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Proline-Glycine Dipeptidic Derivatives of Chiral Phosphoramides as Organocatalysts for the Enantiodivergent Aldol Reaction of Aryl Aldehydes and Isatins with Cyclohexanone in the Presence of Water

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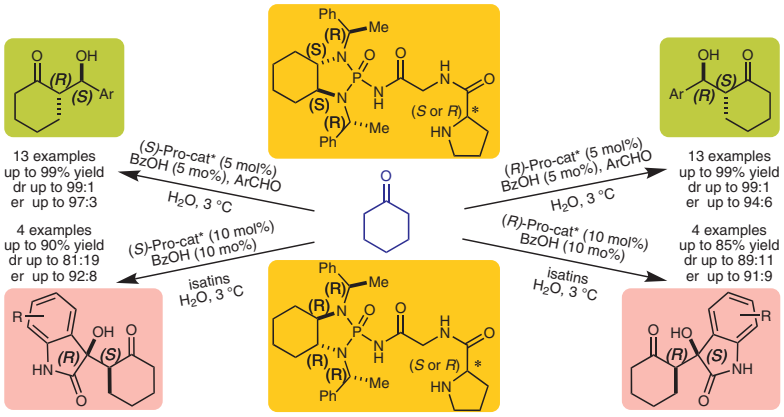

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Abstract The synthesis of several novel organocatalysts derived from (*R*)- and (*S*)-proline-glycine dipeptides and incorporating a chiral phosphoramide fragment was accomplished. These chiral compounds catalyze the enantioselective aldol addition reaction of cyclohexanone to prochiral aryl aldehydes and isatins in the presence of water. These chiral organocatalysts represent some of the few proline-derived compounds capable to catalyze aldol-type addition of cyclohexanone to isatins, a C–C bond forming transformation for which chiral primary amines are usually more successful. Additionally, these phosphoramide-containing catalysts afforded excellent results in the addition of cyclohexanone to aryl aldehydes, as anticipated by the presence of the proline moiety. The present report includes a detailed evaluation of the new multifunctional catalysts that are able to afford either enantiomer of the chiral product by adequate selection of the configuration of the proline residue.

Key words asymmetric organocatalysis, double hydrogen bond donor, dipeptides, hydrophobic interactions, Brønsted acid, Lewis base

Organocatalysis has become a powerful methodology to increase both rate and stereoselectivity in asymmetric organic transformations. Since its rediscovery[1] in the year 2000 by List et al.[2a] and MacMillan et al.[2b] a great number of studies have been undertaken to improve the organocatalyst's performance as well as to expand the range of stereoselective transformations catalyzed by (usually small) chiral organic compounds.[3] In this regard, the asymmetric aldol reaction has been extensively investigated owing to its importance in the selective formation of new C–C bonds accompanied by the creation of one or two new centers of chirality.[4]

In this context, a milestone advance in asymmetric aldol additions consisted in the clarification of the catalytic cycle of proline-catalyzed processes by List, Houk et al.[5] who noted the importance of an acidic hydrogen adjacent to the proline residue to ensure reactivity and selectivity.[5,6] Also relevant in this regard, is the realization by Gong, Wu et al.[7a] that more than one hydrogen bonding interaction in the transition state can fix and activate more efficiently the electrophile leading to a more reactive and stereoselective catalytic process.[7] Figure 1 shows some successful examples of this type of catalysts, where a pyrrolidinic proline fragment is essential to ensure enamine activation, whereas different functional groups act as hydrogen bond donors.

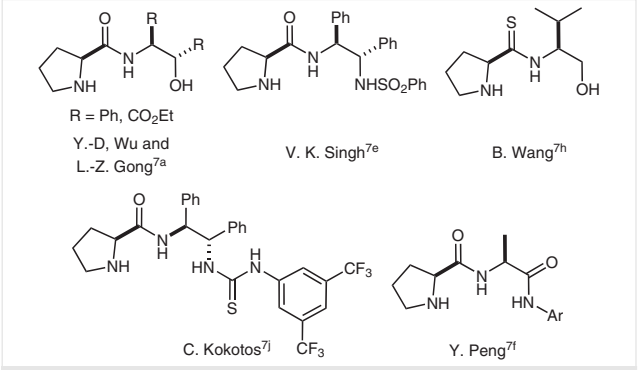


Figure 1 Successful double hydrogen bond donor organocatalysts used in the enantioselective addition of cyclohexanone to aldehydes

For example, Wu's[7a] and Wang's[7g] catalysts incorporate an amide N–H group in addition to a hydroxy group. By contrast, Singh's,[7e] Kokotos's,[7j] and Peng's[7h] catalysts also present an amide N–H function, but in combination with a sulfonamide, thiourea, or a second amide function (Figure 1).

On the other hand, the pursuit of environmentally friendlier organocatalytic processes gave rise to the development of hydrophobic derivatives, which could perform the reactions in aqueous media. This strategy was pioneered by Barbas, et al.[8a] and is now widely developed (Figure 2).[8] Generally, these organocatalysts incorporate large hydrophobic groups that in the presence of water create a lipophilic microenvironment, such as the one found in micelles. This brings organic substrates closer together giving rise to an increased reaction rate and at the same time rendering tighter, more robust transition states, which enhance steric interactions and improve stereoselectivity.[8m]

In this context, recently we reported the synthesis of novel prolinamide catalyst **I** incorporating a chiral phosphoramido group.[9] Application of **I** as organocatalyst in the asymmetric aldol addition of cyclohexanone to isatins in the presence of water afforded quite good stereoselectivities; nevertheless, organocatalyst **I** proved less efficient in the corresponding aldol addition to *p*-nitrobenzaldehyde (Figure 3).[10]

Inspired by the fact that double hydrogen bond donor functionality in organocatalysts has proved rather convenient,[7] and the successful application of small peptides in organocatalysis,[11,12] we decided to synthesize dipeptide-containing derivatives **II** (Figure 4), which offer several desirable characteristics: (1) the large benzodiazaphosphole moiety provides the desired hydrophobic environment;[8,13] (2) the (*R*)- or (*S*)-Pro-Gly dipeptidic fragment constitutes the catalytically active core, with a pyrrolidine fragment able to perform enamine activation,[14] as well as two quite acidic NH hydrogens for activation of electrophiles;[7] and (3) the glycine spacer joining the proline and the phosphoramide segments could help create a sufficiently large 'cavity' for the fixation and activation of electrophiles. Finally, the *N*-phosphonylimine segment has proven to be very useful for the development of GAP (group-assisted purification) chemistry and technology,[15] which can convert oils into solids and avoid the use of column chromatography, thereby minimizing the use of silica gel and solvents.

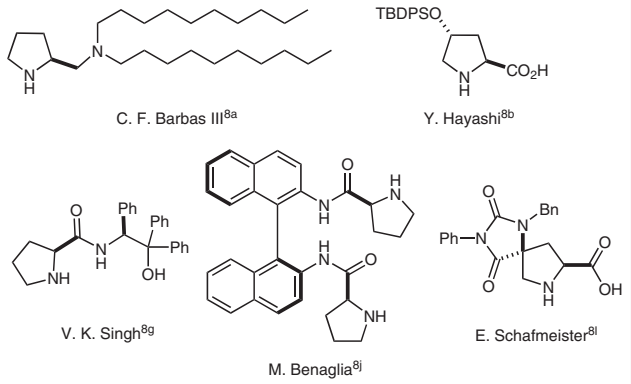


Figure 2 Some successful hydrophobic organocatalysts used in enantioselective aldol additions in the presence of water

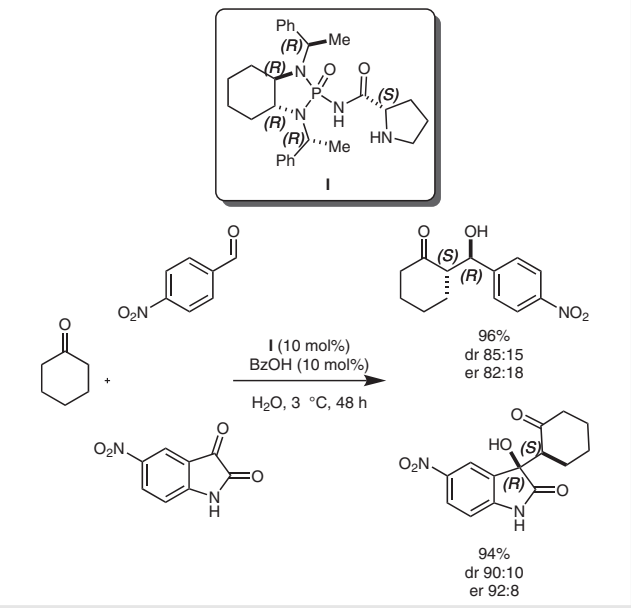


Figure 3 Chiral phosphoramide **I** and its application in the asymmetric aldol addition of cyclohexanone to aromatic aldehydes and isatins[9]

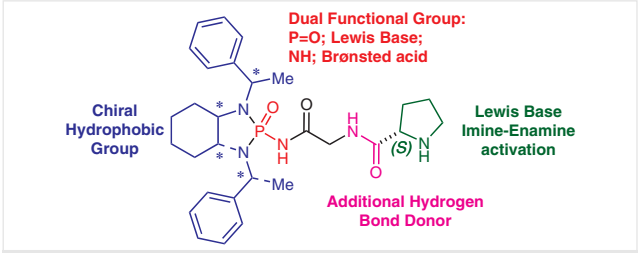
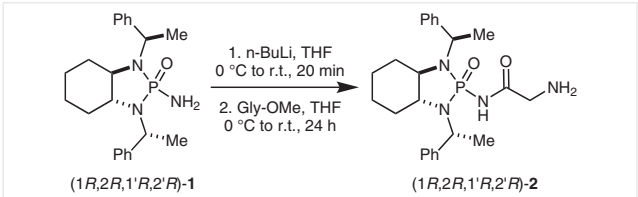
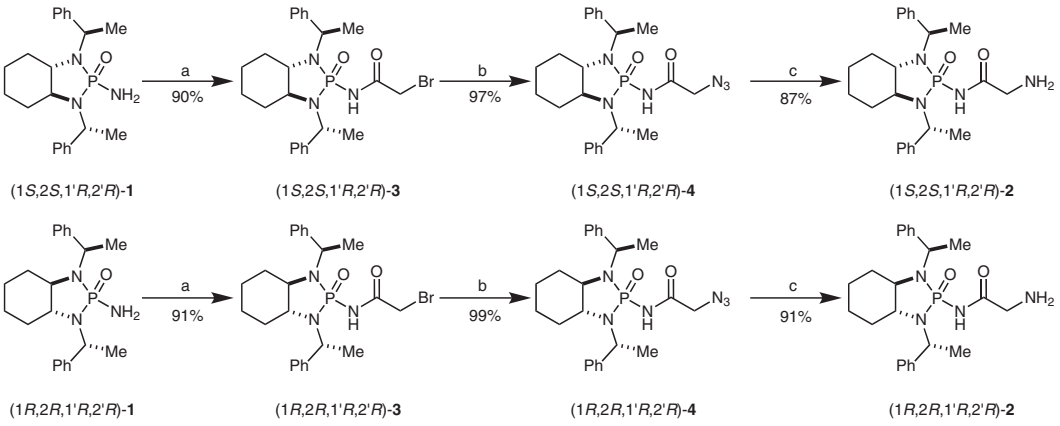


Figure 4 Structural characteristics of the proposed organocatalyst **II**

In the initial approach to synthesize the proposed organocatalysts, initial condensation of previously described phosphoramide (1*R*,2*R*,1′*R*,2′*R*)-**1**[9,15] with glycine methyl ester using *n*-BuLi as a base was carried out (Scheme 1); nevertheless, the yield of (1*R*,2*R*,1′*R*,2′*R*)-**2** was quite low



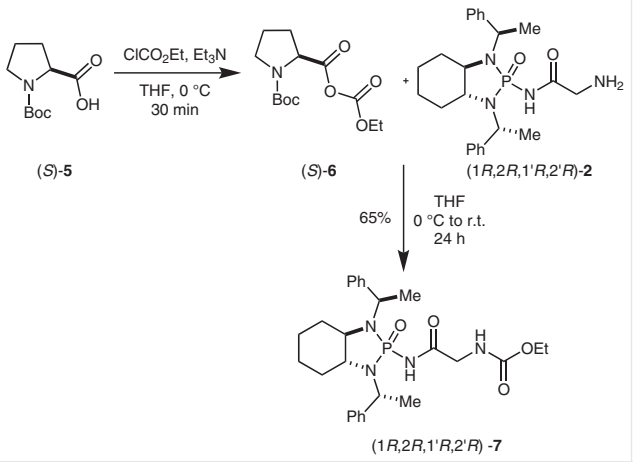
Scheme 1 Initial preparation of (1*R*,2*R*,1′*R*,2′*R*)-**2**



Scheme 2 Synthesis of *N*′-phosphoryl glycine amides (1*S*,2*S*,1′*R*,2′*R*)-**2** and (1*R*,2*R*,1′*R*,2′*R*)-**2**. *Reagents and conditions*: a) 1. *n*-BuLi, THF, 0 °C, 20 min, 2. Methyl bromoacetate, THF, 0 °C, r.t., 24 h, 90–91%; b) NaN_3, DMSO/DMF (9:1), r.t., 24 h, 97–99%; c) H_2, Pd/C, MeOH, r.t., 12 h, 87–91%.

(10%) in spite of the fact that an excess (5 equiv) of glycine methyl ester were employed. Indeed, self-condensation of this glycine derivative apparently competes with the desired reaction.

Gratifyingly, condensation of (1*S*,2*S*,1′*R*,2′*R*)-**1** with methyl 2-bromoacetate afforded (1*S*,2*S*,1′*R*,2′*R*)-**3** in high yield (90%, Scheme 2). This process was chemoselective as addition-elimination reaction at the carbonyl group in methyl bromoacetate took place instead of S_N2 reaction at the alkyl halide fragment. The bromine atom in (1*S*,2*S*,1′*R*,2′*R*)-**3** was then substituted by an azido group via S_N2 displacement reaction with sodium azide at room temperature in a mixture of DMF/DMSO (9:1) solvent. The azido group in (1*S*,2*S*,1′*R*,2′*R*)-**4** was reduced by palladium-catalyzed hydrogenation under mild reaction conditions to afford the desired compound (1*S*,2*S*,1′*R*,2′*R*)-**2** in good yield (Scheme 2).

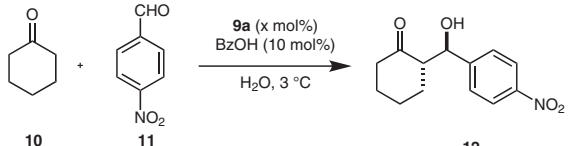


Scheme 3 Initial attempt to couple (1*R*,2*R*,1′*R*,2′*R*)-**4** with *N*-Boc-protected (*S*)-proline

In order to obtain the desired catalyst, we first tried to couple *N*-Boc-(*S*)-proline, (*S*)-**5**, with (1*R*,2*R*,1′*R*,2′*R*)-**4** using ethyl chloroformate as activating agent; nevertheless, carbamate **7** was obtained instead (Scheme 3).

