EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201300629

One-Pot Transformation of Carboxylic Acids into Nitriles

Kotaro Miyagi,[a] Katsuhiko Moriyama,[a] and Hideo Togo*[a]

Keywords: Carboxylic acids / Cyanides / Iodine / Ammonia / One-pot reactions

A variety of aromatic and aliphatic carboxylic acids were smoothly converted into the corresponding nitriles in good yields in a one-pot procedure by treatment with ethyl iodide/K_2CO_3/18-crown-6, followed by sodium diisobutyl-*tert*-butoxyaluminium hydride (SDBBA-H), and finally treatment with molecular iodine or 1,3-diiodo-5,5-dimethylhydantoin (DIH), and aqueous ammonia. This method is useful for the conversion of various aromatic and aliphatic carboxylic acids into the corresponding nitriles in a one-pot procedure.

Introduction

Nitriles are very useful and important intermediates in organic chemistry.[1] The nitrile group is one of the most important and versatile functional groups, as it can be easily converted into numerous other functional groups, such as aldehydes, ketones, amines, and amides, and also into nitrogen-containing heterocycles, such as oxazoles,[2a–2c] thiazoles,[2d,2e] tetrazoles,[2f–1] triazolo[1.5-*c*]pyrimidines,[2j] 1,2-diarylimidazoles,[2k] etc. One-carbon homologated nitriles are typically obtained by the reaction of alkyl halides with toxic metal cyanides.[3] Alternatively, the dehydration of primary amides and aldoximes, or the oxidation of primary amines, provide the corresponding nitriles while retaining the same number of carbon atoms. Thus, nitriles are generally prepared by the dehydration of primary amides with $SOCl_2$, TsCl/pyridine, P_2O_5, $POCl_3$, $COCl_2$, $TiCl_4$, $(CF_3CO)_2O$/pyridine, $(EtO)_3P/I_2$, or Ph_3P/CCl_4,[3] and recently, aromatic nitriles have been prepared by the dehydration of aromatic amides with $(CH_2O)_n/HCO_2H$,[4a] $(COCl)_2$/DMSO,[4b] dibutyltin oxide/microwave irradiation,[4c] $Cp_2Zn(CH_3)_2$,[4d] $Cl_2P(O)OEt$/DBU (1,8-diazabicycloundec-7-ene),[4e] or $Ru_3(CO)_7/R_3SiH$.[4f] The oxidative conversion of primary amines into the corresponding nitriles has also been studied well using AgO,[5a] $Pb(OAc)_4$,[5b–5e] cobalt peroxide,[5f] nickel peroxide,[5g] $Na_2S_2O_8$ or $(Bu_4N)_2S_2O_8$ together with metals,[5h–5k] NaOCl,[5l–5n] $K_3Fe(CN)_6$,[5o] Cu^I or Cu^{II} together with oxygen,[5p–5s] $RuCl_3$ or related Ru reagents,[5t–5x] PhIO,[5y] or trichloroisocyanuric acid toegther with TEMPO [(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl].[5z] Aromatic nitriles, meanwhile, are usually prepared from aromatic amines by treatment with $NaNO_2$ and aqueous HCl, followed by CuCN (the Sandmeyer reaction).[6] On the other hand, the one-pot preparation of nitriles from carboxylic acids is a very attractive concept, as various carboxylic acids are commercially available. Today, nitriles can be directly prepared by the reaction of carboxylic acids with $TsNH_2$ and PCl_5 at 200 °C;[7a] the reaction of carboxylic acids with NH_3 and silica gel at 500 °C;[7b] the carboxylic acid–nitrile exchange reaction at 285 °C;[7c] the reaction of carboxylic acids with NH_3 and ethyl polyphosphate (PPE) at 80 °C;[7d] the reaction of carboxylic acids with $(COCl)_2$, followed by reaction with 2,4-dinitrobenzenesulfonamide and Et_3N at r.t.–70 °C;[7e] the reaction of carboxylic acids with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor), NaN_3, and Ph_3P via acyl azides at room temperature;[7f] the reaction of carboxylic acids with P_2I_4 and ammonium carbonate at room temperature;[7g] and the reaction of arenecarboxylic acids with cyanohydrins, $Pd(OTf)_2$, and Ag_2CO_3 in a decarboxylation reaction at 100 °C,[7h] etc. However, those reactions have drawbacks, such as high reaction temperatures, the requirement for acidic dehydration reagents, or the use of toxic metal azides, moisture-sensitive reagents, or expensive reagents such as palladium, etc. Thus, practical and mild methods for the one-pot preparation of nitriles from easily available carboxylic acids are still required.

In this paper, as part of our basic research into molecular iodine and related iodine reagents for organic synthesis,[8] we would like to report the mild one-pot conversion of a wide range of carboxylic acids into the corresponding nitriles. The reaction proceeds through ethylation of carboxylic acids, subsequent reduction with sodium diisobutyl-*tert*-butoxyaluminium hydride (SDBBA-H),[9] and then treatment with molecular iodine and aqueous ammonia.

Results and Discussion

Recently, we reported the one-pot conversion of isopropyl esters and of *N*,*N*-disubstituted amides into the corresponding nitriles by treatment with diisobutylaluminium

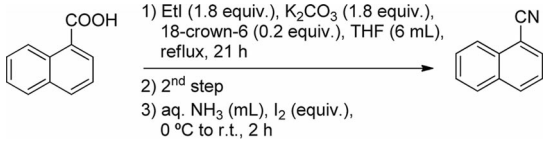
[a] Graduate School of Science, Chiba University,
Yayoi-cho 1-33, Japan
E-mail: togo@faculty.chiba-u.jp
Homepage: http://reaction-2.chem.chiba-u.jp/index.html

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300629.

hydride (DIBAL-H), followed by reaction with molecular iodine and aqueous Ammonia.[8o] We also reported the one-pot conversion of ethyl esters into the corresponding nitriles by treatment with sodium diisobutyl-*tert*-butoxyaluminium hydride (SDBBA-H), followed by reaction with molecular iodine and aqueous ammonia.[8q] Based on those studies, we planned to perform a one-pot conversion of carboxylic acids into nitriles, through esterification. Thus, 1-naphthoic acid was treated with ethyl iodide in the presence of K_2CO_3 and 18-crown-6, and subsequently the reducing agent SDBBA-H was added. This was followed by treatment with molecular iodine and aqueous ammonia at 0 °C to room temperature to give 1-naphthonitrile, as shown in Table 1, entries 1–5.

