OL Organic Letters

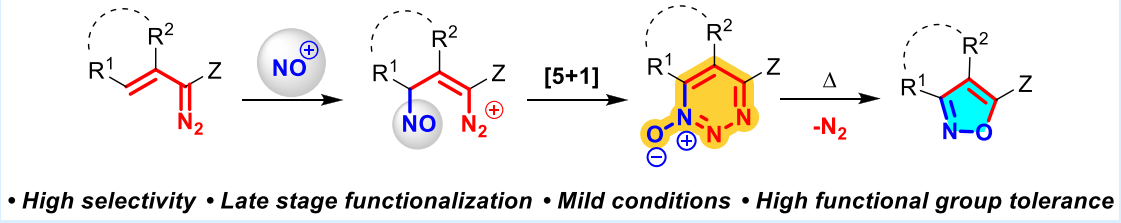
pubs.acs.org/OrgLett Letter

Intermolecular [5 + 1]-Cycloaddition between Vinyl Diazo Compounds and *tert*-Butyl Nitrite to 1,2,3-Triazine 1-Oxides and Their Further Transformation to Isoxazoles

Luca De Angelis, Haifeng Zheng, Matthew T. Perz, Hadi Arman, and Michael P. Doyle*

Cite This: *Org. Lett.* 2021, 23, 6542−6546 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

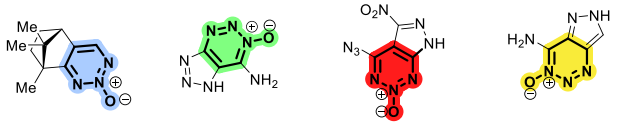


• High selectivity • Late stage functionalization • Mild conditions • High functional group tolerance

ABSTRACT: 1,2,3-Triazine 1-oxides are formed by nitrosyl addition from *tert*-butyl nitrite to the vinylogous position of vinyl diazo compounds. This transformation, which is a formal intermolecular [5 + 1] cycloaddition, occurs under mild conditions, with high functional group tolerance and regioselectivity, and can be employed for late-stage functionalization. Upon heating at refluxing chlorobenzene temperature, these triazine-*N*-oxides undergo dinitrogen extrusion to form isoxazoles in very high yields.

Triazine *N*-oxides are a special class of heterocyclic compounds that have proven to be valuable synthetic scaffolds.[1] Among the possible isomers of triazine *N*-oxides, 1,2,3-triazine-*N*-oxides have gained increased attention compared with their 1,2,4- and 1,3,5-triazine-*N*-oxide counterparts due their potential biological and fluorescent properties or high energy content (Scheme 1).[1,2] 1,2,3-Triazines are most directly accessed by *N*-amination of pyrroles followed by oxidative ring expansion,[3] but other multistep processes are also available.[4] 1,2,3-Triazine-*N*-oxides are commonly obtained by peracid oxidations of 1,2,3-triazines,[5] or diazotization of 2-aminoaryl oximes followed by cyclization.[3a,6] However, these methods suffer from low functional group tolerance, overoxidation, and multiple byproducts. They appear to be limited to bicyclic systems and, generally, have low selectivity for *N*-oxide formation.

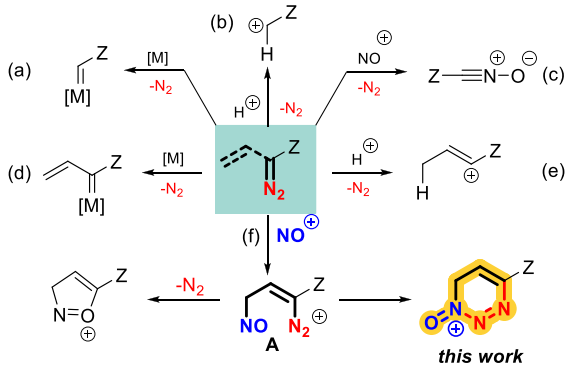
Scheme 1. Diverse applications of 1,2,3-triazine *N*-oxide compounds



(a) CNS *stimulant* (b) *fluorescent material* (c) *energetic material* (d) *energetic material*

