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The Goldilocks Principle in Phase Labeling. Minimalist and Orthogonal Phase Tagging for Chromatography-free Mitsunobu Reaction

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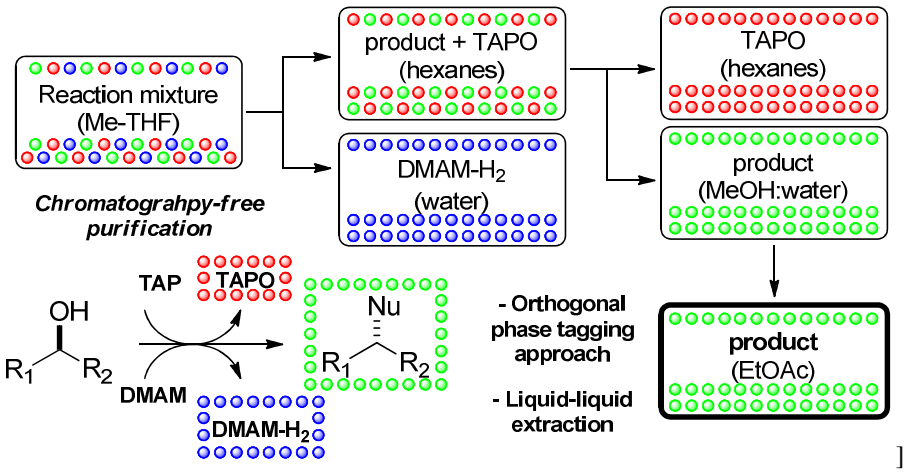

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ABSTRACT: An inexpensive and chromatography-free Mitsunobu methodology has been developed using low molecular weight and orthogonally phase tagged reagents, a *t*-butyl-tagged highly apolar phosphine and a water-soluble DIAD analogue. The by-product of the Mitsunobu reactions can be removed by sequential liquid-liquid extractions using traditional solvents such as hexanes, MeOH, water and EtOAc. Owing to the orthogonal phase labeling, the spent reagents can be regenerated. This new variant of Mitsunobu reaction promises to provide an alternative and complementary solution for the well-known separation problem of Mitsunobu reaction without having to resort to expensive, large molecular weight reagents and chromatography.

1. INTRODUCTION

The Mitsunobu reaction has a privileged position within current toolbox of synthetic organic chemists owing to its scope, reliability, stereospecificity and mild reaction conditions. Employing azocarboxylate and phosphine reagents (Figure 1), convenient synthesis of C-O, C-S, C-N, or even C-C bonds become possible from primary or secondary alcohols.[1] However, despite its many attractive features, the use of Mitsunobu reaction is inherently associated with serious practical concerns. Because of the applied redox activation mode, vast amount of triphenylphosphine oxide and dicarboethoxyhydrazine by-products are generated and their removal is not only an idiosyncratic problem, but also often require column chromatography. Defined by the polarity and solubility of the employed Mitsunobu reagents and their by-products, there is a"polarity/solubility-window" for product separation. Thus, using classical reagents, chromatography-free and large-scale Mitsunobu reactions are viable for synthesizing highly apolar or highly polar products.[2] However, Mitsunobu reaction affording medium polarity "common organic molecules", that are often the target of medicinal chemistry programs, often impose significant hurdles on purification and those methods are less amenable for scale-up. These shortcomings have provided impetus for the development of creative modifications in Mitsunobu reagents and methods. To improve the stoichiometry of the reagents, various catalytic version of Mitsunobu reactions were described.[3] Typically, one of the reagents was regenerated in a parallel reaction. Even, a fully catalytic system for both reagents has been reported,[4] nevertheless, this advancement was recently challenged.[5] Alternatively, efforts have been made to modify both the azocarboxylate and phosphine reactants with phase labels to facilitate the removal of the excess and spent reagents in the purification process.[6] Various approaches have been explored, including soluble and insoluble supports, fluorous, and ionic tagging.[7,8,9] Despite promising advances in chromatography-free Mitsunobu methods, the relatively high cost of the modified reagents and/or their often tedious synthesis limit their widespread utility both at laboratory and industrial scales. The work we report herein was prompted by the desire to address this gap in practicality, thus, inexpensive and easily accessible phase labeled Mitsunobu reagents were targeted.

As part of our interest to develop new methodology for catalyst and reagent immobilization,[10] we have embarked upon developing an operational simple and cost-effective methodology for Mitsunobu reaction purification. We wish to extend the "polarity/solubility window" of the reagents toward both ends of the polarity scale leaving a large window for common organic molecules. We also envisioned that the "Goldilocks Principle" should be employed at the design of the phase labels. Thus, instead of following the widely explored practice of appending large molecular weight phase labels, we aimed to utilize minimal-size phase tags which still ensure the effective separation of the reagents from a "common organic molecule" without compromising their molecular weight, complexity and reagent cost. Additionally, a parallel use of polar and apolar phase labels was conceived for the azocarboxylate and phosphine reagents to offer the potential of regeneration.

