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SHORT COMMUNICATION

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Oxime-Mediated Oxychlorination and Oxybromination of Unactivated Olefins

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Keywords: Oximes / Halogenation / Oxybromination / Isoxazolines / Palladium / Homogeneous catalysis

An oxime-mediated oxychlorination and oxybromination of unactivated olefins relying on palladium catalysis has been developed. A wide range of chlorinated and brominated isoxazolines has been synthesized in moderate to good yields. To demonstrate the value of the method, the brominated isoxazoline has been further converted to other useful synthetic feedstock.

Introduction

Isoxazolines are extensively found in natural products and molecules with biological activity.[1] They also frequently serve as intermediates in organic synthesis, since they can be easily transformed to β-hydroxy ketones and other useful building blocks by virtue of the easy cleavage of the N–O bond.[2] The conventional synthesis methods of isoxazolines mainly rely on the 1,3-dipolar cycloaddition of nitrile oxides and olefins, in which certain oxidants are generally required for the initial oxidation of aldoximes to nitrile oxides.[3] However, these conversions sometimes pose challenges in terms of the tolerance of sensitive functional groups and the achievement of satisfactory regioselectivities. Recently, a variation was presented by which a variety of functionalized isoxazolines were regioselectively furnished by the palladium-catalyzed annulation of β,γ-unsaturated oximes.[4–7] Chen et al. firstly reported the palladium-catalyzed oxyarylation of β,γ-unsaturated oximes with aryl bromides. Intramolecular 5-*exo*-*trig* ring closure occurred, giving rise to sole regioselectivities.[4] Later, Mosher et al. and Loh et al. developed the regioselective methoxycarbonylation and intramolecular dioxygenation of β,γ-unsaturated oximes, respectively.[5,6]

Transition-metal-catalyzed vicinal difunctionalization of unactivated olefins provides a powerful tool for olefin transformations. We have a long-term interest in the palladium-catalyzed functionalization of unactivated olefins to construct heterocycles.[8] Very recently, we developed the palladium-catalyzed synthesis of 5-methylisoxazoles from oximes.[9] A variety of 5-methylisoxazoles were obtained for evaluation of their bioactivity. To enlarge the library of heterocycles for the purpose of medicinal chemistry, we need to establish efficient access to a series of functionalized 3,5-disubstituted isoxazolines. Herein, we wish to report the oxime-mediated oxyhalogenation of unactivated olefins by means of palladium catalysis in the presence of copper salt.[10,11] The resulting halogenated isoxazolines can serve as a versatile feedstock for diols, triols, and amino alcohols.

Results and Discussion

We commenced by the oxychlorination of olefins. At the outset, the reaction parameters were systematically surveyed. It was found that by using palladium acetate as catalyst, copper chloride did not only serve as chlorine source but also as oxidant for the redox cycle. Among the solvents examined, DMSO showed the best performance in terms of chemical yield (Table 1, entries 1–8). The addition of inorganic or organic base accelerated the reaction, but did not improve the chemical yields (entries 9–11). Reducing the catalyst loadings or replacing the catalyst compromised the chemical yields (entries 12–15).

With the optimized reaction conditions on hand, we turned to define the substrate scope of β,γ-unsaturated oximes. As depicted in Figure 1, the broad generality was obtained with a wide range of oximes regardless of their electronic and steric properties. Most of the reactions were complete in a few hours, giving the corresponding isoxazolines in moderate to good yields. Aryl substrates with electron-rich (**2b**–**2f**) or electron-deficient (**2g**–**2k**) substituents did not have apparent impact on chemical yields and reaction rates. Polyaryl (**2l**) and heteroaryl (**2m**) oximes were also adaptable to the reaction conditions. Not only aryl but

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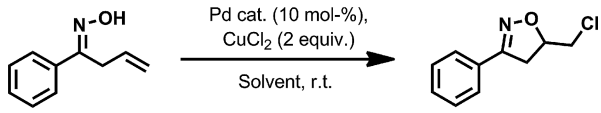
Table 1. Survey of reaction parameters.[a]