Diazo compounds are recognized to be excellent building blocks in the construction of organic compounds due to the diversity of their reactions and their amphiphilic reactivity.[7] They are inherently susceptible to electrophilic addition with transition metal complexes to form metal carbenes,[8] with Brønsted acids to form carbocations,[9] and by nitrosonium ion transfer to form nitrile oxides[10] (Scheme 2a−c). We reasoned that increasingly abundant vinyldiazo compounds might enable selective electrophilic addition to form vinyl diazonium ions and, in doing so, provide a convenient entry to valuable reactive intermediates. Indeed, metallo-vinyl carbenes have

Scheme 2. Background and This Work



Received: July 14, 2021
Published: August 9, 2021

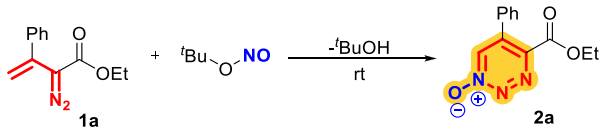
https://doi.org/10.1021/acs.orglett.1c02352
Org. Lett. 2021, 23, 6542−6546

made possible highly stereoselective [3+*n*]-cycloaddition reactions (Scheme 2d)[11] and, recently, bis(trifluoromethanesulfonyl)imide ($HNTf_2$) has been found to be an effective Brønsted acid catalyst to exclusively protonate the vinylogous position of vinyldiazo compounds to form highly reactive vinyl carbocations after the loss of dinitrogen (Scheme 2e).[12] Cycloadditions involving dinitrogen from the diazo functional group, including widely established [3 + 2] dipolar cycloadditions[13] and the rare [4 + 2] Diels–Alder reaction,[14] have been reported, and the nucleophilic trapping of diazonium ions is a classic transformation.[15] Also, alkyl nitrites are well-known to be effective nitrosyl transfer reagents.[16] Inspired by these reports, we speculated that *tert*-butyl nitrite (TBN) would serve as a nitrosyl donor to vinyldiazo compounds producing nitroso-vinyl diazonium ion **A**, which could either undergo loss of dinitrogen to form a precursor to isoxazole or deliver a cationic precursor to 1,2,3-triazine-1-oxide by nucleophilic reaction of the nitrosyl nitrogen with the vinyl diazonium ion through intermolecular [5 + 1] cycloaddition (Scheme 2f). We now report a general method for the formation of 4-substituted carboxylates of 1,2,3-triazine 1-oxide that is performed under very mild conditions, shows high functional group tolerance and regioselectivity, can be employed for late-stage functionalization, and has no limitation to bicyclic systems. In addition, these triazine *N*-oxides undergo thermal dedinitrogenation to form isoxazoles in high yields.

Ethyl 3-phenyl-2-diazo-3-butenoate **1a** and TBN were selected as substrates to test this hypothesis. Their reactions in halogenated solvents using only a modest excess of TBN with or without an ether cosolvent at room temperature formed 1,2,3-triazine 1-oxide **2a** only in trace amounts (Table 1, entries 1 and 2). However, combining dichloromethane with more polar solvents under the same reaction conditions increased the yield of this product (entries 3–6), but neither increasing the ratio of reactants nor decreasing the reaction temperature had a significant influence on product yield. Further efforts to optimize the yield of **2a** revealed that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) with its high electric constant, its ability to stabilize electrophiles,[17] and suggested by its activation of cycloadditions,[18] was found to be the perfect cosolvent along with DCM. Triazine *N*-oxide **2a** was formed in quantitative yield in only 30 min by slow addition of **1a** into a solution of TBN containing only 20:1 v/v DCM/HFIP (entry 7). Increasing the relative amount of HFIP did not increase the rate of conversion.

With the optimized reaction conditions in hand, the scope of the synthesis of 4-substituted carboxylates of 1,2,3-triazine 1-oxide **2** was explored, and these results are presented in Scheme 3. An array of 3-aryl-2-diazo-3-butenoates bearing either electron-donating groups (EDG) (**2a–2e**) or electron-withdrawing groups (EWG) (**2f** and **2g**) delivered the corresponding triazine 1-oxides in excellent yields, although a lower yield was obtained with the *ortho*-methoxy derivative **2e**.

