SYTHESIS OF ADAMANTYL *H*-PHOSPHINATE ESTERS

by

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SYNTHESIS OF ADAMANTYL *H*-PHOSPHINATE ESTERS

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ABSTRACT

Adamantyl *H*-phosphinate esters were first introduced by Yiotakis et al. as a protecting group in the synthesis of phosphinopeptides. Gatineau et al. later found adamantyl *H*-phosphinate esters to be useful in the synthesis of *P*-stereogenic compounds. Phosphorus compounds have a broad range of applications including pharmaceuticals, agricultural products, and flame retardants, making them an area of interest in synthetic chemistry. However, methods for their preparation that achieve high enantioselectivity are limited. Gatineau et al. discovered that adamantyl *H*-phosphinate esters serve as precursors that facilitate this preparation, which they attributed to the ability of the esters to resist racemization when displaced with organometallics. However, their methods were limited by the necessity of chlorophosphine starting materials. In this project, we aimed at developing novel synthetic methods for the preparation of adamantyl *H*-phosphinate esters which are not limited in terms of available reagents and are less expensive than current known methods. EDC, PivCl, and T3P were utilized in the esterification reactions. Methods were developed to prepare these esters in good yield on a multigram scale without the need for chromatography. An alternative method to the esterification of *H*-phosphinic acids was also employed that involved the preparation of adamantyl hypophosphite and its conversion into a variety of *H*-phosphinate esters. However, adamantyl hypophosphite was shown to have limited reactivity.

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LIST OF ABBREVIATIONS

Abbreviation	Full Name
^{13}C NMR	Carbon Nuclear Magnetic Resonance
^{1}H NMR	Proton Nuclear Magnetic Resonance
^{31}P NMR	Phosphorus Nuclear Magnetic Resonance
AdBr	Bromoadamantane
AdOH	1-adamantanol
AdOP(O)H_2	Adamantyl Hypophosphite
Ag_2O	Silver Oxide
AHP	Anilinium Hypophosphite
aq.	Aqueous
ATP	Adenosine Triphosphate
CaH_2	Calcium Hydride
$CDCl_3$	Deuterated Chloroform
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIPEA	N,N-Diisopropylethylamine
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDC	1-Ethyl-3-(dimethylaminopropyl)carbodiimide
EI	Electron Ionization
eq	Equivalent
EtOAc	Ethyl Acetate
g	Grams
h	Hours
H	Hydrogen
HCl	Hydrogen Chloride
HPLC	High Performance Liquid Chromatography
HRMS	High-resolution Mass Spectrometry
Hz	Hertz
i-Pr_2NEt	N,N-Diisopropylethylamine
J	Coupling Constant
K_2CO_3	Potassium Carbonate
$KMnO_4$	Potassium Permanganate
LiHMDS	Lithium bis(trimethylsilyl)amide
m	Multiplet
M	Molar
MeI	Iodomethane
Me_4Si	Tetramethylsilane
$MgSO_4$	Magnesium Sulfate
MHz	Megahertz
mL	Milliliters
mmol	Millimoles
M.p.	Melting Point

m/z	Mass-to-chargo Ratio
N_2	Nitrogen Gas
NaH	Sodium Hydride
$NaHCO_3$	Sodium Bicarbonate
NaOH	Sodium Hydroxide
P	Phosphorus
Pd_2dba_3	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(OAc)_2$	Palladium (II) Acetate
$PhPO_2H_2$	Phenyl Phosphinic Acid
PivCl	Pivaloyl Chloride
Ppm	Parts Per Million
Rf	Retention Factor
rt	Room Temperature
s	Singlet
TLC	Thin Layer Chromatography
TOF	Time-of-flight
T3P	1-propanephosphinic Acid Cyclic Anhydride
UV	Ultraviolet
wt%	Weight Percent

INTRODUCTION

Phosphorus is a crucial element for all known life forms. For example, it is a core component of adenosine triphosphate (ATP), a vital energy carrier in every organism, as well as the phospholipids that form the membranes of cells. It is also a vital element in the nucleic acids DNA and RNA. The ubiquity of phosphorus in biological molecules allows scientists to create phosphorus compounds that mimic those found in living systems. Of particular importance are *P*-stereogenic compounds, those with phosphorus at the chiral center. These compounds have numerous applications, ranging from pharmaceuticals to agriculture.[1] For example, the *P*-stereogenic compound Remdesivir, an ATP analogue, acts as an inhibitor of the SARS-CoV-2 RNA polymerase.[2]

