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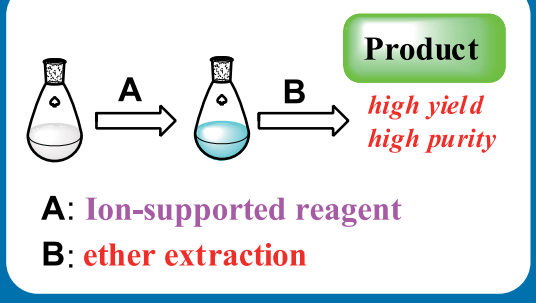

Contribution

Study of Ion-supported Reagents for Organic Synthesis: IS-Ph_3P, IS-MSO, IS-MS, and IS-DIB

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1. Introduction

In organic synthesis, most reactions require organic reagents and therefore, after each reaction, the desired product must be purified by column chromatography to remove organic co-products derived from organic reagents. In view of environmentally benign organic synthesis, novel ion-supported reagents, such as ion-supported Ph_3P (IS-Ph_3P **A** and **B**), ion-supported methyl sulfoxide (IS-MSO **C** and **D**), ion-supported methyl sulfide (IS-MS **E** and **F**), ion-supported (diacetoxyiodo)-benzene (IS-DIB **G** and **H**), and super-DIB (**I**) were developed for easy isolation of desired products from the reaction mixture and reuse of those ion-supported reagents for the same reactions, as shown in Fig. 1. The great advantages of these ion-supported reagents are the simple isolation of the desired products by diethyl ether extraction of the reaction mixture and subsequent removal of the solvent, and their recyclable use for the same reactions through high recovery and efficient regeneration, and therefore those ion-supported reagents are user-friendly and environmentally benign. Experimental procedure for the reaction with ion-supported reagents, isolation of the products, and regeneration and reuse of the ion-supported reagents is shown in Fig. 2

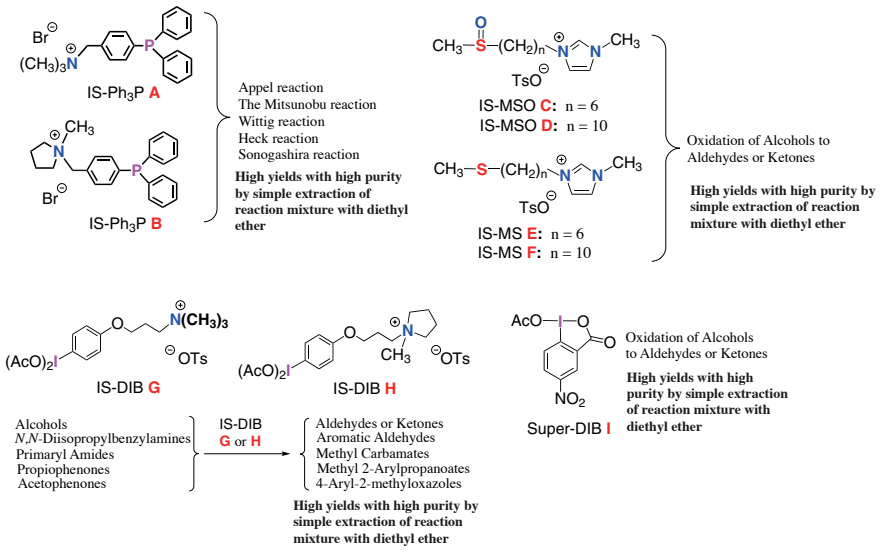


Figure 1. Ion-supported reagents.

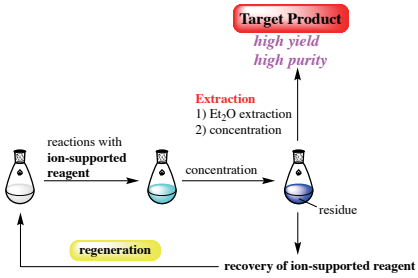


Figure 2. Reaction, recovery, regeneration, and reuse of ion-supported reagents.

2. Ion-supported Ph_3P (IS-Ph_3P)

Ph_3P is one of the most important reagents for organic synthesis, because it can be used for the halogenation of alcohols with CBr_4 or I_2 / imidazole (Appel reaction),[1] esterification of carboxylic acids with alcohols and diethyl azodicarboxylate (DEAD) (Mitsunobu reaction),[2] olefination of aldehydes with phosphonium ylide (Wittig reaction),[3] Pd-catalyzed reaction as a ligand (Sonogashira reaction, Mizoroki-Heck reaction),[4] *etc*. However, Ph_3PO as a co-product is formed in the Appel reaction, the Mitsunobu reaction, and the Wittig reaction, and therefore, it must be removed by column chromatography carefully. Even for the Pd-catalyzed reaction with Ph_3P as a ligand, the reaction mixture must be purified by column chromatography.

2-1. Halogenation of alcohols

IS-Ph_3P **A** and **B** are solid, respectively, and IS-Ph_3P **A** and **B** are efficient reagents for the bromination and iodination of alcohols with CBr_4 and I_2 / imidazole, respectively. After the reaction, diethyl ether was added to the reaction mixture to separate the IS-Ph_3PO and the oil. After filtration and removal of ether solvent from the filtrate, the corresponding alkyl halides were obtained in high yields with high purity (>90%) in both IS-Ph_3P **A** and **B**, without chromatography, by simple diethyl ether extraction of the reaction mixture and subsequent removal of the solvent, as shown in Table 1. Moreover, ion-supported Ph_3PO, 4-(diphenylphosphino)benzyltrimethylammonium bromide and *N*-methyl-*N*-[4-(diphenylphosphino)benzyl]-pyrrolidinium bromide, were recovered in over 90% yield. After the *O*-methylation of the recovered ion-supported Ph_3PO with dimethyl sulfate and the subsequent reduction with $LiAlH_4$, IS-Ph_3P **A** and **B** could be regenerated in high yield, and could be reused for the same halogenation reaction, keeping high yield and high purity of alkyl halides under the same conditions and procedure.[5]

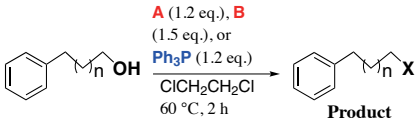
2-2. Mitsunobu reaction

IS-Ph_3P **A** and **B** could be also used for esterification of 3-(4'-methoxyphenyl)propanoic acid with 2-phenylethanol and diisopropyl azodicarboxylate (DIAD) in dichloromethane to provide the corresponding 2"-phenylethyl 3-(4'-methoxyphenyl)-propanoate in good yields, as shown in Table 2. After the reaction, diethyl ether was added to the reaction mixture to separate the IS-Ph_3PO and the oil. After filtration and removal of ether solvent from the filtrate, the corresponding ester was obtained in high yields with high purity (>90%) in both IS-Ph_3P **A** and **B**, respectively, without chromatography. Each IS-Ph_3PO was recovered in over 90% yield. Again, after the *O*-methylation of the recovered ion-supported Ph_3PO with dimethyl sulfate and the subsequent reduction with $LiAlH_4$, IS-Ph_3P **A** and **B** could be regenerated and reused for the same esterification reaction, maintaining good yield with high purity.[5] On the other hand, when Ph_3P was used for the same esterification of 3-(4'-methoxyphenyl)propanoic acid under the same conditions, Ph_3PO was recovered only in 30% yield, together with the ester in 87% yield after purification from ether extracts, as shown in Table 2. This result indicates again IS-Ph_3P **A** and **B** are efficiently recyclable reagents for the esterification of carboxylic acids and the purity of ether extracts from the reaction mixture is enough high.

2-3. Wittig reaction

IS-Ph_3P **A** and **B** were used for the Wittig reaction. Thus, ion-supported phosphonium salts **A1** and **B1**, which were prepared from the reactions of IS-Ph_3P **A** and **B** with ethyl bromoacetate, respectively, reacted with aromatic and aliphatic aldehydes in the presence of K_2CO_3 to give the corresponding α,β−unsaturated ethyl esters in good yields with high purity by simple filtration of the reaction mixture and subsequent removal of the solvent from the filtrate, as shown in Table 3. Similarly, ion-supported phosphonium salts **A2** and **B2**,

Table 1. Halogenation of alcohols.



Bromination: CBr_4 (1.1 eq.) and **A**, **B**, or Ph_3P
Iodination: I_2 (1.5 eq.), imidazole (1.5 eq.), KI (5 eq.)

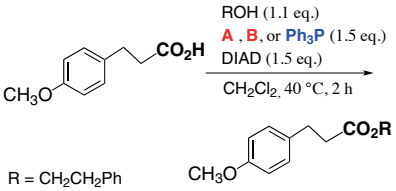
A	**Product** / %		
	n = 0	n = 1	n = 2
X = Br	86	95, 88[a], 76[b]	91
X = I	85	80	80

B	**Product** / %		
	n = 0	n = 1	n = 2
X = Br	89	95, 93[a], 87[b]	97
X = I	83	85	83

Ph_3P	**Product** / %		
	n = 0	n = 1	n = 2
X = Br	72[c]	68[c]	53[c]

[a] Yield of product with the first regenerated **A** or **B**.
[b] Yield of product with the second regenerated **A** or **B**.
[c] Purity of the product after removal of ether from the extracts was 14%~43%. Ph_3PO was recovered in 42~44% yield.

Table 2. Esterification of carboxylic acid.

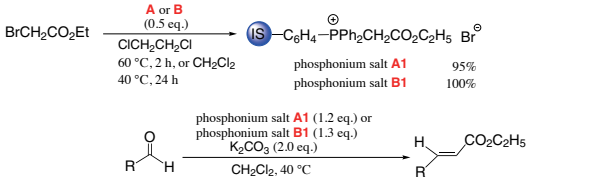


	Yield of Ester / %		
Reuse	0	1	2
A	84	79[a]	70[b]
B	87	80[a]	77[b]
Ph_3P	87[c]	-	-

[a] Yield of ester with the first regenerated **A** or **B**.
[b] Yield of ester with the second regenerated **A** or **B**.
[c] Ph_3PO was recovered in 30% yield.

which were prepared from the reactions of IS-Ph_3P **A** and **B** with *p*-methylbenzyl bromide, respectively, reacted with aromatic and aliphatic aldehydes in the presence of NaH to provide the corresponding *p*-methylstyrene derivatives in good yields with high purity by simple filtration of the reaction mixture and the subsequent removal of the solvent from the filtrate. In both reactions, the co-product, ion-supported Ph_3PO, could be obtained quantitatively by simple filtration, and was converted into the corresponding IS-Ph_3P **A** and **B** again in high yields using dimethyl sulfate, followed by the reduction with $LiAlH_4$. Recovered and regenerated IS-Ph_3P **A** and **B** could be reused for the same Wittig reaction while maintaining good yields of ethyl (*E*)-3-(4'-chlorophenyl)-2-propenoate and 1-(4'-chlorophenyl)-2-(4"-methylphenyl)ethene with high purity by simple filtration and removal of the solvent from the filtrate, as shown in Tables 3 and 4, respectively.[6)]

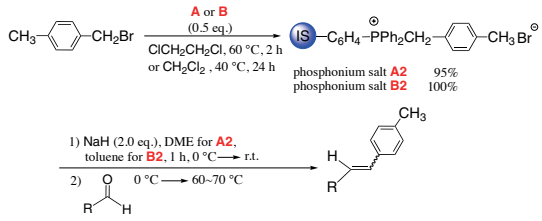
Table 3. Wittig reaction with IS-Ph_3P **A** and **B**.



