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Iron-Catalyzed Direct Olefin Diazidation via Peroxyester Activation Promoted by Nitrogen-Based Ligands

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ABSTRACT: We herein report an iron-catalyzed direct diazidation method via activation of bench-stable peroxyesters promoted by nitrogen-based ligands. This method is effective for a broad range of olefins and *N*-heterocycles, including those that are difficult substrates for the existing olefin diamination and diazidation methods. Notably, nearly a stoichiometric amount of oxidant and TMSN₃ are sufficient for high-yielding diazidation for most substrates. Preliminary mechanistic studies elucidated the similarities and differences between this method and the benziodoxole-based olefin diazidation method previously developed by us. This method effectively addresses the limitations of the existing olefin diazidation methods. Most notably, previously problematic non-productive oxidant decomposition can be minimized. Furthermore, X-ray crystallographic studies suggest that an iron-azide–ligand complex can be generated in situ from an iron acetate precatalyst and that it may facilitate peroxyester activation and the rate-determining C–N₃ bond formation during diazidation of ustrained olefins.

Keywords: iron catalyst, peroxyesters, olefins, N-heterocycles, diazidation, diamination.

Fe^{ll} catalyst/ligand $R^{1} = R^{2} + Q^{1} + TMSN_{3} = COM (1.2 equiv)$ $R^{3} = 1.2 - 1.4 equiv (2.4 - 2.5 equiv) = 0.2 + 0.2$ R^3 Peroxyester Activation R¹, R², R³, R⁴: alkyl or aryl Promoted by Nitrogen-Based Ligands

Vicinal primary diamines are incorporated in a large number of small-molecule pharmaceuticals and biological probes; therefore, extensive efforts have been devoted to the development of selective and general olefin diamination methods, and a variety of powerful methods have been invented.¹ However, there are still significant synthetic challenges that cannot be fully addressed by these methods. These challenges include: a) it is still difficult to directly convert aliphatic isolated olefins, especially internal olefins, to vicinal primary diamines; b) methods for selective diamination of highly functionalized olefins have remained underdeveloped; and c) direct diamination of *N*-heterocycles to afford vicinal primary diamines for complex-alkaloid synthesis has been under-explored.²

Alternatively, both *stoichiometric*³ and *catalytic*^{4–5} olefin diazidation methods have emerged with unique value. These methods complement the olefin diamination methods and provide a convenient approach to producing synthetically important vicinal primary diamines that are otherwise difficult to obtain. Although an array of olefin diazidation methods have been reported to date,^{3–5} the vast majority of them are predominantly restricted to certain limited types of olefins.^{3,4c-d} Furthermore, many of them involve the usage of super-stoichiometric amount of NaN₃ in acidic media. Additionally, selective diazidation methods for functionalized *N*-heterocycles have been under-developed.⁶

In 2015, we reported an iron-catalyzed direct diazidation method for a broad range of olefins, in which an iron catalyst activates TMSN₃ in the presence of bench-stable benziodoxole **1a** to achieve direct olefin diazidation (Scheme 1).^{4a} This reaction occurs at room temperature with low catalyst loading and it is effective for a wide variety of olefins, including those that are incompatible with the existing methods.³ Notably, the *anti-selectivity* for cyclic olefins can be

modulated by iron catalysts (dr up to >20:1). Coupled with facile reduction, this method readily provides an array of valuable vicinal primary diamines.



Scheme 1. Iron-catalyzed olefin diazidation with benziodoxole 1a and the proposed mechanistic working hypothesis

The preliminary mechanistic analysis has revealed that $TMSN_3$ may reversibly convert the insoluble benziodoxole **1a** to azidoiodinane **1b**, and then to a transient iodine(III)–diazide species **1c**, with which an iron catalyst may be oxidized to a high-valent iron-azide species that promotes the stepwise olefin diazidation (Scheme 1).^{4a–b} A variety of control experiments corroborate that the iron–ligand complexes are involved in the rate-, and diastereoselectivity-determining C–N₃ bond forming step in diazidation of unstrained olefins.^{4a}

Identification of the high-valent iron-azide species as a possible reactive intermediate has inspired us to develop a new method that significantly improves upon the reported method. There are two outstanding challenges in this benziodoxole-based diazidation method.



First, *in the absence of an olefin*, an iron catalyst completely decomposes benziodoxole **1a** together with TMSN₃ in 3 h (eq 1a), presumably through the iron-promoted decomposition of

iodine(III)–diazide species 1c.⁷ In contrast, 1a is stable towards TMSN₃ in the absence of an iron catalyst in CH₂Cl₂ (eq 1b).⁷ *This competing pathway can be particularly problematic for substrates with low reactivity since an excess amount of oxidant* 1a *would be necessary to achieve a synthetically useful yield*. Some of these problematic substrates include electronically deactivated allylic esters and carbamates. Therefore, a new catalytic method has yet to be developed such that this non-productive oxidant-decomposition pathway may be suppressed or even eliminated.