The reduction of the ethyl ester to the hemiacetal anion is the key point. SDBBA-H should be added at –40 °C, and then the mixture should be slowly warmed to 0 °C, to suppress the over-reduction to the alcohol. When DIBAL-H was used instead of SDBBA-H, mainly the alcohol was obtained, together with ethyl ester (Table 1, entry 6). Other monohydride reducing agents, such as $LiAlH(OtBu)_3$ and $NaBH(sBu)_3$, were used at –78 to 0 °C, or at 0 °C to room temperature. However, 1-naphthonitrile was not formed at all because no reduction occurred (Table 1, entries 7–10). The effect of changing the alkylating agent used for 1-naphthoic acid was studied under the same conditions and using the same procedure for the conversion of 1-naphthoic acid into 1-naphthonitrile. Methyl iodide, ethyl iodide, propyl iodide, isobutyl iodide, butyl iodide, and methoxymethyl bromide were tested, and ethyl iodide was found to give the best result (Table 1, entries 5 and 11–15). Based on these results, and using the best reaction conditions and procedure, a variety of arenecarboxylic acids were treated with ethyl iodide, K_2CO_3, and 18-crown-6, then with SDBBA-H, and finally with molecular iodine and aqueous ammonia, to give the corresponding aromatic nitriles in good yields, as shown in Table 2, entries 2–12. These arenecarboxylic acids included 2-naphthoic acid, *p*-nitrobenzoic acid, *p*-fluorobenzoic acid, *p*-chlorobenzoic acid, *p*-bromobenzoic acid, *m*-bromobenzoic acid, *o*-bromobenzoic acid, *p*-iodobenzoic acid, *o*-iodobenzoic acid, *p*-trifluoromethylbenzoic acid, and *p*-cyanobenzoic acid. For *m*-bromobenzoic acid, *p*-iodobenzoic acid, *o*-iodobenzoic acid, and *p*-trifluoromethylbenzoic acid, which have an electron-withdrawing group on the aromatic ring, the reduction of the esters with SDBBA-H (in the second step) was carried out at –70 to 0 °C over 4 h, to improve the yields of the aromatic nitriles (Table 2, entries 7 and 9–11). When the reduction of the esters with SDBBA-H was carried out at –40 to 0 °C over 4 h, the yields of aromatic nitriles were in the range 54–61%, and the corresponding benzylic alcohols were formed with yields of 12–25%. On the other hand, ethyl esters derived from electron-rich arenecarboxylic acids, such as benzoic acid, *p*-methylbenzoic acid, *p*-methoxybenzoic acid, benzofuran-2-carboxylic acid, and benzothiophene-2-carboxylic acid, did not react with SDBBA-H at –40 °C. Therefore, for those substrates, the reduction of the esters with SDBBA-H was carried out at 0 °C or at 0 °C to room temperature, and then the reaction mixtures were treated with molecular iodine and aqueous ammonia at 0 °C to room temperature to give the corresponding aromatic nitriles in good yields (Table 2, entries 13–17). Next, aliphatic carboxylic acids bearing an sp^3 hybridized alkyl group, such as 3-phenylpropanoic acid, palmitic acid, stearic acid, oleic acid, and adamantane-1-carboxylic acid, were treated with ethyl iodide, K_2CO_3, and 18-crown-6, then

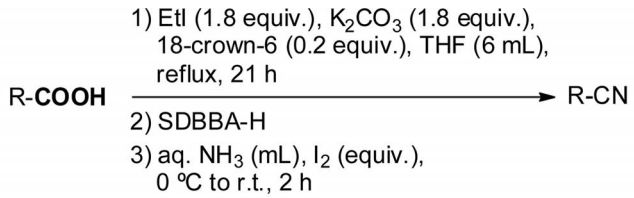
Table 1. Transformation of 1-naphthoic acid into 1-naphthonitrile.

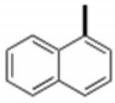
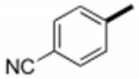
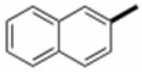
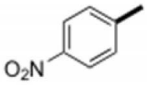
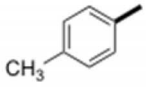
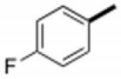
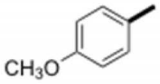
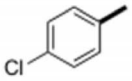
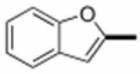
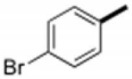
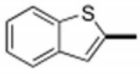
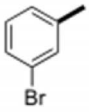
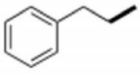
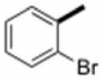
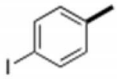
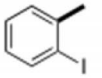
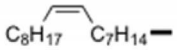
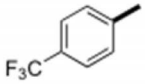
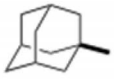
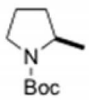


