Organic Letters

pubs.acs.org/OrgLett

Letter

Ru-Catalyzed [3 + 2] Cycloaddition of Nitrile Oxides and Electron-Rich Alkynes with Reversed Regioselectivity

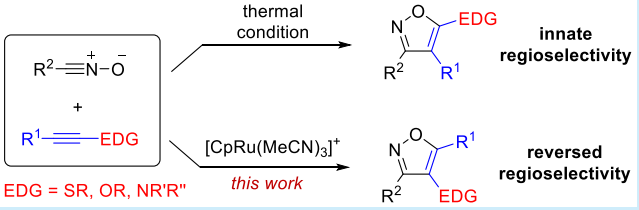
Qiang Feng, Hai Huang, and Jianwei Sun*

Cite This: *Org. Lett.* 2021, 23, 2431−2436

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Polarity reversal ("umpolung") of a functional group can override its inherent reactivity and lead to distinct bond-forming modes. Herein we describe a rarely studied cycloaddition between nitrile oxides and electron-rich alkynes with reversed regioselectivity, leading to the useful 4-heterosubstituted isoxazoles. The use of a ruthenium catalyst completely overrides the inherent polarity of nitrile oxides. This reversed regioselectivity was also observed for their reactions with a range of electron-deficient alkynes.



Polarity reversal ("umpolung") is a powerful strategy that enables a functional group to reverse its polarity and override its inherent reactivity, resulting in a distinct bond-forming mode.[1] In the past half century or so, this concept has underwent significant development.[1a] A number of functional groups can exhibit this type of umpolung by either stoichiometric or catalytic manipulation, among which the carbonyl group is probably the most studied. For example, a carbonyl group can be rendered nucleophilic by converting into dithiane or other acyl anion equivalents by means of cyanide or N-heterocyclic carbene catalysis (Scheme 1a). Recently, Deng and co-workers have also demonstrated an elegant example of organocatalytic asymmetric umpolung of imine functionality.[1j] Despite such impressive progress in the studies of umpolung reactivity, functional groups capable of umpolung are rather limited. Moreover, the majority of current catalytic examples are based on organocatalysis. The development of metal-catalyzed umpolung reactions remains in high demand.

Nitrile oxide is a versatile functionality that can participate in various dipolar cycloaddition reactions for the synthesis of a wide range of heterocycles.[2−4] In particular, its cycloaddition with terminal alkynes to form isoxazoles has been well-studied.[3−5] However, cycloaddition of nitrile oxides is relatively difficult to control regarding chemoselectivity and regioselectivity, which is partly due to the typical requirement for *in situ* generation of this reactive nitrile oxide intermediate and its facile dimerization.[2,6]

Nevertheless, significant progress has been achieved. For example, Fokin and co-workers have pioneered copper- and ruthenium-catalyzed systems that provided complementary regioselectivity for terminal alkynes and haloalkynes.[3a−c,4f] In contrast, cycloaddition of nitrile oxides with electron-rich alkynes have not been systematically studied.[7] Current sporadic examples mostly focus on terminal ones under thermal conditions. A mild catalytic protocol with high regiocontrol remains undeveloped.

The innate reactivity of nitrile oxide normally engages the oxygen motif as the nucleophilic site and the carbon as the electrophilic unit.[2−7] Therefore, the regioselectivity of their thermal [3 + 2] cycloaddition with polarized alkynes is inherently governed by matching the well-defined polarity of the alkyne triple bond (Scheme 1b). Thus, in the few thermal reactions with electron-rich alkynes (e.g., thioalkynes, ynamines), the 5-heterosubstituted isoxazoles were formed as the major regiosomer (Scheme 1b).[7] However, 4-heterosubstituted isoxazoles, the opposite regioisomer, are important subunits in biologically active molecules that lack efficient access (e.g., **I**−**III**, Scheme 1c).[8] Thus, the development of such an efficient cycloaddition process with reversed regioselectivity would be highly useful.

In continuation of our interest in electron-rich alkynes, particularly for cycloaddition,[9] we began this study with internal thioalkyne **1a** as the model substrate.[10] *N*-Hydroxybenzimidoyl chloride **2a** was employed as the model precursor for the *in situ* generation of nitrile oxide in the presence of base Et_3N. In the absence of a catalyst, the reaction using DCE as solvent did not lead to any isoxazole formation (Table 1, entry 1). Instead, dimerization of the nitrile oxide was observed as the major pathway. Next, we evaluated various transition-metal-based catalysts that proved effective for similar cycloadditions.[2−8] While most of these catalysts still led to only

Received: January 24, 2021
Published: March 22, 2021

Downloaded via RUTGERS UNIV on May 15, 2021 at 19:45:44 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

ACS Publications © 2021 American Chemical Society

https://doi.org/10.1021/acs.orglett.1c00273
Org. Lett. 2021, 23, 2431−2436

Scheme 1. Introduction to Umpolung of Nitrile Oxides for Cycloaddition with Electron-Rich Alkynes

