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Diazo Activation with Diazonium Salts: Synthesis of Indazole and 1,2,4-Triazole

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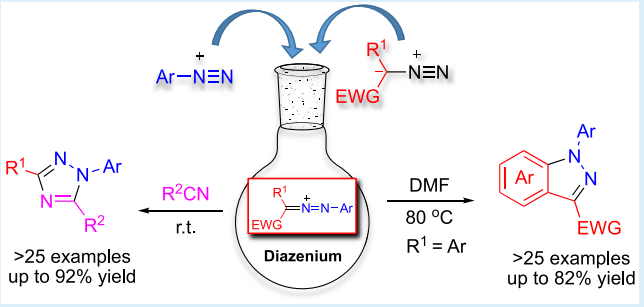
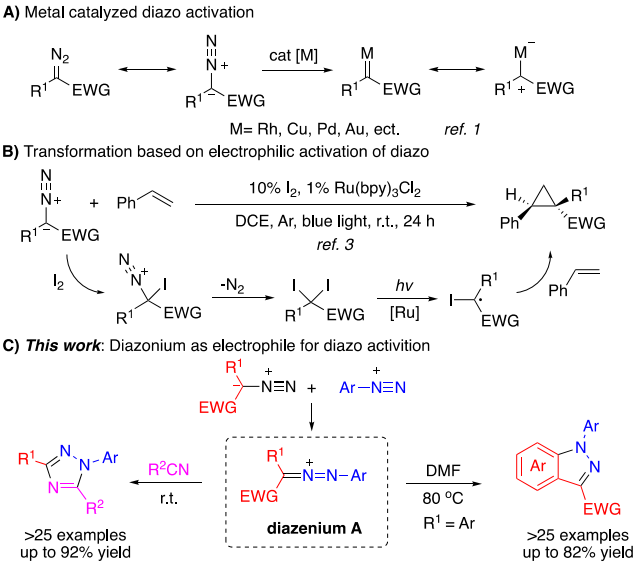
ABSTRACT: A donor/acceptor diazo activation strategy, processing via condensation using diazonium salts without the addition of any other catalysts or reagents, is reported. The diazenium intermediate was found to undergo cyclization to give indazoles in excellent yields. Alternatively, in the presence of nitriles, substituted 1,2,4-triazoles were obtained in good to excellent yields. This interesting diazenium route provides a new approach to achieve complex heterocycle synthesis under mild conditions.



Diazo compounds have been of great interest over the past several decades as excellent carbene precursors. Transition metal catalyzed carbene transfer from diazo compounds is considered to be a typical reaction pathway, providing a powerful strategy for the construction of carbon−carbon or carbon−heteroatom bonds (Scheme 1A).[1] Furthermore, diazo carbon can serve as a nucleophile to react with Lewis acid activated aldehydes (Roskamp reaction), giving the corresponding C−C bonded product.[2] Inspired by these ideas, our group recently reported diazo activation by iodide and the application of an *in situ* formed diiodide ester to the preparation of cyclopropane under mild conditions (Scheme 1B).[3] Herein, we report the formation of diazenium **A** as a key intermediate through diazo activation by diazonium salt. Sequential cyclization/condensation (with nitriles) of this intermediate offers an alternative route to achieve the synthesis of substituted indazoles and 1,2,4-triazoles with high efficiency under mild conditions (Scheme 1C).

Scheme 1. Diazo as Important Synthon for Efficient Transformations



In the past decade, our group has focused on developing new chemical transformations using homogeneous gold catalysts.[4] These efforts have led to discoveries of gold(I)-catalyzed diazo activation[5] and gold(I)/(III) redox catalysis with base-assisted diazonium salt activation as the oxidants.[6] According to the literature, the coupling of diazo compounds with aryl diazonium salts has received extensive attention. As shown in Figure 1A, pioneering work by Huisgen and Koch demonstrated the possibility of electrophilic attack of diazonium salts by diazo carbon. When $ArN_2^+Cl^-$ salt was applied, a fast sequential denitrogenation was caused by chloride anion addition, producing chlorohydrazones.[7] Wan and Shao extended this strategy to generate nitrilimines in situ, leading to pyrroles by coupling with 1,3-dicarbonyl compounds.[8] Under copper-catalyzed conditions, the three-component coupling of ethyl diazoacetate, aryl diazonium salts, and nitriles resulted in 1,2,4-triazoles through a metal carbene intermediate.[9] Similarly, a silver-catalyzed [3 + 2]