Next, an excess amount of TMSN₃ (3.6–4.0 equiv) is often applied to achieve high yields in the aforementioned iron-catalyzed olefin diazidation, in order to effectively activate benziodoxole 1a.^{4a} A stoichiometric amount of TMSN₃ (2.0–2.5 equiv) often led to incomplete conversion for certain substrates in the aforementioned method, especially aliphatic isolated olefins. Ideally, nearly a stoichiometric amount of TMSN₃ should be sufficient for a more sustainable and efficient olefin diazidation method.

Herein, we report a new iron-catalyzed direct diazidation method via nitrogen-based ligandpromoted activation of bench-stable peroxyesters that effectively address the limitations of the previously developed method (Scheme 2). In this method, *nearly a stoichiometric amount of oxidant and TMSN₃ are sufficient for effective diazidation of a broad range of olefins and Nheterocycles at room temperature.* Notably, a variety of previously difficult substrates are compatible with this new method, some of which include allylic esters and carbamates, β -pinene, highly functionalized indoles, pyrroles that are prone to rapid re-aromatization, as well as β , γ unsaturated ketones.

Fe^{ll} catalyst/ligand ⁱPrOH (1.2 equiv) TMSN₃ room temperature *dr* up to >20:1 1.2-1.4 equiv 2.4 equiv R², R³, R⁴: alkyl or aryl

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Scheme 2. Iron-catalyzed olefin diazidation via nitrogen-based ligand-promoted peroxyester activation

Compared with the benziodoxole-based method, preliminary mechanistic studies revealed that the previously problematic non-productive oxidant-decomposition pathway can be effectively suppressed with this new method. X-ray crystallographic studies further suggest that an iron-azide–ligand complex can be generated in situ from an iron acetate precatalyst and it may facilitate peroxyester activation and the rate-determining C–N₃ bond formation during diazidation of unstrained olefins.

Table 1. Catalyst discovery for indene diazidation via nitrogen-based ligand-promoted

peroxyester activation

	Fe(OAc) ₂ + 3a + TMSN ₃ 1.2 equiv 2.4 equiv CH ₂ Cl; (22 22 °C	(5 mol %) mol %) 2/MeCN 2/1) 2/2 cquiv) 2/MeCN 3:1) 92% yield dr: 10:1
^t Bu ^{_0} _0	L _{Ph}	^t Bu ^{−O} −O [⊥] Ar
3a	3b	Ar: 2,4-Cl ₂ -phenyl 3c
	Me Me ^{win} L2 Me	le L3 Me
entry ^a	variation from the standard condition	observations ^{b,c}
1	in the absence of L1	<5% yield <5% conversion
2	in the absence ⁱ PrOH	48% yield, <i>dr</i> : 10:1 59% conversion
3	replace ⁱ PrOH with H ₂ O	52% yield, <i>dr</i> : 10:1 65% conversion in 4 h
4	replace 3a with 3b	75% yield, <i>dr</i> : 6.7:1 87% conversion in 4 h
5	replace 3a with 3c	87% yield, <i>dr</i> : 10:1 95% conversion in 1 h
6	replace L1 with L2	6% yield, <i>dr</i> : 16:1 <i>ca.</i> 10% conversion
7	replace L1 with L3	8% yield, <i>dr</i> . 7:1 <i>ca.</i> 16% conversion
8	replace Fe(OAc) ₂ with Fe(NTf ₂) ₂ (2.5 mol %)	42% yield, <i>dr</i> . 4.2:1 68% conversion
9	replace Fe(OAc) ₂ with Fe(NTf ₂) ₂ (2.5 mol %) and replace L1 with L2	52% yield, <i>dr</i> . 3.5:1 87% conversion

^{*a*}Reactions were carried out under N₂ and subsequently quenched with saturated Na₂CO₃ solution. ^{*b*}Conversion was measured by ¹H NMR analysis. ^{*c*}Isolated yield. Standard safety precautions about handling TMSN₃ should be taken; see SI for details.

Bench-stable *tert*-butyl peroxyesters have been extensively applied in a variety of oxygenatom transfer reactions;⁸ however, room-temperature olefin diazidation via ligand-promoted peroxyester activation using nearly a stoichiometric amount of azide source has not been developed.⁹ To explore the possible new reactivity through iron catalysis, we select indene (**2**) as a model substrate in catalyst discovery for both synthetic and mechanistic considerations (Table

1). Extensive exploration of a range of iron catalysts and ligands revealed that the $Fe(OAc)_2$ bidentate ligand L1 complex effectively activates bench-stable *tert*-butyl peroxybenzoate **3a** in the presence of TMSN₃ (2.4 equiv) and ^{*i*}PrOH (1.2 equiv), and that it catalyzes efficient indene diazidation with excellent *dr* at room temperature (Table 1).

