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Intramolecular Fe(II)-Catalyzed N−O or N−N Bond Formation from Aryl Azides

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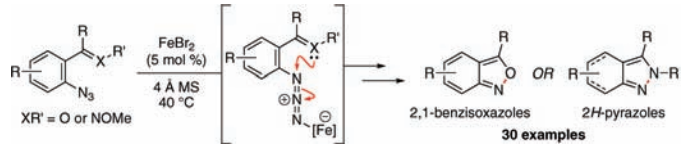
ABSTRACT



Iron(II) bromide catalyzes the transformation of aryl and vinyl azides with ketone or methyl oxime substituents into 2,1-benzisoxazoles, indazoles, or pyrazoles through the formation of an N−O or N−N bond. This transformation tolerates a variety of different functional groups to facilitate access to a range of benzisoxazoles or indazoles. The unreactivity of the *Z*-methyloxime indicates that N-heterocycle formation occurs through a nucleophilic attack of the ketone or oxime onto an activated planar iron azide complex.

Despite the prevalence of nitrogen−heteroatom bonds in biologically active N-heterocycles, methods that form these bonds remain rare. 2,1-Benzisoxazoles[1,2] or indazoles[3,4] typically originate from starting materials with pre-existing N−O or N−N bonds such as oximes, nitrile oxides, or hydrazines. Direct construction of the N−O[5] or N−N[6] bond provides an attractive alternative approach to these *N*-heterocycles. Surprisingly, there are no prior examples of transition-metal-catalyzed routes to these bonds even though such complexes promote the oxidation[7,8] or imination[9] of sulfides. Since we established that benzimidazoles could be produced from *N*-aryl imines with *ortho*-azido substituents upon exposure to $FeBr_2$ (Scheme 1),[10] we were curious if nitrogen−heteroatom bond formation could be achieved by transposing the *ortho*-heteroatom substituent from the α-position to the β-position. While thermolysis of **3** affords the new nitrogen−heteroatom bond,[5a,b,6a−c] the high temperature

(1) Recent reviews, see: (a) Elguero, J. *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 4, p 167. (b) Stadlbauer, W. *Sci. Synth.* **2002**, *12*, 243. (c) Smalley, R. K. *Sci. Synth.* **2002**, *11*, 337.

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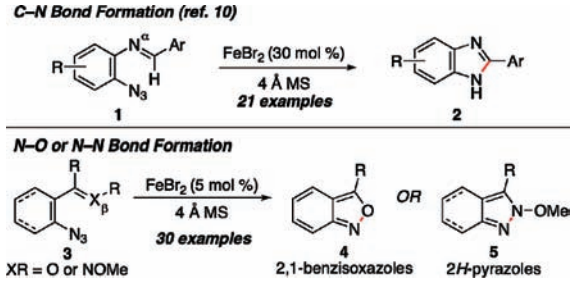
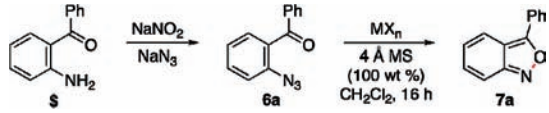
Scheme 1. Iron(II) Bromide-Catalyzed *N*-Heterocycle Formation



limits the functional group tolerance of the reaction. Herein, we report that iron(II) bromide catalyzes the formation of N−O or N−N bonds to transform azides **3** into 2,1-benzisoxazoles **4** or pyrazoles **5** under markedly benign conditions.

To achieve transition-metal-catalyzed nitrogen−heteroatom bond formation, the reactivity of 2-azidobenzophenone toward a variety of transition metal complexes was investigated (Table 1). This aryl azide is available in one step

Table 1. Optimization of Metal-Catalyzed N−O Bond Formation



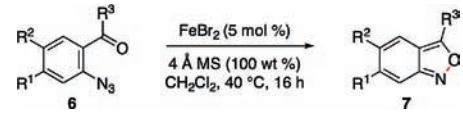
entry	catalyst	mol %	temp (°C)	yield (%)[a]
1[b]	none	n.a.	120	92
2	$Rh_2(O_2CC_3F_7)_4$	5	25	trace
3	CuCl	10	25	no reaction
4	$Cu(OTf)_2$	10	25	trace
5[b]	$RuCl_3{\cdot}H_2O$	10	25	trace
6	ZnI_2	10	25	no reaction
7	$Fe(acac)_2$	10	25	8
8	$FeCl_3$	10	25	20
9	$FeCl_2$	10	25	97
10	$FeBr_2$	10	25	97
11	$FeBr_2$	5	40	99
12[b]	$FeBr_2$	5	40	90

