Studies on Effective Molecular Conversion from Carboxylic Acids to Alkyl Bromides and Alkyl Iodides with an Indium Compound and a Hydrosilane and Its Applications

(インジウム化合物とヒドロシランによる
カルボン酸から臭化アルキル及び
ヨウ化アルキルへの効率的分子変換法と
その応用に関する研究)

東京理科大学大学院　理工学研究科
工業化学専攻　博士後期課程

森谷　敏光

Preface

The studies presented in this thesis have carried out under the direction of Associate Professor Dr. Norio Sakai at the Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science (RIKADAI) during 2011-2014.

The objects of this thesis are the studies on effective molecular conversion from carboxylic acids to alkyl bromides and alkyl iodides with an indium compound and a hydrosilane and its applications. The author hopes that this basic work described in this thesis contributes to the further development of novel indium(III) catalyzed functional group interconversions in organic chemistry, pharmaceutical chemistry, and material science.

Toshimitsu Moriya

Department of Pure and Applied Chemistry

Faculty of Science and Technology

Tokyo University of Science (RIKADAI)

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General Introduction

General

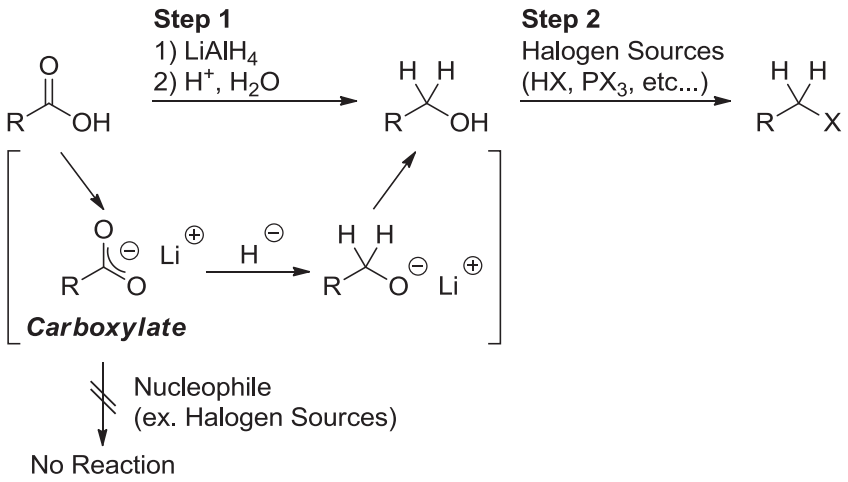
Functional group interconversions with carbonyl compounds, such as aldehydes, ketones, esters, and carboxylic acids, have been occupied a central and important position of synthetic organic chemistry.[1] Among them, a reductive functional group interconversion from carboxylic acids to alkyl halides has attracted considerable attention in author's field because the produced alkyl halides can be easily converted to organic chemicals such as Grignard reagents and organolithium compounds or highly valuable organic compounds such as amines, ethers, and nitriles.[2] Also, because carboxylic acids generally show tolerance to the common reducing reagents, achievement of the functional group interconversion with this reducible reagent is of interest from the viewpoint of molecular conversion.

A conventional method for the preparation of alkyl halides from carboxylic acids generally requires the following troublesome two steps (Scheme 1): first, the carbonyl moiety must be reduced to a primary alcohol with a strong reducing agent, such as lithium aluminum hydride ($LiAlH_4$); second, the primary alcohol obtained is treated with a hydrogen halide or a phosphorus halide.[3] However, the transformation with $LiAlH_4$ declines chemoselectivity toward other functional groups because of its high reducing ability and moisture sensitivity.

On the other hand, a direct preparation of alkyl halides from carboxylic acids is a challenging problem, because the carboxylate, which is generated from a

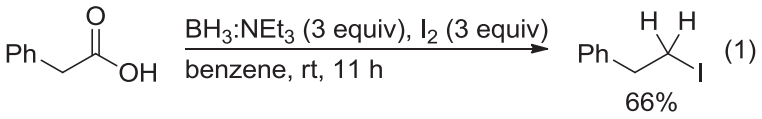
carboxylic acid by the treatment of $LiAlH_4$, has low reactivity and cannot react to nucleophiles except for a hydride ion. Therefore, single step or one-pot procedure for transformation from carboxylic acids to alkyl halides has been required recently.

Scheme 1. Conventional Method for Reduction of Carboxylic Acids

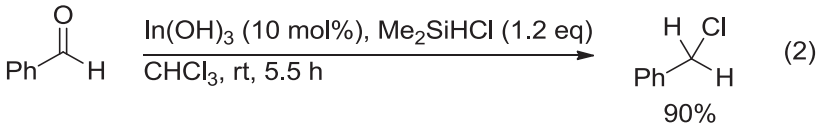


Single Step Procedure for Alkyl Halides from Carbonyl Compounds

Although a number of methods have been developed for the synthesis of alkyl bromides or alkyl iodides, a single-step bromination or iodination from other functional groups has not been studied extensively.[4] Especially, the transformation of carbonyl compounds, such as aldehydes and ketones, into their corresponding organic halides represents one of the most important examples of a functional group interconversion in organic synthesis.[5] However, a direct conversion from carboxylic acids has not yet been studied, and only one research was reported in author's knowledge (Eq. 1).[6]



On the other hand, Yasuda and Baba's group reported the direct interconversion of aldehydes and ketones to alkyl halides by the indium(III) catalyst and halosilane combination system (Eq. 2).[7] This reaction system tolerates some functional groups such as nitriles, halogens, esters, and hydroxy carbonyl groups. However, the substrate scope of carbonyl compounds is limited to benzoyl groups, naphthyl carbonyl groups, and aralkyl ketones.

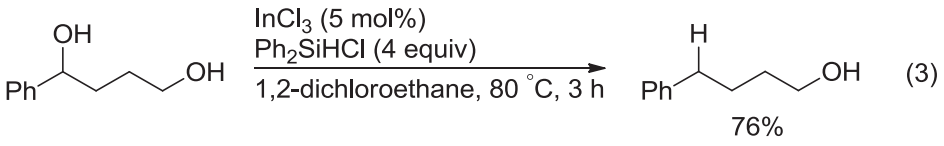


(2)

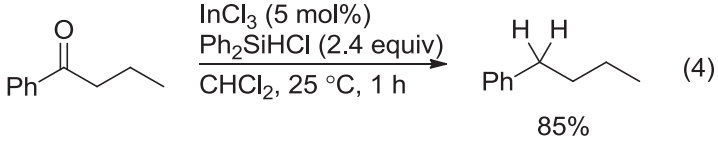
Reduction by Combination of Indium(III) Catalyst and Hydrosilanes

Indium(III) salts are stable to air and moisture, and tolerate some functional groups containing such as N, S, O atoms due to the low heterophilicity of the indium (III) salts.[8] The reductive conversion of various functional groups by a combination of indium(III) salts and hydrosilanes have been developed by several groups.

For example, Yasuda and Baba's group has also reported the $InCl_3$-Ph_2SiHCl combination reaction such as the reduction of secondary or tertiary alcohols (Eq. 3),[9] and the deoxygenation of carbonyl moiety of aryl ketones (Eq. 4).[10]

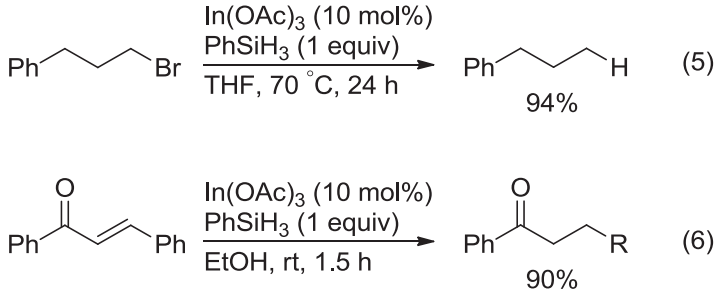


(3)

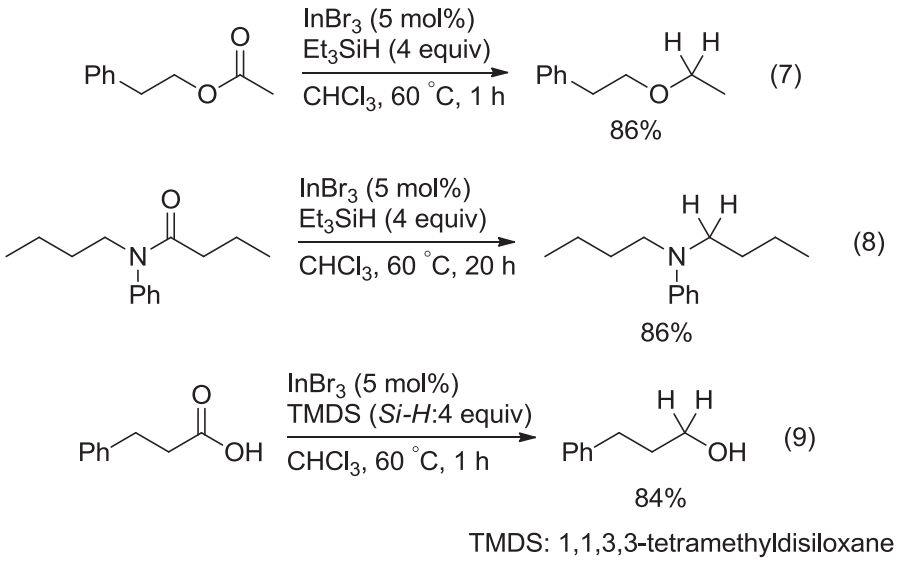


(4)

Miura and Hosomi's group has reported the dehalogenation of organic halides (Eq. 5),[11] and the 1,4-reduction of enones (Eq. 6)[12] using the $In(OAc)_3$-$PhSiH_3$ combination reaction system.

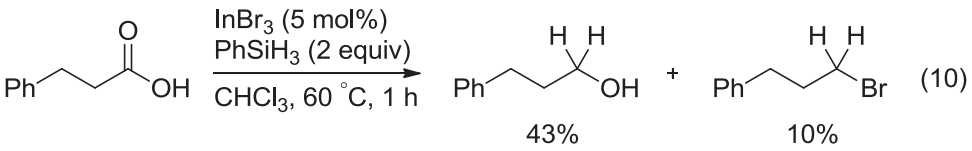


Sakai's group developed the reducing system with $InBr_3$ and Et_3SiH or 1,1,3,3-tetramethyldisiloxane (TMDS) to undertake the deoxygenation of esters (Eq. 7)[13], amides (Eq. 8),[14] and carboxylic acids (Eq. 9),[15] leading to the preparation of ethers, secondary amines, and primary alcohols, respectively. With this reducing reagent, the reductive functional group interconversions of several reducing reagents, such as ketones and acetals, and esterification of carboxylic acids have also been achieved.[16,17]

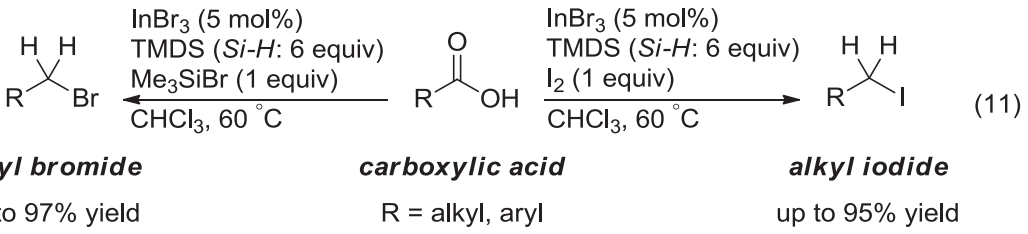


This Work

In the reduction of carboxylic acids to primary alcohols by the $InBr_3$ and hydrosilane combination system, it was found that the product was not only primary alcohols but also alkyl bromides (Eq. 10).



As a result of various experiments, the author found that the unprecedented direct preparation of alkyl bromides and alkyl iodides via the indium(III)-catalyzed reduction of carboxylic acids with a hydrosilane and a bromine or iodine source (Eq. 11).[18]



Additionally, the author showed that this reaction system could be applied to the one-pot conversion from aliphatic carboxylic acids to various compounds, such as alkyl chlorides, fluorides, amines, and nitriles.[18b,19]

This thesis dwells on the conversion from carboxylic acids to alkyl bromide and alkyl iodides treated by indium(III) compounds, hydrosilanes, and bromine or iodine sources, and the application to the one-pot synthesis of various compounds from carboxylic acids.

Chapter 1 describes the detail of the indium(III)-catalyzed reductive bromination or iodination of a variety of carboxylic acids with 1,1,3,3-tetramethyldisiloxane (TMDS) and a source of bromine or iodine. And the author elucidated the reaction mechanism by the time course of ^{1}H and ^{13}C NMR monitoring experiments and the corresponding stepwise reactions.

Chapter 2 deals with the one-pot synthesis of alkyl halides, amine derivatives, and nitrile derivatives as the application of indium(III)-catalyzed reductive bromination or iodination.

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Chapter 1.

Indium(III)-Catalyzed Conversion from Carboxylic Acids to Alkyl Bromide and Alkyl Iodides

Introduction

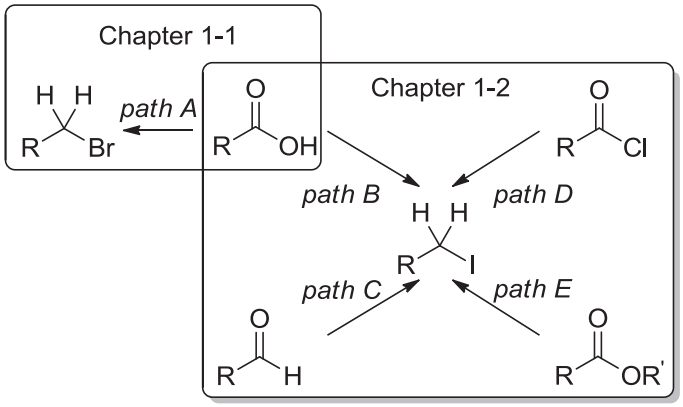
Alkyl halides are useful building blocks that can be converted to various compounds such as Grignard reagents, organic lithium compounds, amines, ethers, and nitriles.[1,2] Although a number of procedures have been developed for the synthesis of alkyl halides, the one-pot, single-step transformation from carboxylic acids have not been studied extensively. Achievement of the method is quite valuable to the aspects of decreasing the synthetic steps and the environmental load of organic synthesis.

To date, the indium(III)-catalyzed reductive functional group transformation of alcohols,[4] ketones,[5] aldehydes,[5] and acyl halides,[6] the radical reduction of organic halides,[7] and the 1,4-reduction of enones,[8] have been developed by several groups. Also, Sakai's group developed the reducing system with indium tribromide ($InBr_3$) and triethylsilane (Et_3SiH) to undertake the deoxygenation of carboxylic acids and amides, leading to the preparation of primary alcohols and secondary amines.[9,10] However, the reductive halogenation of carboxylic acid leading to alkyl halide with indium(III) salts and hydrosilane has not yet been reported regardless of the report

about many reductive functional group interconversions.

