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Contribution

Utilization of Iodine Resources
Syntheses & Reactions of Hypervalent Organoiodanes

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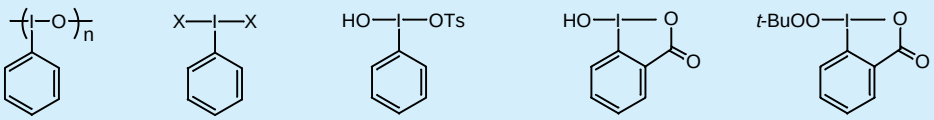
As Japan is not blessed with abundant natural resources, the Japanese are dependent on the importation of the majority of our raw materials from overseas. However, Japan can be proud for its production of iodine, where it is a leading manufacturer in the world. Fossil seawater obtained from underground is the material for producing industrial iodine. More than 80% of the produced iodine is exported to various countries of the world. However, we have to rely on the United States and Europe for importation of the majority of the products into which iodine is incorporated, for instance, an X-ray contrast medium or a photosensitive agent for photographic film. Because of this, our iodine resource is not fully utilized. Accordingly, it becomes very important to develop an effective method for utilization of iodine to its full extent by producing high value organoiodane. Our attention has been directed to trivalence hypervalent organoiodanes (λ^3-organoiodane) with low toxicity and we are making a study of its full use in the synthetic organic chemistry.

Iodine is large-sized halogen element, easily polarizable and low in electronegativity. It forms hypervalent organoiodanes beyond the octet theory by readily extending its valence.

The representative λ^3-organoiodanes are iodosylbenzene (polymer) **1**, (diacetoxyiodo)benzene **2**, [bis(trifluoroacetoxy)iodo]benzene **3**, [hydroxy(tosyloxy)iodo]benzene (Koser reagent) **4**, *o*-iodosylbenzoic acid **5**. They have been widely used as oxidants for active methylene groups, double and triple bonds, alcoholic and phenolic hydroxyl groups, sulphur and amino compounds [1]. More than twenty kinds of λ^3-organoiodanes including the above-noted iodanes, are available from Tokyo Kasei Kogyo Co. Ltd.

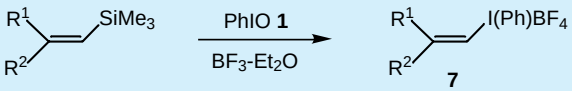


1 **2:** X = OAc **3:** X = $OCOCF_3$ **4** **5** **6**

The λ^3-organoiodane which contains an alkylperoxy group as a ligand has not been synthesized probably because of its high tendency to decompose. We have recently found [2] that the Lewis acid-catalyzed ligand exchange of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one **5** with *tert*-butyl hydroperoxide affords the crystalline peroxyiodane **6**. The peroxyiodane **6** is very stable in the solid state, no decomposition whatever is found, and its cystalline form stores well at room temperature for over one year. This product is an interesting compound since it contains *tert*-butylperoxy group and a trivalent iodine atom, in the same molecule, both of which are powerful oxidants. The purpose of this review is to describe the usefulness of λ^3-peroxyiodanes and their wide applications as radical oxidants.

1. Syntheses & Reactions of Alkenyliodanes and Alkynyliodanes

In 1985 it was found that when iodosylbenzene **1** was activated with BF_3 in dichloromethane, and is reacted with vinylsilane or vinylstannane, the silicon or tin is replaced with trivalent iodine and λ^3-alkenyliodane **7** can be synthesized in good yield (Figure 1) [3]. The generation of λ^3-alkenyliodane is stereospecific and the stereochemistry of vinylsilane or vinylstannane is maintained. The λ^3-alkenyliodane **7** can also be obtained through boron-iodine exchange reaction, employing vinylboronic acid as a substrate [4].



7

Fig.1

The trivalent iodine group exhibits very high leaving group ability and, therefore, nucleophilic substitution reactions of alkenyliodane **7** at vinylic carbons proceed at room temperature under mild conditions. Enolate anions, R_2CuLi, CuCN, ArSNa, *n*-Bu_4NCl, etc. act as good nucleophiles in these reactions. Especially, an S_N2 reaction at vinylic carbons accompanied by the stereochemical inversion of configuration, which was regarded as not to proceed before, is made possible through use of alkenyliodane **7**. In alkenyliodane **7**, the acidity of α-hydrogens is high enough for the α-elimination to take place followed by reductive elimination of iodobenzene, in the presence of a base, leading to the generation of an alkylidene carbene in good yield [5].

In a similar way as the synthesis of alkenyliodanes, alkynyliodane **8** can be synthesized from alkynylsilane and stannane (Figure 2). Synthesis of alkynyliodanes can also be performed directly from the terminal alkyne [5]. The Michael addition reaction of the alkynyliodane **8** with enolate anions, leads to the formation of cyclopentene skeletons. As shown in Figure 2, the alkynyliodane **8** (R=H) is a good ethynylation reagent [6] and available from Tokyo Kasei. The alkylidene carbene is a reaction intermediate and an ethynylated product can be obtained via 1,2-hydrogen rearrangement of the α-hydrogen.

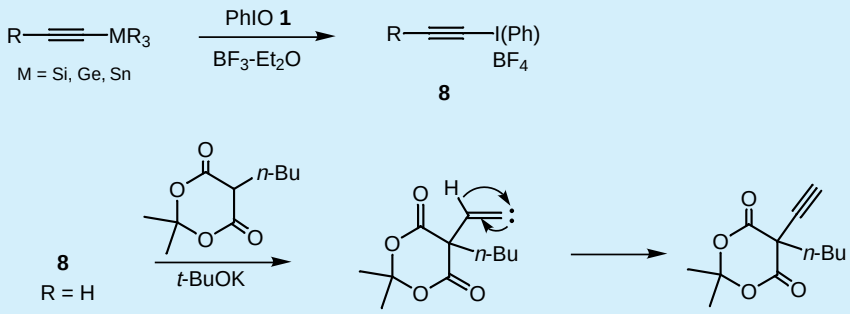


Fig.2

2. Generation of Allenyliodanes & Their Reductive Iodonio-Claisen Rearrangement

The application of the silicone-iodane exchange reaction to propargylsilane leads to the generation of λ^3-allenyliodane via an S_E2' reaction. When (diacetoxyiodo)benzene **2** was treated with propargylsilane **9** in the presence of BF_3, the propargyl group was introduced at the ortho-position of iodobenzene and *o*-propargyliodobenzene **10** was obtained in high yields [7] (Figure 3). After a number of other reactions were studied, the followiing observations were made:

1) The trivalent iodine is always reduced to univalent iodide.
2) Regioselective propargylation occurs at the ortho-position of iodoarenes.
3) The new carbon-carbon bond is formed regioselectively at the α–carbon of the propargyl group.
4) The reaction proceeds at a low temperature.
5) Propargylgermane and stannane can also be used.
6) Hydroxy- and acetoxy-propargylsilanes can be used.

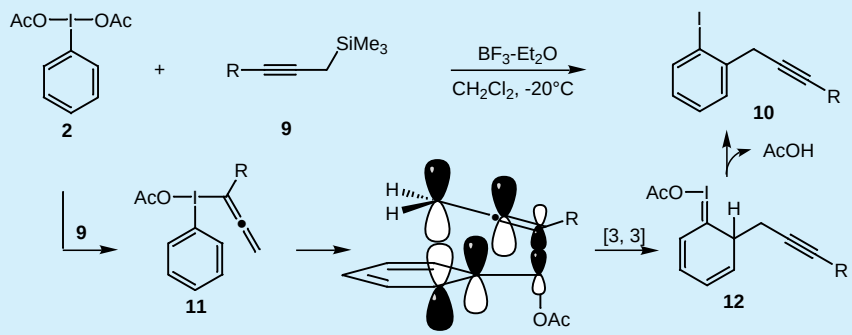


Fig.3

The reaction mechanism, taking into account the above observations, is shown in Figure 3. Reactions of propargylsilane with electrophiles, such as halogens and acyl chlorides, are known to proceed via S_E2' process. To start with, the reaction affords λ^3-allenyliodane **11**. Subsequently, a propargyl group is introduced regioselectively at the ortho-position via intramolecular [3,3]sigmatropic rearrangement, and acetic acid is then released by means of the subsequent reductive elimination of **12** with the formation of the *o*-propargyliodobenzene **10**. Intramolecular nature for the rearrangement of λ^3-allenyliodane **11** is strongly supported by the cross reaction in the presence of univalent iodoarene. Although heating at 150-250°C is required for ordinary Claisen rearrangement reactions, the reductive iodonio-Claisen rearrangement proceeds at a low temperature. The rate determining step of the reaction is presumed to be a [3,3]sigmatropic rearrangement of the λ^3-allenyliodane **11**. The lower activation energy associated with the iodonio-Claisen rearrangement of **11** can be interpreted in terms of the small bond energy needed to break the apical carbon-iodine(III) bond. In general, aryliodanes $ArIX_2$ adopt a T-shaped geometry, the hypervalent I(III)-X bonds being well overlapped with the aromatic π bond. This favorable orbital interaction could facilitate the rearrangement of **11**.