[a] As determined using ^{1}H NMR spectroscopy. [b] No molecular sieves were added.

from commercially available 2-aminobenzophenone.[11] While a plethora of methods have been reported to generate an electrophilic nitrogen atom from aryl azides,[12] we found that only iron salts promoted 2,1-benzisoxazole **7a** formation at significantly reduced temperatures. Screening other metal complexes known to decompose azides—including Cu(I) and Cu(II) salts—did not result in nitrogen−oxygen bond formation.[13] Our data show that the oxidation state of iron affected the efficiency of the reaction because lower conversions were observed when more Lewis acidic iron(III) salts were used. If the reaction temperature was increased to 40 °C, the catalyst loading could be reduced to 5 mol %. The low catalyst loading contrasted with benzimidazole formation, which required 30 mol % $FeBr_2$ for satisfactory conversions.[10] Molecular sieves, while not required, were added to eliminate any adventitious water.

With these optimized conditions, the scope and limitations of iron(II)-catalyzed N−O bond formation were examined (Table 2).[14] 2,1-Benzisoxazole formation depended on the

Table 2. Scope of Fe(II)-Catalyzed N−O Bond Formation



entry	**6**	R^1	R^2	R^3	yield (%)[a]
1	a	H	H	Ph	98
2	b	Me	H	Ph	89
3	c	OMe	H	Ph	57
4	d	CF_3	H	Ph	trace
5	e	H	Cl	Ph	90
6	f	H	NO_2	Ph	dec.[b,c]
7	g	H	H	4-ClC_6H_4	78
8	h	H	H	4-BrC_6H_4	86
9	i	H	Cl	2-FC_6H_4	91
10	j	H	Cl	2-ClC_6H_4	97
11	k	H	H	Me	83
12	l	H	H	*i*-Pr	72[b,d]
13	m	H	H	*c*-C_6H_{11}	74[b]
14	n	H	H	H	no reaction

[a] After SiO_2 chromatography. [b] 10 mol % of $FeBr_2$ used. [c] 10% aniline formed. [d] Isomerization to the 1*H*-benzisoxazole tautomer occurred upon SiO_2 purification.

electronic nature of the azide. While the reaction tolerated a range of R^1- or R^2-substituents, strong electron-withdrawing groups are incompatible with the reaction conditions (entries 1−7). The effect of the R^3-substituent on the reaction was briefly surveyed. 2,1-Benzisoxazoles were made from substrates bearing aryl or alkyl R^3-groups (entries 8−14). Our data suggest that a carbon R^3-substituent is necessary to achieve N−O bond formation because aldehydes, such as **6n**, did not react. Varying the electronic nature of *o*-azidobenzaldehyde **6n** (R^1 = OMe or CF_3) did not result in benzisoxazole formation.

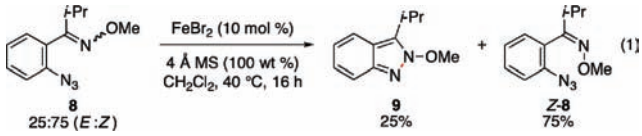
(11) Many 2-amino-substituted aryl ketones are commercially available. Alternatively, the substrates were synthesized from 2-aminobenzaldehyde derivatives. See the Supporting Information for the details of their synthesis.

(12) For reviews, see: (a) Katsuki, T. *Chem. Lett.* **2005**, *34*, 1304. (b) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (c) Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Piangiolino, C. *Coord. Chem. Rev.* **2006**, *250*, 1234.

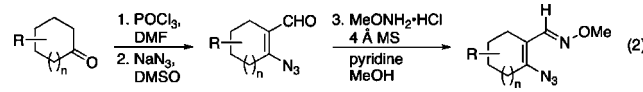
(13) The use of other transition metal complexes resulted in attenuated conversions. Please refer to the Supporting Information for more details.

(14) To a mixture of aryl azide **6** (0.1 mmol), 100% w/w of crushed 4 Å molecular sieves, and metal salt (5−10 mol %) in a conical vial with Teflon septum was added 0.250 mL of solvent. The resulting mixture was heated, and after 16 h, the heterogenous mixture was filtered through SiO_2. The filtrate was concentrated in vacuo. Purification by MPLC afforded the desired product.

