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# Brønsted Acids Enable Three Molecular Rearrangements of One 3-Alkylidene-2*H*-1,2-oxazine Molecule into Distinct Heterocyles

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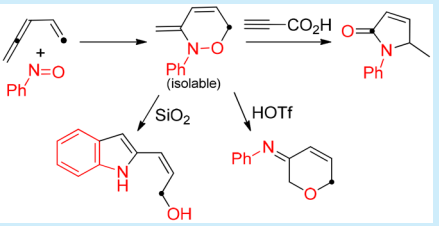
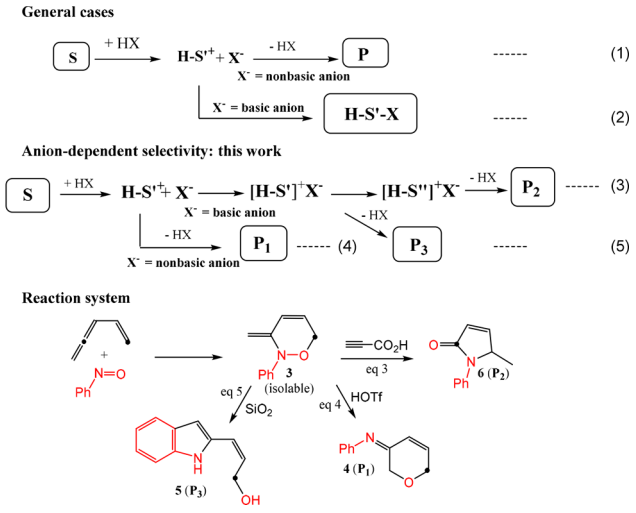
Supporting Information

**ABSTRACT:** This work describes three different strategies to structurally rearrange one 3-alkylidene-2*H*-1,2-oxazine molecule into three distinct heterocycles using HOTf, propiolic acid, and silica gel, respectively. The mechanisms of these rearrangement reactions involve three independent routes, including (i) Brønsted acid catalysis, (ii) a synergetic action of Brønsted acids and anions, (iii) a surface-directed chemoselectivity.



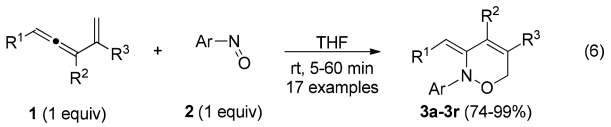

Brønsted acids ($H^+X^-$) are versatile at mediating numerous rearrangement reactions via carbocation intermediates,[1] including the well-known pinacol, Wagner−Meervein, Nazorav, Mannich−aza-Cope, and epoxide/carbonyl rearrangement. A recent advance in Brønsted acid catalysis is to employ chiral anions $X^-$ to induce high enantioselectivity by ion pairing.[2] In the context of acid-catalyzed rearrangements, the reaction efficiency, chemoselectivity, and stereoselectivity rely largely on the cation centers (eq 1). Anions typically alter the chemoselectivity




through an interception or deprotonation of carbocations (eq 2). This work assesses anion- and surface-directed chemoselectivity, in addition to a traditional route. Herein, anions catalyze the transformation of initial cations ($[\mathbf{H\text{-}S'}]^+\mathbf{X}^-$) into new carbocations $[\mathbf{H\text{-}S''}]^+\mathbf{X}^-$ (eq 3), whereas catalyst surface controls the conformation of the ion pair ($[\mathbf{H\text{-}S'}]^+\mathbf{X}^-$) to activate a new chemoselectivity.

