catalysts

MDPI

Article

Iminosugar-Phosphines as Organocatalysts in the [3 + 2] Cycloaddition of Allenoates and *N*-Tosylimines

Pilar Elías-Rodríguez, Ana T. Carmona *, Antonio J. Moreno-Vargas and Inmaculada Robina *

Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, 41012 Sevilla, Spain
* Correspondence: anatere@us.es (A.T.C.); robina@us.es (I.R.)

Abstract: Iminosugar derivatives containing a pyrrolidine-phosphine moiety were prepared from carbohydrates and used as catalysts in the [3 + 2] cycloaddition reaction between alkyl allenoates and electron-deficient imines. The corresponding 1,2,3,5-tetrasubstituted pyrrolines were obtained in good yields and diastereoselectivities but with moderate enantiocontrol. The stereochemical outcome of the reaction depends on the substituent at the nitrogen atom and hydroxyl groups, the configuration of the stereogenic centers and the distance between the diphenylphosphine group and the pyrrolidine skeleton of the catalyst. The preparation of both enantiomers of the catalyst allowed the corresponding enantiomeric pyrrolines to be obtained with similar yields, diastereo- and enantioselectivities.

Keywords: [3 + 2]-cycloaddition; allenes; pyrrolidines; phosphines; organocatalysis

Citation: Elías-Rodríguez, P.; Carmona, A.T.; Moreno-Vargas, A.J.; Robina, I. Iminosugar-Phosphines as Organocatalysts in the [3 + 2] Cycloaddition of Allenoates and *N*-Tosylimines. *Catalysts* **2022**, *12*, 876. https://doi.org/10.3390/catal12080876

Academic Editors: Jose A. Sordo and Chandra M. R. Volla

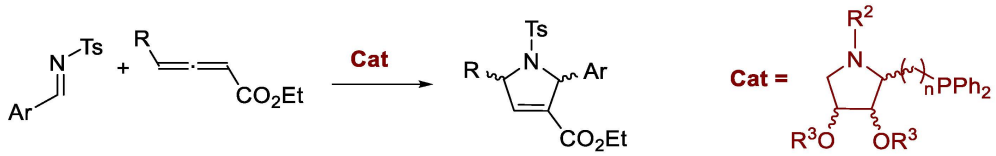
Received: 20 July 2022
Accepted: 1 August 2022
Published: 9 August 2022

1. Introduction

Chirality is an essential characteristic for a large number of industrial and biological compounds such as agrochemicals, drugs or natural products. Over the past few decades, enantioselective catalysis has become the main approach for the asymmetric synthesis of chiral molecules [1]. In this field, chiral tertiary phosphines play a significant role and have been widely used as organocatalysts or ligands in many types of catalytic asymmetric reactions [2,3]. The catalytic activity of tertiary phosphines is due to the free lone pair of electrons on the phosphorus atom, which enables them to be more nucleophilic than their corresponding amine analogues. A wide variety of nucleophilic phosphine-catalyzed annulation reactions has been established as powerful tools for the synthesis of carbo- and heterocycles from readily simple building blocks [4]. In particular, the phosphine-catalyzed [3 + 2] annulation reactions of allenoates and electron-deficient imines is one of the most attractive methods for the synthesis of substituted pyrrolines [5]. In 1998, Lu and co-workers reported the pioneering development of phosphine-catalyzed [3 + 2] cycloadditions of 2,3-butadienoates and electron-deficient imines to afford 2-substituted-3-pyrrolines [6]. Kwon and co-workers [7] extended the reaction to γ-substituted allenoates affording 2,5-disubstituted-3-pyrrolines with high diastereoselectivities. Since then, this reaction has been investigated by several research groups in order to develop an asymmetric variant using chiral catalysts, such as the readily available phosphines with axial and planar chirality [8–10], rhenium-based phosphines [11], phosphinothiourea derivatives [12,13], dipeptide-based phosphines [14] or planar [2.2]paracyclophane-based phosphine-phenol [15], among others [16]. Recently, a diversity of axially chiral phosphines has been prepared and preliminarily applied to several asymmetric transformations [17,18]. It is noteworthy that the first phosphine-catalyzed asymmetric synthesis of 2,5-disubstituted pyrrolines using γ-substituted allenoates was reported by Kwon and co-workers [19]. Two new diastereoisomeric rigid chiral [2.2.1]bicyclophosphines were developed as organocatalysts for this reaction. Both phosphines behaved as pseudoenantiomers and yielded the corresponding enantiomeric pyrrolines with good yields and excellent enantioselectivities. In addition,

these authors have recently reported [20] the use of the natural terpenoid carvone as the starting material for the synthesis of novel P-stereogenic chiral phosphines. These organocatalysts have been used in the asymmetric synthesis of a library of pyrrolines with high yields and enantioselectivities, including the biologically active compound (*R*)-efsevin.

Although carbohydrates are inexpensive and readily available compounds, relatively abundant in enantiomerically pure form and easily modulated with well-established carbohydrate chemistry, their use as starting materials for the synthesis of organocatalysts remains scarce [21]. We have recently reported [22,23] the synthesis of a novel class of pyrrolidine-based phosphine/phosphinite/aminophosphite ligands from readily available sugars. These compounds were used in the enantioselective Pd-allylic substitution and Ir-catalyzed hydrogenation reactions of minimally functionalized olefins, obtaining excellent enantioselectivities. Herein, we disclose the synthesis of iminosugar derivatives containing a pyrrolidine-phosphine moiety from commercial carbohydrates. These compounds have been used as catalysts in the [3 + 2] cycloaddition between alkyl allenoates and electron-deficient imines, affording 2,5-disubstituted-3-pyrrolines with good yields and diastereoselectivities but with moderate enantioselectivities (Scheme 1). The possibility of using the phosphine catalyst in both enantiomeric forms has allowed the corresponding enantiomeric 3-pyrrolines to be obtained with similar yields, diastereo- and enantioselectivities.

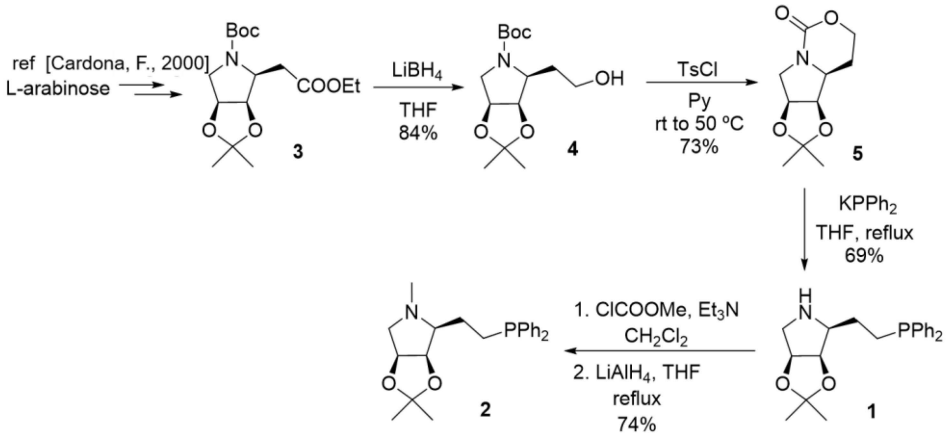


Scheme 1. [3 + 2] Cycloaddition between alkyl allenoates and electron-deficient imines catalyzed by chiral pyrrolidine-phosphines.

2. Results and Discussion

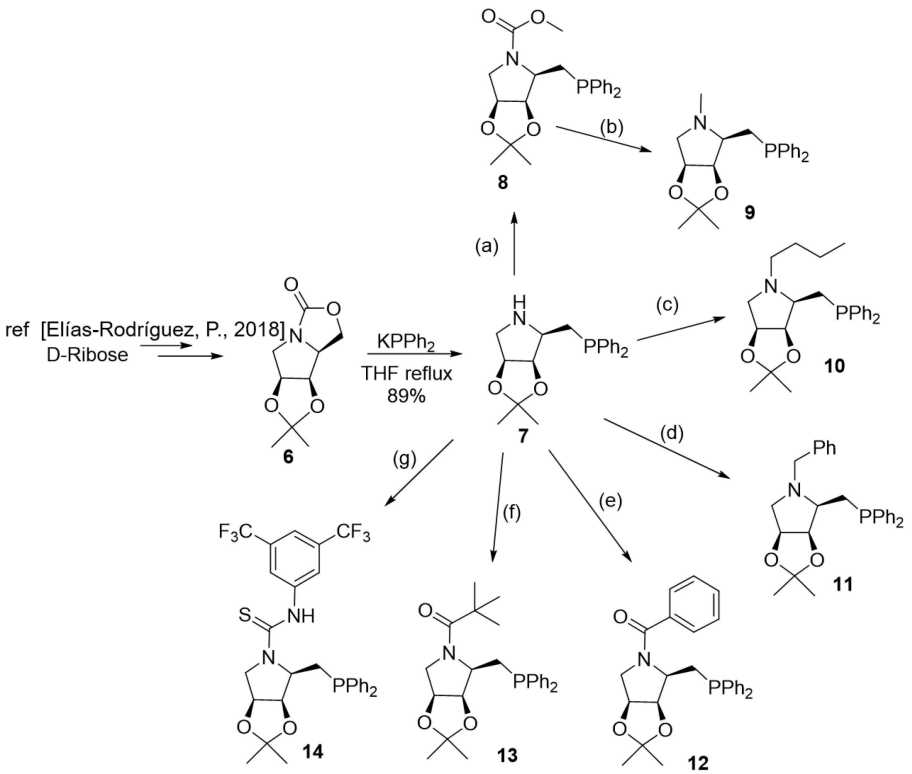
2.1. Synthesis of Pyrrolidine-Based Phosphine Organocatalysts

The new organocatalysts were easily prepared from available and inexpensive carbohydrates, such as L-arabinose, D-ribose and D-mannose. Starting from L-arabinose (Scheme 2), the organocatalysts **1** and **2** were obtained. Their synthesis started from the previously reported *N*-Boc-pyrrolidine **3** [24]. Reduction of **3** with $LiBH_4$ gave the *N*-Boc protected alcohol **4**. Standard tosylation of **4** afforded the cyclic carbamate **5**, as previously described for ***ent*-5** [25]. Nucleophilic ring opening of **5** by treatment with $KPPh_2$ in THF at reflux gave the amino-phosphine catalyst **1** (δ_P = −23.2 ppm). Reaction with methoxycarbonyl chloride gave the corresponding carbamate which, after reduction with $LiAlH_4$ in THF at reflux, afforded the *N*-methyl derivative **2** in 74% yield (two steps).



