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Fe(III)-Catalyzed Aerobic Intramolecular N−N Coupling of Aliphatic Azides with Amines

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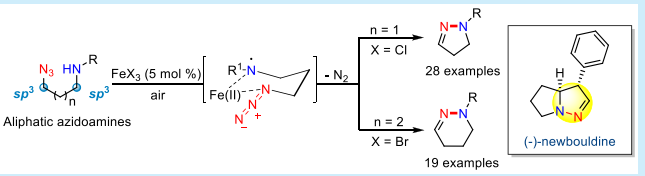
Supporting Information

ABSTRACT: An Fe(III)-catalyzed intramolecular N−N coupling of aliphatic azidoamines that forms diverse five- and six-membered semisaturated diazoheterocycles using air as an oxidant is reported, providing an alternative to hydrazine-based methods. Mechanistic studies suggest that a N-radical induced intramolecular homolytic substitution (S_H2) is involved in ring closure. The power of this N−N bond-forming method is also demonstrated by using it as the final step in a total synthesis of (−)-newbouldine.



Semisaturated heterocycles containing nitrogen−nitrogen (N−N) bonds, such as 2-pyrazolines and tetrahydropyridazines, are ubiquitous in natural products and pharmacologically active agents.[1,2] N−N bonds are most often incorporated from hydrazine.[2c,3] An attractive alternative—intramolecular N−N bond formation—has generally been limited to the formation of aromatic five-membered heterocycles.[5−12] Herein, we describe the first catalytic synthesis of semisaturated five- and six-membered diazo-containing rings from aliphatic azidoamine adducts, employing an Fe(III)-catalyzed intramolecular N−N coupling using air as the oxidant.

Compared to the direct construction of C−C bonds, there are relatively few examples of transition metal-catalyzed or metal-free N−N bond formation,[4] despite the appeal of such a strategy as an atom-economical and straightforward way to prepare diazo compounds. Most intramolecular N−N bond formation methods are limited to the synthesis of aromatic five-membered diazo heterocycles using stabilized aryl or vinyl nitrogen-centered reactive intermediates (e.g., nitrenes, N-radicals, and nitrenium) which are trapped by imines or amides (Figure 1a). For example, copper has been used to build up N−N bonds for the synthesis of aromatic five-membered diazo-heterocycles from benzaldimine substrates.[5] Such heterocycles have also been prepared via N−N formation by oxidative cyclization of an acylnitrenium intermediate from amides with hypervalent iodine.[6] Other achievements include reductive N−N cyclization of *ortho*-nitrobenzaldimines through a phosphine oxide intermediate with organophosphorus[7] or a hydroxylamine intermediate with Sn(II)[8] or Ru(III)/visible light.[9] While thermolysis and photolysis of aryl azides to give nitrene intermediates can also form N−N bonds, they suffer from either harsh reaction conditions or a long reaction time, which limits substrate diversity.[10] Iron- or copper-catalyzed cyclizations of *ortho*-azido benzaldimines can afford aromatic 2*H*-indazoles via planar reactive intermediates.[5a,11,12]

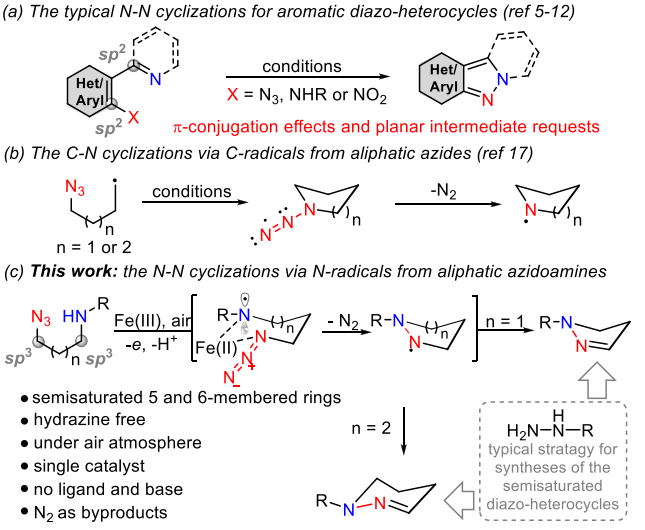


Figure 1. N−N bond formation using aliphatic azidoamines to synthesize semisaturated diazoheterocycles.

