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AgOTf and TfOH co-catalyzed isoquinoline synthesis via redox reactions of *O*-alkyl oximes

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ABSTRACT

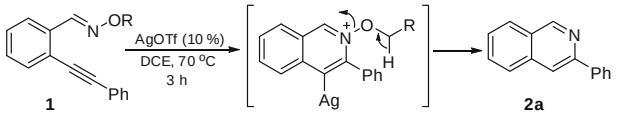
Under AgOTf and Brønsted acid co-catalysis, *O*-alkyl *o*-alkynylbenzaldoxime derivatives undergo a cyclization-induced N–O cleavage to produce isoquinolines with the simultaneous oxidation of *O*-alkyl group. This redox-based method provides a general access to diverse isoquinoline-derived heterocycles that are simple, efficient, and tolerant of various functional groups from readily available and hydrolytically stable oxime precursors.

Recently, there has been a notable progress in the electrophilic metal-catalyzed or electrophile-promoted annulation of alkyne.[1] These methods have provided powerful means to assemble a variety of biologically important heterocycles. Various metal salts, Pd(II), Ag(I), Cu(I), Au(I), Au(III), Hg(II), and Pt(II) salts as well as stoichiometric electrophile (I_2, ICl, and PhSeCl) have been shown to initiate these electrophilic cyclizations. Particularly notable are the processes that occur with additional C–C or C–X bond formation, which leads to the increased product diversity.[2] However, relatively little attention has been paid toward electrophilic cyclization that occurs with the concurrent bond rupture. Prototypical transition metal-catalyzed procedure of the latter type is Larock's cyclization of *o*-alkynyl *t*-butylaldimine that led to an efficient entry to isoquinolines.[3] Considering the medicinal importance of isoquinolines, novel methods that are simple, efficient, and general and that can be mild alternative to classical procedures[4] will be highly desirable.

In the course of our recent study on the reactions of substrates having N–O bonds under electrophilic metal catalysis,[5] we recognized an interesting synthetic potential of the redox chemistry displayed by these N–O substrates. For example, in our synthesis of isoquinoline-*N*-oxides from *o*-alkynyl benzaldoximes,[5b] the *preset* oxidation state that is available from inexpensive hydroxylamine derivatives, obviate the need for extra oxidation step. Furthermore, in our gold-catalyzed azomethine generation and [3+2] cycloaddition cascade,[5c] the cleavage of the N–O bond mediates the required oxidation of alkyne into α-oxo carbenoid and simultaneous reduction of nitrone into imine. Along this line, development of redox reactions mediated by oxime derivatives toward novel redox transformations will be a worthwhile objective,[6] particularly because they are readily prepared from stable and cheap hydroxylamine derivatives, and their redox chemistry could often occur under a mild condition. Moreover, the hydrolytic instability of imines[3a,3b,12] that were observed in some cyclizations of *t*-butylaldimines could be prevented by using more hydrolytically robust oxime precursors. Herein we report a cyclization-induced N–O cleavage leading to isoquinolines and the details of its development.[7]

The required *O*-alkyl oxime derivatives **1** were prepared from the alkylation (NaH, BnBr in THF) or Pd-catalyzed allylation of parent oximes,[8] or more conveniently by the condensation of commercially available *O*-alkyl hydroxylamines (AllylNHOH or BnNHOH) with the corresponding aldehydes.[9] When **1a** was heated with AgOTf (10 mol %) in CH_2Cl_2 at 70 °C (sealed tube), the isoquinoline **2a** was obtained in 85% isolated yield after 3 h (entry 1, Table 1). Inspection of the reaction mixture also revealed the presence of cinnamaldehyde (70%), indicating simultaneous

Table 1
Redox-mediated isoindole synthesis



1 2a

Entry[a]	R	**2a**[b] (%)	Remarks
1	$CH_2CH{=}CHPh$ (**1aa**)	85	Cinnamaldehyde (70%)[b]
2	$CH_2CH{=}CH_2$ (**1ba**)	90	Acrolein[c]
3	CH_2Ph (**1ca**)	93	PhCHO[c]
4	$CH(Me)CH{=}CH_2$ (**1da**)	82	$CH_3C(O)CH{=}CH_2$[c]

[a] DCE (1,2-dichloroethane).
[b] Isolated yields after chromatography.
[c] The presence of these products was confirmed from the crude ^1H NMR spectra but their yields were not determined due to volatility.