Substrate	**A** α,β–Unsaturated Ester				**B** α,β–Unsaturated Ester			
	Time (h)	Yield (%)[a]	Purity (%)[b]	*E*:*Z*	Time (h)	Yield (%)[a]	Purity (%)[b]	*E*:*Z*
Cl–C6H4–CHO	8	94	97	96:4	8	98	98	94:6
	8[c]	95	97	96:4	8[c]	95	90	96:4
	8[d]	92	97	96:4	8[d]	91	90	96:4
	8[e]	99	43	96:4				
CH3–C6H4–CHO	10	95	98	97:3	8	96	90	96:4
CH3O–C6H4–CHO	50	98	97	96:4	24	91	90	95:5
CH3(CH2)6CHO	24	100	97	97:3	20	90	86	93:7
C6H5–CH=CH–CHO	24	93	89	90:10	20	92	95	92:8
(CH3)2C=CH–CHO	24	92	90	95:5	16	88	80	94:6

[a] Isolated yield of *E* and *Z* alkenes. Ion-supported Ph_3PO was recovered in 92%~100% yields.
[b] Purity of product after removal of solvent from the extracts.
[c] The first regenerated IS-Ph_3P **A** or **B** was used.
[d] The second regenerated IS-Ph_3P **A** or **B** was used.
[e] **Ph_3P** was used instead of IS-Ph_3P **A** or **B**, and Ph_3PO was recovered in 50% yield.

Table 4. Wittig reaction with IS-Ph_3P **A** and **B**.



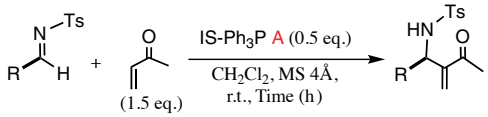
Substrate	**A** Styrene Derivative				**B** Styrene Derivative			
	Time (h)	Yield (%)[a]	Purity (%)[b]	*E*:*Z*	Time (h)	Yield (%)[a]	Purity (%)[b]	*E*:*Z*
Cl–C6H4–CHO	8	95	95	75:25	9	91	90	75:25
	8[c]	94	95	75:25	9[c]	90	85	75:25
	8[d]	92	95	75:25	9[d]	90	81	75:25
	9[e]	90	46	50:50				
CH3–C6H4–CHO	10	95	95	75:25	9	100	90	78:28
CH3O–C6H4–CHO	50	91	96	79:21	24	90	95	81:19
CH3(CH2)6CHO	24[f]	86	91	71:29	24[f]	77	70	74:26
C6H5–CH=CH–CHO	24	91	94	90:10	24	82	90	84:16
(CH3)2C=CH–CHO	24[f]	71	64	78:22	24[f]	85	56	71:29

[a] Isolated yield of *E* and *Z* alkenes. Ion-supported Ph_3PO was recovered in 93%~100% yields.
[b] Purity of product after removal of solvent from the extracts .
[c] The first regenerated IS-Ph_3P **A** or **B** was used.
[d] The second regenerated IS-Ph_3P **A** or **B** was used.
[e] **Ph_3P** was used instead of IS-Ph_3P **A** or **B**, and Ph_3PO was recovered in 46% yield.

2-4. *aza*-Morita-Baylis-Hillman reaction

Various *N*-tosyl arylimines reacted with methyl vinyl ketone in the presence of IS-Ph_3P **A** and **B** to give adducts, *N*-(2'-methylene-3'-oxo-1'-arylbutyl)-4-methylbenzenesulfonamides, in good yields with high purity by simple diethyl ether extraction of the reaction mixture and subsequent removal of the solvent, as shown in Table 5 and 6. Moreover, IS-Ph_3P **A** and **B** could be repeatedly used for the same reaction to provide the corresponding adducts while maintaining good yields with high purity.[7)]

Table 5. *aza*-Morita-Baylis-Hillman Reaction with IS-Ph_3P **A**.



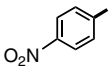
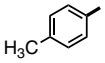
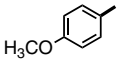
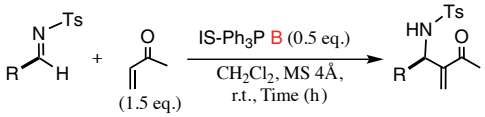
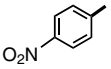
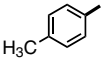
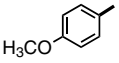
R	Time (h)	Yield (%)	Purity (%)
	24	100	92
	24	95	91
	5	97	94
	3	94	90
	24	96	97
	24	94	95
	24	87	90
	48	74	86
	50	80	85
	48	60	80

Table 6. *aza*-Morita-Baylis-Hillman Reaction with IS-Ph_3P **B**.



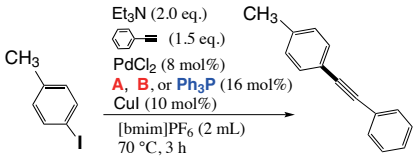
R	Time (h)	Yield (%)	Purity (%)
	24	95	99
	24	94	90
	5	100	95
	3	92	93
	24	97	99
	24	95	92
	24	90	90
	48	66	50
	50	85	80
	48	62	78

2-5. Sonogashira reaction

Ionic liquid reaction media containing $Pd(OAc)_2$ or $PdCl_2$ and IS-Ph_3P **A** and **B** as catalysts could be used and reused for the Sonogashira reaction and the Mizoroki-Heck reaction maintaining high yields of products, using iodotoluene with phenylacetylene and methyl acrylate, respectively. The Sonogashira reaction with IS-Ph_3P **A** and **B** are shown in Table 7.[5)]

Today, IS-Ph_3P **B** is commercially available from Tokyo Chemical Industry Co., Ltd.

Table 7. Sonogashira reaction.



Reuse	Yield of product / %		
	A	**B**	**Ph_3P**
0	100[a]	100[a]	91[b]
1[c]	100[a]	100[a]	92[b]
2[c]	97[a]	100[a]	99[b]
3[c]	100[a]	100[a]	76[b]
4[c]	100[a]	100[a]	41
5[c]	96[a]	90[a]	18
6[c]	96[a]	95[a]	-
7[c]	100[a]	94[a]	-

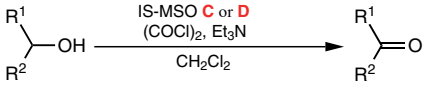
[a] Yield of product. Purity of the product after removal of ether from the extracts was 95~85%.
[b] Yield of product. Each ether extract contains 2~3% of Ph_3P.
[c] Only iodotoluene, phenylacetylene, and Et_3N were added.

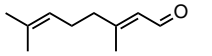
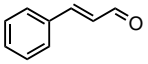
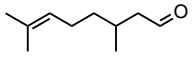
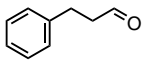
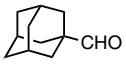
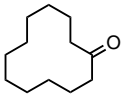
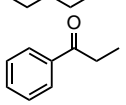
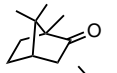
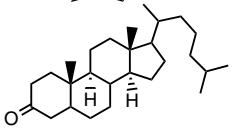
3. Ion-supported Methyl Sulfoxide (IS-MSO) and Ion-supported Methyl Sulfide (IS-MS)

The Swern oxidation[8] of various benzylic and allylic alcohols, primary alcohols, and secondary alcohols with IS-MSO **C** or **D**, and oxalyl chloride in the presence of triethylamine in dichloromethane, followed by simple diethyl ether extraction of the reaction mixture and subsequent removal of the solvent, gave the corresponding aldehydes and ketones, respectively, in good yields with high purity, as shown in Table 8.[9] Here, IS-MSO **C** is odorless viscous oil and IS-MSO **D** is a odorless solid. On the other hand, IS-MS **E** and **F** are odorless solid, respectively. The Corey-Kim oxidation[10] of various benzylic and allylic alcohols, primary alcohols, and secondary alcohols with IS-MS **E** or **F**, and *N*-chlorosuccinimide in the presence of triethylamine in dichloromethane, followed by simple diethyl ether extraction of the reaction mixture and subsequent removal of the solvent, furnished the corresponding aldehydes and ketones, respectively, in good yields with high purity, as shown in Table 9.[11] Both reactions did not produce any unpleasant odor at all. In the Swern oxidation, ion-supported methyl sulfides were recovered in high yields and could be re-oxidized to produce IS-MSO **C** and **D** with hydrogen peroxide, for reuse in the same oxidation. In the Corey-Kim oxidation, IS-MS **E** and **F** were recovered in high yields and could be also reused for the same oxidation.

Today, IS-MSO **C** and IS-MS **E** is commercially available from Tokyo Chemical Industry Co., Ltd.

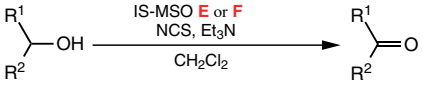
Table 8. Swern oxidation with IS-MSO **C** and **D**.

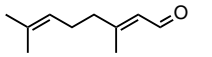
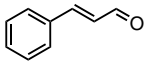
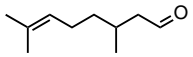
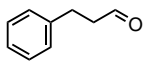
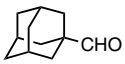
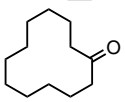
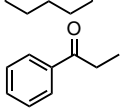
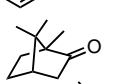
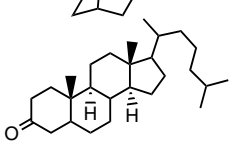


IS-MSO C or D	Product	Yield	Purity
C	MeO–C6H4–CHO	92	99
D		98	98
C	Cl–C6H4–CHO	84	88
D		84	96
C	1,3-benzodioxole-5-CHO	99	98
C[a]		95	99
D		94	89
D[a]		84	99
C	tBu-O-C(=O)-O-C6H4–CHO	93	99
D		86	99
C		99	99
D		94	94
C		99	98
D		92	93
C		83	82
D		89	99
C		85	85
D		92	99
C		78	90
D		90	99
C	TBSO–C6H4=O	96	99
D		95	99
C	TsHN–C6H4=O	99	99
D		99	99
C		99	99
D		91	99
C		99	99
D		91	99
C		99	99
D		92	99
C		88	99
D		99	99

[a] Ion-supported methyl sulfide that was recovered and regenerated, was reused.

Table 9. Corey-Kim oxidation with IS-MS **E** and **F**.



IS-MSO E or F	Product	Yield	Purity
E	MeO–C6H4–CHO	97	99
F		83	84
E	Cl–C6H4–CHO	85	96
F		81	95
E	1,3-benzodioxole-5-CHO	93	97
F		81	94
E	tBu-O-C(=O)-O-C6H4–CHO	89	96
F		88	99
E		82	94
F		74	99
E		94	96
F		75	78
E		80	99
F		90	80
E		94	97
F		92	91
E		92	98
F		87	99
E	TBSO–C6H4=O	86	86
F		86	99
E	TsHN–C6H4=O	85	99
F		78	99
E		99	99
F		83	99
E		99	98
F		88	99
E		99	99
E[a]		90	99
F		85	99
F[a]		84	97
E		88	99
F		90	99

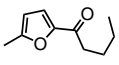
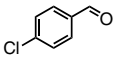
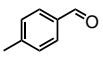
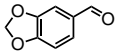
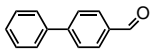
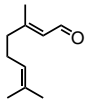
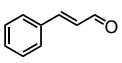
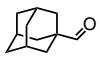
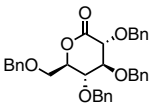
[a] Ion-supported methyl sulfide that was recovered, was reused.