Metal-catalyzed [4 + 2]-cycloadditions of dienes with nitrosoarenes deliver 5,6-dihydro-4*H*-1,2-oxazines[3] that are powerful building units to access many naturally occurring products.[4] To expand the utility of this renowned system, we report three new rearrangements of a closely related family, 3-alkylidene-2*H*-1,2-oxazines, using HOTf, propiolic acid, and $SiO_2$, respectively, furnishing new useful heterocycles, including *Z*-configured *N*-phenyl pyran-3(6*H*)-imine **4** ($\mathbf{P_1}$), pyrrolidin-2-one **6** ($\mathbf{P_2}$), and *Z*-configured 3-(1*H*-indol-2-yl)prop-2-en-1-ol **5** ($\mathbf{P_3}$). Mechanistically, the HOTf reaction (**3** → **4**, eq 4) follows a typical Brønsted acid catalysis, and the $SiO_2$ reaction (**3** → **5**, eq 5) is implemented by silica surface. Particularly notable is the internal redox rearrangement (**3** → **6**, eq 3), activated by a synergetic action of $H^+/X^-$.[5]

Regioselective [4 + 2]-cycloadditions of alkenylallenes with nitrosoarenes in 1:1 molar ratio proceeded smoothly in THF (25 °C, 5−60 min). In a typical operation, the solution were evaporated to dryness, followed by washing with hexane to afford pure 3-alkylidene-2*H*-1,2-oxazines **3a−r** in 74−99% yields (see Table S1). The reactions proceeded also well in other solvents; compound **3a** ($R^1$ = Ph, $R^2$ = $R^3$ = Me) was obtained in satisfactory yields in $CH_3CN$ (99%), dichloromethane (DCM, 99%), toluene (87%) and $CHCl_3$ (99%). The structure of compound **3a** was confirmed by X-ray diffraction to reveal a *Z*-olefin configuration. This regioselectivity is consistent with a 1,4-diradical path, according to our recent investigation.[6]




We explored new rearrangements of nitroxy species **3a** using varied Brønsted acids (see Table S2); selected examples are provided in Table 1. A strong acid such as HOTf (1.0 equiv, 25 °C, 5 min) afforded of *Z*-configured *N*-phenylpyran-3(6*H*)-imine (**4a**) in 83% yield (entry 1), but moderate acids such as 4-nitrobenzoic acid, trifluoroacetic acid, *N*-triflateproline, and

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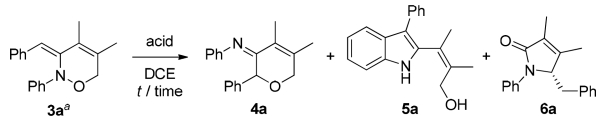
**Table 1. Acidity versus Chemoselectivity**



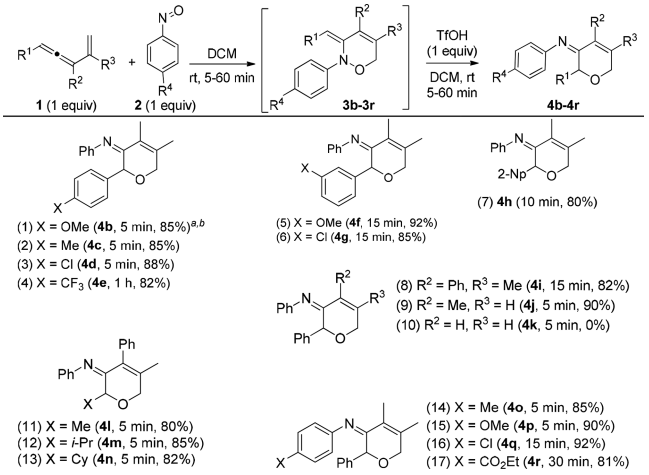

| entry | acids | equiv | t °C / time | 3a | 4a | 5a | 6a | |
|---|---|---|---|---|---|---|---|---|
| 1 | HOTf | 1 | 25 °C / 5 min | -- | 83 | -- | -- | |
| 2 | $CF_3CO_2H$ | 0.2 | 25 °C / 10 h | -- | -- | 20 | 41 | |
| 3 | ≡—$CO_2H$ | 0.2 | 60 °C / 1 h | -- | -- | 14 | 61 | |
| 4 | 4-$NO_2PhCO_2H$ | 1 | 60 °C / 10 h | -- | -- | 17 | 43 | |
| 5 |  | 1 | 60 °C / 28 h | -- | -- | -- | 60 | |
| 6 | silica gel | 10 | 25 °C / 1 h | -- | -- | (67/65)[c] | -- | |
| 7[b] | silica gel[d] | 10 | 60 °C / 24 h | 95 | -- | -- | -- | |