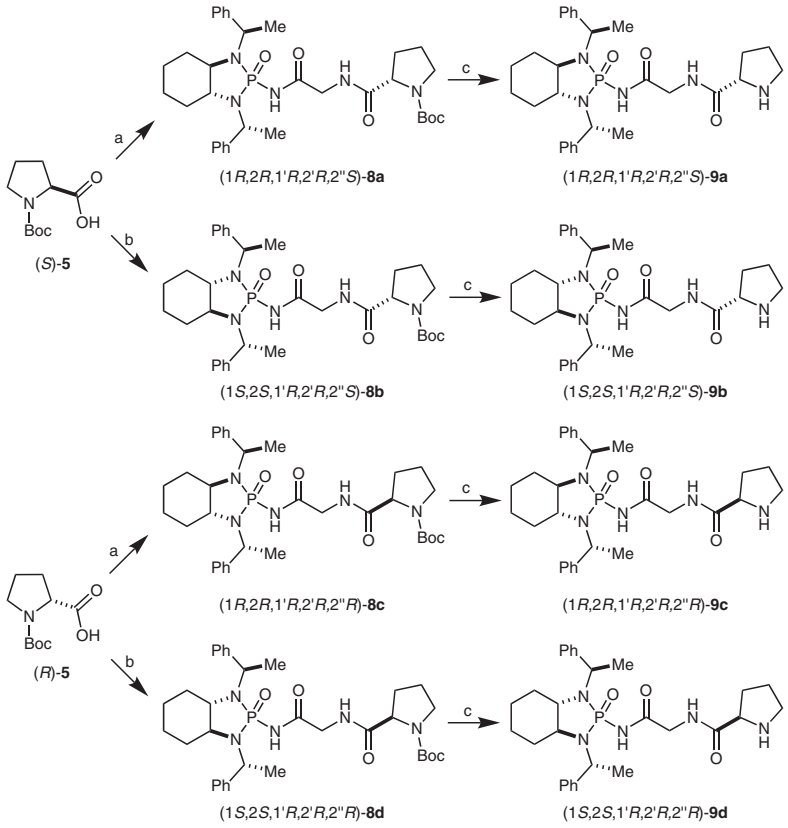
Fortunately, when propylphosphonic anhydride (T3P®)[16] was employed as coupling reagent, the desired products **8a–d** were obtained in good yield. The *N*-Boc protecting group was removed with trifluoroacetic acid and the resulting salt was neutralized with ammonium hydroxide or 1 M sodium hydroxide to afford free catalysts **9a–d** (Scheme 4). Because our previous work with prolinamide catalyst **I**[9] showed that the configuration of the α-phenylethyl moiety has no influence on the reaction stereochemical outcome, only the stereochemistry at the octahydrobenzodiazaphosphole and pyrrolidine moieties was varied.

Table 1 Optimization of the Asymmetric Aldol Reaction Between Cyclohexanone and 4-Nitrobenzaldehyde Catalyzed by (1*R*,2*R*,1′*R*,2′*R*,2′′*S*)-**9a**



Entry	**9a** (mol%)	Time (h)	Yield (%)[a]	dr (*anti*/*syn*)[b]	er[c]
1	10	10	99	93:7	91:9
2	5	24	91	93:7	91:9
3[d]	**5**	**24**	**90**	**91:9**	**94:6**
4[d]	2	96	98	92:8	90:10

[a] Yield of pure, isolated product containing both diastereomers.
[b] Determined by ^1H NMR analysis of the crude product.
[c] Determined by chiral HPLC of the isolated products.
[d] In the presence of 5 mol% of BzOH.

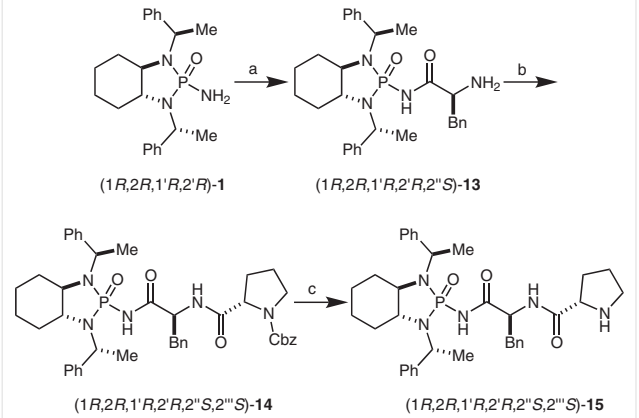


Scheme 4 Synthesis of the desired diastereomeric catalysts **9a–d**. *Reagents and conditions*: 1. T3P® NMM, MeCN, 0 °C, 30 min, 2. (1*R*,2*R*,1′*R*,2′*R*)-**2**, THF, 0 °C → r.t., 24 h, 72–75%; b) 1. T3P® NMM, MeCN, 0 °C, 30 min, 2. (1*S*,2*S*,1′*R*,2′*R*)-**2**, THF, 0 °C → r.t., 24 h, 71–84%; c) 1. CF_3CO_2H, CH_2Cl_2, 0 °C → r.t., 48 h, 2. NH_4OH, EtOAc, 88–95%.

Evaluation of organocatalysts **9a–d** was carried out under the reaction conditions that had been used with catalysts **I**[9] namely, 10 mol% of catalyst and benzoic acid (BzOH) as additive with water as reaction medium at 3 °C (Table 1, entry 1), obtaining the expected aldol products in excellent yields with very good stereoselectivities. Furthermore, catalyst loading could be reduced to 5 and 2 mol% (entries 2–4).

Once the optimum reaction conditions had been established (Table 1, entry 3), the effect of the catalyst's configuration, as well as the potential influence of an additional stereogenic center at the spacer, was evaluated. Regarding this last structural feature, catalyst (1*R*,2*R*,1′*R*,2′*R*,2″*S*,2‴*S*)-**15** incorporates an (*S*)-phenylalanine residue instead of the glycine segment. The synthesis of this catalyst was carried out according to the procedure described for the preparation of catalysts **9a–d**, that is initial condensation of lithium phosphoramide with (*S*)-phenylalanine methyl ester was followed by T3P®-mediated coupling to *N*-Cbz-(*S*)-proline. Finally, the *N*-Cbz- protecting group was removed by hydrogenolysis under mild reaction conditions (Scheme 5).

At this point it was possible to obtain suitable crystals of the intermediate (1*R*,2*R*,1′*R*,2′*R*,2″*S*)-**13**, which were analyzed by X-ray crystallographic diffraction analysis (Figure



Scheme 5 Synthesis of (*S*)-Pro-(*S*)-Phe derivative (1*R*,2*R*,1′*R*,2′*R*,2″*S*,2‴*S*)-**15**. *Reagents and conditions*: a) 1. *n*-BuLi, THF, 0 °C, 20 min, 2. (*S*)-Phe-OMe, THF, 0 °C → r.t., 24 h, 52%; b) *N*-Cbz-(*S*)-Pro, NMM, T3P®, MeCN, 0 °C → r.t., 48 h, 71%; c) H_2, Pd/C (15% w/w), MeOH, r.t., 12 h, 94%.

5).[17] As previously observed in structurally related compounds,[9] both phenyl groups are oriented *syn* to the phosphoryl oxygen atom owing to a non-classical hydrogen bonding interaction with the *ortho*-hydrogens (Figure 5A).[9,18] Another interesting feature observed in this crystallographic structure is the *anti*-relationship between the phosphoryl and carbonyl groups, probably to minimize dipole-dipole repulsion. Finally, the *syn*-orientation between the phosphoryl and the acidic N–H bond (Figure 5B), which may be the consequence of intermolecular hydrogen bonds involving both groups (cf. Figure 5C). Indeed, the intermolecular distances for these interactions are shorter (1.98 Å and 2.05 Å) than those found in the intramolecular hydrogen bonds (2.72 Å and 3.25 Å), which suggests a rather strong interaction.

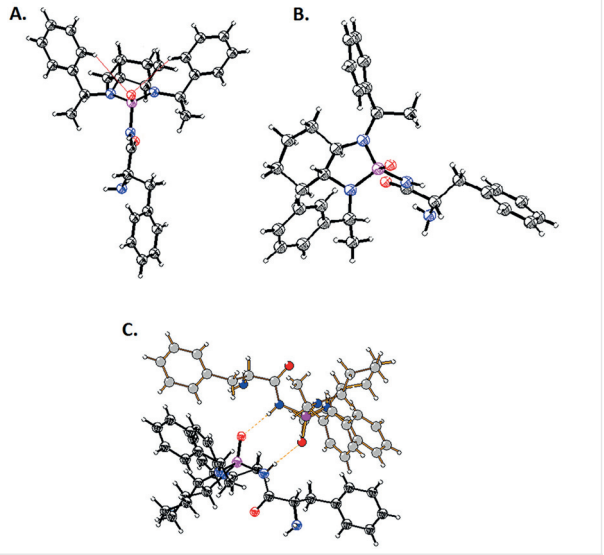
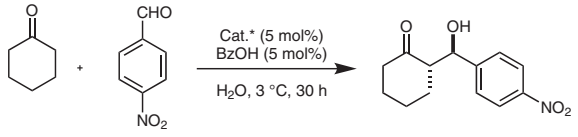


Figure 5 X-Ray diffraction crystallographic structure of derivative (1*R*,2*R*,1′*R*,2′*R*,2′′*S*)-**13**[17]

The efficacy of the five novel catalysts **9a–d** and **15** was then examined at a concentration of 5 mol%, in the presence of 5 mol% benzoic acid as additive, and employing five equivalents of cyclohexanone as substrate and solvent. As shown in Table 2, all five catalysts exhibited good efficiency in the reaction. It is also clear that the configuration of the proline segment dictates the stereochemistry of the product. Indeed, (*S*)-proline-derived catalysts **9a** and **9b** afforded stereoisomer (*S*,*R*)-**12** as the major product (Table 2, entries 1, 2), whereas (*R*)-proline-derived catalysts **9c** and **9d** produced (*R*,*S*)-**12** (*ent*-**12**) as the major product (entries 3, 4). Finally, the presence of an additional center of chirality in catalysts **15** does not have a noticeable effect in the stereochemical course of the reaction, (compare entry 5 vs entries 1 and 2 in Table 2).

Table 2 Influence of the Configuration of Catalysts **9a–d**, and the Effect of the Presence of an Additional Stereocenter in Catalyst **15** on the Asymmetric Aldol Reaction Between Cyclohexanone and 4-Nitrobenzaldehyde



10 5 equiv + **11** 1 equiv → **12**

Entry	Cat.*	Yield (%)[a]	dr (*anti*/*syn*)[b]	er[c]
1	(1*R*,2*R*,1′*R*,2′*R*,2′′*S*)-**9a**	90	91:9	94:6
2	(1*S*,2*S*,1′*R*,2′*R*,2′′*S*)-**9b**	95	92:8	93:7
3	(1*R*,2*R*,1′*R*,2′*R*,2′′*R*)-**9c**	90	91:9	6:94
4	(1*S*,2*S*,1′*R*,2′*R*,2′′*R*)-**9d**	92	94:6	6:94
5	(1*R*,2*R*,1′*R*,2′*R*,2′′*S*,2′′′*S*)-**15**	95	94:6	94:6

[a] Yield of isolated product (both diastereoisomers).
[b] Determined by ^{1}H NMR analysis of the crude product.
[c] Determined by chiral HPLC of the isolated products.

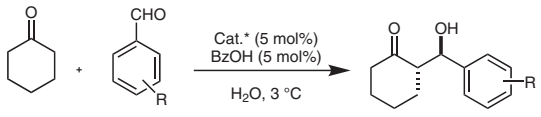
Organocatalysts **9b** and **9d** were selected to examine their performance in reactions with a variety of aryl aldehydes, both activated (containing electron-withdrawing groups) and inactivated (containing electron-donating groups). As it turned out, reactions with activated aldehydes **11a–j** (Table 3, entries 1–20) required less time of reaction than electron-rich aldehydes **11k–l** (entries 21–26). Nevertheless, all reactions proceeded to give the aldol products with good diastereoselectivity and enantioselectivity. The diastereomeric pair of organocatalysts **9b** and **9d** presenting opposite configuration at the proline residue were able to generate enantiomeric products of **12**, depending on the configuration of the proline moiety (cf. er and $[\alpha]_D$ data in Table 3). In this regard, Ellman's,[19a] Hao's,[19b] and our group[9,19c] have reported similar observations, where the proline's stereochemistry dictates the final configuration of the product.

A plausible activation mechanism with catalyst (1*R*,2*R*,1′*R*,2′*R*,2′′*S*)-**9a** is presented in Figure 6. It is considered that cyclohexanone is activated by the pyrrolidine amino group via a nucleophilic enamine. Simultaneously, the aryl aldehyde is activated by a double (bidentate) hydrogen bond interaction as suggested in related catalytic systems[7a,[i–m]] (cf. TS*-**A** in Figure 6). The bidentate interaction could explain the higher stereoselectivity observed in the addition of cyclohexanone to 4-nitrobenzaldehyde activated with catalyst **9b** – 98% yield, 90:10 dr, and 93:7 er – relative to the same reaction catalyzed by analogue **I** (Figure 3) – 96% yield, 85:15 dr, and 82:18 er.[9] For comparison purposes, Figure 6 also includes a plausible transition state (TS*-**B**) with catalyst **I**, presenting a single (monodentate) hydrogen bond interaction.

In this context, Kokotos, et al.[11k] have reported asymmetric aldol additions catalyzed by (*S*)-Pro-Gly-O*t*-Bu and (*S*)-Pro-Gly-NHBn in a mixture of MeCN/water and brine, respectively. Excellent results are found with both systems (up to 100% yield, up to 97:3 dr, and up to 99% ee); nevertheless, larger amounts of catalyst (20 mol%) are required. By comparison, only 5 mol% of catalysts **9a–d** or (1*R*,2*R*,1′*R*,2′*R*,2″*S*,2‴*S*)-**15** are needed here (cf. Tables 2 and 3).

We next turned our attention to the evaluation of catalysts **9a** and **9c** in the asymmetric aldol addition of cyclohexanone to isatins, a transformation that is receiving great attention due to the significant value of the corresponding products.[20] Salient catalysts employed in this processes,[21] usually incorporate a primary amino group that activates the potential aldol donor by means of enamine formation, whereas a variety of Brønsted acid functional groups fix and activate the corresponding isatin by means of non-covalent interactions such as hydrogen bonding. As shown in

Table 3 Scope of Diastereomeric Catalysts **9b** and **9d** in the Aldol Addition of Cyclohexanone to Aryl Aldehydes **11a–m**



10 5 equiv + **11a–m** 1 equiv → **12a–m**

Entry	Cat.*	R	Product	Time (h)	Yield (%)[a]	dr (*anti*/*syn*)[b]	er[c]	$[\alpha]_D^{25}$ ($CHCl_3$)
1	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	2-Cl	**12a**	96	96	89:11	91:9	+20.4
2	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	2-Cl	*ent*-**12a**	96	93	92:8	7:93	–21.6
3	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	3-Cl	**12b**	96	96	93:7	92:8	+12.8
4	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	3-Cl	*ent*-**12b**	96	93	93:7	11:89	–13.6
5	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	4-Cl	**12c**	96	83	91:9	89:11	+20.3
6	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	4-Cl	*ent*-**12c**	96	80	93:7	13:87	–17.3
7	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	3-Br	**12d**	96	99	92:8	90:10	+10.3
8	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	3-Br	*ent*-**12d**	96	99	93:7	9:91	–10.6
9	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	4-Br	**12e**	96	87	92:8	90:10	+18.6
10	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	4-Br	*ent*-**12e**	96	85	90:10	8:92	–17.4
11	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	4-CN	**12f**	40	93	93:7	92:8	+20.8
12	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	4-CN	*ent*-**12f**	40	92	94:6	8:92	–20.3
13	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	3-NO_2	**12g**	40	98	96:4	92:8	+28.4
14	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	3-NO_2	*ent*-**12g**	40	95	94:6	14:86	–27.1
15	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	4-NO_2	**12h**	30	95	90:10	93:7	+12.4
16	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	4-NO_2	*ent*-**12h**	30	92	94:6	6:94	–12.4
17	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	2-CF_3	**12i**	96	72	91:9	87:13	+2.0
18	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	2-CF_3	*ent*-**12i**	96	70	91:9	11:89	–1.2
19	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	4-CF_3	**12j**	24	99	93:7	93:7	+16.8
20	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	4-CF_3	*ent*-**12j**	24	97	94:6	8:92	–16.3
21	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	H	**12k**	168	80	90:10	90:10	+13.9
22	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	H	*ent*-**12k**	168	77	89:11	12:88	–11.2
23	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	4-Me	**12l**	168	44	88:12	86:14	+13.2
24	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	4-Me	*ent*-**12l**	168	41	88:12	15:85	–14.4
25	(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**9b**	4-Ph	**12m**	168	46	89:11	87:13	+10.8
26	(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**9d**	4-Ph	*ent*-**12m**	168	40	89:11	16:84	–9.9

[a] Yield of isolated product (both diastereoisomers).
[b] Determined by ^{1}H NMR analysis of the crude product.
[c] Determined by chiral HPLC of the isolated products.

