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N-Heterocyclic Carbene-Catalyzed Cyclization of Aldehydes with α-Diazo Iodonium Triflate: Facile Access to 2,5-Disubstituted 1,3,4-Oxadiazoles

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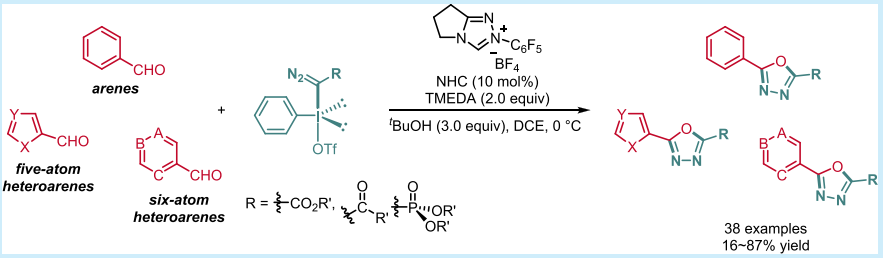

ABSTRACT: Herein, we report a novel organocatalytic process for synthesis of complex 1,3,4-oxadiazoles from readily accessible aldehydes. By exploiting the nucleophilicity of the putative Breslow intermediate and the inherent electrophilicity of α-diazo iodonium triflate, we have found that *N*-heterocyclic carbene catalyst promotes efficient cyclization of various aldehydes and α-diazo iodonium triflates. The reaction proceeds under mild conditions with a wide range of functional group tolerance. The heterocyclic products can be readily further functionalized, rendering the protocol highly valuable.

Because of their unique properties, 1,3,4-oxadiazole derivatives[1] hold a distinctive place in medicinal chemistry[2] and functional materials,[3] which account for the significance of exploitation of practical synthetic approaches to access oxadiazole-containing molecules.[4,5]

The previous established methods for the construction of 1,3,4-oxadiazole cores involve the use of carbonyl derivatives, such as acyl hydrazide,[4a−e] acyl chloride,[4f] hydrazone,[4b,g,h] 2-oxo-2-arylacetaldehyde,[4d] and acetophenone.[4c] Very recently, the synthesis of 2,5-diaryl 1,3,4-oxadiazoles though *N*-acylation of aryl tetrazoles with readily available aldehydes in the presence of oxidant DTBP (^{t}BuOO^{t}Bu) has been reported by He and co-workers (Scheme 2a).[4i] The choice of benzoyl formic acid and α-diazo iodonium salt[5,6] as the cyclization partners to synthesize 2,5-disubstituted 1,3,4-oxadiazoles via a photocatalyzed decarboxylative radical cyclization derives from the study of Li and Liu (Scheme 2b).[4j] On the other hand, *N*-heterocyclic carbenes (NHCs) are versatile organocatalysts[7] that can reverse the polarity (umpolung) of aldehydes to form carbon−carbon bonds[8−10] via the formal acyl anion equivalents.

Although remarkable progress has been made, the problem still exists. Most previous established methods suffer from limitations of using strong oxidants or transition metal, high reaction temperature, as well as limited substrate scope. One-step formation of 1,3,4-oxadiazoles from aldehydes in terms of metal-free organocatalysis is underdeveloped. Taken together with the nucleophilicity of acyl anion equivalents and the electrophilicity of α-diazo iodonium salts,[9] herein, we report a novel metal-free cyclization approach to prepare 1,3,4-oxadiazoles from readily available aldehydes under mild conditions (Scheme 2c).

We began our investigations by subjecting 4-iodobenzaldehyde (**1a**) as a representative substrate in combination with α-diazo iodonium triflate (**2a**) and selection of commonly encountered precursors of NHC catalyst (Table 1, entries 1−4). We found that NHC **A**, reported by the Rovis group,[11] was the only effective catalyst to promote this reaction, giving **3a** in 58% NMR yield (entry 1). A study of diazo sources quickly revealed the reaction specificity of α-diazo iodonium triflate. α-Diazo benziodoxole **2b** (entry 5), α-diazo sulfonium salt **2c** (entry 6),[12] and α-diazo ammonium salt **2d** (entry 7)[13] were demonstrated to be ineffective. To our surprise, ^{i}PrOH had a visible positive effect on the yield (entry 8). We observed a modest yield improvement by slightly increasing the amount of **2a** to 1.05 equiv (entry 9), whereas an excess amount of **2a** was used, resulting in lower yields (entries 10−13). By replacing ^{i}PrOH with ^{t}BuOH, the NMR yield was subtly increased to

