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Facile transformation of esters to nitriles

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ABSTRACT

Various esters were efficiently converted into the corresponding nitriles in good yields by the treatment with sodium diisobutyl-*tert*-butoxyaluminium hydride (SDBBA-H), followed by treatment with molecular iodine in aq ammonia. The present one-pot method is very efficient and practical for the conversion of various aromatic and aliphatic esters into the corresponding nitriles.

1. Introduction

Nitrile is one of the most important and versatile functional groups that can be easily diversified into numerous important functionalized products, such as aldehydes, ketones, amines, amides, and acids, and nitrogen-containing heterocycles, such as tetrazoles and oxazoles. Practically, nitriles are used as synthetic intermediates for agrochemicals, pharmaceuticals, and functional materials,[1] and Citalopram hydrobromide® (treatment of alcohol dependency), Periciazine® (anti-psychotic drug), Fadrozole® (oncolytic drug), and Letrozole® (breast cancer therapy) are pharmaceutically important aromatic nitriles, and 4-cyano-4′-pentylbiphenyl is a typical liquid crystal material.[2] The most typical methods for the preparation of aliphatic and aromatic nitriles are the dehydration of *N*-free amides with $SOCl_2$, TsCl/Py, P_2O_5, $POCl_3$, $COCl_2$, $TiCl_4$, $(CF_3CO)_2O$/Py, or Ph_3P/CCl_4,[3] and recently, aromatic nitriles were prepared by the dehydration of aromatic amides with $(CH_2O)_n/HCO_2H$,[4a] $(COCl)_2$/DMSO,[4b] dibutyltin oxide/microwave, [4c] $Cp_2Zn(CH_3)_2$,[4d] $Cl_2P(O)OEt$/DBU,[4e] and $Ru_3(CO)_7/R_3SiH$.[4f] On the other hand, aromatic nitriles are conventionally prepared from aromatic amines with $NaNO_2$ and aq HCl, followed by the treatment with CuCN (Sandmeyer reaction).[5] Recently, the direct conversion of aromatic bromides into the corresponding aromatic nitriles has been actively studied with CuCN at DMF refluxing temperature,[6a] $Pd(OAc)_2 \cdot K_4[Fe(CN)_6]$ at 120 °C,[6b] Pd·(binaphthyl)P(^{t}Bu)$_2$·$Zn(CN)_2$·Zn at 80–95 °C,[6c] $Pd_2(dba)_3 \cdot Zn(CN)_2$·DPPF at 80–120 °C,[6d] $Pd(tmhd)_2 \cdot K_4[Fe(CN)_6]$ at 80 °C,[6e] $Zn(CN)_2 \cdot Pd_2(dba)_3$ at 100 °C,[6f] Pd/C·CuI·$K_4[Fe(CN)_6] \cdot 3H_2O$ at 130–140 °C,[6g] CuI·alkylimidazole·Pd/C·CuI·$K_4[Fe(CN)_6]$ at 140–180 °C,[6h] $Zn(CN)_2 \cdot Pd_2(dba)_3$·dppf·$Zn \cdot ZnBr_2$ at 95 °C,[6i] CuO·Pd·$K_4[Fe(CN)_6]$ at 120 °C,[6j] Pd$(OAc)_2 \cdot Cu(OAc)_2 \cdot K_4[Fe(CN)_6]$[6k] at 130 °C, and CuI·$K_4[Fe(CN)_6]$[6l] at 175 °C. Thus, today less expensive and less toxic methods for the preparation of nitriles from easily available compounds are required. Esters are one of the most easily available compounds. However, to the best of our knowledge, only a few methods for the direct conversion of esters into nitriles are known. One method is the conversion of esters into the corresponding nitriles with dimethylaluminium amide via the formation of amide intermediate in xylene refluxing conditions,[7a,b] and another method is the conversion of aromatic methyl esters into the aromatic nitriles with $NaN(SiMe_3)_2$ in a sealed tube at 185 °C.[7c] Thus, there are no practical, mild, and efficient methods for the conversion of esters into the corresponding nitriles.

On the other hand, molecular iodine (I_2) is one of the simplest oxidants currently available and can be used for various oxidative reactions, as well as introduction and removal of protecting groups.[8]

As part of our ongoing studies on the use of molecular iodine for organic synthesis,[9] we would like to report herein the one-pot conversion of esters into the corresponding nitriles.

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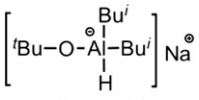
2. Results and discussion

Recently, we have reported the direct conversion of isopropyl esters into the corresponding nitriles by the treatment with diisobutylaluminium hydride (DIBAL-H), followed by the reaction with molecular iodine in aq NH_3.[10] We believe this method is very useful and practical, as it uses less toxic reagent and a simple experimental procedure. However, there are some drawbacks, i.e., isopropyl ester, a sterically hindered alkyl group, is required as an ester substrate, and the reaction is limited to aliphatic isopropyl esters, as aromatic isopropyl esters give a mixture of starting ester and benzylic alcohol even if an equivalent amount of DIBAL-H is used at low temperature (−78 °C). This indicates that the formed aromatic acetal *O*-Al^{i}Bu$_2$ rapidly decomposes into aromatic aldehyde and Al(O^{i}Pr)^{i}Bu$_2$. Once aromatic aldehyde is formed, it reacts with DIBAL-H to provide benzylic alcohol even if the reaction is carried out at −78 °C. To solve this problem, the stabilization of the acetal *O*-Al^{i}Bu$_2$ adduct is required.