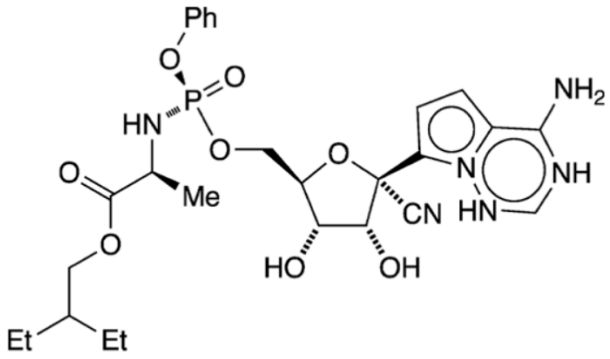
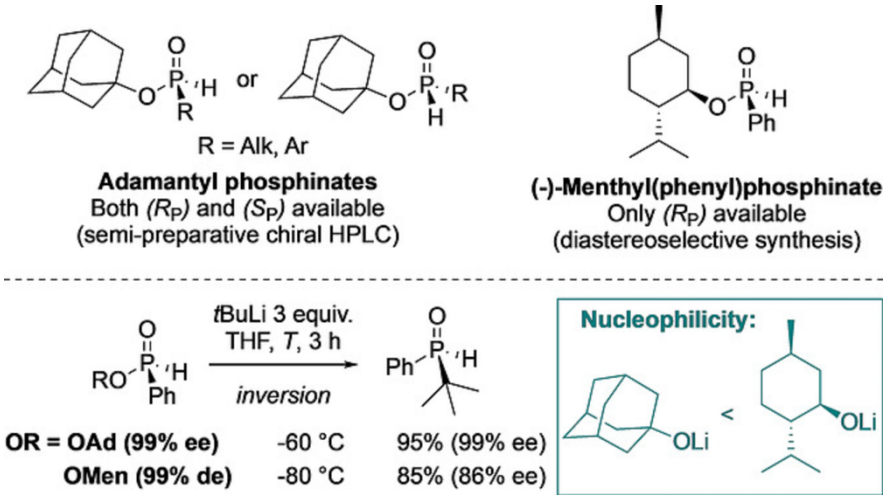


Figure 1: Chemical structure of Remdesivir.[3]

Due to the wide array of possibilities presented by chiral phosphorus compounds, and the relatively limited portfolio of methods for their synthesis in comparison to their counterparts with a carbon backbone, recent research has been devoted to creating methodologies for their production. Chiral resolution has traditionally been used to obtain one enantiomer but leads to significant waste of the other.[4] Therefore, synthetic methods that achieve high enantioselectivity

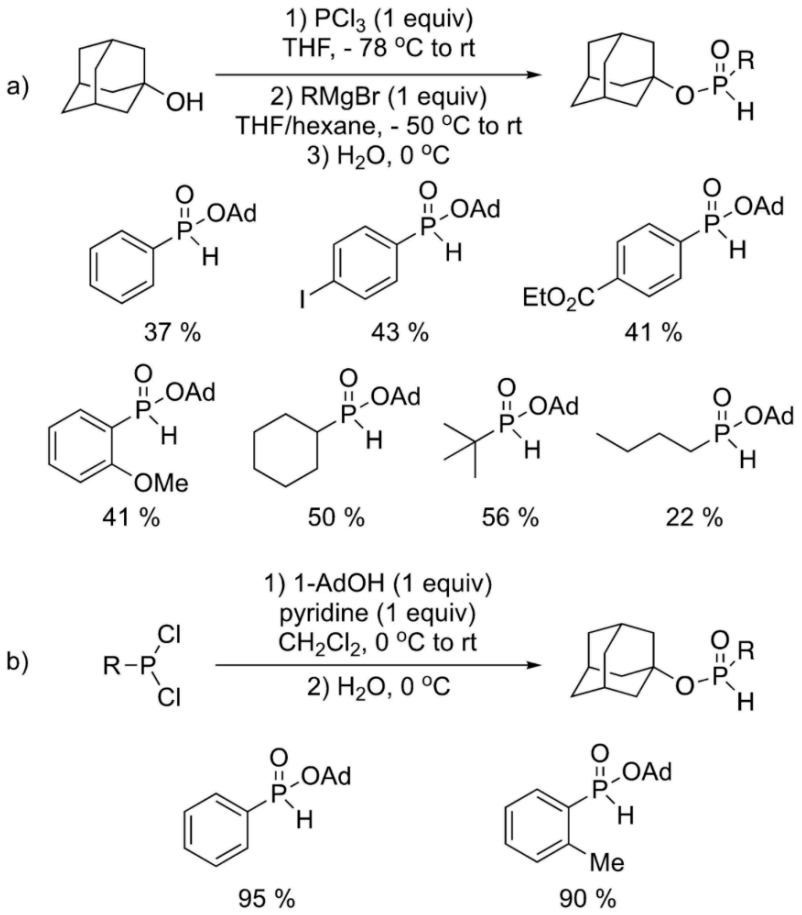
are being investigated. In 1970, Mislow and coworkers made great progress in this investigation through the preparation of menthyl phosphinates as precursors for *P*-stereogenic synthesis from commercially available (-)-menthol.[5] However, isolation of these precursors required multiple difficult crystallizations at low temperature.[6] In 2013, Berger and Montchamp made further progress in methods using menthol through the preparation of menthyl-(hydroxymethyl) phosphinate precursors that were obtained through simpler crystallization procedures.[6]