[a]**3a** = 0.025 M. [b]Acetic acid, benzoic acid and proline were inactive catalysts to give **3a** in 95−98% recovery. [c]Silica gel was obtained from Silicycle (silicaflash G60) and Merck (Geduran Si 60) respectively. [d]Silica gel (Silicycle) was treated with $Et_3N$ (2 mol %) in THF (8 h) before filtration and washing with hexane.

propiolic acid preferably gave the distinct pyrrolidin-2-one **6a** in 41−61% yields, with propiolic acid being the most effective (entries 2−5, Table 1). Weak acids, including acetic acid, benzoic acid, and proline (1 equiv) in hot DCE (60 °C, 36 h), led to only a 95−98% recovery of initial **3a** (Table S2). Astonishingly, silica gel (10 equiv, Silicycle) in DCE enabled another new rearrangement of species **3a** to furnish *Z*-configured 3-(1*H*-indol-2-yl)prop-2-en-1-ol (**5a**) in 67% yield. Silica gel from a different source (Merck) showed a similar result (entry 6). Notably, $Et_3N$-pretreated silica gel became inactive (entry 7). In the case of compound **4a**, its treatment with silica gel (10 equiv) and propiolic acid (20 mol %) in DCE (25 °C, 10 h) did not yield the other two heterocycles, but afford the its hydration product. Accordingly, Brønsted acid ($H^+$) alone was responsible for the formation of *N*-phenyl pyran-3(6*H*)-imine (**4a**) whereas pyrrolidin-2-one **6a** requires a cooperative action of Brønsted acid and carboxylate anion. For indole derivative **5a**, its formation is presumably relevant to the surface structure of silica gel with its very weak acidity being indispensable.

Shown in Scheme 1 is the rearrangement of nitroxy compounds **3b−r** using HOTf; all of these instances gave satisfactory results. In a standard operation, compounds **3** were first produced from alkenylallenes and nitrosoarenes in equilmolar proportion in DCM (25 °C, 5−60 min); the solution was subsequently treated with HOTf (1 equiv) to afford *Z*-configured *N*-phenyl pyran-3(6*H*)-imine (**4b−r**) in 82−92% yields. A small loading of HOTf (20 mol %) led to the imine hydration of products **4**. We examined the rearrangement of trisubstituted nitroxy heterocycles **3b−e** bearing various 4-phenyl groups (X = OMe, Me, Cl, $CF_3$) that were satisfactorily rearranged to compounds **4b−e** in 82−88% yields (entries 1−4); $^1$H NOE confirmed a *Z*-configured imine of compound **3a**. This rearrangement worked well with nitroxy species **3f,g** bearing 3-phenyl groups (X = OMe, Cl) and a 2-naphthyl group to afford desired compounds **4f−h** in 80−92% yields (entries 5−7). The reactions were applicable to species **3i** and **3j** bearing alterable $R^2$ and $R^3$ substituents, producing pyran-3(6*H*)-imines **4i** and **4j** in

**Scheme 1. HOTf-Mediated Rearrangement of Nitroxy Species 3**

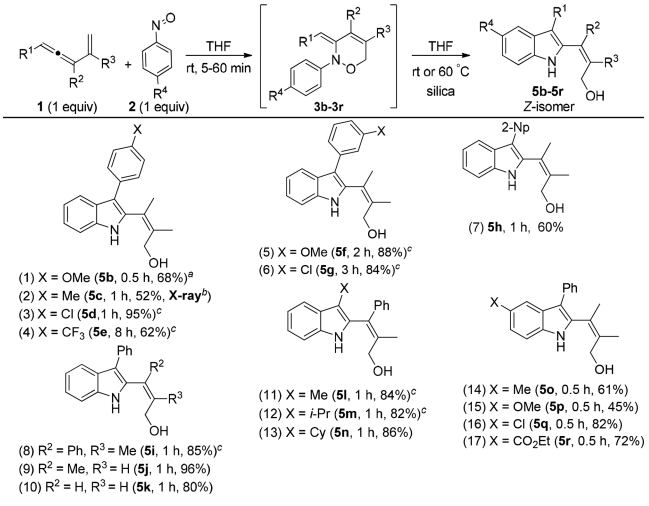



[a]**3** = 0.025 M. [b]Product yields are reported after purification from a silica column.