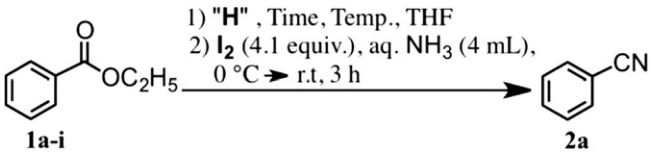
Recently, the preparation of aldehydes from ethyl esters with sodium diisobutyl-*tert*-butoxyaluminium hydride (SDBBA-H), which was prepared from NaO^{t}Bu and DIBAL-H in situ, at 0 °C was reported.[11] This method is extremely interesting and has encouraged us to prepare nitriles from esters.

As mentioned above, when ethyl benzoate (**1a**–**i**) was treated with DIBAL-H alone, followed by the treatment with molecular iodine and aq NH_3, a mixture of ethyl benzoate and benzyl alcohol was obtained, and benzonitrile (**2a**) was not obtained at all even if the reaction was carried out at −78 °C, as shown in Table 1 (entry 1). LiAlH(O^{t}Bu)$_3$ did not react with ethyl benzoate at 0 °C (entry 2). Then, SDBBA-H instead of DIBAL-H was used as the reductant, and the optimization for the formation of benzonitrile (**2a**) was studied as shown in Table 1 (entries 3–16). Thus, to a solution of NaO^{t}Bu in THF was added DIBAL-H at 0 °C under argon atmosphere and the obtained mixture was stirred for 1 h at room temperature. Then, ethyl benzoate (**1a**–**i**) in THF (4 mL) was added to the solution at 0 °C, and the mixture was stirred for 4 h at the same temperature. Then, aq NH_3 (concentration: 28.0%–30.0%) and molecular iodine were added at 0 °C, and the obtained mixture was stirred for 3 h at room temperature to provide benzonitrile (**2a**) in 76% yield (entry 9). KO^{t}Bu and LiO^{t}Bu did not work as well as NaO^{t}Bu (entries 12, 13). As regards the solvent effect, the reaction with SDBBA-H in THF, followed by the treatment with molecular iodine and aq NH_3, provided benzonitrile in higher yield than those in dichloromethane, ether, and toluene (entries14–16). Then, the effect of alkyl group (Me, Et, Pr, ^{i}Pr, Bn, allyl) in alkyl benzoates (**1a**) under the optimal conditions was studied and the results are shown in Table 2. Little difference was noted in the yields of benzonitrile (**2a**); ethyl group (**1a**–**i**) showed the best result providing benzonitrile (**2a**) in good yield. Based on these results, various aromatic ethyl esters (**1-i**) bearing electron-withdrawing groups, such as F, Cl, Br, and NO_2, and electron-donating groups, such as CH_3, CH_3O, and $(CH_3)_3C$, were treated with SDBBA-H (1.7 equiv) at 0 °C, followed by the reaction with molecular iodine and aq NH_3 at 0 °C to room temperature to generate the corresponding aromatic nitriles (**2**) in good yields, as shown in Table 3 (entries 2–6, 8–15, 18–23). Ethyl 3-pyridinecarboxylate (**1r**–**i**) and ethyl 2-thiophenecarboxylate (**1s**–**i**) bearing a heteroaromatic group also provided 3-cyanopyridine (**2r**) and 2-cyanothiophene (**2s**) in good yields, respectively (entries 24, 25). However, the same treatment of ethyl cinnamate (**1t**–**i**) under the same conditions gave cinnamonitrile (**2t**) in low yield, together with many by-products containing 1,4-reduction products (entry 26).



SDBBA-H

Table 1
Transformation of ethyl benzoate to benzonitrile

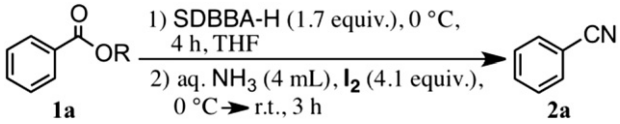


1a-i **2a**

Entry	'H' (equiv)	Temp (°C)	Time (h)	Yield (%) (**2a**:**1a**–**i**:alcohol)
1	DIBAL-H (1.25)	−78 °C	1.5	0:66:40
2	LiAlH(O^{t}Bu)$_3$ (1.25)	0 °C	1.5	0:98:0
3[a]	DIBAL-H (1.25) NaO^{t}Bu (1.30)	0 °C to rt	2	60:23:8
4[a]	DIBAL-H (1.40) NaO^{t}Bu (1.50)	0 °C to rt	2	65:11:10
5[a]	DIBAL-H (1.40) NaO^{t}Bu (1.50)	0 °C	4	51: 19: 6
6[a]	DIBAL-H (1.50) NaO^{t}Bu (1.60)	0 °C	4	65:11:8
7[a]	DIBAL-H (1.40) NaO^{t}Bu (1.50)	−78 °C to rt	2	54:40:4
8[a]	DIBAL-H (1.40) NaO^{t}Bu (2.00)	0 °C	2	44:22:4
9[a]	DIBAL-H(1.70) NaO^{t}Bu(1.80)	0 °C	4	76:2:14
10[a]	DIBAL-H (2.00) NaO^{t}Bu (2.10)	0 °C	4	72: 0: 13
11[a]	DIBAL-H (1.70) NaO^{t}Bu (1.80)	−40 °C	15	63: 16: 6
12	DIBAL-H (1.70) KO^{t}Bu (1.80)	0 °C	4	40:18:1
13	DIBAL-H (1.70) LiO^{t}Bu (1.80)	0 °C	4	48:14:30
14[a,b]	DIBAL-H (1.70) NaO^{t}Bu (1.80)	0 °C	4	51:4:34
15[a,c]	DIBAL-H (1.70) NaO^{t}Bu (1.80)	0 °C	4	50:0:39
16[a,d]	DIBAL-H (1.70) NaO^{t}Bu (1.80)	0 °C	4	48:14:31

[a] SDBBA-H was generated in situ from the reaction of DIBAL-H and NaO^{t}Bu.
[b] CH_2C1_2 was used instead of THF.
[c] Et_20 was used instead of THF.
[d] Toluene was used instead of THF.