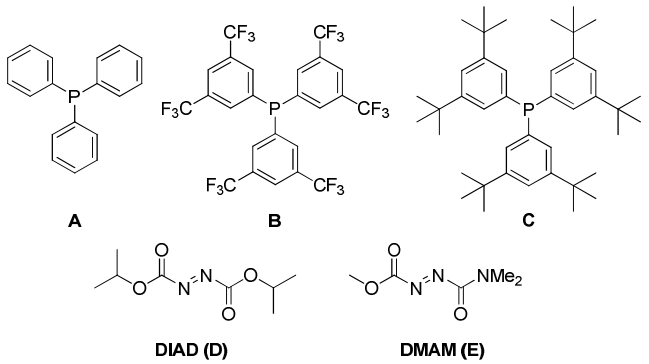


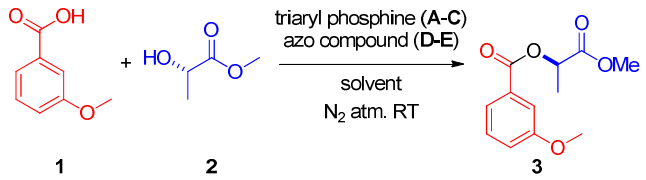
Figure 1. Classical and minimally phase tagged Mitsunobu reagents

We began our investigation to select appropriate reagents for the envisioned low molecular weight and orthogonal-phase-labeled Mitsunobu methodology. For the DEAD analog, we built upon a recently developed water soluble low-molecular weight (dimethylamino)methylazocarbonamide carboxylate DMAM (**E**, Figure 1). As Furkert and Brimble reported, their modified azomonocarboxylate **E** has a similar reactivity to DEAD and it is easily prepared from commercially available starting materials[9f] in a scalable manner. Regarding the phosphine reagent, a highly apolar one was targeted which enables its binary separation from a "common organic molecule". As we have recently reported that trifluoromethyl groups (essentially 6 of them) render triphenylphosphine so apolar that the immobilization of its Pd(0) complex is possible,[10a] we set out our investigation with this phosphine **B** (Figure 1).

2. RESULTS AND DISCUSSION

First, we sought to examine the utility of modified reagents, thus, we explored the Mitsunobu reaction of *m*-anisic acid (**1**) and (*S*)-methyl lactate (**2**). In control experiments, we performed the Mitsunobu reaction with the most common PPh_3/DIAD reagents in THF and Me-THF (Table 1, entries 1, 2). Then the applicability of the selected CF_3 tagged phosphine (**B**) with combination of DIAD (**D**) (Table 1, Entry 3) was investigated. The reaction was found to be sluggish, after 24 hours, the product was isolated with rather poor yield. We reasoned that the nucleophilicity of the phosphine should be enhanced via replacing the CF_3 groups with electron donating and highly lipophilic alkyl tags. To minimize the steric and electronic interference with the nucleophilic site, we envisaged an alkylated analogue **C** that has *t*-butyl tags in all *meta* positions of the phenyl residue.[11a] Then, we were pleased to observe that the modified phosphine **C** exhibited activity parallel to that of PPh_3 in Mitsunobu esterification (Table 1, Entry 4). Finally, the water-soluble azocarboxylate compound DMAM (**E**) was tested in combination with the alkylated phosphine **C**. Gratifyingly, this combination afforded the expected Mitsunobu product in yields close to previous test reaction (Table 1, entry 4 vs. 5). It is worth mentioning that phosphine **C** has received enhanced interest in cross-coupling reactions,[11b] although it is not yet commercially available. Nevertheless, it is readily prepared from inexpensive starting materials in 40 g scale without having to resort to chromatography.

Table 1. Screening of the Mitsunobu reagents[a]



1 2 3

Entry	Phosphine	Azo compound	Solvent	Yield (%)[b]
1	PPh_3(**A**)	DIAD (**D**)	THF	89
2	PPh_3(**A**)	DIAD (**D**)	Me-THF	87
3[c]	**B**	DIAD (**D**)	Me-THF	46
4	**C**	DIAD (**D**)	Me-THF	80
5	**C**	DMAM (**E**)	Me-THF	81

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol, 1.0 equiv), triaryl phosphine (1.0 mmol, 1.0 equiv), azocarboxylate compound (1.0 mmol, 1.0 equiv), solvent (2.0 mL), 2 h reaction time. [b] Isolated yield after chromatography. [c] 24 h reaction time.

Encouraged by the above results, we next sought to examine the feasibility of the chromatography-free and orthogonal separation of the minimally decorated Mitsunobu reagents **C/E** from the product. Among the possible separation methodologies, we wished to employ the liquid–liquid extraction. Thus, using traditional solvents, the separation would be not only inexpensive and simple but also more amenable to scale up.[12] To assess the possibility of binary separation of tagged phosphine **C** from a "common organic molecule", its polarity and solubility was evaluated. The *t*-butylated phosphine **C** and surprisingly its oxide are such highly apolar compounds that they travel near the solvent front when they are subjected to thin layer chromatography (silica/hexanes). Furthermore, they are soluble in hexanes and insoluble in methanol-water (3:2) mixture. Importantly, this aqueous-organic blended solvent is able to dissolve common organic molecules positioned across a broad polarity range.[10c] Based on this, a sequential extractive procedure could be developed (Figure 2). The Mitsunobu reaction was performed in Me-THF and the reaction mixture was diluted with hexanes and extracted with water to remove the excess of the water-soluble azocarboxylate **E** and its spent hydrazine derivative (DMAM-H_2). Then, the hexanes solution was extracted with methanol-water (3:2). Owing to the unrivaled hydrophobicity of the water, the *t*-butyl tagged phosphine **C** and its oxide remained in the hexanes phase and the Mitsunobu product moved to the aqueous-organic phase. Finally, the aqueous phase was diluted with brine and then extracted with ethyl acetate. After evaporation of the organic phase, the Mitsunobu product was obtained.