82−90% yields (entries 8 and 9). We observed no reaction for species **3k** bearing $R^2 = R^3 = H$ (entry 10). We varied the $R^1$ group with methyl, isopropyl and cyclohexyl as in compounds **3l-3n**, rendering compounds **4l−n** in 80−85% yields (entries 11−13). Various nitrosoarenes (X = Me, OMe, Cl, and $CO_2Et$) were applicable to these reactions to afford desired products **4o−r** in high yields (81−92%, entries 14−17).

A silica-mediated rearrangement proceeded well with all nitroxy species **3b−r** to yield *Z*-configured indole products **5b−r** smoothly (Scheme 2). This new rearrangement was applicable to additional 4-phenyl **3b−e** (X = OMe, Me, Cl, $CF_3$) and 3-phenyl **3f,g** (X = OMe, Cl) and 2-naphthyl **3h** analogues, affording the desired indole analogues **5b−e**, **5f,g**, and **5h** with yields exceeding 52% (entries 1−7). The molecular structure of the acyl derivative of species **5c** was characterized with X-ray diffraction to reveal a *Z*-configured allylic alcohol. This indole

**Scheme 2. Silica-Mediated Rearrangement of Cyclic Nitroxy Species 3**




[a]**3** = 0.02 M. [b]X-ray diffraction was performed on the acyl derivative of compound **5c** [c]The reaction was performed at 60 °C under standard conditions.



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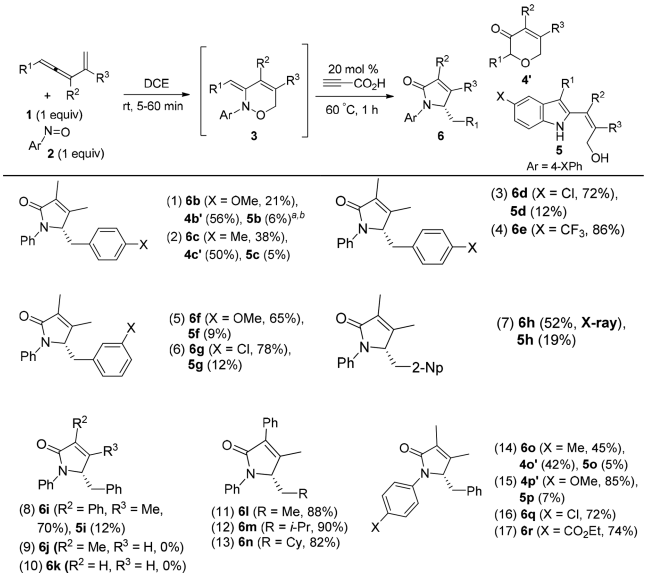
synthesis was applicable also to nitroxy species **3i–k** bearing variable $R^2$ and $R^3$ substituents, delivering compounds **5i–k** in high yields (entries 8–10). For species **3l–n** bearing variable alkyl substituents at the $R^1$ position ($R^1$ = methyl, isopropyl and cyclohexyl), the reactions delivered indole products **5l–n** in 82–86% yields (entries 11–13). Various 4-substituted nitrosobenzenes allowed a substituent onto the C(5)-carbon of indole derivatives **5o–r** over a broad scope (X = Me, OMe, Cl, $CO_2Et$, entries 14–17).

