Metal–catalysed azidation of tertiary C–H bonds suitable for late-stage functionalization

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Many enzymes oxidize unactivated aliphatic C–H bonds selectively to form alcohols; however, biological systems do not possess enzymes that catalyse the analogous aminations of C–H bonds1–2. The absence of such enzymes limits the discovery of potential medicinal candidates because nitrogen-containing groups are crucial to the biological activity of therapeutic agents and clinically useful natural products. In one prominent example illustrating the importance of incorporating nitrogen-based functionality, 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 treatment time3–5. For such reasons, synthetic chemists have sought catalysts that directly convert C–H bonds to C–N bonds. Most currently used catalysts for C–H bond amination are ill suited to the intermolecular 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 atom6–14. Among C–H bond amination reactions, those forming a C–N bond at a tertiary alkyl group would be particularly valuable, because this linkage is difficult to form from ketones or alcohols that might be created in a biosynthetic pathway by oxidation15. Here we report a mild, selective, iron–catalysed azidation of tertiary C–H bonds that occurs without excess of the valuable substrate. The reaction tolerates aqueous environments and is suitable for the functionalization of complex structures in the late stages of a multistep synthesis. Moreover, this azidation makes it possible to install a range of nitrogen-based functional groups, including those from Huisgen ‘click’ cycloadditions and the Staudinger ligation16–19. We anticipate that these reactions will create opportunities to modify natural products, their precursors and their derivatives to produce analogues that contain different polarity and charge as a result of 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 on 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). Such a reagent is related to hypervalent reagents commonly used for oxidation20 and is thermally stable (up to 130 °C)21. It has sufficient thermodynamic potential to convert alkyl C–H bonds to alkyl azides, but the published reactions have been limited to simple hydrocarbons, typically used in excess amounts, or activated C–H bonds at high temperatures in the presence of radical initiators21. Thus, the current azidations of C–H bonds by this reagent22 are not suitable for late-stage functionalization of complex molecules. 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–porphyrin complexes were reported to catalyse the formation of alkyl azides using sodium azide and iodosobenzene or βBuOOH as oxidants, but the reactions were limited to hydrocarbons, an excess of the alkane (10 equiv.) was required, and a major by-product was the corresponding alcohol22–24.

To identify a metal complex that would catalyse 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

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Figure 1 | Development of a catalyst for the azidation of aliphatic C–H bonds. Top row, reactions studied. *Conditions: 10.0 mol% Fe(OAc)2, 11.0 mol% ligand (L1–L11), cis-decalin (0.2 mmol, 1.0 equiv.) and 1 (0.4 mmol, 2.0 equiv.), 23 °C, 1 ml of CH3CN. †The relative configuration of the major diastereomer of 3a was confirmed by X-ray crystallographic analysis of 4a. ‡Combined yield of isomers. Middle and bottom rows, structural formulae of ligands L1–L11. Also shown are yields and the ratios of isomers determined by gas chromatography analysis with dodecane as internal standard; ratios are not corrected for response factors of minor isomers.

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tested as catalysts with the hydrocarbon as limiting reagent; only iron complexes provided measurable yields of azide product at 23 °C (Supplementary Table 1). Combinations of Fe(OAc)$_2$ and various bi-, tri- and tetra-dentate nitrogen ligands (L1–L5 in Fig. 1), including those that catalyse the selective hydroxylation of aliphatic C–H bonds (L1 and L3)$^{25,26}$, provided low yields 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 in Fig. 1). Finally, we found that reactions of iron complexes containing tridentate nitrogen ligands of the pybox family (L10 and L11 in Fig. 1) 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 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; Supplementary Table 2). 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 (Supplementary Table 3), 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 Fig. 2a. These reactions revealed the inherent electronic selectivity of the azidation reaction

![Image](image-url)

