Accepted Manuscript

Cascade reaction of propargylic alcohols with hydroxylamine hydrochloride: facile synthesis of α,β-unsaturated oximes and nitriles

Qi Zhang, Linjing Zhang, Chaojun Tang, Huan Luo, Xuediao Cai, Yonghai Chai

PII: S0040-4020(16)30917-6

DOI: 10.1016/j.tet.2016.09.010

Reference: TET 28081

To appear in: *Tetrahedron*

Received Date: 30 June 2016

Revised Date: 6 September 2016

Accepted Date: 9 September 2016

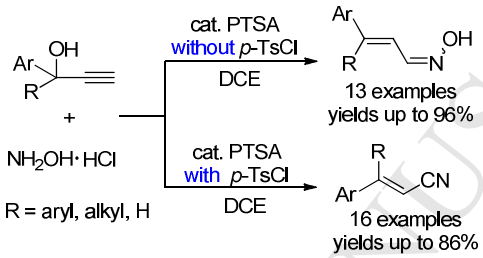
Please cite this article as: Zhang Q, Zhang L, Tang C, Luo H, Cai X, Chai Y, Cascade reaction of propargylic alcohols with hydroxylamine hydrochloride: facile synthesis of α,β-unsaturated oximes and nitriles, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.09.010.

Graphical Abstract

Cascade reaction of propargylic alcohols with hydroxylamine hydrochloride: facile synthesis of α,β-unsaturated oximes and nitriles

Leave this area blank for abstract info.

Qi Zhang[a,*] , Linjing Zhang[a] , Chaojun Tang[b] , Huan Luo [a] , Xuediao Cai[a] and Yonghai Chai[c,*]
[a]*School of Chemistry and Chemical Engineering, Shaanxi Normal University*
[b]*Chongqing Huapont Pharm. CO., LTD.*
[c]*Key Laboratory of Applied Surface and Colloid Chemistry, MOE, Shaanxi Normal University*



Tetrahedron
journal homepage: www.elsevier.com

Cascade reaction of propargylic alcohols with hydroxylamine hydrochloride: facile synthesis of α,β-unsaturated oximes and nitriles

Qi Zhang[a,*], Linjing Zhang[a], Chaojun Tang[b], Huan Luo[a], Xuediao Cai[a] and Yonghai Chai[c,*]

[a]*School of Chemistry and Chemical Engineering, Shaanxi Normal University, No. 199 South Chang'an Road, Xi'an 710062, P. R. of China*
[b]*Chongqing Huapont Pharm. CO., LTD., No. 69 Xingguang Avenue, Chongqing 401121, P. R. of China*
[c]*Key Laboratory of Applied Surface and Colloid Chemistry, MOE, Shaanxi Normal University, No. 199 South Chang'an Road, Xi'an 710062, P. R. of China*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

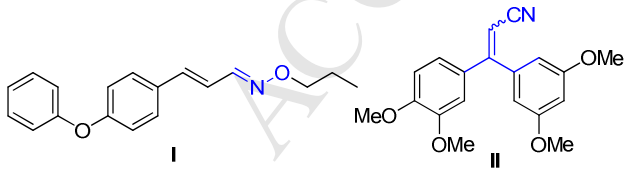
Keywords:
α,β-unsaturated oximes
α,β-unsaturated nitriles
propargylic alcohols
hydroxylamine hydrochloride
organic acid
dehydrating promoter

ABSTRACT

We have developed an easy and practical method for the synthesis of α,β-unsaturated oximes and nitriles from readily available propargylic alcohols with hydroxylamine hydrochloride ($NH_2OH·HCl$) under metal-free conditions. By using or not using *p*-toluenesulfonyl chloride (*p*-TsCl) as the dehydrating promoter, the desired nitriles or oximes could be obtained respectively via a three-step one-pot or two-step one-pot process in moderate to excellent yields with good functional group compatibility.

1. Introduction

α,β-Unsaturated oximes and nitriles are of significant interests as intermediates in organic synthesis for diverse functional group transformations and carbon-carbon/carbon-heteroatom bond formations due to their bifunctional and dipolar nature.[1-3] Furthermore, this type of structures often serves as a core structural skeleton in a variety of natural products, pharmaceuticals, and other useful materials[4,5] such as oxime **I**[4c], a potential insecticide, and nitile **II**[5b], a tubulin polymerization inhibitor.



I II

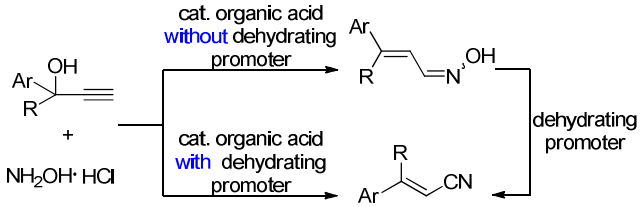
The classical method for the preparation of α,β-unsaturated oximes lies in the condensation between a corresponding carbonyl compound and hydroxylamine hydrochloride ($NH_2OH·HCl$) in the presence of a stoichiometric amount of a base.[6] Recently, new protocols, such as the oxidation of primary amines, the direct conversion of alcohols into oximes, etc, have also been reported.[7] With regard to the synthesis of α,β-unsaturated nitriles, apart from the strategy of the functional transformation of other nitrogen-containing compounds (e.g. oximes, azides, amide, etc),[8] this type of compounds can also be prepared by means of the installation of the cyano group[9] or the formation of the carbon-carbon double bond[10]. In recent years, the synthetic approaches to α,β-unsaturated nitriles through a cascade reaction have also been established.[11,12] Among those, the efficient and atom-economic preparation of α,β-unsaturated nitriles from readily available propargylic alcohols have attracted considerable attention.[12] The Zhan and Jiao groups have reported the direct transformation of propargylic alcohols to the desired nitriles with 4-methylbenzenesulfonohydrazide ($TsNHNH_2$) and azidotrimethylsilane ($TMSN_3$) as the nitritrogen source respectively.[12b,c] Very recently, the Liang group has also accomplished this transformation by using more stable and inexpensive $NH_2OH·HCl$ instead.[12a] In Liang's method, 3 equiv of chlorotrimethylsilane (TMSCl) was employed as the promoter.

In view of the significance of unsaturated nitrogen-containing compounds and encouraged by the above-mentioned work, we were interested in developing a facile and low-cost protocol for the nitrogenation of propargylic alcohols. Herein, we reported an organic acid-catalyzed direct formation of α,β-unsaturated oximes and nitriles from propargylic alcohols with $NH_2OH·HCl$

* Corresponding author. Tel.: +86-29-81530782; fax: +86-29-81530783; e-mail: qiqizhang@snnu.edu.cn (Q. Zhang)

* Corresponding author. Tel.: +86-29-81530783; fax: +86-29-81530783; e-mail: ychai@snnu.edu.cn (Y. Chai)

as the nitrogen source. With or without the addition of a dehydrating promoter, nitriles or oximes could be readily prepared respectively via a three-step one-pot or two-step one-pot process (Scheme 1).

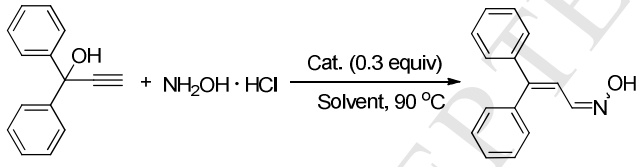


Scheme 1 This work: Nitrogenation of propargylic alcohols.

2. Results and discussion

We initially chose 1,1-diphenylprop-2-yn-1-ol (**1a**) as the model substrate to explore the suitable reaction condition for the transformation of propargylic alcohol to α,β-unsaturated oxime (Table 1). In the presence of 0.3 equiv of trifluoroacetic acid (TFA) in DCE, **1a** could react with $NH_2OH{\cdot}HCl$, giving the expected α,β-unsaturated oxime **2a** in 13% yield after 12 h at 90 °C along with the α,β-unsaturated nitrile, a further dehydrated product from **2a** (Table 1, entry 1). The yield was slightly increased when (±)-camphor-10-sulfonic acid ((±)-CSA) was used instead of TFA, and interestingly, the major side-product is the α,β-unsaturated aldehyde (Table 1, entry 2). To our delight, when 0.3 equiv of *p*-toluenesulfonyl acid (PTSA) was employed as the catalyst, the reaction time was shortened to 4 h and the yield of **2a** experienced a dramatic upgrade to 96% (Table 1, entry 3). 4-Toluenesulfonic acid pyridine salt (PPTS), a weaker organic acid, could not catalyze the cascade reaction and **1a** was recovered almost quantitatively (Table 1, entry 4). Solvents were proved to have great effect on this transformation. Among commonly used solvents, DCE was the most effective one (Table 1, entry 5-8). It is noteworthy that all oximes were obtained as a mixture of two stereoisomers.

