TCIMAIL
number 123

Contribution

New Mitsunobu Reagents

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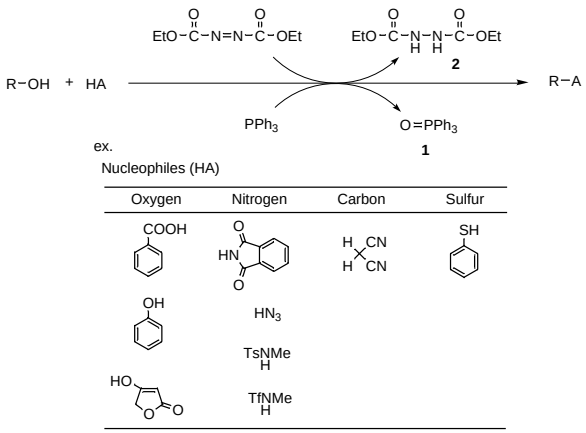
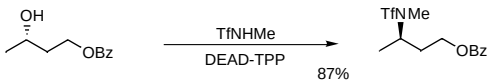
1. Introduction

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)]



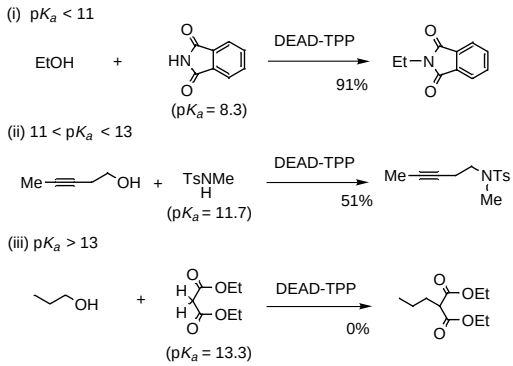
Scheme 1.

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.

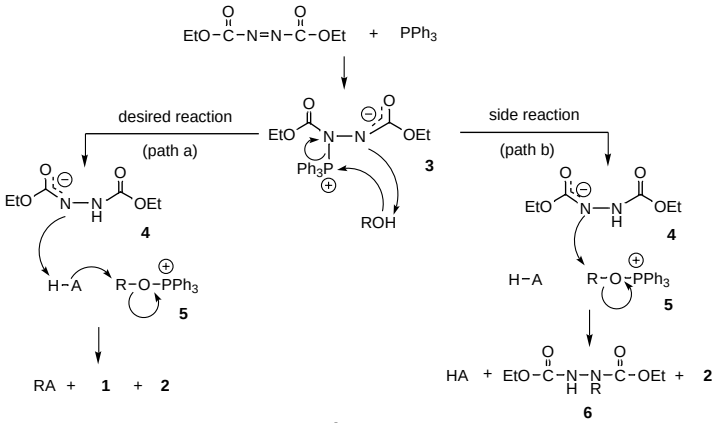


Scheme 3.

2. Development of New Mitsunobu Reagents

2.1. New Azo-type Reagents

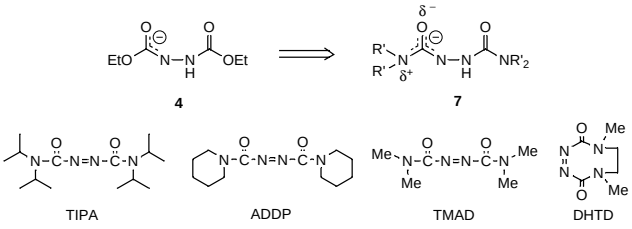
To develop improved redox system, we considered the mechanism of the Mitsunobu reaction and its side reaction. The desired Mitsunobu reaction proceeds probably through the generally accepted path a shown in Scheme 4.[2)]



Scheme 4.

