



Published in final edited form as:

Nature. 2015 January 29; 517(7536): 600–604. doi:10.1038/nature14127.

Metal-Catalyzed Azidation of Tertiary C–H Bonds Suitable for Late-Stage Functionalization

Ankit Sharma and John F. Hartwig

Department of Chemistry, University of California, Berkeley, CA 94720

John F. Hartwig: jhartwig@berkeley.edu

Abstract

Some enzymes are able to selectively oxidize unactivated aliphatic C-H bonds to form alcohols; however biological systems do not possess enzymes that are able to catalyze the analogous amination of a C-H bond.^{1,2} The absence of such chemistry is limiting because nitrogen-containing groups are found in therapeutic agents and clinically useful natural products. In one prominent example, the conversion of the ketone of erythromycin to the –N(Me)CH₂– group in azithromycin leads to a compound that can be dosed once daily with a shorter length of treatment.^{3,4} For such reasons, synthetic chemists are very interested in identifying catalysts that can directly convert C-H bonds to C-N bonds. Most currently used catalysts for C-H bond amination are ill suited for the functionalization of complex molecules, because they require excess substrate or directing groups, harsh reaction conditions, weak or acidic C-H bonds, or reagents containing specialized groups on the nitrogen atom.⁵⁻¹⁴ Among C-H bond amination reactions, those forming a carbon-nitrogen bond at a tertiary alkyl group would be particularly valuable, because this linkage is difficult to generate enzymatically from ketone or alcohol precursors.¹⁵ In this manuscript, we report a mild, selective, iron-catalyzed azidation of tertiary C-H bonds with substrate as limiting reagent. The reaction tolerates aqueous environments and is suitable for “late-stage” functionalization of complex structures. Moreover, this azidation creates the ability to install a range of nitrogen functional groups, including those from bio-orthogonal Huisgen “click” cycloadditions and the Staudinger ligation.¹⁶⁻¹⁹ For these reasons, we anticipate this methodology will create opportunities to easily modify natural products, their precursors, and their derivatives to analogs that contain distinct polarity and charge from nitrogen-containing groups. It could also be used to help identify targets of biologically active molecules by creating a point of attachment, for example to fluorescent tags or ‘handles’ for affinity chromatography, directly onto complex molecular structures.

To develop a mild method for the conversion of an alkyl C-H bond to an alkyl C-N bond, we focused on reactions of the hypervalent iodine reagent **1** containing an azide unit (Fig. 1).

Reprints and permissions information is available at www.nature.com/reprints

Correspondence to: John F. Hartwig, jhartwig@berkeley.edu.

Author Contributions: A.S. conducted the experiments. A.S. and J. F. H. conceived, and designed the project, analyzed the data and prepared this manuscript. X-ray crystal structures were deposited in the Cambridge crystallographic data Centre (CCDC 1027821-1027822).

Author Information: The authors declare no competing financial interests.

Readers are welcome to comment on the online version of the paper.

Such a reagent is related to hypervalent reagents commonly used for oxidation,²⁰ and is thermally stable (up to 130 °C).²¹ It has sufficient thermodynamic potential to convert alkyl C-H bonds alkyl azides, but the published reaction is limited to simple hydrocarbons, typically used in excess amounts, or activated C-H bonds at high temperatures in the presence of radical initiators. Thus, the current reactions of this reagent are not suitable for late-stage functionalization of complex molecules.²¹ If an appropriate transition metal catalyst for C-H bond functionalization with this hypervalent iodine reagent could be identified, then C-H bond amination reactions that incorporate an azide into complex molecules with site selectivity could be devised. Previously, iron and manganese porphyrins were reported to form alkyl azides from sodium azide and iodosobenzene or *t*-BuOOH as oxidants, but the reactions were limited to hydrocarbons, excess of the alkane (10 equiv) was required, and formation of the corresponding alcohol was a major by-product.²²⁻²⁴

