Deoxycyanation of Alkyl Alcohols

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Abstract

Cyano groups represent an important class of functional motifs in medicinal chemistry given their synthetic versatility and capacity to engage in essential interactions with biological targets. However, the synthesis of sterically hindered alkyl nitriles using non-toxic reagents remains challenging. Traditional methods often rely on toxic cyanide sources and suffer from limited substrate scope. Herein, we report a photoredox catalyzed, metal-free deoxycyanation of alkyl alcohols that allows rapid access to a wide array of 1°, 2°, and 3° cyanides using non-toxic cyanide reagents.

Cyanide-containing compounds exhibit unique chemical properties and are important to various industries, including pharmaceuticals, materials science, and agrochemicals.[1,2] In medicinal chemistry, cyanides are particularly valued for their ability to engage in critical hydrogen bonding or covalent interactions with biological targets.[3] This attribute, combined with their metabolic stability, polarity, and linear shape, renders the cyano group a distinctive and highly sought-after scaffold in drug design (Figure 1A). Cyano groups are found in over 70 approved drugs, with many more in clinical development each year.[4] Beyond their role as instrumental functional groups in drug molecules, cyano groups exhibit remarkable synthetic versatility, as they can be readily transformed into other functional groups such as amines, amides, acids, and tetrazoles.[5] Consequently, there is considerable interest in developing methods for synthesizing aryl and alkyl nitriles under mild conditions using non-toxic reagents. While the synthesis of aryl nitriles is well-established, the preparation of alkyl nitriles, especially those that are sterically hindered, remains a significant challenge. Traditional approaches, such as hydrocyanation of alkenes, transition metal-catalyzed cross-coupling, and cyanide addition to electrophiles,[3] are often limited in their ability to deliver sterically encumbered alkyl cyanides and typically require the use of toxic cyanide reagents.

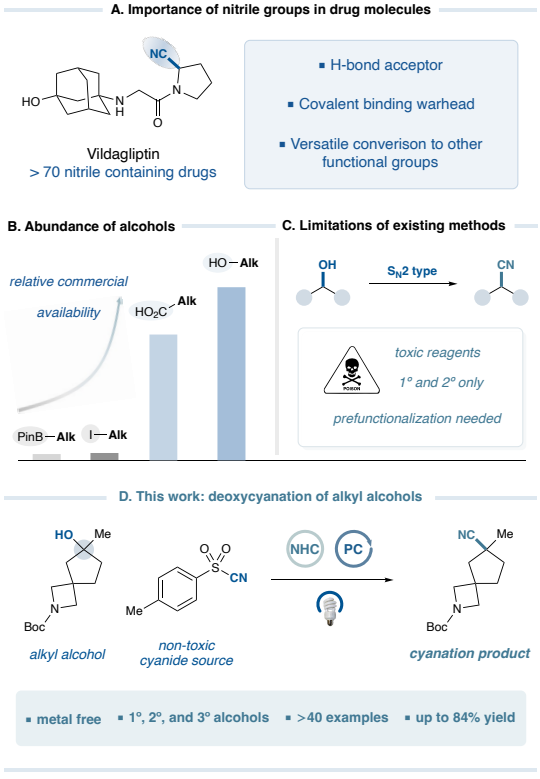


Figure 1. Deoxycyanation of alkyl alcohols

Radical intermediates offer a promising solution for the synthesis of sterically encumbered tertiary alkyl cyanides due to their versatility and high reactivity. Over the past two decades, photoredox catalysis has emerged as a powerful tool for generating radical intermediates and enabling challenging bond formations. Various photoredox-based approaches have been explored for the construction of C(sp^3)–CN bonds, including decarboxylation,[6789] hydrogen atom transfer (HAT)[10111213] /oxidation-deprotonation,[14,15] radical substitution,[14] ring opening,[14,16] and olefination.[17,18] However, many of these methods continue to rely on toxic cyanide reagents, suffer from limited substrate scope, or require specific substrate modalities.

Alcohols, among the most abundant sources of functional C(sp^3) carbon atoms (**Figure 1B**),[192021] are highly attractive starting materials for building block synthesis and late-stage functionalization (**Figure 1C**). Recently, pioneering work by the Kim group demonstrated the synthesis of secondary alkyl cyanides from SuFEx-activated alcohols via an S_N2-type mechanism.[22] Similarly, Han and coworkers successfully synthesized tertiary alkyl cyanides using α-N-phthalimido-oxy isobutyrate (NPIB)-activated alcohols under copper-mediated metallaphotoredox conditions.[23] These approaches, while inspiring, are limited by a narrow substrate scope and the use of toxic TMSCN reagents. We envisioned that a non-toxic, general one-step method for the deoxycyanation of alkyl alcohols would be highly desirable.

