An efficient method for the synthesis of enol ethers and enecarbamates. Total syntheses of isoindolobenzazepine alkaloids, lennoxamine and chilenine[†]

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An efficient method for the synthesis of enol ethers and enecarbamates has been developed based on catalytic hydrosilane reduction of α -phosphonoxy enol ethers and α phosphonoxy enecarbamates. This method has been applied to the total syntheses of two isoindolobenzazepine alkaloids, lennoxamine and chilenine.

Enol ethers and enecarbamates play significant roles in organic synthesis as useful reactants in a variety of fundamental transformations including the Heck reaction,¹ radical cyclisation,² olefin metathesis,³ Diels–Alder cycloaddition,⁴ and oxidation.⁵ We have recently found that α -phosphonoxy enol ethers and α -phosphonoxy encarbamates act as versatile reactants in several palladium(0)-catalysed transformations and we have developed efficient strategies for the synthesis of marine polyether natural products⁶ and nitrogen-containing heterocycles.⁷ In this communication, we describe a palladium(0)-catalysed hydrosilane reduction of α -phosphonoxy enol ethers and α -phosphonoxy enecarbamates as a new, mild method for the synthesis of enol ethers and enecarbamates. Its application to the total syntheses of (\pm)-lennoxamine and (\pm)-chilenine, isoindolobenzazepine alkaloids, is also demonstrated.

It is well known that enol triflate (e.g., 1) can be reduced with *n*-Bu₃SnH and a catalytic amount of $Pd(PPh_3)_4$ to give an olefin (e.g., 2) (Scheme 1, eqn 1).⁸ However, instability of enol triflates is sometimes problematic, and it is generally difficult to synthesise α-heteroatom substituted acyclic enol triflates.^{6a} In addition, their preparation requires expensive reagents such as trifluoromethanesulfonic anhydride or N-phenyl bis(trifluoromethanesulfonimide). On the other hand, the phosphate counterpart is much easier to handle due to its stability and can be prepared by the less expensive diphenylphosphoryl chloride.[‡] Greene and co-workers have reported that treatment of acyclic α -phosphonoxy enol ether 3 with Et_3Al and $Pd(PPh_3)_4$ gave enol ether 4 in moderate yield (eqn 2).9a This method has been applied to the synthesis of a cyclic enecarbamate.9b On the other hand, we envisioned that α -phosphonoxy enol ethers 5a and α -phosphonoxy enecarbamates 5b can be reduced with a combination of hydrosilane and palladium catalyst under neutral conditions to provide the corresponding enol ethers 6a and enecarbamates 6b, respectively (eqn 3).10



Scheme 1 Concept of the present work.

As a model substrate, we used α -phosphonoxy enol ether 7, which was derived from the corresponding propionate by treatment with LDA followed by (PhO)₂P(O)Cl. Reduction of 7 was screened with several hydrosilanes in the presence of a palladium catalyst under various conditions, and the results are summarised in Table 1. Treatment of 7 with 5 equiv. of Et₃SiH and catalytic Pd(PPh₃)₄ in DMF at 60 °C provided (Z)-enol ether **8a** along with its (*E*)-isomer **8b** in 86% combined yield (**8a–8b** = ca. 2:1) (entry 1). Unfortunately, stereochemical scrambling of the double bond was significant in this case. We then surveyed several reaction conditions. Among the hydrosilanes examined, Me₂PhSiH provided the best result (entry 2). Thus, exposure of 7 to 5 equiv. of Me₂PhSiH and 10 mol% of Pd(PPh₃)₄ in DMF at 50 °C gave enol ethers 8a,b in 89% yield as a ca. 5.6 : 1 mixture of stereoisomers. The stereoselectivity of the reduction was increased by the use of the less bulky Me₂PhSiH and was significantly reduced using the more bulky MePh₂SiH or Ph₃SiH (entries 3 and 4). (Me₃Si)₃SiH was ineffective as a hydride source (entry 5). An attempt to use Ph_2SiH_2 resulted in significant isomerisation of the double bond (entry 6). When the reaction was performed using Me₂PhSiH at room temperature, isomerisation of the double bond was further suppressed, but the yield of 8a,b declined slightly (entry 7). Although we have also attempted the reduction of 7 with *n*-Bu₃SnH or *n*-Bu₃GeH, these hydride sources proved to be ineffective; we only observed extensive homocoupling of these reagents under the conditions

