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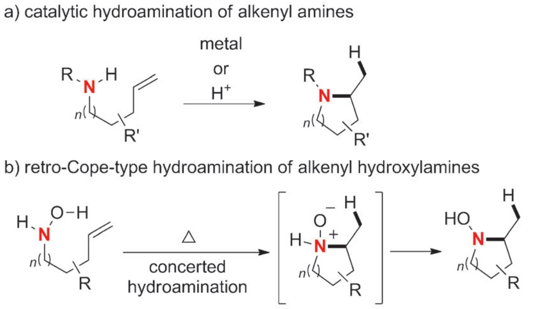
Inorganic-Base-Mediated Hydroamination of Alkenyl Oximes for the Synthesis of Cyclic Nitrones**

Xingao Peng, Benny Meng Kiat Tong, Hajime Hirao, and Shunsuke Chiba**

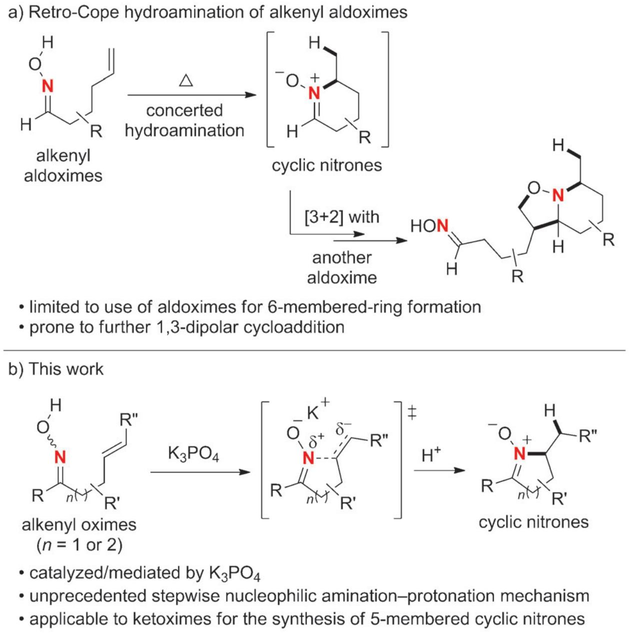
***Abstract:** A method based on hydroamination mediated by inorganic base was developed for the synthesis of cyclic nitrones from alkenyl oximes. DFT calculations of the reaction pathway suggested that this hydroamination could proceed through an unprecedented nucleophilic amination of the unactivated alkene by the oxime nitrogen atom. The transition state of this reaction is stabilized by an ionic interaction between a metal cation such as K^+ and the oxime oxygen and negatively charged alkene moiety.*

Hydroamination of unsaturated carbon–carbon bonds (alkenes or alkynes) is one of the most efficient methods to construct nitrogen-containing heterocyclic scaffolds in an atom- and step-economical manner.[1] The catalytic hydroamination of alkenyl amines has been extensively developed using various metal catalysts (alkali metals, transition metals, and f-block elements) as well as Brønsted acids (Scheme 1a). An analogous type of hydroamination, retro-Cope-type hydroamination (1,3-azaprotio cyclotransfer) of alkenyl hydroxylamines, is a powerful but mechanistically distinct alternative that proceeds through a concerted pericyclic mechanism whereby C−N and C−H bonds are formed concurrently to afford hydroxylamines (Scheme 1b).[2–6]



Scheme 1. Hydroamination of alkenyl amines and alkenyl hydroxylamines.

Retro-Cope hydroamination of alkenyl oximes has also been studied. This reaction could potentially provide cyclic nitrones through N_{sp^2}–C_{sp^3} bond formation, but the oxime substrates have been limited mostly to aldoximes for the formation of 6-membered rings (Scheme 2a).[7–11] Moreover, owing to their 1,3-dipole reactivity, the resulting nitrones are prone to further intermolecular [3+2] cycloaddition with another molecule of the alkenyl oxime. Given that cyclic nitrones are versatile synthons for various synthetic transformations[12] and for medicinal and biological applications,[13] it would be highly desirable to develop an efficient and controllable hydroamination of alkenyl ketoximes that enables the selective synthesis of cyclic nitrones. Herein, we report an operationally simple yet mechanistically distinct hydroamination of alkenyl oximes in a reaction catalyzed or mediated by an inorganic base (especially K_3PO_4), which allows the facile construction of a variety of cyclic nitrones (Scheme 2b).



