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Photochemically Induced Radical Transformation of $C(sp^3)-H$ Bonds to $C(sp^3)-CN$ Bonds

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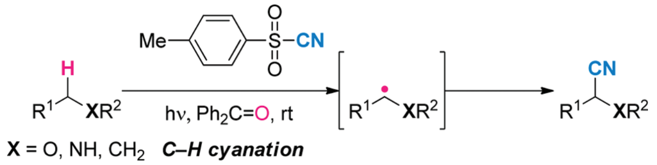
ABSTRACT



A general protocol for direct transformation of unreactive $C(sp^3)-H$ bonds to $C(sp^3)-CN$ bonds has been developed. The C–H activation was effected by photoexcited benzophenone, and the generated carbon radical was subsequently trapped with tosyl cyanide to afford the corresponding nitrile in a highly efficient manner. The present methodology is widely applicable to versatile starting materials and, thus, serves as a powerful tool for selective one-carbon elongation for construction of architecturally complex molecules.

The formation of new carbon–carbon bonds is one of the most important transformations in organic chemistry. The direct transformation of C–H bonds to C–C bonds has attracted much interest in recent years, because it avoids prior functional group manipulations for the synthesis of a preactivated precursor and thus greatly streamlines synthetic sequences. Among such reactions, functionalization of unreactive $C(sp^3)-H$ bonds is particularly advantageous for the construction of highly complex natural products, which generally contain a high ratio of sp^3-hybridized carbon centers. However, this extremely useful reaction remains challenging mainly due to the lack of general strategies for activating inert $C(sp^3)-H$ bonds in comparison to $C(sp^2)-H$ bonds of aromatic compounds.[1,2] Here we report a simple, yet powerful, protocol for direct conversion of $C(sp^3)-H$ bonds to $C(sp^3)-CN$ bonds.[3] The present cyanation has a broad substrate scope. Alkanes, benzylic compounds, ethers, alcohols, and amine derivatives all react to generate nitriles **2** under photochemical conditions using benzophenone ($Ph_2C{=}O$) as a C–H activator and tosyl cyanide (TsCN) as a radical acceptor (Scheme 1).[4,5] Since the attached nitrile moieties can be utilized as handles for

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(1) For recent reviews on direct C–H transformations, see: (a) *Handbook of C–H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; Vols. 1 and 2. (b) *Handbook of Reagents for Organic Synthesis: Reagents for Direct Functionalization of C–H Bonds*; Paquette, L. A., Fuchs, P. L., Eds.; Wiley: Chichester, 2007. (c) Special issue on `C–H Functionalizations in organic synthesis': *Chem. Soc. Rev.* **2011**, *40* (4).

(2) For recent reviews on direct $C(sp^3)-H$ transformation to form C–C bonds, see: (a) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393. (b) Fokin, A. A.; Schreiner, P. R. *Adv. Synth. Catal.* **2003**, *345*, 1035. (c) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795. (d) Davies, H. M.; Manning, J. R. *Nature* **2008**, *451*, 417. (e) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (f) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (g) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (h) Akindele, T.; Yamada, K.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345. (i) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (j) Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2011**, *40*, 2761. (k) Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, 353. (l) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293.

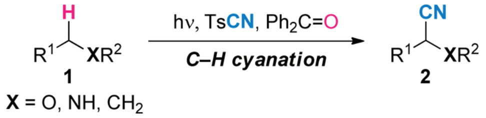
(3) We recently reported direct photoinduced $C(sp^3)-H$ acylation and carbamoylation. (a) Kamijo, S.; Hoshikawa, T.; Inoue, M. *Tetrahedron Lett.* **2010**, *51*, 872. (b) Kamijo, S.; Hoshikawa, T.; Inoue, M. *Tetrahedron Lett.* **2011**, *52*, 2885.