Table 1. Optimization of reaction conditions from **1a** and $NH_2OH{\cdot}HCl$[a]

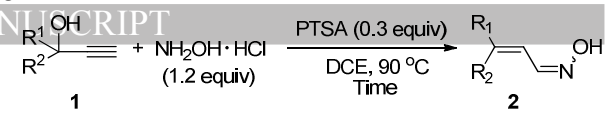


Entry	Cat.	Solvent	Time (h)	Yield[b]
1	TFA	DCE	12	13%
2	(±)-CSA	DCE	12	28%
3	**PTSA**	**DCE**	**4**	**96%**
4	PPTS	DCE	12	0%
5	PTSA	Toluene	24	58%
6	PTSA	MeCN	24	28%
7	PTSA	Dioxane	48	27%
8	PTSA	THF	48	5%

[a]Unless otherwise noted, all reactions were performed with **1a** (0.2 mmol) and $NH_2OH{\cdot}HCl$ (1.2 equiv) in the presence of an organic acid (0.3 equiv) in solvent (1 mL) at 90 °C.

[b]Yields are given for isolated products.

Table 2. Transformation of propargylic alcohols to α,β-unsaturated oximes[a]



Entry	Product	Time (h)	Yield[b]
1	R = H (**2a**)	4	96%
2	R = *o*-Me (**2b**)	16	75%
3	R = *m*-Me (**2c**)	3	81%
4	R = *p*-Me (**2d**)	2	80%
5	R = *p*-F (**2e**)	6	87%
6	R = *p*-Cl (**2f**)	5	81%
7	(**2g**)	5	86%
8	(**2h**)	4	57%
9	(**2i**)	4	39%
10	R = H (**2j**)	4	30%
11[c]	R = H (**2j**)	3.5	85%
12[c]	R = *p*-Me (**2k**)	3.5	73%
13[c]	R = *p*-Cl (**2l**)	8	64%
14	(**2m**)	5	89%
15	(**2n**)	12	18%

[a]Unless otherwise noted, all reactions were performed with **1a** (0.2 mmol) and $NH_2OH{\cdot}HCl$ (1.2 equiv) in the presence of PTSA (0.3 equiv) in DCE (1 mL) at 90 °C for an appropriate time.

[b]Yields are given for isolated products.

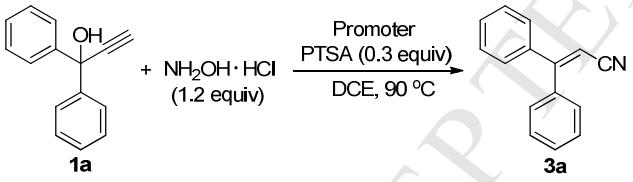
[c]The reactions were performed using a modified procedure: **1a** (0.2 mmol), PTSA (0.3 equiv) and DCE (1 mL) were first stirred at 90 °C for 30 min; then $NH_2OH{\cdot}HCl$ (1.2 equiv) was added to the reaction system and the resulting mixture was stirred at 90 °C for an appropriate time.

Next, we examined the substrate scope of the new method (Table 2). Under the optimal condition, various 1,1-diaryl-substitued tertiary propargylic alcohols were readily transformed to the corresponding α,β-unsaturated oximes in moderate to excellent yields irrespective of the aryl substitution, showing

little electric and/or steric dependence (Table 2, entry 1-8). This approach was also applicable to the propargaylic alcohols with an aryl substitute and an alkyl substitute in C-1 position, such as 2-phenylbut-3-yn-2-ol **1i**, but the corresponding oximes were obtained in relatively low yield (39%). The decrease in the yield probably resulted from other acid-catalyzed competing reactions (e.g. Rupe rearrangement and β-elimination) (Table 2, entry 9). The direct oximation of secondary propargylic alcohol **1j** also occurred, affording the desired oxime **2j** in 30% yield (Table 2, entry 10). To improve the yield, a slightly modified procedure was employed: propargylic alcohol was first stirred under the condition of PTSA (0.3 equiv)/DCE/90 °C for 30 min to give the α,β-unsaturated aldehyde through Meyer-Schuster rearrangement; then 1.2 equiv of $NH_2OH{\cdot}HCl$ was introduced into the reaction mixture. As a result, **2j** was obtained with a dramatic increase of the yield to 85% (Table 2, entry 11). The following exploration showed that secondary propargylic alcohols bearing electron-withdrawing or -donating substituents on the aryl ring were compatible with this modified procedure, and produced the desired oximes in moderate to good yields (Table 2, entry 12-13). When using *O*-alkylhydroxylamine hydrochloride (e.g. $NH_2OMe{\cdot}HCl$) as the nitrogen source, alkenyl *O*-alkyl oxime could also be prepared successfully (Table 2, entry 14). However, the yield decreased palpably when a substrate with an alkyl group in C-3 position was used, implying that the steric hindrance surrounding the oximido group has a significant effect on this transformation (Table 2, entry 15). In consistent with the stereo-outcome of **2a** (Table 1), all prepared oximes consist of two stereoisomers.

After establishing the one-pot synthetic approach to α,β-unsaturated oximes, we subsequently focused our attention on exploring the possibility of preparation of α,β-unsaturated nitriles from propargylic alcohols by means of introducing a dehydrating promoter into the current reaction system. Different promoters were investigated into the formation of **3a** from **1a**, and the results are shown in table 3.

Table 3. Screening dehydrating promoters[a]



1a **3a**

Entry	Promoter (equiv)	Time (h)	Yield[b] (%)
1	Ac_2O (1)	18	56
2	TFAA (1)	18	21
3	TsCl (1)	20	68
4	TsCl (1.5)	20	67
5	TsCl (2)	20	79
6	TsCl (2)/4 A MS	20	73

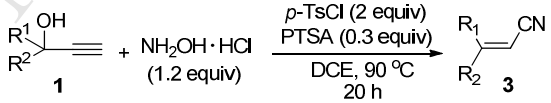
[a]All reactions were performed with **1a** (0.2 mmol), $NH_2OH{\cdot}HCl$ (1.2 equiv), PTSA (0.3 equiv), and promoter in DCE (1 mL) at 90 °C.

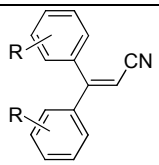
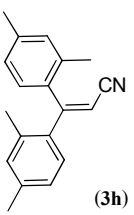
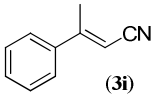
[b]Yields are given for isolated products.

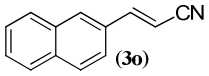
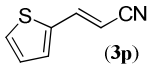
Acetic anhydride (Ac_2O), a known dehydrating reagent in the conversion of oxime to nitrile,[8c] was first examined. Treatment of **1a** with Ac_2O (1 equiv)/PTSA (0.3 equiv)/$NH_2OH{\cdot}HCl$ (1.2 equiv) in DCE at 90 °C for 18 h afforded the desired 3,3-diphenylacrylonitrile **3a** in 56% yield. Interestingly, we also isolated a heterocyclic compound, 4-phenylquinoline, which is believed to be generated via the intramolecular electrophilic substitution of the benzene moiety with *O*-acetyl-oxime moiety[13] (Table 3, entry 1). When trifluoroacetic anhydride (TFAA) was used, the reaction became complicated and **3a** was only obtained in 21% yield (Table 3, entry 2). It has been reported that *p*-toluenesulfonyl chloride (*p*-TsCl), a common and cheap reagent, can also promote the dehydration of oximes in the presence of a stoichiometric amount of a base, usually NEt_3 or pyridine.[8h,i] Gratifyingly, when *p*-TsCl was employed under the acidic condition, the formation of nitrile also proceeded smoothly, providing **3a** in 68% (Table 3, entry 3). The further investigation of the amount of the promoter showed that the use of 2 equiv of *p*-TsCl was the best choice and gave the expected product in 79% (Table 3, entry 3-5). Addition of 4Å molecular sieve didn't lead to any beneficial effect (Table 3, entry 6).

With the optimal condition in hand, the scope of this transformation was explored (Table 4). A variety of 1,1-diaryl-substitued propargylic alcohols were easily converted into the corresponding α,β-unsaturated nitriles in moderate to good yields, which indicates that the substituents on the aryl ring have little electric and/or steric effect (Table 4, entry 1-8). However, the propargylic alcohol with methyl group at C-1 position led to complicated mixtures along with the desired product in low yield probably due to other acid-catalyzed competing reactions (Table 4, entry 9). The cascade reaction of secondary propargylic alcohols also performed well and gave the (*E*)-acrylonitriles selectively via a little changed procedure, introducing *p*-TsCl and $NH_2OH{\cdot}HCl$ into the reaction system after the completion of the PTSA-catalyzed Meyer-Schuster rearrangement (Table 4, entry 10-14). In addition, polycyclic aromatic and heteroaromatic substituted propargylic alcohols were suitable in this transformation, but the yields of the expected nitriles were relatively low (Table 4, entry 15-16).