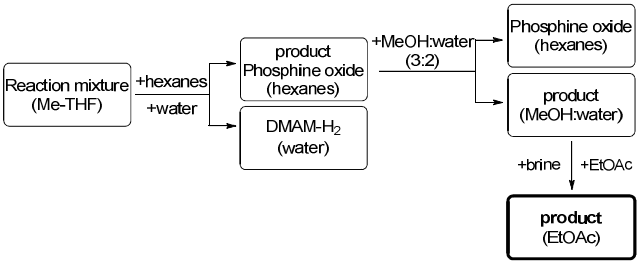
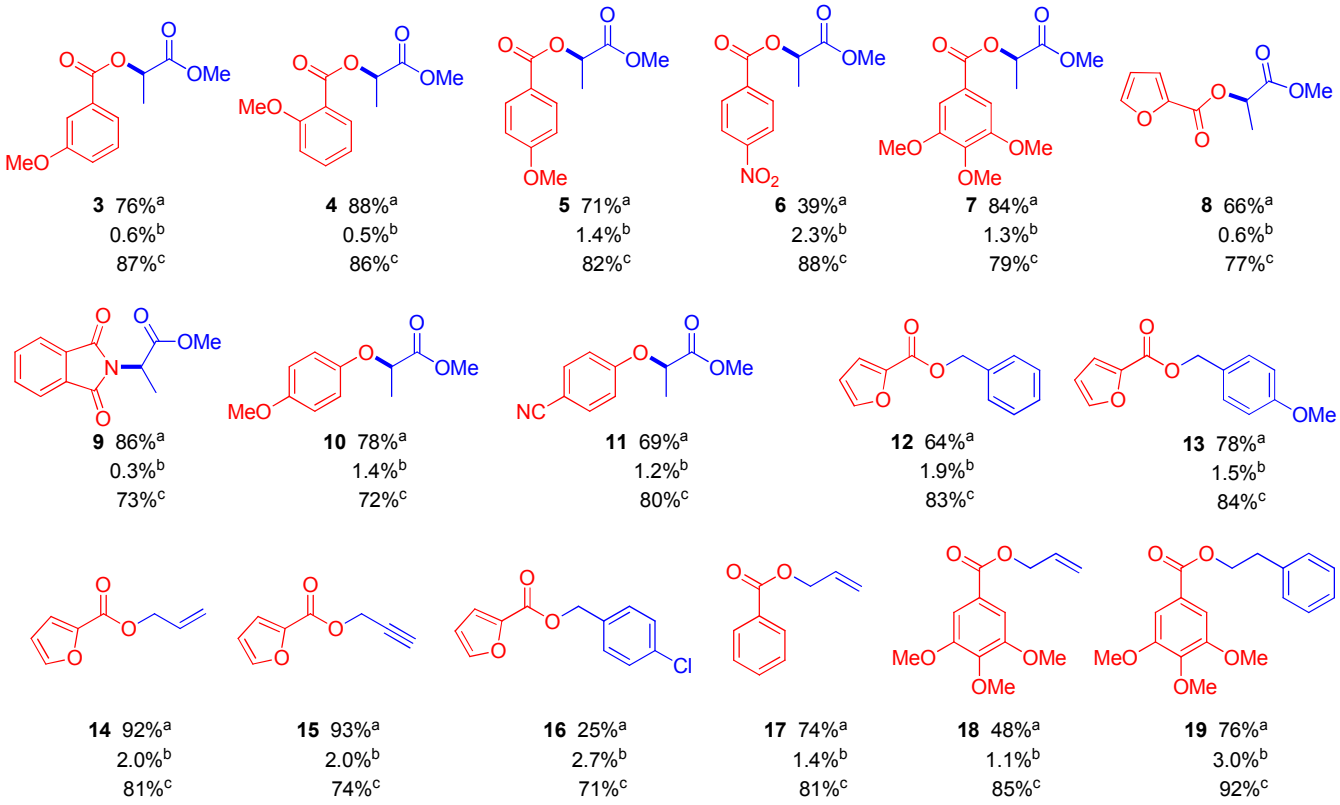


Figure 2. Flowchart of the work-up process for low molecular weight and orthogonally tagged Mitsunobu methodology.

