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[5.5]-*P*-Spirocyclic Chiral Triaminoiminophosphorane-Catalyzed Asymmetric Hydrophosphonylation of Aldehydes and Ynones

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Abstract

Development of highly efficient and enantioselective hydrophosphonylations of aldehydes and ynones mediated by [5.5]-*P*-spirocyclic chiral triaminoiminophosphoranes as base catalysts is described. The strong basicity of the iminophosphoranes and hydrogen-bond donating ability of their conjugate acids, tetraaminophosphonium ions, are critical for the facile generation of aminophosphonium phosphites with substantial nucleophilicity as well as for the subsequent selective, yet productive, P-C bond formation by suppressing undesired side reactions. The scope and limitations of these catalytic asymmetric methodologies are also reported.

1. Introduction

Among various enantioselective phosphorus-carbon (P-C) bond formations, hydrophosphonylation of carbonyl compounds (Pudovik reaction) has garnered particular attention from the chemical science community, because it provides a straightforward access to a wide variety of optically active α-hydroxy phosphonates, a biologically important class of compounds that has structural similarity to α-hydroxy carboxylic acids and exhibits unique activity.[1–3] While dialkyl phosphonate (dialkyl phosphite) is commonly employed as a phosphorus nucleophile for coupling with carbonyl electrophiles, effecting facile P-C bond formation is rather difficult due to the intervention of the phosphonate-phosphite tautomerization.[4,5] Specifically, dialkyl phosphonates exist largely, if not entirely, in the phosphonate form under neutral conditions and the contribution of the phosphite form to the equilibrium is extremely low ($\sim 10^{-4}$%), even though it is considered to be a nucleophilic tautomer. Therefore, the efficiency of the nucleophilic addition of dialkyl phosphonates to carbonyl compounds depends on this unfavorable equilibrium, suggesting that activation of dialkyl phosphonates would be crucial for attaining sufficient reactivity. In fact, Wynberg used a basic organic molecule, quinine, as a sole catalyst capable of activating dialkyl phosphonates for promoting asymmetric hydrophosphonylation for the first time in 1983, though it was only applicable to a highly reactive aromatic aldehyde, 2-nitro benzaldehyde.[6] A decade lapsed before asymmetric hydrophosphonylation was revisited in the arena of Lewis acid chemistry, leading to the identification of several effective catalysts, but with limited success.[7,8] In 1996, Shibasaki developed the first highly enantioselective and general protocol based on the use of an aluminum-based chiral heterobimetallic complex and later introduced a complementarily effective, lanthanide-derived heterobimetallic catalyst for expanding the aldehyde scope.[8c,8e] In most of the reported Lewis acid-catalyzed systems, the Lewis acidic metal center is engaged in the activation of a carbonyl electrophile and phosphonate is simultaneously activated through the formation of a metallophosphite. However, the generally observed moderate catalytic efficiency implies that the expected generation of the metallophosphite is sluggish. The benefit of accelerating the metallophosphite generation for enhancing the reaction rate was indeed substantiated by the addition of external inorganic base, and Katsuki significantly improved the catalytic activity of an aluminum-salalen complex by combined use of K_2CO_3.[7h] Simultaneous activation of carbonyl functionality and the phosphonate by a bifunctional chiral catalyst was also found to be efficacious for facilitating

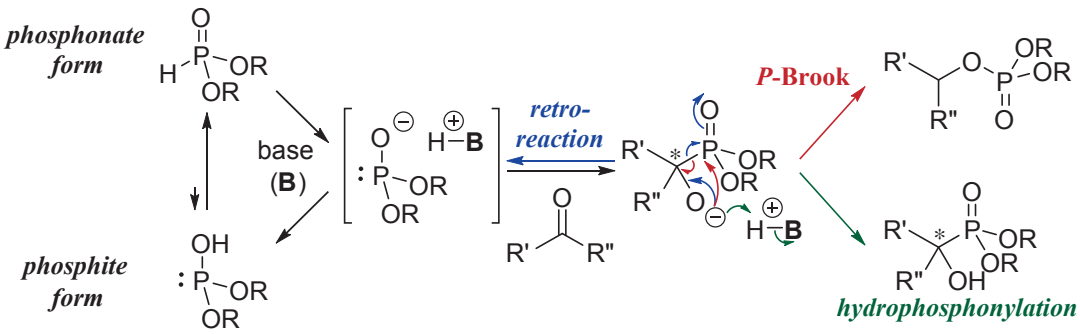
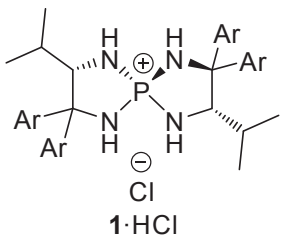


Figure 1. Hydrophosphonylation of carbonyl compounds.

smooth P-C bond formation while controlling the absolute stereochemistry.[9–11] Although these contributions clearly indicate the importance of increasing the concentration of the phosphite tautomer in the hydrophosphonylation, simple activation of dialkyl phosphonates via deprotonation with a basic catalyst remains an inaccessible tactic due to the lack of suitable chiral, non-racemic molecular entities that exert adequately strong basicity, thus leaving the intrinsic reactivity of the phosphite form obscure.[12]

Upon considering not only the generation of a reactive phosphorus nucleophile, but also the inherent features of the subsequent P-C bond-forming process under basic conditions, it appears to be associated with the side reactions; those are retro-hydrophosphonylation (blue arrows) and phospha-Brook rearrangement (red arrows) (Figure 1).[13] These reactions are particularly problematic in the addition of phosphites to ketone carbonyls, presumably because of the following reasons: 1) steric repulsion between ketone substituents (R′, R″) and the $P(O)(OR)_2$ moiety in the transiently generated alkoxide intermediate, and 2) the geminal dialkyl effect (Thorpe–Ingold effect) on the propensity for the rearrangement via three-membered ring formation.[14,15] Since the P-C bond formation is reversible, the presence of an alkoxide ion at the α-position to a phosphoryl group assists the cleavage of the P-C bond, which points out that rapid protonation of the alkoxide ion in the base-catalyzed hydrophosphonylation is essential to suppress the undesired retro-reaction. Protonation is also beneficial for avoiding the intramolecular nucleophilic attack of the oxyanion to the phosphorus center to cause the subsequent rearrangement. This important requirement for regulating the reaction pathway could be fulfilled if the conjugate acid of the basic promoter has high proton-transfer ability.

Currently, triaminoiminophosphorane, introduced by Schwesinger as a P1-phosphazene, is recognized as one of the strongest organic bases.[16,17] In 2007, we disclosed the molecular design and preparation of [5.5]-*P*-spirocyclic chiral triaminoiminophosphorane **1** consisting of four primary amino moieties and uncovered its significant potential as a chiral organic base catalyst through the development of the **1**-catalyzed highly stereoselective Henry reaction (Figure 2).[18] The key to the prominent catalytic performance of **1** was not only its strong basicity, but also the double hydrogen-bond donating ability of its conjugate acid, tetraaminophosphonium ion **1**·H, to recognize and control nucleophilic anionic species.[19,20] We hypothesized that chiral iminophosphoranes **1** featuring these



1a: Ar = Ph
1b: Ar = 4-$CF_3C_6H_4$
1c: Ar = 4-ClC_6H_4
1d: Ar = 4-FC_6H_4
1e: Ar = 4-MeC_6H_4
1f: Ar = 4-$MeOC_6H_4$

1·HCl

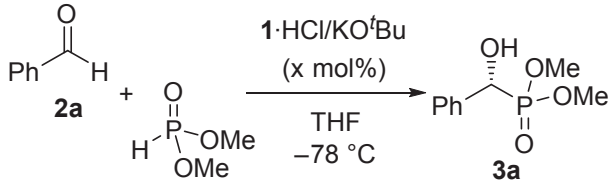
Figure 2. [5.5]-*P*-Spirocyclic chiral tetraaminophosphonium chlorides **1**·HCl.

characteristics would be suitable for the activation of dialkyl phosphonate by deprotonation to generate chiral aminophosphonium phosphite. This activation allows us to shift the phosphonate-phosphite equilibrium and evaluate the intrinsic reactivity of the phosphite ion, leading to highly efficient asymmetric hydrophosphonylation. In addition, the pK_a value of the intermediary α-phosphonyl alkoxide is expected to be higher than that of the N-H proton of **1**·H and thus pseudo-intramolecular proton transfer would effectively suppress the undesired pathways to liberate the desired product. Herein, we report the remarkable catalytic activity and stereocontrolling ability of **1** in the hydrophosphonylation of aldehydes and ynones via the generation of chiral tetraaminophosphonium phosphite.[21] The effect of chirality at the α-position of aliphatic aldehydes on the stereochemical outcome is also discussed for experimentally understanding the transition state of the present catalysis.