Table 4. Transformation of propargylic alcohols to α,β-unsaturated nitriles[a]



Entry	Product	Yield[b] (%)
		
1	R = H (**3a**)	79
2	R = *o*-Me (**3b**)	77
3	R = *m*-Me (**3c**)	73
4	R = *p*-Me (**3d**)	70
5	R = *p*-OMe (**3e**)	56
6	R = *p*-F (**3f**)	80
7	R = *p*-Cl (**3g**)	77
8	 (**3h**)	86
9	 (**3i**)	30

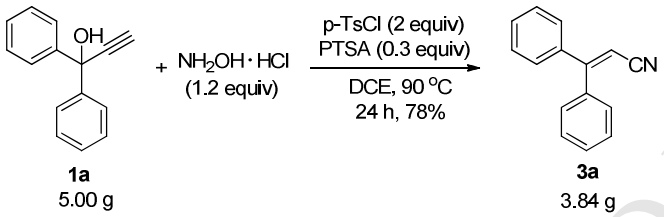
10[c]	R = H (**3j**)	72
11[c]	R = *o*-Me (**3k**)	76
12[c]	R = *m*-Me (**3l**)	64
13[c]	R = *p*-Me (**3m**)	70
14[c]	R = *p*-Cl (**3n**)	59
15[c]	 (**3o**)	32
16[c]	 (**3p**)	22

[a]Unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), $NH_2OH{\cdot}HCl$ (1.2 equiv), PTSA (0.3 equiv), and *p*-TsCl (2 equiv) in DCE (1 mL) at 90 °C for 20 h.

[b]Yields are given for isolated products.

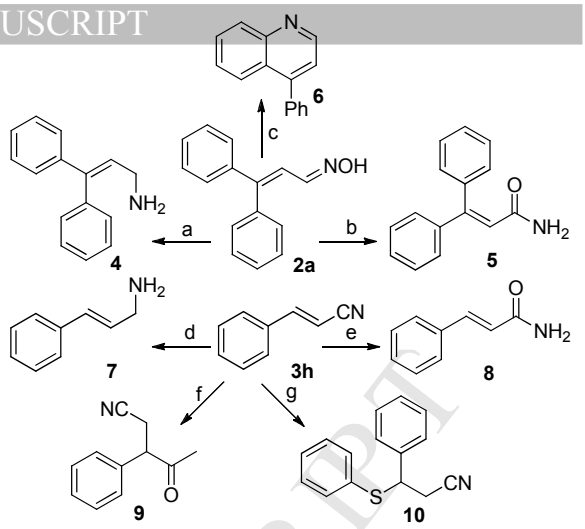
[c]The reactions were performed using a modified procedure: **1a** (0.2 mmol), PTSA (0.3 equiv) and DCE (1 mL) were first stirred at 90 °C for 30 min; then $NH_2OH{\cdot}HCl$ (1.2 equiv) and *p*-TsCl (2 equiv) were added to the reaction system, and the resulting mixture was stirred at 90 °C for another 20 h.

Our one-pot approach was proved to be applicable for the gram-scale preparation of α,β-unsaturated nitriles from propargylic alcohols. As shown in Scheme 2, **3a** could be synthesized on a scale of more than 3.5 g in one batch without any decrease in the yield.



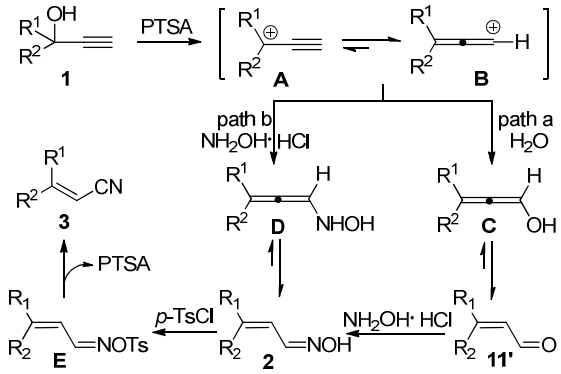
Scheme 2 Gram-scale preparation of α,β-unsaturated nitrile **3a**.

The application of those prepared α,β-unsaturated oxime and nitrile, which are versatile building blocks in organic synthesis, were also carried out (Scheme 3). Oxime **2a** was readily converted into various nitrogen-containing compounds, for example, amine **4** and amide **5** (Scheme 3, a and b)[14,15]. Notably, this kind of β, β-diaryl-α,β-unsaturated oximes could also be used as the starting materials in the construction of the useful quinoline skeleton (Scheme 3, c)[16]. In addition to transformation to other nitrogen-containing derivatives (e.g. Scheme 3, d and e)[17,18], α,β-unsaturated nitrile **3c** could be widely utilized in the formation of new carbon-carbon or carbon-hetero atom bond (e.g. Scheme 3, f and g)[19,20].



Scheme 3 Further application of the products: (a) $LiAlH_4/Et_2O$, r.t., 81%; (b) $Cu(OAc)_2$/Toluene, 80 °C, 94%; (c) i. AcCl/pyridine, r.t.; ii. ^{t}BuOH, Hg lamp, 50% (two steps); (d) $LiAlH_4/AlCl_3/Et_2O$, 0 °C -r.t., 85% (e) K_2CO_3/EtOH-H_2O (v/v 1:20), MW 150 °C, 92%; (f) Ac_2O/Mg/TMSCl/DMF, r.t., 76%; (g) LiOH/PhSH, r.t., 95%.

The plausible mechanism of the cascade reaction has been proposed according to the literatures[8h,8i,12a,21] (Scheme 4). First, propargylic alcohol **1** is dehydrated under the catalysis of PTSA to generate the cation **A**. Then, either H_2O (path a) or $NH_2OH{\cdot}HCl$ (path b) may attack the allenyl cation **B**, resulting in the formation of the α,β-unsaturated aldehyde **11'** via the allenic alcohol **C** or the α,β-unsaturated oxime **2** via the *N*-allenic hydroxylamine **D**, respectively. In path a, **11'** then reacts with $NH_2OH{\cdot}HCl$ to produce the oxime **2**. Finally, when *p*-TsCl is employed to the reaction mixture, **2** can be transformed to the final α,β-unsaturated nitrile **3** through tosylation of the oximido group in **2**, followed by the elimination of PTSA from the intermediate **E**.



Scheme 4 Plausible mechanism for the formation of α,β-unsaturated oximes and nitriles.

To further investigate the mechanism, a control experiment was conducted with the standard condition using **1a** as the substrate (seen the supporting information for details). During the reaction's proceeding, small portions of the reaction solution were taken periodically to determine the key intermediates at different time (5 min, 30 min, 4 h, and 20 h). The ^{1}H NMR spectra were listed in Figure 1. It can be seen that the predominant product in 5 min's sample was aldehyde (90%) and only a trace of other products was observed. This result proved that under the standard condition, propargylic alcohol **1a** underwent path a to form α,β-unsaturated aldehyde first (Figure 1, 1a). As the reaction proceeded, some of aldehyde were consumed

(30% left), and meanwhile, a large number of oxime **2a** (44%) and nitrile **3a** (19%) were generated (Figure 1, 1b). After 4 h, no aldehyde was left. The amount of **2a** decreased slightly (40%) while that of **3a** increased remarkably (48%) (Figure 1, 1c). When the reaction was prolonged to 20 h, most of oxime **2a** was converted into the final product **3a** (76%) (Figure 1, 1d). Based on the above experiment, we concluded that path a is the most possible pathway of this one-pot formation of nitrile from propargylic alcohol.

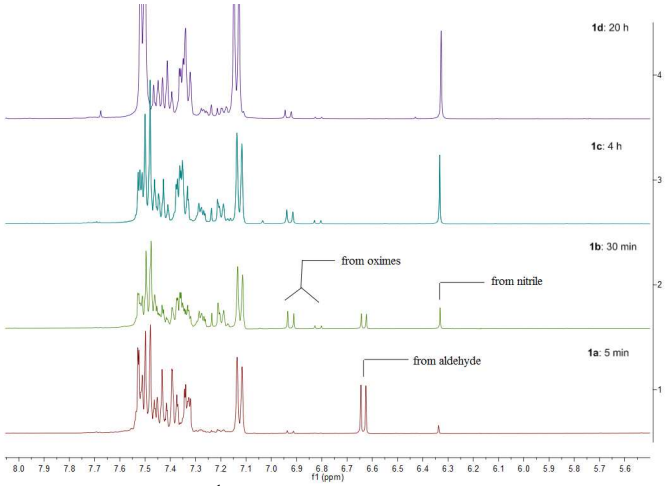


Figure 1 The crude ^{1}H-NMR spectra (in DMSO-d6) of the formation of nitrile **1c** from **1a** at different time: (1a) 5 min; (1b) 30 min; (1c) 4 h; (1d) 20 h.