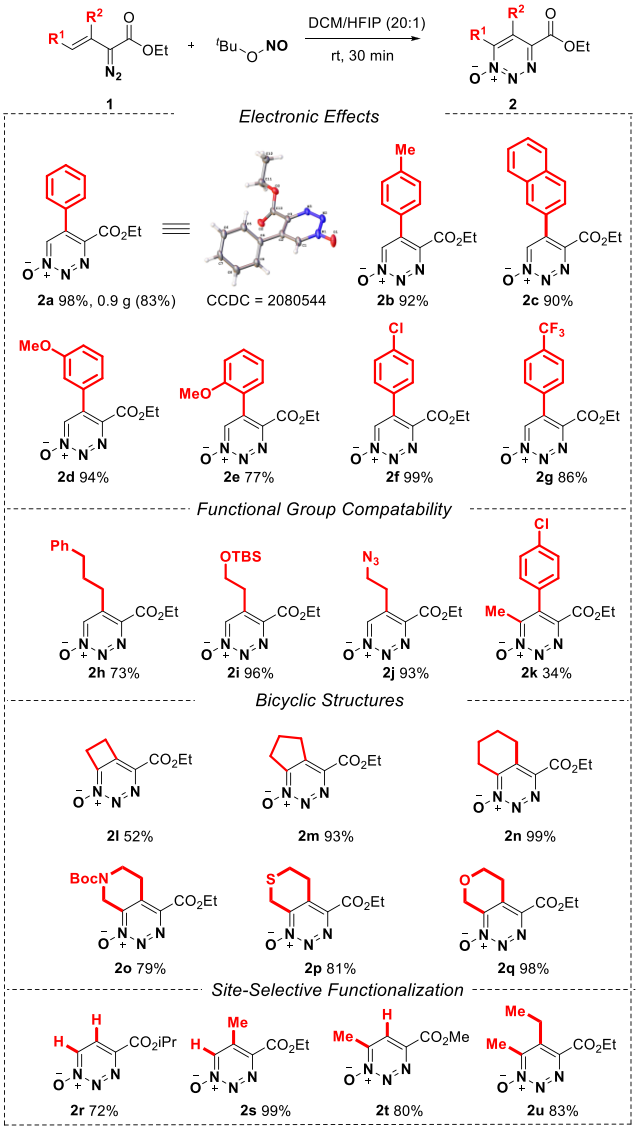
Table 1. Optimization for the Reaction Conditions for the Synthesis of 1,2,3-Triazine *N*-Oxide 2a[a]



Entry	Conditions	Yield of **2a** (%)[b]
1	$CHCl_3$[c], rt, 12 h	<5
2	DCM/MTBP (1:1), rt, 12 h	<5
3	DCM/ACN[c] (1:1), rt, 12 h	22(16)[f]
4	DCM/ACN[d] (1:1), rt, 3 h	77
5	DCM/ACN[e] (1:1), 5 h	68
6	DCM/CH_3NO_2 (1:1), rt, 3 h	58
7	DCM/HFIP (20:1), rt, 0.5 h	99(96)[f]

[a]Reaction conditions: **1a** (0.25 mmol, 0.1 M in *x* solvent) was added to ^{t}BuONO (1.3 equiv., 0.1 M in *x* solvent) dropwise at rt. The reaction was continued for the indicated time at room temperature. [b]The percentage of **2a** compared with the initial amount of **1a** was determined by ^{1}H NMR analysis using $CHBr_3$ as internal standard. [c]3.5 equiv of ^{t}BuONO was used. [d]1.3 equiv of **1a** was used. [e]0 °C to rt. [f]Isolated yields.

