Heterogeneous Fe-N-C Catalyst for Aerobic Dehydrogenation of Hydrazones to Diazo Compounds Used for Carbene Transfer

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ABSTRACT: Organic diazo compounds are versatile reagents in chemical synthesis and would benefit from improved synthetic accessibility, especially for larger scale applications. Here, we report a mild method for the synthesis of diazo compounds from hydrazones using a heterogeneous Fe-N-C catalyst, which has Fe ions dispersed within a graphitic nitrogen-doped carbon support. The reactions proceed readily at room temperature using O_2 (1 atm) as the oxidant. Aryl diazoesters, ketones, and amides are accessible, in addition to less stable diaryl diazo compounds. Initial-rate data show that the Fe-N-C catalyst achieves faster rates than a heterogeneous Pt/C catalyst. The oxidative dehydrogenation of hydrazones may be performed in tandem with Rh-catalyzed enantioselective C–H insertion and cyclopropanation of alkenes, without requiring isolation of the diazo intermediate. This sequence is showcased by using a flow reactor for continuous synthesis of diazo compounds.

M-N-C materials, which feature transition-metal ions dispersed within nitrogen-doped graphitic carbon, have been extensively studied as electrocatalysts for the oxygen reduction reaction (ORR) in fuel cells (**Figure 1a**).[1,2] More recently, the same class of catalysts has been explored for thermal aerobic oxidation reactions, using protons and electrons from chemical bonds in organic molecules to promote O_2 reduction, exemplified in alcohol oxidation and oxidative coupling reactions (**Figure 1b**).[3–5] This reactivity should be general, and we postulated that M-N-C catalysts could address other important challenges in synthetic chemistry. Diazo compounds are carbenoid reagents that undergo catalytic cyclopropanation and C–H functionalization reactions, among other useful reactions,[6,7] but their high reactivity introduces safety hazards that complicate their isolation, storage, and large-scale application.[8] Traditional methods to access diazo compounds include Regitz diazo transfer using a sulfonyl azide[9,10] and the Bamford-Stevens base-promoted reaction of tosylhydrazones.[11,12] Oxidative dehydrogenation of hydrazones offers an atom-economical alternative to these methods, but most precedents use undesirable oxidants, such as stoichiometric metal (HgO,[13] Ag_2O,[14] MnO_2,[15] $Pb(OAc)_4$[16]), sulfonium,[17] or hypervalent iodine reagents.[18,19] Recent advances have led to molecular homogeneous catalysts that enable use of more appealing oxidants (O_2, $NaBO_3$)[20–26] or electrochemical oxidation methods.[27] A heterogeneous catalyst could offer significant practical advantages that could support broader use of diazo compounds. Here, we demonstrate that a Fe-N-C catalyst, originally developed as an ORR electrocatalyst, enables aerobic dehydrogenation of hydrazones (**Figure 1c**). Diazo compounds obtained from this reaction may be used directly in enantioselective Rh-catalyzed cyclopropanation and C–H insertion reactions, without isolation or purification.

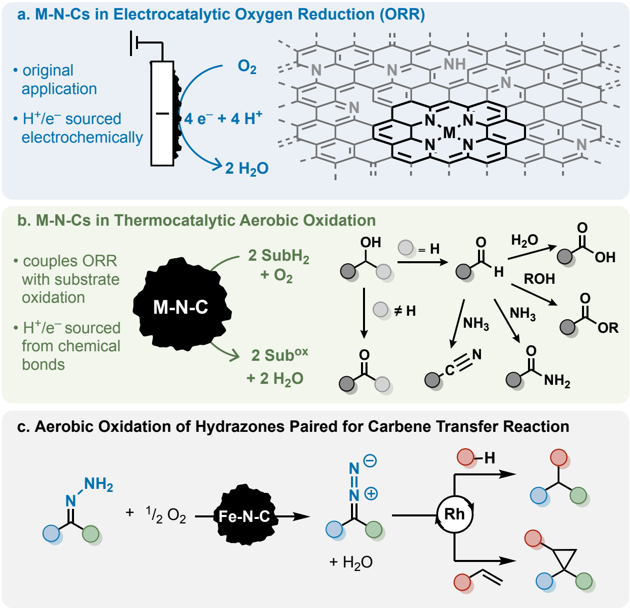
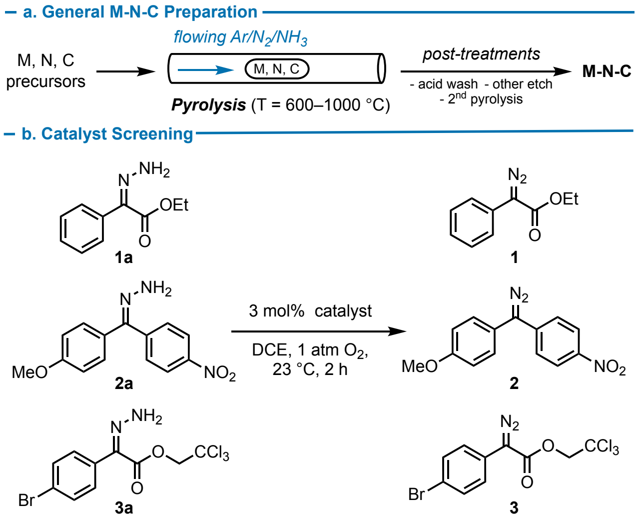