**Figure 2 | Evaluation of the effect of the steric and electronic environment on site selectivity for the azidation of aliphatic tertiary C–H bonds.** Top row, reaction studied. *Conditions: 10.0 mol% Fe(OAc)$_2$, 11.0 mol% ligand L11, substrate (on left: 0.2 mmol, 1.0 equiv.) and 1 (0.6 mmol, 3.0 equiv.), 23 °C, 1 ml of CH$_3$CN. Isolated yields of major azide products are reported unless otherwise mentioned. The ratios of isomers were determined by gas chromatography analysis with dodecane as internal standard, and are not corrected for response factors of minor isomers. a, Evaluation of site selectivity for C–H bond azidation. The ratios reported reflect the site selectivity for reaction at the two tertiary C–H bonds (3k to 3r) or the two benzylic C–H bonds (3s,3t). 3k–3t are the products formed from the azidation. †FeOAc was used as solvent. b, C–H bond azidation of complex molecular scaffolds containing multiple tertiary centres. Yields of products 3u–3z were also compared to those of the benzyl-peroxide-initiated reaction, as follows. ‡Conditions: 10.0 mol% Br2O2Bz, substrate (0.2 mmol, 1.0 equiv.) and 1 (0.6 mmol, 3.0 equiv.), 84 °C and 1,2-dichloroethane (1.0 ml) as solvent. The yield and ratios of isomers were determined by gas chromatography analysis with dodecane as internal standard. The ratios refer to the major product versus minor product determined to be isomers by mass spectrometry. c, Late-stage C–H bond azidation of a tetrahydrogibberellic acid derivative. As reaction at top, except substrate is 5, and 6 is product. §Diastereoselectivity was measured by $^1$H NMR of crude reaction mixture. || Unidentifiable mixture of products.
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 (3k–3q in Fig. 2a). The regioselectivity of azidation at the two electronically distinct tertiary C–H bonds was influenced by the distance of the electron-withdrawing group from the 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.67 Functional groups—such as an alcohol protected as an acetoxy group (3k and 3l), a bromide (3m), a nitrite (3n), an ester (3o), a carboxylic acid (3p) and an amide (3q)—were tolerated. Functional groups like a 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-Proplylcyclohexane underwent azidation with high regioselectivity for the more electron-rich of the two tertiary C–H bonds (3r in Fig. 2a). 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 in Fig. 2a).

Having revealed high regioselectivity for 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 instead of a C–H bond or influence the identity of the C–H bond that undergoes azidation (Fig. 2b). 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 isolated yields (3u–3w in Fig. 2b). 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 (2b, 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 preferential at the iso-propyl side chain to provide one major constitutional isomer in moderate isolated yield (3x in Fig. 2b). This selectivity, presumably, results from the greater conformational flexibility of the iso-propyl side chain. Isomeric products from azidation of a different C–H bond were observed as minor products; again, these products were formed in quantities too low for full characterization, but were shown to be isomers by mass spectrometry.

Unlike the stereoretentive property of the metal-catalysed insertions of nitrenes or carbenes into C–H bonds,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 one to use mixtures of diastereomeric reactants (see Supplementary Table 3 and Fig. 2; explicitly, 2b to form 3b and 5 to form 6) to provide one major diastereomer of the azide product (see below).

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 antileukaemic 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 in Fig. 2b). Similar selectivity was also observed for the azidation of an oestrone (3z in Fig. 2b).

The reaction of a gibberellic acid derivative illustrates the ability to conduct the azidation of complex structures (Fig. 2c). 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–H bond, the one at carbon 8, should react selectively. In addition, the stereochemical outcome of the azidation of cis- and trans-decalin and α-dihydropinene (Supplementary Table 3 and Fig. 2b) suggested that the configuration of the reactive centre in substrate 5 would have a negligible influence on the diastereomeric ratio of product 6 (Fig. 2c). Indeed, the azidation of a mixture of diastereomers 5 provided the corresponding azide 6 as a single isolated diastereoisomer in 75% yield (Fig. 2c) from exo-attack of the azide unit at C(8).

Finally, we also tested functionalizations of the complex scaffolds shown in Fig. 2b and c by 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. 2b 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 (Supplementary Table 3 and Fig. 2b). Attempts to use radical clocks to assess more directly a potential alkyl radical were

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**Table 1 | Experiments to evaluate the involvement of radical intermediates and the role of the iron catalyst**

| Entry | Substrate | Catalyst | Temperature (°C) | Additive | Yield (%) | Selectivity |
|-------|-----------|----------|-----------------|----------|-----------|------------|
| 1     | cis       | Fe(OAc)₂/L11 | 23               | TEMPO⁻ | 3         | NA         |
| 2     | cis       | Fe(OAc)₂/L11 | 23               | BHT⁺ | 3         | NA         |
| 3†    | cis       | Fe(OAc)₂/L11 | 80               | NA     | 55        | 3.2        |
| 4†    | trans     | Fe(OAc)₂/L11 | 80               | NA     | 43        | 3.2        |
| 5†    | cis       | BzOOBz    | 80               | ABCN⁻ | 40        | 1.7        |
| 6†    | trans     | BzOOBz    | 80               | ABCN⁻ | 33        | 1.7        |

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 analysis with dodecane as internal standard and not corrected for response factors of minor isomers. NA, not applicable.