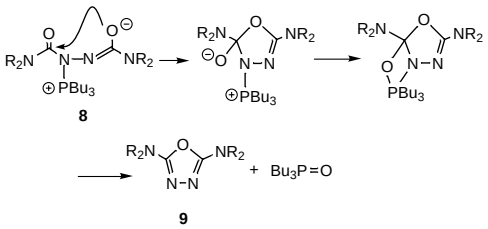
On the contrary, in the case of the reaction of less acidic HA, the hydrazo anion **4** attacks the alkoxyphosphonium **5** directly to afford alkylated the hydrazine derivative **6** as a by-product (Scheme 4, path b),[3] since the anion **4** is not efficient in deprotonating the weakly acidic HA. 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.

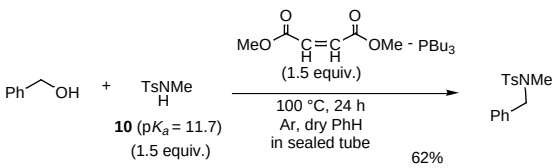
Those new azo compounds were combined with a more nucleophilic phosphine than TPP, such as tributylphosphine (TBP), because of the lower reactivity of the azodicarboxamides as Michael acceptors, compared with DEAD. In the course of our study, we found that most of the new azo compounds and TBP used was 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

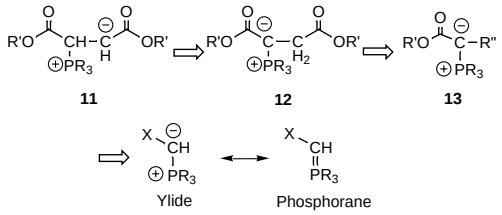
When the azo-type reagents were developed, it was found that maleic and fumaric acid derivatives, which were identified as carbon analogs of DEAD and/or TMAD, mediated the condensation of benzyl alcohol with tosyl amide **10** (*ex.* Scheme 7).[6]



Scheme 7.

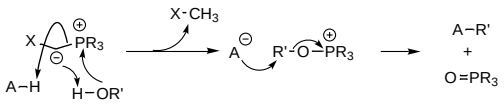
Unfortunately, difficulty in reproducibility of the reaction and in product isolation forced us to abandon this investigation. However, consideration of this reaction mechanism revealed that the betaine **11** was formed instead of the Mitsunobu intermediate **3** (Scheme 8). **11** might easily convert 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.



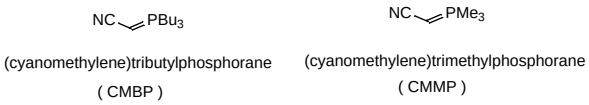
Scheme 8.

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.



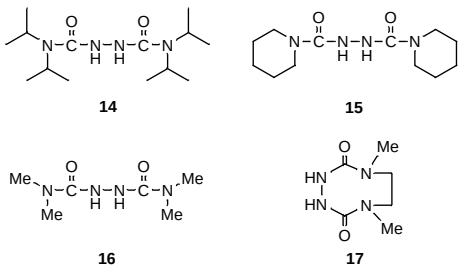
Scheme 10.

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.



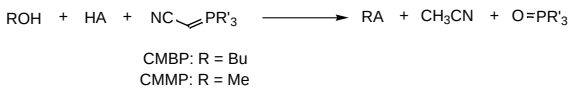
Scheme 11.

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.

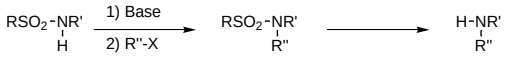


Scheme 12.

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).

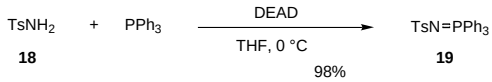


Scheme 13.

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]

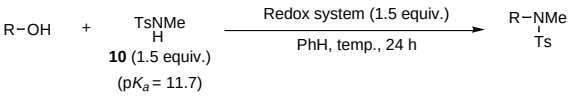
The reaction of *p*-toluenesulfonamide (**18**) was noted. Although **18** (pK_a = 10.2)[16] was expected to react with alcohols under the Mitsunobu conditions because of its pK_a value, **18** was actually converted to tosylimide **19** without any alkylated products (Scheme 14).[15,17,18]



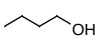
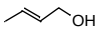
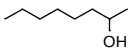
Scheme 14.

