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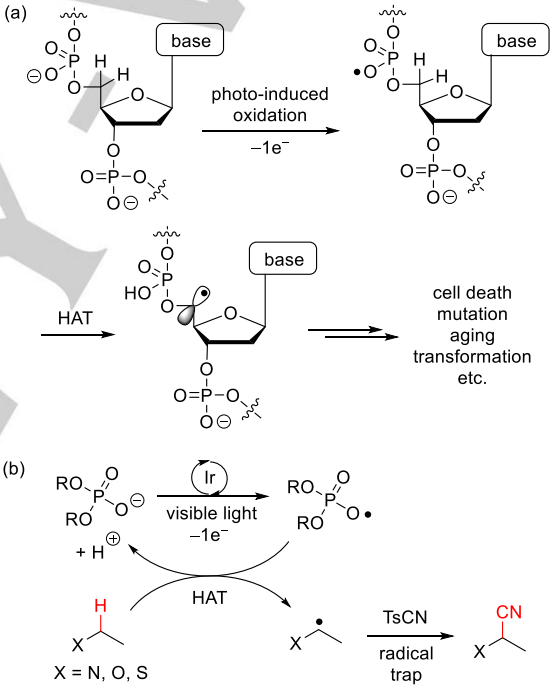
C(sp^3)–H Cyanation Promoted by Visible-Light Photoredox/Phosphate Hybrid Catalysis

Takayuki Wakaki, Kentaro Sakai, Takafumi Enomoto, Mio Kondo, Shigeyuki Masaoka, Kounosuke Oisaki*, Motomu Kanai*

Abstract: Inspired by the reaction mechanism of photo-induced DNA-cleavage in nature, a C(sp^3)–H cyanation reaction promoted by visible-light photoredox/phosphate hybrid catalysis was developed. Phosphate radicals, generated by one-electron photooxidation of phosphate salt, functioned as a hydrogen atom transfer catalyst to produce nucleophilic carbon radicals from C(sp^3)–H bonds with a high bond dissociation energy. The resulting carbon radicals were trapped by a cyano radical source (TsCN) to produce the C-H cyanation products. Due to the high functional-group tolerance and versatility of the cyano group, the reaction will be useful for realizing streamlined building block syntheses and late-stage functionalization of drug-like molecules.

Transformation of unactivated C(sp^3)–H bonds, which are ubiquitously present in organic compounds, can facilitate streamlined syntheses of complex organic molecules.[1] The method is also promising for expanding the structural diversity of drug-like lead molecules through late-stage derivatizations.[2,3] Specifically, C(sp^3)–H functionalization involving a hydrogen atom transfer (HAT) process driven by photoenergy is attractive due to the mild reaction conditions and high functional group-tolerance.[4] In combination with a visible-light photoredox catalysis, structurally distinct HAT catalysts, such as thiols,[5] thiophosphoric acids and imides,[6] quinuclidines,[7] sulfonamides,[8] chloride[9] and bromide[10] ions, aryl carboxylates,[11] and *N*-hydroxy compounds[12] were developed. The currently-available HAT catalysts have limitations, however, such as (1) limited scope of cleavable C-H bonds,[13] (2) catalyst decomposition due to the inherent nucleophilicity[14] and/or reactivity with carbon–carbon multiple bonds,[15] and (3) insufficient stability,[16] thus leaving room for improvement. HAT catalysts that can cleave C(sp^3)–H bonds with a relatively high bond dissociation energy (BDE: 95–105 kcal/mol) and high catalyst turnover are in high demand.

Photocleavage of DNA chains is a chemical process that may lead to cell death, mutation, aging, and transformation.[17] Sevilla *et al.* recently proposed that DNA-photocleavage is initiated by an intramolecular HAT from the deoxyribose moiety to phosphate radicals generated under high-energy light irradiation (Scheme 1a).[18] Our study, inspired by this mechanism, has demonstrated that *in situ*-generated phosphate radicals through one-electron photooxidation act as powerful HAT catalysts capable of cleaving strong C(sp^3)-H bonds with high BDE values (Scheme 1b).[19] This novel HAT catalysis promotes C(sp^3)-H cyanation at the α-position of heteroatoms.