Scheme 2. Hydroamination with alkenyl oximes.

It appears from the previously accumulated knowledge about retro-Cope hydroamination of alkenyl oximes that the conversion of γ,δ-unsaturated ketoximes into the corresponding 5-membered cyclic nitrones is particularly challenging. Indeed, heating oxime **1a**[14] in various solvents at 110–150 °C for 24 h resulted in the recovery of **1a** and provided only

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[*] Dr. X. Peng, B. M. K. Tong, Prof. H. Hirao, Prof. S. Chiba
Division of Chemistry and Biological Chemistry
School of Physical and Mathematical Sciences
Nanyang Technological University, Singapore 637371 (Singapore)
E-mail: shunsuke@ntu.edu.sg

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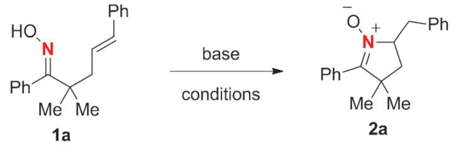
a very small amount of cyclic nitrone **2a** (0–6%; Table 1, entry 1). By contrast, the treatment of oxime **1a** with K_3PO_4 (10 mol%) in toluene at 110 °C brought the reaction to completion in 12 h, thereby yielding cyclic nitrone **2a** in 98% yield (entry 2). Solvent screening (entries 3–6) revealed that chlorobenzene was optimal for this transformation (at 120 °C for 4 h, 98% yield; entry 4) and the reactions in polar solvents such as DMSO and DMF became very sluggish (entries 5 and 6). With K_2CO_3 as the catalyst, the reaction was less efficient than with K_3PO_4 (entry 7). The use of a stronger base, KO*t*Bu, as the catalyst allowed the reaction temperature to be lowered to 60 °C (entries 8 and 9). Other stronger inorganic bases such as NaH and NaOMe also worked reasonably well (entries 10 and 11).

Table 1: Hydroamination of γ,δ-unsaturated ketoxime **1a**.[a]



Entry	Base [equiv]	Solvent	T [°C]	t [h]	Yield of **2a** [%][b]
1	none	various solvents[c]	110–150	24	0–6 (58–92)[d]
2	K_3PO_4 (0.1)	toluene	110	12	98
3	K_3PO_4 (0.1)	*o*-xylene	120	10	98
4	K_3PO_4 (0.1)	PhCl	120	4	98
5	K_3PO_4 (0.1)	DMSO	120	24	59 (29)[d]
6	K_3PO_4 (0.1)	DMF	120	24	12 (72)[d]
7	K_2CO_3 (0.1)	PhCl	120	24	21 (77)[d]
8	KO*t*Bu (0.1)	PhCl	120	0.6	96
9	KO*t*Bu (0.1)	PhCl	60	20	97
10	NaOMe (0.1)	PhCl	120	7	67 (30)[d]
11	NaH (0.1)	PhCl	120	7	88

[a] The reactions were carried out using 0.2 mmol of **1a** in the solvents (0.1 M). [b] Yield of isolated product. [c] The reactions were examined in toluene (110 °C, no product, 92% recovery of **1a**), *o*-xylene (150 °C, 4% yield of **2a** with 70% recovery of **1a**), PhCl (130 °C, 5% yield of **2a** with 78% recovery of **1a**), and DMSO (120 °C, 6% yield of **2a** with 58% recovery of **1a**). [d] Yield of recovered **1a** shown in parentheses.