The aforementioned established N−N bond-forming methods are incapable of building up semisaturated diazoheterocycles. To overcome this, we envisioned tethering aliphatic azides and amines to achieve intramolecular N−N

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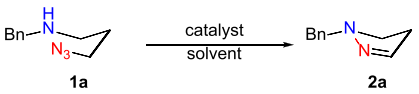
coupling to generate five- or six-membered rings. Although aliphatic azides cannot be the proper and stable entrance to the generation of nitrenes due to lack of stabilization through vicinal conjugation,[13−15] they have been used as alkyl radical acceptors leading to aminyl radicals,[16] affording 5-*exo* and 6-*exo* C−N cyclization products (Figure 1b). Considering that secondary alkyl amines can convert into a N-centered radical through successively removing one electron and one proton under proper oxidative conditions with transition metals or added oxidants,[17] we proposed that a N-centered radical stemming from an amine precursor could attack an azide and achieve N−N formation. However, the single-electron transfer (SET) to an amine is usually followed by generation of an imine,[18] which poisons transition metals. We envisioned skirting the above problems through *in situ* formation of a cyclometal intermediate (Figure 1c). This coordination could serve to stabilize an N-centered radical, thereby suppressing the oxidation of amines into imines.

To validate the catalytic system for *in situ* metal complex formation and N−N cyclization, we initially investigated the reaction of benzyl protected linear γ-azidoamine **1a** in the presence of various transition metal catalysts (Table 1). First, we evaluated catalysts widely utilized for the generation of metal nitrenes from aryl azides. No N−N cyclization product was observed in the presence of $Rh_2(OAc)_4$, $Rh_2(O_2CCF_3)_4$, or CoTPP at 100 °C in sealed tubes for 2 h (entries 1, 2, and 3). $Cu(OAc)_2$ and CuI also failed to form the desired N−N bond (entries 5 and 6). To our delight, **1a** underwent a desired N−N cyclization in the presence of 20 mol % Fe(TPP)Cl(III) (entry 4) that was accompanied by a conversion of the C−N_3 single bond into a C−N double bond to afford 2*H*-pyrazoline product **2a** in 11% yield. Further study identified iron(III) salts as superior agents for the formation of the desired N−N cyclization products, including $FeCl_3$, $FeBr_3$, $Fe(acac)_3$, and $Fe(OTf)_3$, among which 20 mol % of $Fe(acac)_3$ gave 28% yield in refluxing THF under an air atmosphere (entry 15). To our surprise, a lower loading of $FeCl_3$ (5.0 mol %) in the presence of air as an oxidant at 100 °C in a sealed tube led to a 75% yield (entry 11). A nearly identical yield was obtained with 1 atm of O_2 (entry 13). Reactions using dichloroethane or toluene induced lower yields. Alternative oxidants, such as $Cu(OAc)_2$ or $PhI(OAc)_2$ (entries 16 and 17), as well as various N- or P-containing ligands were ineffective (entry 18).

Using our optimized conditions, the scope of the intramolecular N−N bond formation of aminoazides was evaluated. As shown in Scheme 1, a variety of alkyl and aryl amines were found to be amenable to five-membered ring formation. 3-Azidobenzylamines with various arene substituents were efficiently converted into pyrazolines (**2a**−**2g**) in moderate yields, and benzyl group cleavage was not observed. The acetal group of **2g** was also stable under the reaction conditions. In