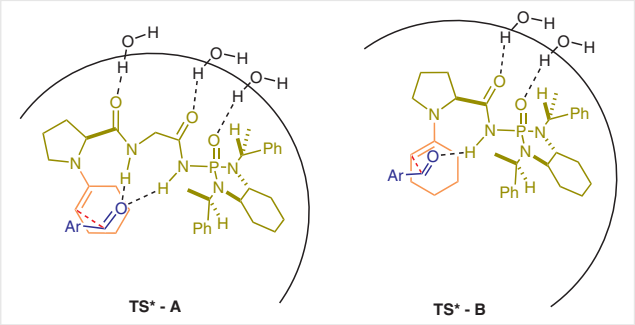


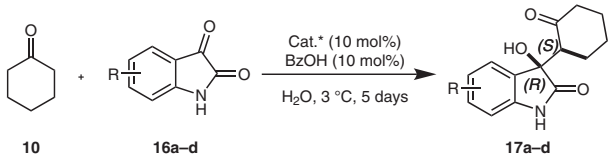
Figure 6 Plausible transition states for cyclohexanone enamine addition to aryl aldehydes catalyzed by catalysts **9a–d** and by catalyst **I**

Table 4, reaction rate and stereoselectivity proved better in aqueous media relative to neat reaction conditions (compare entries 1–3 in Table 4). To improve stereoselectivity the reaction temperature was lowered to 3 °C, observing very good selectivity at the cost of lower yields and longer reaction times (entry 4 in Table 4). To increase reaction rates, both catalyst and additive charges were increased to 10 mol%, while the quantity of cyclohexanone was also raised from 7 to 10 equivalents (Table 4, entries 5 and 6).

With the best reaction conditions at hand (Table 4, entry 5) we proceeded to evaluate the catalyst's scope in the asymmetric aldol addition of cyclohexanone to various substituted isatins. As shown in Table 5, catalysts **9a–c** required longer reaction times and afforded lower yields when compared with catalyst **I**. Nevertheless, with the 5-nitroisatin as substrate the observed enantioselectivity was very good. By contrast, with chlorine-, bromine- and fluorine-substituted isatins the observed enantioselectivities turned out to be poor.

Three different transition states for the aldol reaction involving isatin as acceptor substrate may be plausible (TS*-**A–C**, Figure 7). Transition states TS*-**A** and TS*-**B** involve hydrogen bonding interactions that orient the isatin molecule upon approach to the enamine function; however, in TS*-**A** both acidic N–H hydrogens in the catalyst are bound to the

Table 5 Scope of Diastereomeric Catalysts **9a** and **9c** in the Asymmetric Aldol Addition of Cyclohexanone to Isatins **16a–m**

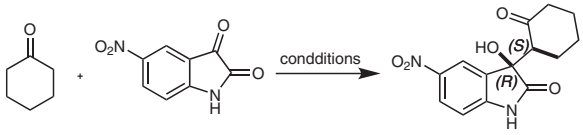


10 7 equiv + **16a–d** 1 equiv → **17a–d**

Catalyst	R	Product	Yield (%)[a]	dr (*u*/*l*)[b]	er[c]
9a	5-NO_2	**17a**	90	80:20	92:8
9c	5-NO_2	*ent*-**17a**	85	85:15	9:91
9a	5-Br	**17b**	60	80:20	74:26
9c	5-Br	*ent*-**17b**	52	89:11	19:81
9a	5-F	**17c**	80	77:23	70:30
9c	5-F	*ent*-**17c**	69	82:18	18:82
9a	7-Cl	**17d**	90	81:19	74:26
9c	7-Cl	*ent*-**17d**	83	82:18	17:83

[a] Yield of pure product (both diastereoisomers).
[b] Determined by ^{1}H NMR analysis of the crude product.
[c] Determined by chiral HPLC of the isolated products.

Table 4 Optimization of Reaction Conditions in the Asymmetric Aldol Reaction Between Cyclohexanone and 5-Nitroisatin Catalyzed by Chiral Phosphoramide (1R,2R,1'*R*2'*R*, 2''*S*)-**9a**.



10 5 equiv + **16** 1 equiv → **17**

Entry	(1*R*,2*R*,1'*R*,2'*R*,2''*S*)-**9a** (mol%)	BzOH (mol%)	Solvent	Temp (°C)	Time (days)	Yield (%)[a]	dr (*u*/*l*)[b]	er[c]
1	5	5	neat	25	5	70	72:28	55:42
2	5	5	brine	25	3	78	76:24	72:28
3	5	5	H_2O	25	3	81	66:34	78:22
4	5	5	H_2O	3	7	64	82:18	95:5
5[d]	**10**	**10**	**H_2O**	**3**	**5**	**90**	**80:20**	**92:8**
6[e]	10	10	H_2O	3	3	93	80:20	92:8

[a] Yield of pure product (both diastereoisomers).
[b] Determined by ^{1}H NMR analysis of the crude product.
[c] Determined by chiral HPLC of the isolated products.
[d] Seven equiv of **10** were used.
[e] Ten equiv of **10** were used.

α-carbonyl group, whereas in TS*-**B** one N–H is interacting with the isatin's α-carbonyl while the other N–H is binding to the amide carbonyl group. Transition state **C** is based on dual activation,[22] and involves hydrogen bonding between the isatin's N–H bond and the phosphoryl group in the catalyst. Simultaneously, the amide carbonyl group in isatin participates in hydrogen bonding with both acidic N–H bonds in the catalyst. All transition state structures are in line with the observed configuration of the major product but it seems that structure TS*-**C** is most likely as suggested by geometry optimization with computational methods at the DFT level of theory (See Supporting Information).

Interestingly, Li and co-workers have developed a methodology called group-assisted purification (GAP), where incorporation of a *N*-phosphonyl substituent in suitable substrates facilitates product isolation in solid form without the need of traditional chromatography.[15] In the present work, the presence of the phosphoryl segment could in principle facilitate isolation of the product by precipitation of the organocatalyst, nevertheless similar solubility properties of products **12a–m** and organocatalysts **17a–d** prevented application of such strategy.

In conclusion, novel multifunctional chiral organocatalysts **9a–d**, which incorporate a dipeptidic (*R*)- or (*S*)-proline-glycine moiety in combination with a previously developed chiral phosphoramide segment[9] were synthesized. These catalysts promoted the diastereo- and enantioselective aldol addition of cyclohexanone to various aryl aldehydes and isatins in the presence of water in good yield and stereoselectivity. These catalysts exhibited better performance in the addition to aryl aldehydes, relative to previously developed analogues. It appears that the second hydrogen bond donor present in chiral organocatalysts **9a–d** is relevant for the observed higher stereoinduction and activity.[7] Finally, proper selection of the configuration of the proline residue gives rise to either enantiomer of the product. The stereochemical outcome of the reaction may be explained in terms of bifunctional activation by the catalyst.

Commercially available reagents were used as received. Anhyd solvents were obtained by distillation under the described conditions.[23] Column chromatography was carried out with Merck silica gel (0.040–0.063 mm). TLC was performed with Merck DC-F254 plates employing UV light and I_2 vapor for visualization. Melting points were measured with a Büchi B-540 apparatus, and are uncorrected. Optical rotations were measured in an Anton Paar MCP-100 Polarimeter with reagent grade solvents. IR spectra were recorded on a Varian-640 apparatus. NMR spectra were obtained with JEOL GSX-270 (270 MHz), Bruker Avance 300 (300 MHz), JEOL Eclipse 400 (400 MHz), and JEOL ECA-500 (500 MHz) spectrometers. High-resolution mass spectra (HRMS) were obtained with a HPLC 1100 coupled to a MSD-TOF Agilent Technologies HR-MSTOF 1069A. Crystallographic data were collected with Enraf-Nonius CAD-4 X-ray diffractometer. Diastereoselectivity and enantioselectivity were measured by chiral HPLC in a Dionex HPLC Ultimate 3000 equipment with UV/Visible detector, diode array, at 210 and 254 nm.

Chiral Catalyst (1*R*,2*R*,1′*R*,2′*R*)-2

One-Step Preparation

In a 100 mL round-bottomed flask equipped with a stirring bar, (1*R*,2*R*,1′*R*,2′*R*)-**1** (0.4 g, 1.0 mmol) was dissolved in anhyd THF (30 mL) under an argon atmosphere and cooled to 3 °C before the dropwise addition of *n*-BuLi (2.8 M in hexanes, 0.08 g, 0.46 mL, 1.3 mmol) via syringe. The resulting mixture was stirred at 3 °C for 20 min before the addition of glycine methyl ester (0.48 g, 5.2 mmol) dissolved in anhyd THF. The reaction mixture was allowed to reach r.t., and then stirred for 24 h. Subsequently, the mixture was poured over ice/water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, the solvent was removed by distillation, and the crude product was purified by column chromatography on silica gel (eluent: hexane/EtOAc 8:2 to 7:3). The pure product was obtained as a white foam; yield: 0.043 g (0.10 mmol, 10%). See below for a complete characterization.

Preparation of Chiral Catalysts 2 via Bromoacetates 3 and Azides 4

Bromoacetates 3; General Procedure

In a round-bottomed flask equipped with a stirring bar, the corresponding trisphosphoramide **1** (1 equiv) was dissolved in anhyd THF under an argon atmosphere and cooled to 3 °C before the dropwise addition of *n*-BuLi (2.8 M in hexanes, 1.3 equiv) via syringe. The mixture was stirred at 3 °C for 20 min. before the addition of methyl 2-bromoacetate (1.3 equiv). The reaction mixture was allowed to reach r.t., and stirring was continued for 24 h. The mixture was then poured over ice/water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, the solvent was removed by distillation, and the crude product was purified by column chromatography on silica gel (eluent: hexane/EtOAc 8:2 to 7:3).

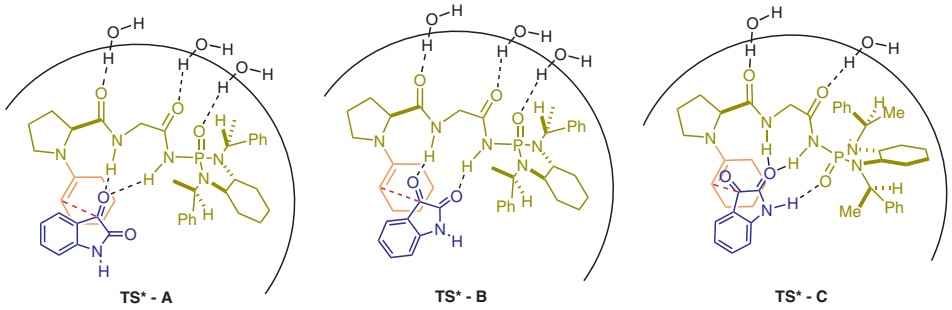


Figure 7 Plausible transition states for the enamine-catalyzed addition of cyclohexanone to isatins

(3a*S*,7a*S*)-2-Oxide-*N*-(2-bromoacetyl)octahydro-1,3-bis[(1*R*)-1-phenylethyl]-2*H*-1,3,2-benzodiazaphosphol-2-amine [(1*S*,2*S*,1′*R*,2′*R*)-3]

The general procedure was used with phosphoramide (1*S*,2*S*,1′*R*,2′*R*)-**1** (0.77 g, 1.97 mmol), *n*-BuLi (2.8 M, 0.16 g, 0.89 mL, 2.56 mmol), and methyl 2-bromoacetate (0.39 g, 0.20 mL, 2.56 mmol) to afford the title compound; yield: 0.91 g (1.77 mmol, 90%); pale yellow foam; $[\alpha]_D^{25}$ +65.6 (*c* 0.387, $CHCl_3$).

IR (ATR): 3084.0, 2921.1, 2853.2, 1703.0, 1475.3, 1454.1, 1377.1, 1299.6, 1278.0, 1208.4, 1194.3, 1182.8, 1151.8, 1102.3, 1081.1, 1058.0, 1019.0, 992.5, 968.7, 931.5, 911.0, 848.4, 780.8, 764.7, 732.9, 698.1, 664.9, 624.8 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.9 (s, 1 H), 7.49 (d, $J_{H,H}$ = 7.8 Hz, 2 H), 7.45 (d, $J_{H,H}$ = 7.8 Hz, 2 H), 7.24–7.31 (m, 4 H), 7.16–7.22 (m, 2 H), 4.50 (dq, $^3J_{H,H}$ = 6.7 Hz, $^3J_{P,H}$ = 13.5 Hz, 1 H), 4.39 (dq, $^3J_{H,H}$ = 7.2 Hz, $^3J_{P,H}$ = 17.3 Hz, 1 H), 3.94 (d, $J_{H,H}$ = 11.9 Hz, 1 H), 3.88 (d, $J_{H,H}$ = 11.7 Hz, 1 H), 3.62–3.70 (m, 1 H), 2.74–2.83 (m, 1 H), 1.65 (d, $J_{H,H}$ = 7.3 Hz, 3 H), 1.54–1.61 (m, 1 H), 1.56 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.42–1.53 (m, 3 H), 1.14–1.22 (m, 2 H), 0.88–0.95 (m, 1 H), 0.68–0.76 (m, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 168.3, 143.5 (d, $^3J_{P,C}$ = 6.0 Hz), 143.2 (d, $^3J_{P,C}$ = 3.6 Hz), 128.6, 128.2, 127.2, 127.15, 127.1, 127.0, 61.5 (d, $J_{P,C}$ = 11.7 Hz), 59.1 (d, $J_{P,C}$ = 12.4 Hz), 53.1 (d, $J_{P,C}$ = 3.7 Hz), 49.6 (d, $J_{P,C}$ = 5.5 Hz), 30.6 (d, $J_{P,C}$ = 9.6 Hz), 30.0, 29.9 (d, $J_{P,C}$ = 4.1 Hz), 28.8 (d, $J_{P,C}$ = 9.3 Hz), 24.4 (d, $J_{P,C}$ = 6.1 Hz), 20.0, 16.8.

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 15.3.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for $[C_{24}H_{32}BrN_3O_2P + H]^+$: 504.14155 and 506.139296 (1:1); found: 504.141690 and 506.140157 (error: 1.36171 ppm).

(3a*R*,7a*R*)-2-Oxide-*N*-(2-bromoacetyl)octahydro-1,3-bis[(1*R*)-1-phenylethyl]-2*H*-1,3,2-benzodiazaphosphol-2-amine [(1*R*,2*R*,1′*R*,2′*R*)-3]

The general procedure was followed with phosphoramide (1*R*,2*R*,1′*R*,2′*R*)-**1** (1.0 g, 2.6 mmol), *n*-BuLi (2.8 M, 0.22 g, 1.2 mL, 3.38 mmol), and methyl 2-bromoacetate (0.52 g, 0.31 mL, 3.38 mmol) to afford the title compound; yield: 1.19 g (2.36 mmol, 91%); pale yellow foam; $[\alpha]_D^{25}$ –35.6 (*c* 1.02, $CHCl_3$).

