1-Cyano-1,2-benziodoxol-3(1*H*)-one

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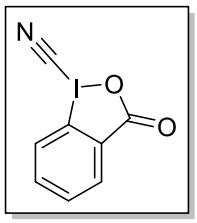
Abstract

This comprehensive review discusses the properties, synthesis, and applications of 1-cyano-1,2-benziodoxol-3(1H)-one, a versatile cyanating agent. Various preparative methods are detailed, highlighting its synthesis through different reactions. The review emphasizes its stability and safe handling, making it a preferred choice over other cyanating agents due to its lower toxicity and ease of use. It plays a crucial role in electrophilic cyanation reactions, contributing to the synthesis of diverse organic molecules, including biologically active compounds and pharmaceuticals. The article also explores its application in metal-free, photoredox, and electrochemical methods, underscoring its broad utility in synthetic chemistry. The versatility of 1-cyano-1,2-benziodoxol-3(1H)-one is further demonstrated in its application in the synthesis of metal complexes and its potential in lignin degradation and heterocycle formation. The review concludes by comparing it with other hypervalent iodine reagents, highlighting its superior performance in various cyanation reactions.



[127541-15-8] $C_8H_4INO_2$ (MW 273.03)

InChI = 1/C8H4INO2/c10-5-9-7-4-2-1-3-6(7)8(11)12-9/h1-4H

InChIKey = AOTJNSUBRSAHHW-UHFFFAOYAC

Alternative Names: 1-Cyano-3-iodoxybenzene, (1-Cyano-1,2-benziodoxol-3-yl)acetonitrile, CBX, IBX-CN, Cyanobenziodoxolone, 1-Cyano-1,2-benzeniodoxol-3-one, 1-Cyano-1,2-benziodoxoline-3-one, 1-Cyano-1,2-iodobenziodoxol-3-one, 1-Cyano-3-iodoxy-1,2-benziodoxole-3(1*H*)-one, 1-Cyano-3-iodoxy-1,2-benziodoxol-3-ol.

Physical data: yellow or light brown solid.

Redox potential: -0.92 V vs saturated calomel electrode (SCE).[1]

Solubility: slightly soluble in water (less than 1 mg/mL) and Et_2O; soluble in DCM, chloroform, AcOEt, DMF, DMSO, HFIP, MeCN; ~~is~~ insoluble in hexane, toluene, MeOH at room temperature.

Form Supplied in: 1-cyano-1,2-benziodoxol-3(1*H*)-one is commercially available from several manufacturers as a dry powder.

Analysis of Reagent Purity: mp 173-175 ^{o}C (dec.); IR (CCl_4): 3090 (Ar), 2161 (CN), 1685, 1632 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.27 (d, 1H, J = 8 Hz), 8.10 (d, 1H, J = 8 Hz), 7.98 (t, 1H, J = 8 Hz), 7.86 (t, 1H, J = 8 Hz); ^{13}C NMR (DMSO-d_6): δ 166.7 (C=O), 136.4, 132.0, 131.8, 130.1, 127.7, 117.4 (Ar), 87.8 (CN). Anal. Calc. for $C_8H_{41}N0_2$*0.5H_20: C, 34.07; H 1.79; N, 4.97. Found: C, 33.98; H, 1.76; N, 4.91.

Preparative Methods:

Method 1[2]. Cyanotrimethylsilane (0.785 ml, 5.886 mmol) was added to a stirred suspension of 2-iodosylbenzoic acid (0.777 g, 2.943 mmol) in dry CH_3CN (20 ml) under nitrogen at room temperature. The reaction mixture was additionally stirred for 3 h until the formation of a clear, colorless solution. This solution was cooled to -18 ^{o}C and kept at this temperature for 2 h until a white microcrystalline precipitate was formed. The precipitate was filtered off, washed with anhydrous CH_2Cl_2 (5 ml) and dried in vacuo to afford 0.755 g (94%) of analytically pure product.

Method 2[3].

Synthesis of 1-hydroxy-1,2-benziodoxol-3-(1H)-one.[4] $NaIO_4$ (25.8 g, 121 mmol, 1.05 eq.) and 2-iodobenzoic acid (28.5 g, 115 mmol, 1.00 eq.) were suspended in 30% (v:v) aq. AcOH (175 ml). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (500 ml) and allowed to cool to room temperature, while protecting it from light. After 1 h, the crude product was collected by filtration. The crystals were washed with ice water (3 x 100 ml) followed by acetone (3 x 100 ml) and then air-dried in the dark affording 29.3 g, (111 mmol, 96.5%) of 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one as a white solid.

Synthesis of 1-acetoxy-1,2-benziodoxol-3-(1H)-one.[5] 1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (10.3 g, 39.1 mmol, 1.00 eq.) was suspended in acetic anhydride (35 ml) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up to room temperature and then cooled to 0 ^{o}C for 30 minutes. The white suspension was filtered, and the filtrate was again cooled to 0 ^{o}C for 30 minutes. The suspension was once again filtered and the combined two batches of the solid product were washed with hexane

(2x20 ml) and dried in vacuo affording 10.8 g, (35.3 mmol, 90.2%) of 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one as a white solid.

Synthesis of 1-cyano-1,2-benziodoxol-3-(1H)-one[6]. 1-Acetoxy-1,2-benziodoxol-3-(1*H*)-one (10.5 g, 34.3 mmol, 1.00 eq.) was dissolved under nitrogen in dry dichloromethane (80 ml). To the clear colorless solution trimethylsilyl cyanide (TMSCN, 9.20 ml, 68.6 mmol, 2.00 eq.) was added *via* a syringe over a five-minute period. The reaction mixture was stirred at room temperature and under nitrogen for 72 h. The resulting thick white suspension was filtered and the solid was washed with hexane (3x20 ml) and dried in vacuo affording 8.89 g (32.6 mmol, 95.0%) of 1-cyano-1,2-benziodoxol-3-(1*H*)-one as an off-white solid.

Method 3[7]. Following a reported procedure[8], 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (11.8 g, 38.6 mmol, 1.00 eq.) was dissolved under nitrogen in dry dichloromethane (200 ml). To the clear colorless solution trimethylsilyl cyanide (TMSCN, 10 ml, 77 mmol, 2.00 eq.) was added *via* a syringe over a five minute period followed by trimethylsilyl trifluoromethanesulfonate (TMSOTf, 70 µL, 0.386 mmol, 0.01 eq.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure completion of the reaction. The resulting thick white suspension was diluted with hexane (5 ml) before being filtered and the solid was washed with hexane (3x20 ml) and dried in vacuo affording (10.3 g, 37.7 mmol, 98 %) as a white solid.

Handling, Storage, and Precautions:

1-Cyano-1,2-benziodoxol-3(1*H*)-one is stable under ambient conditions and can be stored at room temperature for several months without any noticeable decomposition. It should be stored in a cool, dry place and protected from light. This compound is known to be an oxidizing agent and should be handled with care.

Introduction. The CBX cyanating reagent offers several advantages over other reagents such as bromocyane and tosyl cyanide, making it a preferred choice in various chemical reactions. One major advantage is its ease of handling, as CBX is typically available as a stable and crystalline solid, simplifying storage and transportation. Furthermore, CBX exhibits lower toxicity compared to its counterparts, ensuring safer handling for researchers. Additionally, CBX demonstrates remarkable versatility in its reactivity, enabling it to participate in a wide range of cyanation reactions, thereby expanding its applicability in diverse synthetic processes.

Electrophilic (oxidative) cyanation at carbon atom. The formation of C-CN bonds through electrophilic cyanation reactions employing hypervalent iodine reagents has emerged as an efficient and eco-friendly method for synthesizing a wide range of valuable organic molecules with high precision and productivity. This approach has been effectively utilized for the direct electrophilic cyanation of β-keto esters (**A**, **2a-j,r**) and amides (**B**, **2k-q**) with cyano benziodoxole, enabling the rapid, catalyst-free, and room temperature synthesis of highly functionalized quaternary carbon-centered nitriles (Figure 1)[9].