There are several key observations that are mechanistically important (Table 1). First, the ironcatalyzed peroxyester activation and olefin diazidation are enabled by nitrogen-based ligands: *in the absence of a ligand, essentially no reaction was observed and both 2 and 3a were fully recovered* (entry 1). Next, mild proton donors are critical for catalyst turnover and ^{*i*}PrOH leads to a more efficient reaction than H₂O (entries 2–3). Furthermore, the iron catalyst can activate a range of peroxyesters (entries 4–5): a more electron-deficient peroxyester **3c** leads to a faster reaction and distinct *dr* values were observed with different peroxyesters (**3b** vs **3c**). These observations suggest that the corresponding carboxylate ligand, presumably generated through the iron-mediated O–O bond cleavage, may be involved in the *dr*-determining transition state.

To our surprise, the Fe(OAc)₂-tridentate ligand L2 complex, an effective catalyst in our previously reported, benziodoxole-based olefin diazidation method,^{4a} is almost inactive in this reaction: only a small amount of product was observed (entry 6, 6% yield, *dr*: 16:1). Furthermore, another Fe(OAc)₂-tridentate ligand L3 complex also suffers from low reactivity (entry 7). Interestingly, both the Fe(NTf₂)₂-L1 and Fe(NTf₂)₂-L2 complexes catalyze a rapid reaction; however, the desired indene diazide 4 was isolated in only moderate yields (entries 8–9). These results suggest that there may be mechanistic nuances between the Fe(OAc)₂- and Fe(NTf₂)₂-catalyzed reactions.

$$\begin{array}{c} Fe^{ii} \text{ catalyst} \\ \text{bidentate or tridentate} \\ \text{igand} \\ \text{'Bu} \xrightarrow{\text{O}} Ph \\ \textbf{2.0 equiv} \\ \text{recovery of 3a} \end{array} \begin{array}{c} 90-95\% \\ \text{recovery of 3a} \end{array} (2)$$

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Most notably, *in the absence of an olefin*, the vast majority of 3a is recovered under the reaction condition (eq 2),⁷ which suggests that *the non-productive oxidant decomposition has been minimized with this new method*.

Upon the discovery of active iron catalysts, we explored this method with a range of unfunctionalized olefins (Table 2). First, we evaluated olefins with electron-rich allylic C–H bonds which tend to undergo C–H azidation.¹⁰ We observed that both the Fe(OAc)₂–L1 and Fe(NTf₂)₂–L2 complexes are effective for allylsilane diazidation; however, the Fe(NTf₂)₂–L2 catalyst promotes a more rapid reaction with low catalyst loading (entry 1). It is noteworthy that a slight excess of peroxyester **3a** (1.4 equiv) is used to ensure reaction reproducibility since a strong Lewis-acidic Fe(NTf₂)₂ catalyst is applied. Allylbenzene, a substrate prone to undergo direct C–H azidation, is selectively converted to the corresponding diazide (entry 2). We also observed that this method is effective for isolated olefins, including mono-substituted, 1,1-disubstituted, and *trans*-di-substituted olefins (entries 3–5). Notably, the iron-catalyzed diazidation of (+)-camphene diastereoselectively affords the camphene diazide with excellent *dr* (entry 6, *dr* >20:1).¹¹

Since norbornane diamines are valuable synthetic building blocks and their previous syntheses are less-straightforward,¹² we evaluated norbornene in this iron-catalyzed diazidation and discovered that the $Fe(OAc)_2$ –L1 complex catalyzes norbornene diazidation with a good overall yield, albeit in moderate *dr* (entry 7). Gratifyingly, a facile reduction–*N*-Boc protection procedure furnishes the readily separable *N*-Boc norbornane diamines **6a** and **6b** in an excellent overall yield (eq 3).



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$R^1 \xrightarrow{R^2} R^2$	+ + TMSi 'Bu ^{-O} OPh 1.2–1.4 equiv 2.4–2.5 c	N ₃ Fe ^{II} catalyst/ligand /PrOH (1.2 equiv) equiv CH ₂ Cl ₂ /MeCN, 22 °C	R^3 R^1 R^2
entry ^a	olefins	diazidation products	yield ^b
1 ^c	TIPS		81%
2 ^c	Ph	PhN ₃	70%
3°	C ₁₀ H ₂₁	C ₁₀ H ₂₁ N ₃ N ₃	83%
4 ^c	Me C ₇ H ₁₅	Me N ₃ C ₇ H ₁₅ N ₃	86%
5 ^c	C ₅ H ₁₁ Me	C_5H_{11} $\xrightarrow{N_3}$ Me N_3 $dr. 1.3:1$	88%
6 ^{<i>d</i>}	Me	Ma Me Me	87%
7 ^d	A	$\int_{I = 1 \\ I = 1 \\$	81%
8 ^d	Ph	Ph N ₃	82%
9 ^d	Me Ph	Me N ₃ Ph N ₃	86%
10 ^d	Ph	Ph N ₃ Me N ₃ dr: 1.4:1	92%
11 ⁴	Ph	$Ph \xrightarrow{\mathbb{N}_{3}}_{\mathbb{N}_{3}} Ph dr. 2:1$	89%
12 ^{d,e}		N ₃ <i>dr</i> : 10:1	92%
13 ^d	\bigcirc	N ₃ <i>dr.</i> 12:1	82%
14 ^d	Ph	Ph N ₃ N ₃	81%
15 [°]	C ₆ H ₁₃	$\begin{array}{c} N_{3} \\ C_{6}H_{13} \\ + \\ N_{3} \\ C_{6}H_{13} \\ \end{array} $	78%

