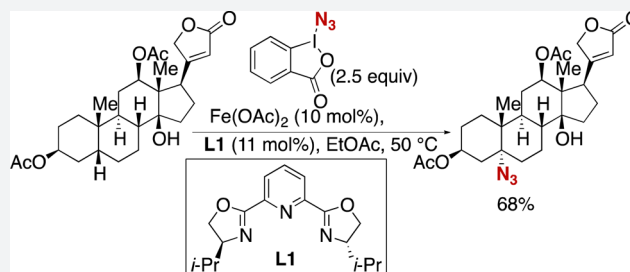# Late Stage Azidation of Complex Molecules

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S *Supporting Information*

ABSTRACT: Selective functionalization of complex scaffolds is a promising approach to alter the pharmacological profiles of natural products and their derivatives. We report the site-selective azidation of benzylic and aliphatic C−H bonds in complex molecules catalyzed by the combination of $Fe(OAc)_2$ and a PyBox ligand. The same system also catalyzes the trifluoromethyl azidation of olefins to form derivatives of natural products containing both fluorine atoms and azides. In general, both reactions tolerate a wide range of functional groups and occur with predictable regioselectivity. Azides obtained by functionalization of C−H and C═C bonds were converted to the corresponding amines, amides, and triazoles, thus providing a wide variety of nitrogen-containing complex molecules.

INTRODUCTION

Natural products and complex molecular architectures are underrepresented in modern screening efforts, in part due to the difficulty in accessing these types of molecules in large numbers.[1] These numbers are limited because the isolation of new natural products is slow. Thus, researchers have sought approaches to create collections of compounds that have structures like those of natural products. Several strategies have been followed to create these molecules, including pathway engineering[2] and diversity-oriented synthesis.[3−5]

Another approach that is beginning to be followed is the direct functionalization of natural products to create structures with precise, but substantial, perturbations to the structures of these molecules.[6−12] This approach can create complex molecules in a fashion that is suitable for programs in which libraries of molecules are screened for a biological activity.[13−23] This approach also can improve the pharmacological profiles of natural products or alter biological activities of specific lead structures.

However, the direct functionalization of complex molecules faces several challenges. These challenges include (1) the difficulty in conducting a reaction at one of many identical functional groups or at one of many unactivated C−H bonds, (2) the need to control or overcome the dependence of the reactivity of one functional group or C−H bond on the position and identity of nearby functional groups, (3) the difficulty in isolating a pure product from product mixtures, and (4) the need to identify the site at which the reaction occurs in a complex structure. A reaction that could be suitable for the direct functionalization of complex natural products would, therefore, need to occur under mild conditions, in the presence of a wide range of functional groups, to form one product or a tractable mixture of just a few products.

Amines and other nitrogen-containing functionalities are present in a majority of U.S. FDA approved small molecule pharmaceuticals.[24] This fact highlights the importance of the attractive interactions between nitrogen-containing functional groups in small molecules with proteins, as well as the effect of these functional groups on the pharmacological properties of the small molecules. Thus, late-stage introduction of a substituent into a complex molecule that can be used to generate a range of nitrogen-containing functionalities would be valuable to medicinal chemistry.

We have pursued a method to introduce azides into complex molecules.[25] We have pursued the introduction of this functional group because azides can be easily converted to a range of nitrogen-containing functional groups, such as amines and amides, as well as heterocycles, such as pyridines, triazoles, and tetrazoles.[26−28] Thus, the introduction of an azido group to complex molecules could enable the syntheses of structurally complex scaffolds containing various nitrogen-based functional groups. The azide functional group is more lipophilic and stable metabolically than a primary amine, and azides have been investigated in medicinal chemistry as prodrugs of primary amines.[29−33] In addition, the azide could serve as a point of attachment for various probes through Huisgen "click" cycloadditions and Staudinger ligations.[27,28] Recently, such reactions have been used to visualize biochemical processes in living cells and organisms.[34−36]

Many methods are available for the syntheses of aliphatic azides.[26,37,38] Recently developed methods include nucleophilic substitution reactions of tertiary alcohols,[39] trapping of the carbon-centered radicals generated through decarboxylation reactions,[40,41] radical functionalizations of olefins,[42−47] and azidation through C−C bond cleavage.[48] In addition to these methods, azides have been prepared by reactions at C−H bonds that are catalyzed by manganese−porphyrin complexes,
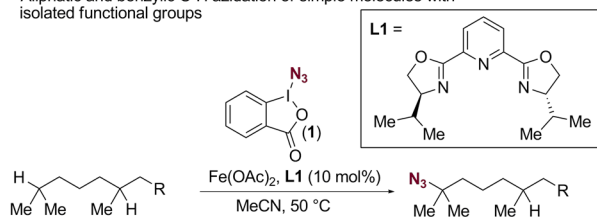
that are photoinduced or promoted by visible light, or that are conducted with an oxidant such as $K_2S_2O_8$.[25,49−54] Although diverse methods have been reported, the functionalization of natural products and complex pharmaceutical ingredients by these reactions has been limited to examples containing a minimum of functional groups.

We recently reported[25] the azidation of alkyl C−H bonds with a hypervalent iodine reagent catalyzed by an iron complex and demonstrated its tolerance for a range of functional groups (Chart 1). We also reported[25] the azidation of a derivative of

Chart 1. Fe(OAc)$_2$/i-Pr-PyBox Catalyzed Azidation Reactions

gibberellic acid, showing that this process has the potential to modify complex structures selectively. On this foundation, we have recently investigated the application of this reaction for the functionalization of representative examples of natural products drawn from a series of common classes. Through these studies, we sought to reveal the strengths and potential

limitations of this azidation of various complex molecules containing multiple functional groups. In parallel, we have conducted studies to extend this azidation of C−H bonds to the azidation of C=C bonds in natural products.