Figure 1. (a) Electrocatalytic oxygen reduction reaction using M-N-Cs and representative catalytic active site. (b) Thermocatalytic aerobic oxidation using M-N-Cs and representative applications. (c) Aerobic oxidation of hydrazones using a Fe-N-C catalyst paired with Rh-catalyzed cyclopropanation of alkenes and C–H insertion.

M-N-C materials are prepared by high-temperature pyrolysis of mixtures of carbon-, nitrogen-, and metal-containing precursors (**Figure 2a**).[28,29] One Fe-N-C ORR electrocatalyst is now available commercially from Pajarito Powder (PAJ-Fe-N-C).[30] We initiated the present study by preparing a series of Co-N-C and Fe-N-C materials, designated Co-ZIF-8-C,[31] Co-Phen-C,[32] Fe-Phen-C,[33] Co-Pc-C,[34] and Fe-Pc-C[35] to reflect the identity of the metal ion (Co or Fe) and the source of nitrogen (ZIF = zeolitic imidazolate framework, Phen = 1,10-phenanthroline, Pc = phthalocyanine; see Section 3 in the Supporting Information for full synthetic protocols). Three representative hydrazones **1a**–**3a** were selected for evaluation under aerobic oxidation conditions using commercially sourced Ru/C, Pt/C, and PAJ-Fe-N-C, in addition to the synthetic M-N-C catalysts (**Figure 2b**). Mild reaction conditions were used to conduct the initial catalyst evaluations: room temperature, 1 atm O_2, and 1,2-dichloroethane (DCE) as the solvent. The noble metal catalysts show modest reactivity in the oxidation of **1a** and **3a**, but negligible reactivity with diarylhydrazone **2a** (entries 1 and 2). Of the synthetic M-N-C catalysts, Fe-Pc-C exhibits the best performance (entries 3–7), including moderate reactivity with **2a**. The PAJ-Fe-N-C catalyst is unique, promoting good reactivity with all three substrates to afford diazo compounds **1–3** in high yields (entry 8).



Entry	Catalyst	% Yield **1**	% Yield **2**	% Yield **3**	
		no DBU	*no DBU*	*no DBU*	*+ 2 mol% DBU*
1	Ru/C	25	5	27	7
2	Pt/C	32	1	29	26
3	Co-ZIF-8-C	3	1	2	7
4	Co-Phen-C	6	11	6	30
5	Fe-Phen-C	8	7	6	23
6	Co-Pc-C	10	4	9	13
7	Fe-Pc-C	25	21	12	21
8	**PAJ-Fe-N-C**	**99**	**99**	**76**	**99**

Figure 2. (a) Schematic representation of the pyrolysis method for preparation of M-N-C materials. (b) Results of hydrazone oxidation with various heterogeneous catalysts (0.05 mmol scale). Yields determined by ^{1}H NMR spectroscopy (int. std. = 1,3,5-trimethoxybenzene). Catalyst loading (3 mol%) is defined with respect to the total metal in each catalyst relative to substrate.