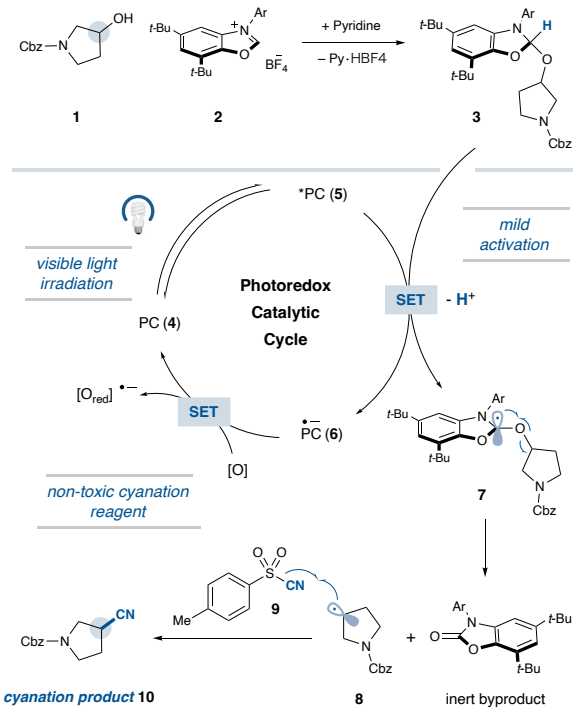
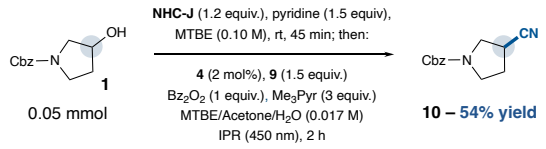


Figure 2. Proposed mechanism for deoxycyanation

Our laboratory recently introduced benzoxazolium salt ("NHC") as a convenient alcohol-activating reagent.[24] Under this strategy, alcohol-NHC adducts are formed under mild conditions and readily undergo photoredox-mediated deoxygenation to generate reactive alkyl radicals, without the need for purification or workup. We envisioned radical addition of the nucleophilic alkyl radical species with a non-toxic tosyl cyanide electrophilic partner in order to achieve efficient, clean formation of the cyanation product.

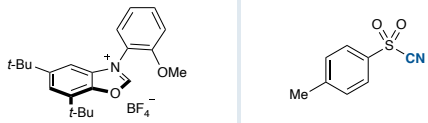
The proposed mechanistic design is outlined in **Figure 2.** First, the alkyl alcohol **1** is condensed with the benzoxazolium salt **2** *in situ* to form an NHC–alcohol adduct **3**. Blue light irradiation of photocatalyst

Table 1. Optimized Conditions and Control Reactions[a]



entry	deviation	yield[b]
1	none	54%
2	no purging	15%
3	O_2 instead of Bz_2O_2	25%
4	no oxidant	8%
5	no filtration	41%
6	no water	40%
7	no collidine base	10%
8	no photocatalyst	8%

standard reagents and catalysts



[a]Reactions performed on 0.05 mmol scale with alcohol (1.0 equiv), NHC-J (1.2 equiv), pyridine (1.5 equiv), methyl *tert*-butly ether (MTBE, 0.10 M), 45 min; 4-CzPN (**4**, 2 mol %), tosyl cyanide (**9**, 1.5 equiv), benzoyl peroxide (Bz_2O_2, 1 equiv), 2,3,6-trimethylpyridine (Me_3Pyr, 3 equiv), 15:15:1 MTBE/Acetone/H_2O (0.017 M), integrated photoreactor. (IPR, 450 nm, 100% light intensity), 2 h. [b]Yield determined by UPLC analysis.

4 4-CzPN generates a highly oxidizing excited species **5**[25] that can be quenched by adduct **3** via single-electron transfer (SET). Subsequent deprotonation of the now acidified methine C–H (pK_a ~10)[21] would provide *α*-amino radical **7**, which can then undergo facile *β*-scission[26] of the alcohol C–O bond to afford the alkyl radical **8** and an inert byproduct. The nucleophilic alkyl radical would then add to the electrophilic tosyl cyanide **9** to afford the desired cyanation product **10**, while the reduced photocatalyst **6** would be oxidized back to **4** through an external oxidant.

