Tetrahedron 65 (2009) 6109–6114

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# DMEAD: a new dialkyl azodicarboxylate for the Mitsunobu reaction

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ARTICLE INFO

*Article history:*
Received 13 April 2009
Received in revised form 20 May 2009
Accepted 20 May 2009
Available online 27 May 2009

*Keywords:*
Mitsunobu reagent
DAD
Separation-friendly reagent
Aqueous extraction

ABSTRACT

Di-2-methoxyethyl azodicarboxylate (DMEAD) is prepared in 65% yield in two steps as a crystalline solid. Use of DMEAD in the Mitsunobu reaction of a variety of alcohols with pronucleophiles results in good yields of the products under sufficient stereospecificity of inversion, as conventional diisopropyl azodicarboxylate (DIAD) does. Isolation of the product is, however, much easier with DMEAD than that with DIAD, because the hydrazine produced from DMEAD is highly hydrophilic and is completely separable by a simple extraction into neutral water. Purification of the organic layer, after separation of the other by-product, triphenylphosphane oxide, by filtration, easily provides high purity of the product in a good yield. Concentration of the water layer yields the hydrazine, which can be reused for the preparation of DMEAD. One-step removal of the two by-products by the aqueous extraction was also possible when trimethylphosphane and DMEAD were employed.



## 1. Introduction

Dialkyl azodicarboxylate esters (DADs) are electrophilic reagents that react with olefins as dienophiles to result in the [4+2] cycloadditions, or as enophiles to perform ene reactions.[1] A more important use of a DAD in organic synthesis is as one of the reagents in the Mitsunobu reaction, where cooperation of the oxidative nature of DAD and the reducing nature of a phosphane promotes dehydration between an alcohol and a carboxylic acid (or one of other acidic pronucleophiles) to give an ester with complete stereo-inversion at the alcoholic carbon.[2] The reaction generally proceeds smoothly at rt under almost neutral conditions using a common DAD, the ethyl ester (DEAD) or the isopropyl ester (DIAD), the latter of which is now more popular due to the stability during storage and handling.

A major drawback of the Mitsunobu reaction is the formation of two by-products, hydrazinedicarboxylate and phosphane oxide, which must be removed from the reaction mixture to isolate a target compound. The separation of the phosphane oxide is usually an insignificant matter, due to low solubility of the oxide produced from the commonly employed triphenylphosphane (=triphenylphosphine). As a matter of fact, concentration of the mixture of the Mitsunobu reaction often provides crystals of triphenylphosphane oxide, which can be removed by filtration with a proper solvent such as petroleum ether.

In contrast, the hydrazinedicarboxylate is problematic during the separation of the product. Diethyl and diisopropyl hydrazinedicarboxylates are not so volatile to remove by evaporation, and their chromatographic separation from the product is also difficult due to the moderate polarity. In addition, side-reactions of DAD also produce moderately polar compounds. For those reasons, the Mitsunobu reaction potentially involves difficulty in the isolation process of the product.

To solve the separation problem, various modified reagents have been developed.[3] That is, DAD is supported on a polymer, and the produced hydrazine is separated by filtration.[4] An acidic,[5,6] basic,[7] or fluorous[8,9] group is attached to a DAD, and the produced hydrazine is separated by extraction into a basic or acidic aqueous layer or into a fluorous solvent, respectively. A DAD incorporating a proper cyclic olefin can be polymerized by metathesis after the Mitsunobu reaction.[10] A particular hydrazine can be removed as a crystalline product from the reaction mixture and can be reused for the preparation of the DAD.[11–13] Azodicarboxamides are also the reagents, the hydrazines of which can be removed by the filtration[14] or the extraction,[15] though their properties are somewhat different form those of DAD. Use of DAD as a catalyst is also one of the solutions because the amount of the produced hydrazine can be reduced.[16] Even with the development of such DAD analogues, the classic DEAD and DIAD are still major reagents in the Mitsunobu reactions, due to the availability of the reagent. DEAD and DIAD are the simplest DADs, but are already costly (e.g., 65 USD for 100 g of DIAD), and their separation-friendly analogues are still more expensive.[17]