3. Conclusion

In conclusion, we have developed a practical and efficient PTSA-catalyzed cascade reaction of propargylic alcohols with $NH_2OH{\cdot}HCl$ to afford α,β-unsaturated nitriles or oximes by using or not using *p*-TsCl as the dehydrating promoter. Notable features of this reaction include readily available starting material, non-toxic and stable nitrogen source, common and inexpensive catalyst and reagents, convenient operations, good functional group compatibility, and suitability for large-scale preparations. The reaction should therefore have widespread applications in the construction of α,β-unsaturated oximes and nitriles either as versatile building blocks or as a privileged motif in useful natural and designed compounds.

4. Experimental section

4.1 General

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Avance 400 or 600 instrument. Chemical shifts (δ) are referenced to internal TMS, DMSO-d_6 or $CDCl_3$. High-resolution mass spectra were recorded on a Bruker axis Impact mass spectrometer. Melting points were determined by using a Stuart Scientific SMP10 instrument and are uncorrected. IR spectra were recorded in the ATR mode on a Nicolet 6700 FT-IR Thermo Scientific spectrometer; only the more significant peaks are reported. All reagents and solvents were obtained commercially and used as received without further purification. Reactions were monitored by TLC on glass-backed plates coated with a 0.2 mm thickness of silica gel 60 F254; chromatograms were visualized by UV radiation (254 nm) or by staining with phosphomolybdic acid, 2,4-dinitrophenylhydrazine and $KMnO_4$. Flash column chromatography was performed on 300–400 mesh silica gel.

*4.2.1 General procedure for the synthesis of compounds **2a–2i**, **2m-2n***

PTSA (0.06 mmol, 0.3 equiv) and $NH_2OH{\cdot}HCl$ (0.24 mmol, 1.2 equiv) were successively added to a solution of propargylic alcohol (0.20 mmol, 1 equiv) in DCE (1 mL). The reaction mixture was stirred at 90 ^{o}C and monitored periodically by TLC. After completion of the reaction, the mixture was cooled to room temperature, and sat. aq $NaHCO_3$ (1 mL) and CH_2Cl_2 (5 mL) were added. The organic layer was separated and washed successively with sat. aq $NaHCO_3$ (2 × 1 mL), H_2O (1 mL), and brine (1 mL), then dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the resulting residue was purified by flash column chromatography [silica gel, EtOAc–PE] to give the α,β-unsaturated oxime. Compound **2a**[13] is known compounds.

*4.2.2 General procedure for the synthesis of compounds **2j–2l***

PTSA (0.06 mmol, 0.3 equiv) were added to a solution of propargylic alcohol (0.20 mmol, 1 equiv) in DCE (1 mL). The reaction mixture was stirred at 90 ^{o}C until propargylic alcohol was completely disappeared (about 30 min). Then $NH_2OH{\cdot}HCl$ (0.24 mmol, 1.2 equiv) was added. The resulting mixture continued to be stirred at 90 ^{o}C and monitored periodically by TLC. After completion of the reaction, the mixture was cooled to room temperature, and sat. aq $NaHCO_3$ (1 mL) and CH_2Cl_2 (5 mL) were added. The organic layer was separated and washed successively with sat. aq $NaHCO_3$ (2 × 1 mL), H_2O (1 mL), and brine (1 mL), then dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the resulting residue was purified by flash column chromatography [silica gel, EtOAc–PE] to give the α,β-unsaturated oxime. Compounds **2j**, **2l**,[22] and **2k**[23] are known compounds.

*4.2.3 3,3-Diphenyl-2-propenal oxime (**2a**)*

(More polar, 36%, E): Yellow solid; mp: 164-165 ^{o}C. ^{1}H-NMR (DMSO-d_6, 600MHz) δ 11.41 (s, 1H), 7.50-7.44 (m, 3H), 7.37-7.36 (m, 3H), 7.29-7.27 (m, 2H), 7.24 (d, *J* = 9.6 Hz, 1H), 7.20-7.18 (m, 2H), 6.92 (d, *J* = 9.6 Hz, 1H). ^{13}C-NMR (DMSO-d_6, 150 MHz) δ 147.8, 144.6, 140.6, 137.7, 129.9, 128.8, 128.6, 128.5, 128.4, 127.6, 114.2.

(Less polar, 60%, Z): Yellow solid; mp: 129-131 ^{o}C. ^{1}H-NMR (DMSO-d_6, 600 MHz) δ 11.22 (s, 1H), 7.52 (d, *J* = 10.2 Hz, 1H), 7.49-7.40 (m, 3H), 7.34-7.28 (m, 5H), 7.19-7.18 (m, 2H), 6.83 (d, *J* = 10.2 Hz, 1H). ^{13}C-NMR (DMSO-d_6, 150 MHz) δ 148.1, 146.5, 140.4, 138.1, 129.7, 128.6, 128.5, 128.3, 128.1, 127.2, 121.1.

*4.2.4 3,3-Bis(2-methylphenyl)-2-propenal oxime (**2b**)*

(More polar, 32%): Yellow solid; mp: 142-143 ^{o}C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.37 (s, 1H), 7.31-7.21 (m, 5H), 7.18-7.15 (m, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 9.6 Hz, 1H), 6.80 (d, *J* = 9.6 Hz, 1H), 2.18 (s, 3H), 2.01 (s, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 147.6, 144.3, 140.8, 138.1, 135.7, 135.1, 131.1, 130.6, 130.5, 129.5, 128.2, 128.0, 125.9, 125.7, 118.6, 20.6, 19.6. IR (KBr, cm^{-1}) γ 3220.4, 1636.0, 1589.8, 1446.7, 898.2, 751.5. ESI-HRMS calcd for $C_{17}H_{18}NO$ ($[M+H]^+$) 252.1388, found 252.1381.

(Less polar, 43%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.21 (s, 1H), 7.41 (d, *J* = 10.4 Hz, 1H), 7.29-7.11 (m, 7H), 7.03 (d, *J* = 7.6 Hz, 1H) , 6.43 (d, *J* = 10.0 Hz, 1H), 2.22 (s, 3H), 2.00 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 147.7, 146.3, 140.6, 138.5, 135.6, 135.1, 131.0, 130.5, 130.4, 129.3, 128.0, 127.7, 125.8, 125.7, 125.2, 20.6, 19.6. IR (KBr, cm^{-1}) γ 3233.0, 1618.7, 1480.1, 1455.9, 1379.7, 1036.7, 973.2, 764.2, 730.7. ESI-HRMS calcd for $C_{17}H_{18}NO$ ($[M+H]^+$) 252.1388, found 252.1389.

*4.2.5 3,3-Bis(3-methylphenyl)-2-propenal oxime (**2c**)*

(More polar, 29%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.36 (s, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.26-7.23 (m, 2H), 7.20-7.13 (m, 3H), 7.03-6.97 (m, 3H), 6.92 (d, *J* = 9.6 Hz, 1H), 2.34 (s, 3H), 2.29 (s, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 148.1, 144.1, 140.7, 137.8, 137.7, 130.2, 129.4, 129.0, 128.4, 128.3, 127.9, 127.0, 125.0, 114.1, 20.94, 20.91. IR (KBr, cm^{-1}) γ 3224.9, 3022.9, 1602.6, 1446.7, 985.9, 880.9, 785.0, 705.3. ESI-HRMS calcd for $C_{17}H_{18}NO$ ($[M+H]^+$) 252.1388, found 252.1382.

(Less polar, 52%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.20 (s, 1H), 7.50 (d, *J* = 10.4 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.23-7.19 (m, 2H), 7.13-7.11 (m, 2H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.97-6.95 (m, 2H), 6.77 (d, *J* = 10.4 Hz, 1H), 2.32 (s, 3H), 2.26 (s, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 148.2, 146.8, 140.5, 138.2, 137.8, 137.6, 130.1, 129.0, 128.7, 128.40, 128.38, 127.6, 126.8, 124.5, 120.9, 21.00, 20.96. IR (KBr, cm^{-1}) γ 3261.9, 2251.5, 1602.5, 1455.9, 1342.7, 973.2, 788.5, 700.7. ESI-HRMS calcd for $C_{17}H_{18}NO$ ($[M+H]^+$) 252.1388, found 252.1392.

*4.2.6 3,3- Bis(4-methylphenyl)-2-propenal oxime (**2d**)*

(More polar, 33%): Yellow solid; mp: 138.3-140.0 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.34 (s, 1H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.17-7.15 (m, 5H), 7.06 (d, *J* = 7.6 Hz, 2H), 6.93 (d, *J* = 9.6 Hz, 1H), 2.34 (s, 3H), 2.29 (s, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 147.8, 144.8, 138.4, 138.1, 137.7, 134.9, 129.9, 129.2, 129.1, 127.6, 113.4, 20.9, 20.8. IR (KBr, cm^{-1}) γ 3250.3, 1606.0, 1581.8, 1505.6, 1430.5, 1379.7, 1027.5, 901.6, 822.0, 755.0. ESI-HRMS calcd for $C_{17}H_{18}NO$ ($[M+H]^+$) 252.1388, found 252.1385.

