Photoinduced Direct Cyanation of C(sp^3)–H Bonds

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Abstract: A general and practical synthetic protocol for the direct transformation of unreactive C(sp^3)–H bonds to C(sp^3)–CN bonds has been developed. The homolytic cleavage of the C–H bond is initiated by photo-excited benzophenone, and the resulting carbon radical subsequently reacts with tosyl cyanide to afford the corresponding nitrile in a highly efficient manner. The present methodology is widely applicable to various starting materials including ethers, alcohols, amine derivatives, alkanes, and alkylbenzenes. This newly developed C–H cyanation protocol provides a powerful tool for selective one-carbon elongation for the construction of architecturally complex molecules.

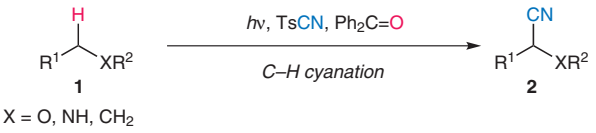
Key words: radical reaction, nitriles, photochemistry, cyanation, C–H functionalizations

Introduction

The carbon–carbon (C–C) bond forming reaction is one of the most important transformations in synthetic organic chemistry. The direct transformation of C–H bonds to C–C bonds has attracted particularly intense interest in recent years, because it avoids prior functional group manipulations for the activation of the substrate and thus greatly simplifies synthetic schemes. Among such reactions, the functionalization of unreactive C(sp^3)–H bonds is especially advantageous for the construction of highly complex natural products, which generally contain a high proportion of sp^3-hybridized carbon centers.[2] Development of this extremely useful reaction has, however, remained challenging largely due to the lack of general strategies for functionalizing inert C(sp^3)–H bonds in comparison to the methods available for functionalization of the C(sp^2)–H bonds of aromatic compounds.[3,4] For this reason, we undertook a research program to develop a new strategy for the direct transformation of C(sp^3)–H bonds to C(sp^3)–C bonds.

We have been particularly interested in the introduction of highly oxidized carbon units, since such groups can be universally utilized as a versatile handle for further carbon elongations or for various standard functional group manipulations.[5] Accordingly, the cyano group was selected as a versatile one-carbon unit.[6] Aside from its utility in organic synthesis, the cyano group is a component functional group of numerous natural products[7] and pharmaceutical agents.[8] Although many efficient methods for the introduction of cyano groups have been developed to date, methods for the direct conversion of an unreactive C(sp^3)–H bond into a C(sp^3)–CN bond are still limited.[9]

We recently found that a combination of benzophenone and tosyl cyanide can effectively convert C(sp^3)–H bonds in a variety of compounds into C(sp^3)–CN bonds under photoirradiation conditions (Scheme 1).[10] The present cyanation is applicable to a broad range of substrates **1**; alkanes, alkylbenzenes, ethers, alcohols, and amine derivatives are all converted in a highly chemoselective manner into the corresponding nitriles **2** in good to excellent yields. In this article, we report the full details of our simple, yet powerful, protocol for the direct cyanation of C(sp^3)–H bonds.[11]



Scheme 1 Direct photochemical transformation of a C(sp^3)–H bond to a C(sp^3)–CN bond

Direct C–H Cyanation of Ethers and Alcohols

We began our investigations into direct C–H cyanation using saturated ethers as the starting materials, since the electron-rich ethereal C–H bonds showed relatively high reactivities toward direct functionalization in our previous studies.[5] From among the saturated ethers, we selected 1,4-dioxane (**1a**) for the purpose of an initial screening to establish the optimal photochemical conditions. Although the C–H bonds of **1a** are not as reactive as those of other cyclic ethers such as tetrahydrofuran and tetrahydropyran,[12] the presence of four equivalent methylene units in **1a** was expected to simplify the analysis of the experimental results.

First, **1a** together with various cyanide sources was mixed with benzophenone in benzene and irradiated with a medium pressure mercury lamp. While cyanogen bromide,[9a,b] trichloroacetonitrile, methyl cyanoformate,[9f,13] or diethyl cyanophosphonate[14] did not function as cyanide donors, the use of tosyl cyanide did result in efficient cyanation of the C–H bond of **1a**.[15] Namely, a reagent combination of tosyl cyanide (1 equiv) and benzophenone (1 equiv) was found to promote the conversion of **1a** (8 equiv) into nitrile **2a** in benzene after six hours (74% yield, Table 1, entry 1). Under these conditions, recovery of benzophenone (59%) and formation of benzopinacol

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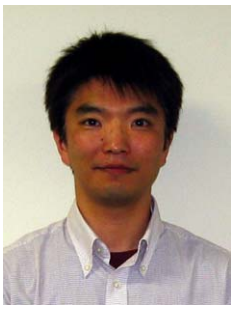
(1,1,2,2-tetraphenylethane-1,2-diol) were observed in addition to formation of **2a**. While the transformation of **1a** to **2a** was not accelerated by employing increased amounts of benzophenone (2 equiv, entry 2), the use of a reduced amount of benzophenone (0.5 equiv, entry 3) slightly lowered the yield of **2a**. In the absence of benzophenone, no product was formed, and a significant amount of tosyl cyanide was recovered (entry 4), indicating that the photo-excited benzophenone functions as the hydrogen abstraction agent. A notable retardation of the reaction and a decrease in the yield were observed upon reducing the amount of **1a** (2 equiv, entry 5). On the other hand, when **1a** was employed as the solvent, the cyanation reaction was complete within one hour and gave **2a** in

Biographical Sketches

Tamaki Hoshikawa was born in 1985 in Shenyang, China, and raised in Kanagawa, Japan. He received his bachelor degree from the University of Tokyo in 2008. He is currently carrying out his Ph.D. studies under the guidance of Prof. M. Inoue at the same university. At present, his research is focused on the development of direct transformations of unreactive chemical bonds and their applications to organic syntheses.

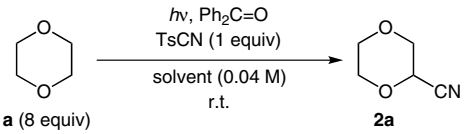
Shun Yoshioka was born in 1990 in Kyoto, Japan. He received his bachelor's degree from the University of Tokyo in 2012. He is currently studying for a master's degree under the guidance of Professor M. Inoue at the same university. His current research is focused on the development of new reactions for syntheses of highly functionalized organic molecules.



Shin Kamijo was born in 1973 in Yamaguchi, Japan. He received his B.Sc. (1997) and Ph.D. (2002) degrees from Tohoku University under the supervision of Prof. Y. Yamamoto. He was then appointed as a Research Associate in the same group (2002–2004). After spending two years as a JSPS Postdoctoral Fellow with Prof. G. B. Dudley at Florida State University (2004–2006) and one year as a Postdoctoral Associate with Prof. M. Shibasaki at The University of Tokyo (2006–2007), he joined the research group of Prof. M. Inoue at The University of Tokyo as an Assistant Professor (2007–2012). In 2012, he moved to the Graduate School of Science and Engineering, Yamaguchi University as an Associate Professor. His research interests focus on methodology developments involving activation and functionalization of unreactive bonds and their utilizations in organic synthesis.

Masayuki Inoue was born in 1971 in Tokyo, Japan. He received a B.Sc. degree in chemistry from the University of Tokyo in 1993. In 1998, he obtained his Ph.D. from the same university, working under the supervision of Profs. K. Tachibana and M. Sasaki. After spending two years with Prof. S. J. Danishefsky at the Sloan-Kettering Institute for Cancer Research (1998–2000), he joined the Graduate School of Science at Tohoku University as an assistant professor in the research group of Prof. M. Hirama. At Tohoku University, he was promoted to associate professor in 2004. He concurrently served as a PRESTO researcher of the Japan Science and Technology Agency (2005–2008). In 2007, he moved to the Graduate School of Pharmaceutical Sciences, University of Tokyo as a full professor. He has been honored with the First Merck-Banyu Lectureship Award (2004), The Chemical Society of Japan Award for Young Chemists (2004), the Thieme Journal Award 2005, the Novartis Lectureship 2008/2009, and the 5th JSPS Prize (2009). His research interests include the synthesis, design, and study of biologically important molecules, with particular emphasis on the total synthesis of structurally complex natural products.

