Copper-Catalyzed Iminohalogenation of γ, δ-Unsaturated Oxime Esters with Halide Salts: Synthesis of 2-Halomethyl Pyrrolines

Chen Chen, Jie Ding, Yuebo Wang, Xiaonan Shi, Dequan Jiao, Bolin Zhu

PII: S0040-4039(19)30757-9
DOI: https://doi.org/10.1016/j.tetlet.2019.151000
Reference: TETL 151000

To appear in: *Tetrahedron Letters*

Received Date: 23 April 2019
Revised Date: 21 June 2019
Accepted Date: 31 July 2019

Please cite this article as: Chen, C., Ding, J., Wang, Y., Shi, X., Jiao, D., Zhu, B., Copper-Catalyzed Iminohalogenation of γ, δ-Unsaturated Oxime Esters with Halide Salts: Synthesis of 2-Halomethyl Pyrrolines, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151000

Tetrahedron Letters
journal homepage: www.elsevier.com

Copper-Catalyzed Iminohalogenation of γ, δ-Unsaturated Oxime Esters with Halide Salts: Synthesis of 2-Halomethyl Pyrrolines

Chen Chen*, Jie Ding, Yuebo Wang, Xiaonan Shi, Dequan Jiao* and Bolin Zhu*

Tianjin Key Laboratory of Structure and Performance for Functional Molecules, MOE Key Laboratory of Inorganic-Organic Hybrid Functional Material Chemistry, College of Chemistry, Tianjin Normal University, Tianjin 300387, P. R. China. Email: hxxycc@tjnu.edu.cn, hxxyjdq@tjnu.edu.cn, hxxyzbl@tjnu.edu.cn

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

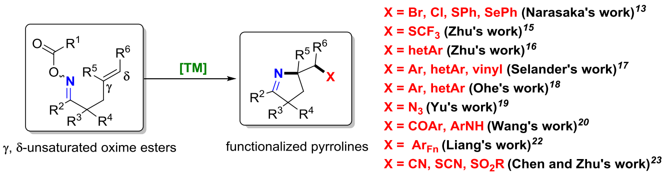
Keywords:
γ, δ-Unsaturated Oxime Esters
Iminohalogenation
Copper-Catalyzed
Pyrrolines

ABSTRACT

A copper-catalyzed iminohalogenation of unactivated alkenes of γ, δ-unsaturated oxime esters is achieved by using readily available halide salts. Utilizing this protocol, a sequence of structurally diversiform 2-halomethyl pyrrolines are efficiently synthesized and a mechanism involving iminyl radical intermediates, which were initiated by Cu(I) species, was proposed.

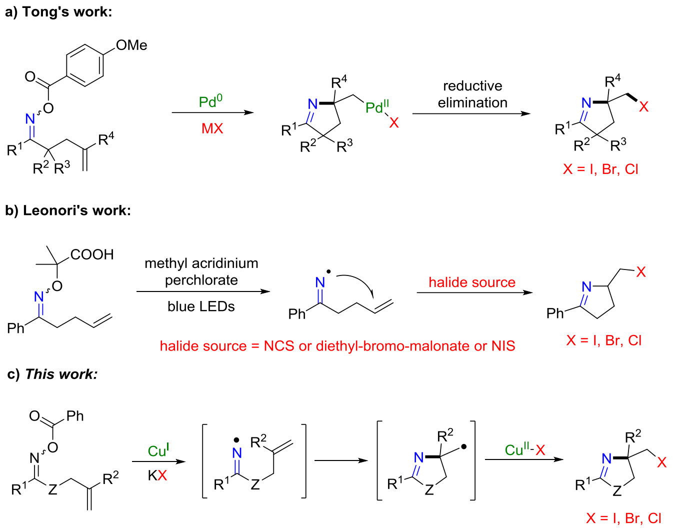
Organic halides are essential functional groups present in a variety of pharmaceuticals,[1] agrochemicals,[2] natural products,[3] and materials,[4] which can easily undergo transformations to a variety of useful functional groups.[5] Furthermore, they can be used as starting materials in transition metal catalysis due to their facile oxidative addition to low valent metal centers.[6] Traditional routes to synthesize organic halides have commonly involved many drawbacks, such as multiple steps, harsh reaction conditions, and the use of toxic reagents. Therefore, the development of efficient approaches for the formation of carbon-halide bonds has been the topic of extensive investigation.[5-9] For examples, Lautens[5, 8] and Tong[9] provided a new concept to construct carbon-halide bonds by highly endothermic C-Pd^{II}-X (X = halide) reductive elimination. Cook[10] and others[11] developed palladium-catalyzed atom transfer radical cyclization reactions for the formation of carbon-halide bonds.