(Less polar, 47%): Yellow solid; mp: 131.0-132.0 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.14 (s, 1H), 7.53 (d, *J* = 10.4 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.74 (d, *J* = 10.0 Hz, 1H), 2.35 (s, 3H), 2.28 (s, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 148.3, 146.5, 137.82, 137.83, 137.4, 135.3, 129.7, 129.1, 127.1, 120.0, 20.8, 20.7. IR (KBr, cm^{-1}) γ 3241.1, 1593.3, 1510.2, 1405.1, 1342.7, 960.5, 818.5, 730.7. ESI-HRMS calcd for $C_{17}H_{18}NO$ ($[M+H]^+$) 252.1388, found 252.1380.

*4.2.7 3,3-Bis(4-fluorophenyl)-2-propenal oxime (**2e**)*

(87%, dr = 1:1.89): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.48 (s, 0.53H), 11.29 (s, 1H), 7.50 (d, *J* = 10.4 Hz, 1H), 7.31-7.14 (m, 13H), 6.93 (d, *J* = 9.6 Hz, 0.51H), 6.80 (d, *J* = 10.4 Hz, 1H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 163.6 (d, J_{C-F} = 148 Hz), 163.3 (d, J_{C-F} = 108 Hz), 161.0 (d, J_{C-F} = 140 Hz), 160.8 (d, J_{C-F} = 104 Hz), 147.9, 145.6, 144.5, 144.2, 137.1 (d, J_{C-F} = 12 Hz), 136.9 (d, J_{C-F} = 12 Hz), 134.3 (d, J_{C-F} = 12 Hz), 133.9 (d, J_{C-F} = 12 Hz), 132.1 (d, J_{C-F} = 32 Hz), 131.85 (d, J_{C-F} = 32 Hz), 129.8 (d, J_{C-F} = 36 Hz), 129.3 (d, J_{C-F} = 32 Hz), 121.7, 115.63 (d, *J* = 164 Hz), 115.60 (d, *J* = 84 Hz), 115.5, 115.3, 114.8. IR (KBr, cm^{-1}) γ 3241.1, 2855.4, 1597.5, 1510.2, 1346.2, 1229.6, 1158.0, 977.8, 839.3. ESI-HRMS calcd for $C_{15}H_{11}NOF_2Na$ ($[M+Na]^+$) 282.0706, found 282.0795.

*4.2.8 3,3-Bis(4-chlorophenyl)-2-propenal oxime (**2f**)*

(81%, dr = 1:2.27): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.54 (s, 0.44H), 11.37 (s, 1H), 7.54-7.48 (m, 4H), 7.43-7.39 (m, 3H), 7.30-7.26 (m, 3H), 7.23-7.20 (m, 3H), 6.94 (d, *J* = 9.6 Hz, 0.42H), 6.86 (d, *J* = 10.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 147.7, 145.1, 144.2, 143.7, 139.1, 138.9, 136.5, 136.1, 133.6, 133.3, 133.1, 133.0, 131.8, 131.6, 129.4, 128.9, 128.8, 128.73, 128.68, 128.6, 122.3, 115.2. IR (KBr, cm^{-1}) γ 3161.4, 2868.1, 1623.3, 1585.2, 1489.4, 1400.5, 1346.2, 1091.0, 1006.7, 944.4, 831.2. ESI-HRMS calcd for $C_{15}H_{11}NOCl_2Na$ ($[M+Na]^+$) 314.0115, found 314.0110.

*4.2.9 3,3-Bis(2,4-dimethylphenyl)-2-propenal oxime (**2g**)*

(More polar, 30%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.26 (s, 1H), 7.04-7.01 (m, 3H), 6.97-6.94 (m, 2H), 6.92-6.87 (m, 2H), 6.79 (d, *J* = 9.6 Hz, 1H), 2.28 (s, 3H), 2.24 (s, 3H), 2.13 (s, 3H), 1.95 (s, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 147.8, 144.6, 138.2, 137.3, 137.2, 135.5, 135.4, 134.9, 131.7, 131.1, 130.4, 129.5, 126.5, 126.2, 118.1, 20.7, 20.6, 20.5, 19.5. IR (KBr, cm^{-1}) γ 3250.4, 2918.9, 1610.6, 1497.5, 1451.3, 1027.5, 906.5, 822.0, 755.0. ESI-HRMS calcd for $C_{19}H_{21}NONa$ ($[M+Na]^+$) 302.1521, found 302.1520.

(Less polar, 56%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.11 (s, 1H), 7.42 (d, *J* = 10.0 Hz, 1H), 7.03-6.88 (m, 6H), 6.37 (d, *J* = 10.0 Hz, 1H), 2.27 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H), 1.94 (s, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 147.9, 146.5, 130.1, 137.1, 136.8, 135.8, 135.4, 134.9, 131.6, 131.1, 130.3, 129.3, 126.4, 126.2, 124.6, 20.7, 20.6, 20.5, 19.5. IR (KBr, cm^{-1}) γ 3250.4, 2918.9, 1610.6, 1492.9, 1451.3, 1379.7, 1338.1, 1275.8, 1027.5, 981.3, 821.9, 751.5. ESI-HRMS calcd for $C_{19}H_{21}NONa$ ($[M+Na]^+$) 302.1521, found 302.1516.

*4.2.10 2-(5H-Dibenzo[a,d][7]annulen-5-ylidene)-2-propenal oxime (**2h**)*

(More polar, 32%): Yellow solid; mp: 118-119 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.40 (s, 1H), 7.49-39 (m, 7H), 7.30 (d, *J* = 7.6 Hz, 1H), 6.97 (AB system, *J* = 12.0 Hz, 2H), 6.93 (d, *J* = 9.6 Hz, 1H), 6.68 (d, *J* = 10.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 147.7, 143.6, 140.3, 134.8, 134.1, 133.4, 131.1, 130.9, 129.4, 129.3, 128.9, 128.6, 128.5, 128.3, 128.0, 127.0, 119.5. IR (KBr, cm^{-1}) γ 3204.2, 2922.4, 2855.4, 1719.2, 1623.3, 1593.3, 1484.8, 1430.5, 1304.6, 1263.1, 1132.6, 1024.0, 898.2, 801.2, 772.3, 738.8. ESI-HRMS calcd for $C_{17}H_{13}NONa$ ($[M+Na]^+$) 270.0895, found 270.0896.

(Less polar, 25%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.25 (s, 1H), 7.55 (d, *J* = 10.4 Hz, 1H), 7.47-7.37 (m, 7H), 7.29-7.26 (m, 1H), 6.95 (AB system, *J* = 12.0 Hz, 2H), 6.19 (d, *J* = 10.4 Hz, 1H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 146.9, 146.4, 140.6, 135.2, 134.2, 133.4, 131.2, 130.9, 129.3, 129.2, 128.9, 128.6, 128.4, 128.1, 127.8, 127.0, 125.9. IR (KBr, cm^{-1}) γ 3233.0, 1723.8, 1623.3, 1484.8, 1430.5, 1304.6, 1137.2, 1027.5, 901.6, 801.2, 772.3, 734.2. ESI-HRMS calcd for $C_{17}H_{13}NONa$ ($[M+Na]^+$) 270.0895, found 270.0890.

*4.2.11 3-Phenyl-2-butenal oxime (**2i**)*

(More polar, 24%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.19 (s, 1H), 7.61 (d, *J* = 9.6 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.41-7.34 (m, 3H), 6.98 (d, *J* = 9.6 Hz, 1H), 2.24 (s, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 144.8, 143.1, 142.1, 129.0, 128.8, 126.3, 114.4, 16.3. ESI-HRMS calcd for $C_{10}H_{11}NONa$ ($[M+Na]^+$) 184.0738, found 184.0744.

(Less polar, 15%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.90 (s, 1H), 8.19 (d, *J* = 10.0 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.39-7.40 (m, 3H), 6.49 (d, *J* = 10.0 Hz, 1H), 2.18 (s, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 148.0, 141.8, 141.0, 128.9, 128.3, 125.9, 120.8, 16.3. ESI-HRMS calcd for $C_{10}H_{11}NONa$ ($[M+Na]^+$) 184.0738, found 184.0740.

*4.2.12 3-Phenyl-2-propenal oxime (**2j**)*

(More polar, 64%): Yellow solid; mp: 135-137 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.29 (s, 1H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.40-7.35 (m, 5H), 6.95 (d, *J* = 15.2 Hz, 1H). ^{13}C-NMR (DMSO-d6, 100 MHz) δ 147.3, 138.0, 136.0, 129.1, 128.9, 127.3, 116.2.