To identify a metal complex that would catalyze the azidation of C-H bonds with **1** under mild conditions, we investigated the reaction of cis-decalin. Various metal complexes, including metal-porphyrins, were tested as catalyst with the hydrocarbon as limiting reagent; only iron complexes provided measurable yield of azide product (yield <5%) at 23 °C (SI, Table S1). Combinations of Fe(OAc)₂ and various bi-, tri- and tetra-dentate nitrogen ligands (**L1** – **L5**), including those that catalyze the selective hydroxylation of aliphatic C-H bonds (**L1** and **L3**),^{25,26} provided low yield of the product **3a** (Fig 1, 3-11%). However, substantial yields of **3a** were observed with iron complexes of oxazoline-derived ligands, particularly with those possessing larger N-Fe-N “bite” angles (**L6-L9**). Finally, we found that reactions of iron complexes containing tridentate nitrogen ligands of the pybox family (**L10** and **L11**) provided product **3a** in good yield with high selectivity for reaction at a tertiary C-H bond (75%, 4.3:1 ratio of diastereomers). Reactions conducted in ethyl acetate (EtOAc) with the catalyst containing ligand **L11** proceeded in good yield and higher *trans:cis* selectivity (65%, 6.3:1, SI, Table S2). Reactions in acetonitrile were faster, but occurred with lower selectivity. Reactions in a mixture of EtOAc and water (5:1) occurred similarly to those in pure EtOAc (63%, 6:1).

The azidation of the C-H bond of a series of hydrocarbons occurred in excellent yields with high selectivity for a tertiary C-H bond over the secondary and primary C-H bonds (SI, Table S3), setting the stage for azidation of the tertiary C-H bonds in molecules containing a series of functional groups. The azidation reaction with derivatives of dihydrocitronellol containing two electronically distinct tertiary C-H bonds and many secondary C-H bonds is shown in part A of Fig. 2. These reactions revealed the inherent electronic selectivity of the azidation reaction and its functional group compatibility. The C-H bond azidation was selective for reaction at the more electron-rich, remote, tertiary C-H bond resulting in good isolated yields of the pure major isomers formed by the reaction (Fig. 2, **3k-3q**). The regioselectivity of azidation at the two electronically distinct tertiary C-H bond was influenced by the distance of the electron-withdrawing group from proximal tertiary C-H bond (**3k** and **3l**). In these cases, the regioselectivity of the C-H bond azidation reaction mirrors the regioselectivity of a wide range of oxidation reactions.²⁷ Functional groups such as an alcohol protected as an acetoxy group (**3k** and **3l**), a bromide (**3m**), a nitrile (**3m**), an ester (**3o**), a carboxylic acid (**3p**), and an amide (**3q**), were tolerated. Functional groups like

carboxylic acid (**3p**) and an amide (**3q**) that could act as directing groups, influenced the selectivity by their electronic properties, rather than by coordination to the catalyst. This higher reactivity of more electron-rich C-H bonds was also observed for cyclic structures. 4-*iso*-propylcyclohexanone underwent azidation with high regioselectivity for the more electron-rich of the two tertiary C-H bonds (**3r**). Investigation of the reactions of substituted arenes showed that tertiary and secondary benzylic C-H bonds were functionalized selectively in the presence of primary benzylic C-H bonds (**3s** and **3t**).

Having revealed high regioselectivity for the C-H bond azidation, we assessed the potential of this reaction for azidation of the C-H bonds in more complex scaffolds containing several functional groups and strained rings that could react over the C-H bonds (Fig 2, B). Cyclic ketones prepared from (–)-carvone underwent azidation at the tertiary C-H bond remote from the ketone with high regioselectivity. These reactions occurred in the presence of epoxides, aziridines and cyclopropanes in good isolated yields (**3u-3w**). Minor azidation products were also observed by gas chromatography–mass spectrometry. These products were formed in amounts too small for isolation and were not characterized. A mixture of diastereomers of α -dihydropinene (5:1) containing three electronically similar, but sterically distinct, tertiary C-H bonds reacted to give 80% isolated yield of a single isomer of azide **3b** at room temperature. The strained four-membered ring was tolerated, suggesting a fast recombination of the likely radical intermediates. Acetoxymenthol containing two electronically similar tertiary C–H bonds reacted preferentially at the *iso*-propyl side chain to provide one major constitutional isomer in moderate isolated yield (**3x**). This selectivity, presumably, results from the greater conformational flexibility of the isopropyl side chain. Isomeric products from azidation of a different C-H bond were observed as minor products; again, these products could be diastereomers formed from azidation of the other tertiary C-H bonds.

