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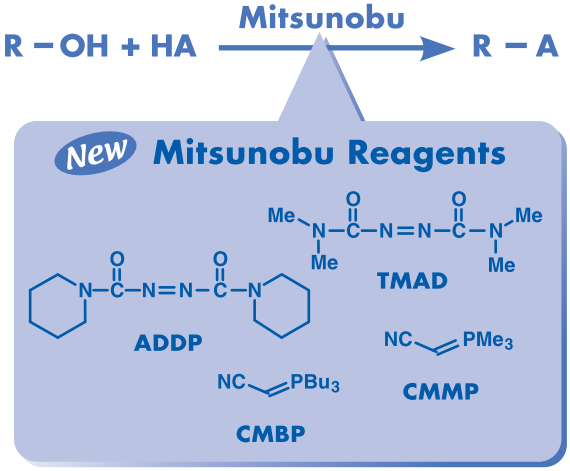

Contribution

New Mitsunobu Reagents

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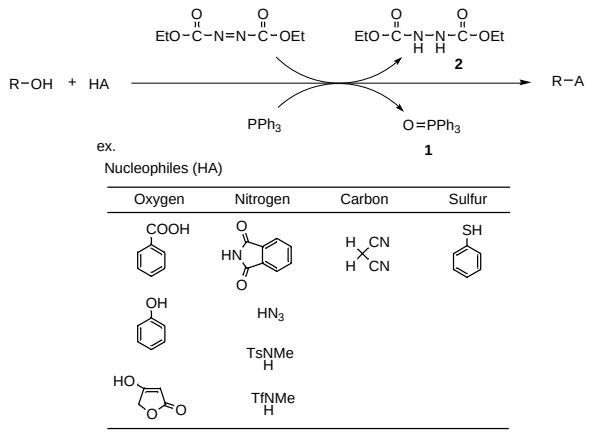
Tokushima Bunri University, Pharmaceutical Sciences

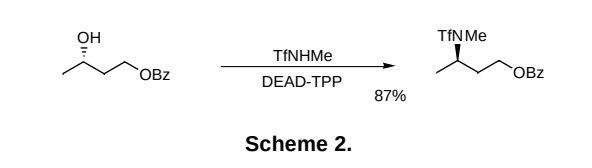
1. Introduction

The Mitsunobu reaction is a well-established fundamental reaction and has been applied widely in organic synthesis. In the Mitsunobu reaction, a unique dehydration occurs between alcohols and various Brønsted-Lowry acids (HA) utilizing a combination of diethyl azodicarboxylate (DEAD) - triphenylphosphine (TPP) (Scheme 1).[1,2]



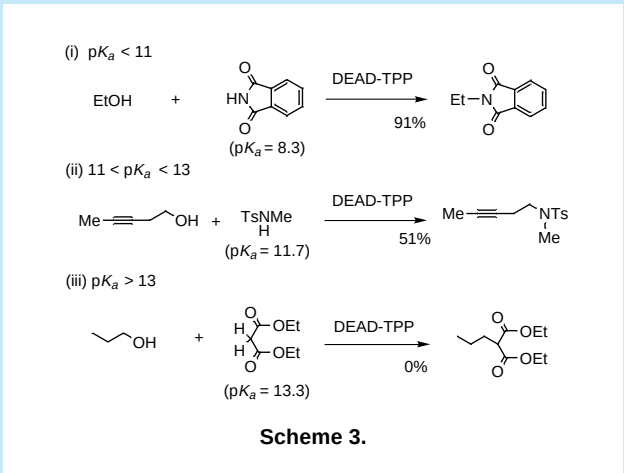
Scheme 1.

Without any prerequisite activation of the alcohol, this redox condensation reaction proceeds under mild conditions with complete Walden inversion of stereochemistry (for example: Scheme 2),[3] while DEAD is reduced to dihydro-DEAD (**2**) and TPP is oxidized totriphenylphosphine oxide (**1**) (Scheme 1).



Scheme 2.

Organic chemists have enjoyed these advantages of the Mitsunobu reaction in organic synthesis. However, the reaction has a serious limitation (the so-called "the restriction of pK_a"); the acidic hydrogen in HA has to have a pK_a of less than 11 for the reaction to proceed satisfactorily. If HA has a pK_a higher than 11, the yield of RA is considerably lower, and with HA having a pK_a higher than 13, the desired reaction does not occur (for example: Scheme 3).[1, 2, 4] In order to overcome "the restriction of pK_a", we have developed new Mitsunobu reagents and applied them to organic synthesis.[5] In this article, we would like to describe the results.

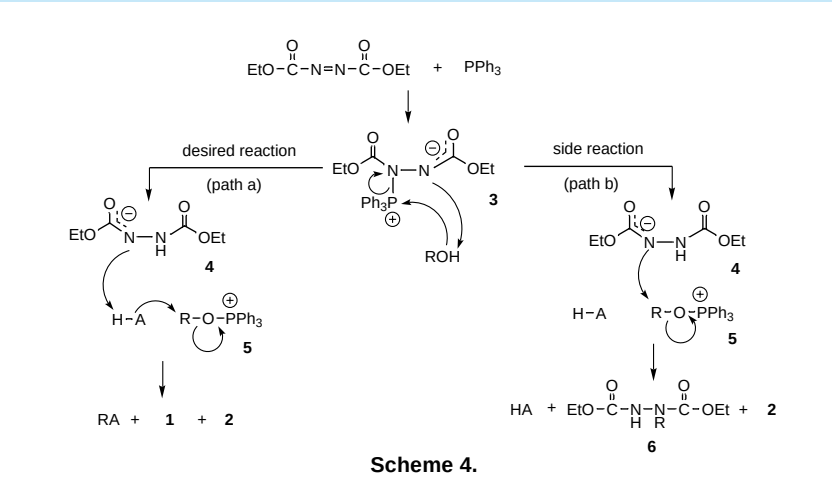


Scheme 3.

2. Development of New Mitsunobu Reagents

2.1. New Azo-type Reagents

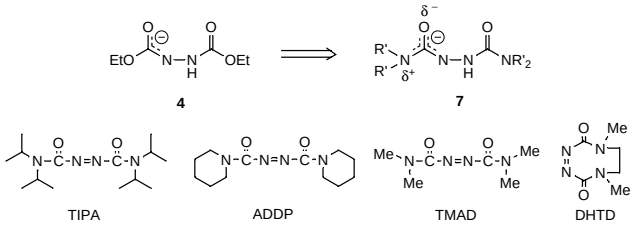
To develop improved redox system, we considered the mechanism of the Mitsunobu reaction and its side reaction. The desired Mitsunobu reaction proceeds probably through the generally accepted path a shown in Scheme 4.[2]



Scheme 4.

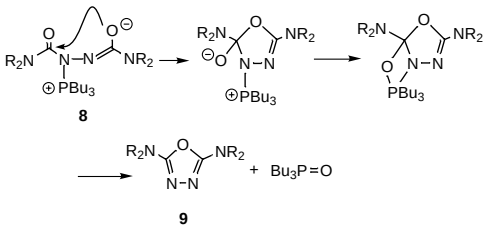
On the contrary, in the case of the reaction of less acidic HA, the hydrazo anion **4** attacks the alkoxyphosphonium **5** directly to afford alkylated the hydrazine derivative **6** as a by-product (Scheme 4, path b),[3] since the anion **4** is not efficient in deprotonating the weakly acidic HA. In order to overcome these drawbacks, "the restriction of pK_a", and expand the versatility of the original Mitsunobu reaction, new reagents which can be protonated by the less acidic HA have been developed to replace the DEAD-TPP system.

One way to improve the redox system would be to enhance the basicity of the anion **4** by replacement of the alkoxy group OEt in DEAD with a strong electron-donating group such as NR_2 in a new anion **7** (Scheme 5).[6,7] Furthermore, it was also considered that the bulkiness of the alkyl substituents on the NR_2 group influenced the reactivity of new azo-type reagents. Thus, *N,N,N′,N′*-tetraisopropylazodicarboxamide (TIPA),[8] 1,1′-(azodicarbonyl)dipiperidine (ADDP),[7] *N,N,N′,N′*-tetramethylazodicarboxamide (TMAD) [8,9] have been developed as the new reagents.



Scheme 5.