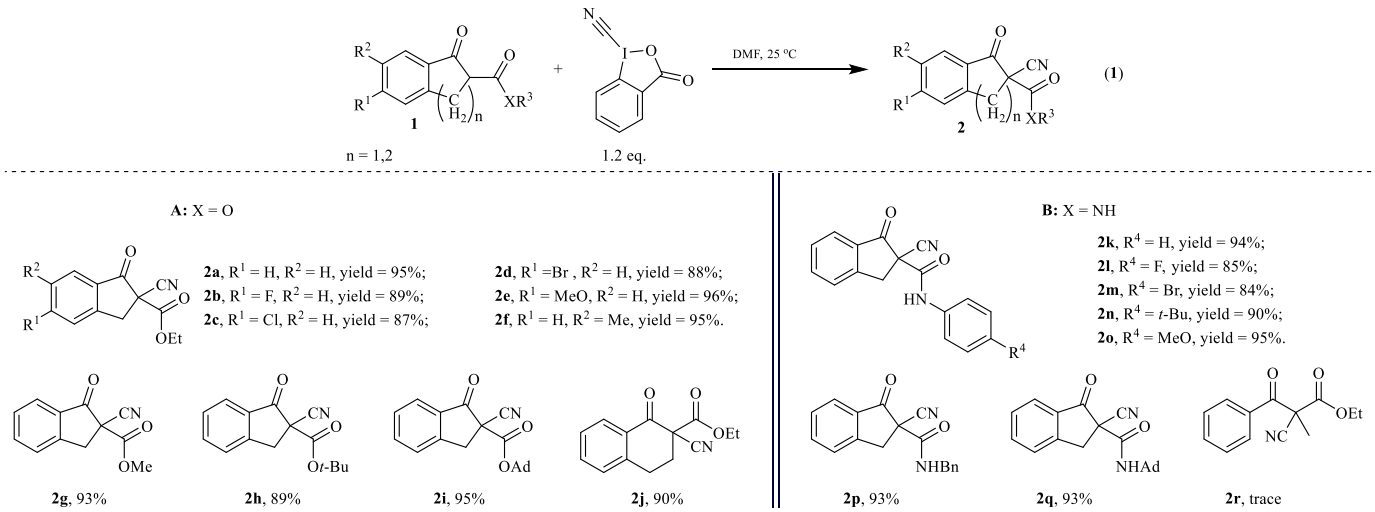


Figure 1.

It has been particularly successful for the selective C-H cyanation of an extensive scope of 3-substituted 2-oxindoles (**4a-k**, **A** and **6a-d**, **B**)[10]. Adding the organic base like *N,N,N′,N′*-tetramethylguanidine (TMG) in cases of less reactive *N*-alkylated oxindoles allowed to achieve highly chemoselective C-H cyanation retaining good preparative yields (**6e-j**, **C**). Derivatives of these compound classes hold potential as biologically active molecules and active pharmaceutical ingredients (API, Figure 2)[11].

Employing copper(I)-catalyzed ring-opening cyanation of cyclopropanols with CBX as a cyano group source, an efficient method for synthesizing β-cyano ketones was developed, exhibiting good functional group compatibility, tolerance, and scalability under mild conditions.[12] The cyclopropanoles transformations (**7** to **8**) showcase the potential of free radical processes, in C-C bond cleavage and formation strategies (Figure 3).

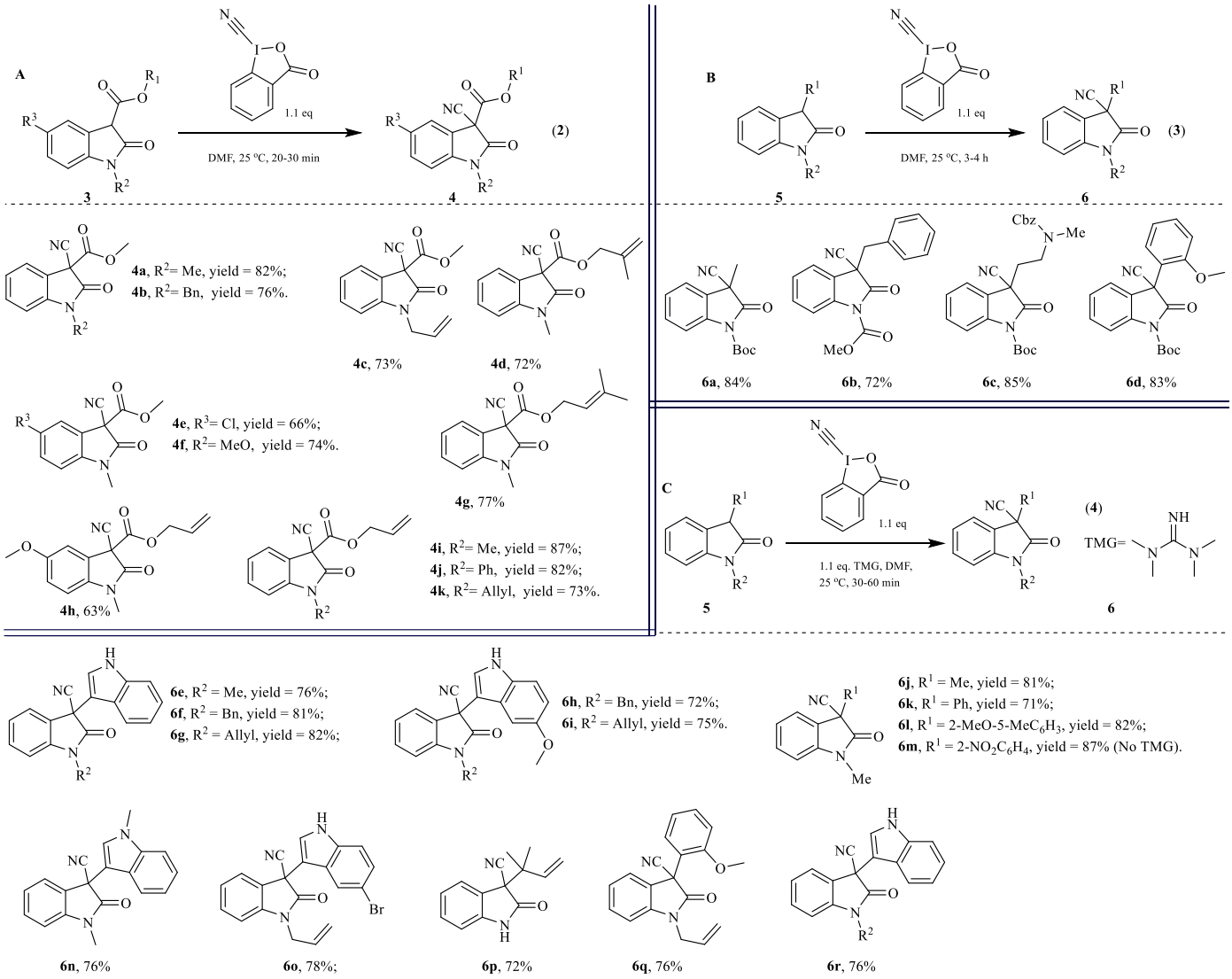


Figure 2.

A metal-free method for direct C(sp^3)–H cyanation of organic substrates using cyanobenziodoxolones (CBX or CDBX) and a catalytic amount of tert-butyl-peroxybenzoate (TBPB) as the initiator has been suggested. This approach demonstrates broad substrate tolerance, encompassing alkanes (**10a-f**, **A**), ethers (**10g-m**, **A**), and tertiary amines (**12a-o**, **B**) with moderate to high yields, while operating under mild reaction conditions. The organocatalytic strategy highlights the potential of expanding the scope and applicability of cyanation reactions in synthetic chemistry (Figure 4)[13].

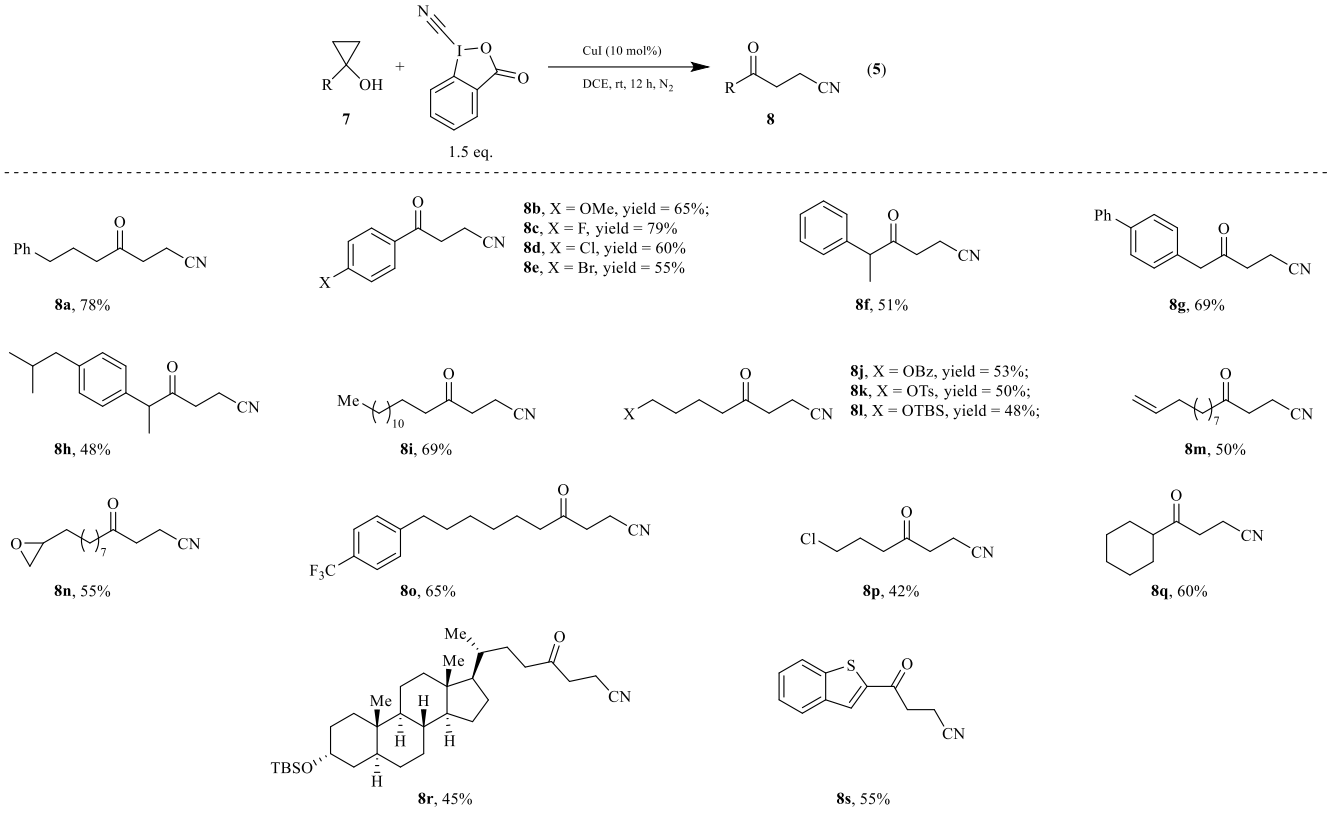


Figure 3.