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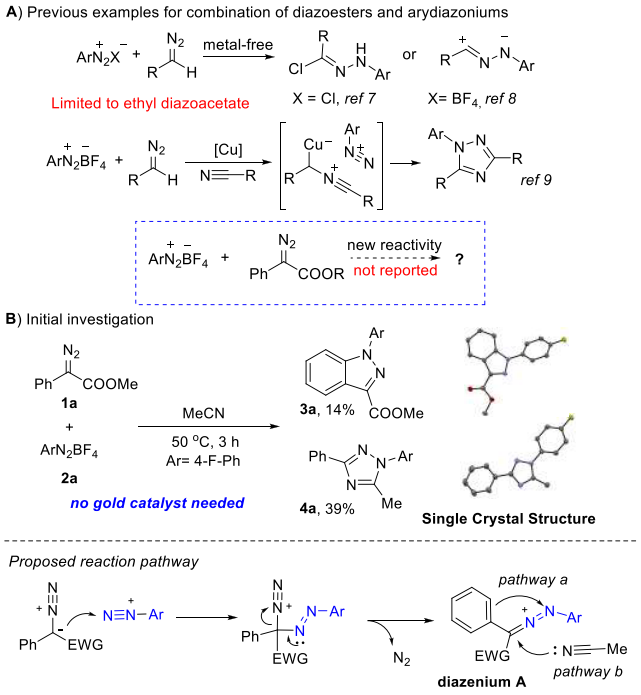


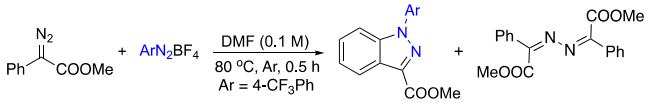
Figure 1. Diazo activation by diazonium: formation of diazenium.

cycloaddition of diazo compounds (CF_3CHN_2) with aryl diazonium salts has been reported for the synthesis of tetrazoles.[10] Surprisingly, the scope of the diazo component has largely been limited to ethyl diazoacetate (acceptor diazo), while aryl diazoesters (acceptor/donor diazo) have received less attention. Since gold(I) complexes can react with both diazo and diazonium salts, we considered exploring gold-catalyzed C−C bond coupling by combining these two reagents and the resulting potential new chemical transformations.[11]

With this idea in mind, we explored the reaction between diazo compound **1a** and diazonium salt **2a** under various conditions. However, heating the mixture of **1a** and **2a** at 50 °C in MeCN, two new compounds were isolated. Their structures were determined as indazole **3a** (14%; CCDC 1989187) and 1,2,4-triazole **4a** (39%; CCDC 1989189) by X-ray crystallography analysis (Figure 1). Notably, this transformation occurred without the presence of gold catalysts. Based on this result, an interesting reaction pathway between the diazonium salt and diazo compound was proposed via nucleophilic addition of a diazo compound to the diazonium salts, followed by denitrogenation to form diazenium intermediate **A**. Intramolecular electrophilic cyclization (pathway a) then gives indazole **3a**. In addition, the addition of nitrile to diazenium **A**, with sequential cyclization and decarboxylation, yields 1,2,4-triazole **4a**. Diazenium salts are known to be generated by Lewis acid (MCl_n) promoted elimination from 1-chloroalkyl-azo compounds ($R_2ClC-N{=}N-Ar$). It requires multiple steps, and the resulting alkyl substituted diazenium species is highly reactive and allows less controllable product formation.[12] To the best of our knowledge, this is the first example of aryl diazonium salts condensation with donor/acceptor diazo compounds for the formation of a diazenium intermediate compound reported and applied in chemical synthesis.[13]