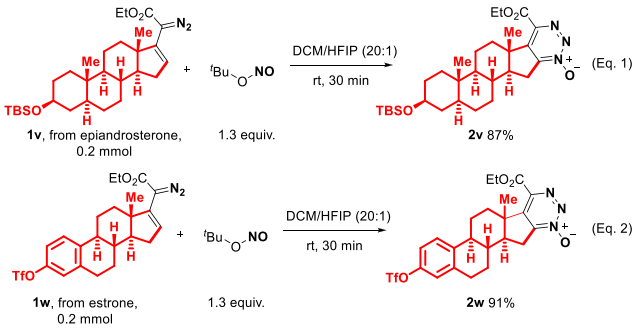
Scheme 3. Direct TBN Reactions with Vinyldiazo Compounds: Synthesis of 1,2,3-Triazine 1-oxides[a]



[a]Reaction conditions: **1** (0.25 mmol, 0.1 M in DCM) was added to ^{t}BuONO [1.3 equiv., 0.1 M in DCM/HFIP (20:1)] dropwise at rt. The reaction was continued for the indicated time at rt. Isolated yields.

https://doi.org/10.1021/acs.orglett.1c02352
Org. Lett. 2021, 23, 6542–6546

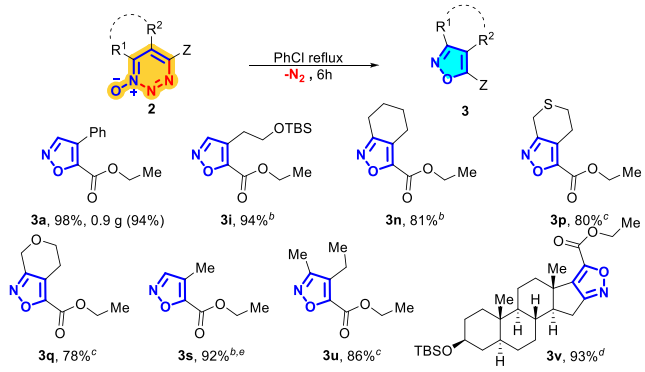
1,2,3-Triazine 1-oxide **2a**, whose structure was confirmed by X-ray crystallography, was prepared in 83% isolated yield in a gram-scale reaction. This method also demonstrates high functional group tolerance with vinyldiazo reactants having phenylalkyl, *tert*-butyldimethylsilyl ether (OTBS), azide, and 4-alkyl-3-aryl substituents that produced triazine 1-oxides **2h−2k** in good to excellent yield. For the synthesis of bicyclic triazine *N*-oxides, four, five, and six membered vinyl groups linked to diazoacetates (**1l−q**) were suitable substrates to furnish the desired products. To further demonstrate the generality of this method, 1,2,3-triazine *N*-oxides bearing one substituent in the 4-position (**2r**), two substituents in the 4,5- or 4,6-positions (**2s** and **2t**), or fully substituted in the 4,5,6-positions (**2u**) were selectively prepared in excellent yield, suggesting the opportunity provided by this methodology for the placement of substituents at the 5- and 6-positions, in addition to the carboxylate group at the 4-position. Surprisingly, the reaction of styryl diazoacetate with TBN produced a complex mixture of byproducts that were not further analyzed. Potential late-stage functionalization was examined with this method using vinyldiazo compounds **1v** and **1w** derived from epiandrosterone and estrone, respectively. They were converted to the corresponding 1,2,3-triazine 1-oxides **2v** and **2w** in 87% and 91% isolated yield, respectively, by simple evaporation of the solvent without chromatography (eqs 1 and 2).



Isoxazoles represent another important class of heterocycles due to their biological activities and therapeutic applications.[17] Their most direct synthesis is the [3 + 2]-cycloaddition of nitrile oxides and alkynes.[10,19] We recognized that 1,2,3-triazine 1-oxides **2** bearing an EWG at 4-position might undergo thermal decomposition with loss of dinitrogen to furnish isoxazole **3**. Indeed, in refluxing chlorobenzene, 5-phenyl-1,2,3-triazine 1-oxide **2a** was thermally converted to 4-phenyl isoxazole **3a** in 98% isolated yield in 6 h (Scheme 4). Notably, no loss of yield was observed when **3a** was prepared in a gram-scale reaction.