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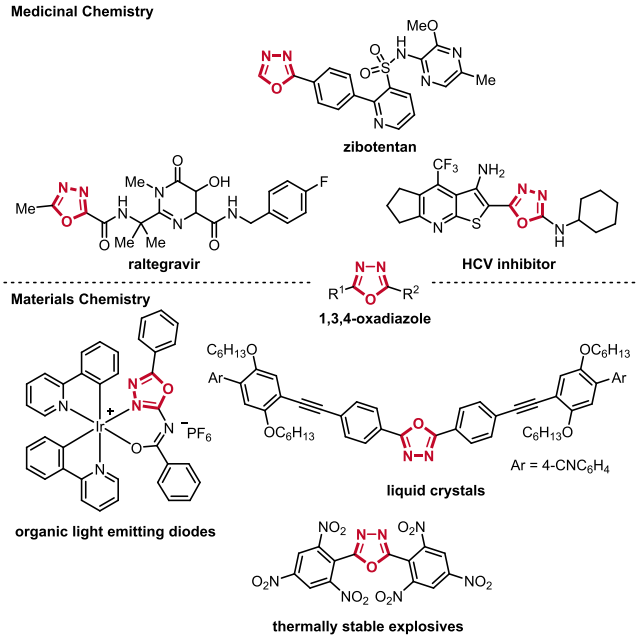
Scheme 1. Representative 1,3,4-Oxadiazole Derivatives Applied in Medicinal Chemistry and Material Chemistry



Scheme 2. Recent Progress on the Synthesis of 1,3,4-Oxadiazoles

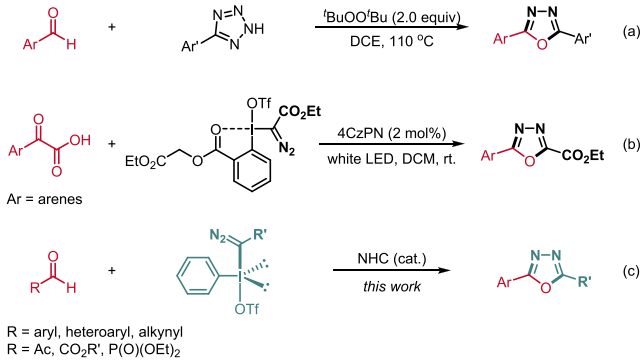
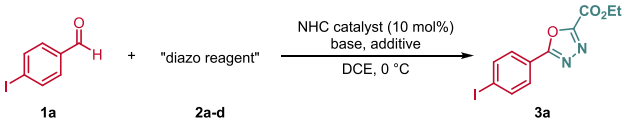
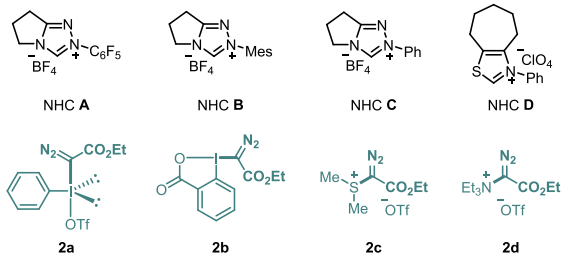


Table 1. Reaction Optimization



entry[a]	2 (equiv)	NHC	base	additive	yield[b]
1	**2a** (1.0)	**A**	TMEDA	none	58%
2	**2a** (1.0)	**B**	TMEDA	none	ND
3	**2a** (1.0)	**C**	TMEDA	none	ND
4	**2a** (1.0)	**D**	TMEDA	none	ND
5	**2b** (1.0)	**A**	TMEDA	none	ND
6	**2c** (1.0)	**A**	TMEDA	none	ND
7	**2d** (1.0)	**A**	TMEDA	none	ND
8	**2a** (1.0)	**A**	TMEDA	^{i}PrOH	62%
9	**2a** (1.05)	**A**	TMEDA	^{i}PrOH	72%
10	**2a** (1.1)	**A**	TMEDA	^{i}PrOH	68%
11	**2a** (1.2)	**A**	TMEDA	^{i}PrOH	63%
12	**2a** (1.3)	**A**	TMEDA	^{i}PrOH	60%
13	**2a** (1.6)	**A**	TMEDA	^{i}PrOH	29%
14	**2a** (1.05)	**A**	TMEDA	^{t}BuOH	74% (70%)[c]
15	**2a** (1.05)	**A**	DIPEA	^{t}BuOH	ND
16	**2a** (1.05)	**A**	Et_3N	^{t}BuOH	ND
17	**2a** (1.05)	**A**	Cs_2CO_3	^{t}BuOH	ND
18	**2a** (1.05)	none	TMEDA	^{t}BuOH	ND



[a]Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), **2**, NHC (0.020 mmol, 10 mol %), base (0.30 mmol, 1.5 equiv), additive (0.60 mmol, 3.0 equiv), DCE (4 mL), 0 °C, 10 h. [b]The yield was determined by ^{1}H NMR analysis using methylene dibromide as an internal standard. "ND" stands for "not detected". [c]Isolated yield.