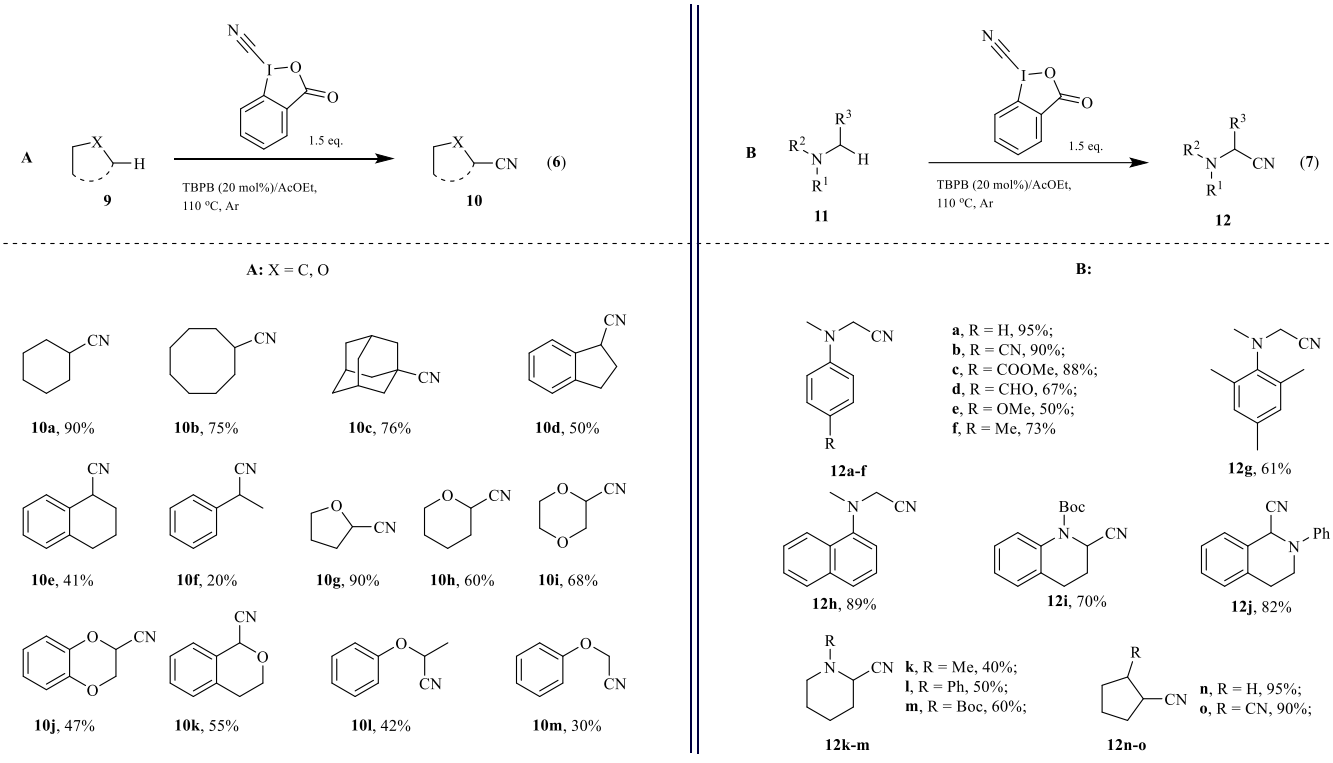


Figure 4.

Another study presents an enantioselective electrophilic α-cyanation of 1-indanone-derived β-keto esters (**13**) and β-keto amides (**14**) using hypervalent iodine as a cyanide-transfer reagent. The reaction highlights the power of chiral organocatalysis, employing a bifunctional chiral *N*,*N*'-dioxides-based organocatalyst (**17**) in conjunction with an inorganic base to achieve high yields and good enantioselectivities. This method demonstrates the versatility and potential of chiral organocatalysis with CBX for strereoselective transformations (Figure 5)[14].

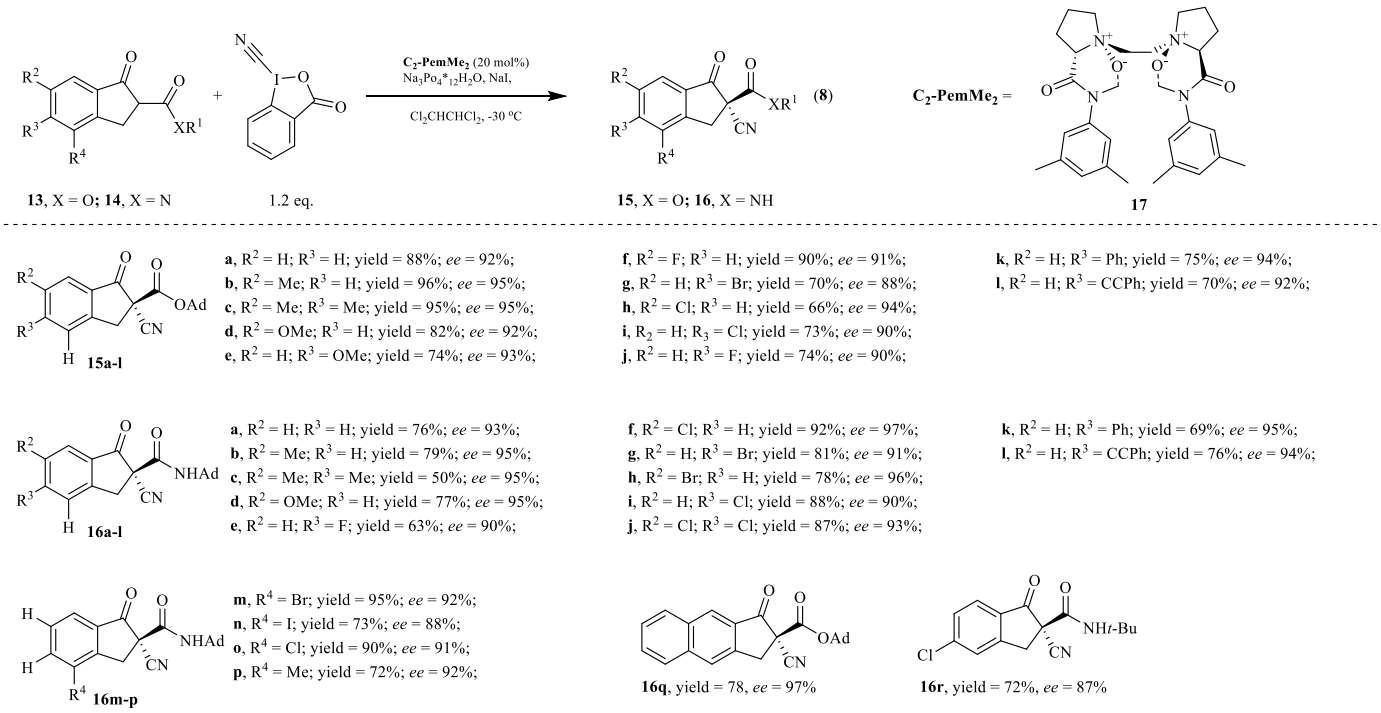


Figure 5.

The electrochemical approach provides a clean, green, and efficient method for the synthesis of functionalized nitriles from alkenes. This versatile strategy allows for the conversion of a wide range of alkenes, including aliphatic derivatives, while maintaining excellent functional group tolerance. The electrocatalytic method, suitable for both acylcyanation (**A**) and, aminocyanation (**B**) can be conducted at room temperature and is easily scalable. This innovative approach offers a promising alternative to traditional methods, paving the way for the development of new reactions and applications (Figure 6)[15].

Photocyanation at carbon atom. The approach based on a radical imino-Michael cascade enables an efficient, metal-free photoredox protocol to synthesize polyfunctionalized nitrogen heterocycles through imino cyanation[16].

