.02 M DMF solution.
b) Isolated yields.

In most cases listed in Table 3, we also noted the formation of 1-phenyl-pent-4-en-1-one (10-47% and 10% for entry 7) arising from the hydrolysis of **1a**. According to the literature reports,[9,14] such type of side reactions can be minimized in the presence of molecular sieves. To our surprise, the addition of

molecular sieves (MS) 4 Å to the reaction under the conditions of $Pd(PPh_3)_4$/DIPEA/DMF caused no apparent reduction of the ketone but a dramatic change in regioselectivity to give **2a** in 29% yield and a trace amount of **3a** (~ 3%) (**3a**:**2a** 9:91). To verify if this 5-*exo* promoting effect of MS was common, we combined a few above-described catalytic conditions [$Pd(PPh_3)_4/Et_3N$/DMF (Table 1, entry 1), $Pd(PPh_3)_4/K_2CO_3$/DMF (Table 3, entry 1) and $Pd(PPh_3)_4$/DBU/DMF (Table 3, entry 4)] with the use of MS and applied to **1a**. In contrast to the examples given in Table 1 and 3, these reactions were all overwhelmingly dominated by the 5-*exo* cyclization with MS, resulting in the drastically decreased ratios between **3a** and **2a** (Table 4, entries 2-4). The underlying causes of the above-mentioned base and MS effects on the regiochemistry are still not fully understood for us and will be subjected to our further exploration.

Table 4. Effect of molecular sieves 4 Å on the Pd(0)-catalyzed cyclization of **1a**



entry[a]	catalytic condition[b]	yield (%)[c]		ratio of **3a**:**2a**
		3a	**2a**	
1	$Pd(PPh_3)_4$/DIPEA	3	29	9:91
2	$Pd(PPh_3)_4/Et_3N$	16	56	22:78
3	$Pd(PPh_3)_4/K_2CO_3$	13	54	19:81
4	$Pd(PPh_3)_4$/DBU	3	42	7:93

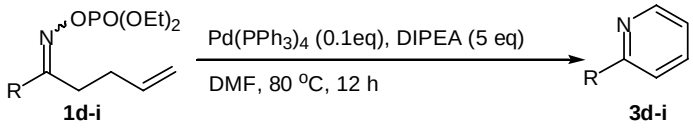
a) All reactions were performed using one equivalent of **1a** in a 0.02 M DMF solution.
b) 100 mg of MS 4 Å was used for 1 mmol of **1a**. c) Isolated yields.

The reaction conditions indicated in entry 7 of Table 3 were subsequently applied into a range of γ,δ-unsaturated ketone *O*-diethylphosphinyloximes with various substitutions (**1d-i**), which were all readily prepared from the corresponding aldehydes following the procedure given in Scheme 3. Among which, **1d-f** and **1h-i** were previously used for the preparation of the pyrroles,[9] while **1g** were synthesized for the first time.[13] As shown in Table 5, under the reaction conditions, the substrates possessing the aromatic (**1d**, **1f-g**) and heteroaromatic (**1e**) substituents cyclized preferentially in a 6-*endo* pathway to give rise to the 2-substituted pyridines **3d-g** as the major products in good yields (50-61%) (entries 1-4). These compounds could be easily separated from pyrrole byproducts (5-16%) by flash chromatography on basic aluminium oxide. We additionally observed that the electronic natures of the 4-substituents on the phenyl moiety seemed to have no effect on the 6-*endo* cyclization as illustrated by the almost equal yields of **3f** and **3g** (entries 3 and 4). However, the current catalytic system appeared to be less applicable to the cycloalkyl or alkyl substituted substrates. The cyclization reactions of **1h** and **1i** did not show

strong regioselective bias to furnish pyridines **3h** and **3i** in 26% and 20% yield, respectively (entries 5 and 6), together with the corresponding pyrroles in almost equal yields (23% and 18%, respectively).

To further extend the utility of the cyclization process, we also investigated the possibility of using the homologated δ,ε-unsaturated ketone *O*-diethylphosphinyloxime precursors for the generation of substituted methylpyridines. It was expected that by using these hitherto unexplored substrates, the complete control of the regioselectivity of the cyclization could be achieved. At first, several δ,ε-unsaturated ketone *O*-diethylphosphinyloxime **7a-e** were prepared in the analogous manner as for synthesizing **1**, except using pent-4-enylmagnesium bromide for the first addition step (Scheme 4).[13]

Table 5. Preparation of 2-substituted pyridines **3d-i** via the Pd(0)-catalyzed cyclization of **1d-i**

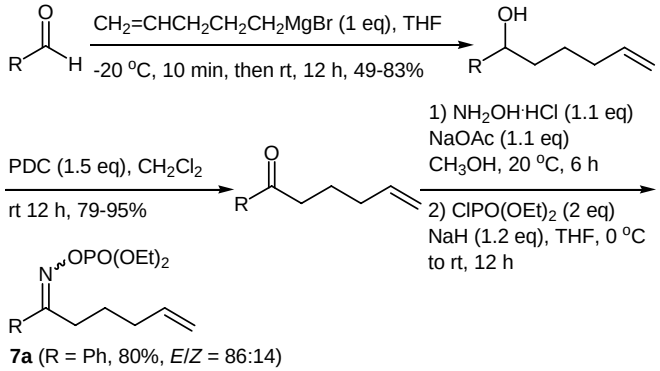


1d-i **3d-i**

entry[a]	starting material	product	yield (%)[b]
1	**1d** (R = 2-naphthalyl, *E*/*Z* = 93:7)	**3d**	60
2	**1e** (R = 4-pyridinyl, *E*/*Z* = 83:17)	**3e**	61
3	**1f** (R = 4-methoxyphenyl, *E*/*Z* = 70:30)	**3f**	51
4	**1g** (R = 4-fluorophenyl, *E*/*Z* = 84:16)	**3g**	50
5	**1h** (R = cyclohexyl, *E*/*Z* = 68:32)	**3h**	26
6	**1i** (R = *n*-heptyl, *E*/*Z* = 50:50)	**3i**	20

a) All reactions were performed using one equivalent of substrate in a 0.02 M DMF solution. b) Isolated yields.

