

Copper-Catalyzed Oxidation of Hydrazones to Diazo Compounds Using Oxygen as Terminal Oxidant

Wenbin Liu,¹‡ Jack Twilton,²‡ Bo Wei,¹ Maizie Lee,¹ Melissa N. Hopkins,² John Bacsa,¹ Shannon S. Stahl,²* and Huw M. L. Davies¹*

¹Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322.

²Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue, Madison, Wisconsin 53706.

Supporting Information Placeholder

ABSTRACT: A mild method for accessing diazo compounds via aerobic oxidation of hydrazones is described. This catalytic transformation employs a Cu(OAc)₂/pyridine catalyst and molecular oxygen from ambient air as the terminal oxidant, generating water as the sole byproduct and affording the desired diazo compounds within minutes at room temperature. A broad array of electronically diverse aryl diazo esters, ketones and amides can be accessed. Pyridine dramatically enhances the rate of the reaction by solubilizing the copper catalyst and serving as Brønsted base in the turnover-limiting proton-coupled oxidation of hydrazone by copper(II). Insights gained from mechanistic studies led to expansion of the scope of this method to include diaryl hydrazones, delivering diaryl diazomethane derivatives, which cannot be accessed via established diazo transfer methods. The products of this method may be employed in rhodium carbene catalysis without isolation of the diazo intermediate to afford cyclopropane products in good yield with high enantioselectivity. **Keywords:** copper, aerobic oxidation, dehydrogenation, hydrazones, diazo compounds, mechanism

Introduction

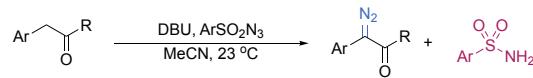
α-Diazo carbonyl compounds and diaryl diazomethane derivatives are versatile reagents with broad synthetic utility. Release of dinitrogen from diazo compounds is thermodynamically very favorable, enabling facile generation of carbene or metal carbene species via thermolysis,¹ photolysis² or activation by metal complexes.³ Carbene intermediates are very reactive and engage in diverse synthetically useful transformations, including insertion into C–H and X–H bonds (X = N, S, O, Si),⁴ cycloadditions,⁵ and other coupling reactions.⁶ One of the challenges with the use of diazo compounds on scale is the intrinsic high energy of these compounds,^{1d,7} and there is considerable interest in preparing diazo compounds *in situ* to avoid safety hazards associated with their generation and isolation in large quantities.⁸ Traditional approaches for the synthesis of diazo compounds use reactive starting materials, such as azides (i.e., diazo transfer) or stoichiometric oxidants, which generate undesirable byproducts (Scheme 1a-i).⁹ Base-induced fragmentation of sulfonylhydrazones (Bamford-Stevens reaction) represents another method (Scheme 1a-ii).¹⁰ The stoichiometric sulfinate byproduct is an undesirable feature, especially for large scale applications, and the common need for strong base or elevated temperatures can lead to decomposition or undesired reactivity of diazo product. The development of more practical methods for synthesis of diazo compounds could bypass these limitations and expand the utility of synthetic methods employing diazo reagents.

Simple hydrazones are appealing precursors to diazo compounds because they are readily accessible and stable. Their oxidation to diazo compounds, however, typically employs stoichiometric metal-based oxidants, such as HgO,¹¹ Ag₂O,¹²

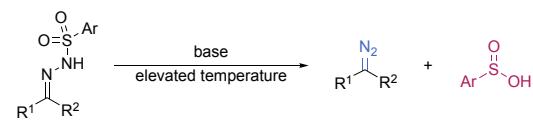
Scheme 1. Previous and Current Work on α-Diazocarbonyl Synthesis

a. Traditional approaches to diazocompounds.

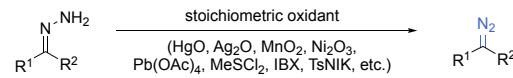
i. Diazo Transfer



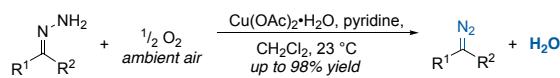
ii. Bamford-Stevens



b. Conventional approaches to hydrazone oxidation



c. This study: Cu-catalyzed hydrozone oxidation under mild conditions



R¹ = aryl, alkyl groups; R² = ester, amide, ketone, aryl groups

• benign terminal oxidant • H₂O as sole byproduct • broad substrate scope

MnO₂,¹³ Ni₂O₃,¹⁴ and Pb(OAc)₄ (Scheme 1b).¹⁵ This challenge has been addressed, in part, by the development of alternative oxidation methods. Examples include the use of chlorodimethylsulfonium chloride (generated from DMSO and oxalyl chloride),¹⁶ iodine-based oxidants, such as IBX¹⁷ and *N*-iodo-*p*-toluenesulfonamide (TsNIK),¹⁸ and a catalytic system using TEMPO and NaOCl as terminal oxidant.¹⁹ Molecular oxygen

(O₂) would be an ideal oxidant; however, catalytic methods demonstrating the feasibility of aerobic oxidation of hydrazone exhibit very limited scope.²⁰

Herein, we describe a copper-catalyzed method for the oxidation of hydrazones with O₂, in which water is the only by-product. It operates efficiently under mild conditions, reaching completion within minutes at room temperature with ambient air as the oxidant, and shows excellent scope in reactions with hydrazones bearing adjacent donor and acceptor substituents (electron-donating and withdrawing groups respectively) (Scheme 1c). The resulting diazo compounds are precursors to synthetically versatile donor/acceptor carbenes employed in diverse stereoselective and synthetically useful transformations.²⁻⁶ Pyridine derivatives play a crucial role in the catalytic reactions, and kinetic and mechanistic studies show that electron-rich pyridines significantly increase catalytic rate and support expansion of the substrate scope to diaryl hydrazones, accessing diaryl diazomethane derivatives. The utility of these advances is highlighted in tandem processes that feature *in situ* generation and use of the diazo compounds in catalytic enantioselective cyclopropanation of alkenes.

