Csp^3-Csp^2 Coupling of Isonitriles and (Hetero)arenes through a Photoredox-Catalyzed Double Decyanation Process

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Abstract: Herein we demonstrate the ability of isonitriles to be used as alkyl radical precursors in a photoredox-catalyzed transformation involving selective C-N cleavage and Csp^3-Csp^2 bond formation. This protocol allows for the preparation of functionalized heteroarenes from readily available isonitriles through a decyanation process. The reaction is general for primary, secondary and terciary substrates, including amino acid derivatives and druglike molecules.

Introduction

Isonitriles are one of the most intriguing functional groups in synthetic chemistry.[1-3] Their chameleonic electronic properties allow them to act as nucleophiles, electrophiles, carbenes and radical acceptors. They can be easily prepared in one or two steps from primary amines,[4,5] alkenes[6] and tertiary alcohols,[7] which are three of the most abundant functional groups in chemistry (Figure 1). Moreover, isonitriles are present in hundreds of secondary metabolites with a growing interest in medicinal chemistry.[8-10] The reactivity of the multiple N≡C bond in isonitriles has been extensively studied through the Ugi and Passerini multicomponent reactions,[11,12] metal coordination,[13] biorthogonal [4+1] cycloaddition,[14] polymerization reactions[15] and *N*-formyl amide formation for the synthesis of complex peptides.[16] In contrast, the selective cleavage and functionalization of the single C-N bond in isonitriles is mostly limited to the formal hydrodeamination reaction (Figure 1).[17-19] Despite their availability from feedstock material, the use of isonitriles in catalytic C-N cleavage/C-C bond formation remains virtually unexplored.[20] We recently disclosed that isonitriles can undergo a mild and general formal hydrodeamination reaction promoted by visible-light irradiation in the presence of a silyl radical precursor.[21] In most cases, the reaction proceeded in the absence of a photocatalyst through a radical chain process. With the aim of further expanding the use of isonitriles in reactions involving C-N cleavage, we envisioned that they could participate in a photoredox catalytic cycle to promote a Csp^3-Csp^2 coupling with cyanopyridines[22-33] through a double decyanation process.

We hypothesized that upon visible-light irradiation, a photocatalyst could induce the formation of a silyl radical through a single electron oxidation (Figure 1).[34-38] The silyl radical could add to the isonitrile to form an imidoyl radical that would generate a carbon-centered radical upon β-fragmentation. The reduced photocatalyst could then reduce a cyanopyridine to provide an aryl radical anion that could react with the alkyl radical through a radical-radical coupling to afford the desired product. The products would be functionalized pyridines, which are the second most common nitrogen-containing heterocyles present in small-molecule drugs.[39]

We recognized from the outset that the choice of the silyl radical precursor would be key to avoid three undesired potential pathways: the hydrodeamination, the silicon-pyridine coupling and the oxidation of the imidoyl radical prior to β-fragmentation. We identified *N*-adamantyl aminosupersilane reagent **3** (Si−NHAd), introduced by MacMillan to promote halide abstractions in the cross-electrophile coupling of unactivated chlorides,[40] as the reagent of choice. The bond dissociation energy of the Si-H bond of a silyl amide (~111 kcal/mol)[41] is significantly higher than that of supersilane $(TMS)_3SiH$ (79 kcal/mol),[42] suppressing the dehydrodeamination pathway. Additionally, the increased nucleophilic character of the amino silyl radical generated compared to supersilane could minimize the formation of the silicon-pyridine coupling product. Importantly, this reagent shows much lower oxidation potentials (E_{pa}[Si−NHAd/Si−NHAd$^{+\bullet}$]= +0.75V vs SCE in 10:1 DMA:H_2O)[43] than supersilane [E_p (Si-H/Si-H$^{+\bullet}$) = +1.67V vs Ag/AgCl, 3M, KCl][44] or supersilanol [E_p (Si-OH/Si-OH$^{+\bullet}$) = +1.54V vs SCE in CH_3CN],[36] which could prevent the overoxidation of the imidoyl radical.[45] For the photocatalyst, we identified the organocatalyst 3DPA2FBN[46] as a suitable catalyst, capable of oxidizing the amino supersilane reagent ($E_{1/2}^{red}$ (**PC*/PC**$^{\bullet-}$) = +0.92 V vs. SCE in CH_3CN) and reducing ($E_{1/2}^{red}$ (**PC/PC**$^{\bullet-}$) = –1.92 V vs. SCE in CH_3CN)[46] the 4-cyanopyridine **2a** ($E_{1/2}^{red}$ = –1.75 V vs. SCE in CH_3CN).[47]