74% and **3a** was isolated in 70% yield (entry 14). The use of Hünig's base (entry 15), Et_3N (entry 16), and Cs_2CO_3 (entry 17) failed to generate the desired oxadiazole **3a**. Ultimately, the control experiment showed that the conversion requires NHC catalyst (entry 18).

Our studies on the scope of the reaction began with the variation of the aryl and heteroaryl aldehydes, as summarized in Table 2. The electronic perturbation on the aryl moiety affects the efficiency of the reaction: generally, the aromatic aldehydes bearing an electron-withdrawing group provided the corresponding oxadiazoles **3a**−**3g** in moderate to good yield, whereas only 22% yield of **3h** was observed through the conversion of *p*-anisaldehyde. The aldehydes bearing a methoxy and acetoxy group at the meta-position on arene reacted cleanly to afford **3i** and **3j**. The tolerance of aromatic ortho substituents, especially large steric bulk, was an additional benefit of this novel process (**3k**, **3l**). Multi-substituted benzaldehydes were suitable substrates (**3m**−**3o**). Also of note, polycyclic aromatic aldehydes were successfully engaged in the reaction, giving synthetic useful yield of **3p** and **3q**. For 3-arylpropiolaldehyde, the reaction gave only a low yield of the product **3r**. Next, we turned our attention to heterocycle substrates with the knowledge that these moieties are potentially valuable pharmacophores. We found that six-atom heterocyclic aldehydes bearing pyridine, pyridazine, quinoline, and quinoxaline were smoothly converted into corresponding heterocycle substituted oxadiazoles (**3s**−**3z**). Besides, the successful application of this approach in the synthesis of various oxadiazoles substituted with five-atom heterocycles, such as thiazole, imidazole, pyrazole, furan, benzofuran, and benzothiazole, further highlighted the good compatibility of the reaction (**3aa**−**3af**).

The scope of the reaction with respect to the α-diazo iodonium triflate was summarized in Table 3 and further exhibited universality of the approach to the synthesis of 1,3,4-oxadiazoles. The ester moiety on hypervalent iodonium salt **2** can be modified: alternative alkyl substituents such as benzyl, *t*-butyl, allyl, and (−)-menthyl groups were tolerated (**3ee**−**3eh**), albeit in somewhat diminished yields of **3ee** and **3eg**. The ester group can also be replaced by a ketone with a small impact on the yield of **3ei**. We were delighted to observe the formation of the corresponding **3ej** by using phosphonate substituted α-diazo iodonium triflates **2ej**.

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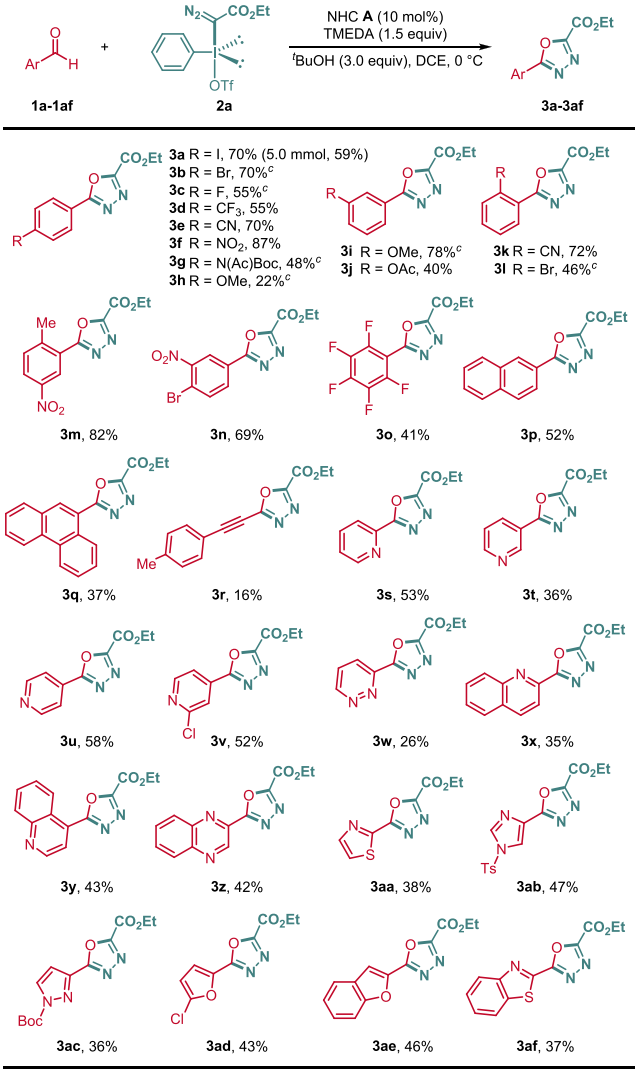
Table 2. Substrate Scope of Aldehydes[a,b]

