# CHEMISTRY
## A European Journal

## Accepted Article

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## COMMUNICATION

# A C-H Cyanation of 6-Ring *N*-Containing Heteroaromatics

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**Abstract:** Heteroaromatic nitriles are important compounds in drug discovery, both for their prevalence in the clinic and due to the diverse range of transformations they can undergo. As such, efficient and reliable methods to access them have the potential for far-reaching impact across synthetic chemistry and the biomedical sciences. Here we report an approach to heteroaromatic C-H cyanation through triflic anhydride activation, nucleophilic addition of cyanide, and concomitant elimination of trifluoromethanesulfinate to regenerate the cyanated heteroaromatic ring. This one-pot protocol is simple to perform, is applicable to a broad range of decorated 6-ring *N*-containing heterocycles and has been shown to be suitable for late-stage functionalization of complex drug-like architectures.

The nitrile group is an important chemical motif, commonly found in molecules throughout chemistry, biology and medicine. In chemistry, it is a versatile intermediate that can act as precursor to a number of functional groups such as amides, amines and carboxylic acids, and to five- and six-membered heterocycles *via* cycloaddition or condensation reactions.[1] In medicine, the polarity, directionality, and low molecular weight of the nitrile moiety make it a substituent of choice in SAR studies, both as a diverse isostere capable of precise hydrogen bonding, and as a beneficial modifier of physicochemical properties.[2] As a result of these properties it can be found attached to *N*-containing heterocycles in a host of important pharmaceuticals including the tyrosine kinase inhibitor bosutinib (**1**), xanthine oxidase inhibitor topiroxostat (**2**), and MIV-150 (**3**), a nonnucleoside reverse transcriptase inhibitor (Scheme 1a). Owing to their synthetic relevance and prevalence in biologically active heterocyclic compounds, there is demand for new and effective methods to install this important functional group. To this end recent efforts have largely focused on the discovery of metal-catalysed coupling procedures[3] as well as the invention of direct C–H activation protocols.[4] Despite the many advances in the field we recognized that the development of a complementary and direct C-H cyanation protocol that was



Scheme 1. (a) Nitrile containing drugs: bosutinib (**1**), tyrosine kinase inhibitor; topiroxostat (**2**), xanthine oxidase inhibitor; MIV-150 (**3**) nonnucleoside reverse transcriptase inhibitor. (b) proposed three-stage protocol for one-pot C-H cyanation.
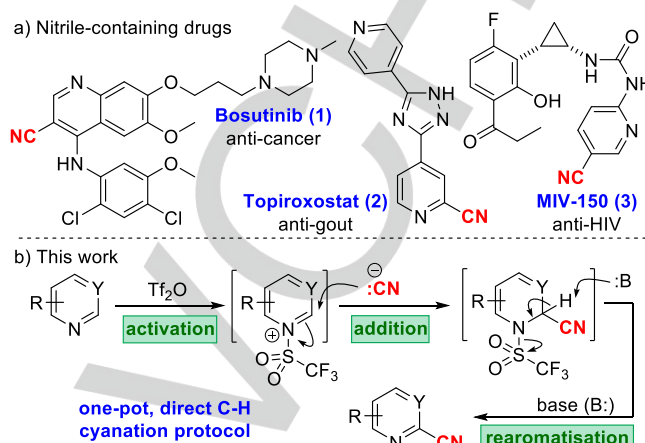
general to many classes of *N*-containing heterocycles would likely find application in library generation and target synthesis and herein we wish to report our findings.

Our plan was to exploit the nucleophilicity of the *N*-atom contained within various 6-ring heterocycles as a general activation mode to introduce the nitrile moiety. Following initial nucleophilic addition to a suitable electrophilic species (such as triflic anhydride), the heteroaromatic ring would be activated towards subsequent nucleophilic attack of cyanide and concomitant base mediated elimination of trifluoromethanesulfinate anion could generate the cyanated heteroaromatic ring (Scheme 1b).[5] The activation of *N*-containing heteroaromatic species *via* reaction of various electrophiles at nitrogen has previously been deployed to effect a range of transformations, and examples of carbon-, phosphorus-, and sulfur-based activating groups have been reported.[6] We hoped to build on this approach to develop a mild and convenient one-pot cyanation protocol that would be both general to many 6-ring *N*-containing heterocycles and useful for late stage functionalization of drug-like molecules.