This method offers a green strategy for constructing complex and valuable building blocks under mild conditions (Scheme 1).

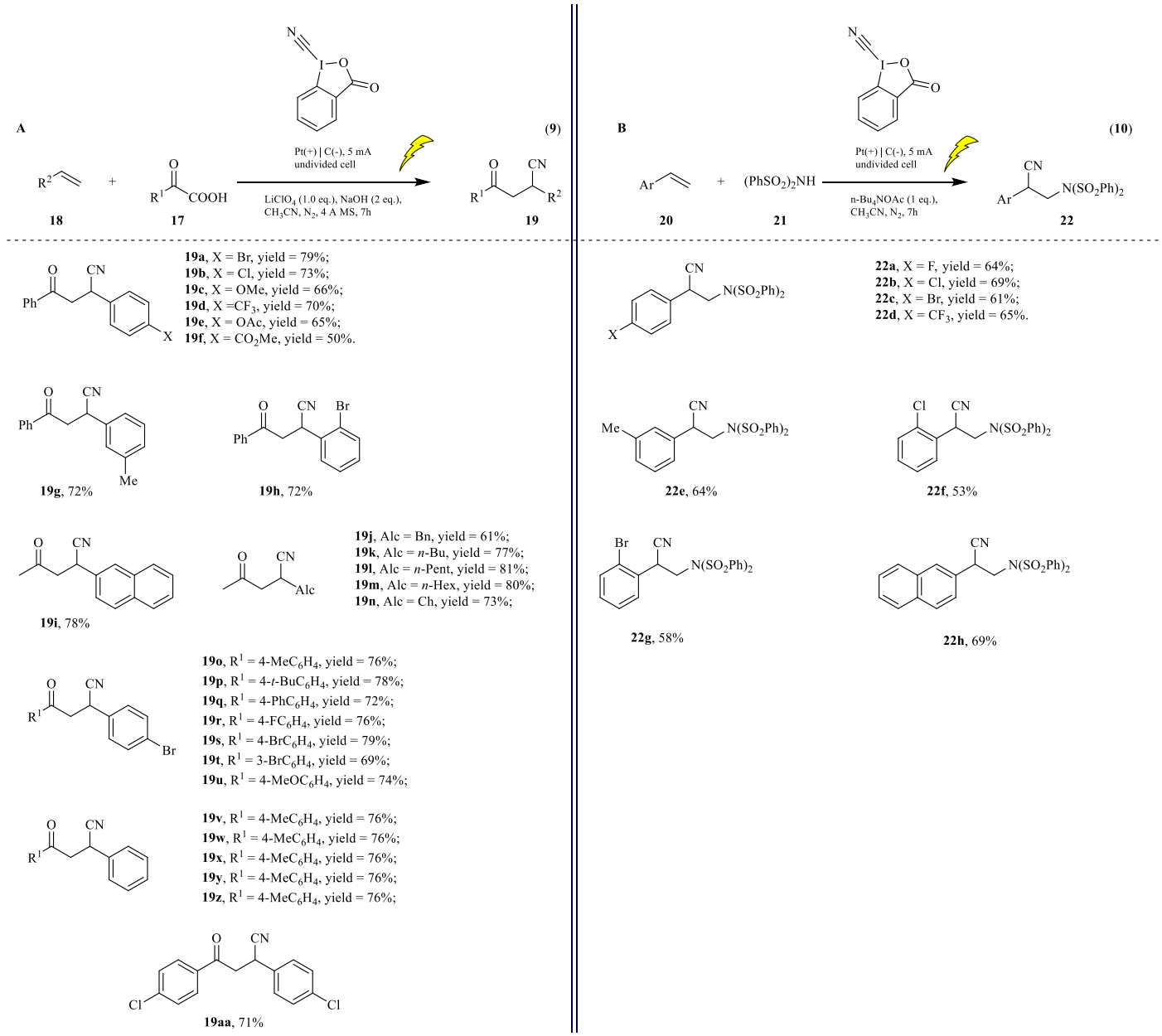
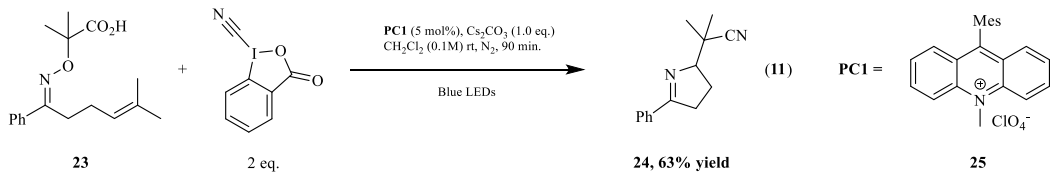


Figure 6.



Scheme 1.

Visible light-induced photocyanation of tertiary amines using the CBX reagent, provides an efficient, catalyst-free, and environmentally friendly alternative to existing methods. The photocyanation process displays a broad substrate scope and functional groups tolerance and operates under extremely mild reaction conditions without the need for a photocatalyst, oxidant, base, or additives. Notably, this method is compatible with both challenging tertiary aliphatic amines (**A**) and N-aryl amine derivatives (**B**), further expanding its applicability in synthesizing valuable α-amino nitriles (Figure 7)[17].

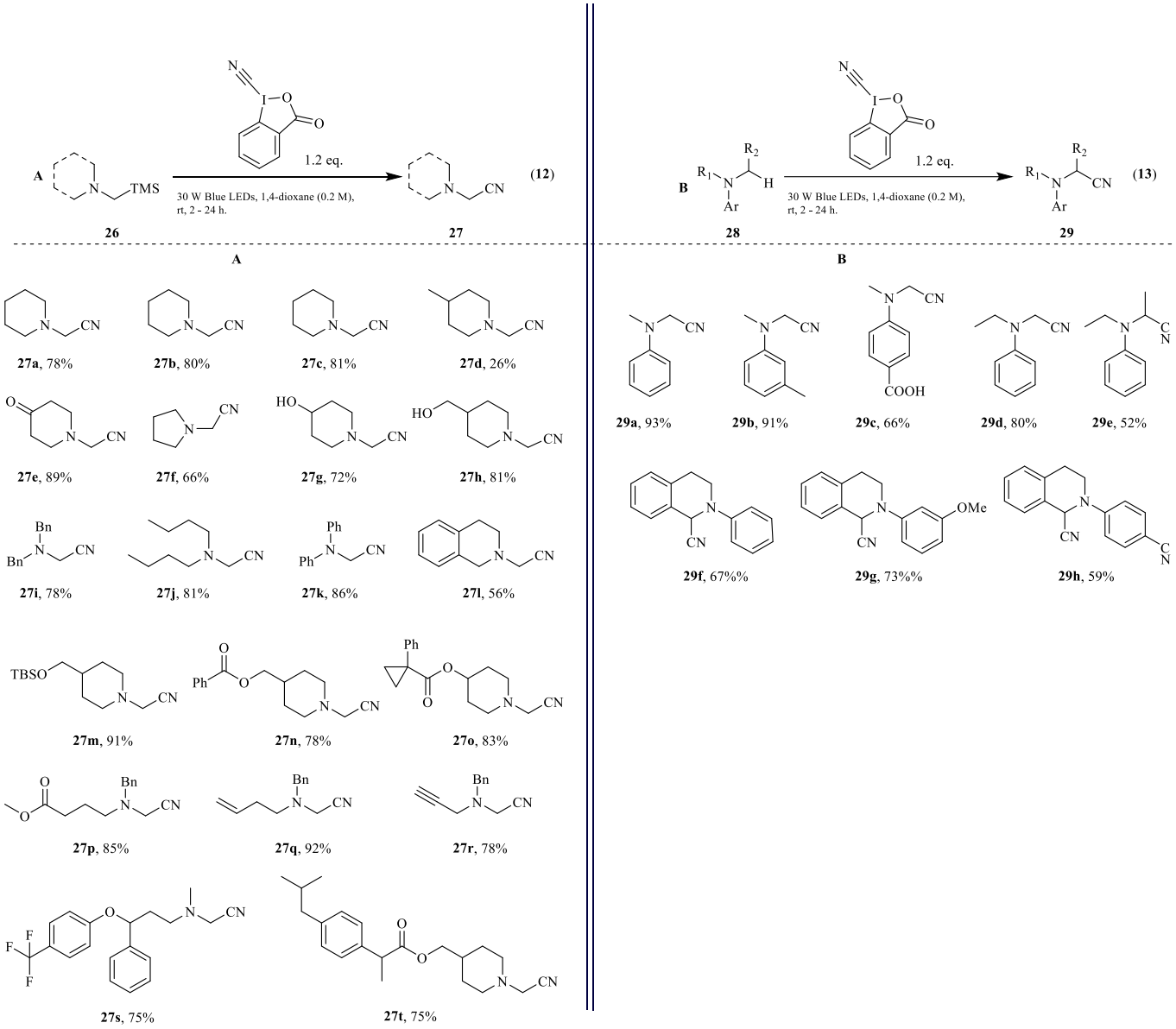
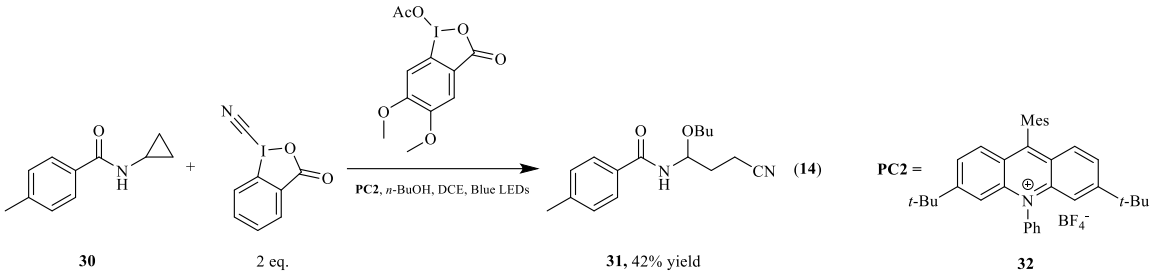