Here, we report the application of the iron-catalyzed C−H azidation to the site-selective azidation of 15 natural products to form pure azide derivatives and the extension of this process to the trifluormethylazidation of the alkenes in seven natural products. The products have been converted to the corresponding amines, amides, and triazoles; the examples we report create a framework for predicting the suitability of the azidation processes for the functionalization of complex, polyfunctional molecules.

■ RESULTS AND DISCUSSION

To begin our studies on the azidation of natural products, we applied the conditions that we recently reported for the azidation of C−H bonds in test substrates and a tetrahydrogibberellic acid. These conditions involved the combination of Fe(OAc)$_2$ and a PyBox ligand as catalyst and the readily available hypervalent iodine reagent 1 as the source of azide.[25] We found that benzylic, allylic, and alkyl C−H bonds were functionalized by this procedure. We also found that the combination of Fe(OAc)$_2$ and a PyBox ligand catalyzed diazidation and trifluoromethylazidation of olefins in related natural products. The following sections describe reactions that led to the functionalization of these three types of C−H bonds and to the C=C bonds of complex molecules. In general, the reactions tolerated a wide range of functional groups and occurred with regioselectivities that could be predicted by the steric accessibility and electronic properties of the C−H and C=C bonds.

Azidation of Benzylic C−H Bonds in Natural Product Derivatives. The azidation of benzylic C−H bonds in a series

Chart 2. Products from Azidation of Benzylic and Heterobenzylic C−H Bonds[a]
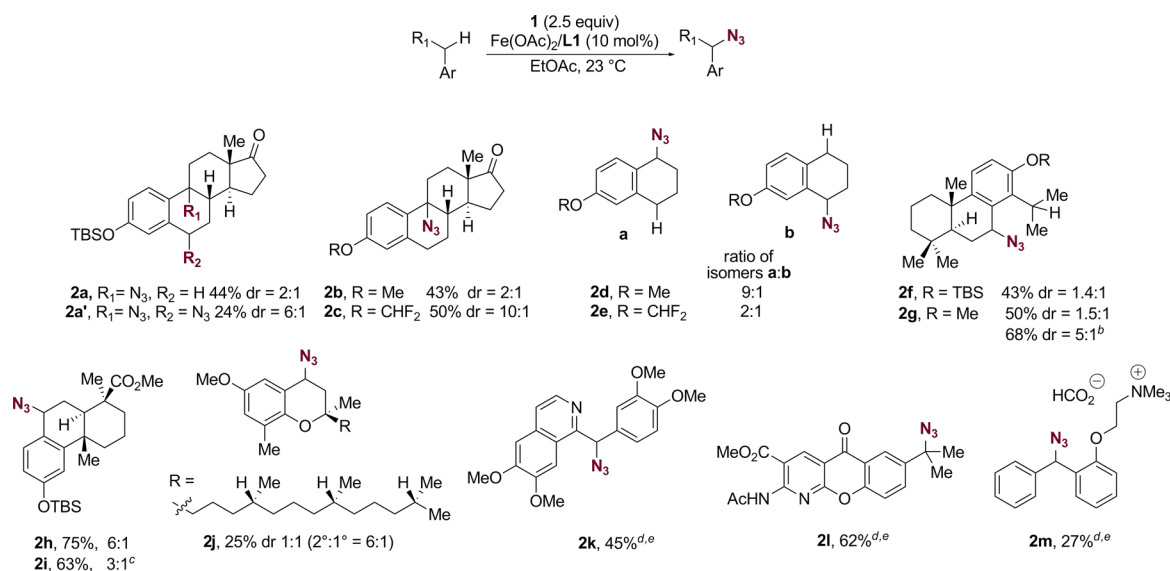
[a]Conditions: 1 (2.5 equiv),10 mol % Fe(OAc)$_2$, 11 mol % ligand L1, and 0.1 mmol of the substrate in EtOAc at 23 °C. Isolated yields of major azide products were reported unless mentioned otherwise. The ratios of isomers were determined by ^{1}H NMR analysis of the crude reaction mixtures. [b]Reaction was conducted with 80 mol % Fe(OAc)$_2$ and 88 mol % L1. [c]Reaction was conducted in heptane:EtOAc mixture (9:1) with enantiomer of the ligand L1. [d]CH$_3$CN was used as a solvent. [e]Reaction was conducted at 50 °C.

of natural products and pharmaceutical agents are shown in Chart 2. Derivatives of biologically active natural products and active pharmaceutical ingredients containing primary, secondary, and tertiary benzylic C–H bonds underwent site-selective azidation at the benzylic C–H bond. The specific examples include phenol derivatives containing a series of protecting groups or alkyl substituents on oxygen, and nitrogen heterocycles containing basic nitrogen atoms that could poison the catalyst or be subject to oxidation. These examples also include natural products containing both sterically accessible and sterically hindered benzylic C–H bonds.

These examples begin to reveal the rules guiding site selectivity and show that the azidation of complex molecules occurs at secondary and tertiary benzylic C–H bonds over primary benzylic C–H bonds. These examples also show that the selectivity between secondary and tertiary benzylic C–H bonds is controlled by the electronic and steric properties of those C–H bonds.

For example, estrone derivatives reacted to give the products from azidation of a benzylic C–H bond in good yields (**2a**–**2c**). The products from azidation of the tertiary benzylic C–H bond were obtained as the major product in the formation of **2a** or exclusive products in the formation of **2b** or **2c**. This selectivity is due to the electron-donating groups *para* to the tertiary C–H bond and higher stability of the tertiary benzylic radical over the secondary benzylic radical. Reaction of the TBS-protected estrone gave measurable amounts of the bis-azidation product (**2a**, R_1, R_2 = N_3) from reaction of the secondary benzylic C–H bonds of monoazidation product (**2a**, R_1 = N_3, R_2 = H), in addition to formation of the major product from reaction at the tertiary benzylic C–H bond. Formation of this bis-azidation product can be avoided by stopping the reaction at low conversion.