2-Phenylpyridine (**4**) was chosen as a model substrate to enable us to study reactivity *and* product isomeric ratio distribution in the planned three-stage, one-pot cyanation protocol. An initial survey of variables such as electrophilic activator, cyanide source and base was performed. Inspired by the work of Corey, triflic anhydride (Tf$_2$O) was found to be uniquely effective as an activator,[7] while trimethylsilyl cyanide was identified as the most convenient and effective cyanide source for productive C-C bond formation. Following full consumption of the activated pyridinium species, addition of *N*-methylmorpholine (NMM) ensured conversion to the final,

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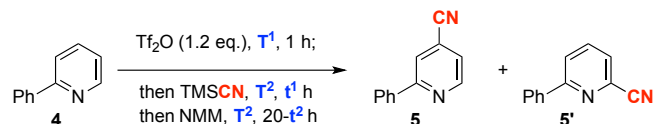[+]  These authors contributed equally to this work
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heteroaromatic product. Using this combination of reagents, nitrile **5** was produced as a mixture of isomers in moderate yield,

**Table 1.** Selected reaction optimisation data.[a]



| Entry | $T^1$ (° C) | $T^2$ (° C) | $t^1$ (h) | Solvent | Yield[b] | Ratio **5:5'**[c] |
|---|---|---|---|---|---|---|
| 1 | -78 | 40 | 0 | $CH_2Cl_2$ | 30% | 53:47 |
| 2 | -78 | 40 | 3 | $CH_2Cl_2$ | 61% | 59:41 |
| 3 | 21 | 40 | 3 | $CH_2Cl_2$ | 75% | 61:39 |
| 4 | 21 | 110 | 3 | PhMe | 59% | 62:38 |
| 5 | 21 | 80 | 3 | DCE | 69% | 61:39 |
| **6** | **21** | **60** | **3** | **CHCl$_3$** | **80%** | **61:39** |
| 7[d] | 21 | 60 | 3 | CHCl$_3$ | 74% | 59:41 |

[a] Conditions: Tf$_2$O (1.2 eq) added to substrate (100 mg) in solvent (0.1 M) at T$^1$, stirred 1 h, then TMSCN (5.0 eq) added, warmed to T$^2$ for t$^1$. NMM (1.3 eq.) added, stirred for 20-t$^1$ h before quench with NaHCO$_3$. Fully rearomatised in each case. [b] Isolated yield. [c] Determined following isolation by flash column chromatography. [d] Performed on 1 g scale. NMM = *N*-methylmorpholine.

but importantly in the absence of any non-aromatized intermediates (Table 1, entry 1). The timing and temperature of the different steps in the procedure were found to be important for reaction yield: delaying addition of base (entry 2) significantly improved production of **5**, with further improvement afforded by warming the first step of the reaction from –78 °C to room temperature (entry 3). Switching to higher boiling solvents allowed us to assess the effect of temperature in the rearomatization step (entries 4, 5 and 6), and CHCl$_3$ at 60 °C was identified as optimal, with high yield retained upon scale up (entry 7). It is noteworthy that the ratio of **5:5'** remained essentially constant throughout our studies despite temperature and solvent variation, with a slight preference for cyanation in the 4-position over the 6-position (**5:5'**; ~60:40). Products of cyanation at the 2-, 3- or 5-position of **4** were not observed.

With an optimized general procedure in hand, the substrate scope of the cyanation was investigated (Scheme 2). Pyridines are extremely widespread motifs in bioactive compounds, both in nature and in the clinic, and as such methods for their functionalization are highly sought after. We were delighted to see that this practical, one-pot protocol was effective across a diverse range of heteroaromatic ring systems, giving aromatic cyanated products in up to 96% yield (Scheme 2a). Substrates possessing aromatic (**5**, **6**) and electron-withdrawing (**8**-**13**) substituents gave excellent yields, with no competitive addition to the ester group in **11** observed. Halide (**14**, **15**) and alkyl (**7**, **16**-**19**) substituents were also well-tolerated in various positions. The alkyl substituents demonstrate compatibility with electron-donating groups, while the halopyridines are particularly