The rearrangement of nitroxy species **3b–r** into pyrrolidin-2-ones **6** with propiolic acid (20 mol %) is very striking; herein, three instances were unsuccessful (entries 9, 10, and 14, Scheme 3). The propiolate anion catalyzed a redox rearrangement via a

**Scheme 3. Propiolic Acid-Catalyzed Rearrangement**

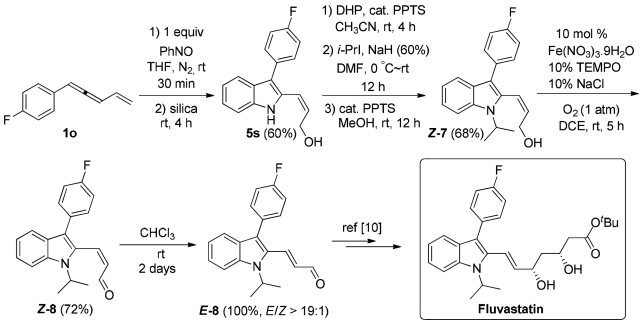



[a]Three = 0.025 M. [b]Product yields are reported after purification from a silica column.

transfer of two $OCH_2$ protons to the $R^1HC{=}N$ olefin. This rearrangement was applicable to species **3b–e** bearing various $R^1$ = 4-$XC_6H_4$ substituents, with X = Cl, $CF_3$ being more effective than X = OMe and Me (entries 1–4). For their 3-phenyl and 2-naphthyl analogues **3f,g** and **3h**, their expected products **6f,g** and **6h** were obtained in 52–78% yields (entries 5–7). The molecular structure of compound **6h** was elucidated with X-ray diffraction. We varied $R^2$ and $R^3$ substituents as in species **3i–k** (entries 8–10); only species **3i** was an applicable substrate to form compound **6i** in 70% yield. For nitroxy species **3l–n** bearing $R^1$ = methyl, isopropyl and cyclohexyl, their internal redox products **6l–n** were obtained in high yields (82–90%, entries 11–13). For various nitrosobenzenes, we found that electron-rich phenyl species **3o** and **3p** were less efficient than their electron-deficient analogues; their respective yields were 0–45% and 72–74%, respectively (entries 14–17). Based on these data, this redox rearrangement is more favorable for those nitroxy species bearing an electron-deficient $R^1HC$ = N bond to avoid an N–O cleavage as for the HOTf reaction.

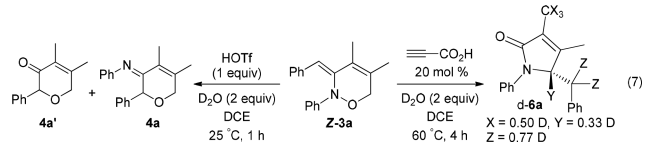
Fluvastatin (Lescol) is an important member of the class of statin drugs which is used for the treatment of hypercholesterolemia.[7] We employed our silica gel reaction on allenylalkene **1o** to synthesize an indole derivative **5s** in 60% yield (Scheme 4). This species was treated with *i*-PrI, followed by

**Scheme 4. A Formal Synthesis of Fluvastatin**



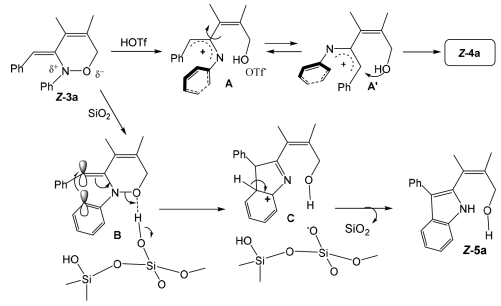

a suitable oxidation to afford *Z*-7 selectively.[8] The *Z* → *E* isomerization was nearly complete when species *Z*-**8** was dissolved in $CDCl_3$ for 2 days. A formal synthesis of fluvastatin with species *E*-**8** is well documented.[9]

We added $D_2O$ in the two rearrangement reactions as depicted in eq 7. In the cases of HOTf, the resulting products **4a** and **4a′** contained no deuterium at all, but in the case of propiolic acid, resulting compound *d*-**6a** contained three deuterium contents (*X* = 0.50 D, *Y* = 0.33 D, and *Z* = 0.77 D). This information indicates that product **4a** arises from the protonation of the N–O oxygen of species *Z*-**3a**, whereas propiolic acid preferably protonates at the PhHC═ carbon, reflecting two distinct mechanisms.