Table 2
Effect of *O*-alkyl group in alkyl benzoates



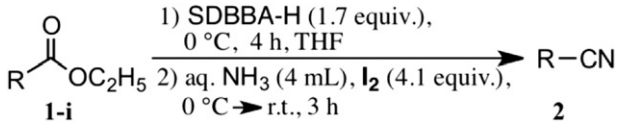
1a **2a**

R	Me	Et (**1a**–**i**)	Pr	^{i}Pr	Bn	Allyl
Yield (%)	68	76	74	68	67	69

The present reaction can be used for a large-scale experiment. Thus, treatment of ethyl *p*-bromobenzoate (4.58 g, 20 mmol, **1d**–**i**) with SDBBA-H (1.7 equiv), followed by the reaction with molecular iodine (4.1 equiv) and aq NH_3 (40 mL) provided *p*-bromobenzonitrile (**2d**) in 85% yield (entry 7). As an additional attempt, the competitive reactions of amides and esters were carried out under the same conditions with DIBAL-H and SDBBA-H, as shown in Tables 4 and 5, respectively.

Thus, treatment of a mixture of ethyl *p*-bromobenzoate (**1d**–**i**) and *N*,*N*-dimethylbenzamide (**I**) with DIBAL-H at −78 °C, followed by the reaction with molecular iodine in aq NH_3 gave benzonitrile

Table 3
Transformation of aromatic esters to aromatic nitriles



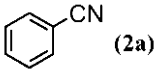
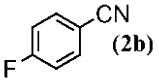
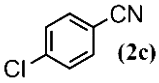
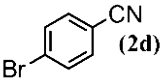
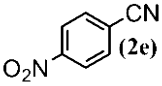
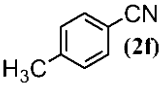
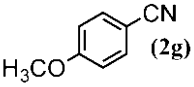
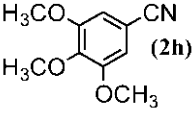
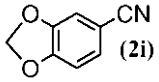
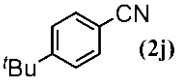
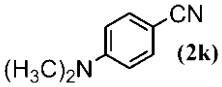
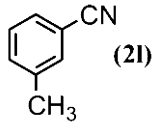
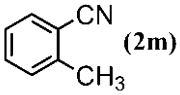
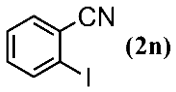
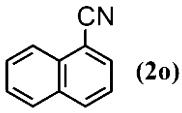
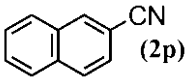
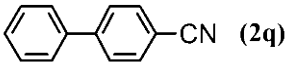
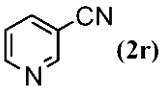
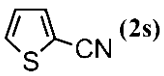
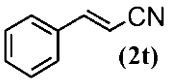
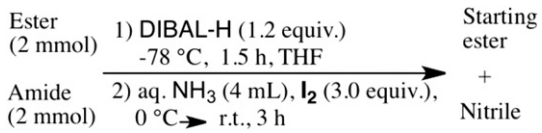
Entry	Product	Yield (%)
1[c]	 (2a)	0(61)[a](38)[b]
2		76
3	 (2b)	73
4[c]	 (2c)	0 (42)[a](33)[b]
5		80
6	 (2d)	86
7		85[d]
8[c]	 (2e)	1 (57)[a](42)[b]
9		88
10	 (2f)	76
11	 (2g)	59 (30)[a](1)[b]
12[e]		83
13[e]	 (2h)	72
14[e]	 (2i)	74
15	 (2j)	84
16	 (2k)	17 (49)[a](5)[b]
17[e]		48 (9)[a](9)[b]
18	 (2l)	74
19	 (2m)	82

Table 3 (*continued*)

Entry	Product	Yield (%)
20	 (2n)	78
21	 (2o)	85
22	 (2p)	74
23	 (2q)	85
24	 (2r)	75
25	 (2s)	72
26	 (2t)	28

[a] Yield of starting material.
[b] Yield of benzylic alcohol.
[c] DIBAL (1.25 equiv) was used as a reductant.
[d] Reaction was carried out at 20 mmol scale.
[e] SDBBA (2.0 equiv) was used.

Table 4
Competitive reaction of esters and amides



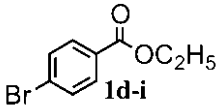
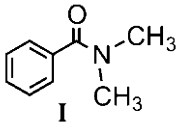
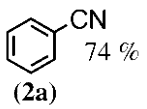
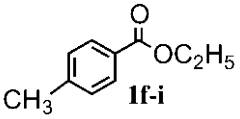
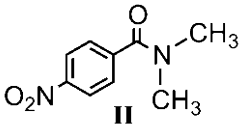
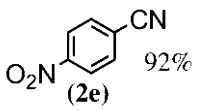
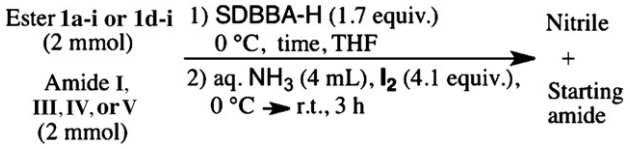
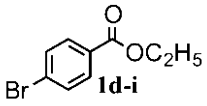
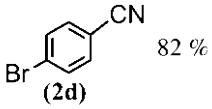
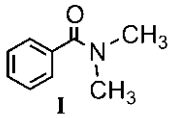
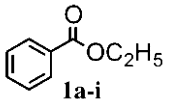
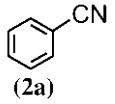
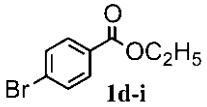
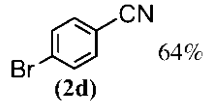
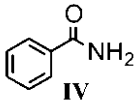
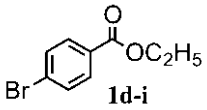
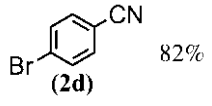
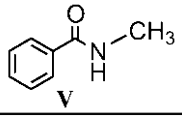
Entry	Substrates	Major products
1	 1d-i	**Id–i** 99%
	 I	 74 % (2a)
2	 1f-i	**If–i** 99%
	 II	 92% (2e)