IR (ATR): 3091.4, 2925.1, 2865.5, 1699.6, 1480.8, 1448.8, 1426.2, 1375.8, 1338.1, 1300.9, 1278.6, 1238.8, 1206.1, 1191.8, 1184.9, 1157.8, 1136.9, 1101.1, 1077.9, 1060.6, 1022.5, 965.4, 931.3, 911.2, 849.3, 762.5, 732.8, 700.0, 657.9, 642.0, 583.8 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.8 (s, 1 H), 7.41 (d, $J_{H,H}$ = 7.6 Hz, 2 H), 7.33 (d, $J_{H,H}$ = 7.7 Hz, 2 H), 7.23 (q, $J_{H,H}$ = 7.4 Hz, 4 H), 7.12 (q, $J_{H,H}$ = 6.5 Hz, 2 H), 4.41 (dq, $^3J_{H,H}$ = 7.0 Hz, $^3J_{P,H}$ = 18.1 Hz, 1 H), 4.15 (dq, $^3J_{H,H}$ = 7.1 Hz, $^3J_{P,H}$ = 9.6 Hz, 1 H), 3.61 (s, 3 H), 2.73 (td, $J_{H,H}$ = 2.6, 10.4 Hz, 1 H), 1.70 (d, $J_{H,H}$ = 10.9 Hz, 1 H), 1.59 (d, $J_{H,H}$ = 7.0 Hz, 3 H), 1.47–1.53 (m, 2 H), 1.46 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.39–1.43 (m, 1 H), 1.22 (qd, $J_{H,H}$ = 3.7, 12.2 Hz, 1 H), 1.09 (qt, $J_{H,H}$ = 3.3, 13.2 Hz, 1 H), 0.90 (qt, $J_{H,H}$ = 3.6, 13.4 Hz, 1 H), 0.62 (qd, $J_{H,H}$ = 3.0, 12.1 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 167.6 (d, $J_{P,C}$ = 2.3 Hz), 146.6 (d, $^3J_{P,C}$ = 3.9 Hz), 140.8 (d, $^3J_{P,C}$ = 1.7 Hz), 128.5, 128.4, 128.3, 127.4, 126.9, 126.6, 62.5 (d, $J_{P,C}$ = 12.3 Hz), 61.7 (d, $J_{P,C}$ = 11.0 Hz), 55.1 (d, $J_{P,C}$ = 4.7 Hz), 51.4 (d, $J_{P,C}$ = 4.3 Hz), 30.2 (d, $J_{P,C}$ = 8.9 Hz), 29.9 (d, $J_{P,C}$ = 9.4 Hz), , 29.5 (d, $J_{P,C}$ = 9.3 Hz), 24.5, 24.2, 22.6 (d, $J_{P,C}$ = 4.5 Hz), 18.8 (d, $J_{P,C}$ = 3.0 Hz).

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 13.8.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for $[C_{24}H_{32}BrN_3O_2P + H]^+$: 504.14155 and 506.139296 (1:1); found: 504.140803 and 506.139344 (error: –0.397713 ppm).

Azides 4; General Procedure

Compound **3** (1 equiv) was dissolved in a 9:1 DMF/DMSO mixture in a round-bottomed flask equipped with magnetic stirrer, and the resulting solution was treated with NaN_3 (1.2 equiv). The reaction mixture was stirred for 24 h at r.t., and then cooled to 3 °C before the addition of 3 volumes of distilled H_2O (exothermic process). The mixture was extracted with Et_2O (3 ×), the organic layers were combined, dried (anhyd Na_2SO_4), and concentrated. The crude product was purified by column chromatography (SiO_2: hexane/EtOAc 95:5).

(3a*S*,7a*S*)-2-Oxide-*N*-(2-azidoacetyl)octahydro-1,3-bis[(1*R*)-1-phenylethyl]-2*H*-1,3,2-benzodiazaphosphol-2-amine [(1*S*,2*S*,1′*R*,2′*R*)-4]

The general procedure was followed with 1*S*,2*S*,1′*R*,2′*R*-**3** (0.5 g, 0.97 mmol) and NaN_3 (0.076 g, 1.16 mmol) to afford the desired azide; yield: 0.44 g (0.94 mmol, 97%); white foam; $[\alpha]_D^{25}$ +83.6 (*c* 0.36, $CHCl_3$).

IR (ATR): 3090.5, 2930.5, 2869.9, 2104.0, 1710.0, 1661.3, 1600.7, 1494.0, 1452.4, 1381.6, 1299.3, 1282.7, 1210.5, 1179.5, 1152.5, 1136.5, 1080.7, 1057.8, 1019.3, 994.4, 967.7, 931.1, 915.4, 848.2, 780.8, 763.2, 730.9, 697.8, 664.1, 625.8, 593.2, 559.0 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.37 (s, 1 H), 7.47 (d, $J_{H,H}$ = 4.9 Hz, 2 H), 7.46 (d, $J_{H,H}$ = 4.8 Hz, 2 H), 7.27–7.33 (m, 4 H), 7.20–7.24 (m, 2 H), 4.50 (dq, $^3J_{H,H}$ = 6.9 Hz, $^3J_{P,H}$ = 13.8 Hz, 1 H), 4.41 (dq, $^3J_{H,H}$ = 7.2 Hz, $^3J_{P,H}$ = 17.1 Hz, 1 H), 3.86 (s, 2 H), 3.68 (t, $J_{H,H}$ = 9.6 Hz, 1 H), 2.79–2.87 (m, 1 H), 1.63 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.58 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.54–1.56 (m, 1 H), 1.51 (br, 1 H), 1.48 (br, 1 H), 1.35 (t, $J_{H,H}$ = 6.8 Hz, 1 H), 1.15–1.25 (m, 2 H), 0.90–0.99 (m, 1 H), 0.79 (qd, $J_{H,H}$ = 3.2, 12.3 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 169.4, 143.4 (d, $^3J_{P,C}$ = 5.7 Hz), 143.2 (d, $^3J_{P,C}$ = 3.7 Hz), 128.6, 128.2, 127.2, 127.1, 127.0, 126.9, 61.4 (d, $J_{P,C}$ = 11.5 Hz), 59.2 (d, $J_{P,C}$ = 12.3 Hz), 52.9 (d, $J_{P,C}$ = 9.3 Hz), 52.7, 49.7 (d, $J_{P,C}$ = 5.2 Hz), 30.6 (d, $J_{P,C}$ = 9.3 Hz), 29.0 (d, $J_{P,C}$ = 9.2 Hz), 24.4, 24.3, 19.8, 16.7.

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 15.8.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for $[C_{24}H_{31}N_6O_2P + H]^+$: 467.231890; found: 467.231900 (error: 0.022626 ppm).

(3a*R*,7a*R*)-2-Oxide-*N*-(2-azidoacetyl)octahydro-1,3-bis[(1*R*)-1-phenylethyl]-2*H*-1,3,2-benzodiazaphosphol-2-amine [(1*R*,2*R*,1′*R*,2′*R*)-4]

The general procedure was followed with (1*R*,2*R*,1′*R*,2′*R*)-**3** (0.35 g, 0.69 mmol) and NaN_3 (0.054 g, 0.83 mmol) to afford the desired azide; yield: 0.32 g (0.68 mmol, 99%); white foam; $[\alpha]_D^{25}$ –44.9 (*c* 0.36, $CHCl_3$).

IR (ATR): 3085.1, 2932.6, 2867.6, 2103.6, 1708.4, 1477.4, 1450.1, 1374.4, 1353.5, 1297.8, 1278.2, 1205.8, 1178.2, 1134.8, 1076.4, 1059.6, 1020.9, 964.6, 930.9, 916.5, 848.3, 793.5, 762.5, 731.3, 698.7, 653.4, 621.4, 599.7 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.64 (br, 1 H), 7.47 (d, $J_{H,H}$ = 7.7 Hz, 2 H), 7.38 (d, $J_{H,H}$ = 7.6 Hz, 2 H), 7.30 (q, $J_{H,H}$ = 7.1 Hz, 4 H), 7.17–7.25 (m, 2 H), 4.46 (dq, $^3J_{H,H}$ = 7.0 Hz, $^3J_{P,H}$ = 19.3 Hz, 1 H), 4.22 (dq, $^3J_{H,H}$ = 7.1 Hz, $^3J_{P,H}$ = 4.9 Hz, 1 H), 3.65 (s, 3 H), 2.85 (td, $J_{H,H}$ = 2.9, 10.3 Hz, 1 H), 1.81 (d, $J_{H,H}$ = 10.7 Hz, 1 H), 1.65 (d, $J_{H,H}$ = 6.9 Hz, 3 H), 1.53–1.61 (m, 2 H), 1.49 (d, $J_{H,H}$ = 7.0 Hz, 3 H), 1.31 (qd, $J_{H,H}$ = 3.1, 11.8 Hz, 1 H), 1.10–1.27 (m, 2 H), 0.95–1.07 (m, 1 H), 0.73 (qd, $J_{H,H}$ = 2.7, 12.2 Hz, 1 H).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 168.8, 146.5, 140.7 (d, $^3J_{P,C}$ = 1.6 Hz), 128.5, 128.4, 127.3, 127.4, 127.0, 126.5, 62.4 (d, $J_{P,C}$ = 12.3 Hz), 61.7 (d, $J_{P,C}$ = 10.7 Hz), 54.9 (d, $J_{P,C}$ = 5.0 Hz), 52.7, (d, $J_{P,C}$ = 8.9 Hz), 51.3 (d, $J_{P,C}$ = 4.2 Hz), 30.2 (d, $J_{P,C}$ = 8.8 Hz), 29.3 (d, $J_{P,C}$ = 9.2 Hz), , 24.5, 24.2, 22.7, 18.5.

^{31}P NMR (161.8 MHz, $CDCl_3$): δ = 13.4

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for [$C_{24}H_{31}N_6O_2P$ + H]$^+$: 467.231890; found: 467.231900 (error: 0.022626 ppm).

Chiral Catalysts 2 via Catalytic Hydrogenation of Azides 4

The corresponding azide **4** (1 equiv) was dissolved in MeOH in a round-bottomed flask equipped with magnetic stirrer under argon atmosphere. Pd/C (15% w/w of 1% Pd/C) was added with care and the reaction flask was charged with H_2 gas using balloons and syringes. The reaction mixture was stirred at r.t. for 12 h until the complete consumption of the starting material (corroborated by TLC). The mixture was poured onto a Celite pad to remove the catalyst, and the filtrate was concentrated under vacuum. The product was purified by column chromatography (SiO_2: CH_2Cl_2/MeOH 98:2).

(3a*S*,7a*S*)-2-Oxide-*N*-(2-aminoacetyl)octahydro-1,3-bis[(1*R*)-1-phenylethyl]-2*H*-1,3,2-benzodiazaphosphol-2-amine [(1*S*,2*S*,1′*R*,2′*R*)-2]

The general procedure for catalytic hydrogenation was followed with azide (1*S*,2*S*,1′*R*,2′*R*)-**4** (0.4 g, 0.86 mmol) and Pd/C (0.060 g) to afford the title compound; yield: 0.33 g (0.75 mmol, 87%); white foam; $[\alpha]_D^{25}$ +92.4 (*c* 0.34, $CHCl_3$).

IR (ATR): 3068.2, 2936.4, 1699.0, 1447.8, 1380.7, 1299.5, 1207.7, 1182.5, 1152.6, 1080.3, 1058.2, 1018.8, 992.3, 968.3, 931.1, 900.1, 851.5, 754.0, 732.0, 967.9, 664.3, 617.3, 597.5, 576.3 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.98 (br, 1 H), 7.44–7.52 (m, 4 H), 7.25–7.32 (m, 4 H), 7.12–7.22 (m, 2 H), 4.51 (dq, $^3J_{H,H}$ = 7.0 Hz, $^3J_{P,H}$ = 13.6 Hz, 1 H), 4.42 (dq, $^3J_{H,H}$ = 7.1 Hz, $^3J_{P,H}$ = 16.9 Hz, 1 H), 3.60–3.72 (m, 1 H), 3.33 (d, $J_{H,H}$ = 17.8 Hz, 1 H), 3.28 (d, $J_{H,H}$ = 17.8 Hz, 1 H), 2.81(td, $J_{H,H}$ = 2.7, 10.5 Hz, 1 H), 1.76 (br, 2 H), 1.64 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.58–1.62 (m, 1 H), 1.56 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.34–1.53 (m, 3 H), 1.10–1.20 (m, 2 H), 0.93 (qt, $J_{H,H}$ = 3.9, 13.2 Hz, 1 H), 0.75 (qd, $J_{H,H}$ = 3.4, 12.3 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 175.6, 143.6 (d, $^3J_{P,C}$ = 6.1 Hz), 143.6 (d, $^3J_{P,C}$ = 4.1 Hz), 128.5, 128.1, 127.4, 127.1, 127.0, 126.9, 61.3 (d, $J_{P,C}$ = 11.5 Hz), 59.2 (d, $J_{P,C}$ = 12.3 Hz), 52.7 (d, $J_{P,C}$ = 3.8 Hz), 49.6, (d, $J_{P,C}$ = 5.4 Hz), 46.2 (d, $J_{P,C}$ = 8.4 Hz), 30.5 (d, $J_{P,C}$ = 9.5 Hz), 29.1 (d, $J_{P,C}$ = 9.4 Hz), 24.4, 24.3, 19.7 (d, $^3J_{P,C}$ = 1.9 Hz), 16.8.

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 15.5.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for [$C_{24}H_{33}N_4O_2P$ + H]$^+$: 441.241392; found: 441.241613 (error: 0.502010 ppm).

(3a*R*,7a*R*)-2-Oxide-*N*-(2-aminoacetyl)octahydro-1,3-bis[(1*R*)-1-phenylethyl]-2*H*-1,3,2-benzodiazaphosphol-2-amine [(1*R*,2*R*,1′*R*,2′*R*)-2]

The general procedure for catalytic hydrogenation was followed with azide (1*R*,2*R*,1′*R*,2′*R*)-**4** (0.29 g, 0.63 mmol) and Pd/C (0.030 g) to afford the title compound; yield: 0.25 g (0.57 mmol, 91%); white foam; $[\alpha]_D^{25}$ –60.9 (*c* 0.35, $CHCl_3$).

IR (ATR): 3092.7, 2934.4, 2868.8, 1698.8, 1449.8, 1374.7, 1298.5, 1204.3, 1182.3, 1135.4, 1076.3, 1059.5, 1020.7, 964.0, 930.6, 900.2, 855.8, 762.3, 730.8, 699.0, 653.9, 599.2 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (br, 1 H), 7.50 (d, $J_{H,H}$ = 7.5 Hz, 2 H), 7.40 (d, $J_{H,H}$ = 7.4 Hz, 2 H), 7.25–7.33 (m, 4 H), 7.13–7.23 (m, 2 H), 4.42 (dq, $^3J_{H,H}$ = 6.9 Hz, $^3J_{P,H}$ = 21.9 Hz, 1 H), 4.18 (dq, $^3J_{H,H}$ = 7.2, $^3J_{P,H}$ = 8.5 Hz, 1 H), 3.66 (td, $J_{H,H}$ = 2.3, 10.6 Hz, 1 H), 3.04 (s, 2 H), 2.89 (td, $J_{H,H}$ = 3.2, 10.5 Hz, 1 H), 1.88(d, $J_{H,H}$ = 12.1 Hz, 1 H), 1.65 (d, $J_{H,H}$ = 7.0 Hz, 3 H), 1.62 (br, 1 H), 1.51–1.55 (m, 2 H), 1.50 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.30 (qd, $J_{H,H}$ = 3.6, 12.0 Hz, 1 H), 1.17 (qt, $J_{H,H}$ = 3.8, 13.3 Hz, 1 H), 1.06 (qt, $J_{H,H}$ = 3.8, 13.2 Hz, 1 H), 0.70 (qd, $J_{H,H}$ = 3.7, 12.4 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 174.7, 147.0 (d, $^3J_{P,C}$ = 4.6 Hz), 141.0 (d, $^3J_{P,C}$ = 1.8 Hz), 128.8, 128.4, 128.2, 128.1, 127.1, 126.8, 126.6, 62.5 (d, $J_{P,C}$ = 12.0 Hz), 61.5 (d, $J_{P,C}$ = 10.6 Hz), 55.2 (d, $J_{P,C}$ = 4.6 Hz), 51.4 (d, $J_{P,C}$ = 4.0 Hz), 45.8 (d, $J_{P,C}$ = 7.6 Hz), 30.3 (d, $J_{P,C}$ = 8.7 Hz), 29.0 (d, $J_{P,C}$ = 9.3 Hz), 24.6 (d, $J_{P,C}$ = 1.2 Hz), 24.2, 22.7 (d, $^3J_{P,C}$ = 4.5 Hz), 17.5 (d, $J_{P,C}$ = 2.2 Hz).