Scheme 1. (a) In the natural system: DNA-strand cleavage by a phosphate radical-mediated HAT process induced by photoenergy. (b) This work: C(sp^3)-H activation by a phosphate radical-mediated HAT process induced by visible-light photoredox catalysis.

Methods for efficient and facile introduction of a cyano group to organic molecules are valuable due to the high synthetic versatility of cyano groups.[20,21] Many precedents of C(sp^3)-H cyanations, however, often required harsh conditions, such as high temperature and/or strong oxidizing reagents, and can only be applied to substrates bearing electron-donating substituents on the adjacent heteroatoms.[21,22] Inoue[23] and Hill[24] groups reported precedents of cyanation targeting C(sp^3)-H bonds with high BDE values, although the reactions required ultraviolet (UV) irradiation. C-H cyanation proceeding under mild visible light-irradiation has not been reported.

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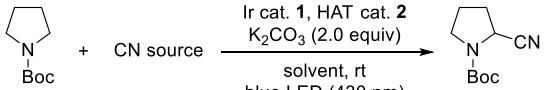
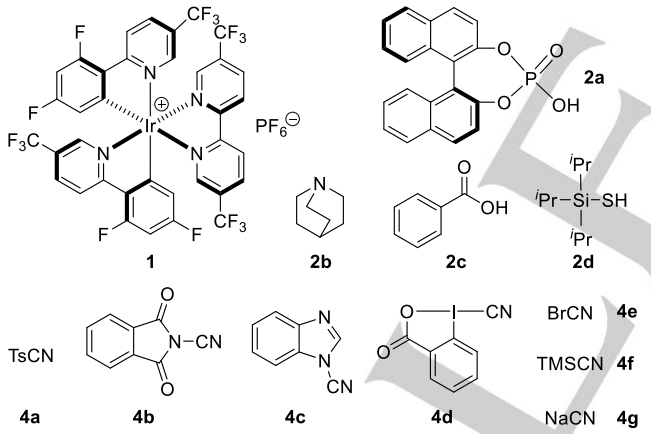
We first searched for a suitable combination of a photoredox catalyst and phosphoric acid using a mechanism-based screening method.[25] Fluorescent quenching was observed when 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (**2a**) and $Ir(dFCF_3ppy)_2(5,5'\text{-}dCF_3bpy)(PF_6)$ (**1**, $dFCF_3ppy$ = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, 5,5'-dCF_3bpy = 5,5'-bis(trifluoromethyl)-2,2'-bipyridine)[26] were irradiated with 430-nm LED light in acetonitrile.

Table 1. Optimization of Reaction Conditions



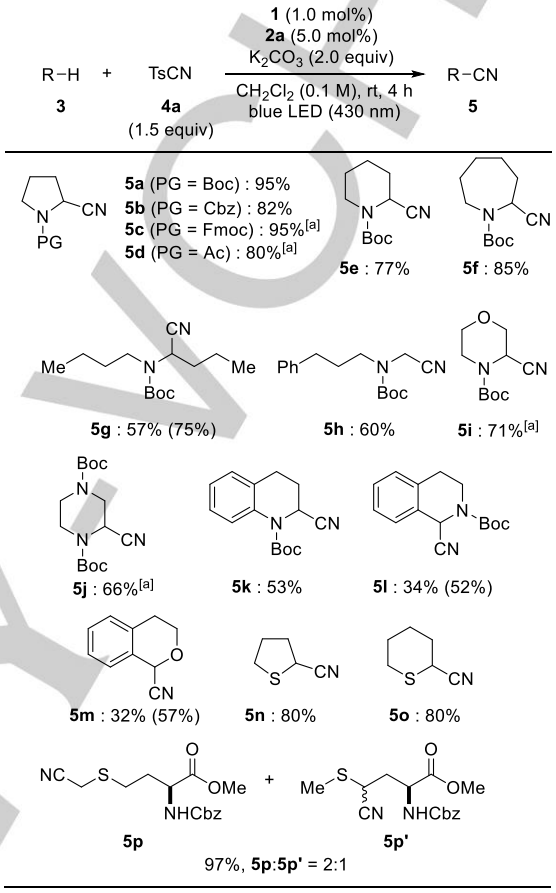
entry	condition[a]	HAT	CN source	yield/%
1	A	**2a**	**4a**	56
2	A	**2b**	**4a**	<1
3	A	**2c**	**4a**	<1
4	A	**2d**	**4a**	9
5	B	**2a**	**4a**	95
6	B	**2a**	**4b**	<1
7	B	**2a**	**4c**	<1
8	B	**2a**	**4d**	21
9	B	**2a**	**4e**	23
10	B	**2a**	**4f**	<1
11	B	**2a**	**4g**	<1
12[b]	A	**2a**	**4a**	<1
13[c]	A	**2a**	**4a**	<1
14[d]	A	**2a**	**4a**	<1
15	A	none	**4a**	17