The diastereomeric excess of the products **2a** and **2b** formed from the two substrates bearing strong electron-donating OTBS and OMe substituents (**2a** and **2b**) is different from the diastereomeric excess of the product **2c** formed from reaction of the substrate bearing the weak electron-donating OCHF$_2$ substituent. This difference in selectivity could result from a change in the nature of the reaction intermediate. It is plausible that the initially formed benzylic radicals derived from the electron-rich TBS and Me ethers undergo oxidation to the corresponding carbocations and that trapping of this carbocation with azide results in a diastereoselectivity that is different from that from trapping of the initial benzylic radical. The diastereoselectivity from a reported azidation of the estrone 3-methyl ether involving a carbocationic benzylic intermediate was similar to that we observed for reaction of the **2a** and **2b**.[55]

Given these results with **2a**–**2c**, we conducted reactions on the simpler substrates **2d** and **2e** to reveal the effect of the electronic properties of the substrate on the azidation of benzylic C–H bonds. These examples underscore the preferential reaction at electron-rich C–H bonds over electron-deficient C–H bonds. The benzylic methylene C–H bonds of **2d** that are located *para* to the electron-donating OMe group reacted preferentially over the benzylic methylene C–H bonds located *meta* to the OMe group. In contrast, the reaction of the analogous tetralin derivative containing a more weakly electron-donating OCHF$_2$ substituent on the arene ring gave a 2:1 mixture of isomers **2e**.

The reaction of the TBS and Me ether derivatives of totarol revealed the influence of the steric environment on the regioselectivity of the benzylic C–H azidation. These TBS and methyl ether derivatives of totarol reacted to form products **2f** and **2g** resulting from azidation of the secondary C–H bonds; no reaction at the exocyclic tertiary C–H bond was observed. This selectivity for secondary over tertiary C–H bonds contrasts the selectivity for secondary versus tertiary C–H bonds in the estrone derivatives **2a**–**2c**. We hypothesize that allylic (A$_{1,3}$) strain forces the isopropyl substituent to adopt a conformation that aligns the tertiary C–H bond with the σ-plane of the aromatic ring, even with the small size of the phenol protecting group in **2g**. In this conformation, the emerging radical resulting from homolysis of this C–H bond would not be stabilized by the π-system of the aromatic ring.

Changing the reaction conditions can alter the diastereoselectivity of the benzylic azidation. For example, the diastereoselectivity and yield of the C–H azidation of the methyl ether derivative of totarol were higher when a higher loading of the catalyst was used. Diastereomers **2g** were obtained in 5:1 ratio when 80 mol % catalyst was used, as opposed to a 1.5:1 ratio when 10 mol % of catalyst was used. We do not have an explanation for the origin of this difference in selectivity, but it can be used to synthetic advantage.

Changing the absolute configuration of the ligand altered the diastereoselectivity of the azidation reaction. Podocarpic acid underwent azidation at a benzylic C–H bond in the presence of the catalyst containing the (*S*,*S*)-ligand to give derivative **2h** in excellent yield and 6:1 diastereoselectivity. Azidation of the same substrate in the presence of the enantiomer of the *i*-Pr-PyBox ligand **L1** occurred with only 3:1 diastereoselectivity (entry **2i**). Although small, these changes in diastereoselectivity imply that the iron center is involved in the formation of the C–N bond.

The reaction of the δ-tocopherol derivative **2j** showed that benzylic C–H bonds undergo the catalytic azidation reaction in preference to tertiary alkyl C–H bonds. This example also shows that a secondary benzylic C–H bond is significantly more reactive than a primary benzylic C–H bond. The azidation of **2j** occurred to give a 6:1 ratio of products from reaction at the secondary benzylic C–H bond over reaction at the primary benzylic C–H bonds, even though the molecule contains more primary C–H bonds than secondary C–H bonds.

Azidation of Benzylic C–H Bonds in Active Pharmaceutical Ingredients. Active pharmaceutical ingredients often contain heterocycles. Basic nitrogen atoms in these heterocycles can poison a catalyst by coordinating to the metal center, and they can undergo oxidation reactions. However, this azidation protocol tolerates basic nitrogens, such as those in a pyridine or those in 2-amidopyridine. As shown in Chart 2, azidation of active pharmaceutical ingredients containing pyridyl and 2-amidopyridyl groups formed products **2k** and **2l** in good to moderate yield. The balance of the material was mostly unreacted substrate.

Ethers and tertiary amines are not tolerated by most C–H functionalization reactions that occur through free radicals. Typically, hydrogen atom abstraction occurs from C–H bonds located alpha to the oxygen or nitrogen in these functional groups. We hypothesized that conversion of a tertiary amine to the corresponding quaternary ammonium salt would electronically deactivate C–H bonds proximal to nitrogen, thereby enabling selective azidation of distal C–H bonds.[56,57] Indeed, conversion of the tertiary amine to its corresponding quaternary ammonium salt to create a strong electron-

withdrawing group inhibited the reaction at the positions alpha to both the nitrogen and proximal oxygen atoms. Thus, azidation of this ammonium salt occurred at the secondary benzylic C−H bonds to form product **2m**. Procedures to induce demethylation of quaternary methylammonium salts under mild conditions are known.[58,59] Methyl aryl ethers were also tolerated under the conditions for azidation of benzylic C−H bonds (entries **2c**, **2d**, **2g**, **2j**, **2k**).