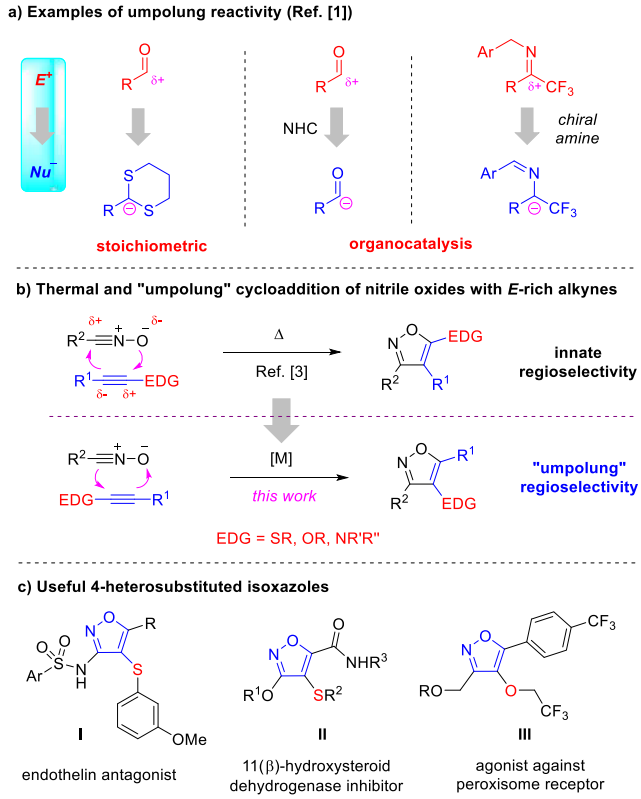
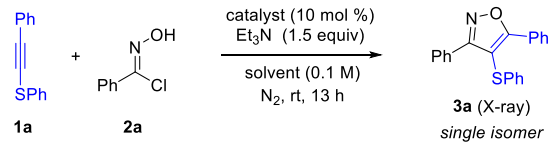


Table 1. Condition Optimization[a]



entry	catalyst	solvent	yield (%)[b]
1	–	DCE	<5
2	$CuSO_4{\cdot}5H_2O$	DCE	<5
3	$Ni(cod)_2$	DCE	<5
4	$Pd(PPh_3)_4$	DCE	<5
5	$Rh(cod)Cl_2$	DCE	<5
6	$[Ir(cod)Cl_2]_2$	DCE	<5
7	$Ru(cod)Cl_2$	DCE	<5
8	Cp*Ru(cod)Cl	DCE	55
9	$Cp^*Ru(PPh_3)_2Cl$	DCE	14
10	$Cp^*Ru(MeCN)_3PF_6$	DCE	31
11	$CpRu(MeCN)_3PF_6$	DCE	79 (76)[c]
12	CpRu(cod)Cl	DCE	80
13	$CpRu(MeCN)_3PF_6$	THF	75
14	$CpRu(MeCN)_3PF_6$	MeOH	23
15	$CpRu(MeCN)_3PF_6$	1,4-dioxane	65
16	$CpRu(MeCN)_3PF_6$	MeCN	84
17[d]	**$CpRu(MeCN)_3PF_6$**	**MeCN**	**92**

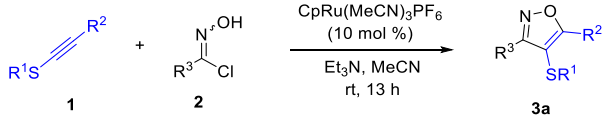
[a]Reaction scale: **1a** (0.1 mmol), **2a** (0.15 mmol). [b]Yield was based on ^{1}H NMR analysis of the crude mixture using mesitylene as the internal standard. [c]Isolated yield. [d]Run at 0.05 M concentration.

dimerization of the nitrile oxide (entries 2−7), we were pleased to find that the [Cp*Ru]-based system could lead to isoxazole **3a**, albeit with low efficiency (entries 8−10). The structure of **3a** was confirmed by X-ray crystallography. After further considerable efforts in screening various ruthenium-based catalysts, we were able to identify [CpRu]-based catalysts $CpRu(MeCN)_3PF_6$ and CpRu(cod)Cl as the superior catalysts, giving essentially the same yields (entries 11−12). The commercially more accessible catalyst $CpRu(MeCN)_3PF_6$ was used for further optimization.

Next, different solvents were compared (entries 13−16). Although protic solvents were less effective, the aprotic polar solvent MeCN could slightly improve the efficiency (entry 16). Finally, the use of a lower concentration further improved the reaction yield to 92% (entry 17). It is worth noting that this reaction exhibited complete regioselectivity opposite to the thermal condition.