Extensive optimization revealed that mixing benzyl 3-hydroxypyrrolidine-1-carboxylate (**1**) with **NHC-J** (1.2 equiv) and pyridine (1.5 equiv) in methyl *tert*-butyl ether (MTBE) [0.1M] followed by filtration and subsequent irradiation with 450 nm light in the presence of tosyl cyanide **9** (1.5 equiv), 4-CzPN **4** (2 mol%), benzoyl peroxide (Bz_2O_2,1 equiv), and 2,4,6-trimethylpyridine (Me_3Pyr) in a solvent mixture of MTBE/acetone/water (15:15:1) [0.017 M] afforded the desired cyanation product in 54% yield (**Table 1**, entry 1). Control experiments demonstrated that additional air is detrimental to the reaction (entry 2). The use of oxygen as the oxidant or performing the reaction in the absence of an oxidant is also detrimental (entries 3-4). Filtration of the NHC condensate mixture or using water as a co-solvent is beneficial but not necessary for the reaction (entries 5-6). At the same time, the collidine base and the photocatalyst are both essential for efficient product formation (entries 7-8).

With optimized conditions in hand, we proceeded to explore the alcohol scope of our method (**Figure 3**). Primary alcohols performed with moderate efficiency under our reaction conditions (**11–15**, 30–39% yield), likely due to the relative instability and reduced nucleophilicity of the corresponding radical species. However, we were delighted to find that a variety of unactivated secondary alcohols are well-tolerated, affording the desired cyanation products in good yields (**10, 16–22**, 53–71% yield). In addition, substrates containing stereogenic centers near the reactive alcohol were observed to retain their original stereochemistry (**23–24,** 50–53% yields). The synthesis of high-value tertiary cyanides has been a long-standing challenge. Given the prevalence of tertiary alcohols and their accessibility through simple nucleophilic addition into ketones and esters, we wondered whether our method could be used to access tertiary cyanides from their corresponding alcohols. To our delight, cyclic tertiary alcohols on four, five, six, and seven-membered saturated heterocycles were converted to their corresponding nitriles in good yields (**25–30**, 51–67% yield). Additionally, linear alcohols underwent efficient deoxycyanation (**31–33**, 51–84%). A variety of spirocycles and strained cyclic alcohol-containing scaffolds were well-tolerated, affording the desired products in synthetically useful to excellent yields. (**34–39**, 57–75% yield).

Next, we explored the applicability of our methodology to pharmaceutical molecules and biomolecules (**Figure 4**). We were excited to observe that deoxycyanation analogues of saxagliptin (**40**, 58% yield) and ibuprofen derivative (**41**, 44% yield) could be successfully synthesized, demonstrating the applicability of our method to the late-stage modification of complex, medicinally relevant molecules. Drug molecules containing activated alkenes and electron-rich heterocycles were also well tolerated (**42–44**, 48–57% yield), indicating the mild nature of our reaction conditions. Furthermore, biomolecules such as unnatural sugar (**45**, 41% yield), hydroxyproline (**46**, 50% yield), and nucleotides (**47**, 32% yield) were also tolerated.

To further demonstrate the versatility of our reaction, we sought to construct complex, C(sp^3)-rich structures using diols in an iterative, modular fashion. Taking note of the high chemoselectivity of the NHC condensation process (1º > 2º ≫ 3º), we first subjected 3-methylbutane-1,3-diol to reaction with olefins via either alkene dialkylation[27] (**48**) or MHAT-mediated olefin-alcohol cross-coupling[28] (**50**, **52**), utilizing methods previously developed within our lab. As expected, olefin alkylation occurred exclusively at the primary alcohol, forming quaternary carbon centers on spirocycles, piperidines, and Febuxostat derivatives in good to excellent yields (56–85% yield). Each alkylated adduct possessed a tertiary alcohol that had remained untouched during the previous functionalization. These intermediates were then subjected to deoxycyanation to afford the desired tertiary alkyl nitriles in synthetically useful yields (**49, 51, 53**, 51–64% yield).

In conclusion, we have developed a metal-free deoxycyanation of alcohols utilizing non-toxic cyanide sources. This novel method demonstrates robust reactivity, excellent functional group tolerance, and the capacity to achieve late-stage functionalization. Given the importance of cyano groups in bioactive compounds, we expect that this reaction will find broad use across the synthetic community.