In the above reductive iodine(III) Claisen rearrangememt reaction, we had no direct evidence for the generation of λ^3-allenyliodane **11**, which has been considered to be an intermediate. Therefore, we have carried out the reaction of dimethylpropargylsilane **13** with hydroxyiodane **5** in order to isolate or detect the intermediate, allenyliodane **14** (Figure 4). It seems reasonable to assume that the [3,3]-sigmatropic rearrangement of allenyliodane **14** proceeds with difficulty, probably because the hypervalent C-I(III) bond being cleaved during the [3,3]-sigmatropic rearrangement could not overlap with the aromatic π orbitals and because of the steric hindrance of the terminal two methyl groups and their electronic effects. As expected, no propargylation at the ortho-position by [3,3] sigmatropic rearrangement was observed. To our regret, we could not detect the generation of allenyliodane **14**. Contrary to our expectation, the present reaction generated alkylperoxyiodane **15** [8]. Peroxyiodane **15** has an alkylperoxy group and hypervalent iodine(III) in a same molecule, both acting as oxidants, but is stable in a solid state. X-ray analysis revealed that the iodine atom has a typical T-shaped geometry specific to hypervalent compounds with some distortion in shape.

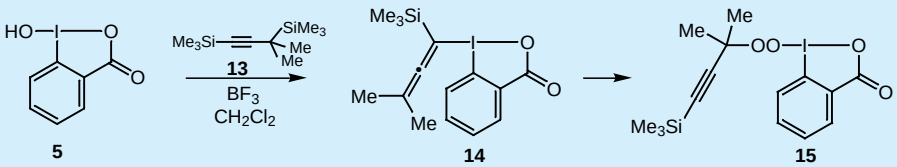


Fig.4

3. Synthesis of *tert*-Butylperoxyiodanes

Hypervalent λ^3–organoiodanes having an alkylperoxy group as a ligand are very unstable. In 1968 Milas and Plesnicar reported that reaction of iodosylbenzene **1** with *tert*-butylhydroperoxide in methylene chloride at -80°C generated *tert*-butylperoxy radical and iodobenzene . It was assumed that in this reaction, an initial ligand exchange on the iodine atom afforded bis(alkylperoxy)iodane, which was so unstable, resulting in homolytic bond cleavage of the hypervalent O-I bond, even at -80°C, to give a *tert*-butylperoxy radical. Accordingly, isolation of alkylperoxyiodane **15** is very interesting because it is stable even at room temperature. This is attributed to fixation of both the apical heteroatom ligands and equatorial aromatic ligand in the same plane by the formation of five-membered heterocycles. This arrangement to form an iodoxolone leads to enhanced stability of the alkylperoxyiodanes **15** because orbital interaction between the easily cleaved I-O bond and π-orbitals of phenyl group is not feasible.

The alkylperoxyiodanes with unique structure were expected to be utilized as new oxidants in organic synthesis. Hereby, iodane **6**, in which the *tert*-butylperoxy group was introduced, was designed as a representative compound and its synthesis attempted. Reaction of hydroxyiodane **5** with *tert*-butylhydroperoxide did not take place at room temperature and hydroxyiodane was recovered because of its poor reactivity. However, on addition of Lewis acid to the reaction mixture, the desired ligand exchange on the iodine atom proceeded effectively to afford peroxyiodane **6** in good yield (Figure 5) [2]. Coordination of BF_3 on the oxygen atoms of hydroxyiodanes **5** causes activation. The product *tert*-butylperoxyiodane **6** is stable in the solid state and no decomposition is seen when the crystalline form is stored over a year at room temperature.

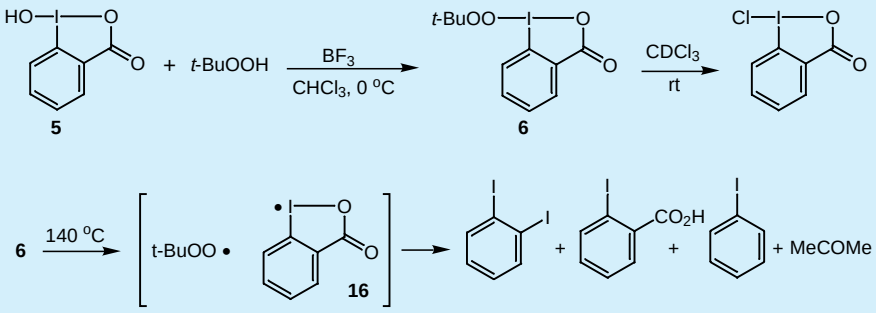


Fig.5

The peroxyiodane **6**, though stable in the solid state, is readily decomposed in solution. When the peroxyiodane **6** is dissolved in chloroform and allowed to stand at room temperature, a ligand exchange takes place to give chloroiodane, and the half life of **6** is about 4 days. Heating crystalline peroxyiodane at 140°C causes it to decompose explosively to generate 1,2-diiodobenzene (46%), iodobenzene (6%), *o*-iodobenzoic acid (14%) and acetone (43%). In this thermal decomposition reaction, the decomposition is considered to take place via the generation of *tert*-butylperoxy radical and 9-I-2 σ-iodanyl radical **16** due to cleavage of the weak hypervalent bond between the oxygen of the peroxy group and iodine atom.

4. Benzylic Oxidation Reaction by *tert*-Butylperoxyiodane [9)]

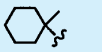
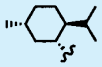
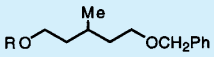
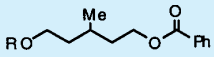
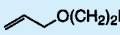
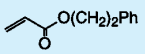
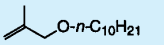
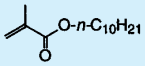
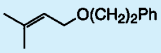
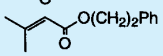
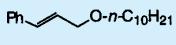
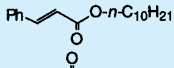
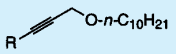
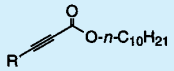
tert-Butylperoxyiodane **6** is effective for the oxidation of the benzylic methylene group of benzyl ethers **17**, to form esters of benzoic acid **18**. Reactions are performed at room temperature under a nitrogen atmosphere using a rubber balloon. The yields of esters are highly dependent upon the dielectric constant of the solvents and the best results were obtained in benzene which has a small dielectric constant, although, the reaction at room temperature was very slow. However, the reaction in benzene was considerably accelerated with the addition of alkali metal carbonates (K_2CO_3, Cs_2CO_3 *etc.*).

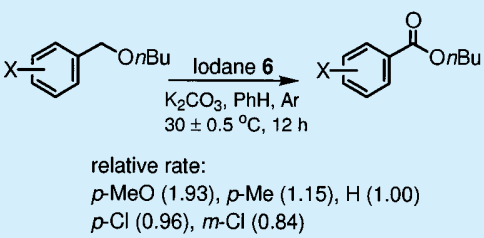
The benzyl group is frequently used as a protecting group for alcohols in organic synthesis. Since esters are readily hydrolized to alcohols, peroxyiodane **6** provides an oxidative deprotection method for the benzyl group. One of the common problems associated with deprotection reactions is their chemoselectivity. Chemoselective oxidation at the benzylic site proceeds even in the presence of MOM group, silyl group, acetyl group or tetrahydropyranyl group. The allyl group is used as a protecting group for alcohols and peroxyiodane **6** is useful for the oxidation of allyl ether to the corresponding α,β-unsaturated esters. Furthermore, the benzylic oxidations of other hydrocarbons also proceed readily and indan, tetrahydronaphthalene, dihydroanthracene, fluorene,*etc.* are efficiently oxidized. The results of these reactions are partly shown in Table 1.