4. Ion-supported (Diacetoxyiodo)benzene (IS-DIB)

Recently, oxidation of alcohols with (diacetoxyiodo)-benzene (DIB) in the presence of 2,2,6,6-tetramethylpiperidine-1-oxy radical (TEMPO) at room temperature has become very popular,[12] due to the mild metal-free oxidation of alcohols. The oxidation of secondary alcohols and primary alcohols with IS-DIB **G** and **H** in the presence of a catalytic amount of TEMPO in dichloromethane at room temperature proceeded efficiently to provide the corresponding ketones and aldehydes, respectively, in good yields with high purity by simple diethyl ether extraction of the reaction mixture and subsequent removal of the solvent, as shown in Table 10. Oxidative reaction of *p*-substituted *N*,*N*-diisopropylbenzylamines with IS-DIB **G** and **H** was also carried out to generate the corresponding aromatic aldehydes in good yields with high purity by simple diethyl ether extraction of the reaction mixture and subsequent removal of the solvent, as shown in Table 11. In addition, the Hofmann reaction of primary amides in methanol under basic conditions and oxidative 1,2-rearrangement reaction of propiophenones in trimethyl orthoformate under acidic conditions with IS-DIB **G** and **H** provided the corresponding methyl carbamates and methyl 2-arylpropanoates, respectively, in good yields with high purity again, by simple diethyl ether extraction of the reaction mixture and subsequent removal of the solvent, as shown in Table 12 and Table 13. Moreover, treatment of *p*-substituted acetophenones with IS-DIB **G** and **H** in the presence of trifluoromethanesulfonic acid in acetonitirle generated the corresponding 5-aryl-2-methyloxazoles in good yields with high purity, as shown in Table 14. In those five reactions, the products were obtained in good yields with high purity by simple diethyl ether extraction of the reaction mixture and subsequent removal of the solvent from the extract. Moreover, ion-supported iodobenzenes, which were co-products derived from IS-DIB **G** and **H** in the present oxidative reactions, were recovered in good yields and could be re-oxidized to IS-DIB **G** and **H** by the reaction with *m*-chloroperoxybenzoic acid (*m*CPBA)[13] and regenerated IS-DIB **G** and **H** could be reused for the same oxidative reactions.[14] On the other hand, when DIB was used for these reactions under the same conditions and procedure, the corresponding products were obtained in good yields, however, the purity of the products was less than 50% due to the presence of iodobenzene, as shown in Tables 10~14.

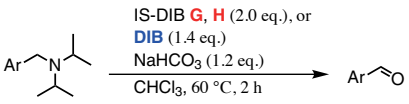
Table 10. Oxidation of alcohols with IS-DIB **G** and **H**.

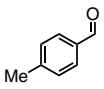
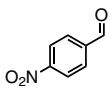
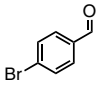
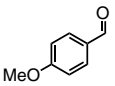
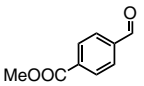
Alcohol —(IS-DIB **G**, **H** or **DIB** (1.5 eq.), TEMPO (10 mol%), CH_2Cl_2 (0.25 M), r.t., Time (h))→ **Aldehyde or Ketone**

IS-DIB **G**, **H**, or **DIB**	Aldehyde or Ketone Time (h), Yield (%), [Purity (%)]	
		
IS-DIB **G** IS-DIB **H**	8, 97, [97] 4.5, 99, [99]	9, 99, [99] 10.5, 93, [98]
		
IS-DIB **G** IS-DIB **H**	6, 98, [99] 2, 98, [99]	4, 98, [99] 1.5, 98, [99]
		
IS-DIB **G** IS-DIB **H**	8, 95, [92] 3.5, 97, [99]	6, 98, [98] 6, 99, [99]
		
IS-DIB **G** IS-DIB **H** **DIB**	6, 99, [99] 3, 99, [99] 1.5, 99, [48]	2, 99, [98] 1.5, 94, [99]
		
IS-DIB **G** IS-DIB **H** IS-DIB **A**[a] IS-DIB **B**[a]	4, 98, [99] 2, 98, [99] 4, 99, [98] 2, 99, [99]	18, 91, [88] 12, 84, [83]
		
IS-DIB **G** IS-DIB **H** **DIB**	12, 99, [99] 6, 95, [99] 4.5, 99, [48]	6, 94, [94] 5, 99, [99] 1.5, 97, [48]

[a] Recovered and regenerated IS-DIB was used.

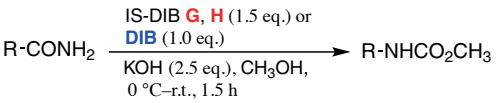
Table 11. Oxidation of *N*,*N*-diisopropylbenzylamines with IS-DIB **G** and **H**.

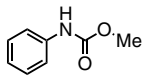
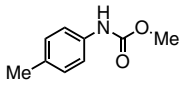
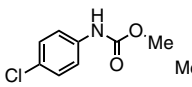
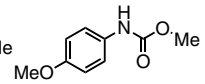
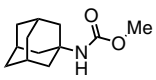
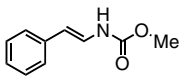


IS-DIB **G**, **H**, or **DIB**	Aldehyde Yield (%), [Purity (%)]	
		
IS-DIB **G** IS-DIB **H** **DIB** IS-DIB **G**[a] IS-DIB **H**[a]	94, [99] 97, [98] 82, [33] 95, [97] 96, [94]	94, [99] 93, [97] 87, [45]
		
IS-DIB **G** IS-DIB **H** **DIB**	92, [99] 93, [98] 88, [45]	91, [99] 92, [97] 87, [40]
		
IS-DIB **G** IS-DIB **H** **DIB**	93, [98] 92, [98] 86, [42]	87, [86] 88, [87] 81, [33]

[a] Recovered and regenerated IS-DIB was used.

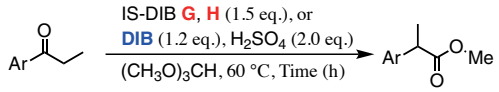
Table 12. Hofmann reaction with IS-DIB **G** and **H**.



IS-DIB G, H, or DIB	Methyl carbamate Yield (%), [Purity (%)]	
		
IS-DIB G	99, [99]	97, [98]
IS-DIB H	99, [99]	98, [99]
DIB	99, [68]	99, [70]
IS-DIB G[a]	99, [99]	
IS-DIB H[a]	99, [99]	
		
IS-DIB G	99, [99]	98, [98]
IS-DIB H	97, [99]	97, [98]
DIB	98, [67]	98, [66]
		
IS-DIB G	99, [99]	97, [99]
IS-DIB H	99, [99]	96, [97]
DIB	99, [65]	98, [66]

[a] Recovered and regenerated IS-DIB was used.

Table 13. Oxidative reaction of propiophenones with IS-DIB **G** and **H**.



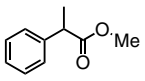
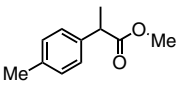
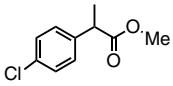
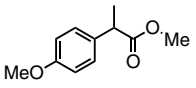
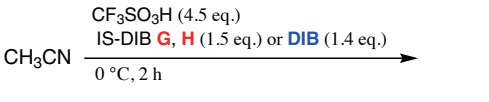
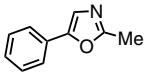
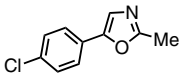
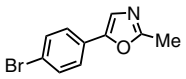
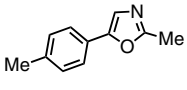
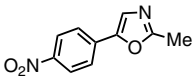
IS-DIB G, H, or DIB	Methyl ester Time (h), Yield (%), [Purity (%)]	
		
IS-DIB G	3, 95, [95]	3, 98, [99]
IS-DIB H	3, 99, [99]	3, 94, [97]
DIB	2, 94, [52]	2, 95, [47]
IS-DIB G[a]	3, 97, [97]	3, 94, [96]
IS-DIB H[a]	3, 96, [96]	3, 94, [97]
		
IS-DIB G	5, 96, [99]	3, 99, [99]
IS-DIB H	5, 95, [98]	3, 95, [97]

Table 14. Formation of oxazoles with IS-DIB **G** and **H**.



IS-DIB G,H, or DIB	Oxazole Time (h), Yield (%), [Purity (%)]	
		
IS-DIB G	5, 93, [95]	5, 92, [93]
IS-DIB H	5, 92, [96]	5, 91, [92]
DIB	3, 91, [38]	3, 94, [40]
IS-DIB G[a]	5, 92, [94]	
IS-DIB H[a]	5, 92, [95]	
		
IS-DIB G	5, 94, [94]	7, 92, [94]
IS-DIB H	5, 93, [93]	7, 90, [90]
DIB	3, 92, [39]	6, 92, [41]
		
IS-DIB G	5, 94, [95]	
IS-DIB H	5, 93, [93]	
DIB	3, 97, [42]	

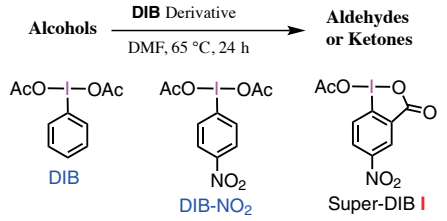
[a] Recovered and regenerated IS-DIB was used.

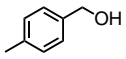
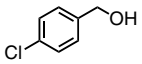
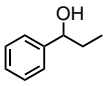
5. Super-DIB

DMP (Dess-Martin Periodinane) [I(V)] is one of the most excellent reagents for the oxidation of alcohols to aldehydes or ketones.[15] However, it is explosive and therefore, it is very difficult to carry out the oxidation of alcohols with DMP in large preparative scale. To break through this problem, super-DIB **I** [I(III)] was prepared and the oxidation of alcohols was carried out to give the corresponding aromatic aldehydes and ketones in good yields with high purity, as shown in Table 15.[16] After the reaction, water was added to the reaction mixture, and the product could be obtained by simple diethyl ether extraction of the reaction mixture and subsequent removal of the solvent. *p*-Nitro-*o*-iodobenzoic acid, co-product, could be also extracted and recovered by chloroform in high yield from the water by acidification. Super-DIB **I** could be regenerated by the treatment with *m*CPBA in acetic acid[13] and could be reused for the same reactions to give the product in good yield with high purity.

Now, Super-DIB **I** is under way as a commercially available reagent in Tokyo Chemical Industry Co., Ltd.

Table 15. Oxidation of alcohols with Super-DIB **I**.



Alcohol	DIB Derivative	Aldehyde or Ketone Yield (%)	[Purity (%)]
	DIB (2.0 eq.)	16	[3]
	DIB-NO_2 (2.0 eq.)	35	[14]
	Super-DIB **I** (2.0 eq.)	97	[98]
	DIB (2.0 eq.)	23	[8]
	DIB-NO_2 (2.0 eq.)	35	[15]
	Super-DIB **I** (2.0 eq.)	87	[86]
	DIB (2.0 eq.)	20	[5]
	DIB-NO_2 (2.0 eq.)	31	[12]
	Super-DIB **I** (2.0 eq.)	87	[86]

Acknowledgement

Financial support in the form of a Grant-in–Aid for Scientific Research (No. 23655142, 20550033) from the Ministry of Education, Culture, Sports, Science, and Technology in Japan, Futaba Memorial Foundation, and Iodine Research Project in Chiba University is gratefully acknowledged.

References

1) R. Appel, *Chem. Ber.* **1971**, *104*, 1030; **1975**, *108*, 2680.
2) O. Mitsunobu, *Synthesis* **1981**, 1.
3) (a) G. Wittig, U. Schollkopf, *Chem. Ber.* **1954**, *87*, 1318. (b) G. Wittig, W. Haag, *Chem. Ber.* **1955**, *88*, 1654.
4) (a) T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320. (c) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467.
5) M. Imura, N. Shimojuh, Y. Kawano, H. Togo, *Tetrahedron* **2010**, *66*, 3421; H. Togo, Y. Imura, K. Tahara, JP Pat. Appl. 2010-11476.
6) N. Shimojuh, Y. Imura, K. Moriyama, H. Togo, *Tetrahedron* **2011**, *67*, 951.
7) Y. Imura, N. Shimojuh, K. Moriyama, H. Togo, *Tetrahedron* **2012**, *68*, 2319.
8) (a) A. J. Mancuso, S. L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480. (b) K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651. (c) A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165.
9) D. Tsuchiya, K. Moriyama, H. Togo, *Synlett* **2011**, 2701; H. Togo, D. Tsuchiya, M. Tabata, K. Moriyama, Y. Mitsumoto, JP Pat. Appl. 2011-183102.
10) E. J. Corey, C. U. Kim, *J. Am. Chem. Soc.* **1972**, *94*, 7586.
11) D. Tsuchiya, M. Tabata, K. Moriyama, H. Togo, *Tetrahedron* **2012**, *68*, 6849; H. Togo, D. Tsuchiya, M. Tabata, K. Moriyama, K. Takatsuki, JP Pat. Appl. 2011-290627.
12) A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974.
13) M. Iinuma, K. Moriyama, H. Togo, *Synlett* **2012**, *21*, 2663.
14) Y. Suzuki, M. Iinuma, K. Moriyama, H. Togo, *Synlett* **2012**, 1250; H. Togo, Y. Suzuki, M. Iinuma, K. Moriyama, K. Takatsuki, JP Pat. Appl. 2011-290626; M. Iinuma, K. Moriyama, H. Togo, *Tetrahedron* **2013**, *69*, 2961.
15) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.
16) H. Togo, M. Iinuma, K. Moriyama, K. Takatsuki, JP Pat. Appl. 2013-028323.