Unlike the stereoretentive property of the metal-catalyzed insertions of nitrenes or carbenes into C-H bonds,^{8,9,28} the configuration of the carbon bound to the azide is independent of the configuration in the reactant. However, this stereochemical outcome of our reactions allows us to use mixtures of diastereomeric reactants (Table S3 and Fig 2 **2b**, **5**) to provide one major diastereomer of the azide product (*vide infra*).

Biologically active molecules containing multiple benzylic and tertiary C-H bonds also reacted selectively. Podocarpic acid and its derivatives have been reported to exhibit a wide variety of biological activities, including antileukemic activity, inhibition of plant cell growth, and anti-inflammatory properties. A podocarpic acid derivative underwent selective azidation at the benzylic C-H bond in high yields and good diastereoselectivity (**3y**). Similar selectivity was also observed for the azidation of an estrone (**3z**).

The reaction of a gibberellic acid derivative illustrates the ability to conduct the azidation of complex structures (Fig. 2, C). Gibberellic acid is a plant hormone that regulates growth and influences developmental processes including cell elongation and germination. The gibberellic acid derivative (**5**) is a pentacyclic diterpene containing four tertiary C-H bonds. Based on the data just presented, the most electron-rich and sterically least hindered tertiary C-H⁴ bond should react selectively. In addition, the stereochemical outcome of the azidation

of *cis*- and *trans*- decalin and α -dihydropinene (Table S3 and Fig 2, B) suggested that the configuration of the reactive center (C-H⁴) in substrate **5** would have a negligible influence on the diastereomeric ratio of product **6**. Indeed, the azidation of a mixture of diastereomers of **5** provided the corresponding azide **6** as a single isolated diastereoisomer in 75% yield (Fig. 2, C) from *exo*-attack of the azide unit at the reactive carbon.

Finally, we also tested functionalizations of the complex scaffolds in parts B and C of Fig 2 by the reactions initiated with benzoyl-peroxide. In all cases, poor yields and selectivities were observed from the reactions initiated by the peroxide. The yields of the products from reaction of the substrates in Fig 2, B were low in all cases and formed mixtures of isomeric products with poor selectivity. In addition, gibberellic acid derivative (**5**) decomposed to form a complex mixture of products in the presence of azide **1** and the peroxide. This distinct reaction course in the presence and absence of the iron catalyst suggests that the C-N bond is formed by two different processes in the two systems and underscores the importance of the iron catalyst to create a reaction that is suitable for late-stage functionalization of complex molecules.

Although detailed mechanistic studies have not yet been conducted, several observations reveal the general features of the mechanism. The site selectivities and stereochemical outcome of the azidation of *cis*- and *trans*-decalin and α -dihydropinene strongly suggest that a tertiary alkyl radical is generated (Table S3 and Fig 2, B). Attempts to use radical clocks to assess more directly a potential alkyl radical were hampered by the poor reactivity of the appropriate substrates (see SI for more details), but the proposed radical intermediate is consistent with the selectivity for azidation of the more electron-rich, less polarized, and thus weaker, tertiary C-H bonds (Fig. 2).²⁷ Furthermore, addition of 1 equiv of BHT and TEMPO, which are known to quench radicals, resulted in complete inhibition of the azidation reaction (Table 1, entries 1 and 2). Finally, the KIE for azidation of ethylbenzene and ethylbenzene-*d*₁₀ in separate vessels from initial reaction rates was observed to be 5.0±0.3, implying that the cleavage of C-H bond is the overall turnover-limiting step.

