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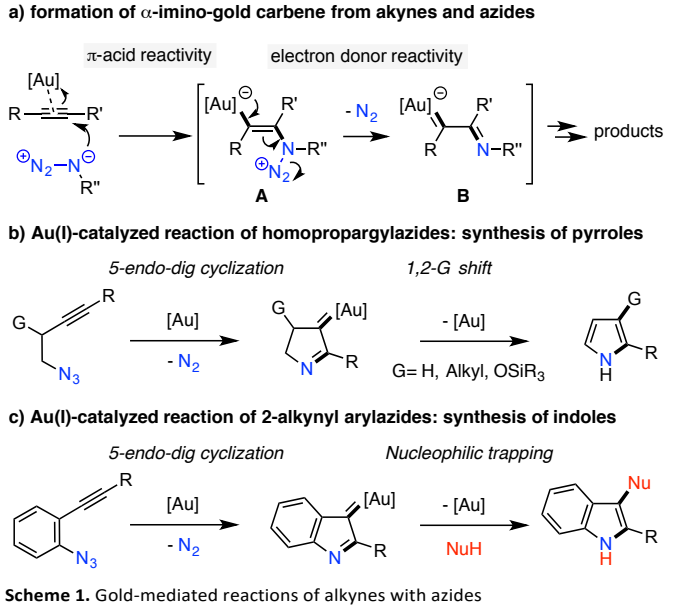
Denitrogenative 6-*endo-dig* azide-yne cyclization of α-propargyloxy-β-haloalkylazides was enabled by gold catalysis, thus providing 2*H*-1,3-oxazines. This rare cyclization mode in gold-catalyzed reactions of azide-yne substrates was demonstrated to be facilitated and controlled by electronic and resonance effect of the alkyne substituents. Molecular transformations of as-prepared 2*H*-1,3-oxazines were also investigated.

Gold catalysis is capable of enhancing molecular complexity through activation and functionalization of carbon-carbon unsaturated bonds.[1] This remarkable ability originates from the π-Lewis acidic properties of electrophilic gold complexes and various nucleophilic functionalization modes of carbon π-systems have been disclosed over the past ten years. For example, gold-mediated reactions of alkynes with azides have been developed as one of the most promising methods for the synthesis of nitrogen-containing molecules.[2] In such a type of process, the nucleophilic addition of the internal nitrogen atom of the azido moiety onto the electrophilically activated alkyne-gold complex enables the simultaneous construction of a C-N bond and a C-Au bond to initially form an organogold intermediate **A** (Scheme 1a).[3] Subsequently, by taking advantage of the electron-donor character of the resulting vinyl-gold moiety, expulsion of dinitrogen proceeds to generate a new intermediate **B**, which can be depicted as an α-imino gold carbene species. This key intermediate **B** can then evolve and be further functionalized in the following different reaction pathways. The group of Toste demonstrated in his pioneering work in the field[2j] that homopropargylazides could be converted into pyrroles following a gold(I)-catalyzed 5-*endo-dig* cyclization followed by a 1,2-H or group shift onto the resulting α-imino gold carbene intermediate (Scheme 1b).



Scheme 1. Gold-mediated reactions of alkynes with azides

Later on, the groups of ours and Zhang disclosed another way to functionalize α-imino gold carbenes derived from 2-alkynyl arylazides by reacting them with carbon and oxygen nucleophiles. This led to the development of an expedient synthesis of functionalized indole derivatives (Scheme 1c).[2f,g] More recently, the same general principle of the reactivity was exploited by different groups to access various *N*-containing heterocycles such as indoles,[2d] oxindoles,[2b] pyrroles,[2a,c] indoloquinolines[2e] and carbolines.[2d] It is worth noting that the so far reported gold-mediated azide-yne cyclizations are, however, almost exclusively proceeding in a 5-*endo-dig* mode thus leading to the construction of 5-membered ring nitrogen-heterocycles.[4,5]

Zhang's seminal studies on gold-catalyzed intermolecular oxidation reactions of internal alkynes revealed that electronic