Clearly, both indazole[14] and 1,2,4-triazole[15] are valuable heterocyclic structures. Their derivatives are a versatile class of compounds found in numerous natural products and biologically active compounds. Therefore, new methodology to facilitate the synthesis of these compounds is highly desired. One general concern is how to achieve the overall selectivity for the formation of indazole vs triazole. Based on the proposed reaction mechanism, it is reasonable to rationalize that the formation of 1,2,4-triazole can be avoided if non-nitrile solvents are applied. After exploring various other solvents, DMF was identified as the optimal solvent. The reaction was conducted at 80 °C under Ar, giving the desired indazole **3b** in 78% yield. Some alternative conditions examined in the reaction are summarized in Table 1, and detailed screening conditions are included in the Supporting Information (SI).

Table 1. Screening Conditions for Indazole Synthesis[a]



Entry	Variation from "standard conditions"	3 (%)	5 (%)
1	none	78	<5
2	DCE as Solvent	0	82
3	NMP as solvent	<5	<5
4	DMSO as solvent	37	<5
5	1.0 equiv of **2b**	68	<5
6	1.5 equiv of **1a**	55	10
7	50 °C	62	8
8	0.05 M	77	<5
9	0.5 M	41	20

[a]Conditions: **1a** (0.2 mmol, 1.0 equiv) and **2b** (0.6 mmol, 3.0 equiv) were added to DMF (2 mL, 0.1 M) at 80 °C. Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

To facilitate nucleophilic addition of the diazo compound to diazonium salts, we initiated the screening of polar aprotic solvents. First, DCE failed to promote the desired reaction owing to the poor solubility of the diazonium salts. Instead, dimeric azine compound **5** (CCDC 2000393, structure confirmed by X-ray analysis; see Table S5 in Supporting Information) was observed as the major product (entry 2). Polar solvents, such as NMP and DMSO, gave poor yields of the desired products, which is likely due to the decomposition of the diazonium salt at high temperature (entries 3−4). Finally, DMF was found to be the optimal solvent. Notably, formation of the dimeric azine compound **5** is a major competitive reaction pathway, as reported previously.[16] Accordingly, 3 equiv of diazonium salt, a reasonable concentration (0.1 M), and a high temperature were necessary to suppress the self-dimerization of the diazo compound, ensuring a good yield and selectivity (entries 6−9). With optimal conditions in hand, we then explored the indazole substrate scope (Scheme 2).

As shown in Scheme 2, most aryl diazonium salts containing electron-withdrawing substituents were suitable for this transformation, giving good to excellent yields (**3a**−**3f**). Aryl diazonium salts with electron-donating substituents failed to produce any desired product. *para*-Methyl substituted aryl diazoesters reacted smoothly to afford the cyclized products (**3g**−**3k**). As expected, two regioisomers (**3o** and **3p**) were

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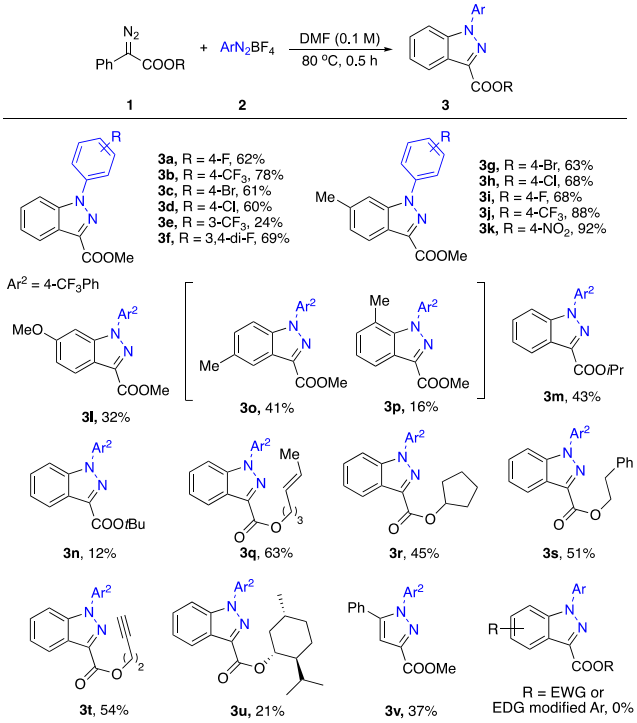
Scheme 2. Substrate Scope of Indazole[a,b]