(Less polar, 21%): Yellow solid; mp: 69-71 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.14 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.38-7.27 (m, 3H), 6.91 (dd, *J* = 7.6,

16.0 Hz, 1H), 6.88 (d, *J* = 16.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 150.3, 136.7, 136.1, 128.8, 128.5, 126.8, 123.1.

*4.2.13 3-(4-Methylphenyl)-2-propenal oxime (**2k**)*

(More polar, 43%): Yellow solid; mp: 102-104 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.20 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.33-7.26 (m, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 6.90 (d, *J* = 15.6 Hz, 1H), 2.30 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 147.4, 138.8, 137.9, 133.2, 129.5, 127.2, 115.3, 20.9. IR (KBr, cm^{-1}) γ 3182.2, 2847.3, 1631.4, 1602.5, 1446.7, 1379.7, 1309.2, 1137.1, 977.8, 919.0, 801.2. ESI-HRMS calcd for $C_{10}H_{11}NONa$ ([M+Na]$^+$) 184.0738, found 184.0739.

(Less polar, 30%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.08 (s, 1H), 7.89 (d, *J* = 5.6 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.85 (dd, *J* = 6.0, 16.0 Hz, 1H), 6.83(d, *J* = 16.0 Hz, 1H), 2.29 (s, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 150.4, 138.0, 136.7, 133.4, 129.4, 126.7, 122.1, 20.9.

*4.2.14 3-(4-Chlorophenyl)-2-propenal oxime (**2l**)*

(More polar, 35%): Yellow solid; mp: 138-139 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.33 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.36 (dd, *J* = 9.2, 16.0 Hz, 1H), 7.30 (d, *J* = 9.2 Hz, 1H), 6.94 (d, *J* = 15.6 Hz, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 147.0, 136.5, 134.9, 133.4, 128.92, 128.89, 116.9.

(Less polar, 29%): Yellow solid; mp: 116-117 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.20 (s, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H) , 7.40 (d, *J* = 8.4 Hz, 2H), 6.95 (dd, *J* = 8.8, 16.0 Hz, 1H), 6.78 (d, *J* = 16.0 Hz, 1H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 150.1, 135.2, 135.1, 132.8, 128.8, 128.5, 124.0.

*4.2.15 3,3-Diphenyl-O-methyl-2-propenal oxime (**2m**)*

(More polar, 38%): Yellow solid; mp: 75-76 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, *J* = 10.4 Hz, 1H), 7.40-7.36 (m, 3H), 7.30 (br s, 5H), 7.24-7.22 (m, 2H), 6.77 (d, *J* = 10.0 Hz, 1H), 3.88 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 149.4, 149.2, 140.9, 138.3, 130.2, 128.5, 128.3, 128.1, 127.7, 120.3, 61.8. IR (KBr, cm^{-1}) γ 3057.5, 2935.1, 2898.2, 2818.5, 1602.6, 1559.8 1489.4, 1446.7, 1363.5, 1174.2, 1049.4, 893.6, 767.7, 734.2, 700.7. ESI-HRMS calcd for $C_{16}H_{15}NONa$ ([M+Na]$^+$) 260.1051, found 260.1058.

(Less polar, 51%): Yellow solid; mp: 53-54 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.37 (m, 3H), 7.31-7.30 (m, 5H), 7.24-7.22 (m, 2H), 7.20 (d, *J* = 10.0 Hz, 1H), 7.07 (d, *J* = 10.0 Hz, 1H), 3.95 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 150.6, 146.1, 141.0, 138.0, 130.4, 128.8, 128.4, 128.28, 128.26, 114.6, 62.0. IR (KBr, cm^{-1}) γ 3052.9, 2931.63, 1606.0, 1492.9, 1443.2, 1049.4, 868.1, 772.3, 700.7. ESI-HRMS calcd for $C_{16}H_{15}NONa$ ([M+Na]$^+$) 260.1051, found 260.1053.

*4.2.16 1,1-Diphenylhept-1-en-3-one oxime (**2n**)*

(More polar, 7%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 10.98 (s, 1H), 7.42-7.36 (m, 3H), 7.35-7.26 (m, 3H), 7.21-7.16 (m, 4H), 6.55 (s, 1H), 1.92 (t, *J* = 7.6 Hz, 2H), 1.23-1.15 (m, 2H), 0.99-0.89 (m, 2H), 0.69 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 157.7, 143.5, 142.2, 139.7, 129.5, 128.3, 128.2, 127.8, 127.6, 127.1, 125.1, 27.6, 25.5, 22.3, 13.5. IR (KBr, cm^{-1}) γ 3405.1, 2955.9, 2922.4, 2855.4, 1644.1, 1492.9, 1446.7, 1024.0, 990.6, 764.2, 697.2. ESI-HRMS calcd for $C_{19}H_{21}NONa$ ([M+Na]$^+$) 302.1521, found 302.1519.

(Less polar,11%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 10.78 (s, 1H), 7.41-7.39 (m, 3H), 7.35-7.33 (m, 3H), 7.24-7.22 (m, 2H), 7.13-7.11 (m, 2H), 6.75 (s, 1H), 1.65 (t, *J* = 7.2 Hz, 2H), 1.24-1.17 (m, 2H), 1.05-0.95 (m, 2H), 0.67 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 155.1, 144.5, 141.4, 139.4, 129.3, 128.4, 128.32, 128.28, 128.1, 127.6, 120.3, 31.3, 28.9, 21.6, 13.5. IR (KBr, cm^{-1}) γ 3430.5, 2955.9, 2927.0, 2860.0, 1636.0, 1443.2, 1024.0, 990.6, 764.2, 697.2. ESI-HRMS calcd for $C_{19}H_{21}NONa$ ([M+Na]$^+$) 302.1521, found 302.1517.

*4.3.1 General procedure for the synthesis of compounds **3a–3i***

PTSA (0.06 mmol, 0.3 equiv), $NH_2OH{\cdot}HCl$ (0.24 mmol, 1.2 equiv), and *p*-TsCl (0.40 mmol, 2 equiv) were successively added to a solution of propargylic alcohol (0.20 mmol, 1 equiv) in DCE (1 mL). The reaction mixture was stirred at 90 °C for 20 hrs. Then it was cooled to room temperature, and sat. aq $NaHCO_3$ (2 mL) and CH_2Cl_2 (5 mL) were added. The organic layer was separated and washed successively with sat. aq $NaHCO_3$ (2 × 2 mL), H_2O (2 mL), and brine (1 mL), then dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the resulting residue was purified by flash column chromatography [silica gel, EtOAc–PE] to give the α,β-unsaturated nitrile. Compound **3a**, **3d**, **3f**,[12a] **3b**,[24] **3c**, **3g**,[25] **3e**,[26] and **3i**[12c] is known compounds.

*4.3.2 General procedure for the synthesis of compounds **3j–3p***

PTSA (0.06 mmol, 0.3 equiv) were added to a solution of propargylic alcohol (0.20 mmol, 1 equiv) in DCE (1 mL). The reaction mixture was stirred at 90 °C until propargylic alcohol was completely disappeared (about 30 min). Then $NH_2OH{\cdot}HCl$ (0.24 mmol, 1.2 equiv) and *p*-TsCl (0.40 mmol, 2 equiv) were added. The resulting mixture continued to be stirred at 90 °C for an 20 hrs. Then it was cooled to room temperature, and sat. aq $NaHCO_3$ (2 mL) and CH_2Cl_2 (5 mL) were added. The organic layer was separated and washed successively with sat. aq $NaHCO_3$ (2 ×2 mL), H_2O (2 mL), and brine (1 mL), then dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the resulting residue was purified by flash column chromatography [silica gel, EtOAc–PE] to give the α,β-unsaturated nitrile. Compounds **3j**-**3o**[12b] are known compounds.

*4.3.3 3,3-Diphenyl-2-propenenitrile (**3a**)*

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.46-7.42 (m, 6H), 7.39-7.35 (m, 2H), 7.30-7.28 (m, 2H), 5.73 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 163.1, 138.8, 137.0, 130.4, 130.0, 129.5, 128.6, 128.5, 128.4, 117.9, 94.8.

*4.3.4 3,3-Dis(2-methylphenyl)-2-propenenitrile (**3b**)*

Yellow solid; mp: 80-81 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.32-7.21 (m, 5H), 7.20-7.16 (m, 2H), 7.12 (d, *J* = 7.6 Hz, 1H), 5.64 (s, 1H), 2.17 (s, 3H), 2.13 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 164.2, 138.9, 137.5, 136.0, 135.9, 131.4, 131.0, 129.7, 129.6, 129.432, 129.425, 126.1, 125.9, 117.3, 100.2, 20.8, 20.1.