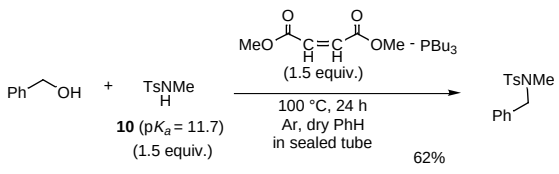
Those new azo compounds were combined with a more nucleophilic phosphine than TPP, such as tributylphosphine (TBP), because of the lower reactivity of the azodicarboxamides as Michael acceptors, compared with DEAD. In the course of our study, we found that most of the new azo compounds and TBP used was consumed even in cases where no desired product was obtained. In such cases, a large amount of the oxadiazole **9** was obtained probably through a new competitive side reaction pathway, in which the betaine **8** produced in the first step of the reaction cyclized intramolecularly as shown in Scheme 6.[8] Thus, cyclic 1,6-dimethyl-1,5,7-hexahydro-1,4,6,7-tetrazocin-2,5-dione (DHTD)[10] was also designed to prevent the cyclization of acyclic azodicarboxamides to **9**.



Scheme 6.

2.2. New Phosphorane-type Reagents

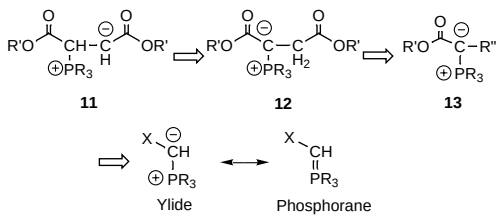
When the azo-type reagents were developed, it was found that maleic and fumaric acid derivatives, which were identified as carbon analogs of DEAD and/or TMAD, mediated the condensation of benzyl alcohol with tosyl amide **10** (*ex.* Scheme 7).[6]



Scheme 7.

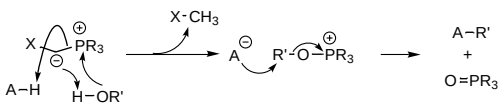
Unfortunately, difficulty in reproducibility of the reaction and in product isolation forced us to abandon this investigation. However, consideration of this reaction mechanism revealed that the betaine **11** was formed instead of the Mitsunobu intermediate **3** (Scheme 8). **11** might easily convert to **12**, whose structure can be generalized as **13**. This is a phosphorus ylide, namely,

phosphorane. After this discovery, it was suspected that the Mitsunobu reagent, the combination of an azo compound and a phosphine, could be replaced with an ylide.



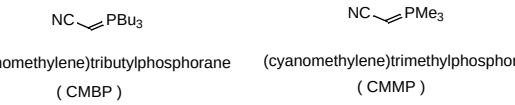
Scheme 8.

If ylides could mediate the Mitsunobu-type reactions, the reaction would proceed through the following reaction pathway illustrated in Scheme 9, which does not take into consideration the problem of acid-base equilibrium. 1) The alcohol is deprotonated by the ylide, then 2) the resulting alcoholate attacks the phosphonium part in the ylide to afford the alkoxy phosphonium. 3) The X-substituted methyl anion is protonated by the acidic HA, and then 4) the resulting conjugate base A^- reacts with the alkoxy phosphonium to give the desired A-R' along with the phosphine oxide.[5,6,11)]



Scheme 9.

On the basis of the above working hypothesis, we examined the reaction of several phosphoranes[6)] and found that (cyanomethylene)tributylphosphorane (CMBP)[6,11)] and less bulky (cyanomethylene)trimethylphosphorane (CMMP)[6,12,13)] had sufficient reactivity (Schemes 10). Especially, CMMP gave excellent results. In this article, we describe the C-N, C-C, and C-O bond forming reactions as examples to reveal the features of the new reagents.



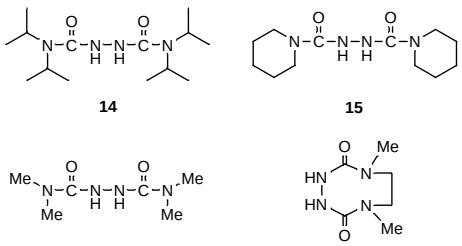
Scheme 10.

3. General Features of New Mitsunobu Reagents

3.1. New Azo-type Reagents

All of the new azo-type reagents, which could be purified by recrystallization, were easier to handle than DEAD which should be distilled for purification. They could be kept for several years under a dry atmosphere; however, they decomposed slowly in protic solvents such as methanol and water with the generation of amines. The reaction was carried out usually under an anhydrous argon atmosphere at 0 °C to room temperature. When the results were not satisfactory, the reaction shown in Scheme 6 may take place as a competitive reaction. In such cases, heating and/or usage of a large amount of the reagents was often ineffective.

The desired products were purified by column chromatography. In the traditional Mitsunobu reaction using DEAD and TPP, one major problem was the laborious purification of the product from dihydro-DEAD and triphenylphosphine oxide because of their moderate polarity and half-crystalline nature. On the other hand, in the reaction of the new azo-type reagents, removal of the hydrazo-compounds **14**-**17** (in place of dihydro-DEAD) and tributylphosphine oxide could be easily accomplished by SiO_2 column chromatography because of their high polarity. Furthermore, since the crystalline **14**-**17** were hardly soluble in many organic solvents, filtration of the reaction mixture after the addition of a solvent (such as hexane, ether, and so on) was quite effective to remove them. As an alternative work-up for the reaction of TMAD and DHTD, aqueous treatment of the reaction mixture was also quite effective because of the good aqueous solubility of **16** and **17**. The hydrazo-compounds **14**-**17** could be recycled by reoxidation.



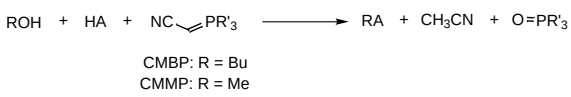
Scheme 11.

3.2. Phosphorane Reagents

Since CMBP and CMMP are very sensitive to air and moisture, all procedures for their purification should be carried out under a dry argon atmosphere, even for analysis by NMR, IR, and Mass spectra. CMBP was purified by distillation under reduced pressure. CMMP was recrystallized from benzene (toluene is unsuitable). When CMBP is sealed in an ampule and CMMP is stored in a screw-top vial with a rubber septum, the reagents could be kept for months at 10 °C under an argon atmosphere without decomposition. CMBP can be handled with a syringe technique. Reweighing of CMMP should be avoided even in an argon glovebag, because of its sensitivity to air and moisture. Thus, CMMP (1-10 mmol) stored in a vial should be used in one portion for the Mitsunobu-type reaction. CMMP could also be stored as a solution in dry THF (about 1 M, 4 mL) in a brown sealed ampule for months at 10 °C under an argon atmosphere without decomposition.[13)] Since CMMP precipitated from the THF solution at low temperature, the ampule was warmed slightly to completely dissolve the precipitate prior to use for the reaction. Of course, CMBP and CMMP behaved as a Wittig reagent to react with carbonyl compounds even with esters.[14)]

The reaction was carried out under an anhydrous argon atmosphere. The phosphorane reagents could also mediate the condensation of *sec*-alcohols more effectively under high-temperature reaction conditions using an Ace pressure tube (max. 200 psi) as a sealed reactor (Comparable results were also obtained using general glassware in refluxing toluene or xylene).

As mentioned above, one problem in the traditional Mitsunobu reaction was the laborious purification of the product from dihydro-DEAD and triphenylphosphine oxide, whereas the use of the phosphoranes led to an easy workup. In this reaction, acetonitrile and tributyl- or trimethylphosphine oxide were produced (Scheme 12). The former produced in place of dihydro-DEAD could be easily evaporated, and the removal of the latter could be attained by SiO_2 column chromatography because of its high polarity. As an alternative workup for the reaction with CMMP, aqueous treatment of the reaction mixture was also quite effective because of the good aqueous solubility of trimethylphosphine oxide.

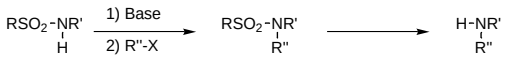


Scheme 12.

4. Reaction of Various Nucleophiles

4.1. Reaction of Nitrogen Nucleophiles (C-N bond formation)

Sulfonamides which were alkylated under the basic conditions in general were utilized as substrates to synthesize amines (Scheme 13).

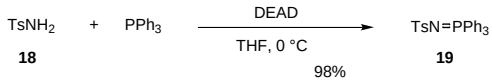


Scheme 13.

They were expected also to react with alcohols under the Mitsunobu conditions, since the common sulfonamides have a pK_a around 11. Unfortunately, however, yields were practically not so high because of "the restriction of pK_a".

On the contrary, the new reagents mediated satisfactorily the reaction of sulfonamides such as tosylamide **10** (pK_a = 11.7),[15] which gave only moderate yields when the DEAD-TPP system was used (Table 1). Primary alcohols were sufficiently activated by TIPA, ADDP and TMAD. DHTD, CMBP and CMMP could also mediate the reaction of secondary alcohols. Furthermore, it was shown that CMMP had sufficient reactivity compared with CMBP even at room temperature owing to the decreased steric hindrance.[5-12]

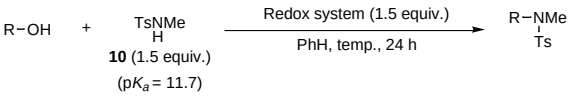
The reaction of *p*-toluenesulfonamide (**18**) was noted. Although **18** (pK_a = 10.2)[16] was expected to react with alcohols under the Mitsunobu conditions because of its pK_a value, **18** was actually converted to tosylimide **19** without any alkylated products (Scheme 14).[15,17,18]



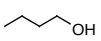
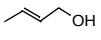
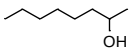
Scheme 14.