In this chapter, first, the author reports the unprecedented direct preparation of alkyl bromides via the indium(III)-catalyzed reduction of carboxylic acids with a hydrosilane and a bromine source (path A in Scheme 1). Second, as an extension of reductive bromination of carboxylic acids, the author examined the direct preparation of alkyl iodides via the indium catalyzed reduction of carboxylic acids and derivatives, such as aldehydes, acyl halides, and esters, with a siloxane and an iodine source (paths B−E). Finally, the author elucidated the reaction mechanism of a reductive transformation series from a carboxylic acid to an alkyl halide by the NMR monitoring of the reaction system.

Scheme 1. $InBr_3$-Catalyzed Reductive Bromination and Iodination of Carboxylic Acids and Its Derivatives



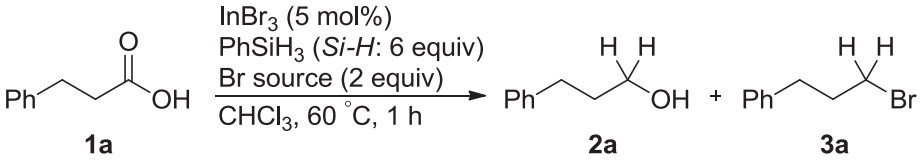
1-1. Indium(III)-Catalyzed Reductive Bromination

Optimization of the Reductive Bromination of Carboxylic Acids

When 3-phenylpropanoic acid (**1a**) was initially treated with $InBr_3$ (5 mol%) and $PhSiH_3$ (*Si–H*: 6 equiv) in $CHCl_3$ at 60 ˚C, an unexpected alkyl bromide **3a** was obtained in a 10% yield with 43% of the primary alcohol **2a** (Table 1, entry 1).

Interestingly this result showed that a counterion of the indium catalyst functioned as a bromine source. Also this type of direct preparation of an alkyl bromide is quite an unusual example. Thus, improvement of the bromination yield was attempted with several bromine sources. For example, the use of a common bromine source (2 equiv for 3-phenylpropanoic acid (**1a**), such as Br_2, PBr_3, and *N*-bromosuccinimide (NBS), resulted in the formation of a complex mixture (entries 2-4). In the case with lithium bromide (LiBr) or tetrabutylammonium bromide (TBABr), the reduction did not proceed (entries 5 and 6). When the counterion of a copper salt was used as a bromine source, the yield of the alkyl bromide **3a** was increased to 32% (entry 7). It was noted that when the reaction was carried out with a typical silyl halide, trimethylbromosilane (Me_3SiBr), the bromination proceeded cleanly, and the yield of the corresponding alkyl bromide **3a** was remarkably improved to 89% (entry 8).

Table 1. Examination of Bromine Sources[a]



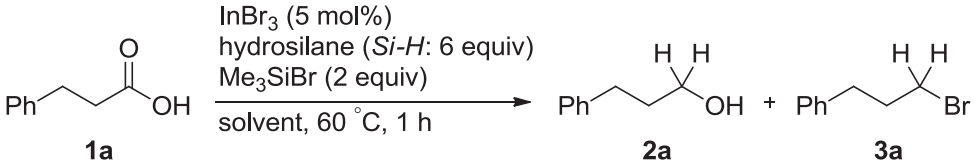
1a **2a** **3a**

		yield (%)[b]	
entry	Br source	**2a**	**3a**
1	none	43	10
2	Br_2	complex mixture	
3	PBr_3	complex mixture	
4	NBS	complex mixture	
5	LiBr	no reaction	
6	TBABr	no reaction	
7	$CuBr_2$	ND[c]	32
8	Me_3SiBr	ND[c]	89
9	Et_3SiBr	ND[c]	69

[a] The reaction was carried out with 3-phenylpropanoic acid (**1a**) (0.6 mmol), $InBr_3$ (5 mol%), $PhSiH_3$ (2 equiv), and a Br source (2 equiv) in $CHCl_3$ at 60 °C for 1 h. [b] NMR yield. [c] ND: not detected.

The use of triethylbromosilane (Et_3SiBr) also showed a moderate effect (entry 9). Table 2 shows the details of the optimal conditions for hydrosilanes and solvents. First, when 3-phenylpropanoic acid (**1a**) was treated with 5 mol % $InBr_3$, 6 equiv (*Si–H*) of $PhSiH_3$, and 2 equiv of Me_3SiBr in $CHCl_3$ at 60 °C, the corresponding alkyl bromide **3a** was obtained in 89% yield (Table 2, entry 1). The reactions with dimethyl(phenyl)silane ($PhMe_2SiH$), methyldiphenylsilane (Ph_2MeSiH), and Et_3SiH resulted in a significant decrease in the yield of **3a** (entries 2-4). When the reaction was conducted with triethoxysilane [$(EtO)_3SiH$], the corresponding bromide **3a** was

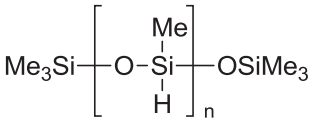
Table 2. Reaction Conditions for Reductive Bromination of Carboxylic Acid **1a**[a]



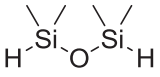
1a **2a** **3a**

			yield (%)[b]	
entry	hydrosilane	solvent	**2a**	**3a**
1	$PhSiH_3$	$CHCl_3$	ND[d]	89
2	$PhMe_2SiH$	$CHCl_3$	ND[d]	21
3	Ph_2MeSiH	$CHCl_3$	ND[d]	19
4	Et_3SiH	$CHCl_3$	ND[d]	36
5	$(EtO)_3SiH$	$CHCl_3$	no reaction	
6	PMHS	$CHCl_3$	ND[d]	94
7	TMDS	$CHCl_3$	ND[d]	99(96)
8	TMDS	toluene	ND[d]	99
9	TMDS	THF	no reaction	
10	TMDS	CH_3CN	no reaction	
11	TMDS	MeOH	no reaction	
12	TMDS	DMF	no reaction	
13[c]	TMDS	$CHCl_3$	ND[d]	99

[a] The reaction was carried out with **1a** (0.6 mmol), $InBr_3$ (5 mol%), hydrosilane (*Si-H:* 6 equiv), and Me_3SiBr (2 equiv) at 60 °C for 1 h. [b] NMR (isolated) yield. [c] Me_3SiBr (1 equiv) was used. [d] ND: not detected.



PMHS : Polymethyl(hydro)siloxane



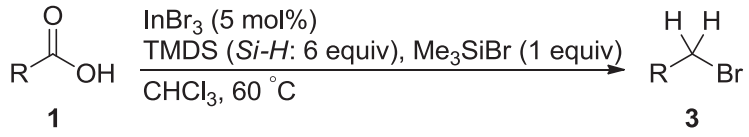
TMDS : 1,1,3,3-Tetramethyldisiloxane

not obtained at all (entry 5). In contrast, ethereal hydrosilanes such as polymethyl(hydro)siloxane (PMHS) and 1,1,3,3-tetramethyldisiloxane (TMDS) were very effective, and the corresponding bromide **3a** was obtained in excellent yield (entries 6 and 7). The screening of hydrosilanes for the bromination of **1a** identified TMDS as the optimal hydrosilane source. The solvent effect was remarkable for this reaction. The use of chloroform and toluene resulted in satisfactory bromination of the carboxylic acid (entries 7 and 8). However, the reaction did not proceed at all in tetrahydrofuran (THF), acetonitrile (CH_3CN), methanol (MeOH), or dimethylformamide (DMF) (entries 9-12). The bromination proceeded in quantitative yield even when 1 equiv of Me_3SiBr was used (entry 13). Consequently, the results of our examinations showed that the optimal conditions for the bromination of carboxylic acid **1a** are $InBr_3$ (5 mol%), TMDS (*Si–H*: 6 equiv), and Me_3SiBr (1 equiv) in $CHCl_3$ at 60 °C.

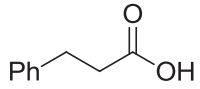
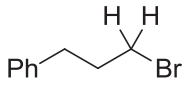
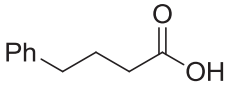
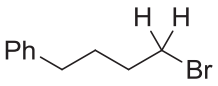
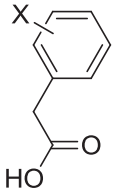
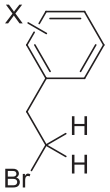
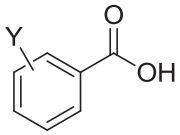
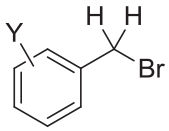
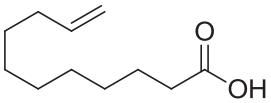
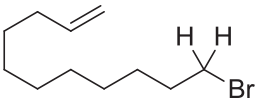
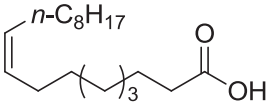
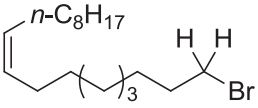
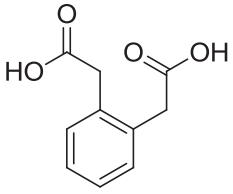
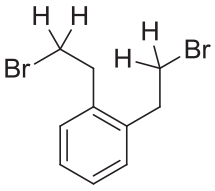
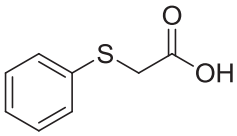
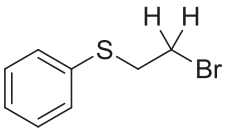
Substrate Scope of the Reductive Bromination of Carboxylic Acids

To generalize this reaction, the direct bromination of various carboxylic acids was carried out under optimized conditions (Table 3). The direct bromination of aliphatic carboxylic acids **1a** and **1b**, with different lengths of the alkyl chain, was completed in a short time and produced the corresponding bromides **3a** and **3b** in excellent yields (entries 1 and 2). Functional groups such as a methyl, halogens, and a hydroxy group were tolerated under the reducing conditions (entries 3-7). The substrate **1h** with a nitro group gave only 3-(4-nitrophenyl)propanol in a 49% yield without the desired bromide **3h** (entry 8). Also, a remarkable substituent effect was observed for an aromatic carboxylic acid. For example, the use of benzoic acid **1i**

Table 3. $InBr_3$-Catalyzed Reductive Bromination of Carboxylic Acids[a]



1 **3**

entry	carboxylic acid		product		time (h)	yield (%)[b]
1		**1a**		**3a**	1	96
2		**1b**		**3b**	4	97
3		**1c**		X = *o*-Me **3c**	1	91
4		**1d**		X = *p*-Cl **3d**	2	95
5		**1e**		X = *p*-Br **3e**	1	95
6		**1f**		X = *o*-I **3f**	1	92
7		**1g**		X = *p*-OH **3g**	1	90
8		**1h**		X = *p*-NO_2 **3h**	1	0[c]
9		**1i**		Y = *p*-OMe **3i**	5	NR[d]
10		**1j**		Y = *p*-Cl **3j**	1	86
11		**1k**		Y = *p*-CH_3 **3k**	2	85
12		**1l**		**3l**	0.5	80
13		**1m**		**3m**	0.5	82
14[e]		**1n**		**3n**	1	89
15		**1o**		**3o**	1	93

[a] The reaction was carried out with carboxylic acid **1** (0.6 mmol), $InBr_3$ (5 mol%), TMDS (*Si-H*: 6 equiv), and Me_3SiBr (1 equiv) in $CHCl_3$ at 60 °C. [b] Isolated yield. [c] 3-(4-Nitrophenyl)propanol was obtained in a 49% yield. [d] NR: no reaction. [e] $InBr_3$ (10 mol%), TMDS (*Si-H*: 12 equiv) and Me_3SiBr (2 equiv) were employed.

with an electron-donating group, a methoxy group, did not produce the expected bromide **3i** (entry 9). When the reductive bromination of **1a** was conducted in the presence of methoxybenzene (1 equiv), a decrease in the yield (60%) of the alkyl bromide **2a** was observed. Although there was no clear explanation for this result, the indium catalyst preferentially coordinated to the methoxy group on the benzene ring to retard the activation of the carbonyl group. In contrast, when the reaction was conducted with benzoic acids **1j** and **1k**, which have an electron-withdrawing group, a chloride or a trifluoromethyl group, the corresponding bromides **3j** and **3k** were obtained in good yields (entries 10 and 11). These results suggested that the electrophilicity of the carbonyl group was reduced by the electron-donating effect of the methoxy group to retard the subsequent reduction. The carboxylic acids bearing a terminal or internal alkene gave the corresponding bromides **3l** and **3m** in good yields (entries 12 and 13). The bromination of dicarboxylic acid **1n** was effectively achieved by double doses of the reagent (entry 14). This reductive bromination system was applicable to phenylthioacetic acid (**1o**), giving the corresponding sulfide **3o** in an excellent yield (entry 15). On the other hand, the bromination of the substrate containing a heterocyclic compound, such as furan, thiophene, and pyridine, did not proceed at all.

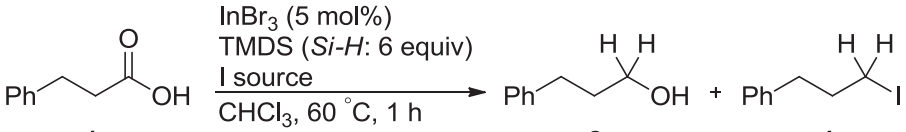
1-2. Indium(III)-Catalyzed Reductive Iodination

Optimization of Reductive Iodination of Carboxylic Acids

To apply this procedure to a reductive iodination, several iodine sources were examined. When trimethyliodosilane (Me_3SiI), which was prepared *in-situ* from iodine and hexamethyldisilane,[11] was used, the corresponding iodide **4a** was obtained in quantitative yield (Table 4, entry 1). However, when 1 equiv of

molecular iodine was used, an excellent yield of the corresponding iodide **4a** was obtained (entry 2). This result emphatically showed that the iodosilane was generated *in-situ* and that the species behaved as an iodide anion source in the iodination series.[12] When 0.5 equiv of I_2 was used, a good yield of the corresponding iodide was obtained (entry 3). In short, these results showed that the iodide cation *in-situ*-generated in the reaction mixture was efficiently reduced to an iodo anion in the reaction. Other iodine sources, such as copper(I) iodide and potassium iodide, were ineffective for this reductive iodination (entries 4 and 5). From the viewpoints of experimental handling and cost, molecular iodine was a more useful iodine source than Me_3SiI and thus was the best iodine source used in this reaction.