2. Results and Discussion

With the strong basicity of L-valine-derived triaminoiminophosphorane **1a** ($pK_a = 25.0$ in MeCN) in mind, we anticipated that **1a** could deprotonate from dimethyl phosphonate ($pK_a = 18.4$ in DMSO) to form the corresponding chiral aminophosphonium phosphite **1a**·$HOP(OMe)_2$.[22] The validity of this assumption was verified by ^{31}P NMR analysis of a mixture of **1a** and $HP(O)(OMe)_2$ at −98 °C, where an equilibrium between the ion pair **1a**·$HOP(OMe)_2$ and the two parent species was observed.[21a] This information prompted us to apply **1a**, which was generated in situ from **1a**·HCl and KO^{t}Bu at −40 °C, to the addition of dimethyl phosphonate to benzaldehyde (**2a**) at −78 °C (Table 1, Entry 1). As expected, the P-C bond formation occurred smoothly to produce α-hydroxy phosphonate **3a** almost quantitatively within 1 h. Enantiomeric excess of **3a** was

Table 1. Optimization of reaction conditions for hydrophosphonylation of aldehydes[a)]



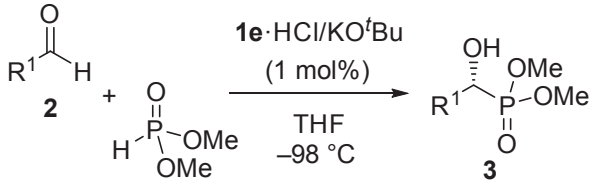
Entry	**1**	*x*	Time (h)	Yield (%)[b)]	*ee* (%)[c)]
1	**1a**	5	1	97	85
2	**1b**	5	4	98	78
3	**1c**	5	2.5	93	74
4	**1d**	5	1.5	90	76
5	**1e**	5	0.5	92	92
6	**1f**	5	0.25	99	78
7	**1e**	1	1	99	91
8[d)]	**1e**	1	4	97	98

a) Unless otherwise noted, the reaction was performed with 1.0 mmol of **2a**, 1.05 equiv of dimethyl phosphonate, *x*.*x* mol% of **1**·HCl, and *x* mol% of KO^{t}Bu in THF (5.0 mL) at −78 °C. b) Isolated yield. c) Enantiomeric excesses were analyzed by HPLC with chiral stationary phase column. Absolute stereochemistry of **3a** was assigned by comparison with literature data.[8c] d) The reaction was conducted at −98 °C.

determined to be 85% by HPLC with chiral stationary phase column and its absolute configuration was determined to be *R* by comparison of the sign of its optical rotation with the literature data.[8c,23] The correlation between the structure of **1** and its catalytic activity was reflected in the reaction rate, and the general tendency was that the more basic iminophosphorane catalyzed the reaction with higher efficiency (Entries 1–6). Interestingly, introduction of an electron-withdrawing group to the 4-position of the geminal aromatic substituents of **1** caused a slight decrease in enantioselectivity. In consideration of the enantiocontrolling ability, iminophosphorane **1e** bearing 4-tolyl groups was selected as an optimal catalyst for further investigations (Entry 5). Importantly, the significantly high catalytic performance allowed us to reduce the catalyst loading to 1 mol% and lower the reaction temperature to −98 °C (Entries 7 and 8). Even under these conditions, essentially enantiopure **3a** was obtained in near quantitative yield, again emphasizing the prominent activity of **1e** as an organic base catalyst.

The scope and limitations of the **1e**-catalyzed asymmetric hydrophosphonylation of aldehydes were then evaluated, and the results are summarized in Table 2. Both electron-rich and electron-deficient 4-substituted benzaldehydes **2b**–**2e** were tolerated, and the corresponding α-hydroxy phosphonates **3b**–**3e** were obtained almost quantitatively with excellent enantioselectivity, although the reactivity was variable depending on the substituent (Entries 1–4). Incorporation of a strongly electron-withdrawing methoxycarbonyl group at the 4-position (**2f**) did not affect the reaction outcome (Entry 5). With 3-substituted benzaldehydes of different electronic attributes, the P-C bond formation proceeded with similar levels of efficiency and stereoselectivity (Entries 6–8). The catalysis of **1e** was insensitive to the steric demand of aromatic aldehydes as it was applicable to 2-substituted benzaldehydes **2j** and **2k** without

Table 2. Substrate scope of hydrophosphonylation of aldehydes[a)]



Entry	R^1 (**2**)	Time (h)	Yield (%)[b)]	*ee* (%)[c)]	**3**
1	4-MeOC$_6$H$_4$ (**2b**)	8	99	94	**3b**
2	4-MeC$_6$H$_4$ (**2c**)	3	91	96	**3c**
3	4-FC$_6$H$_4$ (**2d**)	4	97	97	**3d**
4	4-ClC$_6$H$_4$ (**2e**)	5.5	99	95	**3e**
5	4-MeOCOC$_6$H$_4$ (**2f**)	6	95	97	**3f**
6	3-MeOC$_6$H$_4$ (**2g**)	7	99	95	**3g**
7	3-BrC$_6$H$_4$ (**2h**)	6.5	98	98	**3h**
8	3-CF$_3$C$_6$H$_4$ (**2i**)	9	94	98	**3i**
9	2-MeC$_6$H$_4$ (**2j**)	4	98	96	**3j**
10	2-FC$_6$H$_4$ (**2k**)	3	97	98	**3k**
11	1-naphthyl (**2l**)	3	96	99	**3l**
12[d)]	2-furyl (**2m**)	2	90	98	**3m**
13[e)]	2-thienyl (**2n**)	24	81	96	**3n**
14	(*E*)-PhCH=CH (**2o**)	13	90	96	**3o**
15[e)]	(*E*)-Me(CH$_2$)$_2$CH=CH (**2p**)	16	98	89	**3p**
16	Ph(CH$_2$)$_2$ (**2q**)	6	99	91	**3q**
17[e)]	Me(CH$_2$)$_8$ (**2r**)	16	99	85[f)]	**3r**
18[e)]	cyclohexyl (**2s**)	9.5	99	78[f)]	**3s**

a) Unless otherwise noted, the reaction was performed with 1.0 mmol of **2**, 1.05 equiv of dimethyl phosphonate, 1.1 mol% of **1e**·HCl, and 1 mol% of KO^{t}Bu in THF (5.0 mL) at −98 °C. b) Isolated yield. c) Enantiomeric excesses were analyzed by HPLC with chiral stationary phase column. Absolute stereochemistry of **3** was assigned or assumed by comparison with literature data.[7,8] d) The reaction was conducted at −78 °C. e) 5.5 mol% of **1e**·HCl and 5 mol% of KO^{t}Bu were used. f) Enantiomeric excess was determined after benzoylation.

any detrimental effect on the reactivity and selectivity profiles (Entries 9 and 10). Similarly, 1-naphthaldehyde (**2l**) underwent smooth hydrophosphonylation with rigorous stereocontrol (Entry 11). Heteroaromatic aldehydes **2m** and **2n** also appeared to be good candidates as electrophilic partners, albeit a slight decrease in reactivity was observed (Entries 12 and 13). Notably, catalytically generated chiral aminophosphonium phosphite, a key reactive species, reacted with α,β-unsaturated aldehydes such as **2o** and **2p** preferentially in a 1,2-fashion to give enantiomerically enriched α-hydroxy allylic phosphonates **3o** and **3p**, respectively, without any detectable formation of the 1,4-adducts (Entries 14 and 15). While linear aliphatic aldehydes were accommodated with a comparable degree of reactivity and selectivity, α-branched aliphatic aldehydes were found to be challenging substrates and a considerable decrease in the enantioselectivity seemed inevitable (Entries 16–18).

