Iron-catalyzed site- and regioselective 1,2-azidoamidations of 1,3-dienes.

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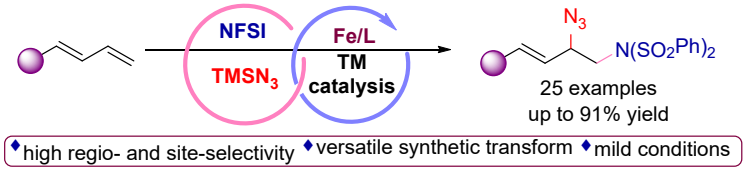
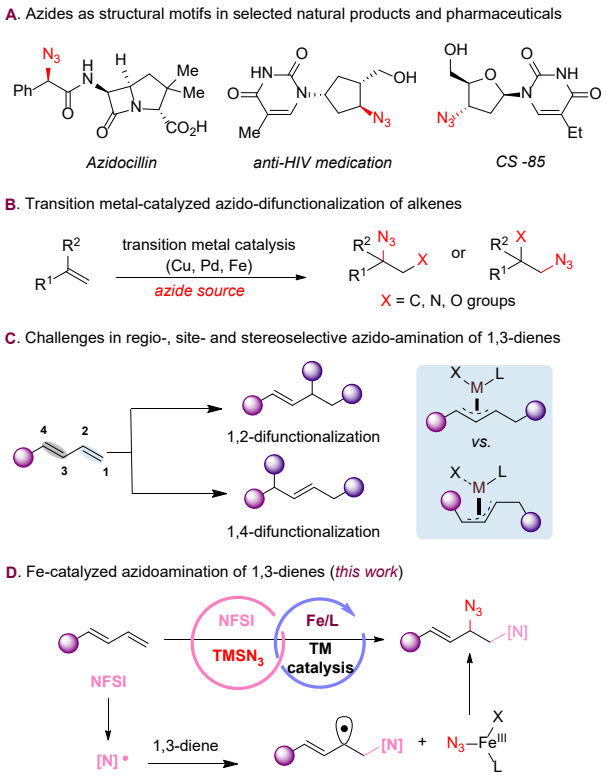
Supporting Information Placeholder



ABSTRACT: The direct 1,2-azidoamidation of unsaturated precursors represents an advantageous approach for the facile synthesis of β-functionalized azides from readily available starting materials. In this paper, we describe a convenient and mild iron-catalyzed 1,2-azidoamidation of 1,3-dienes that shows excellent functional group compatibility to furnish versatile precursors to 1,2-diamine products with high levels of site-, regio- and stereoselectivity. The reaction is proposed to proceed via a single electron transfer (SET)/radical addition/C–N bond formation relay process.

Azide-containing compounds are important due to their potential as precursors of amine-containing structural motifs, but also for their remarkable biological activity in pharmaceutically relevant compounds (Scheme 1A).[1-4] Moreover, organoazides serve as useful reagents for diverse transformations that include aza-Wittig reactions[5], Curtius rearrangements[6] and click chemistry,[7] among others.[8,9] Due to their synthetic utility,[10-12] many methods have been developed for the synthesis of organoazides.[3,13-15] Transition metal-catalyzed radical additions of azido groups to alkenes[14] represents a robust and versatile strategy for the assembly of complex molecular skeletons from easily accessible chemical building blocks, while simultaneously introducing two functional groups across the π-system. Over the last decade, several groups have made advances in copper-, palladium-, and iron-catalyzed azido-difunctionalizations of alkenes, including those of Studer[16], Greaney[17], Liu[18] and Bao.[19] These methods provide a convenient strategy to introduce azido groups into unsaturated bonds with concomitant formation of C–C[20], C–N[21], and other C–heteroatom bonds[22] (Scheme 1B).

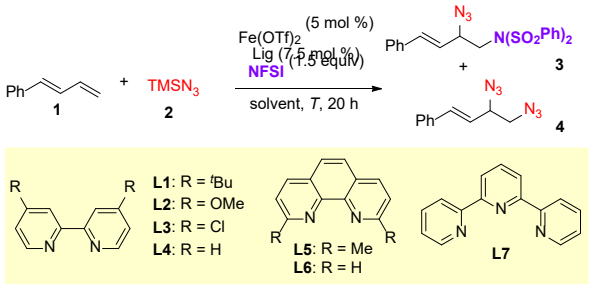
Despite the recent progress in alkene azidation, it is desirable to expand the scope of this chemistry. Readily available 1,3-dienes are known to participate in a wide range of transformations to facilitate the synthesis of value-added compounds;[23, 24] however, the conjugated nature of 1,3-dienes raises challenges with regioselectivity, as they can undergo competing 1,2- and 1,4-additions. Moreover, the stepwise mechanistic pathways operative in radical additions can result in isomerization of highly reactive intermediates, leading to a lack of control over the regio- and stereoselectivity of these transformations (Scheme 1C).