Table 1 Optimization of Cyanation Conditions[a]



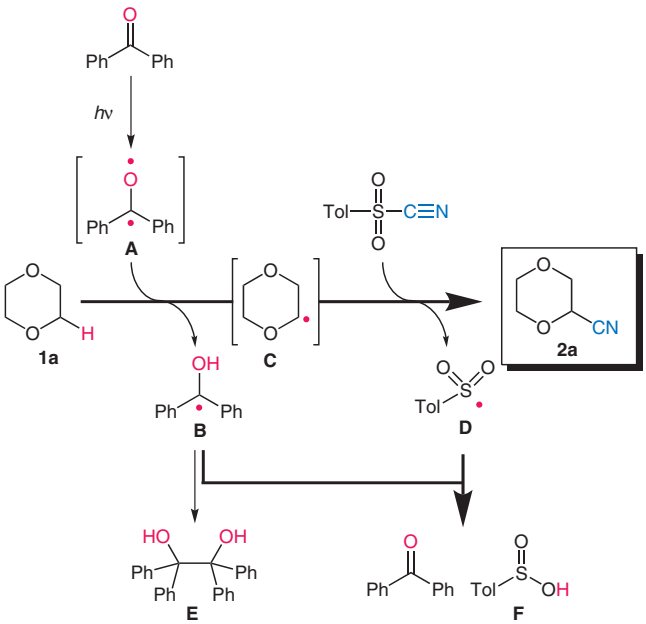
Entry	Solvent	Equiv of benzophenone	Time (h)	Yield[b] (%) of **2a**	Recovery (%) of benzophenone
1	benzene	1	6	74[c]	59
2	benzene	2	6	80	66
3	benzene	0.5	12	64[c]	<4
4	benzene	0	12	0[d]	–
5[e]	benzene	1	24	46	48
6[f]	dioxane	1	1	85	90
7	MeCN	1	6	72 (63)[c,g]	87
8	*t*-BuOH	1	18	63	<5
9	MeCN	0.5	6	74	88

[a] Reaction conditions: **1a**/TsCN (8:1), solvent (0.04 M), r.t., *hν*.
[b] Yield was determined by NMR analysis of the crude mixture; the 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 performed using **1a** (2 equiv). Recovery of TsCN (21%) was observed after the reaction.
[f] Dioxane **1a** was employed as a solvent; **1a**/TsCN (~300:1).
[g] Due to its volatile nature, the isolated yield of **2a** was lower than that indicated by NMR analysis.

85% yield (entry 6). The reaction also proceeded in both aprotic and protic polar solvents, such as acetonitrile (entry 7) and *tert*-butyl alcohol (entry 8). Judging from the high yield of **2a** and the high recovery of benzophenone even upon using a catalytic amount of benzophenone (entry 9), acetonitrile appeared to be the most favorable solvent for the transformation.

The present photoinduced C–H cyanation of 1,4-dioxane (**1a**) to the nitrile product **2a** is considered to consist of a sequence of radical reactions (Scheme 2). Electrophilic oxyl radical **A**, photochemically generated from benzophenone, abstracts hydrogen from the electron-rich ethereal C(sp^3)–H bond of **1a** to furnish carbon radicals **B** and **C**.[16] Subsequently, although there are several potentially reactive species present, the nucleophilic α-alkoxy radical **C** selectively reacts with tosyl cyanide, which is both electron-deficient and the radical acceptor with the least steric hindrance. This reaction leads to nitrile **2a** with concurrent expulsion of sulfonyl radical **D**.[17] If **D** then abstracts the hydrogen from ketyl radical **B**, it regenerates benzophenone to provide sulfinic acid **F**. It is also possible, however, for the ketyl radical **B** to dimerize to afford benzopinacol **E**. Noteworthily, high yielding transformation from **1a** to **2a** (Table 1, entry 7) indicates that all the reactive radical species **A**, **B**, **C**, and **D** properly follow the series of these reactions.

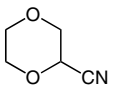
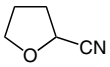
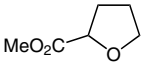
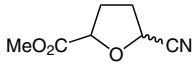
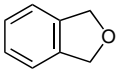
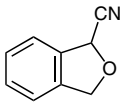
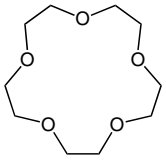
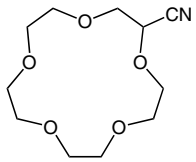
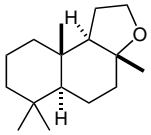
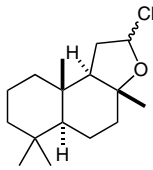
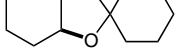
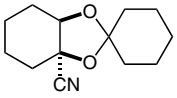
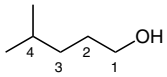
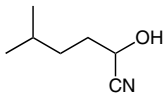
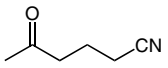
Having successfully determined the optimal reaction conditions for C–H cyanation, we next investigated the chemoselective transformation of a variety of electron-rich C–H bonds adjacent to oxygen-based functionalities (Table 2). The cyanation of tetrahydrofuran (**1b**) proceeded readily and nitrile **2b**[18] was formed in three hours (entry 2). When the ester-attached cyclic ether **1c** was subjected to the same conditions, the O-substituted methylene carbon was selectively cyanated to give nitrile **2c** (entry 3).



Scheme 2 Proposed mechanism for transformation of C(sp^3)–H bonds to C(sp^3)–CN bonds

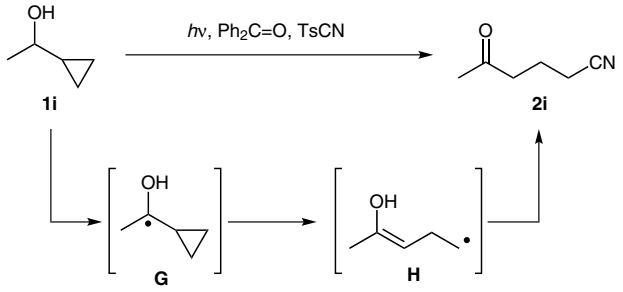
In contrast to the results typically observed with base-induced C–C bond formation, the less acidic position of **1c** was functionalized in this case, demonstrating the unique chemoselectivity of the present reaction.

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

Entry	Starting material	Time (h)	Product	Yield[b] (%)
1	 **1a**	6	 **2a**	63 (72)
2	 **1b**	3	 **2b**	(92)
3	 **1c**	10	 **2c**	80[c]
4[d]	 **1d**	10	 **2d**	91
5	 **1e**	3	 **2e**	84
6	 **1f**	2	 **2f**	89[e]
7[f]		24		71[e]
8[g]	 **1g**	1	 **2g**	84
9	 **1h**	3	 **2h**	72
10	 **1i**	10	 **2i**	97

[a] Reaction conditions: **1**/TsCN/benzophenone (8:1:1), MeCN (0.04 M), r.t., *hv*.
[b] Isolated yield; NMR yield is shown in parentheses.
[c] Mixture of diastereomers (dr 9:2).
[d] Benzene was employed as a solvent instead of MeCN.
[e] Mixture of diastereomers (dr 4:3).
[f] Reaction conditions: **1f**/TsCN/benzophenone (1:4:1).
[g] The reaction was conducted using 2,6-di-*tert*-butylpyridine (2 equiv).

Phthalan (**1d**) gave the corresponding benzyl cyanide **2d** in 91% yield (entry 4), and monocyanation occurred exclusively in the case of 15-crown-5 ether (**1e**), despite the presence of many potentially reactive ethereal C–H bonds (entry 5). Cyanation of structurally complex (–)-ambroxide (**1f**) exhibited high chemoselectivity at the ethereal C–H bond, giving the corresponding nitrile **2f** in 89% yield without affecting the other aliphatic methylene and methine C–H bonds (entry 6). As shown in entry 7, only a slight decrease in yield (71%) was observed even upon treating a limited amount of **1f** (1 equiv) with excess tosyl cyanide (4 equiv). When the acetal-protected *cis*-1,2-diol **1g** was subjected to the reaction in the presence of two equivalents of 2,6-di-*tert*-butylpyridine (acting as an acid scavenger of sulfinic acid), *cis*-fused nitrile **2g** was obtained in 84% yield as the sole isomer (entry 8).[19] This reaction, therefore, allowed the stereoselective formation of the hindered tetrasubstituted carbon center of **2g** in a single step.