(4) Representative examples of direct $C(sp^3)-H$ cyanation, which are mostly limited to amine derivatives, with allylic and benzylic compounds as starting material. (a) Müller, E.; Huber, H. *Chem. Ber.* **1963**, *96*, 670. (b) Müller, E.; Huber, H. *Chem. Ber.* **1963**, *96*, 2319. (c) Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* **1987**, 1811. (d) Lemaire, M.; Doussot, J.; Guy, A. *Chem. Lett.* **1988**, 1581. (e) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J. *Tetrahedron Lett.* **1995**, *36*, 7975. (f) Zheng, Z.; Hill, C. L. *Chem. Commun.* **1998**, 2467. (g) Tajima, T.; Nakajima, A. *J. Am. Chem. Soc.* **2008**, *130*, 10496. (h) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005. (i) Singhal, S.; Jain, S. L.; Sain, B. *Chem. Commun.* **2009**, 2371. (j) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 5024. (k) Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 7464. (l) Allen, J. M.; Lambert, T. H. *J. Am. Chem. Soc.* **2011**, *133*, 1260. (m) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852.

10.1021/ol202659e

syntheses of various carbon-branched skeletons via further chain extension, this methodology holds promise for application to complex molecule synthesis.

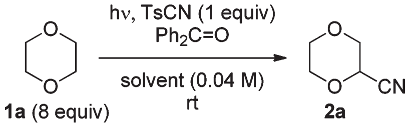
Scheme 1. Direct Photochemical Transformation of C(sp^3)–H Bonds to C(sp^3)–CN Bonds



To screen efficient photochemical conditions[6] for the direct C–H cyanation, we first selected dioxane **1a** as a substrate, based on the expectation that the symmetry of **1a** would simplify the outcome of the reaction.[7] Among a variety of reactants, it was found that a reagent combination of TsCN[8] (1 equiv) and $Ph_2C{=}O$ (1 equiv) efficiently promoted the conversion of **1a** (8 equiv) to nitrile **2a** in benzene (74% yield, entry 1, Table 1). In this reaction, recovery of $Ph_2C{=}O$ (59%) and formation of its dimer (1,1,2,2-tetraphenylethane-1,2-diol) were observed. Whereas the absence of $Ph_2C{=}O$ resulted in no product formation and recovery of TsCN (entry 2), using different amounts of $Ph_2C{=}O$ (0.5 equiv, entry 3) or **1a** (2 equiv, entry 4) led to generation of **2a** in reasonable yields. When dioxane **1a** was also employed as the solvent, the cyanation was complete within 1 h to provide **2a** in 85% yield (entry 5). The reaction also proceeded in both MeCN (entry 6) and *t*-BuOH (entry 7). Judging from the high yield of **2a** and recovered $Ph_2C{=}O$ even when using a reduced amount (entry 8), use of MeCN as the solvent appeared to be the most favorable for the photochemical reaction.

The direct photoinduced C–H cyanation of dioxane **1a** to **2a** should consist of a series of well-ordered radical reactions (Scheme 2).[3] Electrophilic oxyl radical **A**, photochemically generated from $Ph_2C{=}O$, abstracts the hydrogen of the electron-rich C(sp^3)–H bond of **1a** to furnish carbon radicals **B** and **C**. Next, the nucleophilic α-alkoxy radical **C** selectively reacts with the electron-deficient and sterically most accessible radical acceptor, TsCN, in the presence of other potentially reactive species, leading to nitrile **2a** with expulsion of sulfinyl radical **D**.[9] When **D** abstracts the hydrogen from ketyl radical **B**, it regenerates $Ph_2C{=}O$ to provide sulfinic acid and closes the cycle.