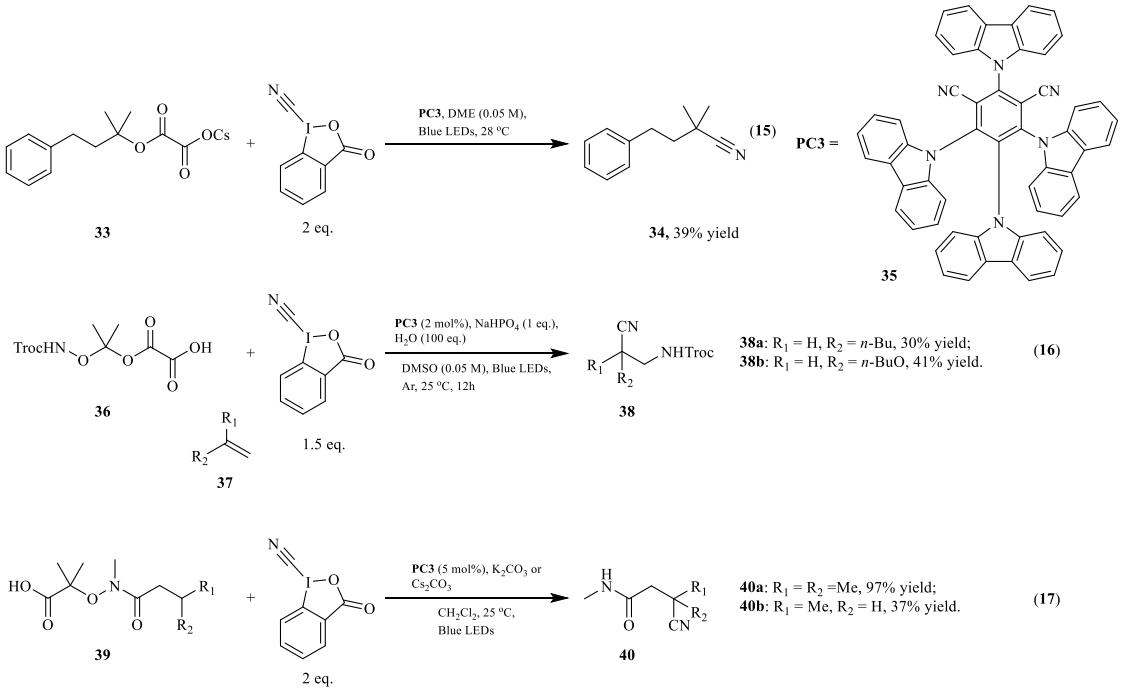
Figure 7.

The photocatalytic approach allows for the cyclopropane ring opening cyanation reaction with CBX under mild photoredox conditions in the presence of iridium-free photocatalyst (**PC2, 32**) and catalytic amount of 5,6-dimethoxybenziodoxolone-3-acetate with a reasonable yield (Scheme 2)[18].



Scheme 2.

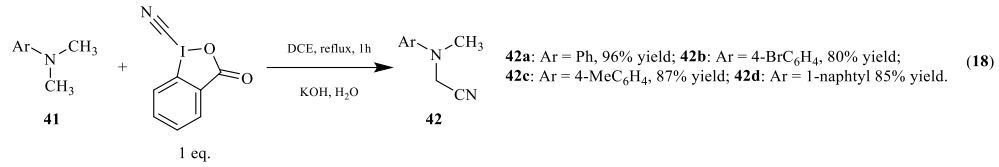
The photoredox-based reactions enabled deoxycyanation process for cesium oxalates using CBX reagents and low intensity irradiation (blue LEDs). These transition-metal-free photoredox systems, which utilize the **PC3** catalyst **35**, enables cyanation reactions using CBX as a cyano group source reagent tolerates many functional groups and allows for the functionalization of ethers (**equation 15**)[19], unactivated alkenes (**equation 16**)[20] and oxamides (**equation 17**)[21], however, in the majority of cases suffers from low yields (Scheme 3).



Scheme 3.

Electrophilic N(S)-cyanation: Cyanation of N,N-Dimethylanilines with Cyanobenziodoxole. Cyanobenziodoxole serves as an effective cyanating agent for N,N-dialkylarylamines. In a representative

example, CBX reacts with N,N-dimethylanilines in 1,2-dichloroethane at reflux, yielding N-cyanomethyl-N-methylanilines in good yields (**equation 18**, Scheme 4)[2].



Scheme 4.

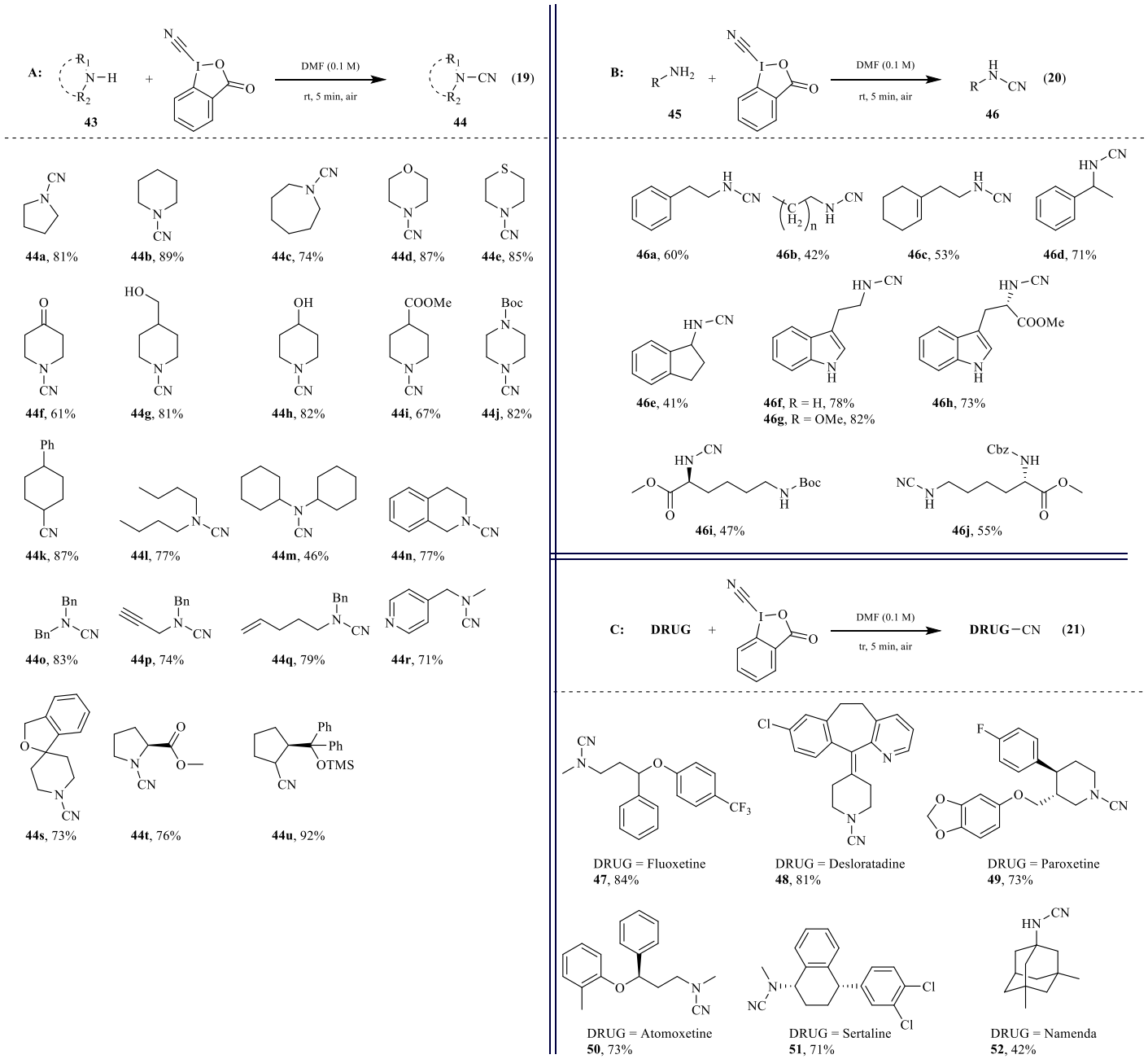


Figure 8.