Table 5
Competitive reaction of esters and amides



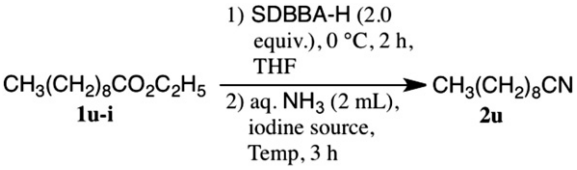
Entry	Substrates	Time	Major products
1	 **1d-i**	1 h	 **(2d)** 82 %
	 **I**		**I** 97%
2	 **1a-i**	4 h	 **(2a)** 72 %
	 **III**		**III** 93%
5[a]	 **1d-i**	4 h	 **(2d)** 64%
	 **IV**		**IV** 97%
6[b]	 **1d-i**	4 h	 **(2d)** 82%
	 **V**		**V** 97%

[a] SDBBA-H (2.3 equiv) was used.
[b] SDBBA-H (2.0 equiv) was used.

(**2a**) in 74% yield, together with the starting ethyl *p*-bromobenzoate (**1d**–**i**) in 99% yield (entry 1), and treatment of a mixture of ethyl *p*-methylbenzoate (**1f**–**i**) and *N*,*N*-dimethyl *p*-nitrobenzoamide (**II**) with DIBAL-H at −78 °C, followed by the reaction with molecular iodine in aq NH_3 gave *p*-nitrobenzonitrile (**2e**) in 92% yield, together with the starting ethyl *p*-methylbenzoate (**1f**–**i**) in 99% yield (entry 2), as shown in Table 4. On the other hand, reaction of a mixture of ethyl *p*-bromobenzoate (**1d**–**i**) and *N*,*N*-dimethylbenzamide (**I**) with SDBBA-H, followed by the reaction with molecular iodine and aq NH_3 gave *p*-bromobenzonitrile (**2d**) in 82% yield, together with the starting *N*,*N*-dimethylbenzamide (**I**) in 97% yield, as shown in Table 5 (entry 1). The same treatment of a mixture of ethyl benzoate (**1a**–**i**) and *N*,*N*-dimethyl *p*-bromobenzamide (**III**) generated benzonitrile (**2a**) in 72% yield, together with the starting *N*,*N*-dimethyl *p*-bromobenzamide (**III**) in 93% yield (entry 2). Moreover, the treatment of a mixture of ethyl *p*-bromobenzoate (**1d**–**i**) and benzamide (**IV**) with SDBBA-H, followed by the reaction with molecular iodine and aq NH_3 provided *p*-bromobenzonitrile (**2d**) in 64% yield, together with the starting benzamide (**IV**) in 97% yield, and the same treatment of a mixture of ethyl *p*-bromobenzoate (**1d**–**i**) and *N*-methylbenzamide (**V**) gave *p*-bromobenznitrile (**2d**) in 82% yield, together with the starting *N*-methylbenzamide (**V**) in 97% yield. Thus, esters (**1**) in the presence of *N*,*N*-disubstituted amides can be smoothly and selectively converted into the corresponding nitriles (**2**) by the treatment with SDBBA-H, followed by the reaction with molecular iodine in aq NH_3, although *N*,*N*-disubstituted amides in the presence of esters are selectively converted into the corresponding nitriles (**2**) by the treatment with DIBAL-H, followed by the reaction with molecular iodine in aq NH_3. So, we can choose the present method with SDBBA-H and the previous method with DIBAL-H.[10] We believe that SDBBA-H is a direct hydride reducing agent and therefore, more electrophilic esters than amides are selectively reduced to the acetal *O*-Al^{i}Bu$_2$(O^{t}Bu)$^-$ Na$^+$ adducts by SDBBA-H. Once the acetal *O*-Al^{i}Bu$_2$(O^{t}Bu)$^-$ Na$^+$ adducts are formed, they react with molecular iodine in aq NH_3 to generate the corresponding nitriles through the formations of aldehydes, aldemines, and *N*-iodo imines.

Then, the present reaction was used for the same conversion of aliphatic ethyl carboxylates into the corresponding aliphatic nitriles. Thus, ethyl decanoate (**1u**–**i**) was treated with SDBBA-H at 0 °C, followed by the reaction with molecular iodine and aq NH_3. However, a mixture of nitrile, ester, and alcohol was obtained, and the yield of decanenitrile (**2u**) was low, as shown in Table 6 (entries 1–4). To improve the yield of decanenitrile (**2u**), 1,3-diiodo-5,5-dimethylhydantoin (DIH), which is more effective oxidant than molecular iodine, was used, and decanenitrile (**2u**) was obtained in 79% yield (entry 11), after optimization experiments. Based on these conditions, various aliphatic ethyl esters (**1-i**) were treated with SDBBA-H (2.0 equiv) at 0 °C, followed by the reaction with DIH (3.0 equiv) and aq NH_3 to give the corresponding aliphatic nitriles (**2**) in good yields as shown in Table 7. The olefinic group of ethyl *cis*-9-octadecenoate (**1aa**–**i**) is not affected to form the corresponding *cis*-9-octadecenenitrile (**2aa**) in good yield (entry 7). A plausible reaction mechanism is shown in Scheme 1. The initial step

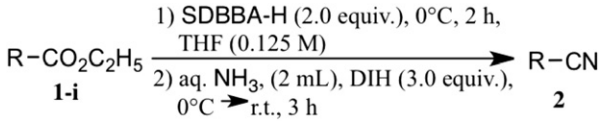
Table 6
Transformation of ethyl decanoate into decanenitrile