Table 4. Reaction Conditions for Reductive Iodination of Carboxylic Acid **1a**[a]



1a **2a** **4a**

		yield (%)[b]	
entry	I source (equiv)	**2a**	**4a**
1	Me_3SiI (1)	ND[c]	99
2	I_2 (1)	ND[c]	98
3	I_2 (0.5)	ND[c]	86
4	CuI (1)	88	8
5	KI (1)	no reaction	

[a] The reaction was carried out with **1a** (0.6 mmol), $InBr_3$ (5 mol%), TMDS (*Si-H*: 6 equiv), and the indicated amount of an iodine source in $CHCl_3$ at 60 °C for 1 h. [b] NMR yield. [c] ND: not detected.

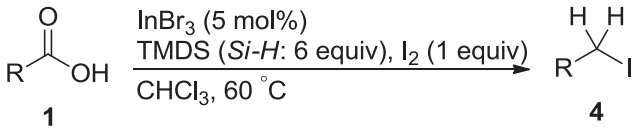
Substrate Scope of Reductive Iodination of Carboxylic Acids

With the optimal conditions, the scope of the direct iodination of various carboxylic acids was investigated (Table 5). The iodination of the aliphatic carboxylic acid **1a** was complete within 1 h and afforded the corresponding iodide

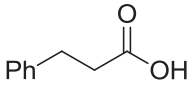
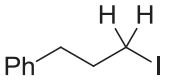
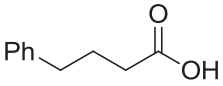
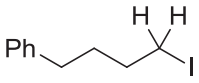
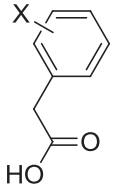
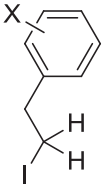
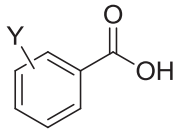
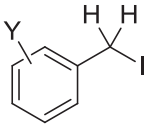
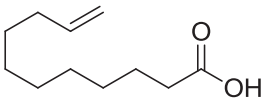
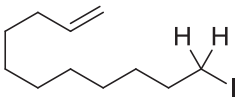
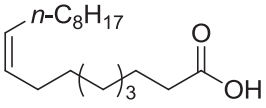
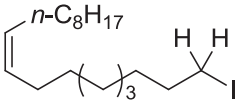
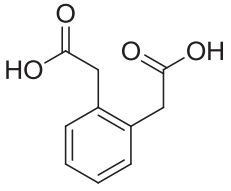
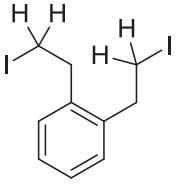
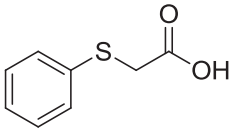
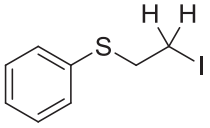
4a in a high yield (entry 1). However, when 4-phenylbutanoic acid (**1b**) was used, the intramolecular cyclization product 1,2,3,4-tetrahydronaphthalene (**4b'**) was obtained as the major product rather than the desired alkyl iodide **4b** (entry 2). It was suggested that although the iodination of carboxylic acid **1b** was rapidly completed, $InBr_3$, which remained intact in the reaction mixture, further accelerated the annulation of the intermediate, alkyl iodide **4b**. The reducing system did not affect functional groups on the benzene ring, such as a methyl group, halogens, and a hydroxy group (entries 3-7). Carboxylic acid **1h** containing a nitro group was transformed into the corresponding iodide **4h** in moderate yield with $InBr_3$ (10 mol%), TMDS (*Si–H*: 12 equiv), and Me_3SiI (1 equiv) in 1,2-dichloroethane at 80 °C (entry 8). Interestingly, this result was in clear contrast with the results of the previous bromination. The use of an iodine source with a nucleophilicity that was stronger than that of bromotrimethylsilane succeeded in halogenation of the carboxylic acid. Application of the procedure to aromatic carboxylic acids was then examined. The iodination of *p*-methoxybenzoic acid (**1i**) did not occur, probably because of a decrease in the electrophilicity of the carbonyl carbon (entry 9). When reactions were performed with benzoic acids **1j** and **1k**, which had either a chlorine or a trifluoromethyl group in the expected iodides **4j** and **4k**, respectively, were obtained in high yields (entries 10 and 11). Carboxylic acids with terminal or internal alkenes were consumed within a short time but did not give the corresponding iodides **4l** and **4m** (entries 12 and 13). Unlike the bromination of **1l** and **1m**, an olefin moiety was also reduced, but the desired products were not detected. The iodination of dicarboxylic acid **1n** was undertaken using $InBr_3$ (10 mol %), TMDS (*Si–H*: 12 equiv), and I_2 (1 equiv) and gave the corresponding iodide **4n** in 88% yield (entry 14). This iodination was applicable to the carboxylic

acid with a thioether moiety, **1o**, which produced the corresponding sulfide **4o** in 92% yield (entry 15).

Table 5. Preparation of Alkyl Iodides from Carboxylic Acids[a]



1 **4**

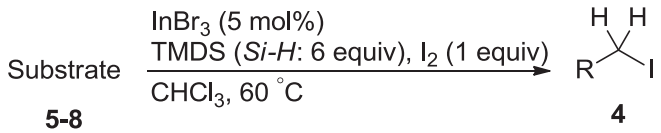
entry	carboxylic acid		product		time (h)	yield (%)[b]
1		**1a**		**4a**	1	91
2		**1b**		**4b**	0.5	0[c]
3		**1c**		X = *o*-Me **4c**	1	91
4		**1d**		X = *p*-Cl **4d**	1	94
5		**1e**		X = *p*-Br **4e**	1	95
6		**1f**		X = *o*-I **4f**	1	91
7		**1g**		X = *p*-OH **4g**	1	89
8[d]		**1h**		X = *p*-NO_2 **4h**	1	50
9		**1i**		Y = *p*-OMe **4i**	5	NR[e]
10		**1j**		Y = *p*-Cl **4j**	1	93
11		**1k**		Y = *p*-CH_3 **4k**	1	87
12		**1l**		**4l**	1	CM[f]
13		**1m**		**4m**	1	CM[f]
14[g]		**1n**		**4n**	1	88
15		**1o**		**4o**	0.3	92

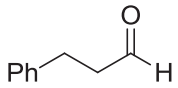
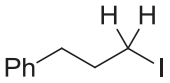
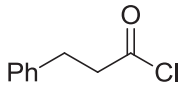
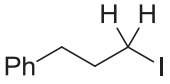
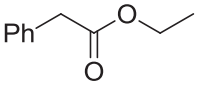
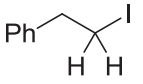
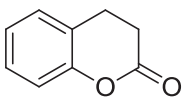
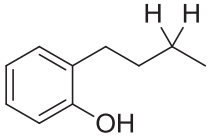
[a] The reaction was carried out with carboxylic acid **1** (0.6 mmol), $InBr_3$ (5 mol%), TMDS (*Si-H*: 6 equiv), and I_2 (1 equiv) in $CHCl_3$ at 60 °C, unless otherwise noted. [b] Isolated yield. [c] 1,2,3,4-Tetrahydronaphthalene (**4b'**) was obtained in 90 % yield. [d] $InBr_3$ (10 mol%) and Me_3SiI (1 equiv) were esed in 1,2-dichloroethane at 80 °C. [e] NR: no reaction. [f] CM: a complex mixture. [g] TMDS (*Si-H*: 12 equiv) and I_2 (2 equiv) were employed.

Reductive Iodination of Carbonyl Compounds and Carboxylic Acid Derivatives

As an application, iodinations of an aldehyde and carboxylic acid derivatives, such as an acyl chloride and an ester, were conducted (Table 6). When both aldehyde **5** and acyl chloride **6** were subjected to the optimal conditions, the corresponding iodide **4a** was obtained in good yields (entries 1 and 2). Similarly, when the iodination was performed with alkyl ester **7**, both deoxygenation of the carbonyl moiety and substitution of the ethoxy group occurred smoothly, producing 2-phenylethyl iodide (**4p**) in 92% yield (entry 3). When this iodination was also examined with a cyclic ester, 3,4-dihydrocoumarin (**8**), the ring-opening product **4q** was obtained in a practical yield (entry 4). These results proved that cleavage of the C−O single bond on the ester proceeded selectively.

Table 6. Reductive Transformations of Various Compounds to Alkyl Iodides[a]



entry	carboxylic acid		product		time (h)	yield (%)[b]
1		**5**		**4a**	1	(85)[c]
2		**6**		**4a**	1	(99)[c]
3		**7**		**4p**	1	92
4		**8**		**4q**	2	70

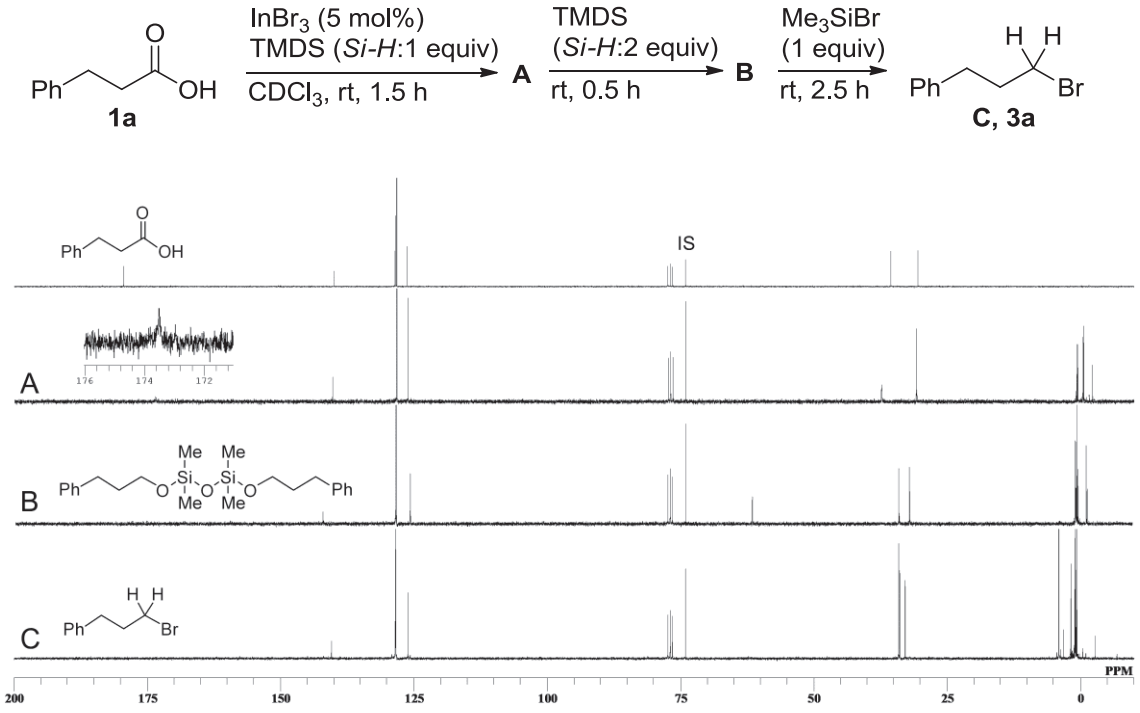
[a] The reaction was carried out with the substrate (0.6 mmol), $InBr_3$ (5 mol%), TMDS (*Si-H*: 6 equiv), and I_2 (1 equiv) in $CHCl_3$ at 60 °C. [b] Isolated yields (GC yields are shown in parentheses).

1-3. Reaction Mechanism

Reaction Mechanism of Reductive Bromination of Carboxylic Acids

To investigate the reaction mechanism, the reaction system comprising 3-phenylpropanoic acid (**1a**), $InBr_3$ (5 mol%), TMDS (*Si–H*: 1 equiv), and d^1-chloroform was monitored by ^{13}C NMR (Figure 1). Initially, when the starting carboxylic acid **1a** was treated with TMDS (*Si–H*: 1 equiv) in the presence of $InBr_3$ (5 mol %), both the clear disappearance of the carbonyl peak (179.4 ppm) of **1a** and the appearance of a new peak (173.5 ppm), which was derived from the corresponding silyl ester **A**, were observed (**A** in Figure 1). Then, when 2 more equivalents (*Si–H*) of TMDS were added to the resultant mixture, both the disappearance of the peak of the silyl ester **A** and the formation of the new peak (61.5 ppm), which was derived from the silyl ether **B**, were observed (**B** in Figure 1). Finally, when 1 equiv of Me_3SiBr as a bromine source was added to the NMR tube, the quantitative formation of 3-phenylpropyl bromide (**3a**) was observed (**C** in Figure 1). To support the reaction mechanism from a different aspect, mass analysis of the solution was also conducted. A high resolution-mass spectral peak of the compound in solution **B** was observed at m/z 425.1947 $[M + Na]^+$. This was in good agreement with the exact mass of the corresponding silyl ester (calculated for $C_{22}H_{34}NaO_3Si_2$: 425.1944). Thus, the results proved that the silyl ether was one of the intermediates through the reductive bromination series. However, Characterization of the silyl ester could not be well established due to the lack of detection of the mass peak.[13] And neither the silyl ester nor the silyl ether prepared from TMDS could be isolated due to their instability.