The observed erosion of stereoselectivity in the hydrophosphonylation of α-branched aliphatic aldehydes led us to examine the reaction with α-chiral aldehyde **2t** to figure out the effect of the α-stereocenter on the facial discrimination of the aldehyde carbonyl by the catalyst (Figure 3). When **2t** was treat-

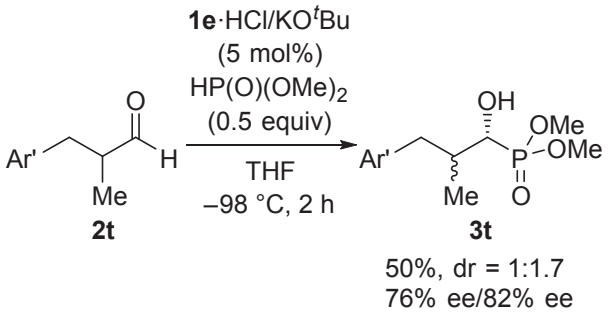


Figure 3. Effect of chirality at α-position of aldehyde on stereoselectivity of hydrophosphonylation catalyzed by chiral iminophosphorane **1e** (Ar′ = 4-^{t}BuC$_6$H$_4$).

ed with 0.5 equiv of dimethyl phosphonate under the influence of 5 mol% of in situ-generated **1e** at −98 °C, a diastereomeric mixture of α-hydroxy phosphonate **3t** was obtained in 50% yield (Figure 3). Enantiomeric excess of each diastereomer was determined to be 76% and 82%, respectively. Although a certain difference in enantioselectivity between the two diastereomers and a detectable degree of kinetic resolution were observed, this result suggested that essentially the catalyst-controlled hydrophosphonylation took place.

In order to understand the origin of poor kinetic resolution in the **1e**-catalyzed addition of dimethyl phosphonate to α-chiral aldehyde **2t**, we conducted a density functional theory (DFT) calculation using a model structure of **2t**, where a 4-*tert*-butylphenyl group was replaced with a simple phenyl group.[24] According to the elegant computational studies reported by Simón and Paton (using benzaldehyde as an electrophile),[25] transition states (TS) of P-C bond formation, giving rise to *anti*- and *syn*-adducts (**TS-*SR*** and **TS-*RR***), were located at B3LYP/6-31G** (Figure 4).[26] Thermodynamic parameters (175.15 K and 1 atm) estimated at the same level and single point energies at SMD(THF)-ωB97XD/6-31++G(d,p) were used to calculate Gibbs free energies. The Gibbs free energy difference of these TSs was 0.2 kcal·mol^{-1}, which consistently reproduced the experimental finding that almost no kinetic resolution was observed in the reaction with **2t**. As shown in Figure 4, **1e**·H donates two N-H protons to interact with oxygen atoms of the phosphite and carbonyl groups concomitantly, and the nucleophilic phosphorus approaches the carbonyl carbon from the open side, as indicated by the Felkin–Anh model. The α-stereocenter of the aldehyde was directed away from the chiral space created by **1e**·H in both diastereomeric TSs; therefore, its direct influence on the chiral environment was unlikely. Since the phenyl group of α-chiral aldehyde could be oriented *anti* with respect to the C$_\alpha$-CHO bond, the steric demand of the benzyl moiety in the carbonyl addition would be very similar to that of the methyl group. Consequently, **1e** could not distinguish the benzyl and methyl groups on **2t**, resulting in the lack of kinetic resolution.

Having seen the uniquely high catalytic activity of iminophosphorane **1**, we were intrigued with its application to hydrophosphonylation of ketones. Because ketones are far less reactive than aldehydes and existing catalytic systems are not effective enough to promote P-C bond formation, the hydrophosphonylation of ketones could offer a vital platform to

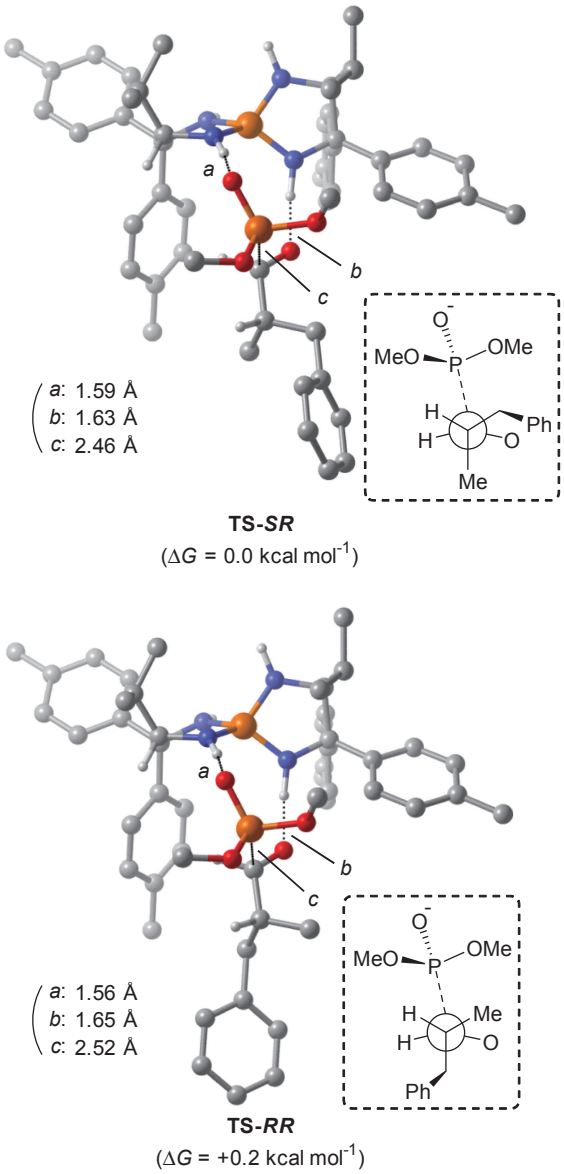


Figure 4. Optimized TS structures, **TS-*SR*** and **TS-*RR***, of the P-C bond formation (unimportant hydrogen atoms are omitted from the structures for clarity).

demonstrate the power of the present iminophosphorane catalysis.[14,15] Although the possible side reactions (retro-reaction and phospha-Brook rearrangement) would likely become more critical, we expected that the N-H moieties of the conjugate acid of **1** would be capable of rapidly protonating the intermediary alkoxide, thereby minimizing the intervention of those undesired pathways.