* 1.0 equiv. was added.
† 1.0 mol% was added.
‡ 6%DAc was used as solvent.
These reactions were lower than those of the iron-catalysed reactions. The selectivities for formation of the azidation product from poor yields were observed in all cases from the reactions initiated by the and c with the reactions initiated by benzoyl peroxide. As noted above, the overall turnover-limiting step. (Fig. 3)16–19. The primary amine formed from azides reaction of an alkyl radical with an iron azide intermediate. ence is formation of the C–N bond in the iron-catalysed process by 80 electron-rich, less polarized, and thus weaker, tertiary C–H bonds intermediate is consistent with the selectivity for azidation of the more complementary Information for more details), but the proposed radical hampered by the poor reactivity of the appropriate substrates (see Supplementary Information for more details), but the proposed radical much development of this C–H bond functionalization method remains to be accomplished, 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 the 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 proceed by distinct mechanisms with distinct selectivities for primary, secondary and tertiary C–H bonds. As rhodium-catalysed 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 content of the ligand creates the potential for enantioselective natural products30.

Much development of this C–H bond functionalization method remains to be accomplished, 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 the 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 proceed by distinct mechanisms with distinct selectivities for primary, secondary and tertiary C–H bonds. As rhodium-catalysed 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.

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1. Bollinger, J. M. & Broderick, J. B. Frontiers in enzymatic C-H-bond activation. Curr. Opin. Chem. Biol. 13, 51–57 (2009).
2. Lewis, J. C., Coelho, P. S. & Arnold, F. H. Enzymatic functionalization of carbon-hydrogen bonds. Chem. Soc. Rev. 40, 2003–2021 (2011).
3. Ploffe, J. et al. Clinical efficacy of intravenous followed by oral azithromycin monotherapy in hospitalized patients with community-acquired pneumonia. Antimicrob. Agents Chemother. 44, 1796–1802 (2000).
4. O’Doherty, B., Muller, O. & Grp, A. S. 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. Infect. Dis. 17, 828–833 (1998).
5. Jeffrey, J. L. & Sarpong, R. Intramolecular C(sp3)–H amination. Chem. Sci. 4, 4092–4106 (2013).
6. Ochiai, M., Miyamoto, K., Kaneaki, T., Hayashi, S. & Nakanishi, W. Highly regioselective amination of unactivated alkanes by hypervalent sulfonylelimino-Λ3-bromane. Science 332, 448–451 (2011).