To assess the role of the iron catalyst for this transformation, we compared the iron-catalyzed azidations of the complex scaffolds in parts B and C of Fig 2 with the reactions initiated by benzoyl-peroxide. In all cases, poor yields were observed from the reactions initiated by the peroxide. Of the product formed, the selectivities were distinct from those of the iron-catalyzed product. In addition, the diastereomeric ratio of product **3a** formed from decalin and azide **1** in the presence of catalytic iron and an organic radical initiator at the 80 °C required for the peroxide-initiated process (SI, Table S1) gave distinct ratios of the *cis*- and *trans*- decalin products (Table 1, entries 3-6). These differences in selectivities are all consistent with a different species forming the C-N bond during the iron-catalyzed reaction and the radical-initiated process. One possibility is that the C-N bond is formed by reaction of an alkyl radical with an iron azide intermediate.

This C-H bond azidation creates access to a range of synthetically useful functionalities attached to the original substrate by a C-N bond (Fig. 3).¹⁶⁻¹⁹ The primary amine formed from the azides **3a** and **3z** containing a fully or partially substituted carbon atom (**4a** and **10**) and heterocycles, such as tetrazole **9**, form in good yields from azide **3f** (SI, table S3).²⁹ The

azides (**3d** and **3e**, SI, table S3) also undergo intramolecular cyclization under conditions reported recently to form various heterocycles, creating a route to nitrogen heterocycles from alkanes by two C-H bond amination chemistries (**11**).¹⁹ Finally, the azide functionality undergoes Huisgen cycloaddition reactions. For example, an alkyne tethered to a fluorescent tag coupled with azido gibberilic acid derivative **6** and an alkyne attached to biotin coupled with azido podocarpic acid derivative **3y**. These reactions illustrate how azidation and cycloaddition can create bioconjugation methods for visualization and identification of cellular targets of biologically active natural products.³⁰

Much development of this C-H bond functionalization method remains, but a wide range of applications and extensions of the azidation reaction can be envisioned. The modularity of the catalyst creates further opportunities for site selectivity, and the stereochemical content of the ligand creates the potential for enantioselective azidation. The cycloadditions of azides could make possible conjugation to antibodies, and the simple reduction of the azide and tolerance of the reaction to water creates the potential to intercept biosynthetic sequences and install an amino group in place of a hydroxyl group in the final stages. Finally, we anticipate that this process will spur development of new classes of catalysts for the azidation of C-H bonds that could occur by distinct mechanisms with distinct selectivities for primary, secondary, and tertiary C-H bonds. As rhodium-catalyzed amination reactions develop further, the two classes of systems for C-H bond amination should begin to provide a set of tools for incorporation of nitrogen atoms that parallels the existing set of tools for the chemical and enzymatic oxidation of C-H bonds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the NIH (4R37GM055382 to JFH) and the Swiss National Science Foundation (SNSF) (PBGEP2_145544 to AS) for financial support. We thank Dr. Antonio DiPasquale for assistance with crystallographic data and NIH shared instrumentation grant S10-RR027172.

References and Notes

1. Bollinger JM, Broderick JB. Frontiers in enzymatic C-H-bond activation. *Curr Opin Chem Biol.* 2009; 13:51–57. [PubMed: 19362514]
2. Lewis JC, Coelho PS, Arnold FH. Enzymatic functionalization of carbon-hydrogen bonds. *Chem Soc Rev.* 2011; 40:2003–2021. [PubMed: 21079862]
3. Plouffe J, et al. Clinical efficacy of intravenous followed by oral azithromycin monotherapy in hospitalized patients with community-acquired pneumonia. *Antimicrob Agents Ch.* 2000; 44:1796–1802.
4. O'doherty B, Muller O, Grp AS. Randomized, multicentre study of the efficacy and tolerance of azithromycin versus clarithromycin in the treatment of adults with mild to moderate community-acquired pneumonia. *Eur J Clin Microbiol.* 1998; 17:828–833.
5. Jeffrey JL, Sarpong R. Intramolecular C(sp³)-H amination. *Chem Sci.* 2013; 4:4092–4106.
6. Ochiai M, Miyamoto K, Kaneaki T, Hayashi S, Nakanishi W. Highly Regioselective Amination of Unactivated Alkanes by Hypervalent Sulfonylimino-lambda(3)-Bromane. *Science.* 2011; 332:448–451. [PubMed: 21512029]