Here, we have studied a new approach to address the separation problem by a molecular design to enable the separation of a hydrazinedicarboxylate by extraction with neutral water. The advantage of this reagent design is that both the hydrazine-free product and impurity-free hydrazine can be obtained by simply the extraction/concentration process. The former purity is important to

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0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.05.048

achieve a separation-friendly or even a separation-free process, and the latter purity affects the effectiveness of the reuse of the recovered hydrazine. The production cost is another key issue in the reagent design. DIAD is cheaper than all other DAD analogues due to their simple structure. However, the purification of DIAD as well as DEAD, that are potentially explosive, necessitates distillation under reduced pressure, and the total cost of a DAD production can be reduced if the distillation is omitted. Di-2-methoxyethyl azodicarboxylate (DMEAD, **1**) is our newly designed reagent that can be produced by a commercially viable process, and its advantage as a Mitsunobu reagent will be presented in this report (Fig. 1).[18]

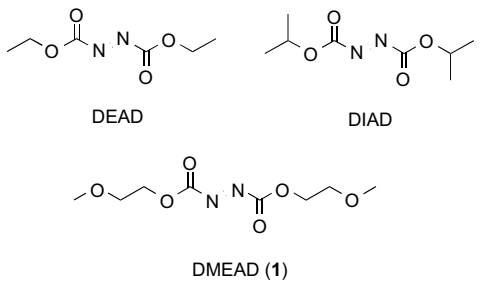
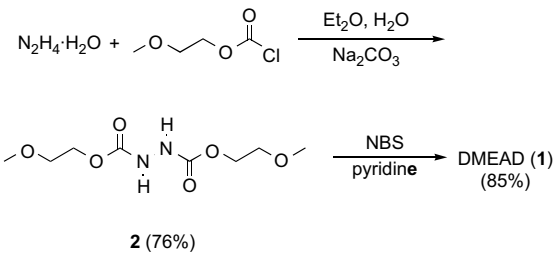



**Figure 1.** DEAD and DIAD, the classic DAD analogues, and DMEAD (**1**), the new analogue.

## 2. Results and discussion

### 2.1. Preparation and physical properties of DMEAD

Di-2-methoxyethyl hydrazinedicarboxylate (**2**) was prepared by mixing commercially available reagents, hydrazine hydrate, 2-methoxyethyl chloroformate, and sodium carbonate in aqueous ethanol in 76% yield after recrystallization (Scheme 1). The hydrazine **2** is a precursor of DMEAD but also the by-product of the Mitsunobu reaction with DMEAD; therefore, the properties of **2** are of importance for the separation and recycling process. The solubility of **2** is very poor (<0.01 g/mL, rt) in ether or toluene, moderately high in ethyl acetate (0.1) and chloroform (0.25) and very high in water (0.55). The solubility in water is better than that of the methyl analogue (0.15) and much better than those of the ethyl and isopropyl analogues (<0.01), which are the hydrazines formed from DEAD and DIAD, respectively. The partition coefficient $K_d$ of **2** at 23 °C was 0.045 for ether/water and 0.025 for toluene/water. From these properties, it was expected that **2** of the by-product in the Mitsunobu reaction with DMEAD could be removed from the reaction mixture by a simple extraction.




**Scheme 1.** Preparation of DMEAD (**1**).

The $R_f$ value of **2** on a silica gel TLC plate was very small, 0.08 (elution with a mixture of ethyl acetate and hexane=1/1) compared with the ethyl ($R_f$=0.44) or the isopropyl analogue (0.65) and is sufficiently smaller than common carboxylic esters (>0.5) of the Mitsunobu product. The high polarity of **2** promised an easy and complete separation of the product by column chromatography.