One important aspect of our method, which is unprecedented in the field of homolytic C_α-N cleavage, is that it would provide a general way to interconvert an alkyl primary amine into pyridine derivatives, in substrates with a C_α-primary, secondary or tertiary carbon. This approach complements the use of pyridinium salts[48] in transition metal-catalyzed cross-coupling reactions to prepare functionalized pyridines (limited to C_α-primary and C_α-secondary)[49-54] or the use of ammonium salts in

photoinduced processes, limited to the use of benzylic substrates.[55,56]

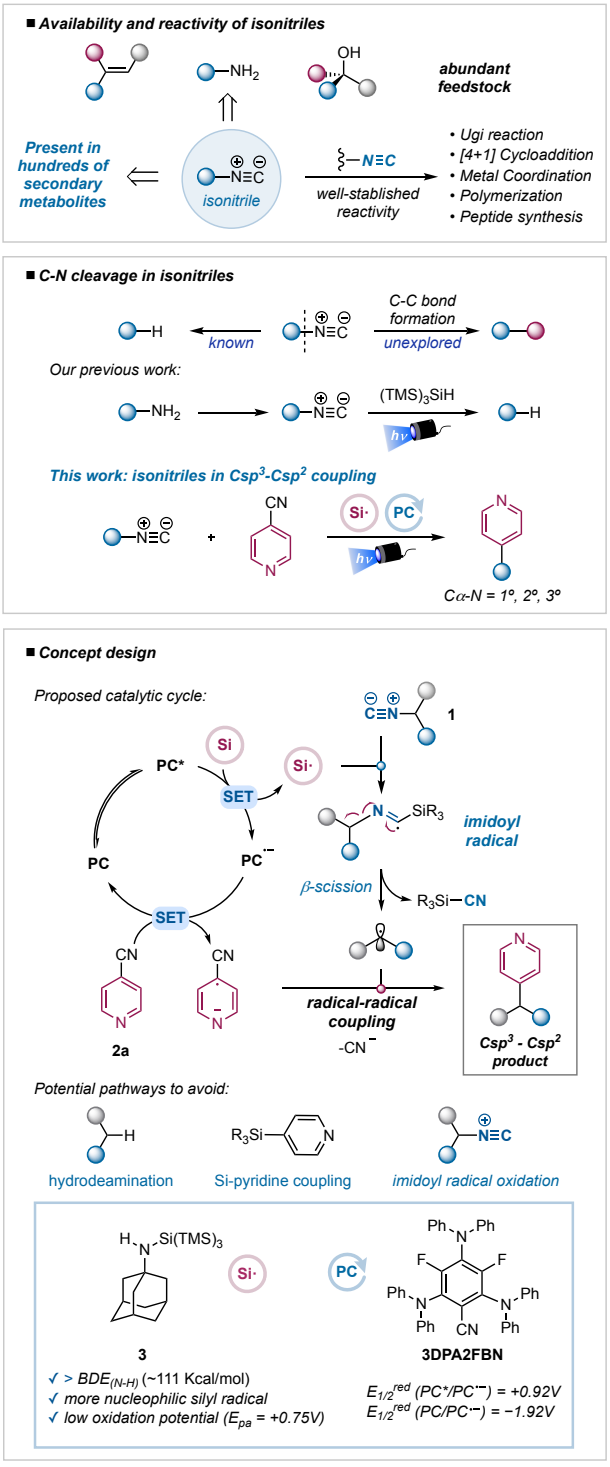
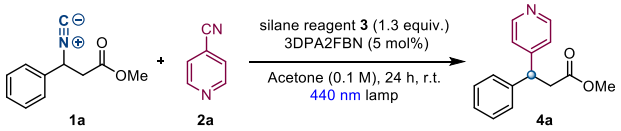


Figure 1. Availability and Reactivity of Isonitriles and Plan Design.

Results and Discussion

Based on this mechanistic considerations, isonitrile **1a** and 4-cyanopyridine (**2a**) were chosen as model substrates. After optimization of different parameters, optimal conditions were found involving silane **3** and photocatalyst 3DPA2FBN (5 mol%) in acetone under blue light irradiation. With these conditions pyridine **4a** was obtained in 84% isolated yield without detecting any hydrodeamination product (table 1, entry 1). Other more commonly used silyl radical sources (table 1, entries 2-3) proved to be less effective. Control experiments revealed that blue light, photocatalyst 3DPA2FBN, and silyl derivative **3** were all individually necessary (table 1, entries 4–6). The presence of oxygen in the reaction mixture led to a decreased 20% yield (table 1, entry 7). The reaction was scaled up to the use of 1 g of isonitrile **1a** with good reproducibility (table 1, entry 8). Moreover, detailed studies, including Stern-Volmer quenching, quantum yield determination and detection of R_3SiCN species supported the catalytic cycle proposed in Figure 1.[57]