In aerobic oxidation reactions of this type, protons derived from the substrate are used in the reduction of O_2 to water,[36] but many reactions are performed with a Brønsted base to enhance the kinetics of proton transfer. Inclusion of catalytic quantities of the organic base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene; 2 mol%) in the oxidation of **3a** had little or deleterious impact on the reactions with noble catalysts (**Figure 2b**, entries 1–2) but led to improved yields of diazo compound **3** with the M-N-C catalysts (**Figure 2b**, entries 3–8). Nearly quantitative yield of **3** was observed with PAJ-Fe-N-C as the catalyst in the presence of DBU (entry 8). The influence of base in M-N-C-catalyzed oxidation of hydrazones is also evident from kinetic studies. The oxidation of **1a** was examined by initial rate methods using the PAJ-Fe-N-C, Co-Pc-C, and Pt/C catalysts in the absence and presence of 2 mol% DBU (**Figure 3**). PAJ-Fe-N-C and Pt/C show comparable initial rates in the absence of DBU, while Co-Pc-C exhibits negligible reactivity (**Figure 3** inset, blue bars). The initial rates with PAJ-Fe-N-C and Co-Pc-C catalysts increase significantly in the presence of 2 mol% DBU, while the Pt/C-catalyzed reaction is slower (**Figure 3**, green bars). The beneficial effect of DBU is especially prominent with PAJ-Fe-N-C.

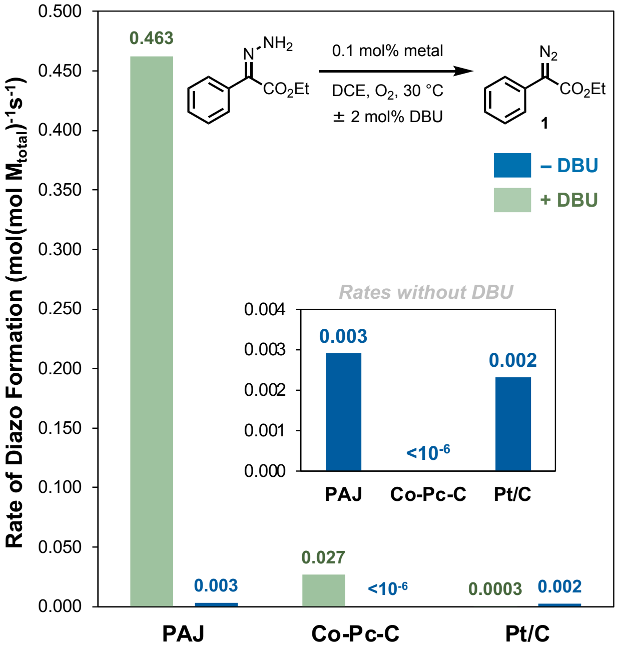


Figure 3. Initial rates of product formation with three different catalysts in the presence (green) and absence (blue) of 2 mol% DBU. Inset shows expansion of rate data obtained in the absence of DBU. The reactions were monitored by UPLC analysis with 1,3,5-trimethoxybenzene as an internal standard.

These results provided a foundation for testing PAJ-Fe-N-C as a catalyst for oxidation of a series of different hydrazones (**Figure 4**). Each of the substrates was first evaluated in the absence of added base, and most reactions proceeded to full conversion within 2 h at room temperature. Good reactivity was also observed with several diaryl hydrazones, which often require more forcing conditions (cf. **2**, **13**, and **14**).[23] With a few substrates, however, only partial conversion was observed in the absence of base (cf. **7** and **10**–**12**), but addition of 2 mol% DBU to these reactions led to high yields of the desired diazo compounds. These two reaction conditions allowed nearly all of the desired diazo compounds to be accessed in excellent yields.

This hydrazone oxidation process was then evaluated in a tandem one-pot sequence, pairing synthesis of the diazo compound with enantioselective carbene-transfer reactions using one of three chiral dirhodium catalysts[37–39] (**Figure 5**). The solvent was changed from DCE to dichloromethane (DCM) for these reactions, reflecting previous reports showing that DCM is the optimal solvent for the Rh-catalyzed reactions.[40]