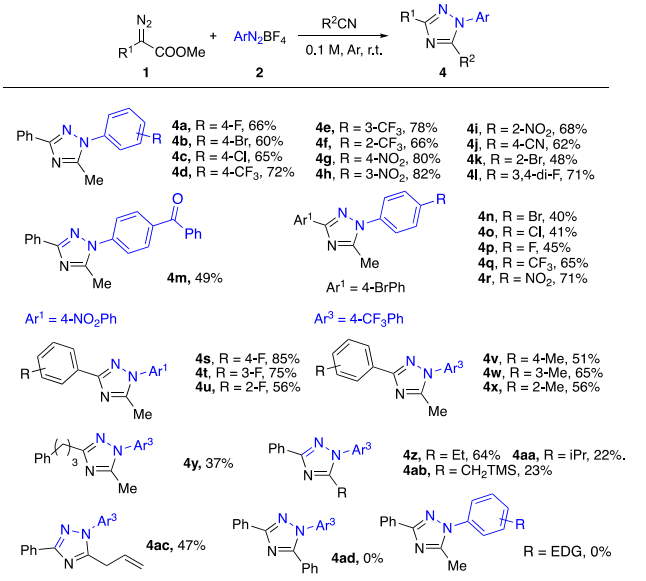
[a]Conditions: **1** (1.0 mmol, 1.0 equiv) and **2** (3.0 mmol, 3.0 equiv) were added to DMF and stirred at 80 °C for 0.5 h under argon. [b]Isolated yield.

isolated when a *meta*-methyl substituted aryl diazoester was employed in the reaction. An electron-donating group (−OMe) modified aryl diazoester (**3l**) resulted in a low yield, and the dimeric compound **5l** was obtained as the major product (55% yield). We next examined the different sizes of ester groups of the diazo ester component. Thus, changing the methyl ester to bulkier *i*Pr and *t*Bu esters reduced the yield of the product indazoles **3m** and **3n** to 43% and 12%, respectively. Diazoesters with modified ester chain containing functional groups, such as alkene (**3q**), saturated ring system (**3r**), benzyl (**3s**), alkyne (**3t**), and menthol (**3u**), were compatible with this reaction. Furthermore, vinyl diazoester was also explored, giving the corresponding *N*-arylpyrazole in moderate yield under metal-free conditions (**3v**). When electron-withdrawing groups were present on the diazo aryl ring, no product was formed.

Encouraged by the successful synthesis of various indazoles, we turned our attention to the selective synthesis of 1,2,4-triazoles. We anticipated that nitrile addition to the diazenium intermediate would be dominant in acetonitrile solvent, while the cyclization pathway would be more kinetically favored over pathway b (Figure 1B). Accordingly, the reaction between **1a** and **2b** afforded desired 1,2,4-triazole **4d** in 74% yield, and with indazole obtained in 5% yield (for more details of conditions optimization, see Table S2 in the SI). The reaction scope is shown in Scheme 3.