The mechanism of the HOTf-mediated rearrangement likely involves a typical N–O bond cleavage because of the high acidity (Scheme 5).[10] The resulting aza-allylic cation **A** undergoes a

**Scheme 5. HOTf and Silica-Mediated Reactions**




facile C–C rotation to form its conformer **A′**, which is subsequently attacked by the hydroxyl group to form *N*-phenylpyran-3(6*H*)-imine **4a** with an observed *Z*-geometry. In the case of the silica reaction, the N–O group of species **3a** interacts easily with the hydroxyl group of silica surface without a N–O cleavage. The increasing electrophilicity of the nitroxy oxygen induces an intramolecular cyclization as shown in state **B** to generate species **C** and ultimately the observed indole product *Z*-**5a**.

The relevant mechanism in the **3a** → **6a** rearrangement became resolved with a $D_2O$ experiment (eq 7). The three distinct contents of *d*-**6a** indicate the varied stages of the $D_2O$ deuteration. Propiolic acid is a weak acid that cannot cleave the N–O bond, but its carboxylic anion is a weak base to show a synergetic effect, as depicted in state **D** (Scheme 6). We believe



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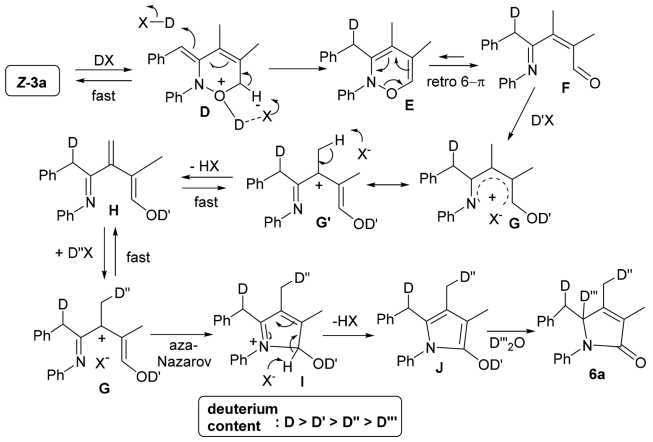
**Scheme 6. Cooperative Action for Propiolic Acid**




that the weakly O-bound propiolic acid **D** abstracts one O−$CH_2$ proton, whereas another propiolic acid delivers a proton to the PhC═ carbon, affording a hypothetical 2*H*-1,2-oxazine species **E** that remains unknown.[11] A 6$\pi$ retro-electrocyclization[12] of highly unstable species **E** generates 4-imino-2-en-1-al species **F** that undergoes protonation to yield azapentadienyl cations **G** or **G′**. The C(3)-methyl of species **G′** can undergo a deuterium exchange via intermediate **H**. A final aza-Nazarov cyclization[13] of cation **G** or **G′** affords pyrrole product **J** and, ultimately, the observed product **6a**. According to this reaction sequence, the deuterium content of compound **6a** follows the decreasing order **D** > **D′′** > **D′′′**, compatible with our observed data of species *d*-**6a**.

In summary, we have successfully developed three molecular rearrangements of 3-alkylidene-2*H*-1,2-oxazines using HOTf, silica gel and propiolic acid, affording *N*-phenyl pyran-3(6*H*)-imine **4**, pyrrolidin-2-one **6**, and *Z*-configured 3-(1*H*-indol-2-yl)prop-2-en-1-ol **5**, respectively. Our experimental data suggest that the reactions with HOTf represent a typical acid catalysis, enabling a N−O cleavage of cyclic nitroxy species. Silica enables a distinct rearrangement with its surface acidic sites to increase the electrophilicity of the nitroxy oxygen. The reaction with propiolic acid involves a synergetic action of $H^+$ and $X^-$.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03985.

Experimental details and spectral data of all compounds (PDF)

### Accession Codes

CCDC 1582436−1582438 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES

(1) (a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (b) Terada, M. *Synthesis* **2010**, *2010*, 1929. (c) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277.

