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# Amino Acid Based Phosphoramidite Ligands for the Rhodium-Catalyzed Asymmetric Hydrogenation

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Two sets of amino acid based phosphoramidite ligands with either a BINOL backbone ($S_b$-**1a–e** and $R_b$-**1a**) or a flexible biphenol backbone (**2a–c** and **2f**) were synthesized and evaluated in the rhodium-catalyzed hydrogenation of different functionalized alkenes: dimethyl itaconate (**3**), methyl 2-acetamidoacrylate (**4**), methyl α-acetamidocinnamate (**5**) and *N*-(3,4-dihydro-2-naphthalenyl)acetamide (**6**). The amino acid fragment can be modified at three positions ($R^1$–$R^3$) giving rise to modular ligands. Initial experiments varying the $R^1$ position of the amino acid fragment, showed that the valine-based phosphoramidite ligand $S_b$-**1b** forms the most selective rhodium catalyst for three of the four substrates of the current study. The modifications at the other positions ($R^2$ and $R^3$) tweaked the ligand structure such that enhanced selectivities were obtained; up to 97 % *ee* is obtained for the asymmetric hydrogenation of **4** with $S_b$-**1e**. For ligands with two sources of chirality match/mismatch effects are observed, the diastereoisomer $S_b$-**1b** giving higher selectivity than the diastereoisomer $R_b$-**1b** for most of the substrates. The set of phosphoramidite ligands having the flexible and cheap biphenol backbone is developed to study the ability of the amino acid derivatives as the sole source of chirality in the ligand to steer enantioselectivity in rhodium-catalyzed hydrogenation. This study shows their capacity to compete with their BINOL-based analogues and even to outclass them depending on the substrate evaluated.
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## Introduction

The generally accepted dogma introduced in the 1970s that bidentate ligands perform better than the monodentate analogues in asymmetric transition-metal catalysis has been overturned. Indeed the seminal reports of Reetz, Pringle, Feringa and de Vries demonstrated that monodentate phosphite,[1a] phosphonite[1b] and phosphoramidite[1c] ligands can be as active and selective as bidentate ligands in the rhodium-catalyzed asymmetric hydrogenation reaction, which is demonstrated for different substrates. The successful applications of phosphoramidite ligands in various asymmetric metal-catalyzed reactions[2] proved that they form a new class of effective ligands. The so-called (*S*)-MonoPhos[3] emerged as the archetypical phosphoramidite ligand used in asymmetric catalysis. Despite the broad applicability, a single catalyst can address effectively the selective transformation of a limited number of substrates.[4] Therefore, a time-consuming tweaking of the ligand structure by covalent modification is necessary to obtain acceptable levels of enantioselectivities for a given substrate. As finding the best catalyst is still based on trial-and-error and sophisticated guesses, a combinatorial approach in which chiral catalysts are prepared and screened in a parallel fashion is a frequently applied strategy.[5] De Vries et al.[6] developed an instant library of phosphoramidite ligands in a combinatorial approach, affording 96 ligands in one day by varying the amine moiety. Among the amines commercially available, the amino acids taken from the chiral pool are in principle particularly attractive. They provide a versatile and natural source of chiral building blocks with structural diversity and are therefore especially suited for fine-tuning of ligands. In addition, the functional groups can be utilized for formation of supramolecular ligands[7] or for substrate orientation via supramolecular interactions between substrates and ligands.[8] Surprisingly, there has been no systematic investigation on the use of phosphoramidite ligands derived from α-amino acids[9] and they have only been scarcely used in catalysis.[10]

Herein, we report the straightforward synthesis of monodentate phosphoramidite ligands derived from cheap and readily available α-amino acid derivatives. A set of ligands having a rigid enantiopure BINOL backbone ($S_b$-**1** or $R_b$-**1**) has been synthesized and their activity and selectivity were evaluated in the rhodium-catalyzed hydrogenation of functionalized alkenes. Thanks to the versatility of the amino acid moieties we modified the $R^1$, $R^2$ and $R^3$ positions (Figure 1) and studied their impact on the catalytic outcome. In addition, we developed a set of ligands having

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a *tropos* biphenol backbone. We studied the ability of the amino acids to steer enantioselectivity in the rhodium-catalyzed hydrogenation using such ligands. Depending on the substrate studied, those ligands proved their capacity to compete with the corresponding more expensive BINOL-based analogues.

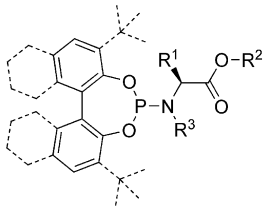



Figure 1. General structure of the amino acid based phosphoramidite ligands.

## Results and Discussion

The ligands were synthesized in a two-step fashion starting from commercially available hydrochloride salts of ester derived amino acids (see Figure 2, **a**–**f**). Two synthetic routes (Scheme 1, Routes a and b) were used for the synthesis of the phosphoramidite ligands starting from BINOL. Yields up to 92% were obtained using route a, whereas route b gave up to 76% yield, in both cases after purification. The synthesis of the phosphoramidite ligands based on 3,3′-di-*tert*-butyl-2,2′-dihydroxy-5,5′-dimethoxy-1,1′-biphenyl (*tropos* backbone **2**) gave up to 92% yield using route a.

It should be noted that the phosphoramidite ligands derived from BINOL ($S_b$-**1a**–**d** and $R_b$-**1b**) are rather sensitive to hydrolysis and should be handled with care, while those having the biphenol backbone (**2a**–**c** and **2f**) and the *N*-methylated phosphoramidite $S_b$-**1e** are only moderately sensitive. All new ligands were fully characterized (see Experimental Section) and then applied in the rhodium-catalyzed hydrogenation of different functionalized alkenes.