As an alternative to menthol derivatives, Gatineau et. al investigated 1-adamantanol for the creation of *H*-adamantylphosphinate precursors for *P*-stereogenic synthesis.[4] With both the menthyl and adamantyl precursors, reaction with organometallic reagents leads to the production of phosphine oxides via an S_N2 mechanism.[1] However, unlike with the secondary menthyl oxide anion, the hindrance provided by the adamantyl oxide anion leaving group makes it a poorer nucleophile and prevents inversion of stereochemistry after displacement with the organometallic reagent.[1,7]



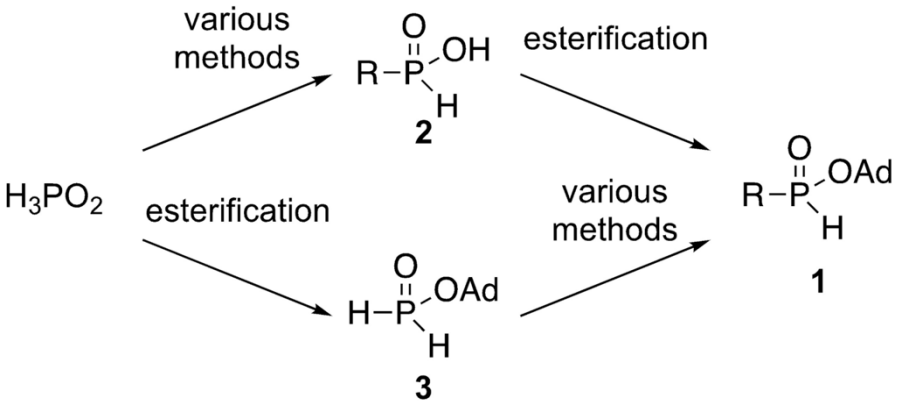
Scheme 1: Comparison of adamantyl phosphinates and menthyl phosphinates as precursors for *P*-stereogenic synthesis.[1]

Gatineau et al. utilized two methods for the synthesis of adamantyl *H*-phosphinate esters.[7] In the first method, 1-adamantanol was reacted with phosphorus trichloride, followed by a Grignard reaction and hydrolysis. The second method involved the reaction of a dichlorophosphine with 1-adamantanol followed by hydrolysis. Both methods allowed for the obtention of enantiopure adamantyl *H*-phosphinates after resolution via chiral semipreparative high performance liquid chromatography (HPLC), with the first resulting in very good yield. However, this method is limited by the lack of commercially available dichlorophosphines.[7] The first (a) and second (b) method are shown in Scheme 2 below.



Scheme 2: Literature methods for the preparation of adamantyl H-phosphinate esters.[8]

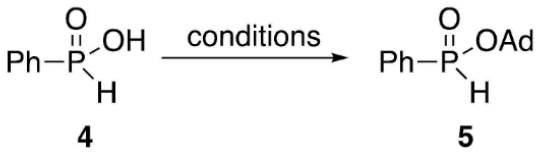
This project focused on the development of novel methods for the synthesis of adamantyl *H*-phosphinate esters that are less expensive and are not limited by the availability of starting materials. A method was also developed that does not require chromatographic purification. Two general techniques were used, the first in which an *H*-phosphinic acid **2** is esterified into the corresponding adamantyl *H*-phosphinate **1**. Our laboratory has extensive experience in synthesizing *H*-phosphinic acids, which are a greener alternative to phosphorus trichloride and dichlorophosphines and can be made in large variety.[9] The second method utilized esterification first to produce adamantyl hypophosphite **3** which is then converted into adamantyl *H*-phosphinate **1** using various methods (Scheme 3).