Table 1. Selected Optimization Data on Iron-Catalyzed N−N Cyclization

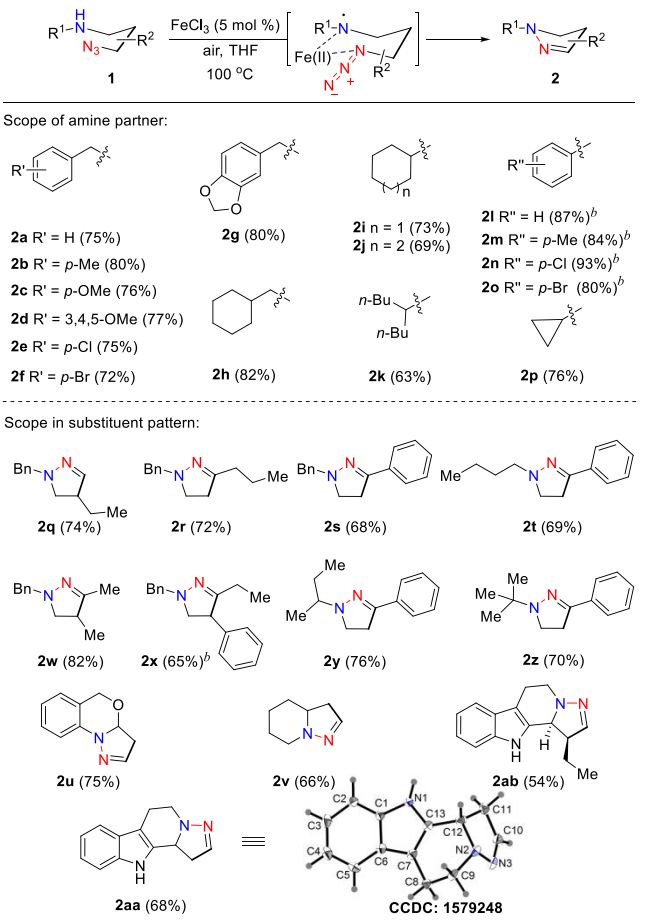


1a **2a**

entry[a]	catalyst (equiv)	solvent	temp (°C)/time (min)/atmosphere	yield (%)[b]
1	$Rh_2(OAc)_4$ (0.2)	DCE	100/120/argon	n.d.
2	$Rh_2(CF_3CO_2)_4$ (0.2)	DCE	100/120/argon	n.d.
3	CoTPP (0.2)	DCE	100/120/argon	n.d.
4	Fe(TPP)Cl (0.2)	THF	100/120/argon	11
5	$Cu(OAc)_2$ (0.2)	DCE	100/120/argon	n.d.
6	CuI (0.2), TMEDA (0.2)	DCE	100/120/argon	n.d.
7	$FeBr_2$ (0.2)	THF	100/120/argon	trace
8	$FeCl_3$ (0.2)	THF	rt/24 h/argon	12
9	$FeCl_3$ (0.2)	THF	reflux/30/argon	14
10	$FeBr_3$ (0.2)	THF	reflux/30/argon	10
11	**$FeCl_3$ (0.05)**	**THF**	100/30/**air**	**75**
12	$FeCl_3$ (0.05)	PhMe	100/120/air	20
13	$FeCl_3$ (0.05)	THF	100/30/O_2	76
14	$Fe(acac)_3$ (0.2)	THF	100/30/air	28
15	$Fe(OTf)_3$ (0.2)	THF	100/30/air	22
16	$FeCl_3$ (0.2), $PhI(OAc)_2$ (0.5)	THF	100/120/argon	n.d.
17	$FeCl_3$ (0.2), $Cu(OAc)_2$ (0.5)	THF	100/120/argon	n.d.
18	$FeCl_3$ (0.2), 4,4′-bipyr (0.2)	THF	100/120/argon	n.d.

[a]Conditions: **1a** (0.2 mmol), solvent (0.125 M), sealed tube (25 mL). [b]Isolated yield of **2a** after purification by flash column chromatography. DCE, 1,2-dichloroethane; TPP, tetraphenylporphyrin; n.d., not detected.

Scheme 1. Scope of Fe(III)-Catalyzed N−N Cyclization for Construction of Five-Membered Diazoheterocycles[a]



[a]Conditions: **1** (0.5 mmol), $FeCl_3$ (0.025 mmol), air (1 atm), THF (4 mL), 100 °C in sealed tube (100 mL), 0.5 h; isolated yields are reported with flash column chromatography (average of two runs). [b]Reaction time was prolonged to 1 h.