As an initial attempt, acetophenone was selected as a representative substrate and reacted with dimethyl phosphonate (1.05 equiv) in the presence of 5 mol% of **1a**·HCl/KO^{t}Bu in THF at −78 °C. The hydrophosphonylation did proceed and the desired adduct was isolated in 59% yield after 34 h of stirring (Figure 5). However, its enantiomeric excess was unfortunately very low. Since an additional trial with 1′-acetonaphthone resulted in only a slight improvement of the reaction outcome, we turned our attention from aromatic ketones to ynones with

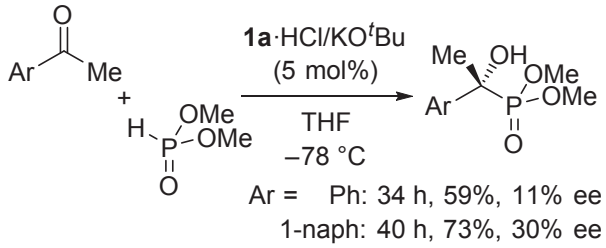
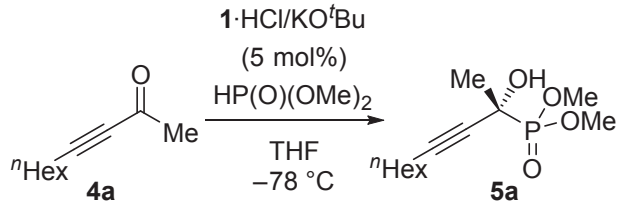


Figure 5. Attempt of hydrophosphonylation of aromatic ketones under the catalysis of iminophosphorane **1a**.

Table 3. Optimization of catalyst structure for hydrophosphonylation of ynones[a)]

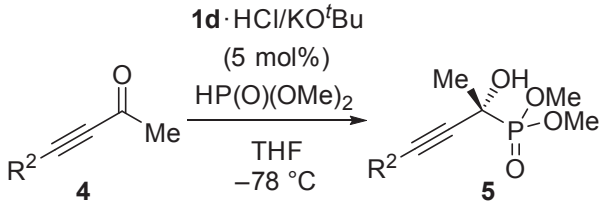


Entry	**1**	Time (h)	Yield (%)[b)]	*ee* (%)[c)]
1	**1a**	24	99	83
2	**1b**	68	53	76
3	**1c**	24	87	83
4	**1d**	19	99	88
5	**1e**	21	99	71
6	**1f**	21	94	81

a) The reaction was performed with 0.2 mmol of **4a**, 0.4 mmol of dimethyl phosphonate, 5.5 mol% of **1**·HCl, and 5 mol% of KO^{t}Bu in THF (2.0 mL) at −78 °C. b) Isolated yield. c) Enantiomeric excesses were analyzed by HPLC with chiral stationary phase column. Absolute stereochemistry was assigned as analogy of **5i** (see Table 4, Entry 8).

anticipation that their keto-carbonyls would be more reactive because of the electronegativity of the *sp*-hybridized carbon atom and less bulkiness of the alkyne component. In addition, we considered the synthetic utility of the products, optically active propargylic alcohols, which are versatile building blocks for the asymmetric synthesis of various biologically important molecules owing to the rich chemistry of carbon-carbon triple bonds that can be derivatized into numerous other functional groups.[27,28] As expected, dec-3-yn-2-one (**4a**) was converted into the corresponding α-tetrasubstituted α-hydroxy propargylic phosphate **5a** quantitatively within 24 h under similar reaction conditions to those of the reactions with aromatic ketones except for using 2 equiv of dimethyl phosphonate (Table 3, Entry 1).[29] The enantiomeric excess of **5a** was determined to be 83%; this result encouraged us to investigate the relationship between the steric/electronic properties of **1**, particularly with respect to the geminal aromatic substituents, and enantioselectivity. Introduction of the strongly electron-withdrawing and relatively bulky trifluoromethyl group to the 4-position of the aromatic appendages (**1b**) diminished the catalytic activity with a slight deterioration of enantioselectivity (Entry 2). While the attachment of electron-releasing groups (**1e** and **1f**) caused a negative impact, the installation of 4-halogenated aromatic groups was revealed to be beneficial, and **1d** with 4-fluorophenyl substituents was identified as an optimal catalyst (Entries 3–6).

Table 4. Substrate scope for hydrophosphonylation of ynones[a)]



Entry	R^2 (**4**)	Time (h)	Yield (%)[b)]	*ee* (%)[c)]	**5**
1	Et (**4b**)	76	73	90	**5b**
2	$Me(CH_2)_8$ (**4c**)	22	98	88	**5c**
3	cyclohexyl (**4d**)	17	96	90	**5d**
4	Me_2CHCH_2 (**4e**)	16	97	79	**5e**
5	$BnOCH_2$ (**4f**)	17	97	81	**5f**
6	^{t}Bu$Me_2SiO(CH_2)_2$ (**4g**)	19	96	87	**5g**
7	$Me_3SiO(Me)_2C$ (**4h**)	19	96	88[d)]	**5h**
8	Me_3Si (**4i**)	17	96	91[e)]	**5i**

a) The reaction was performed with 0.2 mmol of **4**, 0.4 mmol of dimethyl phosphonate, 5.5 mol% of **1d**·HCl, and 5 mol% of KO^{t}Bu in THF (2.0 mL) at −78 °C. b) Isolated yield. c) Enantiomeric excesses were analyzed by HPLC with chiral stationary phase column. Absolute stereochemistry was assigned as analogy of **5i**. d) Enantiomeric excess was determined after desilylation. e) Absolute stereochemistry was determined by X-ray diffraction analysis (CCDC 772834).

Substrate generality was then explored with regard to the terminal substituent of ynone **4** using iminophosphorane **1d** as a catalyst (Table 4). The reactions with ynones possessing linear alkyl groups such as ethyl (**4b**) and *n*-octyl (**4c**) showed a similar profile to that observed with **4a** (Entries 1 and 2). Although **4d** with sterically hindered cyclohexyl substituent was smoothly converted to the corresponding adduct **5d** with high enantioselectivity, β-branching from the alkyne terminus (**4e**) caused a slight decrease in the level of stereocontrol (Entries 3 and 4). The substrates incorporating benzyl and *tert*-butyldimethylsilyl ethers were also amenable to the present system (Entries 5 and 6). Furthermore, the presence of 2-silyloxy-2-propyl and trimethylsilyl groups, which are often used as protective groups of terminal alkynes, were well tolerated (Entries 7 and 8), and thus, products **5h** and **5i** could be readily transformed to the corresponding terminal alkynes, enhancing the synthetic utility of this asymmetric hydrophosphonylation protocol.

3. Conclusion

Establishment of the [5.5]-*P*-spirocyclic chiral iminophosphorane-catalyzed highly efficient and enantioselective hydrophosphonylations of aldehydes and ynones was fully described. These catalytic asymmetric methods relied on the following distinct features of the iminophosphoranes as organic base catalysts: 1) their strong basicity that enabled the facile and substantial generation of reactive chiral aminophosphonium phosphite, and 2) the hydrogen-bond donating ability of their conjugate acids, the aminophosphonium ions, that was crucial

not only for rigorously controlling the absolute stereochemistry in the addition of the phosphite ion to the carbonyls, but also for suppressing the undesired side reactions by rapid protonation of the alkoxide intermediates. This study experimentally proves the inherently high nucleophilicity of phosphite ions, and it provides a tactic for accelerating P-C bond formation with dialkyl phosphonates. We believe that the clear advantages of utilizing strongly basic organic molecules for the activation of dialkyl phosphonates will stimulate further research efforts for the development of chiral catalysts that are effective for improving and inventing various phosphonylation reactions.