With the optimized conditions, we examined the reaction scope. As shown in Table 2, a diverse range of internal

Table 2. Reaction Scope[a]



entry	R^1	R^2	R^3	3	yield (%)[b]
1	Ph	Ph	Ph	**3a**	88
2	Ph	(*p*-OMe)C_6H_4	"	**3b**	92
3	Ph	(*p*-Cl)C_6H_4	"	**3c**	84
4	Ph	(*p*-F)C_6H_4	"	**3d**	82
5	Ph	(*m*-F)C_6H_4	"	**3e**	85
6	Ph	(*o*-F)C_6H_4	"	**3f**	90
7	Ph		"	**3g**	93
8	(*p*-OMe)C_6H_4	Ph	"	**3h**	89
9	(*p*-Br)C_6H_4	Ph	"	**3i**	95
10	(*p*-Cl)C_6H_4	Ph	"	**3j**	94(92)[c]
11	(*p*-F)C_6H_4	Ph	"	**3k**	98
12	(*p*-Me)C_6H_4	Ph	"	**3l**	86
13	(*p*-NO_2)C_6H_4	Ph	"	**3m**	82
14	(*o*-Cl)C_6H_4	Ph	"	**3n**	78
15	^{n}Bu	^{n}Bu	"	**3o**	54
16	Ph	^{n}Bu	"	**3p**	61
17	^{n}Bu	Ph	"	**3q**	91
18	Ph	Ph	(*p*-OMe)C_6H_4	**3r**	89
19	"	"	(*p*-Me)C_6H_4	**3s**	91
20	"	"	(*m*-Me)C_6H_4	**3t**	88
21	"	"	(*p*-Cl)C_6H_4	**3u**	93
22	"	"		**3v**	87

[a]Reaction scale: **1** (0.2 mmol), **2** (0.3 mmol), Et_3N (0.3 mmol), MeCN (4.0 mL). [b]Isolated yield. [c]Run at 5.0 mmol scale.

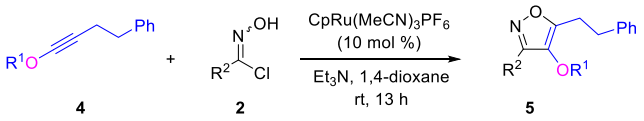
thioalkynes participated smoothly in the mild intermolecular cycloaddition reactions to provide the 3,4,5-trisubstituted isoxazoles bearing a 4-sulfenyl group with good to excellent efficiency (entries 1−17). Both aliphatic and aromatic substituents on the thioalkynes were suitable substrates. Moreover, electron-donating and electron-withdrawing groups on the thioalkynes did not show obvious influence on the

https://doi.org/10.1021/acs.orglett.1c00273
Org. Lett. 2021, 23, 2431−2436

reaction efficiency. A thiophene heterocycle could also be successfully incorporated in the isoxazole product. In addition, this protocol was also amenable to various hydroximoyl chlorides with different electronic properties, including an alkenyl-substituted example (entries 18−22). The reaction was equally efficient at gram scale (entry 10). Moreover, all these reactions produced only one regioisomer.

Intrigued by the above success with thioalkynes, we further extended this protocol to other electron-rich alkynes. Indeed, direct use of the above standard conditions for the reaction between ynol ether **4a** (R^1 = *m*-tolyl) and hydroximoyl chloride **2a** could give the desired isoxazole **5a**, but only with moderate efficiency (42% NMR yield; see the Supporting Information (SI) for details). The low yield was mainly due to the competing dimerization of the nitrile oxide. Next, we further optimized the conditions (see the SI for details). By replacing the solvent with 1,4-dioxane, the reaction yield could be improved to 75%. As solvents can influence the reaction rates of the desired cycloaddition and the competing dimerization of nitril oxide differently, the superior performance of 1,4-dioxane in this case might originate from the change in this rate comparison. Next, various ynol ethers and nitrile oxide precursors were examined, and they all provided the desired 4-alkoxyl isoxazoles with moderate to good yields (Table 3). Again, only one regioisomer was observed in these

Table 3. Reaction of Ynol Ethers[a]

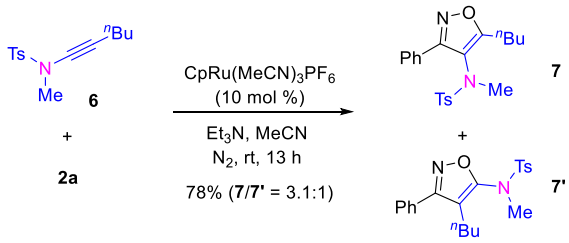


entry	R^1	R^2	5	yield (%)[b]
1	(*m*-Me)C_6H_4	Ph	**5a**	64
2	"	(*m*-Me)C_6H_4	**5b**	60
3	"	(*p*-MeO)C_6H_4	**5c**	69
4	"	(*p*-Cl)C_6H_4	**5d**	73
5	"	Ph	**5e**	49
6	(*m*-Br)C_6H_4	Ph	**5f**	62

[a]Reaction scale: **4** (0.2 mmol), **2** (0.3 mmol), Et_3N (0.3 mmol), 1,4-dioxane (4.0 mL). [b]Isolated yield.

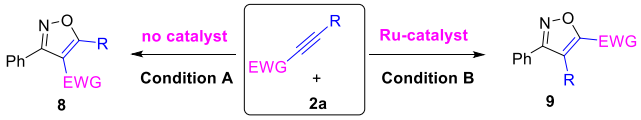
cases. In addition to thioalkynes and ynol ethers, ynamide **6** could also participate in this cycloaddition but with moderate regioselectivity, favoring the umpolung 4-amino isoxazole **7** (Scheme 2). The relatively low regioselectivity might be due to either the lower polarization of the triple bond and/or the weak coordination ability of sulfinamide unit (*vide infra*).