Scheme 4. Synthesis of δ,ε-unsaturated ketone *O*-diethylphosphinyloxime precursors **7a-e**



7a (R = Ph, 80%, *E*/*Z* = 86:14)

7b (R = 4-pyridinyl, 79%, *E*/*Z* = 75:25)

7c (R = 4-methoxyphenyl, 81%, *E*/*Z* = 88:12)

7d(R = 4-fluorophenyl, 73%, *E*/*Z* = 85:15)

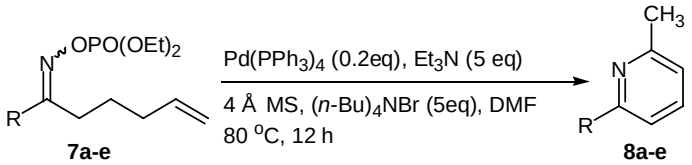
7e (R = *n*-heptyl, 63%, *E*/*Z* = 50:50)

We then explored the suitable cyclization conditions by using **7a** as the substrate**.** However, with the extension of one carbon unit, **7a** was found to be more difficult to cyclize than **1a** under most of the

reaction conditions given in Table 3 (entries 1 and 2, 4-7) and Table 1, to provide only small amounts of 2-methyl 6-phenylpyridine (**8a**) (< 10%) plus 60-86% of 1-phenyl-hex-5-en-1-one resulting from the hydrolysis. After several unsuccessful attempts, we discovered that the addition of 5 equivalents of tetrabutylammonium chloride [(*n*-Bu)$_4$NCl] to the reaction under the catalytic system of Pd(PPh$_3$)$_4$ (0.2 eq)/Et$_3$N (5 eq)/MS 4 Å/DMF could result in the generation of **8a** in 50 % yield. Based on this, it was further found that the yield of **8a** could be improved to 63% when (*n*-Bu)$_4$NCl was replaced by tetrabutylammonium bromide [(*n*-Bu)$_4$NBr]. The reaction conditions of Pd(PPh$_3$)$_4$ (0.2 eq)/Et$_3$N (5 eq)/MS 4 Å/DMF/(*n*-Bu)$_4$NBr (5eq) were then applied to **7b-e** and the results are compiled in Table 6. For **7b-d** bearing the aryl and heteroaryl substituents, the reactions offered the desired pyridines **8b-d** in modest to good yields (36-50%), as well as the ketone byproducts in 26-54% yields (entries 2-4). The relatively low-yielding formation of the pyridine was observed for **7e** substituted with an alkyl group. The reaction of which afforded **8e** in 21% yield, along with a large amount of the ketone (74%) (entry 5).

The cyclization products **3a**, **3d-i** and **8a-e** were all purified by flash chromatography on basic aluminium oxide and satisfactory spectra (^{1}H, ^{13}C-NMR, IR and HRMS) were obtained for them. For those known compounds (**3a**, **3d-h**, **8a-c**), the NMR data were found to agree well with those reported in the literature.[15]

Table 6. Preparation of substituted methylpyridines **8a-e** via the Pd(0)-catalyzed cyclization of **7a-e**



7a-e **8a-e**

entry[a,b]	substrate	product	yield (%)[c]
1	**7a**	**8a** (R = Ph)	63
2	**7b**	**8b** (R = 4-pyridinyl)	36
3	**7c**	**8c** (R = 4-methoxyphenyl)	50
4	**7d**	**8d** (R = 4-fluorophenyl)	42
5	**7e**	**8e** (R = *n*-heptyl)	21

a) All reactions were performed using one equivalent of substrate in a 0.02 M DMF solution. b) 100 mg of MS 4 Å was used for 1 mmol of oxime substrate. c) Isolated yields.

In conclusion, we have demonstrated that the regioselectivity of the amino-Heck reactions of γ,δ-unsaturated ketone *O*-diethylphosphinyloximes, particularly for those bearing aromatic or heteroaromatic substituents, could be deliberately controlled to a large extend with the adjustment of catalytic conditions. Thus, these compounds can serve as the versatile and useful precursors for the preparation of either substituted methylpyrroles or 2-substituted pyridines. Under the catalytic conditions

of $Pd(PPh_3)_4$/DIPEA/DMF, they were shown to preferentially undergo the 6-*endo* cyclization to afford 2-substituted pyridines in moderate to good yields. During the course of the studies, several interesting aspects regarding the effects of phosphinyl groups, solvents, bases and molecular sieves on the regioselectivity have also been observed, and the further investigation to disclose the true reasons behind these observations should be necessary. The synthetic scope of the protocol has been further expanded to the synthesis of substituted methylpyridines form δ,ε-unsaturated ketone *O*-diethylphosphinyloximes, thereby providing a new entry into this type of heterocyclic compounds.

EXPERIMENTAL

All of starting materials were obtained from commercial suppliers and used without further purification. Reactions were performed under an atmosphere of Nitrogen. Tetrahydrofuran was distilled from sodium-benzophenone, and dichloromethane, triethylamine, dimethylformamide, 1,4-dioxane, dimethyl sulfoxide and *N,N*-dimethylacetamide were distilled from calcium hydride before use. TLC analysis was carried out on Merck 25 DC-Alufolien Kieselgel 60F254 aluminum-backed plates visualised by using UV light, or by means of ethanolic solution of vanillin (5%) with sulphuric acid (5%). All of the compounds were purified by flash chromatography on Merck Art.9385 Kiesegel 60 silica gel (230-400 mesh) or Brockmann I basic aluminum oxide (~150 mesh). NMR spectra (^1H, ^{13}C) were recorded on a Bruker 400 spectrometer using deuteriochloroform ($CDCl_3$) as solvent. Chemical shifts measurements are reported in delta (δ) units. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants (J) are reported in Hertz (Hz). Infrared (IR) spectra were recorded on an IR-FT JASCO 410 spectrophotometer (neat) and resonances are reported in wave numbers (cm-1). High resolution mass spectra (HRMS) were determined by using a A. E. I. model MS-50 mass spectrometer in fast atom bombardment (FAB) or electron impact (EI) mode. Elemental analyses were performed on Perkin Elmer 240C apparatus.

General Procedure for the Preparation of γ,δ- and δ,ε-Unsaturated Phosphinyl Oxime Substrates from the Corresponding Ketones; 1-Phenyl-4-penten-1-one *O*-diethylphosphinyloxime (1a): To a solution of 1-phenyl-4-penten-1-one (317 mg, 1.98 mmol) in MeOH (8 mL), NaOAc (179 mg, 2.18 mmol) and $NH_2OH{\cdot}HCl$ (152 mg, 2.18 mmol) were successively added. The reaction mixture was stirred at 20 °C for 6 h, then diluted with CH_2Cl_2 (30 mL) and washed sequentially with H_2O (2 x 10 mL) and saturated NaCl aq soln (10 mL). After dried over anhydrous Na_2SO_4 and concentrated at ambient temperature, the crude hydroxyoxime was dissolved in anhyd THF (13 mL). The solution was cooled to 0 °C and added with NaH (60%, 95 mg, 2.38 mmol). Stirring was continued at 0 °C for another 20 min under N_2, before $(EtO)_2POCl$ (0.61 ml, 3.96mmol) was added dropwise in 3 min. The reaction mixture was allowed to warm to rt and continued to stir for 12 h. After concentration, the crude residue was

subjected to chromatographic purification on silica gel (hexane-EtOAc 5:1, 1:1) to afford **1a** as a mixture of two isomers (*E*/*Z* = 87:13) (513 mg, 83%).