4. Experimental

General Information. Infrared spectra were recorded on a JASCO FT/IR-300E or Shimadzu IRAffinity-1 spectrometer. ^{1}H NMR spectra were recorded on a Varian INOVA-500 (500 MHz), JEOL JNM-ECA600II (600 MHz), or JEOL JNM-ECS400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane (0.0 ppm) resonance as the internal standard ($CDCl_3$). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, m = multiplet, br = broad) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian INOVA-500 (126 MHz), JEOL JNM-ECA600II (151 MHz), or JEOL JNM-ECS400 (101 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$; 77.16 ppm). ^{31}P NMR spectra were recorded on a Varian INOVA-500 (202 MHz), Varian Mercury-300BB (121 MHz), or JEOL ECA500II (202 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from H_3PO_4 (0.0 ppm) resonance as the external standard. The high-resolution mass spectra (HRMS) were measured on a BRUKER DALTONICS microTOF focus-KR (ESI-TOF), JEOL JMS-700 (MStation) (FAB), or Thermo Fisher Scientific Exactive (ESI) spectrometer. Optical rotations were measured on a HORIBA SEPA-500 polarimeter. Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was performed on silica gel 60 (spherical, 40–50 μm; Kanto Chemical Co., Inc.). Enantiomeric excesses were determined by HPLC analysis using chiral columns [ϕ 4.6 mm × 250 mm, DAICEL CHIRALPAK AD-H (ADH), CHIRALCEL OD-H (ODH), CHIRALCEL OD-3 (OD3), CHIRALPAK IA (IA), CHIRALPAK AS-H (ASH), CHIRALPAK AS-3 (AS3), CHIRALPAK IF-3 (IF3), or CHIRALCEL OJ-H (OJH)].

All reactions were carried out under an Argon (Ar) atmosphere in dried glassware. All substrates were purified by column chromatography, recrystallization, or distillation prior to use. Tetrahydrofuran (THF) was supplied from Kanto Chemical Co., Inc. as "Dehydrated solvent system". Chiral aminophosphonium salts **1**[18a] and ynones **4**[30] were prepared by following the literature procedure. Other simple chemicals were purchased and used as such.

General Procedure for Chiral Triaminoiminophosphorane-Catalyzed Asymmetric Hydrophosphonylation of Aldehydes. To a dried test tube was weighted phosphonium salt **1**·HCl (0.011 equiv, 11 μmol) under Ar atmosphere and THF (5.0 mL) was introduced. Then, a 1.0 M THF solution of potassium *tert*-butoxide (10.0 μL, 0.010 equiv, 10.0 μmol) was added to the suspension at −78 °C and the resulting mixture was stirred for 30 min at −40 °C. Aldehyde **2** (1.0 equiv, 1.0 mmol) and dimethyl phosphonate (96.3 μL, 1.05 equiv, 1.05 mmol) were introduced dropwise slowly at −98 °C and the stirring was continued for the reaction time given in Tables 1 and 2 of the manuscript. A solution of trifluoroacetic acid in toluene (0.5 M, 100 μL) was added to the reaction mixture and it was poured into ice-cooled water. The aqueous phase was extracted with ethyl acetate (EA). The combined organic extracts were dried over Na_2SO_4 and filtered. All volatiles were removed by evaporation and the purification of the residue by column chromatography on silica gel gave the corresponding α-hydroxy phosphonate **3**, whose enantiomeric excess was determined by chiral stationary phase HPLC analysis. Absolute configurations of **3a** and **3s** were determined to be *R* by comparison of their optical rotations and/or HPLC retention times to the literature data[7e,7h,8c,31] and that of **3b**–**3r** were assigned by analogy.[23] Compounds **3a**–**3e**, **3g**–**3i**, **3l**–**3m**, and **3o**–**3s** were identified by comparison with their reported spectral data.[7,8,21a]

Characterization of α-Hydroxy Phosphonate 3. Methyl 4-((Dimethoxyphosphoryl)(hydroxy)methyl)benzoate (3f): HPLC OD3, hexane (H)/Ethanol (EtOH) = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 15.4 min (minor enantiomer), 18.9 min (major enantiomer); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (2H, d, J = 8.4 Hz), 7.57 (2H, dd, $J_{H\text{-}H}$ = 7.8 Hz, $J_{P\text{-}H}$ = 1.8 Hz), 5.14 (1H, dd, $J_{P\text{-}H}$ = 12.6 Hz, $J_{H\text{-}H}$ = 5.2 Hz), 4.13 (1H, dd, $J_{P\text{-}H}$ = 8.4 Hz, $J_{H\text{-}H}$ = 5.2 Hz), 3.92 (3H, s), 3.72 (3H, d, $J_{P\text{-}H}$ = 10.2 Hz), 3.71 (3H, d, $J_{P\text{-}H}$ = 10.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.9, 141.5, 130.1 (d, $J_{P\text{-}C}$ = 2.9 Hz), 129.8, 127.0 (d, $J_{P\text{-}C}$ = 5.9 Hz), 70.6 (d, $J_{P\text{-}C}$ = 159.0 Hz), 39.3 (d, $J_{P\text{-}C}$ = 7.1 Hz), 53.9 (d, $J_{P\text{-}C}$ = 7.2 Hz), 52.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ 23.2; IR (film): 3227, 2957, 1719, 1611, 1435, 1414, 1283, 1236, 1190, 1113, 1034, 837 cm^{-1}; HRMS (ESI) Calcd for $C_{11}H_{15}Na_1O_6P_1^+$ ([M+Na]$^+$) 297.0498. Found 297.0495; $[\alpha]_D^{23}$ +58.020° (c = 1.00, $CHCl_3$).

Dimethyl (Hydroxy(*o*-tolyl)methyl)phosphonate (3j): HPLC ASH, H/2-propanol (IPA) = 5:1, flow rate = 0.5 mL/min, λ = 210 nm, 18.6 min (major enantiomer), 31.4 min (minor enantiomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (1H, d, J = 7.5 Hz), 7.27 (1H, t, J = 7.5 Hz), 7.23 (1H, tt, J = 7.5, 1.5 Hz), 7.17 (1H, d, J = 7.5 Hz), 5.30 (1H, dd, $J_{P\text{-}H}$ = 10.8 Hz, $J_{H\text{-}H}$ = 4.3 Hz), 3.72 (3H, d, $J_{P\text{-}H}$ = 10.5 Hz), 3.65 (3H, d, $J_{P\text{-}H}$ = 10.5 Hz), 3.17 (1H, br), 2.39 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.9 (d, $J_{P\text{-}C}$ = 7.2 Hz), 134.9 (d, $J_{P\text{-}C}$ = 1.9 Hz), 130.5 (d, $J_{P\text{-}C}$ = 1.1 Hz), 128.3 (d, $J_{P\text{-}C}$ = 3.3 Hz), 127.3 (d, $J_{P\text{-}C}$ = 4.4 Hz), 126.4 (d, $J_{P\text{-}C}$ = 3.3 Hz), 67.2 (d, $J_{P\text{-}C}$ = 160.7 Hz), 54.0 (d, $J_{P\text{-}C}$ = 6.7 Hz), 53.7 (d, $J_{P\text{-}C}$ = 7.7 Hz), 19.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 24.9; IR (film): 3269, 2958, 2854, 1588, 1490, 1457, 1228, 1052, 837, 818, 858 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{10}H_{15}Na_1O_4P_1^+$ ([M+Na]$^+$) 253.0600. Found 253.0609.