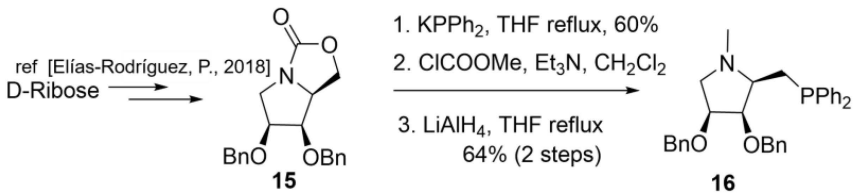
Scheme 2. Synthesis of organocatalysts **1** and **2** derived from L-arabinose [24].

Starting from D-ribose (Scheme 3), pyrrolidine phosphine **7**, which presents a shorter phosphine alkyl chain, was prepared following the procedure reported by us [23] that implies the ring opening of the cyclic carbamate **6** by reaction with $KPPh_2$ in THF. *N*-methyl derivative **9** [22] was prepared by reaction of **7** with methoxycarbonyl chloride affording **8** and subsequent reduction with $LiAlH_4$ in THF at reflux. The reductive amination of **7** with butanal and benzaldehyde afforded *N*-butyl- and *N*-benzyl-pyrrolidine derivatives **10** and **11**, respectively. Standard acylation of **7** using benzoyl and pivaloyl chloride afforded the pyrrolidine derivatives **12** and **13**, respectively, in excellent yields. Finally, the reaction of **7** with 3,5-bistrifluoromethylisothiocyanate gave the thiourea-phosphine derivative **14** [23] in moderate yield.



Scheme 3. Synthesis of organocatalysts **7**–**14** derived from D-Ribose [23]. Reaction conditions: (**a**) ClCOOMe, Et_3N, CH_2Cl_2, 70%; (**b**) $LiAlH_4$, THF reflux; (**c**) BuCHO, $NaBH_4$, 2,2,2-trifluoroethanol 35 °C, 66%; (**d**) PhCHO, $NaBH(OAc)_3$, 1,2-dichloroethane, 58%; (**e**) PhCOCl, Et_3N, CH_2Cl_2, 98%; (**f**) ^{t}BuCOCl Et_3N, CH_2Cl_2, 94%; (**g**) Ar-NCS, CH_2Cl_2, 66%.

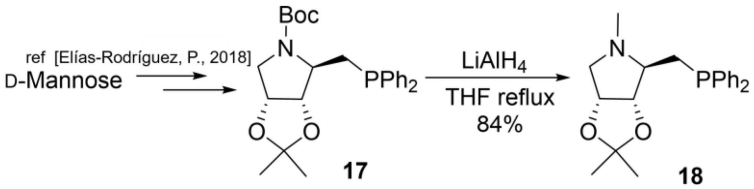
Moreover, pyrrolidine **16** bearing a less rigid backbone skeleton compared with pyrrolidine **9**, was prepared from **15** [23] by reaction with $KPPh_2$ in THF at reflux followed by treatment with methoxycarbonyl chloride and final reduction with $LiAlH_4$ in THF at reflux (Scheme 4).



Scheme 4. Synthesis of organocatalyst **16** derived from D-Ribose [23].

Finally, starting from D-mannose (Scheme 5), the *N*-Boc protected pyrrolidine-phosphine **17** [23], with a 2,3-*cis* configuration in the pyrrolidine backbone, was prepared.

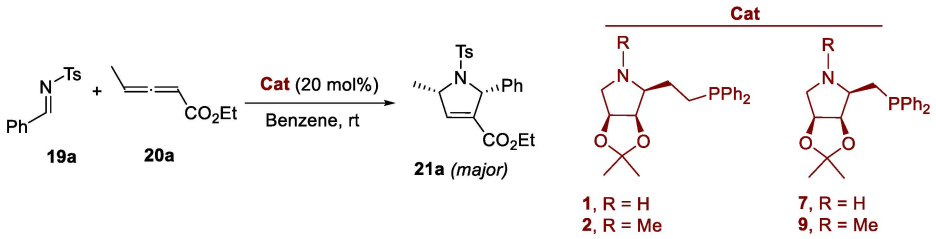
Then, reduction with $LiAlH_4$ in THF at reflux afforded the *N*-methyl derivative **18** in good overall yield.



Scheme 5. Synthesis of organocatalysts **17** and **18** derived from D-Mannose [23].

2.2. Pyrrolidine-Phosphines as Organocatalysts in [3 + 2] Cycloadditions between Alkyl Allenoates and Electron-Deficient Imines

The library of pyrrolidine-based phosphine organocatalysts was evaluated in the [3 + 2] cycloadditions between alkyl allenoates and electron-deficient imines. Preliminary experiments were carried out following Kwon's procedure [19]. Thus, model substrates *N*-tosylimine **19a** [26] and ethyl allenoate **20a** [27] were made to react in benzene at room temperature with 20 mol% of organocatalyst (Scheme 6). We first tested the reactivity of catalysts **1**, **2**, **7** and **9** which differ in the distance between the diphenylphosphine group and the pyrrolidine backbone (**1**, **2** vs. **7**, **9**) and the substitution at the nitrogen atom of the pyrrolidine moiety (**1**, **7** vs. **2**, **9**) (Table 1). In all cases the *cis*-2,5-substituted-3-pyrrolines were obtained with good yields and excellent diastereomeric ratio (dr).



Scheme 6. Phosphine-organocatalyzed reaction between imine **19a** and allenoate **20a** (model reaction).

The enantioselectivity depended on the substitution at the nitrogen atom of the pyrrolidine as the corresponding racemic 3-pyrroline was obtained with catalysts **1** and **7** while moderate enantiomeric excesses (ees) were observed with *N*-methyl pyrrolidines **2** and **9** (entries 2 and 4). Furthermore, it was observed that the stereochemical outcome of the reaction depends on the length of the phosphine alkyl chain (entries 2 and 4). The highest enantioselectivity was achieved with organocatalyst **9** (entry 4). The absolute configuration was assigned by comparison with data previously reported [19].

Table 1. Preliminary screening for the model reaction [1].

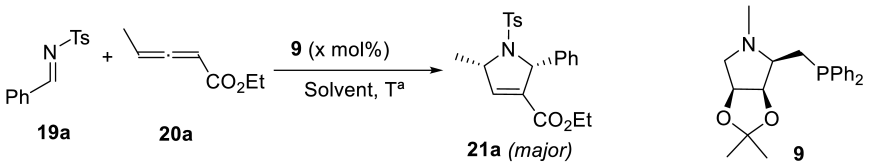
Entry	Cat	Yield (%) [2]	ee (%) [3]	*cis*/*trans* [4]
1	**1**	77	*rac.*	92:8
2	**2**	84	27	95:5
3	**7**	62	*rac.*	92:8
4	**9**	80	50	94:6

[1] Reaction conditions: **19a** (1 equiv), **20a** (1.2 equiv) and Cat (20 mol%) were stirred in benzene (0.6 mL) at rt for 9 h. [2] Yield of isolated product. [3] Determined by HPLC. [4] Determined by ^{1}H NMR of the reaction crude.

As a moderate enantioselectivity was observed, we envisaged an optimization of the reaction conditions. The results are summarized in Table 2. We noticed that the solvent had a slight influence on the yield and on the enantio- and diastereoselectivity of the reaction (entries 1–10). The best results were obtained using benzene, toluene or ethereal solvents (entries 1, 2, 7, 10–12) whereas CH_2Cl_2, MeCN and 1,2-dichlorobenzene led to a decrease in yield, ees and drs (entries 4, 5 and 6). The addition of H_2O and Et_3N as additives resulted

in a reduction of yield (entry 3) and the use of mixtures THF:EtOH resulted in a decrease in diastereoselectivity (entries 8, 9). Et_2O was identified as the best solvent, affording the desired product **21a** in 84% yield, 59% ee and excellent 93:7 dr (entry 10). Moreover, the amount of catalyst could be reduced to 10 mol% without affecting enantioselectivity, but a longer reaction time was needed with a significant reduction of yield (entry 11). Instead, a higher catalyst load (40 mol%) speeded up the reaction and increased the yield. However, no improvement in the enantioselectivity was observed (entry 12).

Table 2. Optimization screening for the model reaction [1].

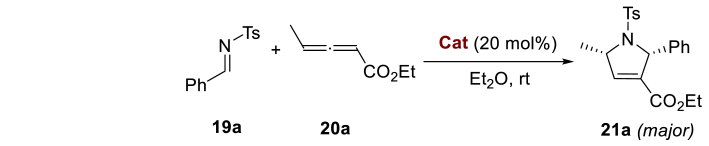


Entry	x mol%	Solvent	T	t (h)	Yield (%) [2]	ee (%) [3]	*cis*/*trans* [4]
1	20	Benzene	rt	7	80	50	94:6
2	20	Toluene	rt	7	88	55	94:6
3	20	Toluene [5]	rt	7	67	53	93:7
4	20	CH_2Cl_2	rt	7	47	45	81:19
5	20	MeCN	rt	7	46	27	77:23
6	20	1,2-DCB	rt	7	51	46	87:13
7	20	THF	rt	7	80	50	93:7
8	20	THF:EtOH 10:1	rt	7	85	53	89:11
9	20	THF:EtOH 5:1	rt	7	72	53	87:13
10	20	Et_2O	rt	7	84	59	93:7
11	10	Et_2O	rt	24	63	59	95:5
12	40	Et_2O	rt	2	95	58	95:5

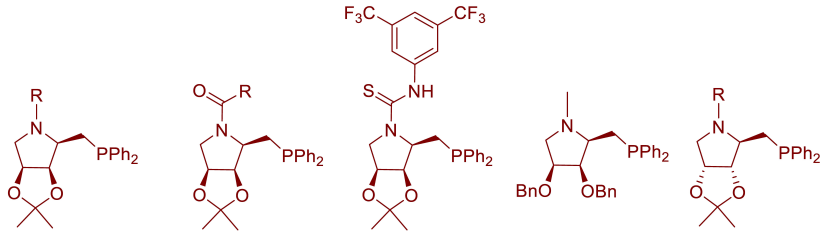
[1] Reaction at 0.154 mmol scale. [2] Yield of isolated product. [3] Determined by HPLC. [4] Determined by ^{1}H NMR of the reaction crude. [5] 20 mol% of H_2O and 5 mol% of Et_3N were used as additive. 1,2-DCB = 1,2-diclorobenzene.