IR (neat): 2983 , 1276 , 1034 , 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *Z*-isomer : δ 1.30 (td, J_1 = 7.1 Hz, J_2 = 0.7 Hz , 6H), 2.24 (dt, J_1 = 7.4 Hz, J_2 = 7.2 Hz , 2H), 2.74 (broad t, J = 7.6 Hz, 2H), 4.10-4.19 (m, 4H), 4.96-5.09 (m, 2H), 5.70-5.83 (m, 1H), 7.31-7.37 (m, 2H), 7.37-7.48 (m, 3H) ppm; *E*-isomer: δ 1.38 (td, J_1 = 7.1 Hz, J_2 = 0.7 Hz , 6H), 2.32 (dt, J_1 = 7.8 Hz, J_2 = 7.3 Hz , 2H), 2.95 (broad t, J = 7.9 Hz, 2H), 4.21-4.34 (m, 4H), 5.00 (broad d, J = 11.5 Hz, 1H), 5.04 (broad d, J = 17.1 Hz, 1H), 5.82 (dm, J = 17.1 Hz, 1H), 7.37-7.45 (m, 3H), 7.65 (broad d, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *Z*-isomer: δ 16.1 (d, J = 6.1 Hz), 30.2, 34.7, 64.5 (d, J = 5.5 Hz), 115.8, 127.5, 128.3, 129.6, 132.1, 136.5, 166.9 (d, J = 13.0 Hz) ppm; *E*-isomer: δ 16.2 (d, J = 6.3 Hz), 27.0, 30.5, 64.6 (d, J = 6.0 Hz), 115.8, 127.1, 128.7, 130.5, 133.6, 136.6, 166.7 (d, J = 13.4 Hz) ppm; HRMS-FAB: *m/z* $[M + H]^+$ calcd. for $C_{15}H_{23}O_4NP$: 312.1365; found: 312.1357.

1-Phenyl-4-penten-1-one *O*-diphenylphosphinyloxime (1b):The typical procedure for the preparation of **1a** was followed by using $ClPO(OPh)_2$ instead of $ClPO(OEt)_2$. From 210 mg (1.31 mmol) of 1-phenyl-4-penten-1-one, **1b** was obtained as a pale yellow oil after flash chromatography on silica gel (hexane-EtOAc 3:1, 1:1, 1:2) (422 mg, *E*/*Z* = 78:22, 79%).

IR (neat): 3074, 1687, 1591, 1489, 1442, 1298, 1188, 766, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 2.21 (td, J_1 = 7.8 Hz, J_2 = 7.3 Hz, 2H), 2.90 (broad t, J = 7.9 Hz, 2H), 4.96 (broad d, J = 9.0 Hz, 1H), 4.99 (broad d, J = 17.3 Hz, 1H), 5.72 (dm, J = 17.3 Hz, 1H) 7.17-7.24 (m, 3H), 7.27-7.53 (m, 10H), 7.63 (broad d, J = 8.1 Hz, 2H) ppm; *Z*-isomer: δ 2.18-2.26 (m, 2H), 2.76 (broad t, J = 7.5 Hz, 2H), 5.01-5.13 (m, 2H), 5.79-5.93 (m, 1H), 7.15-7.22 (m, 3H), 7.27-7.53 (m, 10H), 7.52 (broad d, J = 8.0Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 27.3, 30.4, 115.9, 120.4 (d, J = 4.7 Hz), 125.5, 127.3, 128.7, 129.8, 130.8, 133.0, 136.3, 150.6 (d, J = 7.3 Hz), 168.0 (d, J = 13.6 Hz) ppm; *Z*-isomer: δ 30.0, 34.7, 115.7, 119.8 (d, J = 4.1 Hz), 125.4, 127.3, 128.9, 129.6, 129.7, 131.9, 137.0, 150.5 (d, J = 7.3 Hz), 168.2 (d, J = 12.5 Hz) ppm; HRMS-FAB: *m/z* $[M + H]^+$ calcd. for $C_{23}H_{23}O_4NP$: 408.1365; found: 408.1367.

1-Phenyl-4-penten-1-one *O*-dimethylphosphinyloxime (1c): The typical procedure for the preparation of **1a** was followed by using $ClPO(OMe)_2$ instead of $ClPO(OEt)_2$. From 157 mg (0.98 mmol) of 1-phenyl-4-penten-1-one, **1c** was obtained as a yellow oil after flash chromatography on silica gel (hexane-EtOAc 4:1, 2:1) (236 mg, *E*/*Z* = 90:10, 85%).

IR (neat): 2954, 1641, 1572, 1444, 1281, 1043, 764, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 2.30 (td, J_1 = 7.7 Hz, J_2 = 7.2 Hz, 2H), 2.95 (broad t, J = 7.9 Hz, 2H), 3.88 (d, J = 11.1 Hz, 6H), 4.99 (broad d, J = 9.8 Hz, 1H), 5.02 (broad d, J = 17.0 Hz, 1H), 5.80 (dm, J = 17.0 Hz, 1H), 7.35-7.46 (m, 3H), 7.59-7.68 (m, 2H) ppm; *Z*-isomer: δ 2.21 (td, J_1 = 7.6 Hz, J_2 = 6.8 Hz, 2H), 2.73 (broad t, J = 7.6 Hz, 2H),

3.78 (d, J = 11.2 Hz, 6H), 4.95-5.06 (m, 2H), 5.70-5.81 (m, 1H), 7.30-7.34 (m, 2H) 7.35-7.46 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 27.0, 30.5, 55.1 (d, J = 6.1 Hz), 115.9, 127.2, 128.7, 130.6, 133.4, 136.5, 167.2 (d, J = 13.2 Hz) ppm; *Z*-isomer: δ = 30.2, 34.7, 54.9 (d, 6.0 Hz), 127.5, 128.3, 129.7, 131.9, 136.4, 167.3 (d, 12.5 Hz) ppm; HRMS-EI: *m/z* $[M]^+$ calcd. for $C_{13}H_{18}O_4NP$: 283.0973; found: 283.0979.

1-(2-Naphthalyl)-4-penten-1-one *O*-diethylphosphinyloxime (1d):The typical procedure for the preparation of **1a** was followed; 1-(2-naphthalyl)-4-penten-1-one (120 mg, 0.57 mmol) was used as starting material. Flash chromatography on silica gel (hexane-EtOAc 5:1, 1:1) gave **1d** as a yellow oil. Yield: 200 mg (97%) (*E*/*Z* = 93:7).