Supporting Information

Experimental results, optimization studies, characterization data, and NMR spectra

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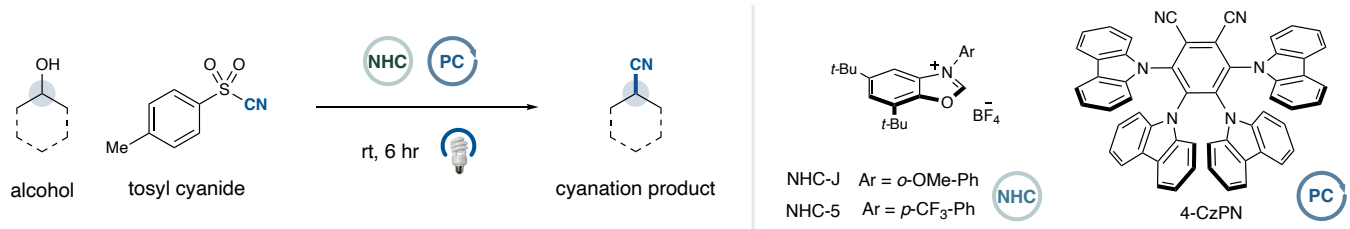
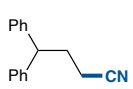
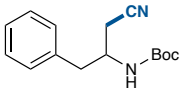


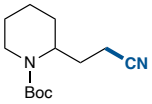
Primary alcohols[a]



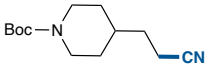
11, 39% yield



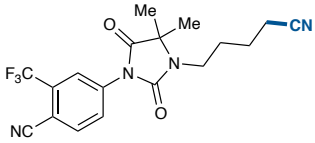
12, 34% yield



13, 36% yield

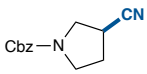


14, 34% yield

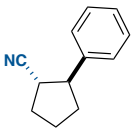


15, 30% yield

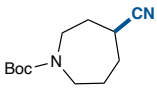
Secondary alcohols[a]



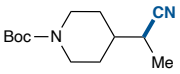
10, 59% yield



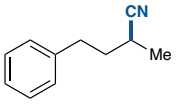
16, 65% yield



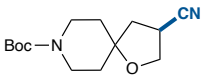
17, 58% yield



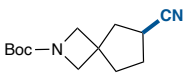
18, 62% yield



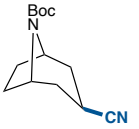
19, 66% yield



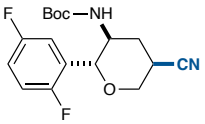
20, 66% yield



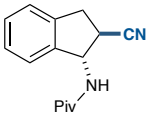
21, 71% yield



22, 53% yield (6.6:1 dr)

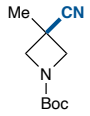


23, 53% yield (1.6:1 dr)

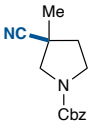


24, 50% yield (5:1 dr)

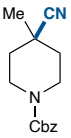
Tertiary alcohols[c]



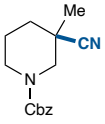
25, 51% yield



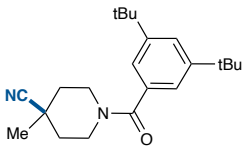
26, 67% yield



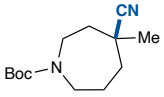
27, 66% yield



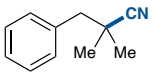
28, 59% yield



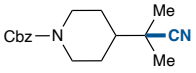
29, 63% yield



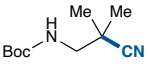
30, 63% yield



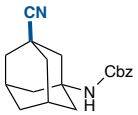
31, 60% yield (84%[b])



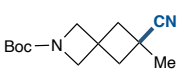
32, 51% yield



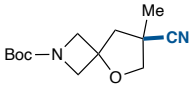
33, 52% yield



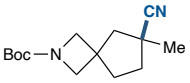
34, 75% yield



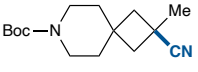
35, 65% yield



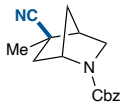
36, 57% yield



37, 72% yield



38, 59% yield



39, 59% yield (1:1 d.r.)

Figure 3 | Scope of alcohol building blocks. A range of alcohols can be used for cyanation. All yields are isolated unless otherwise specified. [a]Standard conditions: Alcohol (0.5 mmol, 1 equiv.), NHC-J (1.2 equiv.), pyridine (1.5 equiv.), MTBE (0.10 M), 45 min; Tosyl cyanide (1.5 equiv.), 4-CzPN (2 mol%), Bz_2O_2 (1 equiv.), Me_3Pyr (3 equiv.), 15:15:1 MTBE/Acetone/H_2O (0.016 M), IPR 450 nm (100% intensity) for 6 hours. See SI for full experimental details. [b]Yield determined by Ultra-performance liquid chromatography (UPLC) analysis using mesitylene as an internal standard. [c]Reaction performed with NHC-5 and in solvent α,α,α-trifluorotoluene (TFT). See the Supporting Information for experimental details.