^{*a*}Reactions were carried out under N₂ unless stated otherwise. ^{*b*}Isolated yield. ^{*c*}Fe(NTf₂)₂ (5 mol %), L2 (5 mol %), ^{*t*}BuOOBz (1.4 equiv), TMSN₃ (2.5 equiv), ^{*i*}PrOH (1.2 equiv). ^{*d*}Fe(OAc)₂ (10

mol %), **L1** (10 mol %), ^{*t*}BuOOBz (1.2 equiv), TMSN₃ (2.4 equiv), ^{*i*}PrOH (1.2 equiv). ^{*e*}Catalyst loading (5 mol %).

This method also proves compatible with styrenyl olefins. We observed that the Fe(OAc)₂–L1 complex catalyzes high-yielding diazidation of styrene, α , and β -methyl styrenes, as well as *trans*-stilbene (entries 8–11). Furthermore, the same catalyst also promotes diazidation of indene and dihydronaphthalene with excellent diastereoselectivity (entries 12–13).

Both 1,2- and 1,4-allylic primary diamines are important building blocks in synthesis; however, expedient synthesis of 1,4-allylic primary diamines through direct 1,4-diene diamination has been difficult.¹³ Likewise, methods for vicinal diamination of the terminal olefin in a 1,4-diene for primary diamine synthesis have also been under-developed.¹⁴ To achieve expedient synthesis of these allylic primary diamines, we explored the iron-catalyzed diazidation with 1,3-dienes (entries 14–15). We observed that the Fe(OAc)₂–L1 complex catalyzes vicinal diazidation of a phenyl-substituted 1,3-diene and that the Fe(NTf₂)₂–L2 complex rapidly catalyzes alkyl-substituted 1,3-diene diazidation to afford a 1:1 mixture of 1,2- and 1,4-diazides that are in equilibrium, presumably through a facile allylic azide rearrangement.¹⁵ A standard reduction–*N*-Boc protection procedure can convert the diazide mixture **7a/b** to readily separable 1,2- and 1,4-*N*-Boc-diamines **8a** and **8b** (eq 4).¹⁵



With the success of this new method for selective diazidation of unfunctionalized olefins, we subsequently evaluated a wide variety of *N*-heterocycles as well as highly functionalized olefins (Table 3).

 Table 3. Iron-catalyzed peroxyester activation for diazidation of N-heterocycles and highly

 functionalized olefins

2				
3	B^1 R^2	ö	Fe ^{ll} catalyst/ligand N ₃	R ¹
4	``)=/``	+ $t_{Bu} - 0$ + TMSN ₃	[/] PrOH (1.2 equiv)	\mathbf{x}^{R^2}
5	R ³	1.2–1.4 equiv 2.4–2.5 equi	V CH ₂ Cl ₂ /MeCN, 22 °C	N ₃
6	entry ^a	olefins	diazidation products	yield ^b
7			N ₃	
8	1 ^c			81%
9		N Troc	N_{N}	0170
10		Me	Troc dr>20:1	
11	20	WIE (VIE	Me	
12	2		N_3	78%
13		Troc	Troc <i>dr</i> >20:1	
14			N3 NHCO ₂ Me	
15	$3^{c,d}$			76%
16		N Boc	N Boc $dr > 20:1$	
17		500	D00 U/ 20.1	
18	∧ c.e.f	CO ₂ H	∧ ^N 3 CO ₂ Me	
19	4		$\left(\sum_{n} \right) - N_3$	74%
20			Boc <i>dr</i> >20:1	
21		<u> </u>	N ₃	
22	5 ^c			85%
23				
24			1roc <i>ar</i> . 12:1	
25	6 ^c			0.00/
26	Ū	N Boc	N_3 "" N_3 Boc $dr > 20:1$	0270
27				
28		Me Me	N ₃ Me Me	
29	7 ^c	Methodac	Me	72%
30			N ₃	
31		0	0 I	
32	8 ^c	Me	Me N ₃	67%
33			dr. 1:1	
34		 Me	Me N ₃	
35		Mo Mo O	N₃ Me Me O	
36	9^g			76%
37		Me • • • H	$N_3 dr. 1:1$	
38				
39	10 ^c	Ŭ "		84%
40		Phr 🗸 📎	Ph VV	
41		0	N ₃ O	
42	11 ⁰		Ph	72%
43		Ph Y Olvie	■ <i>dr</i> : 1.6:1 N ₃	1270
44		0	Q №3	
45	4.07	NN NN	$N \sim N_3$	01%
46	125			5170
47			М	
40 40	13 ^{c,e,f}	∕∕со₂н		73%
49 E0		2	CO ₂ Me	
5U E1			Na	
51	14 ^h	BzO	BzO N3	85%
52			* *	
5 5	a ch	TrocHN	N ₃	770/
54 FF	15''			11%
22				