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Table 1 Screening of conditions

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	Entry	Hydrosilane	Cone angle/deg	D (Si-H)/kJ mol ⁻¹	Yield (%)	$Z-E^a$
	1	Et ₃ SiH	132	398.0	86	2.0:1
	2	Me ₂ PhSiH	122	364.0	89	5.6 : 1
	3	MePh ₂ SiH	136	359.2	78	2.5:1
	4	Ph ₃ SiH	145	354.8	87	1.3:1
	5	(Me ₃ Si) ₃ SiH	182	351.0	Trace	N/A
	6	Ph ₂ SiH ₂		377.8	89	1.4:1
	7 ^b	Me ₂ PhSiH	122	364.0	70	9.1 : 1

"Ratio of **8a** and **8b** was determined based on ¹H NMR spectra (500 MHz) of a purified mixture of **8a,b**. ^{*b*} The reaction was performed at room temperature.

established for Me₂PhSiH. In addition, we examined the use of additives such as LiCl or CuI, but these additives were found to inhibit the reaction completely.¹¹ Screening of catalysts including Pd(PPh₃)₄, Pd(OAc)₂-(2-furyl)₃P, Pd(OAc)₂-Cy₃P, and Pd(OAc)₂-(*o*-dicyclohexylphosphino)biphenyl revealed that Pd(PPh₃)₄ was the catalyst of choice.

We postulated a plausible reaction mechanism of the present process based on several related literature precedents¹² (Scheme 2). Thus, the present catalytic reaction starts with oxidative addition of a hydrosilane (R₃Si–H) into a palladium(0) complex to form a R₃Si–Pd(II)–H intermediate. Two pathways are possible for association of the intermediate with R'–X (*e.g.*, **7**) and subsequent σ -bond metathesis. Finally, reductive elimination affords the product R'–H (*e.g.*, **8**) and regenerates the initial palladium(0) complex.



Scheme 2 Plausible mechanistic considerations.

Interestingly, it seems that the degree of isomerisation of the double bond moderately correlates with the steric bulkiness of hydrosilanes, except for Ph_2SiH_2 .¹³ The steric bulkiness of the R group should be detrimental for association of $R_3Si-Pd(II)-H$ with R'X and subsequent σ -bond metathesis, thereby lowering the rate of these steps and possibly resulting in unfavourable isomerisation. It can be considered that re-addition of the $R_3Si-Pd(II)-H$ complex to the product R'-H followed by elimination would also cause isomerisation of the double bond. Thus, the

degree of isomerisation may also depend on the activity of the R_3Si –Pd(II)–H complex adding to the product R'–H. We speculate that the observed isomerisation may be attributed to these two factors. The bond strength of hydrosilanes is another factor that might influence the stereochemical outcome, because the catalytic cycle of the present reaction should start with oxidative insertion of a palladium(0) catalyst into an Si–H bond. However, as shown in Table 1, the bond strength of the hydrosilanes¹⁴ does not correlate with the observed stereoselectivity.

It should be noted here that another catalytic cycle that involves oxidative addition of 7 into a palladium(0) complex to form a R'-Pd(II)-X intermediate, followed by transmetallation with a hydrosilane, may also be possible. At present, we cannot rule out the possibility of this catalytic cycle operating in our case, although Masuda *et al.* have demonstrated that oxidative addition of a silane bond into a palladium(0) complex must be the key for the catalytic silylation of aryl halides with triethoxysilane.^{12c}