7. Louillat ML, Patureau FW. Oxidative C-H amination reactions. *Chem Soc Rev.* 2014; 43:901–910. [PubMed: 24217419]
8. Roizen JL, Harvey ME, Du Bois J. Metal-Catalyzed Nitrogen-Atom Transfer Methods for the Oxidation of Aliphatic C-H Bonds. *Acc Chem Res.* 2012; 45:911–922. [PubMed: 22546004]
9. Dequierez G, Pons V, Dauban P. Nitrene Chemistry in Organic Synthesis: Still in Its Infancy? *Angew Chem Int Ed.* 2012; 51:7384–7395.
10. Lescot C, Darses B, Collet F, Retailleau P, Dauban P. Intermolecular C-H Amination of Complex Molecules: Insights into the Factors Governing the Selectivity. *J Org Chem.* 2012; 77:7232–7240. [PubMed: 22892031]
11. Roizen JL, Zalatan DN, Du Bois J. Selective Intermolecular Amination of C-H Bonds at Tertiary Carbon Centers. *Angew Chem Int Ed.* 2013; 52:11343–11346.
12. Michaudel Q, Thevenet D, Baran PS. Intermolecular Ritter-Type C-H Amination of Unactivated sp³ Carbons. *J Am Chem Soc.* 2012; 134:2547–2550. [PubMed: 22276612]
13. Li J, et al. Simultaneous structure-activity studies and arming of natural products by C-H amination reveal cellular targets of eupalmerin acetate. *Nat Chem.* 2013; 5:510–517. [PubMed: 23695633]
14. McNally A, Haffemayer B, Collins BSL, Gaunt MJ. Palladium-catalysed C-H activation of aliphatic amines to give strained nitrogen heterocycles. *Nature.* 2014; 510:129–133. [PubMed: 24870240]
15. Pronin SV, Reiher CA, Shenvi RA. Stereoinversion of tertiary alcohols to tertiary-alkyl isonitriles and amines. *Nature.* 2013; 501:195–199. [PubMed: 24025839]
16. Brase S, Gil C, Knepper K, Zimmermann V. Organic azides: An exploding diversity of a unique class of compounds. *Angew Chem Int Ed.* 2005; 44:5188–5240.
17. Schilling CI, Jung N, Biskup M, Schepers U, Brase S. Bioconjugation via azide-Staudinger ligation: an overview. *Chem Soc Rev.* 2011; 40:4840–4871. [PubMed: 21687844]
18. Lallana E, Riguera R, Fernandez-Megia E. Reliable and Efficient Procedures for the Conjugation of Biomolecules through Huisgen Azide-Alkyne Cycloadditions. *Angew Chem Int Ed.* 2011; 50:8794–8804.
19. Hennessy ET, Betley TA. Complex N-Heterocycle Synthesis via Iron-Catalyzed, Direct C-H Bond Amination. *Science.* 2013; 340:591–595. [PubMed: 23641113]
20. Zhdankin, VV. Hypervalent iodine chemistry : preparation, structure and synthetic applications of polyvalent iodine compounds. John Wiley & Sons Ltd; 2013.
21. Zhdankin VV, et al. Preparation, X-ray crystal structure, and chemistry of stable azidoiodinanes - Derivatives of benziiodoxole. *J Am Chem Soc.* 1996; 118:5192–5197.
22. Hill CL, Smegal JA, Henly TJ. Catalytic Replacement of Unactivated Alkane Carbon Hydrogen-Bonds with Carbon-X Bonds (X = Nitrogen, Oxygen, Chlorine, Bromine, or Iodine) - Coupling of Intermolecular Hydrocarbon Activation by Mn-IIitppx Complexes with Phase-Transfer Catalysis. *J Org Chem.* 1983; 48:3277–3281.
23. Kojima T, Leising RA, Yan SP, Que L. Alkane Functionalization at Nonheme Iron Centers - Stoichiometric Transfer of Metal-Bound Ligands to Alkane. *J Am Chem Soc.* 1993; 115:11328–11335.
24. Costas M. Selective C-H oxidation catalyzed by metalloporphyrins. *Coord Chem Rev.* 2011; 255:2912–2932.
25. Kim C, Chen K, Kim JH, Que L. Stereospecific alkane hydroxylation with H₂O₂ catalyzed by an iron(II)-tris(2-pyridylmethyl)amine complex. *J Am Chem Soc.* 1997; 119:5964–5965.
26. Chen MS, White MC. A predictably selective aliphatic C-H oxidation reaction for complex molecule synthesis. *Science.* 2007; 318:783–787. [PubMed: 17975062]
27. Newhouse T, Baran PS. If C-H Bonds Could Talk: Selective C-H Bond Oxidation. *Angew Chem Int Ed.* 2011; 50:3362–3374.
28. Davies HML, Morton D. Guiding principles for site selective and stereoselective intermolecular C-H functionalization by donor/acceptor rhodium carbenes. *Chem Soc Rev.* 2011; 40:1857–1869. [PubMed: 21359404]