Scheme 3 Ring-opening reaction from **1i** to **2i**

Unprotected alcohols were also directly functionalized under the same conditions. While the C–H bond adjacent to the primary hydroxy group of **1h** was chemoselectively cyanated to afford cyanohydrin **2h** (entry 9), treatment of 1-cyclopropylethanol (**1i**) under the same conditions quantitatively furnished 5-oxohexanenitrile (**2i**) (entry 10). As shown in Scheme 3, this transformation proceeded via ring opening of the cyclopropane of secondary radical **G** and subsequent CN trapping by the primary carbon radical **H**.[20] The formation of **2i** therefore provides evidence of the involvement of the α-oxy radical intermediate during this reaction.

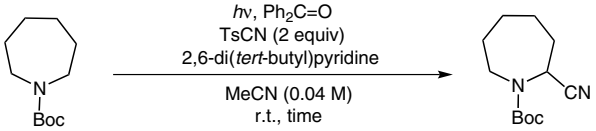
Here direct C–H cyanation of various ethers and alcohols was achieved. The cyanation occurred chemoselectively at the C(sp^3)–H bonds adjacent to oxygen atoms with no reactions at the aliphatic methylene and methine C–H bonds in the same molecule.

Direct C–H Cyanation of Amine Derivatives

α-Amino nitriles play an important role in organic chemistry, especially as the synthetic equivalents of α-amino acids.[21] In addition, several pharmaceutical agents containing α-amino nitrile moieties have recently been designed and manufactured.[8] The Strecker reaction is one of the most useful methods for the preparation of α-amino nitrile derivatives from the corresponding imines.[22] After having established a direct method for the synthesis of α-oxy nitriles, we envisaged that the same radical-based C–H cyanation process would allow the direct synthesis of α-amino nitriles from readily available amine derivatives.

The reaction conditions for the C–H cyanation of amine derivatives were first re-optimized using Boc-protected azepane **3a** (Table 3). The reaction between **3a** and tosyl cyanide (8:1) under the same conditions used for the ethers proceeded via the chemoselective hydrogen abstraction of the electron-rich N-substituted methylene, leading to the corresponding nitrile **4a** in 85% yield (entry 1). The high efficiency of this transformation from **3a** to **4a** prompted us to reduce the ratio of the starting material **3a** to tosyl cyanide. However, modifying this ratio from 8:1 to 1:2 without altering any other factors resulted in a low yield of the desired product **4a** (17%, entry 2). As this disappointing result was attributed to removal of the Boc group by sulfinic acid generated in situ, we examined the addition of 2,6-di-*tert*-butylpyridine as an acid scavenger (entries 3–5). Through varying the amounts of the base, the addition of four equivalents was found to be optimal in terms of the product yield (78%, entry 4). It also should

Table 3 Optimization of Cyanation Conditions for C–H Bonds Adjacent to Nitrogen-Based Functionalities[a]



3a (1 equiv) **4a**

Entry	Equiv		Time (h)	Yield[b] (%)
	Benzophenone	2,6-Di-*tert*-butylpyridine		
1[c]	1	–	6	95 (85)
2	1	–	4.5	17
3	1	2	15	58
4	1	4	10	83 (78)
5[d]	1	8	9	84 (83)
6	0.5	4	5	80
7	0.2	4	8	85 (79)
8	0.5[e]	4	24	77
9	0.5[f]	4	24	74

[a] Reaction conditions: **3a**/TsCN/benzophenone (1:2:1), MeCN (0.04 M), r.t., *hν*.
[b] Yield was determined by NMR analysis of the crude mixture; the isolated yield is shown in parentheses.
[c] **3a**/TsCN/benzophenone (8:1:1).
[d] The reaction was conducted using TsCN (4 equiv).
[e] The reaction was conducted using 4,4′-dimethoxybenzophenone instead of benzophenone.
[f] The reaction was conducted using xanthone instead of benzophenone.

be noted that a second cyanation of **4a** did not take place upon use of two equivalents of tosyl cyanide, reflecting the relatively low reactivity of the N-substituted methylene of the cyanated product **4a**. Even when the amount of benzophenone was reduced from one equivalent (entry 4) to 0.5 or 0.2 equivalents (entries 6 and 7), the cyanation of **3a** in the presence of the base proceeded efficiently with high yields, demonstrating the robustness of the present procedure. Interestingly, other oxyl radical precursors, 4,4′-dimethoxybenzophenone (entry 8) and xanthone (entry 9) required longer reaction times and gave the product in somewhat lower yields.

To explore the applicability, we next examined the cyanation of a variety of nitrogen-containing substrates (Table 4); this was done by applying the two optimized conditions in Table 3: conditions A (entry 1, **3**/TsCN/benzophenone, 8:1:1) and conditions B (entry 4, **3**/TsCN/benzophenone/2,6-di-*tert*-butylpyridine, 1:2:1:4). Under both of these conditions, Boc-protected pyrrolidine **3b** and piperidine **3c** were cyanated to give the corresponding nitriles **4b** and **4c** in high yields (entries 3–6). In the case of *N*-Boc-morpholine **3d**, C–H cyanation chemoselectively occurred at the methylene proximal to the nitrogen atom, and nitrile **4d** was produced in 70% yield (entry 7). This result indicates that the C–H bond adjacent to the nitrogen atom is more reactive than that next to oxygen. Cyclic carbamates **3e** and **3f** were stereoselectively converted into *trans*-substituted nitriles **4e** and **4f**, respectively (entries 8–10). Similarly, cyanation of Boc-protected L-proline derivative **3g** afforded *trans*-substituted nitrile **4g** in a completely stereoselective fashion (entries 11 and 12). The stereochemistry of the ester-attached carbon center in **4g** was retained, showing that the C–H bond adjacent to the electron-withdrawing group was resistant to hydrogen abstraction.[23]

The effect of varying the substituent on the nitrogen atom was examined using several N-protected azepane derivatives. Similarly to Boc-protected **3a** (entry 2), Troc-protected **3h**, and Ac-protected **3i** were successfully transformed to their corresponding nitriles **4h** (entry 13) and **4i** (entry 14), respectively. Whereas the Ts-protected amine **3j** gave the cyanated product **4j** (entry 15), the 4-nitrophenylsulfonyl (Ns) group of **3k** inhibited the reaction, and a significant amount of the starting material **3k** was recovered (entry 16).

Despite the substantial steric hindrance, the cyanation of several cyclohexane derivatives proceeded smoothly to introduce the N-substituted tetrasubstituted carbons (entries 17–19). The methine C–H bond of Boc-protected cyclohexylamine **3l** was chemoselectively functionalized to provide **4l** (entry 17). Monocyanation of *cis*- and *trans*-diaminocyclohexane derivatives **3m** and **3n** took place stereoselectively, resulting in the formation of the same *cis*-fused bicyclic compound **4m** as the sole product (entries 18 and 19). The stereochemical interconversion from the *trans*-fused **3n** to the *cis*-fused **4m** again supported the involvement of a radical intermediate during the course of the reaction.

Direct cyanation of the methylene carbons of acyclic carbamate derivatives **3o–q** was also achieved even when applying conditions B (entries 20–23). The α-amino positions in each of these linear and branched carbon chains were chemoselectively functionalized to generate the amino acid derivatives **4o–q**. When the starting materials possessed asymmetric carbons (entries 24–27), acyclic carbamates **4r** and **4s** were obtained as approximately 1:1 diastereomeric mixtures.

The results presented thus far confirm that the present protocol is capable of direct cyanation of the N-substituted methylene and methine carbons within both cyclic and acyclic structures in a highly efficient fashion, even when the starting materials are present as the limiting reagent. Since the generated N-protected α-amino nitriles serve as the synthetic equivalents of α-amino acids, this methodology provides an expeditious way to access natural and artificial α-amino acids starting from readily available amine derivatives.