Results and Discussion

Catalyst Optimization. Prior work by Ibata and Singh demonstrated that Cu(acac)₂ (acac = acetylacetone) catalyzes aerobic oxidation of narrow set of benzil-derived diarylhydrazones; however, the products are susceptible to further oxidation to benzophenone azines if the reaction time and temperature is not strictly controlled.^{20b} In spite of these limitations, this precedent prompted us to consider simple Cu salts as catalysts for aerobic oxidation of hydrazones bearing donor/acceptor substituents. Initial efforts focused on oxidation of hydrazone (Z)-1 to 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate 2 (Table 1). This substrate was used because the resulting diazo compound has found broad application in catalyst-controlled C–H functionalization reactions.^{4c} A double oxygen balloon and vigorous stirring (800 rpm) with a large magnetic stir bar were used to support efficient oxygen mixing between the headspace and reaction solution. Ibata and Singh used Cu(acac)₂ as the catalyst,^{20b} but the hydrazone starting material 1 was completely unreactive under the previously reported conditions. Similar behavior was observed under modified conditions with several different Cu sources, including Cu(acac)₂, copper(I) iodide, copper(I) oxide, and copper(II) triflate (Table 1, entries 2–5). The triflate salts of copper(I) resulted in hydrazone decomposition but no desired diazo compound was observed (entry 6). The known activity of copper(I) triflate salts activation of diazo compounds,²¹ accounts for the observed byproducts derived from carbene intermediates, such as O–H insertion with H₂O, N–H insertion with the hydrazone (Z)-1 and dimerization. Copper(II) acetate showed the greatest promise and was found to facilitate both formation and retention of the diazo compound 2, affording a 20% yield of 2 with 40% unreacted hydrazone (Z)-1 (entry 7). Use of the less expensive hydrated copper acetate, Cu(OAc)₂·H₂O, was similarly effective (entry 9). However, addition of approximately 10% water by volume to the reaction mixture inhibited the reaction and resulted in complete recovery of (Z)-1 (entry 8). Both molecular sieves and silica were found to be slightly beneficial, affording the desired product in comparable yield, likely due to removal of deleterious water. The use of silica resulted in significantly reduced formation of undesirable byproducts (entry 10 and 12). MgSO₄

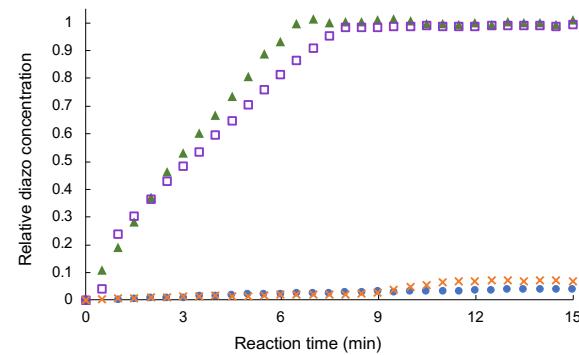
Table 1. Optimization of Hydrazone Oxidation^a

Entry	[Cu]	x	additive	recovered 1, %	yield (2), %
1 ^b	Cu(acac) ₂	20	—	100	0
2	Cu(acac) ₂	20	—	100	0
3	CuI	20	—	100	0
4	Cu ₂ O	20	—	100	0
5	Cu(CF ₃ SO ₃) ₂	20	—	100	0
6	Cu(CF ₃ SO ₃)	20	—	0 ^c	0
7	Cu(OAc) ₂	20	—	40 ^c	20
8	Cu(OAc) ₂	20	H ₂ O (0.1 mL)	98	0
9	Cu(OAc) ₂ ·H ₂ O	20	—	45 ^c	21
10	Cu(OAc) ₂ ·H ₂ O	20	3A molecular sieve (100 mg)	55	24
11	Cu(OAc) ₂ ·H ₂ O	20	MgSO ₄ (100 mg)	86	<5
12	Cu(OAc) ₂ ·H ₂ O	20	silica (100 mg)	63	26
13	Cu(OAc) ₂ ·H ₂ O	20	NEt ₃ (1 equiv), silica	<1	80
14	Cu(OAc) ₂ ·H ₂ O	20	pyridine (1 equiv), silica	3	92
15	Cu(OAc) ₂ ·H ₂ O	10	pyridine (0.6 equiv), silica	nd	95
16 ^d	Cu(OAc) ₂ ·H ₂ O	10	pyridine (0.6 equiv), silica	nd	94

^aReaction conditions: a solution of (Z)-1 (0.5 mmol) in 1 mL of CH₂Cl₂ was added in 1-pot to a vial with [Cu] and additive in 4 mL of CH₂Cl₂ under 1 atm O₂ (balloon) at 23 °C. The mixture was stirred vigorously for 1 h. ^bReaction run in Et₂O at 0 °C. ^cOxidation byproducts were observed in the ¹H NMR spectrum of the crude reaction mixture. ^dAmbient air used instead of a pure O₂ balloon. was also tested as a desiccant, but it inhibited reactivity (entry 11).

Addition of base, such as NEt₃ or pyridine, led to dramatically improved conversion of hydrazone (Z)-1 to the desired diazo compound 2 (80% and 92% yield in entries 13 and 14, respectively). Excellent yield was maintained with reduced loading of Cu(OAc)₂·H₂O and pyridine (10 mol % and 0.6 equiv, respectively; entry 15). In addition, ambient air proved to be compe-

A.



B.

Entry	Legend	Additive (1.0 equiv.)	time (h)	yield, %
1	blue ●	none	21	60
2	green ▲	NEt ₃	0.5	81
3	purple □	pyridine	0.5	90
4	orange ×	2,6-di-tert-butylpyridine	4	25

Figure 1. React-IR analysis of the formation of diazo product 2 from hydrazone 1 (A), together with reaction outcomes observed at longer reaction times with the different base additives (B).

tent as the source of O_2 , affording **2** in a yield nearly identical to that obtained with pure O_2 (entry 16). The beneficial effect of NEt_3 and pyridine is especially clear from React-IR studies of the reaction progress, using the IR absorbance of diazo functionality at $\sim 2100\text{ cm}^{-1}$ (Figure 1A). The reactions conducted with NEt_3 and pyridine reached completion in less than 10 min. The reactions with no base and with the bulky base, 2,6-*t*Bu₂py, showed very little conversion during the same time period, albeit with moderate product formation over longer time periods (Figure 1B).

