C–H Activation

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Site-Selective Catalytic C(sp^2)–H Bond Azidations**

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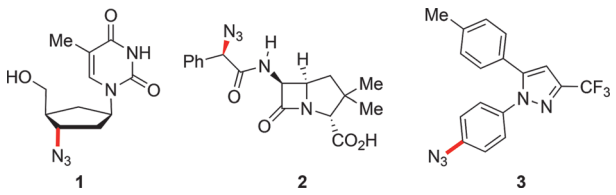
arenes · azides · C–H activation · heterocycles · homogeneous catalysis

Organic azides are key structural motifs in compounds of relevance to biology, medicinal chemistry, and materials science.[1] Thus, various azido-substituted compounds, such as azidothymidine (**1**, AZT), azidocillin (**2**), or the COX-2 inhibitor and colecoxib derivative **3**, exhibit valuable biological activities (Scheme 1). Moreover, the unique reactivity of organic azides resulted in numerous applications as versatile



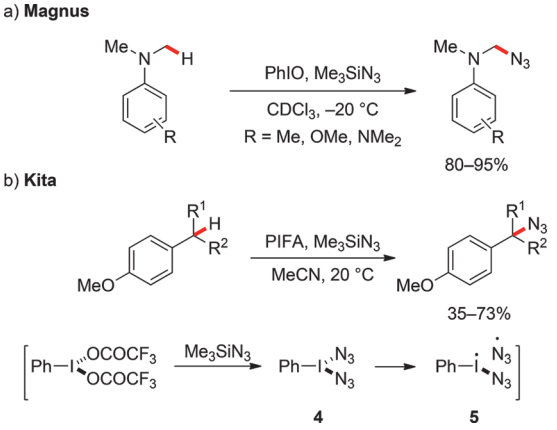
Scheme 1. Selected azido-substituted bioactive compounds.

intermediates in organic synthesis, most notably in the copper-catalyzed 1,3-dipolar Huisgen cycloaddition.[2]

As a consequence, protocols for the chemoselective preparation of organic azides continue to be in high demand. While traditional methods, such as the Sandmeyer reaction, have proven valuable, they are unfortunately accompanied by the formation of stoichiometric amounts of potentially hazardous by-products. On the contrary, more step-economical direct azidations through the cleavage of unactivated C–H bonds[3] represent a significantly more attractive strategy, with notable recent progress being achieved in intermolecular C–N bond formations.[4]

The considerable strength (438.9 kJ mol^{-1} for CH_4, 472.4 kJ mol^{-1} for PhH) and low acidity (pK_a = 43–59 in DMSO) of unactivated C–H bonds[5] calls for the use of rather strong oxidants for direct C–H bond azidations.[6] Thus, iodosylbenzene or phenyliodonium bis(trifluoroacetate) (PIFA), in combination with Me_3SiN_3, allowed C(sp^3)–H bond azidations (Scheme 2),[7] which were proposed to occur by homolytic bond cleavage through key intermediates **4** and **5**.

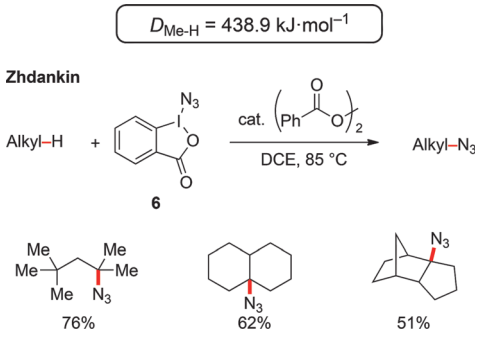
Likewise, related radical azidations proved viable with stable, crystalline reagent **6** and catalytic amounts of benzoyl



Scheme 2. Radical-based azidations of C(sp^3)–H bonds.[7]

peroxide, thereby even enabling efficient C–H bond azidations on simple hydrocarbons (Scheme 3).[8]

A significantly altered chemoselectivity was however observed by Kita and co-workers in 1991, when they utilized polar protic solvents, such as hexafluoroisopropanol. Hence, stoichiometric amounts of hypervalent iodine(III) reagents allowed the direct azidation of more stable C(sp^2)–H bonds in electron-rich arenes at ambient reaction temperature, with π-



Scheme 3. Azidations of alkanes with the well-defined reagent **6**.[8]