As shown in Scheme 3, aryl diazonium salts containing electron-withdrawing substituents worked well in this transformation, providing the desired 1,2,4-triazoles in good to excellent yields (**4a**−**4l**). Carbonyl groups (**4m**) were well tolerated under this condition. As expected, aryl diazonium salts containing an electron-donating group on the aromatic

Scheme 3. Substrate Scope of 1,2,4-Triazole[a,b]



[a]Conditions: **1** (1.5 mmol, 1.5 equiv) and **2** (1.0 mmol, 1.0 equiv) were added to RCN (10 mL), and the mixture was stirred at 25 °C for 48 h under argon. [b]Isolated yield.

ring did not promote the reaction due to rapid decomposition. The presence of both electron-withdrawing/-donating groups on the aromatic ring of the aryl diazo esters did not influence the reaction outcome, and the products were formed in good yields. Notably, alkyl diazoester (**4y**) also participated in the reaction affording the product in 37% yield, which was likely caused by fast decomposition. Employing different nitriles, such as EtCN (**4z**), *i*PrCN (**4aa**), and $TMSCH_2CN$ (**4ab**), furnished the substituted 1,2,4-triazoles in moderate yields. However, less nucleophilic nitriles, such as PhCN (**4ad**), did not promote this reaction. Notably, allylic nitrile (**4ac**) produced the product in moderate yield, highlighting the mild conditions and synthetic potential for further modification.

To probe the possible reaction pathway, we monitored the reaction using in-operando infrared spectroscopy analysis. The mixing of diazo compound **1a** and diazonium salt **2b** (1:1 ratio) in MeCN at room temperature resulted in the N_2 gas bubbling out of the reaction mixture. As shown in Figure 2A, the characteristic C═O stretch absorption peak of **1a** at 1705 cm^{-1} disappeared, along with the formation of a new absorption peak at 1751 cm^{-1}. HRMS analysis of the reaction mixture indicated the formation of **6**, which was formed through simultaneous trapping the diazenium intermediate by MeCN. This result accounted for the higher selectivity for 1,2,4-triazoles over indazoles at room temperature. To understand the subsequent decarboxylation step, the reaction was conducted with a more sterically demanding *tert*-butyl ester (Figure 2B). A decreased yield was observed with the *tert*-butyl ester, indicating a Krapcho-type decarboxylation process. This process was unlikely to proceed via the hydrolysis of the ester to carboxylic acid with subsequent decarboxylation.

In summary, we have disclosed the first example of donor/acceptor diazo activation by diazonium salts under metal-free conditions, via the corresponding diazenium intermediate. This transformation provides a synthetic route for the formation of either indazole or 1,2,4-triazole derivatives in good to excellent

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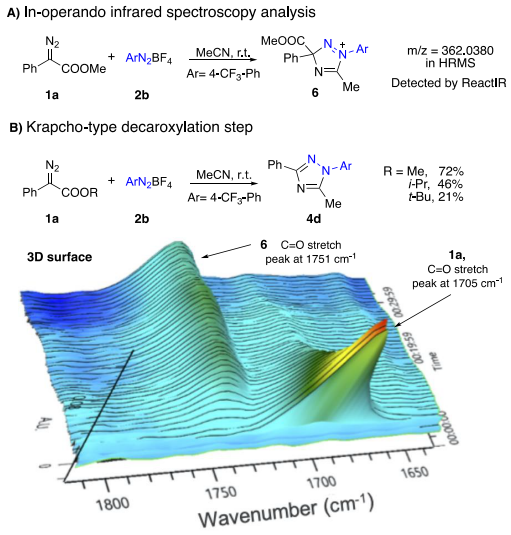

Figure 2. Kinetic profile of diazenium intermediate.

yields. Further applications of this diazenium intermediate to complex molecular synthesis and more detailed mechanistic insight into this transformation are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01232.

Experiment procedures, conditions optimization, X-ray single-crystal diffraction, in-operando infrared spectroscopy, and characterization for all products (PDF)

Accession Codes

CCDC 1989187, 1989189, and 2000393 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.