To further improve the enantioselectivity, we studied the reaction with pyrrolidine phosphines **8**–**14** that present different substituents at the nitrogen atom. Moreover, the influence of the pyrrolidine backbone rigidity and the configuration of carbons bearing the isopropylidenedioxy group in the catalyst (compounds **16**–**18**) were also studied. Model [3 + 2] cycloaddition reaction using the optimized reaction conditions was used in these studies (Table 3). Similar yield, enantio- and diastereoselectivities were observed for derivatives **9**–**11** bearing alkyl substituents at the pyrrolidinic nitrogen (entries 2–4). The best results were obtained for R = Me (**9**) (entry 2, 84% yield, 59% ee and 93:7 dr). The ees dropped to 31 and 33% with *N*-acyl catalysts **12** and **13**, respectively (entries 5 and 6). The presence of a bulky ^{t}Bu group at the nitrogen atom (**13**) led to lower yield (58%). The use of thiourea derivative **14** was also studied, affording the 3-pyrroline with good yield and excellent diastereoselectivity (74% and 95:5 dr) but with a complete loss of enantioselectivity (entry 7). The results with catalyst **16** which bears benzyl groups instead of the isopropylidine group indicated that the enantioselectivity is very sensitive to the rigidity of the pyrrolidine moiety, affording **21a** with an excellent yield and dr (97:3) but a poorer enantiomeric excess (30%, entry 8). Surprisingly, 3-pyrroline ***ent*-21a** was obtained as major product in this case. A significant decrease of enantioselectivity was also observed for 2,3-*cis* derivatives **17** and **18** (12 and 11% ee, respectively, entries 9 and 10), which present different configurations at C-3 and C-4 of the pyrrolidine backbone compared to **8**–**14**.

Table 3. Screening of organocatalysts [1].



Cat =

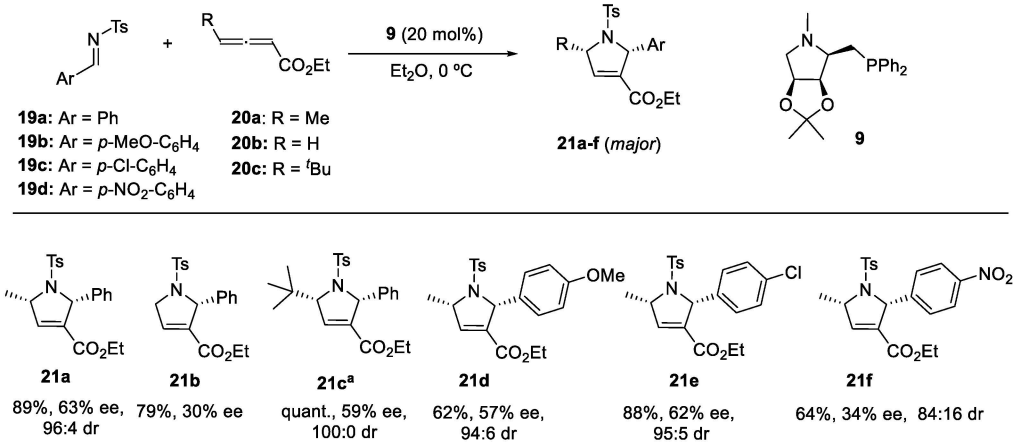


Entry	Cat	T	t (h)	Yield (%) [2]	ee (%) [3]	*cis*/*trans* [4]
1	**8**	rt	7	90	52	93:7
2	**9**	rt	7	84	59	93:7
3	**10**	rt	7	74	56	95:5
4	**11**	rt	7	88	55	94:6
5	**12**	rt	7	82	31	95:5
6	**13**	rt	7	58	33	90:10
7	**14**	rt	7	74	rac.	95:5
8	**16**	rt	7	quant.	−30	97:3
9	**17**	rt	7	96	12	94:6
10	**18**	rt	7	80	−11	97:3
11	**9**	0 °C	30	89	64	96:4
12	**9**	−30 °C	160	63	67	91:9

[1] Reaction at 0.154 mmol scale. [2] Yield of isolated product. [3] Determined by HPLC. [4] Determined by ^{1}H NMR of the reaction crude.

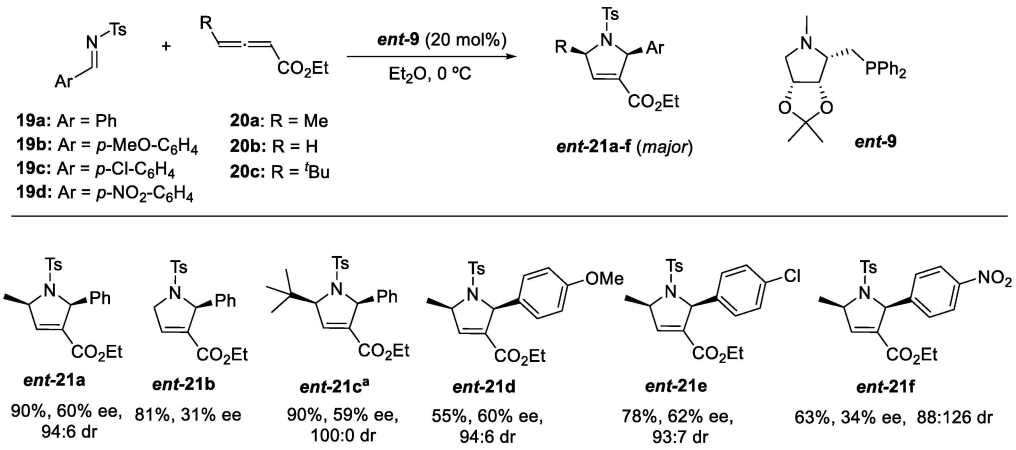
It was also found that in these 2,3-*trans*-3,4-*cis*-*N*-substituted catalysts, the substituent at the nitrogen atom of the pyrrolidine controlled the type of enantioselectivity, obtaining one or another enantiomer in each case (entry 9 vs. entry 10). A study of the influence of the temperature in the model reaction with the most promising catalyst **9** (entries 2, 11 and 12) was then performed. A marked decrease of the reaction rate, yields and dr was observed at –30 °C (entries 2 vs. 11–12). The best general results were obtained at 0 °C (entry 11) without a significative difference in the ee obtained at –30 °C (64 and 67% ee, respectively).

We next moved to explore the scope of the reaction using different alkyl allenoates and electron-deficient imines (Scheme 7). In general, [3 + 2] cycloadditions between a variety of alkyl allenoates (**20a**–**c**) and electron-deficient imines (**19a**–**d**) afforded the corresponding 3-pyrrolines **21a**–**f** in good-to-high yields and diastereoselectivities. When employing the allenoates **20a**,**c** and *N*-tosylimine **19a**, the reactions proceeded with higher enantioselectivities (63 and 59% ee, respectively) than when using the unsubstituted allenoate **20b** (30% ee). Arylimines bearing electron-donating or electron-withdrawing groups (OMe, **19b** and Cl, **19c**) were suitable substrates, furnishing similar yield, enantio- and diastereoselectivities than for imine **19a**. However, the enantioselectivity significantly decreased upon using the *p*-NO_2-arylimine **19d** (34% ee). The assignment of the absolute configuration of 3-pyrrolines **21a**–**c** was carried out by comparison with literature [19], while the absolute configuration of 3-pyrrolines **21d**–**f** was assumed to be the same as that of **21a**.



Scheme 7. Reactions with catalyst **9**. Substrate scope (Reactions performed at 0.154 mmol scale. Yield of isolated product, ee (%) determined by HPLC, dr determined by ^{1}H NMR of the reaction crude. [a] Reaction carried out in toluene at 0 °C).

When using catalyst ***ent*-9** [28], these reactions proceeded with similar yields, diastereo- and enantioselectivities, obtaining the corresponding enantiomeric 3-pyrrolines ***ent*-(21a–f)** (Scheme 8 and Supplementary Materials).



Scheme 8. Reactions with catalyst ***ent*-9**. Substrate scope (Reactions performed at 0.154 mmol scale. Yield of isolated product, ee (%) determined by HPLC, dr determined by ^{1}H NMR of the reaction crude. [a] Reaction carried out in toluene at 0 °C).

Although moderate enantioselectivities were observed in these reactions, the possibility of generating both 3-pyrroline enantiomers using enantiomeric pyrrolidine phosphines as catalysts is an undoubted advantage. A theoretical study to explain the enantioselection of these reactions is underway in our laboratory.

3. Materials and Methods

3.1. General Methods

Optical rotations were measured in a 1.0 cm or 1.0 dm tube with a Jasco P-2000 spectropolarimeter (Tokyo, Japan). Infrared spectra were recorded with a Jasco FTIR-410 spectrophotometer (Tokyo, Japan). ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded with Bruker AMX300 (Billerica, MA, USA), AV300 and AV500 spectrometers (Billerica, MA, USA) for solutions in $CDCl_3$, C_6D_6, and DMSO-d_6 at room temperature, except when indicated. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as an internal standard or H_3PO_4 (^{31}P) as an external standard. δ values are given in ppm and *J* in hertz (Hz). *J* are assigned and not repeated. All the assignments were confirmed by COSY and HSQC experiments. High resolution mass spectra were recorded on a Thermo Scientific

Q-Exactive spectrometer (Waltham, MA, USA). NMR and mass spectra were registered in CITIUS (University of Seville). TLC was performed on silica gel 60 F254 (Merck), with detection by UV light, charring with *p*-anisaldehyde, vanillin, ninhydrin, or Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. Silica gel 60 (Merck, 40−60 and 63−200 μm) was used for preparative chromatography. THF was distilled over Na/benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2. The enantio- and diastereomeric ratios of the products were determined by chiral stationary phase HPLC (Daicel Chiralpak IA, IC, ID IF columns, Osaka, Japan).

