Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201400601

3-Methyl-4-oxa-5-azahomoadamantane as an Organocatalyst for the Aerobic Oxidation of Primary Amines to Oximes in Water

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Received: June 20, 2014; Revised: November 27, 2014; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400601.

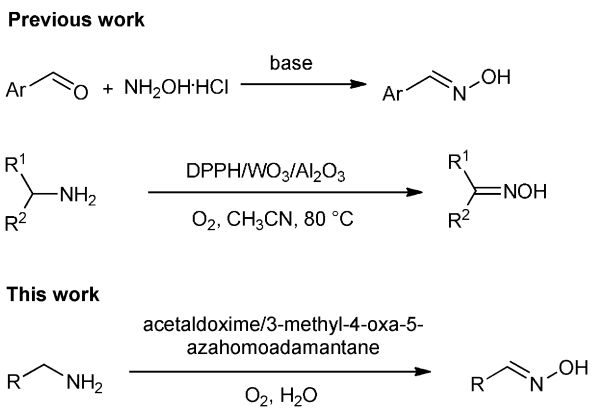
Abstract: A simple and efficient catalytic system for the aerobic oxidation of primary amines into corresponding oximes has been developed, with 3-methyl-4-oxa-5-azahomoadamantane as catalyst, acetaldoxime as co-catalyst and water as solvent. This process, which uses oxygen (O_2) as an economic and green oxidant and water as a green solvent, tolerates a wide range of substrates, affording the target oximes in moderate to excellent yields. It was found that high selectivity was achieved when 3-methyl-4-oxa-5-azahomoadamantane was used, and *E*-type oximes were the only detected products. A possible mechanism for this catalytic process is proposed.

Keywords: aerobic oxidation; amines; 3-methyl-4-oxa-5-azahomoadamantane; oximes; water

Oximes have been widely utilized in medicine, industry, and analytical chemistry, and they are also widely used as intermediates in the synthesis of commodity products, fine chemicals, medicines, and biologically active compounds.[1–5] Moreover, oximes are valuable synthetic tools, which can be either reduced to amines or oxidized to nitrile oxides,[6,7] and they can also be dehydrated to nitriles or undergo an acid-catalyzed Beckmann rearrangement to afford amides.[8] Furthermore, oximes are very important ligands in the formation of mono- and polynuclear metal complexes.[9] In addition, oximes are highly crystalline compounds that find applications not only for protection, but also for purification and characterization of carbonyl compounds.[10,11] The traditional way to obtain oximes is the reaction of a carbonyl compound with hydroxylamine hydrochloride in the presence of a stoichiometric amount of base.[12,13] However, this method has some drawbacks that restrict its further application: (i) the cost of stoichiometric or excess amounts of hydroxylamine salt relative to the respective substrates, (ii) an equal mol equivalent of base should be used relative to the hydroxylamine salt, (iii) large amounts of by-products are generated during the oximation reaction, (iv) yields of the oximes are relatively low because the resulting oximes can undergo either dehydration to nitriles or acid-catalyzed Beckmann rearrangement to amides.

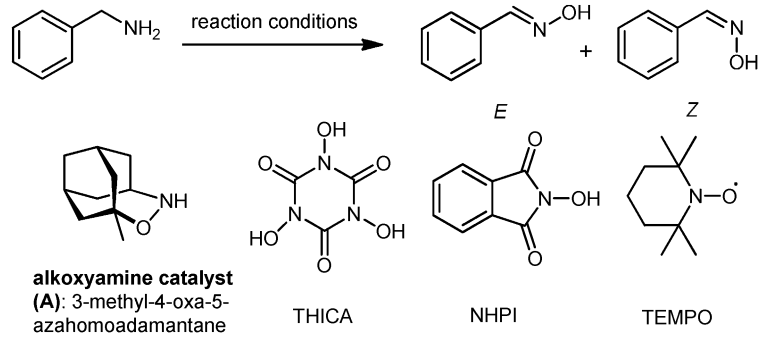
Recently, some studies have been performed to obtain oximes *via* the aerobic oxidation of primary amines by employing 1,1-diphenyl-2-picrylhydrazyl (DPPH) and tungsten-alumina (WO_3/Al_2O_3) as catalyst.[14] (Scheme 1). Nonetheless, this method suffers from some limitations: (i) it is only applicable for aliphatic primary amines, (ii) it requires metal compounds or organic solvent. Therefore, it is of significant importance to develop a mild, convenient and efficient method that can suppress the formation of by-products and increase the yields of the corresponding oximes.