Scheme 1. Radical azido-difunctionalization of alkenes.

We were interested in exploring the use of sustainable first-row transition metals, as opposed to expensive precious metal catalysts,[25] for catalyzing the selective functionalization of 1,3-dienes to furnish valuable allyl azide synthetic building blocks.[26] Herein, we describe a 1,2-azidoamidation of 1,3-dienes using simple Fe(II) salts supported by bidentate *N*-ligands.[25,26] The reaction is proposed to occur through single electron transfer (SET)/radical addition/C–N bond formation (Scheme 1D) to furnish the products with high site-, regio- and stereoselectivities, although selective 1,4-azidoamidation still remains a challenge.

Table 1. Optimization of reaction conditions.[a]

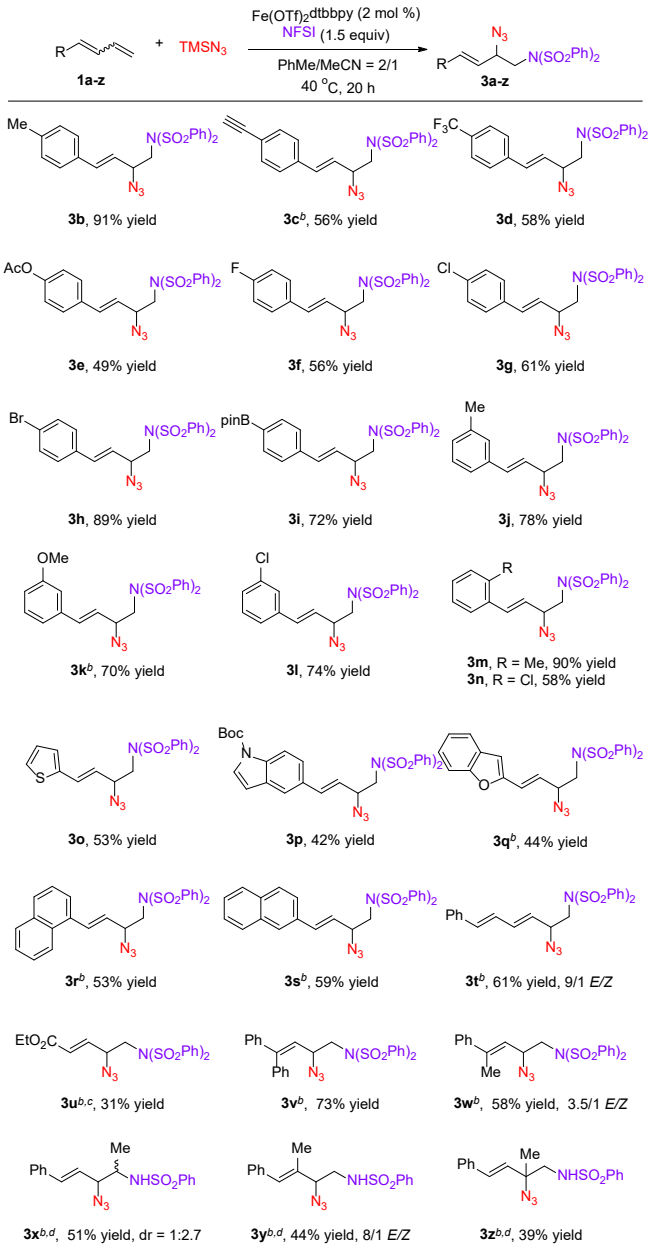


entry	ligand	T (°C)	solvent	yield 3/4 (%)[b]
1	**L1**	23	MeCN	10/2
2	**L1**	23	PhMe	45/7
3	**L1**	23	DCM	47/5
4	**L1**	23	1:2 MeCN:PhMe	59/5
5	**L1**	40	1:2 MeCN:PhMe	74/5
6	**L2**	40	1:2 MeCN:PhMe	59/7
7	**L3**	40	1:2 MeCN:PhMe	68/9
8	**L4**	40	1:2 MeCN:PhMe	61/13
9	**L5**	40	1:2 MeCN:PhMe	57/13
10	**L6**	40	1:2 MeCN:PhMe	53/10
11	**L7**	40	1:2 MeCN:PhMe	N.R.
12	--	40	1:2 MeCN:PhMe	18/5
13[c]	**L1**	40	1:2 MeCN:PhMe	76/4