Cyanamides can be found in many biologically active compounds, including natural products, pharmaceuticals, and agrochemicals. The use of CBX introduces an efficient electrophilic N-cyanation method for synthesizing cyanamides utilizing a stable and less-toxic reagent. The approach allows for the construction of a wide variety of cyanamides under mild, simple conditions with broad functional group compatibility (**A**, **B**, **C**), showcasing its potential for late-stage modification of complex molecules (**C**, Figure 8)[22].

Adding an organic base (DBU) and tuning the reaction conditions allowed authors to significantly expand the scope of the secondary amine substrates (**54a-q**), as well as successfully modify secondary sulfonamides (**56a-r**) using CBX. All the transformations displayed good-to-excellent yields (Figure 9)[23].

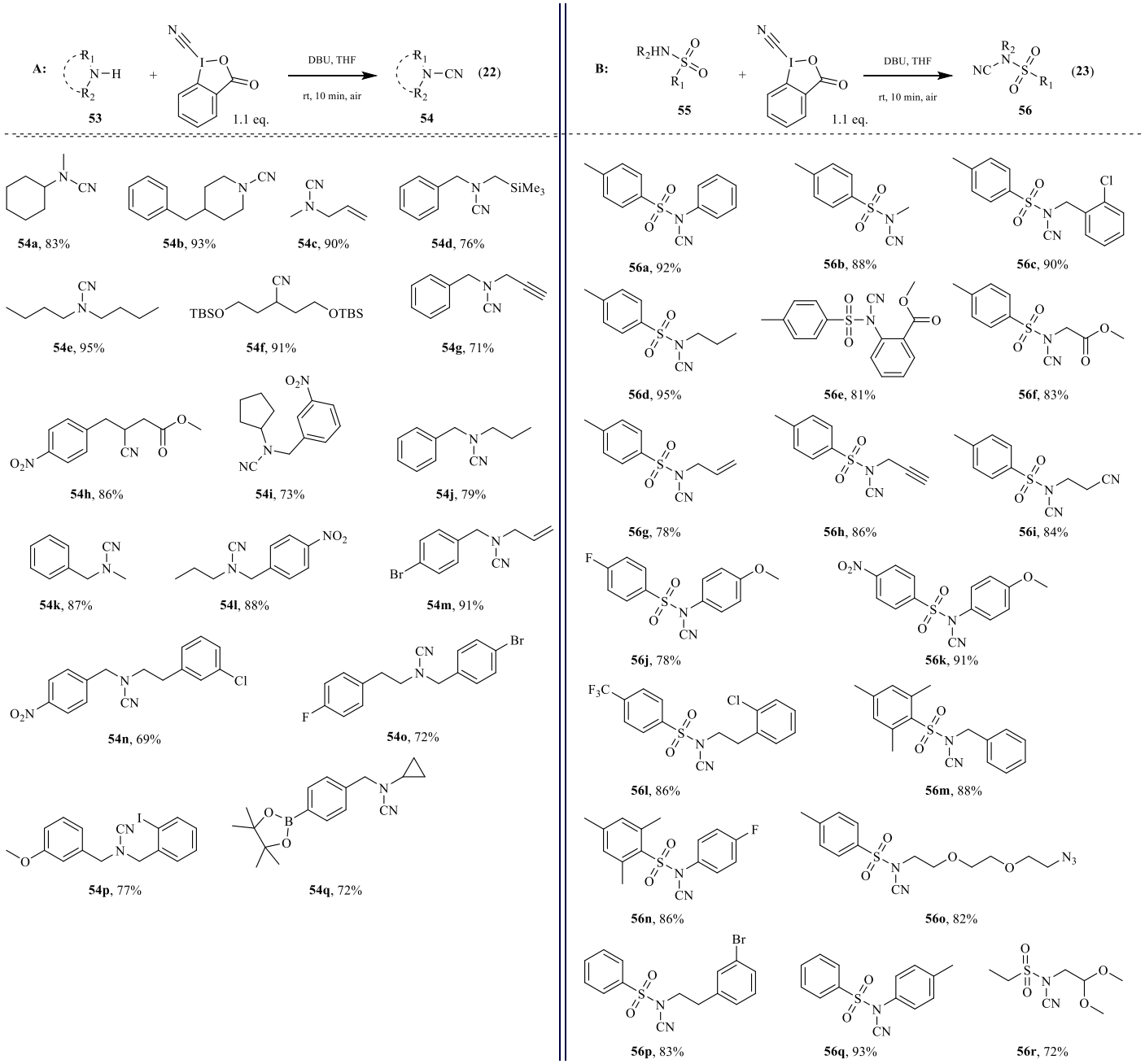


Figure 9.

Cyanobenziodoxol(on)e hypervalent iodine reagents can also be efficiently used for cyanating thiols. The technique enables the synthesis of both aliphatic and aromatic thiocyanates (**58a-g**) from a wide range of thiols , with high chemoselectivity, in just minutes at room temperature. This new thiocyanate synthesis approach holds significant potential for applications in synthetic chemistry, chemical biology, and materials science (Figure 10)[3].

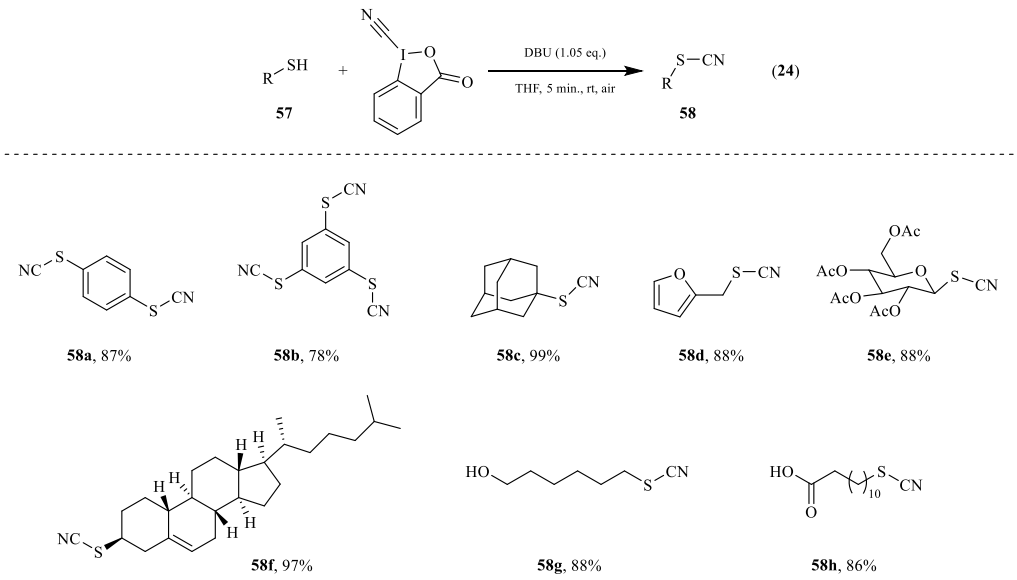


Figure 10.