Due to their unique behavior and eminent reactivity, nitrogen oxides (such as TEMPO, NHPI and THICA) have drawn considerable attention in the



Scheme 1. The aerobic oxidation of primary amines catalyzed by 3-methyl-4-oxa-5-azahomoadamantane/acetaldoxime.

Table 1. Oxidation of the benzylamine under various conditions.[a,b]



Entry	Catalyst (mol%)	Co-catalyst (mol%)	Solvent	Temperature [°C]	Gas	Yield[b] [%] (*E*/*Z*)
1	**A** (2.5)	acetaldoxime (10)	H_2O	refluxing	O_2	92/0
2	THICA (2.5)	acetaldoxime (10)	H_2O	refluxing	O_2	76/4
3	NHPI (2.5)	acetaldoxime (10)	H_2O	refluxing	O_2	50/11
4	TEMPO (2.5)	acetaldoxime (10)	H_2O	refluxing	O_2	45/8
5	**A** (2.5)	acetoxime (10)	H_2O	refluxing	O_2	81/0
6	**A** (2.5)	dimethylglyoxime (10)	H_2O	refluxing	O_2	76/0
7	**A** (2.5)	cyclohexanone oxime (10)	H_2O	refluxing	O_2	71/0
8	**A** (2.5)	acetaldoxime (10)	DMSO	refluxing	O_2	–
9	**A** (2.5)	acetaldoxime (10)	DMF	refluxing	O_2	–
10	**A** (2.5)	acetaldoxime (10)	EtOH	refluxing	O_2	–
11	**A** (2.5)	acetaldoxime (10)	MeCN	refluxing	O_2	–
12	**A** (2.5)	acetaldoxime (10)	H_2O	80	O_2	84/0
13	**A** (2.5)	acetaldoxime (10)	H_2O	60	O_2	63/0
14	**A** (2.5)	acetaldoxime (10)	H_2O	40	O_2	36/0
15	**A** (2.5)	acetaldoxime (10)	H_2O	r.t.	O_2	trace
16	**A** (5)	acetaldoxime (10)	H_2O	refluxing	O_2	92/0
17	**A** (1)	acetaldoxime (10)	H_2O	refluxing	O_2	92/0
18	**A** (0.5)	acetaldoxime (10)	H_2O	refluxing	O_2	83/0
19	**A** (0)	acetaldoxime (10)	H_2O	refluxing	O_2	trace
20	**A** (1)	acetaldoxime (0)	H_2O	refluxing	O_2	trace
21	**A** (1)	acetaldoxime (5)	H_2O	refluxing	O_2	80/0
22	**A** (1)	acetaldoxime (20)	H_2O	refluxing	O_2	92/0
23	**A** (1)	acetaldoxime (10)	H_2O	refluxing	air	79/0
24	**A** (1)	acetaldoxime (10)	H_2O	refluxing	N_2	trace

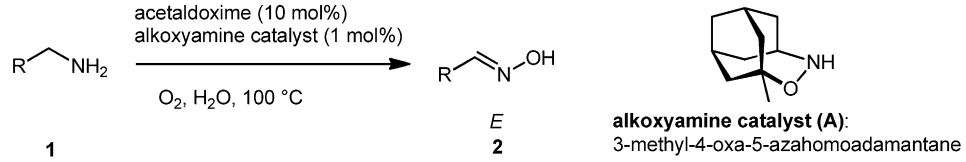
[a] *Reaction conditions:* 1 mmol benzylamine was dissolved in 5 mL solvent. The catalyst and co-catalyst were then added, and the mixture stirred for 24 h under different gas atmosphere at different temperatures.
[b] The reported yields were determined by ^{1}H NMR.

aerobic oxidation of hydrocarbons, alcohols, and amines over the last decade.[15] Recently, 3-methyl-4-oxa-5-azahomoadamantane,[16] which is a novel alkoxyamine-type organocatalyst, was found to enable the highly efficient oxidation of primary and secondary alcohols into the corresponding carbonyl compounds using NaOCl as the terminal oxidant. Based on this work, we tried to extend the application of this alkoxyamine-type organocatalyst for other oxidations.