Assessment of Substrate Scope. The optimized conditions identified for oxidation of hydrazone (*Z*)-**1** provided a starting point for evaluation of a broader range of substrates, using ambient air as the source of oxidant and pyridine as an additive (Table 2). In most of these cases, the diazo products could be obtained in good purity simply by passing the crude reaction mixture through a plug of silica gel. The *Z* isomer is the dominant isomer obtained from the synthesis of hydrazone **1** and was used in the optimization studies in Table 1. The *E* isomer proved to be equally effective, generating **2** in 96% isolated yield. Hence, the other hydrazone substrates were evaluated as mixtures of *E/Z* isomers without extensive separation. Efficient hydrazone oxidation was observed with different ester substituents, generating **3–5** in high yields (89–97%). The oxidation was similarly effective for the synthesis of a variety of aryl diazoacetates, as illustrated for **6–13**. The reaction was especially effective when the aryl substituents were electron-withdrawing or slightly electron-donating, with products isolated in $\geq 93\%$ yield. The reaction yield was diminished for substrates with the electron-donating methoxy group (88% yield of **8** and 69% yield of **13**). This result is consistent with previous observations showing that aryl diazoacetates with strongly donating groups decompose more rapidly.^{1d, 22} In the reaction affording **13**, by-products observed from further reaction of the carbene with oxygen and water were detected. The reaction was also effective in the formation of pyridyl diazoacetate **14** and even an alkyldiazoacetate **15** in high yields (94% and 82%, respectively).

Table 2. Substrate Scope of Diazo Compounds from $Cu(OAc)_2$ -Catalyzed Oxidation of Hydrazones Under Ambient Air

$\begin{array}{c} N-NH_2 \\ \\ R^1-C(=O)-R^2 \end{array}$		$\xrightarrow{\begin{array}{c} Cu(OAc)_2 \cdot H_2O \text{ (10 mol\%)} \\ \text{pyridine (0.6 equiv), air} \\ SiO_2, CH_2Cl_2, 23^\circ C, 1\text{ h} \end{array}}$	$\begin{array}{c} N \\ \\ R^1-C(=O)-R^2 \end{array}$
2	94%, from (<i>Z</i>)- 1		
2	96%, from (<i>E</i>)- 1		
3	89%		
4	97%		
5	93% ^b		
6	95%		
7	96%		
8	88%		
9	96%		
10	97% ^c		
11	93%		
12	96%		
13	69%		
14	94% ^c		
15	82% ^c		
16	92% ^d		
17	99% ^e		
18	98% ^f		

^aReaction condition: a solution of (*Z*)-hydrazone (0.5 mmol) in 1 mL of CH_2Cl_2 (0.5% pyridine) was added to a vial with $Cu(OAc)_2 \cdot H_2O$ (10 mol %) and SiO_2 (100 mg) in 4 mL of CH_2Cl_2 (0.5% pyridine) under ambient air (without cap) at $23^\circ C$. The mixture was stirred vigorously for 1 h before silica plug. ^b1:1 (*Z*:*E*)-hydrazone was used. ^c(*E*)-hydrazone was used. ^dReaction was conducted using 2.4 equiv of pyridine with O_2 balloon in dark (aluminum foil). ^e2:1 (*Z*:*E*)-hydrazone was used. ^f17:1 (*Z*:*E*)-hydrazone was used.

Diazoketone **16** was obtained in good yield, necessitating minor modification of the reaction conditions due to the instability of the product. Specifically, the reaction was conducted in the dark using an O_2 balloon with higher loading of the pyridine additive to minimize the decomposition of the diazoketone product via Wolff rearrangement.²³ Furthermore, the isatin-derived hydrazones were converted to the corresponding diazoamides **17** and **18** in near-quantitative yields.

Mechanistic studies. Additional studies provided valuable insights into these reactions. The addition of 1 equiv of pyridine to a solution of $Cu(OAc)_2$ in dichloromethane formed the previously reported pyridine-capped $Cu(OAc)_2$ dimer, $Cu_2(OAc)_4(py)_2$.²⁴ This complex was found to be a competent catalyst for the aerobic oxidation hydrazone **1**, without the inclusion of additional pyridine, affording diazo compound **2** in nearly quantitative yield (Figure 2).

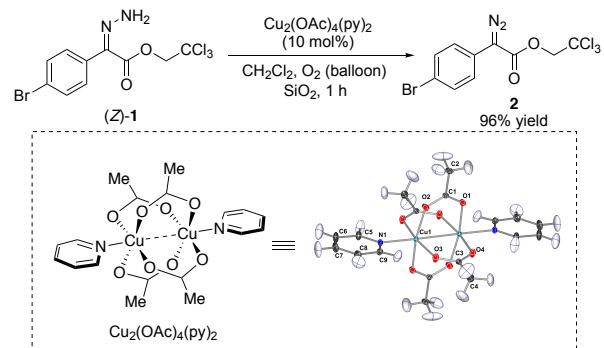


Figure 2. Oxidation of hydrazone (*Z*)-**1** catalyzed by $Cu(OAc)_2 \cdot 2py$, which was characterized by X-ray crystallography.

In order to probe the mechanism of this Cu-catalyzed hydrazone oxidation, the rate of the catalytic reaction was then monitored under standard conditions with a series of 4-substituted pyridine derivatives (Figure 3). The reaction of hydrazone **19** was

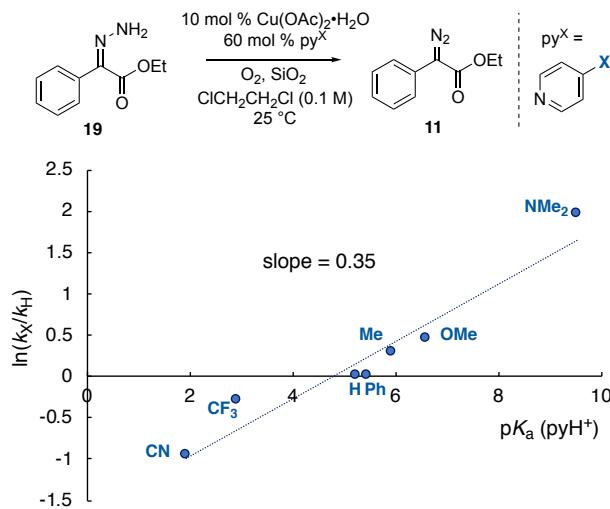
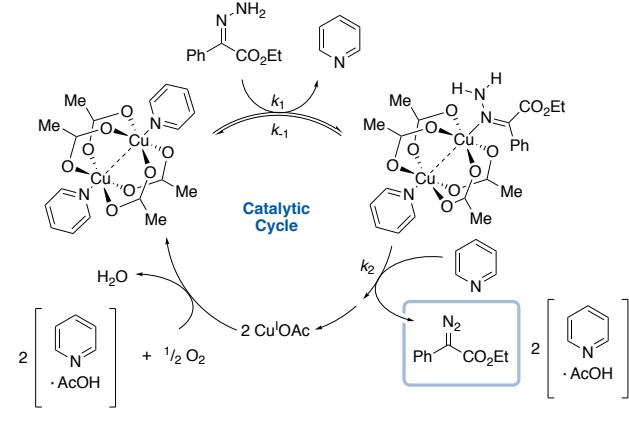


Figure 3. Analysis of pyridine electronic effects on the rate of hydrazone oxidation to afford diazo compound **11**. See Supporting Information for experimental details.

analyzed by following O_2 consumption via gas-uptake methods, and well-behaved time-course data were amenable to initial-rate analysis (see Supporting Information for details). A Brønsted plot correlating the logarithm of the relative rates with the pyridinium pK_a values²⁵ exhibits a linear fit with a positive slope,²⁶ showing that more basic pyridine derivatives lead to faster rates. Use of 4-(*N,N*-dimethylamino)pyridine (DMAP) as the base led to complete conversion of **19** into diazo compound **11** within 2 min at room temperature.