DMEAD was synthesized from hydrazine **2** by several oxidation methods,[19] and found to be a crystalline compound. A reaction with chlorine or sodium hypochlorite yielded DMEAD, but the purity obtained after the extraction was not sufficiently high to allow crystallization from the reaction mixture. The oxidation with NBS in the presence of pyridine in toluene produced less side-products, and the reaction mixture after the extraction/drying/concentration process was crystallized in a mixture of toluene and hexane to give pure DMEAD in 85% yield as yellow prisms (mp 39.9–40.4 °C).

The thermal stability of DMEAD was evaluated by the decomposition temperature. By the differential scanning calorimetry (DSC) measurement, DMEAD was found to decompose at 210 °C (927 J/g, exothermic), while DEAD and DIAD decomposed at 227 °C (1088 J/g) and 249 °C (999 J/g), respectively. The lower decomposition temperature of DMEAD indicates less stability at high temperatures, but at room temperature, the crystalline DMEAD must have an advantage in the stability relative to the liquid DEAD and DIAD. As a matter of fact, DMEAD maintained its crystalline form for more than three months at rt and over a year at 5 °C.

### 2.2. Mitsunobu reaction with reagent recycles

The recovery process of both the by-products of the Mitsunobu reaction was demonstrated by using DMEAD. Optically active (*S*)-2-octanol (2 g) of 96% enantiomeric excess (ee) was converted to (*R*)-2-benzoyloxyoctane (**3a**) by the reaction with 1.1 molar amounts each of benzoic acid, triphenylphosphane, and DMEAD in diethyl ether (120 mL) at rt. Consumption of the reagents proceeded smoothly, and the reaction was completed within 2 h. The reaction mixture was washed with water, and the aqueous layer obtained was re-extracted with diethyl ether (Fig. 2). The aqueous layer then contained only the hydrazine **2** (>98% pure by $^1$H NMR) in 94% yield based on the employed amount of DMEAD, which is 100% of the theoretical value. Recovery of sufficiently pure **2** to reuse was accomplished by a single recrystallization from a mixture of acetone and toluene in 75% yield.

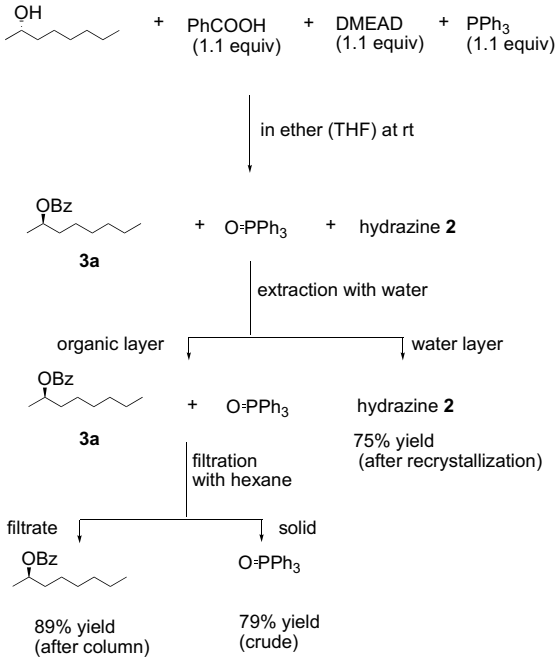



**Figure 2.** Separation process of the Mitsunobu reaction using DMEAD.

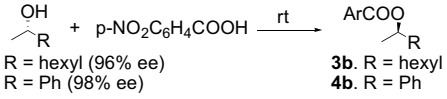
The organic layer was dried, concentrated, and suspended in hexane. Unreacted triphenylphosphane was consumed during this process, and most of the phosphane oxide was recovered by filtration of the suspension in a crystalline form at 79% based on the employed amount of triphenylphosphane (>90% pure by $^1$H NMR). Some side-products produced from DMEAD were also included in the crystalline part. The filtrate consisted mostly of **3a**, ca. 80% (mol/mol), with accompanying some triphenylphosphane oxide and a trace amount of **2** deduced from the $^1$H NMR. Application of the mixture to a short silica gel column afforded chemically pure (*R*)-**3a** in 89% yield.