Radical inhibitors such as α-tocopherol and galvinoxyl inhibit the oxidation of the benzylic methylene group, which suggests the involvement of radical species. To verify that radicals are generated at the benzylic positions, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), which reacts very rapidly with carbon radicals, was used as a trap for any benzylic radicals. The substituent effect on the oxidation reaction of benzyl butyl ethers **17a** was investigated (Figure 6). The introduction of electron-withdrawing chlorine in *p*- or *m*-position decreased the rate of the reaction, while introduction of *p*-MeO group or *p*-Me group accelerated the reaction. Hammett correlation was established between the relative reaction rate and substituent constant σ^+ with ρ = -0.30. This ρ value appears to be comparable to ρ = -0.65 for benzylic hydrogen abstractions from dibenzyl ethers by benzoyloxy radical. An examination of the deuterium primary isotope effect resulted in a very large value (K_H/K_D =12-14). This large isotope effect also strongly indicated that the cleavage of the benzylic C-H bond is involved in the rate-determining step.

The effect of molecular oxygen on this reaction was also investigated. Very interestingly, in the presence of a large excess of benzyl butyl ether **17a** relative to the peroxyiodane **6**, the prolonged reactions (410 h) under nitrogen rubber balloons afforded more than stoichiometric amounts of benzoate ester **18a** (*ca.* 600%), while the reaction in the absence of oxygen (a degassed argon tube experiment) gave 24% of benzoate ester **18a** and 72% of peroxyacetal **19**, which has *tert*-butylperoxy group at the benzylic position. This result would indicate the formation of two kinds of reaction intermediates: the peroxyacetal **19** and hydroperoxyacetal **20** derived from the reaction with molecular oxygen. It is assumed that both of these intermediates are converted into esters of benzoic acid. The reaction mechanism is shown in Figure 7.

Table 1. Oxidation of Benzyl, Allyl, and Propargyl Ethers **17** with the Peroxyiodane **6**

entry	ether	17	time (h)	product	18	yield (%)
	$PhCH_2OR$			$PhCO_2R$		
1	R = *n*-Bu	**17a**	24		**18a**	95
2	*tert*-Bu	**17b**	24		**18b**	80
3	*cyclo*-C_6H_{11}	**17c**	48		**18c**	79
4		**17d**	31		**18d**	74
5		**17e**	30		**18e**	74
6		**17f**	23		**18f**	78
7		**17g**	17		**18g**	86
						
8	R = MOM	**17h**	72		**18h**	78
9	THP	**17i**	47		**18i**	61
10	TBDMS	**17j**	100		**18j**	68
11		**17k**	42		**18k**	60
12		**17l**	72		**18l**	73
13		**17m**	46		**18m**	76
14		**17n**	51		**18n**	72
						
15	R = H	**17o**			**18o**	51
16	TMS	**17p**			**18p**	65



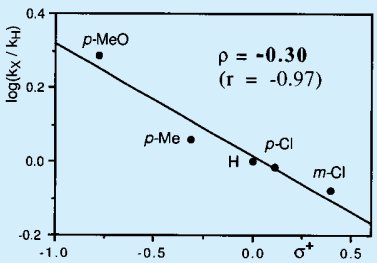


Fig.6

Initially, the weak hypervalent bond between the oxygen atom of the peroxy group and the iodine atom of the peroxyiodane **6** is cleaved to generate *tert*-butylperoxy radical and 9-I-2 σ- iodanyl radical **16**. The benzylic radical **21** is generated when the electrophilic iodanyl radical **16** abstracts the benzylic hydrogen of the benzyl ether **17a**. The benzylic radical **21** further reacts with the peroxyiodane **6** to yield *tert*-butylperoxyacetal **19**, which decomposes to the corresponding ester **18a**. On the other hand, in the presence of molecular oxygen in the reaction system, the reaction of the benzylic radical **21** with oxygen yields the peroxy radical **22**. The peroxy radical **22** further abstracts the benzylic hydrogen of **17a** to yield hydroperoxyacetal **20** and the benzylic radical **21** is regenerated as well. The hydroperoxyacetal **20** is converted to the corresponding ester **18a** under reaction conditions.

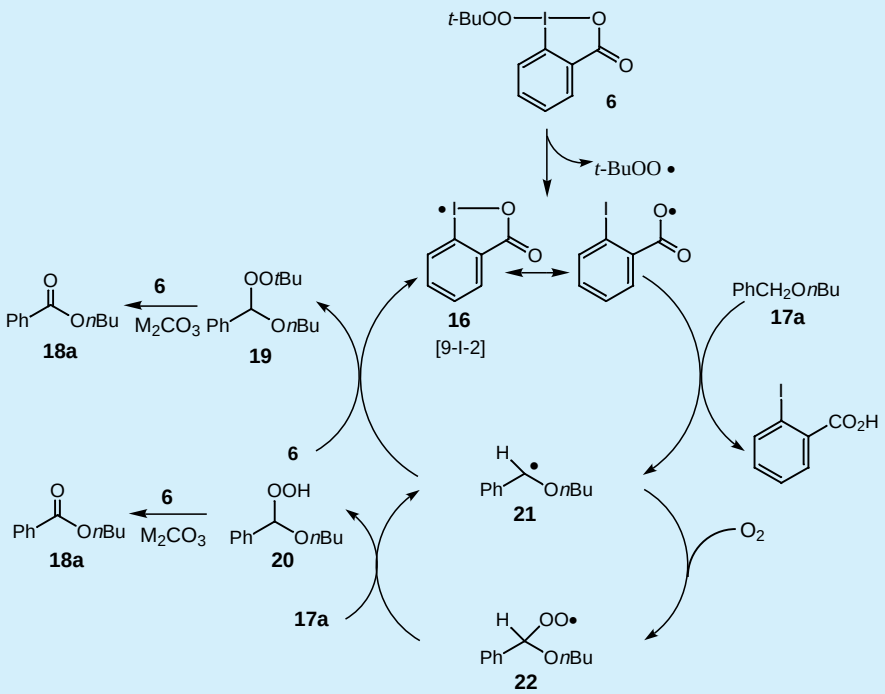
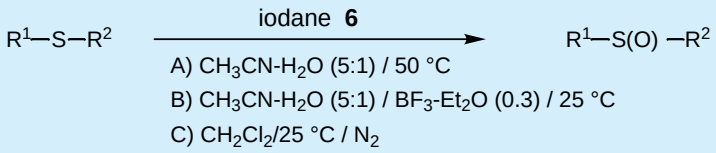


Fig.7

5. Oxidation of Sulfides by *tert*-Butylperoxyiodane [10)]

tert-Butylperoxyiodane **6** oxidizes sulfides to sulfoxides. Dialkyl sulfides and alkyl aryl sulfides are converted to sulfoxides in good yields in aqueous acetonitrile (method A). Diaryl sulfides are converted in good yields to sulfoxides in dichloromethane (method C). Addition of BF_3-Et_2O (method B) to aqueous acetonitrile accelerated the reaction (Figure 8).



n-BuSBn, *i*-BuSBn, *s*-BuSBn, BnSBn, $Me(CH_2)_4SPh$,

CH_2=$CHCH_2SPh$, *p*-$MeOC_6H_4SMe$, *p*-MeC_6H_4SMe,

p-ClC_6H_4SMe, $PhSCH_2P(O)(OEt)_2$, PhSPh, (*p*-$ClC_6H_4)_2S$

Fig.8

Our studies on the substituent effects for the reaction of substituted thioanisoles in aqueous acetonitrile exhibited a large negative ρ value (-3.35) toward the substituent constants σ. The corresponding BF_3-Et_2O mediated reaction exhibited the ρ value -2.23, with a better correlation toward the substituent constants σ^+. It seems reasonable to assume that the reaction in aqueous acetonitrile is an ionic reaction from the following observations.