Table 1. Optimization of Cyanation Conditions[a]



entry	solvent	$Ph_2C{=}O$ equiv	*t*, h	yield, %[b] **2a**	$Ph_2C{=}O$ recovery
1	benzene	1	6	74[c]	59
2	benzene	0	12	0[d]	–
3	benzene	0.5	12	64[c]	<4
4[e]	benzene	1	24	46	48
5[f]	dioxane	1	1	85	90
6	MeCN	1	6	72 (63)[c,g]	87
7	*t*-BuOH	1	18	63	<5
8	MeCN	0.5	6	74	88

[a] Reaction conditions: **1a**/TsCN/$Ph_2C{=}O$ = 8:1:1, solvent (0.04 M), rt, irradiated using a Riko 100 W medium pressure mercury lamp unless otherwise noted. [b] Yield was determined by NMR analysis of the crude mixture. Isolated yield is shown in parentheses. [c] TsCN was recovered in ca. 10% yield. [d] TsCN was recovered in 83% yield. [e] The reaction was conducted using 2 equiv of **1a**. Recovery of TsCN (21%) was observed after the reaction. [f] Dioxane **1a** was employed as a solvent; **1a**/TsCN/Ph_2CO = ~300:1:1. [g] Due to its volatile nature, the isolated yield of **2a** was lower than that indicated by NMR analysis.

Having successfully developed this high-yielding cyanation protocol, we next investigated chemoselective functionalization of a variety of electron-rich C–H bonds adjacent to oxygen- and nitrogen-based functional groups (Table 2). The photoreactions of THF **1b** and phthalan **1c** proceeded smoothly to produce nitriles **2b**[10] and **2c**, respectively, in excellent yields (entries 2 and 3). Monocyanation took place exclusively for 15-crown-5 ether **1d**, despite the presence of many potentially reactive ethereal C–H bonds (entry 4). While the C–H bond adjacent to the primary hydroxyl group of **1e** was selectively functionalized to afford cyanohydrin **2e** (entry 5), treatment of 1-cyclopropylethanol **1f** under the same conditions quantitatively furnished 1-cyano-4-pentanone **2f** via radical-promoted ring opening of the cyclopropane and subsequent CN trapping (entry 6). Exclusive formation of **2f** instead of the corresponding cyanohydrin confirmed the radical formation at the OH-substituted carbon during the course of the reaction.

The single-step conversion of the amine derivatives **1g**–**1i** to the α-amino acid analogues was realized under the same conditions (entries 7–9, Table 2). Both the Boc-protected pyrrolidine **1g** and isobutylamine **1h** were cyanated selectively at the carbon center adjacent to the nitrogen atom, affording proline analogue **2g** (entry 7) and valine analogue

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(5) Nitrile-containing pharmaceuticals have recently been highlighted. Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.

(6) For recent reviews on photochemical reactions, see: (a) Fagnoni, M.; Dondi, D.; Ravelli, D.; Albini, A. *Chem. Rev.* **2007**, *107*, 2725. (b) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052. See also references in ref 3a.

(7) Dioxane has less reactive α-oxy C–H bonds in comparison to cyclic ethers such as tetrahydrofuran and tetrahydropynan. (a) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609. (b) Jenkins, I. D. *J. Chem. Soc., Chem. Commun.* **1994**, 1227. (c) Busfield, W. K.; Grice, D.; Jenkins, I. D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1079.

(8) For representative examples of radical reactions using TsCN as a cyanogen source, see: (a) Barton, D. H. R.; Jaszberenyl, J. C.; Theodorakis, E. A. *Tetrahedron* **1992**, *48*, 2613. (b) Kim, S.; Song, H.-J. *Synlett* **2002**, 2110. (c) Kim, S.; Cho, C. H.; Kim, S.; Uenoyama, Y.; Ryu, I. *Synlett* **2005**, 3160. (d) Schaffner, A.-P.; Darmency, V.; Renaud, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5847. (e) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4519.