Table 4 C–H Cyanation Adjacent to Nitrogen-Based Functionalities[a]

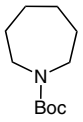
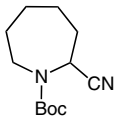
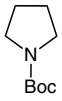
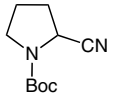
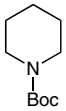
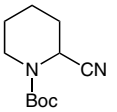
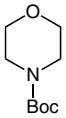
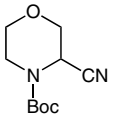
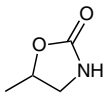
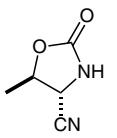
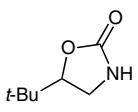
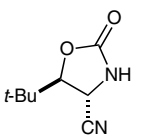
Entry	Starting materials	Conditions, time	Product	Yield[b] (%)
1		A, 6 h		85
2		B, 10 h		78
	3a		**4a**	
3		A, 2 h		94
4[c]		B, 8 h		86
	3b		**4b**	
5		A, 5 h		74
6[c]		B, 10 h		69
	3c		**4c**	
7[c]		B, 44 h		70
	3d		**4d**	
8		A, 10 h		83
9[c]		B, 48 h		23 (30)
	3e		**4e**	
10[c]		B, 24 h		42 (43)
	3f		**4f**	

Table 4 C–H Cyanation Adjacent to Nitrogen-Based Functionalities[a] (continued)

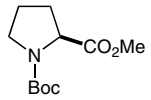
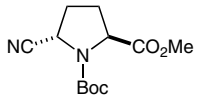
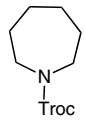
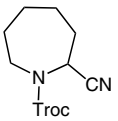
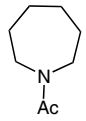
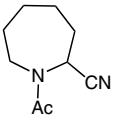
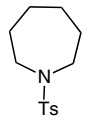
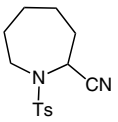
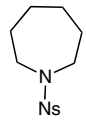
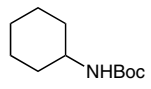
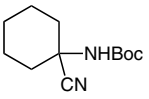
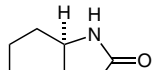
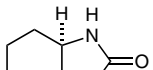
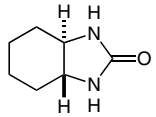
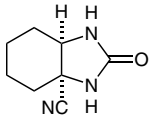
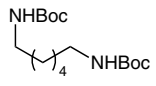
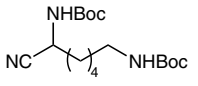
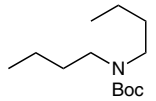
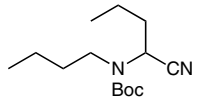
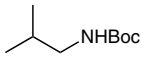
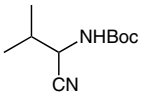
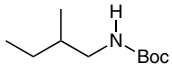
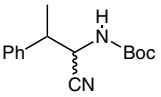
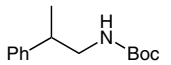
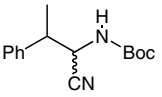
Entry	Starting materials	Conditions, time	Product	Yield[b] (%)
11		A, 24 h		91
12		B, 48 h		67
	3g		**4g**	
13		B, 8 h		75
	3h		**4h**	
14		B, 10 h		75
	3i		**4i**	
15		B, 22 h		30 (24)
	3j		**4j**	
16		B, 22 h	–	0 (61)
	3k			
17		B, 48 h		27 (38)
	3l		**4l**	
18		B, 30 h		43
	3m		**4m**	
19		B, 21 h		51
	3n		**4m**	
20		B, 24 h		57
	3o		**4o**	
21		B, 48 h		55
	3p		**4p**	

Table 4 C–H Cyanation Adjacent to Nitrogen-Based Functionalities[a] (continued)

Entry	Starting materials	Conditions, time	Product	Yield[b] (%)
22		A, 12 h		73
23		B, 48 h		41 (33)
	3q		**4q**	
24		A, 10 h		76
25		B, 48 h		35 (44)
	3r		**4r**[d]	
26		A, 12 h		69
27		B, 48 h		44 (31)
	3s		**4s**[e]	

[a] Conditions A: **3**/TsCN/benzophenone (8:1:1), MeCN (0.04 M), r.t., *hν*; Conditions B: **3**/TsCN/benzophenone (1:2:1), 2,6-di-*tert*-butylpyridine (4 equiv), MeCN (0.04 M), r.t., *hν*.
[b] Isolated yield; the recovery of starting material **3** is shown in parentheses.
[c] The reaction was conducted using benzophenone (0.2 equiv).
[d] Mixture of diastereomers (dr 1:1).
[e] Mixture of diastereomers (dr 6:5).

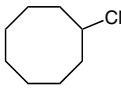
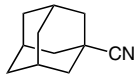
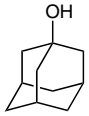
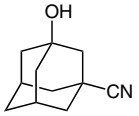
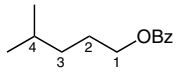
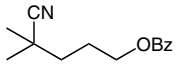
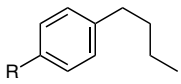
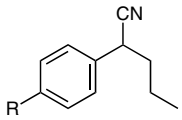
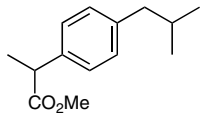
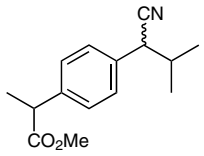
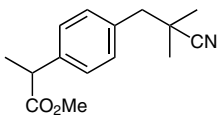
Direct C–H Cyanation of Alkanes and Alkylbenzenes

Compared with the C–H bonds adjacent to heteroatoms such as oxygen and nitrogen, the C–H bonds of unfunctionalized alkanes are generally less reactive toward hydrogen abstraction by the oxyl radical. In fact, the highly chemoselective cyanation results presented in Tables 2–4 clearly show the relative inertness of the non-heteroatom substituted methylene and methine groups. In an attempt to expand the scope of our newly developed cyanation protocol, we investigated the functionalization of a number of unactivated aliphatic and benzylic C–H bonds (Table 5).

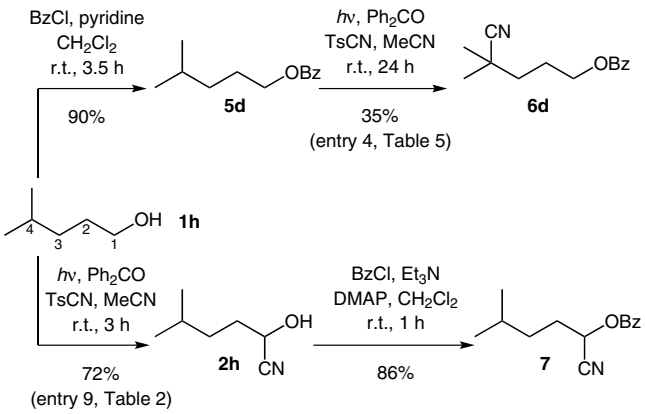
As shown in Table 5, treatment of cyclooctane (**5a**) under our standard conditions (**5**/TsCN/benzophenone, 8:1:1) provided cyclooctanecarbonitrile **6a** in 87% yield (entry 1). This result indicated that the present cyanation protocol was applicable even to the functionalization of unactivated aliphatic methylene groups, in which the carbon is not next to oxygen or nitrogen. The cyanations of both adamantane (**5b**) (entry 2) and its hydroxylated derivative **5c** (entry 3) occurred exclusively at the tertiary C–H bond, installing the quaternary carbons of **6b** and **6c**, respectively. The reaction of benzoate **5d** also produced nitrile **6d** with the quaternary carbon (entry 4). The evidently greater reactivities of the methine C–H bonds in these molecules (entries 2–4), as compared to the methylene C–H bonds, should originate from their more electron-rich nature. Accordingly, the more substituted tertiary C–H bond was selectively converted into the C–CN bond in the pres-

ence of primary and secondary C–H bonds, resulting in selective formation of the sterically encumbered quaternary carbon.[16]

Table 5 C–H Cyanation of Alkanes and Alkylbenzenes[a]

Entry	Starting materials	Time (h)	Product	Yield[b] (%)
1	 **5a**	10	 **6a**	87
2	 **5b**	16	 **6b**	82
3	 **5c**	24	 **6c**	87
4	 **5d**	24	 **6d**	35[c]
				
5[d]	**5e** R = H	18	**6e**	41 (37)
6[d]	**5f** R = OMe	15	**6f**	72 (14)
7[d]	**5g** R = OAc	18	**6g**	27 (55)
8[d]	 **5h**	18	 **6h**[e]	45 (27)
			 **6i**	10

[a] Reaction conditions: **5**/TsCN/benzophenone (8:1:1), MeCN (0.04 M), r.t., *hν*.
[b] Isolated yield; the recovery of TsCN is shown in parentheses.
[c] Trace amount of product cyanated at the methylene C–H bond was observed.
[d] Benzene was employed as a solvent instead of MeCN.
[e] Mixtures of diastereomers (dr = 1:1).