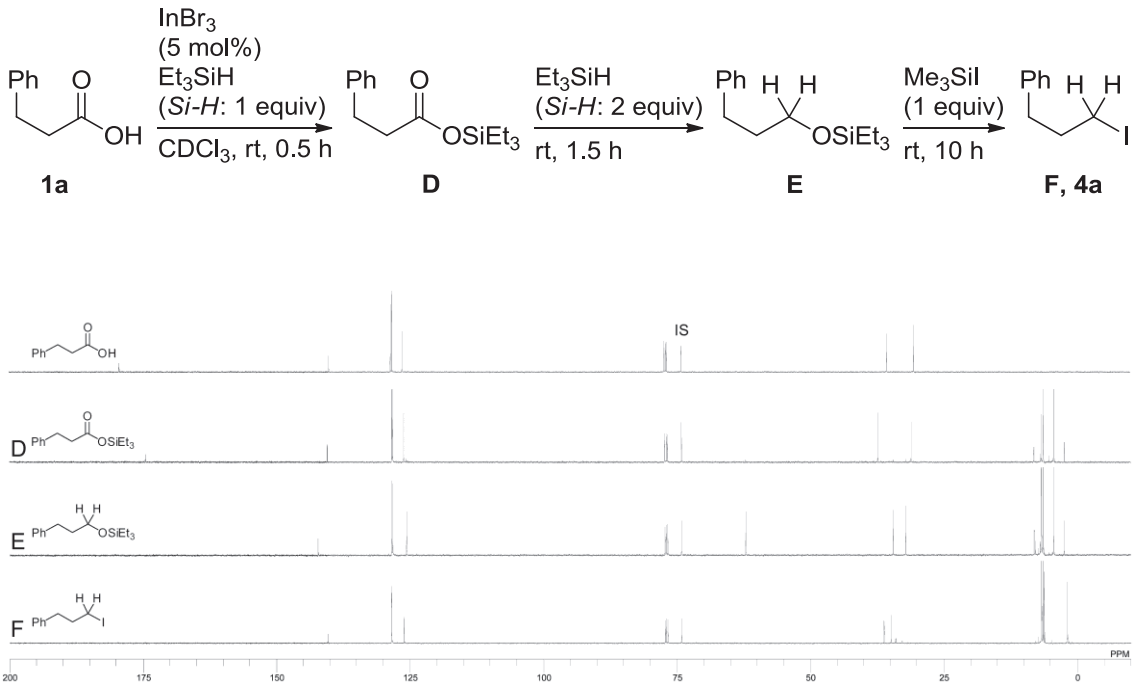
Figure 1. Monitoring of Reductive Bromination of Carboxylic Acid **1a** by ^{13}C NMR



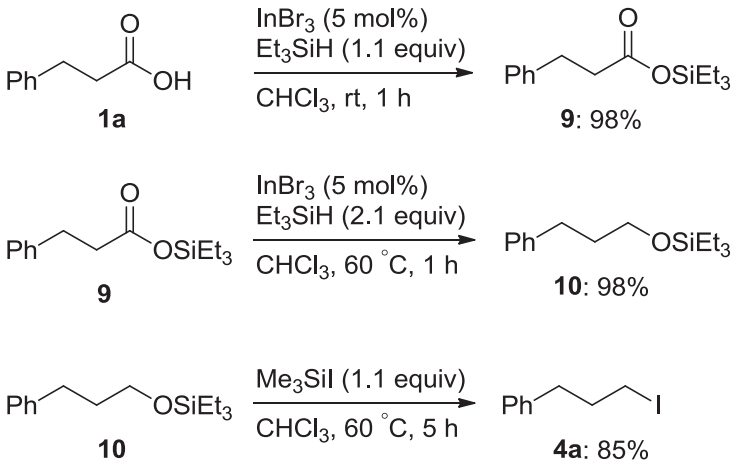
Reaction Mechanism of Reductive Iodination of Carboxylic Acids

To clarify the reaction mechanism of the $InBr_3$-catalyzed reductive iodination of a carboxylic acid series, both ^1H NMR and ^{13}C NMR monitoring of the iodination of 3-phenylpropanoic acid (**1a**) were conducted with triethylsilane instead of TMDS. Each intermediate of the iodination series could be easily isolated, and the NMR results are presented in Figures 2 and 3. In addition, the results from the synthesis of 3-phenylpropyl iodide (**4a**) that was separately synthesized from **1a** by the stepwise reaction shown in Scheme 2 agreed with the results of NMR monitoring of the series of control experiments. First, in the ^{13}C NMR monitoring, when the reaction was carried out with **1a** and 1 equiv of Et_3SiH in the presence of $InBr_3$ (5 mol%), the carbonyl peak of **1a** (179.4 ppm) disappeared as the reaction proceeded, and a new peak appeared at 174.5 ppm, which was assigned to the corresponding silyl ester (**D**

Figure 2. Monitoring of Reductive Iodination of Carboxylic Acid **1a** by ^{13}C NMR

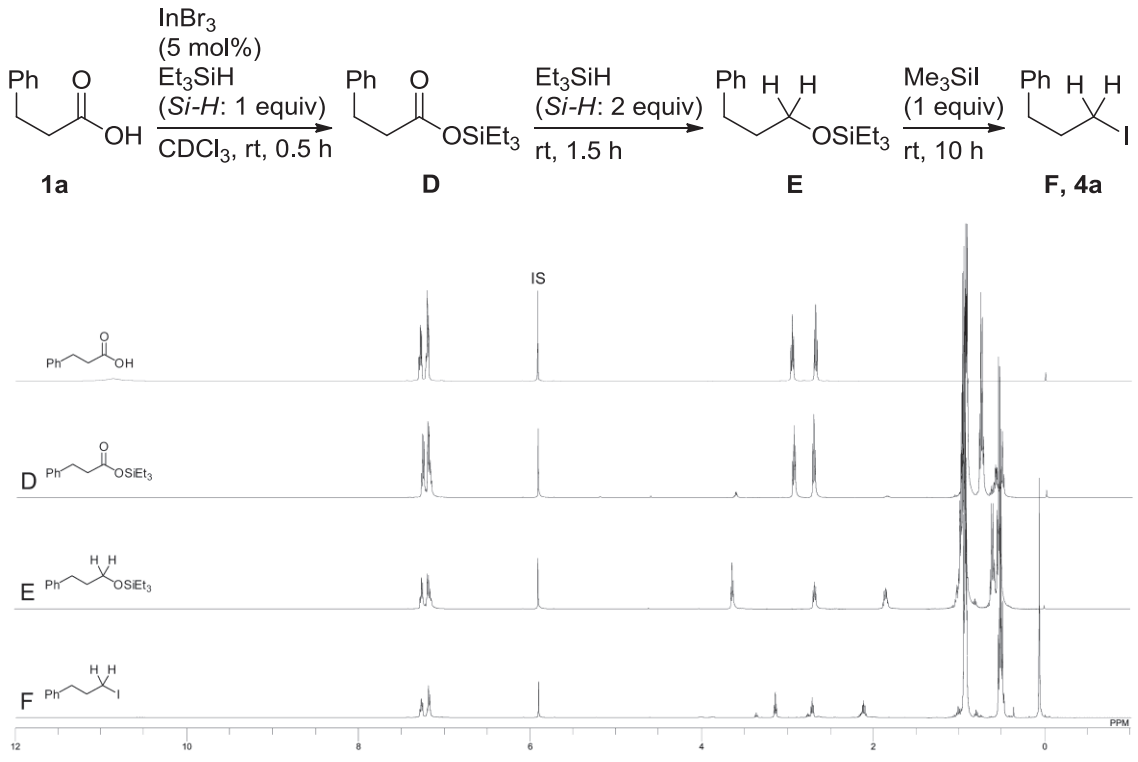


Scheme 2. Stepwise Conversion of Carboxylic Acid **1a** to Alkyl Iodide **4a**



in Figure 2). In the ^{1}H NMR monitoring, the proton peak of the corresponding carboxylic acid (10.87 ppm) disappeared (**D** in Figure 3). The spectrum of the intermediate **D** agreed with that of the isolated triethyl(3-phenylpropyl)silyl ester (**9**) prepared from 3-phenylpropanoic acid (**1a**) with $InBr_3$ and Et_3SiH.

Figure 3. Monitoring of Reductive Iodination of Carboxylic Acid **1a** by ^{1}H NMR



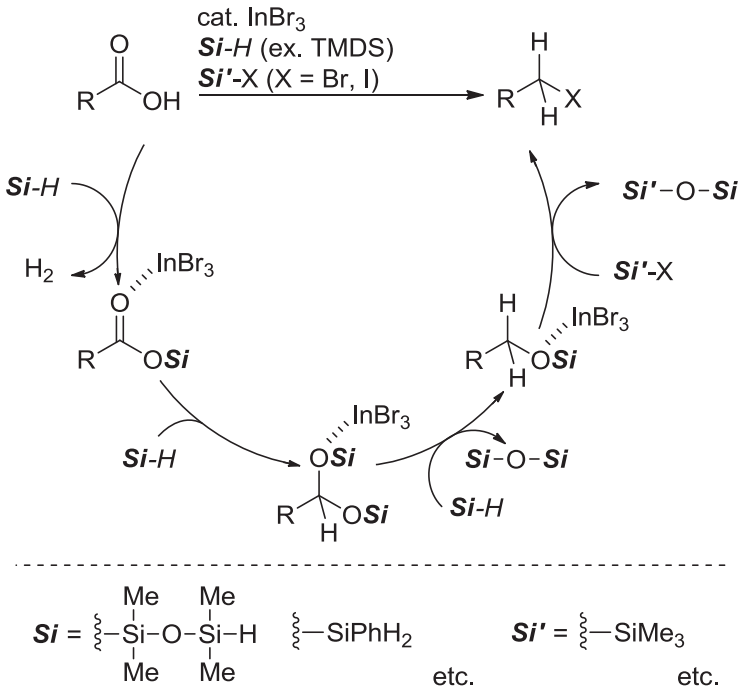
Further addition of 2 equiv of Et_3SiH to the resultant NMR tube resulted in the disappearance of the peak of the silyl ester **D** and the formation of a new peak at 62.1 ppm, which was derived from the corresponding C−O bond of silyl ether **E** (**E** in Figure 2). The ^{1}H NMR spectrum of the silyl ether corresponded to that of silyl ether **10** (**E** in Figure 3). In the final step, the addition of 1 equiv of Me_3SiI to the resultant NMR tube showed a quantitative transformation to 3-phenylpropyl iodide (**4a**) (**F** in Figures 2 and 3).

Plausible Reaction Pathway

On the basis of the NMR monitoring experiments and the several control experiments involving the corresponding intermediates, the plausible mechanistic aspects of the reductive halogenation series are shown in Scheme 3. Initially, the

reaction of the carboxylic acid and the hydrosilane generates a silyl ester with the liberation of H_2 gas. Then, 2 equiv of the hydrosilane is added to form a silyl ether intermediate through the formation of a silyl acetal. In final step, the formed silyl ether is substituted with an appropriate halogen source (Me_3SiBr or Me_3SiI), leading to the preparation of the alkyl halide.

Scheme 3. Plausible Reaction Pathway



Conclusion

The author found that a combination of $InBr_3$, TMDS, and a bromine or iodine source, achieves direct bromination or iodination of a variety of carboxylic acids and their derivatives, such as an acyl chloride, an aldehyde, and an ester. This indium catalyst system is tolerant of a variety of reducible substrates involving common electron-withdrawing groups, such as halogens, a hydroxy group, and a thioether. Insight into the reaction mechanism was gained via the time course of

NMR monitoring experiments and the corresponding stepwise reactions.

Experimental Section

***CAUTION*:** During examinations of the reaction conditions for bromination, when the author added bromine (Br_2) to a chloroform solution containing $InBr_3$, $PhSiH_3$, and a reducible substrate under atmosphere, the author encountered a small explosion with combustion.[14]

General

^1H NMR spectra were measured at 500 or 300 MHz using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were measured at 125 or 75 MHz using the respective residual solvent resonances. High-resolution mass spectra (FAB or ESI) were measured using *p*-nitrobenzyl alcohol (FAB) as a matrix. Infrared (IR) spectra were recorded under neat conditions. Thin-layer chromatography (TLC) was undertaken using silica gel 60 F_{254}. Column chromatography was performed using silica gel 60 F_{254}. Manipulations were carried out under a nitrogen atmosphere unless otherwise noted. Chloroform was distilled from P_2O_5, and the distillate was redistilled from K_2CO_3 and then finally kept dry on molecular sieves (4 Å). Indium tribromide, bromine sources, iodine sources, hydrosilanes, carboxylic acids **1a-o**, aldehyde **5**, acyl chloride **6**, and esters **7** and **8** were commercially available and were used without further purification. With the exception of the compounds **4e**, **4q**, **9**, and **10** the compounds prepared with this method were identified in comparison with spectroscopic data reported in the corresponding literature.

Typical Procedure for the Reductive Bromination of Carboxylic Acids

In a glove box, $InBr_3$ (0.0300 mmol, 10.6 mg) was placed in a screw vial. The vial was sealed with a PTFE-sealed screw cap under a N_2 atmosphere and removed

from the glove box. Then 3-phenylpropanoic acid (**1a**) (0.600 mmol, 90.1 mg), 1,1,3,3-tetramethyldisiloxane (1.80 mmol, 318 μL), and trimethylbromosilane (0.600 mmol, 78.0 μL) were successively added to a distilled chloroform (600 μL) solution containing $InBr_3$. The solution was stirred at room temperature for 5 min. The resultant solution was further stirred under the conditions shown in Table 3. After the reaction, the mixture was cooled to room temperature and quenched with H_2O (2 mL). The organic layer was washed with dichloromethane, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 99:1) to afford the corresponding alkyl bromide **3a** in 96% yield (114.7 mg).

Typical Procedure for the Reductive Iodination of Carboxylic Acids

In a glove box, $InBr_3$ (0.0300 mmol, 10.6 mg) was placed in a screw vial. The vial was sealed with a PTFE-sealed screw cap under a N_2 atmosphere and removed from the glove box. Then 3-phenylpropanoic acid (**1a**) (0.600 mmol, 90.1 mg), 1,1,3,3-tetramethyldisiloxane (1.80 mmol, 318 μL), and iodine (0.600 mmol, 152 mg) were successively added to a distilled chloroform (600 μL) solution containing $InBr_3$. The solution was stirred at room temperature for 5 min. The resultant solution was further stirred under the conditions shown in Tables 5 and 6. After the reaction, the mixture was cooled to room temperature and quenched with H_2O (2 mL). The organic layer was washed with dichloromethane, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 99:1) to afford the corresponding alkyl iodide **4a** in 91% yield (134.4 mg).

^{13}C NMR Monitoring of the ReductiveBromination of 3-Phenylpropanoic Acid

In a glove box, $InBr_3$ (0.0100 mmol, 3.60 mg) was placed in a screw capped NMR tube. The tube was sealed with a septum cap under N_2 atmosphere and was removed from the glove box. 3-Phenylpropionic acid (**1a**, 0.200 mmol, 29.4 mg), 1,1,2,2-tetrachloroethane (21.3 mg, 0.130 mmol) as an internal standard and a dried $CDCl_3$ (400 μL) were successively added. The NMR tube was measured at room temperature with the following procedure: (1) addition of 1 equivalent (*Si–H* for **1a**) of 1,1,3,3-tetramethyldisiloxane (0.100 mmol, 17.6 μL) (the second row spectrum **A** shown in Figure 1), (2) addition of 2 equivalents (*Si–H* for **1a**) of 1,1,3,3-teteramethyldisiloxanae (0.200 mmol, 35.2 μL) (the third row spectrum **B** shown in Figure 1), (3) addition of trimethylbromosilane (0.200 mmol, 26.0 μL) (the bottom spectrum **C** shown in Figure 1).

^{1}H and ^{13}C NMR Monitoring of the Reductive Iodination of 3-Phenylpropanoic Acid

In a glove box, $InBr_3$ (0.0100 mmol, 3.5 mg) was placed in a screw-capped NMR tube. The tube was sealed with a septum cap under a N_2 atmosphere and removed from the glove box. Then 3-phenylpropanoic acid (**1a**, 0.200 mmol, 29.4 mg), 1,1,2,2-tetrachloroethane (0.130 mmol, 21.3 mg) as an internal standard, and dried $CDCl_3$ (400 μL) were successively added. The NMR spectra were measured at room temperature using the following procedure: (1) addition of 1 equiv (*Si–H* for **1a**) of triethylsilane (0.200 mmol, 31.9 μL) (the second-row spectra **D** shown in Figures 2 and 3); (2) addition of 2 equiv (*Si–H* for **1a**) of triethylsilane (0.400 mmol, 63.7 μL) (the third row spectra **E** shown in Figures 2 and 3); and (3) addition of trimethyliodosilane (0.200 mmol, 28.0 μL) (the bottom spectra **F** shown in Figures 2 and 3).