The same conversion was also demonstrated in THF, another popular solvent for the Mitsunobu reaction having higher dissolving power. The reactivity was similar to that in diethyl ether, and by the same procedure, except for exchange of the solvent to toluene prior to the extraction, **2** was recovered in 71% yield after recrystallization. The product was also isolated in 83% yield after chromatography. During the reactions both in diethyl ether and THF, the complete stereochemical inversion was confirmed by chiral HPLC analysis as well as the optical rotation of **3a**.

### 2.3. Stereospecificity with DMEAD

Stereospecific inversion of the Mitsunobu reaction is usually observed, but in some cases, the reaction accompanies an $S_N1$ process[20] or the retention process via the acyloxy phosphonium ion.[21] The stereospecificity of the reaction with DMEAD was studied using different reaction solvents and two optically active substrates, (*S*)-2-octanol (96% ee) and (*S*)-1-phenylethylalcohol (98% ee). Through this series, 4-nitrobenzoic acid was used as a nucleophile (Table 1). Some reactions were also performed with DIAD; the results are shown in parentheses.

**Table 1**
Stereospecificity in the reaction of optically active alcohols with DMEAD (or DIAD, shown in parentheses) and $PPh_3$[a]




| Entry | R | Solvent | Time/h | Yield/% | ee/%[b] |
|---|---|---|---|---|---|
| 1 | $C_6H_{13}$ | Toluene | 3.5 | 96 | 96 |
| 2 | $C_6H_{13}$ | $CH_2Cl_2$ | 1.5 | 89 | 96 |
| 3 | $C_6H_{13}$ | THF | 2.5 (2) | 90 (96) | 96 (96) |
| 4 | $C_6H_{13}$ | $CH_3CN$ | 21 | 54 | 95 |
| 5 | Ph | Toluene | 6 (5) | 91 (90) | 95 (97) |
| 6 | Ph | $CH_2Cl_2$ | 46 | 74 | 86 |
| 7 | Ph | THF | 4 (4) | 84 (89) | 80 (80) |
| 8 | Ph | $CH_3CN$ | 40 | 30 | 54 |

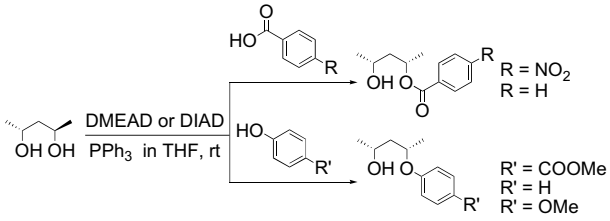
[a] All reactions were carried out at rt in a reagent ratio of alcohol/pronucleophile/DMEAD/$PPh_3$=1/1.2/1.2/1.2.
[b] Determined by HPLC.

The reactions with 2-octanol occurred smoothly except in acetonitrile (entry 4), and ester **3b** was obtained under complete stereochemical inversion (entries 1–3). In contrast, the reaction of (*S*)-1-phenylethanol resulted in a loss of the original stereochemical purity in all the solvents during the conversion to **4b**.[2d] The degree of the loss was strongly dependent on the solvent polarity; 3% loss in toluene (entry 5) but 44% loss in acetonitrile (entry 8). Comparing with DIAD, isolated yields in THF are slightly lower (entries 3 and 7), which might be improved by the optimization of the reaction conditions. A drawback of DMEAD is seen in the reaction in toluene (entry 5). DMEAD and its hydrazine increase the polarity of the reaction media to reduce the stereospecificity in 3%, which is larger than that with DIAD (1%). The observed imperfect stereo-inversion occurred at the benzylic position in the polar media should be attributable to the $S_N1$ mechanism.[20]

### 2.4. Reaction with different pronucleophiles (efficiency of product isolation)

The difference between DMEAD and DIAD in the Mitsunobu reaction was further studied with a symmetric diol, where a selectivity of the reaction is required for the mono-derivation. Stereochemically pure (2*R*,4*R*)-2,4-pentanediol (>99% de and ee) was employed, and thus, the stereospecificity of the reaction could be verified as a diastereomeric purity of the product (Table 2). Pronucleophiles having different acidity in a $pK_a$ range between 3.4 and 10.2 were tested because the acidity is a key issue for efficiency of the Mitsunobu reaction.[2,22] In addition, this series of experiments indicate a usability of DMEAD in the Mitsunobu reaction because the expected products having a remaining hydroxy group are properly polar in different degree, and are considered to be good models to test the efficiency of the product separation from a moderately polar hydrazinedicarboxylate by the conventional chromatography.