(9) Formation of $ArSO_2SO_2Ar$, dimerized sulfinyl radical **D**, was observed in some cases. For the reported ^{1}H NMR data of the disulfone, see: (a) Liu, Y.; Zhang, Y. *Tetrahedron Lett.* **2003**, *44*, 4291. (b) Weber, W. G.; McLeary, J. B.; Sanderson, R. D. *Tetrahedron Lett.* **2006**, *47*, 4771.

(10) Bailey, S.; Humphries, P. S.; Skalitzky, D. J.; Su, W.-G.; Zehnder, L. R. Patent WO 2004/092145 A1, 2004.

Scheme 2. Proposed Mechanism for Transformation of C(sp^3)–H Bonds to C(sp^3)–CN Bonds

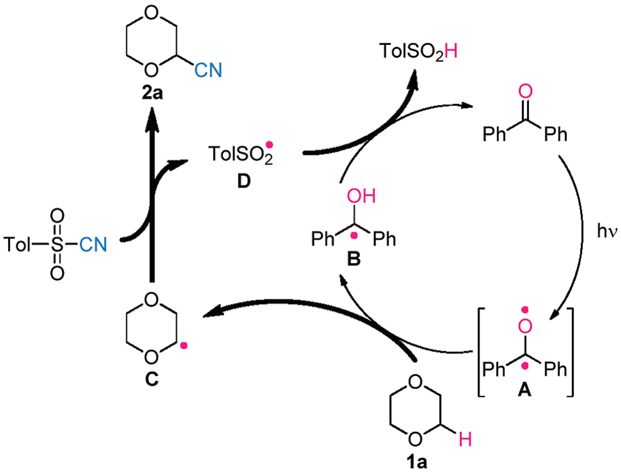
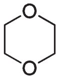
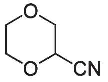
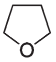
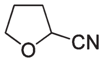
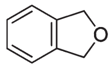
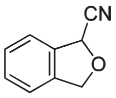
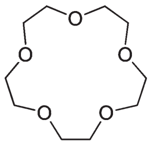
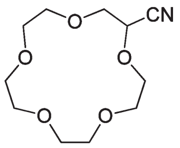
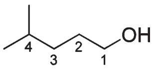
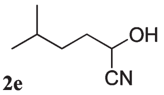
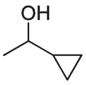
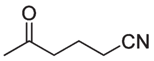
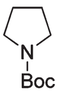
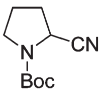
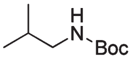
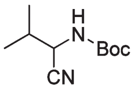
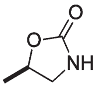
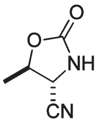


Table 2. C–H Cyanation Adjacent to Heteroatom-Based Functionalities[a]

entry	starting material	t,h	product	yield, %[b]
1	 **1a**	6	 **2a**	63 (72)
2	 **1b**	3	 **2b**	(92)
3[c]	 **1c**	10	 **2c**	91
4	 **1d**	3	 **2d**	84
5	 **1e**	3	 **2e**	72
6	 **1f**	10	 **2f**	97
7	 **1g**	2	 **2g**	94
8	 **1h**	12	 **2h**	73
9	 **1i**	10	 **2i**	83

[a] Reaction conditions: **1**/TsCN/Ph$_2$C=O = 8:1:1, MeCN (0.04 M), rt, irradiated using a Riko 100 W medium pressure mercury lamp unless otherwise noted. [b] Isolated yield. NMR yield is shown in parentheses. [c] Benzene was employed as a solvent instead of MeCN.

2h (entry 8), respectively, in high yields. The reaction of cyclic carbamate **1i** in turn generated threonine derivative **2i** as a single isomer through 1,2-stereoinduction (entry 9).