Table 1. Optimization of the Reaction Conditions

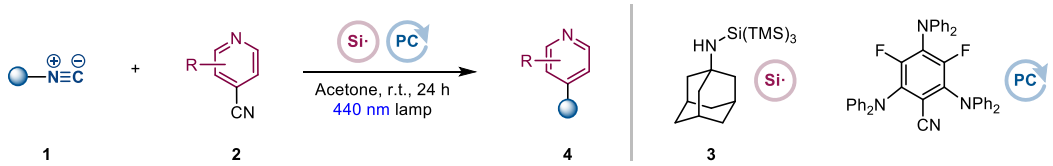


entry	deviation from conditions	yield (%)
1	none	85[a] (84)[b]
2	TMS_3SiH instead of **3**	24[a]
3	TMS_3SiOH instead of **3**	47[a]
4	no light	0
5	no 3DPA2FBN	0
6	no silane	0
7	open air	20[a]
8[c]	1 g scale	73[b]

[a]Yield determined by ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yields within brackets. See SI for experimental details. [c]Reaction time = 48 h.

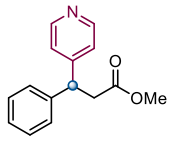
With the optimal conditions in hand, we first explored the scope of the decyanative arylation with benzylic derivatives (Scheme 1). We were pleased to find that the optimized conditions worked efficiently for a wide array of C_α-primary (**4l-4y**), secondary (**4a-4i**, **4k**) and tertiary (**4j**) isonitriles. The reaction scope revealed as a general trend that electron donating substituents on the aromatic ring afforded the corresponding products in higher yields than those bearing electron-withdrawing groups. The steric hindrance in *alpha*-position of the alkyl radical (**4g**, **4h**) or *ortho* substituents (**4f**, **4s, 4t**) on the aryl ring, did not affect the yield. The presence of the morpholine moiety (**4m**), which is often not compatible with other photocatalytic conditions due to oxidative degradation in alpha-position of the tertiary amine, was not affected under our reaction conditions highlighting the broad functional group compatibility. Isonitriles bearing an alkyl or aromatic boronic ester were also successfully used, providing a handle for further functionalization (**4i**, **4o**). Interestingly, bis- isonitrile **1u,** prepared from the corresponding diamine, was selectively mono- (**4u**) or difunctionalized (**4v**) adjusting the equivalents of the reagents. Moreover, indol (**4w**), thiophenyl (**4x**) and pyridyl (**4y**) derived isonitriles afforded the decyano arylation products in moderate to good yields.

Scheme 1. Substrate Scope with Benzylic Isonitriles[a]

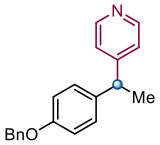


1 + 2 → 4 (3)