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 13.8.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for [$C_{24}H_{33}N_4O_2P$ + H]$^+$: 441.241392; found: 441.241320 (error: –0.162024 ppm).

(3a*R*,7a*R*)-2-Oxide-*N*-(2-amino-*N*-ethoxycarbonylacetyl)octahydro-1,3-bis[(1*R*)-1-phenylethyl]-2*H*-1,3,2-benzodiazaphosphol-2-amine [(1*R*,2*R*,1′*R*,2′*R*)-7]

In a 50 mL round-bottomed flask equipped with a stirring bar, *N*-Boc-(*S*)-Proline (0.1 g, 0.48 mmol) was dissolved in anhyd THF (25 mL) under an argon atmosphere before the addition of Et_3N (0.05 g, 0.07 mL, 0.48 mmol). The reaction mixture was cooled to 3 °C before the dropwise addition of ethyl chloroformate (0.06 g, 0.05 mL, 0.52 mmol) and the resulting mixture was stirred at 3 °C for 30 min before the addition of 0.21 g (0.48 mmol) of (1*R*,2*R*,1′*R*,2′*R*)-**2** in anhyd THF. The reaction mixture was allowed to reach r.t. and stirred for an additional 16 h until the starting material was consumed (checked by TLC). The mixture was poured into H_2O and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (anhyd Na_2SO_4) and concentrated. The crude product was purified by column chromatography (SiO_2: CH_2Cl_2/MeOH 95:5) to afford ethyl carbamate **7**; yield: 0.16 g (0.31 mmol, 65%); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, $J_{H,H}$ = 7.4 Hz, 2 H), 7.39 (d, $J_{H,H}$ = 7.3 Hz, 2 H), 7.35–7.11 (m, 6 H), 5.29 (s, 1 H), 4.44 (dq, $^3J_{H,H}$ = 6.7 Hz, $^3J_{P,H}$ = 19.9 Hz, 1 H), 4.26–4.16 (m, 1 H), 4.14 (q, $J_{H,H}$ = 7.1 Hz, 2 H), 3.70–3.60 (m, 2 H), 2.85 (t, $J_{H,H}$ = 9.2 Hz, 1 H), 1.88–1.77 (m, 1 H), 1.63 (d, $J_{H,H}$ = 6.8 Hz, 3 H), 1.59–1.54 (m, 2 H), 1.50 (d, $J_{H,H}$ = 6.9 Hz, 3 H), 1.35–1.12 (m, 3 H), 1.23 (t, $J_{H,H}$ = 7.0 Hz, 3 H), 1.08–0.95 (m, 1 H), 0.94–0.82 (m, 1 H), 0.81–0.58 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.7, 158.6, 146.3, 140.5, 128.3, 127.2, 126.7, 126.4, 62.4 (d, $J_{P,C}$ = 10.8 Hz), 61.3, 55.0, 51.2, 45.2, 30.1, 29.7, 29.1, 24.4, 24.0, 23.3, 17.9, 14.6.

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 14.1.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for [$C_{27}H_{37}N_4O_4P$ + H]$^+$: 513.262521; found: 513.262522 (error: 0.002080 ppm).

N-Boc-Protected Catalysts 8a–d; General Procedure

In a round-bottomed flask equipped with a stirring bar, *N*-Boc-(*R*)- or *N*-Boc-(*S*)-proline (2.0 equiv) was dissolved in anhyd MeCN under an argon atmosphere, before the addition of *N*-methylmorpholine (3.0 equiv). The resulting mixture was cooled to 3 °C and then propylphosphonic anhydride (T3P®, 50% wt. in EtOAc; 2.4 equiv) was added slowly. The reaction mixture was stirred at 3 °C for 30 min before the addition of the corresponding compound **2** (1 equiv) and stirred at r.t. for 24 h until the complete consumption of the starting material (corroborated by TLC). The crude product was diluted with EtOAc and washed with aq 1.0 M HCl (3 ×), aq sodium potassium tartrate (50% wt.), and finally with brine. The organic layer was dried (anhyd Na_2SO_4) and concentrated. The crude product was purified by column chromatography (SiO_2: hexanes/EtOAc 95:5 to 7:3).

(1*R*,2*R*,1′*R*,2′*R*,2″*S*)-8a

The general procedure was used with (1*R*,2*R*,1′*R*,2′*R*)-**2** (0.15 g, 0.34 mmol), *N*-Boc-(*S*)-proline (0.15 g, 0.68 mmol), *N*-methylmorpholine (0.11 g, 0.12 mL, 1.02 mmol), and T3P® (0.26 g, 0.49 mL, 0.82 mmol) to afford **8a**; yield: 0.16 g (0.26 mmol, 75%); white foam; $[\alpha]_D^{25}$ –70.3 (*c* 0.37, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, $J_{H,H}$ = 7.6 Hz, 2 H), 7.39 (d, $J_{H,H}$ = 7.5 Hz, 2 H), 7.25–7.33 (m, 4 H), 7.13–7.22 (m, 2 H), 4.45 (dq, $^3J_{H,H}$ = 7.1 Hz, $^3J_{P,H}$ = 19.4 Hz, 1 H), 3.92–4.36 (m, 2 H), 3.27–3.80 (m, 5 H), 3.52–3.04 (m, 2 H), 2.11–2.26 (m, 1 H), 1.72–1.96 (m, 3 H), 1.61 (d, $J_{H,H}$ = 6.6 Hz, 3 H), 1.38–1.56 (m, 15 H), 1.20–1.29 (m, 2 H), 1.10–1.18 (m, 1 H), 0.96–1.05 (m, 1 H), 0.64–0.77 (m, 1 H).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 172.7, 169.9, 146.5, 140.4, 128.5 (2 C), 128.4 (4 C), 127.5, 126.9, 126.6 (2 C), 80.7, 62.5 (d, $J_{P,C}$ = 12.2 Hz), 61.4 (d, $J_{P,C}$ = 10.6 Hz), 60.1, 55.2, 53.6, 51.2, 47.3, 43.8, 31.3, 30.2, 29.3, 28.6, 24.6, 24.2, 22.6, 18.2.

^{31}P NMR (161.8 MHz, $CDCl_3$): δ = 13.9.

^{1}H NMR (400 MHz, DMSO-d_6, r.t.): δ = 8.96 (d, $J_{H,H}$ = 7.9 Hz, 1 H), 7.98 (br, 1 H), 7.45 (d, $J_{H,H}$ = 7.6 Hz, 2 H), 7.41 (d, $J_{H,H}$ = 7.2 Hz, 2 H), 7.32 (t, $J_{H,H}$ = 7.6 Hz, 2 H), 7.26 (t, $J_{H,H}$ = 7.6 Hz, 2 H), 7.21 (t, $J_{H,H}$ = 7.3 Hz, 1 H), 7.15 (t, $J_{H,H}$ = 7.3 Hz, 1 H), 4.44 (dq, $^3J_{H,H}$ = 7.1 Hz, $^3J_{P,H}$ = 14.4 Hz, 1 H), 4.05–4.20 (m, 2 H), 3.34–3.39 (m, 1 H), 3.24–3.29 (m, 1 H), 2.45–2.55 (m, 2 H), 2.03–2.15 (m, 1 H), 1.70–1.85 (m, 3 H), 1.55–1.67 (m, 1 H), 1.49 (d, $J_{H,H}$ = 7.3 Hz, 3 H), 1.46 (d, $J_{H,H}$ = 7.2 Hz, 3 H), 1.32–1.43 (m, 13 H), 0.95–1.09 (m, 2 H), 0.70–0.79 (m, 1 H), 0.45 (q, $J_{H,H}$ = 12.0 Hz, 1 H).

^{13}C NMR (100.5 MHz, DMSO-d_6, r.t.): δ = 173.4, 170.9, 154.1, 148.0, 141.5, 128.7 (2 C), 128.6 (2 C), 128.1 (2 C), 127.4, 127.0, 126.6 (2 C), 79.4, 62.3 (d, $J_{P,C}$ = 11.6 Hz), 61.5 (d, $J_{P,C}$ = 11.0 Hz), 60.3, 55.3, 54.7, 51.0 (d, $J_{P,C}$ = 3.8 Hz), 47.0, 43.2 (d, $J_{P,C}$ = 10.7 Hz), 31.6, 30.1, 28.5, 24.6, 24.1, 23.7, 22.8, 20.0.

^{31}P NMR (161.8 MHz, DMSO-d_6, r.t.): δ = 13.8.

^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ = 8.44 (br, 1 H), 7.61 (br, 1 H), 7.47 (d, $J_{H,H}$ = 7.6 Hz, 2 H), 7.42 (d, $J_{H,H}$ = 7.4 Hz, 2 H), 7.32 (t, $J_{H,H}$ = 7.6 Hz, 2 H), 7.26 (t, $J_{H,H}$ = 7.6 Hz, 2 H), 7.21 (t, $J_{H,H}$ = 7.4 Hz, 1 H), 7.16 (t, $J_{H,H}$ = 7.3 Hz, 1 H), 4.48 (dq, $^3J_{H,H}$ = 7.2 Hz, $^3J_{P,H}$ = 14.6 Hz, 1 H), 4.12–4.24 (m, 2 H), 3.369 (t, $J_{H,H}$ = 5.7, 16.9 Hz, 2 H), 3.49–3.58 (m, 1 H), 3.28–3.39 (m, 2 H), 2.55–2.64 (m, 1 H), 2.44–2.54 (m, 1 H), 2.04–2.16 (m, 1 H), 1.73–1.91 (m, 3 H), 1.62–1.68 (m, 1 H), 1.53 (d, $J_{H,H}$ = 7.0 Hz, 3 H), 1.51 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.32–1.47 (m, 12 H), 1.11 (qd, $J_{H,H}$ = 3.4, 12.0 Hz, 1 H), 1.02 (qt, $J_{H,H}$ = 3.6, 13.1 Hz, 1 H), 0.84 (qt, $J_{H,H}$ = 3.2, 13.2 Hz, 1 H), 0.59 (qd, $J_{H,H}$ = 3.2, 12.2 Hz, 1 H).

^{13}C NMR (100.5 MHz, DMSO-d_6, 100 °C): δ = 173.2, 170.8 (d, $J_{P,C}$ = 3.5 Hz), 154.4, 147.3 (d, $J_{P,C}$ = 4.0 Hz), 141.7 (d, $J_{P,C}$ = 2.6 Hz), 128.5 (2 C), 128.4 (2 C), 128.2 (2 C), 127.3, 126.9, 126.8 (2 C), 79.6, 62.1 (d, $J_{P,C}$ = 12.3 Hz), 61.9 (d, JP,C = 10.8 Hz), 60.5, 54.6 (d, JP,C = 4.6 Hz), 51.5 (d, $J_{P,C}$ = 4.5 Hz), 47.2, 43.8 (d, $J_{P,C}$ = 9.0 Hz), 31.0, 30.2 (d, $J_{P,C}$ = 9.1 Hz), 28.7, 24.6, 24.2, 23.9, 22.5 (d, $J_{P,C}$ = 4.3 Hz), 19.8 (d, $J_{P,C}$ = 4.0 Hz).

^{31}P NMR (161.8 MHz, DMSO-d_6, 100 °C): δ = 14.0.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for $[C_{34}H_{48}N_5O_5P + H]^+$: 638.346585; found: 638.346941 (error: 0.557658 ppm).

(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-8b

The general procedure was followed with (1*S*,2*S*,1′*R*,2′*R*)-**2** (0.4 g (0.91 mmol), *N*-Boc-(*S*)-proline (0.39 g, 1.82 mmol), *N*-methylmorpholine (0.28 g, 0.3 mL, 2.73 mmol), and T3P® (0.7 g, 1.31 mL, 2.18 mmol) to afford **8b** (0.42 g, 0.65 mmol, 71%); white foam; $[\alpha]_D^{25}$ +36.3 (*c* 0.347, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.52 (br, 1 H), 7.46 (d, $J_{H,H}$ = 7.6 Hz, 2 H), 7.43 (d, $J_{H,H}$ = 7.7 Hz, 2 H), 7.30 (t, $J_{H,H}$ = 7.6 Hz, 2 H), 7.25 (t, $J_{H,H}$ = 7.5 Hz, 2 H), 7.19 (d, $J_{H,H}$ = 7.6 Hz,), 7.16 (d, $J_{H,H}$ = 7.3 Hz, 2 H), 4.47 (dq, $^3J_{H,H}$ = 6.7 Hz, $^3J_{P,H}$ = 13.3 Hz, 1 H), 4.28–4.41 (m, 1 H), 4.24 (br, 1 H), 4.01–4.16 (m, 1 H), 3.85–3.96 (m, 1 H), 3.25–3.63 (m, 3 H), 2.78 (t, $J_{H,H}$ = 9.7 Hz, 1 H), 2.09–2.20 (m, 1 H), 1.76–1.94 (m, 2 H), 1.60 (d, $J_{H,H}$ = 7.0 Hz, 3 H), 1.36–1.57 (m, 7 H), 1.46 (s, 9 H), 1.19–1.31 (m, 1 H), 1.05–1.17 (m, 2 H) 0.91 (br q $J_{H,H}$ = 12.8 Hz, 1 H), 0.70 (br q, $J_{H,H}$ = 10.6 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 172.6, 171.2, 170.7, 155.1, 143.4, 128.6 (2 C), 127.0 (2 C), 126.9 (2 C), 126.8 (2 C), 80.5, 61.3 (d, $J_{P,C}$ = 11.7 Hz), 60.7, 59.9 (d, $J_{P,C}$ = 12.2 Hz), 52.9 (d, $J_{P,C}$ = 3.3 Hz), 49.3 (d, $J_{P,C}$ = 5.1 Hz), 47.1, 43.8, 31.2, 30.5 (d, $J_{P,C}$ = 9.5 Hz), 29.2, 28.8 (d, $J_{P,C}$ = 9.3 Hz), 28.5, 24.3, 24.2, 19.9, 16.2.

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 15.9.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for $[C_{34}H_{48}N_5O_5P + H]^+$: 638.346585; found: 638.34665 (error: 0.101794 ppm).

(1*R*,2*R*,1′*R*,2′*R*,2″*R*)-8c

The general procedure was followed with (1*R*,2*R*,1′*R*,2′*R*)-**2** (0.3 g, 0.68 mmol), *N*-Boc-(*R*)-proline (0.29 g, 1.36 mmol), *N*-methylmorpholine (0.21 g, 0.23 mL, 2.04 mmol), and T3P® (0.52 g, 0.97 mL, 1.63 mmol) to afford **8c**; yield: 0.31 g (0.49 mmol, 72%); white foam; $[\alpha]_D^{25}$ –2.9 (*c* 0.347, $CHCl_3$).