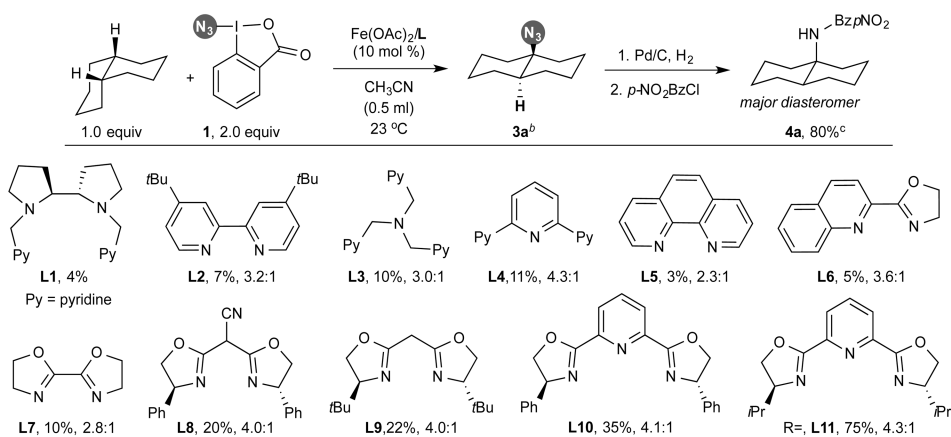
29. Demko ZP, Sharpless KB. A click chemistry approach to tetrazoles by Huisgen 1,3-dipolar cycloaddition: Synthesis of 5-acyltetrazoles from azides and acyl cyanides. *Angew Chem Int Ed.* 2002; 41:2113–2116.
30. Trippier PC. Synthetic Strategies for the Biotinylation of Bioactive Small Molecules. *Chem med chem.* 2013; 8:190–203. [PubMed: 23303486]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

**Fig. 1.**

Development of a catalyst for the azidation of aliphatic C–H bonds.

^a Conditions: 10.0 mol % $\text{Fe}(\text{OAc})_2$, 11.0 mol % ligand, cis-decalin (0.2 mmol, 1.0 equiv) and **1** (0.4 mmol, 2.0 equiv), 23 °C. The yields and the ratios of isomers were determined by gas chromatography (GC) analysis with dodecane as internal standard and not corrected for response factors of minor isomers. ^b The relative configuration of the major diastereomer of **3a** was confirmed by X-ray crystallographic analysis of **4a**.