These data were complemented by additional kinetic analysis to determine a catalytic rate law. The catalytic rate for oxidation of **19** exhibited a first-order dependence on $[Cu(OAc)_2]$ and **[19]**, but little-to-no dependence on $[py]$ or pO_2 (3–28 psi) (see Figure S6 in the Supporting Information). These results provide the basis for the proposed catalytic mechanism shown in Figure 4. The reaction is initiated by reversible substitution of a pyridine ligand on $Cu_2(OAc)_4(py)_2$ by the hydrazone substrate, followed by turnover-limiting deprotonation of the coordinated



$$\text{rate} = \frac{k_1 k_2 [\text{Cu}][(\text{Z}-19)[\text{pyridine}]}{k_1 [\text{pyridine}]} \quad (1)$$

$$\text{rate} = k_{\text{obs}}[\text{Cu}][(\text{Z}-19)] \quad (2)$$

$$k_{\text{obs}} = \frac{k_1 k_2}{k_1} \quad (3)$$

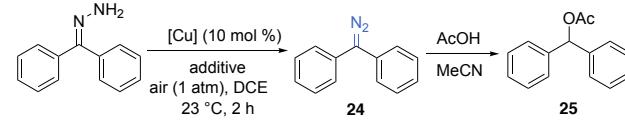
Figure 4. Proposed catalytic mechanism and rate law.

hydrazone by pyridine. The latter step is expected to be coupled to reduction of the Cu^{II} centers, resulting in formation of the diazo compound and 2 equiv of $Cu^{I}OAc$. The catalyst can then be re-oxidized by O_2 , supported by protons derived from the substrate oxidation step. A rate law derived for this mechanism (Figure 4, eq 2) rationalizes the zero-order kinetic dependence on $[py]$, even while pyridine is crucial to enable the reaction to proceed (cf. Figure 1). The influence of the electronic properties of pyridine (cf. Figure 3)²⁷ may be rationalized by electronic contributions to the fundamental rate constants incorporated in the k_{obs} term (Figure 4, eq 3: k_1 , k_1 , and k_2). The positive slope in Figure 3 suggests the influence of pyridine basicity on turnover-limiting proton transfer (k_2) is the most significant electronic contribution.

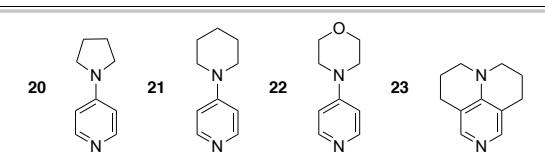
Expansion of reactivity to diaryl hydrazones. Diaryl hydrazones are precursors to diaryldiazomethane derivatives. The latter compounds are noteworthy because they behave as donor-acceptor carbenes in rhodium-catalyzed cyclopropanations, affording the desired products with high stereoselectivity.²⁸ Catalytic methods for aerobic dehydrogenation of diarylhydrazones to prepare diazo compounds have not been reported, and the catalytic conditions shown in Table 2 are unreactive with these substrates (cf. Table S2 in the Supporting Information).²⁹ Nonetheless, we wonder whether the more reactive catalyst systems featuring electron-rich pyridines might be effective with these substrates.

A range of copper carboxylate salts and basic pyridine derivatives were evaluated for the oxidation of benzophenone hydrazone (Table 3). The diphenyl diazomethane product (**24**) is relatively unstable, and to facilitate product quantitation, AcOH was added to the reaction mixture at the end of the reaction to convert the diazo compound **24** to the corresponding acetate **25**. Moderate reactivity was observed with $Cu(OAc)_2$ in combination with DMAP or another electron-

Table 3 Optimization of Diaryl Hydrazone Oxidation^a



Entry	[Cu]	additive	yield (25), %
1	$Cu(OAc)_2 \cdot H_2O$	pyridine (0.5 equiv), silica	7
2	$Cu(OAc)_2 \cdot H_2O$	DMAP (0.5 equiv)	34
3	$Cu(OAc)_2 \cdot H_2O$	20 (0.5 equiv)	38
4	$Cu(OAc)_2 \cdot H_2O$	21 (0.5 equiv)	34
5	$Cu(OAc)_2 \cdot H_2O$	22 (0.5 equiv)	24
6	$Cu(OAc)_2 \cdot H_2O$	23 (0.5 equiv)	59
7	5 mol % $Cu(O_2CCF_3)_2 \cdot H_2O$	23 (0.20 equiv)	87



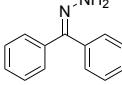
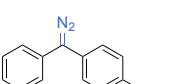
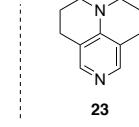
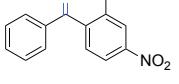
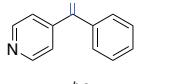
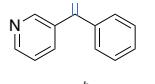
^aReaction conditions: a solution of hydrazone (0.01 mmol) in 0.05 mL of solvent was added in 1 to a vial with $[Cu]$ and additive in 0.05 mL of DCE under air at 23 °C. The mixture was stirred vigorously for 2 hrs then cooled to 0°C and quenched with AcOH (20 μ L in 200 μ L MeCN). Product **24** was converted to the acetate to facilitate UPLC analysis. A stock solution of IS (1,3,5-trimethoxybenzene) was added and assay yield was determined by calibrated UPLC analysis. DCE = 1,2-dichloroethane.