1a 2a

Entry	Pd Cat.	Solvent	Additive	Time[b]	Yield[c]
1	$Pd(OAc)_2$	THF	–	3	24
2	$Pd(OAc)_2$	acetonitrile	–	13	74
3	$Pd(OAc)_2$	dioxane	–	7	71
4	$Pd(OAc)_2$	DCE	–	5	35
5	$Pd(OAc)_2$	toluene	–	9	63
6	$Pd(OAc)_2$	chlorobenzene	–	3	80
7	$Pd(OAc)_2$	DMF	–	2.5	42
8	$Pd(OAc)_2$	DMSO	–	3	82
9	$Pd(OAc)_2$	DMSO	K_2CO_3	1	74
10	$Pd(OAc)_2$	DMSO	NaOH	1	80
11	$Pd(OAc)_2$	DMSO	Et_3N	2	69
12[d]	$Pd(OAc)_2$	DMSO	–	4	69
13	$Pd(TFA)_2$	DMSO	–	12	42
14	$PdCl_2$	DMSO	–	6	65
15	$Pd(CH_3CN)Cl_2$	DMSO	–	10	58

[a] Reaction conditions: **1a** (0.15 mmol), $CuCl_2$ (0.30 mmol), and Pd catalyst (0.015 mmol) in solvent (5 mL). [b] Based on entire conversion (hours). [c] Isolated yield (%). [d] 5 mol-% $Pd(OAc)_2$.

alkyl oximes were suitable substrates (**2n**–**2p**). Compound **2q** is noteworthy, as the olefin unit in cyclohexene did not compete with the allyl group in Wacker-type oxypalladation. Reactions with oximes that have substitutions on the allyl group gave rise to fully functionalized isoxazolines (**2r**–**2u**) in good yields. Compound **2t** was obtained as a mixture of two diastereomers (*dr* 3:2), but compound **2u** was generated as a single 4,5-*syn*-isomer due to the stereocontrol of the five-membered ring. In the case of oximes with internal olefins (**2v**–**2x**), the transformation uniformly gave the corresponding oxychlorination products in *anti*-form which was deduced from the conformation of the analogous **3j**.

Inspired by these results, we considered whether the strategy could be applied to the oxybromination of olefins by simply replacing copper chloride with copper bromide (Figure 2). Under similar reaction conditions, a variety of oximes were readily converted into the desired oxybromination products in satisfactory yields. Both electron-rich and electron-poor oximes (**3a**–**3d**) were compatible with the reaction conditions. The chemical yield did not decrease when thienyl oxime (**3e**) was employed. Polysubstituted oximes furnished products **3f**–**3h** in good yields in spite of their more crowded chemical environment. Similarly to the oxychlorination reaction, the transformation of oximes with internal olefins also generated the sole *anti* product (**3i, 3j**), which was unambiguously confirmed by the crystal structure of **3j**.[12] It was in agreement with the conformation of adduct produced by Wacker-type reaction.

To demonstrate the utility of the method, brominated isoxazoline **3f** was explored as a versatile precursor for diols and amino alcohols. As shown in Scheme 1, the nucleophilic substitution of bromine in **3f** with pyrrolidine or acetate gave rise to the resulting isoxazolines **4** and **5** with diol