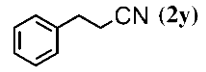
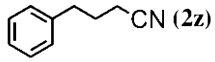
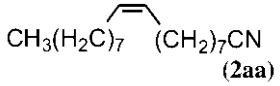
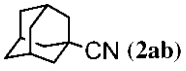


Entry	Iodine source (equiv)	Temp (°C)	Yield (%) (nitrile:ester:alcohol)
1[a]	I_2 (4.1 equiv)	−78 °C	50:12:28
2[b]	I_2 (4.1 equiv)	rt	17:5:14
3	I_2 (4.1 equiv)	40 °C	38:0:9
4	I_2 (4.1 equiv)	60 °C	37:12:6
5	DIH (3.0 equiv)	rt	65:7:8
6	DIH (3.0 equiv)	60 °C	50:3:11
7	DIH (3.0 equiv)	0 °C	46:12:9
8	DIH (3.0 equiv)	15→20 °C	44:0:12
9[c]	DIH (3.0 equiv)	rt	50:17:8
10	DIH (3.0 equiv)	rt	43:0:11
11[d]	DIH (3.0 equiv)	rt	79:0:12

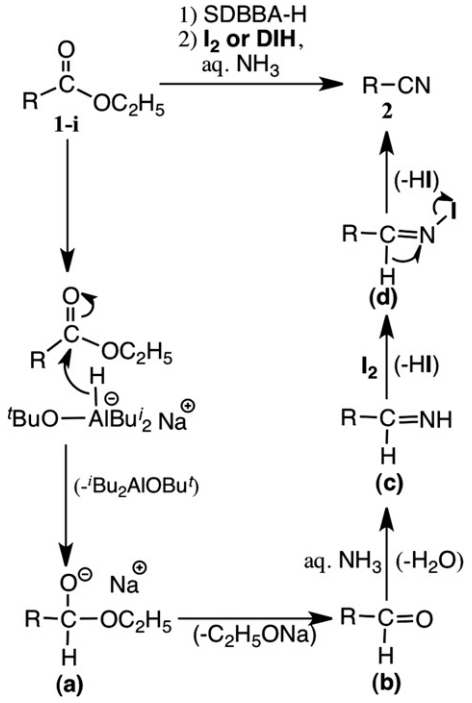
[a] D1BAL-H (1.25 equiv) was used instead of SDBBA-H.
[b] Reaction time was 12 h at the first step.
[c] Reaction was carried out under dark conditions.
[d] DIH was added, then NH_3, aq (2 mL) was added in second step.

Table 7
Transformation of aliphatic esters to aliphatic nitriles



Entry	Product	Yield (%)
1	$CH_3(CH_2)_8CN$ (**2u**)	79
2	$CH_3(CH_2)_{10}CN$ (**2v**)	79
3	$CH_3(CH_2)_{12}CN$(**2w**)	84
4	$CH_3(CH_2)_{14}CN$ (**2x**)	86
5	 CN (**2y**)	76
6	 CN (**2z**)	83
7	 $CH_3(H_2C)_7$ $(CH_2)_7CN$ (**2aa**)	75
8	 CN (**2ab**)	70

is the direct reduction of ethyl ester (**1-i**) by SDBBA-H, to form aldehyde (**b**) via the β-cleavage of acetal (**a**). Aldehyde (**b**) further reacts with aq NH_3 to form imine (**c**). Imine (**c**) further reacts with molecular iodine or DIH in aq NH_3 to form *N*-iodo imine (**d**). Once *N*-iodo imine (**d**) is formed, HI elimination smoothly occurs by the reaction with NH_3 to generate nitrile (**2**). On the other hand, amides do not react with SDBBA-H due to the less electrophilicity of the carbonyl group.



Scheme 1. Plausible reaction mechanism.

3. Conclusion

Various aromatic and aliphatic ethyl esters were smoothly converted into the corresponding aromatic and aliphatic nitriles, respectively, in good yields, with SDBBA-H, followed by the treatment with molecular iodine or DIH in aq NH_3. The present reaction is practical one-pot method for the conversion of both aromatic and aliphatic esters into the corresponding nitriles.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were obtained with JEOL-JNM-ECX400, JEOL-JNM-ECS400, and JEOL-JNM-ECA500 spectrometers. Chemical shifts are expressed in parts per million downfield from TMS in δ units. Mass spectra were recorded on 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 60 (Kanto Kagaku Co.) was used for column chromatography and Wakogel B-5F was used for preparative TLC.

4.2. Typical procedure for conversion of aromatic ethyl esters into aromatic nitriles

NaO^tBu (98% purity, 353 mg, 3.6 mmol) was dried by a vacuum pump for 30 min at room temperature. To a solution of NaO^tBu in THF (3 mL) was added DIBAL-H (1.04 M, 3.27 mL, 3.4 mmol) at 0 °C under argon atmosphere and the obtained mixture was stirred for 1 h at room temperature. Then, ethyl benzoate (150.06 mg, 2.0 mmol) in THF (4 mL) was added to the solution at 0 °C, and the obtained mixture was stirred for 4 h. Finally, aq NH_3 (concentration: 28.0%–30.0%, 4 mL) and I_2 (2.08 g, 4.1 equiv) were added at 0 °C, and the obtained mixture was stirred for 3 h at room temperature. Then the reaction mixture was poured into saturated aq Na_2SO_3 solution (10 mL) and extracted with ethyl acetate (15 mL×3). The organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was treated with flash short column chromatography on silica gel (eluent: hexane/ethyl acetate=9:1) to afford benzonitrile (156.7 mg, 76% yield).