3.2. Synthesis of Phosphine Catalysts

(2S,3R,4S)-N-terc-Butyloxycarbonyl-2-hydroxyethyl-3,4-O-isopropylidene pyrrolidine-3,4-diol (**4**). To a solution of **3** [24] (1.74 g, 5.27 mmol) in anh. THF (22 mL) cooled at 0 °C, $LiBH_4$ (9.3 mL, 2 M in THF, 18.5 mmol) was added dropwise under Ar. The reaction mixture was stirred at room temperature for 4 d and then cooled at 0 °C. Then, a saturated aqueous solution of $NaHCO_3$ (30 mL) was added slowly and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered and evaporated. The resulting residue was purified by chromatography column on silica gel (Et_2O:cyclohexane, 1:2→2:1), to give **4** (1.28 g, 4.44 mmol, 84%) as a white solid. $[\alpha]_D^{23}$ + 33.9 (*c* 0.80, CH_2Cl_2). IR (ν cm^{-1}) 3431 (OH), 2981, 2935, 1662 (C=O), 1403, 1242, 1160, 859. ^{1}H NMR (300 MHz, DMSO-d_6, 363 K, δ ppm, *J* Hz) δ 4.73–4.66 (m, 2H, H-3, H-4), 3.98 (t, 1H, $J_{OH,2'}$ = 5.4, OH), 3.88–3.81 (m, 1H, H-2), 3.72–3.62 (m, 1H, H-5a), 3.55–3.45 (m, 2H, H-2′), 3.18–3.13 (m, 1H, H-5b), 2.03–1.92 (m, 1H, H-1′a), 1.87–1.78 (m, 1H, H-1′b), 1.44 (s, 3H, -C(CH_3)$_2$), 1.42 (s, 9H, -C(CH_3)$_3$), 1.30 (s, H, -C(CH_3)$_2$). ^{13}C NMR (75.4 MHz, DMSO-d_6, 363 K, δ ppm) δ 153.4 (C=O), 111.2 (-*C*(CH_3)$_2$), 79.3 (C-3 or C-4), 78.4 (-*C*(CH_3)$_3$), 76.6 (C-3 or C-4), 58.1 (C-2′), 56.4 (C-2), 50.1 (C-5), 32.1 (C-1′), 27.7 (-C(*C*H_3)$_3$), 26.0 (-C(*C*H_3)$_2$), 24.7 (-C(*C*H_3)$_2$). HRMS (ESI) *m/z* found 310.1621, calc. for $C_{14}H_{25}NO_5Na$ $[M + Na]^+$: 310.1625.

(7S,8R,8aS)-7,8-O-Isopropylidene-pentahydropyrrolo [1,2-c]-oxazol-4-ona-7,8-diol (**5**). To a solution of **4** (816 mg, 2.84 mmol) in dry pyridine (15 mL) at 0 °C, TsCl (1.4 g, 7.1 mmol) was slowly added. After stirring at room temperature for 4 h, the mixture was heated at 50 °C for 4.5 h. The solvent was then removed, and the resulting residue was purified by chromatography column on silica gel (EtOAc), to give **5** (441 mg, 2.07 mmol, 73%) as a white solid. $[\alpha]_D^{20}$ – 48.0 (*c* 0.72, CH_2Cl_2). IR (ν cm^{-1}) 2982, 2937, 1664 (C=O), 1399, 1160, 1091, 858. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 4.74–4.70 (m, 1H, H-7), 4.62 (dd, 1H, *J* = 6.0, *J* = 4.5, H-8), 4.35 (ddd, 1H, $J_{2a,2b}$ = 10.8, *J* = 4.2, *J* = 2.7, H-2a), 4.22–4.15 (m, 1H, H-2b), 4.14 (d, 1H, $J_{6a,6b}$ = 13.2, H-6a), 3.57–3.51 (m, 1H, H-8a), 3.21 (dd, 1H, $J_{6b,7}$ = 4.8, H-6b), 2.31–2.17 (m, 1H, H-1a), 2.03–1.94 (m, 1H, H-1b), 1.42 (s, 3H, -C(CH_3)$_2$), 1.30 (s, 3H, -C(CH_3)$_2$). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 153.1 (C=O), 112.4 (-*C*(CH_3)$_2$), 80.8 (C-8), 78.6 (C-7), 65.8 (C-2), 58.8 (C-8a), 52.2 (C-6), 26.5 (-C(*C*H_3)$_2$)), 24.8 (-C(*C*H_3)$_2$)), 22.0 (C-1). HRMS (ESI) *m/z* found 236.0894, calc. for $C_{10}H_{15}NO_4Na$ $[M + Na]^+$: 236.0893.

(2S,3R,4S)-2-Diphenylphosphinoethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (**1**). To a solution of **5** (192 mg, 0.90 mmol) in anh. THF (9.5 mL) at 0 °C was slowly added $KPPh_2$ (0.5 M in THF, 2.2 mL, 1.1 mmol) under Ar. The mixture was heated at reflux for 1.5 h and then warmed to room temperature IRA-120H^+ was added, and the resulting mixture was filtered through Celite and washed with CH_2Cl_2. The solvent was evaporated, and the residue was purified by chromatography column on silica gel (CH_2Cl_2:acetone, 5:1, 1% Et_3N) to give **1** (221 mg, 0.623 mmol, 69%) as a colourless oil. $[\alpha]_D^{23}$ + 66.2 (*c* 1.0, CH_2Cl_2). IR (ν cm^{-1}) 3320 (NH), 2982, 2924, 1662, 1276, 1042, 695. ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.49–7.45 (m, 2H, H-arom.), 7.43–7.39 (m, 2H, H-arom.), 7.34–7.29 (m, 6H, H-arom.), 4.65 (dd, 1H, $J_{4,3}$ = 5.5, $J_{4,5b}$ = 4.0, H-4), 4.51 (dd, 1H, $J_{3,2}$ = 4.0, H-3), 3.04 (d, 1H, $J_{5a,5b}$ = 13.5, H-5a), 2.72–2.69 (m, 1H, H-2), 2.57 (dd, 1H, H-5b), 2.29–2.23 (m, 1H, H-2′a), 2.19–2.13 (m, 1H, H-2′b), 1.79–1.72 (m, 3H, H-1′, NH), 1.40 (s, 3H, -C(CH_3)$_2$), 1.30 (s, 3H, -C(CH_3)$_2$). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 139.1 (d, $J_{C,P}$ = 12.6, C_{arom}-P), 138.3 (d, $J_{C,P}$ = 12.6, C_{arom}-P), 133.1 (d, $J_{C,P}$ = 18.5, C-arom.), 132.7 (d, $J_{C,P}$ = 18.1, C-arom.), 128.7 (C-arom.),

128.6–128.5 (m, C-arom.), 110.5 (-*C*(CH_3)$_2$), 82.3, 81.6 (C-3, C-4), 65.1 (d, $J_{C,P}$ = 13.4, C-2), 53.1 (C-5), 25.9 (-C(*C*H_3)$_2$), 25.6 (d, $J_{C,P}$ = 11.4, C-2′), 25.2 (d, $J_{C,P}$ = 16.8, C-1′), 24.1 (-C(*C*H_3)$_2$). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ 15.8 (s). HRMS (ESI) *m/z* found 356.1762, calc. for $C_{21}H_{27}NO_2P$ $[M + H]^+$: 356.1774.

(2S,3R,4S)-N-Methyl-2-diphenylphosphinoethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (**2**). To a solution of **1** (80 mg, 0.23 mmol) in anh. CH_2Cl_2 (1.0 mL) at 0 °C was successively added Et_3N (34 µL, 0.25 mmol) and $ClCO_2CH_3$ (20 µL, 0.25 mmol). The mixture was stirred at 0 °C for 2 h. Then, HCl 0.1 M (5 mL) was added and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried with Na_2SO_4, filtered and evaporated. The resulting crude was dissolved in anh. THF (1.5 mL) and added to a suspension of $LiAlH_4$ (25 mg, 0.66 mmol) in anh. THF (0.5 mL) at 0 °C. The mixture was heated at reflux for 2.5 h and then cooled at 0 °C. Et_2O and a saturated aqueous solution of Na_2SO_4 were successively added and the mixture was filtered through Celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (EtOAc:cyclohexane, 1:2) to give **2** (60 mg, 0.16 mmol, 74%, 2 steps) as a colourless oil. $[\alpha]_D^{23}$ + 154.5 (*c* 0.56, CH_2Cl_2). IR (ν cm^{-1}) 2935, 2774, 1432, 1150, 1077, 695. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.55–7.50 (m, 2H, H-arom.), 7.43–7.38 (m, 2H, H-arom.), 7.34–7.29 (m, 6H, H-arom.), 4.63–4.56 (m, 2H, H-4, H-3), 3.15 (d, 1H, $J_{5a,5b}$ = 11.1, H-5a), 2.42–2.37 (m, 1H, H-1a′), 2.15 (s, 3H, *N*-C*H*$_3$), 2.04 (dd, 1H, $J_{5b,4}$ = 3.9, H-5b), 2.00–1.90 (m, 2H, H-2, H-1′b), 1.87–1.63 (m, 2H, H-2′a, H-2′b), 1.45 (s, 3H, -C(C*H*$_3$)$_2$), 1.32 (s, 3H, -C(C*H*$_3$)$_2$). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 139.7 (d, $J_{C,P}$ = 12.7, C_{arom}-P), 137.9 (d, $J_{C,P}$ = 12.7, C_{arom}-P), 133.3 (d, $J_{C,P}$ = 18.7, C-arom.), 132.5 (d, $J_{C,P}$ = 17.8, C-arom.), 128.8 (C-arom.), 128.5–128.4 (m, C-arom.), 110.8 (-*C*(CH_3)$_2$), 80.6 (C-3 or C-4), 78.0 (C-3 or C-4), 71.2 (d, $J_{C,P}$ = 14.3, C-2), 62.2 (C-5), 40.5 (*N*-*C*H$_3$), 26.1 (-C(*C*H$_3$)$_2$), 24.9 (-C(*C*H$_3$)$_2$), 24.3(d, $J_{C,P}$ = 10.9, C-1′), 24.0 (d, $J_{C,P}$ = 16.0, C-2′). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ 15.0 (s). HRMS (ESI) *m/z* found 370.1932, calc. for $C_{22}H_{29}NO_2P$ $[M + H]^+$: 370.1930.