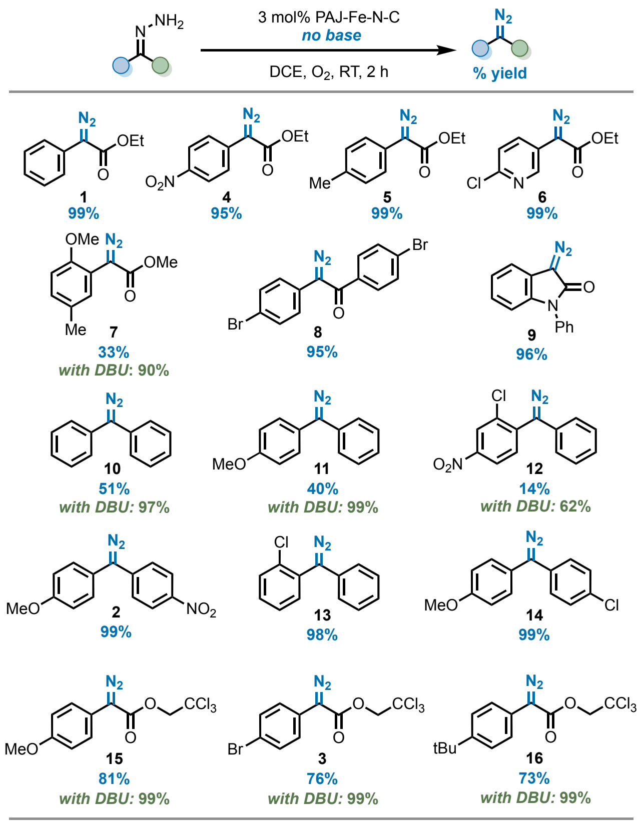
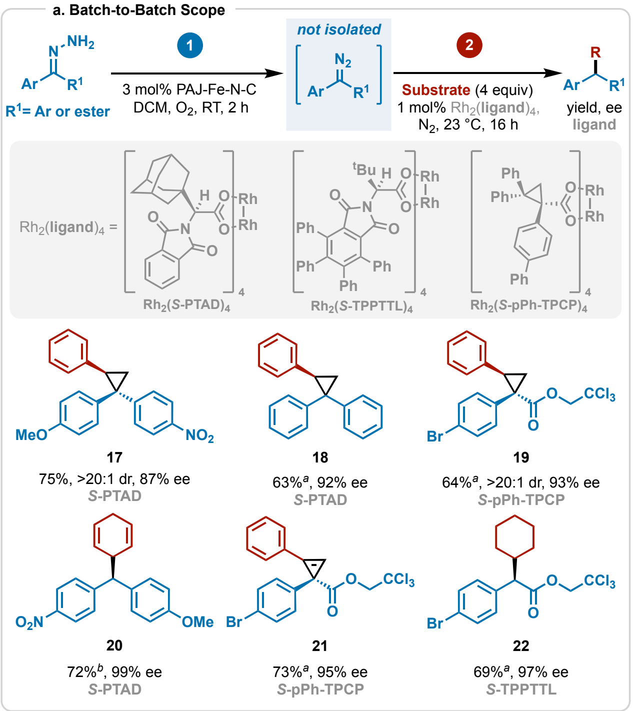


Figure 4. Substrate scope of diazo compounds obtained from PAJ-Fe-N-C-catalyzed aerobic oxidation of hydrazones (0.05 mmol scale). Diazo products were quantified by ^1H NMR spectroscopy (int. std. = 1,3,5-trimethoxybenzene) following filtration of catalyst through a PTFE membrane.

After completion of the hydrazone oxidation reactions, the crude mixture containing the diazo compound and PAJ-Fe-N-C catalyst was sparged with N_2 and added to a solution of substrate and a dirhodium catalyst. Control experiments showed that the PAJ-Fe-N-C catalyst does not impact the Rh-catalyzed reactions (Figure S4). For cases in which catalytic DBU is needed to form the diazo compound, 20 equiv of HFIP (1,1,1,3,3,3-hexafluoroisopropanol) were added to the second step to sequester DBU through hydrogen bonding and prevent its interference with the dirhodium-catalyzed reaction.[41]

The tandem sequence was first evaluated for the synthesis of cyclopropanes (**Figure 5a**). The optimized oxidation conditions were used to form diazo compound **2** and subsequent Rh-catalyzed cyclopropanation afforded **17** in 75% yield and 87% enantiomeric excess (ee). When the same sequence was repeated on 1 mmol scale, the yield increased to 83% while maintaining 87% ee (**Figure 5b**). The formation and reaction of unsubstituted diaryl diazo compound **10** afforded cyclopropane **18** in 63% yield and 92% ee. This sequence was also demonstrated with the donor-acceptor diazo compound **3**, which underwent reactions with styrene and phenylacetylene in 64% yield/93% ee (**19**) and 73% yield/95% ee (**21**) respectively. The former reaction was also performed on 3 mmol scale using lower PAJ-Fe-N-C catalyst loading (1.5 mol%), with no DBU, and with air rather than pure O_2 as the oxidant. The intermediate diazo compound was formed in nearly quantitative yield, and it then underwent Rh-catalyzed cyclopropanation of styrene in 65% yield and 97% ee (**Figure 5b**). No HFIP was required in the second step since DBU was excluded in the hydrazone oxidation reaction. The tandem sequence was also demonstrated in C–H insertion reactions with 1,4-cyclohexadiene and cyclohexane. These reactions exhibit similarly good outcomes, forming **20** and **22** in 72% yield/99% ee and 69% yield/97% ee, respectively.