Stepwise Reductive Iodination Reaction

In a glove box, $InBr_3$ (0.0300 mmol, 10.6 mg) was placed in a screw vial. The vial was sealed with a PTFE-sealed screw cap under a N_2 atmosphere and removed from the glove box. Then 3-phenylpropanoic acid (**1a**) (0.600 mmol, 90.1 mg) and triethylsilane (0.660 mmol, 105 μL) were successively added to a distilled chloroform (600 μL) solution containing $InBr_3$. The solution was stirred at room temperature for 1 h. After the reaction, the mixture was quenched with H_2O (2 mL). The organic layer was washed with dichloromethane, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 97:3) to afford triethyl(3-phenylpropyl)silyl ester (**9**) (155.5 mg, 98% yield). In a glove box, $InBr_3$ (0.0300 mmol, 10.6 mg) was placed in a screw vial. The vial was sealed with a PTFE-sealed screw cap under a N_2 atmosphere and removed from the glove box. Then triethyl(3-phenylpropyl)silyl ester (**9**) (0.600 mmol, 159 mg) and triethylsilane (1.26 mmol, 201 μL) were added to a distilled chloroform (600 μL) solution containing $InBr_3$. The solution was stirred at 60 °C for 1 h. After the reaction, the mixture was quenched with H_2O (2 mL). The organic layer was washed with dichloromethane, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 99:1) to afford triethyl(3-phenylpropyl)silyl ether (**10**) (147.3 mg, 98% yield). In a glove box, $InBr_3$ (0.0300 mmol, 10.6 mg) was placed in a screw vial. The vial was sealed with a PTFE-sealed screw cap under N_2 atmosphere and removed from the glove box. Then triethyl(3-phenylpropyl)silyl ether (**10**) (0.600 mmol, 150 mg) and trimethyliodosilane (0.660 mmol, 91.1 μL) were successively added to a distilled chloroform (600 μL) solution containing $InBr_3$. The solution was

stirred at 60 °C for 5 h. After the reaction, the mixture was quenched with H_2O (2 mL). The organic layer was washed with dichloromethane, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 99:1) to afford 3-phenylpropyl iodide (**4a**) (125.5 mg, 85% yield).

Compound Characterization

3-Phenylpropyl bromide (3a)[15]

96% yield; a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (quint, 2H, *J* = 7.5 Hz), 2.76 (t, 2H, *J* = 7.5 Hz), 3.38 (t, 2H, *J* = 7.5 Hz), 7.18-7.21 (m, 3H) 7.27-7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.0, 33.9, 34.1, 126.1, 128.4, 128.5, 140.5; MS (EI) *m/z* 199 (M^+, 2%), 201 (M^++2, 2%), 91 (M^+-108, 100%).

4-Phenylbutyl bromide (3b)[16]

97% yield; a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72-1.80 (m, 2H), 1.86-1.92 （m, 2H), 2.64(t, 2H, *J* = 7.0 Hz), 3.42 (t, 2H, *J* = 7.0 Hz), 7.16-7.20 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.8, 32.2, 33.6, 34.9, 125.9, 128.4 (2C), 141.8 (One signal was not observed due to overlapping.); MS (EI) *m/z* 213 (M^+, 10%), (M^++2, 10%), 132 (M^+-81, 100%).

***o*-Methylphenethyl bromide (3c)**[17]

91% yield; a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.17 (t, 2H, *J* = 8.1 Hz), 3.52 (t, 2H, *J* = 8.1 Hz), 7.16 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 31.6, 36.9, 126.2, 127.1, 129.3, 130.5, 136.1, 137.1; MS (EI) *m/z* 199 (M^+,15%), 201 (M^++2, 12%), 119 (M^+-80, 100%).

***p*-Chlorophenethyl bromide (3d)**[18]

95% yield; a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (t, 2H, *J* = 7.5 Hz), 3.54 (t, 2H, *J* = 7.5 Hz), 7.15 (d, 2H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 32.6, 38.5, 128.7, 130.0, 132.7, 137.2; MS (EI) *m/z* 220 (M^+, 100%), 224 (M^++4, 15%).

***p*-Bromophenethyl bromide (3e)**[19]

95% yield; a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.11 (t, 2H, *J* = 7.5 Hz), 3.53 (t, 2H, *J* = 7.5 Hz), 7.08 (d, 2H, *J* = 8.4 Hz), 7.44 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.5, 38.6, 120.8, 130.4, 131.7, 137.7; MS (EI) *m/z* 264 (M^+, 100%), 268 (M^++4, 10%).

***o*-Iodophenethyl bromide (3f)**[20]

92% yield; a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.27 (t, 2H, *J* = 7.5 Hz), 3.55 (t, 2H, *J* = 7.5 Hz), 6.91-6.97 (m, 1H), 7.25-7.33 (m, 2H), 7.81-7.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.2, 43.9, 100.2, 128.4, 128.8, 130.2, 139.7, 141.4; MS (EI) *m/z* 311 (M^+, 10%), 313 (M^++2, 10%), 217 (M^+-94, 100%).

***p*-Hydroxyphenethyl bromide (3g)**[21]

90% yield; a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.08 (t, 2H, *J* = 7.5 Hz), 3.52 (t, 2H, *J* = 7.5 Hz), 5.08 (s, 1H), 6.79 (d, 2H, *J* = 8.4 Hz), 7.08 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.4, 38.5, 115.4, 129.9, 131.2, 154.3; MS (EI): *m/z* 201 (M^+, 100%), 203 (M^++2, 100%).

***p*-Chlorobenzyl bromide (3j)**[22]

86% yield; a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 4.45 (s, 2H), 7.29-7.34 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.4, 129.0, 130.4, 134.3, 136.3; MS (EI): *m/z* 205 (M^+, 2%), 207 (M^++2, 1%), 125 (M^+-81, 100%).

***p*-(Trifluoromethyl)benzyl bromide (3k)**[23]

85% yield; a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 4.47 (s, 2H), 7.49 (d, 2H, *J* = 8.0 Hz), 7.59 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.7, 123.9 (q, J_{C-F} = 272.0 Hz), 125.8 (q, J_{C-F} = 3.8 Hz), 129.3, 130.5 (q, J_{C-F} = 32.6 Hz), 141.6 (d,

$J_{C\text{-}F}$ = 1.5 Hz); MS (EI): *m/z* 239 (M^+, 2%), 241 (M^++2, 1%), 159 (M^+-80, 100%).

11-Bromo-1-undecene (3l)[24]

80% yield; a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28-1.45 (m, 13H), 1.82-1.88 (m, 2H), 2.01-2.06 (m, 2H), 3.40 (t, 2H), 4.91-4.95 (m, 1H), 4.96-5.02 (m, 1H), 5.76-5.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 28.1, 28.7, 28.9, 29.0, 29.3, 32.8, 33.7, 33.9, 114.1, 139.1; MS (EI): *m/z* 233 (M^+, 1%), 235 (M^++2, 1%), 151 (M^+-81, 100%).

1-Bromooctadecane-9-ene (3m)[25]

82% yield; a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.0 Hz), 1.26-1.31 (m, 22H), 1.82-1.89 (m, 2H), 1.99-2.04 (m, 4H), 3.41 (t, 2H, *J* = 7.0 Hz), 5.33-5.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 27.1, 27.2, 28.2, 28.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 31.9, 32.8, 34.0, 129.8, 130.0; MS (EI): *m/z* 331 (M^+, 5%), 333 (M^++2, 5%), 97 (M^+-234, 100%)

1,2-Bis(2-bromoethyl)benzene (3n)[26]

89% yield; a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.20 (t, 4H, *J* = 7.5 Hz), 3.54 (t, 4H, *J* = 7.5 Hz), 7.19-7.26 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.0, 36.0, 127.4, 129.8, 137.0; MS (EI): *m/z* 292 (M^+, 30%), 294 (M^++2, 13%), 117 (M^+-175, 100%).

Phenylthioethyl bromide (3o)[27]

93% yield; a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.25-3.29 (m, 2H), 3.42-3.46 (m, 2H), 7.21-7.25 (m, 1H), 7.28-7.32 (m, 2H), 7.36-7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.8, 36.0, 127.0, 129.1, 130.5, 134.0; MS (EI): *m/z* 217 (M^+, 8%), 219 (M^++2, 8%), 137 (M^+-80, 100%)

3-Phenylpropyl iodide (4a)[28]

91% yield (134.4 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (quint, 2H,

J = 7.0 Hz), 2.73 (t, 2H, *J* = 7.0 Hz), 3.17 (t, 2H, *J* = 7.0 Hz), 7.19-7.23 (m, 3H) 7.27-7.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.3, 34.9, 36.2, 126.2, 128.4, 128.5, 140.4; MS (EI): *m/z* 246 (M^+, 42%), 91 (M^+ -155, 100%).

1,2,3,4-Tetrahydronaphthalene (4b')[29]

90% yield (71.4 mg); a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48-1.81 (m, 4H), 2.74-2.76 (m, 4H), 7.03-7.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 29.4, 125.4, 129.1, 137.1; MS (EI): *m/z* 132 (M^+, 75%), 104 (M^+ -18, 100%).

***o*-Methylphenethyl iodide (4c)**[30]

91% yield (134.4 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.20 (t, 2H, *J* = 8.0 Hz) , 3.30 (t, 2H, *J* = 8.0 Hz), 7.14-7.17 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.9, 19.2, 38.0, 126.2, 127.0, 128.9, 130.5, 135.7, 139.0; MS (EI): *m/z* 246 (M^+, 10%), 119 (M^+ -127, 100%).

***p*-Chlorophenethyl iodide (4d)**[31]

94% yield (150.3 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.15 (t, 2H, *J* = 7.5 Hz), 3.32 (t, 2H, *J* = 7.5 Hz), 7.13 (d, 2H, *J* = 8.5 Hz), 7.29 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.2, 39.4, 128.8, 129.7, 132.7, 138.9; MS (EI): *m/z* 266 (M^+, 13%), 268 (M^++2, 4%), 139 (M^+ -127, 100%).

***p*-Bromophenethyl iodide (4e)**

95% yield (177.2 mg); a colorless oil; IR (neat) ν/cm^{-1} 2959, 1067, 800; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.12 (t, 2H, *J* = 7.5 Hz), 3.31 (t, 2H, *J* = 7.5 Hz), 7.06 (d, 2H, *J* = 8.0 Hz), 7.43 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.9, 39.5, 120.7, 130.0, 131.7, 139.4; HRMS (FAB): Calcd for C_8H_8BrI: 309.8854, Found 309.8845.

***o*-Iodophenethyl iodide (4f)**[32]

91% yield (195.4 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.26-3.30 (m, 2H), 3.31-3.35 (m, 2H), 6.94-6.98 (m, 1H), 7.23-7.26 (m, 1H), 7.29-7.33 (m, 1H),

7.81-7.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.3, 45.0, 99.9, 128.5, 128.7, 129.8, 139.8, 143.3; MS (EI): *m/z* 358 (M^+, 18%), 221 (M^+ -137, 100%).

***o*-Hydroxyphenethyl iodide (4g)**[33]

89% yield (132.5 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.10 (t, 2H, *J* = 8.0 Hz), 3.31 (t, 2H, *J* = 8.0 Hz), 4.93 (s, 1H), 6.76-6.80 (m, 2H), 7.04-7.08 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.4, 39.5, 115.4, 129.5, 133.0, 154.4; MS (EI): *m/z* 248 (M^+, 36%), 121 (M^+ -127, 100%).

***p*-Nitrophenethyl iodide (4h)**[34]

50% yield (83.1 mg); a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.30 (t, 2H, *J* = 7.0 Hz), 3.39 (t, 2H, *J* = 7.0 Hz), 7.37 (d, 2H, *J* = 8.5 Hz), 8.20 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.6, 39.4, 123.9, 129.3, 147.0, 147.6; MS (EI): *m/z* 277 (M^+, 100%).

***p*-Chlorobenzyl iodide (4j)**[22]

93% yield (140.9 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (s, 2H), 7.24-7.27 (m, 2H), 7.29-7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.2, 129.0, 130.0, 133.6, 137.8; MS (EI): *m/z* 252 (M^+, 25%), 254 (M^++2, 5%). 121 (M^+ -127, 100%).

***p*-(Trifluoromethyl)benzyl iodide (4k)**[35]

87% yield (149.3 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (s, 2H), 7.48 (d, 2H, *J* = 8.0 Hz), 7.55 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.15, 123.9 (q, $J_{C\text{-}F}$ = 272.5 Hz), 125.8 (q, $J_{C\text{-}F}$ = 3.9 Hz), 129.0, 130.0 (q, $J_{C\text{-}F}$ = 32.7 Hz), 143.3 (d, $J_{C\text{-}F}$ = 1.0 Hz); MS (EI): *m/z* 286 (M^+, 10%), 159 (M^+ -127, 100%).

1,2-Bis(2-iodoethyl)benzene (4n)[36]

88% yield (203.8 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.20 (t, 4H, *J* = 8.0 Hz), 3.31 (t, 4H, *J* = 8.0 Hz), 7.17-7.19 (dd, 2H, *J* = 3.0 Hz, 3.0Hz), 7.23-7.26

(dd, 2H, J = 3.0 Hz, 3.0Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.2, 37.0, 127.4, 129.5, 138.5; MS (EI): *m/z* 386 (M^+, 10%), 259 (M^+ -127, 100%).

Phenylthioethyl iodide (4o)[37]

92% yield (145.8 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.24-3.29 (m, 2H), 3.30-3.35 (m, 2H), 7.23-7.27 (m, 1H), 7.30-7.34 (m, 2H), 7.36-7.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 2.5, 37.0, 127.1, 129.2, 130.6, 134.0; MS (EI): *m/z* 264 (M^+, 25%), 137 (M^+ -127, 100%).

2-Phenylethyl iodide (4p)[38]

92% yield (128.1 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.18 (t, 2H, J = 8.0 Hz), 3.35 (t, 2H, J = 8.0 Hz), 7.19 (d, 2H, J = 7.5 Hz), 7.25-7.28 (m, 1H), 7.30-7.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.6, 40.3, 126.8, 128.3, 128.6, 140.6; MS (EI): *m/z* 232 (M^+, 10%), 105 (M^+ -127, 100%).

***o*-Hydroxyphenylpropyl iodide (4q)**

70% yield (110.1 mg); a colorless oil; IR (neat) ν/cm^{-1} 3518, 2930, 1452, 1212, 753; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (quint, 2H, J = 7.0 Hz), 2.74 (t, 2H, J = 7.0 Hz), 3.21 (t, 2H, J = 7.0 Hz), 4.76 (brs, 1H), 6.74 (d, 1H, J = 7.5 Hz), 6.88 (t, 1H, J = 7.5 Hz), 7.10 (t, 1H, J = 7.5 Hz), 7.14 (d, 1H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.8, 30.7, 33.3, 115.3, 120.9, 127.5, 130.6, 153.5; HRMS (FAB): Calcd for $C_9H_{11}IO$: 385.9028, Found 385.9028.