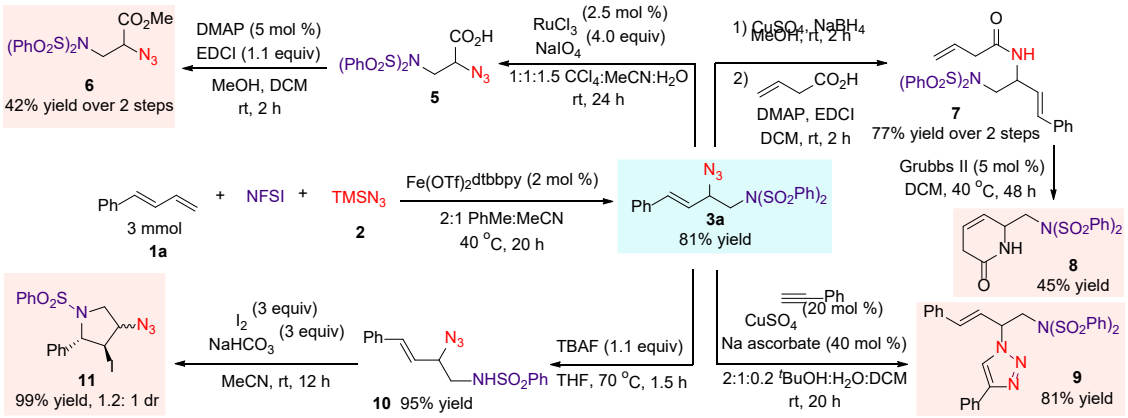
[a] Reaction conditions: **1** (0.10 mmol), $TMSN_3$ **2** (0.15 mmol), NFSI (0.15 mmol), ligand (7.5 mol %), $Fe(OTf)_2$ (5 mol %), solvent (1.5 mL), 20 h, under N_2. [b] Determined by ^1H NMR analysis using 1,3,5-$Me_3C_6H_2CO_2H$ as an internal standard. [c] 2 mol % $Fe(OTf)_2$dtbbpy instead of [Fe] and ligand.

Initial studies employed 1-phenyl-1,3-butadiene **1a** as the model substrate, *N*-fluorobenzenesulfonimide (NFSI) as a dual oxidant and radical precursor, $TMSN_3$ as the azide source and acetonitrile as the solvent. A $Fe(OTf)_2$ salt supported by a 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbbpy) ligand was chosen as the initial catalyst. The mixture was stirred at room temperature under N_2 for 20 h; however, the desired azidoamidation product **3a** was furnished in only 10% yield, along with the diazidated compound **4a** in 2% yield and full conversion of the diene **1a** (Table 1, entry 1). The poor yield was hypothesized to arise from side reactions, most likely competing radical polymerizations. Toluene and DCM were examined next, resulting in improved yields of **3a** (entries 2-3). Due to the poor solubility of the iron complex in toluene alone, we employed a mixed 1:2 MeCN/PhMe solvent system, which proved to be more effective than any other individual solvent (entry 4), furnishing **3a** in 59% yield. An increase in the temperature from 23 °C to 40 °C resulted in an improvement in the yield of **3a** to 74%, while no increase in the amount of **4a** was noted (entry 5). Subsequently, a variety of other achiral ligands **L2-L7** were investigated to support the $Fe(OTf)_2$ catalyst (entries 6–11); however, **L1** proved to be the best ligand. In the absence of any ligand (entry 12), **3a** was afforded in a significantly eroded yield of 18%. Finally, the use of a pre-formed complex of $Fe(OTf)_2$dtbbpy instead of separate metal and ligand components resulted in a slightly increased yield to 76% of the desired **3a** (entry 13).