To determine if our method could be used to form N−N bonds, aryl azide **8**, bearing a β-nitrogen atom in the tether, was screened (eq 1). In addition to testing the possibility of N−N bond formation, this substrate would also allow an examination of the stereochemical requirements of the reaction. When a mixture of **8** (25:75, *E*:*Z*) was exposed to $FeBr_2$, the *E*-isomer reacted quantitatively to form 2*H*-indazole **9**, while *Z*-**8** was entirely recovered from the reaction mixture.[15] Isomerization of *Z*-**8** was never observed, even when the reaction conditions were substantially altered.[16]



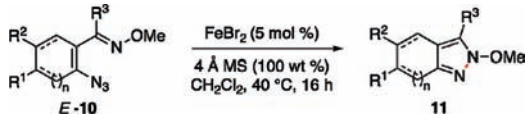
Iron(II)-catalyzed N−N bond formation from *E*-methyl oximes **10** exhibited a broader substrate scope than our benzisoxazole study (Table 3).[17] Biaryl ketoximes (**10a**−**10f**) bearing either electron-donating or electron-withdrawing R^1- and R^2-substituents were cleanly transformed into **11** (entries 1−6). The reaction also tolerated aryl-, alkyl-, and hydrogen R^3-substituents (entries 7−11). As with **7m**, indazole **11h**, which contained a secondary alkyl substituent, isomerized to the 1*H*-aromatic product upon exposure to SiO_2 (entry 9). The identity of the imine nitrogen substituent affected the reaction outcome. While methyl ketoximes were competent substrates, no reaction was observed for ketoximes. The reaction was not limited to aryl azide substrates: trisubstituted pyrazoles **11m**−**11p** could be accessed from vinyl azides upon exposure to 5 mol % of $FeBr_2$ (entries 12−16). Vinyl azides **10m**−**10p** are readily synthesized from the cycloalkanone via a three-step procedure (eq 2).[18]

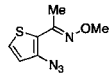
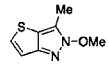
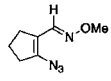
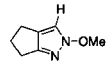
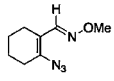
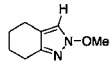
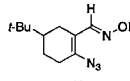
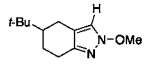
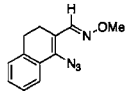
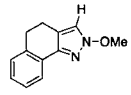


The reactivity of diazides **10q** and **10r** showcases the mildness of our Fe(II) process (Scheme 2). Whereas thermolysis of either diazide produced a thick tar containing trace amounts of indazole (<5%) and aldoximine, exposure of diazide **10q** or **10r** to $FeBr_2$ cleanly afforded the 4- or 6-azido-substituted indazole. In contrast to the thermal process, the second azide group remained intact in our Fe(II)-catalyzed process.

N-Heterocycles **7** or **11** can be elaborated into other synthetically valuable products (Scheme 3). SmI_2-mediated reduction of the N−O bond in benzisoxazole **7a** in the presence of acetophenone or acetone formed quinolines **12a** and **12b**.[19] Palladium-catalyzed hydrogenolysis of the N−OMe bond present in **11q** and **11p** produced 1*H*-indazole **13** and

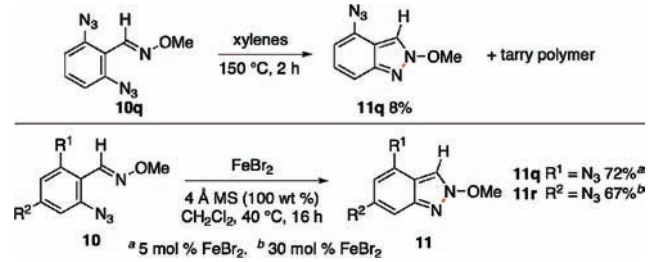
Table 3. Scope of Fe(II)-Catalyzed N−N Bond Formation



entry	**10**	R^1	R^2	R^3	yield (%)[a]
1	a	H	H	Ph	99
2[b]	b	Me	H	Ph	58[c]
3	c	OMe	H	Ph	44[c]
4	d	H	NO_2	Ph	80[c,d]
5[b]	e	H	Cl	2-ClC_6H_4	99
6[b]	f	H	Cl	2-FC_6H_4	63[c,d]
7	g	H	H	Me	72[c,d]
8[b]	h	H	H	*c*-C_6H_{11}	80[c,e]
9	i	OMe	H	H	76[c]
10	j	H	H	H	84
11	k	SO_2Me	H	H	97
		E-**10**		**11**	yield (%)[a]
12[b]	l				99
13	m				91
14	n				86
15	o				86
16	p				79

[a] After SiO_2 chromatography. [b] Reaction performed using an *E*-/*Z*-mixture of **10**. [c] The remainder of the reaction mixture was unreacted **10**. [d] 10 mol % of $FeBr_2$ used. [e] Isomerization to the 1*H*-benzisoxazole tautomer occurred upon SiO_2 purification.