Triethyl(3-phenylpropyl)silyl ester (9)

98% yield (155.5 mg); a colorless oil; IR (neat) ν/cm^{-1} 1239, 1100; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.59 (q, 6H, J = 8.0 Hz), 0.96 (t, 9H, J = 8.0 Hz), 2.66 (t, 2H, J = 7.5 Hz), 2.94 (t, 2H, J = 7.5 Hz), 7.18-7.21 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.6, 6.5, 30.6, 35.6, 126.3, 128.2, 128.5, 140.2, 178.4; HRMS (ESI): Calcd for $C_{15}H_{24}O_2Si$ (M^++Na): 287.1443, Found 287.1421.

Triethyl(3-phenylpropyl)silyl ether (10)

98% yield (147.3 mg); a colorless oil; IR (neat) ν/cm^{-1} 1710, 1252, 1076; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.60 (q, 6H, *J* = 8.0 Hz), 0.97 (t, 9H, *J* = 8.0 Hz), 1.85 (quint, 2H, *J* = 7.5 Hz), 2.68 (t, 2H, *J* = 7.5 Hz), 3.64 (t, 2H, *J* = 7.5 Hz), 7.15-7.20 (m, 3H), 7.22-7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.5, 6.8, 32.1, 34.5, 62.1, 125.6, 128.3, 128.4, 142.2; HRMS (ESI): Calcd for $C_{15}H_{26}OSi$ (M^++Na): 273.1651, Found 273.1651.

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Chapter 2.

One-Pot Conversion from Carboxylic Acids to Other Functional Group Compounds

Introduction

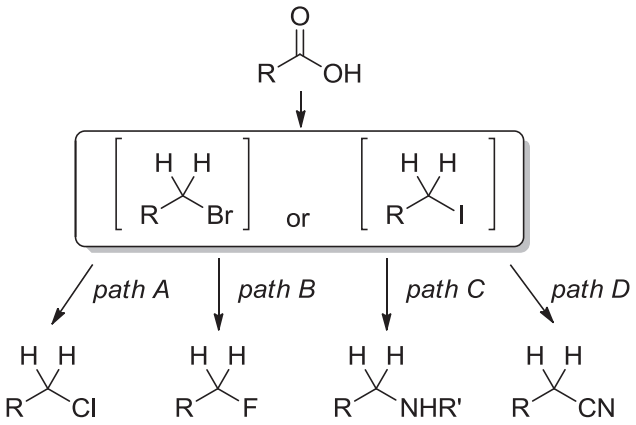
Alkyl halides are useful building blocks, because the producing alkyl halides can be easily converted to organic chemicals, such as Grignard reagents and organic lithium compounds, or highly valuable organic compounds, such as amines, ethers, nitriles, and so on.[1]

Especially, cyanides behave as a central building block or precursor for an easy preparation of ketones, aldehydes, primary amines, and carboxylic acids in organic synthesis and pharmaceutical chemistry.[2] For example, cyanides are easily converted to primary amines by hydrogenation, or can be transformed to a carboxylic acid and its derivative by hydrolysis under basic conditions.[3] Also, the conventional method for the preparation of cyanides has been an S_N2 reaction of alkyl halides with metal cyanides, such as potassium cyanide and sodium cyanide.[4] Metal cyanides generally have high toxicity, which has led to an avoidance of their use even in laboratory-scale synthesis. To overcome these problems, in the past two decades, trimethylsilyl cyanide (Me_3SiCN), which has low toxicity but less reactivity than metal cyanides, has been used as a nitrile surrogate.[5] Thus far,

various functional group conversions by the combination of an indium(III) compound and Me_3SiCN have been achieved. For instance, the Indium(III)-catalyzed direct conversion of α-aryl alcohols into α-aryl cyanides, and the 1,2- or 1,4-addition of Me_3SiCN to enones have been disclosed.[6,7] To the best of our knowledge, however, there has been no report on the reductive one-pot conversion of carboxylic acids to nitriles.

In this chapter, to show the utility of alkyl iodides prepared by the method described in Chapter 1, the author developed the consecutive transformation of *in-situ*-prepared alkyl iodides to alkyl chlorides, fluorides and amine derivatives using a one-pot method (paths A-C in Scheme 1). And, the author reports first example of a one-pot synthesis of alkyl cyanides via the $InBr_3$-catalyzed reductive bromination or iodination of carboxylic acids (path D).

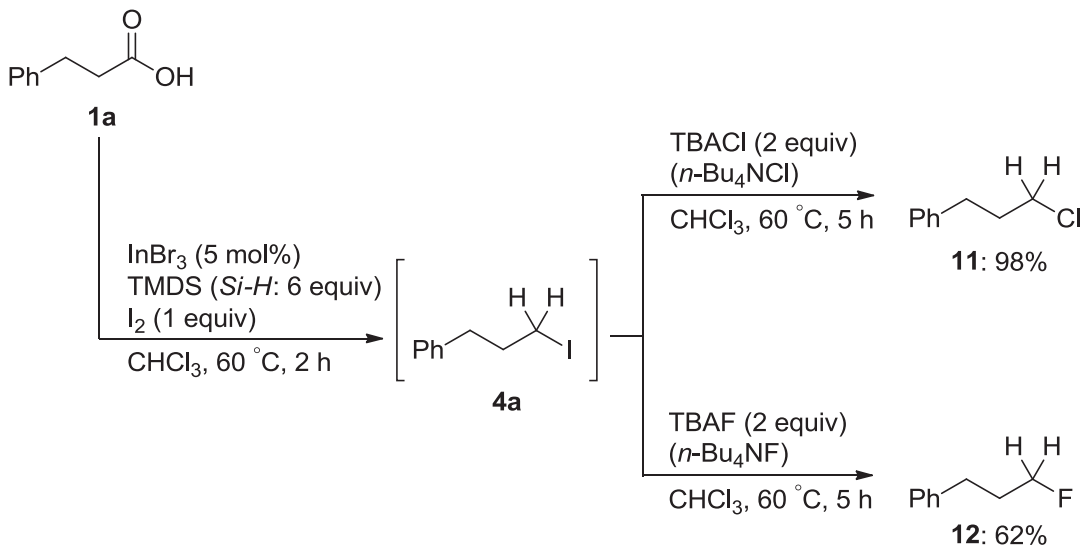
Scheme 1. Consecutive Transformation of the *in-situ*-Prepared Alkyl Bromides or Alkyl Iodides



2-1. One-Pot Conversion to Alkyl Fluorides and Chlorides from Carboxylic Acids

To show the utility of the reductive iodination, the author then attempted a one-pot conversion to alkyl chlorides, fluorides and amine derivatives via *in-situ*-generated alkyl iodides.[8] As shown in Scheme 2, the iodination of 3-phenylpropanoic acid (**1a**) was initially carried out with the standard conditions consisting of $InBr_3$ (5 mol%), 1,1,3,3-tetramethyldisiloxane (TMDS) (*Si–H*: 6 equiv), and I_2 (1 equiv), followed by treatment with tetrabutylammonium chloride (TBACl) (2.0 equiv) to produce the 3-phenylpropyl chloride (**11**) in a nearly quantitative yield. Similarly, when carboxylic acid **1a** was treated with tetrabutylammonium fluoride (TBAF) after the iodination series, the corresponding alkyl fluoride **12** was obtained in a 62% yield. These results demonstrated that this catalytic system could transform carboxylic acids into alkyl fluoride, chloride, bromide, and iodide by the combination of $InBr_3$, a hydrosilane and an appropriate halogen source.

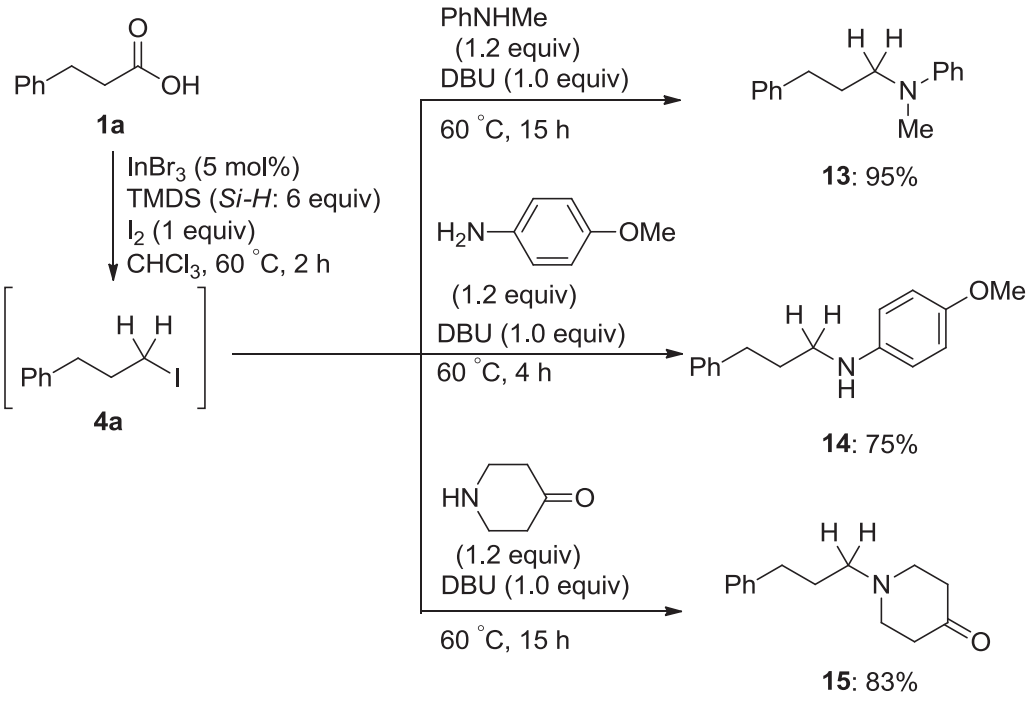
Scheme 2. One-Pot Conversion of Carboxylic Acids to Alkyl Chloride and Fluoride



2-2. One-Pot Conversion to Amine Derivatives from Carboxylic Acids

To the intermediate **4a** was added an aniline derivative (1.2 equiv) and treatment with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) (1 equiv), and the corresponding secondary amine **13** was obtained in a 95% yield. The reaction with a primary amine, 4-methoxyaniline, also produced the corresponding secondary amine **14** in a 75% yield with a 21% yield of tertiary amine **14'** as a by-broduct. When 4-piperidinone was used as a nucleophile, the corresponding *N*-(3phenylpropyl)-4-piperidone (**15**) was obtained in an 83% yield. In this context, Elpern et al. reported the synthetic route of the compound **15**, as a strong analgesics precursor.[9] The conventional method for compound **15** required multi-step operations, and the total yield of the desired compound was rather low. This procedure is practicable synthetic method in the cut down of the reaction steps.

Scheme 3. One-Pot Conversion of Carboxylic Acids to Amine Derivatives

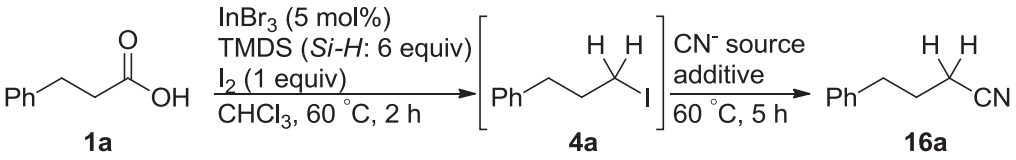


2-3. One-Pot Conversion to Alkyl Cyanides from Carboxylic Acids

Reaction Conditions

When 3-phenylpropanoic acid (**1a**) was initially treated with $InBr_3$ (5 mol%), TMDS (*Si–H*: 6 equiv), and I_2 (1 equiv) at 60 ˚C in chloroform for 1 h, the corresponding iodide **4a** was formed in a quantitative yield. Then, to directly transform the alkyl iodide into a nitrile in the same pot, tetrabutylammonium cyanide (TBACN) (2 equiv) was added to the reaction mixture, which led to a conversion of the desired 3-phenylpropyl cyanide (**16a**) in a 60% yield (Table 1, entry 1). Instead of TBACN, which has high toxicity and hygroscopicity, Me_3SiCN was then used as a cyanide ion source not to produce the expected alkyl cyanide **16a**, but to recover the alkyl iodide **4a** in a quantitative yield (entry 2). This result showed that cleavage of the Si–C bond of Me_3SiCN did not occur under the conditions. Thus, to generate a free cyanide, a mixture of potassium fluoride (2 equiv) and 18-crown-6-ether (2 equiv), which captures the potassium cation, were added to the resultant solution, and, as expected, the yield of the alkyl cyanide **16a** was improved to 93% (entry 3). Similarly, the use of TBAF also had the predictive effect of producing alkyl cyanide **16a** in a quantitative yield (entry 4). These results showed that a hypervalent cyanosilicate,[10] which functioned as a nucleophilic cyanide source, was *in-situ*-generated from TBAF and Me_3SiCN. However, in the case of using one equivalent of TBAF, the yield of the alkyl cyanide declined to a moderate amount, possibly because the remaining silane deactivated the TBAF (entry 5). Hence, the fluoride anion source required 2 equivalents to complete the cyanation.

Table 1. Examination of CN^- Sources[a]

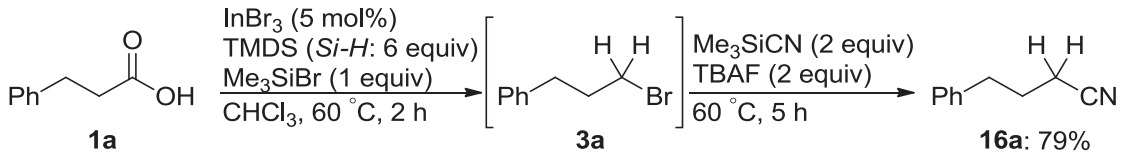


entry	CN^- source (equiv)	additive (equiv)	yield (%)[b] 4a	yield (%)[b] 16a
1	TBACN (2)	none	ND[c]	60
2	Me_3SiCN (2)	none	99	ND[c]
3	Me_3SiCN (2)	KF (2) 18-crown-6-ether (2)	ND[c]	93
4	Me_3SiCN (2)	TBAF (2)	ND[c]	95[d]
5	Me_3SiCN (2)	TBAF (1)	trace	51

[a] The reaction was carried out with **1a** (0.6 mmol), $InBr_3$ (5 mol%), TMDS (*Si-H*: 6 equiv), and I_2 (1 equiv) in $CHCl_3$ at 60 °C for 2 h. Then a CN^- source and an additive were added to the reaction mixture, and stired at 60 °C for 5h. [b] GC yield. [c] ND: Not detected. [d] Isolated yield.

Instead, when a trimethylbromosilane (Me_3SiBr) was used, as the bromide source, a similar alkyl cyanide **16a** was obtained in a good yield through the alkyl bromide intermediate **3a** (Scheme 4).