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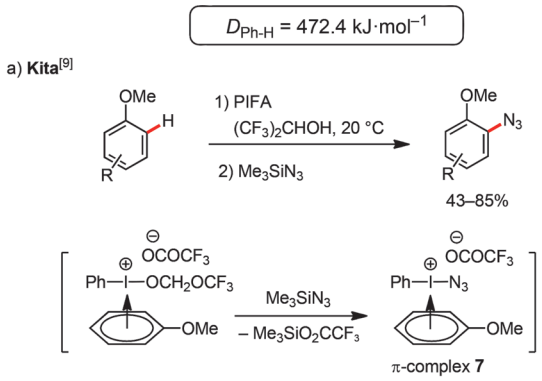
complex **7** as a proposed key intermediate (Scheme 4a).[9] Conversely, the azidation of electron-rich heteroaromatic substrates required a one-pot multistep protocol involving copper catalysis, as reported by Suna in 2012.[10a] Thus, the

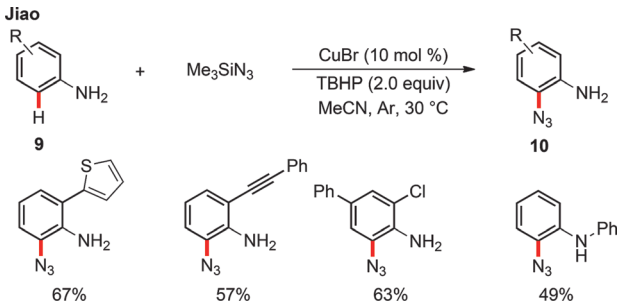


Scheme 4. Direct azidations of C(sp^2)–H bonds.

in situ generated heteroaryl(phenyl)iodonium azides **8** underwent a copper(I)-catalyzed regioselective fragmentation to furnish heteroaromatic azides (Scheme 4b), thereby indicating the potential of copper complexes for C–N_3 bond forming processes. The azides were subsequently transformed into the corresponding 1,2,3-triazoles or amines by cycloaddition or reduction, respectively.

One of the key challenges in the direct intermolecular functionalization of arenes is the achievement of site-selectivity, which is predominantly accomplished through the assistance of chelation. Particularly, removable and/or modifiable Lewis basic directing groups are highly attractive. Hence, a considerable advance in direct C(sp^2)–H bond azidations was accomplished in 2012 by Tang and Jiao through the development of copper(I)-catalyzed direct C–N bond formations, exploiting readily available amino[11] substituents as the site-selectivity-ensuring directing groups.[10b] Thus, use of inexpensive CuBr as the catalyst, in combination with Me_3SiN_3, site-selectively delivered the *ortho*-azidated products **10** under remarkably mild reaction conditions (Scheme 5). Notably, hypervalent iodine(III) reagents were not required as the sacrificial oxidants, but *tert*-butylhydroperoxide (TBHP) was found to be a cost-effective alternative, even though it is utilized in a superstoichiometric fashion.

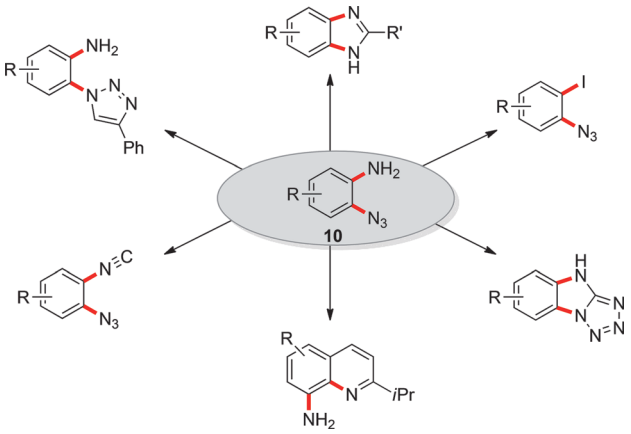
The catalytic system displayed an outstanding chemoselectivity, which was inter alia illustrated by a remarkable functional-group tolerance.[10b] Moreover, both primary as well as secondary amines proved to be suitable substrates. As to the catalyst working mode, preliminary studies with radical inhibitors indicated a reaction manifold involving a sequence of single-electron-transfer (SET) steps. The power of the amino-directed C–H bond azidation approach was elegantly



Scheme 5. Copper(I)-catalyzed direct azidations of anilines **9**.[10b]

illustrated by the subsequent diversification of the thus obtained *ortho*-azidoanilines **10** (Scheme 6).[10b]

In summary, considerable progress has recently been made in the challenging direct azidations through C–H bond cleavages. Thus, inexpensive copper(I) catalysts enabled site-



Scheme 6. Diversification of *ortho*-azidoanilines **10**.[10b]

selective direct C–N bond formations on readily available aniline derivatives with broad substrate scope. In consideration of the increasing practical importance of organic azides, further progress is expected in this rapidly evolving research area.

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