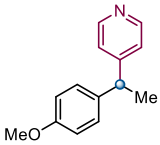
from benzylic isonitriles



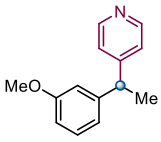
4a, 84%



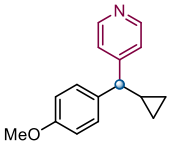
4b, 75%



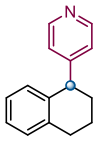
4c, 80%



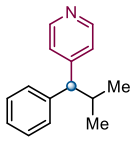
4d, 94%



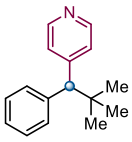
4e, 71%



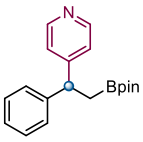
4f, 87%



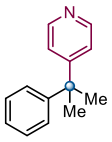
4g, 75%



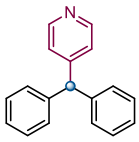
4h, 71%



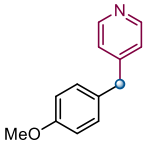
4i, 58%



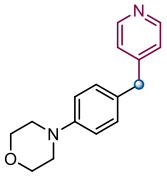
4j, 75%



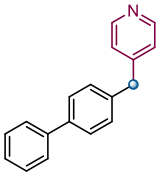
4k, 61%



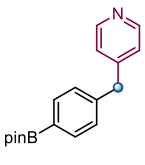
4l, 76%



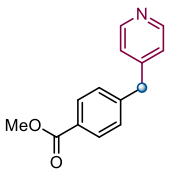
4m, 63%



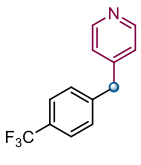
4n, 41%



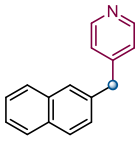
4o, 48%



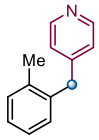
4p, 54%



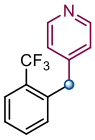
4q, 50%



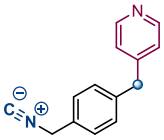
4r, 91%



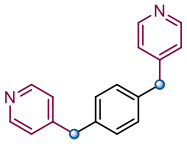
4s, 82%



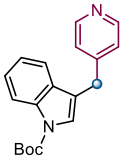
4t, 66%



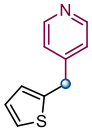
4u, 51%



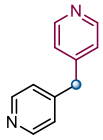
4v, 39%



4w, 75%

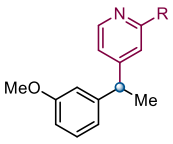


4x, 65%

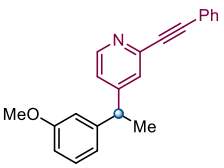


4y, 45%

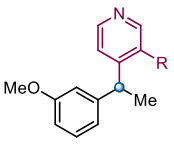
(hetero)aryl nitriles



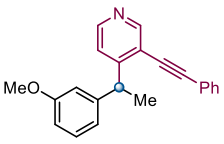
4z, R = Me, 70%
4aa, R = F, 47%
4ab, R = Cl, 40%
4ac, R = OMe, 43%
4ad, R = Ph, 59%



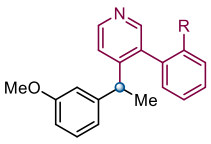
4ae, 27%



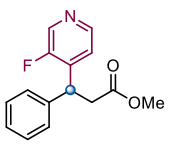
4af, R = OMe, 61%
4ag, R = Ph, 66%
4ah, R = *p*-MeOPh, 68%



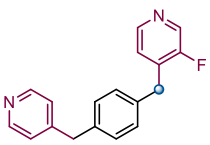
4ai, 36%



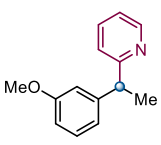
4aj, R = F, 59%
4ak, R = OMe, 80%



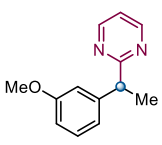
4al, 77%



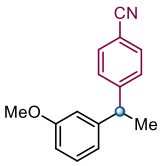
4am, 53% (70% brsm)



4an, 55%



4ao, 27%



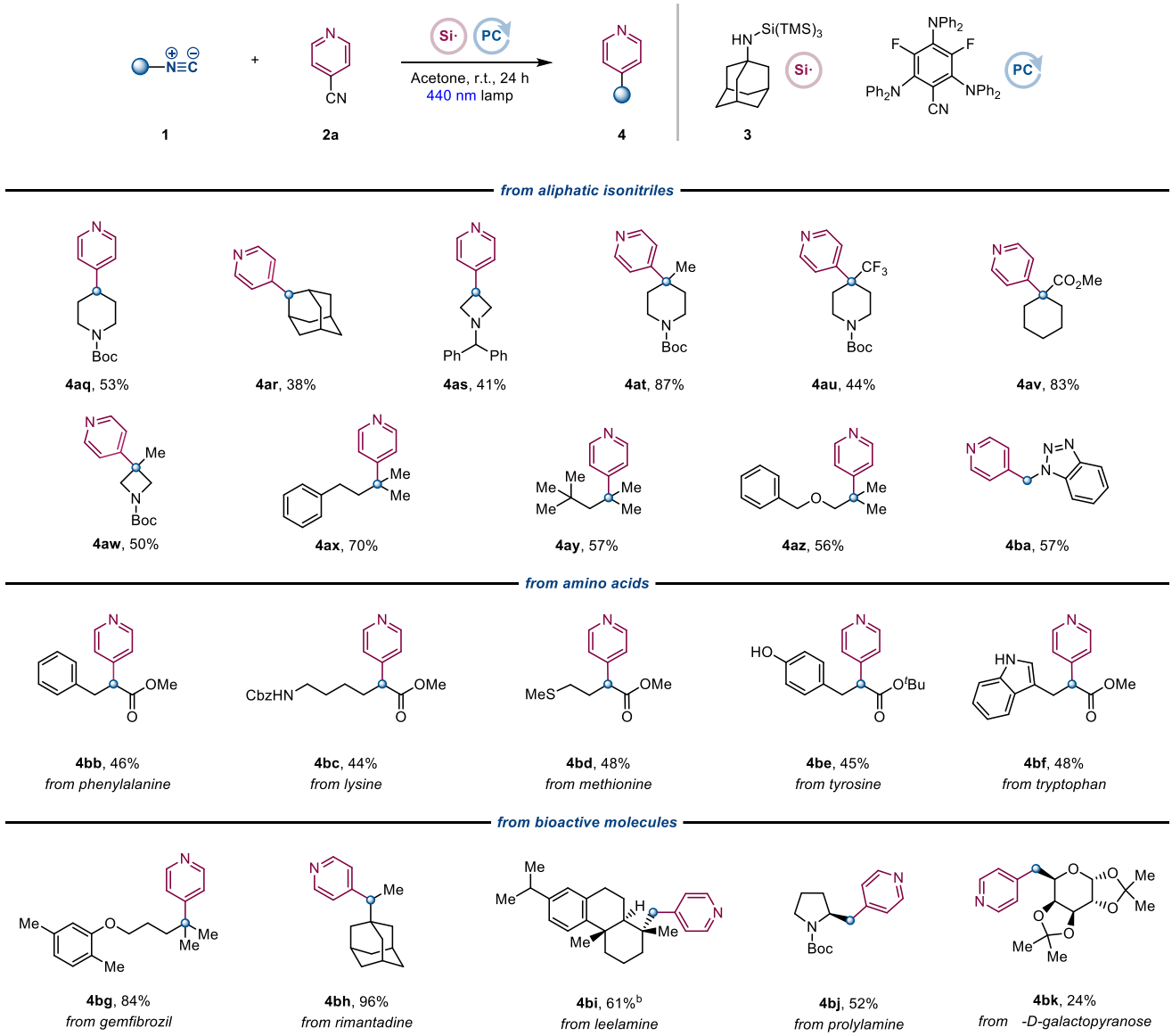
4ap, 44%[b]