Dimethyl ((2-Fluorophenyl)(hydroxy)methyl)phosphonate (3k): HPLC ASH, H/IPA = 3:1, flow rate = 0.5 mL/min, λ = 210 nm, 14.2 min (major enantiomer), 22.1 min (minor enantiomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (1H, t,

$J = 8.0$ Hz), 7.33–7.28 (1H, m), 7.20 (1H, t, $J = 8.0$ Hz), 7.05 (1H, t, $J = 8.0$ Hz), 5.44 (1H, d, $J_{P\text{-}H} = 11.5$ Hz), 4.69 (1H, br), 3.79 (3H, d, $J_{P\text{-}H} = 10.5$ Hz), 3.71 (3H, d, $J_{P\text{-}H} = 10.5$ Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8 (dd, $J_{F\text{-}C} = 247.7$ Hz, $J_{P\text{-}C} = 6.8$ Hz), 129.9 (dd, $J_{F\text{-}C} = 8.3$ Hz, $J_{P\text{-}C} = 3.0$ Hz), 129.0 (t, $J_{P\text{-}C} = 3.6$ Hz, $J_{F\text{-}C} = 3.6$ Hz), 124.5 (t, $J_{P\text{-}C} = 3.1$ Hz, $J_{F\text{-}C} = 3.1$ Hz), 124.4 (dd, $J_{F\text{-}C} = 13.5$ Hz, $J_{P\text{-}C} = 1.5$ Hz), 115.2 (dd, $J_{F\text{-}C} = 21.9$ Hz, $J_{P\text{-}C} = 2.1$ Hz), 63.7 (dd, $J_{P\text{-}C} = 163.8$ Hz, $J_{F\text{-}C} = 3.7$ Hz), 54.3 (d, $J_{P\text{-}C} = 6.7$ Hz), 53.8 (d, $J_{P\text{-}C} = 7.2$ Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 23.8 (d, $J_{F\text{-}P} = 5.9$ Hz); IR (film): 3270, 2955, 2852, 1488, 1463, 1235, 1041, 834 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_9H_{12}F_1Na_1O_4P_1^+$ ([M+Na]$^+$) 257.0349. Found 257.0354.

Dimethyl (Hydroxy(thiophen-2-yl)methyl)phosphonate (3n): HPLC AS3, H/IPA = 5:1, flow rate = 1.0 mL/min, $\lambda = 210$ nm, 10.4 min (major enantiomer), 13.6 min (minor enantiomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (1H, dd, $J_{H\text{-}H} = 4.0$ Hz, $J_{P\text{-}H} = 1.5$ Hz), 7.21 (1H, t, $J_{H\text{-}H} = 3.5$ Hz, $J_{P\text{-}H} = 3.5$ Hz), 7.01 (1H, dd, $J = 4.0$, 3.5 Hz), 5.27 (1H, d, $J_{P\text{-}H} = 10.5$ Hz), 4.41 (1H, br), 3.78 (3H, d, $J_{P\text{-}H} = 11.0$ Hz), 3.74 (3H, d, $J_{P\text{-}H} = 10.0$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5 (d, $J_{P\text{-}C} = 4.8$ Hz), 127.0 (d, $J_{P\text{-}C} = 1.9$ Hz), 126.3 (d, $J_{P\text{-}C} = 7.7$ Hz), 125.9, 66.7 (d, $J_{P\text{-}C} = 169.4$ Hz), 54.2 (d, $J_{P\text{-}C} = 6.8$ Hz), 53.9 (d, $J_{P\text{-}C} = 7.7$ Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.5; IR (film): 3235, 2957, 1449, 1202, 1121, 1038, 845 cm^{-1}; HRMS (ESI) Calcd for $C_7H_{11}Na_1O_4P_1S_1^+$ ([M+Na]$^+$) 245.0008. Found 245.0007; $[\alpha]_D^{22}$ +26.143° (c = 1.03, $CHCl_3$).

Dimethyl (3-(4-(*tert*-Butyl)phenyl)-1-hydroxy-2-methylpropyl)phosphonate (3t): HPLC *minor-isomer* OD3, H/EtOH = 97:3, flow rate = 0.5 mL/min, $\lambda = 210$ nm, 17.6 min (major enantiomer), 23.2 min (minor enantiomer); *major-isomer* IF3, H/EtOH = 97:3, flow rate = 0.5 mL/min, λ = 210 nm, 27.5 min (major enantiomer), 29.7 min (minor enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) *minor-isomer* δ 7.29 (2H, d, $J = 8.8$ Hz), 7.13 (2H, d, $J = 8.8$ Hz), 3.83 (6H, d, $J_{P\text{-}H}$ = 10.4 Hz), 3.80 (1H, td, $J_{P\text{-}H} = 12.1$ Hz, $J_{H\text{-}H} = 12.1$, 6.0 Hz), 3.44 (1H, br), 3.10 (4H, dd, $J = 13.4$, 3.6 Hz), 2.45 (1H, dd, $J = 13.4$, 9.2 Hz), 2.30–2.12 (1H, m), 1.30 (9H, s), 0.98 (3H, d, $J = 6.8$ Hz); *major-isomer* δ 7.30 (2H, d, $J = 8.0$ Hz), 7.11 (2H, d, $J = 8.0$ Hz), 3.89 (1H, ddd, $J_{P\text{-}H} = 8.4$ Hz, $J_{H\text{-}H} = 7.4$, 3.2 Hz), 3.77_3 (3H, d, $J = 10.4$ Hz), 3.77_0 (3H, d, $J = 10.4$ Hz), 2.90 (1H, br), 2.79 (1H, dd, $J = 13.4$, 7.4 Hz), 2.57 (1H, ddd, $J = 13.4$, 7.4, 2.8 Hz), 2.22 (1H, sept-d, $J = 7.4$, 3.2 Hz), 1.30 (9H, s), 1.08 (3H, d, $J = 7.4$ Hz); ^{13}C NMR (151 MHz, $CDCl_3$) *minor-isomer* δ 148.9, 137.1, 129.2, 125.2, 7.20 (d, $J_{P\text{-}C}$ = 156.1 Hz), 53.3 (d, $J_{P\text{-}C} = 7.2$ Hz), 53.2 (d, $J_{P\text{-}C} = 7.2$ Hz), 37.8 (d, $J_{P\text{-}C} = 8.6$ Hz), 37.5, 34.5, 31.6, 16.0 (d, $J_{P\text{-}C} = 7.2$ Hz); *major-isomer* δ 149.1, 137.1, 129.0, 125.4, 69.7 (d, $J_{P\text{-}C}$ = 157.6 Hz), 53.2 (d, $J_{P\text{-}C} = 7.2$ Hz), 39.7 (d, $J_{P\text{-}C} = 14.5$ Hz), 36.7, 34.5, 31.5, 14.4, one carbon atom was not found probably due to overlapping; ^{31}P NMR (202 MHz, $CDCl_3$) *monor-isomer* δ 28.1; *major-isomer* δ 28.0; IR (film): 3294, 2957, 2866, 1512, 1460, 1364, 1219, 1034, 829 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{27}Na_1O_4P_1^+$ ([M+Na]$^+$) 337.1539. Found 337.1531.

General Procedure for Chiral Triaminoiminophosphorane-Catalyzed Asymmetric Hydrophosphonylation of Ynones. To a suspension of phosphonium salt **1**·HCl (0.055 equiv, 11 µmol) in THF (2.0 mL) was added a 1.0 M THF solution of potassium *tert*-butoxide (10.0 µL, 0.050 equiv, 10 µmol) at −78 °C under Ar atmosphere. The resulting mixture was stirred for 30 min at −40 °C. Ynone **4** (1.0 equiv, 0.2 mmol) and dimethyl phosphonate (36.7 µL, 2.0 equiv, 0.4 mmol) were introduced dropwise slowly at −78 °C and the stirring was continued for the reaction time given in Tables 3 and 4 of the manuscript. After addition of a solution of trifluoroacetic acid in toluene (0.5 M, 100 µL), the reaction mixture was poured into ice-cooled water. The aqueous phase was extracted with EA three times and the combined organic extracts were dried over Na_2SO_4. Filtration and concentration were performed to afford the crude residue. The residue was purified by column chromatography on silica gel to give the α-tetrasubstituted α-hydroxy phosphonate **5**, whose enantiomeric excess was determined by HPLC analysis. Absolute configuration of **5i** was determined by X-ray crystallographic analysis (CCDC 772834) and that of other **5** was estimated as analogy.