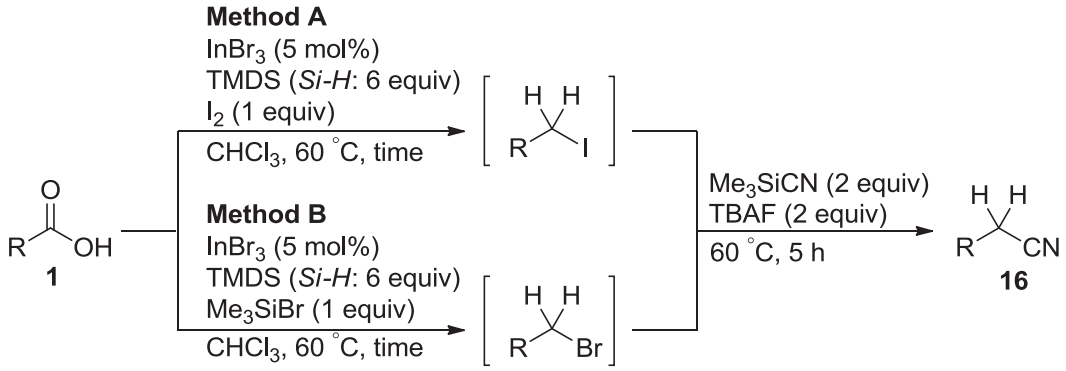
Scheme 4. One-Pot Synthesis of the Cyanide via the Alkyl Bromide

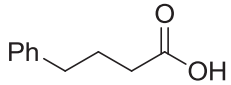
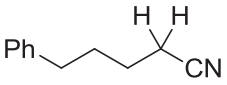
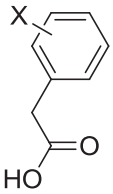
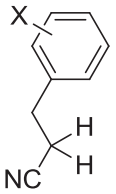
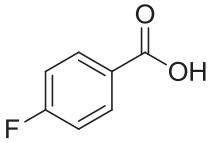
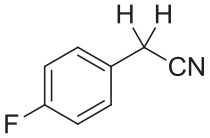
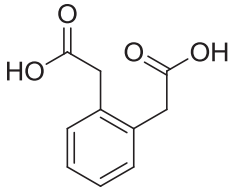
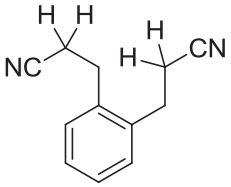
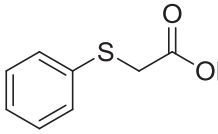
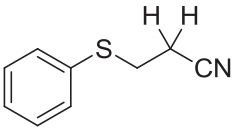


Substrate Scope of One-Pot Synthesis of Alkyl Cyanide

To generalize this reaction, a one-pot synthesis of various alkyl cyanides from carboxylic acids was carried out under optimal conditions (Table 2). The reaction was carried out with two methods through either alkyl iodides (Method A) or alkyl bromides (Method B). The reactivity and handling of the cyanation by either

Table 2. One-Pot Synthesis of Alkyl Cyanides from Carboxylic Acids[a]



entry	carboxylic acid	Method	time (h)	product	yield (%)[b]
1	 **1b**	A	0.5	 **16b**	ND[c]
		B	4		76
2	 **1c**	B	1	 X = *o*-Me **16c**	96
3	**1d**	A	3	X = *p*-Cl **16d**	81
4	**1e**	A	2	X = *p*-Br **16e**	83
5	**1f**	B	1	X = *o*-I **16f**	72
6	**1g**	B	1	X = *p*-OH **16g**	91
7	 **1k**	B	2	 **16k**	79
8[d]	 **1n**	B	2	 **16n**	66
9	 **1o**	A	0.5	 **16o**	34
		B	0.5		31

[a] The reaction was carried out with **1** (0.6 mmol), $InBr_3$ (5 mol%), TMDS (*Si-H*: 6 equiv), and I_2 or Me_3SiBr (1 equiv) in $CHCl_3$ at 60 °C. Then Me_3SiCN (2 equiv) and TBAF (2 equiv) were added to the reaction mixture, and stired at 60 °C for 5 h. [b] Isolated yield. [c] ND: Not detected. [d] Double doses of catalyst and reagent were used.

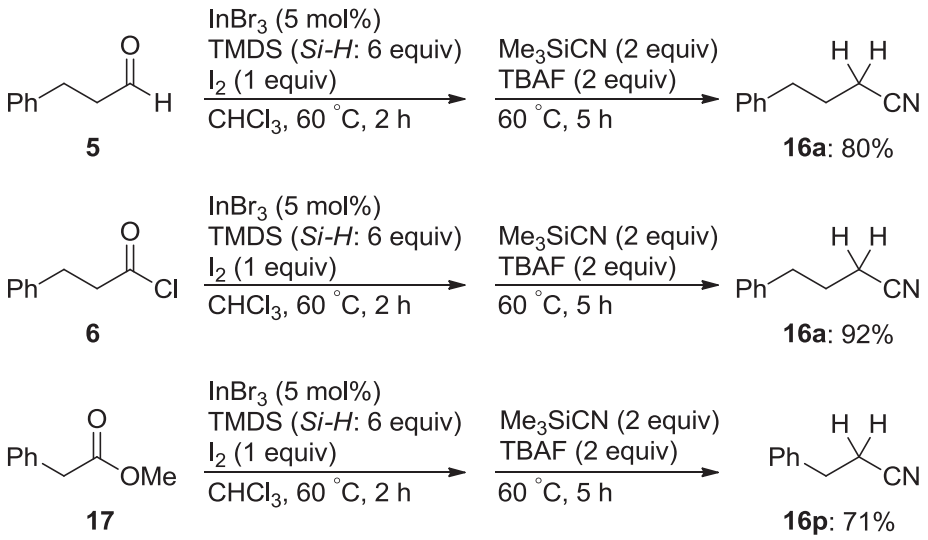
Method A or Method B were almost equivalent. However, in several cases, Method A produced the unidentified by-products, which precluded to isolation the desired alkyl cyanides. When the reaction was conducted with an aliphatic carboxylic acid

1b, the corresponding cyanide **16b** was obtained in an 87% yield via the alkyl bromide (Method B) (entry 1). However, a similar reaction via an alkyl iodide (Method A) did not form the desired product **16b**, but instead a 1,2,3,4-tetrahydronaphthalene (**4b'**), the annurated product, was formed in a quantitative yield. Functional groups, such as a methyl, halogens, and a hydroxy group, tolerated the reducing conditions (entries 2-6). Benzoic acids bearing an electron-withdrawing group, such as a trifluoromethyl group, undertook cyanation to produce the expected cyanide **16k** in practical yields (entry 7). The cyanation of dicarboxylic acid, **1n**, was effectively achieved by double doses of the reagents (entry 8). Although the yield of the cyanide **16o** was low, the synthesis of the cyanide with a thioether moiety was also successful (entry 9).

In addition, as application, this cyanation was extended to a large-scale synthesis, 10 mmol (1.50 g) of 3-phenylpropanoic acid (**1a**) was used under Method A. The reaction proceeded smoothly, and 3-phenylpropyl cyanide (**16a**) was obtained in 1.23 g (85% yield).

To expand applicable substrates, various carbonyl compounds, such as an aldehyde, an acyl halide and an ester, were applied to this reaction system (Scheme 5). For instance, 3-phenylpropanal (**5**) was treated with $InBr_3$ (5 mol%), TMDS (*Si–H*: 6 equiv), and I_2 (1 equiv) in chloroform at 60 ˚C for 2 h *in-situ* to form the corresponding alkyl iodide. The successive addition of TBAF (2 equiv) and Me_3SiCN (2 equiv) to the iodide and stirring at 60 ˚C for 5 h gave the expected alkyl cyanide **16a** in an 80% yield. With the same treatment, the acyl chloride **6** and the ester **17** also produced the corresponding alkyl cyanides **16a** and **16p** in good to high yields.

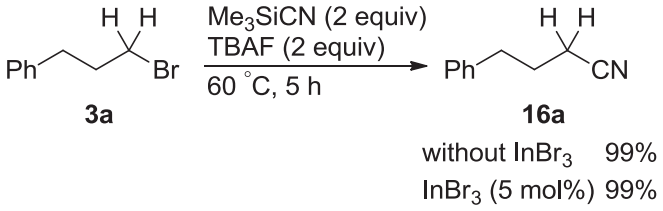
Scheme 5. One-Pot Synthesis of Cyanides from Various Carbonyl Compounds



Reaction Mechanism

To demonstrate the role of $InBr_3$ in the nucleophilic cyanation series 3-phenylpropyl bromide (**3a**), TBAF (2 equiv), and Me_3SiCN (2 equiv) was reacted either with $InBr_3$ or without the catalyst (Scheme 6). Because cyanation also proceeded to produce cyanide **16a** without $InBr_3$ in quantitative yields, $InBr_3$ did not participate in the cyanation step.

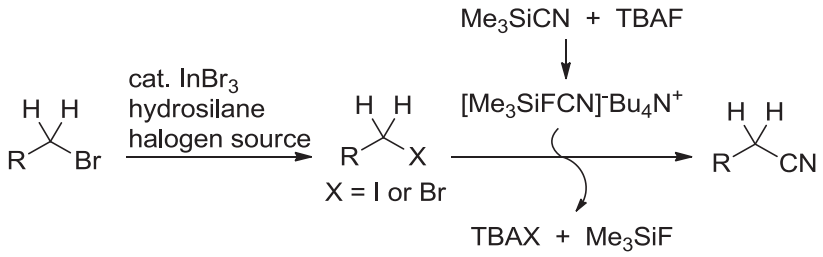
Scheme 6. Control Experiments for the Cyanation of Alkyl Bromides



Based on these control experiments, a reaction pathway for the one-pot synthesis of alkyl cyanides from carboxylic acids is shown in Scheme 7. First, the $InBr_3$-catalyzed reductive bromination or iodination of carboxylic acids occurred to

form the corresponding alkyl bromides or iodides.[11] Then, nucleophilic substitution with $[Me_3SiFCN]^-Bu_4N^+$, which was *in-situ*-generated from Me_3SiCN and TBAF,[10] produced the desired alkyl cyanides.

Scheme 7. Plausible Reaction Pathway



Conclusion

In chapter 2-1 and 2-2, the author demonstrated the one-pot synthesis of alkyl halides and amine derivatives via the addition of nucleophiles into the reductive bromination or iodination of carboxylic acid.

In chapter 2-3, the author demonstrated the one-pot synthesis of alkyl cyanides from carboxylic acids via alkyl bromides or iodides by $InBr_3$-catalyzend reductive bromination or iodination. The procedure could also apply to the transformation of other carbonyl compounds, such as an aldehyde, an acyl chloride and an ester.

Experimental Section

General

^1H NMR spectra were measured at 500 (or 300) MHz using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were measured at 125 (or 75) MHz using the respective residual solvent resonances. High-resolution mass spectra (FAB or ESI) were measured using *p*-nitrobenzyl alcohol (FAB) as a matrix. Infrared

spectra (IR) were recorded under neat conditions. Thin-layer chromatography (TLC) was undertaken using silica gel 60 F_{254}. Column chromatography was performed using silica gel 60 F_{254}. Manipulations were carried out under nitrogen atmosphere unless otherwise noted. Chloroform was distilled from P_2O_5, and the distillate was re-distilled from K_2CO_3 then finally kept dry on molecular sieves (4 Å). Indium tribromide, Me_3SiBr, I_2, hydrosilanes, bromine sources, hydrosilanes, tetrabutylammonium fluoride (1 M THF solution), Me_3SiCN, and carboxylic acids **1a-o**, aldehyde **5**, acyl chloride **6**, and esters **17** were commercially available, and were used without further purification. With the exception of the compounds **13**, **14**, **14'**, **15**, **16c**, **16e**, **16f**, and **16n**, the compounds prepared with this method were identified in comparison with spectroscopic data reported in the corresponding literature.

One-Pot Synthesis of Alkyl Halides via Reductive Iodination of Carboxylic Acids

In a glove box, $InBr_3$ (0.0300 mmol, 10.6 mg) was placed in a screw vial. The vial was sealed with a PTFE sealed screw cap under N_2 atmosphere and was removed from the glove box. Then, 3-phenylpropanoic acid (**1a**) (0.600 mmol, 90.1 mg), 1,1,3,3-tetramethyldisiloxane (1.80 mmol, 318 μL), and iodine (0.600 mmol, 152.3 mg) were successively added to a distilled chloroform (600 μL) solution containing $InBr_3$. The solution was stirred at room temperature for 5 minutes. The resultant solution was further stirred at 60 ˚C for 2 h. The reaction mixture was cooled to room temperature, then either tetrabutylammonium chloride or tetrabutylammonium fluoride (1.20 mmol) was added. The resultant solution was stirred at 60 ˚C for 5 h. After the reaction, the mixture was cooled to room temperature and was quenched with H_2O (2 mL). The organic layer was washed

with dichloromethane, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 80 : 20) to afford the corresponding alkyl halide.

One-Pot Synthesis of Amine Derivatives via Reductive Iodination of Carboxylic Acids

In a glove box, $InBr_3$ (0.0300 mmol, 10.6 mg) was placed in a screw vial. The vial was sealed with a PTFE sealed screw cap under N_2 atmosphere and was removed from the glove box. Then, 3-phenylpropanoic acid (**1a**) (0.600 mmol, 90.1 mg), 1,1,3,3-tetramethyldisiloxane (1.80 mmol, 318 μL), and iodine (0.600 mmol, 152.3 mg) were successively added to a distilled chloroform (600 μL) solution containing $InBr_3$. The solution was stirred at room temperature for 5 minutes. The resultant solution was further stirred at 60 ˚C for 2 h. The reaction mixture was cooled to room temperature, then an amine (0.720 mmol) and 1,8-diazabicyclo [5.4.0]-7-undecene (0.600 mmol, 91.3 mg) was added. The resultant solution was stirred at 60 ˚C. After the reaction, the mixture was cooled to room temperature and was quenched with H_2O (2 mL). The organic layer was washed with dichloromethane, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 80 : 20) to afford the corresponding amine.

Typical Procedures for the One-Pot Synthesis of Alkyl Cyanides from Carboxylic Acids

Method A: To a 5 mL screw-capped vial under an N_2 atmosphere containing freshly distilled $CHCl_3$ (0.6 mL) were successively added 3-phenylpropanoic acid (**1a**) (0.600 mmol), indium tribromide (0.0300 mmol, 10.6 mg), 1,1,3,3-tetramethyldisiloxane (1.80 mmol, 318 μL) and iodine (0.0600 mmol, 152

mg). The resultant mixture was heated at 60 ˚C (bath temperature) and the consumption of the starting acid was monitored via GC analysis during the reaction time, as shown in Table 2. After this process, to the resultant mixture was added a THF solution (1 mol/L) of tetrabutylammonium fluoride (1.20 mmol, 1.20 mL) and trimethylsilyl cyanide (1.20 mmol, 149 μL). The resultant mixture was further heated at 60 ˚C (bath temperature) for 5 h. The reaction was quenched with a Na_2CO_3 aqueous solution (1 mL). The aqueous layer was extracted with AcOEt (5 mL × 3), and the combined organic phases were dried over anhydrous Na_2SO_4, then filtered and evaporated under reduced pressure. The crude product was purified via silica gel chromatography (hexane/AcOEt = 99:1) to give 3-phenylpropyl cyanide (**16a**) in 95% yield.