Entry	Second step			Third step		Yields [%][a]	
	Red. agent[b] [equiv.]	Temp.	Time [h]	NH_3 (aq.) [mL]	I_2 [equiv.]	Nitrile	Ester
1	1.5	–40 to 0 °C	4	4	4.1	37	56
2	1.8	–40 to 0 °C	4	4	4.1	58	22
3	2.0	–40 to 0 °C	4	4	4.1	44	18
4	2.2	–40 to 0 °C	4	4	5.0	73	10
5	2.2	–40 to 0 °C	4	6	5.0	77	trace
6	DIBAL-H, 1.5	–78 °C	4	6	5.0	trace (45)[c]	48
7	$LiAlH(OtBu)_3$, 1.5	–70 to 0 °C	4	6	5.0	0	95
8	$LiAlH(OtBu)_3$, 1.5	0 °C to r.t.	4	6	5.0	0	83
9	$NaHB(sBu)_3$, 1.5	–70 to 0 °C	4	6	5.0	0	86
10	$NaHB(sBu)_3$, 1.5	0 °C to r.t.	4	6	5.0	0	78
11[d]	2.2	–40 to 0 °C	4	6	5.0	47	11
12[e]	2.2	–40 to 0 °C	4	6	5.0	15	42
13[f]	2.2	–40 to 0 °C	4	6	5.0	50	27
14[g]	2.2	–40 to 0 °C	4	6	5.0	47	39
15[h]	2.2	–40 to 0 °C	4	6	5.0	35	15

[a] Isolated yields. [b] SDBBA-H unless otherwise stated. [c] Yield of 1-naphthalenemethanol. [d] CH_3I was used instead of EtI. [e] *n*PrI was used instead of EtI. [f] *i*BuI was used instead of EtI. [g] *n*BuI was used instead of EtI. [h] CH_3OCH_2Br was used instead of EtI.

Table 2. Transformation of carboxylic acids into nitriles.

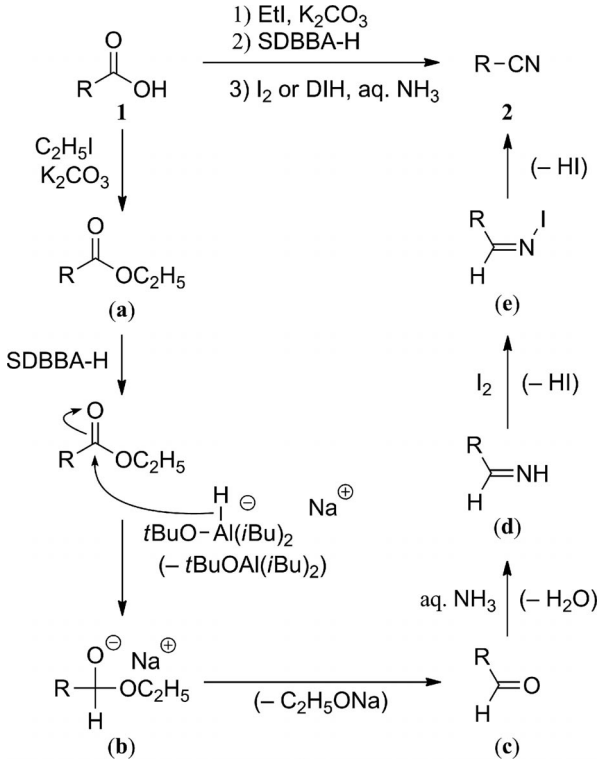


Entry	R	2nd step SABBA–H (equiv.) Temp., time	Yield (%)[a]	Entry	R	2nd step SABBA–H (equiv.) Temp., time	Yield (%)[a]
1		(2.2), –40 to 0 °C, 4 h	77	12[c]		(2.2), –40 °C, 2 h	70
2		(2.2), –40 to 0 °C, 4 h	70	13[b]		(2.5), 0 °C, 4 h	73
3		(2.2), –40 to 0 °C, 3 h	77	14[b, d]		(2.7), 0 °C to r.t., 6 h	73
4		(2.2), –40 to 0 °C, 4 h	82	15[b, d, e]		(2.7), 0 °C, 6 h	69
5		(2.2), –40 to 0 °C, 3 h	82	16[f]		(2.5), 0 °C, 4 h	74
6		(2.2), –40 to 0 °C, 4 h	80	17[f]		(2.5), 0 °C, 4 h	62
7		(2.2), –70 to 0 °C, 4 h	75	18[g]		(2.2), 0 °C, 4 h	75
8[b]		(2.2), –40 to 0 °C, 4 h	74	19[g]	$CH_3(CH_2)_{14}$—	(2.7), 0 °C, 4 h	74
9		(2.2), –70 to 0 °C, 4 h	79	20[g]	$CH_3(CH_2)_{16}$—	(2.7), 0 °C, 4 h	71
10		(2.2), –70 to 0 °C, 4 h	76	21[g]		(2.7), 0 °C, 4 h	73
11		(2.2), –70 to 0 °C, 4 h	71	22[g]		(2.7), 0 °C, 4 h	62
				23[g]		(2.2), 0 °C, 2 h	80 (99% *ee*)

[a] Isolated yields. [b] SDBBA-H was prepared with additional NaO*t*Bu (0.25 equiv.). [c] Reaction was carried out on a 1 mmol scale. [d] I_2 (6.0 equiv.) was used. [e] THF (4 mL) was used in the first step. [f] First step conditions: EtI (1.8 equiv.), K_2CO_3 (1.8 equiv.), 18-crown-6 (0.5 equiv.), THF/CH_2Cl_2 (3:1; 6 mL), reflux, 21 h. [g] DIH (3.0 equiv.) was used instead of I_2, and reaction was carried out at 0 °C in the third step.

with SDBBA-H at 0 °C, and finally with DIH (1,3-diiodo-5,5-dimethylhydantoin) and aqueous ammonia, to give the corresponding nitriles in good yields (Table 2, entries 18–22). Here, molecular iodine was not an efficient oxidant, but the iodination ability of DIH is stronger than that of molecular iodine. An olefinic group was not affected in the reaction (Table 2, entry 21). However, treatment of cinnamic acid under the same conditions and with the same procedure provided cinnamonitrile only in 20% yield, due to reduction of the α,β-unsaturated carbon–carbon double bond by SDBBA-H. The same treatment of *N*-Boc-protected L-proline (Boc = *tert*-butyloxycarbonyl) with ethyl iodide and K_2CO_3, then with SDBBA-H at 0 °C, and finally with DIH and aqueous ammonia gave the corresponding nitrile in good yield, and retaining a high *ee* (Table 2, entry 23).