Azidation of Alkyl C−H Bonds in Complex Molecules. Natural products containing electron-rich, tertiary alkyl C−H bonds and lacking benzylic C−H bonds underwent azidation at the tertiary C−H bond. The azidation process tolerated ketone, ester, amide, tertiary alcohol, and epoxide functional groups. Alkyl C−H bonds located farther from an electron-withdrawing group reacted selectively over tertiary C−H bonds located closer to an electron-withdrawing group (Chart 3). For

Chart 3. Products from Azidation of the Aliphatic C−H Bonds of Natural Products[a]
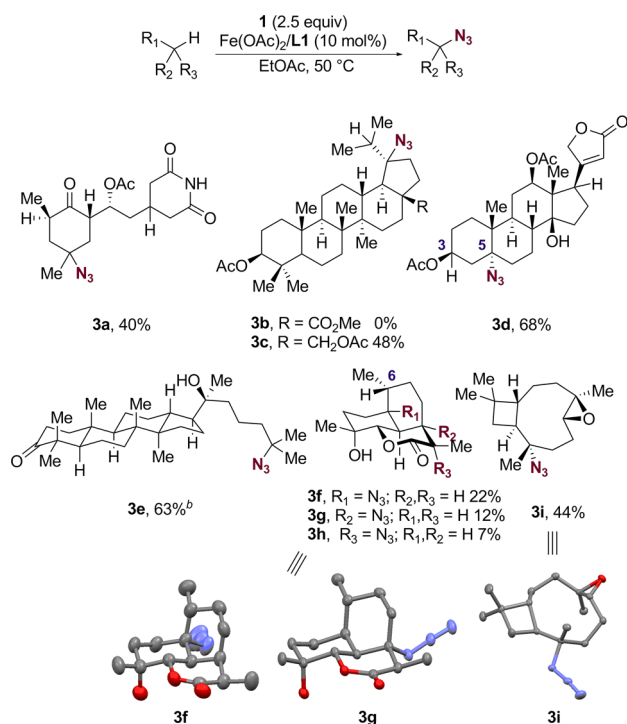
- Sterically accessible, electron rich C-H bonds react preferentially
- *Cis*-decalin fragments are particularly reactive.

[a]Conditions: **1** (2.5 equiv), 10 mol % Fe(OAc)₂, 11 mol % ligand **L1**, and 0.1 mmol of the substrate in EtOAc at 50 °C. Isolated yields of major azide products were reported unless mentioned otherwise. [b]Reaction was run in MeCN at 50 °C.

example, cycloheximide acetate gave the C−H azidation product **3a** exclusively. Azidation of the betulinic acid derivative containing an electron-withdrawing alkoxycarbonyl group did not give azidation product **3b** (no reaction was observed), but a structurally similar betulin derivative containing a more electron-donating acetoxymethyl group at the position of the ester gave azide **3c** in good yield.

Like the azidations of benzylic C−H bonds, the azidations of alkyl C−H bonds are sensitive to steric effects. Tertiary C−H bonds at the ring junction of *trans*-decalin motifs did not react (**3b**, **3d**, **3e**), but the more sterically accessible tertiary C−H

bonds at the ring junctions of *cis*-decalin motifs were particularly reactive. For example, the tertiary C5−H bond in digoxigenin diacetate reacted to yield the azide **3d** in good yield. In addition to the difference in steric properties of the *cis*- and *trans*-decalin ring structures, the C−H bond of the *cis*-decalin is weaker than that of *trans*-decalin because of the effects of conformation. Hydrogen atom abstraction from *cis*- and *trans*-decalin gives the same radical intermediate, but *cis*-decalin is the less stable starting structure.[60]

Consistent with a process occurring through a radical intermediate, the configuration of the carbon atom at the reaction site in *cis*-decalin structures inverts during the reaction. For example, the *cis*-decalin A/B ring system of digoxigenin was converted to its more stable *trans*-decalin stereoisomer during the azidation process, resulting in azide **3d** that contains a trans A/B ring system. This azidation causes the acetate at C3 to occupy an equatorial position, instead of the axial position in the starting digoxigenin diacetate. The size of the acetate, presumably, helps bias the reaction toward exclusive formation of the *trans*-decalin product.

The reaction of a derivative of artemisinic acid allowed us to probe a more complex interplay between steric and electronic effects on the regioselectivity of this azidation reaction. Azidation of this substrate gave a mixture of three main products (**3f**–**3h**). Although the hydrogen atom on C6 is the tertiary C−H bond that is located furthest from an electron-withdrawing group, it did not undergo C−H azidation. We reason that a reaction did not occur at this position because this C−H bond is located on the concave face of the molecule. Thus, the tertiary C−H bonds on the more sterically accessible convex face of the molecule reacted, and they reacted according to the general trends of the other molecules: The most abundant product resulted from reaction at the more electron rich tertiary C−H bond. The identities of products **3f**, **3g**, and **3h** were unambiguously determined by X-ray diffraction. (Chart 3; for the ORTEP of **3h** and data for all structures see the Supporting Information).

The reaction of dihydrocaryophyllene oxide also occurred with regioselectivity in accord with that of the reactions of the other natural products. The reaction of dihydrocaryophyllene oxide occurred at the most electron-rich C−H bond to give the corresponding azide **3i** without significant opening of the strained cyclobutane and epoxide rings. The identity of **3i** was unambiguously determined by single crystal X-ray analysis.

Azidation of Complex Molecules Containing Alkene Units. Alkenes in natural products can be the site of a reaction or, in C−H bond functionalization processes, weaken juxtaposed C−H bonds and cause them to be the site of reaction. To assess the factors controlling whether the alkene, the allylic C−H bond, or a non-allylic C−H bond is the site of reaction, we conducted azidation reactions on a series of natural products containing alkenes. These results are shown in Chart 4 and as the example of digoxigenin azidation (**3d**) in Chart 3.

As noted in the previous section, the azidation of a digoxigenin derivative containing an unsaturated butenolide unit occurred at an electron-rich tertiary C−H bond over the allylic C−H bond to form azide **3d** (Chart 3). We propose that the reaction occurs at the stronger tertiary C−H bond over the weaker allylic C−H bond of the butenolide because the allylic C−H bond in this structure is electron poor.