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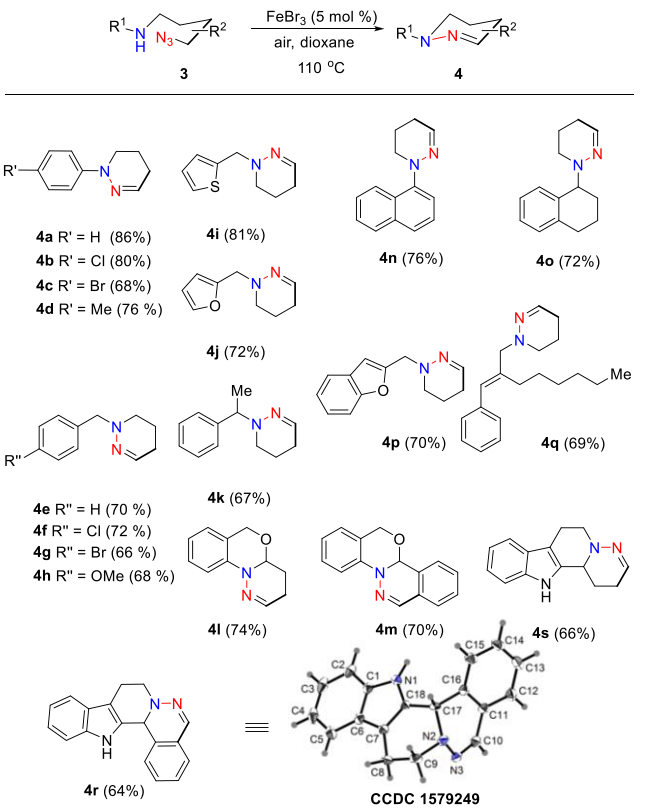
addition, aliphatic amine adducts also cyclized in good yield (**2h**–**2k**). In comparison, **2j** and **2k** converted minimally, which may be a result of steric hindrance about the amine due to the alkyl side chains. Furthermore, substrates bearing electron-donating or electron-withdrawing N-aryl groups were smoothly converted into the desired products (**2l**–**2o**) in higher yields than either aliphatic or benzylic amines.

We next investigated the scope of the reaction using γ-azidoamine substrates bearing substituents within their alkyl linkers (as shown in Scheme 1). First, we focused on γ-azido benzylamines varying in their β- or γ-substituent and found methyl, ethyl, propyl, and phenyl groups to be well tolerated (**2q**, **2r**, **2s**, **2w**, and **2x**). Among these examples, benzylic secondary azides (as in **1s** and **1t**), which are typically Lewis acid sensitive, proved to be robust. The transformation even worked for more sterically hindered *sec*- and *tert*-butyl groups, affording the corresponding products **2y** and **2z** in moderate yields. Additionally, 1,3-benzoxazine **1u** and piperidine **1v** afforded [6,6,5]- and [6,5]-fused products **2u** and **2v** in 75% and 66% yields. For tryptamine derivatives, cyclization onto the aliphatic amines afforded tetracyclic products **2aa** and **2ab**, again in good yields. X-ray diffraction analysis confirmed the structure of **2aa**. Critically, in all cases, the new five-membered rings resisted dehydrogenation to unsaturated heterocycles.

Next, we evaluated whether six-membered-ring formation could be achieved by using δ-azidoamine substrates (Scheme 2). We began by optimizing reactions of δ-azidoamines containing either aryl or benzyl amines and found that $FeBr_3$ in dioxane at 110 °C efficiently catalyzed intramolecular N–N bond formation to afford the corresponding tetrahydropyridazines (**4a**–**4h**, **4k**, **4n**, and **4o**). To the best of our knowledge, this intramolecular N–N formation approach for construction of the six-membered heterocycles using azides is unprecedented. Heterocycle-substituted azidoamines, including those bearing thiophene, furan, and benzofuran heterocycles, were also smoothly converted to products **4i**, **4j**, and **4p**, despite their sensitivity to Lewis acids. Cinnamylamine-derived product **4q** was synthesized in 69% yield; the conjugated olefin did not interrupt the cyclization. Similarly, several fused cyclic products, particularly **4l**, **4m**, **4r**, and **4s**, were constructed in synthetically useful yields from the heterocyclic precursors. Single-crystal X-ray diffraction confirmed the polycyclic structure of **4r**.