If the new reagents can mediate the condensation of **18** and alcohols, the reaction can provide an excellent route to primary and secondary amines when coupled with the known methods of desulfurization.[15,19] Although all of the azo reagents and CMMP failed in the alkylation of **18**, CMBP accomplished it, satisfactorily. The results are listed in Table 2.[18] Primary alcohols reacted at room temperature in excellent yields. Benzylic and allylic alcohols were too reactive under the same conditions and gave double alkylation products to some extent. The reaction of a secondary alcohol, 2-octanol proceeded at higher temperature (80 °C) with complete Walden inversion.

Table 1. Reaction of *N*-Methyl-*p*-tosylamide (**10**).

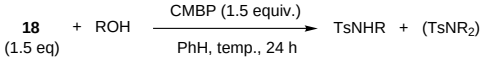


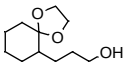
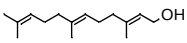
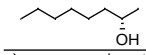
% yield

R-OH	Redox system temp. DEAD-TPP*) r.t.	TIPA-TBP r.t.	ADDP-TBP r.t.	TMAD-TBP r.t.	DHTD-TBP r.t.	CMBP r.t.	CMBP 100 °C	CMMP r.t.	CMMP 80 °C
	65	70	90	100	100	99	100	—	—
	66	98	86	99	97	81	100	—	—
	51	100	99	96	97	83	100	—	—
	53	6	34	40	85	60	89	98	95

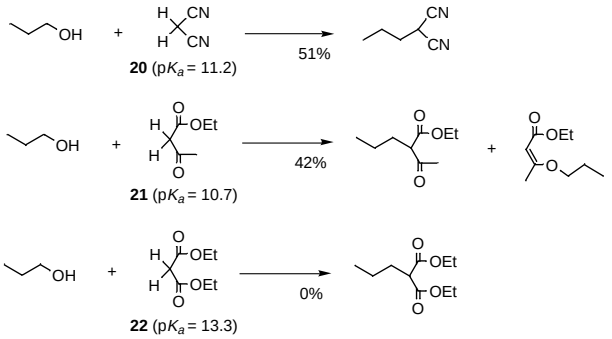
*) The reaction was carried out in THF.

Table 2. Reaction of *p*-tosylamide (**18**).



ROH	r.t. yield (%)	80 °C yield (%)
	93	—a)
	88	—
	70 (22)	—
	85 (12)	—
	45	89

a) – : no experimental result.



Scheme 15.

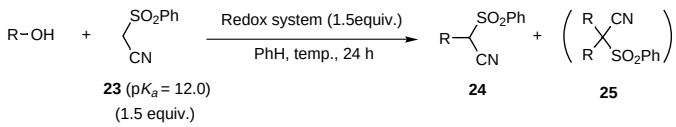
4.2. Reaction of Carbon Nucleophiles (C-C bond formation)

The carbon-carbon bond formation utilizing the Mitsunobu reaction has been attempted by Mitsunobu himself. He reported that malononitrile (**20**, pK_a = 11.2) was alkylated in 51% yield.[4] In the case of **21** (pK_a = 10.7), the *O*-alkylated product was obtained as the major product.[4] Further, **22** (pK_a = 13.3) could not yield any desired product (Scheme 15).[4] Although many researchers were looking for the Mitsunobu-type C-C bond forming reaction, they could not find and/or devise synthetically useful carbon nucleophiles, active methylene compounds in general, which could overcome "the restriction of pK_a".

This background prompted us to investigate the Mitsunobu C-C bond forming reaction employing the new reagents. And so, we found that the reagents dramatically improved the reaction of phenylsulfonylacetonitrile (**23**, pK_a = 12.0). The results are shown in Table 3. [5,10,12] Yields in parentheses are for the dialkylated products. In the reaction with primary alcohols, DHTD gave the best results among the azo-type reagents. Though the reaction of CMBP at ambient temperature afforded poor yields, the treatment at higher temperature gave the desired products in satisfactory yields, except in the case of benzyl alcohol which yielded the double alkylated product **25**. The reaction of 2-octanol was not affected satisfactorily by any of azo-type reagents including DHTD. On the contrary, CMBP mediated the reaction at 120 °C to give the desired product in 79% yield. When CMMP was used, the alkylation was accomplished in 94% yield. Thus, CMMP was the most suitable mediator for the carbon-carbon bond-forming reaction.

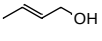
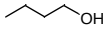
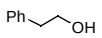
The finding that the double alkylation of **23** took place to some extent prompted us to study further the alkylation of some active methine compounds. In fact, CMMP promoted the reaction of 3-methyl-2-phenylsulfonylnonanenitrile (**26**) with butanol in excellent yield. This result suggested that a cyclic compound was formed, when the reaction was applied to diol (**27**) with **23**. Furthermore, the stereochemical outcome of this reaction, the formation of a *cis*-decaline derivative, verified the complete Walden inversion in the C-C bond formation using secondary alcohols with CMMP (Scheme 16).[12]

Table 3. Reaction of Phenylsulfonylacetonitrile (**23**).

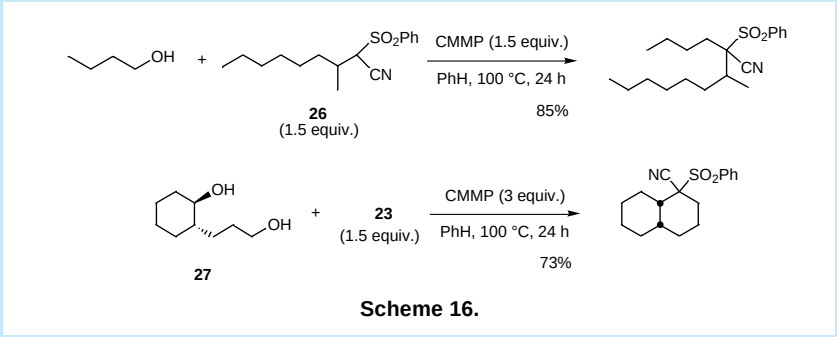


23 (pK_a = 12.0) (1.5 equiv.) **24** **25**

% yield

ROH	Redox system: DEAD-TPP r.t.	TMAD-TBP r.t.	DHTD-TBP r.t.	CMBP r.t.	CMBP 100 °C	CMBP 120 °C	CMMP 100 °C
	57 (22)	59 (3)	46 (51)	75 (21)	72 (28)	—	—
	—1)	64 (16)	52 (22)	76	89	—	—
	—	63	97	66	96	—	—
	—	85	94	83	95	—	—
	29	23	67	4	66	79	94

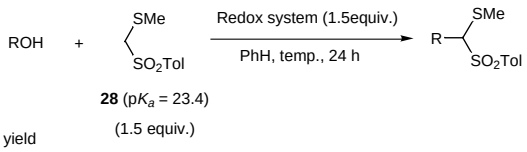
1) – : no experimental result.



Scheme 16.

It became clear that the phosphorane-type reagents mediated the alkylation of carbon nucleophiles with a pK_a higher than 20. For example, the reaction of MT sulfone (**28**, pK_a = 23.4) is summarized in Table 4. While none of the azodicarboxamides was effective for the reaction of **28** as anticipated because of its high pK_a, the phosphoranes were found to be quite effective for the *C*-alkylation of **28**. Even in the reaction of secondary alcohol, e.g. 2-octanol, CMBP afforded the desired product at 150 °C in 85% yield and CMMP increased satisfactorily the yield to 88% at lower temperature (100 °C). In the reaction of benzyl alcohol, the formation of dibenzyl ether decreased the yield of the desired product.[5,10]

Table 4. Reaction of MT Sulfone (**28**).



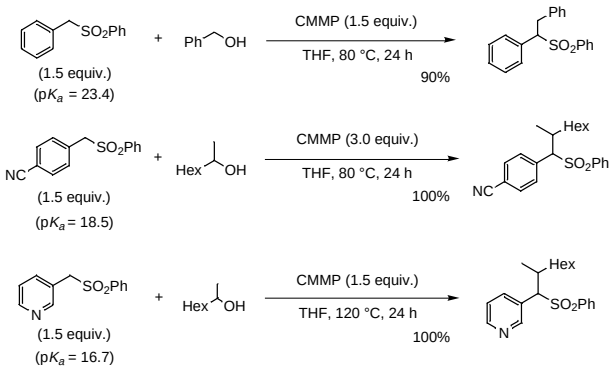
28 (pK_a = 23.4)
(1.5 equiv.)