Characterization of Ynone 4. Tridec-3-yn-2-one (4c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (2H, t, $J = 7.3$ Hz), 2.32 (3H, s), 1.57 (2H, quin, $J = 7.3$ Hz), 1.39 (2H, quin, $J = 7.3$ Hz), 1.27 (10H, br), 0.88 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.2, 94.4, 81.5, 32.9, 32.0, 29.5, 29.4, 29.2, 29.0, 27.8, 22.8, 19.1, 14.3; IR (film) 2925, 2855, 2209, 1679, 1466, 1421, 1358, 1227, 960, 722 cm^{-1}; HRMS (FAB) Calcd for $C_{13}H_{23}O_1^+$ ([M+H]$^+$) 195.1749. Found 195.1752.

6-((*tert*-Butyldimethylsilyl)oxy)hex-3-yn-2-one (4g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (2H, t, $J = 6.9$ Hz), 2.58 (2H, t, $J = 6.9$ Hz), 2.32 (3H, s), 0.90 (9H, s), 0.09 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9, 91.1, 82.2, 60.9, 32.9, 26.0, 23.5, 18.4, −5.2; IR (film) 2929, 2857, 2213, 1681, 1471, 1360, 1227, 1110, 838, 778 cm^{-1}; HRMS (FAB) Calcd for $C_{12}H_{23}O_2Si_1^+$ ([M+H]$^+$) 227.1467. Found 227.1477.

5-Methyl-5-((trimethylsilyl)oxy)hex-3-yn-2-one (4h): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 1.53 (6H, s), 0.21 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.4, 96.0, 82.6, 66.5, 32.6, 32.3, 1.9; IR (film) 2987, 2213, 1683, 1418, 1361, 1250, 1167, 1038, 843, 756 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{10}H_{18}Na_1O_2Si_1^+$ ([M+Na]$^+$) 221.0974. Found 221.0982.

Characterization of α-Tetrasubstituted α-Hydroxy Phosphonate 5. Dimethyl (1-Hydroxynon-2-yn-1-yl)phosphonate (5a): HPLC ODH, H/IPA = 100:1, flow rate = 0.5 mL/min, $\lambda = 210$ nm, 30.2 min (major enantiomer), 33.2 min (minor enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, d, $J_{P\text{-}H} = 10.1$ Hz), 3.88 (3H, d, $J_{P\text{-}H} = 10.5$ Hz), 3.50 (1H, br), 2.24 (1H, t, $J = 7.3$ Hz), 2.23 (1H, t, $J = 7.3$ Hz), 1.66 (3H, d, $J_{P\text{-}H} = 15.6$ Hz), 1.52 (2H, quin, $J = 7.3$ Hz), 1.41–1.34 (2H, m), 1.33–1.24 (4H, m), 0.89 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 88.2 (d, $J_{P\text{-}C} = 8.7$ Hz), 78.5, 65.9 (d, $J_{P\text{-}C} = 176.1$ Hz), 54.7_3 (d, $J_{P\text{-}C} = 6.8$ Hz), 54.6_6 (d, $J_{P\text{-}C}$ = 6.8 Hz), 31.4, 28.6, 28.4 (d, $J_{P\text{-}C} = 2.9$ Hz), 25.4, 22.6, 19.0 (d, $J_{P\text{-}C} = 1.9$ Hz), 14.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3; IR (film): 3284, 2932, 2857, 2242, 1455, 1365, 1238, 1185, 1034, 834 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{12}H_{23}Na_1O_4P_1^+$ ([M+Na]$^+$) 285.1226. Found 285.1240; $[\alpha]_D^{25}$ +25.0° (c = 0.58, MeOH).

Dimethyl (1-Hydroxypent-2-yn-1-yl)phosphonate (5b): HPLC OJH, H/IPA = 50:1, flow rate = 0.5 mL/min, $\lambda = 210$ nm, 20.2 min (major enantiomer), 23.2 min (minor enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (6H, d, $J_{P\text{-}H} = 10.1$ Hz),

3.23 (1H, br), 2.27 (2H, qd, $J_{H\text{-}H} = 7.5$ Hz, $J_{P\text{-}H} = 4.0$ Hz) 1.65 (3H, d, $J_{P\text{-}H} = 15.6$ Hz), 1.15 (3H, t, $J = 7.5$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 89.6 (d, $J_{P\text{-}C} = 8.7$ Hz), 77.8, 65.9 (d, $J_{P\text{-}C} = 176.1$ Hz), 54.8 (d, $J_{P\text{-}C} = 7.7$ Hz), 54.7 (d, $J_{P\text{-}C} = 6.8$ Hz), 25.3, 13.6, 12.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3; IR (film) 3290, 2958, 2243, 1645, 1456, 1366, 1237, 1031, 835, 754 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_8H_{15}Na_1O_4P_1^+$ ($[M+Na]^+$) 229.0600. Found 229.0595; $[\alpha]_D^{25}$ +26.2° (c = 0.75, MeOH).

Dimethyl (1-Hydroxydodec-2-yn-1-yl)phosphonate (5c): HPLC ODH, H/IPA = 100:1, flow rate = 0.5 mL/min, λ = 210 nm, 26.5 min (major enantiomer), 30.8 min (minor enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, d, $J_{P\text{-}H} = 10.1$ Hz), 3.88 (3H, d, $J_{P\text{-}H} = 10.5$ Hz), 2.51 (1H, d, $J_{P\text{-}H} = 4.1$ Hz), 2.25 (2H, qd, $J_{H\text{-}H} = 7.2$ Hz, $J_{P\text{-}H} = 4.0$ Hz), 1.65 (3H, d, $J_{P\text{-}H} = 15.6$ Hz), 1.53 (1H, q, $J = 7.3$ Hz), 1.51 (1H, q, $J = 7.3$ Hz), 1.37 (2H, quin, $J = 7.3$ Hz), 1.32–1.23 (10H, br), 0.88 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 88.0 (d, $J_{P\text{-}C} = 9.7$ Hz), 78.6, 65.8 (d, $J_{P\text{-}C} = 175.1$ Hz), 54.7 (d, $J_{P\text{-}C} = 7.7$ Hz), 54.6 (d, $J_{P\text{-}C} = 6.8$ Hz), 31.9, 29.5, 29.3, 29.2, 28.9, 28.5, 25.4, 22.7, 18.9, 14.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.2; IR (film) 3282, 2926, 2854, 2242, 1462, 1238, 1185, 1033, 834, 764 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{15}H_{29}Na_1O_4P_1^+$ ($[M+Na]^+$) 327.1696. Found 327.1683; $[\alpha]_D^{25}$ +21.1° (c = 1.79, MeOH).

Dimethyl (3-Cyclohexyl-1-hydroxyprop-2-yn-1-yl)-phosphonate (5d): HPLC IA, H/IPA = 100:1, flow rate = 0.5 mL/min, λ = 210 nm, 58.0 min (minor enantiomer), 61.2 min (major enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, d, $J_{P\text{-}H} = 10.0$ Hz), 3.88 (3H, d, $J_{P\text{-}H} = 10.1$ Hz), 3.55 (1H, br), 2.48–2.38 (1H, m), 1.84–1.75 (2H, m), 1.74–1.65 (2H, m), 1.65 (3H, d, $J_{P\text{-}H} = 15.1$ Hz), 1.56–1.38 (3H, m), 1.37–1.24 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 92.0 (d, $J_{P\text{-}C} = 9.7$ Hz), 78.6, 65.9 (d, $J = 174.6$ Hz), 54.8 (d, $J_{P\text{-}C} = 8.7$ Hz), 54.7 (d, $J_{P\text{-}C} = 7.7$ Hz), 32.4, 29.1, 25.9, 25.5, 24.8, two carbon atoms were not found due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3; IR (film) 3283, 2931, 2853, 2233, 1448, 1237, 1185, 1033, 835, 757 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{12}H_{21}Na_1O_4P_1^+$ ($[M+Na]^+$) 283.1070. Found 283.1083; $[\alpha]_D^{25}$ +20.0° (c = 3.28, MeOH).