noteworthy for their potential for further downstream orthogonal transformations. Of the pyridines surveyed, substitution was generally favored at the 4-position, with minor, separable quantities of other isomers produced in some cases. The isolation of these additional compounds could be valuable as further analogues for inclusion in SAR studies. Quinolines and isoquinolines represent an important class of ring system in medicinal chemistry and accordingly were attractive substrates to investigate.[8] Pleasingly, cyanated quinolines **20-22** were produced in excellent yields (Scheme 2b), with substitution at the 2-position predominating (a reversal of the selectivity observed for pyridines). Isoquinolines were also highly effective substrates yielding fully rearomatized 1-substituted nitriles **23** and **24** as single isomers. Diazines (pyridazine, pyrimidine and pyrazine) represent a diverse class of heterocycle where the presence of the second nitrogen atom in the 6-membered ring provides electronically distinct examples; it is thus not unsurprising that no single reported cyanation procedure is applicable to members of each class. However, our protocol proved successful across a diverse range, with cyanated pyridazine (**25**-**27**, **34**), pyrimidine (**28**-**30**, **35**) and pyrazine (**31**-**33**) examples produced in moderate to excellent yields (Scheme 2c). Bidentate ligands are ubiquitous in organometallic chemistry and new methods to modify and tune them are in constant demand. We observed straightforward cyanation of **36**-**38**, with only traces of di-cyanated products observed for **36**, allowing facile synthesis of useful unsymmetrical cyanated ligands.

To further demonstrate the general applicability of our methodology we examined more complex heterocyclic structures which are commonly found in commercial pharmaceuticals and agrochemicals (Scheme 2e).[8] A series of cyanated heterocycles were produced (**39**-**51**), with excellent yields obtained in the presence of halides (**40**, **42**, **44**, **46**, **47**), and non-reactive heterocycles (**48**, **49**, **51**). The production of cyanated analogues of such diverse heterocyclic structures demonstrates the power of this methodology as a tool for medicinal chemistry and It is worthy of note that all of the examples described in Scheme 2 were produced using a single experimental protocol.