^{*a*}Reactions were carried out under N₂ unless stated otherwise. ^{*b*}Isolated yield. ^{*c*}Fe(NTf₂)₂ (5 mol %), ^{*t*}BuOOBz (1.4 equiv), TMSN₃ (2.5 equiv), ^{*i*}PrOH (1.2 equiv). ^{*d*}10 mol % Catalyst was applied. ^{*e*}Neither ^{*i*}PrOH nor other proton donor was applied. ^{*f*}MeI (5.0 equiv), K₂CO₃ (3.0 equiv). ^{*g*}Fe(OAc)₂ (10 mol %), L1 (10 mol %), ^{*t*}BuOOBz (1.2 equiv), TMSN₃ (2.4 equiv), ^{*i*}PrOH (1.2 equiv). ^{*h*}Fe(NTf₂)₂ (10 mol %), L2 (10 mol %), ^{*t*}BuOOBz (3.0 equiv), TMSN₃ (4.0 equiv).

We discovered that both *N*-Troc indole and 3-methyl *N*-Troc indole are excellent substrates and the corresponding *trans*-diazides were isolated as a single diastereomer (entries 1–2).⁹ We further observed that the iron catalyst is sufficiently functional group-tolerant such that tryptamine carbamate, indole propionic acid, and *N*-Troc dihydroquinoline are all readily converted to the corresponding *trans*-diazides with excellent *dr* (entries 3–5). Interestingly, the Fe(NTf₂)₂–L2 complex also catalyzes a previously difficult 1,4-selective *N*-Boc pyrrole diazidation, affording a *trans*-pyrrol diazide with excellent *dr* (entry 6, *dr* >20:1).¹⁶

Highly functionalized terpenes are important building blocks for organic synthesis; however, selective terpene diazidation has been difficult since redox-labile functional groups are less-compatible with the vast majority of the existing diazidation methods. Therefore, we further explored this iron-catalyzed method with a range of complex terpenes. We observed that a more electron-rich olefin at the distal position in geranyl acetate can be preferentially functionalized, affording a geranyl diazide (entry 7). Likewise, two olefinic moieties within (–)-carvone can be differentiated and the azido-group is selectively transferred to the less electron-deficient olefin (entry 8). Notably, the labile aliphatic aldehyde group in (\pm)-citronellal is compatible with the method without detrimental aldehyde oxidation (entry 9). Furthermore, a β , γ -unsaturated ketone can readily undergo diazidation without olefin isomerization (entry 10). Moreover, this method is effective for both electron-deficient methyl cinnamate and an electron-rich enamide (entries 11–12). It is also compatible with a carboxylic acid functional group without lactone formation (entry 13).

Multi-functional vicinal diamino alcohols and tri-amines are valuable building blocks for organic synthesis; however, diamination methods for allylic esters and carbamates have not been developed.^{17,18} Additionally, electronically deactivated allylic esters and carbamates present low reactivity under the standard reaction condition in our previously reported method. As a result, we explored the new method with these challenging substrates and discovered that the $Fe(NTf_2)_2$ –L2 complex catalyzes high-yielding diazidation of these electronically deactivated substrates (entries 14–15). A straightforward reduction–protection sequence can thereby afford the functionalized vicinal diamino alcohol 10 and tri-amine 12 (eqs 5 and 6).



The unique synthetic strength of this iron-catalyzed method has inspired us to probe for its mechanistic details with a series of control experiments and to elucidate the similarities and differences between this olefin diazidation method and the previously reported, benziodoxole-based method.^{4a}



Scheme 3. Mechanistic experiments to probe for the intermediacy of a carbo-radical species

^{*a*}Fe(NTf₂)₂ (10 mol %), **L2** (10 mol %), **3a** (1.4 equiv), TMSN₃ (2.5 equiv), ^{*i*}PrOH (1.2 equiv), TEMPO (1.0 equiv); ^{*b*}Fe(OAc)₂ (10 mol %), **L1** (10 mol %), **3a** (1.2 equiv), TMSN₃ (2.4 equiv), ^{*i*}PrOH (1.2 equiv), TEMPO (1.0 equiv); ^{*c*}Fe(NTf₂)₂ (5 mol %), **L2** (5 mol %), **3a** (1.4 equiv), TMSN₃ (2.5 equiv), ^{*i*}PrOH (1.2 equiv); ^{*d*}Fe(OAc)₂ (10 mol %), **L1** (10 mol %), **3a** (1.2 equiv), TMSN₃ (2.4 equiv), ^{*i*}PrOH (1.2 equiv); ^{*d*}Fe(OAc)₂ (10 mol %), **L1** (10 mol %), **Ja** (1.2 equiv), TMSN₃ (2.4 equiv), ^{*i*}PrOH (1.2 equiv).