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**).

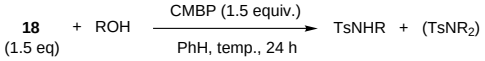


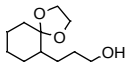
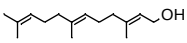
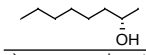
% yield

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

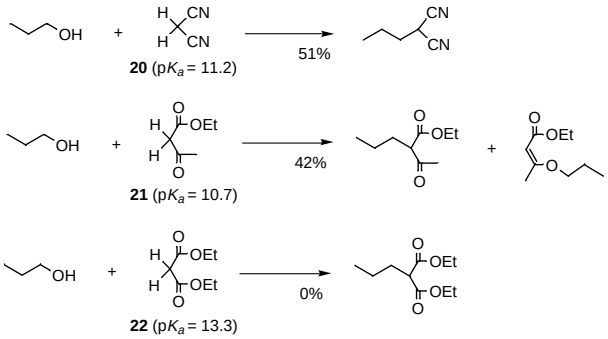
*) The reaction was carried out in THF.

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.

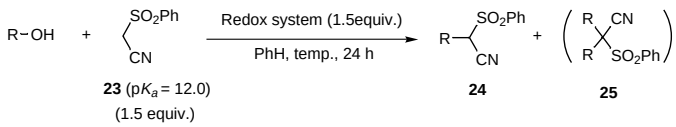
4.2. Reaction of Carbon Nucleophiles (C-C bond formation)

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.

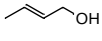
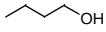
The finding that the double alkylation of **23** took place to some extent prompted us to study further the alkylation of some active methine compounds. In fact, CMMP promoted the reaction of 3-methyl-2-phenylsulfonylnonanenitrile (**26**) with butanol in excellent yield. This result suggested that a 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**).

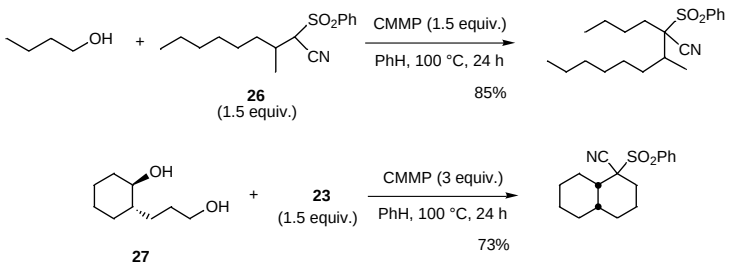


23 (pK_a = 12.0) (1.5 equiv.) **24** **25**

% 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

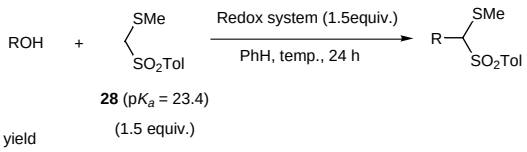
1) – : no experimental result.



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**).



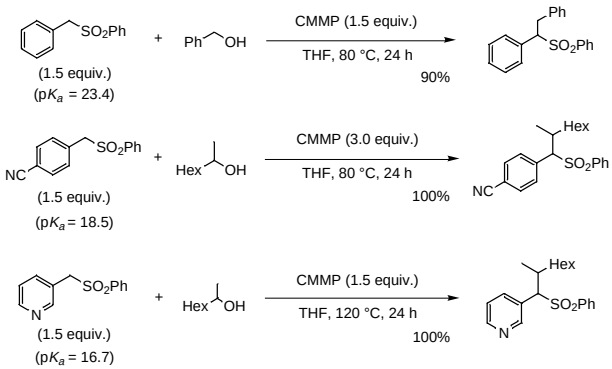
28 (pK_a = 23.4)
(1.5 equiv.)

% 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.