Table 2. Substrate scope.[a]



[a] Unless indicated, reactions were run with 1,3-diene (0.1 mmol), $TMSN_3$ **2** (0.15 mmol), NFSI (0.15 mmol), $Fe(OTf)_2$dtbbpy (0.002 mmol), PhMe (1 mL), MeCN (0.5 mL), 40 °C, under N_2, 20 h. [b] DCM as solvent. [c] 50 °C, 48 h. [d] Workup with TBAF (1 M in THF, 1.0 equiv).



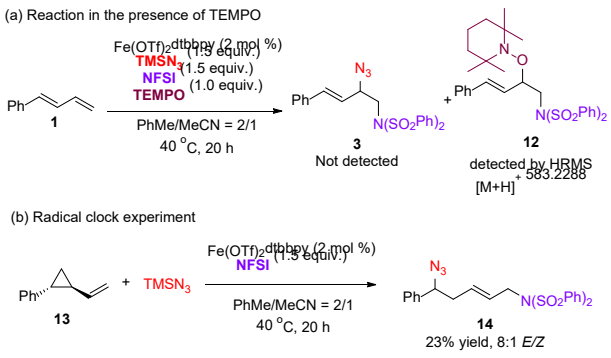
Scheme 2. Product derivatizations.

With optimized conditions in hand, we next focused on examining the scope of the reaction (Table 2). A wide range of 1-phenyl-1,3-butadienes, bearing both electron-donating (methyl **1b,** ethynyl **1c**) and electron-withdrawing substituents (**1d, 1f-1i**) at the *para-*, *meta-*, or *ortho* positions of the phenyl group, were suitable substrates in this protocol. The corresponding azidoamidated products **3b-3i** and **3k** were obtained in good yields with high levels of regio-, site- and stereocontrol, favoring 1,2- over 1,4-addition and installation of the azide at the more substituted C3 carbon of the diene. Moving the substituent on the aryl ring to the *meta* (**3j-3l**) position decreased the yield when an electron-rich Me group was present, but increased yield resulted using a Cl group; the opposite trend was observed when these groups were located in the *ortho* position in **3m-3n**. The heteroaryl-substituted 1,3-butadienes **1o-1q** smoothly underwent the reaction to furnish the desired products **3o-3q** in moderate yields. Interestingly, although naphthyl-derived 1,3-butadienes **1r** and **1s** performed poorly using a mixed solvent system, employing dichloromethane alone generated the corresponding azidoamidated products **3r** and **3s** in good yields. The 1,3,5-triene **1t** was found to be a viable precursor for the azidoamidation, delivering the desired **3t** in 61% yield with excellent regio- and site-selectivity and in an *E*:*Z* ratio of 9:1. A challenging electron-poor diene **1u** containing an ester substituent yielded the corresponding adduct **3u** in acceptable yield, although a prolonged reaction time and increased temperature was required. Notably, geminal C1 disubstitution on the dienes **1v** and **1w** lead to smooth conversion to the desired products **3v** and **3w** in 73% yield (3.5:1 *E*/*Z*) and 58% yield, respectively. Substitution on C4 of the diene could be tolerated, as **1x** gave the deprotected **3x** in good regio- and site-selectivity with a 2.7:1 *dr* after workup with TBAF. Substitution at C2 and C3 of the diene in **1y** and **1z**, respectively, gave moderate yields of **3y** and **3z** with good regio- and site-selectivities.[27]

To demonstrate the synthetic utility of the diene azidoamidation chemistry, a gram-scale reaction and a series of transformations of a representative product **3a** were carried out (Scheme 2). A gram-scale reaction of 1-phenyl-1,3-butadiene **1** conducted under slightly adjusted conditions furnished **3a** in an 81% yield (Table 1, entry 14). The α-azido acid derivative **4** was directly prepared from oxidation of **3a** with $RuCl_3/NaIO_4$, followed by condensation with MeOH to give the α-azido ester **5** in 42% yield over the two steps. Compound **3a** was readily reduced with $NaBH_4$ and subjected to amidation to deliver **6**. A subsequent ring-closing metathesis of **6** employing Grubbs II at low concentration successfully generated lactam **7**. A click reaction[28] of **3a** with phenylacetylene produced the expected triazole **8**[29] in 81% yield. Finally, mono-desulfonylation of **3a** was achieved upon treatment with n-Bu_4NF to afford the α-azido sulfonamide derivative **10** in 95% yield. In the presence of $NaHCO_3$ and I_2, **10** underwent cyclization to the iodosubstituted pyrrolidine **11**, containing three contiguous chiral centers, in 95% yield and in a 1.2:1 *dr*.[30]