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First, TEMPO radical was introduced in the iron-catalyzed dodecene (13) diazidation and a TEMPO-addition product 14 was observed when either $Fe(NTf_2)_2$ or $Fe(OAc)_2$ was used as a catalyst (Scheme 3). Next, we evaluated a substituted vinylcyclopropane 15 with this iron-catalyzed method and isolated the ring-opening product 1,5-diazide 16 in excellent yields with either iron catalyst (Scheme 3). *These results suggest that azido radical is likely involved in the first C–N₃ bond forming step, which may initiate radical addition to an olefin and afford a carbo-radical species.*

After the first C–N₃ bond formation, the second C–N₃ bond forming step can proceed through azido group transfer to either a carbo-radical or a carbocation species. In order to differentiate these two mechanistic possibilities, we explored diazidation of (-)- β -pinene 17 (Scheme 4). Notably, the exocyclic olefin of (-)- β -pinene can be selectively 1,2-difunctionalized using both iron catalysts, which exclusively affords a vicinal diazide 18 with excellent *dr* (Scheme 4, *dr* >20:1). Facile reduction and protonation of 18 furnishes diaminium salt 19.



Scheme 4. Iron-catalyzed regio- and diastereo-selective diazidation of (-)- β -pinene

^{*a*}Fe(NTf₂)₂ (5 mol %), **L2** (5 mol %), **3a** (1.4 equiv), TMSN₃ (2.5 equiv), ^{*i*}PrOH (1.2 equiv); ^{*b*}Fe(OAc)₂ (10 mol %), **L1** (10 mol %), **3a** (1.2 equiv), TMSN₃ (2.4 equiv), ^{*i*}PrOH (1.2 equiv); ^{*c*}Pd/C (10 wt. %) in MeOH, 12 h, then *p*-TsOH·H₂O; ^{*d*}Fe(OAc)₂ (20 mol %), **L1** (20 mol %), **3a** (1.2 equiv), TMSN₃ (2.4 equiv), ^{*i*}PrOH (1.2 equiv), TEMPO (0.5 equiv).

To our surprise, neither a ring-contraction nor a ring-fragmentation product (**20a** or **20b**) was detected. Since ring-contraction from the (-)- β -pinene scaffold has been well-precedented in carbocation-mediated reactions,¹⁹ *the absence of 20a suggests that the second C–N₃ bond formation likely proceeds through a carbo-radical instead of a carbocation species.* Additionally, the lack of the ring-fragmentation product **20b** suggests that the rate of the second C–N₃ bond C–N₃ bond formation is faster than the one of carbo-radical fragmentation.

Unlike dodecene (Scheme 3), the diazidation of highly strained (-)- β -pinene in the presence of TEMPO radical affords both the TEMPO-addition product **21** and the diazidation product **18**, *which suggests that the second C*– N_3 *bond forming step is not rate-limiting for this highly strained substrate*.



Scheme 5. Control experiments to determine the rate-limiting step for diazidation of unstrained olefins

^{*a*}Fe(NTf₂)₂ (5 mol %), **L2** (5 mol %), **3a** (1.4 equiv), TMSN₃ (2.5 equiv); ^{*b*}1 M aq. H₂SO₄, 15 min; ^{*c*}Fe(OAc)₂ (10 mol %), **L1** (10 mol %), **3a** (1.2 equiv), TMSN₃ (2.4 equiv); ^{*d*}Fe(OAc)₂ (10 mol %), **L1** (10 mol %), **3c** (1.2 equiv), TMSN₃ (2.4 equiv).

In order to determine which C–N₃ bond forming step is rate-limiting for *unstrained olefins*, we carried out a few control experiments (Scheme 5). First, we evaluated (*Z*)-hex-3-en-1-ol **22a** in the Fe(NTf₂)₂-catalyzed diazidation with **3a** and identified a significant amount of the

isomerization product *(E)*-hex-3-en-1-ol **22b** along with the diazide **23** within 5 min. Notably, both **22a** and **22b** were converted to diazide **23** in a stereo-convergent manner in 2 h. Interestingly, when the Fe(OAc)₂–L1 complex was used as the catalyst, only the isomerization product **22b** was observed. Notably, the Fe(OAc)₂ catalyst promotes a faster reaction with a more electron-deficient oxidant **3c**: both **22b** and **23** were observed within 2 h. *These results suggest that the second C–N₃ bond forming step is rate-limiting in the iron-catalyzed diazidation of unstrained olefins.*



Scheme 6. Control experiments to probe for mechanistic insights of azido-radical generation

^{*a*}**1a** (1.2 equiv), TMSN₃ (4.0 equiv), 2 h; ^{*b*}**3a** (1.2 equiv), TMSN₃ (2.4 equiv), ^{*i*}PrOH (1.2 equiv).