The examples in Chart 4 summarize our results on azidation reactions of more electron-rich trisubstituted and disubstituted alkenes. These data show that derivatives of natural products

Chart 4. Products from Azidation of Natural Products Containing Alkenes[a]

4a, 42%   **4b**, 26%[b]

4c, 56%
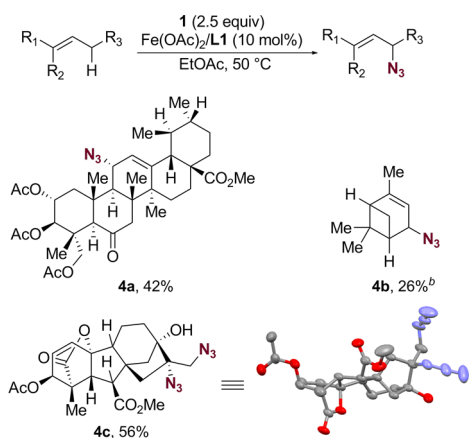
- Trisubstituted olefins undergo allylic C-H azidation
- 1,1-disubstituted olefins undergo bis-azidation

[a]Conditions: **1** (2.5 equiv), 10 mol % Fe(OAc)$_2$, 11 mol % ligand **L1**, and 0.1 mmol of the substrate in EtOAc at 50 °C. [b]Reaction was run at 23 °C. Isolated yields of major azide products were reported.

containing trisubstituted olefins reacted to give the corresponding products of allylic azidation. For example, the madecassic acid derivative, as well as α-pinene, reacted to give the allylic azides **4a** and **4b**, although in modest yields. In addition to allylic C−H azidation product **4a**, the madecassic acid derivative yielded 16% of a diene side product (see the [Supporting Information](#)). This 1,3-diene side product, presumably, arises from oxidation of the allylic radical to the corresponding allylic carbocation, which is then deprotonated to deliver the diene.
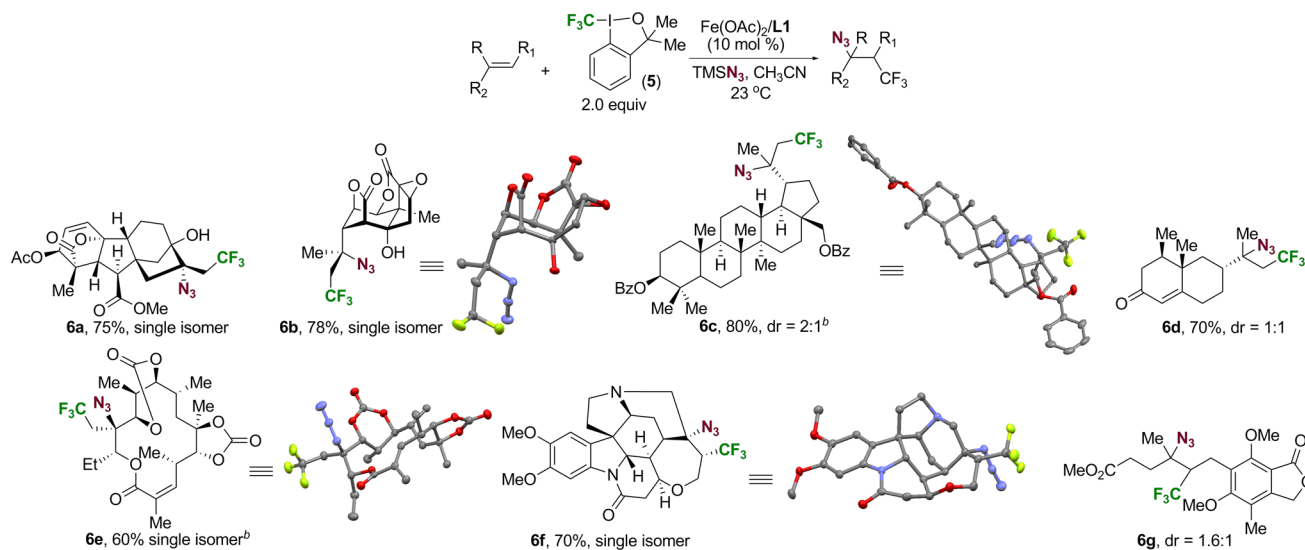
In contrast to these allylic azidations of trisubstituted alkenes, a gibberellic acid derivative that contains 1,2- and 1,1-disubstituted olefins reacted selectively at the 1,1-disubstituted olefin to yield diazide **4c**. This diazidation of the alkene, presumably, occurs by initial addition of the azidyl radical to the 1,1-disubstituted double bond. Single crystal X-ray analysis unambiguously confirmed the structural assignment of diazide **4c**.

Trifluoromethylazidation of Olefins in Complex Molecules. The high yielding diazidation reaction of the gibberellic acid derivative to produce diazide **4c** suggested that olefin difunctionalization reactions, in addition to C−H azidation reactions, could be catalyzed by the combination of Fe(OAc)$_2$ and the PyBox ligand. We sought to conduct the concomitant installation of an azide and a fluoroalkyl group at an alkene catalyzed by this iron complex because fluoroalkyl groups are often present in pharmaceutical agents and agrochemicals due to the unique properties of fluorine.[61,62] Moreover, small molecule screening for drug discovery based on ^{19}F HMR spectroscopy allows rapid and simultaneous screening of large numbers of targets and small molecules,[63] and the azide functional group is amenable to bioorthogonal "click reactions" for target identification. Finally, concurrent installation of the trifluoromethyl and azide groups would enable the syntheses of beta-trifluoromethyl amines.

Copper-catalyzed trifluoromethyl azidation of olefins with Togni's reagent and TMSN$_3$ was recently reported.[43] Although this method has broad functional group tolerance, examples of trifluoromethylazidation were limited to substrates containing a single functional group and relatively simple natural products or their derivatives.

We found that the combination of Fe(OAc)$_2$ and **L1** catalyzed trifluoromethylazidation of olefins in complex natural products with Togni's reagent (**5**) and TMSN$_3$ as the source of the CF$_3$ and azide groups (Chart 5). In all products, the trifluoromethyl group is bonded to the less-substituted carbon atom, and the azide group is bonded to the tertiary carbon atom. This regioselectivity suggests that addition of a trifluoromethyl radical to the alkene occurs to generate a tertiary alkyl radical, which was trapped by a source of azide to form the observed products.