4.3. Typical procedure for conversion of aliphatic ethyl ester into aliphatic nitriles

NaO^tBu (98% purity, 206 mg, 2.1 mmol) was dried by a vacuum pump for 30 min at room temperature. To a solution of NaO^tBu in THF (3 mL) was added DIBAL-H (1.04 M, 1.92 mL, 2.0 mmol) at 0 °C under argon atmosphere and the obtained mixture was stirred for 1 h at room temperature. Then, ethyl decanoate (200.32 mg, 1.0 mmol) in THF (4 mL) was added to the solution at 0 °C, and the obtained mixture was stirred for 2 h. Then, DIH (1.13 g, 3.0 equiv) and aq NH_3 (concentration: 28.0%–30.0%, 2 mL), were added at 0 °C, and the obtained mixture was stirred for 3 h at room temperature. Then, the reaction mixture was poured into saturated aq Na_2SO_3 solution (10 mL) and extracted with ethyl acetate (15 mL×3). The organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was treated with flash short column chromatography on Silica gel (eluent: hexane/ethyl acetate=9:1) to afford decanenitrile (119.5 mg, 79% yield).

*4.3.1. Benzonitrile (**2a**).* Colorless oil (commercial); IR (neat): 2230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.48 (t, 2H, *J*=7.70 Hz),

7.61 (t, 1H, J=7.70 Hz), 7.67 (d, 2H, J=7.70 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=112.43, 118.81, 129.09, 132.13, 132.73.

*4.3.2. 4-Fluorobenzonitrile (**2b**).* Mp 34–35 °C (commercial, mp 35 °C); IR (Nüjol): 2233 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.18 (dd, J_{H-H}=9.1 Hz, J_{H-F}=8.4 Hz, 2H), 7.69 (dd, J_{H-H}=9.1 Hz, J_{H-F}=5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=108.54 (d, J_{C-F}=3.81 Hz), 116.83 (d, J_{C-F}=22.89 Hz), 118.00, 134.66 (d, J_{C-F}=8.58 Hz), 165.01 (d, J_{C-F}=257.49 Hz).

*4.3.3. 4-Chlorobenzonitrile (**2c**).* Mp 92–94 °C (commercial, mp 92 °C); IR (Nüjol): 2225 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.47 (d, 2H, J=8.61 Hz), 7.61 (d, 2H, J=8.61 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=110.77, 117.94, 129.67, 133.35, 139.54.

*4.3.4. 4-Bromobenzonitrile (**2d**).* Mp 114–115 °C (commercial, mp 113 °C); IR (Nüjol): 2223 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.53 (d, 2H, J=8.59 Hz), 7.64 (d, 2H, J=8.59 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=111.23, 118.03, 128.00, 132.63, 133.39.

*4.3.5. 4-Nitrobenzonitrile (**2e**).* Mp 145–147 °C (commercial, mp 147 °C); IR (Nüjol): 2232 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.90 (d, 2H, J=8.90 Hz), 8.37(d, 2H, J=8.90 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=116.77, 118.32, 124.27, 133.45, 150.02.

*4.3.6. 4-Methylbenzonitrile (**2f**).* Colorless oil (commercial); IR (neat): 2228 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.42(s, 3H), 7.27 (d, 2H, J=8.60 Hz), 7.53 (d, 2H, J=8.60 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=21.74, 109.21, 119.07, 129.76, 131.95, 143.63.

*4.3.7. 4-Methoxybenzonitrile (**2g**).* Mp 60–62 °C (commercial, mp 60 °C); IR (Nüjol): 2217 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.86(s, 3H), 6.95 (d, 2H, J=8.38 Hz), 7.59 (d, 2H, J=8.38 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=55.51, 103.94, 114.71, 119.19, 133.94, 162.81.

*4.3.8. 3,4,5-Trimethoxybenzonitrile (**2h**).* Mp 92–94 °C (lit.[12] Mp 92–94 °C); IR (Nüjol): 2224 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.88 (s, 6H), 3.90 (s, 3H), 6.87 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=56.33, 60.99, 106.65, 109.39, 118.90, 142.29, 153.51.

*4.3.9. Piperonylonitrile (**2i**).* Mp 90–92 °C (commercial, mp 91–93 °C). IR (Nüjol): 2222 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.07 (s, 2H), 6.87 (d, 1H, J=8.15 Hz), 7.04 (d, 1H, J=1.59 Hz), 7.22 (dd, 1H, J=8.15, 1.59 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=102.18, 104.96, 109.11, 111.40, 118.87, 128.21, 148.02, 151.51.

*4.3.10. 4-(tert-Butyl)benzonitrile (**2j**).* Colorless oil (commercial); IR (neat): 2227 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 9H), 7.46 (d, 2H, J=8.60 Hz), 7.57 (d, 2H, J=8.60 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.88, 35.20, 109.24, 119.11, 126.11, 131.90, 156.58.

*4.3.11. 4-(Dimethyl)aminobenzonitrile (**2k**).* Mp 75–77 °C (commercial, mp 75 °C). IR (Nüjol): 2210 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.04 (s, 6H), 6.64 (d, 2H, J=7.00 Hz), 7.46 (d, 2H, J=7.00 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=39.91, 97.35, 111.36, 120.71, 133.27, 152.43.

*4.3.12. 3-Methylbenzonitrile (**2l**).* Colorless oil (commercial); IR (neat): 2229 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.39 (s, 3H), 7.33–7.37 (m, 1H), 7.40 (d, 1H, J=8.05 Hz), 7.43–7.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=21.01, 112.11, 118.90, 128.88, 129.13, 132.33, 133.53, 139.11.

*4.3.13. 2-Methylbenzonitrile (**2m**).* Colorless oil (commercial); IR (neat): 2225 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.55 (s, 3H), 7.27 (t, 1H, J=7.73 Hz), 7.32 (d, 1H, J=7.73 Hz), 7.48 (t, 1H, J=7.73 Hz), 7.59 (d, 1H, J=7.73 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=20.43, 112.74, 118.10, 126.17, 130.19, 132.47, 132.59, 141.90.