% yield

ROH	Redox system						
	TMAD-TBP	DHTD-TBP	CMBP				CMMP
	r.t.	r.t.	r.t.	100 °C	120 °C	150 °C	100 °C
Ph–OH	0	2	6	40 [2]	41 [2]	—	—
OH	— [1]	<1	12	50	68	—	—
OH	—	0	2	85	94	—	—
Ph–OH	2	<1	2	56 [2]	73 [2]	—	—
OH, Hex	—	0	0	44	71	88	88

1) – : no experimental result. 2) Dimeric ether was obtained.

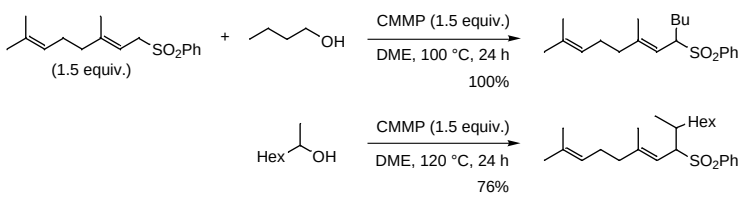
The phosphorane-type reagents could also be used for the alkylation of various carbon nucleophiles with a high pK_a. One of these was arylmethyl phenyl sulfones (pK_a = 16 ~ 23), whose methylene was activated by both an aromatic ring and a sulfonyl group. They reacted efficiently with alcohols (Scheme 17).[20]



Scheme 17.

Further, allylic phenyl sulfones (pK_a = ~ 23) with a tri-substituted olefin such as prenyl and geranyl phenyl sulfone were alkylated in satisfactory yield in the presence of CMMP. The results of the geranyl phenyl sulfone are illustrated in Scheme 18 as an example.[21]

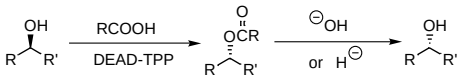
Carbon nucleophiles introduced in this chapter were generally converted to carbanions under basic conditions, and then were subjected to the reaction with alkylating agents such as alkyl halides. However, the alkylation with secondary halides suffered some drawbacks such as 1) disappointing yield because of competitive elimination reaction, and 2) the difficulty of the complete Walden inversion. On the contrary, as mentioned above, the new Mitsunobu C-C bond forming reaction was much more versatile than ever and could be applied in various stages of organic syntheses.



Scheme 18.

4.3. Reaction of Oxygen Nucleophiles (C-O bond formation)

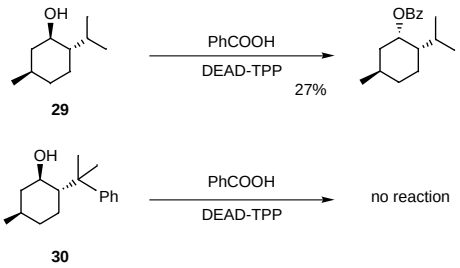
Herein we would also like to describe the reaction of carboxylic acids having a lower pK_a value. The Mitsunobu reaction of carboxylic acids with chiral secondary alcohols affords the corresponding esters with complete inversion of the configuration. Hence this reaction has been widely used for the preparation of the enantiomers and/or the epimers of the parent alcohols *via* removal of the acyl group from the resulting esters by hydrolysis or hydride reduction (Scheme 19).[2)]



Scheme 19.

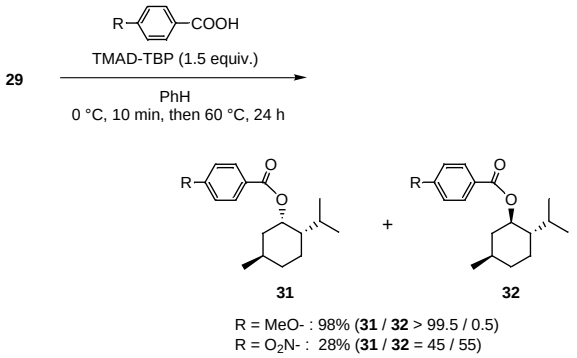
The reaction, however, is very sensitive to the steric situation around the carbinyl carbon; increasing steric hindrance leads to sharp decreases in the yield of the corresponding esters. For example, although cholestanol was acylated with benzoic acid to give the corresponding benzoate in 100% yield, the yield of the reaction of menthol (**29**) decreased to only 27% and phenylmenthol (**30**) with greater steric hindrance was not converted to the desired product (Scheme 20).[22)]

This difficulty has partly been overcome by changing the solvent (e.g. benzene)[23)] or applying carboxylic acids with stronger acidity.[22,24)] However, further improvement is still needed for the reaction of sterically congested secondary alcohols.



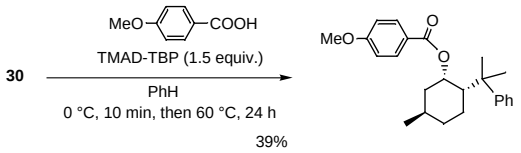
Scheme 20.

Detailed studies suggested that the combination of the TMAD-TBP system and *p*-methoxybenzoic acid was the reaction of choice for the Mitsunobu inversion of sterically congested alcohols. For example, **29** reacted with *p*-methoxybenzoic acid to give the corresponding ester in high yield. On the contrary, use of *p*-nitrobenzoic acid with a lower pK_a value decreased both yields and inversion ratios (Scheme 21). As mentioned above, the results were contrasted with the reaction using DEAD-TPP, which achieved the complete Walden inversion even when yields were low.



Scheme 21.

Unfortunately, the acylation of **30** proceeded in only moderate yield (39%) even when using the combination TMAD-TBP system and *p*-methoxybenzoic acid (Scheme 22). However, it should be noted that considerable progress was made in the Mitsunobu acylation utilizing the new reagent system, when considering the DEAD-TPP system which could not completely mediate the desired reaction of **30**.[6,25)]

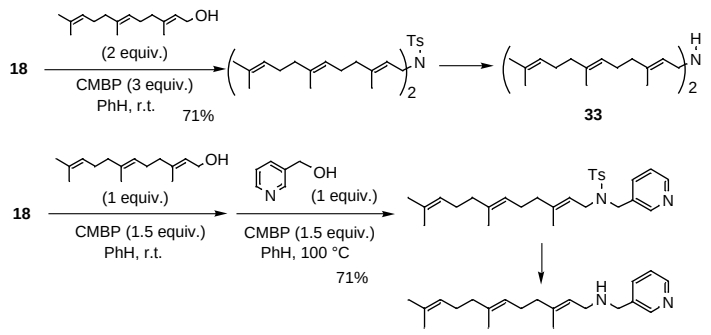


Scheme 22.

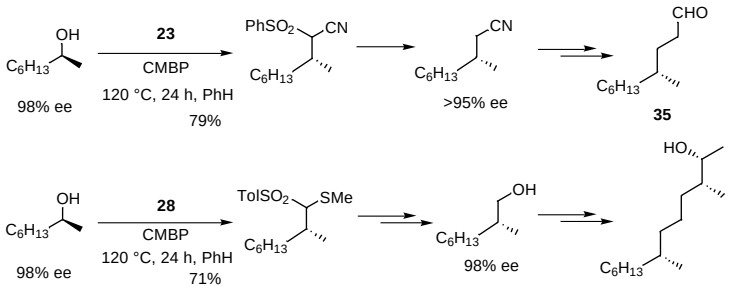
5. Application to Organic Syntheses

The usefulness of the new reagents was demonstrated by effective synthesis of some of interesting compounds. The amines **33**, **34** which were proposed as squalene synthetase inhibitors by Prashad and his co-workers[26)] were synthesized easily by the reaction of **18** with the corresponding alcohols in the presence of CMBP, followed by desulfurization of the tosyl group. For the synthesis of unsymmetrical secondary amines, the second alcohol and CMBP were added to the reaction mixture of the first alkylation and the desired *N,N*-disubstituted tosylamide was obtained in one pot (Scheme 23).[18)]

The new C-C bond forming reaction was successfully employed in asymmetric formal synthesis of pheromone analogs **35**[27)] and **36**[28)]. By these syntheses, the Walden inversion was verified even in the reaction of carbon nucleophiles, and so the chirality of (*S*)-2-octanol, which is an optically active, cheap, and commercially available compound, was nicely reflected in the stereochemistry of the products.[5,6,10)]



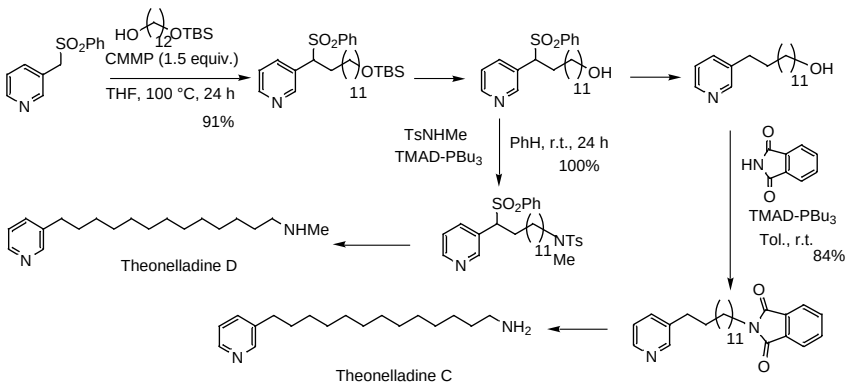
Scheme 23.