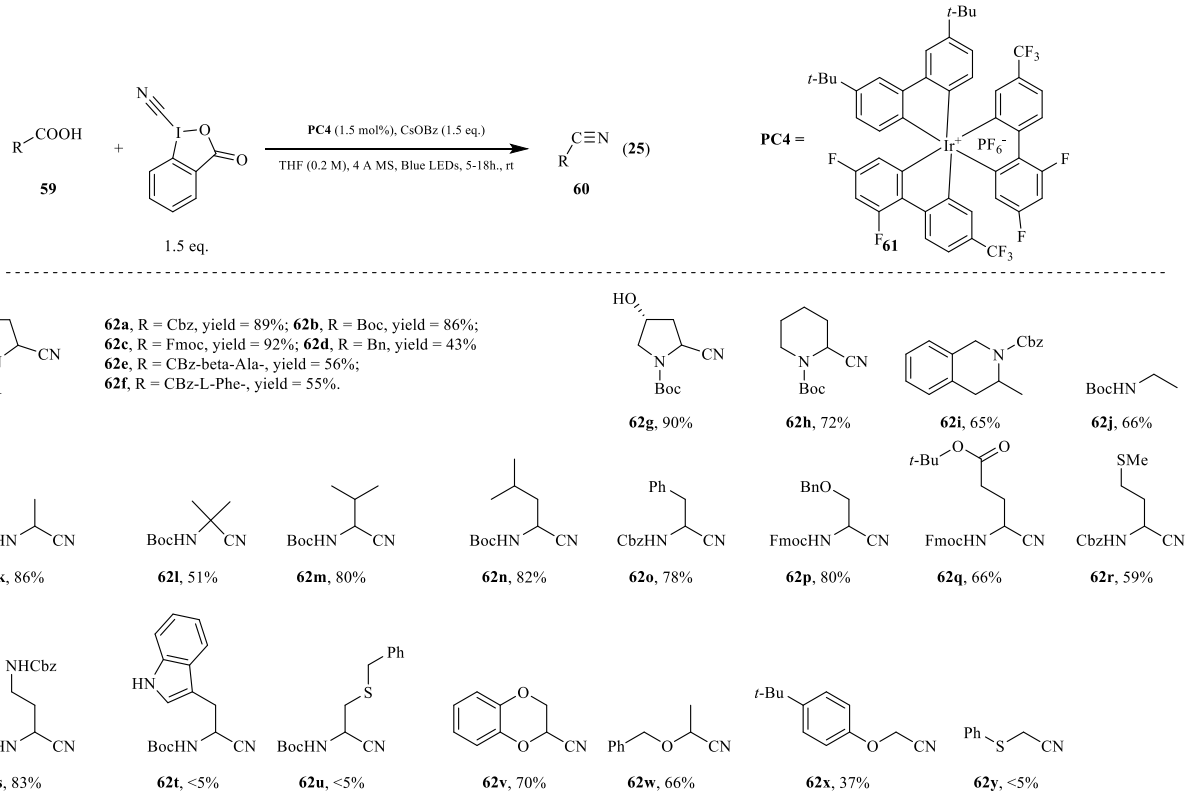


Figure 11.

Photoredox C-C bond cleavage. This type of reactions facilitates one-step conversion of aliphatic carboxylic acids to corresponding nitriles by combining visible light-mediated photoredox and cyanobenziodoxolone reagent (**equation 25**). The process enables high-yield production of a wide array of nitriles from natural and non-natural α-amino and α-oxy acids, as well as direct cyanation of dipeptides and drug precursors (Figure 11)[1].

Cyanobenziodoxolone has emerged as a promising reagent for visible-light-induced C-C bond cleavage in lignin, opening new pathways for transforming this abundant biopolymer into value-added chemicals. CBX-promoted selective cleavage of C-C bonds in β-O-4 lignin model compounds **62**, CBX enables the production of aldehydes (**63**) and acetal esters (**64**), which can be further converted into phenols and formaldehyde. This novel approach offers a mild and efficient strategy for lignin degradation, paving the way for a more sustainable utilization of this renewable resource in various industrial applications (Figure 12, 13)[24].

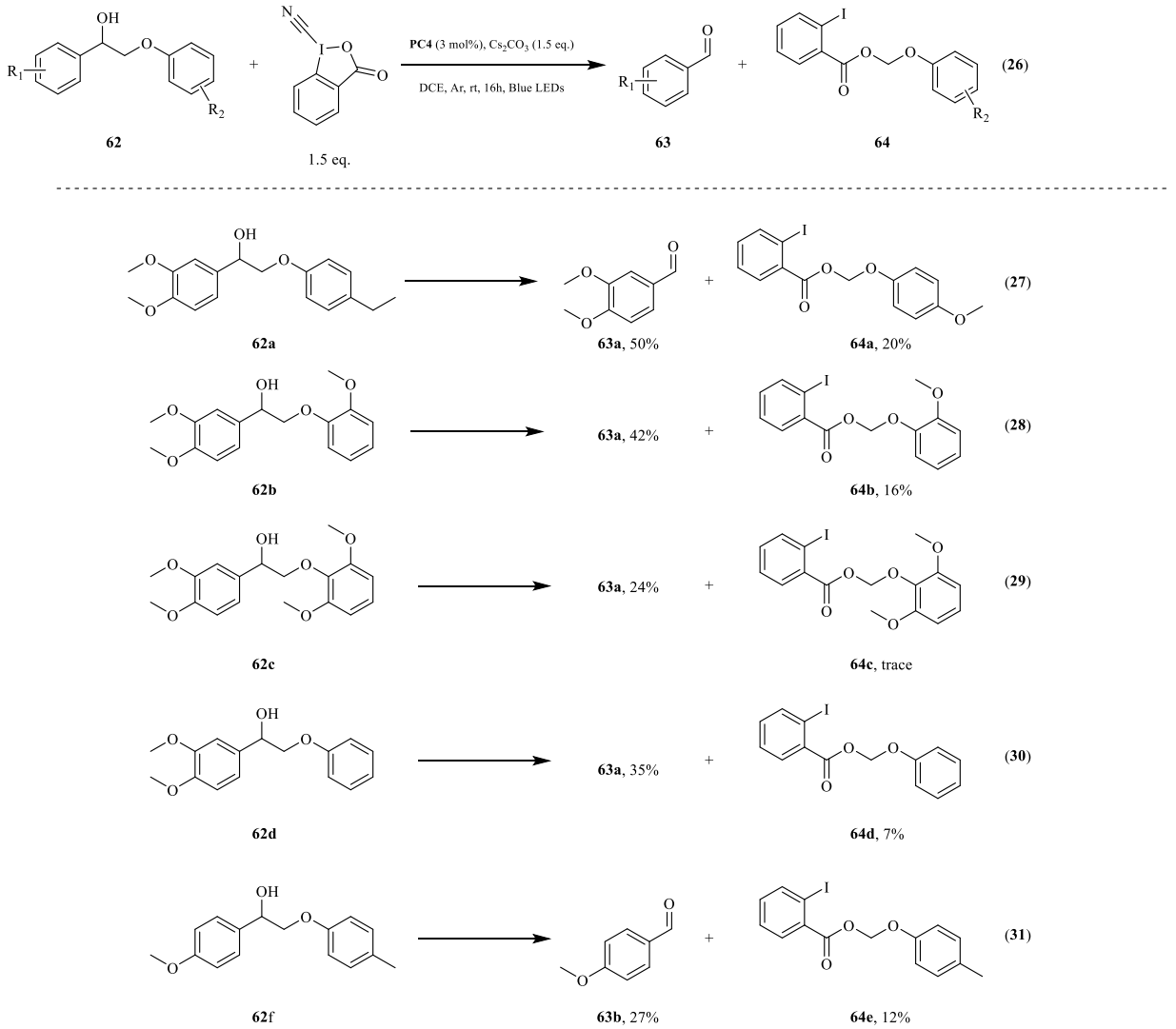


Figure 12.

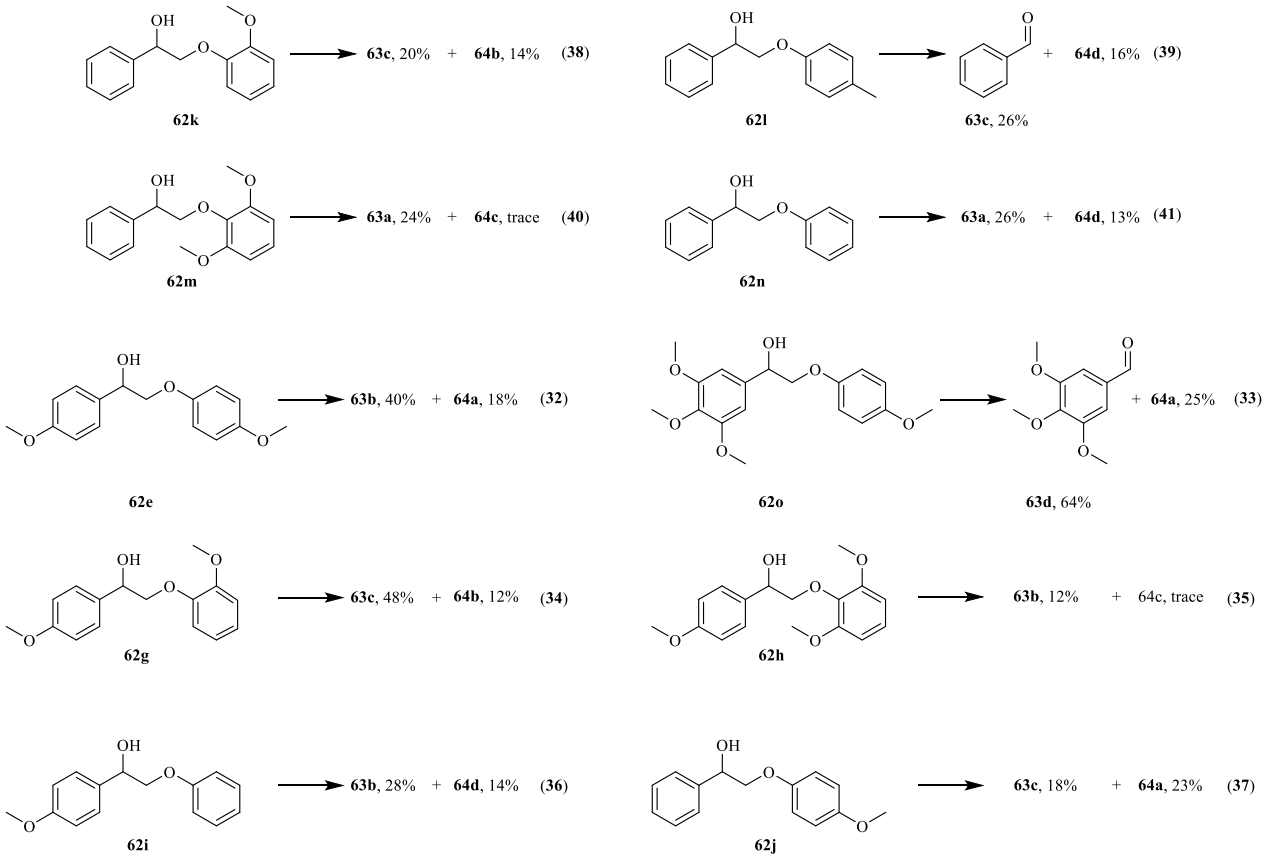


Figure 13.