A plausible reaction mechanism is shown in Scheme 1. Initially, ethyl ester **a** is formed by the reaction of carboxylic acid **1** with ethyl iodide in an S_N2 reaction. Then, the reduction of ethyl ester **a** by SDBBA-H takes place to form aldehyde **c** by β-cleavage of hemiacetal anion **b**. Aldehyde **c** reacts further with aqueous ammonia to form imine **d**. Imine **d** reacts further with molecular iodine or DIH in aqueous ammonia to form *N*-iodo imine **e**. Once *N*-iodo imine **e** has been formed, HI elimination occurs smoothly by reaction with ammonia to generate nitrile **2**. Practically, treatment of 1-napthoic acid with ethyl iodide (1.8 equiv.), K_2CO_3 (1.8 equiv.), and 18-crown-6 (0.2 equiv.) in THF under refluxing conditions for 21 h gave ethyl 2-naphthoate in 94% yield (first step of the overall reaction). Treatment of ethyl 2-naphthoate with SDBBA-H (2.2 equiv.) at –40 to 0 °C over 4 h, followed by treatment with molecular iodine (5.0 equiv.) and aqueous ammonia (4 mL) at 0 °C to room temperature over 2 h (second and third steps of the overall reaction) generated 1-naphthonitrile in 86% yield. We have previously reported the direct conversion of alcohols into nitriles, maintaining the same number of carbon atoms.[10] In that process, aldehydes were rapidly converted into the corresponding nitriles at room temperature on treatment with molecular iodine and aqueous ammonia. These results support that the present reaction proceeds by the reaction pathway shown in Scheme 1.



Scheme 1. Plausible reaction mechanism.

Conclusions

In conclusion, a variety of aromatic and aliphatic carboxylic acids were smoothly converted into the corresponding nitriles in good yields in a one-pot procedure by treatment with ethyl iodide/K_2CO_3/18-crown-6, and subsequently with sodium diisobutyl-*tert*-butoxyaluminium hydride (SDBBA-H), and finally with molecular iodine or DIH, and aqueous ammonia. This reaction is another useful method for the one-pot conversion of various aromatic and aliphatic carboxylic acids into the corresponding nitriles.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were obtained with JEOL-JNM-ECX400, JEOL-JNM-ECS400, and JEOL-JNM-ECA500 spectrometers. Chemical shifts are expressed in ppm downfield from TMS in δ units. Mass spectra were recorded with JMS-T100GCV, JMS-HX110, and Thermo LTQ Orbitrap XL spectrometers. IR spectra were measured with a JASCO FT/IR-4100 spectrometer. Melting points were determined with a Yamato melting-point apparatus model MP-21. Silica gel $60F_{254}$ (Merck) was used for TLC, and Silica gel 60 (Kanto Kagaku Co.) was used for short column chromatography.

Preparation of SDBBA-H Solution:[9] NaO*t*Bu (96.10 g/mol, 98% purity; 441.28 mg, 4.5 mmol) was dried using a vacuum pump for 30 min at room temperature. The NaO*t*Bu was dissolved in THF (3 mL), and DIBAL-H (1.02 M; 4.31 mL, 4.4 mmol) was added at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h at room temperature to give SDBBA-H. This solution was used directly for the reduction of esters.

Typical Procedure 1 for the Conversion of Aromatic Carboxylic Acids into Aromatic Nitriles: Iodoethane (561 mg, 1.8 equiv.) was added to a mixture of 1-naphthoic acid (344 mg, 2 mmol), 18-crown-6 (106 mg, 0.2 equiv.), and K_2CO_3 (332 mg, 1.8 equiv.) under an argon atmosphere. The mixture was stirred for 21 h at reflux. Then, SDBBA-H (2.2 equiv.) in dry THF (4 mL) was added at –40 °C. The resulting mixture was stirred for 4 h under an argon atmosphere at –40 °C, and gradually warmed to 0 °C. Finally, NH_3 (28.0–30.0% aq.; 6 mL) and I_2 (2.54 g, 5.0 equiv.) were added at 0 °C, and the resulting mixture was stirred for 2 h at room temperature. Then the reaction mixture was poured into Na_2SO_3 (saturated aq.; 10 mL) and the mixture was extracted with ethyl acetate (3 × 15 mL). The organic phase was dried with Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by flash short column chromatography on silica gel (hexane/diethyl ether, 30:1) to give 1-naphthonitrile (236 mg, 77%).

Typical Procedure 2 for the Conversion of Aromatic Carboxylic Acids into Aromatic Nitriles: Iodoethane (561 mg, 1.8 equiv.) was added to a mixture of 4-iodobenzoic acid (496 mg, 2 mmol), 18-crown-6 (106 mg, 0.2 equiv.), and K_2CO_3 (332 mg, 1.8 equiv.) in dry THF (6 mL) under an argon atmosphere. The mixture was stirred for 21 h at reflux. Then, SDBBA-H (2.2 equiv.) in dry THF (4 mL) was added at –70 °C. The resulting mixture was gradually warmed to 0 °C and stirred for 4 h under an argon atmosphere. Finally, NH_3 (28.0–30.0% aq.; 6 mL) and I_2 (2.54 g, 5.0 equiv.) were added at 0 °C, and the resulting mixture was stirred for 2 h at room temperature. Then the reaction mixture was poured into Na_2SO_3 (saturated aq.; 10 mL), and the mixture was extracted with ethyl acetate (3× 15 mL). The organic phase was dried with Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by flash short column chromatography on silica gel (hexane/diethyl ether, 30:1) to give 4-iodobenzonitrile (362 mg, 79%).