Since azido-radical is likely involved in the first C–N₃ bond forming step, we further investigated the mechanistic details of the ligand-promoted peroxyester activation for azido-radical generation (Scheme 6). We observed that benziodoxole **1a** and TMSN₃ promote isomerization of *cis*-stilbene **24a** to *trans*-stilbene **24b** in the absence of an iron catalyst.^{4a} However, without an iron catalyst, *cis*-stilbene **24a** is completely unreactive towards peroxyester **3a** with TMSN₃, and no isomerization is observed. *These results suggest that, unlike the benziodoxole-based method, azido-radical generation is iron catalyst-dependent in this new method.*

Likewise, in the absence of an olefin, an iron catalyst completely decomposes benziodoxole **1a** with TMSN₃, furnishing *o*-iodobenzoic acid **25** (eq 1a in introduction).⁷ However, we observed that the vast majority of peroxyester **3a** is recovered with either iron catalyst in the absence of an

olefin using this new method (eq 2 on page 8).⁷ These observations suggest that the nonproductive peroxyester decomposition pathway can be suppressed in this new method.



Scheme 7. Control experiments to corroborate the involvement of a carboxylate ligand in the rate-determining $C-N_3$ bond forming step for unstrained olefins

^{*a*}Fe(NTf₂)₂ (10 mol %), **L2** (10 mol %), **3a** (3.0 equiv), TMSN₃ (4.0 equiv), ^{*i*}PrOH (0.5 equiv); ^{*b*}Fe(NTf₂)₂ (10 mol %), **L2** (10 mol %), **3c** (3.0 equiv), TMSN₃ (4.0 equiv), ^{*i*}PrOH (0.5 equiv).

The observed electronic effect of a peroxyester over the reaction rate in an Fe(OAc)₂-catalyzed diazidation (Scheme 5) has inspired us to re-evaluate the Fe(NTf₂)₂-catalyzed diazidation of challenging substrates, such as allyl benzoate **26**. As a result, we observed an evidently faster reaction using a more electron-deficient peroxyester **3c** compared with the standard oxidant **3a** (Scheme 7). Since the O–O bond cleavage of electronically distinct **3a**/**3c** is less-likely to be rate-limiting (Scheme 5), this result suggests that the carboxylate ligand, presumably generated through the O–O bond cleavage, is likely involved in the rate-determining transition state in both $Fe(NTf_2)_2$ - and $Fe(OAc)_2$ -catalyzed reactions.

Not only can an oxidant affect the diazidation rate, a ligand can also evidently modulate the reactivity. In particular, the observed ligand effect in the $Fe(OAc)_2$ -catalyzed olefin diazidation is mechanistically intriguing: while the $Fe(OAc)_2$ -bidentate ligand L1 complex is effective for indene diazidation, the $Fe(OAc)_2$ -tridentate ligand L2 complex is almost inactive (Table 1, entry 6). Since the first C–N₃ bond formation is reversible for diazidation of unstrained olefins, the observed rate retardation with the $Fe(OAc)_2$ -L2 complex may be *attributed to either ineffective peroxyester O–O bond cleavage or inefficient carbo-radical oxidation*.



Scheme 8. Control experiments to probe for ligand effect

^{*a*}Fe(OAc)₂ (10 mol %), **L2** (10 mol %), **1a** (1.2 equiv), TMSN₃ (4.0 equiv); ^{*b*}Fe(OAc)₂ (10 mol %), **L2** (10 mol %), **3d** (1.2 equiv), TMSN₃ (2.4 equiv), ^{*i*}PrOH (1.2 equiv).

To differentiate these two possibilities, we carried out a few control experiments (Scheme 8). First, we observed that the $Fe(OAc)_2$ -tridentate L2 complex rapidly catalyzes dodecene diazidation using benziodoxole 1a; however, *it is completely inactive when tert-butyl peroxy 2iodobenzoate 3d* is used as the oxidant. *These results suggest that the inefficient O-O bond cleavage by the Fe(OAc)_2-L2 complex is likely the reason for the observed low reactivity.*

Since the $Fe(OAc)_2$ - and $Fe(NTf_2)_2$ -catalyzed reactions present distinct reactivity profiles (Table 1), we suspect that different active catalytic species may be involved. Therefore, we further studied the coordination chemistry of the $Fe(OAc)_2$ - and $Fe(NTf_2)_2$ -ligand complexes in the presence of TMSN₃ (Scheme 9).



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Scheme 9. Structure–reactivity relationship studies of the $Fe(OAc)_2$ and $Fe(NTf_2)_2$ catalysts in the presence of TMSN₃

^{*a*}**28** (10 mol %), **3a** (1.2 equiv), TMSN₃ (2.4 equiv), ^{*i*}PrOH (1.2 equiv); ^{*b*}**28** (10 mol %), **3a** (1.2 equiv), ^{*i*}PrOH (1.2 equiv); ^{*c*}**28** (25 mol %), **3c** (1.2 equiv).