Introduction of the author :

Hideo Togo
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Hideo Togo was born in Ibaraki in 1956. He completed his doctoral thesis in 1983, at Tsukuba University. Then, he became a post-doctoral fellow at University of Lausanne in Switzerland, and ICSN (Professor Sir, Derek H. R. Barton) of CNRS in France. He became a research associate in Chiba University in 1989, an associate professor in 1994, and a full professor in 2005. His research interests are organic iodine chemistry and radical chemistry, and green chemistry.

TCI Related Compounds

M2103	IS-Ph_3P (**B**) [=1-Methyl-1-[4-(diphenylphosphino)benzyl]pyrrolidinium Bromide]	1g
M2274	IS-MSO (**C**) [=1-Methyl-3-[6-(methylsulfinyl)hexyl]imidazolium *p*-Toluenesulfonate]	1g, 5g
M2321	IS-MS (**E**) [=1-Methyl-3-[6-(methylthio)hexyl]imidazolium *p*-Toluenesulfonate]	1g, 5g

Chemistry Chat -Focusing on the Elements-

Elements for the Fight against Cancer

Kentaro Sato

The twentieth century saw an extraordinary extension of human life in industrialized countries. For example, the Japanese average longevity was around 44 years in 1900 and improved to over 80 years by 2000. The centenarian population was only 198 in 1965, but surpassed the 10,000 mark in 1998 and is now over 50,000 in 2012. In the next few decades, there may come a time when it isn't rare to live longer than 100 years.

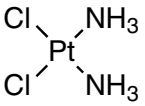
The advancement of medicine has been a big factor contributing to the dramatic extension of life. The discovery of antibiotics in particular was a revolutionary event, helping eradicate many of infectious diseases which had plagued mankind since the dawn of time. Also, our knowledge of taking care of our health such as controlling lifestyle diseases has advanced over the years along with the invention of many effective medicines.

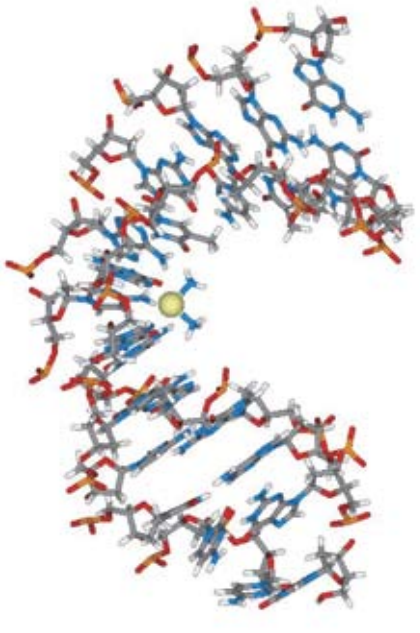
The advancement of medicine in turn is largely attributed to that of chemical science, which studies the potentials of chemical elements and finds their most useful applications. No drug development can be separated from the science of chemical elements. In this column, let us look at some of the cancer drugs as examples to see what kind of roles chemical elements play in each case.

Platinum

As a cancer-fighting element, the first one that comes to one's mind is probably platinum. Cisplatin, a platinum complex in which the central metal is coordinated with two ammonias and two chlorides, is a potent growth inhibitor of cancerous cells (the figure shown on the right). It is somewhat unusual that a purely inorganic complex like cisplatin is used as a medicine. It was discovered almost half a century ago, but it still has an important place in contemporary chemotherapy.

In 1965, an American chemist Barnett Rosenberg observed an unusually strong inhibition of the division of *E. coli* cells under certain conditions while he was studying the effects of electric field on the bacteria. To his surprise, the cause turned out to be not the electric field but the platinum



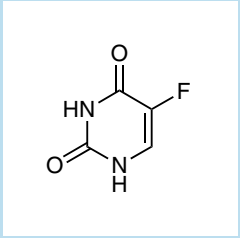


Cisplatin

electrodes used in the experiment. A trace concentration of platinum metal dissolved into the culture solution from the electrode and formed platinum complex, which reacted with the DNA of *E. coli* cells to interfere with their growth.

This effect was later demonstrated against cancer cells and cisplatin became a widely used drug for the treatment of mainly kidney, bladder, and ovarian cancers. There have also been structural analogues of cisplatin having modified ligands such as carboplatin and oxaliplatin, which are both important chemotherapeutics today.

Fluorine



5-FU

Fluorine is a common element in drug molecules, and one of the most famous F-containing drugs for cancer treatment is probably 5-fluorouracil (5-FU). Uracil is one of the nucleobases constituting human genes and 5-FU is its modified version in which one of the hydrogen atoms is replaced by a fluorine atom. This medicine works by sneaking into the biochemical process of nucleic acid and hinders DNA synthesis, thereby inhibiting cancer cell growth.

In nucleic acid biosynthesis, uracil first reacts to form a chemical bond with a sugar molecule and then gets methylated at the 5-position to become thymidylic acid. 5-FU, being almost the same size as uracil, enters this biosynthetic pathway as a camouflaged uracil. However, because its 5-position is blocked by the fluorine atom the methylation cannot take place, resulting in the inhibition of the enzyme responsible for thymidylic acid synthesis and DNA biosynthesis is stopped consequently.

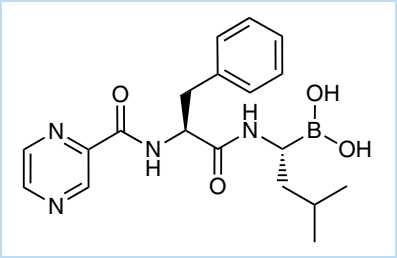
By the way, fluorine is of course the most electronegative element in all elements. Therefore, the introduction of fluorine into a drug candidate molecule in place of hydrogen can drastically alter the electronic property of the molecule. Also, compounds with low metabolic stability can be fluorinated at the metabolized position as a protection to improve their stability. For these reasons, fluorine has strengthened its presence in medicinal chemistry in recent years and this is also why the development of fluorination chemistry is progressing very fast.

Arsenic

Arsenic is an element typically known to be toxic, but surprisingly it has medicinal application. The solution of arsenic trioxide (As_2O_3) is actually sold as anticancer drug! It was originally used in parts of China as a traditional medicine. When clinical trials were done using purified As_2O_3 to test its efficacy against different types of cancer, it was proven to be effective against a certain form of leukemia. It is now available in many countries.

It remains unclear exactly why arsenic trioxide, a supposed poison, possesses anticancer activity. But after all, all other anticancer drugs are similar in a way, in a sense that they are good medicine to our body by being poisonous to cancer cells. As the proverb goes, this is a good example of "fight poison with poison."

Boron



Bortezomib

Boron (the "fifth element" in the periodic table) used to be an element rarely used in medicinal chemistry. The recent arrival of the boron-containing multiple myeloma drug Bortezomib (marketed as the name Velcade®), however, could change the tradition.

Bortezomib is a dipeptide molecule in which the carboxylic acid on the C-terminus is replaced by boronic acid, and it targets the proteasome whose function is cleaning up of misfolded proteins. The boronic acid group of Bortezomib binds to the threonine residue of the proteasome's active site to inhibit its function. The boron atom therefore plays a central role in the mechanism of action of this drug.

Many of common boron containing compounds are stable and have low toxicity. For chemists, boron is a very familiar element found in the reagent for hydroboration reaction or in the reactants of Suzuki-Miyaura reaction. It has never been a popular element in drug design, but its value possibly will change after the success of Bortezomib.

In another application, boron is used as a key component of BNCT (boron neutron capture therapy) research. In BNCT, boron is delivered to cancer cells and the cells are irradiated by neutrons. When boron-10 is hit by neutrons, it undergoes the nuclear fission reaction that gives lithium-7 and helium-4. The travel distance of these high energy particles is no more than a few nanometers long therefore they attack the cancer cells without damaging surrounding healthy cells. Because preferential delivery of the boron to the malignant cells is the key in BNCT, a variety of boron compounds are being developed.

Elements Used in Radiation Therapy

Radiation therapy is an important cancer treatment along with chemotherapy and surgery. The most famous type is probably gamma ray irradiation by radioactive cobalt-60. Cobalt-60 is formed from cobalt-59, its stable isotope, by neutron activation in a nuclear reactor. Cobalt-60 emits a beta ray with the half-life of 5.27 years to become nickel-60, then emits two gamma rays which attacks the cancer cells.

The type of nuclei that can be used for radiation therapy is specified by the law and it includes a wide range of nuclei from tritium to radon-226. The list includes even artificial elements such as technetium and notorious ones of late such as iodine and cesium.

Ideally, radiation therapy targets only malignant cells and keeps healthy cells intact, but in reality simple irradiation cannot be completely cell-specific. Therefore, there are therapies in which a small radiation source is delivered to the affected tissue to treat it from inside.

The newest weapon of radiation therapy is a combination with antibody which works like a missile. For example, the adduct of a radioactive element such as yttrium-90 with an antibody was developed as a chemotherapeutic for lymphatic cancer. The drug utilizes the ability of antibodies to recognize the protein expressed on the surface of cancer cells, which reduces the chance of affecting untargeted areas of the body. Antibody technology is advancing fast and further development of this therapy in close future can be expected.

As we discussed so far, we humans employ all sorts of chemical elements to defend ourselves in the war against our biggest health threat, cancer. Because cancer is an ailment that has direct influence on our life and death, new medicines with even high risk of side effects tend to get government approval relatively easily. For this reason, a number of different approaches of drug development are being taken. Accordingly, we can look forward to seeing unusual elements utilized in future therapies based on innovative medical (and chemical) concepts.

Introduction of the author :

Kentaro Sato

[Brief career history] He was born in Ibaraki, Japan, in 1970. 1995 M. Sc. Graduate School of Science and Engineering, Tokyo Institute of Technology. 1995-2007 Researcher in a pharmaceutical company. 2007-Present Freelance science writer. 2009-2012 Project assinstant professor of the graduate school of Science, the University of Tokyo.
[Specialty] Organic chemistry
[Website] The Museum of Organic Chemistry <http://www.org-chem.org/yuuki/MOC.html>

Technical Glossary

Proteasome

p.11" Elements for the Fight against Cancer"

Proteasome is a protein complex consisting of 19S cap units and a 20S core unit with a molecular weight of about 2000kDa. Proteasome incorporates targeted proteins and degrades them into short peptides or amino acids. The structure of proteasome is the cylindrical 20S core unit in the center and both sides of it bind with a 19S cap unit.