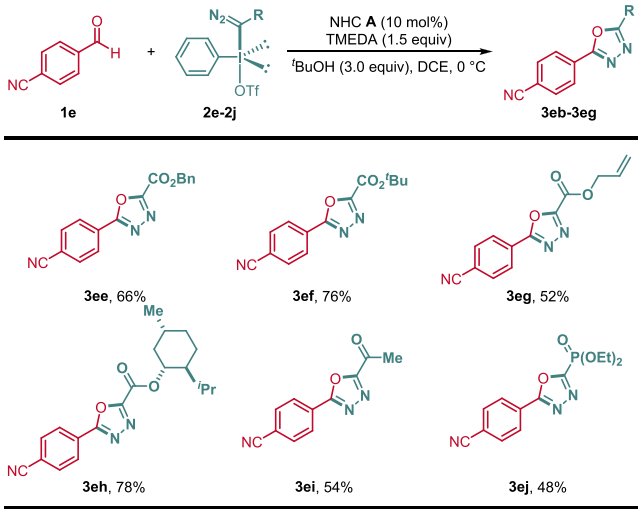


[a]Reaction conditions: **1** (0.20 mmol, 1.0 equiv), **2a** (0.21 mmol, 1.05 equiv), NHC **A** (0.020 mmol, 10 mol %), TMEDA (0.30 mmol, 1.5 equiv), ^{t}BuOH (0.60 mmol, 3.0 equiv), DCE (4 mL), 0 °C, 10 h. [b]Isolated yield. [c]After 10 h, renewed **2a** (0.21 mmol, 1.05 equiv), NHC **A** (0.020 mmol, 10 mol %), and TMEDA (0.30 mmol, 1.5 equiv) addition and continued stirring at 0 °C for another 10 h.

The feasibility of the protocol has been demonstrated by a set of efficient derivatization reactions of product **3a**, including Sonogashira cross-coupling, amidation, and reductive decarboxylation,[14] affording products **4**, **5**, and **6** in good to excellent yield, respectively (Scheme 3).

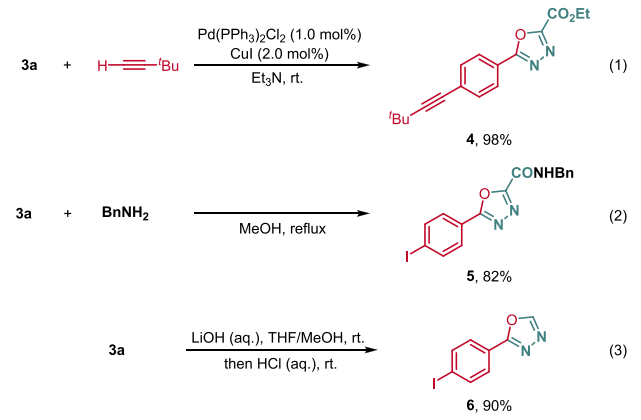
We noticed that further increasing the amount of **2a** led to inhibition of the conversion (Table 1, entries 10−13), whereas, in some cases, the addition of renewed catalyst, **2a** combined with TMEDA, resulted in full conversion of starting materials as well as improved yield (Table 2, **3b**, **3c**, **3g**, **3h**, **3i**), which revealed that **2a** was not the actually active species promoting the formation of oxadiazoles. By mixing **2a** with TMEDA (1.5 equiv) in DCE at 0 °C, we prepared TMEDA supported α-diazo ammonium triflate **7** in 66% yield (Scheme 4a),[15] which underwent cyclization to afford **2c** in 65% yield under the standard conditions (Scheme 4b). These results demonstrated that α-diazo ammonium triflate **7** was the active species in the reaction.