Scheme 3: Novel methods for the synthesis of adamantyl H-phosphinates.[8] Method I is shown along the top of the scheme while Method II is shown along the bottom.

RESULTS AND DISCUSSION

First, we began with the esterification of phenyl-*H*-phosphinic acid using various conditions. The reaction conditions and results are shown in Table 1.



4 **5**

Entry	Conditions	Yield [%][a]
1	$PhPO_2H_2$ (1 eq) AdBr (2.4 eq), $CHCl_3$ and brought to reflux, Ag_2O (2.4 eq) added portion-wise. Refluxed for 2 h	42
2	$PhPO_2H_2$ (1.2 eq) AdBr (1 eq), $CHCl_3$, Ag_2O (1.0 eq) was added portion-wise, rt, 2 h	56
3	$PhPO_2H_2$ (1 eq) AdOH (1 eq) EDC (1.5 eq) DMAP (0.1 eq) CH_2Cl_2, 0 °C to rt, 16 h	55
4	$PhPO_2H_2$ (1.1 eq) AdOH (1.8 eq) EDC (1.5 eq) DMAP (0.1 eq) CH_2Cl_2, 0 °C to rt, overnight	72
5	$PhPO_2H_2$ (1 eq) PivCl (1.5 eq) Pyr (1 eq) AdOH (2 eq) CH_2Cl_2, rt, 16 h	84
6a	$PhPO_2H_2$ (1.2 eq) PivCl (1.2 eq) Pyr (1.5 eq) AdOH (1 eq)	80[b]
6b	CH_2Cl_2, rt, 16 h	94[b,c]
7a	$PhPO_2H_2$ (1.25 eq) T3P (1.5 eq, 50 wt% in EtOAc) AdOH	90[b]
7b	(1.0 eq) CH_2Cl_2, rt, 16 h	85[b,d]

[a] Isolated yield of pure **5** from **4** (1.5 mmol) after column chromatography, unless otherwise noted. [b] No chromatography. [c] 8.5 g (30 mmol) of **5**. [d] 13 g (48 mmol) of **5**.

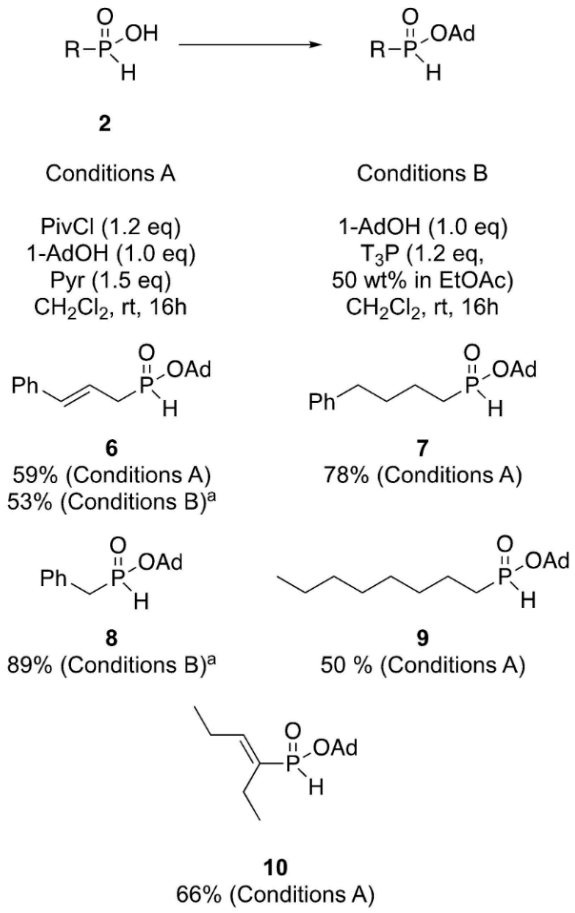
Table 1: Reaction conditions for the esterification of phenyl-*H*-phosphinic acid.[8]

Phenyl phosphinic acid ($PhPO_2H_2$) was first reacted with silver oxide (Ag_2O) and 1-bromoadamantane (AdBr) (entry 1) to produce **5**. In entry 2, a higher yield, as assessed by nuclear magnetic resonance (NMR), was achieved by using a slight excess of $PhPO_2H_2$. As a less expensive alternative to Ag_2O and AdBr, esterification was carried out with 1-adamantanol (AdOH) and 1-ethyl-3-(dimethylaminopropyl) carbodiimide (EDC), leading to an improved yield (entry 3). The yield was further increased by using an excess of AdOH (entry 4).