**Table 2**
Selective mono-derivation of 2,4-pentanediol with varied pronucleophiles[a]




| No. | Nu–H ($pK_a$) | Yield/% (diester/%) | |
|---|---|---|---|
| | | DMEAD | DIAD[b] |
| 1 | 4-Nitrobenzoic acid (3.44) | 45 (26) | 40 (30) |
| 2 | 4-Nitrobenzoic acid (3.44) | 79 (<5) | 83 (<5) |
| 3 | Benzoic acid (4.20) | 74 (<5) | 74 (<5) |
| 4 | 4-Methoxycarbonylphenol (8.74) | 83 (<5) | 91 (<5) |
| 5 | Phenol (9.95) | 84 (<5) | 80 (<5) |
| 6 | 4-Methoxyphenol (10.20) | 82 (<5) | 83 (<5) |

[a] All reactions were carried out at rt in THF by addition of DAD to the mixture of the other reactions in a ratio of diol/pronucleophile/DAD/$PPh_3$=1.2/1/1.2/1.2. For entry 2, 4-nitrobenzoic acid was added to the mixture of the other three reagents.
[b] Estimated yield based on $^1$H NMR.

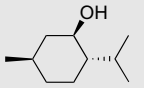
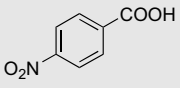
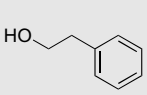
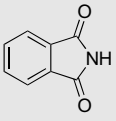
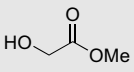
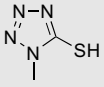
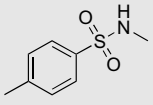
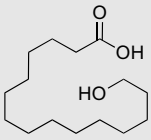
The reactions shown in Table 2 were carried out in THF at rt by addition of DMEAD or DIAD to a mixture of the other three components except for entry 2, where the acid was added to a mixture of the others. The reagent ratio was fixed at diol/pronucleophile/DMEAD(DIAD)/$PPh_3$=1.2/1/1.2/1.2. A sufficiently acidic 4-nitrobenzoic acid is a popular pronucleophile in the Mitsunobu reaction, but in the present case, bis-derivation occurred considerably to give the diester in 26%, and low mono-derivation selectivity (45%) was observed (entry 1). The low mono-selectivity was also observed with DIAD. However, modification of the addition method to reduce the concentration of the acid during the reaction resulted in selective mono-derivation (entry 2). The reactions with the other pronucleophiles are selective by the regular addition method, resulting in only 2–3% of the diesters (entries 3–6). The high mono-derivation selectivity of the 1,3-diol may suggest the formation of a cyclic phosphorane intermediate with the diol. Actually, the reagents were mostly consumed without addition of the pronucleophile deduced from disappearance of the yellow solution color. The phosphorane intermediate should be converted to the phosphonium precursor for the product by the proton transfer from the pronucleophile.

The product mono-alcohols have moderately low $R_f$ values (0.4–0.6 with ethyl acetate/hexane=3/7 to 6/4) on silica gel TLC, and for the same reactions with DIAD, complete separations of the products from the diisopropyl hydrazinedicarboxylate were not possible (except for the reaction in entry 5), but the hydrazine was contaminated in a considerable amount (25–35% of the product) after the silica gel chromatography. These results are contrasting to the easy isolations demonstrated with DMEAD, and it is clearly an advantage of DMEAD in the Mitsunobu reaction. Stereospecificity was also very high with both reagents to give >98% diastereomeric excess of the products in all cases.