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■ REFERENCES

(1) For reviews, see: (a) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935. (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861−2903. (c) Maas, G. *Chem. Soc. Rev.* **2004**, *33*, 183−190. (d) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417−424. (e) Lu, H.; Zhang, X. *Chem. Soc. Rev.* **2011**, *40*, 1899−1909. (f) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236−247. (g) Zhu, S.; Zhou, Q. *Natl. Sci. Rev.* **2014**, *1*, 580−603. (h) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308−1318. (i) Jia, M.; Ma, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 9134−9166. (j) Xia, Y.; Qiu, D.; Wang, J. *Chem. Rev.* **2017**, *117*, 13810−13889. (k) Xiang, Y.; Wang, C.; Ding, Q.; Peng, Y. *Adv. Synth. Catal.* **2019**, *361*, 919−944.

(2) (a) Holmquist, C. R.; Roskamp, E. J. J. *J. Org. Chem.* **1989**, *54*, 3258−3260. (b) Kang, B. C.; Nam, D. G.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2015**, *17*, 4810−4813. (c) Hashimoto, T.; Maruoka, K. *Bull. Chem. Soc. Jpn.* **2013**, *86*, 1217−1230. (d) Li, W.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 8532−8533.

(3) Li, P.; Zhao, J.; Shi, L.; Wang, J.; Shi, X.; Li, F. *Nat. Commun.* **2018**, *9*, 1972.

(4) (a) Duan, H.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Am. Chem. Soc.* **2009**, *131*, 12100. (b) Wang, D.; Ye, X.; Shi, X. *Org. Lett.* **2010**, *12*, 2088−2091. (c) Xi, Y.; Dong, B.; McClain, E. J.; Wang, Q.; Gregg, T. L.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 4657−4661. (d) Xi, Y.; Wang, D.; Ye, X.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Org. Lett.* **2014**, *16*, 306−309. (e) Peng, H.; Akhmedov, N. G.; Liang, Y.; Jiao, N.; Shi, X. J. *J. Am. Chem. Soc.* **2015**, *137*, 8912−8915. (f) Hosseyni, S.; Wojtas, L.; Li, M.; Shi, X. *J. Am. Chem. Soc.* **2016**, *138*, 3994−3997. (g) Wang, J.; Zhang, S.; Xu, C.; Wojtas, L.; Akhmedov, N. G.; Chen, H.; Shi, X. *Angew. Chem., Int. Ed.* **2018**, *57*, 6915−6920. (h) Ye, X.; Peng, H.; Wei, C.; Yuan, T.; Wojtas, L.; Shi, X. *Chem.* **2018**, *4*, 1983−1993.

(5) Xi, Y.; Su, Y.; Yu, Z.; Dong, B.; McClain, E. J.; Lan, Y.; Shi, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 9817−9821. For reviews, see: (a) Wei, F.; Song, C.; Ma, Y.; Zhou, L.; Tung, C.; Xu, Z. *Sci. Bulletin.* **2015**, *60*, 1479−1492. (b) Liu, L.; Zhang, J. *Chem. Soc. Rev.* **2016**, *45*, 506−516.

(6) (a) Cai, R.; Lu, M.; Aguilera, E. Y.; Xi, Y.; Akhmedov, N. G.; Petersen, J. L.; Chen, H.; Shi, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 8772−8776. (b) Peng, H.; Cai, R.; Xu, C.; Chen, H.; Shi, X. *Chem. Sci.* **2016**, *7*, 6190−6196. (c) Dong, B.; Peng, H.; Motika, S. E.; Shi, X. *Chem. - Eur. J.* **2017**, *23*, 11093−11099. (d) Jimoh, A.; Hosseyni, S.; Ye, X.; Wojtas, L.; Hu, Y.; Shi, X. *Chem. Commun.* **2019**, *55*, 8150−8153. For reviews, see (e) Hopkinson, M. N.; Tlahuext-Aca, A.; Glorius, F. *Acc. Chem. Res.* **2016**, *49*, 2261−2272. (f) Akram, M. O.; Banerjee, S.; Saswade, S. S.; Bedi, V.; Patil, N. T. *Chem. Commun.* **2018**, *54*, 11069−11083.