rich pyridine derivative (**20–23**, entries 3–6). 9-Azajulolidine (**23**) showed the best reactivity (59%, entry 6), probably reflecting the coplanarity of the amino group and the pyridine π -system, which enhances the basicity of **23** relative to DMAP and other 4-aminopyridine derivatives.³⁰ Further improvement was observed when $\text{Cu}(\text{OAc})_2$ was replaced with $\text{Cu}(\text{O}_2\text{CCF}_3)_2 \cdot \text{H}_2\text{O}$. The combination of 5 mol% $\text{Cu}(\text{O}_2\text{CCF}_3)_2 \cdot \text{H}_2\text{O}$ and 20 mol% **23** delivered 87% assay yield of acetate derivative **25** (entry 7; see Table S2 for additional screening data).³¹

These optimized conditions were then employed with a series of additional di(hetero)aryl hydrazone derivatives (Table 4). The innate reactivity of the diaryldiazomethane derivatives can lead to relatively large differences between the NMR and isolated yields. For example, benzophenone hydrazone affords the corresponding diazo compound (**24**) in excellent *in situ* yield (98% by NMR), but only 58% isolated yield (see SI for experimental detail). A similar outcome is observed upon substitution of one of the aromatic rings with an electron-donating *p*-OMe group (**26**: 89% NMR, 62% isolated yield). Substrates bearing electron-withdrawing substituents are particularly effective under these conditions, furnishing the diazo compounds in excellent yield (**27** and **28**, 90% and 86% isolated yield respectively). This outcome likely reflects a combination of factors, including the more acidic nature of the N–H bonds of the hydrazone starting materials, which leads to enhanced reactivity, and increased stability of the diazo products under the reaction conditions and during isolation. Finally, benzoylpyridine derived hydrazones were subjected to the optimized reaction conditions and proceeded to the corresponding diazo compounds in moderate to good yield (**29** and **30**, 44 and 79% isolated yield respectively), demonstrating that Lewis basic heterocycles can be tolerated in the substrates.

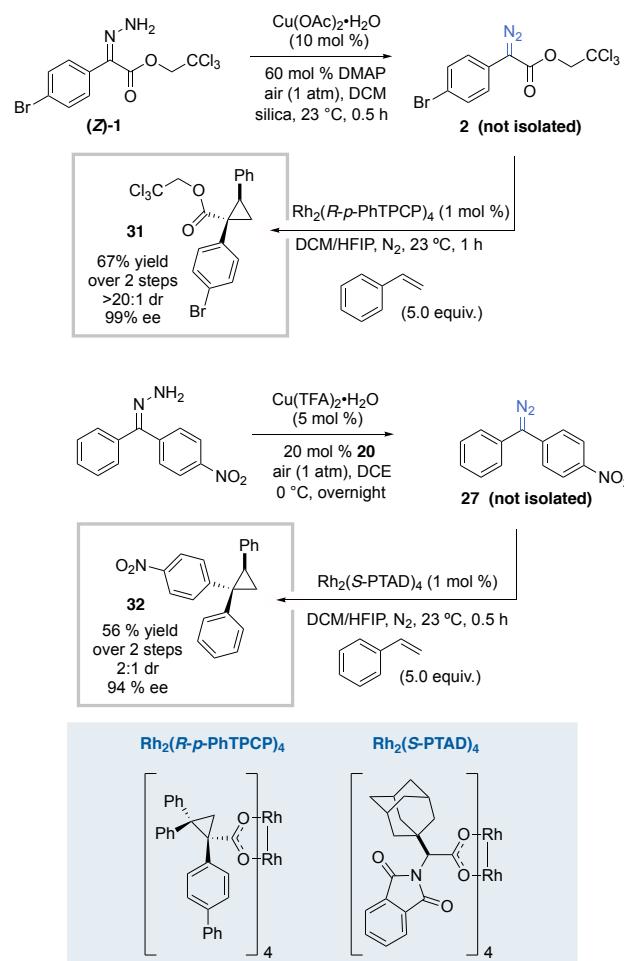
Tandem catalytic diazo synthesis and carbene transfer. The present method provides a means to prepare diazo compounds *in situ* and use, without isolation, in tandem one-pot reactions

Table 4. Diaryl Hydrazone Oxidation^a

		
24 98% (58%)	26 89% (62%)	27 92% (90%)
		
28 91% (86 %)	29^{b,c} 56% (44 %)	30^b 94% (79 %)

^aReaction conditions: Hydrazone (0.20 mmol) was added to a vial with 5 mol% $\text{Cu}(\text{TFA})_2 \cdot \text{H}_2\text{O}$ and 20 mol% 9-azajulolidine (**21**) in 2 mL of DCE under air at 0 °C. The mixture was stirred vigorously for 12 h. Yields shown reflect ¹H NMR analysis of the crude reaction with 1,3,5-trimethoxybenzene as internal standard; yields shown in parenthesis are isolated.³¹ ^bReaction run for 6 h. ^cProduct isolated as an inseparable 4:1 mixture with ketone byproduct.

Scheme 2. Tandem Oxidation-Cyclopropanation^a



^aSee SI for experimental details. Yields of cyclopropanes shown are isolated.

with Rh-catalyzed carbene transfer. This concept was tested using a hydrazone precursor to both classes of diazo compounds (Scheme 2). Hydrazone **1** was converted to the corresponding diazo compound **2** using a $\text{Cu}(\text{OAc})_2$ /DMAP catalyst system. The crude reaction mixture containing **2** and residual copper catalyst was then used directly in the cyclopropanation of styrene with a chiral rhodium carboxylate catalyst, $\text{Rh}_2(R\text{-}p\text{-PhTPCP})_4$.³² The cyclopropane product was obtained in good yield and excellent stereoselectivity (**31**, 67% yield, >20:1 dr, 99% ee). This tandem reactivity has even greater implications for diaryldiazomethanes, owing to their instability and challenges in their isolation (cf. Table 4).²⁸ The crude diaryldiazomethane derivative **27**, obtained from aerobic dehydrogenation of the corresponding hydrazone using a $\text{Cu}(\text{TFA})_2/23$ catalyst system, was used directly in the cyclopropanation of styrene with $\text{Rh}_2(S\text{-PTAD})_4$ as catalyst. The cyclopropane product **32** was obtained in moderate yield and good stereoselectivity (56% yield, 2:1 dr, and 94% ee). These results highlight the potential applicability of sequential Cu-catalyzed aerobic oxidation and Rh-catalyzed carbene transfer without purification of the reactive diazo intermediate.