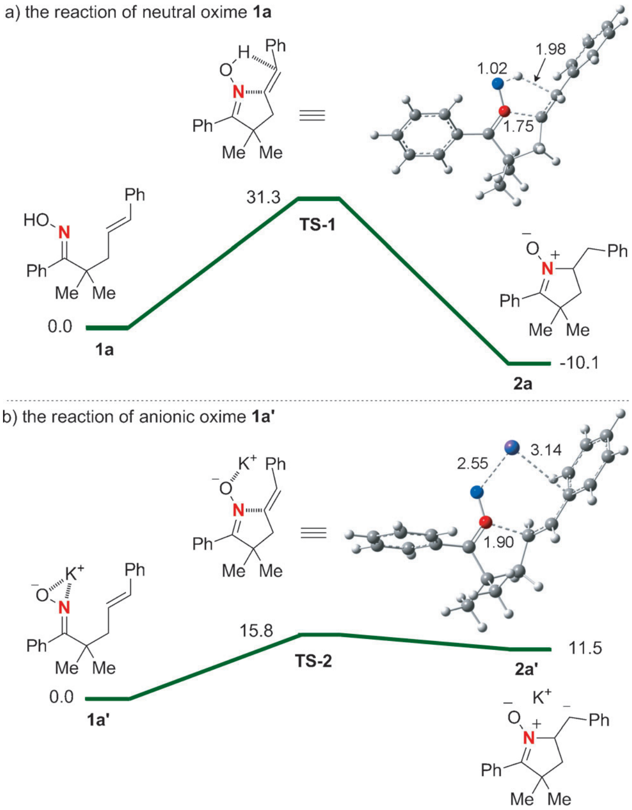
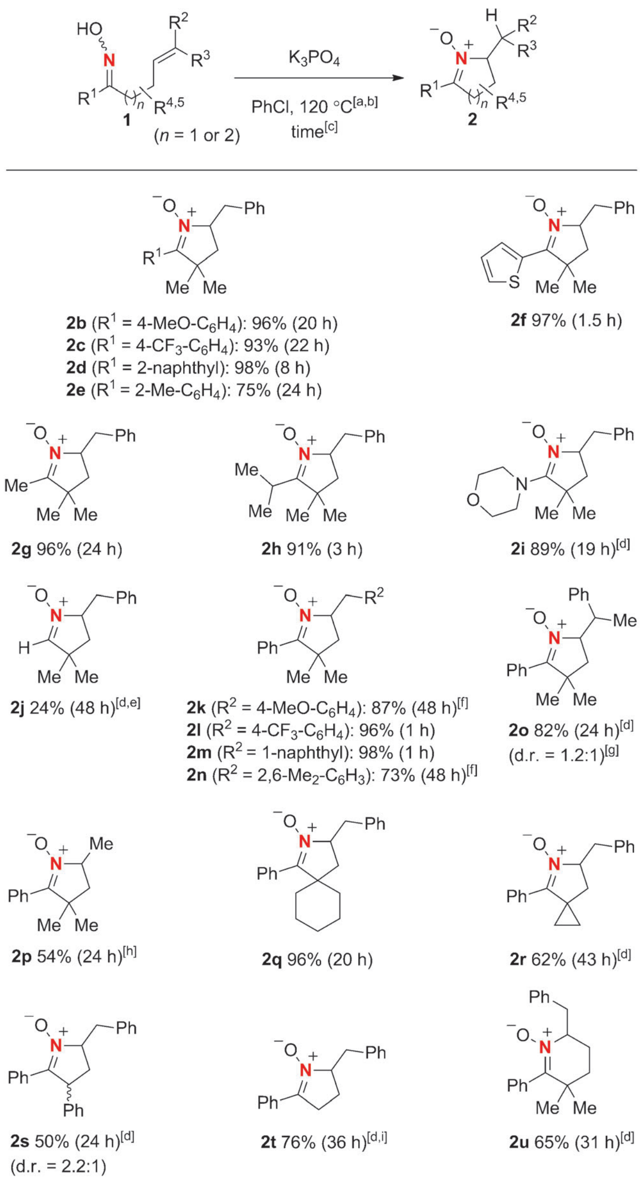


Figure 1. Energy diagrams (in kcal mol^{-1}) for the reaction of neutral oxime **1a** (a) and anionic oxime **1a'** (b), as obtained at the B3LYP-(SCRF)/6-311+G(d,p) level. Zero-point-energy (ZPE) effects are included. Key bond distances are given in Å in the three-dimensional models of the transition states.