### 2.5. Further study on applicability of DMEAD

The performance of DMEAD in the Mitsunobu reaction was further tested for different combinations of alcohols and pronucleophiles, in comparison with that of DIAD. The reactions were carried out in THF at rt with 1.2 molar amounts of the reagents. The results are given in Table 3. Menthol is a less reactive substrate but could be converted to the diastereomerically pure isomenthol ester with 4-nitrobenzoic acid in a good yield, though the reaction took a longer time, similarly to the same reaction with DIAD (entry 1). Phthalimide, a nitrogen pronucleophile, reacted smoothly with a primary alcohol with DMEAD to give the corresponding imide, while the reaction with DIAD proceeded more slowly and resulted in incomplete consumption of the alcohol in the longer reaction time under the present conditions (entry 2). The reaction of 1-methyl-1*H*-tetrazole-5-thiol with glycolic acid methyl ester yielded tetrazolylsulfanyl acetate in 88% yield after short column chromatography on silica gel. For this conversion, use of DIAD caused a problem in the separation of the by-product hydrazine from the product by silica gel column chromatography (entry 3). *N*-Methyltosylamide is a potent nucleophile in the Mitsunobu reaction, but the reaction with 2-octanol was unsatisfactory in the yield of the 2-octyl tosylamide both with DIAD and DMEAD (entry 4). Intramolecular reaction to give a macrolactone is not high yielding for the Mitsunobu reaction. As a matter of fact, the cyclization of the 16-membered ring resulted in only a moderate yield in the reactions with both DMEAD and DIAD (entry 5).

**Table 3**
Different combinations of the pronucleophile and alcohol[a]

| No. | Alcohol | Nu–H | DMEAD | | DIAD | |
|---|---|---|---|---|---|---|
| | | | Time/h | Yield/% | Time/h | Yield/% |
| 1 |  |  | 17 | 73 | 17 | 72 |
| 2 |  |  | 2.5 | 94 | 4 | 67 |
| 3 |  |  | 2 | 88 | 3 | 65[b] |
| 4 |  |  | 21 | 33 | 15 | 55 (53)[c] |
| 5 |  | | 12.5 | 31 | 19 | 38 |

[a] All reactions were carried out at rt in THF with the reagents in a ratio of alcohol/pronucleophile/DMEAD or DIAD/$PPh_3$=1/1.2/1.2/1.2.
[b] The product obtained by the $SiO_2$ chromatography in 97% crude yield contained 32% (w/w) of the hydrazine.
[c] Reported yield with DEAD.

### 2.6. Total separation by aqueous workup

Triphenylphosphane oxide of the other by-product can be removed by the precipitation/filtration process, but this process could not remove all the oxide from the reaction mixture. In addition, total removal of both the by-products by a simple aqueous workup is sometimes preferable; especially when the reaction scale is not so large. To realize this in the Mitsunobu reaction with DMEAD, trimethylphosphane (TMP) was selected because its oxide is known to be removable by the aqueous workup.[23] TMP is a less popular phosphane in the Mitsunobu reaction, and may have a difficulty in its use other than the price. Comparing with conventional triphenylphosphane, the phosphorous atom in TMP is less hindered and more basic ($pK_{BH+}$ of $PMe_3$=8.65, $PPh_3$=2.73), and thus TMP should have stronger nucleophilicity and reducing power. TMP has been employed with the combination of less oxidative urea type DAD (e.g., 1,1′-(azodicarbonyl)dipiperidine), and this combination is effective for the Mitsunobu reaction with reductive substrates such as thiol.[24] In the case of the combination with DMEAD, the Mitsunobu reaction was sluggish to result in less than 20% conversion, presumably due to the too stable nature of the reagents complex. By tuning the reaction conditions, the reaction at 60 °C in toluene was found to result in the high conversion in 12 h. After cooling, the reaction mixture was washed with water (two times), dried, and concentrated under vacuum to give a crude product, which contained no trace TMP nor its oxide. From the reaction of (*S*)-2-octanol (96% ee) with benzoic acid in a reagent ratio of 2-octanol/benzoic acid/DMEAD/$PMe_3$=1/1/1.3/1.3, **3a** was obtained in 82% yield after the column chromatographic purification. The stereoinversion was almost perfect to yield 95% ee of (*R*)-**3a**. Under the same conditions, (*S*)-1-phenylethylalcohol (98% ee) was converted to the benzoate analogue **4a** in 82% yield (96% ee). It should be noted that the same reaction except use of *p*-nitrobenzoic acid instead of benzoic acid resulted in poor results in both the conversion (75% in 18 h) and the inversion (80% ee) to give the low isolated yield (57%). The imperfect stereo-inversion may be caused by the reaction with the acyloxy phosphonium ion and the alcohol.[21] Although the DMEAD/TMP combination is effective to isolate the product by a simple extraction, the applicable range is not so clear yet.