(7) (a) Huisgen, V. R.; Koch, H.-J. *Justus Liebigs Annalen der Chemie.* **1955**, *591*, 200−231. For examples of cyclization to tetrazoles, see: (b) Maas, G.; Gumbel, H.; Weise, G.; Regitz, M. *Chem. Ber.* **1985**, *118*, 2105−21174. (c) Fliege, W.; Huisgen, R.; Clovis, J. S.; Knupfer, H. *Chem. Ber.* **1983**, *116*, 3039−3061.

(8) Shao, Y.; Zheng, H.; Qian, J.; Wan, X. *Org. Lett.* **2018**, *20*, 2412−2415.

(9) Li, H.; Wu, X.; Hao, W.; Li, H.; Zhao, Y.; Wang, Y.; Lian, P.; Zheng, Y.; Bao, X.; Wan, X. *Org. Lett.* **2018**, *20*, 5224−5227.
(10) Chen, Z.; Fan, S.-Q.; Zheng, Y.; Ma, J.-A. *Chem. Commun.* **2015**, *51*, 16545−16548.
(11) Zhang, D.; Xu, G.; Ding, D.; Zhu, C.; Li, J.; Sun, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 11070−11074.
(12) (a) Al-Bataineh, N. Q.; Brewer, M. *Tetrahedron Lett.* **2012**, *53*, 5411−5413. (b) Wang, Q.; Amer, A.; Mohr, S.; Ertel, E.; Jochims, J. C. *Tetrahedron* **1993**, *49*, 9973−9986. (c) Wang, Q.; Jochims, J. C.; Kohlbrandt, S.; Dahlenburg, L.; Al-Talib, M.; Hamed, A.; Ismail, A. E. *Synthesis* **1992**, *1992*, 710−718.
(13) For an example of metal catalyzed condensation between vinyl diazoester and diazonium salts, see: Guo, H.; Zhang, D.; Zhu, C.; Li, J.; Xu, G.; Sun, J. *Org. Lett.* **2014**, *16*, 3110−3113.
(14) (a) Wan, Y.; He, S.; Li, W.; Tang, Z. *Anti-Cancer Agents Med. Chem.* **2019**, *18*, 1228−1234. (b) Zhang, S.-G.; Liang, C.-G.; Zhang, W.-H. *Molecules* **2018**, *23*, 2783. (c) Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; de Ocariz, C. O. *Mini-Rev. Med. Chem.* **2005**, *5*, 869−878.
(15) (a) Malani, A. H.; Makwana, A. H.; Makwana, H. *Mor. J. Chem.* **2017**, *5*, 41−58. (b) Gao, F.; Wang, T.; Xiao, J.; Huang, G. *Eur. J. Med. Chem.* **2019**, *173*, 274−281. (c) Zampieri, D.; Cateni, F.; Moneghini, M.; Zacchigna, M.; Laurini, E.; Marson, D.; De Logu, A.; Sanna, A.; Mamolo, M. G. *Curr. Top. Med. Chem.* **2019**, *19*, 620−632. (d) Wang, H.; Ren, Y.; Wang, K.; Man, Y.; Xiang, Y.; Li, N.; Tang, B. *Chem. Commun.* **2017**, *53*, 9644−9647. (e) Joshi, M. S.; Pigge, F. C. *Org. Lett.* **2016**, *18*, 5916−5919.
(16) (a) Kornecki, K. P.; Briones, J. F.; Boyarskikh, V.; Fullilove, F.; Autschbach, J.; Schrote, K. E.; Lancaster, K. M.; Davies, H. M. L.; Berry, J. F. *Science* **2013**, *342*, 351. (b) He, F.; Li, F.; Koenigs, R. M. *J. Org. Chem.* **2020**, *85*, 1240−1246.

https://dx.doi.org/10.1021/acs.orglett.0c01232
Org. Lett. 2020, 22, 4151−4155