After identification of the minimally decorated azocarboxylate **E** and phosphine **C** as easily and orthogonally removable reagents for Mitsunobu reaction, their utility was explored using various pro-nucleophiles and alcohols. It was also an objective to use the above extractive method for work-up to demonstrate its broad utility. Additionally, within the product, the hydrazine by-product and the phosphine oxide residue were also determined. To gain comparable results, the reactions were also performed with the traditional PPh_3/DIAD reagent combination and in those cases, the products were isolated by chromatography (Scheme 1). First, the model substrates *m*-anisic acid (**1**) and (*S*)-methyl lactate (**2**) were coupled. We found that the Mitsunobu reaction with DEAD/PPh_3 reagent afforded the ester **3** in Me-THF with 87% isolated yield. With the tagged reagents, the above extractive protocol provided the ester **3** with 76% yield, however, the product contained only 0.6% phosphine oxide impurity and no traces of hydrazine by-product could be detected. Next, the extension of the reaction scope toward (*S*)-Methyl lactate (**2**) esterification and amidation were explored (Scheme 1). We were pleased to find that the esterification of *o*-anisic acid (**4**), *p*-anisic acid (**10**), trimethylgallic acid (**7**) and the amidation with phtalimide (**9**) were more efficient with **C**/**E** than with the classical PPh_3/DIAD reagents. Using modified reagents, the esterification of 2-furoic acid with allyl alcohol and propargyl alcohol also afforded esters **14** and **15** in excellent yields, even better yields than with traditional reagent combination after chromatography. The reaction of *m*- or *p*-anisic acid, 2-furoic acid and p-cianophenol with (*S*)-methyl lactate provided esters **3**, **5**, **8**, **11** and the benzylation with benzyl alcohol or with *p*-anisyl alcohol of 2-furoic acid delivered esters **12**, **13** with yields comparable to those of non-tagged DIAD/PPh_3 reagents. Alkylations of trimethylgallic acid proceed smoothly by using allyl alcohol or phenylethanol (**17**, **19**), although a slightly lower isolated yield was observed with modified reagents. It was also established that this minimalist phase tagging method has its own limitations. When the Mitsunobu products have low solubility in aqueous methanol (typically nitro and halogenated compounds), the extraction of the desired compounds was less efficient which lowered the isolated yields (**6**, **16**). Nevertheless, for highly apolar or highly polar products, the classical reagents often enable chromatography-free Mitsunobu reaction.[2] Finally, it is important to note that desired products could be isolated with purities higher than 95% (with high stereoselectivity when chiral lactic ester was used as a substrate), the phosphine oxide residue in the isolated products was in the range of 0.5-3% and the hydrazine by-product was under the detection limit in every case.

Scheme 1. Comparison of classical and low molecular weight phase tagged reagents in Mitsunobu reactions.



[a]Reaction conditions: pro-nucleophile (1.0 mmol, red colored), alcohol (1.0 mmol, 1.0 equiv, blue colored), phase tagged phosphine (**C**) (1.0 mmol, 1.0 equiv), DMAM (**E**) (1.0 mmol, 1.0 equiv), Me-THF (2.0 mL), 2 h reaction time. Crude product was obtained by extraction process. Method A. [b]Residual phosphine oxide content, determined by ^{1}H NMR of the crude products. [c]Reaction conditions: nucleophile (1.0 mmol), alcohol (1.0 mmol, 1.0 equiv), triphenyl phosphine (**A**) (1.0 mmol, 1.0 equiv), DIAD (**D**) (1.0 mmol, 1.0 equiv), Me-THF (2.0 mL), 2 h reaction time. Isolated yields after chromatography. Method B

An additional advantage of this orthogonal phase tagging approach is that it enables the regeneration of spent reagents. Accordingly, after the extractive separation, the hydrazine DMAM-H_2 can be re-oxidize with Oxone according to literature procedure[9f] and the phosphine oxide can be reduced with trichloro-silane in the presence of triethylamine.

3. CONCLUSIONS

In summary, we have demonstrated that a convenient and inexpensive chromatography-free Mitsunobu methodology can be developed using minimal-size and orthogonal phase tags for the reagents. This “tag-economic” approach offers an alternative to the widely explored large-molecular-weight phase-labeled Mitsunobu reagents. The applied reagents are either known

(DMAM, **E**) or conveniently prepared in multidecagram scale from commercially available inexpensive materials. This reagent combination exhibits reactivity that is similar to that of classical PPh_3/DIAD in Mitsunobu reaction. Most importantly, the hydrazine and phosphine oxide by-products formed during the Mitsunobu reactions are easily removed by liquid-liquid extractive protocol using traditional solvents and solvent mixtures and both spent reagents can be easily regenerated due to the orthogonal phase labeling. We anticipate that these advances might result in the further valorization of Mitsunobu reaction and trigger to unlock even more of its potential in organic synthesis and medicinal chemistry. Further studies to explore the utility of minimalist tag approach are ongoing in our laboratory and will be reported in due course.

4. EXPERIMENTAL SECTION

4.1. Materials and Methods. NMR spectra were acquired on Varian spectrometer running at 500 MHz, 125 MHz and 202 MHz for ^{1}H, ^{13}C and ^{31}P, respectively. Chemical shifts (δ) were reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.00 ppm for ^{13}C NMR). The following abbreviations were used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; m, multiplet. ^{13}C NMR spectra were acquired on a broad band decoupled mode. High resolution mass spectra were obtained on a Q-TOF Premier mass spectrometer (Waters Corporation) in positive electronspray mode or EI on a GCTOF spectrometer (Jeol AccuTOF T200GC). Melting points were determined on a SRS MPA100 apparatus and are uncorrected. Column chromatography was performed with RediSep Rf Gold Silica Flash Chromatography Colum (20-40 µm). TLC analysis was performed on silica gel 60 F_{254}-coated aluminium sheets (Merck). Visualization was accomplished by means of ultraviolet (UV) irradiation at 254nm and/or by staining with potassium permanganate. Enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Chiralpak IC or Daicel CHIRALCEL OK columns). Optical rotation measurements were carried out with an ABL$^{\&}$E Jasco P-2000 automatic polarimeter at λ = 589 nm, the concentration (c) expressed in g/100 mL in chloroform. Commercially available materials were purchased from Sigma-Aldrich and were used without further purification. All reactions were carried out under N_2 atmosphere. THF and Me-THF were distillated under nitrogen directly over sodium/benzophenone. DMAM (**E**) was prepared according to literature procedure.[9f]