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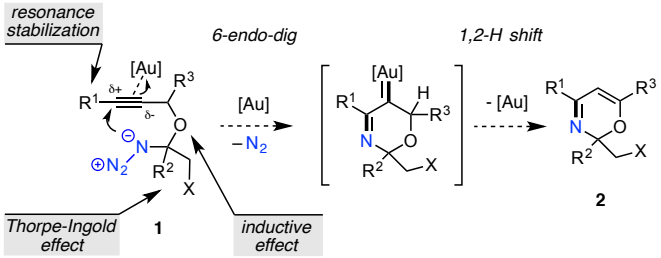
effects of the alkyne substituents, namely resonance stabilization and inductive effect, could help in controlling and enhancing the regioselectivity of the transformation.[6] Given the mechanistic similarities between the two processes (formation of α-oxo gold carbene intermediates / α-imino gold carbene intermediates), we reasoned that a proper installation of such electronic properties on the alkyne substituents might be essential to realize the kinetically disfavoured azide-yne cyclization mode. We recently reported a protocol to produce α-alkoxy-β-haloalkylazides by a fluoro- or bromoalkoxylation of vinyl azides in the presence of respectively Selectfluor®[7] or TBCO[8] (Scheme 2a).[9] We became interested in exploring the reactivity of α-propargyloxy-β-haloalkylazides **1**, and more specifically in the possibility to perform 6-*endo-dig* azide-yne cyclizations by means of gold catalysis (Scheme 2b). We considered that such a type of cyclization should be facilitated in the present case by: 1) the presence of the oxygen atom in **1** that would polarize the C≡C bond by inductive effect, thus rendering the alkyne carbon distal to the oxygen atom more electrophilic, and 2) the presence of R^1 substituents that could stabilize by resonance the resulting δ^+ charge at the distal alkyne carbon (e. g. R^1= aryl, alkenyl). Additionally, the presence of substituents on the carbon atom linking the azido and alkynyloxy moieites was expected to induce a Thorpe-Ingold effect that would enhance the rate of cyclization.[10] The development of this chemistry for synthesis of 2*H*-1,3-oxazines **2** and their molecular transformations are described herein.

a) linking alcohols with vinyl azides by haloalkoxylation (ref 9)

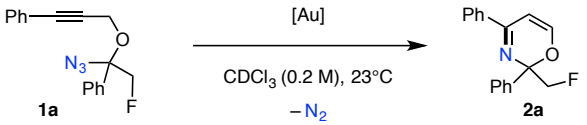
b) reactivity of α-propargyloxy-β-haloalkylazides under Au-catalysis



Scheme 2. Synthesis and reactivity of α-propargyloxy-β-haloalkylazides **1**

With the above working hypothesis, we started our investigations by studying the reactivity of α-propargyloxy-β-fluoroalkylazide **1a** (R^1 = Ph)[11] in the presence of various gold(I) catalysts (Table 1). Substrate **1a** was first treated in $CDCl_3$[12] at 23 °C with a series of three different gold complexes: $[Ph_3PAu(NCCH_3)]SbF_6$ (entry 1), $[IPrAu(NCCH_3)]SbF_6$ (entry 2) and $[XPhosAu(NCCH_3)]SbF_6$ (entry 3). While these complexes were all able to produce 2*H*-1,3-oxazine **2a** *via* the desired 6-*endo-dig* azide-yne cyclization, $[XPhosAu(NCCH_3)]SbF_6$ exhibited a far superior reactivity. In that case, a full conversion was reached within 5 h to afford **2a** in 80% yield. Further screening of biarylphosphine based complexes revealed that the use of the more sterically demanding Me4*t*-BuXPhos ligand could improve both the reaction rate and the yield of **2a** (1.5h, 88% yield, entry 5). A final significant improvement was achieved by replacing the SbF_6^- counter-anion in the gold complex with the more coordinating NTf_2^-. This led to a dramatic acceleration of the reaction: completion was obtained after only 20 min without altering the yield of **2a** (entries 6 and 7). It is worth noting that in no case traces of a triazole product possibly formed by an intramolecular azide-alkyne [3+2]-cycloaddition could be detected.[13]