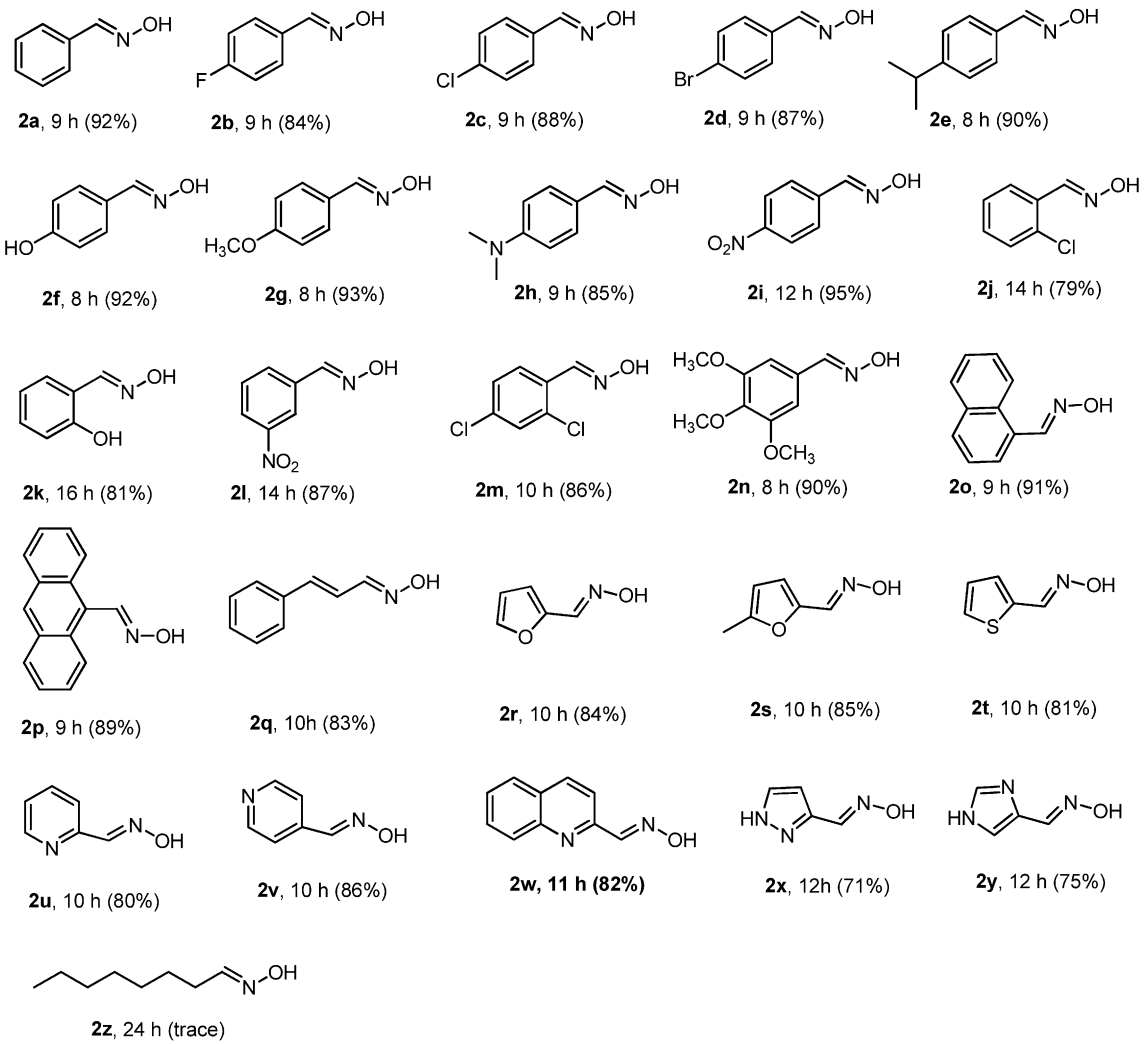
Herein, we report a novel, efficient and metal-free approach for the aerobic oxidation of primary amines into the corresponding oximes. This process with 3-methyl-4-oxa-5-azahomoadamantane as catalyst, acetaldoxime as co-catalyst, O_2 as the terminal oxidant, and water as solvent, tolerates a wide range of substrates, affording the target oximes in moderate to excellent yields.