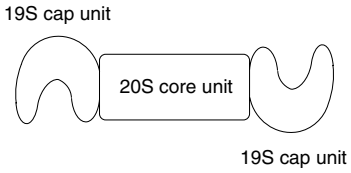
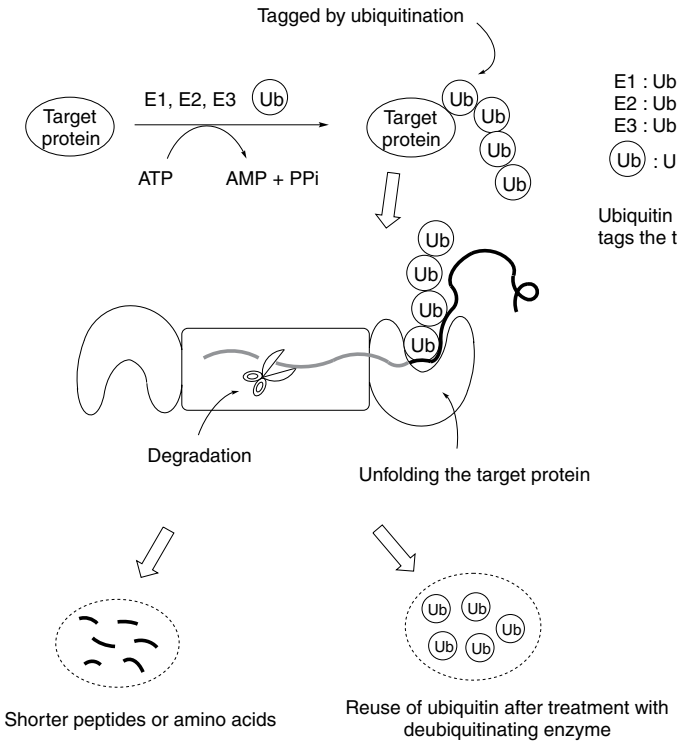


Image of Proteasome

The 19S cap acts to unfold the target proteins for degradation. After unfolding the higher-order structure of the target proteins and incorporating them into the cylindrical 20S core unit, they are degraded into short peptides or amino acids catalyzed by enzymes. This protein degradation process proceeds in three steps as follows: tagging the protein by ubiquitin, incorporation of the tagged proteins into the 19S cap, and enzymatic degradation within the 20S core.



E1 : Ubiquitin-activating enzyme
E2 : Ubiquitin-conjugating enzyme
E3 : Ubiquitin ligase
Ub : Ubiquitin

Ubiquitin is a small protein consisting of 76 amino acids which tags the target proteins to conjugate with their lysine residues.

Degradation of target proteins by proteasome is ATP dependent. Ubiquitins, after using for tagging the proteins, are recycled by a deubiquitinating enzyme and reused for degradation of proteins by proteasome.

Science "Spring" Seminar

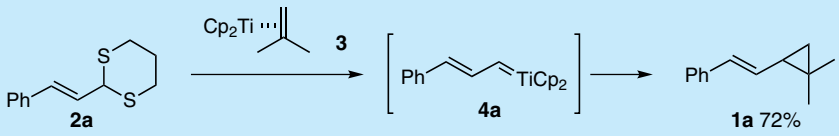
Carbonyl Olefination (2)

Takeshi Takeda

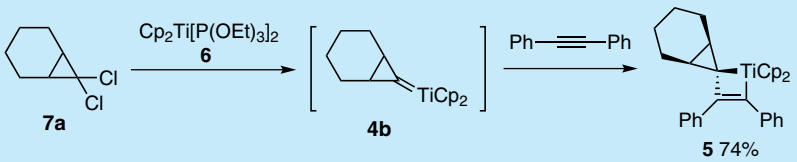
Department of Applied Chemistry, Tokyo University of Agriculture and Technology

1. Titanium-carbene complexes

In 1995, we found that alkenylcyclopropanes **1** were produced by the reaction of β,γ-unsaturated thioacetals **2** with the titanocene(II)-olefin complexes **3** (Scheme 1).[1] Since the active species generated by the desulfurizative titanation of thioacetals were supposed to be the nucleophilic Schrock-type carbene complexes **4**, we have studied their reactions with a variety of unsaturated compounds. Although the direct experimental evidence supporting the intermediary titanium carbene complexes has never been obtained so far, in 2008, we succeeded in the isolation and characterization of titanacyclobutene **5** bearing a spiro-bonded cyclopropane produced by the titanocene(II) **6** -promoted reaction of *gem*-dichloride **7a** with diphenylacetylene (Scheme 2)[2] and this experimental result indirectly but certainly supports the formation of carbene complex **4b**.

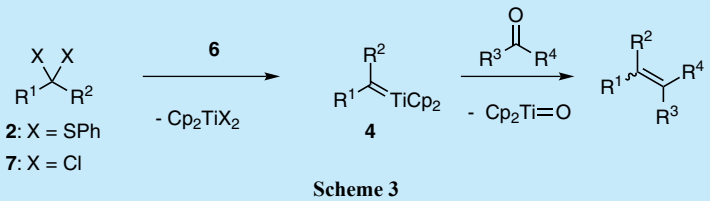


Scheme 1



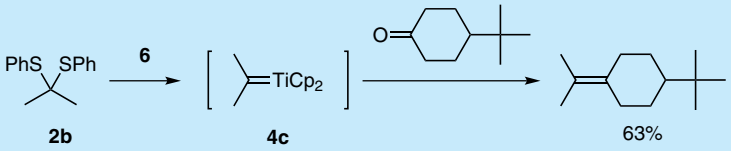
Scheme 2

Similarly to methylidenetitanocene, generated from the Tebbe reagent, the titanium carbene complexes **4** produced by the reductive titanation of thioacetals **2** or *gem*-dichlorides **7** react with various carbonyl compounds (Scheme 3), and we have explored the distinctive advantages of this reaction over conventional carbonyl olefinations such as the Wittig reaction.[3]

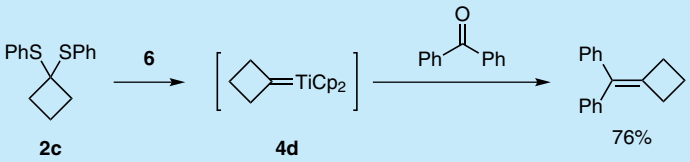


Scheme 3

As described in the previous article, the transformation of ketones into tetrasubstituted olefins is one of the most difficult problems remained in carbonyl olefination, and hence we challenged this problem by using titanium carbene complexes. For the synthesis of tetrasubstituted olefins, highly substituted alkylidene complexes are required. The desulfurizative titanation of certain sterically less crowded thioketals such as those derived from acetone **2b** and cyclobutanone **2c** affords the corresponding tetrasubstituted alkylidene complexes **4c** (Scheme 4)[4] and **4d** (Scheme 5).[5] In contrast, no carbene complexes are generated from more bulky thioketals.

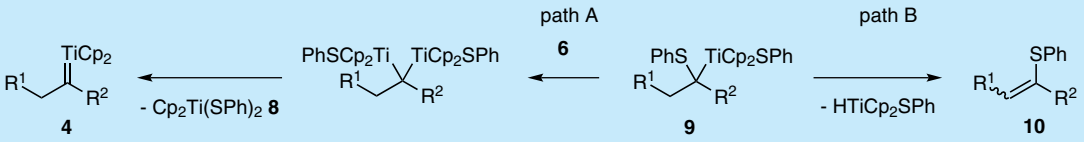


Scheme 4



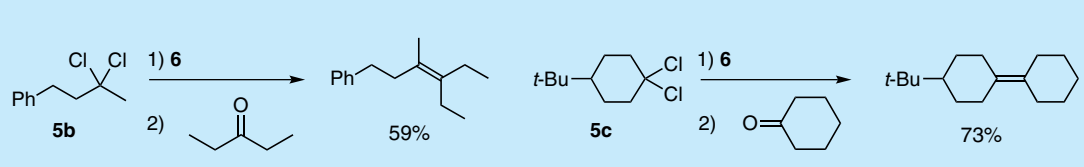
Scheme 5

We assumed that the formation of carbene complexes proceeds through the stepwise reductive titanation of two C-S bonds and following elimination of bis(phenylthio)titanocene **8** (Scheme 6, path A). In the case of thioketals bearing two bulky substituents, its steric hindrance interferes with the second reductive titanation of C-S bond of the alkyltitanium species **9**, and, and instead, the β-hydride elimination preferentially proceeds to produce alkenyl sulfides **10** (path B).



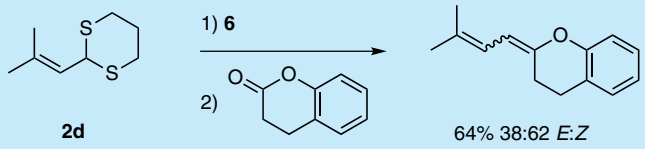
Scheme 6

In view of the fact that a C-Cl bond is more reactive than a C-S bond toward the titanocene(II) reagent, we assumed that the carbene complexes might be produced by using *gem*-dichlorides as starting materials. As we expected, tetrasubstituted olefins were obtained by the reaction of ketones with the organotitanium species generated by the reductive titanation of *gem*-dichlorides (Scheme 7).[6] This olefination, however, still has a limitation in that it cannot be applied to the preparation of ethylenes having four ethyl or more sterically bulky alkyl groups and, to my regret, the conversion of ketones into highly substituted olefins is still a big challenge.

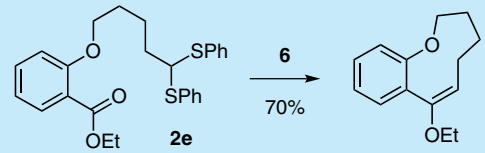


Scheme 7

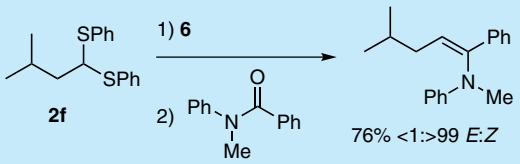
Our carbonyl olefination using carbene complexes also found to be an answer to the several problems remained in the carbonyl olefination of carboxylic acid derivatives. As shown in Schemes 8,[4] 9,[7] 10,[8] and 11,[9] the treatment of esters, lactones, thioesters, and amides with a variety of carbene complexes generated from thioacetals and *gem*-dihalides affords the corresponding heteroatom-substituted olefins. Since thioacetals are generally stable under various conditions, carboxylic acid derivatives bearing a thioacetal moiety are readily prepared and their intramolecular carbonyl olefination enables us to synthesize a range of carbo- and heterocycles as exemplified in Scheme 9



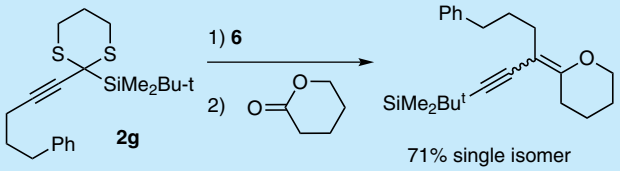
Scheme 8



Scheme 9



Scheme 10

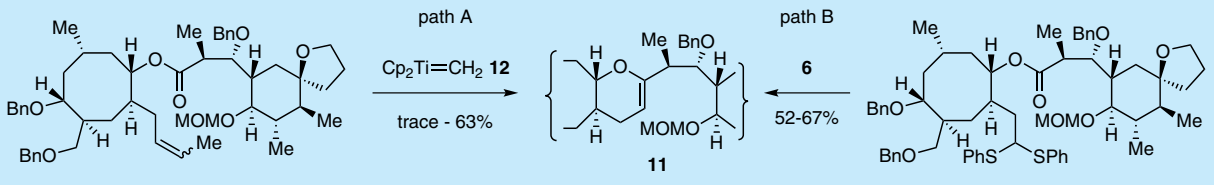


Scheme 11

2. New reactions are rarely used as practical methods

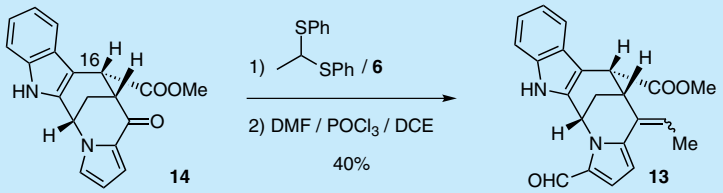
One of my former students, who was involved in the study on the titanium carbene complexes in my group, had to synthesize highly substituted olefins during his post-doctoral work. He tried most of carbonyl olefination reactions including the Wittig reaction, but failed to get the desired product. Finally he decided to use the carbene complex generated from thioacetal and obtained the olefination product in a satisfactory yield. This episode tells us that we should accept the bitter reality that newly developed reactions are rarely used by other chemists as practical synthetic methods.