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Table 2
The Effect of Ag(I)-salts and TfOH co-catalyst (**1ca** → **2a**)

Entry[a]	Catalyst (%)	Time (h)	Yield[b] (%)
1	TfOH (5)	10	0[c]
2	$AgSbF_6$ (5)	10	95
3	AgOTf (5)	10	95
4	$AgBF_4$ (5)	10	25
5	$AgNTf_2$ (5)	10	70
6	Ag_2CO_3 (2.5)	10	15
7	Ag_2O (2.5)	10	94
8	$AgClO_4$ (5)	10	39
9	AgOTf (5)	3	75
10	AgOTf (5)/TfOH (5)	1	>97
11	AgOTf (5)/TfOH (10)	1	>96
12	AgOTf (5)/$HNTf_2$ (5)	1	74

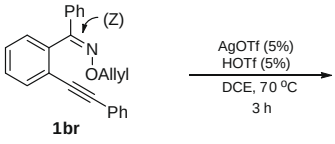
[a] All reactions were carried out at 70 °C for 10 h in DCE using **1b** as substrate, unless otherwise noted.
[b] Determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[c] Starting material remained intact.

oxidation of *O*-cinnamyl group. To optimize the *O*-alkyl group, cinnamyl group was replaced with allyl (**1b**) or benzyl (**1c**) group and these substrates had a slight improvement in terms of yield, with the formation of the respective carbonyl by-products (entries 2 and 3). The reaction presumably proceeds through *6-endo*-dig addition of *N*-atom of oxime on Ag-activated alkyne, followed by N–O cleavage, during which the *O*-alkyl group is oxidized into the corresponding carbonyl compounds.

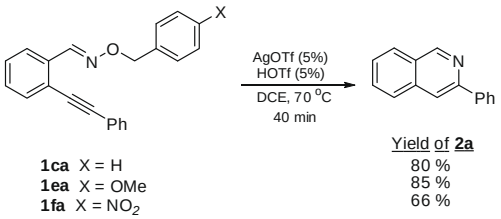
The effect of various silver (I) salts on the cyclization is summarized in Table 2. In the presence of mere Brønsted acid (TfOH, 5%), the reaction did not proceed at all and the starting **1ca** remained intact. Among the silver salts screened, AgOTf, $AgSbF_6$, and Ag_2O (all at 5 mol % catalyst loading) stood out in terms of the reaction time and yield providing **2a** in ~95% yield after 10 h at 70 °C (entries 2, 3, and 7). Use of Brønsted acid co-catalyst (5%) along with AgOTf (5%) further boosted the reactivity, giving **2a** in >97% yield in only 1 h, while the reaction without the co-catalyst gave 75% yield in 3 h (entries 9 and 10). Use of TfOH in more than >30% led to a slightly lower yield due to the decomposition. Change of acid co-catalyst into $HNTf_2$ led to a lower yield of **2a** (entry 12). The reason for this beneficial effect of Brønsted acid is presumably due to a facile proto-demetallation in the turnover step.[10] Surprisingly, however, the use of various gold(I) catalysts of the type Au(-L)OTf showed inferior results compared to AgOTf under a similar reaction condition. We also examined the solvent effect using AgOTf (5%) as a catalyst: Among the solvents screened, CH_2Cl_2 and 1,2-dichloroethane displayed a steady and the highest conversion, while more polar solvents (DMF, CH_3NO_2, or CH_3CN) also showed high initial rates but lower overall conversions. However, the reaction was inefficient in MeOH or in toluene.