To obtain detailed information pertaining to the role of the inorganic base in the formation of cyclic nitrone **2a** from oxime **1a**, we performed density functional theory (DFT) calculations to analyze the energy profiles for the reactions of oxime **1a** in its neutral and anionic forms at the B3LYP-(SCRF)/6-311+G(d,p) level (Figure 1), taking into account the chlorobenzene solvent effect.[15–18] In the cyclization of neutral oxime **1a** (in the absence of the base), the oxime nitrogen and the hydroxy hydrogen attack the two carbon atoms of the alkene in a concerted fashion (i.e. through retro-Cope hydroamination) to yield the five-membered cyclic nitrone **2a**. However, the transition state for this reaction (**TS-1**) is highly unstable, and thus the energy barrier is very high (31.3 kcal mol^{-1}; Figure 1a).

By contrast, the energy barrier for the reaction of anionic oxime **1a'** (with K^+) is much lower (15.8 kcal mol^{-1}; Figure 1b). Interestingly, in the transition state **TS-2**, K^+ interacts with the oxime oxygen atom and stays close to the *ipso*-carbon atom of the phenyl group. While the *ipso*-carbon has a positive charge according to the Mulliken population analysis (Figure S1 in the Supporting Information), the adjacent three carbon atoms are negatively charged. The K^+ ion thus effectively stabilizes these negative charges that accumulate as the cyclization reaction progresses. The resultant carbanion intermediate **2a'** will subsequently accept a proton from oxime **1a** to yield **2a** and regenerate anionic oxime **1a'**. Our computational results therefore suggest an essential role for metal cations such as K^+ and Na^+ in this unprecedented stepwise hydroamination reaction.

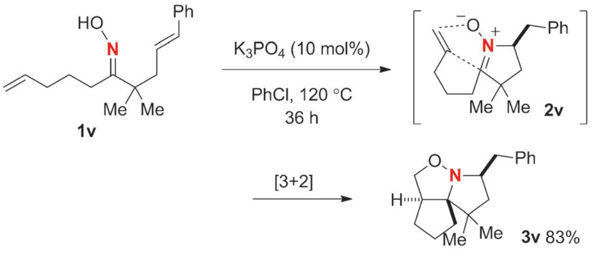
We next explored the substrate scope of this K_3PO_4-mediated hydroamination with regard to the γ,δ-unsaturated ketoximes **1** for the synthesis of 5-membered cyclic nitrones **2** (Scheme 3). For the substituent R^1, the reactions tolerated the installation of not only electron-rich and electron-deficient benzene rings (Scheme 3, **2b** and **2c**) but also sterically bulky aryl groups (**2d** and **2e**), as well as a 2-thienyl moiety (**2f**). Alkyl groups (**2g** and **2h**) and a morpholino moiety (**2i**) could also be introduced at R^1, although the reaction of aldoxime **1j** (R^1 = H) afforded nitrone **2j** in only 24% yield along with the corresponding nitrile in 47% yield through the dehydration of aldoxime **1j**. Investigation into the effect of the substituents attached to the alkene (R^2 and R^3) revealed that the



Scheme 3. Substrate scope for the synthesis of nitrones **2**. [a] Unless otherwise noted, the reactions were carried out using 0.2 mmol of **1** in the presence of K_3PO_4 (10 mol%) in PhCl (0.1 M) at 120°C under an N_2 atmosphere. [b] Yields of isolated product are noted. [c] The reaction time is noted in parantheses. [d] 100 mol% of K_3PO_4 was used. [e] The corresponding nitrile was formed in 47% yield through the dehydration of aldoxime **1j**. [f] 40 mol% of K_3PO_4 was used. [g] From pure *E*-alkenyl oxime **1o**, nitrone **2o** was formed as a 1.2:1 mixture of diastereomers. [h] The reaction was conducted using 100 mol% of K_3PO_4 at 150°C in *o*-xylene and oxime **1p** was recovered in 38% yield. [i] 5 mmol of oxime **1t** was used.