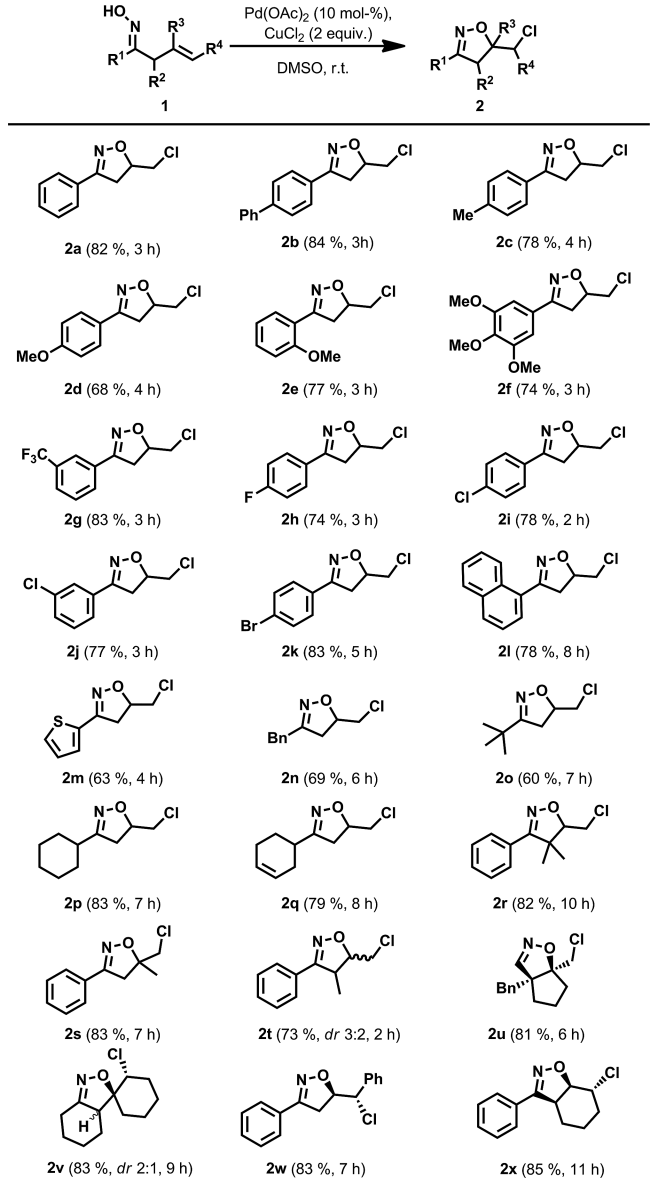


Figure 1. Substrate scope for oxychlorination of olefins.

or amino alcohol structural motifs, respectively. Remarkably, the treatment of **3f** with Fe and aqueous NH_4Cl efficiently led to β,γ-diol ketone **6**, which could be further converted into an important building block, 1,2,4-triol.

Conclusion

In summary, we have developed an oxime-mediated oxychlorination and oxybromination of unactivated olefins relying on palladium catalysis. A vast array of chlorinated and brominated isoxazolines has been divergently synthesized in moderate to good yields. The reaction has been achieved in good regio- and stereoselectivity and with high functional group tolerance. The halogenated isoxazolines can be further transformed into diols, triols, and amino alcohols, which demonstrates the value of the method.