The cyanation protocol developed for the heteroatom-substituted substrates was successfully applied to functionalization of the less reactive C–H bonds of alkanes and benzylic compounds (Table 3). Cyclooctane **1j** was efficiently converted to the corresponding carbon-branched carbocycle **2j** under the optimized conditions (entry 1). The reactions of adamantane **1k** (entry 2) and its hydroxylated derivative **1l** (entry 3) both proceeded exclusively at the methine positions to install the quaternary carbons of **2k** and **2l**, respectively. The cyanation of benzoate **1m** gave rise to compound **2m** with a quaternary carbon (entry 4). The displayed chemoselectivities in entries 2–4 must originate from the higher reactivities of the more alkylated C–H bonds.[11] Thus, the electron-rich tertiary C–H bond was selectively converted to a C–CN bond in the presence of primary and secondary C–H bonds. Intriguingly, the contrasting results in entry 5, Table 2 and entry 4, Table 3 demonstrated that the reaction site can be predictably directed to either the α-alkoxy carbon at C1 or the tertiary carbon at C4 just by detaching or attaching the electron-withdrawing Bz group.

The reactivity of the benzylic C–H bond was next examined. The reaction of butylbenzene **1n** furnished benzyl cyanide **2n** in 41% yield (entry 5, Table 3). Installation of the electron-donating methoxy group on the phenyl ring (**1o**) increased the yield (entry 6), and installation of the electron-withdrawing acetoxy group (**1p**) decreased the yield (entry 7). The cyanation of ibuprofen methyl ester **1q** occurred on the isobutyl substituent to give benzyl nitrile **2q** as the major product along with its regioisomer **2q′** (entry 8). The results in entry 8 showed the higher reactivity of the benzylic C–H bond in comparison to the tertiary C–H bond.[2]

Direct chemoselective cyanation of more complex structures demonstrated the general applicability of the present transformation (Scheme 3). The cyanation of proline derivative **1r** took place chemoselectively at the methylene C–H bond adjacent to the nitrogen atom, providing

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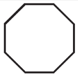
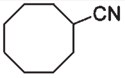
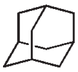
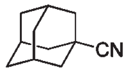
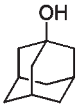
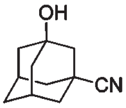
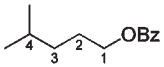
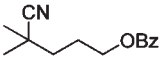
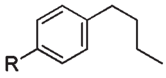
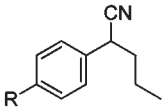
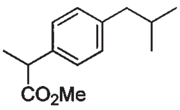
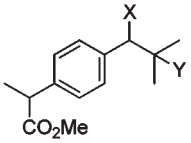
(11) It was often demonstrated that the more electron-rich C–H bonds are more reactive toward C–H bond functionalizations (R$_3$CH > R$_2$CH$_2$ > RCH$_3$) when using electrophilic reactants. For example, see: (a) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749. (b) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (c) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (d) Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, *65*, 3042. (e) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. (f) Kamijo, S.; Amaoka, Y.; Inoue, M. *Synthesis* **2010**, *14*, 2475. (g) Kamijo, S.; Matsumura, S.; Inoue, M. *Org. Lett.* **2010**, *12*, 4195.

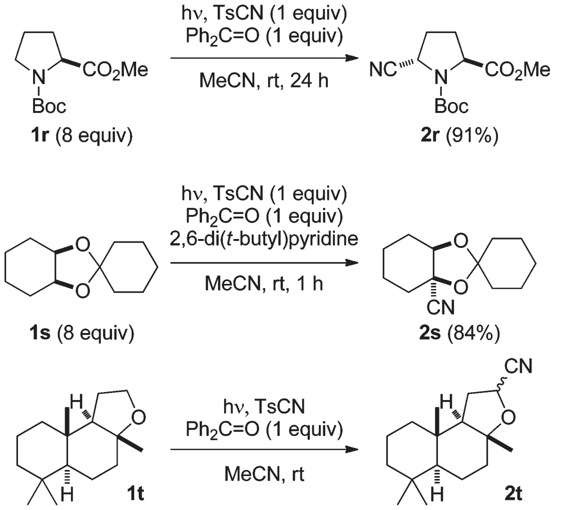
(12) The stereochemistry of the ester-attached carbon of **2r** was confirmed to be retained. Optical rotation of **2r**: $[\alpha]_D^{25}$ –100.0. For comparison, see: (a) Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. *Synthesis* **1993**, 298. (b) Sunilkumar, G.; Nagamani, D.; Argade, N. P.; Ganesh, K. N. *Synthesis* **2003**, 2304.