As a representative example, the aerobic oxidation of benzylamine (Scheme 1) was selected to optimize the reaction conditions (Table 1). It is pleasing that the oxidation of benzylamine with O_2 (1 atm) catalyzed by 3-methyl-4-oxa-5-azahomoadamantane (2.5 mol%) combined with acetaldoxime (10 mol%) gave solely (*E*) benzaldoxime in 92% yield (Table 1, entry 1). Other nitrogen oxides were also examined. Unsatisfactorily, when THICA (*N′,N″,N‴*-trihydroxyisocyanuric acid), NHPI (-hydroxyphthalimide), and TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) were used, the reaction proceeded in low yield, and the (*Z*) benzaldoxime was detected by ^{1}H NMR (entries 2–4). Several acetaldoxime analogues were compared (en-

Table 2. The aerobic oxidation of primary amines into oximes catalyzed by 3-methyl-4-oxa-5-azahomoadamantane and acetaldoxime.[a,b]



1 — *E* 2 — **alkoxyamine catalyst (A)**: 3-methyl-4-oxa-5-azahomoadamantane



[a] *Reaction conditions:* 1 mmol primary amine, 1 mol% 3-methyl-4-oxa-5-azahomoadamantane and 10 mol% acetaldoxime was dissolved in 5 mL H_2O, and the mixture was stirred for several hours under O_2 atmosphere at refluxing temperature.

[b] The reported yields were determined by ^1H NMR.

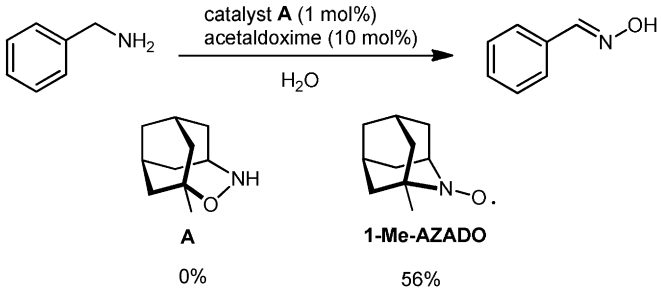
tries 5–7). Substitution by acetoxime, dimethylglyoxime, or cyclohexanone oxime led to lower yields. Screening of different solvents revealed that the solvent played an important role in this reaction. Notably, H_2O was the only effective solvent, benzaldoxime could not form in other solvents such as DMSO, DMF, EtOH, MeCN, which may because the catalyst 3-methyl-4-oxa-5-azahomoadamantane could not form its radical in these solvents (entries 1, 8–11). Reducing the reaction temperature from refluxing conditions to room temperature led to great decrease in the yields (entries 1, 12–15). Subsequently, the amount of the catalyst was screened. And the result showed that the optimum amount of acetaldoxime

was 10 mol% and 1 mol% for 3-methyl-4-oxa-5-azahomoadamantane (entries 1, 16–22). Besides, when using air in the reaction, the yield was reduced slightly (entries 17 and 23). Also the reaction could not be conducted under an N_2 atmosphere (entry 24).

Next, the substrate scope for the aerobic oxidation of the primary amines was examined in detail under the optimized reaction conditions. As shown in Table 2, the reaction could be successfully applied to a range of different substituted benzylamines and gave the corresponding (*E*) products in moderate to excellent yields, with no (*Z*) products formed. The above results indicated that the catalytic oximation of benzylamines with electron-withdrawing substituents gave excellent yields except for the halo-substituted benzylamines (Table 2, entries **b**–**d**, **i**). In the case of benzylamines with electron-donating groups, good yields in the range 85–93% could be achieved (entries **e**–**h**, **n**). When the benzylamines bear the same substituent, the oxime yields from the *ortho* or *meta* substituted compounds are lower than that for *para* substitution (entries **c**, **g**, **i**, **l**). This should be attributed to the steric hindrance effect. Fortunately, 1-naphthalenemethylamine, 9-anthracenemethylamine and 3-phenyl-2-propyleneamine could also be successfully converted into the corresponding oximes in good yields in this catalytic system (entries **o**–**q**). Moreover, we also subjected heterocyclic primary amines to the employed reaction conditions. To our surprise, heterocyclic amines showed high reactivity to give the corresponding oximes in good yields (entries **r**–**y**). This catalytic system was then applied to the oxidation of aliphatic amines to further extend the substrate scope. Unfortunately, merely a trace amount of octanal oxime was detected when octylamine was exposed to this catalytic system for 24 h (entry **z**). The reason may be that the electron-withdrawing effect of the aromatic base was stronger than that of the aliphatic one, when the electron-withdrawing ability of the groups on the α carbon atom was stronger, the reaction proceeded more easily. Secondary amines and aniline type substrates [such as dibenzylamine and aniline (not shown)] were not oxidized under this catalytic system.