Scheme 4 Divergent synthesis of functionalized nitriles

Intriguingly, the cyanated positions of alcohol **2h** (Table 2, entry 9) and its benzoylated derivative **6d** (Table 5, entry 4) were different, demonstrating that the reaction can be predictably directed to either the α-alkoxy carbon at C1 or the tertiary carbon at C4 simply by detaching or attaching the electron-withdrawing benzoyl group. By applying these results, the two structural isomers **6d** and **7** were both synthesized from the same starting material **1h** by switching the reaction order of the cyanation and benzoylation (Scheme 4).

The reactivity of the benzylic C–H bonds was found to be higher than that of their aliphatic counterparts (Table 5). The reaction of butylbenzene (**5e**) provided benzyl cyanide **6e** in 41% yield as the sole product (entry 5). Installation of an electron-donating methoxy group on the phenyl ring **5f** increased the yield (entry 6), and presence of an electron-withdrawing acetoxy group **5g** decreased the yield (entry 7). The cyanation of ibuprofen methyl ester (**5h**) occurred on the isobutyl substituent to give benzyl nitrile **6h** as the major product along with its regioisomer **6i** (entry 8). This result proved the greater reactivity of the benzylic C–H bond in comparison to both the aliphatic tertiary C–H bond and the ester-attached benzylic C–H bond.

These studies have demonstrated that the direct C–H cyanation of both alkanes and alkylbenzenes is possible, thus enabling the preparation of branched carboskeletons, whether starting from cyclic or acyclic compounds. The obtained products would be useful for construction of more complex structures by taking advantage of the installed nitrile as a starting point for further functionalization.

Conclusion

In summary, we have developed a new synthetic methodology for the direct transformation of C(sp^3)–H bonds to C(sp^3)–CN bonds by using a combination of tosyl cyanide and benzophenone under photoirradiation conditions. The C–H cyanation proceeds at ambient temperature and is applicable to various starting materials including ethers, al-

cohols, amine derivatives, alkanes, and alkylbenzenes. In general, the cyano group is selectively attached to the carbon possessing the most electron-rich C–H bond on the starting molecular framework. The obtained compounds possess branched carboskeletons, which are difficult to make by other reactions. The particularly important features of the present methodology include simplicity of the synthetic technique, predictability in terms of the stereo- and chemoselectivity, and efficiency in the single-step construction of hindered tetrasubstituted carbons. Since the introduced nitrile moiety can be universally utilized as a versatile handle for further carbon elongations or functional group manipulations, the present C–H cyanation should serve as a powerful tool for the synthesis of various natural and artificial amino acids, complex natural products, and molecules of pharmaceutical interest.

All reactions sensitive to air or moisture were carried out under an argon atmosphere and in anhydrous conditions unless otherwise noted. Reagents were used as supplied unless otherwise stated. Analytical TLC was performed using E. Merck Silica gel 60 F254 precoated plates. Flash column chromatography was generally performed using 40–50 μm Silicagel 60N (Kanto) or 75 μm Activated Alumina (Wako). ^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM-ECX-500 (500 MHz), JNM-ECA-500 (500 MHz), or a JNM-ECS-400 (400 MHz) spectrometer with reference to residual solvent signals [^{1}H NMR: $CDCl_3$ (δ = 7.26); ^{13}C NMR: $CDCl_3$ (δ = 77.0)]. IR spectra were recorded on a Jasco FT/IR-4100 spectrophotometer. ESI-TOF mass spectra were recorded on a Bruker Daltonics micrOTOF II (HRMS). UV irradiation was carried out by using a Riko 100 W medium-pressure Hg lamp.

Cyclooctanecarbonitrile (6a); Typical Procedure Conditions A for Direct C–H Cyanation of Ethers, Alcohols, Amine Derivatives, Alkanes, and Alkylbenzenes

To a MeCN (5.5 mL) soln of TsCN (40.4 mg, 223 μmol) in a Pyrex test tube were added benzophenone (40.6 mg, 223 μmol) and cyclooctane (**5a**, 240 μL, 1.78 mmol) at r.t. The mixture was degassed by three successive freeze-thaw cycles and purged with argon. The test tube was placed at 5-cm distance from a UV lamp and it was irradiated (Riko 100-W medium-pressure Hg lamp) at r.t. for 10 h. The mixture was then treated with sat. aq $NaHCO_3$ and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified with flash column chromatography (hexane–EtOAc, 50:1) to give **6a**; yield: 26.7 mg (87%).

***tert*-Butyl 2-Cyanoazepane-1-carboxylate (4a); Typical Procedure Conditions B for Direct C–H Cyanation of Amine Derivatives**

To a MeCN (5.0 mL) soln of *tert*-butyl azepane-1-carboxylate (**3a**, 39.9 mg, 200 μmol) in a Pyrex test tube were added benzophenone (36.4 mg, 200 μmol), 2,6-di(*tert*-butyl)pyridine (175 μL, 800 μmol), and TsCN (72.5 mg, 400 μmol). The mixture was degassed by three successive freeze-thaw cycles and purged with argon. The test tube was placed at 5-cm distance from a UV lamp and it was irradiated (Riko 100-W medium-pressure Hg lamp) at r.t. for 10 h. The mixture was treated with sat. aq $NaHCO_3$. The mixture was extracted with EtOAc (3 × 20 mL), washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified with flash column chromatography (hexane–EtOAc 20:1) to give **4a**; yield: 35.0 mg (78%).

1,4-Dioxane-2-carbonitrile (2a)
[CAS Reg. No.: 14717-00-1]

Colorless oil; yield: 16.4 mg (63%).

IR (neat): 2241, 1127, 1103 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.70–3.83 (m, 3 H), 3.87 (d, *J* = 3.2 Hz, 2 H), 4.05 (m, 1 H), 4.54 (t, *J* = 3.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.8, 64.5, 66.5, 67.6, 116.1.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_5H_7NO_2Na$: 136.0369; found: 136.0344.

Tetrahydrofuran-2-carbonitrile (2b)[18]
[CAS Reg. No.: 14631-43-7]

Colorless oil; yield: 92% (based on the analysis of crude ^{1}H NMR spectrum).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95–2.15 (m, 2 H), 2.20–2.30 (m, 2 H), 3.90–4.00 (m, 2 H), 4.68 (dd, *J* = 5.0, 6.8 Hz, 1 H).

Methyl 5-Cyanotetrahydrofuran-2-carboxylate (2c)

Major Isomer
Yellow oil; yield: 23.6 mg (66%).

IR (neat): 2248, 1743, 1213, 1077 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19 (m, 1 H), 2.25–2.50 (m, 3 H), 3.74 (s, 3 H), 4.69 (dd, *J* = 4.5, 8.3 Hz, 1 H), 4.93 (dd, *J* = 4.1, 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.1, 30.6, 52.4, 67.3, 77.5, 118.4, 171.7.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_7H_9NO_3Na$: 178.0475; found: 178.0475.

Minor Isomer
Yellow oil; yield: 4.8 mg (14%).