IR (neat): 2982, 1443, 1275, 1165, 1033, 917 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 1.41 (td, J_1 = 7.1 Hz, J_2 = 0.9 Hz, 6H), 2.39 (td, J_1 = 7.8 Hz, J_2 = 7.8 Hz, 2H), 3.08 (broad t, J = 7.9 Hz, 2H), 4.23-4.38 (m, 4H), 5.02 (broad d, J = 10.1 Hz, 1H), 5.07 (broad d, J = 17.1 Hz, 1H), 5.87 (dm, J = 17.1 Hz, 1H), 7.50-7.58 (m, 2H), 7.82-7.92 (m, 4H), 8.08 (s, 1H) ppm; *Z*-isomer: δ 1.30 (td, J_1 = 7.0 Hz, J_2 = 0.7 Hz, 6H), 2.27 (td, J_1 = 7.7 Hz, J_2 = 7.5 Hz, 2H), 2.85 (broad t, J = 7.6 Hz, 2H), 4.08-4.24 (m, 4H), 4.98-5.11 (m, 2H), 5.69-5.82 (m, 1H), 7.42-7.52 (m, 2H), 7.79-7.89 (m, 4H), 8.08 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 16.2 (d, J = 6.4 Hz), 26.8, 30.7, 64.7 (d, J = 5.8 Hz), 115.8, 123.9, 126.6, 127.3, 127.5, 127.7, 128.4, 128.7, 131.0, 132.9, 134.3, 136.6, 166.6 (d, J = 13.5 Hz) ppm; HRMS-EI: *m/z* $[M]^+$ calcd. for $C_{19}H_{24}O_4NP$: 361.1443; found: 361.1446.

1-(4-Pyridinyl)-4-penten-1-one *O*-diethyl phosphinyloxime (1e): The typical procedure for the preparation of **1a** was followed; 1-(4-pyridinyl)-4-penten-1-one (171 mg, 1.06 mmol) was used as starting material. Flash chromatography on silica gel (hexane-EtOAc 1:1, EtOAc) gave **1e** as a viscous oil. Yield: 262 mg (79%) (*E*/*Z* = 83:17).

IR (neat): 2984, 1595, 1544, 1410, 1274, 1032, 916 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 1.38 (t, J = 7.1 Hz, 6H), 2.31 (td, J_1 = 7.8 Hz, J_2 = 7.0 Hz, 2H), 2.94 (broad t, J = 7.8 Hz, 2H), 4.19-4.35 (m, 4H), 5.00 (broad d, J = 9.2 Hz, 1H), 5.03 (broad d, J = 17.3 Hz, 1H), 5.78 (dm, J = 17.3 Hz, 1H), 7.53 (d, J = 6.1 Hz, 2H), 8.67 (broad d, J = 6.1 Hz, 2H) ppm; *Z*-isomer: δ 1.29 (t, J = 7.1 Hz, 6H), 2.18-2.29 (m, 2H), 2.73 (broad t, J = 7.5 Hz, 2H), 4.08-4.19 (m, 4H), 4.92-5.08 (m, 2H), 5.70-5.90 (m, 1H), 7.21 (d, J = 6.1 Hz, 2H), 8.62-8.72 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 16.2 (d, J = 6.3 Hz), 26.4, 30.3, 64.9 (d, J = 5.9 Hz), 116.3, 121.2, 136.0, 141.3, 150.3, 164.9 (d, J = 13.9 Hz) ppm; *Z*-isomer: δ 16.1 (d, J = 6.0 Hz), 29.8, 34.2, 64.8 (d, J = 6.0 Hz), 116.2, 121.8, 135.9, 140.3, 150.0, 164.8 (d, J = 13.5 Hz) ppm; HRMS-FAB: *m/z* $[M + H]^+$ calcd. for $C_{14}H_{22}O_4N_2P$: 313.1317; found: 313.1318.

1-(4-Methoxyphenyl)-4-penten-1-one *O*-diethylphosphinyloxime (1f): The typical procedure for the preparation of **1a** was followed; 1-(4-methoxyphenyl)-4-penten-1-one (177 mg, 0.93 mmol) was used as starting material. Flash chromatography on silica gel (hexane-EtOAc 5:1, 1:1) gave **1f** as a pale yellow

oil. Yield: 257 mg (81%) (*E*/*Z* = 70:30).

IR (neat): 2974, 2929, 1606, 1514, 1255, 1032, 922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 1.37 (td, J_1 = 7.1 Hz, J_2 = 0.7 Hz, 6H), 2.31 (td, J_1 = 7.4 Hz, J_2 = 7.2 Hz, 2H), 2.91 (broad t, J = 7.9 Hz, 2H), 3.83 (s, 3H), 4.20-4.31 (m, 4H), 4.99 (broad d, J = 10.0 Hz, 1H), 5.03 (broad d, J = 17.2 Hz, 1H), 5.82 (dm, J = 17.2 Hz, 1H), 6.90 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 8.9 Hz, 2H) ppm; *Z*-isomer: δ 1.31 (td, J_1 = 7.0 Hz, J_2 = 0.6 Hz, 6H), 2.22 (td, J_1 = 7.6 Hz, J_2 = 7.4 Hz, 2H), 2.73 (broad t, J = 7.6 Hz, 2H), 3.83 (s, 3H), 4.11-4.20 (m, 4H), 4.95-5.05 (m, 2H), 5.72-5.89 (m, 1H), 6.91 (d, J = 8.9 Hz, 2H), 7.38 (d, J = 8.9 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 16.2 (d, J = 6.5 Hz), 26.8, 30.7, 55.3, 64.5 (d, J = 5.9 Hz), 114.0, 115.7, 125.9, 128.6, 136.7, 161.5, 166.1 (d, J = 13.2 Hz) ppm; *Z*-isomer: δ 16.1 (d, J = 6.4 Hz), 30.5, 34.5, 55.3, 64.4 (d, J = 6.0 Hz), 113.6, 124.0, 129.7, 136.6, 160.5, 165.8 (d, J = 12.1 Hz) ppm; HRMS-EI: *m/z* $[M + H]^+$ calcd. for $C_{16}H_{25}O_5NP$: 342.1470; found: 342.1473.