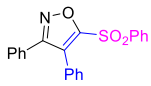
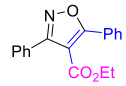
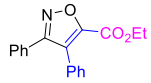
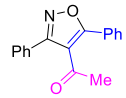
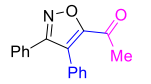
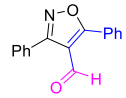
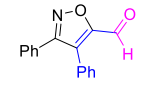
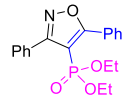
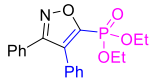
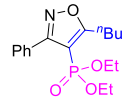
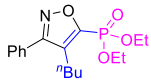
Scheme 2. Reaction of Ynamide 6



In addition to electron-rich alkynes, we were also curious about whether this selectivity switch is general toward electron-deficient alkynes. For direct comparison, we set up both thermal (uncatalyzed) and ruthenium-catalyzed reactions for the same pair of substrates (Table 4). Indeed, a complete

Table 4. Regioselectivity Switch on Electron-Deficient Alkynes[a]



entry	Condition A (**8**)	Condition B (**9**)
1[b]	**8a**, 83% >20:1 *rr*	 **9a**, 89% 7:1 *rr*
2	 **8b**, 86% >20:1 *rr*	 **9b**, 94% >20:1 *rr*
3	 **8c**, 75% 16:1 *rr*	 **9c**, 88% >20:1 *rr* (X-ray)
4	 **8d**, 79% >20:1 *rr*	 **9d**, 92% >20:1 *rr*
5	 **8e**, 55% >20:1 *rr*	 **9e**, 95% >20:1 *rr*
6	 **8f**, <10%[c]	 **9f**, 90% >20:1 *rr*

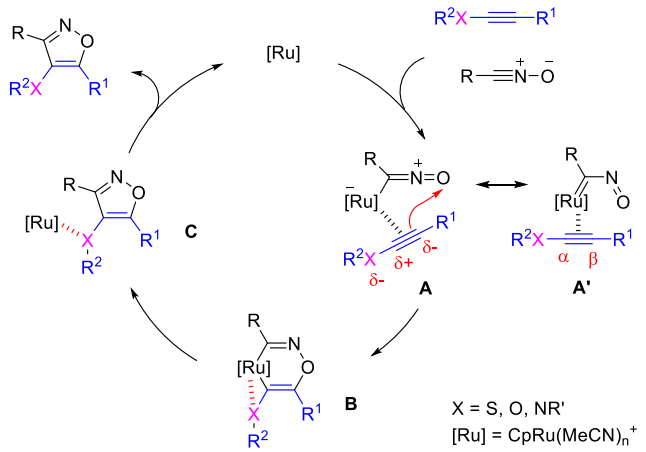
[a]Condition A: alkyne (0.2 mmol), **2a** (0.5 mmol), Et_3N (0.5 mmol), and Et_2O (8 mL), rt, 48 h; Condition B: standard conditions as shown in Table 2, except that THF was used as solvent. Isolated yield. [b]Run with MeCN as solvent. [c]The alkyne was recovered.

switch of regioselectivity was also observed with all these electron-poor alkynes, including alkynyl sulfone, ester, ketone, aldehyde, and phosphonate.[11] Under thermal conditions (condition A), the matched innate polarity of the two partners led to isomers **8** bearing the electron-withdrawing group on the 4-position.[4] In contrast, with Ru-catalysis, isoxazoles **9** with the electron-withdrawing group on the 5-position were uniformly generated with high efficency and regio ratio (*rr*). These results indicate that the Ru-catalyzed umpolung reactivity of nitrile oxides is indeed general.

A possible reaction mechanism is proposed to rationalize the reactivity and regioselectivity employing electron-rich alkynes as an example (Scheme 3). We believe that the catalytic cycle begins with complexation of ruthenium with both alkyne and nitrile oxide.[3c] The resulting complex **A** has several features: (1) The nitrile oxide coordinates with the carbon center rather than the oxygen center, presumably due to the relatively soft nature of ruthenium. (2) The presence of the positive charge on the nitrogen in **A** may easily lead to back-donation from the ruthenium center to form the ruthenium carbene resonance

https://doi.org/10.1021/acs.orglett.1c00273
Org. Lett. 2021, 23, 2431−2436

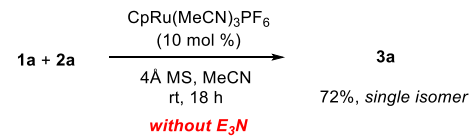
Scheme 3. Proposed Mechanism



structure **A′**, thus minimizing charge separation. (3) Such a bonding mode between nitrile oxide and ruthenium alters the electronic property of the nitrile oxide, leading to subsequent nucleophilic attack onto the oxygen center, rather than the original electrophilic carbon center. Next, an oxidative cyclization step takes place to form Ru-heterocycle **B**, in which the more nucleophilic β carbon of the alkyne approaches the oxygen atom. This step can also be regarded as a Diels–Alder-type [4 + 2] cycloaddition from the Ru-carbene resonance structure **A′**. Finally, a reductive elimination step forms the product via **C** and regenerates the active catalyst. For electron-rich alkynes, there might be additional coordination of the heteroatom (O, S, or N) on the alkyne to the ruthenium center, as shown in intermediate **B**. This interaction may help stabilize this intermediate and thus enhance the reactivity and regioselectivity, particularly in the case of thioalkynes.