4.2. procedure for Mitsunobu reaction with phase tagged phosphine (C) and DMAM (E) (Method A). The pro-nucleophile (1.0 mmol, 1.0 equiv) and tris(3,5-di-tert-butylphenyl)phosphine (1.0 mmol, 1.0 equiv) were dissolved in Me-THF (2 mL) at room temperature. Under N_2 atmosphere, the appropriate alcohol (1.0 mmol, 1.0 equiv) was added followed by the dropwise addition of DMAM (1.0 mmol, 1.0 equiv). When the reaction was completed (monitored by TLC), the general work-up procedure was used to obtain the corresponding product.

4.3. General work-up procedure for Mitsunobu reaction: orthogonal phase tagging approach. The crude reaction mixture was transferred to a separatory funnel and 20 mL of hexanes were added. The mixture was washed with water

(3x5 mL) then the hexanes solution was extracted with methanol-water (3:2) mixture. The combined methanol-water mixture was diluted with brine (50 mL) and was extracted with ethyl acetate (3x20 mL). The combined ethyl acetate phase was dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. In several cases, DCM was used to transfer the products to a 4 mL vial.

4.4. General procedure for Mitsunobu reaction with PPh3 and DIAD (Method B). The appropriate pro-nucleophile (1.0 mmol) and PPh_3 (1.0 mmol, 1.0 equiv) were dissolved in Me-THF (2 mL) at room temperature, under N_2 atmosphere. The appropriate alcohol (1.0 mmol, 1.0 equiv) was added to the mixture followed by the dropwise addition of DIAD (1.0 mmol, 1.0 equiv). When the reaction was completed (monitored by TLC), the solvent was evaporated and the residue was purified by column chromatography (SiO_2, hexanes: ethyl acetate mixture).

Tris(3,5-di-tert-butylphenyl)phosphine[11a] (**C**). An oven dried, 2l, 4-necked round-bottom flask was equipped with KPG stirrer, gas inlet, outlet, thermometer and dropping funnel. Under continuous N_2 flush, 1-bromo-3,5-di-*tert*-butylbenzene (134.62 g, 0.50 mol, 5 equiv) was dissolved in dry THF (600 mL) and the resulting solution was cooled to -78°C. The dropping funnel was charged with 200 mL BuLi solution (2.5M in Hexanes, 0.5 mol, 5 equiv) and the solution was introduced to the reaction mixture dropwise to maintain the temperature below -70°C. The formation of aryllithium compound was monitored by GC (small sample was quenched with water). When the reaction was completed, 8.72 mL (13.73 g, 0.10 mol, 1 equiv) of freshly distillated PCl_3 was dissolved in dry THF (50 mL) and was added to the suspension at -70°C. After stirring at that temperature, the reaction mixture was warmed to room temperature while becoming a yellowish solution. Water (200 mL) was added and the mixture was extracted with ethyl acetate (2x500 mL). The separated organic layer was washed with saturated $NaHCO_3$ (300 mL) and brine (300 mL) then dried over Na_2SO_4 and concentrated. The resulting crude mixture was purified by crystallization from cold methanol to give the product (47.80 g, 80%) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 3H), 7.09 (d, *J*=8.2, 6H), 1.23 (s, 54H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4 (d, *J*=6.7 Hz), 136.7 (d, *J*=7.9 Hz), 128.0 (d, J=19.2 Hz), 122.3, 34.8, 31.4; ^{31}P NMR (202 MHz, $CDCl_3$) δ -3.24 (s)

Tris(3,5-di-tert-butylphenyl)phosphine oxide (**C**-oxide). Synthesized according to literature procedure.[13] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 3H), 7.48 (d, *J*=14.8, 6H), 1.26 (s, 54H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9 (d, *J*=12.1 Hz), 130.2 (d, *J*=105.1 Hz), 126.6 (d, *J*=10.9 Hz), 126.2, 35.0, 31.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ 32.97 (s); HRMS (ESI) calcd for $C_{42}H_{64}OP$ $[M+H]^+$ 615.4695, found: 615.4680

Reduction of Tris(3,5-di-tert-butylphenyl)phosphine oxide.[14] Tris(3,5-di-*tert*-butylphenyl)phosphine oxide (10.76 g, 17.5 mmol) and triethylamine (24.4 mL, 175 mmol, 10 equiv) were dissolved in dry toluene (100 mL) and under N_2 atmosphere at 0°C, $HSiCl_3$ (5.30 mL, 52.5 mmol, 3 equiv) was added. After stirring at 0°C for 30 minutes, the reaction mixture was refluxed and the formation of triarylphosphine was monitored by TLC (Hexanes: Ethyl acetate 3:1). When the reaction

was completed (within 2 hours), the mixture was cooled to 0°C and was quenched with sat. Na_2CO_3 solution (10 mL) then was filtered through a plug of Celite and washed with toluene. The organic layer was separated and dried over Na_2SO_4 and concentrated. The resulting crude mixture was crystallized from cold methanol to afford 9.17 g (87%) of Tris(3,5-di-*tert*-butylphenyl)phosphine.