Pyrrolines and their derivatives are valuable structural motifs in a large number of bioactive molecules,[12] which can be facilely obtained through transition-metal-catalyzed cyclization of γ, δ-unsaturated oxime esters.[13-24] In recent years, Narasaka,[13] Bower,[14] Zhu,[15] Zhu,[16] Selander,[17] Ohe,[18] Yu,[19] Wang,[20] Tong,[21] Liang[22] and our group[23] realized transition-metal-catalyzed imino-functionalization of γ, δ-unsaturated oxime esters to synthesize various functionalized pyrrolines (Scheme 1).



Scheme 1. Transition-Metal-Catalyzed Imino-Functionalization of γ, δ-Unsaturated Oxime Esters

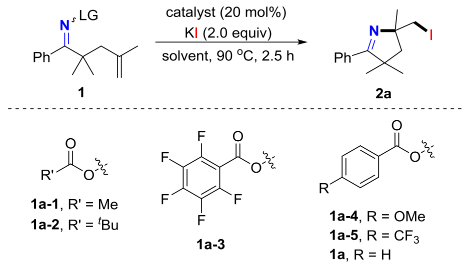
The development of efficient methodologies to synthesize 2-halomethyl pyrrolines has become a subject of great interest during the past few years.[21, 24] In 2015, Tong[21] and co-workers reported a palladium-catalyzed iminohalogenation of alkenes with the assistance of halide salts to provide facile access to synthetically useful 2-halomethyl pyrrolines via C-Pd^{II}-X (X = I, Br, Cl) reductive elimination. Electron-poor phosphine ligand was proved to be essential for promoting this process (Scheme 2a). In 2017, Leonori[24] and co-workers reported a visible-light-mediated radical cascade process for the construction of 2-halomethyl pyrrolines by employing NCS, diethyl-bromo-malonate and NIS as halide source, respectively. However, only three examples were shown in moderate yields (Scheme 2b). Despite a variety of approaches are available, seeking for cheap and readily available reagents/catalysts as well as mild reaction conditions for the synthesis of this type of significant molecules still remains challenge. Inspired by previous works and as our continued interest in the synthesis of halogen-containing heterocycles,[25] we anticipate to realize a copper-catalyzed iminohalogenation of γ, δ-unsaturated oxime esters with halide salts to synthesize 2-halomethyl pyrrolines (Scheme 2c). To the best of our knowledge, such reactions have not been explored.



Scheme 2. Methods of Synthesis of 2-Halomethyl Pyrrolines

For this purpose, we commenced our studies by investigating copper-catalyzed iminoiodination of γ, δ-unsaturated oxime esters for the construction of 2-iodomethyl pyrrolines. To our delight, *O*-acyl oxime **1a-1** was treated with 20 mol% $Cu(OAc)_2{\cdot}H_2O$ in MeCN at 90 °C under N_2 atmosphere for 2.5 h afforded the desired iminoiodination product **2a** in 42% yield (Table 1, entry 1). In order to examine the effect of the leaving group, other derivatives were investigated. The use of *O*-pivaloyl oxime **1a-2** led to a similar yield (Table 1, entry 2). When *O*-pentafluorobenzoyl oxime **1a-3** was used, the yield of **2a** increased to 75%, implying that the aryl substituent might favor this radical cyclization reaction (Table 1, entry 3). Thus, several *O*-aroyl oximes with different substituent groups on the aromatic moiety were examined (Table 1, entries 4-6). The *O*-benzoyl oxime **1a** giving compound **2a** in 76% yield and could be prepared from readily available starting materials. Hence, from the viewpoint of cost and atom economy, **1a** was used for further optimization studies. Investigation of the solvents revealed that MeCN was superior compared to toluene, 1, 4-dioxane and butyronitrile (Table 1, entries 7-9). Amongst the various transition metal catalysts tested, including Cu_2O, CuI, $Cu(OTf)_2$, $FeCl_2$, $Cu(OAc)_2$ was found to be the most effective, giving product **2a** in 81% yield (Table 1, entries 10-14). However, decreasing the catalytic loading of $Cu(OAc)_2$ to 10 mol%, resulted in only 46% yield of **2a**, with remainder being unreacted starting materials (Table 1, entry 15). A similar effect was observed when the reaction temperature was decreased to 60 °C (Table 1, entry 16). Different iodide sources were further tested, such as NaI and ^{n}Bu$_4$NI, but they did not give better results than KI (Table 1, entries 17-18). Hence the optimal reaction conditions are as follows: **1a** (1.0 equiv), $Cu(OAc)_2$ (20 mol%), KI (2.0 equiv), MeCN (2.0 mL) under N_2 atmosphere at 90 °C for 2.5 h.