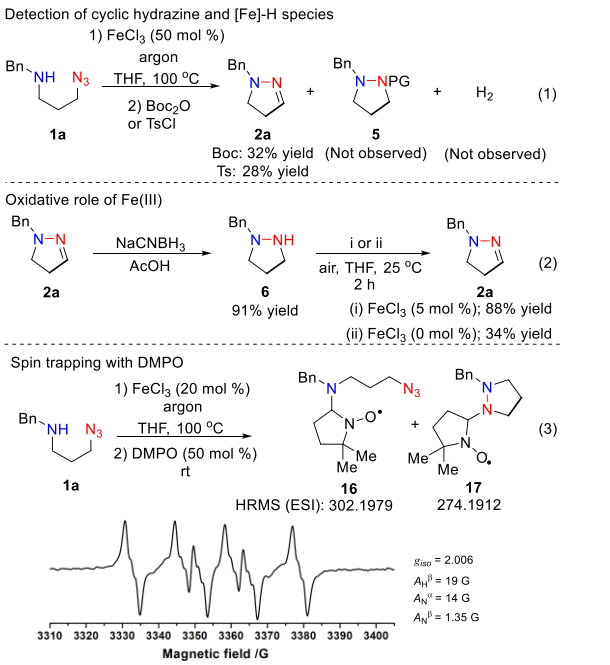
Our subsequent efforts focused on the elucidation of reactive intermediates to aid our interpretation of the mechanism (Scheme 3). Neither the protected product (**5**) nor H_2 were detected by GC under an argon atmosphere with 50 mol % $FeCl_3$; the major product obtained was pyrazoline **2a** (eq 1). This suggests that no iron hydride species is generated, and the reaction does not proceed through a cyclic hydrazine in the absence of O_2 as the oxidant. Next, after reduction of **2a** with $NaBH_3CN$, the resulting saturated tetrahydropyrazole **6** was oxidized at room temperature by either the $FeCl_3$/air system or air only (eq 2). The latter afforded pyrazoline **2a** in relatively low yield compared to the reaction in the presence of $FeCl_3$, indicating that (1) oxidative H-abstraction to produce imines under the optimized reaction conditions is favored by the synergistic effects of $FeCl_3$ and O_2 and (2) the high reaction temperature must be more crucial for the N–N coupling step than oxidation to the imine. Next, we were curious if the reaction proceeds by an initial single-electron transfer from the amine to Fe(III).[18a,19] When **1a** was subjected to modified reaction conditions (20 mol % $FeCl_3$ and subsequent 50 mol % DMPO (5,5-dimethyl-1-pyrroline-*N*-oxide)), the radical trapping products **16** and **17** were observed with an ESI high-

Scheme 2. Scope of Fe(III)-Catalyzed N–N Cyclization for Construction of Six-Membered Diazoheterocycles[a]



[a]Conditions: **3** (0.5 mmol) and $FeBr_3$ (0.025 mmol) in air (1 atm), and dioxane (4 mL) at 110 °C in a sealed tube (100 mL) for 0.5 h. Isolated yields of products purified by flash column chromatography are reported (average of two runs).

Scheme 3. Control Experiments



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resolution mass spectrum (eq 3). Furthermore, electron paramagnetic resonance (EPR) experiments of **1a** as substrate were performed. Strong radical signals were observed with an average *g* value of 2.00609 after addition of DMPO, implying that $FeCl_3$ reacts with substrate to produce N-centered radicals. Taken together, these experiments indicate that the ring-closure step could proceed by an intramolecular homolytic substitution (S_H2) from an N-centered radical to the azide to form N−N bond.

To further unravel the mechanism, a DFT calculation investigation into the Fe(III)-catalyzed N−N coupling of **1a** as the model reaction was carried out (see the Supporting Information for details). Combining with the control experiments, a possible reaction mechanism was proposed in Figure 2. Starting from the γ-azidoamine **1a**, the six-membered

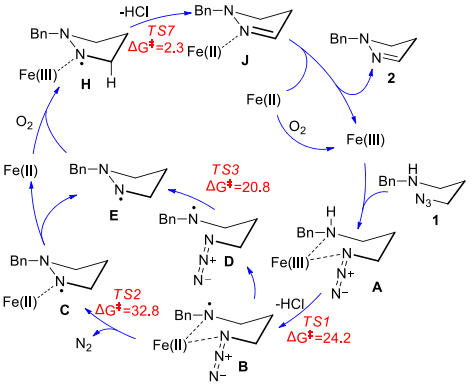
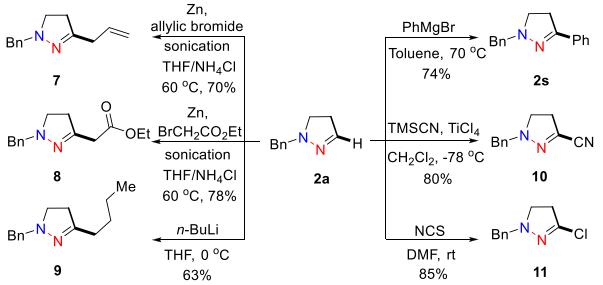


Figure 2. Proposed mechanistic cycle.