Table 3. Substrate Scope of α-Diazo Iodonium Triflates[a,b]

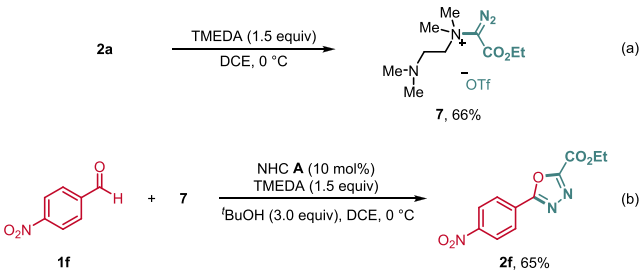


[a]Reaction conditions: **1e** (0.20 mmol, 1.00 equiv), **2** (0.21 mmol, 1.05 equiv), NHC **A** (0.020 mmol, 10 mol %), TMEDA (0.30 mmol, 1.50 equiv), ^{t}BuOH (0.60 mmol, 3.0 equiv), DCE (4 mL), 0 °C, 10 h. [b]Isolated yield.

Scheme 3. Derivatization of 1,3,4-Oxadiazole Products



Scheme 4. Mechanistic Studies



A postulated pathway is illustrated in Scheme 5. Initially, a nucleophilic addition of free NHC **A** to the aldehyde **1** to give adduct, which is in equilibration between its Breslow intermediate **B**[16] and its tautomer tetrahedral intermediate **B′**,[17] undergoes *N*-selective nucleophilic attack at in situ generated α-diazo ammonium triflate **7**,[18] affording the zwitterion adduct **C**. Subsequently, the ammonium **D** is formed by release of catalyst **A** to close the catalytic cycle. Finally, in the presence of base, deprotonation of **D**, followed

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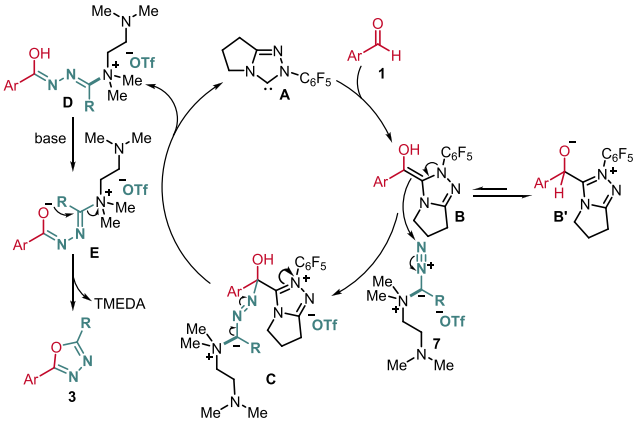
Scheme 5. Proposed Mechanism



by cyclization of **E** via intramolecular nucleophilic attack, produces the desired 1,3,4-oxadiazoles **3** (Scheme 5).

In summary, we have reported a novel strategy for the cyclization of readily accessible aldehydes with α-diazo iodonium triflate. The approach enables straightforward access to various 1,3,4-oxadiazole derivatives under mild conditions. Ongoing efforts will focus on synthetic applications, developing a better understanding of the mechanism, and exploration of the reactivities of α-diazo iodonium triflates newfound α-diazo ammonium triflates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01128.

Synthetic procedures, IR, NMR, and HRMS of the inclusion complexes (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Ainsworth, C. 1,3,4-Oxadiazole. *J. Am. Chem. Soc.* **1965**, *87*, 5800.

(2) (a) Zou, X. J.; Lai, L. H.; Jin, G. Y.; Zhang, Z. X. Synthesis, fungicidal activity, and 3D-QSAR of pyridazinone-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. *J. Agric. Food Chem.* **2002**, *50*, 3757. (b) Somani, R. R.; Shirodkar, P. Y. Oxadiazole: a biologically important heterocycle. *Pharma Chem.* **2009**, *1*, 130. (c) Johns, B. A.; Weatherhead, J. G.; Allen, S. H.; Thompson, J. B.; Garvey, E. P.; Foster, S. A.; Jeffrey, J. L.; Miller, W. H. 1,3,4-Oxadiazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 2: SAR of the C5 position. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1807. (d) Manjunatha, K.; Poojary, B.; Lobo, P. L.; Fernandes, J.; Kumari, N. S. Synthesis and biological evaluation of some 1,3,4-oxadiazole derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 5225. (e) Khanfar, M. A.; Hill, R. A.; Kaddoumi, A.; El Sayed, K. A. Discovery of novel GSK-3β inhibitors with potent in vitro and in vivo activities and excellent brain permeability using combined ligand- and structure-based virtual screening. *J. Med. Chem.* **2010**, *53*, 8534.