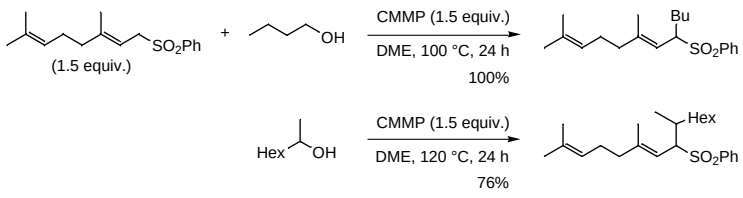
The phosphorane-type reagents could also be used for the alkylation of various carbon nucleophiles with a high pK_a. One of these was arylmethyl phenyl sulfones (pK_a = 16 ~ 23), whose methylene was activated by both an aromatic ring and a sulfonyl group. They reacted efficiently with alcohols (Scheme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



Scheme 17.

Further, allylic phenyl sulfones (pK_a = ~ 23) with a trisubstituted 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]

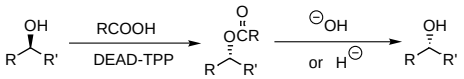
Carbon nucleophiles introduced in this chapter were generally converted to carbanions under basic conditions, and then were subjected to the reaction with alkylating agents such as alkyl halides. However, the alkylation with secondary halides suffered some drawbacks such as 1) disappointing yield because 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)

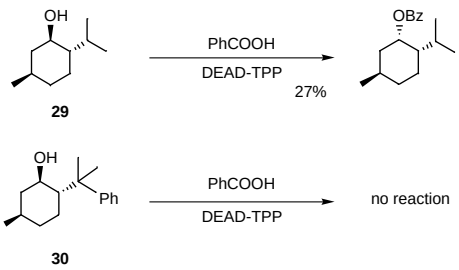
Herein we would also like to describe the reaction of carboxylic acids having a lower pK_a value. The Mitsunobu reaction of carboxylic acids with chiral secondary alcohols affords the corresponding esters with complete inversion of the configuration. Hence this reaction has been widely used for the preparation 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.

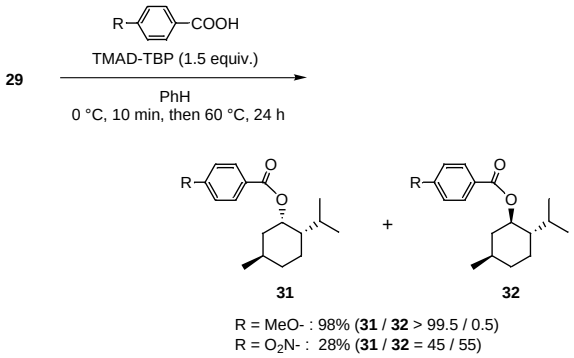
The reaction, however, is very sensitive to the steric situation around the carbinyl carbon; increasing steric hindrance leads to sharp decreases in the yield of the corresponding esters. For example, although cholestanol was acylated with benzoic acid to give the corresponding benzoate in 100% yield, 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.



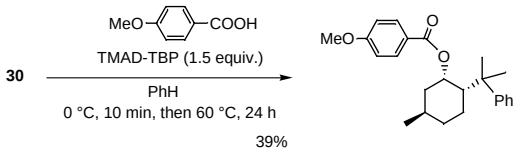
Scheme 20.

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)]

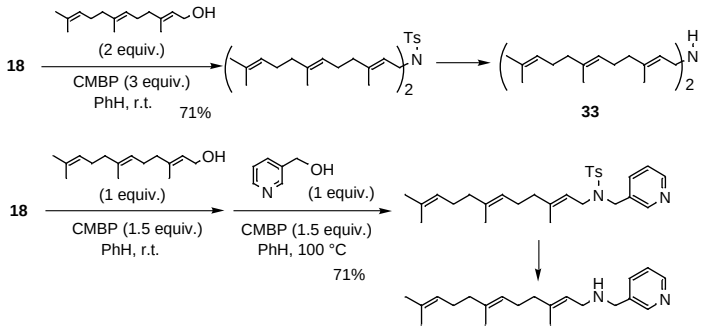


Scheme 22.