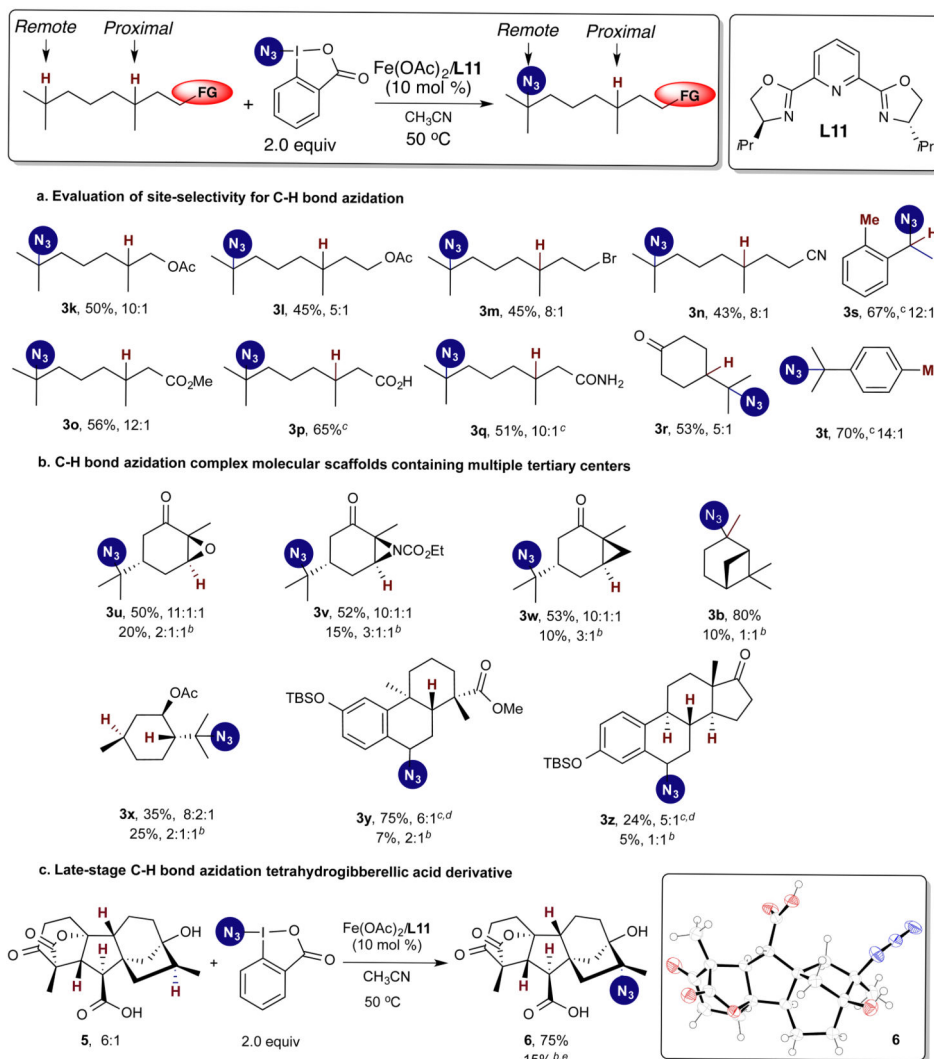
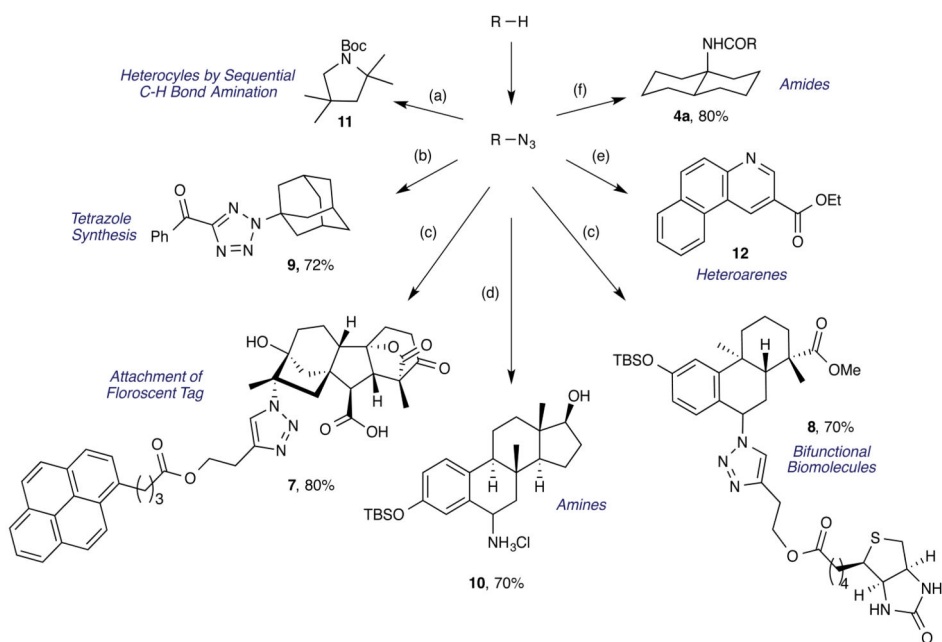