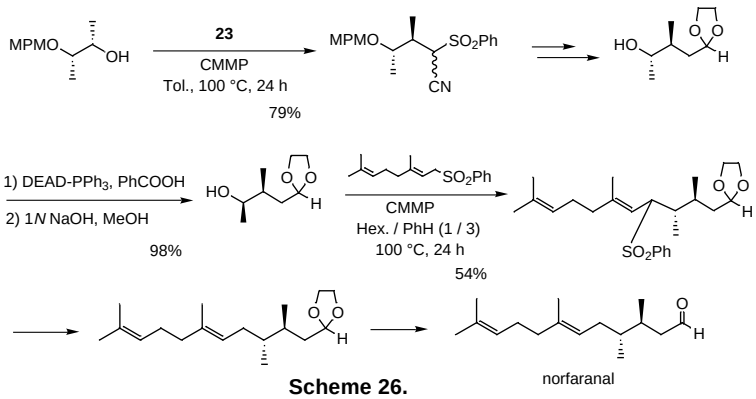
Scheme 24.

The synthesis of novel pyridine alkaloids, isolated as biologically active compounds from marine sponges (*Theonella swinhoei*),[29] was readily accomplished utilizing the Mitsunobu C-C and C-N bond forming reaction (Scheme 25).[5,20]

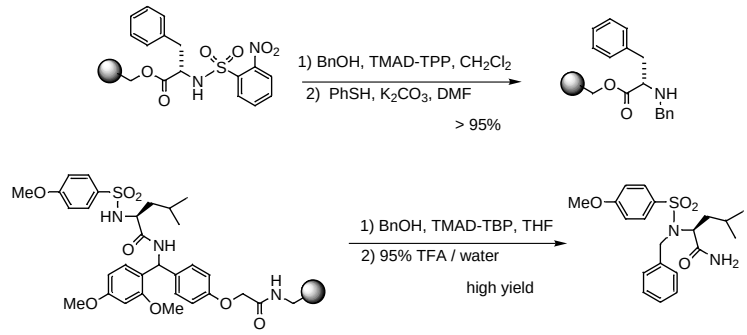
In previous syntheses of (+)-norfaranal, one major problem was how to construct the *anti*-dimethyl structure as an optically active form.[30] This difficulty could be overcome by both the standard and new Mitsunobu reactions, which were employed in three steps of the synthetic route. Commercially available (2*S*,3*S*)-2,3-butanediol was chosen as the starting material and the stereochemistry of the diol was successfully reflected in the 3*S*,4*R*-*anti*-dimethyl structure of the target molecule (Scheme 26).[21]



Scheme 25.



Scheme 26.



Scheme 27.

The new Mitsunobu reagents were also applied to solid-phase synthesis because of higher yields and/or an easier purification than the traditional Mitsunobu reagent. A few examples were shown in Scheme 27.[31,32)]

6. Conclusion

These have application not only in the traditional type of Mitsunobu reactions, but they also provide new methodology for the C-N, C-O, and C-C bond forming reactions, all of which proceeded poorly when the traditional reagents were used. We also described that each of the new reagents showed different reactivity in several cases. Thus, our efforts allow organic chemists to choose the appropriate one among the Mitsunobu reagents to suit their synthetic requirements in the fine organic synthesis, which calls for selectivity and specificity. We hope that this article will help the reader to choose a pertinent reagent.

The authors are deeply indebted to the staff, graduate students, and undergraduate students for their collaboration in Tokushima Bunri University. This work was supported partially by a Grant-Aid for Scientific Research (C) from the Ministry of Education, Science, Sports, and Culture of Japan. A Sankyo Chemical Award in Synthetic Organic Chemistry and A Subor Grant from the Suntory Institute for Bioorganic Research are also gratefully acknowledged.

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He was born in Mishima, Shizuoka, in 1954, and received his B.S. degree in 1977 from Tohoku University. He received his M.S. degree in 1980 from Nagoya University. After earning his Ph.D. in 1984 from Tohoku University, he continued research in Tohoku University as a Research Associate and then as Associate Professor (1988). For one year, he worked as a postdoctoral fellow (1985) at the University of Colorado. In 1988, he moved to the Faculty of Pharmaceutical Sciences at Tokushima Bunri University, and rose to the rank of Full Professor in 1996. He was a recipient of the Progress Award in Synthetic Organic Chemistry, Japan (1993) and the Sankyo Chemical Award in Synthetic Organic Chemistry (1994).

His research interest includes the development of new synthetic methods, asymmetric synthesis, natural product synthesis, and the design of host molecules for molecular recognition.

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He was born in Osaka in 1972, and received his B.S. (1995), M.S. (1997) and Ph.D degrees (2003) from Tokushima Bunri University. In 1997, he was appointed a Research Associate in the Faculty of Pharmaceutical Sciences, Tokushima Bunri University. He was a recipient of the incentive award in the 45th symposium on the chemistry of natural products (2003).

His research interests are in the area of molecular recognition chemistry and synthetic organic chemistry.

Shô Itô, Professor emeritus, *Tokushima Bunri University*

He was born in Tokyo in 1924, and received his B.S. (1950) and Ph.D degrees (1957) from Tohoku University. He became a Research Associate in 1957, Assistant Professor in 1962 and then was promoted to Full Professor at Tohoku University in 1965. He was the Dean of the Faculty of Science from 1979 to 1982. In 1988, he moved to Tokushima Bunri University, where he was the Dean of Pharmaceutical Sciences (1989-2000). He was appointed Professor Emeritus at Tohoku University in 1988 and at Tokushima Bunri University in 2001. He was a Councilor of the Chemical Society of Japan (1977-1979). He was active in IUPAC as the President of the Division of Organic Chemistry (1979-1982), an Elected Member of the Bureau (1985-1993), and a Member of the Executive Committee (1987-1993). He was the Regional Editor of Tetrahedron Letters (1984-1995). He was a recipient of the Chemical Society of Japan Award in 1985.

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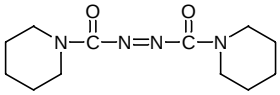
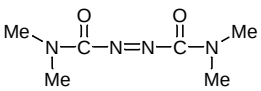
TCI's Related Compounds

New Mitsunobu Reagents

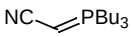


ADDP
1,1′-(Azodicarbonyl)dipiperidine
25g, 5g [A1051]



TMAD
N,N,N′,N′-Tetramethylazodicarboxamide
5g, 1g [A1458]

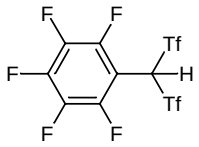
Tsunoda Reagent



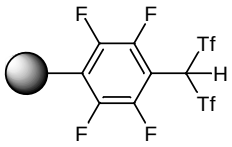
CMBP
(Cyanomethylene)tri-*n*-butylphosphorane
1g [C1500]

SUPER BRØNSTED ACID

B2291	1-[Bis(trifluoromethanesulfonyl)methyl]-2,3,4,5,6-pentafluorobenzene	(1)	1g	100mg
B2292	Bis(trifluoromethanesulfonyl)methyltetrafluorophenyl Polystyrene Resin	(2)		100mg