1) An equilibrium is in existence between the peroxyiodane **6** and hydroxyiodane **5**.
2) Use of either the hydroxyiodane **5** or the *tert*-butyl hydroperoxide as an oxidant by itself causes no reaction to occur, but the use of both in together allows the reaction to proceed almost quantitatively.
3) In addition, the effect of the added galvinoxyl which is a radical scavenger, is small.

Furthermore, it is strongly suggests that *tert*-butylperoxyiodane **6** is the active species and that a reactive intermediate with a considrable positive charge on the sulfur atom is generated . On the other hand, the reaction in dichloromethane (method C) is completely inhibited by the addition of galvinoxyl indicating that the reaction takes place by a radical mechanism.

Oxidative deprotection of dithioacetals also takes place. Treatment of dithioacetals with peroxyiodane **6** in aqueous acetonitrile reacts completely in several minutes with the generation of parent ketones in high yields. The peroxyiodane **6** is useful for the oxidation of selenides to selenoxides and phosphines to phosphine oxides. Furthermore, the peroxyiodane **6** oxidizes 2 mol of triphenylphosphines to the corresponding oxides.

6. Oxidation of Amines by *tert*-Butylperoxyiodane [11)]

The *tert*-butylperoxyiodane **6** is effective for the oxidation of amines. The reaction of secondary amines with the *tert*-butylperoxyiodane **6** causes dehydration to occur, yielding imines. Addition of K_2CO_3 accelerates the reaction. In the oxidation of tetrahydroisoquinoline, dihydroisoquinoline is obtained in high yeild. When an excess amount of peroxyiodane **6** is used, isoquinoline is produced. The reaction with tertiary amines generates peroxy amino acetals with the peroxy group being introduced on the α-carbon atom of the amines (Figure 9).

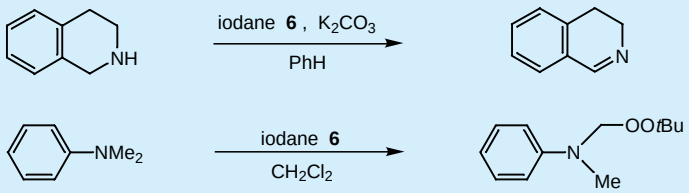


Fig.9

7. Radical Oxidation Reaction of Phenols by *tert*-Butylperoxyiodane [12)]

In reactions with *p*-alkyl substituted phenols, 4-(*tert*-butylperoxy)cyclohexadienone is produced. Treatment of *p*-substituted phenols with peroxyiodane **6**, in the presence of *tert*-butyl hydroperoxide, gives *tert*-butylperoxycyclohexadienones in good yield under mild conditions (ethyl acetate/50°C). It seems reasonable to assume that this reaction is a radical reaction because the oxidation reaction in the presence of galvinoxyl was almost completely inhibited and a small amount of a dimer of *tert*-butylperoxycyclohexadienone was obtained as a by-product. The phenoxy radical, stabilized by resonance, is an intermediate, and its coupling with the *tert*-butylperoxy radical yields *tert*-butylperoxycyclohexadienone.

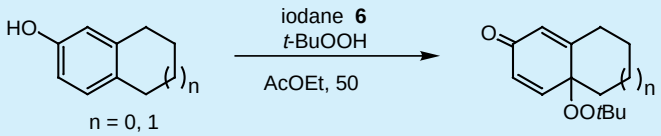


Fig.10

8. Conclusion

In *tert*-butylperoxyiodane **6**, the *tert*-butylperoxy group and the trivalent iodine atom are bonded by a hypervalent bond. An intensive survey of its structure leads us to expect its high reactivity but makes us worry about its potential for explosion. It is likely that a limited number of chemists would actually try to synthesize this compound by themselves. On the contrary, the crystalline *tert*-butylperoxyiodane **6** is a surprisingly stable compound and no decomposition occurs at room temperature. Furthermore, no radical cleavage of the hypervalent bond occurs until it is made into a solution in which case the reaction proceeds slowly. Generally, the reaction is carried out at less than 50°C and no attempts have been made beyond

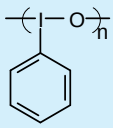
that temperature.

As discussed in the above, the developement of *tert*-butylperoxyiodane has been attributed to our concentrated efforts to seek for new potential utilization of iodine. The results have been generated by many careful experiments carried out by Dr. Takao Ito (Nippon Tobacco Industry K.K. Laboratory). The author wish to extend heartfelt thanks toward many of the students, for their contributions, whose names are listed in the reference literature involved in these studies.

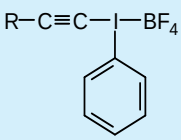
References

1) a)G, F. Koser, in "The Chemistry of Functional Groups, Supplement D2"; Ed. by S. Patai and Z. Rappoport, Wiley, New York (1995); Chapters 21. b) A. Varvoglis, "The Organic Chemistry of Polycoordinated Iodine", VCH, New York (1992).
2) M. Ochiai, T. Ito, Y. Masaki, M. Shiro, *J. Am. Chem. Soc.*, **114**, 6269 (1992).
3) M. Ochiai, *Kagaku Sosetsu*, "Hypervalent Organic Compounds", **34**, 181 (1998).
4) M. Ochiai, M. Toyonari, T. Nagaoka, D.-W. Chen, M. Kida, *Tetrahedron Lett.*, **38**, 6709 (1997).
5) M. Ochiai, in "Chemistry in Hypervalent Compounds"; Ed. by K. Akiba, Wiley-VCH, New York (1999); Chapters 12.
6) M. Ochiai, T. Ito, Y. Takaoka, Y. Masaki, M. Kunishima, S. Tani, Y. Nagao, *J. Chem. Soc., Chem. Commun.*, **1990**, 118.
7) M. Ochiai, T. Ito, Y. Takaoka, Y. Masaki, *J. Am. Chem. Soc.*, **113**, 1319 (1991).
8) M. Ochiai, T. Ito, M. Shiro, *J. Chem. Soc., Chem. Commun.*, **1993**, 218.
9) M. Ochiai, T. Ito, H. Takahashi, A. Nakanishi, M. Toyonari, T. Sueda, S. Goto, M. Shiro, *J. Am. Chem. Soc.*, **118**, 7716 (1996).
10) M. Ochiai, A. Nakanishi, T. Ito, *J. Org. Chem.*, **62**, 4253 (1997).
11) M. Ochiai, D. Kajishima, T. Sueda, *Heterocycles*, **46**, 71 (1997).
12) M. Ochiai, A. Nakanishi, A. Yamada, *Tetrahedron Lett.*, **38**, 3927 (1997).

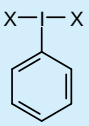
Hypervalent Organoiodanes



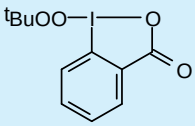
Iodosobenzene
5g JPYen9,300 (I0072)



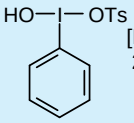
R=H
Ethynyl(phenyl)iodonium Tetrafluoroborate
1g JPYen 10,100 (E0467)
R=Me_3Si
Trimethylsilylethynyl(phenyl)iodonium Tetrafluoroborate
1g JPYen 6,850 (P1239)



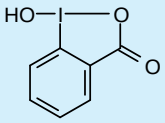
X=OAc
Iodobenzene Diacetate
25g JPYen7,650 10g JPYen3,900 (I0330)
X=$OCOCF_3$
[Bis(trifluoroacetoxy)iodo]benzene
25g JPYen 12,800 10g JPYen7,350 (B1175)



1-(*tert*-Butylperoxy)-1,2-benziodoxol-3(1*H*)-one
1g JPYen 23,800 (B2121)



[Hydroxy(tosyloxy)iodo]benzene
25g JPYen 14,500 5g JPYen 5,550 (P1015)



o-Iodosobenzoic Acid
10g JPYen 16,300 (I0073)

TCIMAIL
July, 1999 number 104

CHEMICALS NOTE

Recently Modified Mitsunobu Reactions

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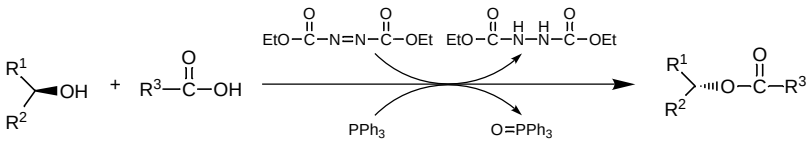
R & D (Information Management) Department,
Tokyo Kasei Kogyo Co., Ltd.