1-methoxy-1-oxopropan-2-yl 3-methoxybenzoate (**3**). Method A: 181 mg (76%); Method B Hexanes: Ethyl acetate 5:1): 207 mg (87%); R_f (Hexanes:Ethyl acetate 5:1)= 0.24; colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.69 (m, 1H), 7.59 (s, 1H), 7.35 (t, *J*=7.9 Hz, 1H), 7.10-7.13 (m, 1H), 5.33 (q, *J*=7.0 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 1.62 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 165.8, 159.6, 130.7, 129.4, 122.3, 119.8, 114.3, 69.1, 55.4, 52.3, 17.0; HRMS (ESI) calcd for $C_{12}H_{14}O_5Na$ $[M+Na]^+$ 261.0739, found: 261.0735; 99% ee (**3**) Enantioselectivity was determined by HPLC analysis with Chiralpak IC column, 10% ethanol in heptane, 1 mL/min, λ=296.4 nm, retention times: minor: 6.623 min, major: 7.328 min; $[\alpha]_D^{20}$-24.6 (c 0.88, $CHCl_3$).

1-methoxy-1-oxopropan-2-yl 2-methoxybenzoate (**4**). Method A: 209 mg (88%); Method B (Hexanes: Ethyl acetate 5:1): 204 mg (86%); R_f (Hexanes:Ethyl acetate 5:1) = 0.18; colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.91 (m, 1H), 7.45-7.49 (m, 1H), 6.98 (t, *J*=7.6 Hz, 2H), 5.33 (q, *J*=7.0 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 1.59 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 165.0, 159.6, 133.9, 132.0, 120.1, 119.1, 112.1, 68.7, 56.0, 52.3, 17.0; HRMS (ESI) calcd for $C_{12}H_{14}O_5Na$ $[M+Na]^+$ 261.0739, found: 261.0741; 99% ee (**4**) Enantioselectivity was determined by HPLC analysis with Chiralpak IC column, 50% ethanol in heptane, 1 mL/min, λ= 296.4 nm, retention times: minor: 4.958 min, major: 5.755 min; $[\alpha]_D^{20}$-3.3 (c 1.01, $CHCl_3$).

1-methoxy-1-oxopropan-2-yl 4-methoxybenzoate (**5**). Method A: 169 mg (71%); Method B (Hexanes: Ethyl acetate 3:1): 195 mg (82%); R_f (Hexanes:Ethyl acetate 3:1) = 0.40; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J*=8.9 Hz, 2H), 6.92 (d, *J*=8.9 Hz, 2H), 5.30 (q, *J*=7.0 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 1.60 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 165.6, 163.7, 131.9, 121.8, 113.6, 68.8, 55.4, 52.3, 17.1; HRMS (ESI) calcd for $C_{12}H_{14}O_5Na$ $[M+Na]^+$ 261.0739, found: 261.0734; 99% ee (**5**) Enantioselectivity was determined by HPLC analysis with Chiralpak IC column, 50% ethanol in heptane, 1 mL/min, λ= 256.4 nm, retention times: minor: 4.583 min, major: 5.410 min; mp.: 61-62°C (EtOAc); $[\alpha]_D^{20}$-36.4 (c 1.02, $CHCl_3$).

1-methoxy-1-oxopropan-2-yl 4-nitrobenzoate (**6**). Method A: 99 mg (39%); Method B (Hexanes: Ethyl acetate 3:1): 222 mg (88%); R_f (Hexanes:Ethyl acetate 3:1) = 0.52; yellowish liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23-8.29 (m, 4H), 5.37 (q, *J*=7.0 Hz, 1H), 3.78 (s, 3H), 1.65 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 164.0, 150.8, 134.8, 130.9, 123.5, 69.8, 52.5, 17.0; HRMS (EI) calcd for $C_{11}H_{11}NO_6$ $[M]^+$ 253.0586, found: 253.0578; 98% ee (**6**) Enantioselec-

tivity was determined by HPLC analysis with Chiralpak IC column, 50% ethanol in heptane, 1 mL/min, λ= 258.4 nm, retention times: minor: 5.433 min, major: 6.941 min; $[\alpha]_D^{20}$-23.3 (c 1.01, $CHCl_3$).

1-methoxy-1-oxopropan-2-yl 3,4,5-trimethoxybenzoate (**7**). Method A: 250 mg (84%); Method B (Hexanes: Ethyl acetate 3:1): 235 mg (79%); R_f (Hexanes:Ethyl acetate 3:1) = 0.19; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 2H), 5.31 (q, *J*=7.0 Hz, 1H), 3.90 (s, 9H), 3.76 (s, 3H), 1.62 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 165.5, 152.9, 142.7, 124.3, 107.2, 69.2, 60.9, 56.2, 52.3, 17.0; HRMS (ESI) calcd for $C_{14}H_{18}O_7Na$ $[M+Na]^+$ 321.0950, found: 321.0956; 98% ee (**7**) Enantioselectivity was determined by HPLC analysis with Chiralpak IC column, 100% ethanol, 1 mL/min, λ= 268.4 nm, retention times: minor: 4.512 min, major: 5.581 min; mp.: 78-79°C (EtOAc); $[\alpha]_D^{20}$-23.8 (c 1.01, $CHCl_3$).