Some preliminary mechanistic studies of the reaction were also conducted. Control experiments showed that no product appeared in the presence of 3-methyl-4-oxa-5-azahomoadamantane or acetaldoxime alone (Table 1, entries 19 and 20). When the reaction was conducted under an N_2 atmosphere, only a trace amount of product was obtained (Table 1, entry 24). Thus, acetaldoxime, 3-methyl-4-oxa-5-azahomoadamantane and O_2 were essential for this reaction.

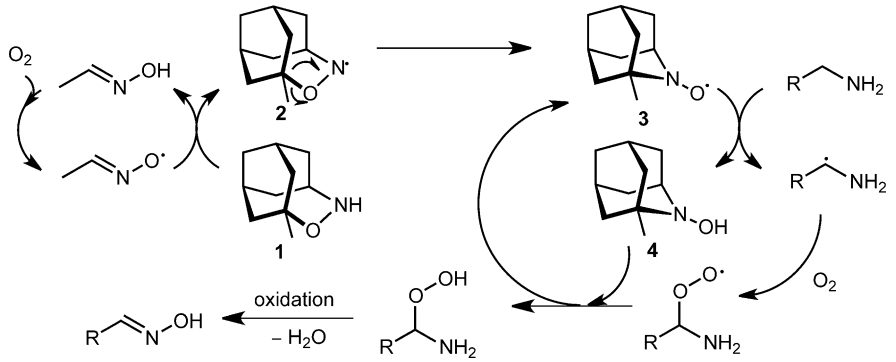
Besides, in order to obtain mechanistic insight into the 3-methyl-4-oxa-5-azahomoadamantane-catalyzed oxidation, attempts to identify the active species generated were undertaken. The aerobic oxidation of benzylamine (10 mmol) catalyzed by 3-methyl-4-oxa-5-azahomoadamantane (0.1 mmol) and acetaldoxime (1 mmol) in water was performed at refluxing conditions. After cooling to room temperature, a residue was obtained after extraction and evaporation. Then the crude product was purified by chromatography to give the product (*E*-benzaldoxime) in 92% yield and 1-Me-AZADO (1-methyl-2-azaadamntane *N*-oxyl, the data of which are available in the Supporting Information) in 56% (based on the equiv. of 3-methyl-4-oxa-5-azahomoadamantane) yield (Scheme 2).



Scheme 2. The aerobic oxidation of benzylamine to oxime catalyzed by 3-methyl-4-oxa-5-azahomoadamantane/acetaldoxime.

Based on these results and previous literature reports,[15,16,18] a possible catalytic mechanism of 3-methyl-4-oxa-5-azahomoadamantane/acetaldoxime in the aerobic oxidation of primary amines was proposed as shown in Scheme 3. The first step of the reaction lies in the generation of the corresponding *N*-oxyl radical of acetaldoxime, through reaction of acetaldoxime and dioxygen. And then this *N*-oxyl radical abstracts hydrogen from 3-methyl-4-oxa-5-azahomoadamantane **1** to recover the acetaldoxime. Simultaneously, **1** is converted to its radical **2**. The rearrangement of **2** gives the N−O radical species **3** (1-Me-AZADO). Radical **3** abstracts a hydrogen atom from the primary amine to form an α-aminobenzyl radical and was transformed to **4** at the same time. Then the α-aminobenzyl radical was readily captured by O_2 to give the α-aminobenzylperoxy radical, which underwent abstraction of hydrogen from **4** to give the α-aminobenzyl hydroperoxide. And **4** was then converted to form **3** again to establish the catalytic cycle. Finally, the α-aminobenzyl hydroperoxide was dehydrated to form the desired product. After analyzing the isolated products by ^{1}H NMR, *E*-type oximes were obtained as the only products.