In 1967 O. Mitsunobu reported the generation of the esters in high yield from the reaction of alcohols and carboxylic acids in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) [1]. This reaction represents an epoch-making reaction which involves the activation of the alcoholic hydroxyl group and the subsequent carbon-oxygen bond cleavage caused by the attacking carboxylate anions to give an ester with complete Walden-inversion of the alcohol component. Furthermore, not only the carboxylic acids as the nucleophilic component but the imide or thiol can also be utilized and the reactions proceed under mild conditions. The above reaction constitutes one of the most important organic reactions and is called “Mitsunobu Reaction” as a token of respect for its developer [2].



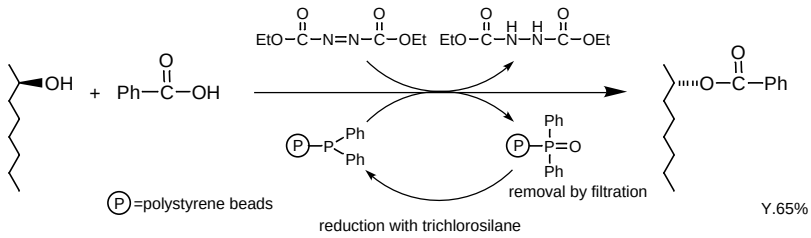
The Mitsunobu reaction has found widespread use in many fields because of its high reliability and extensive applicability. For example, when Chem.abstr. is traced by the keyword "Mitsunobu" from 1967 up to today, one encounters about 1,000 related reports, indicating the high utilization of this reaction.

However, the generation of phosphine oxide and hydrazinedicarboxylate as by-products often prevents the desired product from being isolated. Furthermore, the p*K*a of the usable acid component must be below 13, preferably below 11. Because the Mitsunobu reaction has demonstrated a very excellent reactive ability, efforts have been made toward widening the utilization scope.

1. Removal of By-products

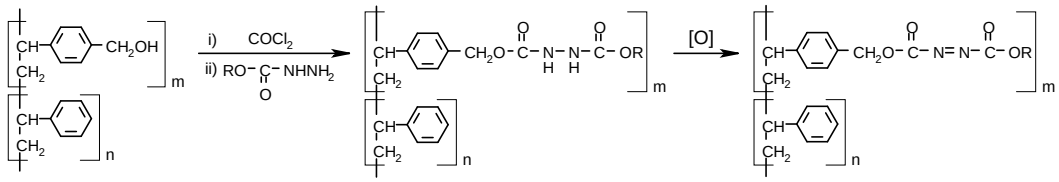
The Mitsunobe reaction is a condensation-dehydration reaction with loss of a water molecule from alcohols and carboxylic acids. This is a result of the strong affinity for oxygen by TPP and for hydrogen by DEAD. This constitutes a simultaneous redox reaction in which TPP is oxidized to an oxide and with DEAD being reduced to hydrazinedicarboxylate. Accordingly, one cannot avoid by-products, phosphine oxide and hydrazinecarboxylate, which are generated. Moreover, these by-products often prevent the desired products from being further isolated.

R.A. Amos and co-workers [3] employed polystyryldiphenylphosphine which constitutes TPP anchored to polystyrene resin in the Mitunobe reaction. In this system, TPP, in excess, and the resulting oxide are anchored to the polystyrene resin, and they can be easily removed by means of filtration. The resulting oxide can be reduced by trichlorosilane to TPP and reused again. The chiral alcohol, 2-octanol, reacts with benzoic acid with complete Walden-inversion to give the corresponding ester, thus, demonstrating that the characteristics of the Mitsunobu reaction are preserved.

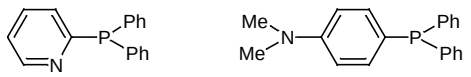


This methodology can also be applied to combinatorial chemistry. For example, A.R. Tunoori and co-workers[4] have configured a library of the aryl alkyl ethers from phenols and alcohols by means of liquid phase synthesis using polystyryldiphenylphosphine.

Similarly, an attempt to anchor dialkyl azodicarboxylate to a resin was also conducted. L.D. Arnold and co-workers [5] reacted hydroxymethylpolystyrene first with phosgene, and second with a carbazilic ester, followed by oxidation to synthesize azodicarboxylate. This resin affords good results in combination with TPP.

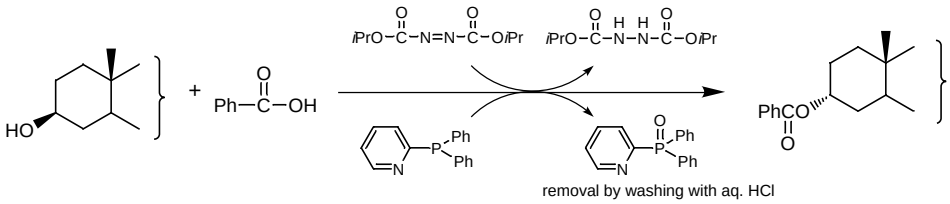


A method to remove the unreacted phosphine and the by-product, phosphine oxide, has also been considered. A basic functional group was introduced into TPP and upon completion of the reaction, it was washed by acid. Diphenyl(2-pyridyl)phosphine **1** and (4-dimethylaminophenyl)diphenylphosphine **2** were developed to contain a basic amine functional group attached to the phosphine group.



1 **2**

D.Camp and co-workers [6] have reported that in the Mitsunobu reaction using diphenyl(2-pyridyl)phosphine **1**, cholestane 3α-ester can be obtained in 80% yield from cholestane-3β-ol and benzoic acid. In this instance, they have removed the by-product, phosphine oxide by washing the organic layer with 2M hydrochloric acid upon completion of the reaction. Furthermore, the reaction has been followed by ^{31}P n.m.r. which showed that the basic component has no effect on the reaction rate nor reaction mechanism.



M.von Itzstein and co-workers [7] have employed (4-dimethylaminophenyl)diphenylphosphine **2** as a replacement for TPP. This phosphine has a basic dimethylamino group. For this reason, the accompanying oxide by-product can be removed by washing with dilute hydrochloric acid. They have also observed the reaction via ^{31}P.n.m.r. and reported the results of their investigation.

2. Application toward Weak Acids

The mechanism of the Mitsunobu reaction is considered as shown in Figure 1. A betaine **3** is formed from TPP and DEAD. This betaine reacts with an alcohol to yield an anion **4** and a phosphonium **5**. An anion **7** is generated by proton abstraction by the anion **4** from acid **6**. This anion **7** attacks the phosphonium **5** to give the desired Walden invertion product **8**. If the acidity of the acid **6** is low and the p*K*a value is over **11**, the proton abstraction by the anion **4** from the acid **6** is inhibited and the anion **4** attacks the phosphonium **5** to yield an undesired product **9**.