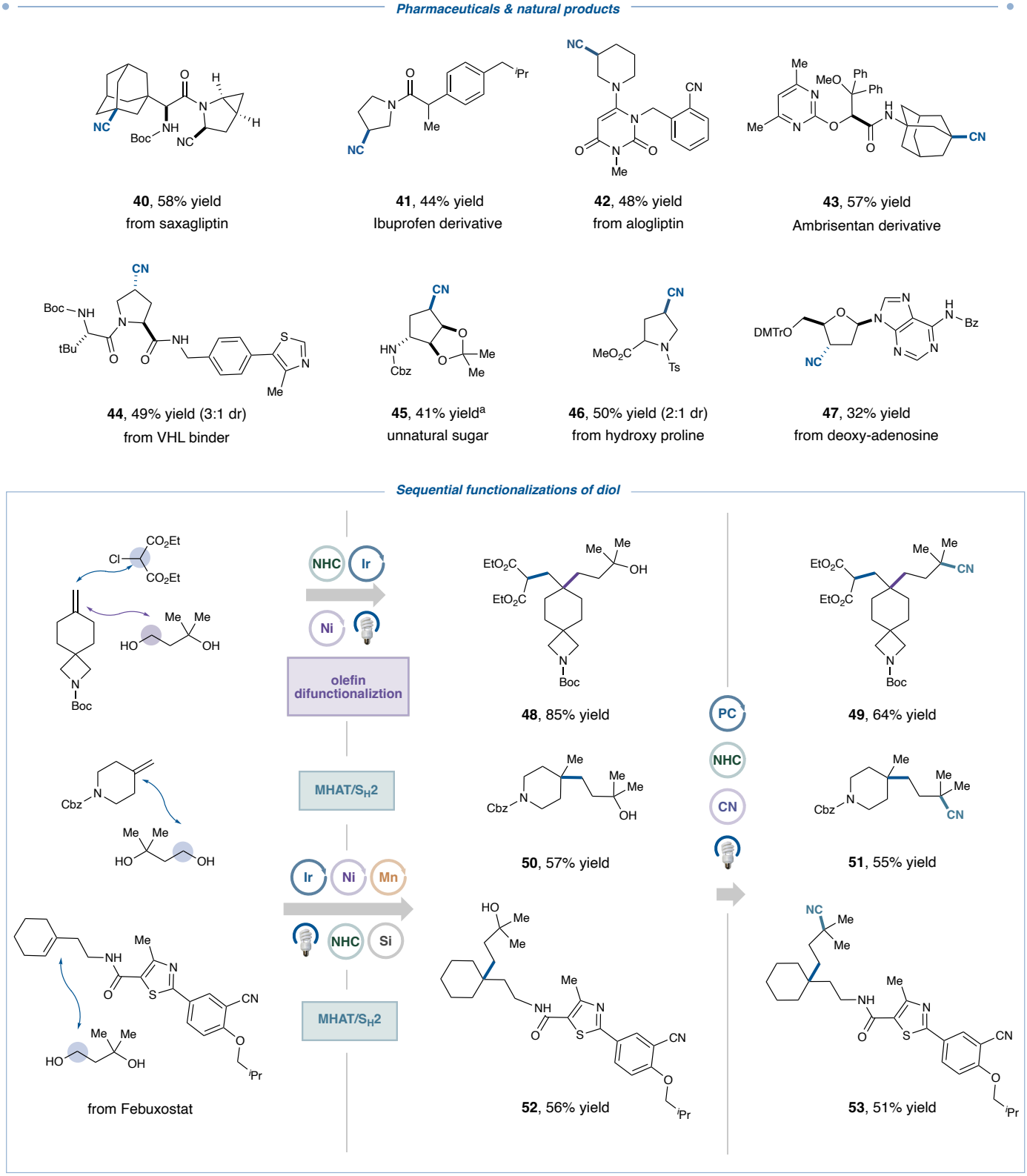


Figure 4 | Complex building block applications and sequential functionalization of diols. All yields are isolated unless otherwise noted. See the Supporting Information for detailed reaction conditions. [a]Assay yield determined by ^{1}H analysis against 1,3,5-trimethoxybenzene as an internal standard.

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Author contributions

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Notes

The authors declare the following competing financial interest(s): D.W.C.M. declares a competing financial interest with respect to the integrated photoreactor.

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