Method B: To a 5 mL screw-capped vial under an N_2 atmosphere containing freshly distilled $CHCl_3$ (0.6 mL) were successively added 3-phenylpropanoic acid (**1a**) (0.600 mmol), indium tribromide (0.0300 mmol, 10.6 mg), 1,1,3,3-tetramethyldisiloxane (1.80 mmol, 318 μL) and trimethylbromosilane (0.600 mmol, 78.0 μl). The resultant mixture was heated at 60 ˚C (bath temperature) and the consumption of the starting acid was monitored via GC analysis during the reaction time, as shown in Table 2. After this process, to the resultant mixture was added a THF solution (1 mol/L) of tetrabutylammonium fluoride (1.20 mmol, 1.20 mL) and trimethylsilyl cyanide (1.20 mmol, 149 μL). The resultant mixture was further heated at 60 ˚C (bath temperature) for 5 h. The reaction was quenched with a Na_2CO_3 aqueous solution (1 mL). The aqueous layer was extracted with AcOEt (5 mL × 3), and the combined organic phases were dried over anhydrous Na_2SO_4, then filtered and evaporated under reduced pressure. The crude product was purified via silica gel chromatography (hexane/AcOEt = 99:1) to give 3-phenylpropyl

cyanide (**16a**) in 79% yield.

Compound Characterization

3-Phenylpropyl chloride (11)[12]

91% yield (84.4 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.08 (quint, 2H, *J* = 7.0 Hz), 2.78 (t, 2H, *J* = 7.0 Hz), 3.52 (t, 2H, *J* = 7.0 Hz), 7.18-7.22 (m, 3H), 7.29-7.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.7, 34.0, 44.2, 126.1, 128.4, 128.5, 140.7; MS (EI): *m/z* 154 (M^+, 100%), 156 (M^++2, 75%).

3-Phenylpropyl fluoride (12)[13]

62% yield (51.4 mg); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93-2.04 (m, 2H), 2.73 (t, 2H, *J* = 7.5 Hz), 4.43 (dt, 2H, *J* = 6.0 Hz), 7.17-7.20 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.3 (d, $J_{C\text{-}F}$ = 5.3 Hz), 32.0 (d, $J_{C\text{-}F}$ = 19.6 Hz), 83.0 (d, $J_{C\text{-}F}$ = 165.0 Hz), 126.0, 128.4, 128.5, 141.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -220.5 (m, 1F); MS (EI): *m/z* 138 (M^+, 70%), 91 (M^+-47, 100%).

***N*-Methyl-*N*-phenyl-3-phenylpropylamine (13)**

95% yield (128.4 mg); a colorless oil; IR (neat) ν/cm^{-1} 2941, 1363; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90 (quint, 2H, *J* = 7.5 Hz), 2.64 (t, 2H, *J* = 7.5 Hz), 2.90 (s, 3H), 3.33 (t, 2H, *J* = 7.5 Hz), 6.64-6.69 (m, 3H), 7.16-7.22 (m, 5H), 7.25-7.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 33.3, 38.2, 52.2, 112.2, 116.0, 125.8, 128.3, 128.4, 129.1, 141.8, 149.3; HRMS (FAB): Calcd for $C_{16}H_{19}N$: 225.1517, Found 225.1543.

***N*-(4-Methoxyphenyl)-3-phenylpropylamine (14)**

75% yield (108.6 mg); an orange oil; IR (neat) ν/cm^{-1} 3412, 2964, 2892, 2840, 1268; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93 (quint, 2H, *J* = 7.5 Hz), 2.72 (t, 2H, *J* = 7.5 Hz), 3.10 (t, 2H, *J* = 7.5 Hz), 3.73 (s, 3H), 6.54 (d, 2H, *J* = 9.0 Hz), 6.76 (d, 2H, *J* = 9.0 Hz), 7.18-7.24 (m, 3H), 7.28 (t, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 31.2, 33.4, 44.4, 55.8, 114.1, 114.9, 125.9, 128.3, 128.4, 141.7, 142.6, 152.0; HRMS (FAB): Calcd for $C_{16}H_{19}NO$: 241.1467, Found 241.1460.

***N*-(4-Methoxyphenyl)-bis(3-phenylpropyl)amine (14')**

21% yield (45.3 mg); a yellow oil; IR (neat) ν/cm^{-1} 3412, 2964, 2892, 2840, 1268; ^{1}H NMR (500 MHz, $CDCl_3$) δ1.84 (quint, 4H, *J* = 7.5 Hz), 2.61 (t, 4H, *J* = 7.5 Hz), 3.19 (t, 4H, *J* = 7.5 Hz), 3.74 (s, 3H), 6.60 (d, 2H, *J* = 8.5 Hz), 6.78 (d, 2H, *J* = 8.5 Hz), 7.14-7.19 (m, 6H), 7.23-7.28 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.8, 33.4, 51.6, 55.8, 114.8, 115.4, 125.8, 128.3, 128.4, 141.9, 143.2, 151.6; HRMS (FAB-Magnetic Sector): Calcd for $C_{25}H_{29}NO$: 359.2249, Found 359.2239.

***N*-(3-Phenylpropyl)-4-piperidone (15)**

83% yield (108.2 mg); a yellow oil; IR (neat) ν/cm^{-1} 2948,1715, 1352; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (quint, 2H, *J* = 7.5 Hz), 2 .43-2.49 (m, 6H), 2.68 (t, 2H, *J* = 7.5 Hz), 2.73 (t, 4H, *J* = 6.5 Hz), 7.19 (t, 3H, *J* = 7.5 Hz), 7.28 (t, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.0, 33.5, 41.2, 53.0, 56.6, 125.8, 128.2, 128.3, 141.9, 209.2; HRMS (FAB): Calcd for $C_{14}H_{20}NO$: 218.1545, Found 218.1559.

3-Phenylpropyl cyanide (16a)[14]

95% yield (82.7 mg); a yellow oil; IR (neat) ν/cm^{-1} 2247 (CN); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90 (quint, 2H, *J* = 7.5 Hz), 2.30 (t, 2H, *J* = 7.5 Hz), 2.77 (t, 2H, *J* = 7.5 Hz), 7.18-7.21 (m, 3H) 7.27-7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 26.8, 34.3, 119.4, 126.4, 128.4, 128.6, 139.6; MS (EI) *m/z* 145 (M^+, 100%)

4-Phenylbutyl cyanide (16b)[15]

87% yield (83.1 mg); a yellow oil; IR (neat) ν/cm^{-1} 2247 (CN); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56-1.72 (m, 2H), 1.75-1.82（m, 2H), 2.34 (t, 2H, *J* = 7.5 Hz), 2.66 (t, 2H, *J* = 7.5 Hz), 7.16-7.20 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.0, 24.8, 30.2, 35.0, 119.5, 126.1, 128.3, 128.4, 141.2; MS (EI) *m/z* 159 (M^+,

100%)

1,2,3,4-Tetrahydronaphthalene (4b')[16]

90% yield (71.4 mg); a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.48-1.81 (m, 4H), 2.74-2.76 (m, 4H), 7.03-7.10 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 23.2, 29.4, 125.4, 129.1, 137.1; MS (EI): *m/z* 132 (M^+, 75%), 104 (M^+ -18, 100%)

***o*-Methylphenethyl cyanide (16c)**

96% yield (83.6 mg); a yellow oil; IR (neat) ν/cm^{-1} 2247 (CN); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.58 (t, 2H, *J* = 7.5 Hz) , 2.98 (t, 2H, *J* = 7.5 Hz), 7.16-7.19 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 19.1, 28.9, 119.1, 126.5, 127.4, 128.7, 130.6, 135.8, 136.2; MS (EI) *m/z* 145 (M^+,100%) HRMS (EI): Calcd for $C_{10}H_{11}N$: 145.0891, Found 145.0908.

***p*-Chlorophenethyl cyanide (16d)**[17]

81% yield (80.5 mg); a yellow oil; IR (neat) ν/cm^{-1} 2247 (CN); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 (t, 2H, *J* = 7.5 Hz), 2.94 (t, 2H, *J* = 7.5 Hz), 7.16-7.20 (m, 2H), 7.30-7.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 30.9, 118.7, 129.0, 129.6, 133.2, 136.4; MS (EI) *m/z* 165 (M^+, 100%), 166 (M^++1, 10%), 167 (M^++2, 30%), 168 (M^++3, 5%).

***p*-Bromophenethyl cyanide (16e)**

83% yield (104.6 mg); a yellow oil; IR (neat) ν/cm^{-1} 2247 (CN); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61 (t, 2H, *J* = 7.5 Hz), 2.9 (t, 2H, *J* = 7.5 Hz), 7.10-7.13 (m, 2H), 7.45-7.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 30.9, 118.7, 121.2, 130.0, 132.0, 136.9; MS (EI) *m/z* 209 (M^+, 70%), 211 (M^++2, 70%), 169 (M^+-40, 100%). HRMS (EI): Calcd for C_9H_8BrN: 208.9840, Found 208.9830.

***o*-Iodophenethyl cyanide (16f)**

72% yield (111.1 mg); a yellow oil; IR (neat) ν/cm^{-1} 2247 (CN); ^{1}H NMR (500 MHz,

$CDCl_3$) δ 2.63-2.68 (m, 2H), 3.05-3.09 (m, 2H), 6.96-6.99 (m, 1H), 7.30-7.36 (m, 2H), 7.83-7.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8, 36.5, 99.7, 118.6, 128.9, 129.2, 129.9, 139.8, 140.4; MS (EI) *m/z* 257 (M^+, 100%) HRMS (EI): Calcd for C_9H_8IN: 256.9701, Found 256.9717.

_p_-Hydroxyphenethyl cyanide (16g)[18]

91% yield (80.4 mg); a yellow oil; IR (neat) ν/cm^{-1} 2253 (CN); ^1H NMR (300 MHz, $CDCl_3$) δ 2.59 (t, 2H, *J* = 7.5 Hz), 2.89 (t, 2H, *J* = 7.5 Hz), 5.17 (s, 1H), 6.77-6.81 (m, 2H), 7.07-7.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 30.7, 115.7, 119.2, 129.5, 130.1, 154.8; MS (EI): *m/z* 147 (M^+, 20%), 107 (M^+-40, 100%).

_p_-(Trifluoromethyl)benzyl cyanide (16k)[19]

79% yield (87.8 mg); a yellow oil; IR (neat) ν/cm^{-1} 2254 (CN); ^1H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 2H), 7.47 (d, 2H, *J* = 8.0 Hz), 7.65 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 117.0, 123.9 (q, J_{C-F} = 271.9 Hz), 126.2 (q, J_{C-F} = 3.9 Hz), 128.4, 130.6 (q, J_{C-F} = 32.6 Hz), 134.0; MS (EI): *m/z* 185 (M^+, 70%), 116 (M^+ -69, 100%)

1,2-Bis(2-cyanoethyl)benzene (16n)

66% yield (73.0 mg); a yellow oil; IR (neat) ν/cm^{-1} 2256 (CN); ^1H NMR (300 MHz, $CDCl_3$) δ 2.64 (t, 4H, *J* = 7.5 Hz), 3.02 (t, 4H, *J* = 7.5 Hz), 7.21-7.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 27.9, 118.8, 128.0, 129.4, 135.8; MS (EI): *m/z* 184 (M^+, 40%), 144 (M^+ -40, 100%) HRMS (EI): Calcd for $C_{12}H_{12}N_2$: 184.1000, Found 184.1022.

Phenylthioethyl cyanide (16o)[20]

34% yield (33.3 mg); a yellow oil; IR (neat) ν/cm^{-1} 2251 (CN); ^1H NMR (500 MHz, $CDCl_3$) δ 2.59 (t, 2H, *J* = 7.5 Hz), 3.13 (t, 2H, *J* = 7.5 Hz), 7.26-7.42 (m, 3H), 7.42-7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 30.2, 117.9, 127.7, 129.3,

131.4, 133.1; MS (EI): *m/z* 163 (M^+, 70%), 123 (M^+ -40, 100%).

2-Phenylethyl cyanide (16p)[21]

71% yield (55.9 mg); a yellow oil; IR (neat) ν/cm^{-1} 2248 (CN); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (t, 2H, *J* = 7.5 Hz), 2.96 (t, 2H, *J* = 7.5 Hz), 7.22-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 31.5, 119.1, 127.2, 128.2, 128.9, 138.0; MS (EI): m/z *131* (M+, 90%), 91 (M+ -40, 100%)

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Conclusion

This thesis dwells on the conversion from carboxylic acids to alkyl bromide and alkyl iodides treated by a indium(III) compound, a hydrosilane, and a bromine source or an iodine source, and application to the one-pot synthesis of various compounds from carboxylic acids.

In ***Chapter 1***, the author found that a combination of $InBr_3$, TMDS, and a bromine source or an iodine source achieves direct bromination or iodination of a variety of carboxylic acids and their derivatives, such as an acyl chloride, an aldehyde, and an ester. And insight into the reaction mechanism was gained via the time course of NMR monitoring experiments and the corresponding stepwise reactions.

In ***Chapter 2***, as the application of the indium(III)-catalyzed reductive bromination or iodination of carboxylic acid, the author demonstrated the one-pot synthesis of alkyl halides, amine derivatives, and alkyl cyanides via the addition of nucleophiles into the reductive bromination or iodination of carboxylic acid.

List of Publications

1. Indium-Catalyzed Reductive Bromination of Carboxylic Acids Leading to Alkyl Bromides

   Toshimitsu Moriya, Shinichiro Yoneda, Keita Kawana, Reiko Ikeda, Takeo Konakahara, Norio Sakai

   Organic Letters, Vol. 14, No. 18, pp 4842-4845 (2012)

2. Indium(III)-Catalyzed Reductive Bromination and Iodination of Carboxylic Acids to Alkyl Bromides and Iodides: Scope, Mechanism, and One-Pot Transformation to Alkyl halides and Amine Derivatives

   Toshimitsu Moriya, Shinichiro Yoneda, Keita Kawana, Reiko Ikeda, Takeo Konakahara, Norio Sakai

   The Journal of Organic Chemistry, Vol. 78, No. 21, pp 10642-10650 (2013)

3. Indium(III)-Catalyzed One-Pot Synthesis of Alkyl Cyanides from Carboxylic Acids

   Toshimitsu Moriya, Kohei Shoji, Shinichiro Yoneda, Reiko Ikeda, Takeo Konakahara, Norio Sakai

   Synthesis, Vol. 45, pp 3233-3238 (2013)

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