T. Tsunoda and co-workers [8] have carried out an additional investigation of DEAD and TPP in order to apply the Mitsunobu reaction to weak acids with high pKa value. This investigation constitutes a new system by converting the ethoxy terminal of DEAD to the amino group in order to increase the basicity of anion **4**. Sterically bulky groups

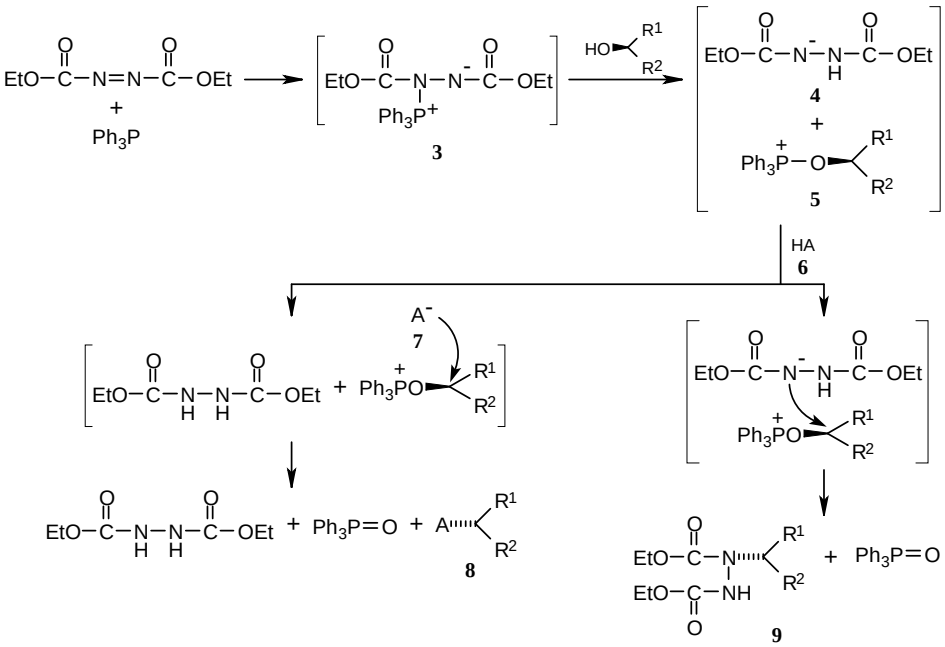
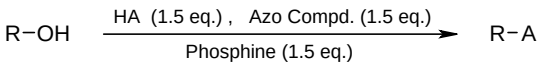


Fig. 1 Mechanism of Mitsunobu reaction

were introduced on the amino group in order to inhibit the increased nucleophilic substitution activity as a result of the increased basicity. This system is able to easily abstract the proton from **6**. To achieve this, they utilized azo compounds such as 1,1′-(azodicarbonyl)dipiperidine **10** and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide **11** in combination with tri-*n*-butylphosphine (TBP).

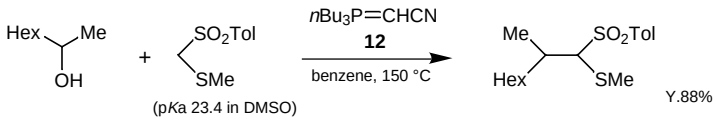
In the systems of 1,1′-(azodicarbonyl)dipiperidine **10** and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide **11**, and TBP as shown in Table **1**, the Mitsunobu reaction proceeds in high yields in spite of the amide having p*K*a value higher than **11**. Accordingly, the method developed by Tsunoda and co-workers attracts a great deal of attention as a method to moderate the limitation of p*K*a and extend the scope in the application of the Mitsunobu reaction.



HA	R−OH	DEAD−TPP	**10**−TBP	**11**−TBP
$CF_3-C(=O)-NHCH_2Ph$ (p*K*a 13.6)	$PhCH_2OH$	3	53	86
		—	56	78
$Ts-NH-Me$ (p*K*a 11.7)	$PhCH_2OH$	65	86	99
		51	99	96

Table 1. Mitsunobu alkylation with some azo compounds (% Yield of RA)

They have further investigated the use of cyanomethylenetri-*n*-butylphosphorane **12** in the Mitsunobu reaction[10]. With cyanomethylenetri-*n*-butylphosphorane **12**, acid components having high p*K*a values can be utilized and the cyanomethylenetri-*n*-butylphosphorane **12** alone can achieve the functions of both DEAD and TPP.



The isolation of the desired product can be readily performed by employing a combination of DEAD anchored to the resin and phosphine **1**,**2** having basic functional group, or that of TPP anchored to a resin and DEAD. The methods developed by Tsunoda and co-workers to use 1,1′-(azodicarbonyl)dipiperidine **10**-TBP, *N*,*N*,*N*′,*N*′-Tetramethylazodicarboxamide **11**-TBP or cyanomethylenetri-*n*-butylphosphorane moderate the limitation of p*K*a and extend the scope of the Mitsunobu reaction beyond the conventional DEAD-TPP system, thus further enhancing the usefulness of the Mitsunobu reaction. Because of its excellent reactivity, cyanomethylenetri-*n*-butylphosphorane **12** especially is expected to be useful in applications for the synthesis of physiologically active compounds.

References

1) O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.*, **40**, 2380 (1967).
2) O. Mitsunobu, *Synthesis*, **1981**, 1; D. L. Hughes, *Org. React.*, **42**, 335 (1992).
3) R. A. Amos, R. W. Emblidge, N. Havens, *J. Org. Chem.*, **48**, 3598 (1983).
4) A. R. Tunoori, D. Dutta, G. I. Georg, *Tetrahedron Lett.*, **39**, 8751 (1998).
5) L. D. Arnold, H. I. Assil, J. C. Vederas, *J. Am. Chem. Soc.*, **111**, 3973 (1989).
6) D. Camp, I. D. Jenkins, *Aust. J. Chem.*, **41**, 1835 (1988).
7) M. von Itzstein, M. Mocerino, *Synth. Commun.*, **20**, 2049 (1990).
8) T. Tsunoda, S. Itô, *J. Synth. Org. Chem. Jpn.*, **52**, 113 (1994); *idem*, *ibid*., **55**, 631 (1997).
9) T. Tsunoda, Y. Yamamiya, S. Itô, *Tetrahedron Lett*., **34**, 1639 (1993); T. Tsunoda, J. Otsuka, Y. Yamamiya, S. Itô, *Chem. Lett.*, **1994**, 539; T. Tsunoda, Y. Yamamiya, Y. Kawamura, S. Itô, *Tetrahedron Lett*., **36**, 2529 (1995).
10) T. Tsunoda, M. Nagaku, C. Nagino, Y. Kawamura, F. Ozaki, H. Hioki, S. Itô, *Tetrahedron Lett*., **36**, 2531 (1995); T. Tsunoda, F. Ozaki, N. Shirakata, Y. Tamaoka, H. Yamamoto, S. Itô, *ibid*., **37**, 2463 (1996).

NEW MITSUNOBU REAGENT / TSUNODA REAGENT

C1500	Cyanomethylenetri-*n*-butylphosphorane		1g JPYen 12,500

PHOSPHINES

D2411	Dicyclohexylphenylphosphine		5g JPYen 12,300
D1019	Diethylphenylphosphine		5ml JPYen 21,400
D2478	(4-Dimethylaminophenyl)diphenylphosphine	5g JPYen 17,400	1g JPYen 5,950
D2471	Diphenyl-2-pyridylphosphine		1g JPYen 9,300
T0361	Tri-*n*-butylphosphine	500ml JPYen 27,700	25ml JPYen 2,000
T1165	Tricyclohexylphosphine (15% in Toluene)	500ml JPYen 50,000	25ml JPYen 5,950
T1005	Tri-*n*-hexylphosphine	500ml JPYen 45,600	25ml JPYen 4,800
T0503	Tri-*n*-octylphosphine	500ml JPYen 50,000	25ml JPYen 4,300
T0519	Triphenylphosphine	500g JPYen 7,650	25g JPYen 1,200

AZODICARBOXYLIC ESTERS / AMIDES

A0776	Dibenzyl Azodiformate (40% in Dichloromethane)		25g JPYen 8,400
A0705	Diethyl Azodiformate (40% in Toluene)	250g JPYen 25,500	25g JPYen 5,000
A1246	Diisopropyl Azodiformate (40% in Toluene)	250g JPYen 13,800	25g JPYen 2,950
A0882	Dimethyl Azodiformate (40% in Toluene)		25g JPYen 9,300
A1051	1,1′-(Azodicarbonyl)dipiperidine		5g JPYen 7,950
A1458	*N*,*N*,*N*′,*N*′-Tetramethylazodicarboxamide		1g JPYen 7,650

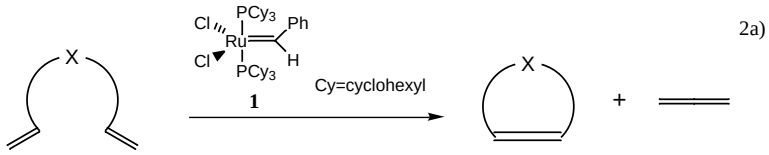
Azodicarboxylic esters are susceptible to explosion when subjected to heat, impact and friction. In order to alleviate the risk, azodicarboxylic esters are available as a 40% solution in organic solvents. We recommend to use them in the solution as received. Under compelling circumstances requiring heating operations such as compression, distillation or drying, please carry out experiments in the required minimum amount only and in addition, to use fully-equipped safety measures such as a safety shield.