Table 1. Optimization of the Reaction Conditions[a]

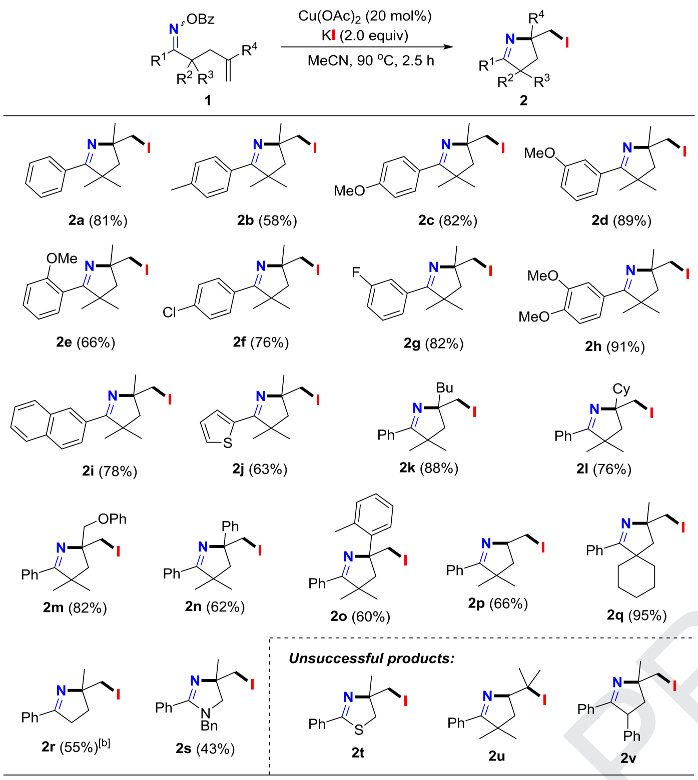


entry	1	catalyst	solvent	yield[b](%)
1	**1a-1**	$Cu(OAc)_2{\bullet}H_2O$	MeCN	42%
2	**1a-2**	$Cu(OAc)_2{\bullet}H_2O$	MeCN	45%
3	**1a-3**	$Cu(OAc)_2{\bullet}H_2O$	MeCN	75%
4	**1a-4**	$Cu(OAc)_2{\bullet}H_2O$	MeCN	71%
5	**1a-5**	$Cu(OAc)_2{\bullet}H_2O$	MeCN	73%
6	**1a**	$Cu(OAc)_2{\bullet}H_2O$	MeCN	76%
7	**1a**	$Cu(OAc)_2{\bullet}H_2O$	Toluene	32%
8	**1a**	$Cu(OAc)_2{\bullet}H_2O$	1,4-Dioxane	53%
9	**1a**	$Cu(OAc)_2{\bullet}H_2O$	PrCN	74%
10	**1a**	Cu_2O	MeCN	65%
11	**1a**	CuI	MeCN	69%
12	**1a**	$Cu(OTf)_2$	MeCN	72%
13	**1a**	$FeCl_2$	MeCN	53%
14	**1a**	$Cu(OAc)_2$	MeCN	81%
15[c]	**1a**	$Cu(OAc)_2$	MeCN	46%
16[d]	**1a**	$Cu(OAc)_2$	MeCN	44%
17[e]	**1a**	$Cu(OAc)_2$	MeCN	70%
18[f]	**1a**	$Cu(OAc)_2$	MeCN	42%

[a] All reactions were performed with **1** (0.2 mmol), catalyst (20 mol%), KI (0.4 mmol) in solvent (2.0 mL) at 90 °C under a nitrogen atmosphere for 2.5 h. [b] isolated yield. [c] 10 mol% $Cu(OAc)_2$ was used. [d] the reaction temperature was 60 °C. [e] NaI as iodine source. [f] ^{n}Bu$_4$NI as iodine source.