A representative array of isoxazoles **3** was prepared in excellent yields suggesting the broad application of this method. However, a limitation in this methodology appears in the attempted failed conversion of **2l** to the corresponding strained isoxazole. However, this method favors the synthesis of fully substituted isoxazoles such as **3u** since the alternative 1,3-dipolar cycloaddition approach of nitrile oxides with asymmetric alkynes suffers from low regioselectivity and often gives mixtures of regioisomers.[20] The preparation of polycyclic isoxazoles proposed by previously reported methods is also challenging;[21] polycyclic isoxazoles **3n**, **3p**, and **3q** were obtained from the thermal decomposition of triazine *N*-oxide **2n**, **2p**, and **2q** in excellent yield. The more complex triazine *N*-oxide **2v** derived from the natural product epiandrosterone

Scheme 4. Synthesis of Isoxazoles by Thermal Decomposition of 1,2,3-Triazine 1-Oxides[a]

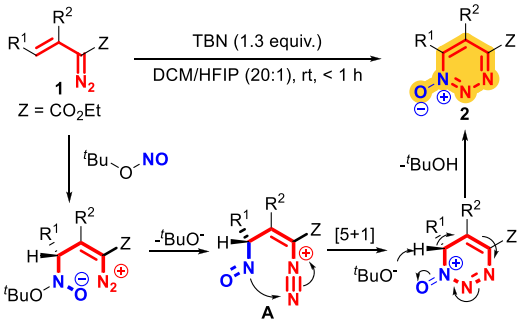


[a]Reaction conditions: a solution of **2** (0.2 mmol, 0.1 M in PhCl) was reflux for 6 h. [b]24 h. [c]72 h. [d]48 h. [e]NMR yield.

was transformed to isoxazole **3v** in 93% yield, demonstrating the effectiveness of this transformation in a late-stage functionalization process.

A probable mechanism for the synthesis of the triazine *N*-oxide **2** through formal intramolecular [5 + 1] cycloaddition is proposed in Scheme 5. Consistent with previous findings on

Scheme 5. Proposed Mechanism for the Formation of 1,2,3-Triazine 1-Oxide



the nucleophilicity of the terminal carbon of vinyldiazo esters,[12,22] **1** selectively undergoes nitrosyl exchange with TBN to generate the nitroso-vinyl diazonium intermediate **A** and *tert*-butoxide, or either its azo-*tert*-butoxide or *tert*-butyl alcohol from proton exchange with HFIP. Then intramolecular nucleophilic association of the nitrosyl nitrogen with the terminal nitrogen of the diazonium ion occurs followed by the deprotonation to furnish the 1,2,3-triazine 1-oxide **2.** The role of HFIP is inexorably linked with stabilization of *tert*-butoxide in its role as the nitrosyl donor and proton removal.

In summary, we have disclosed a novel and practical method for the synthesis of 1,2,3-triazine 1-oxides under mild conditions in high yields from vinyl diazoacetates and TBN. High selectivity of the *N*-oxide position, excellent functional group tolerance, and potential late-stage functionalization have been achieved. Isoxazoles are formed from 1,2,3-triazine 1-oxides by their thermal dinitrogen extrusion in excellent yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02352.

https://doi.org/10.1021/acs.orglett.1c02352
Org. Lett. 2021, 23, 6542−6546

Experimental procedure and spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 2080544 contains 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

Michael P. Doyle − *Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States*; orcid.org/0000-0003-1386-3780; Email: michael.doyle@utsa.edu

Authors

Luca De Angelis − *Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States*

Haifeng Zheng − *Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States*

Matthew T. Perz − *Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States*

Hadi Arman − *Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02352

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Support for this research from the The Welch Foundation (AX−1871) is gratefully acknowledged. We thank W. G. Griffith (The University of Texas at San Antonio), for extensive mass spectral analyses. The X-ray diffractometer used in this research was supported by a grant from the U.S. National Science Foundation (CHE-1920057).

REFERENCES

(1) (a) Mfuh, A. M.; Larionov, O. V. Heterocyclic N-Oxides - An Emerging Class of Therapeutic Agents. *Curr. Med. Chem.* **2015**, *22*, 2819−2857. (b) Larionov, O. V. *Heterocyclic N-Oxides*; Springer International Publishing: Cham, Switzerland, 2018.