Org. Synth., **72**, 273 (1995); *ibid.*, Coll. Vol. 3, 375 (1955); *ibid.*, Coll. Vol. 4, 411 (1963).

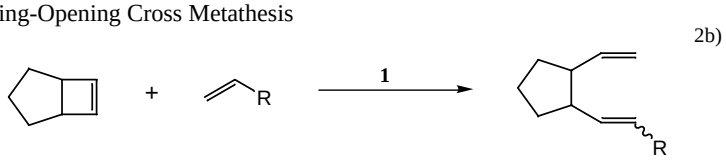
OLEFIN METATHESIS CATALYST

B2036 (Benzylidene)bis(tricyclohexylphosphine)ruthenium(IV) Dichloride 1g JPYen 20,200

Ring-Closing Metathesis

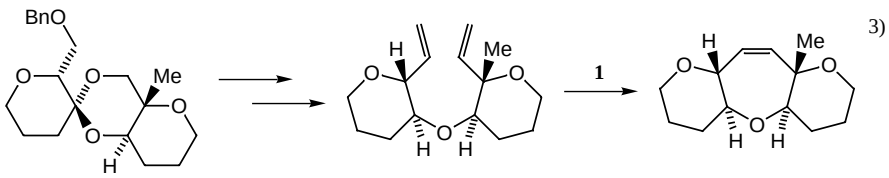


Ring-Opening Cross Metathesis



Recently, olefin metathesis reaction employing metallic carbene complex as a catalyst is attracting a high degree of attention. Metathesis is referred to as a reaction in which an exchange of alkylidene group occurs between two olefin molecules.

In 1995 R.H. Grubbs and co-workers have developed the present reagent 1, as a metathesis catalyst. The catalyst 1 is characterized by being stable toward the oxygen and moisture in the atmosphere and inert to the presence of a variety of functional groups when compared with the conventional metathesis catalysts. The reactions using the catalyst 1 are mainly classified into ring-closing metathesis reaction and ring-opening cross metathesis reaction.



A great number of synthesis examples employing the catalyst 1 for metathesis reactions, have been reported [2] and its application toward synthesizing physiologically active substances have been increasingly carried out. For example, T. Oishi and co-workers have applied the catalyst 1 to the synthesis of polycyclic ethers [3] and K.C. Nicolau and co-workers utilized the catalyst 1 in the synthesis of epothilones A and B [4].

References

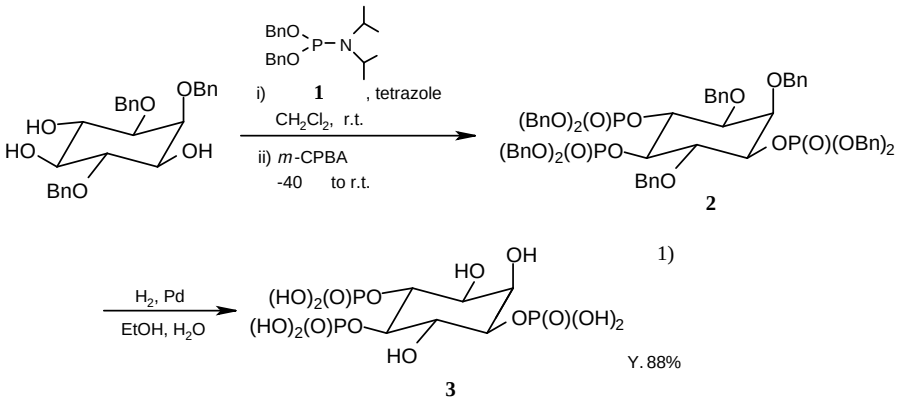
1) Well-defined metathesis catalysts
P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem. Int. Ed. Engl.*, **34**, 2039 (1995).

2) Olefin metathesis catalyst
a) S. J. Miller, H. E. Blackwell, R. H. Grubbs, *J. Am. Chem. Soc.*, **118**, 9606 (1996).
b) M. L. Snapper, J. A. Tallarico, M. L. Randall, *ibid.*, **119**, 1478 (1997).
c) A. Fürstner, K. Langemann, *ibid.*, **119**, 9130 (1997).
d) F. P. J. T. Rutjes, H. E. Schoemaker, *Tetrahedron Lett.*, **38**, 677 (1997).
e) S. E. Gibson, V. C. Gibson, S. P. Keen, *Chem. Commun.*, **1997**, 1107.

3) Synthesis of a *trans*-fused 6-7-6 tricyclic ether system
T. Oishi, Y. Nagumo, M. Hirama, *Synlett*, **1997**, 980.

4) Synthesis of epothilones A and B in solid and solution phase
K. C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature*, **387**, 268 (1997).

D2624 Dibenzyl *N,N*-Diisopropylphosphoramidite 5g JPYen 13,600



The present reagent 1 reacts rapidly with alcohols in the presence of 1*H*-tetrazole at room temperature to generate phosphorous triesters. Subsequent reaction with oxidizing agents such as m-chloroperoxybenzoic acid affords the corresponding phosphoric triesters 2. The triesters thus obtained can be deprotected by cleavage of the benzyl group by catalytic hydrogenolysis using Pd/C to yield the desired derivatives of phosphoric acids 3 [1]. The reagent 1 has high reactivity and its reactions to proceed under mild conditions. It has a wide scope of applications, including the synthesis of biomolecules such as oligonucleotides [2].

References

1) Phosphorylation of cyclitols
K.-L. Yu, B. Fraser-Reid, *Tetrahedron Lett.*, **29**, 979 (1988).
2) The synthesis of oligonucleotides
S. L. Beaucage, R. P. Iyer, *Tetrahedron*, **48**, 2223 (1992).
3) Other applications
a) Phosphorylation of amino acids
W. Bannwarth, A. Trzeciak, *Helv. Chim. Acta*, **70**, 175 (1987).
b) Phosphorylation of peptides
J. W. Perich, R. B. Johns, *Tetrahedron Lett.*, **29**, 2369 (1988).
c) Phosphorylation of sugars
Y. Ichikawa, M. M. Sim, C.-H. Wong, *J. Org. Chem.*, **57**, 2943 (1992).

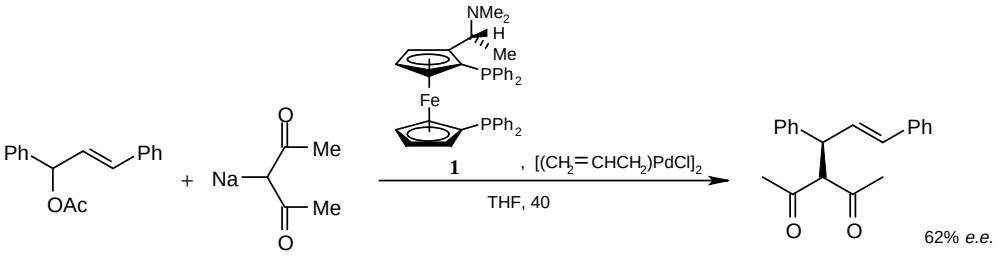
Related Products

C0978	Barium 2-Cyanoethylphosphate	25g	JPYen	13,600	5g	JPYen	4,100
C1210	2-Chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one	25g	JPYen	12,400	5g	JPYen	4,200
C1215	2-Chloro-1,3,2-dioxaphospholane				25g	JPYen	8,400
C1250	2-Chloro-2-oxo-1,3,2-dioxaphospholane				10g	JPYen	13,400
C1018	2-Chlorophenyl-*N*-phenylphosphoramidochloridate	25g	JPYen	30,800	5g	JPYen	10,000
C1019	4-Chlorophenyl-*N*-phenylphosphoramidochloridate	25g	JPYen	29,700	5g	JPYen	9,700
C0976	2-Chlorophenylphosphorodichloridate	25g	JPYen	7,750	5g	JPYen	2,000
C0977	4-Chlorophenylphosphorodichloridate	25g	JPYen	8,250	5g	JPYen	2,250
D1613	*S,S'*-Diphenylphosphorodithioate Monocyclohexylammonium Salt	25g	JPYen	39,500	5g	JPYen	10,200
D1059	Diphenylphosphoryl Chloride	500g	JPYen	26,200	25g	JPYen	3,800
M0904	Methyl Phosphorodichloridate				25g	JPYen	11,700
M0905	Methyl Phosphorodichloridite				10g	JPYen	7,850
P0209	Phenylphosphoryl Dichloride	500g	JPYen	36,600	25g	JPYen	5,450
P1223	Pyrophosphoric Acid Tetrabenzyl Ester				1g	JPYen	21,200