Replacing EDC with pivaloyl chloride (PivCl) and pyridine gave a superior yield (entry 5), which was further improved by using AdOH as the limiting reagent (entry 6a). The crude product did not require chromatographic purification and could be produced on a multigram-scale because the slight excess of acid can simply be removed by extraction (entry 6b).

In entry 7a, a similar reaction was carried out with 1-propanephosphonic acid cyclic anhydride (T3P). This gave a good yield, did not require chromatography, and could be easily scaled up to produce 13 g of **5** (entry 7b).

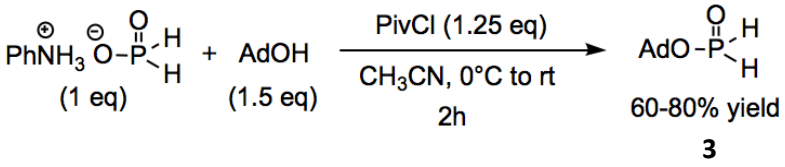
Esterification of various *H*-phosphinic acids was then carried out under the reaction conditions of entries 6a and 7a to see if similar results could be achieved. The resulting adamantyl esters and yields are reported in Scheme 4.



Scheme 4: Conditions and results for the esterification of different *H*-phosphinic acids. Esters labeled with the superscript [a] did not require chromatographic purification.[8]

As illustrated in Scheme 4, exposing various *H*-phosphinic acids to the reaction conditions involving PivCl and T3P led to moderate, and in some cases very good yields of the corresponding adamantyl esters. Esters **6** and **8** were obtained in sufficient purity and did not require chromatography (Scheme 4).

As an alternative approach to the esterification of *H*-phosphinic acids, the novel adamantyl hypophosphite ($AdOP(O)H_2$) was first prepared based on Stawinski's method[10] (Scheme 5) and used in various one-pot reactions with the aim of producing several *H*-phosphinate esters.

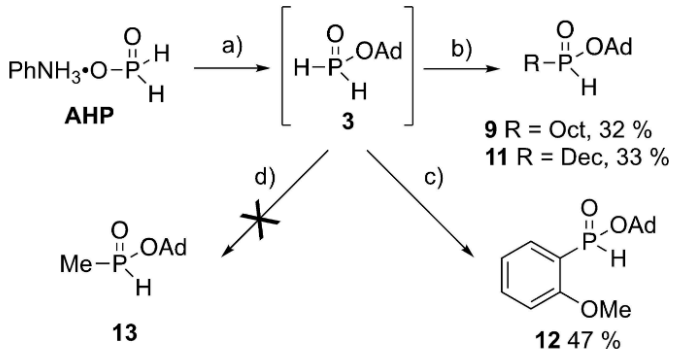


Scheme 5: Stawinski's PivCl method.[10]

First, $AdOP(O)H_2$ **3** (Scheme 6) was prepared from anilinium hypophosphite (AHP) (1 eq), PivCl (1.1 eq), pyridine (1.25 eq), and 1-AdOH (1.5 eq) (0°C to rt, 2h, CH_3CN). Palladium-catalyzed hydrophosphinylation of alkenes (tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3) (1 mol%), xantphos (2 mol %), reflux, 16h)[8] was then carried out with either 1-octene or 1-decene (1 eq) (Scheme 6; **9** and **11**). This was successful but produced low yields. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) promoted alkylation (iodomethane (MeI) (1.1 eq), DBU (1.1 eq), rt)[8] was then conducted on the prepared $AdOP(O)H_2$, but the reaction was unsuccessful (Scheme 6; **13**). DBU-promoted conjugate addition to benzyl acrylate was similarly ineffective.

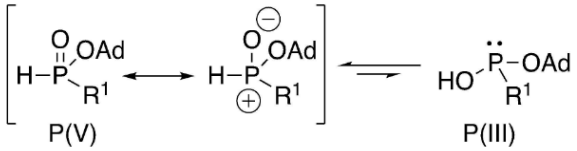
A similar method to prepare $AdOP(O)H_2$ was carried out with toluene instead of acetonitrile (CH_3CN), which was used in a palladium-catalyzed cross-coupling reaction (2-

iodoanisole (1 eq), N,N-diisopropylethylamine (iPr_2NEt) (1.3 eq), palladium (II) acetate ($Pd(OAc)_2$) (2 mol%), (1,1'-bis(diphenylphosphino)ferrocene (dppf) (2 mol%), reflux, 48 h) to give **12** in moderate yield (Scheme 6).