(2) (a) Nagai, S.; Ueda, T. Synthesis and Central Nervous System Stimulant Activity of Camphor-1,2,3-Triazine Fused with Diphenylcyclopropenone and Camphor-1,2,3-Triazine *N*-oxides. *J. Heterocycl. Chem.* **2000**, *37*, 1663−1664. (b) Deng, M.; Feng, Y.; Zhang, W.; Qi, X.; Zhang, Q. A Green Metal-Free Fused-Ring Initiating Substance. *Nat. Commun.* **2019**, *10*, 1339. (c) Tang, Y.; Imler, G. H.; Parrish, D. A.; Shreeve, J. M. Energetic and Fluorescent Azole-Fused 4-Amino-1,2,3-triazine-3-N-Oxides. *ACS Appl. Energy Mater.* **2019**, *2*, 8871−8877.

(3) (a) Kobylecki, R. J.; McKillop, A. In *Adv. Heterocycl. Chem.*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1976; Vol. *19*. (b) Neunhoeffer, H.; Paul, F. *Chemistry of 1,2,3-Triazine and 1,2,4-Triazine, Tetrazines, and Pentazin*; Wiley, John Wiley & Sons: New York, 2009.

(4) (a) Cascioferro, S.; Spagnò, V.; Carbone, A.; Montalbano, A.; Barraja, P.; Diana, P.; Cirrincion, G.; Parrino, B. Synthesis and Antitumor Activities of 1,2,3-Triazine and Their Benzo- and Heterofused Derivates. *Eur. J. Med. Chem.* **2017**, *142*, 74−86. (b) Chen, F. J.; Sugimura, H.; Takeuichi, R.; Ichikawa, S.; Sasaki, I. C-H Insertion by Alkylidene Carbenes to Form 1,2,3-Triazines and Anionic [3 + 2] Dipolar Cycloadditions to Form Tetrazoles: Crucial Roles of Stereoelectronic and Steric Effects. *Org. Lett.* **2018**, *20*, 3434−3437.

(5) (a) Ohsawa, A.; Arai, H.; Ohnishi, H.; Igeta, H. Synthesis, Oxidation, and Reduction of Monocyclic 1,2,3-Triazines. *J. Chem. Soc., Chem. Commun.* **1980**, *24*, 1182−1183. (b) Neunhoeffer, H.; Clausen, M.; Vötter, H.-D.; Ohl, H.; Krüger, C.; Angermund, K. 1,2,3-Triazine, Iii Synthese Von N-Aminopyrazolen Und Deren Oxidation Zu 1,2,3-Triazinen. Molekülstruktur Des 1,2,3-Triazins. *Liebigs Ann. Chem.* **1985**, *1985*, 1732−1751. (c) Ohsawa, A.; Itoh, T.; Yamaguchi, K.; Kawabata, C. Revised Structure of *N*-Oxidation Products of 4,5,6-Triaryltriazines: 1,2,3Triazine 2-Oxides. *Chem. Pharm. Bull.* **1991**, *39* (8), 2117−2119.

(6) Liu, Y.; Qi, X.; Zhang, W.; Yin, P.; Cai, Z.; Zhang, Q. Construction of Bicyclic 1,2,3-Triazine *N*-Oxides from Aminocyanides. *Org. Lett.* **2021**, *23*, 734−738.

(7) (a) Davies, H. M. L.; Lain, Y. J. The Combined C−H Functionalization/Cope Rearrangement: Discovery and Applications in Organic Synthesis. *Acc. Chem. Res.* **2012**, *45*, 923−935. (b) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. Modern Organic Synthesis with α-Diazocarbonyl Compounds. *Chem. Rev.* **2015**, *115*, 9981−10080. (c) Candeias, N. R.; Paterna, P. M. P. Gois, Homologation Reaction of Ketones with Diazo Compounds. *Chem. Rev.* **2016**, *116*, 2937−2981.

(8) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: Hoboken, 1998. (b) Wang, J.; Qiu, D. *Recent Developments of Diazo Compounds in Organic Synthesis*; World Scientific: London, 2020.

(9) Smith, A. B.; Dieter, R. K. The Acid Promoted Decomposition of α-Diazo Ketones. *Tetrahedron* **1981**, *37*, 2407−2439.

(10) De Angelis, L.; Crawford, M. A.; Su, Y.-L.; Wherritt, D.; Arman, H.; Doyle, M. P. Catalytic-Free Formation of Nitrile Oxides and Their Further Transformation to Diverse Heterocycles. *Org. Lett.* **2021**, *23*, 925−929.