1-methoxy-1-oxopropan-2-yl furan-2-carboxylate (**8**). Method A: 131 mg (66%); Method B (Hexanes: Ethyl acetate 3:1): 152 mg (77%); R_f (Hexanes:Ethyl acetate 3:1) = 0.28; colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58-7.59 (m, 1H), 7.24-7.26 (m, 1H), 6.50-6.51 (m, 1H), 5.31 (q, *J*=7.0 Hz, 1H), 3.75 (s, 3H), 1.59 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 157.7, 146.7, 143.9, 118.8, 111.9, 68.8, 52.4, 17.0; HRMS (ESI) calcd for $C_9H_{10}O_5Na$ $[M+Na]^+$ 221.0426, found: 221.0422; 99% ee (**8**) Enantioselectivity was determined by HPLC analysis with Chiralpak IC column, 50% ethanol in heptane, 1 mL/min, λ= 252.4 nm, retention times: minor: 4.758 min, major: 6.360 min; $[\alpha]_D^{20}$-28.2 (c 0.83, $CHCl_3$).

Methyl 2-(1,3-dioxoisoindolin-2-yl)propanoate (**9**). Method A: 200 mg (86%); Method B (Hexanes: Ethyl acetate 3:1): 170 mg (73%); R_f (Hexanes:Ethyl acetate 3:1) = 0.37; colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84-7.86 (m, 2H), 7.72-7.73 (m, 2H), 4.96 (q, *J*=7.3 Hz, 1H), 3.73 (s, 3H), 1.69 (d, *J*=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 167.3, 134.1, 131.9, 123.4, 52.7, 47.4, 15.2; HRMS (ESI) calcd for $C_{12}H_{11}NO_4Na$ $[M+Na]^+$256.0586, found: 256.0584; 99% ee (**9**) Enantioselectivity was determined by HPLC analysis with Daicel CHIRALCEL OKcolumn, 50% ethanol in heptane, 1 mL/min, λ= 240.4 nm, retention times: major: 9.057 min, minor: 10.176 min; $[\alpha]_D^{20}$+8.2 (c 0.98, $CHCl_3$).

Methyl 2-(4-methoxyphenoxy)propanoate (**10**). Method A: 164 mg (78%); Method B (Hexanes: Ethyl acetate 3:1): 151 mg (72%); R_f (Hexanes:Ethyl acetate 3:1) = 0.36; yellowish liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79-6.84 (m, 4H), 4.67 (q, *J*=6.8 Hz, 1H), 3.74 (s, 6H), 1.58 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 154.5, 151.6, 116.5, 114.6, 73.6, 55.6, 52.1, 18.6; HRMS (ESI) calcd for $C_{11}H_{14}O_4Na$ $[M+Na]^+$ 233.0790, found: 233.0800; 96% ee (**10**) Enantioselectivity was determined by HPLC analysis with Daicel CHIRALCEL OK column, ethanol, 1 mL/min, λ= 240.4 nm, retention times: major: 6.127 min, minor: 7.666 min; $[\alpha]_D^{20}$+29.7 (c 1.02, $CHCl_3$).

Methyl 2-(4-cyanophenoxy)propanoate (**11**). Method A: 141 mg (69%); Method B (Hexanes: Ethyl acetate 3:1) : 164 mg (80%); R_f (Hexanes:Ethyl acetate 3:1) = 0.26; yellowish liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J*=9.0 Hz, 2H), 6.91 (d, *J*=9.0 Hz, 2H), 4.81 (q, *J*=6.8 Hz, 1H), 3.77 (s, 3H), 1.65 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

171.5, 160.7, 134.0, 118.9, 115.5, 104.8, 72.4, 52.5, 18.3; HRMS (ESI) calc. for $C_{11}H_{12}NO_3$ $[M+H]^+$ 206.0817, found: 206.0811; 96% ee (**11**) Enantioselectivity was determined by HPLC analysis with Daicel CHIRALCEL OK column, ethanol, 1 mL/min, λ= 246.4 nm, retention times: major: 5.451 min, minor: 7.414 min; $[\alpha]_D^{20}$+42.3 (c 1.02, $CHCl_3$).

Benzyl furan-2-carboxylate[15] (**12**). Method A: 129 mg (64%); Method B (Hexanes: Ethyl acetate 5:1): 168 mg (83%); R_f (Hexanes:Ethyl acetate 5:1) = 0.40; colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J*=0.7 Hz, 1H), 7.43-7.44 (m, 2H), 7.32-7.39 (m, 3H), 7.20 (dd, *J*=3.4, 0.7 Hz, 1H), 6.49 (dd, J=3.4, 1.7Hz, 1H), 5.35 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 146.4, 144.6, 135.6, 128.6, 128.3, 128.3, 118.1, 111.8, 66.5; HRMS (ESI) calcd for $C_{12}H_{10}O_3Na$ $[M+Na]^+$ 225.0528, found: 225.0529.