*4.3.14. 2-Iodobenzonitrile (**2n**).* Mp 53–55 °C (commercial, mp 55 °C); IR (Nüjol): 2224 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.28 (t, 1H, J=7.70 Hz), 7.44 (t, 1H, J=7.70 Hz), 7.60 (d, 1H, J=7.70 Hz), 7.91 (d, 1H, J=7.70 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=98.34, 119.26, 120.58, 128.24, 133.64, 134.20, 139.49.

*4.3.15. 1-Cyanonaphthalene (**2o**).* Mp 35–36 °C (commercial, mp 36–38 °C); IR (neat): 2222 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.51 (dd, 1H, J=7.25, 8.38 Hz), 7.61 (t, 1H, J=8.38 Hz), 7.68 (t, 1H, J=8.38 Hz), 7.88–7.93 (m, 2H), 8.06 (d, 1H, J=8.38 Hz), 8.22 (d, 1H, J=8.38 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=110.09, 117.75, 124.84, 125.05, 127.47, 128.52, 128.59, 132.26, 132.55, 132.83, 133.21.

*4.3.16. 2-Cyanonaphthalene (**2p**).* Mp 66–67 °C (commercial, mp 67 °C). IR (Nüjol): 2225 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.58–7.68 (m, 3H), 7.87–7.95 (m, 3H), 8.24 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=110.09, 117.75, 124.84, 125.05, 127.47, 128.52, 128.59, 132.26, 132.55, 132.83, 133.21.

*4.3.17. 4-Cyanobiphenyl (**2q**).* Mp 84–86 °C (commercial, mp 87 °C). IR (Nüjol): 2226 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.42 (t, 1H, J=7.25 Hz), 7.48 (t, 2H, J=7.25 Hz), 7.59 (d, 2H, J=7.25 Hz), 7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=110.90, 118.91, 127.20, 127.71, 128.63, 129.09, 132.57, 139.16, 145.65.

*4.3.18. 3-Cyanopyridine (**2r**).* Mp 49–51 °C (commercial, mp 50 °C); IR (Nüjol): 2229 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.46 (ddd, 1H, J=7.95, 4.87, 0.86 Hz), 7.99 (dt, 1H, J=7.95, 2.00 Hz), 8.83(dd, 1H, J=4.87, 2.00 Hz), 8.91 (sd, 1H, J=2.00 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=110.13, 116.46, 123.59, 139.20, 152.47, 152.98.

*4.3.19. 2-Cyanothiophene (**2s**).* Colorless oil (commercial); IR (neat): 2222 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.14 (dd, 1H, J=4.98, 3.85 Hz), 7.62 (dd, 1H, J=4.98, 1.13 Hz), 7.64 (dd, 1H, J=3.85, 1.13 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=109.80, 114.14, 127.56, 132.51, 137.34.

*4.3.20. Decanenitrile (**2u**).* Colorless oil (commercial); IR (Nüjol): 2247 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, 3H, J=6.90 Hz), 1.22–1.29 (m, 10H), 1.41–1.48 (m, 2H), 1.62–1.69 (m, 2H), 2.34 (t, 2H, J=7.10 Hz): ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1, 17.1, 22.6, 25.3, 28.6, 28.7, 29.1, 29.2, 31.8, 119.9.

*4.3.21. Dodecanenitrile (**2v**).* Colorless oil (commercial); IR (Nüjol): 2246 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.88 (t, 3H, J=6.90 Hz), 1.24–1.40 (m, 14H), 1.40–1.48 (m, 2H), 1.66 (quintet, 2H, J=7.16 Hz), 2.33 (t, 2H, J=7.16 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.09, 17.11, 22.65, 25.36, 28.65, 28.75, 29.28(d), 29.48, 29.53, 31.86, 119.86.

*4.3.22. Tetradecanenitrile (**2w**).* Colorless oil (commercial); IR (Nüjol): 2247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.88 (t, 3H, J=6.70 Hz), 1.24–1.34 (m, 18H), 1.41–1.48 (m, 2H), 1.62–1.69 (m, 2H), 2.33 (t, 2H, J=7.20 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.08, 17.08, 22.65, 25.34, 28.63, 28.72, 29.26, 29.31, 29.46, 29.55, 29.60(d), 31.88, 119.82.

*4.3.23. Hexadecanenitrile (**2x**).* Oil. IR (neat): 2247 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, 3H, J=6.78 Hz), 1.24–1.34 (m, 22H), 1.40–1.49 (m, 2H), 1.57–1.70 (m, 2H), 2.33 (t, 2H, J=7.13 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.08, 17.08, 22.65, 25.34, 28.63, 28.73, 29.27, 29.32, 29.46, 29.56, 29.61(q), 31.89, 119.82.

*4.3.24. 3-Phenylpropanenitrile (**2y**).* Colorless oil (commercial); IR (neat): 2247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.59 (t, 2H,

J=7.45 Hz), 2.93 (t, 2H, J=7.45 Hz), 7.22 (d, 2H, J=8.30 Hz), 7.26 (t, 1H, J=8.30 Hz), 7.33 (t, 2H, J=8.30 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=19.20, 31.42, 119.04, 127.10, 128.15, 128.74, 137.97.

*4.3.25. 4-Phenylbutanenitrile (**2z**).* Colorless oil (commercial); IR (neat): 2247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.98 (m, 2H), 2.32 (t, 2H, J=7.20 Hz), 2.65 (t, 2H, J=7.20 Hz), 7.15–7.21 (m, 3H), 7.31 (t, 2H, J=7.20 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=16.26, 26.81, 34.26, 119.42, 126.40, 128.35, 128.56, 139.63.