Conclusion

A new Cu-catalyzed method has been developed for aerobic dehydrogenation of hydrazones to the corresponding diazo

compounds. The catalyst is entirely composed of low-cost, commercially available materials, and the reaction proceeds very efficiently at room temperature or below with ambient air as the source of oxidant. React-IR and gas uptake kinetic studies provide valuable insights into the accelerating effect of the pyridine in the reaction, which is proposed to arise from its role as a base for the turnover-limiting proton-coupled oxidation of the Cu^{II}-coordinated hydrazone substrate. Inspired by these mechanistic studies, we extended the scope of this method to the oxidation of diaryl hydrazones to access diazo compounds, which cannot be prepared by diazo transfer, utilizing a more basic pyridine co-catalyst. This method shows exceptionally broad substrate scope and in contrast to many traditionally approaches enables access to multiple classes of structurally diverse diazo compounds. The utility of this new technology was further demonstrated by conducting hydrazone oxidation in tandem with Rh-catalyzed cyclopropanation without isolation of the diazo compound from the crude reaction mixture. These results have important implications for the practical utility of catalytic processes using diazo compounds as synthetic intermediates. Further studies to streamline this method for organic synthesis and extend its utility in flow chemistry are on-going.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Complete experimental procedures and compound characterization are available in the Supporting Information. (PDF).

AUTHOR INFORMATION

Corresponding Author

*stahl@chem.wisc.edu
*hmdavie@emory.edu

Author Contributions

[‡]W.L. and J.T contributed equally.

All authors have given approval to the final version of the manuscript.

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REFERENCES

- (1) (a) Deng, Y. J., C.; Doyle, M. P. Dinitrogen Extrusion from Enoldiazo Compounds under Thermal Conditions: Synthesis of Donor–Acceptor Cyclopropenes. *Chem. Commun.* **2015**, *51*, 12924–12927; (b) Tortoreto, C. R., D.; Davies, H. M. L. Metal-Free C–H Functionalization of Alkanes by Aryldiazoacetates. *Org. Lett.* **2017**, *19*, 770–773; (c) Zhang, X. Z., Y.; Qiu, L.; Xu, X. Thermally Induced N–S Bond Insertion Reaction of Diazo Compounds with N–Sulfonylsuccinimides: Synthesis of Sulfides and Mechanism Studies. *Org. Biomol. Chem.* **2018**, *16*, 70–76; (d) Green, S. P. W., K. M.; Payne, A. D.; Hallett, J. P.; Miller, P. W.; Bull, J. A. Thermal Stability and Explosive Hazard Assessment of Diazo Compounds and Diazo Transfer Reagents. *Org. Process Res. Dev.* **2020**, *24*, 67–84.
- (2) (a) Ciszewski, Ł. W. J., K. R.; Gryko, D. Recent Developments in Photochemical Reactions of Diazo Compounds. *Org. Biomol. Chem.* **2019**, *17*, 432–448; (b) Huang, X. W., R. D.; Harms, K.; Meggers, E. Asymmetric Catalysis with Organic Azides and Diazo Compounds Initiated by Photoinduced Electron Transfer. *J. Am. Chem. Soc.* **2016**, *138*, 12636–12642; (c) Jurberg, I. D. D., H. M. L. Blue Light-promoted Photolysis of Aryldiazoacetates. *Chem. Sci.* **2018**, *9*, 5112–5118.
- (3) (a) Li, P.; Zhao, J.; Shi, L.; Wang, J.; Shi, X.; Li, F. Iodine-catalyzed diazo activation to access radical reactivity. *Nat. Commun.* **2018**, *9*, 1972; (b) Keipour, H.; Jalba, A.; Delage-Laurin, L.; Ollevier, T. Copper-Catalyzed Carbenoid Insertion Reactions of α -Diazoesters and α -Diazoketones into Si–H and S–H Bonds. *J. Org. Chem.* **2017**, *82*, 3000–3010; (c) Davies, H. M. L. Finding Opportunities from Surprises and Failures. Development of Rhodium-Stabilized Donor/Acceptor Carbenes and Their Application to Catalyst-Controlled C–H Functionalization. *J. Org. Chem.* **2019**, *84*, 12722–12745.
- (4) (a) Harada, S. T., K.; Homma, H.; Sakai, C.; Ito, T.; Nemoto, T. Silver-Catalyzed Asymmetric Insertion into Phenolic O–H Bonds using Aryl Diazoacetates and Theoretical Mechanistic Studies. *Chem. Eur. J.* **2019**, *25*, 12058–12062; (b) Tanbouza, N. K., H.; Ollevier, T. Fe^{II}-Catalysed Insertion Reaction of α -Diazocarbonyls into X–H Bonds (X = Si, S, N, and O) in Dimethyl Carbonate as a Suitable Solvent Alternative. *RSC Adv.* **2019**, *9*, 31241–31246; (c) Davies, H. M. L., L., K. Dirhodium Tetracarboxylates as Catalysts for Selective Intermolecular C–H Functionalization. *Nat. Rev. Chem.* **2019**, *3*, 347–360; (d) Gillingham, D. F., N. Catalytic X–H Insertion Reactions Based on Carbenoids. *Chem. Soc. Rev.* **2013**, *42*, 4918–4931.
- (5) (a) Zhang, B. D., H. M. L. Rhodium-Catalyzed Enantioselective [4+2] Cycloadditions of Vinylcarbenes with Dienes. *Angew. Chem., Int. Ed.* **2020**, *59*, 4937–4941; (b) Zheng, H. D., M. P. Catalytic Desymmetric Cycloaddition of Diaziridines with Metalloenolcarbenes: The Role of Donor-Acceptor Cyclopropenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 12502–12506.
- (6) (a) Xia, Y. Q., D.; Wang, J. Transition-Metal-Catalyzed Cross-Couplings through Carbene Migratory Insertion. *Chem. Rev.* **2017**, *117*, 13810–13889; (b) Wang, D. S., K. J. Copper-Catalyzed, Stereoselective Cross-Coupling of Cyclic Allyl Boronic Acids with α -Diazoketones. *Org. Lett.* **2017**, *19*, 1622–1625.
- (7) (a) Bien, J. D., A. H.; DelMonte, A. J.; Fraunhofer, K. J.; Gao, Z.; Hang, C.; Hsiao, Y.; Hu, W.; Katipally, K.; Littke, A.; Pedro, A.; Qiu, Y.; Sandoval, M.; Schild, R.; Soltani, M.; Tedesco, A.; Vanyo, D.; Vemishetti, P.; Waltermire, R. E. The First Kilogram Synthesis of Beclabuvir, an HCV NS5B Polymerase Inhibitor. *Org. Process Res. Dev.* **2018**, *22*, 1393–1408; (b) Jia, M. M., S. New Approaches to the Synthesis of Metal Carbenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 9134–9166.
- (8) (a) Deadman, B. J. C., S. G.; Maguire, A. R. Taming hazardous chemistry in flow: the continuous processing of diazo and diazonium compounds. *Chem. Eur. J.* **2015**, *21*, 2298–2308; (b) Movsisyan, M. D., E. I.; Berton, J. K.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. Taming hazardous chemistry by continuous flow technology. *Chem. Soc. Rev.* **2016**, *45*, 4892–4928; (c) Hock, K. J. K., R. M. The Generation of Diazo Compounds in Continuous-Flow. *Chem. Eur. J.* **2018**, *24*, 10571–10583; (d) Sullivan, R. J. F., G. P. R.; Newman, S. G. Overcoming Scope Limitations in Cross-Coupling of Diazo Nucleophiles by Manipulating Catalyst Speciation and Using Flow Diazo Generation. *ACS Catal.* **2019**, *9*, 5623–5630; (e) Poh, J. S. M., S.; von Keutz, T.; Tran, D. N.; Battilocchio, C.; Pasau, P.; Ley, S. V. Rapid Asymmetric Synthesis of Disubstituted Allenes by Coupling of Flow-Generated Diazo Compounds and Propargylated Amines. *Angew. Chem., Int. Ed.* **2017**, *56*, 1864–1868; (f) Tran, D. N. B., C.; Lou, S. B.; Hawkins, J. M.; Ley, S. V. Flow chemistry as a discovery tool to access sp²–sp³ cross-coupling reactions via diazo compounds. *Chem. Sci.* **2015**, *6*, 1120–1125; (g) Yoo, C. J. R., D.; Liu, W.; Hoyt, C. B.; Pimentel, B.; Lively, R. P.; Davies, H. M. L.; Jones, C. W. An Immobilized-Dirhodium Hollow-Fiber Flow Reactor for Scalable and Sustainable C–H Functionalization in Continuous Flow. *Angew. Chem., Int. Ed.* **2018**, *57*, 10923–10927.