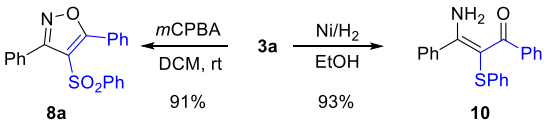
Aiming to further improve the standard protocol, in which a base has to be used, we employed 4 Å molecular sieves to replace the base Et_3N to mediate the *in situ* generation of nitrile oxide. Gratifyingly, the reaction of **1a** and **2a** also proceeded efficiently to form the same product **3a** in 72% yield (Scheme 4).[12] Thus, this nearly neutral condition could provide complementary utility when needed.

Scheme 4. Reaction without Et_3N



The 4-sulfenyl product **3a** could be easily oxidized by *m*CPBA to provide sulfone **8a** (Scheme 5), whose identity was confirmed to be the same as that obtained in entry 1 of Table 4. Moreover, the isoxazole product could undergo ring opening smoothly under Ni-catalyzed hydrogenation conditions to provide highly functionalized enone **10**. It is worth noting that such highly functionalized stereodefined aminosufenyl olefins are useful structural units in bioactive molecules and their synthesis has been an important topic in organic synthesis.[13]

Scheme 5. Product Derivatizations



In summary, we have developed an efficient [3 + 2] cycloaddition of nitrile oxides with electron-rich alkynes, including thioalkynes, ynol ethers, and ynamides. Different from the thermal condition, the ruthenium-catalyzed protocol leads to opposite regioselectivity, providing efficient and mild access to a diverse range of useful 4-heterosubstituted isoxazoles. The observed excellent regioselectivity could be explained by the polarization of the alkyne triple bond as well as the additional complexation of the heteroatom with the ruthenium. In addition to electron-rich alkynes, the ruthenium-induced polarity reversal of nitrile oxides was also applied to the regiodivergent cycloaddition with various electron-deficient alkynes with high efficiency and selectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00273.

Experimental procedures and NMR spectra (PDF)

Accession Codes

CCDC 1914523 and 1935590 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.

■ AUTHOR INFORMATION

Corresponding Author

Jianwei Sun − *Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, Changzhou 213164, China; Department of Chemistry, The Hong Kong University of Science and Technology, Kowloon, China;* orcid.org/0000-0002-2470-1077; Email: sunjw@ust.hk

Authors

Qiang Feng − *Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, Changzhou 213164, China; Department of Chemistry, The Hong Kong University of Science and Technology, Kowloon, China;* orcid.org/0000-0002-7032-0451

Hai Huang − *Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, Changzhou 213164, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00273

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the NSFC (22071210, 91956114) and Hong Kong RGC (16302719) and Jiangsu

specially appointed professors program. We thank Prof. Guochen Jia for helpful discussions.

■ REFERENCES

(1) Selected reviews (a−c) and recent examples (d−j) of umpolung reactivity: (a) Seebach, D. Methods of Reactivity Umpolung. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239−336. (b) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307−9387. (c) Hari, D. P.; Caramenti, P.; Waser, J. Cyclic Hypervalent Iodine Reagents: Enabling Tools for Bond Disconnection via Reactivity Umpolung. *Acc. Chem. Res.* **2018**, *51*, 3212−3225. (d) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. A Highly Enantioselective Catalytic Intramolecular Stetter Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299. (e) Ni, H.; Chan, W. − L.; Lu, Y. Phosphine-Catalyzed Asymmetric Organic Reactions. *Chem. Rev.* **2018**, *118*, 9344−9411. (f) Sohn, S. S.; Rosen, E. L.; Bode, J. W. N-Heterocyclic Carbene-Catalyzed Generation of Homoenolates: γ-Butyrolactones by Direct Annulations of Enals and Aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 14370−14371. (g) Reich, B. J. E.; Justice, A. K.; Beckstead, B. T.; Reibenspies, J. H.; Miller, S. A. Cyanide-Catalyzed Cyclizations via Aldimine Coupling. *J. Org. Chem.* **2004**, *69*, 1357−1359. (h) Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. Cyanide-Catalyzed Cyclizations via Aldimine Coupling. *J. Am. Chem. Soc.* **2006**, *128*, 1472−1473. (i) Smith, A. B., III.; Xian, M. Anion Relay Chemistry: An Effective Tactic for Diversity Oriented Synthesis. *J. Am. Chem. Soc.* **2006**, *128*, 66−67. (j) Wu, Y.; Hu, L.; Li, Z.; Deng, L. Catalytic Asymmetric Umpolung Reactions of Imines. *Nature* **2015**, *523*, 445−450.