The carbonyl olefination using thioacetal-titanocene(II) system was utilized for the construction of J-ring of ciguatoxin **11** (Scheme 12) by Prof. Hirama of Tohoku University.[10] To the best of my knowledge, this is the first application of our carbonyl olefination to the synthesis of natural products. Initially their strategy for the formation of J-ring was based on the method reported by Nicolaou et al., which consists of methylidenation of the ester moiety in the J-ring precursor with methylidenetitanocene **12** generated from the Tebbe reagent and the following ring-closing metathesis (Path A). This approach, however, was poorly reproducible and hence they needed an alternative method. They finally employed our intramolecular carbonyl olefination (Path B) which realized the gram-scale preparation of **11** with good reproducibility.



Scheme 12

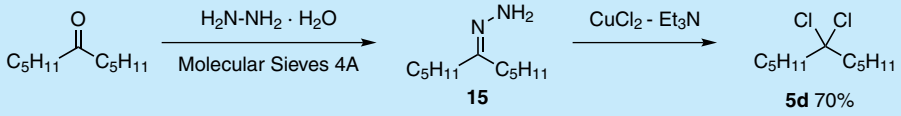
The thioacetal-based carbonyl olefination was also employed as "the last option" for the final ethylidenation in the total synthesis of alstoscholarine**13** (Scheme 13).[11] Since the ketone **14** was completely inactive toward the ylide generated from ethyltriphenylphosphonium salts, the addition of the ethyl Grignard reagent to the BOC-protected **14** and following dehydration was examined. Although such successive transformation gave the ethylidenation product, the epimerization at the C-16 position also proceeded due to high basicity of the Grignard reagent. Then they tried the use of thioacetal-titanocene(II) system and obtained the desired olefination product as a mixture of stereoisomers (*E*:*Z* = ca. 3:1).



Scheme 13

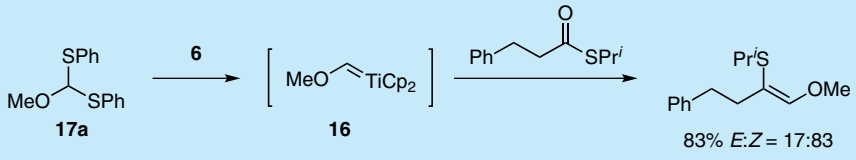
3. We need to explore how to prepare novel starting materials

One of the major factors which determines the utility of synthetic reactions is the availability of starting materials. Even though the reaction itself is excellent, no one wants to use it if the preparation of starting material is troublesome or extremely difficult. As described above, the carbonyl olefination using *gem*-dichlorides is quite useful for the preparation of highly substituted olefins. However, there was no efficient method for the preparation of *gem*-dichlorides from ketones when we started this study. In general, *gem*-dichlorides are prepared by the reaction of ketones with phosphorous trichloride or thionyl chloride,[12] but it is quite difficult to suppress the concomitant formation of alkenyl chlorides due to the acidic reaction conditions. Then we explored an alternative way to obtain *gem*-dichlorides as pure forms and found a new method for their preparation from ketones via hydrazones **15** (Scheme 14).[13] Our new method enables us to prepare highly substituted carbene complexes and their use for carbonyl olefination.

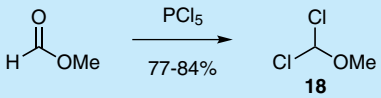


Scheme 14

Another reaction which we disclosed with the preparation of its starting materials is the alkoxymethylenation of carbonyl compounds. In 1998, we reported a new method for the preparation of enol ethers using methoxy group substituted carbene complexes **16** generated from methoxybis(phenylthio)-methane (**17a**) (Scheme 15).[14] The starting material **17a** was prepared by the reaction of thiophenol with dichloromethyl methyl ether (**18**) obtained by the treatment of methyl formate with phosphorus pentachloride (Scheme 16).[15] If appropriate dithioorthoformates **17** are available, a variety of enol ethers which are difficult to prepare by other methods are obtained because any dithioorthformates **17** can be transformed into the corresponding carbene complexes. So a big question is how to obtain dithioorthoformates **17**. Preparation of functionalized dithioorthoformates from the corresponding formats is not feasible because the conversion of formats into dichloromethyl ethers must be carried out under strongly acidic conditions.

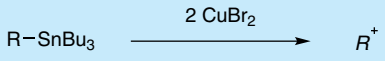


Scheme 15

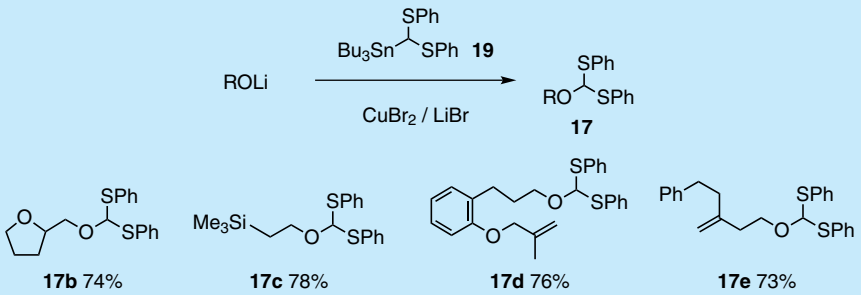


Scheme 16

In this context, after five years or so, we began to explore a new method for the preparation of functionalized dithioorthoformates **17**. Our basic idea for this problem is that *carbocation equivalents must be formed by the two electrons oxidation of organotin compounds* (Scheme 17). Indeed, the simple operation involving the treatment of tributyl[bis(phenylthio)methyl]stannane (**19**) with lithium alkoxides and copper(II) bromide gave acid-labile dithioorthoformates bearing a terminal double bond or β-trimethylsilyl group (Scheme 18).[16] The carbene complexes generated from these organosulfur compounds reacted with a variety of carbonyl compounds to produce enol ethers which are difficult to prepare by the conventional methods.

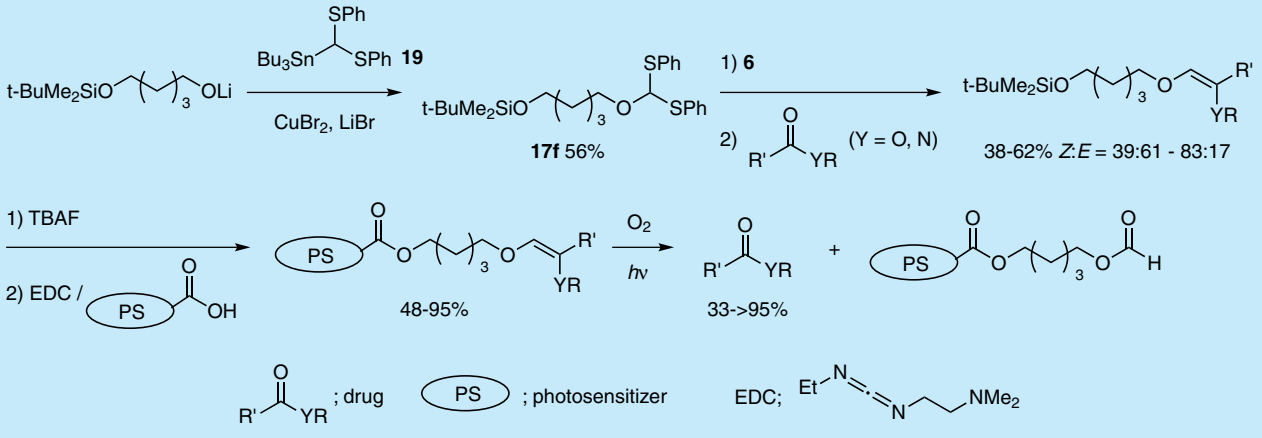


Scheme 17



Scheme 18

This sequence of reactions was employed for the construction of the site-specific prodrug release system (Scheme 19).[17] Drugs are released through the scission of double bond bearing two heteroatoms by visible-light irradiation. The above carbonyl olefination using dithioorthoformates is probably only a method of producing such double bonds, and the preparation of dithioorthoformate **17f** containing a TBDMS-protected hydroxyl group would be achieved only by the method using the organotin compound **19**.



Scheme 19

References

1) Y. Horikawa, T. Nomura, M. Watanabe, I. Miura, T. Fujiwara, T. Takeda, *Tetrahedron Lett.* **1995**, *36*, 8835.
2) T. Shono, T. Nagasawa, A. Tsubouchi, K. Noguchi, T. Takeda, *Chem. Commun.* **2008**, 3537.
3) T. Takeda, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 195; T. Takeda, *Chem. Rec.* **2007**, *7*, 24; T. Takeda, A. Tsubouchi, in *Science of Synthesis Knowledge Updates 2011/3*, eds. by E. M. Carreira, J. Drabowicz, I. Marek, M. Oestreich, E. Schaumann, Thieme, Stuttgart, **2012**, p. 1.
4) Y. Horikawa, M. Watanabe, T. Fujiwara, T. Takeda, *J. Am. Chem. Soc.* **1997**, *119*, 1127.
5) T. Fujiwara, N. Iwasaki, T. Takeda, *Chem. Lett.* **1998**, 741.
6) T. Takeda, R. Sasaki, T. Fujiwara, *J. Org. Chem.* **1998**, *63*, 7286.
7) Md. A. Rahim, H. Sasaki, J. Saito, T. Fujiwara, T. Takeda, *Chem. Commun.* **2001**, 625.
8) T. Takeda, J. Saito, A. Tsubouchi, *Tetrahedron Lett.* **2003**, *44*, 5571.
9) T. Takeda, M. Ozaki, S. Kuroi, A. Tsubouchi, *J. Org. Chem.* **2005**, *70*, 4233.
10) T. Oishi, H. Uehara, Y. Nagumo, M. Shoji, J.-Y. Le Brazidec, M. Kosaka, M. Hirama, *Chem. Commun.* **2001**, 381.
11) T. Gerfaud, C. Xie, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2011**, *50*, 3954.
12) R. D. Rieke, S. E. Bales, P. M. Hudnall, T. P. Burns, G. S. Poindexter, *Org. Synth.* **1988**, Coll. Vol. *VI*, 845.
13) T. Takeda, R. Sasaki, A. Nakamura, S. Yamauchi, T. Fujiwara, *Synlett* **1996**, 273; T. Takeda, R. Sasaki, S. Yamauchi, T. Fujiwara, *Tetrahedron* **1997**, *53*, 557.
14) Md. A. Rahim, H. Taguchi, M. Watanabe, T. Fujiwara, T. Takeda, *Tetrahedron Lett.* **1998**, *39*, 2153.
15) H. Gross, A. Rieche, E. H. Höft, E. Beyer, *Org. Synth.* **1973**, Coll. Vol. *V*, 365.
16) T. Takeda, K. Sato, A. Tsubouchi, *Synthesis* **2004**, 1457.
17) M. Y. Jiang D. Dolphin, *J. Am. Chem. Soc.* **2008**, *130*, 4236.

Introduction of the author :

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Takeshi Takeda obtained his Ph.D. (1977) in chemistry from Tokyo Institute of Technology. He joined the University of Tokyo as an Assistant Professor in 1977. After a half year of postdoctoral work at University of California, Los Angeles, he moved to Tokyo University of Agriculture and Technology as an Associate Professor in 1981. He was appointed to a Professorship in 1994.
He received an Incentive Award in Synthetic Organic Chemistry, Japan (1987) and a Chemical Society of Japan Award for Creative Work (2003).
His current research interests include organic chemistry, organometallic chemistry, and organic synthesis.