Chart 5. Products from Trifluoromethylazidation of Natural Products[a]

6a, 75%, single isomer   **6b**, 78%, single isomer   **6c**, 80%, dr = 2:1[b]   **6d**, 70%, dr = 1:1

6e, 60% single isomer[b]   **6f**, 70%, single isomer   **6g**, dr = 1.6:1

[a]Conditions: **5** (2 equiv), TMSN$_3$ (1.5 equiv), 10 mol % Fe(OAc)$_2$, 11 mol % ligand **L1**, and 0.1 mmol of the substrate in CH$_3$CN at 23 °C. [b]Reaction was conducted in EtOAc. Isolated yields of major CF$_3$/azide products were reported unless mentioned otherwise. The ratios of isomers were determined by ^{19}F NMR analysis of the crude reaction mixtures.

Various natural products including terpenes, alkaloids, and polyketides underwent this difunctionalization. 1,1-Disubstituted olefins in gibberellic acid and picrotoxinin underwent trifluoromethylazidation to yield **6a** and **6b** in excellent yield, diastereoselectivity, and regioselectivity. A betulin derivative gave azidation product **6c** in excellent yield and 2:1 diastereoselectivity. The reaction to form **6a** showed that 1,1-disubstituted olefins reacted preferentially over 1,2-disubstituted olefins (entry **6a**), and the reactions to form **6d** and **6e** showed that 1,1-disubstituted olefins bearing alkyl substituents reacted over trisubstituted olefins bearing electron-withdrawing substituents.

We investigated a two-step strategy involving dehydration and trifluoromethylazidation to prepare macrocyclic polyketide derivatives containing the CF_3 and azide groups. For example, readily available 9-(S)-hydroxyerythronolide was converted to product **6e** in two steps. Dehydration and protection of the secondary alcohols, followed by olefin functionalization, gave **6e** in 46% yield (see the Supporting Information for more details). This sequence represents a practical strategy for the semisynthesis of unnatural polyketide macrocycles.

Brucine, which contains several functional groups that are highly reactive toward free radicals, including a tertiary amine and an ether, underwent trifluoromethylazidation at the olefin to give **6f** in high yield. The acyclic olefin in a mycophenolic acid derivative also reacted in high yield, although the diastereoselectivity of the reaction was low (entry **6g**).

Site-Selective Introduction of an Azide into the Cholesterol Scaffold. Having revealed azidation reactions occurring at tertiary C−H bonds, benzylic C−H bonds, and C−C double bonds, we investigated the ability of these reactions to be conducted selectively on a scaffold containing all of these structural units. The cholesterol scaffold is a common one containing these units and one for which benchmark reactions have been reported. For example, the azidation of the cholesterol scaffold has been reported at both the C3 and C6 positions. Nucleophilic substitution was used to install an azide group at the C3 position (**7a**).[64] A two-step olefin functionalization reaction involving hydroboration and azidation of the resulting B-alkylcatecholborane under free radical conditions led to the product **7b** containing the azide group at the C6 position.[65]

Iron-catalyzed C−H and C=C azidation protocols enabled installation of an azide at positions that are different from those of the stoichiometric, reagent-based methods. Scheme 1 summarizes how iron-catalyzed C−H and C=C functionalization methodologies can be used to install azide groups at the C5, C7, and C25 positions of the cholesterol scaffold. Our iron-catalyzed trifluoromethylazidation reaction gave, in high yield and diastereoselectivity, compound **7c** containing an azide group at the C5 position and a trifluoromethyl group at the C6 position. A cholesterol derivative in which the C3 carbinol has been protected as its corresponding benzoate ester underwent azidation at the allylic C−H bond in the presence of the $Fe(OAc)_2$-PyBox catalyst to form azide **7d**. The azidation was directed to the C−H bond at the C25 position by initial hydrogenation of the C5−C6 olefin. The reaction formed the azide **7e** in 23% isolated yield; this yield was modest because small amounts of product from azidation at C14 also formed, along with various diazidation products. Overall, these transformations illustrate how modern catalytic methods can complement classic transformations to achieve site-selective functionalization of structures based on natural products.

Scheme 1. Azidation of the Scaffold of Cholesterol[a]
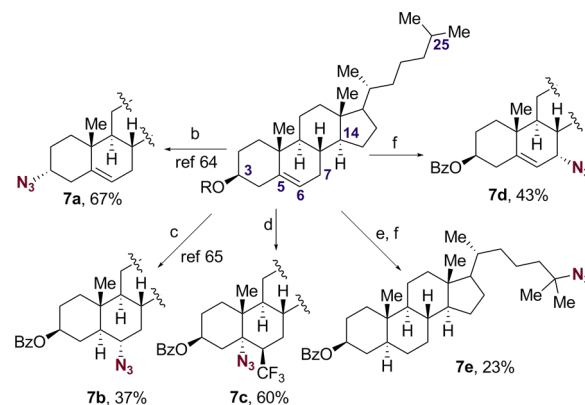
[a]Conditions: (b) R = H; (i) $MeSO_2Cl$, Py, 0 °C; (ii) NaN_3, DMF, reflux; (c) R = Bz; (i) CatBH, MeCONMe₂ (cat); (ii) $PhSO_2N_3$, t-BuON=NOt-Bu, 80 °C; (d) R = Bz; Togni's reagent (**5**), TMSN₃; $Fe(OAc)_2$ (10 mol %), **L1** (11 mol %) 23 °C; (e) H₂, Pd/C (10 mol %), EtOAc, 23 °C; (f) R = Bz; **1**, $Fe(OAc)_2$ (10 mol %), **L1** (11 mol %), 50 °C. Yields of azidation reactions are shown.

Limitations of the Azidation of Natural Products. Although the data we report show that the azidation of C−H bonds in complex molecules occurs with broad scope, certain molecules did not react in high yields or with high site selectivity. In general, molecules containing strong electron-withdrawing groups proximal to the tertiary C−H bonds or containing C−H bonds that are sterically inaccessible did not undergo azidation to give isolable amounts of azidation products. Molecules containing many highly reactive C−H bonds, such as C−H bonds located α to heteroatoms, yielded mixtures of products that we were unable to separate.