Typical Procedure 3 for the Conversion of Aliphatic Carboxylic Acids into Aliphatic Nitriles: Iodoethane (561 mg, 1.8 equiv.) was added to a mixture of 3-phenylpropionic acid (300 mg, 2 mmol), 18-crown-6 (106 mg, 0.2 equiv.) and K_2CO_3 (332 mg, 1.8 equiv.) in dry THF (6 mL) under an argon atmosphere. The mixture was stirred for 21 h at reflux. Then, SDBBA-H (2.2 equiv.) in dry THF (4 mL) was added at 0 °C. The resulting mixture was stirred for 4 h under an argon atmosphere at 0 °C. Finally, NH_3 (28.0–30.0% aq.; 6 mL) and DIH (2.35 mg, 3.0 equiv.) were added at 0 °C, and the resulting mixture was stirred for 2 h at 0 °C. Then, the reaction mixture was poured into Na_2SO_3 (saturated aq.; 10 mL), and the mixture was extracted with ethyl acetate (3× 15 mL). The organic phase was dried with Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by flash short column chromatography on silica gel (hexane/diethyl ether, 30:1) to give 3-phenylpropanenitrile (197 mg, 75%).

Most of the nitriles formed in this study are commercially available (comm. avail.) and they were identified by comparison with authentic samples.

1-Naphthonitrile: Yield 236 mg (77%), m.p. 35–36 °C (comm. avail., m.p. 35 °C). IR (neat): $\tilde{\nu}$ = 2219 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.52 (dd, J = 7.1, 8.3 Hz, 1 H), 7.62 (t, J = 8.3 Hz, 1 H), 7.69 (t, J = 8.4 Hz, 1 H), 7.94–7.89 (m, 2 H), 8.07 (d, J = 8.3 Hz, 1 H), 8.23 (d, J = 8.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 110.2, 117.8, 124.9, 125.1, 127.5, 128.6, 128.6, 132.3, 132.6, 132.9, 133.2 ppm.

2-Naphthonitrile: Yield 214 mg (70%), m.p. 66–68 °C (comm. avail., m.p. 67 °C). IR (neat): $\tilde{\nu}$ = 2225 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.68 (m, 3 H), 7.88–794 (m, 3 H), 8.24 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.4, 119.2, 126.3, 127.6, 128.0, 128.4, 129.0, 129.2, 132.2, 134.1, 134.6 ppm.

4-Nitrobenzonitrile: Yield 228 mg (77%), m.p. 145–147 °C (comm. avail., m.p. 147 °C). IR (neat): $\tilde{\nu}$ = 2233 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.8 Hz, 2 H), 8.36 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.8, 118.3, 124.3, 133.4, 150.0 ppm.

4-Fluorobenzonitrile: Yield 199 mg (82%), m.p. 34–35 °C (comm. avail., m.p. 34 °C). IR (neat): $\tilde{\nu}$ = 2233 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.18 (dd, $J_{H,H}$ = 9.1, $J_{H,F}$ = 8.4 Hz, 2 H), 7.69 (dd, $J_{H,H}$ = 9.1, $J_{H,F}$ = 5.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 108.7 (d, $J_{C,F}$ = 4.0 Hz), 117.0 (d, $J_{C,F}$ = 23.0 Hz), 118.1, 134.8 (d, $J_{C,F}$ = 9.5 Hz), 165.1 (d, $J_{C,F}$ = 257.7 Hz) ppm.

4-Chlorobenzontrile: Yield 226 mg (82%), m.p. 92–94 °C (comm. avail., m.p. 92 °C). IR (neat): $\tilde{\nu}$ = 2225 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.6 Hz, 2 H), 7.61 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.8, 118.0, 129.7, 133.4, 139.5 ppm.

4-Bromobenzonitrile: Yield 291 mg (80%), m.p. 113–115 °C (comm. avail., m.p. 113 °C). IR (neat): $\tilde{\nu}$ = 2224 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 8.2 Hz, 2 H), 7.64 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.2, 118.0, 128.0, 132.6, 133.4 ppm.

3-Bromobenzonitrile: Yield 273 mg (75%), m.p. 42–43 °C (comm. avail., m.p. 40 °C). IR (neat): $\tilde{\nu}$ = 2230 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (t, J = 8.2, 7.7 Hz, 1 H), 7.61 (d, J = 7.7 Hz, 1 H), 7.75 (d, J = 8.2 Hz, 1 H), 7.81 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.2, 117.3, 122.9, 130.6, 130.7, 134.8, 136.1 ppm.

2-Bromobenzonitrile: Yield 269 mg (74%), m.p. 55 °C (comm. avail., m.p. 54 °C). IR (neat): $\tilde{\nu}$ = 2230 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.50 (m, 2 H), 7.65–7.72 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.9, 117.1, 125.3, 127.6, 133.2, 133.9, 134.3 ppm.

4-Iodobenzonitrile: Yield 362 mg (79%), m.p. 125–126 °C (comm. avail., m.p. 127 °C). IR (neat): $\tilde{\nu}$ = 2225 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 8.4 Hz, 2 H), 7.85 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 100.3, 111.8, 118.2, 133.2, 138.5 ppm.