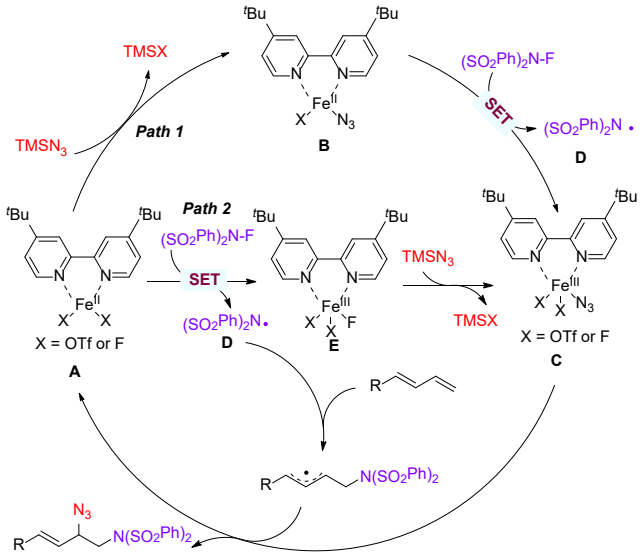
To gain more insight into the reaction, a series of mechanistic probe experiments were conducted (Scheme 4). The addition of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) to the reaction completely inhibited the formation of the desired product **3** under otherwise standard conditions. The radical-trapped product **12** was detected by high-resolution mass spectrometry (Scheme 4a), supporting the intermediacy of an allylic radical, generated from the addition of a disulfonimidyl radical to the diene. A reaction of a (*trans)*-1-phenyl-2-vinylcyclopropane **13** radical clock also supported a radical pathway, as the ring-opened **14** was obtained in 23% yield and an 8:1 *E:Z* ratio,

Scheme 3. Mechanistic studies.



suggesting an *in situ*-generated cyclopropylcarbinyl radical undergoes fast ring-opening to give the benzyl radical, which is then trapped by azide.

Scheme 4. Proposed catalytic cycle.



Based on our and other mechanistic studies,[31,32] we proposed a plausible mechanism for the Fe-catalyzed *E*-selective azidoamidation reaction (Scheme 5). In Path 1, the process is initiated by the iron(II) complex **A**, which can undergo ligand exchange with $TMSN_3$ to form the iron(II) azide complex **B**. Subsequently, a SET of **B** with NFSI results in the generation of an iron(III) azide species **C** and a bis-sulfonylamidyl radical **D**. Alternatively, in Path 2, the SET process may occur first through reaction of complex **A** with NFSI to produce an oxidized iron species **E** and a radical **D**. Intermediate **E** then reacts with $TMSN_3$ to produce the same iron(III) azide species **C** as noted for Path 1. In both paths, radical **D** selectively adds to the terminal carbon atom of the 1,3-diene, exclusively generating the allylic radical intermediate **F**. This intermediate is subsequently captured by **C**, which leads to the formation of the final product via a group transfer pathway[19] to regenerate the active catalyst species **A**. The observation that only products from 1,2-addition were obtained is noteworthy. While no 1,4-addition products were observed by ^1H NMR spectroscopy, the possibility of a 1,4-addition product[25] undergoing a subsequent and rapid Winstein rearrangement cannot be ruled out. Indeed, we found that 1,4-addition competes with 1,2-addition when alkyl-substituted 1,3-dienes are employed in the reaction (see the SI for further details).

In conclusion, we have described a pratical iron-catalyzed azdioamidation of 1,3-dienes using commercially available reagents. The reaction is highly site-selective for the alkene distal from the aryl group, as well as highly regioselective for addition of the azido group to the more substituted carbon. A wide range of β-amidated azides have been prepared to provide access to synthetically significant amines. Further studies on the synthetic applications and asymmetric azidofunctionalizations of feedstocks bearing multiple sites of unsaturation are ongoing in our laboratory.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information.

The Supporting Information is available free of charge at http://pubs.acs.org. Experimental section, characterization data, NMR spectra, crystal data, unsuccessful substrates and relevant references.

Accession Codes

CCDC 2296147 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 1223336033.

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Notes

The authors declare no competing financial interest.

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