(2) Reviews of cycloaddition of nitrile oxides: (a) Belen′kii, L. I. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd ed.; Feuer, H., Ed.; Wiley: Hoboken, NJ, 2008; pp 1−127. (b) Gothelf, K. V.; Jørgensen, K. A. Asymmetric 1, 3-Dipolar Cycloaddition Reactions. *Chem. Rev.* **1998**, *98*, 863−909. (c) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: Chichester, UK, 2002. (d) Pellissier, H. Asymmetric 1, 3-Dipolar Cycloadditions. *Tetrahedron* **2007**, *63*, 3235−3285. (e) Namboothiri, I. N. N.; Rastogi, N. Isoxazolines from Nitro Compounds: Synthesis and Applications. *Top. Heterocycl. Chem.* **2008**, *12*, 1−44. (f) Pasinszki, T.; Westwood, N. P. C. Synthesis, Spectroscopy, and Applications of Small Nitrile Oxides. *Curr. Org. Chem.* **2011**, *15*, 1720−1733. (g) Rane, D.; Sibi, M. Recent Advances in Nitrile Oxide Cycloadditions. Synthesis of Isoxazolines. *Curr. Org. Chem.* **2011**, *8*, 616−627. (h) Heaney, F. Nitrile Oxide/Alkyne Cycloadditions−A Credible Platform for Synthesis of Bioinspired Molecules by Metal−Free Molecular Clicking. *Eur. J. Org. Chem.* **2012**, *2012*, 3043−3058. (i) Ukaji, Y.; Soeta, T. In *Methods and Applications of Cycloaddition Reactions in Organic Synthesis*, 1st ed.; Nishiwaki, N., Ed.; Wiley: 2014; pp 263−281. (j) Roscales, S.; Plumet, J. Metal-Catalyzed 1, 3-Dipolar Cycloaddition Reactions of Nitrile Oxides. *Org. Biomol. Chem.* **2018**, *16*, 8446−8461. (k) Plumet, J. 3-Dipolar Cycloaddition Reactions of Nitrile Oxides under "Non-Conventional" Conditions: Green Solvents, Irradiation, and Continuous Flow. *ChemPlusChem* **2020**, *85*, 2252−2271. (l) Huisgen, R. 1, 3-Dipolar Cycloadditions. Past and Future. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565−598.

(3) Cycloaddition with electron-normal alkynes, mostly terminal alkynes: (a) Hansen, T. V.; Wu, P.; Fokin, V. V. One-Pot Copper(I) − Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles. *J. Org. Chem.* **2005**, *70*, 7761−7764. (b) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates. *J. Am. Chem. Soc.* **2005**, *127*, 210−216. (c) Grecian, S.; Fokin, V. V. Ruthenium−Catalyzed Cycloaddition of Nitrile Oxides and Alkynes: Practical Synthesis of Isoxazoles. *Angew. Chem., Int. Ed.* **2008**, *47*, 8285−8287. (d) Jackowski, O.; Lecourt, T.; Micouin, L. Direct Synthesis of Polysubstituted Aluminoisoxazoles and Pyrazoles by a Metalative Cyclization. *Org. Lett.* **2011**, *13*, 5664−5667. (e) Kankala, S.; Vadde, R.; Vasam, C. S. N-Heterocyclic Carbene−Catalyzed 1,3−Dipolar Cycloaddition Reactions: A Facile Synthesis of 3,5−Di− and 3,4,5−Trisubstituted Isoxazoles. *Org. Biomol. Chem.* **2011**, *9*, 7869−7876. (f) Jawalekar, A. M.; Reubsaet, E.; Rutjes, F. P. J. T.; Van Delft, F. L. Synthesis of Isoxazoles by Hypervalent Iodine-Induced Cycloaddition of Nitrile Oxides to Alkynes. *Chem. Commun.* **2011**, *47*, 3198−3200. (g) Yoshimura, A.; Middleton, K. R.; Todora, A. D.; Kastern, B. J.; Koski, S. R.; Maskaev, A. V.; Zhdankin, V. V. Hypervalent Iodine Catalyzed Generation of Nitrile Oxides from Oximes and their Cycloaddition with Alkenes or AlkyneS. *Org. Lett.* **2013**, *15*, 4010−4013. (h) Zhao, G.; Liang, L.; Wen, C. H. E.; Tong, R. In Situ Generation of Nitrile Oxides from NaCl−Oxone Oxidation of Various Aldoximes and Their 1,3-Dipolar Cycloaddition. *Org. Lett.* **2019**, *21*, 315−319. (i) Yoshimura, A.; Middleton, K. R.; Todora, A. D.; Kastern, B. J.; Koski, S. R.; Maskaev, A. V.; Zhdankin, V. V. Hypervalent Iodine Catalyzed Generation of Nitrile Oxides from Oximes and their Cycloaddition with Alkenes or Alkynes. *Org. Lett.* **2013**, *15*, 4010−4013.