Table 1 Optimization of the reaction conditions



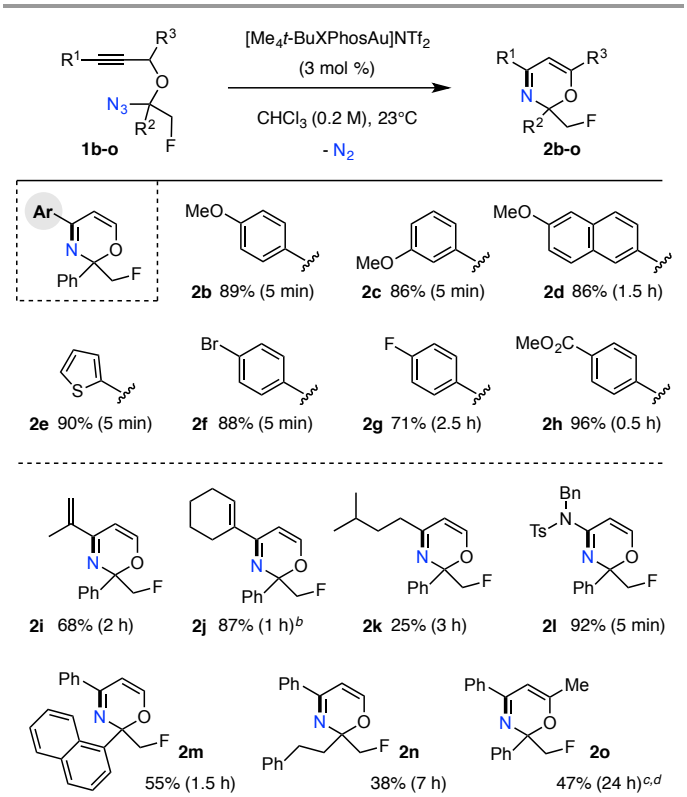
Entry	Au catalysts	Cat. [mol%]	Time [h]	Yield [%][a]
1	$[Ph_3PAu(NCCH_3)]SbF_6$	4	24	10
2	$[IPrAu(NCCH_3)]SbF_6$	4	24	<5
3	$[XPhosAu(NCCH_3)]SbF_6$	4	5	80
4	[*t*-BuXPhosAu(NCCH3)]SbF6	4	3	88
5	[Me4*t*-BuXPhosAu(NCCH3)]SbF6	4	1.5	88
6	[Me4*t*-BuXPhosAu]NTf2	4	0.2	88
7	[Me4*t*-BuXPhosAu]NTf2	3	0.3	89[b]

[a] ^{1}H NMR yields based on an internal standard. [b] Isolated yield.

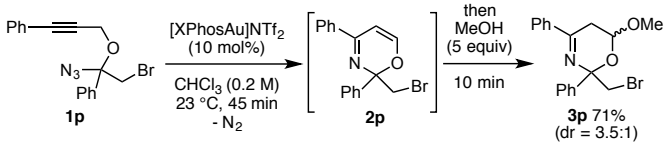
2*H*-1,3-Oxazines are potentially useful scaffolds in synthetic and medicinal chemistry,[14,15] while their application is currently limited due to the fact that they are sensitive to acidic and thermal conditions and that only a few routes therefore exist to access them. Inspired by the unprecedented 6-*endo-dig* azide-yne cyclization for the construction of 2*H*-1,3-oxazine **2a** (Table 1), we further investigated the scope of the transformation (Scheme 3). The nature of the alkyne terminus was first examined. As seen in Scheme 3, the transformation could be applied without noticeable yield deterioration (71-96%) to various aryl groups as R^1 (**2b**-**2h**) with reaction time ranging from 5 min to 2.5 h. Substrates possessing electron-deficient aryl groups (**2g** and **2h**) tend to require a longer reaction time than those with electron-rich (hetero)aryl groups (for **2b**-**2e**). This observation suggests that the activation of the alkyne moiety by the gold catalyst (see mechanistic proposal, Scheme 2) can be the rate-determining step of the transformation. The present 6-*endo-dig* azide-yne cyclization also proceeded smoothly with ene-yne systems (for **2i** and **2j**), whereas a substitution by an alkyl group was detrimental to the reaction probably due to a lack of resonance stabilization effect (for **2k**). Ynamide **1l** was found to be a privilege type of substrate for the transformation as the corresponding 1,3-oxazine **2l** was obtained in excellent yield and short reaction time. With regard to the nature of substituent R^2, a sterically more demanding 1-naphthyl group was tolerated although a drop in yield was observed (for **2m**), whereas an alkyl group was shown to severely impact the process efficiency (for **2n**). Installation of a methyl group at the propargylic position (R^3) did not decrease the chemical yield

(for **2o**) (that is a 2-step yield form the corresponding propargylic alcohol) albeit a longer reaction time was required for completion.