(9) (a) Ford, A. M., 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; (b) Baum, J. S. S., D. A.; Davies, H. M. L.; Smith, H. D. Diazotransfer Reactions with *p*-Acetamidobenzenesulfonyl Azide. *Synth. Commun.* **2006**, *17*, 1709-1716.

(10) (a) Bamford, W. R. S., T. S. The Decomposition of Toluene-*p*-sulphonylhydrazone by Alkali. *J. Chem. Soc.* **1952**, 4735-4740; (b) Fulton, J. R. A., V. K.; de Vicente, J. The Use of Tosylhydrazone Salts as a Safe Alternative for Handling Diazo Compounds and Their Applications in Organic Synthesis. *Eur. J. Org. Chem.* **2005**; (c) Emer, E. T., J.; Tredwell, M.; Calderwood, S.; Collier, T. L.; Liégault, B.; Taillefer, M.; Gouverneur, V. Diversity-Oriented Approach to CF_3CHF_2 -, CF_3CFBr_2 -, CF_3CF_2 -, $(\text{CF}_3)_2\text{CH}$ -, and $\text{CF}_3(\text{SCF}_3)\text{CH}$ -Substituted Arenes from 1-(Diazo-2,2,2-trifluoroethyl)arenes. *Org. Lett.* **2014**, *16*, 6004-6007.

(11) (a) Staudinger, H. G., A. Versuche zur Herstellung isomerer Diazoverbindungen bezw. Hydrazone. *Chem. Ber.* **1916**, *49*, 1961-1968; (b) Day, A. C. R., P.; Southam, R. M.; Whiting, M. C. The preparation of secondary aliphatic diazo-compounds from hydrazones. *J. Chem. Soc. C: Org.* **1966**, *0*, 467-469.

(12) Schroeder, W. K., L. The Use of Silver Oxide in the Preparation of Diaryldiazomethanes. *J. Org. Chem.* **1954**, *19*, 718-720.

(13) (a) Morrison, H. D., S.; Yates, P. Communications- Preparation of α -Diazo Ketones. *J. Org. Chem.* **1961**, *26*, 2617-2618; (b) Doyle, M. P. Y., M. Effective and Highly Stereoselective Coupling with Vinyldiazomethanes To Form Symmetrical Trienes. *J. Org. Chem.* **2002**, *67*, 602-604; (c) Denton, J. R. S., D.; Davies, H. M. L. Enantioselective Synthesis of Trifluoromethyl-Substituted Cyclopropanes. *Org. Lett.* **2007**, *9*, 2625-2628.

(14) Nakagawa, K. O., H.; Minami, K. Oxidation with Nickel Peroxide: the Preparation of Diazo-compounds from Hydrazones. *Chem. Commun. (London)* **1966**, *20*, 730-731.

(15) Holton, T. L. S., H. Advantageous Syntheses of Diazo Compounds by Oxidation of Hydrazones with Lead Tetraacetate in Basic Environments. *J. Org. Chem.* **1995**, *60*, 4725-4729.

(16) Javed, M. I. B., M. Diazo Preparation via Dehydrogenation of Hydrazones with "Activated" DMSO. *Org. Lett.* **2007**, *9*, 1789-1792.

(17) Nicolaou, K. C. M., C. J. N.; Montagnon, T. *o*-Iodoxybenzoic Acid (IBX) as a Viable Reagent in the Manipulation of Nitrogen- and Sulfur-Containing Substrates: Scope, Generality, and Mechanism of IBX-Mediated Amine Oxidations and Dithiane Deprotections. *J. Am. Chem. Soc.* **2004**, *126*, 5192-5201.

(18) Nicolle, S. M. M., C. J. Potassium N-Iodo *p*-Toluenesulfonamide (TsNIK, Iodamine-T): A New Reagent for the Oxidation of Hydrazones to Diazo Compounds. *Chem.: Eur. J.* **2014**, *20*, 4420-4425.

(19) Perusquía-Hernández, C. L.-I., G. R.; Frontana-Uribe, B. A.; Cuevas-Yáñez, E. Synthesis and esterification reactions of aryl diazomethanes derived from hydrazone oxidations catalyzed by TEMPO. *Tetrahedron Lett.* **2013**, *54*, 3302-3305.