a. Batch-to-Batch Scope

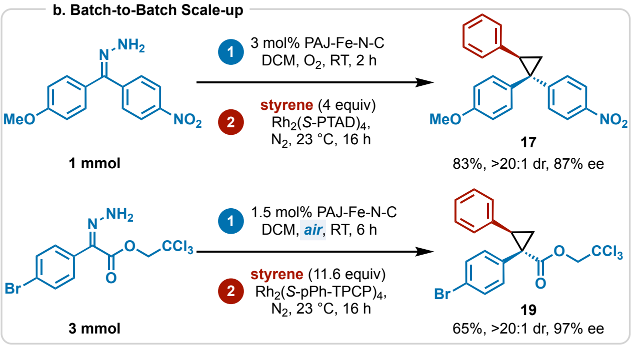

b. Batch-to-Batch Scale-up

Figure 5. (a) Tandem oxidation and cyclopropanation or C–H insertion without workup of diazo intermediate (0.2 mmol scale; isolated yields). ^{a}20 equiv HFIP added in step 2. ^{b}Step 2 performed at –20 °C. (b) Larger scale batch reaction sequences, including the use of air rather than O_2 in step 1 of the preparation of **19**.

Successful identification and demonstration of a heterogeneous catalyst raised the possibility of conducting hydrazone oxidation in a continuous flow process that avoids independent handling of the diazo compound (**Figure 6a**). A packed-bed reactor was constructed from a 1/4" glass tube filled with the PAJ-Fe-N-C catalyst mixed with base-treated silica ($bSiO_2$; 1:9 catalyst:$bSiO_2$ mass ratio) held in place with plugs of glass wool. Use of the $bSiO_2$ ensured good liquid flow through the catalyst bed. Base treatment of the silica ($NaHCO_3$ solution) prevented acid-promoted decomposition of diazo compounds during the reaction (see Section 7 of the Supporting Information for full details of flow reactor design and optimization). The reaction was performed by using an HPLC pump to flow a DCM solution containing 200 mM hydrazone and 4 mM DBU (2 mol%) at 0.1 mL/min, together with flow of O_2 gas at 0.25 mL/min (**Figure 6a**). The gas and liquid streams were separated upon exiting the packed-bed reactor bed. The liquid was collected in a secondary glass column, in which the diazo product solution was sparged with N_2 to remove dissolved O_2 before entering the flask containing the Rh catalyst and substrate for carbene transfer.