*4.3.26. cis-9-Octadecenenitrile (**2aa**).* Colorless oil (commercial); IR 1654, 2247 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3)=0.88 (t, J=6.9 Hz, 3H), 1.26–1.37 (m, 20H), 1.63–1.69 (m, 2H), 1.99–2.03 (m, 4H), 2.33 (t, J=7.2 Hz, 2H), 5.31–5.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$)=14.09, 17.08, 22.64, 25.30, 27.04, 27.17, 28.59, 28.63, 28.87, 29.28(d), 29.48, 29.53, 29.70, 31.86, 111.82, 129.50, 130.08; HRMS (APPI) calcd for $C_{18}H_{33}N$ M=263.2608, obsd M^+=263.2604.

*4.3.27. 1-Cyanoadamantane (**2ab**).* Mp 192–195 °C (commercial, mp 195 °C). IR (neat): 2229 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.70–1.78 (m, 6H), 2.04–2.08 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.0, 30.1, 35.7, 39.8, 125.3.

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References and notes

1. Fabiani, M. E. *Drug News Perspect.* **1999**, *12*, 207.
2. (a) Friedrick, K.; Wallensfels, K. The Chemistry of the Cyano Group In. *Rapoport, Z., Ed.; Wiley-Interscience: New York, NY, 1970; (b) North, M. Comprehensive Organic Functional Group Transformation In. Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; (c) Murahashi, S.-I. Synthesis from nitriles with retention of the cyano group In. Science of Synthesis*; Georg Thieme: Stuttgart, 2004; Vol. 19, pp 345–402; (d) Collier, S. J.; Langer, P. Application of nitriles as reagents for organic synthesis with loss of the nitrile functionality In. *Science of Synthesis*; Georg Thieme: Stuttgart, 2004; Vol. 19, pp 403–425.
3. *Comprehensive Organic Transformation*; Larock, R. C., Ed.; VCH: New York, NY, 1989; pp 976–993.
4. (a) Heck, M.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1996**, *61*, 6486; (b) Nakajima, N.; Ubukata, M. *Tetrahedron Lett.* **1997**, *38*, 2099; (c) Bose, D. S.; Jayalakshmi, B. *J. Org. Chem.* **1999**, *64*, 1713; (d) Ruck, R. T.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 5375; (e) Kuo, C.; Zhu, J.; Wu, J.; Chu, C.; Yao, C.; Shia, K. *Chem. Commun.* **2007**, 301; (f) Hanada, S.; Motoyama, Y.; Nagashima, H. *Eur. J. Org. Chem.* **2008**, *24* 1633, 2650, and 4097.
5. Sandmeyer, T. *Chem. Ber.* **1884**, *17*, 1633.
6. (a) Sharman, W. M.; Van Lier, J. E. In *Porphyrin Handbook*; Kadish, E., Smith, K. M., Guilard, R., Eds.; Academic: New York, NY, 2003; Vol. 15, p 1; (b) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508; (c) Littke, A.; Soumeillant, M.; Kaltenbach, R. F., III; Cherney, R. J.; Tarby, C. M.; Kiau, S. *Org. Lett.* **2007**, *9*, 1711; (d) Martin, M. T.; Liu, B.; Cooley, B. E., Jr.; Eaddy, J. F. *Tetrahedron Lett.* **2007**, *48*, 2555; (e) Nandurkar, N. S.; Bhanage, B. M. *Tetrahedron* **2008**, *64*, 3655; (f) Iqbal, Z.; Lyubimtsev, A.; Hanack, M. *Synlett* **2008**, 2287; (g) Chen, G.; Weng, J.; Zheng, Z.; Zhu, X.; Cai, Y.; Cai, J.; Wan, Y. *Eur. J. Org. Chem.* **2008**, 3524; (h) Schareina, T.; Zapf, A.; Cotte, A.; Müller, N.; Beller, M. *Synthesis* **2008**, 3351; (i) Buono, F. G.; Chidambaram, R.; Mueller, R. H.; Waltermire, R. E. *Org. Lett.* **2008**, *10*, 5325; (j) Chattopadhyay, K.; Dey, R.; Ranu, B. C. *Tetrahedron Lett.* **2009**, *50*, 3164; (k) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 1052; (l) DeBlase, C.; Leadbeater, N. E. *Tetrahedron* **2010**, *66*, 1098.
7. (a) Wood, J. L.; Khatri, N. A.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 4907; (b) Theodore, L. J.; Nelson, W. L. *J. Org. Chem.* **1987**, *52*, 1309; (c) Hwu, J. R.; Hsu, C. H.; Wong, F. F.; Chung, C.; Hakimelahi, G. H. *Synthesis* **1998**, 329.
8. Reviews: (a) Togo, H.; Iida, S. *Synlett* **2006**, 2159; (b) Togo, H. *J. Synth. Org. Chem.* **2008**, *66*, 652.
9. (a) Mori, N.; Togo, H. *Synlett* **2004**, 880; (b) Mori, N.; Togo, H. *Synlett* **2005**, 1456; (c) Mori, N.; Togo, H. *Tetrahedron* **2005**, *61*, 5915; (d) Ishihara, M.; Togo, H. *Synlett* **2006**, 227; (e) Iida, S.; Togo, H. *Synlett* **2006**, 2633; (f) Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474; (g) Iida, S.; Togo, H. *Tetrahedron* **2007**, *63*, 8274; (h) Iida, S.; Togo, H. *Synlett* **2007**, 407; (i) Iida, S.; Togo, H. *Synlett* **2008**, 1639; (j) Iida, S.; Ohmura, R.; Togo, H. *Tetrahedron* **2009**, *65*, 6257.
10. Suzuki, Y.; Yoshino, T.; Moriyama, K.; Togo, H. *Tetrahedron* **2011**, *67*, 3809.
11. Song, J. I.; An, D. K. *Chem. Lett.* **2007**, *36*, 886.
12. Ren, Y. *Tetrahedron Lett.* **2009**, *50*, 4595.