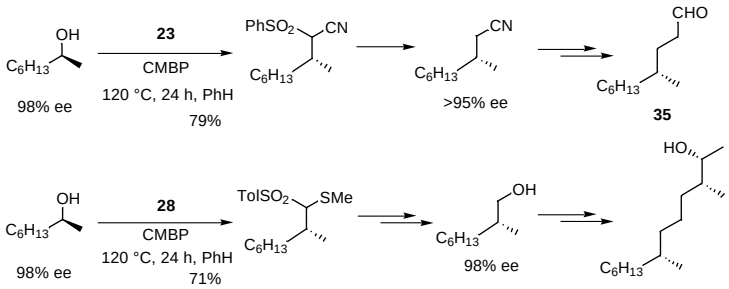
5. Application to Organic Syntheses

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)]



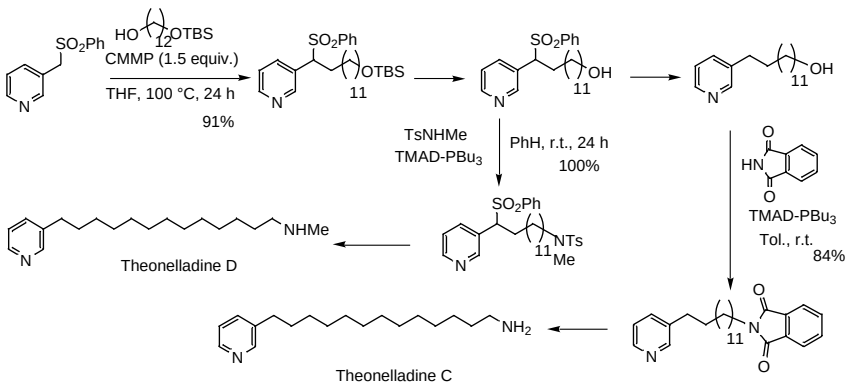
Scheme 23.



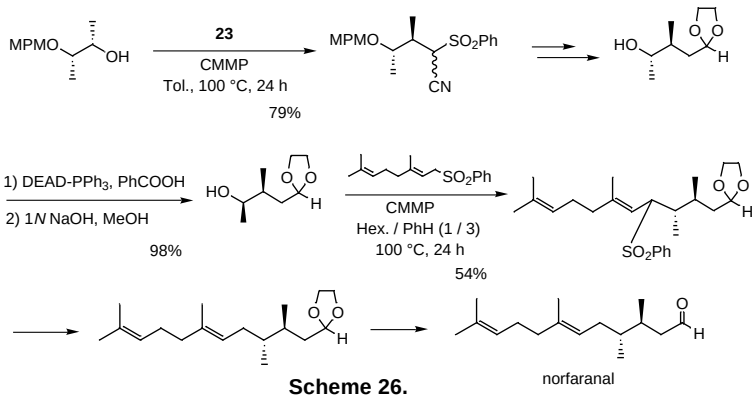
Scheme 24.

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]

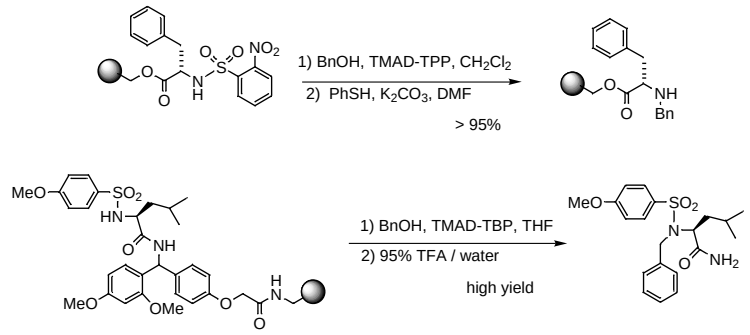
In previous syntheses of (+)-norfaranal, one major problem was how to construct the *anti*-dimethyl structure as an optically active form.[30] This difficulty could be overcome by both the standard and new Mitsunobu reactions, which were employed in three steps of the synthetic route. Commercially available (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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(Received January, 2005)