IR (neat): 2242, 1740, 1213, 1081 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20–2.50 (m, 4 H), 3.80 (s, 3 H), 4.60 (m, 1 H), 4.81 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.5, 31.2, 52.5, 67.3, 78.3, 118.3, 171.7.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_7H_9NO_3Na$: 178.0475; found: 178.0478.

1,3-Dihydroisobenzofuran-1-carbonitrile (2d)[24]
[CAS Reg. No.: 1246678-37-4]

Colorless oil; yield: 28.7 mg (91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.17 (d, *J* = 12.4 Hz, 1 H), 5.30 (dd, *J* = 2.7, 12.4 Hz, 1 H), 5.92 (d, *J* = 2.7 Hz, 1 H), 7.31 (d, *J* = 6.4 Hz, 1 H), 7.35–7.50 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 71.3, 74.2, 117.5, 121.5, 121.8, 128.5, 129.7, 134.0, 138.5.

1-Cyano-15-crown-5 (2e)
[CAS Reg. No.: 1338695-80-9]

Colorless oil; yield: 47.3 mg (84%).

IR (neat): 2239, 1126 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60–3.75 (m, 13 H), 3.78–3.90 (m, 5 H), 4.87 (t, *J* = 6.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.1, 69.3, 70.1, 70.4 (2 ×), 70.5, 70.9, 71.1, 71.6, 71.8, 117.8.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{19}NO_5Na$: 268.1155; found: 268.1152.

Ambroxide-12-carbonitrile (2f)
[CAS Reg. No.: 1338695-82-1]

Colorless solid; yield: 51.0 mg (89%); mixture of 2 diastereomers: ratio 4:5 (^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.826 (s, 3 H), 0.832 (s, 3 H), 0.86 and 0.89 (s, 3 H), 1.00 and 1.03 (d, *J* = 2.8 Hz, 1 H), 1.09 (s, 3 H), 1.13–1.30 (m, 3 H), 1.40–1.85 (m, 7 H), 1.98 (dt, *J* = 3.2, 11.9 Hz, 1 H), 2.05–2.30 (m, 2 H), 4.58 (t, *J* = 8.2 Hz, 4/9 H) and 4.68 (dd, *J* = 2.3, 11.4 Hz, 5/9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer): 15.2, 18.2, 20.6, 21.0, 21.5, 29.7, 33.0, 33.5, 36.3, 39.4, 39.7, 42.3, 56.8, 59.1, 63.3, 83.8, 120.2; δ (minor diastereomer): 15.1, 18.2, 20.4, 21.0, 21.9, 29.6, 33.0, 33.5, 36.4, 39.3, 39.8, 42.2, 57.0, 60.0, 63.1, 83.8, 120.9.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{27}NONa$: 284.1985; found: 284.1979.

cis-Hexahydrospiro[benzo[*d*][1,3]dioxole-2,1′-cyclohexane]-3a-carbonitrile (2g)
[CAS Reg. No.: 1338695-86-5]

Colorless oil; yield: 43.8 mg (84%).

IR (neat): 2241, 1121, 1073 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.90 (m, 16 H), 2.00–2.10 (m, 2 H), 4.41 (t, *J* = 4.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6, 20.0, 23.5, 23.8, 24.9, 25.7, 33.6, 34.8, 37.5, 72.8, 76.2, 111.7, 120.2.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{19}NO_2Na$: 244.1308; found: 244.1301.

2-Hydroxy-5-methylhexan-1-ol (2h)
[CAS Reg. No.: 73683-33-7]

Colorless oil; yield: 20.5 mg (72%).

IR (neat): 3439, 2249, 1071 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.4 Hz, 6 H), 1.39 (m, 2 H), 1.61 (septet, *J* = 6.4 Hz, 1 H), 1.85 (m, 2 H), 2.45 (br d, *J* = 6.4 Hz, 1 H, OH), 4.46 (br dt, *J* = 6.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.31, 22.35, 27.6, 33.2, 33.3, 61.7, 119.9.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_7H_{13}NONa$: 150.0889; found: 150.0896.

5-Oxohexanenitrile (2i)[25]
[CAS Reg. No.: 10412-98-3]

Yellow oil; yield: 24.8 mg (97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (tt, *J* = 7.3, 7.3 Hz, 2 H), 2.17 (s, 3 H), 2.42 (t, *J* = 7.3 Hz, 2 H), 2.63 (t, *J* = 7.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 19.2, 30.0, 41.1, 119.2, 206.8.

***tert*-Butyl 2-Cyanoazepane-1-carboxylate (4a)[26]**
[CAS Reg. No.: 153749-93-0]

Colorless oil; yield: 44.9 mg (85%, conditions A), 35.0 mg (78%, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.43 (m, 2 H), 1.48 and 1.50 (m, 9 H), 1.55–1.60 (m, 1 H), 1.70–1.80 (m, 2 H), 1.80–1.90 (m, 2 H), 2.20–2.32 (m, 1 H), 2.96–3.06 (m, 1 H), 3.79 (br d, *J* = 15.1 Hz, 3/5 H), 3.89 (br d, *J* = 15.1 Hz, 2/5 H), 4.76 (dd, *J* = 6.0, 11.0 Hz, 2/5 H), 5.11 (dd, *J* = 6.9, 10.5 Hz, 3/5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 25.1, 28.3, 28.6, 28.7, 32.6, 32.9, 43.2, 43.8, 45.9, 47.3, 81.0, 81.5, 119.3, 119.4, 155.0.

***tert*-Butyl 2-Cyanopyrrolidine-1-carboxylate (4b)[26]**
[CAS Reg. No.: 144688-70-0]

Colorless solid; yield: 42.9 mg (94%, conditions A), 23.4 mg (86%, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 18/5 H), 1.51 (s, 27/5 H) (9 H), 1.98–2.30 (m, 4 H), 3.25–3.40 (m, 1 H), 3.40–3.60 (m, 1 H), 4.44 (m, 3/5 H), 4.56 (m, 2/5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8, 24.6, 28.1, 28.3, 30.8, 31.6, 45.7, 46.0, 47.1, 80.9, 81.4, 119.1, 153.0.

***tert*-Butyl 2-Cyanopiperidine-1-carboxylate (4c)[26]**
[CAS Reg. No.: 153749-89-4]

Colorless solid; yield: 33.3 mg (74%, conditions A), 21.9 mg (69%, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H), 1.56–1.57 (m, 2 H), 1.68–1.76 (m, 4 H), 2.94 (br m, 1 H), 4.05 (br m, 1 H), 5.23 (br m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 24.5, 28.4, 28.8, 41.4, 43.9, 81.4, 117.7, 154.0.

***tert*-Butyl 3-Cyanomorpholine-4-carboxylate (4d)[27]**
[CAS Reg. No.: 518047-40-0]

Colorless solid; yield: 29.6 mg (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 9 H), 3.25 (br m, 1 H), 3.49 (dt, *J* = 2.7, 11.9 Hz, 1 H), 3.62 (dd, *J* = 3.2, 11.9 Hz, 1 H), 3.81 (m, 1 H), 3.99 (br d, *J* = 11.4 Hz, 1 H), 4.06 (d, *J* = 12.4 Hz, 1 H), 4.91 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 66.5, 67.5, 82.3, 116.5, 153.5.

***trans*-5-Methyl-2-oxooxazolidine-4-carbonitrile (4e)[28]**
[CAS Reg. No.: 144688-70-0]

Colorless solid; yield: 22.8 mg (83%, conditions A), 5.7 mg (23%, conditions B); mp 83–85 °C.

IR (neat): 3290, 2251, 1759, 1222, 1105, 1066 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (d, *J* = 6.4 Hz, 3 H), 4.24 (dd, *J* = 1.4, 5.0 Hz, 1 H), 4.92 (dq, *J* = 5.0, 6.4 Hz, 1 H), 6.28 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 48.6, 76.2, 116.2, 156.9.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_5H_6N_2O_3Na$: 149.0321; found: 149.0318.

***trans*-5-*tert*-Butyl-2-oxooxazolidine-4-carbonitrile (4f)**
Colorless solid; yield: 9.4 mg (42%); mp 135–138 °C.

IR (neat): 3412, 2254, 1771, 1389, 1227, 1044, 1027 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 9 H), 4.39 (d, *J* = 6.4 Hz, 1 H), 4.50 (d, *J* = 6.4 Hz, 1 H), 6.39 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 34.4, 43.3, 87.0, 116.9, 157.3.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{12}N_2O_2Na$: 191.0798; found: 191.0792.