Finally, we sought to demonstrate the potential of the methodology for the late-stage functionalization of complex substrates, a concept that is becoming increasingly popular (Scheme 3).[9,10] Using the standard protocol we were able to cyanate abiraterone acetate (**52**, a treatment for prostate cancer) in excellent yield with three different analogues produced. Protected erlotinib (**53**, a treatment for lung and pancreatic cancer) afforded a good yield of a single isomer, while mirtazapine (**54**, an antidepressant) gave a moderate yield of the 4-CN derivative in the presence of electron-donating groups on the pyridine moiety. Quinine is included on the World Health Organization's List of Essential Medicines for its important anti-malarial properties; following *O*-methylation, it was cyanated in good yield to provide **55** as a single regioisomer. As well as further extending the scope, the latter two examples demonstrate the tolerance of the method to basic amine functionality, although we hypothesize that competitive and reversible coordination of these groups to the activator results in low conversion in the case of **54**.
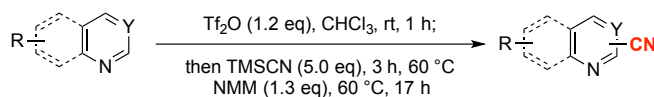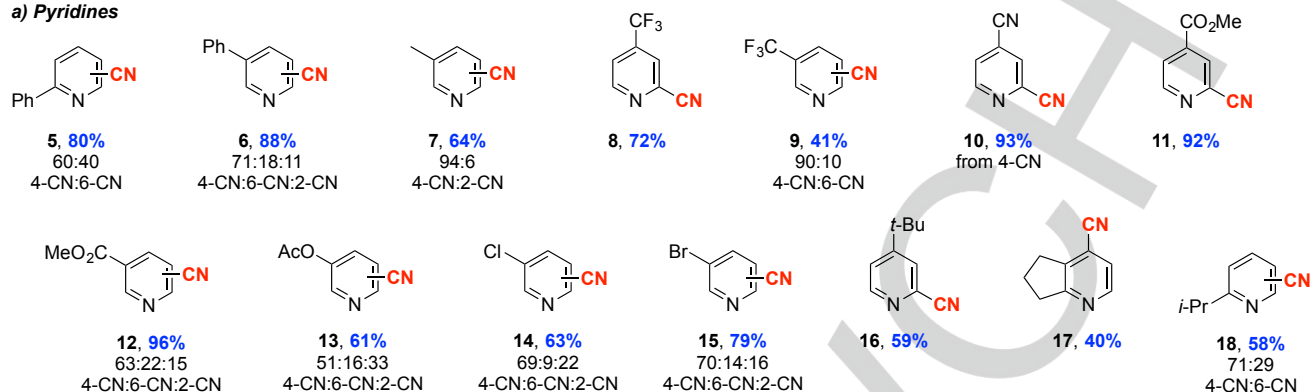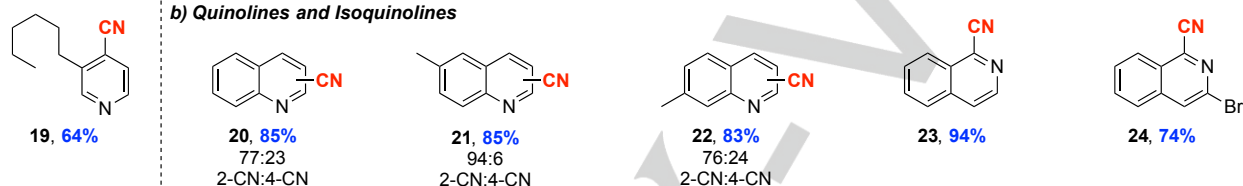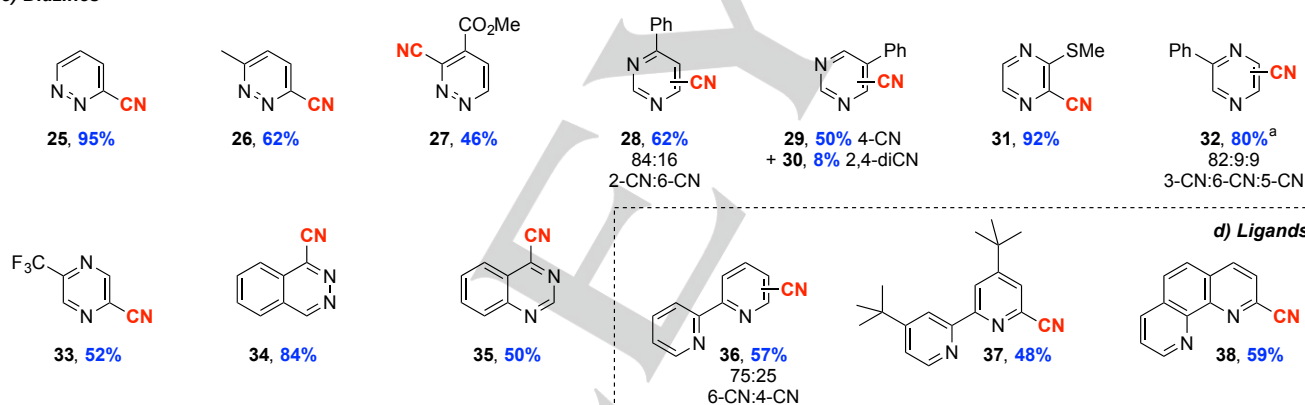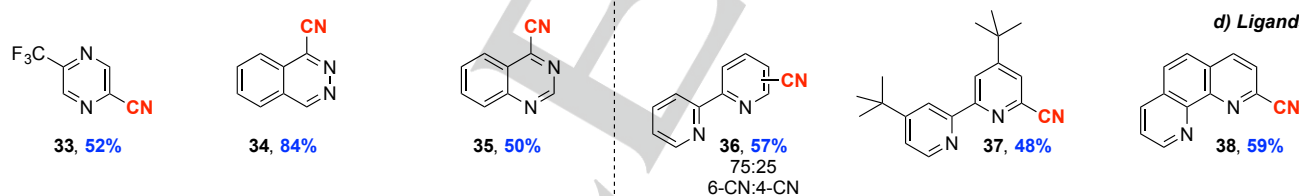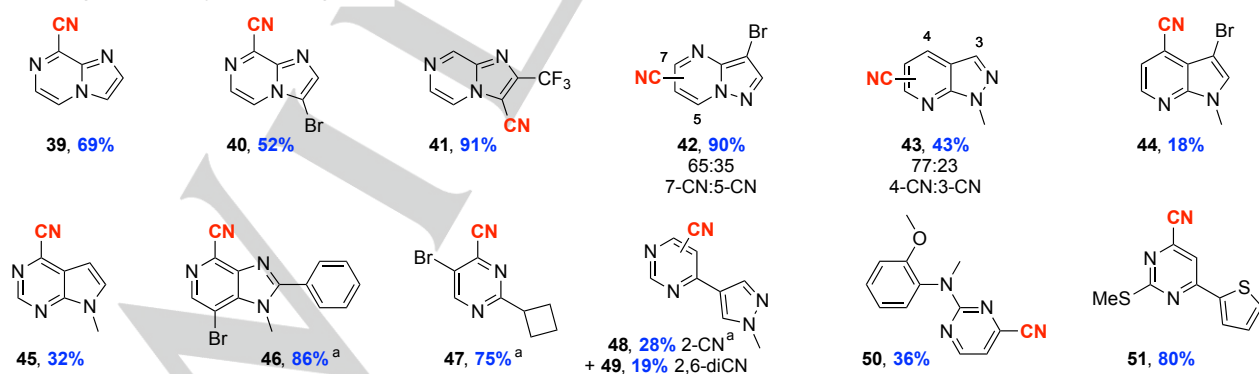
**Scheme 2.** Substrate scope. Conditions: 0.7 mmol scale, Tf$_2$O (1.2 eq.), CHCl$_3$ (0.1 M wrt substrate), 1 h, rt; then TMSCN (5.0 eq.), 3 h at 60 °C; then NMM (1.3 eq.), 17 h at 60 °C. Yields are of isolated materials. Isomeric ratio determined from isolated amounts of purified material. For consistency, numbering of functionalized carbon refers to the starting material. [a] <0.7 mmol scale, see SI for details.
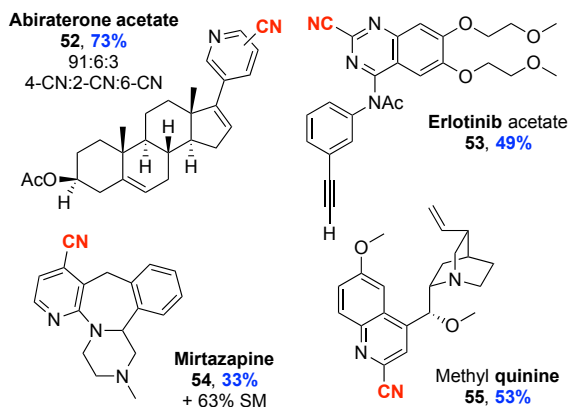
**Scheme 3.** Late-stage cyanation of drug and natural product derivatives. Conditions: $Tf_2O$ (1.2 eq.), $CHCl_3$ (0.1 M wrt substrate), 1 h, rt; then TMSCN (5.0 eq.), 3 h at 60 °C; then NMM (1.3 eq.), 17 h at 60 °C. Isomeric ratio determined from amounts of purified material.