[a] Condition A: **1** (2.0 mol%), HAT **2** (20 mol%), **4** (2.0 equiv), CH_3CN (0.1 M). Condition B: **1** (1.0 mol%), HAT **2** (5.0 mol%), **4** (1.5 equiv), CH_2Cl_2 (0.1 M). [b] In the absence of K_2CO_3. [c] No light irradiation. [d] In the absence of **1**.

Based on this finding, we next investigated several types of C-H functionalization reactions using 2 mol% **1** and 20 mol% **2a** under photoirradiation with blue LEDs (Table 1, condition A). The reaction between *N*-Boc pyrrolidine (**3a**) and *p*-toluenesulfonyl cyanide (TsCN, **4a**) in the presence of K_2CO_3 produced cyanation product **5a** in 56% yield (entry 1). When using previously reported HAT catalysts such as quinuclidine (**2b**),[7] benzoic acid (**2c**),[11] and triisoproplysilylthiol (**2d**)[5] instead of **2a**, **5a** was obtained in low yield (entries 2-4). Further optimization of the reaction conditions improved the yield of **5a** to 95% when the catalyst loadings of **1** and **2a** were reduced to 1 mol% and 5 mol%, respectively, in dichloromethane solvent (condition B, entry 5). Screening of cyanation reagents revealed that **4a** was optimal (entries 5-11). Nucleophilic cyanation reagents, TMSCN (**4f**) or NaCN (**4g**), did not produce **5a** (entries 10 and 11). As control experiments in the absence of any elemental factors, blue LED irradiation, the Ir photocatalyst, K_2CO_3, or phosphoric acid **2a**, the yield remained low (entries 12-15).