(3) (a) He, G. S.; Tan, L.-S.; Zheng, Q.; Prasad, P. N. Multiphoton absorbing materials: molecular designs, characterizations, and applications. *Chem. Rev.* **2008**, *108*, 1245. (b) Rehmann, N.; Ulbricht, C.; Köhnen, A.; Zacharias, P.; Gather, M. C.; Hertel, D.; Holder, E.; Meerholz, K.; Schubert, U. S. Advanced device architecture for highly efficient organic light-emitting diodes with an orange-emitting crosslinkable iridium(III) complex. *Adv. Mater.* **2008**, *20*, 129. (c) Paraschivescu, C. C.; Matache, M.; Dobrotă, C.; Nicolescu, A.; Maxim, C.; Deleanu, C.; Fărcăsanu, I. C.; Hădade, N. D. Unexpected formation of *N*-(1-(2-aryl-hydrazono)isoindolin-2-yl)benzamides and their conversion into 1,2-(bis-1,3,4-oxadiazol-2-yl)benzenes. *J. Org. Chem.* **2013**, *78*, 2670.

(4) (a) Fan, Y.; He, Y.; Liu, X.; Hu, T.; Ma, H.; Yang, X.; Luo, X.; Huang, G. Iodine-mediated domino oxidative cyclization: one-pot synthesis of 1,3,4-oxadiazoles via oxidative cleavage of C(sp^2)-H or C(sp)-H bond. *J. Org. Chem.* **2016**, *81*, 6820. (b) Yu, W.; Huang, G.; Zhang, Y.; Liu, H.; Dong, L.; Yu, X.; Li, Y.; Chang, J. I_2-mediated oxidative C-O bond formation for the synthesis of 1,3,4-oxadiazoles from aldehydes and hydrazides. *J. Org. Chem.* **2013**, *78*, 10337. (c) Gao, Q.; Liu, S.; Wu, X.; Zhang, J.; Wu, A. Direct annulation of hydrazides to 1,3,4-oxadiazoles via oxidative C(CO)-C(methyl) bond cleavage of methyl ketones. *Org. Lett.* **2015**, *17*, 2960. (d) Kumar, D.; Pilania, M.; Arun, V.; Mishra, B. A facile and expeditious one-pot synthesis of α-keto-1,3,4-oxadiazoles. *Synlett* **2014**, *25*, 1137. (e) Chauhan, J.; Ravva, M.; Sen, S. Harnessing Autoxidation of Aldehydes: In Situ Iodoarene Catalyzed Synthesis of Substituted 1,3,4-Oxadiazole, in the Presence of Molecular Oxygen. *Org. Lett.*

2019, *21*, 6562. (f) Huisgen, R.; Sauer, J.; Sturm, H. J. Acylierung 5-substitutierter tetrazole zu 1.3.4-oxdiazolen. *Angew. Chem.* **1958**, *70*, 272. For the condensation/oxidative cyclization sequence, see: (g) Guin, S.; Ghosh, T.; Rout, S. K.; Banerjee, A.; Patel, B. K. Cu(II) catalyzed imine C-H functionalization leading to synthesis of 2,5-substituted 1,3,4-oxadiazoles. *Org. Lett.* **2011**, *13*, 5976. (h) Zhang, G.; Yu, Y.; Zhao, Y.; Xie, X.; Ding, C. Iron(III)/TEMPO-catalyzed synthesis of 2,5-disubstituted 1,3,4-oxadiazoles by oxidative cyclization under mild conditions. *Synlett* **2017**, *28*, 1373. (i) Wang, L.; Cao, J.; Chen, Q.; He, M. One-Pot synthesis of 2,5-diaryl 1,3,4-oxadiazoles via di-*tert*-butyl peroxide promoted *N*-acylation of aryl tetrazoles with aldehydes. *J. Org. Chem.* **2015**, *80*, 4743. (j) Li, J.; Lu, X.-C.; Xu, Y.; Wen, J.-X.; Hou, G.-Q.; Liu, L. Photoredox catalysis enables decarboxylative cyclization with hypervalent iodine(iii) reagents: access to 2,5-disubstituted 1,3,4-oxadiazoles. *Org. Lett.* **2020**, *22*, 9621.

(5) For reviews and selected examples of I(III) reagents, see: (a) Yoshimura, A.; Zhdankin, V. V. Advances in synthetic applications of hypervalent iodine compounds. *Chem. Rev.* **2016**, *116*, 3328. (b) Zhdankin, V. V.; Stang, P. J. Chemistry of polyvalent iodine. *Chem. Rev.* **2008**, *108*, 5299. (c) Peng, J.; Chen, C.; Wang, Y.; Lou, Z.; Li, M.; Xi, C.; Chen, H. Direct Vicinal Disubstitution of Diaryliodonium Salts by Pyridine N-oxides and N-amidates by a 1,3-Radical Rearrangement. *Angew. Chem., Int. Ed.* **2013**, *52*, 7574. (d) Wang, X.; Studer, A. Regio- and Stereoselective Cyanotriflation of Alkynes Using Aryl(cyano)iodonium Triflates. *J. Am. Chem. Soc.* **2016**, *138*, 2977. (e) Wang, X.; Studer, A. Iodine(III) Reagents in Radical Chemistry. *Acc. Chem. Res.* **2017**, *50*, 1712.