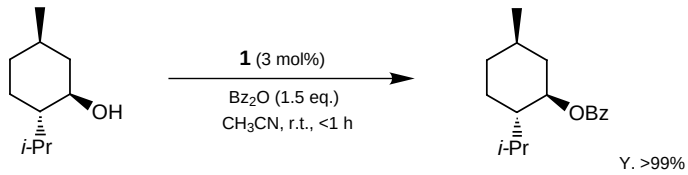


1

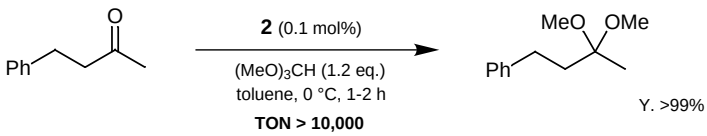


2

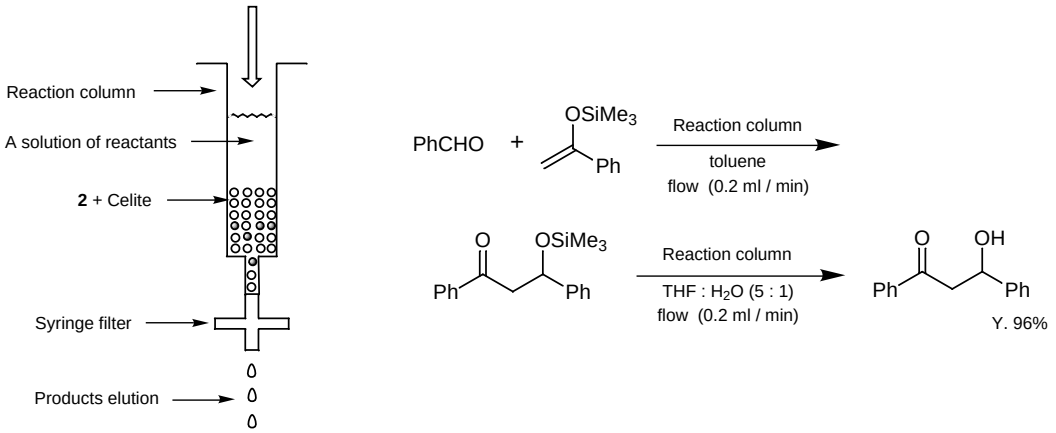
Products **1** and **2** are a super Brønsted acid and a polymer-supported super Brønsted acid, which are developed by Ishihara, Yamamoto and co-workers. These products have two trifluoromethanesulfonyl groups which are strong electron-withdrawing groups and one perfluorophenyl group on the methine carbon. The acidity of the proton on the methine carbon is remarkably high, and both products are utilized as excellent acid catalyst in various reactions.[1a)] For example, **1** has a pK_a = 1.5 (in CD_3CO_2D) and it has been reported to be useful for the acylation of (–)-menthol.



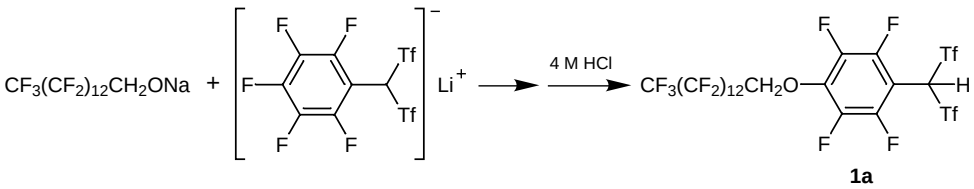
2 is effectively swollen by both polar and nonpolar organic solvents, and it possesses high catalytic activity. It is used as a solid acid catalyst which can be recovered and reused. For example, in the acetalization of benzylacetone, it is quantitatively recovered after the reaction by simple filtration and it can be reused more than 10 times without loss of activity. The turnover number (TON) is greater than 10,000.[1a)]

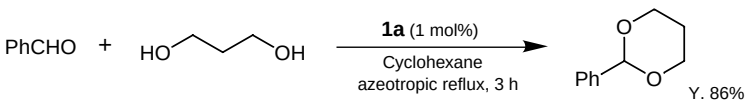


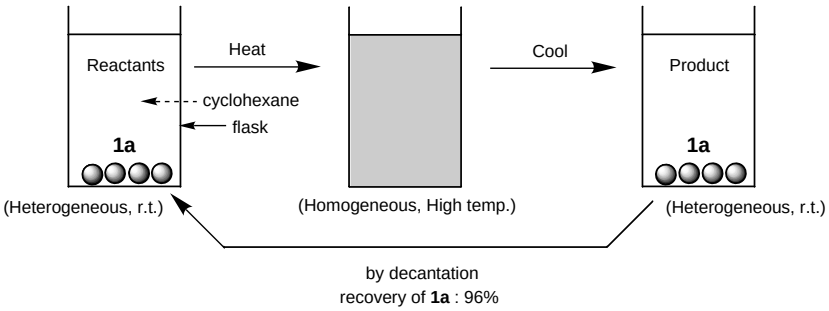
Another application for **2** that has been reported is its use in a packed reaction column.[1b)] The reaction column is a rather simple system that consists of a disposable syringe packed with a mixture of **2** and Celite. Since the catalyst activity of **2** is quite high, it is possible to perform various acid-promoted reactions in high yield and in a single pass requiring just a short reaction time. For example, the Mukaiyama aldol reaction can be successfully performed by passing a mixed solution of benzaldehyde and the silylenol ether of acetophenone into the reaction column just once. The resulting silyl ether of the aldol product is again put through the reaction column as an aqueous THF solution, and hydrolysis progresses smoothly to give the desired aldol product in 96% yield over the 2-steps of procedures. Furthermore, the conversions into acetals and esters also progress readily, thereby making it a very useful reagent for functional group conversions of samples prior to NMR, HPLC and GC analyses. This reaction column can also be coupled to a pump to establish a continuous-flow reaction system.



The lithio product of **1** is known to undergo nucleophilic substitution at the *para*-position. Thus it is possible to create further designs. For example, 1*H*,1*H*-perfluorotetradecyloxy group was introduced at the *para*-position to obtain a product with a high fluorous property, which can be used as a fluorous super Brønsted acid catalyst **1a**.[1c] During the acetalization of benzaldehyde, **1a** dissolves in cyclohexane when it is heated to reflux, and function as a catalyst. After the reaction, **1a** precipitates upon cooling to room temperature, allowing it to be recovered and reused. As described herein, when **1a** is utilized as homogeneous catalyst, its activity is higher than the solid catalyst **2**; furthermore it can also be recovered as a solid catalyst, and there are advantages that it can be recovered and reused the catalyst without fluorous solvens.



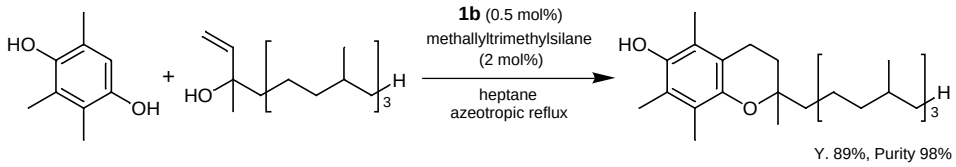




(cont.)

(cont.)

The trimethylsilyl pentafluorophenylbis(trifluoromethanesulfonyl)methide [$(C_6F_5CTf_2)SiMe_3$] **1b** prepared from **1** and allyltrimethylsilane is utilized as a super Lewis acid catalyst in the regioselective condensation of trimethylhydroquinone with isophythol.[1d] When the acidity of **1** is compared with TfOH and Tf_2NH, the order of Brønsted acidity is TfOH > Tf_2NH > **1**, however, when the Lewis acidity of the trimethylated forms of these compounds was compared, the order of Lewis acidity becomes **1b** > Tf_2NSiMe_3 > $TfOSiMe_3$. It is anticipated that the conjugate base of **1** ($C_6F_5C^-Tf_2$) will find utility as a bulky counter anions.



Y. 89%, Purity 98%

References

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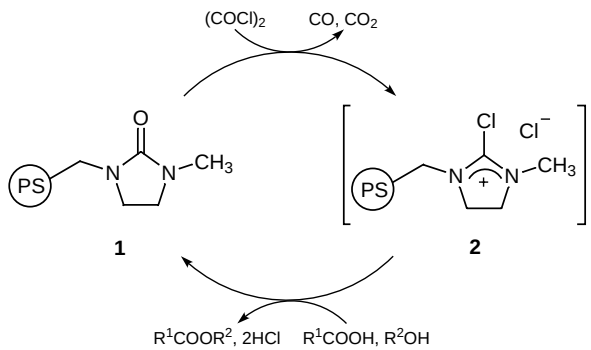
d) A. Hasegawa, K. Ishihara, H. Yamamoto, *Angew. Chem. Int. Ed.*, **42**, 5731 (2003).
e) K. Ishihara, H. Yamamoto, TCI MAIL, **115**, 2 (2002).