## 3. Conclusions

In this report, we have shown that the hydrazine formed during the Mitsunobu reaction with DMEAD could be effectively removed by a simple extraction with neutral water from the reaction mixture and is recovered in sufficiently pure form for reuse. The production cost of DMEAD is clearly less than that of the other alternatives so far reported to solve the separation problem. Compared with conventional DIAD, DMEAD may cost more due to the use of 2-methoxyethyl chloroformate in place of isopropyl chloroformate, but DMEAD has an advantage over DIAD (DEAD) due to the easy purification step (no distillation) that can overcome the cost of the raw materials. DMEAD can be used in the Mitsunobu reaction in almost the same way as DIAD but is a much more preferable reagent that allows easy separation and reagent-reusable processes. DMEAD is now obtainable from a commercial source.

## 4. Experimental section

### 4.1. General

2-Methoxyethyl chloroformate was obtained from Tokyo Chemical Industry Co., Ltd. Substrate in Table 3, entry 5 was obtained by the hydrolysis of the lactone. The other chemicals were obtained from commercial sources. All anhydrous reactions were performed under nitrogen in flame-dried glassware using solvents distilled over proper drying agents. Melting points were obtained on a BUHCI Melting Point B-545. All products were characterized by NMR spectrometry using a JEOL ECA-600 spectrometer or a JEOL AL-400 at 400 MHz, and by IR with a SHIMAZU IR Prestige-21. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Elemental analyses were performed with a Perkin–Elmer CHNS/O Analyzer 2400. High resolution MS was obtained with a JEOL JMS-AX505-HA. Enantiomeric purities were determined by HPLC analysis using a chiral column (DAICEL CHIRALPAK AD for **3a** and CHIRALCEL OJ-H for the others).

### 4.2. Preparation of di-2-methoxyethyl hydrazinedicarboxylate (2)

A solution of hydrazine hydrate (20 g, 400 mmol) and sodium carbonate (46.81 g, 440 mmol) in water (160 mL) and 99.5% ethanol (100 mL) was cooled to 5 °C with an ice–water bath. 2-Methoxyethyl chloroformate (121.83 g, 880 mmol) was added dropwise while keeping the temperature below 10 °C. After 2 h, the mixture was concentrated under vacuum and then treated with acetone (400 mL) to precipitate inorganic salts. The filtrate was concentrated and purified by recrystallization from a mixture of acetone (100 mL) and toluene (160 mL) to give 71.8 g of **2** as a colorless powder (76% yield). Mp 75.0–76.5 °C; IR (KBr) 1755 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.02 (br s, 2H), 4.27–4.25 (m, 4H), 3.58–3.56 (m, 4H), 3.49 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 156.59, 70.40, 64.68, 58.69. Anal. Calcd for $C_8H_{16}N_2O_6$: C, 40.68; H, 6.83; N, 11.96; obsd C, 40.78; H, 7.10; N, 12.00.