With the optimal conditions in hand, we then examined the scope of γ, δ-unsaturated oxime esters. As shown in Table 2. For the aryl-substituted oxime esters with different electronic properties at the *ortho*, *meta*, and *para* position performed well in the reaction, which included methyl, methoxyl, chloro, fluoro, affording the desired iminoiodination products **2a-2h** in 58%-91% yields. Naphthalenyl-substituted oxime ester **1i** showed a positive result, providing **2i** in 78% yield. Notably, this transformation displayed good tolerance towards heterocycle, thiophene-substituted oxime ester **1j** reacted smoothly to give the corresponding product **2j** in 63% yield. The substituent at the alkene part (R^4) was also varied using butyl, cyclohexyl, even bulky groups, producing the corresponding products in good to excellent yields (**2k-2o**). In the case of **1p** bearing a single-substituted alkene afforded **2p** in 66% yield. When **1q,** with cyclohexyl at α position, was used as the substrate, **2q** was obtained in 95% yield. γ, δ-Unsaturated oxime ester without a *gem*-dimethyl group was also examined, prolonged the reaction time to 5 h, the desired product **2r** was obtained in 55% yield when Cu_2O as the catalyst. It should be noted that significant quantities of the corresponding ketone was isolated. This was probably due to the lack of Thorpe-Ingold effect,[26] which aids *gem*-dimethyl substrates, thus favoring radical cyclization. We were also pleased to find that **1s** could be transformed into the imidazoline derivative **2s**, albeit in lower yield. Unfortunately, the thiazoline derivative **2t** was not obtained under our standard conditions.

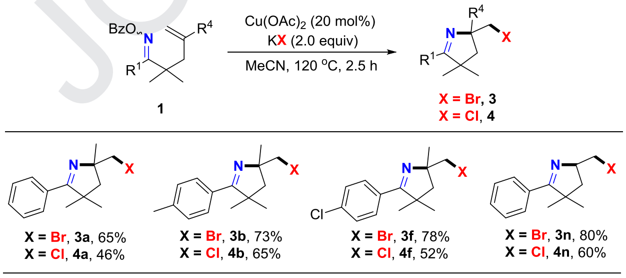
Table 2. The Reaction Scope of the Iminoiodination[a]



[a] All reactions were performed with **1** (0.2 mmol), Cu(OAc)$_2$ (0.04 mmol), KI (0.4 mmol) in MeCN (2.0 mL) at 90 °C under a nitrogen atmosphere for 2.5 h. [b] Cu$_2$O was used instead of Cu(OAc)$_2$, 5 h.

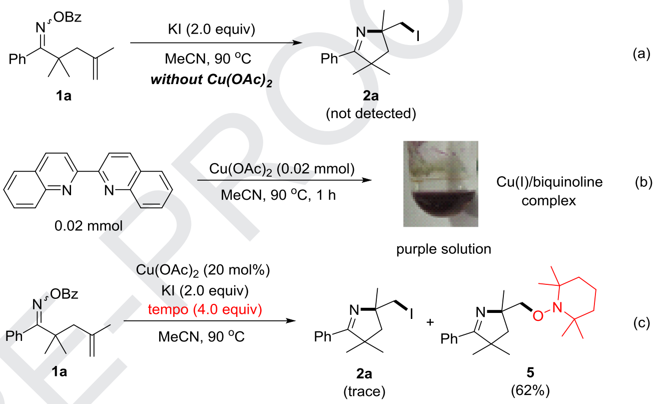
Since we have established the iminoiodination of γ, δ-unsaturated oxime esters, we further investigated iminobromination and iminochlorination. When KBr and KCl were used as the halide source, desired bromo-substituted pyrroline **3a** and chloro-substituted pyrroline **4a** were obtained in 65% and 46% yields, respectively. As shown in Table 3, the corresponding products with various substituents were obtained in 52%-80% yields.