CHIRAL FERROCENYLPHOSPHINE LIGANDS

D2537 (*R*)-*N*,*N*-Dimethyl-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]-ethylamine 1 100mg JPYen 7,450

D2538 (*S*)-*N*,*N*-Dimethyl-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]-ethylamine 2 100mg JPYen 7,450



In the fields of medicinal and agricultural chemicals, a demand for optically active compounds has increased more than ever. Among a variety of methods available for preparing optically active compounds, intensive studies have increasingly been made on the utilization of asymmetric catalysts.

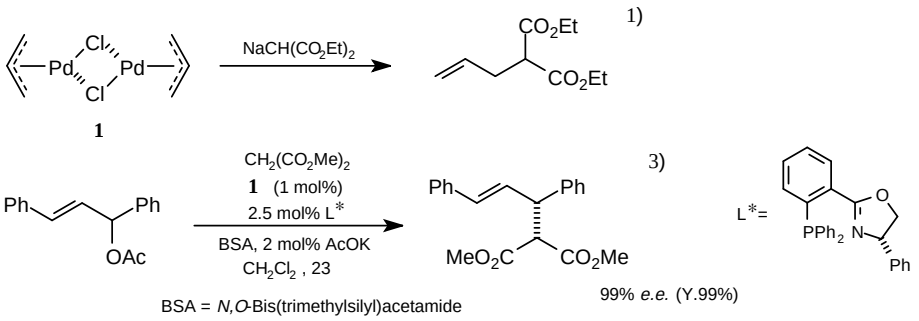
The present reagents 1 and 2 are ligands having both a chiral plane and a chiral center within their molecules and they form asymmetric catalysts having highly controlled configuration with transition metals. Furthermore, the dimethylamino group of reagents 1 and 2 can be easily converted to other functional groups.

References

Asymmetric synthesis catalyzed by chiral ferrocenylphosphine-metal complexes
T. Hayashi, A. Yamamoto, T. Hagihara, Y. Ito, *Tetrahedron Lett.*, **27**, 191 (1986).
T. Hayashi, *Pure & Appl. Chem.*, **60**, 7 (1988).

π-ALLYLPALLADIUM COMPLEX

A1479 Allylpalladium (II) Chloride Dimer 500mg JPYen 9,800



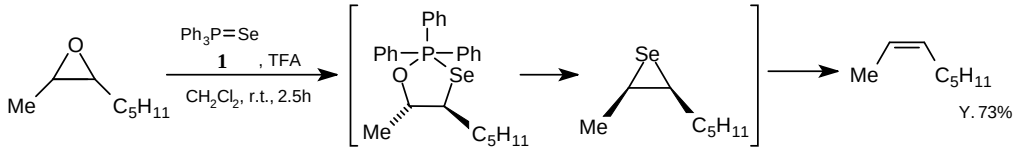
The present reagent 1 performs quantitative allylation with a variety of nucleophiles [1,2]. For example, reaction with malonic acid esters leads to allyl substituted malonate derivatives. Furthermore, addition of reagent 1 and phosphine ligands to the reactions between nucleophiles and olefins leads to the formation of a new Pd-phosphine complex within the system which functions as a catalyst for the allylation reaction to proceed smoothly. In this case using asymmetric phosphine ligands such as L* allows asymmetric allylation reaction to occur [3,4].

References

1) Reaction of π-allylpalladium chloride with nucleophiles
J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.*, **1965**, 4387.
2) Organopalladium intermediates in organic synthesis
B. M. Trost, *Tetrahedron*, **33**, 2615 (1977).
3) Chiral phosphinoaryldihydrooxazoles as ligands in asymmetric catalysis
P. von Matt, A. Pfaltz, *Angew. Chem. Int. Ed. Engl.*, **32**, 566 (1993).
4) Asymmetric catalytic allylation using palladium chiral phosphine complexes
P. R. Auburn, P. B. Mackenzie, B. Bosnich, *J. Am. Chem. Soc.*, **107**, 2033 (1985).

DEOXYGENATION OF EPOXIDES

T1819 Triphenylphosphine Selenide 5g JPYen 5,650



Other Examples:

Epoxides	→	Alkenes	
trans-2,3-Epoxyoctane	→	*trans*-2-Octene	Y. 68%
cis-Stilbene Oxide	→	*cis*-Stilbene	Y. *ca.* 71%

D.L. J. Clive and co-workers have reported the reaction of the present reagent 1 and an epoxide in the presence of trifluoroacetic acid to generate alkene. This reaction is completed in a short time under mild conditions and can be said to be a useful method to sterically retain the C-C bond of an epoxide.

References

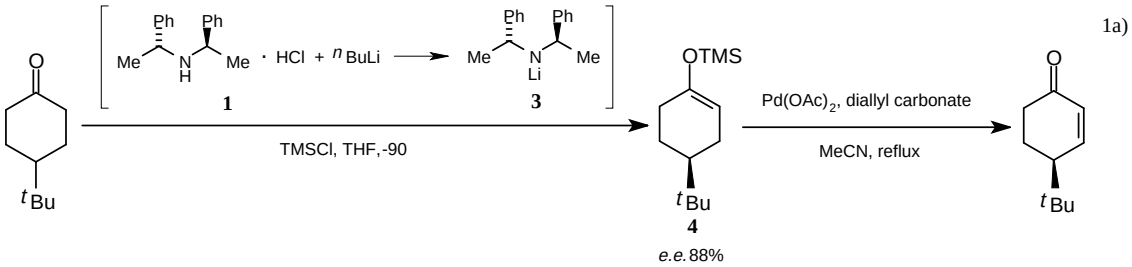
Conversion of epoxides into alkenes

D. L. J. Clive, C. V. Denyer, *J. Chem. Soc., Chem. Commun.*, **1973**, 253.
F. Mathey, G. Muller, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **281**, 881 (1975).

ASYMMETRIC DEPROTONATION

B2034 (*R*,*R*)-(+)-Bis(α-methylbenzyl)amine Hydrochloride 1 5g JPYen13,700

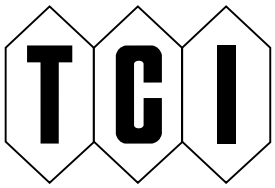
B2035 (*S*,*S*)-(-)-Bis(α-methylbenzyl)amine Hydrochloride 2 5g JPYen12,400



The present reagents 1 and 2 react with *n*-butyllithium and form chiral lithium amides 3 which are used as a chiral base for the generation of optically active enol derivatives from prochiral ketones. Optically active enols or the corresponding silyl enol ethers 4 constitute useful synthetic intermediates for synthesizing optically active compounds which have been subjected to enantioselecitve alkylation, acylation, carboxylation, etc. [1].

References

1) Asymmetric deprotonation of prochiral ketones
a) C. M. Cain, R. P. C. Cousins, G. Coumbarides, N. S. Simpkins, *Tetrahedron*, **46**, 523 (1990).
b) H. Hogeveen, W. M. P. B. Menge, *Tetrahedron Lett.*, **27**, 2767 (1986).
2) Enantioselective conjugate addition to enones with chiral lithium organo(amido)cuprates
a) B. E. Rossiter, M. Eguchi, *Tetrahedron Lett.*, **31**, 965 (1990).
b) B. E. Rossiter, M. Eguchi, G. Miao, N. M. Swingle, A. E. Hernández, D. Vickers, E. Fluckiger, R. G. Patterson, K. V. Reddy, *Tetrahedron*, **49**, 965 (1993).



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