In conclusion, we have developed a simple, efficient and green catalytic system consisting of 3-methyl-4-oxa-5-azahomoadamantane and acetaldoxime for the aerobic oxidative synthesis of oximes from primary amines. This practical reaction with O_2 as green and economic oxidant and water as green solvent, tolerates a wide range of substrates, affording the target



Scheme 3. The possible reaction mechanism of the aerobic oxidation catalyzed by 3-methyl-4-oxa-5-azahomoadamantane and acetaldoxime.

oximes in moderate to excellent yields. Besides, 3-methyl-4-oxa-5-azahomoadamantane showed excellent selectivity as oxidant for the primary amines, and *E*-type oximes were obtained as the only products. Furthermore, a plausible reaction mechanism was proposed based on the experimental observations and literature precedents.

Experimental Section

General Remarks

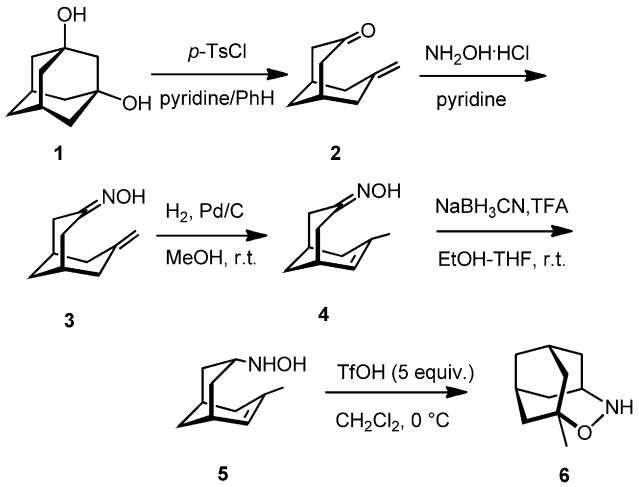
All starting materials were purchased from commercial sources and used without further treatment. All known compounds were identified by appropriate techniques and compared with previously reported data. NMR (500 MHz) spectra were recorded on a Bruker 500 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on an Agilent Technologies 6110 quadrupole MS equipped with electrospray ionization (ESI) probe operating in positive/negative ion mode. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Yields refer to the isolated yields of the products after purification by silica-gel column chromatography (300 mesh). All the analytical data and spectra are available in the Supporting Information.

Preparation of the 3-Methyl-4-oxa-5-azahomoadamantane

3-Methyl-4-oxa-5-azahomoadamantane was prepared by the literature procedure[16,17] as shown in Scheme 4. The detailed procedure is available in the Supporting Information. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.68$ (br s, 1H), 3.58 (s, 1H), 2.07–1.97 (m, 2H), 1.95–1.68 (m, 8H), 1.61–1.47 (m, 2H), 1.23 (s, 3H); ^{13}C NMR (125.72 MHz, $CDCl_3$): $\delta = 80.7$, 55.0, 42.0, 36.8, 34.3, 29.8, 26.3; MS: $m/z = 168$ (M^+).

General Procedure for the Synthesis of Oximes

A mixture of 1 mmol primary amine, 1 mol% 3-methyl-4-oxa-5-azahomoadamantane, 10 mol% acetaldoxime and 5 mL H_2O was placed into a three-necked flask. O_2 was bubbled into the flask at a flow rate of 20 mL min^{-1}. The reaction mixture was stirred at refluxing conditions for several hours and the reaction progress was monitored by TLC. After completion, the final reaction mixture was cooled to room temperature and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. When necessary, the crude product was purified by chromatography with ethyl acetate/petroleum ether (1:8) as eluent.



Scheme 4. The preparation of the 3-methyl-4-oxa-5-azahomoadamantane.

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Adv. Synth. Catal. **2015**, *357*, 1 – 7

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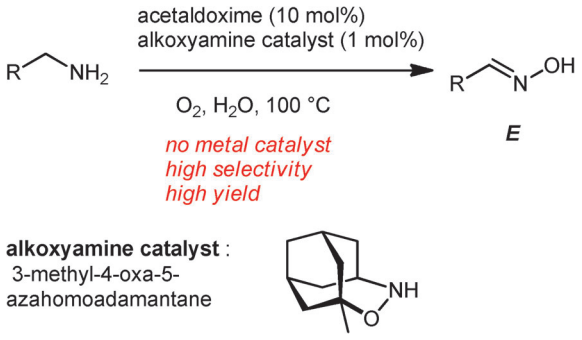

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