2-Iodobenzonitrile: Yield 348 mg (76%), m.p. 55 °C (comm. avail., m.p. 55 °C). IR (neat): $\tilde{\nu}$ = 2225 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (t, J = 7.9 Hz, 1 H), 7.46 (t, J = 7.7 Hz, 1 H), 7.62 (d, J = 7.7 Hz, 1 H), 7.94 (d, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.5, 119.4, 120.8, 128.4, 133.7, 134.4, 139.7 ppm.

4-(Trifluoromethyl)benzonitrile: Yield 243 mg (71%), m.p. 39–40 °C (comm. avail., m.p. 37 °C). IR (neat): $\tilde{\nu}$ = 2225 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.79 (d, J = 8.4 Hz, 2 H), 7.80–7.84 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 116.0, 117.4, 123.0 (q, $J_{C,F}$ = 271.8 Hz), 126.2 (q, $J_{C,F}$ = 3.6 Hz), 132.7, 134.5 (q, $J_{C,F}$ = 33.4 Hz) ppm.

Terephthalonitrile: Yield 179 mg (70%), m.p. 218–220 °C (comm. avail., m.p. 228 °C). IR (neat): $\tilde{\nu}$ = 2231 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (s, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.7, 117.0, 132.8 ppm.

Benzonitrile: Yield 151 mg (73%). Colorless oil (comm. avail., oil). IR (neat): $\tilde{\nu}$ = 2228 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (t, J = 7.7 Hz, 2 H), 7.61 (t, J = 7.7 Hz, 1 H), 7.67 (d, J = 7.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.3, 118.8, 129.0, 132.0, 132.7 ppm.

4-Methylbenzonitrile: Yield 171 mg (73%). Colorless oil (comm. avail., oil). IR (neat): $\tilde{\nu}$ = 2227 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 7.27 (d, J = 8.6 Hz, 2 H), 7.53 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 109.0, 118.9, 129.6, 131.7, 143.5 ppm.

4-Methoxybenzonitrile: Yield 184 mg (69%), m.p. 60–61 °C (comm. avail., m.p. 60 °C). IR (neat): $\tilde{\nu}$ = 2217 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.59 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5, 104.0, 114.7, 119.2, 134.0, 162.8 ppm.

Benzofuran-2-carbonitrile: Yield 212 mg (74%), m.p. 36–38 °C (comm. avail.). IR (neat): $\tilde{\nu}$ = 2227 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (t, J = 7.5 Hz, 1 H), 7.46 (s, 1 H), 7.49–7.58 (m, 2 H), 7.68 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$):

δ = 111.8, 112.0, 118.4, 122.6, 124.5, 125.5, 127.3, 128.4, 155.6 ppm.

Benzothiophene-2-carbonitrile: Yield 197 mg (62%). Oil; (comm. avail., m.p. 24–28 °C). IR (neat): $\tilde{\nu}$ = 2215 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.47 (t, J = 7.5 Hz, 1 H): δ = 7.53 (t, J = 7.5 Hz, 1 H), 7.84–7.58 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 109.6, 114.4, 122.4, 125.2, 125.7, 127.8, 135.0, 137.4, 141.3 ppm.

3-Phenylpropanenitrile: Yield 197 mg (75%). Colorless oil (comm. avail.). IR (neat): $\tilde{\nu}$ = 2247 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.62 (t, J = 7.5 Hz, 2 H), 2.96 (t, J = 7.5 Hz, 2 H), 7.23 (d, J = 8.2 Hz, 2 H), 7.26 (t, J = 8.2 Hz, 1 H), 7.34 (t, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3, 31.5, 119.1, 127.2, 128.2, 128.8, 138.0 ppm.

Hexadecanenitrile: Yield 351 mg (74%), m.p. 32–33 °C (comm. avail., m.p. 27–33 °C). IR (neat): $\tilde{\nu}$ = 2247 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.24–1.34 (m, 22 H), 1.40–1.49 (m, 2 H), 1.57–1.70 (m, 2 H), 2.33 (t, J = 7.1 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 17.1, 22.7, 25.3, 28.6, 28.7, 29.3, 29.3, 29.5, 29.6, 29.6 (4), 31.9, 119.8 ppm.

Octadecanenitrile (Stearonitrile): Yield 335 mg (63%), m.p. 43 °C (comm. avail., m.p. 40 °C). IR (neat): $\tilde{\nu}$ = 2242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.24–1.34 (m, 26 H), 1.39–1.49 (m, 2 H), 1.60–1.70 (m, 2 H), 2.33 (t, J = 7.1 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 17.1, 22.7, 25.4, 28.7, 28.8, 29.3, 29.4, 29.5, 29.6, 29.7 (6), 31.9, 119.9 ppm.

***cis*-9-Octadecenenitrile:** Yield 385 mg (73%). Colorless oil (comm. avail.). IR (neat): $\tilde{\nu}$ = 2242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H): δ = 1.26–1.37 (m, 20 H), 1.63–1.69 (m, 2 H), 1.99–2.03 (m, 2 H), 2.33 (t, J = 7.1 Hz, 2 H), 5.31–5.39 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 17.1, 22.6, 25.3, 27.0, 27.2, 28.6, 28.6, 28.9, 29.3 (2), 29.5, 29.5, 29.7, 31.9, 119.8, 129.5, 130.1 ppm. HRMS (APPI): calcd. for $C_{18}H_{33}N$ $[M]^+$ 263.2608; found 263.2604.

1-Cyanoadamantane: Yield 200 mg (62%), m.p. 191–194 °C (comm. avail., m.p. 195 °C). IR (neat): $\tilde{\nu}$ = 2230 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.70–1.78 (m, 6 H) 2.00–2.08 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0, 30.1, 35.7, 39.8, 125.3 ppm.