(4) Cycloaddition with electron-deficient or highly strained alkynes, such as benzynes and cyclooctynes. For selected recent examples, see: (a) Back, T. G.; Zhai, H. Cyclizations and Cycloadditions of Acetylenic Sulfones on Solid Supports. *Chem. Commun.* **2006**, 326−328. (b) Crossley, J. A.; Browne, D. L. An Alkynyliodide Cycloaddition Strategy for the Construction of Iodoisoxazoles. *J. Org. Chem.* **2010**, *75*, 5414−5416. (c) Zheng, H.; McDonald, R.; Hall, D. G. Boronic Acid Catalysis for Mild and Selective [3 + 2] Dipolar Cycloadditions to Unsaturated Carboxylic Acids. *Chem. - Eur. J.* **2010**, *16*, 5454−5460. (d) Dubrovskiy, A. V.; Larock, R. C. Synthesis of Benzisoxazoles by the [3 + 2] Cycloaddition of in situ Generated Nitrile Oxides and Arynes. *Org. Lett.* **2010**, *12*, 1180−1183. (e) Brian, C.; Sanders, F.; Friscourt, P. A.; Ledin, N. E.; Mbua, S.; Guo, A. J.; Boltje, T. J.; Popik, V. V.; Boons, G. − J. Metal−Free Sequential [3 + 2]-Dipolar Cycloadditions using Cyclooctynes and 1,3-Dipoles of Different Reactivity. *J. Am. Chem. Soc.* **2011**, *133*, 949−957. (f) Oakdale, J. S.; Sit, R. K.; Fokin, V. V. Ruthenium-Catalyzed Cycloaddition of 1−Haloalkynes with Nitrile Oxides and Organic Azides; Synthesis of 4-Halo Isoxazoles and 5−Halo Triazoles. *Chem. - Eur. J.* **2014**, *20*, 11101−11110. (g) Kesornpun, C.; Aree, T.; mahidol, C.; Ruchirawat, S.; Kittakoop, P. Water-Assisted Nitrile Oxide Cycloadditions: Synthesis of Isoxazoles and Stereoselective Syntheses of Isoxazolines and 1,2,4−Oxadiazoles. *Angew. Chem., Int. Ed.* **2016**, *55*, 3997−4001.

(5) Other synthetic methods: (b) Waldo, J. P.; Larock, R. C. Synthesis of Isoxazoles via Electrophilic Cyclization. *Org. Lett.* **2005**, *7*, 5203−5205. (c) Tang, S.; He, J.; Sun, Y.; He, L.; She, X. Efficient and Regioselective One-Pot Synthesis of 3-Substituted and 3,5-Disubstituted Isoxazoles. *Org. Lett.* **2009**, *11*, 3982−3985. (d) Murarka, S.; Studer, A. Transition Metal-Free TEMPO-Catalyzed Oxidative Cross- Coupling of Nitrones with Alkynyl-Grignard Reagents. *Adv. Synth. Catal.* **2011**, *353*, 2708−2714. (e) Gayon, E.; Quinonero, O.; Lemouzy, S.; Vrancken, E.; Campagne, J. Transition-Metal-Catalyzed Uninterrupted Four-Step Sequence to Access Trisubstituted Isoxazoles. *Org. Lett.* **2011**, *13*, 6418−6421. (g) Zhu, L.; Yu, H.; Xu, Z.; Jiang, X.; Lin, L.; Wang, R. Copper-Catalyzed Oxyazidation of Unactivated Alkenes: A Facile Synthesis of Isoxazolines Featuring an Azido Substituent. *Org. Lett.* **2014**, *16*, 1562−1565. (h) Liu, Y.-Y.; Yang, X.-H.; Yang, J.; Song, R.-J.; Li, J.-H. Silver-Mediated Radical Cyclization: Construction of Δ^2-Isoxazolines from α-Halo Ketoximes and 1,3-Dicarbonyl Compounds. *Chem. Commun.* **2014**, *50*, 6906−6908. (i) Gao, P.; Li, H.-X.; Hao, X.-H.; Jin, D.-P.; Chen, D.-Q.; Yan, X.-B.; Wu, X.-X.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. Facile Synthesis of Disubstituted Isoxazoles from Homopropargylic Alcohol via C = N Bond Formation. *Org. Lett.* **2014**, *16*, 6298−6301. (j) Li, C.; Deng, H.; Li, C.; Jia, X.; Li, J. Palladium-Catalyzed Synthesis of Δ^2-Isoxazoline from Toluene Derivatives Enabled by the Triple Role of Silver Nitrate. *Org. Lett.* **2015**, *17*, 5718−5721. (k) Dai, P.; Tan, X.; Luo, Q.; Yu, X.; Zhang, S.; Liu, F.; Zhang, W.-H. Synthesis of 3-Acyl-isoxazoles and Δ^2-

https://doi.org/10.1021/acs.orglett.1c00273
Org. Lett. 2021, 23, 2431−2436

Isoxazolines from Methyl Ketones, Alkynes or Alkenes, and tert-Butyl Nitrite via a Csp^3−H Radical Functionalization/Cycloaddition Cascade. *Org. Lett.* **2019**, *21*, 5096−5100.

(6) Wiley, R. H.; Wakefield, B. J. Infrared Spectra of the Nitrile *N*-Oxides: Some New Furoxans. *J. Org. Chem.* **1960**, *25*, 546−551.