electronic nature of the alkene significantly influences the hydroamination process. It took a very long time (48 h) for the reaction of oxime **1k**, which bears an electron-rich methoxyphenyl group on the alkene, to be completed, even with 40 mol% of K_3PO_4, whereas the reaction of oxime **1l**, which has an electron-deficient group (trifluoromethyl phenyl), proceeded very rapidly and was completed within 1 h. Sterically bulky aryl groups (**2m** and **2n**) could be installed as R^2, but the reaction of oxime **1n**, which bears a 2,6-dimethylphenyl group, was very slow. Oxime **1o**, which is a trisubstituted *E*-alkene with Ph as R^2 and Me as R^3, afforded the corresponding nitrone **2o** as a 1.2:1 diastereomeric mixture, a result that supports a stepwise hydroamination mechanism involving a carbanion intermediate like **2a′** in Figure 1b. Hydroamination of the terminal alkene of oxime **1p** (R^2 and R^3 = H) required a higher temperature (150°C) and a stoichiometric amount of K_3PO_4 to give nitrone **2p** in 54% yield (87% yield based on recovered oxime **1p**).[19] Spirocyclic nitrones were also effectively constructed by using the K_3PO_4-mediated hydroamination (**2q** and **2r**). Besides α-geminal disubstituted oximes, α-monophenyl-substituted and nonsubstituted oximes **1s** and **1t** were also examined. While oxime **1s** is a 1:1 *syn*/*anti* mixture and oxime **1t** is the pure *syn* isomer (the oxime N−O bond lies on the same side as the alkene),[20,21] the stoichiometric use of K_3PO_4 gave the corresponding nitrones **2s** and **2t** in 50% and 76% yields, respectively (the reaction of oxime **1t** was conducted in 5 mmol scale). These results suggest that the stereochemistry of the oxime N−O bond does not influence the hydroamination. The K_3PO_4-mediated hydroamination turned out to be advantageous even for the formation of nitrones with 6-membered rings. The cyclization of δ,ε-unsaturated oxime **1u** proceeded in the presence of 1 equiv of K_3PO_4 to give 6-membered cyclic nitrone **2u** in 65% yield. In the absence of K_3PO_4, the cyclization also occurred through concerted retro-Cope hydroamination, although the reaction was rather sluggish (35% yield of **2u** with 36% recovery of **1u** even after 37 h heating).

Dialkenyl oxime **1v** underwent K_3PO_4-mediated hydroamination to give 5-membered cyclic nitrone **2v**, which subsequently underwent 1,3-dipolar cycloaddition with another alkene tether to give triheterocyclic system **3v** in 83% yield as a single diastereomer (Scheme 4).



Scheme 4. A domino sequence of hydroamination–[3+2] cycloaddition.

The further application of this finding to develop other types of amino functionalization of alkenes with oxime derivatives, as well as asymmetric variants with chiral bases, is currently under investigation.

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Keywords: density functional calculations · 1,3-dipoles · hydroamination · nitrones · oximes

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[19] The energy barrier for the reaction of anionic oxime **1p′** (with K^+) was somewhat higher ($25.5\,\text{kcal}\,\text{mol}^{-1}$) than that for **1a′**, while the energy barrier for the retro-Cope reaction pathway of neutral oxime **1p** ($31.1\,\text{kcal}\,\text{mol}^{-1}$) was as high as that for **1a** (Figure S2 in the Supporting Information).

[20] Unsymmetrical oximes have two stereoisomers; *syn* and *anti* isomers. Herein, the *syn* isomer is defined as oximes bearing the N−O bond on the same side as the alkenyl moiety and vice versa for the *anti* isomer.

[21] Amidoxime **1i** was an inseparable mixture of *syn*/*anti* isomers (1:11), while the stereochemistry of each isomer was not assigned. Except for oximes **1i**, **1s** and **1t**, all the oximes **1** were the *anti* isomer (see the Supporting Information).