Table 2. Scope and Limitations

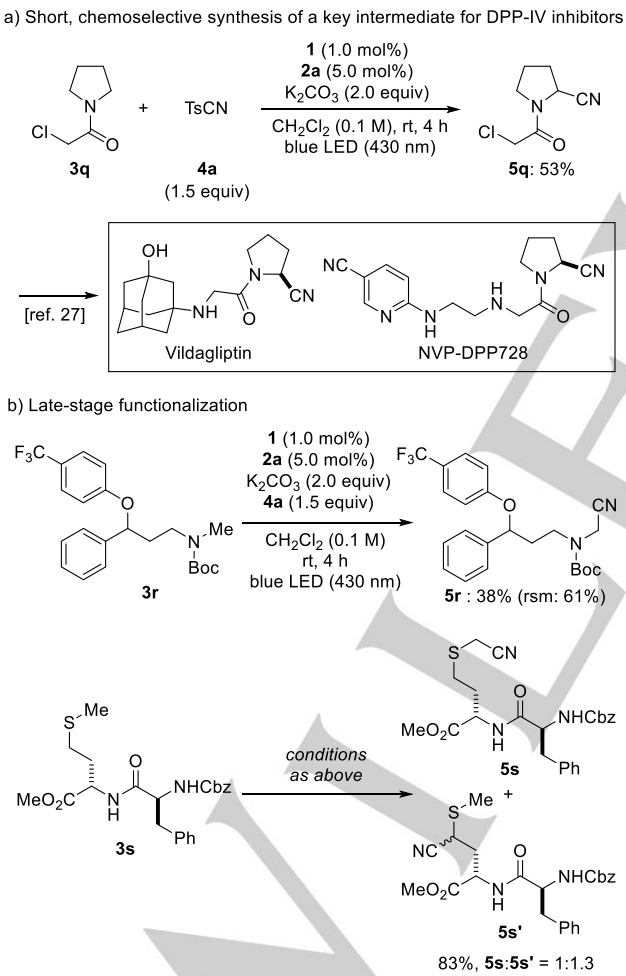


Yields were determined as isolated yields. Yields indicated in parentheses were determined from the ^1H NMR analysis in the presence of 1,1,2,2-tetrachloroethane as an internal standard. [a] **4a** (3.0 equiv), 20 h.

Having determined the optimal conditions, we next investigated the substrate scope (Table 2). For protected amines, pyrrolidines with different carbamate-protecting groups (**3a**-**3d**), *N*-Boc piperidine (**3e**), *N*-Boc azepane (**3f**), and *N*-Boc dibutylamine (**3g**) produced the corresponding cyanation products **5a**-**5g** in good to excellent yields (77%-95%). Using *N*-Boc secondary amine **3h** having methyl and phenylpropyl substituents on the nitrogen atom, C-H cyanation proceeded at the methyl group with excellent selectivity (**5h**: >20:1 regioselectivity). The reaction with *N*-Boc morpholine (**3i**) proceeded selectively at an α-C-H bond of the nitrogen atom, producing **5i** in 71% yield. *N*,*N'*-Di-Boc-piperazine (**3i**) predominantly produced mono-cyanated product **5j** in 66% yield, presumably due to the deactivating effects of the electron-withdrawing cyano group. For *N*-Boc-tetrahydroquinoline (**3k**) and *N*-Boc-tetrahydroisoquinoline (**3l**) having benzylic C-H bonds, the reaction proceeded selectively at the α-position of the nitrogen atom, giving products **5k** and **5l** in 52%-53% yields. As demonstrated in the reaction to isochromane (**3m**), tetrahydrothiophene (**3n**), and thiane (**3o**), an α-C-H bond bound to an oxygen atom or a sulfur atom was successfully converted to

a C-CN bond of **5m**-**5o** in good yield (57%-80%). The reaction with *N*-Boc methionine (**3p**) afforded two regioisomers, **5p** and **5p'**, in an excellent combined yield of 97%.

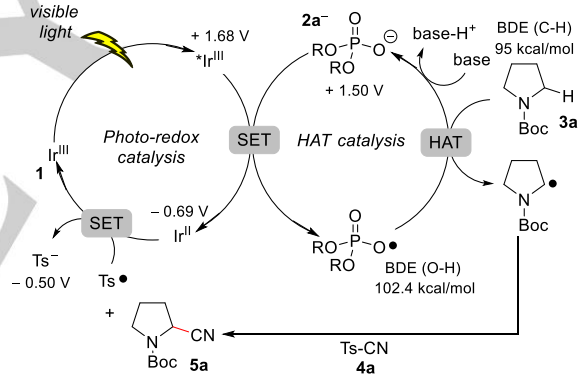
This reaction was applied to a short synthesis of pharmaceuticals and late-stage cyanation of multifunctional molecules, taking advantage of the mild reaction conditions and functional group tolerance. Using commercially available 2-chloro-1-(pyrrolidin-1-yl)ethan-1-one (**3q**) as a substrate, cyanation product **5q** was obtained in 53% yield without affecting the α-chloroacetyl moiety, which is sensitive to nucleophiles or reductants. Amidonitrile **5q** is a key intermediate for the synthesis of dipeptidyl peptidase IV (DPP-IV) inhibitors.[27] When this reaction was applied to *N*-Boc fluoxetine (**3r**), C-H cyanation proceeded regioselectively at the methyl group to produce **5r** in 38% yield. The product derived from methylene cyanation was not detected at all. When methionine-containing dipeptide **3s** was subjected to the same conditions, however, a mixture of **5s** and **5s'** was obtained in a 1:1.3 ratio. Functional groups other than the thioether group, as well as the benzylic C-H bonds, were unaffected.