### 4.3. Preparation of di-2-methoxyethyl azodicarboxylate (DMEAD, 1)

To a solution of **2** (200 g, 847 mmol) and pyridine (67.2 g, 847 mmol) in toluene (2000 mL) was added *N*-bromosuccinimide (165.85 g, 932 mmol) in a small portion at room temperature. After vigorous stirring for 3 h, the reaction mixture was washed with water (800 mL×2), dried over magnesium sulfate, concentrated under vacuum, and then purified by recrystallization from a mixture of toluene (300 mL) and hexane (1500 mL) to give 168.8 g of DMEAD as yellow prisms (85% yield). Mp 39.9–40.4 °C; IR (KBr) 1782 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.51–4.49 (m, 4H), 3.66–3.63 (m, 4H), 3.32 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 160.04, 69.45, 67.85, 58.84. Anal. Calcd for $C_8H_{14}N_2O_6$: C, 41.03; H, 6.03; N, 11.96. Found: C, 41.09; H, 6.29; N, 12.10.

### 4.4. The reaction of (*S*)-2-octanol and benzoic acid in diethyl ether

To a solution of (*S*)-2-octanol (2 g, 15.4 mmol), benzoic acid (2.07 g, 16.9 mmol), and triphenylphosphane (4.44 g, 16.9 mmol) in diethyl ether (80 mL), a solution of DMEAD (3.96 g, 16.9 mmol) in diethyl ether (40 mL) was added dropwise at room temperature. After 2 h, the mixture was treated with water (100 mL). The water layer was separated from the ether layer and re-extracted with diethyl ether (100 mL). The combined organic layer was washed with water (100 mL). The aqueous layers were combined, concentrated under vacuum (60 °C/20 Torr), and purified by recrystallization from a mixture of acetone/toluene (=5/8) to give 3.01 g of **2** as a colorless powder. The organic layer was washed with water (100 mL), brine (100 mL), dried over magnesium sulfate, concentrated, and suspended in hexane (100 mL). Filtration of the suspension afforded triphenylphosphane oxide as a colorless solid (3.69 g). The filtrate was concentrated and purified by a short column on silica gel (elution with 5% ethyl acetate in hexane) to give 3.18 g of **3a** as a colorless liquid (89% yield). $[\alpha]_D^{20}$ −40.6 (*c* 1.06, MeOH). Lit.[25] $[\alpha]_D^{20}$ −39.5 (*c* 0.032, THF).

### 4.5. The reaction of (*S*)-2-octanol and benzoic acid in THF

To a solution of (*S*)-2-octanol (2 g, 15.4 mmol), benzoic acid (2.06 g, 16.9 mmol), and triphenylphosphane (4.44 g, 16.9 mmol) in THF (80 mL), a solution of DMEAD (3.96 g, 16.9 mmol) in THF (40 mL) was added dropwise at room temperature. After 2 h, the mixture was treated with water (0.5 mL), concentrated, and then extracted with toluene (100 mL×2) and water (100 mL). The aqueous layer was concentrated and purified by recrystallization from a mixture of acetone/toluene (=5/8) to give 2.85 g of **2** as colorless powder. The organic layer was washed with water (100 mL), brine (100 mL), dried over magnesium sulfate, concentrated, and mixed with hexane (100 mL). By the filtration, triphenylphosphane oxide was obtained as a colorless solid (4.61 g). The filtrate was concentrated, and purification by a short column on silica gel (elution with 5% ethyl acetate in hexane) gave 2.97 g of **3a** as a colorless liquid (83% yield).

### 4.6. The reaction of (*S*)-2-octanol and benzoic acid with $PMe_3$ (TMP)

To a solution of (*S*)-2-octanol (130 mg, 1 mmol), benzoic acid (159 mg, 1.3 mmol), and DMEAD (159 mg, 1.3 mmol) in toluene (1.5 mL) was added a toluene solution of trimethylphosphane (1.0 M, 1.3 mL) at 60 °C, and the resulting mixture was stirred at the same temperature for 12 h. After cooling, the mixture was diluted with toluene, washed with water (×2), and then dried over sodium sulfate. After the concentration, the concentrate contained only **3a** deduced from the $^1H$ NMR. Purification by a short column on silica gel (elution with 5% ethyl acetate in hexane) gave 192 mg of a colorless liquid (82% yield).

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