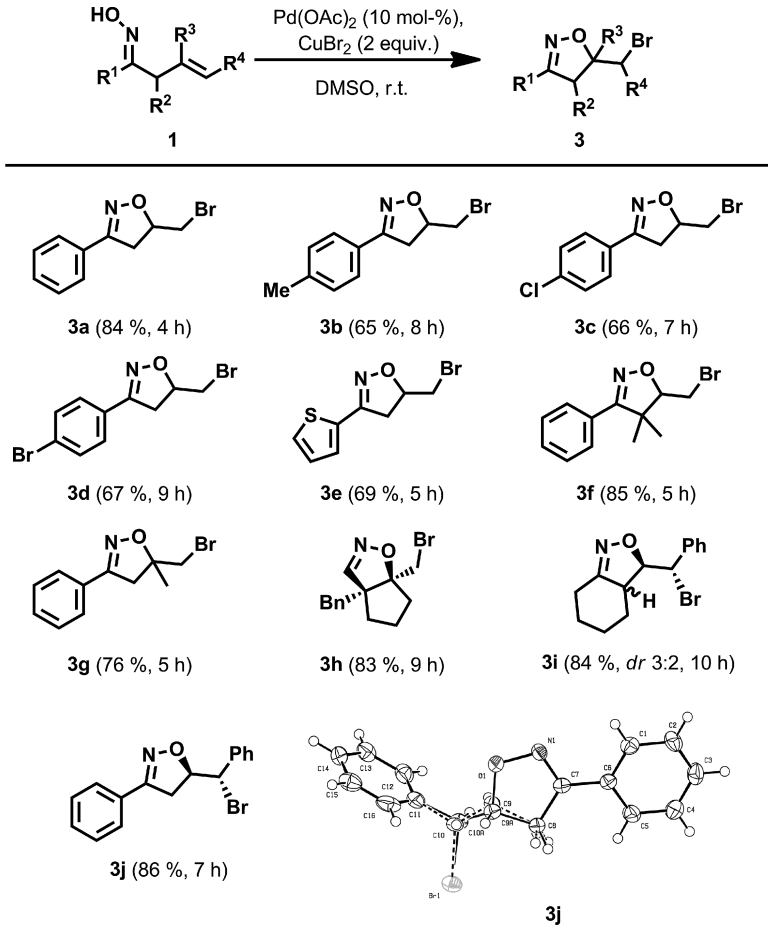
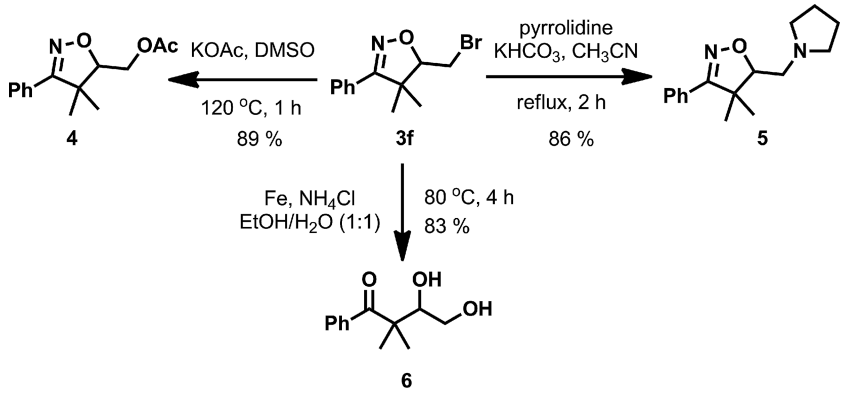


Figure 2. Representative substrates for oxybromination of olefins.



Scheme 1. Chemical transformations of brominated isoxazoline.

Experimental Section

Synthesis Procedure: Oxime 1 (0.15 mmol, 1.0 equiv.), $Pd(OAc)_2$ (0.015 mmol, 0.1 equiv.), and $CuCl_2$ (or $CuBr_2$, 0.3 mmol, 1.2 equiv.) were loaded into a flame-dried flask, which was subjected to evacuation/flushing with dry argon three times. Anhydrous DMSO (5 mL) was added to the mixture by a syringe, and the mixture was then stirred at room temp. until the starting material had been consumed as determined by TLC. The mixture was then extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered, concentrated, and purified by flash chromatography on silica gel (ethyl acetate/hexanes) to give product **2** (or **3**).