1H NMR (500 MHz, CDCl3): δ = 8.26 (br, 1 H), 7.45 (br, 2 H), 7.37 (d, $J_{H,H}$ = 7.5 Hz, 2 H), 7.24–7.31 (m, 4 H), 7.13–7.21 (m, 2 H), 4.44 (dq, $^3J_{H,H}$ = 6.9 Hz, $^3J_{P,H}$ = 18.6 Hz, 1 H), 4.26 (br, 1 H), 4.15 (br, 1 H), 3.30–3.87 (m, 5 H), 2.73–2.88 (m, 1 H), 2.13–2.30 (m, 2 H), 1.95 (br, 1 H), 1.87 (br, 1 H), 1.77 (br, 1 H), 1.60 (d, $J_{H,H}$ = 6.8 Hz, 3 H), 1.38–1.57 (m, 15 H), 1.24 (br q, $J_{H,H}$ = 10.7 Hz, 1 H), 1.14 (qt, $J_{H,H}$ = 4.0, 13.0 Hz, 1 H), 0.97 (br q, $J_{H,H}$ = 13.2 Hz, 1 H), 0.68 (br s, $J_{H,H}$ = 11.8 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 175.5, 170.5, 146.7, 140.7 (d, $^3J_{P,C}$ = 5.8 Hz), 140.64 (d, $^3J_{P,C}$ = 5.0 Hz), 128.4 (2 C), 128.3 (4 C), 127.2, 126.8, 126.5 (2 C), 80.6, 62.4 (d, $J_{P,C}$ = 12.2 Hz), 61.4 (d, $J_{P,C}$ = 10.8 Hz), 60.1, 55.1 (d, $J_{P,C}$ = 3.3 Hz), 51.2 (d, $J_{P,C}$ = 3.5 Hz), 47.2, 31.2 (d, $J_{P,C}$ = 4.0 Hz), 30.2 (d, $J_{P,C}$ = 8.1 Hz), 29.4, 28.7, 28.47, 24.8, 24.5, 24.1, 22.6 (d, $J_{P,C}$ = 3.8 Hz), 18.4.

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 13.9.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for $[C_{34}H_{48}N_5O_5P + H]^+$: 638.346585; found: 638.346953 (error: 0.576457 ppm).

(1*S*,2*S*,1′*R*,2′*R*,2″*R*)-8d

The general procedure was followed with (1*S*,2*S*,1′*R*,2′*R*)-**2** (0.3 g, 0.68 mmol), *N*-Boc-(*R*)-proline (0.29 g, 1.36 mmol), *N*-methylmorpholine (0.21 g, 0.23 mL, 2.04 mmol), and T3P® (0.52 g, 0.97 mL, 1.63 mmol) to afford **8d**; yield: 0.37 g (0.57 mmol, 84%); white foam; $[\alpha]_D^{25}$ +102.2 (*c* 0.365, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.42 (br, 1 H), 7.45 (d, $J_{H,H}$ = 7.5 Hz, 4 H), 7.24–7.32 (m, 4 H), 7.09–7.21 (m, 2 H), 4.43–4.46 (m, 1 H), 4.32 (br, 1 H), 4.23 (br, 1 H), 3.85–4.16 (m, 2 H), 3.24–3.67 (m, 3 H), 2.75–2.85 (m, 1 H), 2.09–2.30 (m, 2 H), 1.92 (br, 1 H), 1.82 (br, 1 H), 1.60 (d, $J_{H,H}$ = 6.8 Hz, 3 H), 1.52 (d, $J_{H,H}$ = 6.5 Hz, 3 H), 2.21 (s, 9 H), 1.35–1.57 (m, 4 H), 1.07–1.19 (m, 2 H), 0.87–0.97 (m, 1 H), 0.72 (br, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 172.6, 170.4, 155.0, 143.5, 143.2, 128.6 (2 C), 128.2 (2 C), 127.2 (2 C), 127.0 (3 C), 126.9, 80.6, 61.3 (d, $J_{P,C}$ = 11.4 Hz), 60.1, 59.0 (d, $J_{P,C}$ = 12.6 Hz), 52.9, 49.5 (d, $J_{P,C}$ = 5.1 Hz), 47.4, 44.3, 43.8, 31.2, 30.5, 28.9, 28.6, 24.4, 24.3, 19.8, 16.5.

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 15.8.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for $[C_{34}H_{48}N_5O_5P + H]^+$: 638.346585; found: 638.346864 (error: 0.437034 ppm).

Hydrolysis of *N*-Boc Protecting Group in 8a–d Leading to 9a–d; General Procedure

Compound **8** was dissolved in CH_2Cl_2 and cooled to 3 °C before the dropwise addition of TFA (10.0 equiv) dissolved in CH_2Cl_2. The resulting mixture was stirred for 12–24 h until the complete consumption of the starting material (corroborated by TLC). The solvent was evaporated, and the crude product was dissolved in EtOAc, before the addition of aq 1 M NaOH or ammonium hydroxide, and the resulting mixture was stirred for an additional 1 h to liberate the trifluoroacetate salt. The phases were separated, and the organic layer was dried (anhyd Na_2SO_4) and concentrated. The crude product was purified by column chromatography (SiO_2: CH_2Cl_2/MeOH 98:2 to 95:5).

(1*R*,2*R*,1′*R*,2′*R*,2″*S*)-9a

The general deprotection procedure was followed with (1*R*,2*R*,1′*R*,2′*R*,2″*S*)-**8a** (0.16 g, 0.25 mmol) and TFA (0.29 g, 0.19 mL, 2.5 mmol) to afford **9a**; yield: 0.12 g (0.22 mmol, 88%); white foam; $[\alpha]_D^{25}$ –57.9 (*c* 0.333, $CHCl_3$).

IR (ATR): 2936.6, 2864.2, 1726.1, 1662.9, 1450.5, 1390.5, 1274.5, 1205.6, 1181.5, 1133.3, 1076.6, 1058.9, 1020.9, 965.0, 930.4, 899.1, 856.2, 767.4, 733.0, 700.1, 651.2, 613.9, 583.1 566.1 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.89 (t, $J_{H,H}$ = 5.2 Hz, 1 H), 7.74 (br, 1 H), 7.49 (d, $J_{H,H}$ = 7.5 Hz, 2 H), 7.40 (d, $J_{H,H}$ = 7.3 Hz, 2 H), 7.33 (t, $J_{H,H}$ = 7.7 Hz, 2 H), 7.29 (t, $J_{H,H}$ = 7.7 Hz, 2 H), 7.23 (t, $J_{H,H}$ = 7.4 Hz, 1 H), 7.19 (d, $J_{H,H}$ = 7.3 Hz, 1 H), 4.45 (dq, $^3J_{H,H}$ = 6.8 Hz, $^3J_{P,H}$ = 20.2 Hz, 1 H), 4.20 (dq, $^3J_{H,H}$ = 7.1 Hz, $^3J_{P,H}$ = 9.4 Hz, 1 H), 3.87 (dd, $J_{H,H}$ = 6.6, 17.8 Hz, 1 H), 3.80 (dd, $J_{H,H}$ = 5.5, 9.2 Hz, 1 H), 3.59–3.68 (m, 1 H), 3.57 (dd, $J_{H,H}$ = 4.5, 17.9 Hz, 1 H), 3.01–3.11 (m, 1 H), 2.91–3.0 (m, 1 H), 2.79–2.90 (m, 1 H), 2.07–2.37 (m, (3 H), 1.91 (sext, $J_{H,H}$ = 6.5 Hz, 1 H), 1.84 (br d, $J_{H,H}$ = 10.4 Hz, 1 H), 1.69–1.78 (m, 2 H), 1.65 (d, $J_{H,H}$ = 7.0 Hz, 3 H), 1.53–1.61 (m, 2 H), 1.51 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.30 (qd, $J_{H,H}$ = 3.4, 12.1 Hz, 1 H), 1.19 (qt, $J_{H,H}$ = 3.6, 13.2 Hz, 1 H), 1.04 (qt, $J_{H,H}$ = 3.7, 13.3 Hz, 1 H), 0.72 (qd, $J_{H,H}$ = 3.3, 12.3 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 175.8, 170.4 (d, $J_{P,C}$ = 2.5 Hz), 146.6 (d, $^3J_{P,C}$ = 4.2 Hz), 140.7 (d, $^3J_{P,C}$ = 1.8 Hz), 128.5 (2 C), 128.4 (2 C), 127.3 (2 C), 127.4, 126.9, 126.6 (2 C), 62.4 (d, $J_{P,C}$ = 12.2 Hz), 61.5 (d, $J_{P,C}$ = 10.9 Hz), 60.7, 55.1 (d, $J_{P,C}$ = 4.6 Hz), 51.4 (d, $J_{P,C}$ = 4.1 Hz), 47.5, 43.5 (d, $J_{P,C}$ = 9.4 Hz), 30.9, 30.3 (d, $J_{P,C}$ = 8.7 Hz), 29.2 (d, $J_{P,C}$ = 9.4 Hz), 26.5, 24.5, 24.2 (d, $J_{P,C}$ = 0.7 Hz), 22.6 (d, $J_{P,C}$ = 4.5 Hz), 18.1 (d, $J_{P,C}$ = 2.6 Hz).

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 13.8.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for $[C_{29}H_{40}N_5O_3P + H]^+$: 538.294156; found: 538.294118 (error: –0.069515 ppm).

(1*S*,2*S*,1′*R*,2′*R*,2″*S*)-9b

The general deprotection procedure was followed with (1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**8b** (0.39 g, 0.61 mmol) and TFA (0.7 g, 0.47 mL, 6.1 mmol) to afford **9b**; yield: 0.31 g (0.58 mmol, 95%); white foam; $[\alpha]_D^{25}$ +52.3 (*c* 0.30, $CHCl_3$).

IR (ATR): 2924.1, 2855.9, 1702.5, 1668.1, 1453.8, 1387.9, 1299.8, 1207.9, 1180.7, 1153.1, 1080.3, 1057.2, 1018.5, 1002.9, 969.4, 931.3, 899.6, 856.6, 781.7, 733.1, 698.3, 666.3 cm^{-1}.

1H NMR (500 MHz, CDCl3): δ = 9.26 (br, 1 H), 8.07 (br, 1 H), 7.49 (d, $J_{H,H}$ = 7.5 Hz, 2 H), 7.45 (d, $J_{H,H}$ = 7.9 Hz, 2 H), 7.30 (t, $J_{H,H}$ = 7.7 Hz, 2 H), 7.27 (t, $J_{H,H}$ = 7.7 Hz, 2 H), 7.15–7.22 (m, 2 H), 4.50 (dq, $^3J_{H,H}$ = 6.9 Hz, $^3J_{P,H}$ = 13.4 Hz, 1 H), 4.38 (dq, $^3J_{H,H}$ = 7.0 Hz, $^3J_{P,H}$ = 17.4 Hz, 1 H), 4.14 (dd, $J_{H,H}$ = 6.1, 17.9 Hz, 1 H), 3.88 (dd, $J_{H,H}$ = 4.6, 17.9 Hz, 1 H), 3.81 (dd, $J_{H,H}$ = 5.5, 9.1 Hz, 1 H), 3.54–3.66 (m, 1 H), 2.85–3.08 (m, 2 H), 2.75–2.82 (m, 1 H), 2.54 (br, 1 H), 2.10–2.19 (m, 1 H), 1.91 (sext, $J_{H,H}$ = 6.7 Hz, 1 H), 1.66–1.77 (m, 2 H), 1.63 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.53–1.60 (m, 2 H), 1.53 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.42–1.51 (m, 2 H), 1.10–1.20 (m, 2 H), 0.92 (qt, $J_{H,H}$ = 3.7, 13.3 Hz, 1 H), 0.71 (qd, $J_{H,H}$ = 3.3, 12.3 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 175.6, 171.1, 143.6 (d, $^3J_{P,C}$ = 6.1 Hz), 143.3 (d, $^3J_{P,C}$ = 3.9 Hz), 128.6 (2 C), 128.1 (2 C), 127.2 (2 C), 127.1 (2 C), 127.0, 126.9, 61.3 (d, $J_{P,C}$ = 11.7 Hz), 60.7, 59.0 (d, $J_{P,C}$ = 12.2 Hz), 52.9 (d, $J_{P,C}$ = 3.5 Hz), 49.5 (d, $J_{P,C}$ = 5.5 Hz), 47.4, 43.8 (d, $J_{P,C}$ = 9.8 Hz), 30.9, 30.5 (d, $J_{P,C}$ = 9.5 Hz), 28.9 (d, $J_{P,C}$ = 9.3 Hz), 26.4, 24.3 (d, $J_{P,C}$ = 13.0 Hz), 19.9, 16.5.

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 15.6.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for $[C_{29}H_{40}N_5O_3P + H]^+$: 538.294156; found: 538.293414 (error: –1.377351 ppm).

(1*R*,2*R*,1′*R*,2′*R*,2″*R*)-9c

The general deprotection procedure was followed with (1*R*,2*R*,1′*R*,2′*R*,2″*R*)-**8c** (0.28 g, 0.45 mmol) and TFA (0.51 g, 0.34 mL, 4.5 mmol) to afford **9c**; yield: 0.22 g (0.41 mmol, 91%); white foam; $[\alpha]_D^{25}$ –11.6 (*c* 0.32, $CHCl_3$).

IR (ATR): 3090.8, 2931.3, 2865.0, 1704.9, 1667.6, 1449.7, 1375.1, 1298.1, 1275.6, 1204.8, 1180.7, 1135.9, 1077.4, 1059.4, 1020.6, 964.0, 931.1, 899.6, 857.7, 765.9, 732.4, 700.0, 648.1, 609.4, 573.0 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.44 (br, 1 H), 7.98 (t, $J_{H,H}$ = 4.9 Hz, 1 H), 7.46 (d, $J_{H,H}$ = 7.7 Hz, 2 H), 7.38 (d, $J_{H,H}$ = 7.8 Hz, 2 H), 7.27 (q, $J_{H,H}$ = 8.1 Hz, 4 H), 7.18 (d, $J_{H,H}$ = 7.3 Hz, 1 H), 7.14 (d, $J_{H,H}$ = 6.7 Hz, 1 H), 4.44 (dq, $^3J_{H,H}$ = 6.9 Hz, $^3J_{P,H}$ = 18.2 Hz, 1 H), 4.17 (dq, $^3J_{H,H}$ = 7.2 Hz, $^3J_{P,H}$ = 9.1 Hz, 1 H), 3.91 (dd, $J_{H,H}$ = 5.8, 17.9 Hz, 1 H), 3.79 (dd, $J_{H,H}$ = 5.5, 9.1 Hz, 1 H), 3.55–3.66 (m, 2 H), 2.90–3.10 (m, 2 H), 2.75–2.84 (m, 1 H), 2.56 (br, 1 H), 2.08–2.19 (m, 1 H), 1.90 (sext, $J_{H,H}$ = 6.4 Hz, 1 H), 1.67–1.80 (m, 3 H), 1.61 (d, $J_{H,H}$ = 7.0 Hz, 3 H), 1.51–1.57 (m, 2 H), 1.49 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.45 (br, 1 H), 1.25 (qd, $J_{H,H}$ = 3.0, 12.1 Hz, 1 H), 1.13 (qt, $J_{H,H}$ = 3.4, 13.2 Hz, 1 H), 0.91–1.01 (m, 1 H), 0.66 (qd, $J_{H,H}$ = 3.1, 12.3 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 175.5, 170.5 (d, $J_{P,C}$ = 2.5 Hz), 146.8 (d, $^3J_{P,C}$ = 4.1 Hz), 140.9 (d, $^3J_{P,C}$ = 2.1 Hz), 128.5 (2 C), 128.3 (2 C), 128.2 (2 C), 127.3, 126.8, 126.5 (2 C), 62.4 (d, $J_{P,C}$ = 12.2 Hz), 61.5 (d, $J_{P,C}$ = 10.9 Hz), 60.6, 55.1 (d, $J_{P,C}$ = 4.7 Hz), 51.4 (d, $J_{P,C}$ = 4.2 Hz), 47.4, 43.4 (d, $J_{P,C}$ = 9.8 Hz), 30.9, 30.2 (d, $J_{P,C}$ = 8.6 Hz), 29.4 (d, $J_{P,C}$ = 9.5 Hz), 26.3, 24.4, 24.1, 22.6 (d, $J_{P,C}$ = 4.6 Hz), 18.7 (d, $J_{P,C}$ = 3.0 Hz).