(2S,3R,4S)-N-Methoxycarbonyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (**8**). To a solution of **7** [22] (330 mg, 0.970 mmol) in anh. CH_2Cl_2 (5.0 mL) at 0 °C, was successively added Et_3N (0.15 mL, 1.1 mmol) and $ClCO_2CH_3$ (84 µL, 1.1 mmol). The mixture was stirred at 0 °C for 2.5 h. Then, HCl (0.1 M) was added and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried with Na_2SO_4, filtered and evaporated. The resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane, 1.4) to give **8** (273 mg, 0.680 mmol, 70%) as a colourless oil. $[\alpha]_D^{25}$ + 77.6 (*c* 0.71, CH_2Cl_2). IR (ν cm^{-1}) 2988, 2940, 1699 (C=O), 1446, 1081, 695. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.63–7.58 (m, 2H, H-arom), 7.46–7.28 (m, 8H, H-arom.), 4.79 (ap.t, 1H, $J_{3,4}$ = $J_{3,2}$ = 6.0, H-3), 4.72–4.67 (m, 1H, H-4), 4.00–3.91 (m, 1H, H-2), 3.80–3.74 (m, 1H, H-5a), 3.61 (s, 3H, OC*H*$_3$), 3.40 (dd, 1H, $J_{5b,5a}$ = 12.3, $J_{5b,4}$ = 4.5, H-5b), 2.99–2.91 (m, 1H, H-1a′), 2.45–2.37 (m, 1H, H-1b′), 1.49 (s, 3H, -C(C*H*$_3$)$_2$), 1.35 (s, 3H, -C(C*H*$_3$)$_2$). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 155.7 (C=O), 139.5 (d, $J_{C,P}$ = 12.6, C_{arom}-P), 138.2 (d, $J_{C,P}$ = 13.3, C_{arom}-P), 133.3 (d, $J_{C,P}$ = 19.7, C-arom.), 132.7 (d, $J_{C,P}$ = 18.6, C-arom.), 128.9 (C-arom.), 128.6 (d, $J_{C,P}$ = 6.8, C-arom.), 128.5 (C-arom.), 128.4 (d, $J_{C,P}$ = 6.9, C-arom.), 113.0 (-*C*(CH_3)$_2$, 80.1 (d, $J_{C,P}$ = 2.3, C-3), 77.8 (C-4), 58.3 (d, $J_{C,P}$ = 23.4, C-2), 52.4 (-O*C*H$_3$),51.1 (C-5), 28.6 (d, $J_{C,P}$ = 11.4, C-1′), 26.9 (-C(*C*H$_3$)$_2$), 25.4(-C(*C*H$_3$)$_2$). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ 20.7 (s). HRMS (ESI) *m/z* found 400.1662, calc. for $C_{22}H_{27}NO_4P$ $[M + H]^+$: 400.1672.

(2S,3R,4S)-N-Butyl-2-diphenylphosfinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (**10**). A solution of butanal (35 µL, 0.38 mmol) in 2,2,2-trifluoroethanol (0.8 mL) was heated at 35 °C for 5 min. Then, **7** [22] (64 mg, 0.19 mmol) was added and the reaction mixture was heated at 35 °C for 1 h. $NaBH_4$ (15 mg, 0.38 mmol) was added and then the mixture was stirred for 1 h. The mixture was filtered through Celite and washed with CH_2Cl_2. The solvent was evaporated, and the residue was purified by chromatography column on silica gel (Et_2O:cyclohexane, 1:5) to give **10** (49 mg, 0.12 mmol, 66%) as a colourless

oil. $[\alpha]_D^{22}$ + 152.2 (*c* 0.65, CH_2Cl_2). IR (ν cm^{-1}) 2952, 2930, 1028, 694. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.55–7.49 (m, 2H, H-arom.), 7.47–7.40 (m, 2H, H-arom.), 7.37–7.28 (m, 6H, H-arom.), 4.62 (dd, 1H, $J_{3,4}$ = 6.3, $J_{3,2}$ = 4.5, H-3), 4.56 (dd, 1H, $J_{4,5b}$ = 4.5, H-4), 3.19 (d, 1H, $J_{5a,5b}$ = 11.1, H-5a), 2.86–2.77 (m, 1H, *N*-CH_2), 2.51–2.43 (m, 1H, H-1′a), 2.38 (dt, 1H, $J_{1'b,1'a}$ = 13.3, $J_{1'b,2}$ = $J_{1'b,P}$ = 3.3, H-1′b), 1.98–1.86 (m, 2H, H-5b, H-2), 1.81–1.73 (m, 1H, *N*-CH_2), 1.52 (s, 3H, -C(CH_3)$_2$), 1.44–1.24 (m, 7H, -C(CH_3)$_2$, -$CH_2CH_2CH_2CH_3$), 0.89 (t, 3H, $^3J_{H,H}$ = 7.0, -CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 139.6 (d, $J_{C,P}$ = 12.2, C_{arom}-P), 138.7 (d, $J_{C,P}$ = 13.6, C_{arom}-P), 133.4 (d, $J_{C,P}$ = 19.8, C-arom.), 132.4 (d, $J_{C,P}$ = 17.7, C-arom.), 129.0 (C-arom.), 128.6 (d, $J_{C,P}$ = 7.1, C-arom.), 128.3 (d, $J_{C,P}$ = 8.3, C-arom.), 128.3 (C-arom.), 111.1 (-*C*(CH$_3$)$_2$), 80.8 (d, $J_{C,P}$ =3.8, C-3), 78.0 (C-4), 66.0 (d, $J_{C,P}$ = 19.8, C-2), 59.4 (C-5), 52.8 (-NCH_2), 29.9 (-NCH_2CH_2), 26.4 (-C(CH_3)$_2$), 26.0 (d, $J_{C,P}$ = 12.4, C-1′), 25.6 (-C(CH_3)$_2$), 20.8 (-$NCH_2CH_2CH_2$), 14.1 (-CH_3). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ 21.4 (s). HRMS (ESI) *m/z* found 398.2243, calc. for $C_{24}H_{33}NO_2P$ [M + H]$^+$: 398.2243.

(2S,3R,4S)-N-Benzyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (**11**). To a solution of **7** [22] (66 mg, 0.19 mmol) in anh. 1,2-dichloroethane (2 mL) were successively added benzaldehyde (40 µL, 0.39 mmol) and $NaBH(OAc)_3$ (87 mg, 0.41 mmol). The mixture was stirred at room temperature for 3 h, and then a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered, and evaporated. The residue was purified by chromatography column on silica gel (Et_2O:cyclohexane, 1.5) to give **11** (48 mg, 0.11 mmol, 58%) as a colourless oil. $[\alpha]_D^{22}$ + 115.2 (*c* 1.0, CH_2Cl_2). IR (ν cm^{-1}) 2985, 1433, 1028, 695. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.45–7.32 (m, 4H, H-arom.), 7.29–7.19 (m, 6H, H-arom.), 7.18–7.10 (m, 5H, H-arom.), 4.59 (dd, 1H, $J_{3,4}$ = 6.3, $J_{3,2}$ = 4.8, H-3), 4.43 (dd, 1H, $J_{4,5b}$ = 4.5, H-4), 3.96 (d, 1H, $^2J_{H,H}$ = 13.8, -CH_2Ph), 2.96–2.88 (m, 2H, H-5a, -CH_2Ph), 2.48–2.32 (m, 2H, H-1′a, H-1′b), 2,04–1.96 (m, 1H, H-2), 1.82 (dd, 1H, $J_{5b,5a}$ = 11.1, H-5b), 1.47 (s, 3H, -C(CH_3)$_2$), 1.23 (s, 3H, -C(CH_3)$_2$). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 139.3 (d, $J_{C,P}$ = 12.0, C_{arom}-P), 138.8 (d, $J_{C,P}$ = 13.8, C_{arom}-P), 133.6 (d, $J_{C,P}$ = 20.1, C-arom.), 132.4 (d, $J_{C,P}$ = 17.8, C-arom.), 129.2 (C-arom.), 128.7–128.3 (m, C-arom.), 126.9 (C-arom.), 111.3 (-*C*(CH$_3$)$_2$), 80.9 (d, $J_{C,P}$ = 3.7, C-3), 77.9 (C-4), 65.2 (d, $J_{C,P}$ = 22.4, C-2), 59.3 (C-5), 56.6 (-CH_2Ph), 26.6 (-C(CH_3)$_2$), 26.4 (d, $J_{C,P}$ = 12.4, C-1′), 25.8 (-C(CH_3)$_2$). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ 21.7 (s). HRMS (ESI) *m/z* found 432.2092, calc. for $C_{27}H_{31}NO_2P$ [M + H]$^+$: 432.2087.

(2S,3R,4S)-N-Benzoyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (**12**). To a solution of **7** [22] (88 mg, 0.26 mmol) in anh. CH_2Cl_2 (2 mL) cooled at 0 °C, was successively added Et_3N (72 µL, 0.52 mmol) and benzoyl chloride (40 µL, 0.34 mmol). The mixture was stirred at room temperature for 2.5 h. Then, a saturated aqueous solution of NH_4Cl was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and evaporated. The resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane, 1.4→1:2) to give **12** (113 mg, 0.250 mmol, 98%) as a colourless oil. $[\alpha]_D^{26}$ + 75.1 (*c* 0.77, CH_2Cl_2). IR (ν cm^{-1}) 2993, 2927, 1631 (C=O), 1078, 695. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.67–7.63 (m, 2H, H-arom), 7.52–7.26 (m, 13H, H-arom.), 4.83 (ap.t, 1H, $J_{3,4}$ = $J_{3,2}$ = 6.0, H-3), 4.62 (q, 1H, $J_{4,5b}$ = $J_{4,5a}$ = 6.3, H-4), 4.57–4.48 (m, 1H, H-2), 3.70 (dd, 1H, $J_{5a,5b}$ = 11.7, H-5a), 3.57 (dd, 1H, H-5b), 3.03–2.91 (m, 1H, H-1a′), 2.51 (dd, 1H, $J_{1b',1a'}$ = 13.2, $J_{1b',2}$ = 10.2, H-1b′), 1.55 (s, 3H, -C(CH_3)$_2$), 1.35 (s, 3H, -C(CH_3)$_2$). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 170.1 (C=O), 139.5 (d, $J_{C,P}$ = 12.4, C_{arom}-P), 137.8 (d, $J_{C,P}$ = 11.6, C_{arom}-P), 136.2 (C-arom.), 133.2 (d, $J_{C,P}$ = 19.5, C-arom.), 132.8 (d, $J_{C,P}$ = 18.9, C-arom.), 130.6 (C-arom.), 128.9–128.4 (m, C-arom.), 128.4 (C-arom.), 127.8 (C-arom.), 113.3 (-*C*(CH$_3$)$_2$), 79.6 (d, $J_{C,P}$ = 2.8, C-3), 78.0 (C-4), 57.7 (d, $J_{C,P}$ = 22.0, C-2), 54.1 (C-5), 28.1 (d, $J_{C,P}$ = 14.3, C-1′), 27.4 (-C(CH_3)$_2$), 25.6 (-C(CH_3)$_2$). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ 20.8 (s). HRMS (ESI) *m/z* found 446.1867, calc. for $C_{27}H_{29}NO_3P$ [M + H]$^+$: 446.1880.