4-methoxybenzyl furan-2-carboxylate (**13**). Method A: 181 mg (78%); Method B (Hexanes: Ethyl acetate 5:1): 195 mg (84%); R_f (Hexanes:Ethyl acetate 5:1) = 0.29; yellowish liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.37 (d, *J*=8.4 Hz, 2H), 7.17-7.18 (m, 1H), 6.90 (d, *J*=8.5 Hz, 2H), 6.48-6.49 (m, 1H), 5.28 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 158.6, 146.3, 144.7, 130.3, 127.8, 118.0, 114.0, 111.8, 66.4, 55.3; HRMS (ESI) calcd for $C_{13}H_{12}O_4Na$ $[M+Na]^+$ 255.0633, found: 255.0635.

Allyl furan-2-carboxylate[16] (**14**). Method A: 140 mg (92%); Method B (Hexanes: Ethyl acetate 5:1): 123 mg (81%); R_f (Hexanes:Ethyl acetate 5:1) = 0.48; yellowish liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.18 (d, *J*=2.9 Hz, 1H), 6.48-6.49 (m, 1H), 5.96-6.01 (m, 1H), 5.38 (dd, *J*=17.2, 1.3 Hz, 1H), 5.26 (dd, *J*=10.4, 1.0 Hz, 1H), 4.78 (d, *J*=5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 146.3, 144.5, 131.8, 118.6, 117.9, 111.7, 65.3; HRMS (ESI) calcd for $C_8H_8O_3Na$ $[M+Na]^+$ 175.0371, found: 175.0371.

Prop-2-yn-1-yl furan-2-carboxylate[16] (**15**). Method A: 139 mg (93%); Method B (Hexanes: Ethyl acetate 3:1): 111 mg (74%); R_f (Hexanes:Ethyl acetate 3:1) = 0.42; yellowish liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57-7.58 (m, 1H), 7.21 (d, *J*=3.5, 1H), 6.50 (dd, *J*=3.4, 1.7 Hz, 1H), 4.87 (d, *J*=2.4Hz, 2H), 2.51 (t, *J*=2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 146.7, 143.9, 118.8, 111.9, 77.3, 75.3, 52.2; HRMS (ESI) calcd for $C_8H_6O_3Na$ $[M+Na]^+$ 173.0215, found: 173.0214.

4-chlorobenzyl furan-2-carboxylate[17] (**16**). Method A: 59 mg (25%); Method B (Hexanes: Ethyl acetate 3:1): 168 mg (71%); R_f (Hexanes:Ethyl acetate 3:1) = 0.43; yellowish liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58-7.59 (m, 1H), 7.34-7.38 (m, 4H), 7.20-7.21 (m, 1H), 6.50-6.51 (m, 1H), 5.30 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 146.5, 144.4, 134.3, 134.1, 129.7, 128.8, 118.3, 111.9, 65.7; HRMS (ESI) calcd for $C_{12}H_9ClO_3Na$ $[M+Na]^+$ 259.0138, found: 259.0138.

Allyl benzoate[18] (**17**). Method A: 120 mg (74%); Method B (Hexanes: Ethyl acetate 5:1): 131 mg (81%); R_f (Hexanes:Ethyl acetate 5:1) = 0.53; colorless liquid;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J*=7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 6.01-6.09 (m, 1H), 5.42 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.29 (dd, *J* = 10.5, 1.2 Hz, 1H), 4.83 (d, *J*=5.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 132.9, 132.2, 130.2, 129.6, 128.3, 118.1, 65.5

Allyl 3,4,5-trimethoxybenzoate[19] (**18**). Method A: 121 mg (48%); Method B (Hexanes: Ethyl acetate 5:1): 214 mg (85%); R_f (Hexanes:Ethyl acetate 5:1) = 0.37; white solid;^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 2H), 6.04 (ddd, *J*=16.1, 10.9, 5.7 Hz, 1H), 5.41 (dd, *J*=17.2, 1.4 Hz, 1H), 5.28 (dd, *J*=10.4, 1.1 Hz, 1H), 4.81 (d, *J*=5.7 Hz, 2H), 3.90 (s, 9H);^{13}C NMR (125 MHz, $CDCl_3$) δ165.8, 152.9, 142.3, 132.3, 125.1, 118.2, 106.9, 65.7, 60.9, 56.2.

Phenethyl 3,4,5-trimethoxybenzoate[20] (**19**). Method A: 240 mg (76%); Method B (Hexanes: Ethyl acetate 3:1): 291 mg (92%); R_f (Hexanes:Ethyl acetate 3:1) = 0.37; colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.33 (m, 7H), 4.52 (t, *J*=6.9Hz, 2H), 3.90 (s, 3H), 3.88 (s, 6H), 3.07 (t, *J*=6.9Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 152.9, 142.2, 137.9, 129.0, 128.5, 126.6, 125.3, 106.8, 65.4, 60.8, 56.2, 35.3.

ASSOCIATED CONTENT

Supporting Information

Supporting Information: Copies of NMR spectra and HPLC chromatograms

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Notes

The authors declare no competing financial interest.

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