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**Figure 3 | Introduction of a series of nitrogen-containing functionalities via C–H bond azidation.** a, Azide (1.0 equiv.), Fe cat., Fmoc-OSuc (1.5 equiv.), 65°C, benzene, 24 h (see ref. 19 for details). b, BrCN (2 equiv.), 130°C, 48 h; c, CuSO4 (10 mol%), alkyn (2 equiv.), DMF, 48 h; d, CuSO4 (10 mol%), N3. e, PhCN (2 equiv.), 130°C, 48 h; f, NaBH4 (3 equiv.), MeOH; g, (1) TBOH (1.0 equiv.), toluene (2.0 equiv.), ethyl 3-ethoxyacrylate; (2) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), EtOAc, 5 min (ref. 18); h, (1) Pd/C, H2, MeOH; (2) Ac2O, dichloromethane, 12 h. with azido gibberellic acid derivative 6, and an azide 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 products19.
7. Loulliat, M. L. & Patureau, F. W. Oxidative C-H amination reactions. Chem. Soc. Rev. 43, 901–910 (2014).
8. Rozen, J. L., Harvey, M. E. & Du Bois, J. Metal-catalyzed nitrogen-atom transfer methods for the oxidation of aliphatic C-H bonds. Acc. Chem. Res. 45, 911–922 (2012).
9. Dequiedt, G., Pons, V. & Dauban, P. Nitrone chemistry in organic synthesis: still in its infancy? Angew. Chem. Int. Edn Engl. 51, 7384–7395 (2012).
10. Lescot, C., Darnés, B., Collet, F., Retailleau, P. & Dauban, P. Intermolecular C-H amination of complex molecules: insights into the factors governing the selectivity. J. Org. Chem. 77, 7232–7240 (2012).
11. Rozen, J. L., Zalatan, D. N. & Du Bois, J. Selective intermolecular amination of C-H bonds at tertiary carbon centers. Angew. Chem. Int. Edn Engl. 52, 11343–11346 (2013).
12. Michaudel, Q., Thevenet, D. & Baran, P. S. Intermolecular Ritter-type C-H amination of unactivated sp3 carbons. J. Am. Chem. Soc. 134, 2547–2550 (2012).
13. Li, J. et al. Simultaneous structure-activity studies and arming of natural products by C-H amination reveal cellular targets of eupalmerin acetate. Nature Chem. 5, 510–517 (2013).
14. McNally, A., Haffemayer, B., Collins, B. S. L. & Gaunt, M. J. Palladium-catalysed C-H amination of tertiary-alkyl isonitriles and amines. Nature 510, 129–133 (2014).
15. Pronin, S. V., Reiher, C. A. & Shenvi, R. A. Stereoinversion of tertiary alcohols to tertiary-α-alkyl isonitriles and amines. Nature 501, 195–199 (2013).
16. Brase, S., Gil, C., Knepper, K. & Zimmermann, V. Organic azides: an exploring diversity of a unique class of compounds. Angew. Chem. Int. Edn Engl. 44, 5188–5240 (2005).
17. Schilling, C. I., Jung, N., Biskup, M., Schepers, U. & Brase, S. Bioconjugation via azide-Staudinger ligation: an overview. Chem. Soc. Rev. 40, 4840–4871 (2011).
18. Lallana, E., Riguera, R. & Fernandez-Mega, E. Reliable and efficient procedures for the conjugation of biomolecules through Huisgen azide-alkyne cycloadditions. Angew. Chem. Int. Edn Engl. 50, 8794–8804 (2011).
19. Henners, E. T. & Betley, T. A. Complex N-heterocycle synthesis via iron-catalyzed, direct C-H bond amination. Science 340, 591–595 (2013).
20. Zhdankin, V. V. Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds (Wiley & Sons, 2013).
21. Zhdankin, V. V. et al. Preparation, X-ray crystal structure, and chemistry of stable azidoiodinanes — Derivatives of benziodoxole. J. Am. Chem. Soc. 118, 5192–5197 (1996).
22. Hill, C. L., Smegal, J. A. & Henly, T. J. 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 Mn4TPPX complexes with phase-transfer catalysis. J. Org. Chem. 48, 3277–3281 (1983).
23. Rozen, J. L., Harvey, M. E. & Du Bois, J. Meta-catalyzed nitrogen-atom transfer methods for the oxidation of aliphatic C-H bonds. Acc. Chem. Res. 45, 911–922 (2012).
24. Zhdankin, V. V. Nitrone chemistry in organic synthesis: still in its infancy? Angew. Chem. Int. Edn Engl. 51, 7384–7395 (2012).
25. Zhdankin, V. V. Intermolecular Ritter-type C-H amination of unactivated sp3 carbons. J. Am. Chem. Soc. 115, 11328–11335 (1993).
26. Costas, M. Selective C-H oxidation catalyzed by metalloporphyrins. Coord. Chem. Rev. 255, 2912–2932 (2011).
27. Kim, C., Chen, K., Kim, J. H. & Que, L. Stereoselective alkane hydroxylation with \( \text{H}_2\text{O}_2 \) catalyzed by an iron(l)-tris(2-pyridylmethyl)amine complex. J. Am. Chem. Soc. 119, 5964–5965 (1997).
28. Chen, M. S. & White, M. C. A predictably selective aliphatic C-H oxidation reaction for complex molecule synthesis. Science 318, 783–787 (2007).
29. Newhouse, T. & Baran, P. S. If C-H bonds could talk: selective C-H bond oxidation. Angew. Chem. Int. Edn Engl. 50, 3362–3374 (2011).
30. Davies, H. M. L. & Morton, D. Guiding principles for site selective and stereoselective intermolecular C-H functionalization by donor/acceptor rhodium carbenes. Chem. Soc. Rev. 40, 1857–1869 (2011).
31. Demko, Z. P. & Sharpless, K. B. A click chemistry approach to tetrazoles by Huisgen 1,3-dipolar cycloaddition: synthesis of 5-acyltetrazoles from azides and acyl cyanides. Angew. Chem. Int. Edn Engl. 41, 2113–2116 (2002).
32. Trippier, P. C. Synthetic strategies for the biotinylation of bioactive small molecules. ChemMedChem 8, 190–203 (2013).

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