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[1] a) C.-B. Xue, J. Wityak, T. M. Sielecki, D. J. Pinto, D. G. Batt, G. A. Cain, M. Sworin, A. L. Rockwell, J. J. Roderick, S. Wang, M. J. Orwat, W. E. Frietze, L. L. Bostrom, J. Liu, C. A. Higley, F. W. Rankin, A. E. Tobin, G. Emmett, G. K. Lalka, J. Y. Sze, S. V. Di Meo, S. A. Mousa, M. J. Thoolen, A. L. Racanelli, E. A. Hausner, T. M. Reilly, W. F. DeGrado, R. R. Wexler, R. E. Olson, *J. Med. Chem.* **1997**, *40*, 2064–2084; b) R. E. Olson, T. M. Sielecki, J. Wityak, D. J. Pinto, D. G. Batt, W. E. Frietze, J. Liu, A. E. Tobin, M. J. Orwat, S. V. Di Meo, G. C. Houghton, G. K. Lalka, S. A. Mousa, A. L. Racanelli, E. A. Hausner, R. P. Kapil, S. R. Rabel, M. J. Thoolen, T. M. Reilly, P. S. Anderson, R. R. Wexler, *J. Med. Chem.* **1999**, *42*, 1178–1192; c) D. G. Batt, G. C. Houghton, W. F. Daneker, P. K. Jadhav, *J. Org. Chem.* **2000**, *65*, 8100–8104; d) J. T. Pulkkinen, P. Honkakoski, M. Peräkylä, I. Berczi, R. Laatikainen, *J. Med. Chem.* **2008**, *51*, 3562–3571; e) P. K. Poutiainen, T. Oravilahti, M. Peräkylä, J. J. Palvimo, J. A. Ihalainen, R. Laatikainen, J. T. Pulkkinen, *J. Med. Chem.* **2012**, *55*, 6316–6327.
[2] K. P. Kozikowski, *Acc. Chem. Res.* **1984**, *17*, 410–416.
[3] For selected examples, see: a) H.-J. Gi, Y. Xiang, R. F. Schinazi, K. Zhao, *J. Org. Chem.* **1997**, *62*, 88–92; b) D. E. Kizer, R. B. Miller, M. J. Kurth, *Tetrahedron Lett.* **1999**, *40*, 3535–3538; c) B. Das, H. Holla, G. Mahender, J. Banerjee, M. R. Reddy, *Tetrahedron Lett.* **2004**, *45*, 7347–7350; d) N. Chatterjee, P. Pandit, S. Halder, A. Patra, D. K. Maiti, *J. Org. Chem.* **2008**, *73*, 7775–7778; e) B. A. Mendelsohn, S. Lee, S. Kim, F. Teyssier, V. S. Aulakh, M. A. Ciufolini, *Org. Lett.* **2009**, *11*, 1539–1542; f) J. L. Frie, C. S. Jeffrey, E. J. Sorensen, *Org. Lett.* **2009**, *11*, 5394–5397; g) S. Minakata, S. Okumura, T. Nagamachi, Y. Takeda, *Org. Lett.* **2011**, *13*, 2966–2969; h) T. Jen, B. A. Mendelsohn, M. A. Ciufolini, *J. Org. Chem.* **2011**, *76*, 728–731; i) A. M. Jawalekar, E. Reubsaet, F. P. J. T. Rutjes, F. L. van Delft, *Chem. Commun.* **2011**, *47*, 3198–3200; j) A. Yoshimura, C. Zhu, K. R. Middleton, A. D. Todora, B. J. Kastern, A. V. Maskaev, V. V. Zhdankin, *Chem. Commun.* **2013**, *49*, 4800–4802; k) A. Yoshimura, K. R. Middleton, A. D. Todora, B. J. Kastern, S. R. Koski, A. V. Maskaev, V. V. Zhdankin, *Org. Lett.* **2013**, *15*, 4010–4013.
[4] D. Jiang, J. Peng, Y. Chen, *Org. Lett.* **2008**, *10*, 1695–1698.
[5] A. L. Norman, M. D. Mosher, *Tetrahedron Lett.* **2008**, *49*, 4153–4155.
[6] M.-K. Zhu, J.-F. Zhao, T.-P. Loh, *J. Am. Chem. Soc.* **2010**, *132*, 6284–6285.