We performed DFT (M06-2X/def2-SVP) calculations to understand the site-selectivity of cyanation in terms of each heterocycle's electronic structure.[11] We found that the condensed Fukui index, $f^+(r)$, is a good quantitative predictor for the position(s) of attack and the level of selectivity observed.[12] A large value of $f^+(r)$ for a given carbon atom is associated with a large change in chemical potential when electron density is added – it indicates greater susceptibility towards nucleophilic attack. Functionalization at the most electrophilic position(s) of the N-triflyl cation is consistent with irreversible, selectivity-determining nucleophilic attack by cyanide. For 29 of the substrates studied experimentally, the largest Fukui index predicts the major site of cyanation 23 times; in the other 6 cases cyanation occurs at the second most electrophilic position. This is attributable to the absence of steric effects in this electronic model (see Figures S2 and S3, Supporting Information). Differences in atomic Fukui indices match the experimental regioselectivities well (particularly for pyridines and quinolines/isoquinolines).
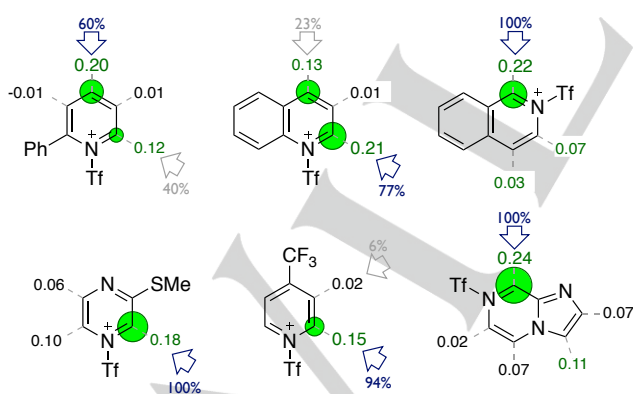