POLYMER-SUPPORTED DEHYDRATING AGENT

M1452 3-Methyl-2-oxoimidazolidin-1-ylmethyl Polystyrene Resin, cross-linked with 1% DVB (1) 1g



Entry	R^1	R^2	Yield (%)
1	^{t}Bu	$Ph(CH_2)_3$	82
2	$Ph(CH_2)_2$	^{t}Bu	80
3	$Ph(CH_2)_2$	^{t}Bu	81[a]
4	$Ph(CH_2)_2$	^{t}Bu	81[b]

condition: **2** (1.5 eq.), NEt_3 (3 eq.), CH_2Cl_2, r.t., 48 h
[a] Used a recycled polymer from entry 2
[b] Used a recycled polymer from entry 3

Polymer-supported 1,3-dimethyl-2-imidazolidinone (**1**), is converted to the dehydrating agent **2** upon chlorination with oxalyl chloride. The chloro compound **2** is a very active esterification agent, and hindered compounds such as pivalic acid or *tert*-butyl alcohol are converted to esters in good yield. After the reaction, **1** is easily recovered through filtration and reused repeatedly. This method, developed by Ishikawa and co-worker, is expected to be an environmentally friendly dehydration condensation method.

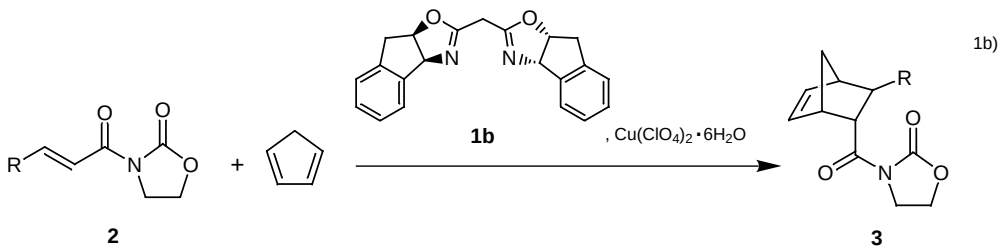
References

Polymer-supported DMI as a potential heterogeneous dehydrating agent
W. Disadee, T. Watanabe, T. Ishikawa, *Synlett*, **2003**, 115.

CHIRAL METHYLENEBIS(OXAZOLINE) LIGANDS

M1401 (+)-2,2′-Methylenebis[(3a*R*,8a*S*)-3a,8a-dihydro-8*H*-indeno-[1,2-*d*]oxazole] (1a) 500mg

M1402 (–)-2,2′-Methylenebis[(3a*S*,8a*R*)-3a,8a-dihydro-8*H*-indeno-[1,2-*d*]oxazole] (1b) 500mg



1b)

	Temp.	Y (%)	*endo*/*exo*	*endo* (% ee)
R=H	-78	88	>99 : 1	98 (2*S*)
R=CH_3	-30	85	95 : 5	99 (2*S*)
R=CO_2Et	-78	95	92 : 8	92 (2*R*)

The chiral bidentate ligands **1** forms stable chiral metal complexes with Lewis acids such as $Cu(ClO_4)_2 \cdot 6H_2O$, $Cu(OTf)_2$, and $Ni(ClO_4)_2$. These chiral metal complexes are Lewis acid catalysts that have excellent stereocontrol and are used in a number of assymmetric reactions. For example, the dienophiles **2** undergo a Diels-Alder reaction with cyclopentadiene in the presence of chiral metal complex derived from **1b** and $Cu(ClO_4)_2 \cdot 6H_2O$ to give the adducts **3** with high enantioselectivity.[1b] Metal complexes of **1** are also effective chiral catalyst for asymmetric hetero-Diels-Alder reactions,[2a] radical reactions,[2b] sigmatropic rearrangements,[2c] and phospho-transfer reaction.[2d] The utility of ligand **1** is expected to increase as various substituents are introduced to methylene position of **1**.[3]

References

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a) I. W. Davies, L. Gerena, D. Cai, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *Tetrahedron Lett.*, **38**, 1145 (1997).
b) A. K. Ghosh, H. Cho, J. Cappiello, *Tetrahedron: Asymmetry*, **9**, 3687 (1998).
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a) T. Saito, K. Takekawa, T. Takahashi, *Chem. Commun.*, **1999**, 1001.
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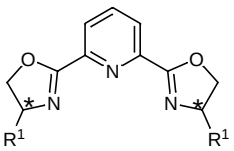
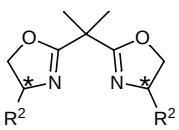
d) M. Jiang, S. Dalgarno, C. A. Kilner, M. A. Halcrow, T. P. Kee, *Polyhedron*, **20**, 2151 (2001).
3) Enantioselective conjugate addition
a) D. M. Barnes, *et al.*, *J. Am. Chem. Soc.*, **124**, 13097 (2002).

Related Compounds



R^1 = ^{i}Pr	(*R*,*R*)	B2217	1g, 250mg
	(*S*,*S*)	B2218	500mg
R^1 = Ph	(*R*,*R*)	B2219	1g, 250mg
	(*S*,*S*)	B2220	250mg

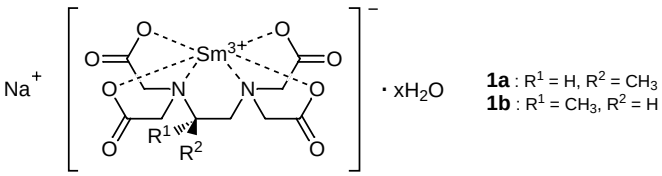


R^2 = ^{t}Bu	(*S*,*S*)	I0567	1g, 100mg
R^2 = Ph	(*R*,*R*)	D2823	1g, 250mg
	(*S*,*S*)	I0582	1g, 250mg

A WATER-SOLUBLE CHIRAL SHIFT REAGENT for USE in HIGH-FIELD NMR

S0473 Sodium [(*R*)-1,2-Diaminopropane-*N,N,N′,N′*-tetraacetato]samarate(III), Hydrate (1a) 100mg

S0474 Sodium [(*S*)-1,2-Diaminopropane-*N,N,N′,N′*-tetraacetato]samarate(III), Hydrate (1b) 100mg



There have been developed various methods of determining the enantiomeric purity and absolute configuration of chiral compounds using NMR, the most common and versatile analytical method in organic chemistry. As one of these, there is the method to resolve enantiomer signals by using paramagnetic chiral lanthanide shift reagents. For example, the europium propylenediaminetetraacetate complex (Eu-pdta) was reported to be useful for assigning the absolute configurations of α-amino acids and α-hydroxy acids in D_2O.[1)] However, it has been well known that lanthanide shift reagents generally have the drawback of causing line broadening, which is more serious when they are used in stronger magnetic field. Eu-pdta often caused heavy line broadening especially for the signals of α-amino acids even with 90 MHz ^1H NMR and it could not be used for these substrates in high-field NMR because of serious line broadening. In recent years, Kabuto and co-workers have demonstrated that the Samarium complex (Sm-pdta) **1** is not as likely to cause line broadening in high-field NMR as Eu-pdta does and can be also used in determining absolute configurations of the α-amino acids.[2)] Observation of the chemical shift nonequivalence for several protons enabled by the use of high-resolution NMR increases the reliability of the assignment as in modified Mosher method.

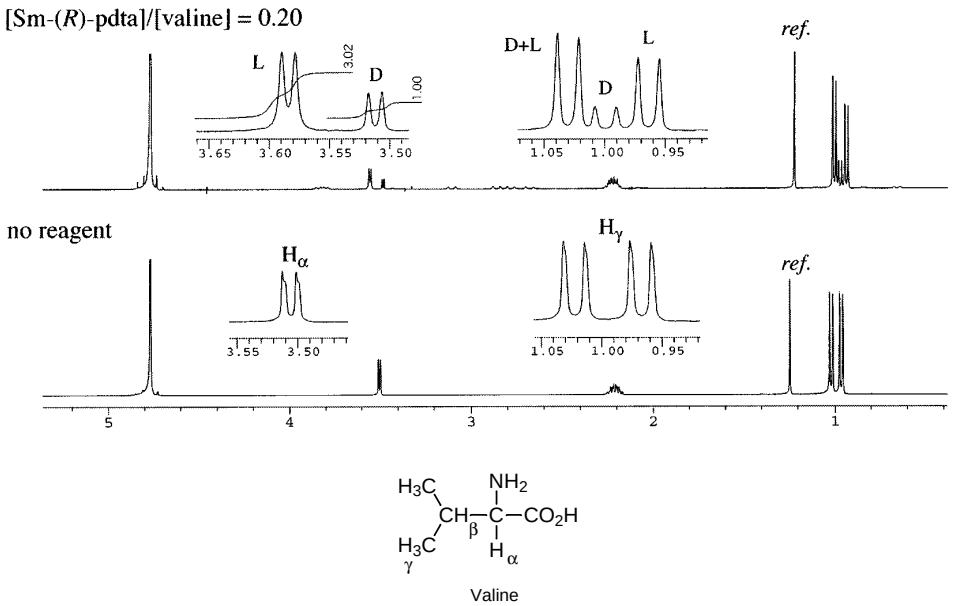


Figure 1. ^1H NMR spectra (400 MHz) of valine (0.06 M, [D]/[L] = 1/2.85) in D_2O at pH 9.4.