(7) Sporadic examples with electron-rich alkynes: (a) Himbert, G.; Kuhn, H.; Barz, M. Cycloadditionen, XVIII: 5−Aminoisoxazole durch Cycloaddition von Nitriloxiden an Inamine. *Liebigs Ann. Chem.* **1990**, *1990*, 403−407. (b) Sukhova, L. N.; Ostroumov, I. G.; Bel'skii, V. K.; Galishev, V. A.; Maretina, I. A. Cycloadditon of 1,3-Dipolar Reagents to 6-Diethylamino-3-hexen-5-yn-2-one. *Russ. J. Org. Chem.* **1994**, *30*, 49−53. (c) Li, J.; Wakefield, B. D.; Ruble, J. C.; Stiff, C. M.; Romero, D. L.; Marotti, K. R.; Sweeney, M. T.; Zurenko, G. E.; Rohrer, D. C.; Thorarensen, A. Preparation of Novel Antibacterial Agents. Replacement of The Central Aromatic Ring with Heterocycles. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2347−2350. (d) Hsung, R. P.; You, L.; Zhang, X.; Johnson, W. L.; Figueroa, R.; Li, H. Syntheses of Amide-substituted Isoxazoles and Pyrazoles via Regioselective [3 + 2] Cycloadditions of Terminally Unsubstituted Ynamides. *Heterocycles* **2007**, *74*, 553−568. (e) Chen, C.; Cui, S. Iterative Assembly of Nitrile Oxides and Ynamides: Synthesis of Isoxazoles and Pyrroles. *J. Org. Chem.* **2019**, *84*, 12157−12164.

(8) (a) Kanda, Y.; Takahashi, T.; Araki, Y.; Konoike, T.; Mihara, S.-i.; Fujimoto, M. Discovery and Synthesis of A Potent Sulfonamide ETB Selective Antagonist. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1875−1878. (b) Fukui, Y.; Sasatani, T.; Matsumura, K.-i.; Ishizuka, N.; Yano, T.; Kanda, Y.; Chomei, N. *Isoxazole Derivative Having Agonistic Activity Against Peroxisome Proliferator-activated Receptor*. PCT, WO 2005/054213A1. (c) Ogawa, T.; Chomei, N.; Masuda, K.; Tanaka, S. *Isoxazole Derivative and Isothiazole Derivative Having Inhibitory Activity on 11β-Hydroxysteroid Dehydrogenase Type 1*. US Patent, 2011, 8017638B2.

(9) (a) Ding, S.; Jia, G.; Sun, J. Iridium-Catalyzed Intermolecular Azide−Alkyne Cycloaddition of Internal Thioalkynes under Mild Conditions. *Angew. Chem., Int. Ed.* **2014**, *53*, 1877−1880. (b) Wang, Y.; Song, L. − J.; Zhang, X.; Sun, J. Metal−Free [2 + 2 + 2] Cycloaddition of Ynamides and Nitriles: Mild and Regioselective Synthesis of Fully Substituted Pyridines. *Angew. Chem., Int. Ed.* **2016**, *55*, 9704−9708. (c) Wu, A.; Feng, Q.; Sung, H. H. Y.; Williams, I. D.; Sun, J. Synthesis of Eight−Membered Lactams through Formal [6 + 2] Cyclization of Siloxy Alkynes and Vinylazetidines. *Angew. Chem., Int. Ed.* **2019**, *58*, 6776−6780.

(10) Sun, J.; Feng, Q. Preparation Method of 3,4,5(4-heteroatom) Full Substituted Isoxazole Compounds for Medicine molecule. Chinese patent, 2020, CN110724110.

(11) Other electron-withdrawing groups (EWGs) were also evaluated with the Ru-catalyzed condition. When EWG = CN, a mixture was formed. When EWG = CO_2H, very low reactivity was observed.

(12) Ryu, E. K.; Kim, J. N. 1, 3-Dipolar Cycloaddition: Molecular Sieves Assisted Generation of Nitrile Oxides from Hydroximoyl Chlorides. *Heterocycles* **1990**, *31*, 1693−1697.

(13) (a) Lavecchia, A.; Cosconati, S.; Limongelli, V.; Novellino, E. Modeling of Cdc25B Dual Specifity Protein Phosphatase Inhibitors: Docking of Ligands and Enzymatic Inhibition Mechanism. *ChemMedChem* **2006**, *1*, 540−546. (b) Pappo, D.; Kashman, Y. β−Turn Mimetic: Synthesis of Cyclic Thioenamino Peptides. *Org. Lett.* **2006**, *8*, 1177−1179. (c) Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782−8785. (d) Wan, J. − P.; Zhong, S.; Xie, L.; Cao, X.; Liu, Y.; Wei, L. KIO_3−Catalyzed Aerobic Cross−Coupling Reactions of Enaminones and Thiophenols: Synthesis of Polyfunctionalized Alkenes by Metal−Free C−H Sulfenylation. *Org. Lett.* **2016**, *18*, 584−587.

https://doi.org/10.1021/acs.orglett.1c00273
Org. Lett. 2021, 23, 2431−2436