We next attempted to cyclize α-propargyloxy-β-bromoalkylazide **1p**. The reaction proved to be more difficult potentially due to the redox compatibility between C(sp^3)–Br bond and gold(I) complexes.[16] However, the use of [XPhosAu]NTf_2 as the catalyst at a slightly higher loading (10 mol%) resulted in the formation of the corresponding 2*H*-1,3-oxazine **2p** (Scheme 4). Due to the instability, **2p** was converted into the corresponding acetal **3p** through sequential treatment with MeOH for isolation.

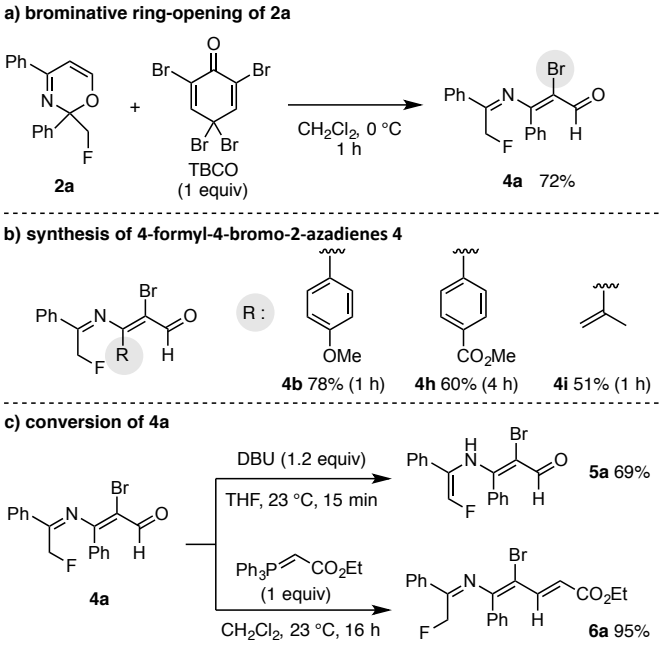


Scheme 3 Substrate scope.[a] The reaction was conducted on 0.2 mmol scale. [b] [*t*-BuXPhosAu($NCCH_3$)]SbF_6 (3 mol%) was used as the catalyst. [c] The synthesis was conducted in 2-steps way from the corresponding vinyl azide and propargyl alcohol *via* alkoxyfluorination and gold(I)-catalyzed azide-yne cyclization (see ESI for more details). [d] 5 mol% of [(Me_4*t*-BuXPhos)Au($NCCH_3$)]SbF_6 was used as the catalyst.



Scheme 4 The reaction of azide **1p**

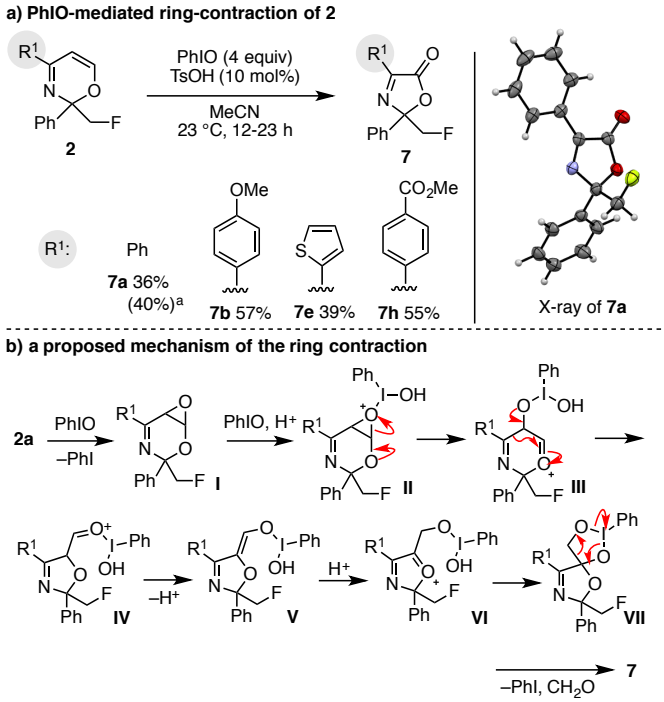
Having developed a new efficient method for the construction of 2*H*-1,3-oxazines **2**, we then focused our attention on exploring their molecular transformations. The electrophilic bromination of **2a** by TBCO led to an interesting ring-opening process and stereoselectively afforded 4-formyl-4-bromo-2-azadiene **4a** in 72% yield (Scheme 5a).[17,18,19] The capability of the brominative ring-opening of 1,3-oxazines **3** in producing multi-functionalized 4-formyl-4-bromo-2-azadienes **4** was demonstrated through the preparation of compounds **4b**, **4h**, and **4i** (Scheme 5b). The treatment of **4a** with DBU resulted in an imine-enamine tautomerization that furnished bisenamine **5a** (Scheme 5c).[20] An elongation of the π-conjugation in **4a** was enabled by reaction with a stabilized phosphonium ylide that delivered 2-aza-triene **6a** in excellent yield (Scheme 5c).