Table 3. The Reaction Scope of Iminobromination and Iminochlorination[a]



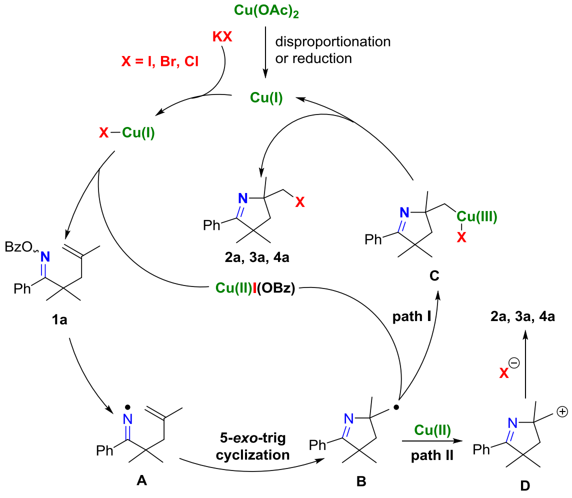
[a] All reactions were performed with 1 (0.2 mmol), Cu(OAc)$_2$ (0.04 mmol), KX (0.4 mmol) in MeCN (2.0 mL) at 120 °C under a nitrogen atmosphere for 2.5 h.

To gain insights into the mechanism of this iminohalogenation process, several control experiments were conducted. In the absence of Cu(OAc)$_2$, **2a** was not detected, demonstrating that the copper salt plays an important role in N-O bond cleavage to form an iminyl radical (Scheme 3a). Heating the MeCN solution of Cu(OAc)$_2$ in the presence of 2, 2'-biquinoline at 90 °C for 1 h, a deep purple solution was observed, which suggested Cu(I)/biquinoline complex formation. This result indicates that this reaction is initiated by Cu(I) species[14b, 15] (Scheme 3b). To further confirm the presence of the iminyl radical, a control experiment was conducted in the presence of 2, 2, 6, 6-tetramethyl-1-piperidinyloxy (TEMPO) under optimal conditions. Only trace amounts of **2a** was detected, and the radical trapping product **5** was obtained in 62% yield. This result clearly demonstrated the reactions are inhibited by TEMPO and iminyl radical might be involved in the iminoiodination process (Scheme 3c).



Scheme 3. Control Experiments

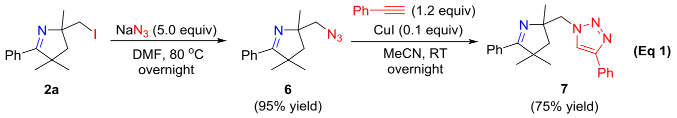
Base on the literature reports[14a, 14b, 15, 17-19] and above results, a plausible mechanism is proposed in Scheme 4, Initially, Cu(I) species was formed in situ via disproportionation or reduction of Cu(OAc)$_2$. Subsequently, CuX was formed via the metathesis between Cu(I) species and KX, which reductively cleaves the N−O bond of the oxime ester **1a** to form iminyl radical. It then undergoes an intramolecular 5-*exo*-trig radical cyclization to form C-centered radical intermediate **B**. Subsequently, **B** is trapped by Cu(II)X(OBz) to produce Cu(III) intermediate **C**, followed by reductive elimination to furnish the iminohalogenation products **2a-4a** and Cu(I) species (Path I). However, alternative Path II cannot be excluded. C-centered radical intermediate **B** can be oxidized to carbocation intermediate **D** by Cu(II) species, which can react with halide ions to afford the 2-halomethyl pyrrolines **2a-4a.**



Ligands on copper complexes have been omitted for clarity

Scheme 4. Proposed Mechanism

To showcase the reactivity of our prepared 2-iodomethyl pyrrolines, we sought to derivatize the carbon-iodine bond by simple synthetic methods (Eq 1). Upon treatment with NaN_3, **2a** could be transformed into **6** now possessing an azido group in 95% yield. This was further converted to triazole-functionalized compound **7** with phenylacetylene via the click reaction in 75% yield.[21]



In conclusion, we have developed a copper-catalyzed iminohalogenation of unactivated alkene of γ, δ-unsaturated oxime esters with halide salts. A variety of substitution patterns and functional groups were tolerated, giving the desired 2-halomethyl pyrrolines in moderate to good yields. A mechanism involving iminyl radical intermediates, which was initiated by Cu(I) species, was proposed. We have exploited subsequent carbon-iodine bond transformations through nucleophilic attack and click reaction, which demonstrated the synthetic potential of our prepared 2-halomethyl pyrrolines.