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 13.9.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for $[C_{29}H_{40}N_5O_3P + H]^+$: 538.294156; found: 538.294492 (error: 0.62527 ppm).

1*S*,2*S*,1′*R*,2′*R*,2″*R*)-9d

The general deprotection procedure was followed with (1*S*,2*S*,1′*R*,2′*R*,2″*R*)-**8d** (0.37 g, 0.57 mmol) and TFA (0.65 g, 0.43 mL, 5.7 mmol) to afford **9d**; yield: 0.28 g (0.52 mmol, 91%); white foam; $[\alpha]_D^{25}$ +103.9 (*c* 0.307, $CHCl_3$).

IR (ATR): 30.85.8, 2940.3, 2871.4, 1710.0, 1662.0, 1470.0, 1447.3, 1386.1, 1299.6, 1208.1, 1185.1, 1152.9, 1081.1, 1058.1, 1018.5, 991.8, 968.5, 931.3, 900.0, 854.6, 781.3, 764.1, 733.1, 698.5, 663.1, 625.7, 607.8, 574.2 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.35 (br, 1 H), 8.05 (t, $J_{H,H}$ = 4.6 Hz, 1 H), 7.48 (d, $J_{H,H}$ = 7.7 Hz, 2 H), 7.45 (d, $J_{H,H}$ = 8.1 Hz, 2 H), 7.31 (t, $J_{H,H}$ = 7.7 Hz, 2 H), 7.26 (t, $J_{H,H}$ = 7.6 Hz, 2 H), 7.20 (d, $J_{H,H}$ = 7.5 Hz, 1 H), 7.16 (d, $J_{H,H}$ = 7.3 Hz, 1 H), 4.50 (dq, $^3J_{H,H}$ = 7.0 Hz, $^3J_{P,H}$ = 13.8 Hz, 1 H), 4.36 (dq, $^3J_{H,H}$ = 7.0 Hz, $^3J_{P,H}$ = 17.6 Hz, 1 H), 4.10 (dd, $J_{H,H}$ = 6.0, 17.9 Hz, 1 H), 3.90 (dd, $J_{H,H}$ = 4.6, 17.9 Hz, 1 H), 3.79 (dd, $J_{H,H}$ = 5.5, 9.1 Hz, 1 H), 3.53–3.63 (m, 1 H), 2.88–3.08 (m, 2 H), 2.74–2.82 (m, 1 H), 2.53 (br, 1 H), 2.00–2.19 (m, 1 H), 1.93 (sext, $J_{H,H}$ = 6.4 Hz, 1 H), 1.64–1.78 (m, 2 H), 1.63 (d,

$J_{H,H}$ = 7.1 Hz, 3 H), 1.57–1.60 (m, 1 H), 1.55 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.41–1.53 (m, 3 H), 1.10–1.20 (m, 2 H), 0.92 (qt, $J_{H,H}$ = 3.8, 13.3 Hz, 1 H), 0.73 (qd, $J_{H,H}$ = 3.0, 12.3 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 175.6, 171.2, 143.6 (d, $^3J_{P,C}$ = 5.8 Hz), 143.3 (d, $^3J_{P,C}$ = 3.7 Hz), 128.6 (2 C), 128.1 (2 C), 127.2 (2 C), 127.1 (2 C), 127.0, 126.9, 61.3 (d, $J_{P,C}$ = 11.7 Hz), 60.7, 59.0 (d, $J_{P,C}$ = 12.2 Hz), 53.0 (d, $J_{P,C}$ = 3.4 Hz), 49.5 (d, $J_{P,C}$ = 5.5 Hz), 47.4, 43.8 (d, $J_{P,C}$ = 9.9 Hz), 30.9, 30.5 (d, $J_{P,C}$ = 9.4 Hz), 28.8 (d, $J_{P,C}$ = 9.3 Hz), 26.4, 24.3 (d, $J_{P,C}$ = 10.3 Hz), 19.9 (d, $J_{P,C}$ = 1.6 Hz), 16.6.

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 15.6.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for [$C_{29}H_{40}N_5O_3P$ + H]$^+$: 538.294156; found: 538.293462 (error: 0.863058 ppm).

(1*R*,2*R*,1′*R*,2′*R*,2″*S*)-13

In a 100 mL round-bottomed flask equipped with a stirring bar (1*R*,2*R*,1′*R*,2′*R*)-**1** (0.82 g (2.1 mmol) was dissolved in anhyd THF (40 mL) under an argon atmosphere and cooled at 3 °C before the dropwise addition of *n*-BuLi (2.8 M in hexanes; 0.18 g, 1.0 mL, 2.7 mmol). The resulting mixture was stirred at 3 °C for 20 min before the addition of phenylalanine methyl ester (0.5 g, 2.7 mmol) dissolved in anhyd THF. The reaction mixture was allowed to reach r.t., and stirring was continued for 24 h. Subsequently, the mixture was poured into ice/water and extracted with EtOAc. The combined organic layers were dried (anhyd Na_2SO_4), filtered, and the solvent was removed by distillation. The crude product was purified by column chromatography on silica gel (eluent: hexane/EtOAc 8:2 to 7:3) to afford pure **13**; yield: 0.58 g (1.1 mmol, 52%); white foam; [α]$_D^{25}$ –44.3 (*c* 0.336, $CHCl_3$).

IR (ATR): 3057.1, 3028.6, 2933.0, 2967.6, 1711.3, 1494.5, 1451.4, 1377.2, 1337.7, 1299.6, 1240.0, 1224.2, 1206.4, 1182.5, 1136.6, 1074.6, 1030.2, 996.1, 963.7, 928.9, 814.8, 766.8, 738.9, 668.4, 667.5, 597.7, 559.2 cm^{-1}.

1H NMR (500 MHz, CDCl3): δ = 8.59 (d, JH,H = 10.4 Hz, 1 H), 7.55 (d, $J_{H,H}$ = 7.5 Hz, 2 H), 7.40 (d, $J_{H,H}$ = 7.8 Hz, 2 H), 7.31 (q, $J_{H,H}$ = 7.8 Hz, 4 H) 7.20–7.27 (m, 6 H), 7.14–7.19 (m, 1 H), 4.50 (dq, 3JH,H = 7.0 Hz, $^3J_{P,H}$ = 19.4 Hz, 1 H), 4.20 (dq, $^3J_{H,H}$ = 7.3 Hz, $^3J_{P,H}$ = 7.5 Hz, 1 H), 3.73 (td, JH,H = 2.5, 10.7 Hz, 1 H), 3.38 (dd, JH,H = 3.6, 10.3 Hz, 1 H), 3.32 (dd, $J_{H,H}$ = 3.8, 13.5 Hz, 1 H), 2.86 (td, $J_{H,H}$ = 3.1, 10.5 Hz, 1 H), 2.38 (dd, $J_{H,H}$ = 10.4, 13.5 Hz, 1 H), 1.83 (d, $^3J_{H,H}$ = 9.9 Hz, 1 H), 1.67 (d, $^3J_{H,H}$ = 6.0 Hz, 3 H), 1.63 (d, 3JH,H = 21.1 Hz, 1 H), 1.47–1.55 (m, 2 H), 1.51 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.33 (qd, $J_{H,H}$ = 3.6, 12.1 Hz, 1 H), 1.19 (qt, $J_{H,H}$ = 3.7, 13.2 Hz, 1 H), 0.90–1.12 (m, 3 H), 0.68 (qd, $J_{H,H}$ = 3.5, 12.3 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 177.2 (d, $J_{P,C}$ = 1.6 Hz), 147.0 (d, $J_{P,C}$ = 3.8 Hz), 141.3 (d, $J_{P,C}$ = 1.7 Hz), 137.9, 129.9, 129.6, 129.3, 129.2, 128.9, 128.8, 128.6, 128.5, 128.3, 127.5, 127.1, 127.0, 126.8, 126.7, 63.8 (d, $J_{P,C}$ = 5.4 Hz), 63.2 (d, $J_{P,C}$ = 7.9 Hz), 62.8 (d, $J_{P,C}$ = 12.1 Hz), 62.1 (d, $J_{P,C}$ = 10.3 Hz), 55.4 (d, $J_{P,C}$ = 4.7 Hz), 51.9 (d, $J_{P,C}$ = 3.4 Hz), 36.3, 30.5 (d, $J_{P,C}$ = 8.5 Hz), 28.7 (d, $J_{P,C}$ = 9.2 Hz), 24.7, 24.4, 22.4 (d, $J_{P,C}$ = 4.7 Hz), 16.6.

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 12.1.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for [$C_{31}H_{39}N_4O_2P$ + H]$^+$: 531.288341; found: 531.288141 (error: –0.37782 ppm).

(1*R*,2*R*,1′*R*,2′*R*,2″*S*,2‴*S*)-14

The general coupling procedure for the preparation of compounds **8a–d** was followed with *N*-Cbz-(*S*)-proline (0.52 g, 2.1 mmol), *N*-methylmorpholine (0.53 g, 0.57 mL, 5.2 mmol), T3P® (0.67 g, 0.57 mL, 2.4 mmol), and (1*R*,2*R*,1′*R*,2′*R*,2″*S*)-**13** (0.92 g, 1.7 mmol) to afford the N-protected catalyst **14**; yield: 0.92 g (1.2 mmol, 71%); white foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.70–7.80 (m, 20 H), 5.15 (d, $^3J_{H,H}$ = 12.2 Hz, 1 H), 4.76 (br, 1 H), 4.42–4.60 (m, 1 H), 4.15–4.21 (m, 1 H), 3.63–3.75 (m, 1 H), 3.36–3.44 (m, 1 H), 3.17–3.29 (m, 1 H), 2.55–2.85 (m, 2 H), 1.85–2.20 (m, 2 H), 1.69–1.79 (m, 2 H), 1.55–1.66 (m, 4 H), 1.43–1.54 (m, 6 H), 1.25–1.37 (m, 2 H), 1.10–1.17 (m, 1 H), 0.91–0.99 (m, 1 H), 0.80–0.90 (m, 2 H), 0.55–0.67 (m, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 172.7, 171.6, 155.8, 147.1 (d, $^3J_{P,C}$ = 4.2 Hz), 140.8 (d, $^3J_{P,C}$ = 3.7 Hz), 137.0, 136.6, 129.4, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.4, 127.3, 127.1, 126.9, 126.8, 126.4, 67.5, 62.6 (d, $J_{P,C}$ = 12.2 Hz), 61.6 (d, $J_{P,C}$ = 10.4 Hz), 61.5, 60.1, 54.9 (d, $J_{P,C}$ = 7.3 Hz), 51.3, 47.7, 38.0, 31.1, 30.1 (d, $J_{P,C}$ = 7.8 Hz), 28.0, 24.4, 23.0, 22.8, 18.9, 14.4 (d, $J_{P,C}$ = 8.0 Hz).

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 14.4.

(1*R*,2*R*,1′*R*,2′*R*,2″*S*,2‴*S*)-15

The general procedure for catalytic hydrogenation to reduce azides **4** was followed with (1*R*,2*R*,1′*R*,2′*R*,2″*S*,2‴*S*)-**14** (0.5 g, 0.66 mmol) and Pd/C (0.07 g) to afford **15**; yield: 0.39 g (0.62 mmol, 94%); white foam; [α]$_D^{25}$ –47.4 (*c* 0.35, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.28 (br, 1 H), 7.87 (d, $J_{H,H}$ = 8.3 Hz, 1 H), 7.53 (d, $J_{H,H}$ = 7.5 Hz, 2 H), 7.18–7.36 (m, 10 H), 7.06–7.15 (m, 3 H), 4.69 (ddd, $J_{H,H}$ = 4.7, 8.4, 10.7 Hz, 1 H), 4.53 (dq, $^3J_{H,H}$ = 7.0 Hz, $^3J_{P,H}$ = 17.0 Hz, 1 H), 4.17 (dq, $^3J_{H,H}$ = 7.2 Hz, $^3J_{P,H}$ = 8.3 Hz, 1 H), 3.66–3.75 (m, 1 H), 3.63 (dd, $J_{H,H}$ = 4.7, 9.2 Hz, 1 H), 3.46 (dd, $J_{H,H}$ = 4.7, 13.9 Hz, 1 H), 2.86 (dt, $J_{H,H}$ = 6.7, 10.1 Hz, 1 H), 2.74–2.81 (m, 1 H), 6.67 (dd, $J_{H,H}$ = 10.8, 13.9 Hz, 1 H), 2.52–2.61 (m, 1 H), 2.00 (br, 1 H), 1.84–1.93 (m, 1 H), 1.70–1.80 (m, 1 H), 1.63 (d, $J_{H,H}$ = 7.1 Hz, 3 H), 1.41–1.55 (m, 6 H), 1.50 (d, $J_{H,H}$ = 7.0 Hz, 3 H), 1.31 (qd, $J_{H,H}$ = 3.5, 12.1 Hz, 1 H), 1.20–1.25 (m, 1 H), 1.15 (qt, $J_{H,H}$ = 3.5, 13.2 Hz, 1 H), 0.95 (qt, $J_{H,H}$ = 3.7, 13.3 Hz, 1 H), 0.62 (qd, $J_{H,H}$ = 3.3, 12.3 Hz, 1 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 175.5, 173.2 (d, $J_{P,C}$ = 3.7 Hz), 147.0 (d, $^3J_{P,C}$ = 4.7 Hz), 140.9 (d, $^3J_{P,C}$ = 2.1 Hz), 137.2, 129.4 (2 C), 128.6 (2 C), 128.4 (4 C), 127.3, 127.0, 126.7, 126.5 (2 C), 62.6 (d, $J_{P,C}$ = 12.3 Hz), 61.6 (d, $J_{P,C}$ = 10.9 Hz), 60.4, 55.4 (d, $J_{P,C}$ = 4.4 Hz), 51.5 (d, $J_{P,C}$ = 4.0 Hz), 47.3, 37.9, 30.7, 30.4 (d, $J_{P,C}$ = 8.8 Hz), 29.8 (d, $J_{P,C}$ = 9.3 Hz), 26.0, 24.5, 24.2, 22.6 (d, $J_{P,C}$ = 4.2 Hz), 19.0 (d, $J_{P,C}$ = 3.1 Hz).

^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 14.5.

HR ESI-TOF: *m*/*z* [M + H]$^+$ calcd for [$C_{36}H_{46}N_5O_3P$ + H]$^+$: 628.341106; found: 628.341492 (error: 0.614856 ppm).

Preparation of Racemic Aldol Products Derived from Aryl Aldehydes; General Procedure

In a vial equipped with magnetic stirrer were mixed 10 equiv of cyclohexanone with 10 equiv of NaOH as a 1.0 M solution in H_2O. Then 1 equivalent of the corresponding aldehyde was added, and the mixture was stirred at r.t. for 3 to 4 h. H_2O was added, and the product was extracted with EtOAc. Aldol products were purified by column chromatography hexane/EtOAc 100–0 to 80–20.

Asymmetric Aldol Reaction with Aryl Aldehydes; General Procedure

In a vial equipped with magnetic stirrer was suspended the corresponding catalyst **9** or **15** (0.01 mmol) and benzoic acid (0.01 mmol) in distilled H_2O (1 mL), before the addition of cyclohexanone (0.10 mL 1.0 mmol). The resulting mixture was stirred at 3 °C for 20 min and then the corresponding aryl aldehyde (0.2 mmol) was added. The reaction mixture was left standing at 3 °C for the required time. The product was extracted with EtOAc (3 ×), the combined organic phases were dried (anhyd Na_2SO_4), concentrated, and the crude product was purified by column chromatography (SiO_2, hexane/EtOAc 8:2 to 1:1).