[a]All yields are isolated. Reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol), aminosilane reagent **3** (0.26 mmol), **PC** (5 mol%), were irradiated by blue Kessil lamp (440 nm) in acetone (0.1M) at r.t. for 24 h. [b]See SI for experimental details.

We then applied the optimized conditions to different 4-cyanopyridines obtaining the corresponding 2,4-disubstituted (**4z-4ae**) and 3,4-disubstituted (**4af-4al**) products. Starting from isonitrile **4u**, previously prepared through the monofunctionalization of bis-isonitrile **1u**, compound **4am** was prepared, with two different pyridine rings. We were also pleased to find that the reaction took place with 2-cyanopyridine, 2-cyanopyrimidine and 1,4-dicyanobenzene as coupling partners to provide compounds **4an-4ap** in moderate yields.

More challenging aliphatic isonitriles were also suitable substrates (Scheme 2). As before, the reaction was general for C_α-primary (**4bi-4bk**), secondary (**4aq-4as**, **4bh**) and tertiary (**4at-4az**, **4bg**) isonitriles, including an isonitrile with C_α-heteroatom (**4ba**). Isonitriles derived from phenylalanine, lysine, methionine, and unprotected tyrosine and tryptophan afforded the corresponding α-pyridyl esters (**4bb-4bf**). Finally, the selective C-N cleavage was tested with different isonitriles prepared from bioactive molecules, showcasing the potential to apply the method in late-stage functionalization (**4bg-4bk**).

Scheme 2. Substrate Scope: Aliphatic Isonitriles, Amino Acid Derivatives and Bioactive Molecules[a]



[a]All yields are isolated. Reaction conditions: **1** (0.20 mmol), **2a** (0.30 mmol), aminosilane reagent **3** (0.26 mmol), **PC** (5 mol%), were irradiated by blue Kessil lamp (440 nm) in acetone (0.1M) at r.t. for 24 h. [b]Reaction time = 48 h.

In summary, we have developed the first protocol that uses isonitriles as alkyl radical precursors in a photoredox-catalyzed transformation involving selective C-N cleavage and subsequent C-C bond formation. This transformation allows for the interconversion of readily available isonitriles into functionalized pyridines under mild conditions, in the presence of an organic photocatalyst and a silyl amine. Mechanistic studies suggest a catalytic cycle with a reductive quenching involved. Importantly, the reaction can be used to functionalize primary, secondary and terciary substrates. Moreover, we envision that this study will enable the development of further photocatalyzed transformations using isonitriles to selectively cleave and functionalize C-N bonds.

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Conflict of Interest

The authors declare no conflict of interest.

Supporting Information

Materials and methods, experimental procedures, complete computational details, ^{1}H and ^{13}C NMR spectra, and HRMS data are available in the Supplementary Information.

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