Acknowledgments

We gratefully acknowledge the Science&Technology Development Fund of Tianjin Education Commission for Higher Education (2018KJ159), Doctoral Program Foundation of Tianjin Normal University (043135202-XB1703), National Natural Science Foundation of China (21572160), the Foundation of Development Program of Future Expert in Tianjin Normal University (WLQR201811) and the Program for Innovative Research Team in University of Tianjin (TD13-5074) for generous financial support.

References and notes

1. a) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992−1012. b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330. c) Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363-1388.
2. a) Jeschke, P. *Pest Manage. Sci.* **2010**, *66*, 10-27. b) Jeschke, P. *ChemBioChem* **2004**, *5*, 570-589.
3. a) Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep.* **2012**, *29*, 144-222. b) Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141-152.
4. a) Tang, M. L.; Bao, Z. *Chem. Mater.* **2011**, *23*, 446-455. b) Amanchukwu, C. V.; Harding, J. R.; Shao-Horn, Y.; Hammond, P. T. *Chem. Mater.* **2015**, *27*, 550-561.
5. Marchese, A. D.; Lind, F.; Mahon, A. E.; Yoon, H.; Lautens, M. *Angew. Chem., Int. Ed.* **2019**, *58*, 5095-5099.
6. a) Petrone, D. A.; Ye, J.; Lautens, M. *Chem. Rev.* **2016**, *116*, 8003-8104. b) Chen, C.; Tong, X. *Org. Chem. Front.* **2014**, *1*, 439-446.
7. For selected examples, see: a) Hao, W.; Wei, J.; Geng, W.; Zhang, W.-X.; Xi, Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 14533-14537. b) Chen, C.; Su, J.; Tong, X. *Chem. Eur. J.* **2013**, *19*, 5014-5018. c) Hou, L.; Zhou, Z.; Wang, D.; Zhang, Y.; Chen, X.; Zhou, L.; Hong, Y.; Liu, W.; Hou, Y.; Tong, X. *Org. Lett.* **2017**, *19*, 6328-6331.
8. For selected examples, see: a) Yoon, H.; Marchese, A. D.; Lautens, M. *J. Am. Chem. Soc.* **2018**, *140*, 10950-10954. b) Petrone, D. A.; Franzoni, I.; Ye, J.; Rodríguez, J. F.; Poblador-Bahamonde, A. I.; Lautens, M. *J. Am. Chem. Soc.* **2017**, *139*, 3546-3557. c) Petrone, D. A.; Lischka, M.; Lautens, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10635-10638. d) Jia, X.; Petrone, D. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9870-9872. e) Newman, S. G.; Howell, J. K.; Nicolaus, N.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14916-14919. f) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 1778-1780.
9. a) Liu, H.; Li, C.; Qiu, D.; Tong, X. *J. Am. Chem. Soc.* **2011**, *133*, 6187-6193. b) Liu, H.; Chen, C.; Wang, L.; Tong, X. *Org. Lett.* **2011**, *13*, 5072-5075. c) Chen, C.; Hu, J.; Su, J.; Tong, X. *Tetrahedron Lett.* **2014**, *55*, 3229-3231.
10. Monks, B. M.; Cook, S. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 14214-14218.
11. For selected examples, see: a) Liu, Q.; Chen, C.; Tong, X. *Tetrahedron Lett.* **2015**, *56*, 4483-4485. b) Liu, H.; Qiao, Z.; Jiang, X. *Org. Biomol. Chem.* **2012**, *10*, 7274-7277. c) Mori, M.; Kubo, Y.; Ban, Y. *Tetrahedron* **1988**, *44*, 4321-4330.
12. a) Magedov, I. V.; Luchetti, G.; Evdokimov, N. M.; Manpadi, M.; Steelant, W. F. A.; Van slambrouck, S.; Tongwa, P.; Antipin, M. Y.; Kornienko, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1392-1396. b) Biava, M.; Porretta, G. C.; Poce, G.; Supino, S.; Deidda, D.; Pompei, R.; Molicotti, P.; Manetti, F.; Botta, M. *J. Med. Chem.* **2006,** *49*, 4946-4952. c) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505-11515.