The optimized reaction condition mentioned above (AgOTf 5 mol % and TfOH 5 mol % in DCE at 70 °C) led us to examine the generality of the reaction in the synthesis of various isoquinoline skeletons (Table 3). As also shown in Table 1, the *O*-benzyl substrate (**1cc**) on the oximes underwent slightly faster reaction than O-allyl substrate (**1bc**) (entries 3 and 4). Electron-demand in the alkynyl terminus had dramatic effect on the efficiency of cyclization. Placing electron-rich aryl group instead of Ph at R^2 significantly shortened the reaction time (entries 1 and 2).[3i] While the substrates with R^2 = aryl led to an efficient cyclization, the substrates with alkenyl or long alkyl group at R^2 underwent sluggish reaction and required relatively longer reaction time at higher catalyst loadings (entries 3–5, 12, and 13).[11] We also explored substrates with varying electron demands in the aromatic core. Substitution with fluoro, chloro, trifluoromethyl, methyl, methoxy, or dimethoxy group could well be accommodated in this cyclization (entries 6–12). Importantly, in contrast to the classical Pictet–Spengler reaction which requires electron-rich aromatic group for effective cyclization, electron-deficient aromatic substrates worked equally well (entries 6–8) or even better than electron-rich aromatic substrates (entries 3 and 5 vs entries 12 and 13).[7] We also explored ketoxime derivatives (entries 14 and 15). In fact, the reactions of ketoximes occurred much faster than those of aldoximes (entries 14 and 15).[12] The efficiency of this cyclization is also demonstrated in the synthesis of 1,6-naphthyridine (entry 16). In addition, double cyclization underwent smoothly with remarkable efficiency to give pyrido[3,4-*g*]isoquinolines and pyrido[4,3-*g*]isoquinolines, although in this case, further catalyst loadings were required for a full conversion (entries 17 and 18). Notably the heterocycles **2o**, **2p**, and **2q** are highly fluorescent and will have important applications in materials science.

The mechanistic course of this reaction deserves further comments. To support the mechanistic proposal in Table 1, the (*Z*)-ketoxime derivative **1br** was prepared and tested under our standard catalytic condition. While (*E*)-ketoxime derivatives **1bm** and **1bn** efficiently cyclized (Table 3), the (*Z*)-**1br** remained intact after 3 h at 70 °C, indicating that (*E*)-geometry is required for the redox cyclization (Eq. 1). In addition, we inspected the nature of N–O cleavage in further detail by preparing electronically tuned *O*-benzyloxime derivatives **1ea** and **1fa**. Comparison of the reaction rates determined after the same reaction time shows that there is a small but discernable electronic effect: Electron-donating –OMe group (**1ea**) had a similar or slightly increased rate of the cyclization, while nitro group (**1fa**) showed a slightly diminished reaction rate (Eq. 2).



(1)

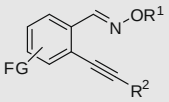
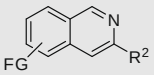
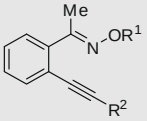
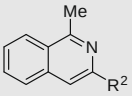
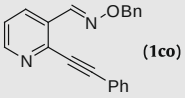
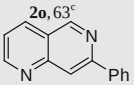
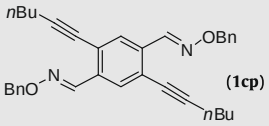
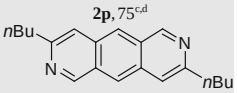
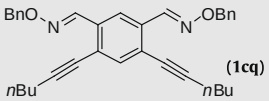
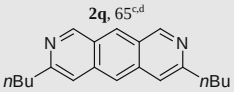


(2)

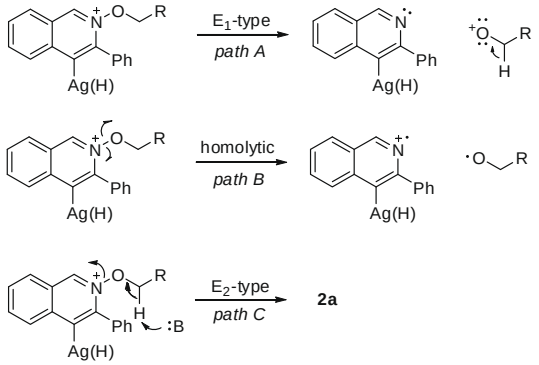
From the above data, the E_{1cb}-type elimination could be ruled out based on the observed slower rate of **1fa** cyclization. Unimolecular (E_1) mechanism would generate a highly reactive alkyloxenium ion[13] and thus could also be disfavored (path A, Scheme 1). Homolytic cleavage of N–O bond (path B) is less likely because such process would require a photolysis condition,[14] and the current reaction proceeds smoothly in the dark or in the presence of 1 equiv of BHT (2,6-di-*tert*-butyl-4-methylphenol) as a radical trap under otherwise identical conditions. With BHT, benzyl alcohol would be expected as a by-product from the cyclization **1ca** under the homolytic condition, but was not observed.[15] Thus bimolecular E_2-type elimination (path C) with concerted bond cleavage seems to be the most likely.