(2S,3R,4S)-N-Pivaloyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (**13**). To a solution of **7** [22] (104 mg, 0.300 mmol) in anh. CH_2Cl_2 (2.5 mL) cooled at 0 °C, was

successively added Et_3N (85 µL, 0.61 mmol) and pivaloyl chloride (50 µL, 0.39 mmol). The mixture was stirred at room temperature for 2 h. Then, a saturated aqueous solution of NH_4Cl was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and evaporated. The resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane, 1:5) to give **13** (121 mg, 0.290 mmol, 94%) as a colourless oil. $[\alpha]_D^{26}$ + 50.1 (*c* 0.79, CH_2Cl_2). IR (ν cm^{-1}) 2988, 2929, 1625 (C=O), 1079, 696. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.69–7.63 (m, 2H, H-arom), 7.46–7.27 (m, 8H, H-arom.), 4.72 (ap.t, 1H, $J_{3,4} = J_{3,2}$ = 6.0, H-3), 4.63 (q, 1H, $J_{4,5b} = J_{4,5a}$ = 6.6, H-4), 4.48–4.39 (m, 1H, H-2), 4.05 (ddd, 1H, $J_{5a,5b}$ = 11.1, *J* = 0.9, H-5a), 3.45 (dd, 1H, H-5b), 2.89 (dt, 1H, $J_{1a',1b'}$ = 13.5, $J_{1a',2} = J_{1a',P}$ = 4.5, H-1a'), 2.37 (dd, 1H, $J_{1b',2}$ = 10.2, H-1b'), 1.49 (s, 3H, -C(CH_3)$_2$), 1.34 (s, 3H, -C(CH_3)$_2$), 1.18 (s, 9H, -C(CH_3)$_3$). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 177.0 (C=O), 140.0 (d, $J_{C,P}$ = 12.4, C_{arom}-P), 138.3 (d, $J_{C,P}$ = 13.9, C_{arom}-P),133.1 (d, $J_{C,P}$ = 19.1, C-arom.), 132.9 (d, $J_{C,P}$ = 19.0, C-arom.), 128.7 (d, $J_{C,P}$ = 6.6, C-arom.), 128.6 (C-arom.), 128.4 (C-arom.), 128.3 (d, $J_{C,P}$ = 6.9, C-arom.), 113.2 (-C(CH_3)$_2$, 78.5 (d, $J_{C,P}$ =2.3, C-3), 78.3 (C-4), 58.7 (d, $J_{C,P}$ = 21.9, C-2), 52.3 (C-5), 39.2 (-C(CH_3)$_3$), 27.8 (C-1′, -C(CH_3)$_3$), 27.4 (-C(CH_3)$_2$), 25.7 (-C(CH_3)$_2$). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ 19.3 (s). HRMS (ESI) *m/z* found 426.2181, calc. for $C_{25}H_{33}NO_3P$ [M + H]$^+$: 426.2193.

(2S,3R,4S)-N-Methyl-3,4-di-O-benzyl-2-diphenylphosphinomethyl-pyrrolidine-3,4-diol (**16**). To a solution of **15** [23] (58 mg, 0.26 mmol) in anh. THF (1.5 mL) at 0 °C was slowly added $KPPh_2$ (0.5 M in THF, 0.52 mL, 0.26 mmol) under Ar. The mixture was heated at reflux for 2 h and then warmed to room temperature IRA-120H$^+$ was added, and the resulting mixture was filtered through Celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (CH_2Cl_2, 1% Et_3N) to give the corresponding diphenylphosphinomethyl-pyrrolidine (49 mg, 0.10 mmol, 60%). To a solution of this compound (49 mg, 0.10 mmol) in anh. CH_2Cl_2 (0.5 mL) at 0 °C, was successively added Et_3N (16 µL, 0.11 mmol) and $ClCO_2CH_3$ (9.0 µL, 0.11 mmol). The mixture was stirred at 0 °C for 4.5 h. Then, HCl (0.1 M) was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried with Na_2SO_4, filtered and evaporated. The resulting crude was dissolved in anh. THF (1.0 mL) and added to a suspension of $LiAlH_4$ (12 mg, 0.29 mmol) in anh. THF (0.5 mL) at 0 °C. The mixture was heated at reflux for 2 h and then cooled at 0 °C. Et_2O and a saturated aqueous solution of Na_2SO_4 were successively added and the mixture was filtered through Celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (EtOAc:cyclohexane, 1:2) to give **16** (33 mg, 0.070 mmol, 64%, 2 steps) as a colourless oil. $[\alpha]_D^{26}$ + 86.5 (*c* 0.73, CH_2Cl_2). IR (ν cm^{-1}) 2916, 2851, 1026, 736, 688. ^{1}H NMR (500 MHz, C_6D_6, δ ppm, *J* Hz) δ 7.59–7.56 (m, 2H, H-arom.), 7.46–7.43 (m, 4H, H-arom.), 7.32–7.31 (m, 2H, H-arom.), 7.18–7.00 (m, 12H, H-arom.), 4.86 (d, 1H, $^2J_{H,H}$ = 11.5, -CH_2Ph(a)), 4.56 (d, 1H, -CH_2Ph(a)), 4.39 (s, 2H, -CH_2Ph(b)), 3.98 (t.a, 1H, $J_{3,4} = J_{3,2}$ = 5.0, H-3), 3.74–3.71 (m, 1H, H-4), 3.26 (dd, 1H, $J_{5a,5b}$ = 10.0, $J_{5a,4}$ = 4.5, H-5a), 2.85–2.81 (m, 1H, H-1′a), 2.63–2.56 (m, 2H, H-2, H-1′b), 2.23 (dd, 1H, $J_{5b,4}$ = 6.5, H-5b), 2.21 (s, 3H, *N*-CH_3). ^{13}C NMR (125.7 MHz, C_6D_6, δ ppm, *J* Hz) δ 140.8 (d, $J_{C,P}$ = 14.0, C_{arom}-P), 140.2 (d, $J_{C,P}$ = 14.8, C_{arom}-P), 139.7 (C-arom.), 139.5 (C-arom.), 133.6 (d, $J_{C,P}$ = 19.4, C-arom.), 133.1 (d, $J_{C,P}$ = 18.0, C-arom.), 128.7–127.6 (m, C-arom.), 80.3 (d, $J_{C,P}$ = 5.6, C-3), 78.8 (C-4), 73.6 (-CH_2Ph(a)), 71.9 (-CH_2Ph(b)), 65.5(d, $J_{C,P}$ = 19.3, C-2), 58.4 (C-5), 42.0 (*N*-CH_3), 28.9 (d, $J_{C,P}$ = 12.9, C-1′). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ 20.4 (s). HRMS (ESI) *m/z* found 496.2384, calc. for $C_{32}H_{35}NO_2P$ [M + H]$^+$: 496.2400.

(2S,3S,4R)-N-Methyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (**18**). To a suspension of $LiAlH_4$ (30 mg, 0.79 mmol) in anh. THF (1.6 mL) at 0 °C was added a solution of **17** [23] (70 mg, 0.16 mmol) in anh. THF (1.6 mL). The mixture was heated at reflux for 2.5 h under Ar and then cooled at 0 °C. Et_2O and a saturated aqueous solution of Na_2SO_4 were successively added and the mixture was filtered through Celite and washed

with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (EtOAc:cyclohexane, 1:3) to give **18** (47 mg, 0.13 mmol, 84%) as a pale yellow oil. $[\alpha]_D^{27}$ + 56.8 (*c* 1.32, CH_2Cl_2). IR (ν cm^{-1}) 2985, 2932, 1206, 1055, 694. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.52–7.43 (m, 4H, H-arom.), 7.34–7.30 (m, 6H, H-arom.), 4.64–4.60 (m, 1H, H-4), 4.49 (dd, 1H, *J* = 6.9, *J* = 4.2, H-3), 3.22 (dd, 1H, $J_{5a,5b}$ = 10.2, $J_{5a,4}$ = 6.3, H-5a), 2.58–2.44 (m, 3H, H-1′a, H-2, H-5b), 2.24 (s, 3H, *N*-CH_3), 2.07–1.99 (m, 1H, H-1′b), 1.44 (s, 3H, -C(CH_3)$_2$), 1.28 (s, 3H, -C(CH_3)$_2$). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 139.1–137.7 (m, C-arom.), 133.3 (d, $J_{C,P}$ = 19.4, C-arom.), 132.9 (d, $J_{C,P}$ = 18.9, C-arom.), 129.0 (C-arom.), 128.8 (C-arom.), 128.6 (d, $J_{C,P}$ = 7.0, C-arom.), 128.5 (d, $J_{C,P}$ = 6.7, C-arom.), 113.3 (-*C*(CH$_3$)$_2$), 85.4 (d, $J_{C,P}$ = 6.5, C-3), 77.9 (C-4), 68.6–68.4 (m, C-2), 61.2 (C-5), 40.0 (*N*-CH_3), 29.4 (d, $J_{C,P}$ = 14.8, C-1′), 27.2 (-C(CH_3)$_2$), 25.1 (-C(CH_3)$_2$). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ 24.3 (s). HRMS (ESI) *m/z* found 356.1756, calc. for $C_{21}H_{27}NO_2P$ $[M + H]^+$: 356.1774.