1-*tert*-Butyl 2-Methyl (2*S*,5*S*)-5-Cyanopyrrolidine-1,2-dicarboxylate (4g)[29]
[CAS Reg. No.: 649728-62-1]

Colorless oil; yield: 51.0 mg (91%, conditions A), 23.8 mg (67%, conditions B); $[\alpha]_D^{25}$ –100.0 (*c* 2.14, $CHCl_3$).[23]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 9/2 H), 1.50 (s, 9/2 H), 2.10–2.60 (m, 4 H), 3.72 (s, 3/2 H), 3.73 (s, 3/2 H), 4.33 (d, *J* = 8.2 Hz, 1/2 H), 4.43 (d, *J* = 8.7 Hz, 1/2 H), 4.65 (d, *J* = 8.2 Hz, 1/2 H), 4.75 (d, *J* = 7.8 Hz, 1/2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 28.2, 28.5, 28.8, 29.6, 29.7, 47.6, 47.7, 52.3, 52.5, 58.5, 58.8, 81.9, 82.4, 118.7, 118.8, 152.56, 152.60, 172.2, 172.4.

1-(3,3,3-Trichloropropanoyl)azepane-2-carbonitrile (4h)
Colorless oil; yield: 31.4 mg (75%).

IR (neat): 2936, 2243, 1718, 1415, 716 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31–1.50 (m, 2 H), 1.60–1.98 (m, 5 H), 2.29–2.40 (m, 1 H), 3.14 (ddt, *J* = 1.8, 5.0, 14.7 Hz, 1 H), 3.98 (dd, *J* = 4.1, 15.1 Hz, 1 H), 4.68 (d, *J* = 12.4 Hz, 7/10 H), 4.69 (d, *J* = 11.9 Hz, 3/10 H), 4.91 (d, *J* = 11.9 Hz, 7/10 H), 4.94 (d, *J* = 11.9 Hz, 3/10 H), 4.98 (dd, *J* = 6.4, 11.0 Hz, 3/10 H), 5.10 (dd, *J* = 6.8, 10.5 Hz, 7/10 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.3, 24.8, 28.2, 28.3, 28.4, 32.6, 32.7, 44.0, 44.3, 47.0, 75.3, 75.4, 95.1, 118.4, 118.5, 153.0, 154.3.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{13}N_2O_2Cl_3Na$: 320.9898; found: 320.9932.

1-Acetylazepane-2-carbonitrile (4i)
Yellow oil; yield: 17.8 mg (75%).

IR (neat): 3490, 2935, 2859, 2239, 1652, 1413, 1207 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32–1.43 (m, 1 H), 1.44–1.65 (m, 2 H), 1.71–1.80 (m, 1 H), 1.81–1.97 (m, 3 H), 2.18 (s, 27/10 H), 2.21 (s, 3/10 H), 2.23–2.31 (m, 1 H), 2.88 (ddd, *J* = 1.8, 11.9, 12.8 Hz, 1/10 H), 3.34 (ddd, *J* = 2.3, 11.0, 15.6 Hz, 9/10 H), 3.72 (dt, *J* = 3.9, 15.6 Hz, 9/10 H), 4.25 (m, 1/10 H), 4.57 (dd, *J* = 6.4, 10.5 Hz, 1/10 H), 5.48 (dd, *J* = 6.4, 10.0 Hz, 9/10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.8, 24.3, 24.5, 27.9, 28.0, 28.7, 28.9, 32.0, 33.3, 42.2, 44.1, 45.1, 48.8, 53.4, 118.8, 170.8.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{14}N_2ONa$: 189.1004; found: 189.0993.

1-Tosylazepane-2-carbonitrile (4j)
Colorless oil; yield: 16.7 mg (30%).

IR (neat): 2238, 1597, 1338, 1159 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44–1.56 (m, 1 H), 1.62–1.72 (m, 1 H), 1.74–1.83 (m, 3 H), 1.85–1.96 (m, 2 H), 2.22–2.32 (m, 1 H), 2.43 (s, 3 H), 2.96 (ddd, *J* = 2.9, 10.9, 14.9 Hz, 1 H), 3.71 (dt, *J* = 4.6, 14.9 Hz, 1 H), 5.01 (t, *J* = 6.9 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 23.9, 27.7, 28.8, 34.1, 45.3, 47.7, 117.3, 127.3, 129.9, 135.3, 144.2.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}N_2O_2SNa$: 301.0998; found: 301.0983.

***tert*-Butyl (1-Cyanocyclohexyl)carbamate (4l)**
Colorless solid; 12.3 mg (27%); mp 96–97 °C.

IR (neat): 3336, 2937, 2239, 1704, 1367, 1166 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 1.54–1.77 (m, 8 H), 2.25–2.37 (m, 2 H), 4.67 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 24.7, 28.3, 35.8, 51.9, 81.1, 120.1, 153.6.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{20}N_2O_2Na$: 247.1398; found: 247.1422.

***cis*-2-Oxooctahydro-1*H*-benzimidazole-3a-carbonitrile (4m)**
Yellow solid; yield: 9.9 mg (43%); mp 109–111 °C.

IR (neat): 3202, 2939, 2231, 1713 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37–1.45 (m, 1 H), 1.49–1.73 (m, 4 H), 1.84–1.95 (m, 1 H), 1.98–2.13 (m, 2 H), 3.93 (t, *J* = 5.5 Hz, 1 H), 5.43 (br s, 1 H), 5.73 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 19.5, 27.5, 32.8, 54.6, 55.7, 120.3, 162.1.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{11}N_3ONa$: 188.0798; found: 188.0797.

Di-*tert*-butyl (1-Cyanohexane-1,6-diyl)dicarbamate (4o)
Colorless oil; yield: 27.4 mg (57%).

IR (neat): 3334, 2979, 2934, 2247, 1691, 1519, 1168 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.52 (m, 6 H), 1.43 (s, 9 H), 1.45 (s, 9 H), 1.75–1.83 (m, 2 H), 3.04–3.18 (m, 2 H), 4.55 (m, 1 H), 4.55 (br s, 1 H), 4.97 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9, 25.8, 28.2, 28.4, 29.8, 33.3, 40.1, 42.1, 79.2, 81.1, 118.9, 156.0.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{31}N_3O_4Na$: 364.2198; found: 364.2231.

***tert*-Butyl Butyl(1-cyanobutyl)carbamate (4p)**
Colorless oil; yield: 19.7 mg (55%).

IR (neat): 2963, 2240, 1700, 1368, 1154 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.3 Hz, 3 H), 0.97 (t, *J* = 7.3 Hz, 3 H), 1.32 (q, *J* = 7.3 Hz, 2 H), 1.47 (s, 9 H), 1.36–1.79 (m, 5 H), 1.80–1.91 (m, 1 H), 3.14–3.29 (m, 2 H), 4.98 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 13.7, 18.9, 20.1, 28.3, 31.2, 34.3, 45.4, 47.3, 81.2, 118.6, 154.5.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{26}N_2O_2Na$: 227.1898; found: 277.1893.

***tert*-Butyl 1-Cyano-2-methylpropylcarbamate (4q)[30]**
[CAS Reg. No.: 130457-35-1]

Colorless solid; yield: 32.7 mg (73%, conditions A), 11.3 mg (41%, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.3 Hz, 6 H), 1.45 (s, 9 H), 2.01 (octet, *J* = 6.9 Hz, 1 H), 4.45 (br m, 1 H), 4.93 (br d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 18.5, 28.2, 31.8, 48.4, 81.1, 118.0, 154.4.