(6) (a) Wang, Z.; Herraiz, A. G.; del Hoyo, A. M.; Suero, M. G. Generating carbyne equivalents with photoredox catalysis. *Nature* **2018**, *554*, 86. (b) Wang, Z.; Jiang, L.; Sarró, P.; Suero, M. G. Catalytic cleavage of $C(sp^2)$-$C(sp^2)$ bonds with Rh-carbynoids. *J. Am. Chem. Soc.* **2019**, *141*, 15509. (c) Jiang, L.; Wang, Z.; Armstrong, M.; Suero, M. G. β-diazocarbonyl compounds: synthesis and their Rh(II)-catalyzed 1,3 C-H insertions. *Angew. Chem., Int. Ed.* **2021**, *60*, 6177.

(7) (a) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by *N*-heterocyclic carbenes. *Chem. Rev.* **2007**, *107*, 5606. (b) Grossmann, A.; Enders, D. *N*-heterocyclic carbene catalyzed domino reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (c) Bugaut, X.; Glorius, F. Organocatalytic umpolung: *N*-heterocyclic carbenes and beyond. *Chem. Soc. Rev.* **2012**, *41*, 3511. (d) Mahatthananchai, J.; Bode, J. W. On the mechanism of *N*-Heterocyclic carbene-catalyzed reactions involving acyl azoliums. *Acc. Chem. Res.* **2014**, *47*, 696. (e) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic reactions enabled by *N*-heterocyclic carbenes. *Chem. Rev.* **2015**, *115*, 9307. (f) Wang, M. H.; Scheidt, K. A. Cooperative catalysis and activation with *N*-heterocyclic carbenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912. (g) Chen, X.-Y.; Gao, Z.-H.; Ye, S. Bifunctional *N*-heterocyclic carbenes derived from *L*-pyroglutamic acid and their applications in enantioselective organocatalysis. *Acc. Chem. Res.* **2020**, *53*, 690.

(8) (a) Biju, A. T.; Glorius, F. Intermolecular *N*-heterocyclic carbene catalyzed hydroacylation of arynes. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761. (b) Hovey, M. T.; Check, C. T.; Sipher, A. F.; Scheidt, K. A. *N*-heterocyclic-carbene-catalyzed synthesis of 2-aryl indoles. *Angew. Chem., Int. Ed.* **2014**, *53*, 9603. (c) Sharma, H. A.; Hovey, M. T.; Scheidt, K. A. Azaindole synthesis through dual activation catalysis with *N*-heterocyclic carbenes. *Chem. Commun.* **2016**, *52*, 9283. (d) Janssen-Müller, D.; Singha, S.; Lied, F.; Gottschalk, K.; Glorius, F. NHC-organocatalyzed C_{Ar}-O bond cleavage: mild access to 2-hydroxybenzophenones. *Angew. Chem., Int. Ed.* **2017**, *56*, 6276.

(9) For examples of NHC-catalyzed carbon−carbon formation through the coupling of aldehydes with hypervalent iodine(III) reagents, see: (a) Toh, Q. Y.; McNally, A.; Vera, S.; Erdmann, N.; Gaunt, M. J. Organocatalytic C-H bond arylation of aldehydes to bis-heteroaryl ketones. *J. Am. Chem. Soc.* **2013**, *135*, 3772. (b) Rajkiewicz, A. A.; Kalek, M. *N*-heterocyclic carbene-catalyzed olefination of aldehydes with vinyliodonium salts to generate α,β-unsaturated ketones. *Org. Lett.* **2018**, *20*, 1906. (c) Rajkiewicz, A. A.; Wojciechowska, N.; Kalek, M. *N*-heterocyclic carbene-catalyzed synthesis of ynones via C-H alkynylation of aldehydes with alkynyliodonium salts-evidence for alkynyl transfer via direct substitution at acetylenic carbon. *ACS Catal.* **2020**, *10*, 831.