(2R,3S,4R)-N-Methyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (***ent*-9**). To a solution of ***ent*-7** (391 mg, 1.15 mmol) in anh. CH_2Cl_2 (5.5 mL) at 0 °C, was successively added Et_3N (175 µL, 1.26 mmol) and $ClCO_2CH_3$ (100 µL, 1.26 mmol). The mixture was stirred at 0 °C for 4.5 h. Then, HCl (0.1 M) was added and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried with Na_2SO_4, filtered and evaporated. The resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane, 1:4) to give the corresponding *N*-methoxycarbonyl pyrrolidine (326 mg, 0.820 mmol, 74%, 2 steps). A solution of this compound (311 mg, 0.790 mmol) was dissolved in anhydrous THF (6.0 mL) and added to a suspension of $LiAlH_4$ (90 mg, 2.4 mmol) in anh. THF (2.0 mL) at 0 °C. The mixture was heated at reflux for 1 h and then cooled at 0 °C. Et_2O and a saturated aqueous solution of Na_2SO_4 were successively added and the mixture was filtered through Celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (EtOAc:cyclohexane, 1:2→1:1) to give ***ent*-9** (257 mg, 0.720 mmol, 92%) as a colourless oil. NMR and IR data are in accordance with those of its enantiomer **9** [18]. $[\alpha]_D^{27}$ – 163.3 (*c* 1.23, CH_2Cl_2). HRMS (ESI) *m/z* found 356.1759, calc. for $C_{21}H_{27}NO_2P$ $[M + H]^+$: 356.1774.

3.3. Enantioselective Phosphine-Catalyzed [3 + 2] Cycloaddition between Allenoates and Electron-Deficient Imines

General procedure: To a solution of the imine **19** (1.0 equiv, 0.154 mmol) and phosphine **9** or ***ent*-9** (0.2 equiv, 0.03 mmol, 11 mg) in Et_2O (0.6 mL) cooled at 0 °C or in toluene (0.6 mL) at r.t. the allenoate **20** (1.2 equiv, 0.185 mmol) was added dropwise in Et_2O or toluene (0.6 mL). The reaction mixture was stirred for the specified time at specific temperature. Then, the solvent was concentrated and the resulting residue was purified by chromatography column on silica gel to give pure **21** or ***ent*-21**. Enantiomeric ratios were determined by HPLC analysis. Diastereomeric ratios were determined by analysis of ^{1}H NMR reaction crudes. Racemic samples were prepared with PPh_3 o PBu_3 (20 mol%) in toluene at room temperature following this general procedure.

(2R,5S) Ethyl 2-phenyl-5-methyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**21a**). Reaction of imine **19a** [26] (40 mg, 0.15 mmol), **9** (11 mg, 0.03 mmol) and allenoate **20a** [27] (24 mg, 0.19 mmol) in Et_2O (1.2 mL) for 30 h at 0 °C and chromatography column (toluene:acetone, 60:1), afforded **21a** (53 mg, 0.14 mmol, 89%, 63% ee, dr 96:4 *cis/trans*) as a pale yellow oil. NMR and IR data are in accordance with literature [7] $[\alpha]_D^{26}$ – 110.8 [*c* 1.0, $CHCl_3$, 63% ee (2*R*,5*S*)]. Lit. [19]. $[\alpha]_D^{20}$ – 18.0 [*c* 1.0, $CHCl_3$, 4% ee (2*R*,5*S*)]. The enantiomeric ratios were determined by HPLC using a Chiralpak ID column [*n*-hexanes/*i*PrOH (70:30)]; flow rate 1.0 mL/min, λ = 210 nm, T = 30 °C; t_R ((2*S*,5*R*), minor) = 15.3 min, t_R ((2*R*,5*S*), mayor) = 24.0 min.

(2R)-Ethyl 2-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**21b**). Reaction of imine **19a** (40 mg, 0.15 mmol), **9** (11 mg, 0.03 mmol) and allenoate **20b** [29] (21 mg, 0.19 mmol) in Et_2O (1.2 mL) for 38 h at 0 °C and chromatography column (EtOAc:cyclohexane, 1:5), afforded

21b (45 mg, 0.12 mmol, 79%, 30% ee (2*R*)) as a colourless oil. NMR and IR data are in accordance with literature [29]. $[\alpha]_D^{24}$ – 63.0 [c 1.0, $CHCl_3$, 30% ee (2*R*)]. Lit. [19]. $[\alpha]_D^{20}$ + 147.4 [*c* 1.0, $CHCl_3$, 72% ee (2*S*)]. The enantiomeric ratios were determined by HPLC using a Chiralpak IC column [*n*-hexanes/*i*PrOH (50:50)]; flow rate 1.0 mL/min, λ = 210 nm, T = 30 °C; t_R (2*S*, minor) = 15.2 min, t_R (2*R*, mayor) = 22.1 min.

(2R,5R) Ethyl 5-(terc-butyl)-2-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**21c**). Reaction of imine **19a** (40 mg, 0.15 mmol), **9** (11 mg, 0.03 mmol) and allenoate **20c** [29] (31 mg, 0.19 mmol) in toluene (1.2 mL) for 48 h at room temperature and chromatography column (EtOAc:cyclohexane, 1:8), afforded **21c** (66 mg, 0.15 mmol, quant., dr 100:0 *cis/trans*, 59% ee (2*R*,5*R*)) as a pale yellow oil. NMR and IR data are in accordance with literature [7]. $[\alpha]_D^{23}$ – 70.8 [*c* 1.0, $CHCl_3$, 59% ee (2*R*,5*R*)]. Lit. [19]. $[\alpha]_D^{20}$ – 84.5 [*c* 1.0, $CHCl_3$, 73% ee (2*R*,5*R*)]. The enantiomeric ratios were determined by HPLC using a Chiralpak IA column [*n*-hexanes/*i*PrOH (80:20)]; flow rate 1.0 mL/min, λ = 210 nm, T = 30 °C; t_R ((2*S*,5*S*), minor) = 5.0 min, t_R ((2*R*,5*R*), mayor) = 6.1 min.

(2R,5S) Ethyl 5-methyl-2-(4-methoxyphenyl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**21d**). Reaction of imine **19b** [30] (45 mg, 0.15 mmol), 9 (11 mg, 0.03 mmol) and allenoate **20a** (24 mg, 0.19 mmol) in Et_2O (1.2 mL) for 44 h at 0 °C and chromatography column (toluene:acetone, 50:1), afforded **21d** (40 mg, 0.10 mmol, 62%, dr 94:6 *cis/trans*, 57% ee (2*R*,5*S*)) as a pale yellow oil. NMR and IR data are in accordance with literature [31]. $[\alpha]_D^{23}$ – 116.1 [*c* 1.0, $CHCl_3$, 57% ee (2*R*,5*S*)]. The enantiomeric ratios were determined by HPLC using a Chiralpak IF column [*n*-hexanes/*i*PrOH (70:30)]; flow rate 1.0 mL/min, λ = 210 nm, T = 30 °C; t_R ((2*S*,5*R*), minor) = 16.4 min, t_R ((2*R*,5*S*), mayor) = 20.8 min.

(2R,5S) Ethyl 2-(4-chlorophenyl)-5-methyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**21e**). Reaction of imine **19c** [30] (46 mg, 0.15 mmol), **9** (11 mg, 0.03 mmol) and allenoate **20a** (24 mg, 0.19 mmol) in Et_2O (1.2 mL) for 38 h at 0 °C and chromatography column (toluene:acetone, 50:1), afforded **21e** (57 mg, 0.14 mmol, 88%, dr 95:5 *cis/trans*, 62% ee (2*R*,5*S*)) as a colourless oil. NMR and IR data are in accordance with literature [31]. $[\alpha]_D^{23}$ – 124.0 [*c* 1.0, $CHCl_3$, 62% ee (2*R*,5*S*)]. The enantiomeric ratios were determined by HPLC using a Chiralpak IC column [*n*-hexanes/*i*PrOH (90:10)]; flow rate 1.0 mL/min, λ = 210 nm, T = 30 °C; t_R ((2*S*,5*R*), minor) = 30.3 min, t_R ((2*R*,5*S*), mayor) = 41.5 min.

(2R,5S) Ethyl 5-methyl-2-(4-nitrophenyl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**21f**). Reaction of imine **19d** [30] (47 mg, 0.15 mmol), **9** (11 mg, 0.03 mmol) and allenoate **20a** (24 mg, 0.19 mmol) in Et_2O (1.2 mL) for 16 h at 0 °C and chromatography column (toluene:acetone, 50:1), afforded **21f** (42 mg, 0.10 mmol, 64%, dr 84:16 *cis/trans*, 34% ee (2*R*,5*S*)) as a colourless oil. NMR and IR data are in accordance with literature [31] $[\alpha]_D^{23}$ – 82.5 [*c* 1.0, $CHCl_3$, 34% ee (2*R*,5*S*)]. The enantiomeric ratios were determined by HPLC using a Chiralpak IC column [*n*-hexanes/*i*PrOH (70:30)]; flow rate 1.0 mL/min, λ = 210 nm, T = 30 °C; t_R ((2*S*,5*R*), minor) = 25.3 min, t_R ((2*R*,5*S*), major) = 31.5 min.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal12080876/s1, experimental procedures for the synthesis of ***ent*-9** and ***ent*-(21a–f)**, copies of ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and HPLC traces [32–35].

Author Contributions: Conceptualization, I.R. and A.T.C.; methodology, I.R. and A.T.C.; formal analysis, A.J.M.-V., P.E.-R.; investigation, I.R., A.T.C., P.E.-R., A.J.M.-V.; resources, I.R., A.J.M.-V.; writing—original draft preparation, I.R., A.T.C., P.E.-R., A.J.M.-V.; writing—review and editing, I.R., A.T.C., P.E.-R., A.J.M.-V.; supervision, I.R. and A.T.C.; project administration, I.R. and A.T.C.; funding acquisition, I.R., A.J.M.-V.; All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the "Ministerio de Ciencia e Innovación", grant numbers CTQ2016–77270-R and PID2020-116460RB-100 (funded by MCIN/AEI/ 10.13039/501100011033) and by "Junta de Andalucía" (FQM-345).

Data Availability Statement: Not applicable.

Acknowledgments: We thank the Spanish Ministry of Education for a FPU fellowship (P.E.R), Elena Moreno-Clavijo for helpful discussions and CITIUS-NMR-MS service of the University of Seville for technical assistance.

Conflicts of Interest: The authors declare no conflict of interest.