For example, attempts to conduct azidation of the monensin derivative **8a** under our standard reaction conditions resulted in a complex mixture of products (Chart 6). We propose that

Chart 6. Molecules That Gave Intractable Mixtures from the Azidation Procedure or Did Not React
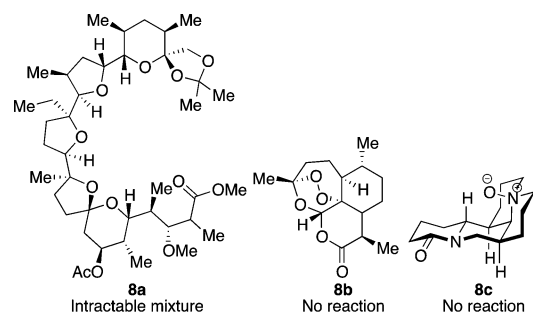
unselective functionalization of the C−H bonds located alpha to the ether oxygen atoms led to this mixture. In addition, natural products that contain electron-deficient tertiary C−H bonds, such as artemisinin (**8b**) and oxymatrine (**8c**), did not react; in these cases the starting material was recovered. Azide derivatives of artemisinin have now been prepared by alternative protocols for the azidation of C−H bonds.[50,51]

**Derivatization of Azide-Containing Natural Products.** Although organic azides are present in select active pharmaceutical ingredients (APIs), most prominently in the anti-HIV medicine 3′-azido-3′-deoxythymidine (AZT),[66] the main application of the products of azidation is as a precursor

to molecules containing various nitrogen-based functional groups.[67] Amines, amides, and heterocycles, which can be readily accessed from the azides, are present in a majority of APIs and are widespread in natural products.

We conducted studies to assess whether the azides in these complex structures can be converted to amines, amides, and triazoles under mild conditions, as is typical for small molecules. As shown in Chart 7, benzylic, alkyl, allyl, and

**Chart 7. Derivatization of Complex Molecule Azides**[a]
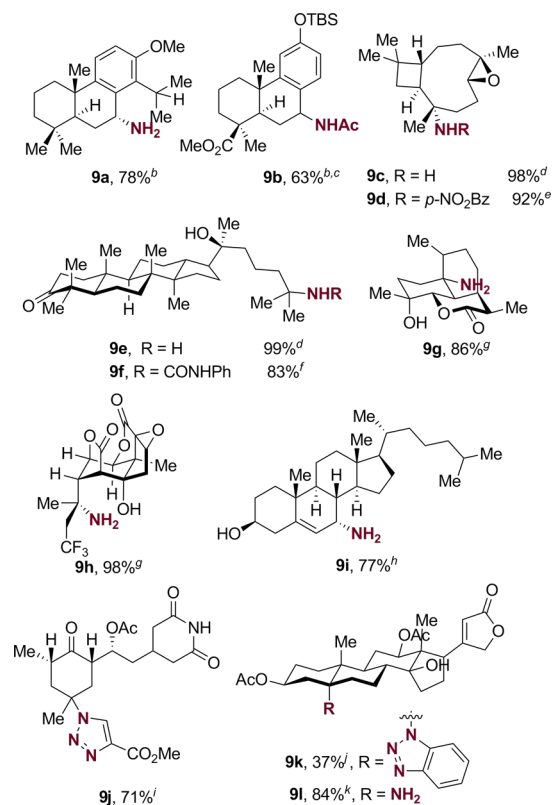
[a]Conditions: (b) Me3P, H2O, THF 23 °C; (c) Ac2O Py; (d) H2 (1 atm), Pd/C (20 mol %) 23 °C; (e) p-NO2BzCl, DMAP, Et3N, CH2Cl2, 23 °C; (f) PhNCO, Py, CH2Cl2 23 °C; (g) H2 (1 atm), PtO2 (20 mol %) 23 °C; (h) LiAlH4, THF 65 °C; (i) HCCO2Me, 65 °C; (j) 2-(trimethylsilyl)phenyl triflate, CsF, MeCN, 23 °C; (k) NaBH4, CuSO4 (20 mol %), MeOH/THF.

beta-trifluoromethyl azides were converted to the corresponding primary amines by the reduction of the azides under mild conditions. Benzylic azides were converted to benzylic amines under the conditions of a Staudinger reduction. For example azide **2g** was converted to **9a** in high yield and isolated as a free amine. Alternatively, one-pot reduction of the azide **2h**, followed by acetylation, gave acetamide (**9b**). Tertiary azides **3i**, **3e**, **3g**, and **6b** were reduced to the corresponding amines under hydrogenation conditions using Pd/C or PtO2 as a catalyst (entries **9c**, **9e**, **9g**, and **9h**). Amines **9c** and **9e** were converted to the corresponding p-NO2Bz amide **9d** and urea **9f** in high yield.

Cycloaddition chemistry of azides is now a classic, reliable reaction. Indeed, the triazole derivative of cycloheximide **9j** and the benzotriazole derivative of digoxigenin **9k** were prepared by [3 + 2] cycloaddition reactions between the azide of cycloheximide **3a** and digoxigenin **3d** generated by our C−H bond azidation and an alkyne or a benzyne generated in situ.

Experimental logD Values for the Nitrogen-Containing, Natural-Product Derivatives. Late-stage functionalization provides the potential to enhance the water solubility of natural products by the introduction of a polar functional group.[68] We investigated the effect of late-stage azidation and derivatization of the azides prepared by our catalytic reactions on the lipophilicity of several natural product derivatives. Chart 8 summarizes the experimental logD values for the azide derivatives of the natural products and several of the products from derivatization of the azide.