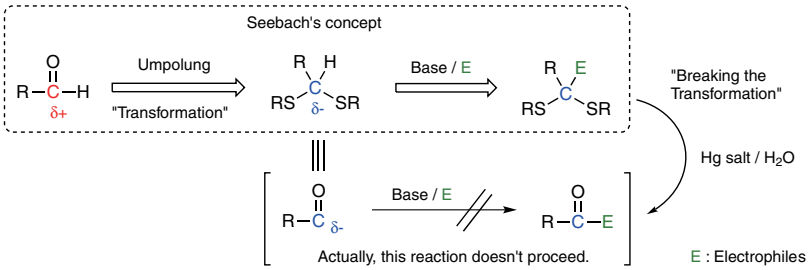
Hydrolysis of Thioacetals Using Oxidizing Reagents

Haruhiko Taguchi

Tokyo Chemical Industry, Co. Ltd.

In this issue of TCI MAIL, the highlighted topic of synthetic methods is dethioacetalization using oxidizing reagents. Professor Takeda has written of the attractive usages of thioacetals, in particular, the preparation of titanium-carbene complexes using thioacetals (see “spring” seminar, page 14). However, there are some serious problems to the use of thioacetals for synthesis, even though they are very useful as building blocks. What are problems? Nasty smell! Of course smells are a problem, but there are other problems that are of greater consequence.

It is well known that thioacetals are used as formyl anion equivalents and Prof. Seebach originally introduced this concept of umpolung.[1)] This idea was very innovative because the carbonyl carbon has an electrophilic character and it acts as a carbocation. Using the concept of umpolung, if the carbonyl group is transformed to the corresponding thioacetal, the character of the carbon changes to a carbanion. And furthermore, treatment of the thioacetal with a strong base generates an anionic species, which reacts with various electrophiles. It is very easy to introduce various electrophiles into a carbonyl carbon after the transformation of the carbonyl group.



The concept of "Umpolung" proposed by Prof. Seebach

Well now, the important question before us, is how to undo this transformation of the carbonyl to the thioacetal? According to Seebach’s umpolung strategy, the method for hydrolysis of thioacetals, has been the use of mercury salts. In 60’s and 70’s, mercury salts had been useful reagents in organic synthesis, but in recent years, environmental concerns have almost completely eliminated there use in the laboratory. Almost all laboratories do not use mercury salts in organic synthesis because chemists tend to avoid their use for environmental reasons.

To resolve the problems associated with the use of mercury, other methods for the hydrolysis of thioacetals have to be developed. Thioacetals are similar to acetals, so can they be hydrolyzed by the treatment with a strong acid? This strategy is effective for the hydrolysis of acetals; however, in the case of thioacetals, this method is not effective. The pK_a value of alcohols are about 16, while that of thiols are between 10 and 11. Since, the pK_a values of thiols are 5 units higher than those of alcohols, protonation of sulfur atom does not occur and dethioacetalizations does not proceed.

Why is mercury so effective in dethioacetalization? The reason why mercury salts have been so effective has to do with the chemical affinity of mercury and sulfur atoms. Why is their affinity for each other so good? It is based on the principle of hard and soft acids and bases, that is the HSAB theory, which provides the answer.

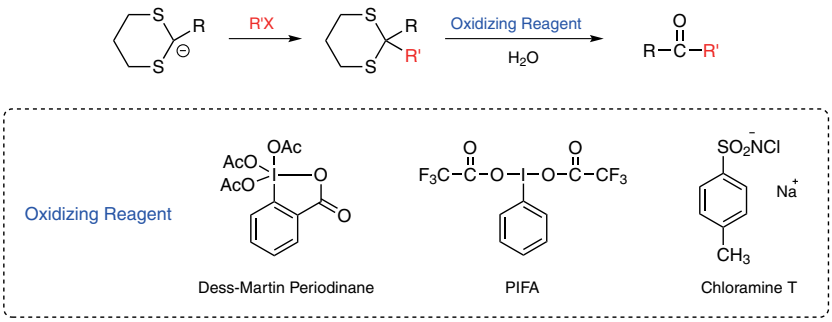
According to HSAB theory, sulfur atoms tends to form ion pairs with soft ions, and it turns out that mercury is a soft ion. The chemical affinity of sulfur and mercury ions is quite strong. This effect enables mercury to form a coordinate bond with sulfur, which activates the carbon-sulfur bond towards hydrolysis.[2)]

Can thioacetals be hydrolyzed by using some other soft substance? Another concept of hydrolysis is to form sulfonium salts. Sulfur compounds, such as sulfides and sulfoxides, react readily with methyl iodide to form methylsulfonium salts. This chemical property is specific to sulfur and oxygen does not react in this way. The formed sulfonium salts have a positive charge and this species can undergo various reactions. By using this technique, the hydrolysis of thioacetals can proceed. In some references, relatively strong alkylating reagents are used to form sulfonium salts, which on subsequent hydrolysis under alkaline conditions regenerate the carbonyl compound.[3)] Interestingly, this type of hydrolysis proceeds using cupper salts,[4)] which are soft ions.

These synthetic techniques provide alternate methods to hydrolyze thioacetals, avoiding the use of mercury salt. It should be noted, that there are problems associated with this method also. For one, it is often necessary to use a strong alkylating reagent, and because these reagents have cancer inducing properties, many chemists do not use them.

Another idea for thioacetal hydrolysis is to use oxidizing reagent. Hypervalent iodine compounds, such as Dess-Martin periodinane,[5)] [Bis(trifluoroacetoxy)iodo]benzene (PIFA)[6)] and 2-iodoxybenzoic acid (IBX)[7)], are used for thioacetal hydrolysis. These oxidizing reagents oxidize the thioacetals to sulfoxides or sulfones, and after oxidation, water-mediated hydrolysis is possible.[8)] If hydrolysis is performed in an alcohol base, the formed carbonyl compound reacts with alcohols to form corresponding acetals. Usually, acetals cannot be derived from thioacetals under acidic conditions, so this result is potentially useful.

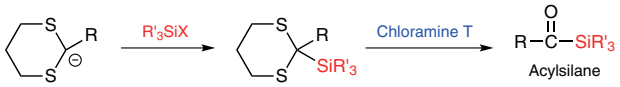
Dethioacetalization by oxidation with IBX is quite structure specific. IBX oxidation of benzyl or allylthioacetals proceed rapidly, while IBX oxidation of other alkyl group thioacetals proceed slowly or not at all.



Examples of dethioacetalizations using oxidizing reagents

Why is the hydrolysis of thioacetals possible using hypervalent iodine? Iodine is a soft ion species, based on the HSAB theory, and thus it readily reacts with sulfur to cause oxidation.

Another unique dethioacetalization is presented. Through the use of chloramine T as an oxidizing reagent,[9)] the hydrolysis of a sensitive silyl thioacetal has been reported to yield a silyl ketone.[10)] Now various acylsilanes are synthesized by this method.



Synthesis of acylsilanes using Chloramine T

Chemical synthesis using thioacetals is a powerful tool for the construction of complex compounds. TCI has many thioacetals and related reagents for making thioacetals and removal of the thioacetal group. The Umpolung technique can be made possible by using a number of TCI reagents.

References

1) D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239.
2) D. Seebach, A. K. Beck, *Org. Synth.* **1971**, *51*, 76.
3) T. Oishi, K. Kamemoto, Y. Ban, *Tetrahedron Lett.* **1972**, *13*, 1085.
4) K. Mori, H. Hashimoto, Y. Takenaka, T. Takigawa, *Synthesis* **1975**, 720.
5) N. F. Langille, L. A. Dakin, J. S. Panek, *Org. Lett.* **2003**, *5*, 575.
6) G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, *30*, 287.
7) Y. Wu, X. Shen, J.-H. Huang, C.-J. Tang, H.-H. Liu, Q. Hu, *Tetrahedron Lett.* **2002**, *43*, 6443.
8) K. Ogura, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.)* **1979**, *37*, 903.
9) W. F. J. Huurdeman, H. Wynberg, D. W. Emerson, *Tetrahedron Lett.* **1971**, *12*, 3449.
10) H. J. Reich, E. K. Eisenhart, R. E. Olson, M. J. Kelly, *J. Am. Chem. Soc.* **1986**, *108*, 7791.

Related Compounds

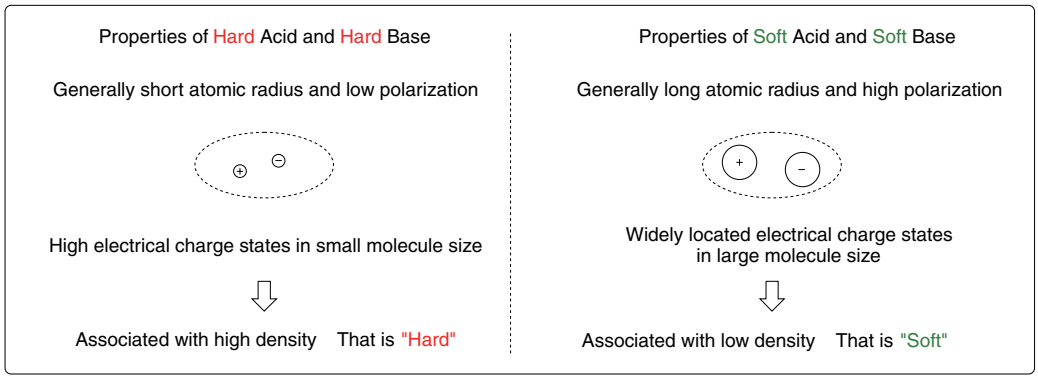
D0119	1,3-Dithiane		5g,	25g
B1444	Bis(phenylthio)methane		5g,	25g
T1514	2-Trimethylsilyl-1,3-dithiane		5g,	25g
T1507	Trimethyloxonium Tetrafluoroborate		5g,	25g
T1606	Triethyloxonium Tetrafluoroborate (15% in Dichloromethane, *ca.* 1mol/L)			100mL
I0060	Iodomethane (stabilized with Copper chip)	10mL,	100mL,	300mL
D2045	Dess-Martin Periodinane	1g,	5g,	25g
B1175	[Bis(trifluoroacetoxy)iodo]benzene		5g,	25g
C0076	Chloramine T Trihydrate		25g,	500g
M0805	Methyl (Methylsulfinyl)methyl Sulfide (= FAMSO)		5g,	25g
M0875	Methylthiomethyl *p*-Tolyl Sulfone (= MT-sulfone)		5g,	25g

Technical Glossary

HSAB Theory

p.20" Hydrolysis of Thioacetals Using Oxidizing Reagents"

The HSAB theory, proposed by Pearson, helps to qualitatively understand the properties of elements. The HSAB theory describes the reactions of acids with bases and defines the chemical character of acids and bases as "Hard" or "Soft".



Hard acids and bases generally have short atomic radius and low polarization while soft acids and soft bases generally have long atomic radius and high polarization. As to chemical properties, hard acids tend to bind with hard bases and soft acids tend to bind with soft bases.

The HSAB theory is a qualitative and experimental rule and it should be considered as one of several factors in understanding the chemical reactions. This rule is useful for approximating the nature of the chemical reaction. In particular, in considering electrostatic properties of elements, it is important to note that hard species tend to form ionic bonds, while soft species tend to form covalent bonds.