In summary, we demonstrated that *O*-alkyl benzaldoxime derivatives undergo a cyclization-induced N–O cleavage to provide isoquinolines and this general protocol is efficiently co-catalyzed by AgOTf and TfOH. The feature of this cyclization is its simplicity, mild reaction conditions, and its generality with regard to aromatic substituent. For example, elaborate aza-aromatics, such as pyrido[4,3-*g*]isoquinolines and pyrido[3,4-*g*]isoquinolines could be readily assembled by this protocol.

Table 3
AgOTf/TfOH-catalyzed synthesis of isoquinolines[a]

Entry	Substrate	Condition[a] (*x* mol %/time)	Product[b] (%)
			
1	R^1 = Bn, R^2 = Ph (**1ca**)	5/1 h	**2a**, 95
2	R^1 = Bn, R^2 = 4-MeO-C_6H_4 (**1cb**)	5/0.5 h	**2b**, 93
3	R^1 = allyl, R^2 = *n*-Hex (**1bc**)	10/10 h	**2c**, 72
4	R^1 = Bn, R^2 = *n*-Hex (**1cc**)	5/7 h	**2c**, 76
5	R^1 = Bn, R^2 = cyclohex-1-enyl (**1cd**)	10/6.5 h	**2d**, 85
6	R^1 = Bn, R^2 = Ph, FG = 5-F (**1ce**)	5/5 h	**2e**, 96
7	R^1 = Bn, R^2 = Ph, FG = 5-Cl (**1cf**)	5/3.5 h	**2f**, 83
8	R^1 = Bn, R^2 = Ph, FG = 5-CF_3 (**1cg**)	5/5.5 h	**2g**, 70
9	R^1 = Bn, R^2 = Ph, FG = 5-CH_3 (**1ch**)	5/3 h	**2h**, 65
10	R^1 = Bn, R^2 = Ph, FG = 5-OCH_3 (**1ci**)	5/4.5 h	**2i**, 82
11	R^1 = Bn, R^2 = Ph, FG = 4,5-di-OCH_3 (**1cj**)	5/4.5 h	**2j**, 81
12	R^1 = allyl, R^2 = *n*-Hex, FG = 5-OCH_3 (**1bk**)	10/17 h	**2k**, 71
13	R^1 = Bn, FG = 4,5-di-OCH_3, R^2 = cyclohex-1-enyl (**1cl**)	10/18 h	**2l**, 57[c]
			
14	R^1 = allyl, R^2 = Me (**1bm**)	5/2 h	**2m**, 86
15	R^1 = allyl, R^2 = cyclohex-1-enyl (**1bn**)	5/0.5 h	**2n**, 92
16	 (**1co**)	10/17 h	**2o**, 63[c] 
17	 (**1cp**)	20/18 h	**2p**, 75[c,d] 
18	 (**1cq**)	20/18 h	**2q**, 65[c,d] 

[a] Equimolar amount (*x* mol %) of AgOTf and TfOH in 1,2-dichloroethane at 70 °C.
[b] Isolated yield after chromatography.
[c] Unreacted starting material remained.
[d] Two portions of AgOTf/TfOH (10 mol %) were added successively at 10 h time interval.



Scheme 1. Possible mechanisms for the N–O redox.

Acknowledgments

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Supplementary data

Experimental details, characterization of substrates and products, and copies of ^{1}H, ^{13}C NMR spectra of all products. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.144.