Dimethyl (1-Hydroxy-5-methylhex-2-yn-1-yl)phosphonate (5e): HPLC ADH, H/IPA = 20:1, flow rate = 0.5 mL/min, λ = 210 nm, 15.1 min (minor enantiomer), 16.0 min (major enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, d, $J_{P\text{-}H} = 10.5$ Hz), 3.88 (3H, d, $J_{P\text{-}H} = 10.1$ Hz), 2.55 (1H, br), 2.15 (2H, dd, $J_{H\text{-}H} = 6.6$ Hz, $J_{P\text{-}H} = 4.0$ Hz), 2.14 (1H, d, J = 6.6 Hz), 1.83 (1H, sept, $J = 6.6$ Hz), 1.66 (3H, d, $J_{P\text{-}H} = 15.6$ Hz), 0.98 (6H, d, $J = 6.6$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 87.1 (d, $J_{P\text{-}C} = 8.7$ Hz), 79.5, 66.0 (d, $J_{P\text{-}C} = 176.1$ Hz), 54.7 (d, $J_{P\text{-}C} = 6.8$ Hz), 54.6 (d, $J_{P\text{-}C} = 6.8$ Hz), 28.0, 25.4, 22.0, two carbon atoms were not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.2; IR (film) 3288, 2958, 2242, 1464, 1368, 1238, 1186, 1034, 832, 762 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{10}H_{19}Na_1O_4P_1^+$ ($[M+Na]^+$) 257.0913. Found 257.0910; $[\alpha]_D^{25}$ +23.6° (c = 1.98, MeOH).

Dimethyl (4-(Benzyloxy)-1-hydroxybut-2-yn-1-yl)phosphonate (5f): HPLC OJH, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 31.4 min (major enantiomer), 33.2 min (minor enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.33 (4H, m) 7.33–7.27 (1H, m), 4.60 (2H, s), 4.22 (2H, d, $J_{P\text{-}H}$ = 4.1 Hz), 3.89 (3H, d, $J_{P\text{-}H} = 10.5$ Hz), 3.88 (3H, d, $J_{P\text{-}H} = 10.6$ Hz), 1.70 (3H, d, $J_{P\text{-}H} = 15.6$ Hz), O-H proton was not found probably due to broadening; ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3, 128.6, 128.3, 128.1, 84.9, 83.2 (d, $J_{P\text{-}C} = 9.7$ Hz), 71.6, 65.8 (d, $J_{P\text{-}C} = 176.1$ Hz), 57.4, 54.9 (d, $J_{P\text{-}C} = 7.7$ Hz), 54.8 (d, $J_{P\text{-}C} = 7.7$ Hz), 25.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.9; IR (film) 3270, 2957, 2855, 1714, 1454, 1355, 1235, 1034, 838, 753 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{14}H_{19}Na_1O_5P_1^+$ ($[M+Na]^+$) 321.0862. Found 321.0856; $[\alpha]_D^{25}$ +20.3° (c = 1.04, MeOH).

Dimethyl (5-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-pent-2-yn-1-yl)phosphonate (5g): HPLC ASH, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 9.1 min (minor enantiomer), 11.3 min (major enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (3H, d, $J_{P\text{-}H} = 10.5$ Hz), 3.87 (3H, d, $J_{P\text{-}H}$ = 10.1 Hz), 3.72 (2H, t, $J = 7.1$ Hz), 2.46 (2H, td, $J_{H\text{-}H} = 7.1$ Hz, $J_{P\text{-}H} = 4.6$ Hz), 1.65 (3H, d, $J_{P\text{-}H} = 15.6$ Hz), 0.89 (9H, s), 0.07 (6H, s), O-H proton was not found probably due to broadening; ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.9 (d, $J_{P\text{-}C} = 9.7$ Hz), 79.6, 65.8 (d, $J_{P\text{-}C} = 175.1$ Hz), 61.6, 54.8 (d, $J_{P\text{-}C} = 7.7$ Hz), 54.7 (d, $J_{P\text{-}C} = 7.7$ Hz), 25.9, 25.4, 23.3, 18.4, −5.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.2; IR (KBr) 3278, 2957, 2240, 1471, 1360, 1240, 1101, 1028, 836, 773 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{14}H_{29}Na_1O_5P_1Si_1^+$ ($[M+Na]^+$) 359.1414. Found 359.1413; $[\alpha]_D^{25}$ +19.8° (c = 1.23, MeOH).

Dimethyl (1,4-Dihydroxy-4-methylpent-2-yn-1-yl)-phosphonate (desilylated 5h): HPLC ASH, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.3 min (minor enantiomer), 11.3 min (major enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (1H, brd, $J_{P\text{-}H} = 1.4$ Hz), 4.62 (1H, br), 3.90 (6H, d, $J_{P\text{-}H} = 10.1$ Hz), 1.61 (3H, d, $J_{P\text{-}H} = 15.1$ Hz), 1.53 (3H, s), 1.50 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 92.7 (d, $J_{P\text{-}C} = 9.7$ Hz), 80.2, 65.3 (d, $J_{P\text{-}C} = 176.1$ Hz), 64.7, 54.9$_9$ (d, $J_{P\text{-}C} = 7.7$ Hz), 54.9$_6$ (d, $J_{P\text{-}C} = 7.7$ Hz), 31.3, 30.8, 24.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.5; IR (film) 3305, 2983, 2243, 1647, 1455, 1365, 1236, 1171, 1035, 787 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_9H_{17}Na_1O_5P_1^+$ ($[M+Na]^+$) 259.0706. Found 259.0696; $[\alpha]_D^{25}$ +21.0° (c = 1.73, MeOH).

Dimethyl (1-Hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl)-phosphonate (5i): HPLC ADH, H/IPA = 50:1, flow rate = 0.5 mL/min, λ = 210 nm, 15.3 min (minor enantiomer), 16.6 min (major enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (3H, d, $J_{P\text{-}H} = 10.6$ Hz), 3.88 (3H, d, $J_{P\text{-}H} = 10.5$ Hz), 3.62 (1H, br), 1.67 (3H, d, $J = 15.6$ Hz), 0.18 (9H,s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 103.4, 92.2 (d, $J_{P\text{-}C} = 7.7$ Hz), 66.1 (d, $J_{P\text{-}C} = 174.2$ Hz), 55.1 (d, $J_{P\text{-}C} = 7.7$ Hz), 54.9 (d, $J_{P\text{-}C} = 7.7$ Hz), 25.2, −0.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.3; IR (KBr) 3287, 2963, 2160, 1252, 1238, 1160, 1054, 1028, 841, 783 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_9H_{19}Na_1O_4P_1Si_1^+$ ($[M+Na]^+$) 273.0682. Found 273.0688; $[\alpha]_D^{25}$ +21.4° (c = 1.03, MeOH). Crystal data for **5i** (CCDC 772834): $C_9H_{19}O_4PSi$ (MW 250.30), Monoclinic, $P2_1$, $a = 9.5228(13)$, $b = 7.4316(11)$, $c = 9.7945(14)$ Å, $\beta = 103.092(3)°$, $V = 675.14(17)$ Å^3, $Z = 2$, $T = 153(2)$ K, Independent reflections 3033 [$R_{int} = 0.0248$], Flack parameter 0.17(10), $R_1(R_w) = 0.0388$ (0.0968) ($I > 2\sigma(I)$), GOF = 1.071.

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30 L. Cao, J. Ding, M. Gao, Z. Wang, J. Li, A. Wu, *Org. Lett.* **2009**, *11*, 3810.

31 M. T. Corbett, J. S. Johnson, *J. Am. Chem. Soc.* **2013**, *135*, 594.