Yields were calculated after purification, the diastereomeric ratio was determined by ^{1}H NMR of the crude product and enantiomeric ratio was determined by chiral HPLC. The aldol products have been already reported, the spectroscopic data were correlated with the literature.[12a,b]

Preparation of Racemic Aldol Products Derived from Isatins; General Procedure

In a sealed tube were mixed the corresponding isatin (0.5 mmol), cyclohexanone (5.0 mmol), Et_2NH (1.0 mmol) and EtOH (5 mL). The reaction mixture was heated to 80 °C for 24 h, the solvent was removed under vacuum, and the products purified by column chromatography (SiO_2: hexane/EtOAc 7:3 to 1:1).

Asymmetric Aldol Reaction with Isatins; General Procedure

In a vial equipped with magnetic stirrer was suspended the corresponding catalyst **9** or **15** (0.02 mmol) and of benzoic acid (0.02 mmol) in distilled H_2O (1 mL), before the addition of cyclohexanone (0.15 mL, 1.4 mmol). The resulting mixture was stirred at 3 °C for 20 min and then of the corresponding isatin (0.2 mmol) was added. The reaction mixture was left standing at 3 °C for 72 h, and then extracted with EtOAc (3 ×), the combined organic phases were dried (anhyd Na_2SO_4), concentrated, and the crude product purified by column chromatography (SiO_2, hexane/EtOAc 8:2 to 1:1). Yields were calculated after purification, the diastereomeric ratio was determined by ^{1}H NMR of the crude product and enantiomeric ratio was determined by chiral HPLC. The aldol products have been already reported, the spectroscopic data were correlated with the literature.[9]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1592005.

References

(1) For some pioneering work, see: (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G. R.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (c) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404. (d) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (e) Denmark, S. E.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 9524. (f) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (g) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982. See also: (h) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726.

(2) (a) List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

(3) (a) List, B. *Tetrahedron* **2002**, *58*, 5573. (b) Notz, W.; Tanaka, F.; Barbas, C. F. III. *Acc. Chem. Res.* **2004**, *37*, 580. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *40*, 1570. (e) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (f) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638. (g) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. (h) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (i) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390. (j) Wang, H.; Lu, H.; Xu, P.-F. *Acc. Chem. Res.* **2015**, *48*, 1832.

(4) (a) Chen, X.-H.; Yu, J.; Gong, L.-Z. *Chem. Commun.* **2010**, *46*, 6437. (b) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600. (c) Bisai, V.; Bisai, A.; Singh, V. K. *Tetrahedron* **2012**, *68*, 4541. (d) Guillena, G. In *Modern Methods in Stereoselective Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, **2013**, 155. (e) Obregón-Zúñiga, A.; Milán, M.; Juaristi, E. *Org. Lett.* **2017**, *19*, 1108.

(5) (a) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911. (b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (c) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558. (d) Cheong, P. H-Y.; Houk, K. N. *Synthesis* **2005**, 1533. See also: (e) Sunoj, R. B. *WIREs Comp. Mol. Sci.* **2011**, *1*, 920.

(6) See, for example: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (c) Sohtome, Y.; Nagasawa, K. *Synlett* **2010**, 1.

(7) (a) Tang, Z.; Jiang, F.; Yu, L-T.; Cui, X.; Gong, L-Z.; Mi, A-Q.; Jiang, Y-Z.; Wu, Y-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262. See also: (b) Tang, Z.; Yang, Z-H.; Chen, X-H.; Cun, L-F.; Mi, A-Q.; Jiang, Y-Z.; Gong, L-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285. (c) Raj, M.; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097. (d) He, L.; Jiang, J.; Tang, Z.; Cui, X.; Mi, A-Q.; Jiang, Y-Z.; Gong, L-Z. *Tetrahedron: Asymmetry* **2007**, *18*, 265. (e) Gandhi, S.; Singh, V. K. *J. Org. Chem.* **2008**, *73*, 9411. (f) Chen, F.; Huang, S.; Zhang, H.; Liu, F.; Peng, Y. *Tetrahedron* **2008**, *64*, 9585. (g) Vishnumaya, M. R.; Singh, V. K. *J. Org. Chem.* **2009**, *74*, 4289. (h) Wang, B.; Chen, G-H.; Liu, L-Y.; Chang, W-X.; Li, J. *Adv. Synth. Catal.* **2009**, *351*, 2441. (i) Tsandi, E.; Kokotos, C. G.; Kousidou, S.; Ragoussis, V.; Kokotos, G. *Tetrahedron* **2009**, *65*, 1444. (j) Fotaras, S.; Kokotos, C. G.; Tsandi, E.; Kokotos, G. *Eur. J. Org. Chem.* **2011**, 1310. (k) Fotaras, S.; Kokotos, C. G.; Kokotos, G. *Org. Biomol. Chem.* **2012**, *10*, 5613. (l) Revelou, P.; Kokotos, C. G.; Moutevelis-Minakakis, P. *Tetrahedron* **2012**, *68*, 8732. (m) Psarra, A.; Kokotos, C. G.; Moutevelis-Minakakis, P. *Tetrahedron* **2014**, *70*, 608.

(8) (a) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2006**, *128*, 734. See also: (b) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 958. (c) Hayashi, Y.; Aratake, S.; Okano, S.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5527. (d) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801. (e) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417. (f) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493. (g) Maya, U.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593. (h) Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji,

M. *Chem. Commun.* **2007**, 957. (i) Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem. Eur. J.* **2007**, *13*, 10246. (j) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247. (k) Hernández, J. G.; Juaristi, E. *Chem. Commun.* **2012**, *48*, 5396. (l) Zhao, Q.; Lam, Y-H.; Kheirabadi, M.; Xu, C.; Houk, K. N.; Schafmeister, C. E. *J. Org. Chem.* **2012**, *77*, 4784. (m) Giacalone, F.; Gruttadauria, M. In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions and Applications*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, **2013**, 1st ed., Vol. 2 673. (n) Obregón-Zuñiga, A.; Juaristi, E. *Tetrahedron* **2017**, *73*, 5373.

(9) Cruz-Hernández, C.; Hernández-González, P. E.; Juaristi, E. *Synthesis* **2018**, *50*, 1827.

(10) A related proline-derived organocatalyst that incorporates a phosphoryl group was reported a few years ago, see: (a) Liu, X-W.; Le, T. N.; Lu, Y.; Xiao, Y.; Ma, J.; Li, X. *Org. Biomol. Chem.* **2008**, *6*, 3997. (b) Yu, G.; Ge, Z-M.; Cheng, T-M.; Li, R-T. *Chin. J. Chem.* **2008**, *26*, 911.

(11) See, for example: (a) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (b) Kofoed, J.; Nielsen, J.; Raymond, J-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445. (c) Shi, L-X.; Sun, Q.; Ge, Z-M.; Zhu, Y-Q.; Cheng, T-M.; Li, R-T. *Synlett* **2004**, 2215. (d) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418. (e) Lei, M.; Shi, L.; Li, G.; Chen, S.; Fang, W.; Ge, Z.; Cheng, T.; Li, R. *Tetrahedron* **2007**, *63*, 7892. (f) D'Elia, V.; Zwicknagl, H.; Reiser, O. *J. Org. Chem.* **2008**, *73*, 3262. (g) Nisco, M.; Pedatella, S.; Ullah, H.; Zaidi, J. H.; Naviglio, D.; Özdamar, Ö.; Caputo, R. *J. Org. Chem.* **2009**, *74*, 9562. (h) Chen, Y-H.; Sung, P-H.; Sung, K. *Amino Acids* **2010**, *38*, 839. (i) Yolacan, C.; Mavis, M. E.; Aydogan, F. *Tetrahedron* **2014**, *70*, 3707. (j) Bisticha, A.; Triandafillidi, I.; Kokotos, C. G. *Tetrahedron: Asymmetry* **2015**, *26*, 102. (k) Triandafillidi, I.; Bisticha, A.; Voutyritsa, E.; Galiatsatou, G.; Kokotos, C. G. *Tetrahedron* **2015**, *71*, 932. (l) Milbeo, P.; Maurent, K.; Moulat, L.; Lebrun, A.; Didierjean, C.; Aubert, E.; Martinez, J.; Calmès, M. *Tetrahedron* **2016**, *72*, 1706. (m) Schnitzer, T.; Wennemers, H. *J. Am. Chem. Soc.* **2017**, *139*, 15356.

(12) (a) Hernández, J. G.; Juaristi, E. *J. Org. Chem.* **2011**, *76*, 1464. (b) Hernández, J. G.; Juaristi, E. *Tetrahedron* **2011**, *67*, 6953. (c) Hernández, J. G.; García-López, V.; Juaristi, E. *Tetrahedron* **2012**, *68*, 92. (d) Machuca, E.; Rojas, Y.; Juaristi, E. *Asian J. Org. Chem.* **2015**, *4*, 46. (e) Machuca, E.; Juaristi, E. *Tetrahedron Lett.* **2015**, *56*, 1144.

(13) (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (b) Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545. (c) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302. (d) Guo, W.; Liu, X.; Liu, Y.; Li, C. *ACS Catal.* **2018**, *8*, 328. (e) Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. *Chem. Rev.* **2018**, *118*, 679.

(14) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

(15) For the synthesis of related phosphoramide derivatives, see: (a) Kattuboina, A.; Li, G. *Tetrahedron Lett.* **2008**, *49*, 1573. (b) Han, J.; Ai, T.; Li, G. *Synthesis* **2008**, 2519. (c) Kaur, P.; Nguyen, T.; Li, G. *Eur. J. Org. Chem.* **2009**, 912. (d) Seifert, C. W.; Pindi, S.; Li, G. *J. Org. Chem.* **2015**, *80*, 447. (e) An, G.; Seifert, C.; Li, G. *Org. Biomol. Chem.* **2015**, *13*, 1600. (f) Qiao, S.; Pindi, S.; Spigener, P. T.; Jiang, B.; Li, G. *Tetrahedron Lett.* **2016**, *57*, 619. (g) Zhang, H.; Yang, B.; Yang, Z.; Lu, H.; Li, G. *J. Org. Chem.* **2016**, *81*, 7654. (h) Qiao, S.; Wilcox, C. B.; Unruh, D. K.; Jiang, B.; Li, G. *J. Org. Chem.* **2017**, *82*, 2992. (i) Qiao, S.; Wu, J.; Mo, J.; Spigener, P. T.; Zhao, B. N.; Jiang, B.; Li, G. *Synlett* **2017**, *28*, 2483. (j) Qiao, S.; Mo, J.; Wilcox, C. B.; Jiang, B.; Li, G. *Org. Biomol. Chem.* **2017**, *15*, 1718.

(16) Wissman, H.; Kleiner, H.-J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 133.

(17) (a) Crystal data for (1*S*,2*S*,1′*R*,2′*R*,2″*S*)-**15**: $C_{31}H_{38}N_4O_2P$, Trigonal, R3; a = 38.985(2) Å, b = 38.985 Å, c = 10.8582(5) Å; α = 90°, β = 90°, γ = 120°; V = 14291.7(10) Å^3; z = 20, z′ = 2.22; R_1 = 6.55%; R_{int} = 7.75%. (b) CCDC 1827531 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(18) (a) Desiraju, G. R.; Kashino, S.; Coombs, M. M.; Glusker, J. P. *Acta Crystallogr., Sec. B* **1993**, *49*, 880. (b) Desiraju, G. R. *Acc. Chem. Res.* **1996**, *29*, 441. (c) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, **1997**, 12.

(19) (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Tetrahedron* **2011**, *67*, 4412. (b) Wan, W.; Gao, W.; Ma, G.; Ma, L.; Wang, F.; Wang, J.; Jiang, H.; Zhu, S.; Hao, J. *RSC Adv.* **2014**, *4*, 26563. (c) Reyes-Rangel, G.; Vargas-Caporali, J.; Juaristi, E. *Tetrahedron* **2017**, *73*, 4707.

(20) (a) Pajouhesh, H.; Parson, R.; Popp, F. D. *J. Pharm. Sci.* **1983**, *72*, 318. (b) Codding, P. W.; Lee, T. A.; Richardson, J. F. *J. Med. Chem.* **1984**, *27*, 649. (c) Kamano, Y.; Zhang, H.-P.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Pettit, G. R. *Tetrahedron Lett.* **1995**, *36*, 2783. (d) Khono, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Juroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990. (e) Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S.; Feng, X.-Z. *Eur. J. Org. Chem.* **2001**, 261. (f) Tokunaga, T.; Home, W. E.; Nagamine, J.; Kawamura, T.; Taiji, M.; Nagata, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1789. (g) Luppi, G.; Monari, M.; Corrêa, R. J.; Violante, F. A.; Pinto, A. C.; Kaptein, B.; Broxterman, Q. B.; Garden, S. J.; Tomasini, C. *Tetrahedron* **2006**, *62*, 12017. (h) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20. (i) Sultan, C.; Mikhail, C.; Shifeng, L.; Jianyu, S.; Vandna, R.; Ray, C.; Wendy, Y.; Rainbow, K.; Jianmin, F.; Jay, C. A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3676. (j) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (k) Kumar, A.; Chimni, S. S. *RSC Adv.* **2012**, *2*, 9748. (l) Parvathaneni, S. P.; Pamanji, R.; Janapala, V. R.; Uppalapati, S. K.; Balasubramanian, S.; Mandapati, M. R. *Eur. J. Med. Chem.* **2014**, *84*, 155. (m) Reddy, U. V. S.; Chennapuram, M.; Seki, K.; Seki, C.; Anusha, B.; Kwon, E.; Okuyama, Y.; Uwai, K.; Tokiwa, M.; Takeshita, M.; Nakano, H. *Eur. J. Org. Chem.* **2017**, 3874.

(21) (a) Ricci, A.; Bernardi, L.; Gioia, C.; Verucci, S.; Robitzer, M.; Quignard, F. *Chem. Commun.* **2010**, *46*, 6268. (b) Raj, M.; Veerasamy, N.; Singh, V. K. *Tetrahedron Lett.* **2010**, *51*, 2157. (c) Shen, C.; Shen, F.; Xia, H.; Zhang, P.; Chen, X. *Tetrahedron: Asymmetry* **2011**, *22*, 708. (d) Guo, Q.; Zhao, J. C.-G. *Tetrahedron Lett.* **2012**, *53*, 1768. (e) Liu, Y.; Gao, P.; Wang, J.; Sun, Q.; Ge, Z.; Li, R. *Synlett* **2012**, *23*, 1031. (f) Kumar, A.; Chimni, S. S. *Tetrahedron* **2013**, *69*, 5197. (g) Tanimura, Y.; Yasunaga, K.; Ishimaru, K. *Eur. J. Org. Chem.* **2013**, 6535. (h) Zhao, H.; Meng, W.; Yang, Z.; Tian, T.; Sheng, Z.; Li, H.; Song, X.; Zhang, Y.; Yang, S.; Li, B. *Chin. J. Chem.* **2014**, *32*, 417. (i) Wang, J.; Liu, Q.; Sun, Y.; Luo, Y.; Yang, H. *Chirality* **2015**, *27*, 314. (j) Kimura, J.; Reddy, U. V. S.; Kohari, Y.; Seki, C.; Mawatari, Y.; Uwai, K.; Okuyama, Y.; Kwon, E.; Tokiwa, M.; Takeshita, M.; Iwasa, T.; Nakano, H. *Eur. J. Org. Chem.* **2016**, 3748. (k) Mohite, P. H.; Drabina, P.; Bureš, F. *Synthesis* **2017**, *49*, 1613.

(22) (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) Terada, M. *Synthesis* **2010**, 1929. (c) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (d) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.

(23) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: London, **1988**.