(2) (a) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603. (b) Zi, W.; Toste, F. D. *Chem. Soc. Rev.* **2016**, *45*, 4567. (c) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534. (d) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518. (e) Jia, M.; Bandini, M. *ACS Catal.* **2015**, *5*, 1638. (f) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.

(3) (a) Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5630. (b) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, *2006*, 2031. (c) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317. (d) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.

(4) Carosso, S.; Miller, M. J. *Org. Biomol. Chem.* **2014**, *12*, 7445.

(5) Cooperative catalysis typically employs metal catalysts bearing a functional ligand; see: (a) Kim, D.-S.; Park, W.-J.; Jun, C.-H. *Chem. Rev.* **2017**, *117*, 8977. (b) Afewerki, S.; Cordova, A. *Chem. Rev.* **2016**, *116*, 13512.

(6) Liu, J.; Skaria, M.; Sharma, P.; Chiang, Y.-W.; Liu, R.-S. *Chem. Sci.* **2017**, *8*, 5482.

(7) (a) Switzer, J. A.; Hess, D. C. *Expert Rev. Neurother.* **2006**, *6*, 195. (b) Davidson, M. H. *Am. J. Med.* **1994**, *96*, 41.

(8) Liu, J.; Ma, S. *Org. Lett.* **2013**, *15*, 5150.

(9) (a) Zacharia, J. T.; Tanaka, T.; Hayashi, M. *J. Org. Chem.* **2010**, *75*, 7514. (b) Tempkin, O.; Abel, S.; Chen, C.-P.; Underwood, R.; Prasad, K.; Chen, K.-M.; Repic, O.; Blacklock, T. J. *Tetrahedron* **1997**, *53*, 10659.

(10) Acid-catalyzed rearrangement of cyclic nitroxy species: (a) Kulandai Raj, A. S.; Kale, B. S.; Mokar, B. D.; Liu, R.-S. *Org. Lett.* **2017**, *19*, 5340. (b) Sharma, P.; Liu, R.-S. *Org. Lett.* **2016**, *18*, 412. (c) Ghorpade, S.; Jadhav, P. D.; Liu, R.-S. *Chem. - Eur. J.* **2016**, *22*, 2915. (d) Sharma, P.; Liu, R.-S. *Chem. - Eur. J.* **2016**, *22*, 15881. (e) Kawade, R. K.; Tseng, C.-C.; Liu, R.-S. *Chem. - Eur. J.* **2014**, *20*, 13927.

(11) For unsaturated six-membered nitroxy species, see: Sukhorukov, A. Y.; Ioffe, S. L. *Chem. Rev.* **2011**, *111*, 5004.

(12) This ring cleavage was well documented for other nitroxy species; see refs 10 and 11 and selected examples: (a) Ioffe, S. L.; Lyapkalo, I. M.; Tishkov, A. A.; Danilenko, V. M.; Strelenko, Y. A.; Tartakovsky, V. A. *Tetrahedron* **1997**, *53*, 13085. (b) Gygax, P.; Das Gupta, T. K.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 2205. (c) Shatzmiller, S.; Shalom, E. *Liebigs Ann. Chem.* **1983**, *1983*, 897. (d) Goldberg, I.; Saad, D.; Shalom, E.; Shatzmiller, S. *J. Org. Chem.* **1982**, *47*, 2192.

(13) For the aza-Nazarov cyclizations, see: (a) Klumpp, D. A.; Zhang, Y.; O'Connor, M. J.; Esteves, P. M.; de Almeida, L. S. *Org. Lett.* **2007**, *9*, 3085. (b) Ma, Z.-X.; He, S.; Song, W.; Hsung, R. P. *Org. Lett.* **2012**, *14*, 5736. (c) Zhou, A.-H.; He, Q.; Shu, C.; Yu, Y.-F.; Liu, S.; Zhao, T.; Zhang, W.; Lu, X.; Ye, L.-W. *Chem. Sci.* **2015**, *6*, 1265. (d) Sahani, R. L.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2017**, *56*, 12736. (e) Pawar, S. K.; Sahani, R. L.; Liu, R.-S. *Chem. - Eur. J.* **2015**, *21*, 10843.



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