complex (**A**) can be generated by coordination of Fe to the internal N atom of azide, releasing −18.1 kcal/mol. Then, a concerted single electron oxidation by Fe(III) and deprotonation of amine with a Cl anion give rise to a neutral N-centered radical (**B**), which is 14.1 kcal/mol higher in free energy with a barrier of 24.2 kcal/mol (via **TS1**). When the N-radical of **B** attacks the internal N of azide, an intramolecular homolytic substitution (S_H2) occurs. It undergoes a concerted loss of N_2 without any intermediate, providing **C** directly. This process (via **TS2**) requires an energy barrier of 32.8 kcal/mol, which is 12.0 kcal/mol higher than **TS3** to form **E** from **D**. However, dissociation of Fe from **B** to give **D** is endergonic by 22.8 kcal/mol. A combined energy comparison prefers the Fe coordinated pathway from **B** to **C**. Fe(II) is detached and further oxidized to Fe(III) by dioxygen. Fe(III) can coordinate with **E** again to afford **H**, which is armed for H-abstraction. Conversion of intermediate **H** to **J** by a second H-abstraction to give imine via oxidation to Fe(III) was calculated to be highly exergonic by 22.8 kcal/mol via transition state **TS7** ($\Delta G^{\ddagger}$ = 2.3 kcal/mol). The intermediate **J** finally undergoes dissociation of Fe(II) to afford desired product **2**. Fe(III) can be regenerated by dioxygen.

With the importance of the semisaturated diazoheterocycles as the useful bioactive moiety and the versatile synthetic building blocks, the N−N coupling products afford great potential for their further derivatizations. For example, when **2a** reacted with various metal-containing nucleophiles, such as allylic zinc bromide, ethyl α-bromozincacetate, *n*-BuLi, and PhMgBr, the corresponding formal C−H functionalization products were observed after quenching of reactions under an air atmosphere, presumably occurring via a nucleophilic addition/oxidative H-abstraction cascade process (Scheme 4). The formation of imine might be caused by a more reactive

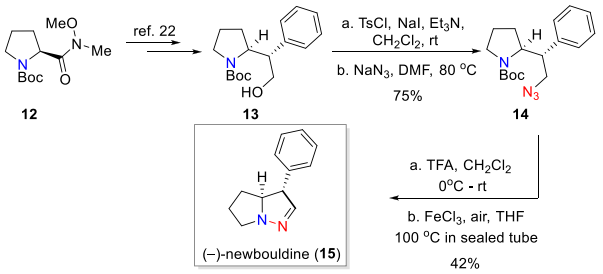
Scheme 4. Further Transformations of Pyrazolines via Formal C−H Functionalizations



secondary amino species bonded to a metal center that is more easily oxidized by air. We also utilized TMSCN to cyanide pyrazoline in the presence of Lewis acid $TiCl_4$.[20] When treated with *N*-chlorosuccinimide, 4-chloropyrazoline **11** was synthesized via a chloronium ion induced oxidation.

Finally, to further illustrate the utility of this method, we were able to apply the N−N cyclization strategy process to the synthesis of (−)-newbouldine (**I**), an alkaloid possessing potent neurological effects (Scheme 5).[2a,21] Grignard reaction,

Scheme 5. Total Synthesis of (−)-Newbouldine Using a Late Stage N−N Cyclization Strategy



Wittig reaction, and subsequent hydroboration−oxidation from the readily available proline precursor **12** proceeded in high yield to construct **13**;[22] azidation of **13** afforded the protected azidoamine **14** in 75% yield (dr = 1.5:1). After Boc deprotection, our N−N cyclization was utilized to construct the [5,5]-bicyclic framework and access (−)-newbouldine in 42% yield. The ability to synthesize diazo-heterocyclic fragments using this method should prove useful in the synthesis of drug candidates and natural products.

We have developed the first synthetic tool for efficient construction of highly functionalized five- and six-membered semisaturated diazo-heterocycles through Fe-catalyzed intramolecular N−N bond formation using aliphatic aminoazides. A series of synthetic applications of the resulting pyrazoline have been described for preparation of valuable derivatives. The catalytic method was also showcased as a key step in the synthesis of (−)-newbouldine. Efforts are underway to extend this method for the construction of more complex heterocycles.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01396.

Experimental procedures, product characterization, copies of NMR spectra, computational data, and crystallographic data for **2aa** and **4r** (PDF)

Accession Codes

CCDC 1579248−1579249 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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