Hypervalent Iodine Compound

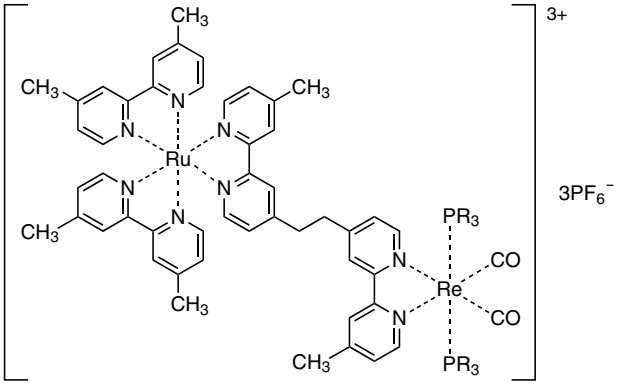
p.21" Hydrolysis of Thioacetals Using Oxidizing Reagents"

Iodine is a soft species having the properties that large molecule size, easily polarizable and low in electronegativity. Generally, iodine acts as a monovalent species to form a single bond with various elements. It can have over eight electrons beyond the octet theory by readily extending its valence. In this expanded valence state, is called hypervalent iodinane. It is known that trivalent and pentavalent iodines are hypervalent iodinane, and each of their structure are pseudo trigonal bipyramidal molecular geometry and square pyramidal molecular geometry.

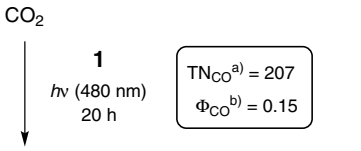
These hypervalent iodine compounds show strong oxidative action because the reduced monovalent iodines possess a more stable octet structure. These chemical properties are useful for oxidation in organic synthesis. Dess-Martin periodinane and [bis(trifluoroacetoxy)iodo]benzene(PIFA) are typical reagents for such purposes.

Ru-Re Supramolecular Complex Photocatalyst Capable of Efficiently Reducing CO_2 to CO

R0100 Ru-Re(FPh) (1) 50mg

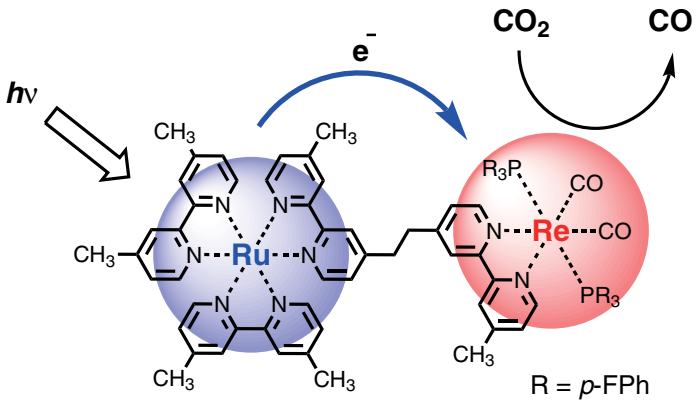


1 (R = *p*-FPh)



a) mol of the CO produced / mol of **1**
b) quantum yield of CO formation

Recently, more and more studies on artificial photosynthesis, in which carbon dioxide is converted into chemical resources by using solar light, have been performed. As part of these studies, the research on photocatalyzed CO_2 reduction into CO has drawn increasing attention. A novel Ru-Re supramolecular photocatalyst, Ru-Re(FPh) (**1**), which was developed in the Ishitani Laboratory, combines the Re complex, which can efficiently reduce CO_2, with the Ru complex, which is an excellent photosensitizer, thus it can reduce efficiently CO_2 to CO using visible light. In addition to its photostability, **1** exhibits tremendous photocatalytic properties (quantum yield of CO formation = 0.15; turnover number of CO formation = 207).



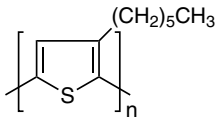
*This product is commercialized under instruction by Professor Osamu Ishitani,
Department of Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, Japan.

Reference

1) Development of highly efficient supramolecular CO_2 reduction photocatalysts with high turnover frequency and durability
Y. Tamaki, K. Watanabe, K. Koike, H. Inoue, T. Morimoto, O. Ishitani, *Faraday Discuss.* **2012**, *155*, 115.

High Regioregular p-type Organic Semiconducting Polymer

P2018 Poly(3-hexylthiophene-2,5-diyl) (= P3HT) (1) 1g



1

Poly(3-hexylthiophene-2,5-diyl) (P3HT, **1**) is a conjugated polymer showing the character of p-type semiconductors. By reason of its excellent photonics and electronics properties, it has been used as a material for organic photovoltaic cells, organic field-effect transistors, organic light-emitting diodes, *etc.*[1-5] In addition, it is able to create devices in coating processes because of its good solubility in organic solvents.

It has been reported that the higher the regioregularity of P3HT is, the better the performance is.[1b] We provide P3HT with 98% regioregularity.

References

1) Organic photovoltaic cell (OPV)
a) G. Li, V. Shrotriya, J. Huang, Y. Yao, T. Moriarty, K. Emery, Y. Yang, *Nat. Mater.* **2005**, *4*, 864. b) C. H. Woo, B. C. Thompson, B. J. Kim, M. F. Toney, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 16324. c) T. Yamanari, T. Taima, K. Hara, K. Saito, *J. Photochem. Photobiol. A.* **2006**, *182*, 269.

2) Organic field-effect transistor (OFET)
a) Z. Bao, A. Dodabalapur, A. J. Lovinger, *Appl. Phys. Lett.* **1996**, *69*, 4108. b) L.-L. Chua, J. Zaumseil, J.-F. Chang, E. C.-W. Ou, P. K.-H. Ho, H. Sirringhaus, R. H. Friend, *Nature* **2005**, *434*, 194.

3) Organic light-emitting diode (OLED)
A. Dodabalapur, Z. Bao, A. Makhija, J. G. Laquindanum, V. R. Raju, Y. Feng, H. E. Katz, J. Rogers, *Appl. Phys. Lett.* **1998**, *73*, 142.

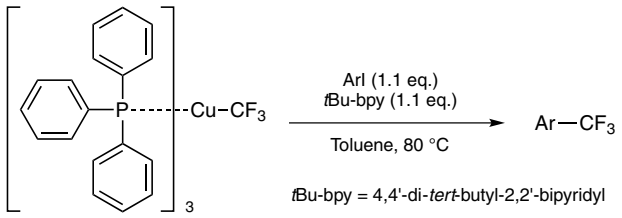
4) Electrochromic device
a) S. D. D. V. Rughooputh, S. Hotta, A. J. Heeger, F. Wudl, *J. Polym. Sci. Part B: Polym. Phys.* **1987**, *25*, 1071. b) A. Aoki, *Hyomen Gijutsu (J. Surf. Finish. Soc. Jpn.)* **2007**, *58*, 762.

5) Photo-thermal-electrical converter
E. Miyako, C. Hosokawa, M. Kojima, M. Yudasaka, R. Funahashi, I. Oishi, Y. Hagihara, M. Shichiri, M. Takashima, K. Nishio, Y. Yoshida, *Angew. Chem. Int. Ed.* **2011**, *50*, 12266.

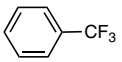
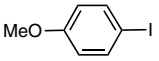
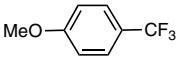
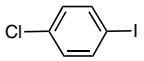
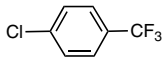
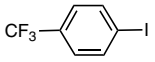
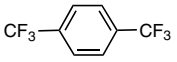
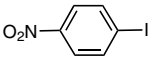
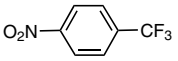
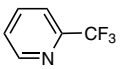
Novel Aromatic Trifluoromethylating Reagent

T2883 (Trifluoromethyl)tris(triphenylphosphine)copper(I) (1) 1g, 5g

Trifluoromethylated aromatic compounds are important intermediates for the synthesis of pharmaceuticals, agrochemicals, and polymer materials, and thus, a number of trifluoromethylating reagents have been developed so far. (Trifluoromethyl)tris(triphenylphosphine)copper(I) (**1**), reported by Komiya and Grushin *et al.*, is an air-stable trifluoromethylating reagent with ease of handling, and the reagent has been reported to trifluoromethylate iodoarenes in the presence of *t*Bu-bpy.



1

ArI	Product	Y. (%) [a]
		60 - 65 [b]
		70 - 75 [b]
		60 [b]
		65 [c]
		90 [c]
		75 [c]

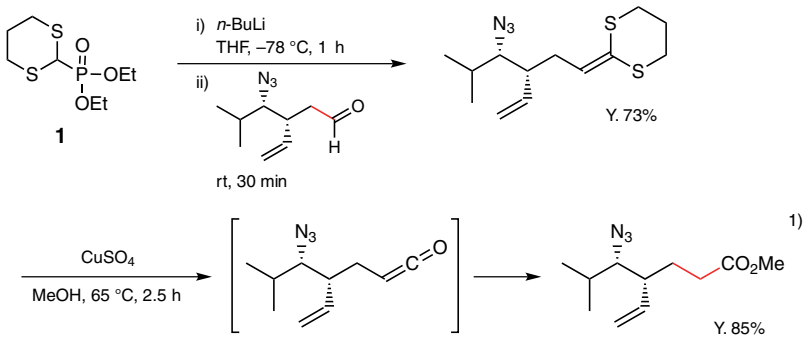
a) Determined by ^{19}F-NMR with 4,4'-difluorobiphenyl as an internal standard.
b) Reaction time: 22 h; c) Reaction time: 2-7 h

References

1) C-Si bond cleavage of trihalomethyltrimethylsilane by alkoxo- and aryloxogold or -copper complexes
Y. Usui, J. Noma, M. Hirano, S. Komiya, *Inorg. Chim. Acta* **2000**, *309*, 151.
2) Simple, stable, and easily accessible well-defined $CuCF_3$ aromatic trifluoromethylating agents
O. A. Tomashenko, E. C. Escudero-Adán, M. M. Belmonte, V. V. Grushin, *Angew. Chem. Int. Ed.* **2011**, *50*, 7655.

Homologation Reaction by Ketene Dithioacetalization

D4074 Diethyl (1,3-Dithian-2-yl)phosphonate (1) 5g



1

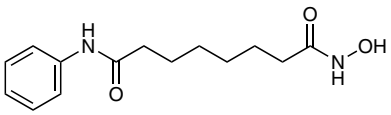
A Horner–Emmons reagent, diethyl (1,3-dithian-2-yl)phosphonate (**1**), reacts with aldehydes and ketones to afford the ketene dithioacetals. After deprotection, followed by hydrolysis or alkolysis, the intermediate ketenes can be converted to the corresponding homologous carboxylic acids or esters in good yields. The one-carbon homologation reaction is an important transformation in organic synthesis.

Reference

1) Substrate-controlled and organocatalytic asymmetric synthesis of carbocyclic amino acid dipeptide mimetics
S. Hanessian, D. K. Maji, S. Govindan, R. Matera, M. Tintelnot-Blomley, *J. Org. Chem.* **2010**, *75*, 2861.

HDAC Inhibitor

H1388 Suberoylanilidehydroxamic Acid (1) 200mg



1

Suberoylanilidehydroxamic acid (SAHA, **1**) is a histone deacetylase (HDAC) inhibitor[1,2] and inhibits both classes I and II enzymes by binding to the pocket of the catalytic site.[3] **1** is one of the hydroxamic acid-based hybrid polar compounds because it has in common two polar groups separated by an apolar 5- to 6-carbon methylene chain.[2] **1** has been demonstrated to inhibit the proliferation of a wide variety of transformed cells *in vitro*.[1]

References

1) Cancer biology: mechanism of antitumor action of vorinostat (suberoylanilide hydroxamic acid), a novel histone deacetylase inhibitor
V. M. Richon, *Br. J. Cancer* **2006**, *95*, S2.
2) A class of hybrid polar inducers of transformed cell differentiation inhibits histone deacetylases
V. M. Richon, S. Emiliani, E. Verdin, Y. Webb, R. Breslow, R. A. Rifkind, P. A. Marks, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 3003.
3) Structures of a histone deacetylase homologue bound to the TSA and SAHA inhibitors
M. S. Finnin J. R. Donigian, A. Cohen, V. M. Richon, R. A. Rifkind, P. A. Marks, R. Breslow, N. P. Pavletich, *Nature* **1999**, *401*, 188.

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