13. a) Koganemaru, Y.; Kitamura, M.; Narasaka, K. *Chem. Lett.* **2002**, *31*, 784-785. b) Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Tetrahedron*, **1999**, *55*, 8915-8930. c) Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1998**, *27*, 1261-1262.
14. a) Race, N. J.; Faulkner, A.; Shaw, M. H.; Bower, J. F. *Chem. Sci.* **2016**, *7*, 1508-1513. b) Faulkner, A.; Race, N. J.; Scott, J. S.; Bower, J. F. *Chem. Sci.* **2014**, *5*, 2416-2421. c) Faulkner, A.; Scott, J. S.; Bower, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 7224-7230.
15. Guo, K.; Zhang, H.; Cao, S.; Gu, C.; Zhou, H.; Li, J.; Zhu, Y. *Org. Lett.* **2018**, *20*, 2261-2264.
16. Bao, X.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2017**, *56*, 9577-9581.
17. Yang, H.-B.; Pathipati, S. R.; Selander, N. *ACS Catal.* **2017**, *7*, 8441-8445.
18. Shimbayashi, T.; Okamoto, K.; Ohe, K. *Chem. - Asian J.* **2018**, *13*, 395-399.
19. Su, H.; Li, W.; Xuan, Z.; Yu, W. *Adv. Synth. Catal.* **2015**, *357*, 64-70.
20. a) Wang, L.; Wang, C. *Org. Chem. Front.* **2018**, *5*, 3476-3482. b) Wang, L.; Wang, C. *J. Org. Chem.* **2019**, *84*, 6547-6556.
21. Chen, C.; Hou, L.; Cheng, M.; Su, J.; Tong, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 3092-3096.
22. Wei, W.-X.; Chen, S.; Xia, Y.; Li, M.; Li, X.-S.; Han, Y.-P.; Wang, C.-T.; Liang, Y.-M. *ChemCatChem* **2019**, DOI: 10.1002/cctc.201900303.
23. Wang, Y.; Ding, J.; Zhao, J.; Sun, W.; Lian, C.; Chen, C.; Zhu, B. *Org. Chem. Front.* **2019**, DOI: 10.1039/c9qo00421a.
24. Davies, J.; Sheikh, N. S.; Leonori, D. *Angew. Chem., Int. Ed.* **2017**, *56*, 13361-13365.
25. a) Han, F.; Yang, W.; Zhao, A.; Zheng, R.; Ji, C.; Liu, X.; Liu, G.; Chen, C. *Asian J. Org. Chem.* **2018**, *7*, 1124-1131. b) Wang, Z.; Li, T.; Zhao, J.; Shi, X.; Jiao, D.; Zheng, H.; Chen, C.; Zhu, B. *Org. Lett.* **2018**, *20*, 6640-6645. c) Bao, Y.; Wang, Z.; Wang, Y.; Zhao, J.; Gong, J.; Han, M.; Liu, C.; Chen, C.; Zhu, B. *Tetrahedron* **2019**, *75*, 1450-1456.
26. a) Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc.* **1922**, *121*, 1177-1198. b) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305-329. c) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080-1106.

- First copper-catalyzed iminohalogenation of γ, δ-unsaturated oxime esters with KX (X = I, Br, Cl)
- Readily available catalyst and halide source
- New method for the efficient synthesis of diversiform 2-halomethyl pyrrolines
- Good functional group compatibility, moderate to excellent yields, simple operations.

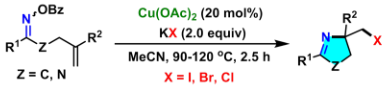
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or alte

Leave this area blank for abstract info.

Copper-Catalyzed Iminohalogenation of γ, δ-Unsaturated Oxime Esters with Halide Salts: Synthesis of 2-Halomethyl Pyrrolines

Chen Chen*, Jie Ding, Yuebo Wang, Xiaonan Shi, Dequan Jiao* and Bolin Zhu*



- 27 examples, up to 95% isolated yield
- good functional group compatibility
- KX(X = I, Br. Cl) as the halide source
- diversiform 2-halomethyl pyrrolines