*4.3.5 3,3-Dis(3-methylphenyl)-2-propenenitrile (**3c**)*

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.33 (t, *J* = 8.0 Hz, 1H), 7.27-7.21 (m, 5H), 7.10-7.07 (m, 2H), 5.69 (s, 1H), 2.38 (s, 3H), 2.34 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 163.5, 139.0, 138.3, 138.1, 137.1, 131.1, 130.7, 130.0, 128.9, 128.4, 128.3, 126.6, 125.7, 118.0, 94.5, 21.32, 21.30.

*4.3.6 3,3-Dis(4-methylphenyl)-2-propenenitrile (**3d**)*

Yellow solid; mp: 110-113 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.20-7.15 (m, 4H), 5.65 (s, 1H), 2.41 (s, 3H), 2.38 (s, 3H), ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 163.1, 140.7, 140.2, 136.3, 134.3, 129.5, 129.3, 129.1, 128.4, 118.3, 93.3, 21.4, 21.3.

*4.3.7 3,3-Dis(4-methoxyphenyl)-2-propenenitrile (**3e**)*

Yellow solid; mp: 105-106 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.54 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 162.3, 161.4, 160.9, 131.6, 131.2, 130.1, 129.5, 118.7, 113.9, 113.8, 91.5, 55.4, 55.3.

*4.3.8 3,3-Dis(4-fluorophenyl)-2-propenenitrile (**3f**)*

Yellow solid; mp: 78-80 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.46-7.41 (m, 2H), 7.31-7.26 (m, 2H), 7.18-7.12 (m, 2H), 7.11-7.05 (m, 2H), 5.68 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 165.1 (d, J_{C-F} = 172 Hz), 162.6 (d, J_{C-F} = 164 Hz), 160.8, 134.9 (d, J_{C-F} = 12 Hz), 132.8 (d , J_{C-F} = 12 Hz), 131.6 (d, J_{C-F} = 32 Hz), 130.4 (d, J_{C-F} = 36 Hz), 117.6, 116.0 (d, J_{C-F} = 24 Hz), 115.7 (d, J_{C-F} = 24 Hz), 94.8.

*4.3.9 3,3-Dis(4-chlorophenyl)-2-propenenitrile (**3g**)*

Yellow solid; mp: 96-97 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 4H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.73 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 160.6, 136.94, 136.87, 136.5, 134.9, 130.8, 129.6, 129.1, 129.0, 117.3, 95.7.

*4.3.10 3,3-Dis(2,4-dimethylphenyl)-2-propenenitrile (**3h**)*

White solid; mp: 81-82 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.17 (d, *J* = 8.0 Hz, 1H), 7.04-6.96 (m, 5H), 5.57 (s, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 164.3, 139.4, 139.3, 136.3, 135.8, 135.7, 135.0, 132.1, 131.7, 129.64, 129.61, 126.8, 126.6, 117.6, 99.2, 21.2, 21.1, 20.7, 20.0. IR (KBr, cm^{-1}) γ 2922.4, 2214.6, 1610.63, 1589.8, 1497.5, 1446.7, 813.9. ESI-HRMS calcd for $C_{19}H_{19}NNa$ ($[M+Na]^+$) 284.1415; found 284.1416.

*4.3.11 3-Phenyl-2-butenenitrile (**3i**)*

*(E)-**3i**:* ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.47-7.40 (m, 5H), 5.62 (s, 1H), 2.47 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 159.7, 138.1, 130.2, 128.7, 125.8, 117.5, 95.5, 20.1.

*(Z)-**3i**:* ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.53-7.42 (m, 5H), 5.40 (s, 1H), 2.28 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 160.9, 137.9, 129.8, 128.6, 127.0, 117.5, 95.5, 24.6.

*4.3.12 (2E)-3-Phenyl-2-propenenitrile (**3j**)*

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.46-7.37 (m, 6H), 5.67 (d, *J* = 16.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 150.5, 133.4, 131.1, 129.0, 127.3, 118.1, 96.2.

*4.3.13 (2E)-3-(2-Methylphenyl)-2-propenenitrile (**3k**)*

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, *J* = 16.4 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.34-7.30 (m, 1H), 7.23 (t, *J* = 7.6 Hz, 2H), 5.80 (d, *J* = 16.8 Hz, 1H), 2.40 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.4, 137.2, 132.5, 131.0, 130.9, 126.6, 125.5, 118.3, 97.2, 19.5.

*4.3.14 (2E)-3-(3-Methylphenyl)-2-propenenitrile (**3l**)*

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, *J* = 16.4 Hz, 1H), 7.29-7.25 (m, 4H), 5.85 (d, *J* = 16.8 Hz, 1H), 2.37 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 150.7, 138.8, 133.4, 132.0, 128.9, 127.9, 124.5, 118.2, 96.0, 21.2.

*4.3.15 (2E)-3-(4-Methylphenyl)-2-propenenitrile (**3m**)*

White solid; mp: 70-71 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.37-7.33 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.81 (d, *J* = 16.4 Hz, 1H), 2.38 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 150.4, 141.8, 130.8, 129.8, 127.3, 118.4, 95.0, 21.4.

*4.3.16 (2E)-3-(4-Chlorophenyl)-2-propenenitrile (**3n**)*

Yellow solid; mp: 85-86 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.38 (br s, 4H), 7.35 (d, *J* = 16.4 Hz, 1H), 5.87 (d, *J* = 16.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 149.0, 137.1, 131.9, 129.3, 128.5, 117.8, 96.9.

*4.3.17 (2E)-3-(2-Naphthalenyl)-2-propenenitrile (**3o**)*

White solid; mp: 131-132 °C. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 7.87-7.86 (m, 4H), 7.56-7.53 (m, 4H), 5.98 (d, *J* = 16.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 150.5, 134.5, 133.1, 131.0, 129.6, 129.1, 128.7, 127.8, 127.7, 127.1, 122.2, 118.3, 96.3.

*4.3.18 (2E)-3-(2-Thienyl)-2-propenenitrile (**3p**)*

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.50-7.23 (m, 2H), 7.24 (s, 1H), 7.08 (s, 1H), 5.65 (d, *J* = 16.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 142.7, 138.3, 131.2, 129.2, 128.3, 118.0, 94.4.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (21302119, 21471093).

References

1. For reviews, see: (a) Yamane, M.; Narasaka, K. In *Science of Synthesis*; Padwa, A., Ed.; Thieme Verlag: Stuttgart, 2004; Vol. 27, pp 605−647; (b) Abele, E.; Abele, R. *Curr. Org. Synth.* **2014**, *11*, 403; (c) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Fucntional Group Preparations*; VCH Publishers: New York, 1989; (d) Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035.
2. (a) Ma, X.-P.; Shi, W.-M.; Mo, X.-L.; Li, X.-H.; Li, L.-G.; Pan, C.-X.; Chen, B.; Su, G.-F.; Mo, D.-L. *J. Org. Chem.* **2015**, *80*, 10098; (b) Chen, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2015**, *17*, 2567; (c) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325; (d) Francois, D.; Maden, A.; Murray, W. V. *Org. Lett.* **2004**, *6*, 1931; (e) Saikia, P.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **2003**, *44*, 8725.
3. (a) Gunes, Y.; Arcelik, N.; Sahin, E.; Fleming, F. F.; Altundas, R. *Eur. J. Org. Chem.* **2015**, *2015*, 6679; (b) Waetzig, J. D.; Swift, E. C.; Jarvo, E. R. T*etrahedron* **2009**, *65*, 3197; (c) Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2003**, *68*, 7133.
4. (a) Qin, H.-L.; Leng, J.; Zhang, C.-P.; Jantan, I.; Amjad, M. W.; Sher, M.; Naeem-ul-Hassan, M.; Hussain, M. A.; Bukhari, S. N. A. *J. Med. Chem.* **2016**, *59*, 3549; (b) DeFalco, J.; Steiger, D.; Gustafson, A.; Emerling, D. E.; Kelly, M. G.; Duncton, M. A. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 276; (c) Nakayama, A., Iwamura, H., Niwa, A., Nakagawa, Y., Fujita, T. *J. Agr. Food Chem.* **1985**, *33*, 1034.
5. (a) Dalisay, D. S., Molinski, T. F. *Org. Lett.* **2009**, *11*, 1967; (b) Zhang, L.-H.; Wu, L.; Raymon, H. K.; Chen, R. S.; Corral, L.; Shirley, M. A.; Krishna Narla, R.; Gamez, J.; Muller, G. W.; Stirling, D. I.; Bartlett, J. B.; Schafer, P. H.; Payvandi, F. *Cancer Res.* **2006**, *66*, 951; (c) Wu, X., Xu, B., Tong, H., Wang, L. *Macromolecules*, **2011**, *44*, 4241.
6. Beckman, E. *Chem. Ber.* **1980**, *23*, 1680.
7. (a) Tanimoto, H., Yokoyama, K., Mizutani, Y., Shitaoka, T., Morimoto, T., Nishiyama, Y., Kakiuchi, K. *J. Org. Chem.* **2016**, *81*, 559; (b) Yu, J.; Lu, M. Synlett, 2014, 25, 1873; (c) Wang, K.; Qian, X.; Cui, J. *Tetrahedron* **2009**, *65*, 10377; (d) Kitahara, K.; Toma, T.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 2259; (e) Andersson, H.; Wang, X.; Bjoerklund, M.; Olsson, R.; Almqvist, F. *Tetrahedron Lett.* **2007**, *48*, 6941; (f) Danilenko, V. M.; Tishkov, A. A.; Ioffe, S. L.; Lyapkalo, I. M.; Strelenko, Y. A.; Tartakovsky, V. A. *Synthesis* **2002**, 635; (g) Palacios, F.; Aparicio, D.; De Los Santos, J. M.; Rodriguez, E. *Tetrahedron* **1998**, *54*, 599.
8. (a) Keita, M.; Vandamme, M.; Paquin, J.-F. *Synthesis* **2015**, *47*, 3758; (b) Zhang, W.; Haskins, C. W.; Yang, Y.; Dai, M. *Org. Biomol. Chem.* **2014**, *12*, 9109; (c) Song, Y.; Shen, D.; Zhang, Q.; Chen, B.; Xu, G. *Tetrahedron Lett.* **2014**, *55*, 639; (d) Zhao, Y.; Chew, X.; Leung, G. Y. C.; Yeung, Y.-Y. *Tetrahedron Lett.* **2012**,