Heterocycle formation. Cyanobenziodoxolone has been successfully employed in the synthesis of enantiopure 1,5-substituted hydantoins (**66**), which are a valuable class of heterocycles. By leveraging CBX's electrophilic carbon source properties, this method starts from readily available chiral amino acids and avoids conventional multistep protocols. This user-friendly approach enables the efficient synthesis of a diverse library of chiral hydantoins (**66a-w**), demonstrating CBX's potential in advancing synthetic and medicinal chemistry applications (Figure 14)[7].

Metal complexes synthesis. The use of cyanobenziodoxolone has been demonstrated to play a dual role in the synthesis of metal complexes, acting as both a ligand donor through its cyano group and a single electron transfer (SET) oxidant. This unique reactivity enables the synthesis of elusive high-valent iron complexes (**71**), paving the way for novel iron-catalyzed group-transfer reactions. Further understanding of CBX's reactivity with iron complexes may unlock new opportunities for environmentally friendly methodologies in organic synthesis (Scheme 5).[25]

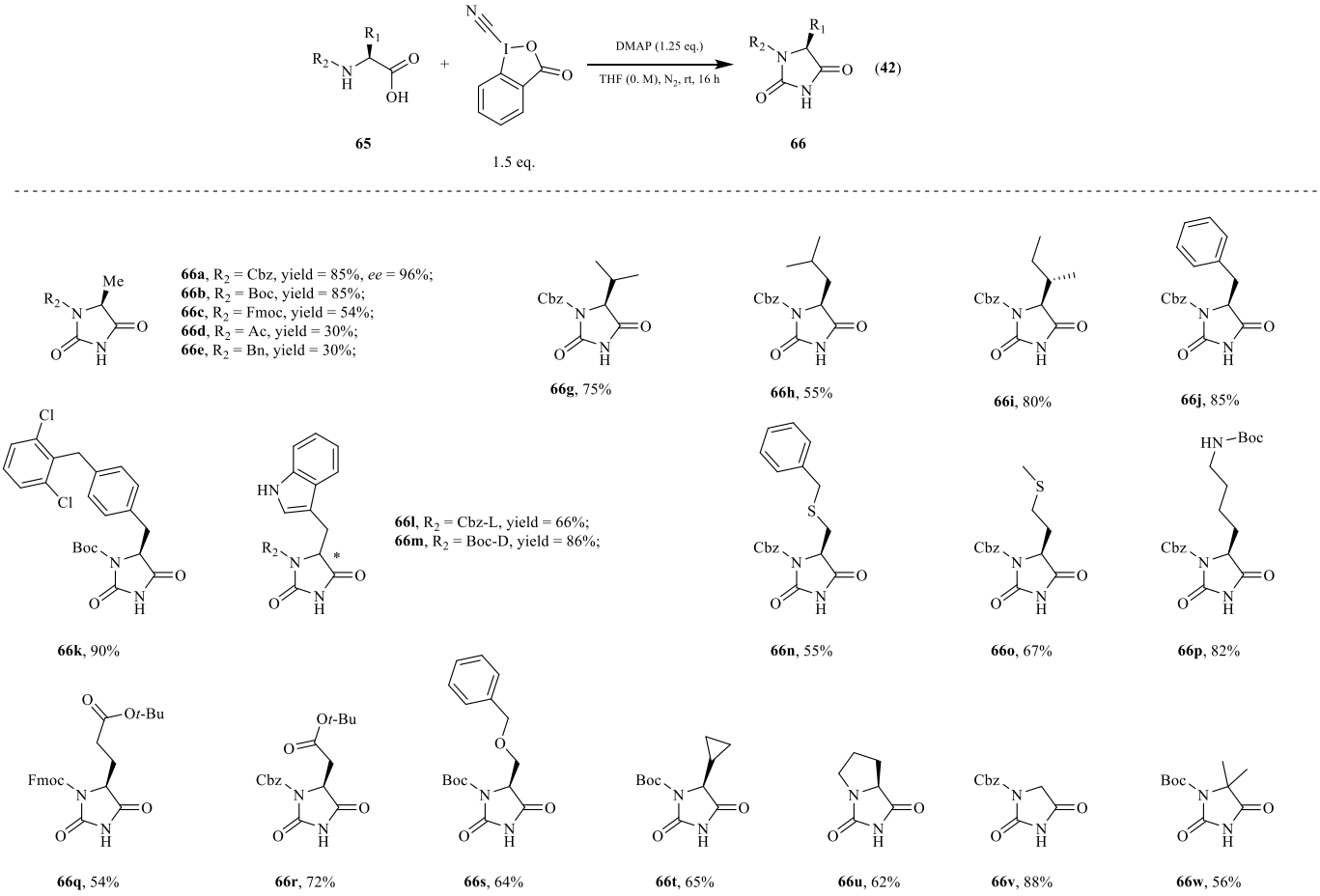
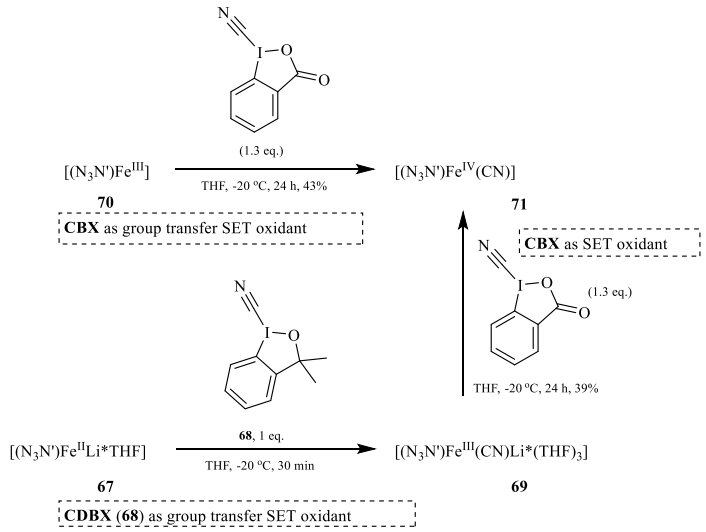


Figure 14.



Scheme 5.

Other cyanation agents from hypervalent iodine reagents (HIRs) family. It is notable that hypervalent iodine reagents (HIRs) structurally related to CBX can find use in the similar cases as CBX and can sometimes expand the scope of CBX reactivity. However still in the majority of cases CBX retains its superiority over modified

analogues. The reactivity of the cyanating HIRs was evaluated by Chen and coworkers in photoredox promoted decarboxylative cyanations[26]. The second most widely used reagent of the family, 1-cyano-3,3-dimethyl-3-(1H)-1,2-benziodoxole (CDBX, **68**) was successfully used in catalytic electrophilic cyanation of silyl enol ethers[27], thiocyanates synthesis [3] and cyano-transfer/SET oxidation of ferric complexes[25]. The less common *tret*-butilated CBX (**76**) showed good yields in organocatalytic base-promoted enantioselective electrophilic cyanation of β-keto esters performed in phase-transfer conditions[8]. At last, dimetoxy-CBX (**74**) showed the best reactivity in class for selective C(sp^3)-C(sp^3) cleavage/alkynylation of cycloalkylamides (Figure 15).

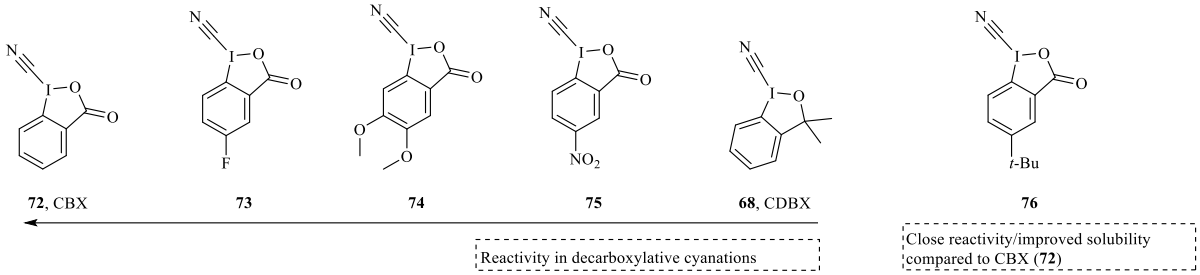


Figure 15.

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