***tert*-Butyl 1-Cyano-2-methylbutylcarbamate (4r)**
White solid; yield: 37.1 mg (76%, conditions A), 10.2 mg (35%, conditions B); mixture of 2 diastereomers, ratio 1:1 (^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.3 Hz, 3 H), 1.05 (t, *J* = 7.3 Hz, 3 H), 1.20–1.60 (m, 11 H), 1.77 (m, 1 H), 4.55 (br m, 1 H), 4.93 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.10, 11.13, 14.9, 15.0, 25.0, 25.6, 28.2, 28.3, 38.0, 38.1, 46.9, 47.2, 81.0, 81.1, 117.9, 118.4, 154.4, 154.5.

***tert*-Butyl 1-Cyano-2-phenylpropylcarbamate (4s)**
Colorless solid; yield: 41.5 mg (69%, conditions A), 23.0 mg (44%, conditions B); mixture of 2 diastereomers, ratio 6:5 (^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 45/11 H), 1.44 (s, 54/11 H), 1.48 (d, *J* = 7.3 Hz, 3 H), 3.11 (dq, *J* = 7.3, 7.3 Hz, 6/11 H), 3.20 (br dq, *J* = 6.4, 6.9 Hz, 5/11 H), 4.60–4.90 (br m, 2 H), 7.27–7.40 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9, 17.6, 28.08, 28.14, 42.3, 42.6, 48.2, 81.2, 117.6, 118.0, 127.6, 127.9, 127.8, 128.1, 128.8, 129.0, 139.1, 139.3, 154.2.

Cyclooctanecarbonitrile (6a)
[CAS Reg. No.: 40636-30-4]

Colorless oil; yield: 26.7 mg (87%).

IR (neat): 2235 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40–1.65 (m, 8 H), 1.70–1.90 (m, 4 H), 1.96 (dddd, *J* = 2.8, 4.1, 9.6, 13.3 Hz, 2 H), 2.75 (tt, *J* = 4.1, 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 25.1, 26.8, 28.7, 29.4, 123.5.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{15}NNa$: 160.1097; found: 160.1092.

Adamantane-1-carbonitrile (6b)[31]
[CAS Reg. No.: 23074-42-2]

Colorless solid; yield: 29.6 mg (82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (br s, 6 H), 2.04 (br s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0, 30.1, 35.7, 39.9, 125.3.

3-Hydroxyadamantane-1-carbonitrile (6c)[32]
[CAS Reg. No.: 59223-70-0]

Colorless solid; yield: 35.2 (87%).

IR (neat): 3261, 2226, 1141, 1034 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61 (d, *J* = 3.2 Hz, 2 H), 1.72 (d, *J* = 3.2 Hz, 4 H), 1.94 (br d, *J* = 2.3 Hz, 4 H), 2.04 (s, 2 H), 2.28 (br dd, *J* = 2.8, 3.2 Hz, 2 H), 1.49 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6, 32.8, 34.3, 38.7, 43.7, 46.9, 67.0, 123.9.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{15}NONa$: 200.1046; found: 200.1046.

5-(Benzoyloxy)-2,2-dimethylpentanenitrile (6d)
[CAS Reg. No.: 1338695-82-1]

Colorless oil; yield: 18.6 mg (35%).

IR (neat): 2234, 1719, 1277, 714 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 6 H), 1.69 (m, 2 H), 1.98 (m, 2 H), 4.37 (t, *J* = 6.4 Hz, 2 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.57 (t, *J* = 7.5 Hz, 1 H), 8.04 (dd, *J* = 1.4, 7.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 26.6, 32.1, 37.6, 64.3, 124.7, 128.4, 129.5, 130.1, 133.0, 166.5.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{17}NO_2Na$: 254.1151; found: 254.1161.

2-Phenylpentanenitrile (6e)[33]
[CAS Reg. No.: 5558-78-1]

Colorless oil; yield: 15.4 mg (41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 3 H), 1.50 (m, 2 H), 1.90 (m, 2 H), 3.78 (dd, *J* = 6.4, 8.7 Hz, 1 H), 7.30–7.40 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 20.3, 37.2, 37.9, 120.9, 127.2, 128.0, 129.0, 136.0.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{13}NNa$: 182.0940; found: 182.0945.

2-(4-Methoxyphenyl)pentanenitrile (6f)[34]
[CAS Reg. No.: 648409-06-7]

Colorless oil; yield: 29.0 mg (72%).

IR (neat): 2238, 1512, 1253, 1034, 831 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.3 Hz, 3 H), 1.50 (m, 2 H), 1.85 (m, 2 H), 3.73 (dd, *J* = 6.4, 8.8 Hz, 1 H), 3.81 (s, 3 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 20.2, 36.3, 37.9, 55.3, 114.3, 121.2, 128.0, 128.3, 159.2.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{15}NONa$: 212.1046; found: 212.1039.

2-(4-Acetoxyphenyl)pentanenitrile (6g)
[CAS Reg. No.: 1338695-83-2]

Colorless oil; yield: 13.2 mg (27%).

IR (neat): 2239, 1760, 1512, 1201, 1015, 846 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 3 H), 1.51 (m, 2 H), 1.85 (m, 2 H), 2.30 (s, 3 H), 3.79 (dd, *J* = 6.4, 8.7 Hz, 1 H), 7.10 (d, *J* = 8.7 Hz, 2 H), 7.33 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 20.3, 21.1, 36.6, 37.8, 120.6, 122.2, 128.3, 133.5, 150.2, 169.3.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{15}NO_2Na$: 240.0995; found: 240.0991.

Methyl 2-[4-(1-Cyano-2-methylpropyl)phenyl]propanoate (6h)
[CAS Reg. No.: 1338695-84-3]

Colorless oil; yield: 24.7 mg (45%); mixture of 2 diastereomers.

IR (neat): 2238, 1737, 1210, 1165, 843 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.9 Hz, 3 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 1.50 (d, *J* = 7.3 Hz, 3 H), 2.11 (dq, *J* = 6.4, 6.9 Hz, 1 H), 3.63 (d, *J* = 6.4 Hz, 1 H), 3.67 (s, 3 H), 3.73 (m, 1 H), 7.25 (d, *J* = 8.7 Hz, 2 H), 7.30 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 18.8, 20.8, 33.7, 44.8, 45.0, 52.1, 119.8, 127.9, 128.1, 133.8, 140.31, 140.33, 174.7.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{19}NO_2Na$: 268.1308; found: 268.1308.

Methyl 2-[4-(2-Cyano-2-methylpropyl)phenyl]propanoate (6i)
[CAS Reg. No.: 1338695-85-4]

Colorless oil; yield: 5.3 mg (10%).

IR (neat): 2233, 1735, 1206, 1163, 847 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (s, 6 H), 1.50 (d, *J* = 7.5 Hz, 3 H), 2.79 (s, 2 H), 3.67 (s, 3 H), 3.72 (q, *J* = 7.5 Hz, 1 H), 7.23 (d, *J* = 8.6 Hz, 2 H), 7.27 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 26.5, 33.5, 45.1, 46.3, 52.0, 124.7, 127.5, 130.5, 134.5, 139.6, 174.9.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{19}NO_2Na$: 268.1308; found: 268.1301.

2-(Benzoyloxy)-5-methylhexanenitrile (7)
To a CH_2Cl_2 (2.5 mL) soln of 2-hydroxy-5-methylhexanenitrile (**2h**, 6.4 mg, 50.3 μmol) were added BzCl (8.5 μL, 75 μmol), Et_3N (14 μL, 100 μmol), and DMAP (0.2 mg) at r.t. The mixture was stirred for 1 h, and then the reaction was quenched with H_2O. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with sat. aq $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was purified with flash column chromatography (hexane–EtOAc, 50:1) to give **7** as a colorless oil; yield: 10.0 mg (86%).

IR (neat): 1732, 1602, 1585, 1266, 1093, 711 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.4 Hz, 6 H), 1.40–1.50 (m, 2 H), 1.66 (septet, *J* = 6.4 Hz, 1 H), 2.00–2.10 (m, 2 H), 5.57 (t, *J* = 6.4 Hz, 1 H), 7.49 (t, *J* = 7.8 Hz, 2 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 8.06 (dd, *J* = 1.6, 7.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.28, 22.32, 27.6, 30.5, 33.4, 61.8, 117.0, 128.3, 128.6, 129.9, 134.0, 164.8.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{17}NO_2Na$: 254.1151; found: 254.1154.

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