***N*-(*tert*-butoxycarbonyl)-L-proline:** Yield 314 mg (80%). Colorless oil. IR (neat): $\tilde{\nu}$ = 2248, 1696 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$-DMSO): δ = 1.42 (s, 9 H), 1.82–1.99 (m, 2 H), 2.08–2.28 (m, 3 H), 3.24 (q, J = 8.3 Hz, 1 H), 4.59–4.65 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 24.5, 28.2, 30.7, 30.8, 31.5, 45.6, 45.9, 46.9, 47.0, 80.8, 81.2, 119.0, 152.9, 153.5 ppm. HRMS (ESI): calcd. for $C_{10}H_{17}N_2O_2$ $[M + H]^+$ 197.1285; found 197.1284.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra of all the nitriles prepared.

Acknowledgments

Financial support by the Ministry of Education, Culture, Sports, Science, and Technology in Japan in the form of a Grant-in-Aid for Scientific Research (grant number 25105710) and by Chiba University (Iodine Research Project) is gratefully acknowledged.

[1] a) K. Friedrick, K. Wallensfels, in: *The Chemistry of the Cyano Group* (Ed.: Z. Rappoport), Wiley–Interscience, New York, **1970**; b) M. North, in: *Comprehensive Organic Functional Group Transformations* (Eds.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees), Pergamon, Oxford, UK, **1995**; c) S.-I. Murahashi, *Synthesis from Nitriles with Retention of the Cyano Group*, in: *Science of Synthesis* vol. 19, Thieme, **2004**, p. 345–402; d) S. J. Collier, P. Langer, *Applications of Nitriles as Reagents for Organic Synthesis with Loss of the Nitrile Functionality*, in: *Science of Synthesis* vol. 19, Thieme, **2004**, p. 403–425.

[2] a) P. Wipf, *Chem. Rev.* **1995**, *95*, 2115–2134; b) P. Wipf, F. Yokokawa, *Tetrahedron Lett.* **1998**, *39*, 2223–2226; c) P. C. Ducept, S. P. Marsden, *Synlett* **2000**, 692–694; d) M. Chihiro, H. Nagamoto, I. Takemura, K. Kitano, H. Komatsu, K. Sekiguchi, F. Tabusa, T. Mori, M. Tominaga, Y. Yabuuchi, *J. Med. Chem.* **1995**, *38*, 353–358; e) X.-H. Gu, X.-Z. Wan, B. Jiang, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 569–572; f) P. K. Kadaba, *Synthesis* **1973**, 71–84; g) G. D. Diana, D. Cutcliffe, D. L. Volkots, J. P. Mallamo, T. R. Bailey, N. Vescio, R. C. Oglesby, T. J. Nitz, J. Wetzel, V. Giranda, D. C. Pevear, F. J. Dutko, *J. Med. Chem.* **1993**, *36*, 3240–3250; h) S. J. Wittenberger, B. G. Donner, *J. Org. Chem.* **1993**, *58*, 4139–4141; i) J.-J. Shie, J.-M. Fang, *J. Org. Chem.* **2003**, *68*, 1158–1160; j) J. B. Medwid, R. Paul, J. S. Baker, J. A. Brockman, M. T. Du, W. A. Hallett, J. W. Hanifin, R. A. Hardy Jr., M. E. Tarrant, L. W. Torley, S. Wrenn, *J. Med. Chem.* **1990**, *33*, 1230–1241; k) I. K. Khanna, R. M. Weier, Y. Yu, X. D. Xu, F. J. Koszyk, P. W. Collins, C. M. Koboldt, A. W. Veenhuizen, W. E. Perkins, J. J. Casler, J. L. Masferrer, Y. Y. Zhang, S. A. Gregory, K. Seibert, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1634–1647.

[3] R. C. Larock, *Nitriles, Carboxylic Acids and Derivatives*, in: *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, New York, **1999**, p. 1621–1996.

[4] a) M. Heck, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1996**, *61*, 6486–6487; b) N. Nakajima, M. Ubukata, *Tetrahedron Lett.* **1997**, *38*, 2099–2102; c) D. S. Bose, B. Jayalakshmi, *J. Org. Chem.* **1999**, *64*, 1713–1714; d) R. T. Ruck, R. G. Bergman, *Angew. Chem.* **2004**, *116*, 5489–5491; *Angew. Chem. Int. Ed.* **2004**, *43*, 5375–5377; e) C. Kuo, J. Zhu, J. Wu, C. Chu, C. Yao, K. Shia, *Chem. Commun.* **2007**, 301–303; f) S. Hanada, Y. Motoyama, H. Nagashima, *Eur. J. Org. Chem.* **2008**, 4097–4100.