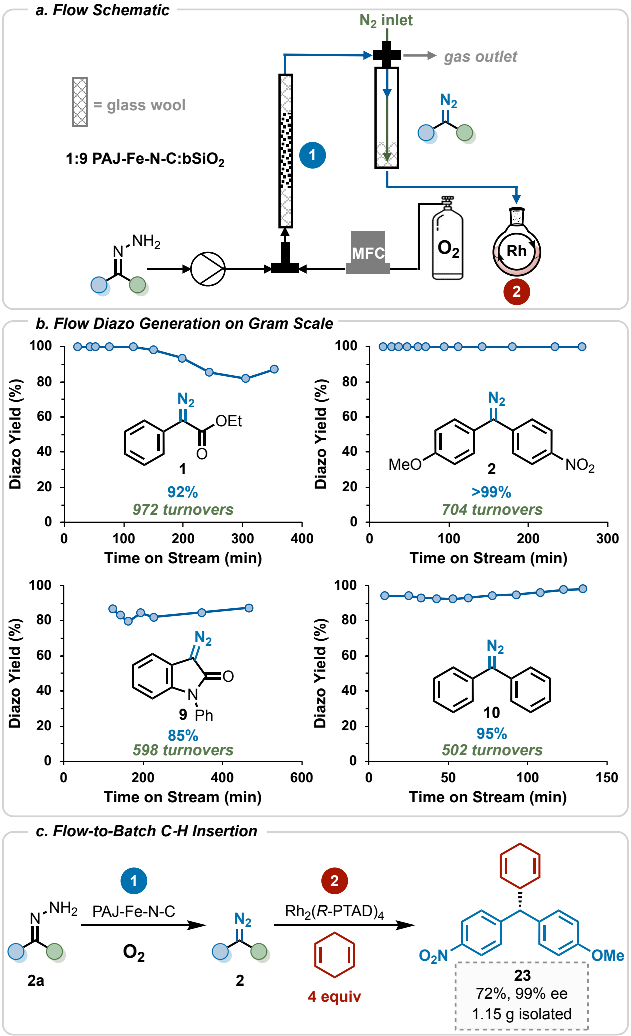


Figure 6. (a) Schematic of flow set-up. MFC = mass flow controller. (b) Time on stream plots for gram-scale flow oxidations: 200 mM hydrazone and 4 mM DBU in DCM at 0.1 mL/min and 0.25 mL/min O_2. (c) Flow-to-batch C–H insertion: 1 mol% $Rh_2(R\text{-PTAD})_4$ (see Figure 5 for structure), 5 equiv HFIP, 4 equiv 1,4-cyclohexadiene under N_2 and maintained at –10 °C.

Four different hydrazones were tested in the flow reactor, packed with the PAJ-Fe-N-C catalyst and $bSiO_2$. Analysis of diazo compound formation by UPLC revealed good steady-state reaction performance and excellent assay yields (85–99%) with donor-acceptor and diaryl hydrazones (**Figure 6b**). The results reflect catalyst turnover numbers of 500-1000 with the Fe-N-C catalyst, on the basis of active-site counts determined by using a recently reported kinetic assay.[42] The continuous-flow oxidation of diaryl hydrazone **2a** to afford the diaryl diazo compound **2** was then paired with Rh-catalyzed carbene insertion into a C–H bond of cyclohexadiene (**Figure 6c**). The solution containing **2** was delivered directly into a flask containing 1,4-cyclohexadiene, 5 equiv HFIP, and $Rh_2(R\text{-PTAD})_4$, without any independent handling of the diazo intermediate. The C–H insertion product **23** was obtained in 72% isolated yield and 99% ee, with respect to the hydrazone **2a**. This result may be compared to the 60% yield/99% ee obtained when using a two-step batch process with isolated diazo compound.[43]

In summary, this work shows that an Fe-N-C heterogeneous catalyst, originally developed as an ORR electrocatalyst for fuel cells, is highly effective for aerobic oxidation of hydrazones to diazo compounds. PAJ-Fe-N-C is the first heterogeneous catalyst shown to be effective for this reaction, and it outperforms noble metal catalysts, such as Pt/C. Numerous donor-acceptor and diaryl hydrazones undergo near-quantitative conversion to the diazo compound, and the crude reaction mixture may be used directly in enantioselective Rh-catalyzed carbene transfer reactions, including cyclopropanation and C–H insertion. The merits of the heterogeneous catalyst are evident from its integration within a pack-bed reactor that enables continuous production of the diazo compound and integration in a tandem process pairing diazo synthesis and Rh-catalyzed carbene transfer.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, kinetic data, and supplementary discussions. This material is available free of charge via the internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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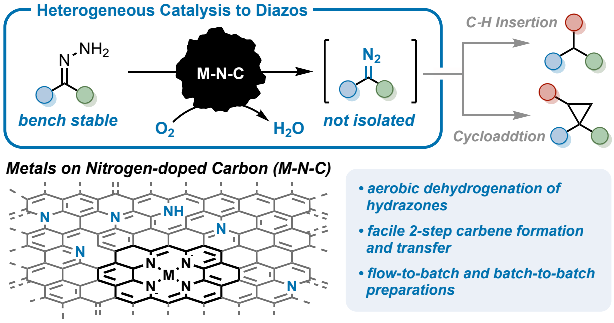
TOC Graphic


Heterogeneous Catalysis to Diazos
N
NH2
bench stable
M-N-C
O2
H2O
N2
not isolated
C-H Insertion
Cycloaddtion
Metals on Nitrogen-doped Carbon (M-N-C)
N
N
NH
N
N
N
N
M
N
N
N
• aerobic dehydrogenation of hydrazones
• facile 2-step carbene formation and transfer
• flow-to-batch and batch-to-batch preparations