(11) (a) Cheng, Q.-Q.; Deng, Y.; Lankelma, M.; Doyle, M. P. Cycloaddition Reaction of Enoldiazo Compounds. *Chem. Soc. Rev.* **2017**, *46*, 5425−5443. (b) Marichev, K. O.; Doyle, M. P. Catalytic asymmetric cycloaddition reactions of enoldiazo compounds. *Org. Biomol. Chem.* **2019**, *17*, 4183−4195.

(12) Zheng, H.; Dong, K.; Wherritt, D.; Arman, H.; Doyle, M. P. Brønstead Acid Catalyzed Friedel-Crafts-type Coupling and Dedinitrogenation Reaction of Vinyldiazo Compounds. *Angew. Chem.* **2020**, *132*, 13715−13719.

(13) (a) Jangra, H.; Chen, Q.; Fuks, E.; Mayer, P.; Ofial, A. R.; Zipse, H.; Mayr, H. Nucleophilicity and Electrophilicity Parameters for Predicting Absolute Rate Constants of Highly Asynchronous 1,3-Dipolar Cycloaddition of Aryldiazomethanes. *J. Am. Chem. Soc.* **2018**, *140*, 16758−16772. (b) Su, Y.-L.; Dong, K.; Zheng, H.; Doyle, M. P. Generation of Diazomethyl Radicals by Hydrogen Atom Abstraction and Their Cycloaddition with Alkenes. *Angew. Chem., Int. Ed.* DOI: **2021** DOI: 10.1002/anie.202105472.

(14) Qiu, H.; Srinivas, H. D.; Zavalij, P. Y.; Doyle, M. P. Unprecedented Intramolecular [4 + 2]-Cycloaddition Between a 1−3-Diene and a Diazo ester. *J. Am. Chem. Soc.* **2016**, *138*, 1808−1811.

(15) Zollinger, H. *Diazo Chemistry I: Aromatic and Heteroaromatic Compounds*; Wiley: New York, 1994.

(16) (a) Doyle, M. P.; Terpstra, J. W.; Pickering, R. A.; LePoire, D. M. Hydrolysis, Nitrosyl Exchange, and Synthesis of Alkyl Nitrites. *J. Org. Chem.* **1983**, *48*, 3379−3382.

(17) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. Hexafluoroisopropanol as a Highly Versatile Solvent. *Nat. Rev. Chem.* **2017**, *1*, No. 0088.

(18) Glinkerman, C. M.; Boger, D. L. Catalysis of Heterocyclic Azadiene Cycloaddition Reactions by Solvent Hydrogen Bonding: Concise Total Synthesis of Methoxatin. *J. Am. Chem. Soc.* **2016**, *138*, 12408−12413.
(19) Feuer, H. *Nitrile Oxides, Nitrones & Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd ed.; John Wiley & Sons Inc.: Hoboken, NJ, 2008; pp 1−128.
(20) Roscales, S.; Plumet, J. Metal-catalyzed 1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides. *Org. Biomol. Chem.* **2018**, *16*, 8446−8461.
(21) (a) Schmitt, D. C.; Lam, L.; Johnson, J. S. Three-Component Coupling Approach to Trachyspic Acid. *Org. Lett.* **2011**, *13* (19), 5136−5139. (b) Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. Facile Construction and Divergent Transformation of Polycyclic Isoxazoles: Direct Access to Polyketide Architectures. *Org. Lett.* **2003**, *5* (4), 391−394. (c) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O.; Wenkert, E. Metal-Catalyzed, Intramolecular Reactions of alpha-Diazo Ketones with Isoxazoles. *J. Org. Chem.* **1994**, *59* (10), 2882−2884.
(22) Barluenga, J.; Lonzi, G.; Riesgo, L.; Tomás, M.; López, L. A. Direct Access to β-Oxodiazo Compounds by Copper(II)-Catalyzed Oxidative Rearrangement of Stabilized Vinyl Diazo Derivates. *J. Am. Chem. Soc.* **2011**, *133*, 18138−18141.

https://doi.org/10.1021/acs.orglett.1c02352
Org. Lett. 2021, 23, 6542−6546