Fig. 2. Evaluation of the effect of the steric and electronic environment on site selectivity for the azidation of aliphatic 3° C–H bonds.^a

^a Conditions: 10.0 mol% Fe(OAc)₂, 11.0 mol% ligand, Substrate (0.2 mmol, 1.0 equiv.) and **1** (0.6 mmol, 3.0 equiv), 23 °C. Isolated yields of major azide products are reported unless mentioned otherwise. The ratios of isomers were determined by gas chromatography (GC) analysis with dodecane as internal standard and not corrected for response factors of minor isomers. ^b Conditions: 10.0 mol% BzOOBz, Substrate (0.2 mmol, 1.0 equiv.) and **1** (0.6 mmol, 3.0 equiv), 23 °C and DCE (0.5 ml) as solvent. The yield and ratios of isomers were determined by gas chromatography (GC) analysis with dodecane as internal standard. ^c EtOAc was used as solvent ^d diastereoselectivity was measured by ¹H NMR of crude reaction mixture. ^e Unidentifiable mixture of products.

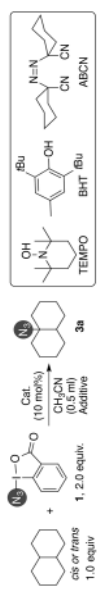
**Fig. 3.**

Introduction of a series of nitrogen-containing functionalities *via* C-H bond azidation.

^a Azide (1.0 equiv), [Fe cat.], Fmoc-OSuc, 65 °C, benzene, 24 h;¹⁶ ^b BzCN (2 equiv), 130 °C, 48 h; ^c CuSO₄ (10 mol%), alkyne (2 equiv), DMF, 48 h; ^d CuSO₄ (10 mol%), NaBH₄ (3 equiv), MeOH; ^e (1) TfOH (1.0 equiv), toluene, (2.0 equiv.) ethyl 3-ethoxyacrylate; (2) DDQ, EtOAc, 5 min;¹⁸ ^f (1) Pd/C, H₂, MeOH; (2) Ac₂O, DCM, 12 h.

Table 1

Experiments to evaluate the potential involvement of radical intermediates and the role of the iron catalyst in the C-H bond azidation reaction.^a



Entry	Substrate	Cat.	Temp. (°C)	Additive	Yield (%)	Selectivity
1	<i>cis</i>	Fe(OAc) ₂ /L11	23	TEMPO ^b	3	-
2	<i>cis</i>	Fe(OAc) ₂ /L11	23	BHT ^b	3	-
3 ^d	<i>cis</i>	Fe(OAc) ₂ /L11	80	-	55	3:2
4 ^d	<i>trans</i>	Fe(OAc) ₂ /L11	80	-	43	3:2
5 ^d	<i>cis</i>	BzOOBz	80	ABCN ^c	40	1:7
6 ^d	<i>trans</i>	BzOOBz	80	ABCN ^c	33	1:7

^a Conditions: 10.0 mol% catalyst, *cis* or *trans*-decalin (0.2 mmol, 1.0 equiv) and **1** (0.4 mmol, 2.0 equiv), 2 h. The yield and ratios of isomers were determined by gas chromatography (GC) analysis with dodecane as internal standard and not corrected for response factors of minor isomers.

^b 1.0 equiv. was added.

^c 1.0 mol% was added.

^d EtOAc was used as solvent.