(20) (a) Tsuji, J. T., H.; Kajimoto, T. Organic Synthesis by Means of Metal Complexes: XII Copper Catalyzed Oxidation of Dihydrazones to Acetylenes. *Tetrahedron Lett.* **1973**, *14*, 4573-4574; (b) Ibata, T. S., G. S. Formation of Diazoketones and Azines by Improved Oxidation of Ketohydrazones Using $\text{Cu}(\text{acac})_2$ as a Catalyst. *Tetrahedron Lett.* **1994**, *35*, 2581-2584; (c) Akira, N. S., Y.; Teruo, M. A Convenient Synthesis of Diazo Compounds by Catalytic Dehydrogenation of Hydrazones with Cobalt Schiff Bass Complex-Oxygen System. *Chem. Lett.* **1986**, *15*, 505-506.

(21) (a) Salomon, R. G. K., J. K. Copper(I) Catalysis in Cyclopropanations with Diazo Compounds. Role of Olefin Coordination. *J. Am. Chem. Soc.* **1973**, *95*, 3300-3310; (b) Evans, D. A. W., K. A.; Scott, M. J. 'Bis(oxazolines)' as Ligands for Self-Assembling Chiral Coordination Polymers – Structure of a Copper(I) Catalyst for the Enantioselective Cyclopropanation of Olefin. *Angew. Chem., Int. Ed.* **1992**, *31*, 430-432; (c) Burgess, K. L., H.-J.; Porte, A.; Sulikowski, G. A. New Catalysts and Conditions for a C-H Insertion Reaction Identified by High Throughput Catalyst Screening. *Angew. Chem., Ind. Ed.* **1996**, *35*, 220-222.

(22) Ovalles, S. R. H., J. H.; Davies, H. M. L. Thermally Induced Cycloadditions of Donor/Acceptor Carbenes. *Org. Lett.* **2011**, *13*, 4284-4287.

(23) Csizmadia, I. G. F. J. S., O. P. Mechanism of the Wolff Rearrangement. *J. Am. Chem. Soc.* **1968**, *90*, 7360-7361.

(24) Uekusa, H. O., S.; Saito, Y. Structural Comparison Between Dimeric Copper(II) Formate and Acetate in Pyridine and Urea Adducts. *Acta Cryst.* **1989**, *45*, 377-380.

(25) Aqueous pyridinium pKa values are predicted and where collected from Sci-Finder.

(26) Anslyn, E. Q. D., D. A., *Modern Physical Organic Chemistry*. 1st ed.; University Science Books: Mill Valley, CA, USA, p 507-524.

(27) The rate constant is dependent on the electronics of the pyridine derivative despite the fact the rate equation shows no concentration dependence. Note pyridine also helps to solubilize $\text{Cu}(\text{OAc})_2$ in DCM and DCE.

(28) (a) Lee, M. R., Z.; Musaev, D. G.; Davies, H. M. L. Rhodium-Stabilized Diarylcarbenes Behaving as Donor/Acceptor Carbenes. *ACS Catal.* **2020**, *10*, 6240-6247. (b) Zhu, D.; Chen, L.; Fan, H.; Yao, Q.; Zhu, S., Recent progress on donor and donor-donor carbenes. *Chem. Soc. Rev.* **2020**, *49*, 908-950. (c) Bergstrom, B. D.; Nickerson, L. A.; Shaw, J. T.; Souza, L. W., Transition Metal Catalyzed Insertion Reactions with Donor/Donor Carbenes. *Angew. Chem. Int. Ed.* **2020**, *in press* doi: 10.1002/anie. 202007001. (d) Yang, L. L.; Evans, D.; Xu, B.; Li, W. T.; Li, M. L.; Zhu, S. F.; Houk, K. N.; Zhou, Q. L., Enantioselective Diarylcarbene Insertion into Si-H Bonds Induced by Electronic Properties of the Carbenes. *J. Am. Chem. Soc.* **2020**, *142*, 12394-12399. (e) Jagannathan, J. R.; Fettinger, J. C.; Shaw, J. T.; Franz, A. K., Enantioselective Si-H Insertion Reactions of Diarylcarbenes for the Synthesis of Silicon-Stereogenic Silanes. *J. Am. Chem. Soc.* **2020**, *142*, 11674-11679.

(29) Reactivity between $\text{Cu}(\text{OAc})_2$ and 2-benzoylpyridine-derived hydrazones has been shown to afford triazole products, presumably via the intermediacy of the corresponding diazo compound: (a) Mori, H. S., K.; Mashito, S.; Matsuoka, Y.; Matsubayashi, M.; Sakai, K. Aerial Oxidation of Some 2-Pyridyl Ketone Hydrazones Catalyzed by Cu^{2+} . Physical Properties of Reaction Products. *Chem. Pharm. Bull.* **1993**, *41*, 1944-1947; (b) Hirayama, T. U., S.; Okada, T.; Tsurue, N.; Okuda, K.; Nagasawa, H. Facile One-Pot Synthesis of [1,2,3,4]Triazolo[1,5-a]Pyridines from 2-Acylpyridines by Copper(II)-catalyzed Oxidative N-N Bond Formation. *Chem. Eur. J.* **2014**, *20*, 4156-4162.

(30) The unique efficacy of 9-azajulolidine in pyridine catalyzed reactions has been observed previous see for select examples: (a) Wong, K.-T. K., S.-Y. Yen, F.-W. Facile synthesis of 9-azajulolidine and its application to post-Ullmann reactions. *Tetrahedron Lett.* **2007**, *48*, 5051-5054; (b) Tsutsumi, T. S., A.; Kasai, T.; Chu, M.; Karanjit, S.; Nakayama, A.; Naba, K. Synthesis and evaluation of 1,1,7,7-tetramethyl-9-azajulolidine (TMAJ) as a highly active derivative of N,N-dimethylaminopyridine. *Tetrahedron Lett.* **2020**, *61*, 152047.

(31) See SI for optimization data. The remaining mass balance was recovered starting material and over-oxidation to benzophenone due to instability of the diazo product under the reaction conditions. During isolation the diazo compound was found to completely decompose to benzophenone and azine on silica, rapid purification on basic alumina afforded isolated material but some decomposition is observed even on this stationary phase.

(32) Wei, B. S., J. C.; Lin, P.; Wilkerson-Hill, S. M.; Fullilove, F. A.; McKinnon, S.; Blackmond, D. G.; Davies, H. M. L. In Situ Kinetic Studies of Rh(II)-Catalyzed Asymmetric Cyclopropanation with Low Catalyst Loadings. *ACS Catal.* **2020**, *10*, 1161-117.

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