References and Note

1. Halpern, J.; Trost, B.M. Asymmetric Catalysis. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5347. [CrossRef] [PubMed]
2. Wei, Y.; Shi, M. Applications of Chiral Phosphine-Based Organocatalysts in Catalytic Asymmetric Reactions. *Chem. Asian J.* **2014**, *9*, 2720–2734. [CrossRef] [PubMed]
3. Wang, T.; Han, X.; Zhong, F.; Yao, W.; Lu, Y. Amino Acid-Derived Bifunctional Phosphines for Enantioselective Transformations. *Acc. Chem. Res.* **2016**, *49*, 1369–1378. [CrossRef] [PubMed]
4. Xiao, Y.; Guo, H.; Kwon, O. Nucleophilic Chiral Phosphines: Powerful and Versatile Catalysts for Asymmetric Annulations. *Aldrichim. Acta* **2016**, *49*, 3–13.
5. Shaikh, A.C.; Kwon, O. Phosphine-Catalyzed [3 + 2] Annulation: Synthesis of Ethyl 5-(*tert*-Butyl)-2-phenyl-1-tosyl-3-pyrroline-3-carboxylate. *Organ. Synth.* **2019**, *96*, 214–231. [CrossRef]
6. Xu, Z.; Lu, X. A Novel [3 + 2] Cycloaddition Approach to Nitrogen Heterocycles via Phosphine-Catalyzed Reactions of 2,3-Butadienoates or 2-Butynoates and Dimethyl Acetylenedicarboxylate with Imines: A Convenient Synthesis of Pentabromopseudilin. *J. Org. Chem.* **1998**, *63*, 5031–5041. [CrossRef]
7. Zhu, X.F.; Henry, C.E.; Kwon, O. A Highly Diastereoselective Synthesis of 3-Carbethoxy-2,5-disubstituted-3-pyrrolines by Phosphine Catalysis. *Tetrahedron* **2005**, *61*, 6276–6282. [CrossRef]
8. Jean, L.; Marinetti, A. Phosphine-Catalyzed Enantioselective [3 + 2] Annulations of 2,3-Butadienoates with Imines. *Tetrahedron Lett.* **2006**, *47*, 2141–2145. [CrossRef]
9. Fleury-Brégeot, N.; Jean, L.; Retailleau, P.; Marinetti, A. Screening of Chiral Phosphines as Catalysts for the Enantioselective [3 + 2] Annulations o *N*-tosylimines with Allenic Esters. *Tetrahedron* **2007**, *63*, 11920–11927. [CrossRef]
10. Zhang, H.-H.; Wang, C.-S.; Li, C.; Mei, G.-J.; Li, Y.; Shi, F. Design and Enantioselective Construction of Axially Chiral Naphtyl Indole Skeletons. *Angew. Chem. Int. Ed.* **2017**, *56*, 116–121. [CrossRef]
11. Scherer, A.; Gladysz, J.A. A Promising new Catalyst Family for Enantioselective Cycloadditions Involving Allenes and Imines: Chiral Phosphines with Transition Metal-CH_2-P: Linkages. *Tetrahedron Lett.* **2006**, *47*, 6335–6337. [CrossRef]
12. Fang, Y.-Q.; Jacobsen, E.N. Cooperative, Highly Enantioselective Phosphinothiourea Catalysis of Imine-Allene [3 + 2] Cycloadditions. *J. Am. Chem. Soc.* **2008**, *130*, 5660–5661. [CrossRef]
13. Nguyen, T.-H.; Toffano, M.; Bournaud, C.; Vo-Thang, G. Synthesis of Chiral Thiourea–Phosphine Organocatalysts derived from L-Proline. *Tetrahedron Lett.* **2014**, *55*, 6377–6380. [CrossRef]
14. Han, X.; Zhong, F.; Wang, Y.; Lu, Y. Versatile Enantioselective [3 + 2] Cyclization between Imines and Allenoates Catalyzed by Dipeptide-Based Phosphines. *Angew. Chem. Int. Ed.* **2012**, *51*, 767–770. [CrossRef]
15. Kitagaki, S.; Nakamura, K.; Kawabata, C.; Ishikawa, A.; Takenaga, N.; Yoshida, K. Planar Chiral [2.2]Paracyclophane-Based Phosphine–Phenols: Use in Enantioselective [3 + 2] Annulations of Allenoates and *N*-Tosylimines. *Org. Biomol. Chem.* **2018**, *16*, 1770–1778. [CrossRef]
16. Wang, D.; Liu, W.; Hong, Y.; Tong, X. Phosphine-Catalyzed (3 + 2) Annulation of δ-Acetoxy Allenoates with 2-Sulfonamidomalonate: Synthesis of Highly Substituted 3-Pyrrolines and Mechanistic Insight. *Org. Lett.* **2018**, *20*, 5002–5005. [CrossRef]
17. Wu, P.; Yu, L.; Gao, C.-H.; Cheng, Q.; Deng, S.; Jiao, Y.; Tan, W.; Shi, F. Design and Synthesis of Axially Chiral Aryl-Pyrroloindoles via the Strategy of Organocatalytic Asymmetric (2 + 3) Cyclization. *Fund. Res.* 2022, *in press*. [CrossRef]
18. Sheng, F.-T.; Yang, S.; Wu, S.-F.; Zhang, Y.-C.; Shi, F. Catalytic Asymmetric Synthesis of Axially Chiral 3,3′-Bisindoles by Direct Coupling of Indole Rings. *Chin. J. Chem.* **2022**, *40*, 2151–2160. [CrossRef]
19. Henry, C.E.; Xu, Q.; Fan, Y.C.; Martin, T.J.; Belding, L.; Dudding, T.; Kwon, O. Hydroxyproline-Derived Pseudoenantiomeric [2.2.1]Bicyclic Phosphines: Asymmetric Synthesis of (+)- and (−)-Pyrrolines. *J. Am. Chem. Soc.* **2014**, *136*, 11890–11893. [CrossRef]
20. Smaligo, A.J.; Vardhineedi, S.; Kwon, O. Carvone-Derived P-Stereogenic Phosphines: Design, Synthesis, and Use in Allene–Imine [3 + 2] Annulation. *ACS Catal.* **2018**, *8*, 5188–5192. [CrossRef]
21. Henderson, A.S.; Bower, J.F.; Galan, M.C. Carbohydrates as Enantioinduction Components in Stereoselective Catalysis. *Org. Biomol. Chem.* **2016**, *14*, 4008–4017. [CrossRef]
22. Borràs, C.; Elías-Rodríguez, P.; Carmona, A.T.; Robina, I.; Pàmies, O.; Diéguez, M. Amino-P Ligands from Iminosugars: New Readily Available and Modular Ligands for Enantioselective Pd-Catalyzed Allylic Substitutions. *Organometallics* **2018**, *37*, 1682–1694. [CrossRef]
23. Elías-Rodríguez, P.; Borràs, C.; Carmona, A.T.; Faiges, J.; Robina, I.; Pàmies, O.; Diéguez, M. Pyrrolidine-Based P,O Ligands from Carbohydrates: Easily Accessible and Modular Ligands for the Ir-Catalyzed Asymmetric Hydrogenation of Minimally Functionalized Olefins. *ChemCatChem* **2018**, *10*, 5414–5424. [CrossRef]
24. Cardona, F.; Robina, I.; Vogel, P. Synthesis of (*Z*)-3-Deoxy-3-(1,2,3,6-Tetradeoxy-3,6-Imino-L-*Arabino*-Hexitol-1-C-Ylidene)-D-*Xylo*-Hexose Derivatives. First Examples of Homo-(1→3)-C-Linked Iminodisaccharides. *J. Carbohydr. Chem.* **2000**, *19*, 555–571. [CrossRef]

25. Elías-Rodríguez, P.; Moreno Clavijo, E.; Carrión Jiménez, S.; Carmona Asenjo, A.T.; Moreno Vargas, A.J.; Caffa, I.; Montecucco, F.; Cea, M.; Nencioni, A.; Robina Ramírez, I. Synthesis and Cancer Growth Inhibitory Activities of 2-Fatty-Alkylated Pyrrolidine-3,4-Diol Derivatives. *Arkivoc* **2014**, *3*, 197–214. [CrossRef]
26. Makoto, H.; Rie, S.; Satoru, O.; Akira, H. Allyl- and Propargylchromium Reagents Generated by A Chromium(III) Ate-Type Reagent as a Reductant and Their Reactions With Electrophiles. *Chem. Commun.* **2001**, *4*, 357–358.
27. Castellano, S.; Fiji, H.D.G.; Kiderman, S.S.; Watanabe, M.; León, P.; Tamanoi, F.; Kwon, O. Small-Molecule Inhibitors of Protein Geranylgeranyltransferase Type, I. *J. Am. Chem. Soc.* **2007**, *129*, 5843–5845. [CrossRef]
28. ***ent*-9** was prepared following the procedure described for **9** using L-Ribose as starting material. See Supporting Information.
29. Li, J.; Wang, N.; Chunju, L.; Jia, X. Multicomponent Reaction to Construct Spirocyclic Oxindoles with a Michael (Triple Michael)/Cyclization Cascade Sequence as the Key Step. *Chem. Eur. J.* **2012**, *18*, 9645–9650. [CrossRef] [PubMed]
30. Sivakumar, A.V.; Babu, G.S.; Baht, S.V. Asymmetric Synthesis of β-Amino Acids Through Application of Chiral Sulfoxide. *Tetrahedron Asymmetry* **2001**, *12*, 1095–1099. [CrossRef]
31. Zhao, G.L.; Shi, M. Aza-Baylis-Hillman Reactions of *N*-Tosylated Aldimines with Activated Allenes and Alkynes in the Presence of Various Lewis Base Promoters. *J. Org. Chem.* **2005**, *70*, 9975–9984. [CrossRef] [PubMed]
32. Martínez-Bailén, M.; Carmona, A.T.; Moreno-Clavijo, E.; Robina, I.; Ide, D.; Kato, A.; Moreno- Vargas, A.J. Tuning of beta-Glucosidase and alpha-Galactosidase Inhibition by Generation and in situ Screening of a Library of Pyrrolidine-Triazole Hybrid Molecules. *Eur. J. Med. Chem.* **2017**, *138*, 532–542. [CrossRef]
33. Castellano, S.; Fiji, H.D.G.; Kiderman, S.S.; Watanabe, M.; León, P.; Tamanoi, F.; Kwon, O. Phosphine-Catalyzed [4 + 2] Annulation: Synthesis of Cyclohexenes. *J. Am. Chem. Soc.* **2007**, *129*, 12632–12633.
34. Lang, R.W.; Hansen, H.J. A Simple Synthesis of Alkyl Allenecarboxylates (Allenic Esters) by the Wittig-Reaction. *Helv. Chim. Acta* **1980**, *63*, 438–455. [CrossRef]
35. Wang, K.; Xing, Z.; Ma, Y.; Wang, Q. One-step Preparation of *N*-tosylimines Using Zeolite Catalysts. *Catal. Lett.* **2008**, *123*, 129–134. [CrossRef]