53, 4766; (e) He, J.; Yamaguchi, K.; Mizuno, N. *J. Org. Chem.* **2011**, *76*, 4606; (f) Lamani, M.; Prabhu, K. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6622, S6622/1; (g) Kuo, C.-W.; Zhu, J.-L.; Wu, J.-D.; Chu, C.-M.; Yao, C.-F.; Shi, K.-S. *Chem. Commun.* **2007**, 301; (h) Oskooie, H. A.; Heravi, M. M.; Jaddi, Z. *Phosphorous. Sulfur.* **2005**, *180*, 1993; (i) Ghiaci, M.; Bakhtiari, K. *Synthetic Commun.* **2001**, *31*, 1803.

9. (a) Su, W.; Gong, T.-J.; Xiao, B.; Fu, Y. *Chem. Commun.* **2015**, *51*, 11848; (b) Pradal, A.; Evano, G. *Chem. Commun.* **2014**, *50*, 11907; (c) Powell, K. J.; Han, L.-C.; Sharma, P.; Moses, J. E. *Org. Lett.* **2014**, *16*, 2158; (d) Zhang, G., Ren, X., Chen, J., Hu, M., Cheng, J., *Org. Lett.* **2011**, *13*, 5004; (e) Zhou, W.; Xu, J.; Zhang, L.; Jiao, N. *Org. Lett.* **2010**, *12*, 2888; (f) Zhang, Z.; Liebeskind, L. S. *Org. Lett.* **2006**, *8*, 4331.
10. (a) Lanari, D.; Alonzi, M.; Ferlin, F.; Santoro, S.; Vaccaro, L. *Org. Lett.* **2016**, *18*, 2680; (b) Gu, Z.; Wang, Y.; Yao, Y.; Xia, X.; Wang, H.; Li, W. *Catal. Lett.* **2015**, *145*, 2046; (c) Wang, R., Falck, J. R. *Chem. Commun.* **2013**, *49*, 6516; (d) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428; (e) Kojima, S., Fukuzaki, T., Yamakawa, A., Murai, Y. *Org. Lett.* **2004**, *6*, 3917; (f) Randl, S., Gessler, S., Wakamatsu, H., Blechert, S. *Synlett* **2001**, 430; (g) Zhang, T. Y., O'Toole, J. C., Dunigan, J. M. *Tetrahedron Lett.* **1998**, *39*, 1461.
11. (a) Huang, X.; Li, X.; Jiao, N. *Chem. Sci.* **2015**, *6*, 6355; (b) Noh, J.-H.; Kim, J. *J. Org. Chem.* **2015**, *80*, 11624; (c) Kelly, C. B.; Lambert, K. M.; Mercadante, M. A.; Ovian, J. M.; Bailey, W. F.; Leadbeater, N. E. *Angew. Chem., Int. Ed.* **2015**, *54*, 4241; (d) An, X.-D.; Yu, S. *Org. Lett.* **2015**, *17*, 5064; (e) Shu, Z.; Zhou, Y.; Zhang, Y.; Wang, *J. Org. Chem. Front.* **2014**, *1*, 1123; (f) Khalafi-Nezhad, A.; Mohammadi, S. *RSC Advances* **2014**, *4*, 13782; (g) Rokade, B. V.; Malekar, S. K.; Prabhu, K. R. *Chem. Commun.* **2012**, *48*, 5506.
12. (a) Han, Y.-P.; Song, X.-R.; Qiu, Y.-F.; Hao, X.-H.; Wang, J.; Wu, X.-X.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2015**, *80*, 9200; (b) Huang, X.; Jiao, N. *Org. Biomol. Chem.* **2014**, *12*, 4324; (c) Hao, L., Wu, F., Ding, Z.-C., Xu, S.-X., Ma, Y.-L., Chen, L., Zhan, Z.-P. *Chem.-Eur. J.* **2012**, *18*, 6453, S6453/1; (d) Zhu, Y.; Wen, S.; Yin, G.; Lu, P.; Wang, Y. *Org. Lett.* **2011**, *13*, 3553.
13. Mohamed, M. A. A.; Siedlecka, U.; Suwinski, J. *Pol. J. Chem.* **2003**, *77*, 577.
14. Weitzberg, M.; Abu-Shakra, E.; Azeb, A.; Aizenshtat, Z.; Blum, J. *J. Org. Chem.* **1987**, *52*, 529.
15. Sharma, S. K.; Bishopp, S. D.; Allen, C. L.; Lawrence, R.; Bamford, M. J.; Lapkin, A. A.; Plucinski, P.; Watson, R. J.; Williams, J. *Tetrahedron Lett.* **2011**, *52*, 4252.
16. Alonso, R.; Campos, P. J.; Garcia, B.; Rodriguez, M. A. *Org. Lett.* **2006**, *8*, 3521.
17. Li, M.-B.; Wang, Y.; Tian, S.-K. *Angew. Chem., Int. Ed.* **2012**, *51*, 2968.
18. Tu, T.; Wang, Z.; Liu, Z.; Feng, X.; Wang, Q. *Green Chem.* **2012**, *14*, 921.
19. Ohno, T.; Sakai, M.; Ishino, Y.; Shibata, T.; Maekawa, H.; Nishiguchi, I. *Org. Lett.* **2001**, *3*, 3439.
20. Azizi, N.; Khajeh-Amiri, A.; Ghafuri, H.; Bolourtchian, M. *Green Chem. Lett. Rev.* **2009**, *2*, 43.
21. (a) Park, J.; Yun, J.; Kim, J.; Jang, D.-J.; Park, C. H.; Lee, K. *Synthetic Commun.* **2014**, *44*, 1924; (b) Song, X.-R.; Han, Y.- P.; Qiu, Y.-F.; Qiu, Z.-H.; Liu, X.-Y.; Xu, P.-F.; Liang, Y.-M. *Chem.-Eur. J.* **2014**, *20*, 12046; (c) Zhang, H.; Tanimoto, H.; Morimoto, T.; Nishiyama, Y.; Kakiuchi, K. *Org. Lett.* **2013**, *15*, 5222; (d) Pennell, M. N.; Unthank, M. G.; Turner, P.; Sheppard, T. D. *J. Org. Chem.* **2011**, *76*, 1479; (e) Trost, B. M.; Luan, X.; Miller, Y. *J. Am. Chem. Soc.* **2011**, *133*, 12824; (f) Wang, D.; Zhang, Y.; Harris, A.; Gautam, L. N. S.; Chen, Y.; Shi, X. *Adv. Synth. Catal.* **2011**, *353*, 2584; (g) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149; (h) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027.
22. González-Liste, P. J.; Cadierno, V.; García-Garrido, S. E. *ACS Sustain. Chem. Eng.* **2015**, *3*, 3004.
23. Unterhalt, B.; Eljabour, S. *Arch. Pharm.* **1986**, *319*, 1146.
24. Mueller, A.; Moe, S.; Balandrin, M. World Patent 2000002551, 2000.
25. Zhou, T.; Luo, F.-X.; Yang, M.-Y.; Shi, Z.-J. *J. Am. Chem. Soc.* **2015**, *137*, 14586.
26. Shil, A. K.; Das, P. *RSC Advances* **2015**, *5*, 24859.