Table 3. Cyanation of Alkanes and Benzylic Compounds[a]

entry	starting material	*t*, h	product	yield, %[b]
1	 **1j**	10	 **2j**	87
2	 **1k**	16	 **2k**	82
3	 **1l**	24	 **2l**	87
4	 **1m**	24	 **2m**	35[c]
				
5[d]	**1n**: R = H	18	**2n**	41[e]
6[d]	**1o**: R = OMe	15	**2o**	72
7[d]	**1p**: R = OAc	18	**2p**	27[e]
8[d]	 **1q**	18	 **2q**: X = CN, Y = H **2q'**: X = H, Y = CN	45[e] 10

[a] Reaction conditions: **1**/TsCN/$Ph_2C{=}O$ = 8:1:1, MeCN (0.04 M), rt, irradiated using a Riko 100 W medium pressure mercury lamp unless otherwise noted. [b] Isolated yield. [c] Trace amount of product cyanated at methylene C–H bond was observed. [d] Benzene was employed as a solvent instead of MeCN. [e] Recovery of TsCN was observed.

Scheme 3. Cyanation of Proline Derivative, Protected Cyclohexane-1,2-Diol, and (−)-Ambroxide



1t:TsCN = 8:1	2 h	89% [dr = 4:3]
1t:TsCN = 1:4	24 h	71% [dr = 4:3]

trans-substituted product **2r** in a completely stereoselective fashion (91% yield).[12] When the acetal-protected *cis*-1,2-diol **1s** was subjected to the reaction in the presence of 2,6-di(*tert*-butyl)pyridine,[13] *cis*-fused nitrile **2s** was obtained in 84% yield as the sole isomer. Thus, this single reaction enabled the introduction of a tetrasubstituted carbon center stereoselectively via functionalization of a hindered tertiary ethereal C–H bond. Cyanation of (−)-ambroxide **1t** again exhibited high chemoselectivity at the ethereal C–H bond, leading to nitrile **2t** in 89% yield without affecting the other methylene and methine C–H bonds. Importantly, only a slight decrease in yield (89% vs 71%) was observed when treating a limited amount of **1t** (1 equiv) with excess amounts of TsCN (4 equiv).

In conclusion, we have developed a photochemical protocol for the direct transformation of unreactive $C(sp^3)$–H bonds to $C(sp^3)$–CN bonds by the action of TsCN and $Ph_2C{=}O$. The C–H cyanation proceeds at ambient temperature with high applicability to various starting materials including alkanes, benzylic compounds, ethers, alcohols, and amine derivatives. Overall, the reaction selectively installs a one-carbon unit onto a starting molecular framework at the most electron-rich C–H bond. Simplicity in the operation, predictability in the stereo- and chemoselectivity, and efficiency in the single-step construction of hindered tetrasubstituted carbons are particularly of note. Since the branched CN moiety can be universally used as a reactive functional group for further carbon elongation, the present C–H transformation should serve as a powerful tool for the synthesis of complex natural products and molecules of pharmaceutical interest.

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Supporting Information Available. Experimental procedures and spectroscopic and analytical data for relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Because of the acid sensitive nature of the acetals of **1s** and **2s**, 2,6-di(*tert*-butyl)pyridine was added for neutralization of the generated sulfinic acid during the reaction (see Scheme 2). The yield of **2s** significantly decreased, when the reaction was performed without addition of 2,6-di(*tert*-butyl)pyridine.