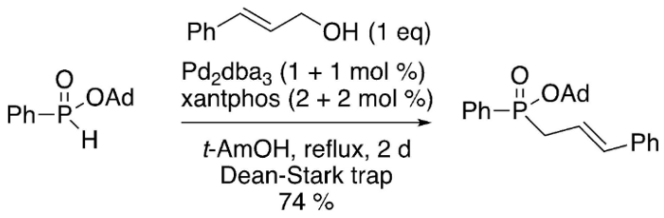
Scheme 6: Preparation of various *H*-phosphinate esters.[8]

An explanation for the limited reactivity of adamantyl hypophosphite may be provided by the findings of Janesko, Montchamp, and coworkers in 2015.[11] In their work, deuteration rates were used to measure the reactivity of phosphinylidene-containing (P(O)H) compounds. These compounds undergo tautomerization, such that both a P(III) and P(V) form are present in the mixture (Scheme 7). The P(III) form is more reactive; however, the electron-donating ability of the adamantyl group stabilizes the P(V) tautomer which predominates even more in the reaction mixture.



Scheme 7: Tautomerization between P(V) and P(III) form.[8]

Despite the limited reactivity of adamantyl *H*-phenylphosphinate, Pd-catalyzed allylation with cinnamyl alcohol was successful when the reaction time was increased and the amount of catalyst was doubled compared with the butyl ester (Scheme 8).



Scheme 8: Pd-catalyzed allylation with cinnamyl alcohol. [8]

The preparation of hypophosphite **3** was also attempted by transesterification of ethyl phosphinate with adamantanol (2 eq, rt, 24h), but it only gave a ^{31}P-NMR yield of 16%. Transesterification of butyl phenylphosphinate (2 eq AdOH, 2 eq sodium hydride (NaH) or lithium bis(trimethylsilyl)amide (LiHMDS)) was also carried out without success. The ability of adamantyl esters to resist racemization during substitution reactions is attributed by Gatineau et. al to the hindrance of the tertiary leaving group,[7] which may also explain the unsatisfactory results of transesterification with AdOH.

CONCLUSION AND FUTURE WORK

This project aimed at creating novel methods for the synthesis of adamantyl *H*-phosphinate esters that are not limited by the availability of starting materials. Two methods were employed, the first involving esterification of an *H*-phosphinic acid. The most satisfactory results were obtained when T3P and PivCl were used as reagents. Using 1-adamantanol as the limiting reagent and *H*-phosphinic acid in slight excess gave a good yield of product and allowed chromatographic purification to be avoided.

The second method involved the preparation of the novel adamantyl hypophosphite and its conversion into various adamantyl esters. However, adamantyl hypophosphite showed limited reactivity, which can likely be attributed to the bulky nature of the adamantyl group and its unfavorable tautomeric equilibrium. Despite this challenge, this project expanded the portfolio of adamantyl *H*-phosphinate esters and discovered methods for their preparation that reduce time, cost, and waste. Future work could focus on finding a large-scale resolution method to avoid the limitations of chiral semi-preparative HPLC.

EXPERIMENTAL PROCEDURES[8]

General:

^{1}H NMR spectra were recorded on a 400 MHz Bruker Avance spectrometer. Chemical shifts for the ^{1}H NMR spectra (in parts per million) are relative to internal tetramethylsilane (Me_4Si), (δ = 0.00 ppm) with deuterated chloroform ($CDCl_3$). $^{13}C\{^{1}H\}$ NMR spectra are recorded at 101 MHz. Chemical shifts for $^{13}C\{^{1}H\}$ NMR spectra are reported (in parts per million) relative to $CDCl_3$ (δ = 77.0 ppm). ^{31}P NMR spectra were recorded at 162 MHz, and chemical shifts reported (in parts per million) are relative to external 85% phosphoric acid (δ = 0.00 ppm). Flash chromatography experiments were carried out on silica gel premium Rf grade (40-75 μm). Ethyl acetate/hexane was used as the eluent for chromatographic purifications. Thin layer chromatography (TLC) plates were visualized by UV or immersion in permanganate (3 g of potassium permanganate ($KMnO_4$), 20 g of potassium carbonate (K_2CO_3), 5 mL of 5% aq. sodium hydroxide (NaOH), 300 mL of water) followed by heating. High-resolution mass spectra (HRMS) were obtained by electro-spray ionization using a time-of-flight (TOF) analyzer. All starting materials were purchased from commercial sources and used as received, unless otherwise noted. Solvents were distilled under nitrogen gas (N_2) and dried according to standard procedures (CH_3CN, toluene, and dichloromethane from calcium hydride (CaH_2)).