Chart 8. Experimental logD$_{7.4}$ Values of Natural Product Derivatives and Their Nitrogen-Containing Derivatives
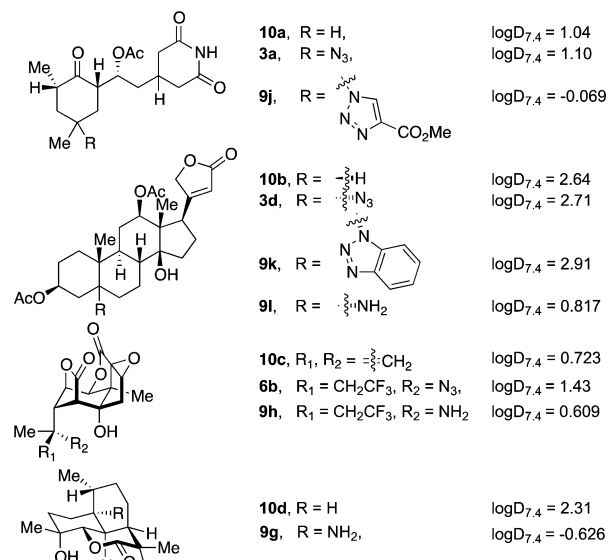
Introduction of ionizable functional groups, which carry a positive or negative charge, increase the water solubility significantly. At neutral pH, the nitrogen-containing functional groups can be charged or neutral depending on the pK_a values of the conjugate acid. Azides are protonated only under strongly acidic conditions and are neutral at physiological pH. Therefore, introduction of the azide group into these complex molecules had little effect on the logD values. The lipophilicity of the products from azidation of cycloheximide and digoxigenin derivatives **3a** and **3d** was slightly higher than that of the starting materials **10a** and **10b**. As expected, trifluoromethylazidation of the olefin in pictoroxinin increased the logD values more than azidation of the tertiary C−H bonds in cycloheximide and digoxigenin derivatives, due to the high lipophilicity of the CF3 group (compare entries **10c** vs **6b** for trifluoromethylazidation of picrotoxinin and entries **10a** vs **3a** and **10b** vs **3d** for C−H azidation of cycloheximide and digoxigenin derivatives).

Nitrogen atoms in triazoles are weakly basic. Thus, only a small fraction of the triazoles are protonated at neutral pH. The partitioning of ester-substituted triazole **9j** into water was significantly higher than that of cycloheximide derivative **10a**, presumably because the nitrogen atoms in the triazole and oxygen atoms in the ester act as hydrogen bond acceptors. In contrast, the partitioning of the benzotriazole derivative of digoxigenin **9k** into water was lower than that of **10b**, due to the presence of hydrophobic benzene ring.

Aliphatic amines are usually protonated at physiological pH. Therefore, introduction of the amines into these natural products by the combination of azidation and reduction of the azides to the primary amine significantly increased the water solubility of the structures. For example, the partitioning of the amine derivatives of both digoxigenin **9l** and artemisinic acid **9g** was significantly higher than that of the starting materials **10b** and **10d**.

Overall, these logD studies revealed that our C−H azidation protocol provides a useful tool for tuning the lipophilicity of the structurally complex scaffolds. Although introduction of the azido group itself had little effect on the lipophilicity of complex molecules, further derivatization of these azides created products with a wide range of logD values (e.g., digoxigenin derivatives **10b**, **3d**, **9k**, and **9l**).

SUMMARY

We have demonstrated that the iron-catalyzed azidation of C−H bonds can lead to the functionalization of a wide range of complex natural products and their derivatives, and that the reactions can occur with high site selectivity in many cases. Benzylic, allylic, and alkyl C−H bonds reacted with the hypervalent iodine reagent **1** in the presence of catalytic amounts of $Fe(OAc)_2$ and the PyBox ligand **L1** to produce the corresponding secondary and tertiary azides in moderate to good yield. The Fe−PyBox system also catalyzes the diazidation of 1,1-disubstituted olefins and the trifluoromethylazidation of a variety of olefins in complex structures.

Our results suggest that both steric and electronic effects strongly influence the site selectivity of the C−H azidation reaction. The following trends can be used to predict the relative reactivity of various C−H bonds.

(1) Electron-rich and sterically accessible C−H bonds are the most reactive sites for azidation.

(2) Secondary and tertiary benzylic C−H bonds are more reactive toward this azidation than are alkyl and primary benzylic C−H bonds.

(3) Among alkyl C−H bonds, only the tertiary C−H bonds reacted.

(4) Trisubstituted olefins underwent allylic C−H bond azidation while 1,1-disubstituted olefins underwent alkene diazidation.

(5) The combination of $Fe(OAc)_2$ and PyBox ligand **L1** catalyzes the trifluoromethylazidation of a variety of olefins in complex molecules. 1,1-Disubstituted olefins are the most reactive olefins toward trifluoromethylazidation, and electron-rich olefins underwent trifluoromethylazidation selectively over electron-poor olefins.

This azidation enables the rapid synthesis of small-molecule probes through introduction of both reactive (N_3 group) and observable handles (CF_3 group). Azides could be used to prepare nitrogen-containing derivatives of natural products for SAR studies. We have shown that azide derivatives of complex molecules can be converted to the corresponding amines, amides, and triazoles in high yield.

The time and expense required for target-based syntheses, especially syntheses of complex natural products, makes it important to develop a lexicon of reactions that are suitable for the late stage functionalization of complex molecules, and this work shows that the azidation of C−H bonds and alkenes is clearly suitable for derivatization of a range of natural products. Such reactions can expand chemical space rapidly for use in medicinal chemistry settings, and further studies on systems that enable late-stage functionalization reactions are underway in our lab.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.6b00214.

Experimental procedures and characterization of all new compounds (PDF)
Crystallographic data for **3f** (CIF)
Crystallographic data for **3g** (CIF)
Crystallographic data for **3h** (CIF)
Crystallographic data for **3i** (CIF)
Crystallographic data for **4c** (CIF)
Crystallographic data for **6b** (CIF)
Crystallographic data for **6c** (CIF)
Crystallographic data for **6e** (CIF)
Crystallographic data for **6f** (CIF)

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Notes
The authors declare no competing financial interest.

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