1-(4-Fluorophenyl)-4-penten-1-one *O*-diethylphosphinyloxime (1g): The typical procedure for the preparation of **1a** was followed; 1-(4-fluorophenyl)-4-penten-1-one (160 mg, 0.90 mmol) was used as starting material. Flash chromatography on silica gel (hexane-EtOAc 6:1, EtOAc) gave **1g** as a yellow oil. Yield: 216 mg (73%) (*E*/*Z* = 84:16); IR (neat): 3078, 2983, 1641, 1603, 1510, 1277, 1034, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 1.37 (t, J = 7.1 Hz, 6H), 2.28 (td, J_1 = 7.8 Hz, J_2 = 7.6 Hz, 2H), 2.91 (broad t, J = 7.9 Hz, 2H), 4.18-4.31 (m, 4H), 4.97 (broad d, J = 9.7 Hz, 1H), 5.01 (broad d, J = 17.4 Hz, 1H), 5.78 (dm, J = 17.4 Hz, 1H), 7.06 (tm, J = 8.5 Hz, 2H), 7.64 (dd, J_1 = 8.8 Hz, J_2 = 5.4 Hz, 2H) ppm; *Z*-isomer: δ 1.29 (t, J = 7.1 Hz, 6H), 2.19 (td, J_1 = 7.6 Hz, J_2 = 7.4 Hz, 2H), 2.71 (broad t, J = 7.6 Hz, 2H), 4.08-4.18 (m, 4H), 4.93-5.02 (m, 2H), 5.69-5.81 (m, 1H), 7.04-7.11 (m, 2H), 7.35 (dm, J = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 16.2 (d, J = 6.4 Hz), 26.9, 30.5, 64.7 (d, J = 6.0 Hz), 115.8 (d, J = 21.8 Hz), 116.0, 129.2 (d, J = 8.5 Hz), 129.6 (d, J = 3.1 Hz), 136.4, 164.1 (d, J = 251.0 Hz), 165.8 (d, J = 13.4 Hz) ppm; *Z*-isomer: δ 16.1 (d, J = 6.5 Hz), 30.2, 34.6, 64.6 (d, J = 6.0 Hz), 115.5 (d, J = 21.9 Hz), 115.9, 127.9 (d, J = 3.4 Hz), 129.8 (d, J = 8.5 Hz), 136.3, 163.1 (d, J = 250.1 Hz), 165.7 (d, J = 12.8 Hz) ppm; HRMS-FAB: *m/z* $[M]^+$ calcd. for $C_{15}H_{21}FO_4NP$: 329.1192; found: 329.1189.

1-Cyclohexyl-4-penten-1-one *O*-diethylphosphinyloxime (1h): The typical procedure for the preparation of **1a** was followed; 1-cyclohexyl-4-penten-1-one (97 mg, 0.58 mmol) was used as starting material. Flash chromatography on silica gel (hexane-EtOAc 10:1, 3:1) gave **1h** as a colourless oil. Yield: 128 mg (69%) (*E*/*Z* = 68:32).

IR (neat): 2981, 2931, 1666, 1641, 1450, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 1.16-1.35 (m, 5H), 1.32 (td, J_1 = 7.0 Hz, J_2 = 0.8 Hz, 6H), 1.63-1.82 (m, 5H), 2.18-2.43 (m, 5H), 4.09-4.25 (m, 4H), 4.97 (broad d, J = 10.2 Hz, 1H), 5.02 (broad d, J = 17.0 Hz, 1H), 5.78 (dm, J = 17.0 Hz, 1H) ppm; *Z*-isomer: δ 1.16-1.35 (m, 5H), 1.32 (td, J_1 = 7.0 Hz, J_2 = 0.8 Hz, 6H), 1.63-1.82 (m, 5H), 2.18-2.43 (m, 5H), 4.09-4.25 (m, 4H), 4.93-5.06 (m, 2H), 5.73-5.83 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$):

E-isomer: δ 16.2 (d, J = 6.3 Hz), 25.7, 25.8, 25.9, 27.3, 30.0, 43.8, 64.4 (d, J = 5.9 Hz), 115.4, 137.0, 172.8 (d, J = 12.2 Hz) ppm; Z-isomer: δ 16.2 (d, J = 6.3 Hz), 28.9, 29.8, 30.2, 30.4, 38.2, 64.4 (d, J = 5.9 Hz), 115.3, 137.4, 172.0 (d, J = 12.5 Hz) ppm; HRMS-FAB: *m/z* $[M + H]^+$ calcd. for $C_{15}H_{29}O_4NP$: 318.1834; found: 318.1829.

Dodec-1-en-5-one *O*-diethylphosphinyloxime (1i): The typical procedure for the preparation of **1a** was followed; dodec-1-en-5-one (136 mg, 0.75 mmol) was used as starting material. Flash chromatography on silica gel (hexane-EtOAc 10:1, 3:1) gave **1i** as a viscous oil. Yield: 162 mg (65%) (*E*/*Z* = 50:50).

IR (neat): 2929, 1277, 1036, 918 cm^{-1}; ^1H NMR of isomeric mixture (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.4 Hz, 3H), 1.21-1.32 (m, 8H), 1.35 (t, J = 7.1 Hz, 6H), 1.45-1.58 (m, 2H), 2.25-2.35 (m, 3H), 2.35-2.42 (m, 2H), 2.48 (broad t, J = 7.8 Hz, 1H) 4.12-4.29 (m, 4H), 5.00 (broad d, J = 10.2 Hz, 1H), 5.05 (broad d, J = 17.1 Hz, 1H), 5.80 (dm, J = 17.1 Hz, 1H) ppm; ^{13}C NMR of isomeric mixture (100 MHz, $CDCl_3$): δ 14.0, 16.1 (d, J = 6.3 Hz), 22.6, 25.8, 26.0, 28.1, 28.9, 29.2, 29.6, 29.8, 30.0, 31.6, 31.7, 33.2, 33.9, 64.3 (d, J = 5.8 Hz), 115.6, 115.7, 136.7, 136.9, 169.7 (d, J = 12.6 Hz), 169.8 (d, J = 11.9 Hz) ppm; HRMS-EI: *m/z* $[M - CH_3]^+$ calcd. for $C_{15}H_{29}O_4NP$: 318.1834; found: 318.1837.

1-Phenyl-5-hexen-1-one *O*-diethylphosphinyloxime (7a): The typical procedure for the preparation of **1a** was followed; 1-phenyl-5-hexen-1-one (160 mg, 0.92 mmol) was used as the starting material. Flash chromatography on silica gel (hexane-EtOAc 8:1, 3:1) gave **7a** as a viscous oil. Yield: 239 mg (80%) (*E*/*Z* = 86:14).