(10) For reviews and selected examples of Stetter reactions, see: (a) Stetter, H.; Kuhlmann, H. The catalyzed nucleophilic addition of aldehydes to electrophilic double bonds. *Org. React.* **1991**, *40*, 407. (b) Ottow, E.; Schollkopf, K.; Schulz, B.-G. Enzymemimetic C-C and C-N bond formations. In *Stereoselective Synthesis*; Enders, D., Ed.; Springer: Heidelberg, Germany, 1993; pp 63. (c) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. A highly enantioselective catalytic intramolecular Stetter reaction. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (d) Myers, M. C.; Bharadwaj, A. R.; Milgram, B. C.; Scheidt, K. A. Catalytic conjugate additions of carbonyl anions under neutral aqueous conditions. *J. Am. Chem. Soc.* **2005**, *127*, 14675. (e) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *N*-heterocyclic carbene-catalyzed hydroacylation of unactivated double bonds. *J. Am. Chem. Soc.* **2009**, *131*, 14190. (f) Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. Enantioselective Stetter reactions of enals and modified chalcones catalyzed by *N*-heterocyclic carbenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 11782. (g) Jia, M.-Q.; You, S.-L. Desymmetrization of cyclohexadienones via D-camphor-derived triazolium salt catalyzed intramolecular Stetter reaction. *Chem. Commun.* **2012**, *48*, 6363.

(11) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. An efficient synthesis of achiral and chiral 1,2,4-triazolium salts: bench stable precursors for *N*-heterocyclic carbenes. *J. Org. Chem.* **2005**, *70*, 5725.

(12) (a) Taylor, M. T.; Nelson, J. E.; Suero, M. G.; Gaunt, M. J. A protein functionalization platform based on selective reactions at methionine residues. *Nature* **2018**, *562*, 563. (b) Li, X.; Golz, C.; Alcarazo, M. *a*-Diazo sulfonium triflates: synthesis, structure, and application to the synthesis of 1-(dialkylamino)-1,2,3-triazoles. *Angew. Chem., Int. Ed.* **2021**, *60*, 6943.

(13) Schnaars, C.; Hennum, M.; Bonge-Hansen, T. Nucleophilic halogenations of diazo compounds, a complementary principle for the synthesis of halodiazo compounds: experimental and the theoretical studies. *J. Org. Chem.* **2013**, *78*, 7488.

(14) Aurelio, L.; Scullino, C. V.; Pitman, M. R.; Sexton, A.; Oliver, V.; Davies, L.; Rebello, R. J.; Furic, L.; Creek, D. J.; Pitson, S. M.; Flynn, B. L. From sphingosine kinase to dihydroceramide desaturase: a structure-activity relationship (SAR) study of the enzyme inhibitory and anticancer activity of 4-((4-(4-chlorophenyl)thiazol-2-yl)amino)-phenol (SKI-II). *J. Med. Chem.* **2016**, *59*, 965.

(15) Bugaenko, D. I.; Yurovskaya, M. A.; Karchava, A. V. *N*-arylation of DABCO with diaryliodonium salts: general synthesis of *N*-aryl-DABCO salts as precursors for 1,4-disubstituted piperazines. *Org. Lett.* **2018**, *20*, 6389.

(16) Breslow, R. On the mechanism of thiamine action. IV. evidence from studies on model systems. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

(17) Langdon, S. M.; Wilde, M. M. D.; Thai, K.; Gravel, M. Chemoselective *N*-heterocyclic carbene-catalyzed cross-Benzoin reactions: importance of the fused ring in triazolium salts. *J. Am. Chem. Soc.* **2014**, *136*, 7539.

(18) (a) Li, W.; Liu, X.; Hao, X.; Hu, X.; Chu, Y.; Cao, W.; Qin, S.; Hu, C.; Lin, L.; Feng, X. New electrophilic addition of α-diazoesters with ketones for enantioselective C-N bond formation. *J. Am. Chem. Soc.* **2011**, *133*, 15268. (b) Santos, F. M. F.; Rosa, J. N.; André, V.; Duarte, M. T.; Veiros, L. F.; Gois, P. M. P. *N*-heterocyclic carbene catalyzed addition of aldehydes to diazo compounds: stereoselective synthesis of *N*-acylhydrazones. *Org. Lett.* **2013**, *15*, 1760. (d) Li, L.; Chen, J.-J.; Li, Y.-J.; Bu, X.-B.; Liu, Q.; Zhao, Y.-L. Activation of *a*-diazocarbonyls by organic catalysts: diazo group acting as a strong *N*-terminal electrophile. *Angew. Chem., Int. Ed.* **2015**, *54*, 12107. (f) Guo, R.; Zheng, Y.; Ma, J.-A. Electrophilic reaction of 2,2,2-trifluorodiazoethane with the in situ generated *N*-heterocyclic carbenes: access to *N*-aminoguanidines. *Org. Lett.* **2016**, *18*, 4170.

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