[5] a) T. G. Clarke, N. A. Hampson, J. B. Lee, J. R. Morley, B. Scanlon, *Tetrahedron Lett.* **1968**, *9*, 5685–5688; b) L. Vargha, M. Remenyi, *J. Chem. Soc.* **1951**, 1068–1069; c) J. Cason, in: *Org. Synth. Coll. Vol. 3*, New York, **1955**, p. 3–7; d) M. L. Mihailovic, A. Stojiljkovic, V. Andrejevic, *Tetrahedron Lett.* **1965**, *6*, 461–464; e) A. Stojiljkovic, V. Andrejevic, M. L. Mihailovic, *Tetrahedron* **1967**, *23*, 721–732; f) J. S. Below, C. Garza, J. W. Mathieson, *J. Chem. Soc. C* **1970**, 634–635; g) K. Nakagawa, T. Tsuji, *Chem. Pharm. Bull.* **1963**, *11*, 296–301; h) E. I. Troyanskii, I. V. Svitanko, V. A. Ioffe, G. I. Nikishin, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 2180–2185; i) S. Yamazaki, Y. Yamazaki, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 301–303; j) D. Biondini, L. Brinchi, R. Germani, L. Goracci, G. Savelli, *Eur. J. Org. Chem.* **2005**, 3060–3063; k) E. Chen, Z. Peng, H. Fu, J. Liu, L. Shao, *J. Chem. Res. Synopses* **1999**, 726–727; l) G. A. Lee, H. H. Freedman, *Tetrahedron Lett.* **1976**, *17*, 1641–1644; m) S. Yamazaki, *Synth. Commun.* **1997**, *27*, 3559–3564; n) B. Jursic, *J. Chem. Res. Synop.* **1988**, 168–169; o) G. I. Nikishin, E. I. Troyanskii, V. A. Joffe, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 2758–2762; p) T. Kametani, K. Takahashi, T. Ohsawa, M. Ihara, *Synthesis* **1977**, 245–248; q) P. Capdevielle, A. Lavigne, M. Maumy, *Synthesis* **1989**, 453–454; r) P. Capdevielle, A. Lavigne, D. Sparfel, J. Baranne-Lafont, K. C. Nguyen, M. Maumy, *Tetrahedron Lett.* **1990**, *31*, 3305–3308; s) Y. Maeda, T. Nishimura, S. Uemura, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2399–2403; t) R. Tang, S. E. Diamond, N. Neary, F. Mares, *J. Chem. Soc., Chem. Commun.* **1978**, 562–563; u) M. Schroder, W. P. Griffith, *J. Chem. Soc., Chem. Commun.* **1979**, 58–59; v) A. J. Bailey, B. R. James, *Chem. Commun.* **1996**, 2343–2344; w) K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani, K. Kaneda, *Chem. Commun.* **2001**, 461–462; x) K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2003**, *115*, 1518–1521; *Angew. Chem. Int. Ed.*

2003, *42*, 1480–1483; y) R. M. Moriarty, R. K. Vaid, M. P. Duncan, M. Ochiai, M. Inenaga, Y. Nagao, *Tetrahedron Lett.* **1988**, *29*, 6913–6916; z) F. Chen, Y. Kuang, H. Dai, L. Lu, M. Huo, *Synthesis* **2003**, 2629–2631.

[6] T. Sandmeyer, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633–1639.

[7] a) C. S. Miller, in: *Org. Synth. Coll. Vol. 3*, **1955**, p. 646–648; b) A. C. Cope, R. J. Cotter, L. L. Estes, in: *Org. Synth. Coll. Vol. 4*, **1963**, p. 62–64; c) D. A. Klein, *J. Org. Chem.* **1971**, *36*, 3050–3051; d) T. Imamoto, T. Takaoka, M. Yokoyama, *Synthesis* **1983**, 142–143; e) V. J. Huber, R. A. Bartsch, *Tetrahedron* **1998**, *54*, 9281–9288; f) C. O. Kangani, B. W. Day, D. E. Kelley, *Tetrahedron Lett.* **2007**, *48*, 5933–5937; g) V. N. Telvekar, R. A. Rane, *Tetrahedron Lett.* **2007**, *48*, 6051–6053; h) K. Ouchaou, D. Georgin, F. Taran, *Synlett* **2010**, 2083–2086.

[8] Review articles: a) H. Togo, S. Iida, *Synlett* **2006**, 2159–2175; b) H. Togo, *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 652–663. Articles: c) N. Mori, H. Togo, *Synlett* **2004**, 880–882; d) N. Mori, H. Togo, *Tetrahedron* **2005**, *61*, 5915–5925; e) M. Ishihara, H. Togo, *Synlett* **2006**, 227–230; f) S. Iida, H. Togo, *Synlett* **2006**, 2633–2635; g) M. Ishihara, H. Togo, *Tetrahedron* **2007**, *63*, 1474–1480; h) S. Iida, H. Togo, *Synlett* **2007**, 407–410; i) S. Iida, H. Togo, *Synlett* **2008**, 1639–1642; j) S. Iida, R. Ohmura, H. Togo, *Tetrahedron* **2009**, *65*, 6257–6262; k) S. Ushijima, H. Togo, *Synlett* **2010**, 1067–1070; l) R. Ohmura, M. Takahata, H. Togo, *Tetrahedron Lett.* **2010**, *51*, 4378–4371; m) Y. Suzuki, Y. Ishiwata, K. Moriyama, H. Togo, *Tetrahedron Lett.* **2010**, *51*, 5950–5953; n) S. Takahashi, H. Togo, *Heterocycles* **2010**, *82*, 593–601; o) Y. Suzuki, T. Yoshino, K. Moriyama, H. Togo, *Tetrahedron* **2011**, *67*, 3809–3814; p) H. Baba, K. Moriyama, H. Togo, *Tetrahedron Lett.* **2011**, *52*, 4303–4307; q) Y. Suzuki, K. Moriyama, H. Togo, *Tetrahedron* **2011**, *67*, 7956–7962; r) S. Ushijima, S. Dohi, K. Moriyama, H. Togo, *Tetrahedron* **2012**, *68*, 1436–1442; s) H. Baba, K. Moriyama, H. Togo, *Synlett* **2012**, *23*, 1175–1180; t) S. Ushijima, K. Moriyama, H. Togo, *Tetrahedron* **2012**, *68*, 4701–4709; u) S. Ushijima, K. Moriyama, H. Togo, *Tetrahedron* **2012**, *68*, 4588–4595; v) S. Dohi, K. Moriyama, H. Togo, *Tetrahedron* **2012**, *68*, 6557–6564; w) H. Kikui, K. Moriyama, H. Togo, *Synthesis* **2013**, 791–797.

[9] J. I. Song, D. K. An, *Chem. Lett.* **2007**, *36*, 886–887.

[10] a) N. Mori, H. Togo, *Synlett* **2005**, 1456–1458; b) S. Iida, H. Togo, *Tetrahedron* **2007**, *63*, 8274–8281.

Received: May 1, 2013
Published Online: August 1, 2013