Scheme 2. Comparison of the Reactivity of Diazides **10**



(15) *Z*-Oximes were reported to be unreactive in the metal-free thermal reaction. See ref 6c.

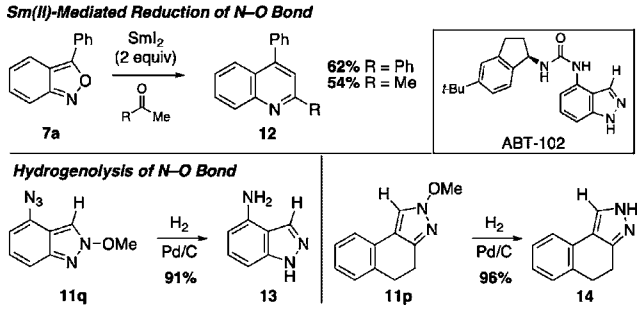
(16) For a complete description of the isomerization conditions screened, refer to the Supporting Information.

(17) *E*-**10** (or a mixture of *E*-, *Z*-**10**), 100% w/w of crushed 4 Å molecular sieves, and metal salt (5−10 mol %) were added to a conical vial, which was sealed with a PTFE septum, followed by the addition of CH_2Cl_2 as solvent. The resulting mixture was heated to 40 °C for 16 h. The heterogeneous mixture was purified by MPLC to afford the product.

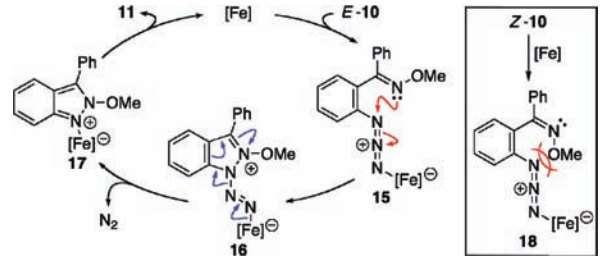
(18) Tabyaoui, B.; Aubert, T.; Farnier, M.; Guilard, R. *Synth. Commun.* **1988**, *18*, 1475. Refer to the Supporting Information for the synthesis of **10m**−**10p**.

(19) For a related SmI_2-mediated pyridine synthesis, see: Fan, X.; Zhang, X.; Zhang, Y. *Heteroatom Chem.* **2005**, *16*, 637.

Scheme 3. Functionalization of *N*-Heterocyclic Products



Scheme 4. Potential Mechanism for 2*H*-Indazole Formation



2*H*-pyrazole **14**.[20] The vanilloid receptor (TRPV1) antagonist, ABT-102,[21] contains 1*H*-indazole **13**. Abbott Pharmaceuticals developed ABT-102 as a clinical candidate for the treatment of chronic pain.

While several mechanisms could account for *N*-heterocycle formation,[22] the reactivity differences between the *E*- and *Z*-oxime isomers of **10** suggest that N−X bond formation occurs through a planar reactive intermediate (Scheme 4).[23] Because the corresponding aniline was unreactive, we assign this reactive intermediate to be iron(II)−azide complex **15**. This intermediate could be produced from *E*-**10** by coordination of the iron(II) catalyst to the terminal *N*-atom of the azide.[24] Planarization then triggers a nucleophilic attack of the oxime on the activated azide to form the N−N bond.[22,25] Extrusion of N_2 from **16** followed by dissociation of the iron catalyst would provide the 2*H*-indazole product. The origin of the *Z*-isomer's inertia can be inferred from examination of the iron azide complex **18**: in addition to the destabilizing steric interactions produced upon planarization of **18**, the lone pair of electrons on the oxime are oriented in the wrong direction for N−N bond formation.

In conclusion, we have demonstrated that iron(II) bromide readily forms N−O or N−N bonds from a range of *ortho*-azide-substituted aryl ketones or *E*-methyl oximes. Future experiments will determine if a contiguous π-system is required for Fe(II)-catalyzed azide decomposition and if any of the reactive intermediates can be trapped by dipolarophiles to produce additional C−C or C−N bonds.

Acknowledgment. We are grateful to the National Institutes of Health NIGMS (R01GM084945), Petroleum Research Fund administered by the American Chemical Society (46850-G), and the University of Illinois at Chicago for their generous support. We also thank Prof. L. Anderson (UIC) for insightful discussions and Mr. Furong Sun (UIUC) for mass spectrometry data.

Supporting Information Available: Complete experimental procedures and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Lower yields of 1*H*-indazoles were obtained when alternative reduction protocols were attempted.

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