References and notes

1. (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395; (b) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174; (c) Larock, R. C. In *Acetylene Chemistry, Biology, and Material Science*; Diedrich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: New York, 2005; pp 51–59. Chapter 2.
2. (a) Asao, N.; Yudha, S. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. and references therein; (b) Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959; (c) Wei, P.; Ding, Y.-X. *Synlett* **2004**, 599; (d) Patil, N. T.; Yamomoto, Y. *J. Org. Chem.* **2004**, *69*, 5139; (e) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 10096; (f) Su, S.; Porco, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 7744; (g) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462.
3. For transition metal catalyzed processes, see: (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86; (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437; (c) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042; (d) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920; (e) Dai, G.; Larock, R. C. *Org. Lett.* **2002**, *4*, 193; (f) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553; (g) Korivi, R. P.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 5179; For electrophile-induced cyclizations, see: (h) Ishikawa, T.; Manabe, S.; Akiwa, T.; Kudo, T.; Saito, S. *Org. Lett.* **2004**, *6*, 2361; (i) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**. doi:10.1021/jo802196r.
4. (a) Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903; (b) Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030; (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431; For $AuCl_3$/AgOTf catalyzed Pictet–Spengler reaction, see: (d) Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521; For related electrophilic cyclization using ketenimine intermediate, see: (e) Yang, Y.-Y.; Shou, W.-G.; Chen, Z.-B.; Hong, D.; Wang, Y.-G. *J. Org. Chem.* **2008**, *73*, 3928.
5. (a) Yeom, H.-S.; Lee, E.-S.; Shin, S. *Synlett* **2007**, 2292; (b) Yeom, H.-S.; Kim, S.; Shin, S. *Synlett* **2008**, 924; (c) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040.
6. For metal-catalyzed redox transformation of oximes into nitriles and amides, see: (a) Yang, S. H.; Chang, S. *Org. Lett.* **2001**, *3*, 4209; (b) Yamaguchi, K.; Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Mizuno, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3922; (c) Fujiwara, H.; Ogasawara, Y.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 5202.
7. While this Letter is in preparation, Zhang et al. has published a communication having a similar approach for the isoquinoline synthesis. However, the demonstrated scope has not been examined with electron-deficient aromatic substrates or for the synthesis of more elaborate heterocycles, such as 1,6-naphthyridine or pyridoisoquinolines. Furthermore, employing TfOH as co-catalyst, we arrived at much milder reaction conditions. See Gao, H.; Zhang, J. *Adv. Synth. Catal.* **2009**, *351*, 85.
8. Miyabe, H.; Yoshida, K.; Krishna, V.; Matsumura, A.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 5630.
9. The starting aldehydes were mixed with $BnONH_2{\cdot}HCl$ (or $AllylONH_2{\cdot}HCl$, 1.1 equiv) and NaOAc (1.1 equiv) in CH_2Cl_2–MeOH (1:1) at rt. After 1 h, the desired *O*-alkyl oximes were obtained in good yields (75–90%) after chromatography.
10. With stoichiometric amount of electrophilic metal, M-bound intermediate (Au-Csp^2) was isolated, which proto-demetallate in the presence of acid, see (a) Liu, L.-P.; Mashuta, M. S.; Hammond, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 17642; For examples of the use of acid co-catalyst in electrophilic metal catalysis, see: (b) Bhunia, S.; Wang, K.-C.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2008**, *47*, 5063; (c) Zhou, C.-Y.; Hong, P. W.; Che, C.-M. *Org. Lett.* **2006**, *8*, 325; (d) Belting, W.; Krause, N. *Org. Lett.* **2006**, *8*, 4489; (e) Dai, L.-Z.; Qi, M.-J.; Shi, Y.-L.; Shi, M. *Org. Lett.* **2007**, *9*, 3191.
11. However, the substrate with $R^2 = n$-Bu similar to **2bc** led to an efficient cyclization in 2 h as indicated by ^1H NMR, although the yield was not determined due to its volatility.
12. One limitation of the procedure using *t*-butylimine precursors is the inaccessibility and/or instability of the corresponding ketimine derivatives, and thus derivatization at C1-position of isoquinolines is not viable (Ref. 3).
13. For characterizations of aryloxenium ions, see: (a) Wang, Y.-T.; Jin, K. J.; Leopard, S. H.; Wang, J.; Peng, H.-L.; Platz, M. S.; Xue, J.; Phillips, D. L.; Glover, S. A.; Novak, M. *J. Am. Chem. Soc.* **2008**, *130*, 16021; (b) Abramovitch, R. A.; Alvernhe, G.; Bartnik, R.; Dassanayake, N. L.; Inbasekaran, N. M.; Kato, S. *J. Am. Chem. Soc.* **1981**, *103*, 4558.
14. Durmaz, Y. Y.; Yilmaz, G.; Yagci, Y. *J. Polym. Sci., Part A.; Polym. Chem.* **2007**, *45*, 423.
15. However, in the presence of BHT, the reaction was much slower due to the effect of phenolate counter anion.