Scheme 5 Molecular transformations of 2*H*-1,3-oxazine **2a**

It was also found that the treatment of 1,3-oxazines **2** with PhIO (4 equiv) in the presence of a catalytic amount of TsOH resulted in an unprecedented and intriguing oxygenative ring-contraction that delivered oxazolones **7** (Scheme 6a).[21] Based on the Plattner's study on oxidative cleavage of aryl epoxides by PhIO,[22] a tentative mechanistic proposal is depicted in Scheme 6b. 2*H*-1,3-Oxazine **2** might initially be oxidized by PhIO to produce epoxide **I**,[23] which is further electrophilically activated in the presence of PhIO and a proton to afford epoxide-λ^3-iodane **II**. Formation of oxonium intermediate **III** with ring-opening of the epoxide may induce a ring-contraction to give **IV**, which is then transformed into spirocyclic intermediate **VII**. Finally, elimination of PhI and formaldehyde affords oxazolone **7**.

In summary, we have developed a gold-catalyzed denitrogenative 6-*endo-dig* azide-yne cyclization of α-propargyloxy-β-haloalkylazides that allows the synthesis of 2*H*-1,3-oxazines. Unique molecular transformations of these relatively unusual products were also demonstrated. We anticipate that the implementation of this rare 6-*endo-dig* azide-yne cyclization mode could light the path to further development of other unprecedented gold-catalyzed cyclizations.



Scheme 6 PhIO-mediated ring-contraction of 2*H*-1,3-oxazines **2**. [a] $Cu(OTf)_2$ (20 mol%) was used instead of TsOH in DMF as a solvent.

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Notes and references

1 For recent reviews, see: (a) Z. Z. Zheng, Z. Wang, Y. Wang and L. Zhang, *Chem. Soc. Rev.*, 2016, **45**, 4448; (b) R. J. Harris and R. A. Widenhoefer, *Chem. Soc. Rev.*, 2016, **45**, 4533; (c) W. Zi and D. F. Toste, *Chem. Soc. Rev.*, 2016, **45**, 4567; (d) A. M. Asiri and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2016, **45**, 4471; (e) M. Jia and M. Bandini, *ACS Catal.*, 2015, **5**, 1638; (d) R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028.

2 For articles on gold catalysis involving alkynes and azides, see: (a) C. Shu, Y-H. Wang, C-H. Shen, P-P. Ruan, X. Lu and L-W. Ye, *Org. Lett.*, 2016, **18**, 3254; (b) N. Li, T-Y. Wang, L-Z. Gong and L. Zhang, *Chem. Eur. J.*, 2015, **21**, 3585; (c) Y. Wu, L. Zhu, Y. Yu, X. Luo and X. Huang, *J. Org. Chem.* 2015, **80**, 11407; (d) C. Shu, Y-H. Wang, B. Zhou, X-L. Li, Y-F. Ping, X. Lu and L-W. Ye, *J. Am. Chem. Soc.*, 2015, **137**, 9567; (e) Y. Tokimizu, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2014, **16**, 3138; (f) M. Gaydou and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2013, **52**, 13468; (g) Z-Y. Yan, Y. Xiao and L. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8624; (h) H. Liu, X. Li, Z. Chen and W.-X. Hu, *J. Org. Chem.*, 2012, **77**, 5184; (i) A. Wetzel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2011, **50**, 7354; (j) B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang and L. Zhang, *Angew. Chem., Int. Ed.* 2011, **50**, 8358; (k) Z. Huo and Y. Yamamoto, *Tetrahedron Lett*. 2009, **50**, 3651; (l) D. J. Gorin, N. R. Davis and D. F. Toste, *J. Am. Chem. Soc*. 2005, **127**, 11260.