Scheme 2. Application of C(*sp*^{3})-H Cyanation

We collected experimental results to gain some insight into the reaction mechanism: (1) No fluorescence-quenching occurred in mixtures of photocatalyst **1** and substrate **3a**, **1** and TsCN (**4a**), or **1** and K_2CO_3. On the other hand, fluorescence-quenching occurred in a mixture of **1**, phosphate **2a**, and K_2CO_3.[28] (2) The reaction proceeded only under photoirradiation (Table 1, entry 13). When the reaction was performed under the photoirradiation-shading cycle, the reaction proceeded only during photoirradiation.[28,29] Those results may suggest that the reaction does not proceed via a radical chain mechanism. (3) Use of sodium *p*-toluenesulfinate (NaO_2Stol) or sodium *p*-toluenesulfonate (NaO_3Stol) instead of **2a** did not afford the cyanation product. These results suggest that *in situ*-generated *p*-toluenesulfonyl radicals ($Ts^{\bullet}$) or *p*-toluenesulfonyloxy radicals ($TsO^{\bullet}$) do not function as HAT species in this reaction.

Based on the above mechanistic insights, we propose a possible mechanism for the present reaction, as depicted in Scheme 3: (1) Photocatalyst **1** ($^*Ir^{III}/Ir^{II}$ = +1.68 V vs. SCE) is excited by visible light irradiation. (2) The excited photocatalyst oxidizes the phosphate anion (**2a**$^{\bullet}$/**2a**$^{-}$: +1.50 V vs. SCE), thus generating a phosphate radical. Without K_2CO_3, the reaction does not proceed because the oxidation of **2a** requires +1.72 V (vs. SCE). (3) The resulting phosphate radical (BDE(O–H) = 102.4 kcal/mol)[30] selectively abstracts the C–H bonds of **3a** (BDE(C–H) = 95 kcal/mol) to produce the corresponding carbon radical. (4) The resulting carbon radical is trapped by **4a**,[14,23,24,31] producing cyanation product **5a**. (5) The thus-generated *p*-toluenesulfonyl radical ($Ts^{\bullet}/Ts^{-}$ = –0.50 V vs. SCE)[31a] is reduced by the photocatalyst (Ir^{III}/Ir^{II} = –0.69 V vs. SCE) to give a sulfinate anion (Ts^{-}), thereby closing the whole hybrid catalytic cycle.



Scheme 3. Proposed Reaction Mechanism

In summary, we developed a catalytic C(*sp*^{3})-H cyanation reaction that proceeded under mild conditions and visible-light irradiation. Identification of a hybrid catalysis comprising iridium photoredox catalyst **1** and phosphate HAT catalyst **2a** was key for the success. Due to the observed functional group tolerance, this reaction was applicable to late-stage functionalization of a bioactive compound and peptide. The extension of this novel phosphate HAT system to other reaction patterns is ongoing.

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Conflict of interests

The authors declare no conflict of interest.

Keywords: C-H activation • photoredox catalysis • cyanation • phosphoric acid • late-stage functionalization

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C(sp^3)-H Cyanation Promoted by a Visible-Light Photoredox/Phosphate Hybrid Catalysis

A C(sp^3)-H cyanation promoted by a visible-light photoredox/phosphate hybrid catalysis is described. The use of phosphate hydrogen atom transfer (HAT) catalysts was essential for the reaction. Nitrile compounds were synthesized in moderate to excellent yields with streamlined synthetic route. This reaction was appreciable to late-stage functionalization of a bioactive molecules and a peptide.