IR (neat): 2981, 1641, 1444, 1275, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 1.38 (td, J_1 = 7.0 Hz, J_2 = 0.8Hz, 6H), 1.63 (m, 2H), 2.14 (td, J_1 = 7.2 Hz, J_2 = 7.0 Hz, 2H), 2.86 (broad t, J = 8.0 Hz, 2H), 4.21-4.38 (m, 4H), 4.99 (broad d, J = 10.1 Hz, 1H), 5.02 (broad d, J = 17.1 Hz, 1H), 5.79 (dm, J = 17.1 Hz, 1H), 7.37-7.47 (m, 3H), 7.66 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 2H) ppm; *Z*-isomer: δ 1.30 (td, J_1 = 7.0 Hz, J_2 = 0.9 Hz, 6H), 1.54 (m, 2H), 2.05-2.13 (m, 2H), 2.65 (broad t, J = 7.7 Hz, 2H), 4.19-4.21 (m, 4H), 4.93-5.04 (m, 2H), 5.66-5.78 (m, 1H), 7.32-7.37 (m, 2H), 7.37-7.47 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 16.2 (d, J = 6.3 Hz), 25.7, 27.0, 33.6, 64.6 (d, J = 5.9 Hz), 115.5, 127.1, 128.6, 130.5, 133.6, 137.5, 167.3 (d, J = 13.2 Hz) ppm; *Z*-isomer: δ 16.1 (d, J = 6.3 Hz), 25.4, 33.0, 34.7, 64.4 (d, J = 5.8 Hz), 115.4, 127.4, 128.3, 129.5, 132.3, 137.6, 167.4 (d, J = 13.4 Hz) ppm; HRMS-FAB: *m/z* $[M + H]^+$ calcd. for $C_{16}H_{25}O_4NP$: 326.1521; found: 326.1514.

1-(4-Pyridinyl)-5-hexen-1-one *O*-diethylphosphinyloxime (7b): The typical procedure for the preparation of **1a** was followed; 1-(4-pyridinyl)-5-hexen-1-one (173 mg, 0.99 mmol) was used as the starting material. Flash chromatography on silica gel (hexane-EtOAc 5:1, EtOAc) gave **7b** as a yellow oil. Yield: 254 mg (79%) (*E*/*Z* = 75:25).

IR (neat): 3078, 2983, 1641, 1595, 1545, 1275, 1032, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 1.38 (t, J = 7.1 Hz, 6H), 1.65 (m, 2H), 2.13 (td, J_1 = 7.2 Hz, J_2 = 7.1 Hz, 2H), 2.83 (broad t, J = 8.0 Hz,

2H), 4.20-4.34 (m, 4H), 5.00 (broad d, J = 10.1 Hz, 1H), 5.02 (broad d, J = 17.5 Hz, 1H), 5.77 (dm, J = 17.5 Hz, 1H), 7.57 (d, J = 6.2 Hz, 2H), 8.67 (broad d, J = 6.2 Hz, 2H) ppm; *Z*-isomer: δ 1.29 (t, J = 7.0 Hz, 6H), 1.54-1.62 (m, 2H), 2.06-2.14 (m, 2H), 2.62 (broad t, J = 7.7 Hz, 2H), 4.09-4.20 (m, 4H), 4.95-5.01 (m, 2H), 5.66-5.76 (m, 1H), 7.21 (broad d, J = 6.2 Hz, 2H), 8.67-8.70 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 16.2 (d, J = 6.3 Hz), 25.5, 26.4, 33.5, 64.9 (d, J = 5.9 Hz), 115.9, 121.1, 137.1, 141.2, 150.4, 165.5 (d, J = 13.8 Hz) ppm; *Z*-isomer: δ 16.1 (d, J = 6.3 Hz), 25.1, 32.9, 34.3, 64.8 (d, J = 5.9 Hz), 115.8, 121.7, 137.2, 140.4, 150.1, 165.4 (d, J = 13.4 Hz) ppm; HRMS-FAB: *m/z* $[M + H]^+$ calcd. for $C_{15}H_{24}O_4N_2P$: 327.1483; found: 327.1474.

1-(4-Methoxyphenyl)-5-hexen-1-one *O*-diethylphosphinyloxime (7c): The typical procedure for the preparation of **1a** was followed; 1-(4-methoxyphenyl)-5-hexen-1-one (210 mg, 1.03 mmol) was used as the starting material. Flash chromatography on silica gel (hexane-EtOAc 10:1, 2:1) gave **7c** as a yellow oil. Yield: 296 mg (81%) (*E*/*Z* = 88:12).

IR (neat): 2981, 1608, 1514, 1255, 1032, 918, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 1.36 (t, J = 7.1 Hz, 6H), 1.65 (m, 2H), 2.12 (td, J_1 = 7.1 Hz, J_2 = 7.1 Hz, 2H), 2.81 (broad t, J = 8.0 Hz, 2H), 3.81 (s, 3H), 4.19-4.31 (m, 4H), 4.97 (broad d, J = 10.2 Hz, 1H), 5.01 (broad d, J = 17.1 Hz, 1H), 5.77 (dm, J = 17.1 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H) ppm; *Z*-isomer: δ 1.30 (t, J = 7.1 Hz, 6H), 1.55 (m, 2H), 2.03-2.10 (m ,2H), 2.63 (broad t, J = 7.6 Hz,, 2H), 3.81 (s, 3H), 4.09-4.21 (m, 4H), 5.01-5.10 (m, 2H), 5.66-5.79 (m, 1H), 6.86-6.93 (m, 2H), 7.37 (d, J = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 16.2 (d, J = 6.4 Hz), 25.9, 26.8, 33.6, 55.3, 64.5 (d, J = 5.9 Hz), 114.0, 115.5, 125.9, 128.6, 137.6, 161.5, 166.6 (d, J = 13.3 Hz) ppm; *Z*-isomer: δ 16.1 (d, J = 6.4 Hz), 25.8, 33.0, 34.5, 55.2, 64.4 (d, J = 6.1 Hz), 113.6, 115.3, 124.1, 129.7, 137.7, 160.5, 166.3 (d , J = 13.3 Hz) ppm; HRMS-FAB: *m/z* $[M]^+$ calcd. for $C_{17}H_{26}O_5NP$: 355.1549; found: 355.1539.

1-(4-Fluorophenyl)-5-hexen-1-one *O*-diethylphosphinyloxime (7d): The typical procedure for the preparation of **1a** was followed; 1-(4-fluorophenyl)-5-hexen-1-one (101 mg, 0.53 mmol) was used as the starting material. Flash chromatography on silica gel (hexane-EtOAc 6:1, 1:1) gave **7d** as a yellow oil. Yield: 132 mg (73%) (*E*/*Z* = 85:15).