**Figure 1.** The magnitude of computed atomic Fukui indices for N-triflyl heterocycles, $f^+(r)$ (green circles), correlate with the site of nucleophilic attack (blue/grey arrows). Results for several other substrates are shown in the Supporting Information.

We also computed $^{13}C$ NMR chemical shifts of the activated pyridines. The most deshielded nucleus matches the site of nucleophilic addition observed in the major (or single) regioisomer formed (Figure S4, Supporting Information). This is consistent with the results obtained using condensed Fukui indices and supports the mechanistic interpretation above. Chemical shifts of other heterocycles do not match well with the observed sites of addition (unlike the Fukui index), presumably due to magnetic effects unrelated to chemical reactivity. We therefore focus on the use of Fukui indices, which can be employed by end-users of this methodology to predict site-selectivity in late-stage heterocycle cyanation. These calculations consider the substrate only and do not require more laborious transition state modelling.

In conclusion we have developed a direct and general one-pot protocol that enables C–H cyanation of a wide range of 6-ring N-containing heterocycles. The procedure is easy to perform and is suitable for late stage functionalization of drug derivatives and advanced intermediates. Work to further expand the generality of this C–H functionalization approach is ongoing and the results will be reported in due course.

## Experimental Section

Triflic anhydride (1.2 eq.) was added dropwise to a 0.1M solution of the substrate (1.0 eq.) in anhydrous $CHCl_3$ in a vial capped with a septum at room temperature under an atmosphere of argon. The resulting solution was stirred for 1 h, then trimethylsilyl cyanide (5.0 eq.) was added. The septum was exchanged for a screw cap and the mixture stirred at 60 °C for 3 h. The reaction was removed from the heating source, and N-methylmorpholine (1.3 eq.) added quickly before the vial was resealed. The mixture was then stirred at 60 °C for a further 17 h before cooling to room temperature and quenching with sat. $NaHCO_3$ solution. The phases were separated, and the organic phase extracted twice with $CH_2Cl_2$. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified via silica flash column chromatography.

## Acknowledgements

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# COMMUNICATION

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## Entry for the Table of Contents

## COMMUNICATION



*Bryony L. Elbert, Alistair J. M. Farley, Timothy W. Gorman, Tarn C. Johnson, Christophe Genicot, Bénédicte Lallemand, Patrick Pasau, Jakub Flasz, José L. Castro, Malcolm MacCoss, Robert S. Paton,\* Christopher J. Schofield,\* Martin D. Smith,\* Michael C. Willis,\* and Darren J. Dixon\**
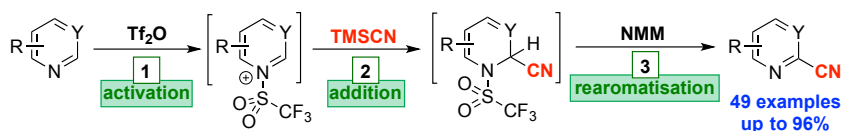
A direct, reliable and general one-pot *N*-heteroaromatic C-H cyanation procedure *via* triflic anhydride *N*-activation, nucleophilic addition of cyanide, and concomitant elimination of trifluoromethanesulfinate, is reported. The protocol is simple to perform, has computationally predictable site selectivity, and is applicable to a broad range of decorated 6-ring *N*-containing heterocycles, including complex drug-like architectures.

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