We next applied the optimal conditions for the reduction of a series of α -phosphonoxy enol ethers and α -phosphonoxy enecarbamates, which were prepared from the corresponding esters and imides, respectively, by treating them with KHMDS-(PhO)₂P(O)Cl (Table 2). A variety of cyclic and acyclic enol ethers and enecarbamates could be synthesised in good to excellent yields according to our method. Reduction of 10a,b (ca. 1 : 1 mixture of stereoisomers) in DMF at 60 °C gave enol ethers 11a (36%) and 11b (9%), and 10b was recovered in 43% yield (entry 1). In DMF at 135 °C, the reduction proceeded smoothly to provide a mixture of 11a and 11b in 58% and 19% yields, respectively (entry 2). These results were attributable to the reactivity difference between 10a and 10b, the latter of which was less reactive due to steric hindrance. The vinyl ether 14§ was synthesised from the corresponding acetate 12 in 82% yield for the two steps (entry 3). In this case, no potentially competitive intramolecular Heck coupling was observed. Sterically encumbered 1-adamantyl acetate 15 was efficiently delivered to vinyl ether 17¹⁵ in 63% overall yield (entry 4). The medium-sized lactam 18 was efficiently transformed to the corresponding cyclic enecarbamate 20 in 68% yield (entry 5). In the case of 22, a moderate reactivity difference between the aryl bromide and the α -phosphonoxy enecarbamate functionalities was observed (entry 6). This selectivity was further enhanced by

Table 2 Application to a variety of substrates



^{*a*} Reaction conditions: KHMDS, (PhO)₂P(O)Cl, THF–HMPA, –78 °C; then Me₂PhSiH (5 equiv.), Pd(PPh₃)₄ (10 mol%), DMF, 60 °C. ^{*b*} The reduction was performed at 135 °C. ^{*c*} The reduction was performed at room temperature. ^{*d*} **10b** was recovered in 43% yield.

performing the reaction with 1.2 equiv. of Me₂PhSiH and 10 mol% of Pd(PPh₃)₄ in DMF at room temperature, giving **23** in 73% yield for the two steps (entry 7). In some cases, a small amount (*ca.* 5%) of over-reduced product was also isolated, although the mechanism underlying its formation is elusive.¹⁶

Finally, we applied our methodology to the total syntheses of (\pm) -lennoxamine (**25**)^{17,18} and (\pm) -chilenine (**26**),^{19,20} isoindolobenzazepine alkaloids isolated from Chilean barberries *Berberis darwinii* and *Berberis empetrifolia*, respectively. Our synthesis plan is illustrated in Scheme 3. The enamide **27** was envisioned as the common intermediate for **25** and **26**. The isoindolinone systems of **25** and **26** were to be constructed by radical cyclisation and palladium-catalysed cyclisation, respectively. Chemoselective reduction of α -phosphonoxy enamide **28** would provide **27**. This reaction was planned based on the observed reactivity difference between the aryl bromide and α -phosphonoxy enecarbamate functionalities of **22** (Table 2, entry 7).

The synthesis started with treatment of 3,4-methylenedioxyphenylacetic acid **29** with thionyl chloride followed by coupling with aminoacetaldehyde dimethylacetal to provide amide **30** in good yield (Scheme 4). The Pomeranz–Fritsch-type cyclisation²¹ of **30** afforded enecarbamate **31** in 59% yield. Hydrogenation of the double bond within **31** gave lactam **32** in 83% yield. Despite several attempts, *N*-acylation of **32** under the standard



Scheme 3 Synthesis plan toward lennoxamine and chilenine.

conditions (*n*-BuLi or LiN(SiMe₃)₂, HMPA, THF; then 2-bromo-5,6-dimethoxybenzoyl chloride^{18b}) met with failure. However, treatment of **32** with 2-bromo-5,6-dimethoxybenzoyl chloride in the presence of 4 Å molecular sieves (ClCH₂CH₂Cl, 65 °C) gave imide **33** in a near-quantitative yield. After conversion of **33** into *a*-phosphonoxy enamide **28**, chemoselective hydrosilane reduction was executed by exposing **28** to Me₂PhSiH and Pd(PPh₃)₄ catalyst in DMF at 80 °C, affording enamide **27**¹⁸ⁱ in 61% yield for the two steps. Finally, according to Funk *et al.*'s procedure, radical