IR (neat): 3076, 2983, 1641, 1602, 1512, 1275, 1063, 918, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 1.37 (td, J_1 = 7.1 Hz, J_2 = 0.7 Hz, 6H), 1.64 (m, 2H), 2.12 (td, J_1 = 7.2 Hz, J_2 = 7.0 Hz, 2H), 2.82 (broad t, J = 8.0 Hz, 2H), 4.19-4.31 (m, 4H), 4.98 (broad d, J = 10.1 Hz, 1H), 5.01 (broad d, J = 17.1 Hz, 1H), 5.76 (dm, J = 17.1 Hz, 1H), 7.07 (t, J = 8.8 Hz, 2H), 7.65 (dm, J = 8.8 Hz, 2H) ppm; *Z*-isomer: δ 1.30 (td, J_1 = 7.0 Hz, J_2 = 0.7 Hz, 6H), 1.55 (m, 2H), 2.03-2.10 (m, 2H), 2.63 (broad t, J = 7.7 Hz, 2H), 4.08-4.19 (m, 4H), 4.91-5.01 (m, 2H), 5.65-5.78 (m, 1H), 7.05-7.12 (m, 2H), 7.36 (dm, J = 8.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 16.2 (d, J = 6.4 Hz), 25.7, 26.9, 33.5, 64.6 (d, J = 6.0 Hz), 115.6, 115.7 (d, J = 22.4 Hz), 129.1 (d, J = 8.5 Hz), 129.7 (d, J = 3.5 Hz), 137.4, 164.2 (d, J = 251.0 Hz),

166.3 (d, J = 13.5 Hz) ppm; *Z*-isomer: δ 16.1 (d, J = 5.9 Hz), 25.5, 32.9, 34.7, 64.5 (d, J = 6.2 Hz), 115.5, 115.5 (d, J = 22.1 Hz), 128.1 (d, J = 3.8 Hz), 129.8 (d, J = 8.4 Hz), 137.5, 163.1 (d, J = 250.1 Hz), 166.2 (d, J = 13.0 Hz) ppm; HRMS-FAB: *m/z* $[M + H]^+$ calcd. for $C_{16}H_{24}FO_4NP$: 344.1427; found: 344.1433.

Tridec-1-en-6-one *O*-diethylphosphinyloxime (7e): The typical procedure for the preparation of **1a** was followed; tridec-1-en-6-one (87 mg, 0.44 mmol) was used as the starting material. Flash chromatography on silica gel (hexane-EtOAc 10:1, 5:1) gave **7e** as a colourless oil. Yield: 97 mg (63%) (*E*/*Z* = 50:50).

IR (neat):2979, 1641, 1277, 1066, 920 cm^{-1}; ^1H NMR of the isomeric mixture (400 MHz, $CDCl_3$): δ 0.85 (t, J = 6.5 Hz, 3H), 1.22-1.30 (m, 8H), 1.33 (td, J_1 =7.1 Hz, J_2 = 0.8 Hz, 6H), 1.44-1.53 (m, 2H), 1.55-1.65 (m, 2H), 2.03-2.10 (m, 2H), 2.22-2.29 (m, 2H), 2.32-2.39 (m, 2H), 4.12-4.23 (m, 4H), 4.96 (broad d, J = 11.6 Hz, 1H), 4.99 (broad d, J = 17.2 Hz, 1H), 5.75 (dm, J = 17.2 Hz, 1H) ppm; ^{13}C NMR of the isomeric mixture (100 MHz, $CDCl_3$): δ = 14.0, 16.2 (d, J = 6.4 Hz), 22.6, 25.0, 25.2, 25.8, 26.1, 28.2, 28.8, 28.9, 29.2, 29.7, 31.6, 31.7, 33.1, 33.2, 33.6, 33.8, 64.3 (d, J = 5.7 Hz), 115.3, 115.4, 137.5, 137.7, 170.3 (d, J = 12.6 Hz), 170.4 (d, J = 12.4 Hz) ppm; HRMS-FAB: *m/z* $[M + H]^+$ calcd. for $C_{17}H_{35}O_4NP$: 348.2304; found: 348.2297.

Typical Experimental Procedure for the Amino-Heck Reactions of γ,δ-Unsaturated O-Diethylphosphinyloximes for the Generation of 2-Substituted Pyridines; 2-Phenylpyridine (3a): Under a nitrogen atmosphere, $Pd(PPh_3)_4$ (37.5 mg, 0.032 mmol) and DIPEA (210 mg, 1.62 mmol) were sequentially added to a solution of **1a** (101 mg, 0.32 mmol) in anhyd DMF (16.2 mL, 0.02 M) at r.t. The resulting yellow suspension was quickly warmed to 80 °C and continued to stir for 12 h. The reaction mixture was then cooled to r.t., filtrated through a Celite pad and washed with EtOAc (80 mL). The filtrate was successively washed with H_2O (2 × 10 mL) and saturated NaCl aq soln (10 mL). After concentration, the crude products were subjected to chromatographic purification on aluminum oxide (hexane-EtOAc 5:1, 3:1) to afford **3a** in 71% yield (35.7 mg).

IR (neat): 1735, 1266, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19-7.26 (m, 1H), 7.40-7.52 (m, 3H), 7.70-7.79 (m, 2H), 8.00 (d, J = 7.3 Hz, 2H), 8.70 (d, J = 4.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.6, 122.1, 126.9, 128.8, 129.0, 136.7, 139.4, 149.7, 157.5 ppm; HRMS-FAB: *m/z* $[M]^+$ calcd. for $C_{11}H_9N$: 155.0735; found: 155.0733.

2-Heptylpyridine (3i): The typical procedure for the preparation of **3a** was followed; **1i** (158 mg, 0.47 mmol) was used as the starting material. Flash chromatography on aluminum oxide (hexane-EtOAc 15:1, 7:1) gave **3i** in 20% yield (16.8 mg).

IR (neat): 2954, 2925, 1591, 1570, 1473, 1435, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 6.9 Hz, 3H), 1.22-1.40 (m, 7H), 1.64-1.76 (m, 3H), 2.77 (t, J = 7.8 Hz, 2H), 7.09 (ddd, J_1 = 7.6 Hz, J_2 = 4.9 Hz, J_3 = 0.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.58 (td, J_1 = 7.6 Hz, J_2 = 1.8 Hz, 1H), 8.52 (broad d, J = 4.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 29.2, 29.4, 30.0, 31.8, 38.5, 120.8, 122.7,

136.2, 149.2, 162.6 ppm; HRMS-EI: *m/z* $[M - Et]^+$ calcd. for $C_{10}H_{14}N$: 148.1126; found: 148.1127.

Typical Experimental Procedure for the Amino-Heck Reactions of δ,ε-unsaturated ketone *O*-diethylphosphinyloximes for the Generation of Substituted Methylpyridines; 2-Methyl-6-phenylpyridine (8a): Under a nitrogen atmosphere, $Pd(PPh_3)_4$ (79.6 mg, 0.069 mmol) and molecular sieves (MS) 4 Å (34 mg) were added to a solution of **7a** (112 mg, 0.34 mmol) in anhyd DMF (17.2 mL, 0.02 M) at rt. The reaction mixture was stirred at r.t. for 10 min, then Et_3N (174 mg, 1.72 mmol) and $(n\text{-}Bu)_4NBr$ (555 mg, 1.72 mmol) were successively added. The mixture was quickly warmed to 80 °C and continued to stir for 12 h. The reaction mixture was then cooled to rt, filtrated through a Celite pad and washed with EtOAc (100 mL). The filtrate was successively washed with H_2O (2 × 15 mL) and saturated NaCl aq soln (15 mL). After concentration, the crude products were subjected to chromatographic purification on aluminum oxide (hexane-EtOAc 5:1, 3:1) to afford **8a** in 63% yield (36.7 mg).