General procedure for the synthesis of adamantyl phenyl-H-phosphinate with PivCl:

To a solution of phenyl-*H*-phosphinic acid (39 mmol, 1.2 eq) and 1-AdOH (33 mmol, 1.0 eq) in dichloromethane (CH_2Cl_2) (0.2 M) was added pyridine (49 mmol, 1.5 eq) and PivCl (39 mmol, 1.2 eq) dropwise at rt under N_2. The reaction was stirred at rt for 16 h. The organic layer was washed with a 0.1 M hydrogen chloride (HCl) aq. solution. The two layers were separated, and the

organic layer was washed with a saturated aq. solution of sodium bicarbonate ($NaHCO_3$). The two layers were separated, and the organic layer was washed with brine, dried over magnesium sulfate ($MgSO_4$), filtered, and concentrated under a vacuum. The product **5** was obtained as a white solid without further purification needed (8.5 g, 30 mmol, 94%) in accordance with literature data.[7]

General procedure for the synthesis of adamantyl phenyl-H-phosphinate with EDC:

To a solution of phenyl *H*-phosphinic acid (1.5 mmol, 1.0 eq) and 1-AdOH (2.7 mmol, 1.8 eq) in CH_2Cl_2 (0.5 M) was added 4-dimethylaminopyridine (0.15 mmol, 0.1 eq) at rt under N_2. The reaction was brought to 0 °C and EDC (2.25 mmol, 1.5 eq) was added. The reaction was brought to rt and stirred for 16 h. The organic layer was washed with a saturated aq. solution of $NaHCO_3$. The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. This crude product was purified by column chromatography (hexanes/ethyl acetate (EtOAc) 90:10) to afford pure adamantyl phenyl-*H*-phosphinate as a white solid (0.3 g, 1.1 mmol, 72%) in accordance with literature data.[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 553.4 Hz, 1H), 7.82-7.71 (m, 2H), 7.61-7.51 (m, 1H), 7.50-7.33 (m, 2H), 2.24-2.16 (m, 3H), 2.12 (d, J = 3.0 Hz, 6H), 1.64 (t, J = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5 (d, J = 2.9 Hz), 131.7 (d, J = 137.9 Hz), 130.9 (d, J = 11.5 Hz), 128.5 (d, J = 13.9 Hz), 82.6 (d, J = 8.5 Hz), 44.1 (d, J = 4.6 Hz), 35.7, 31.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.1 (dt, J = 553.0, 13.5 Hz).

General procedure for the synthesis of adamantyl phenyl-H-phosphinate with T3P:

To a solution of phenyl-*H*-phosphinic acid (70 mmol, 1.25 eq) and 1-AdOH (56 mmol, 1.0 eq) in CH_2Cl_2 (0.5 M) was added T3P (84 mmol, 50 wt% in EtOAc, 1.5 eq) at 0 °C under N_2. The reaction

was brought to rt and stirred for 16 h. The organic layer was washed with a saturated aq. solution of $NaHCO_3$ (2x). The two layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. The product adamantyl phenyl-*H*-phosphinate was obtained as a white solid without further purification needed (13g, 47 mmol, 85%) in accordance with literature data.[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 553.4 Hz, 1H), 7.82-7.71 (m, 2H), 7.61-7.51 (m, 1H), 7.50-7.33 (m, 2H), 2.24-2.16 (m, 3H), 2.12 (d, *J* = 3.0 Hz, 6H), 1.64 (t, *J* = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5 (d, *J* = 2.9 Hz), 131.7 (d, *J* = 137.9 Hz), 130.9 (d, *J* = 11.5 Hz), 128.5 (d, *J* = 13.9 Hz), 82.6 (d, *J* = 8.5 Hz), 44.1 (d, *J* = 4.6 Hz), 35.7, 31.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.1 (dt, *J* = 553.0, 13.5 Hz).