[7] For recent examples of forming isoxazolines from other pathways, see: a) B. Han, X.-L. Yang, R. Fang, W. Yu, C. Wang, X.-Y. Duan, S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 8816–8820; *Angew. Chem.* **2012**, *124*, 8946; b) Y.-T. He, L.-H. Li, Y.-F. Yang, Y.-Q. Wang, J.-Y. Luo, X.-Y. Liu, Y.-M. Liang, *Chem. Commun.* **2013**, *49*, 5687–5689; c) C. B. Tripathi, S. Mukherjee, *Angew. Chem. Int. Ed.* **2013**, *52*, 8450–8453; *Angew. Chem.* **2013**, *125*, 8608; d) W. Li, P. Jia, B. Han, D. Li, W. Yu, *Tetrahedron* **2013**, *69*, 3274–3280; e) X. Zhu, Y.-F. Wang, W. Ren, F.-L. Zhang, S. Chiba, *Org. Lett.* **2013**, *15*, 3214–3217; f) L. Zhu, H. Yu, Z. Xu, X. Jiang, L. Lin, R. Wang, *Org. Lett.* **2014**, *16*, 1562–1565.
[8] a) C. Zhu, J. R. Falck, *Angew. Chem. Int. Ed.* **2011**, *50*, 6626–6629; *Angew. Chem.* **2011**, *123*, 6756; b) C. Zhu, J. R. Falck, *Org. Lett.* **2011**, *13*, 1214–1217.
[9] K.-Y. Dong, H.-T. Qin, X.-X. Bao, F. Liu, C. Zhu, *Org. Lett.* **2014**, *16*, 5266–5268.
[10] For examples of palladium-catalyzed halogenation of alkenes, see: a) C. Jonasson, W. F. J. Karstens, H. Hiemstra, J.-E. Bäckvall, *Tetrahedron Lett.* **2000**, *41*, 1619–1622; b) M. R. Manzoni, T. P. Zabawa, D. Kasi, S. R. Chemler, *Organometallics* **2004**, *23*, 5618–5621; c) A. Lei, X. Lu, G. Liu, *Tetrahedron Lett.* **2004**, *45*, 1785–1788; d) P. Szolcsányi, T. Gracza, *Tetrahedron* **2006**, *62*, 8498–8502; e) G. Broggini, V. Barbera, E. M. Beccalli, E. Borsini, S. Galli, G. Lanza, G. Zecchi, *Adv. Synth. Catal.* **2012**, *354*, 159–170; f) F. E. Michael, P. A. Sibbald, B. M. Cochran, *Org. Lett.* **2008**, *10*, 793–796.
[11] For examples involving Pd/Cu catalytic system, see: a) E. M. Beccalli, G. Broggini, S. Gazzola, A. Mazza, *Org. Biomol. Chem.* **2014**, *12*, 6767–6789; b) E. Borsini, G. Broggini, A. Fasana, S. Galli, M. Khansaa, U. Piarulli, M. Rigamonti, *Adv. Synth. Catal.* **2011**, *353*, 985–994; c) P.-Y. Chen, K.-S. Huang, C.-C. Tsai, T.-P. Wang, E.-C. Wang, *Org. Lett.* **2012**, *14*, 4930–4933; d) K. Funaki, T. Sato, S. Oi, *Org. Lett.* **2012**, *14*, 6186–6189; e) G. Broggini, V. Barbera, E. M. Beccalli, U. Chiacchio, A. Fasana, S. Galli, S. Gazzola, *Adv. Synth. Catal.* **2013**, *355*, 1640–1648; f) Z. Zhang, L. Ouyang, W. Wu, J. Li, Z. Zhang, H. Jiang, *J. Org. Chem.* **2014**, *79*, 10734–10742.
[12] CCDC-1033544 (for **3j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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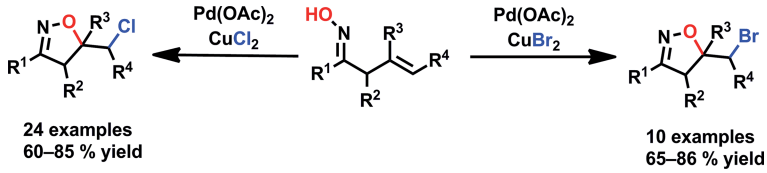

One to two: An oxime-mediated oxychlorination and oxybromination of unactivated olefins relying on palladium catalysis has been developed. A wide range of chlorinated and brominated isoxazolines has been synthesized in moderate to good yields.

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