Resolution of the enantiomer signals of α-amino acids

NMR measurement is carried out on D_2O solutions of α-amino acids of pH 9-10, near the pK_a of the substrates, where the best resolution is possible. The pH of the sample solution is adjusted with D_2O solutions of NaOD (~2M and ~0.2 M for fine adjustment, added with a micropipet), and a D_2O solution of DCl, if necessary. Use of the buffer solutions containing anions such as phosphate and carbonate cannot be recommended because of their possible coordination to the lanthanide ion. When a sample solution contains both D-isomer and L-isomer, **1** is directly added in small amounts to the sample tube (when the concentration of the amino acid is 0.06 M, an amount of reagent is approximately 5-20 mol% of a substrate), and is dissolved by shaking the tube. Figure 1 shows an example of the NMR resolution of the enantiomer signals of valine utilizing the above procedure (^{1}H NMR: 400 MHz; [valine] = 0.06M; D/L ratio = 1/2.85; pH 9.4; [**1a**]/[valine] = 0.2). Since the complex **1** itself also possesses several broad signals in the range of 2-4 ppm, it is not the appropriate reagent to use for determining the enantiomeric purity. However, as in the above example, when the enantiomer signals can be resolved at the baseline without overlapping with the signals of the reagent, then the approximate D/L ratio can be obtained from the ratio of the integration (D/L = 1/3.02 in the above case).

Determination of absolute configuration:

(A) Enantiomeric mixture: When measurements of different types of α-amino acid (D/L = 1/2) are made under the above conditions, resolution of the enantiomer NMR signals yields the following results (See Table 1). The chemical shift differences between the enantiomer signals were determined for the enantiomeric mixtures of various α-amino acids under the conditions described above. Some results are shown in Table 1.

Table 1. Resolution of enantiomer signals of amino acids in the presence of **1a**.

Amino acids	[**1a**]/[amino acid]	pH	signal	ΔΔδ (ppm)	high field
alanine	0.10	10.5	H_α	0.018	D
valine	0.20	10.5	H_α	0.146	D
proline	0.10	11.2	H_α	0.022	D
alanine	0.10	10.5	H_β	–0.007	L
valine	0.20	10.2	H_β	–0.015	L
proline	0.05	11.2	H_δ (hi)	–0.01	L

Here ΔΔδ is δ(L)–δ(D), and δ(L) and δ(D) indicate the chemical shifts of ^{1}H signal due to L- and D-amino acids in the presence of **1a**, respectively. As shown in Figure 2, in the presence of **1a**, the H_α signals of the D-isomers appeared more upfield than those of L-isomers, while the signals of side chain protons of L-isomer resonated upfield compared with those of their counterparts. This relation was observed for almost all of the amino acids examined. Therefore, by observing the separation of H_α and side chain proton signals, it is possible to assign the absolute configuration of α-amino acids including those with unknown configuration.

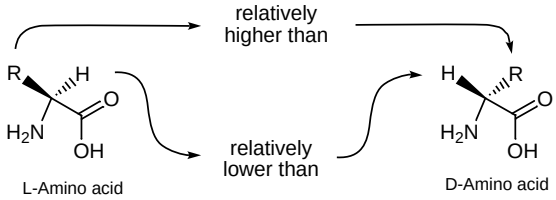


Figure 2. Relative position of proton signals of amino acid enantiomers in the presence of **1a**.

(cont.)

(cont.)

(B) Single enantiomer: Actual samples are often enantiopure. It is possible to determine the absolute configuration of a single enantiomer, by conducting the two separate measurements in the presence of **1a** and **1b** and comparing chemical shifts of the corresponding signals. This is because the chemical shifts of the signals of the enantiomer at hand in the presence of **1b** are the same as those of its enantiomer measured in the presence of **1a**. The chemical shifts of the ^{1}H signals of amino acid are sensitive to concentration, temperature and pH, thus strict control of these conditions is required as well as controlling the equivalence of each reagent. The optimal procedures is to first prepare two sample tubes containing equivalent amounts of a pH-adjusted sample solution. To one and the other tubes, add separately the same amount of D_2O solutions of **1a** and **1b** (pH adjusted to 8), whose concentrations are the same, using microsyringes to conduct the measurements.

This method has also been applied to α-hydroxy acids at pH ~5 and the relation for the side chain protons shown in Figure 2 was consistently observed.[3)]

References

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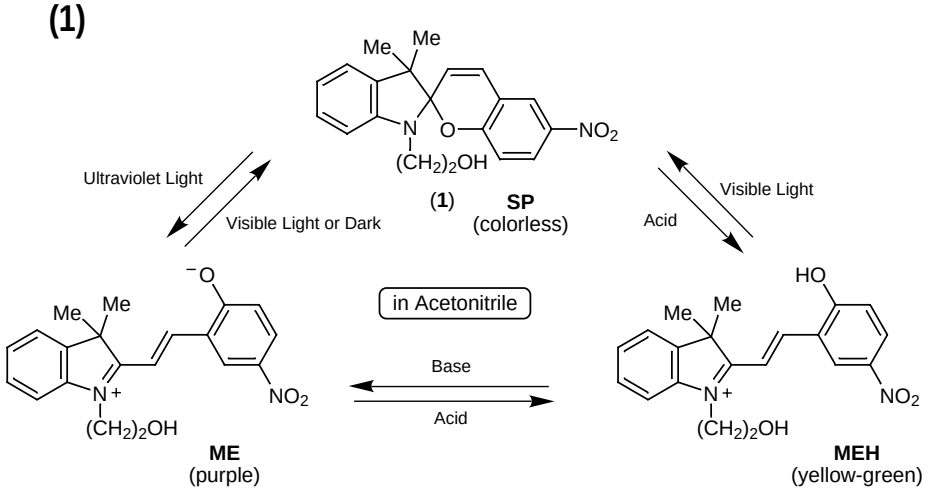
MOLECULAR SWITCH

H1042 1-(2-Hydroxyethyl)-3,3-dimethylindolino-6′-nitrobenzopyrylospiran (1) 1g



1 is a three state photochromic compound that responds to chemical and optical inputs to produce optical outputs. The colorless spiropyran state (SP) switches to the purple merocyanine form (ME) on irradiation with UV light. Alternatively, SP switches to the yellow-green protonated merocyanine (MEH) on acidification. The colored form ME and MEH return to the colorless state SP when they are irradiated with visible light. Similarly, ME returns to the SP state when stored in the dark. The addition of acid to ME produces MEH, and the treatment of MEH with base restores ME. The studies of the molecular switch which applied these properties have been actively carried out.

References

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F. M. Raymo, S. Giordani, *J. Am. Chem. Soc.*, **123**, 4651 (2001).
F. M. Raymo, S. Giordani, *Proc. Natl. Acad. Sci. U. S. A.*, **99**, 4941 (2002).
S. Giordani, F. M. Raymo, *Org. Lett.*, **5**, 3559 (2003).

Acceptable new standard of water-quality in Japan

VOC MIXTURE STANDARD SOLUTIONS

In May 2003, a new "Ministerial Ordinance for Standard of Water-quality" was issued, and executed in April 2004 to improve and maintain the quality, safety, and taste of drinking water in Japan . Due to this revision, the conventional "water quality standard criterion" and "monitoring criterion" were abolished. In their place a new "water quality standard criterion" and "water quality management target criterion" have been set, and new management system has been established. We have introduced several relevant VOC solution standards to aid in the analyses of these new criterion. In addition, we have 54 VOC mixture standard solution for water analysis.

S0677 11 VOC Mixture Standard Solution 502-11 (each 0.5 mg/ml in Methanol)

MHLW Water quality standard criterion – Mixture of 11 diluted solutions

Contents: carbon tetrachloride, 1,1-dichloroethylene, *cis*-1,2-dichloroethylene, dichloromethane, tetrachloroethylene, trichloroethylene, benzene, chloroform, dibromochloromethane, bromodichloromethane, bromoform.

S0678 6 VOC Mixture Standard Solution 502-6 (each 0.5 mg/ml in Methanol)

MHLW Water-quality management target criterion – Mixture of 6 diluted solutions

Contents: 1,2-dichloroethane, *trans*-1,2-dichloroethylene, 1,1,2-trichloroethane, toluene, 1,1,1-trichloroethane, *tert*-Butyl Methyl Ether.

S0679 2 VOC Mixture Standard Solution 502-2 (each 0.5 mg/ml in Methanol)

MHLW Water-quality management target criterion – Mixture of 2 diluted solutions

Contents: *cis*-1,3-dichloropropene, *trans*-1,3-dichloropropene.

S0676 *tert*-Butyl Methyl Ether (1 mg/ml in Methanol)

S0605 54 VOC mixture standard solution (each 1 mg/ml in Methanol)

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