Synthesis of adamantyl-2-methoxyphenyl-H-phosphinate via Pd-catalyzed cross-coupling from AHP:

To a solution of AHP (2mmol, 1.0 eq) and 1-AdOH (3.0 mmol, 1.5 eq) in toluene (0.2 M) was added pyridine (2.5 mmol, 1.25 eq) and PivCl (2.2 mmol, 1.1 eq) dropwise at 0 °C then brought to rt under N_2. The reaction stirred at rt for 2h, then $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 2.0 mol%), dppf (22.2 mg, 0.04 mmol, 2.0 mol%), and 1,2-dimethoxyethane (1mL), N,N-diisopropylethylamine (DIPEA) (2.6 mmol, 1.3 eq) and iodoanisole (1 mmol, 1 eq). The mixture was stirred under a flow of N_2 for 10 min and then heated at 115°C for 24 h before cooling to rt. The solvent was then removed under vacuum and the resulting residue was dissolved in EtOAc and washed with $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexanes/EtOAc 50:50 to 0:100) to afford pure adamantyl-2-methoxyphenyl-*H*-phosphinate as a beige solid (0.29 g, 0.94 mmol, 47%) in accordance with the literature data.[7] ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.59 (d, *J* = 572.0 Hz, 1H), 7.83 (ddd, *J* = 14.4, 7.5, 1.8 Hz, 1H), 7.52 (tdd, *J* = 7.4, 1.8, 0.7 Hz, 1H), 7.11-7.01 (m, 1H), 6.97-6.88 (m, 1H), 3.89 (s, 3H), 2.21 (d, *J* = 2.9 Hz, 3H), 2.12 (d, *J* = 3.4 Hz, 6H), 1.66 (t, *J* = 3.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (d, *J* = 4.5 Hz), 134.3 (d, *J* = 1.9 Hz), 133.1 (d, *J* = 6.7 Hz), 120.7 (d, *J* = 13.0 Hz), 119.5 (d, *J* = 138.6 Hz), 110.8 (d, *J* = 7.2 Hz), 81.9 (d, *J* = 8.4 Hz), 55.6, 44.0 (d, *J* = 4.8 Hz), 35.8, 31.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 9.3 (ddd, *J* = 571.3, 14.5, 6.4 Hz); HRMS (EI+): *m/z* calculated for $C_{17}H_{23}O_3P$: 307.1458 $[M+H]^+$; found: 307.1455.

Synthesis of adamantyl-cinnamylphenyl-phosphinate via Pd-catalyzed allylation of phenyl-H-phosphinic acid:

To a solution of phenyl-*H*-phosphinic acid, (2.0 mmol, 1 eq) in t-amyl alcohol (0.1 M), $Pd_2(dba)_3$ (1.0 mol%), Xantphos (2.0 mol%), and cinnamyl alcohol (1 eq) were added. The reaction mixture was stirred at reflux for 24 h under N_2 in a flask equipped with a Dean-Stark trap. The reaction was brought to rt and another portion of $Pd_2(dba)_3$ (1.0 mol%) and Xantphos (2.0 mol%) was added and brought to reflux for 24 h (48 h total reaction time). The reaction was cooled down to rt. EtOAc was added, the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under a vacuum. This crude product was purified by column chromatography (hexanes/ethyl acetate 80:20) to afford pure adamantyl-cinnamylphenyl-phosphinate as a yellow solid (0.58 g, 1.5 mmol, 74%). M.p. 114-115°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.76 (m, 2H), 7.58-7.50 (m, 1H), 7.48-7.42 (m, 2H), 7.34-7.27 (m, 4H), 7.25-7.19 (m, 1H), 6.42-6.27 (m, 1H), 6.21-6.04 (m,1H), 2.85 (ddd, *J* = 18.5, 7.7, 1.3 Hz, 2H), 2.13 (s, 3H), 2.06 (d, *J* = 3.7 Hz, 6H), 1.59 (d, *J* = 3.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2 (d, *J* = 3.6 Hz), 134.5 (d, *J* = 13.1 Hz), 133.3, 131.7 (d, *J* = 2.9 Hz), 131.6, 128.5, 128.2 (d, *J* = 12.5 Hz), 127.3, 126.1 (d, *J* = 2.0 Hz), 119.7 (d,

J = 10.3 Hz), 82.8, 44.6 (d, *J* = 3.8 Hz), 37.6 (d, *J* = 99.1 Hz), 35.7, 31.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.0; HRMS (EI+): *m/z* calcd for $C_{25}H_{29}O_2P$: 393.1978 $[M+H]^+$; found: 393.1975.

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