3 For a review on gold and nitrenoid species, see: P. W. Davies and M. Garzón, *Asian J. Org. Chem*., 2015, **4**, 694.

4 Zhang and co-workers reported a gold(I)-catalyzed 5-*exo-dig* azide-enyne cyclization enabled by a rationale control of the electronic properties on the substituents, see ref 2f.

5 Yamamoto and co-workers reported a Au(III)-catalyzed 6-*endo-dig* azide-yne cyclization of 2-alkynyl benzyl azides. The process requires a high catalyst loading (30 mol% of $AuCl_3$), a high temperature (100 °C in THF) and competes with the intramolecular azide-alkyne cycloaddition, see: ref 2i.

6 (a) K. Ji, J. Nelson and L. Zhang, *Beilstein J. Org. Chem*., 2013, **9**, 1925; (b) B. Lu, C. Li and L. Zhang, *J. Am. Chem. Soc*., 2010, **132**, 14070.

7 Selectfluor®: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]-octane bis(tetrafluoroborate).

8 TBCO: 2,4,4,6-tetrabromocyclohexa-2,5-dienone.

9 Y-F. Wang, M. Hu, H. Hayashi, B. Xing and S. Chiba, *Org. Lett*., 2016, **18**, 992.

10 M. E. Jung and G. Piizzi, *Chem. Rev*., 2005, **105**, 1735.

11 Substrates **1a-p** were prepared by following the procedure we previously reported (see ref 9). See ESI for more details.

12 Deuterated chloroform ($CDCl_3$) was used in order to monitor the reactions and estimate the yields of products. Reactions can be naturally run in regular $CHCl_3$.

13 Thermal treatment of **1a** in refluxing toluene delivered the corresponding bicyclic triazole in 65% yield, see: ref 9.

14 For selected reports on the construction of 2*H*-1,3-oxazine scaffolds, see: (a) K. V. Zavyalov, M .S. Novikov, A. F. Khlebnikov and V. V. Pakalnis, *Tetrahedron*, 2014, **70**, 3377; (b) A. F. Khlebnikov, M .S. Novikov, Y. G. Gorbunova, E. E. Galenko, K. I. Mikhailov, V. V. Pakalnis and M. S. Avdontceva, *Beilstein J. Org. Chem*., 2014, **10**, 1896; (c) C. François-Endelmond, T. Carlin, P. Thuery, O. Loreau and F. Taran, *Org. Lett*., 2010, **12**, 40; (d) J. R. Manning and H. M. L. Davies, *Tetrahedron*, 2008, **64**, 6901; (e) J. Barluenga, M. Tomás, A. Ballesteros and J.-S. Kong, *Tetrahedron*, 1996, **52**, 3095; (f) J. Barluenga, M. Tomás, A. Ballesteros, J.-S. Kong, S. García-Granda and A. Aguirre, *J. Chem. Soc., Chem. Commun*., 1993, 217.

15 (a) H. Hilpert, R. Narquizian, E. Pinard, A. Polara, M. Rogers-Evans, T. Woltering and W. Wostl, WO 2012/156284 A1; (b) J. B. Chylińska, T. Urbański and M. Mordarski, *J. Med. Chem*., 1963, **6**, 484.

16 For a review, see: M. Joost, A. Amgoune, and D. Bourissou, *Angew. Chem., Int. Ed*. 2015, **54**, 15022.

17 See ESI for a mechanistic proposal of this unprecedented ring-opening.

18 In sharp contrast, treatment of **2a** with Selectfluor® in the presence of MeOH kept the oxazine ring to deliver 5-fluoro-6-methoxy-dihydro-2*H*-1,3-oxazine **8** as an unstable mixture of four diastereomers. See ESI for more details.

19 For a review on synthetic application of azadienes, see: S. Jayakumar, M. P. S. Ishar and M. P. Mahajan, *Tetrahedron* 2002, **58**, 379.

20 For reports on synthesis of bisenamines, see: A. Leyva-Pérez, J. R. Cabrero-Antonino, A. Cantín and A. Corma, *J. Org. Chem*., 2010, **75**, 7769, and references therein.

21 See ESI for the screening of oxidants for the reaction of **2a**.

22 N. Havare and D. A. Plattner, *Helv. Chim. Acta*, 2012, **95**, 2036.

23 For oxygenation of alkene by PhIO, see: J. Barluenga, G. Lonzi, L. Riesgo, M. Tomás and L. A. López, *J. Am. Chem. Soc*. 2011, **133**, 18138.