Scheme 4 Reagents and conditions: (a) SOCl₂, reflux; (b) aminoacetaldehyde dimethylacetal, pyridine, CH₂Cl₂, room temperature, 99%; (c) concentrated HCl, AcOH, room temperature, 59%; (d) H₂, 10% Pd/C, MeOH, room temperature, 83%; (e) 2-bromo-5,6-dimethoxybenzoyl chloride, 4 Å molecular sieves, ClCH₂CH₂Cl, 65 °C, 99%; (f) KHMDS, (PhO)₂P(O)Cl, THF–HMPA, -78 °C; (g) Me₂PhSiH, Pd(PPh₃)₄, DMF, 80 °C, 61% (two steps); (h) *n*-Bu₃SnH, AIBN, benzene, 105 °C, 67% (+ debrominated **27**, 25%); (i) Pd(PPh₃)₄, KOAc, *n*-Bu₄NCl, DMF, 110 °C, 84% (+ recovered **27**, 9%).

cyclisation of **27** under tin hydride conditions (*n*-Bu₃SnH, AIBN, benzene, 105 °C)^{18i,22} furnished (\pm)-lennoxamine **25** in 67% yield along with 25% yield of debrominated **27**. The spectroscopic data (¹H, ¹³C NMR, HRMS) of synthetic **25** were in full accordance with those reported in the literature.¹⁷ Thus, the total synthesis of (\pm)-lennoxamine was accomplished in seven steps (20% overall yield) from commercially available **29**. On the other hand, palladium-catalysed cyclisation of **27** was smoothly achieved using 10 mol% of Pd(PPh₃)₄, KOAc, and *n*-Bu₄NCl in DMF at 110 °C for 14 h,²³ affording dehydrolennoxamine **34** in 84% yield along with 9% of recovered **27**. Since the spectroscopic data (¹H, ¹³C NMR, HRMS) of **34** matched the reported data,^{18k} and since **34** has already been converted to **26** by Danishefsky and Fang,^{20a} the present synthesis constitutes the formal total synthesis of (\pm)-chilenine **26** (seven steps, 25% overall yield from **29**).

In conclusion, we have developed a new method for the synthesis of enol ethers and enecarbamates based on a catalytic hydrosilane reduction of α -phosphonoxy enol ethers and enecarbamates, respectively. The present method is applicable to the synthesis of a variety of cyclic and acyclic enol ethers and enecarbamates. In addition, we found that this reaction displays an interesting functional group selectivity between aryl bromides and α phosphonoxy enecarbamates. The short and highly efficient total syntheses of isoindolobenzoazepine alkaloids (\pm)-lennoxamine and (\pm)-chilenine have been accomplished based on the catalytic hydrosilane reduction of the α -phosphonoxy enamide **28** and subsequent radical cyclisation and palladium-catalysed cyclisation, respectively, as the key transformations. Further application of the present method to the total synthesis of natural products is currently under investigation.

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Notes and references

‡ The prices of these reagents (reagent grade) in the 2007 Aldrich catalogue are: trifluoromethanesulfonic anhydride = 6500 yen per 10 g (184 yen per mmol); *N*-phenyl bis(trifluoromethanesulfonimide) = 9100 yen per 5 g (650 yen per mmol); diphenylphosphoryl chloride (96% purity) = 6000 yen per 100 g (16 yen per mmol).

§ Representative experimental procedures. The synthesis of compound 14. To a solution of acetate 12 (46.6 mg, 0.147 mmol) in THF (4 mL) were added HMPA (0.127 mL, 0.730 mmol) and (PhO)₂P(O)Cl (0.152 mL, 0.733 mmol). The resultant mixture was cooled to -78 °C and treated with KHMDS (0.5 M solution in toluene, 0.88 mL, 0.44 mmol). After being stirred at -78 °C for 0.5 h, the reaction mixture was guenched with 3% NH₄OH, diluted with Et₂O, and allowed to warm to room temperature over 20 min. The resultant mixture was extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to provide crude α -phosphonoxy enol ether 13, which was passed through a short pad of florisil column and used immediately in the next reaction. To a solution of 13 in DMF (2 mL) were added Me₂PhSiH (0.112 mL, 0.731 mmol) and Pd(PPh₃)₄ (16.9 mg, 0.0146 mmol). After being stirred at 60 °C for 1 h, the reaction mixture was cooled to room temperature, diluted with EtOAc, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5 to 10% diethyl ether/hexane) gave 14 (36.1 mg, 82%) as a colourless oil.

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