We observed that the grey solution of the Fe(OAc)₂–L1 complex turned dark when an excess amount of TMSN₃ was introduced. Subsequent ether trituration readily afforded solid **28** and IR analysis revealed strong azido group absorptions (2041 and 2073 cm⁻¹) shifted to lower energy in comparison to free azide, characteristic of iron-azide complexes (Scheme 9).²⁰ We discovered that **28** is catalytic active for indene diazidation. Interestingly, *in the absence of TMSN₃*, **28** *also promotes the diazidation with essentially the same dr, albeit in a low yield* (Scheme 9).²¹ Additionally, **28** promotes diazidation of *(Z)*-hex-3-en-1-ol **22a** *in the absence of TMSN₃*, which readily affords both the diazidation product **23** and olefin isomerization product **22b** (Scheme 9).

Extensive exploration of crystallization conditions of **28** afforded solid **29** that is suitable for X-ray crystallographic analysis, which revealed the bridged dimeric structure of solid **29** as $Fe^{III}_{2}(L1)_{2}(N_{3})_{6}$ (Scheme 9). We suspect that **28** may be oxidized to afford **29** during crystal growth.²² *These experiments suggest that the Fe(OAc)*₂ *catalysts are converted to iron-azide complexes in their resting state by TMSN*₃, and that the iron-azide bond may be involved in the rate-limiting azido-group transfer during diazidation of unstrained olefins.

Interestingly, we did not observe the solid formation of the $Fe(NTf_2)_2-L2$ complex under the analogous condition and IR analysis of the resulting viscous oil revealed lack of characteristic azido-group absorptions (Scheme 9). *This experiment suggests that the Fe(NTf_2)_2 catalysts may not be converted to the corresponding iron-azide complexes by TMSN₃ in their resting state.*

Based upon a variety of collected mechanistic insights, we propose the mechanistic working hypotheses for the $Fe(NTf_2)_2$ - and $Fe(OAc)_2$ -catalyzed olefin diazidation respectively (Scheme 10).



Scheme 10. Mechanistic working hypotheses of the $Fe(NTf_2)_2$ - and $Fe(OAc)_2$ -catalyzed olefin diazidation via ligand-promoted activation of peroxyesters

In an Fe(NTf₂)₂-catalyzed reaction (Scheme 10a), an Fe(NTf₂)₂-ligand complex may reductively cleave the O–O bond in a peroxyester **3** to generate a *tert*-butoxyl radical which is associated with a high-valent iron complex **30** with a carboxylate ligand. ^{*i*}PrOH presumably facilitates gradual release of HN₃ from TMSN₃, and *tert*-butoxyl radical may thereby be rapidly

sequestered by HN₃ to liberate azido radical. The azido radical may readily add to an olefin to afford carbo-radical species **31**. Since the carboxylate ligand is involved in the rate-determining transition state in the Fe(NTf₂)₂-catalyzed diazidation, we propose that TMSN₃ may reversibly convert the iron(III) species **30** to a high-valent iron-azide species **32**, which presumably mediates the rate-determining azido-group transfer to the carbo-radical species **31** and afford the diazidation product.²³ Notably, the Fe(NTf₂)₂–ligand complex can be readily regenerated by the transiently generated TMSNTf₂.

In an Fe(OAc)₂-catalyzed reaction (Scheme 10b), an iron-azide–ligand complex **33** can be generated in situ, which may facilitate the O–O bond cleavage and azido-radical generation in an analogous way. However, the high-valent iron-azide species **34** may directly mediate the rate-limiting azido-group transfer to the carbo-radical species **31** and furnish the diazidation product. Subsequently, TMSN₃ may readily convert the iron(II)-carboxylate complex back to the catalytically active iron-azide complex **33** via anion metathesis.

CONCLUSIONS

In conclusion, we have reported an iron-catalyzed direct diazidation method via nitrogen-based ligand-promoted activation of bench-stable peroxyesters. This method significantly improves upon our previously reported, benziodoxole-based method and it is effective for a broad range of olefins and *N*-heterocycles, including those that are difficult substrates for the existing olefin diamination and diazidation methods. Most notably, nearly a stoichiometric amount of oxidant and TMSN₃ are sufficient for high-yielding diazidation for most substrates. Furthermore, preliminary mechanistic studies were carried out to elucidate the similarities and differences between this new method and the benziodoxole-based diazidation method. It was revealed that,

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unlike the benziodoxole-based-method, azido-radical generation is iron-catalyst-dependent and the non-productive oxidant-decomposition pathway can be effectively suppressed using this new method. X-ray crystallographic studies further suggest that an iron-azide–ligand complex can be generated in situ from an iron acetate precatalyst and it may facilitate peroxyester activation and the rate-determining C–N₃ bond formation for diazidation of unstrained olefins. Our current efforts focus on synthetic applications of this new method for complex-molecule synthesis.

ASSOCIATED CONTENT

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Supporting Information.

Experimental procedure, characterization data for all new compounds, and selected NMR spectra. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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