IR (neat): 2954, 1589, 1448, 1444, 758, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H), 7.10 (d, J = 7.5 Hz, 1H), 7.39 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.4 Hz, 2H), 7.52 (d, J = 7.7 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.97 (d, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 117.6, 121.6, 127.0, 128.6, 128.7, 136.9, 139.8, 157.0, 158.4 ppm; HRMS-EI: *m/z* $[M]^+$ calcd. for $C_{12}H_{11}N$: 169.0891; found: 169.0889.

2-(4-Fluorophenyl)-6-methylpyridine (8d):

The typical procedure for the preparation of **8a** was followed; **7d** (97 mg, 0.28 mmol) was used as the starting material. Flash chromatography on aluminum oxide (hexane-EtOAc 10:1, 1:1) gave **8d** in 42% yield (22.2 mg).

IR (neat): 3062, 2925, 1601, 1456, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.62 (s, 3H), 7.09 (d, J = 7.6 Hz, 1H), 7.14 (tm, J = 8.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H), 7.96 (dm, J = 8.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.7, 115.5 (d, J = 21.5 Hz), 117.3, 121.5, 128.8 (d, J = 8.2 Hz), 135.9 (d, J = 2.9 Hz), 136.9, 155.9, 158.4, 163.4 (d, J = 247.8 Hz) ppm; HRMS-EI: *m/z* $[M]^+$ calcd. for $C_{12}H_{10}FN$: 187.0797; found: 187.0797; Anal. Calcd for $C_{12}H_{10}FN$: C, 76.99; H, 5.38; N, 7.48. Found: C, 76.63; H, 5.34; N, 7.51.

2-Heptyl-6-methylpyridine (8e): The typical procedure for the preparation of **8a** was followed; **7e** (95 mg, 0.27 mmol) was used as the starting material. Flash chromatography on aluminum oxide (hexane-EtOAc 15:1, 10:1) gave **8e** in 20% yield (10.5 mg).

IR (neat):2954, 1593, 1456, 789 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 6.8 Hz, 3H), 1.23-1.29 (m, 4H), 1.31-1.37 (m, 3H), 1.66-1.72 (m, 3H), 2.52 (s, 3H), 2.73 (broad t, J = 7.9 Hz, 2H), 6.94 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 24.6, 29.2, 29.5, 30.3, 31.8, 38.6, 119.4, 120.3, 136.4, 157.6, 162.0 ppm; HRMS-FAB: *m/z* [M +

H]$^+$ calcd. for $C_{13}H_{22}N$: 192.1752; found: 192.1757; Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32. Found: C, 81.64; H, 11.06; N, 7.30.

ACKNOWLEDGEMENTS

We are grateful to the National Science Council of Republic of China (Taiwan) and National Dong-Hwa University for financial support.

REFERENCES AND NOTES

1. For recent reviews, see: a) M. Kitamura and K. Narasaka, *Chem. Record*., 2002, 268; b) K. Narasaka, *Pure Appl. Chem*., 2003, **75**, 19.
2. H. Tsutsui and K. Narasaka, *Chem. Lett*., 1999, 45.
3. K. Sakoda, J. Mihara, and J. Ichikawa, *Chem. Commun*., 2005, 4684.
4. M. Kitamura, H. Yanagisawa, and M. Yamane, *Heterocycles*, 2005, **65**, 273.
5. S. Zaman, M. Kitamura, and A. D. Abell, *Aust. J. Chem*., 2007, **60**, 624.
6. T. Hosokawa, N. Shimo, K. Maeda, A. Sonoda, and S. Murahashi, *Tetrahedron Lett*., 1976, 383; b) H. Tsutsui and K. Narasaka, *Chem. Lett*., 2001, 526.
7. S. Chiba, M. Kitamura, O. Saku, and K. Narasaka, *Bull. Chem. Soc. Jpn*., 2004, **77**, 785.
8. S. Zaman, K. Mitsuru, and A. D. Abell, *Org. Lett*., 2005, **7**, 609.
9. J. L. Zhu and Y. H. Chan, *Synlett*, 2008, 1250.
10. R. A. Sheldon and J. K. Kochi, *Metal-Catalyzed Oxidations of Organic Compound*, Academic Press: New York, 1981; b) R. I. Rudakova, E. S. Rudakov, and A. K. Sheinkman, *Chem. Heterocycl. Compd*., 1976, 713.
11. M. Kitamura, D. Kudo, and K. Narasaka, *ARKIVOC*, 2006 (iii), 148.
12. J. A. Joule and K. Mills, *Heterocyclic Chemstry*, Blackwell Science Ltd, 2000, pp. 71–86.
13. The configurations the *E*, *Z*-isomers were assigned based on the chemical shifts of the α-methylene protons on the ^{1}H NMR spectrum. The *cis*-relationship between α-methylene protons and the phosphinyloxime group causes their signal to appear at higher frequency.
14. M. Kitamura, S. Zaman, and K. Narasaka, *Synlett*, 2001, 974.
15. For the characterization of **3a**, see: a) H. Ohta, M. Tokunaga, Y. Obora, T. Iwai, T. Iwasawa, T.

Fujihara, and Y. Tsuji, *Org. Lett*., 2007, **9**, 89; b) for **3d**, see: A. Núñez, A. Sánchez, C. Burgos, and J. Alvarez-Builla, *Tetrahedron*, 2004, **60**, 6217; c) for **3e**, see: G. Lunn, *J. Org. Chem*., 1992, **57**, 6317; d) for **3f**, see: M. Parmentier, P. Gros, and Y. Fort, *Tetrahedron*, 2005, **61**, 3261; e) for **3g**, see: O. P. Shkurko, S. G. Baram, and V. P. Mamaev, *Chem. Heterocycl. Compd*., 1983, 60; f) for **3h**, see: X. L. Cui and R. S. Brown, *J. Org. Chem*., 2000, **65**, 5653; g) for **5a**, see: H. Anderson, F. Almqvist, and R. Olsson, *Org. Lett*., 2007, **9**, 1335; h) for **5b**, see: I. Minoru, O. Tsukasa, and T. Masanao, *Chem. Pharm. Bull.*, 1985, **33**, 4755; i) for **5c**, see: S. A. Petrich, F. A. Hicks, D. R. Wilkinson, J. G. Tarrant, S. M. Bruno, M. Vargas, K. N. Hosein, J. T. Gupton, and J. A. Sikorski, *Tetrahedron*, 1995, **51**, 1575.