The ligands $S_b$-**1a**–**e**, $R_b$-**1b**, **2a**–**c** and **2f** were evaluated in the rhodium-catalyzed asymmetric hydrogenation of substrates that varied electronically and sterically: dimethyl itaconate (**3**), methyl 2-acetamidoacrylate (**4**), methyl α-acetamidocinnamate (**5**) and *N*-(3,4-dihydro-2-naphthalenyl)acetamide (**6**) (see Figure 3 and Scheme 2). The reactions were carried out in $CH_2Cl_2$ at room temperature under $H_2$ pressure of 10 bar in the presence of 1 mol-% catalysts, which were prepared in situ from $Rh(nbd)_2BF_4$ and 2.2 equiv. of the respective chiral ligand. The catalysis results are summarized in Tables 1, 2, and 3.

Full conversions and good enantioselectivities were obtained (up to 89% *ee*) for the hydrogenation of the dimethyl itaconate (**3**). Increasing the steric bulk around the additional chiral center ($R^1$ = *i*Bu and $R^1$ = *i*Pr) leads to an increase of the selectivity, from 80% *ee* for $S_b$-**1a** to 89% *ee* for $S_b$-**1b** (Table 1, Entries 1 and 2). The ligand $S_b$-**1c** ($R^1$ =

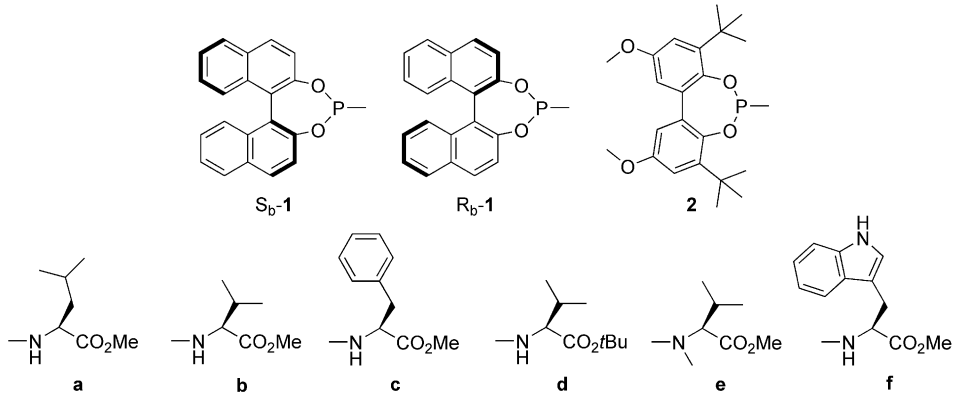
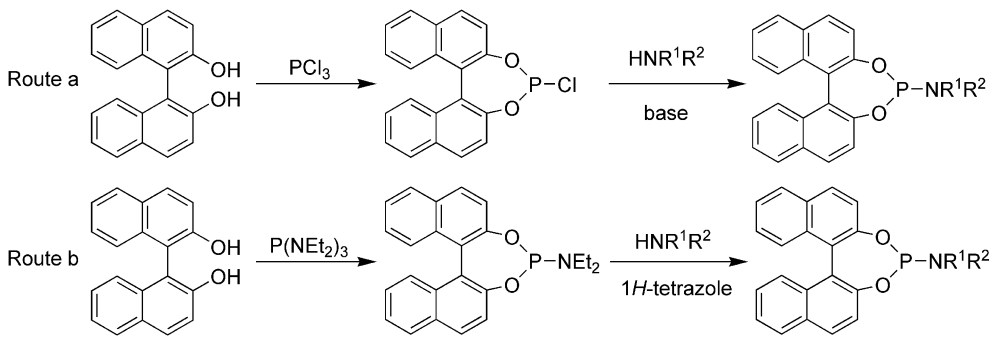



Figure 2. Scope of ligands synthesized and evaluated in asymmetric Rh-catalyzed hydrogenation.




Scheme 1. Two routes used for the synthesis of amino acid based phosphoramidite ligands.

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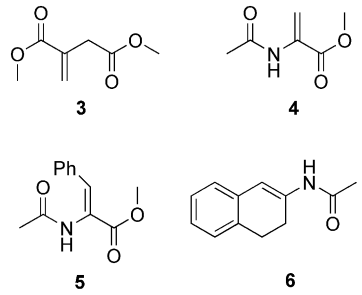
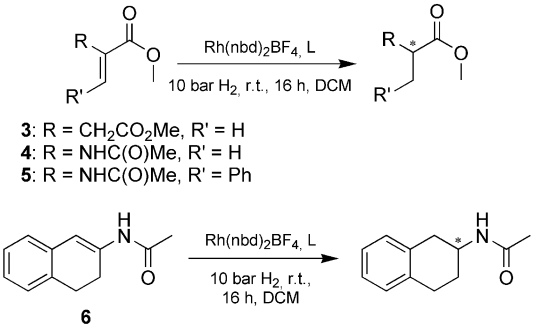



Figure 3. Substrates used to evaluate the hydrogenation properties of rhodium complexes of **1** and **2**.




Scheme 2. Rh-catalyzed asymmetric hydrogenation of substrates **3**, **4**, **5** and **6**.

Bn) provides similar selectivity to the *i*Bu, up to 81% *ee* (Table 1, Entry 3). Full conversions and moderate enantioselectivities were obtained in the hydrogenation of methyl 2-acetamidoacrylate (**4**) (up to 68%). Modifying the alkyl moiety $R^1$ does not affect the catalytic outcome (Table 1, Entries 4 and 5) while a slight drop of selectivity is observed when the benzyl group is introduced. The catalyst based on the ligand $S_b$-**1c** affords 58% *ee* (Table 1, Entry 6). The hydrogenation of the more hindered alkene methyl α-acetamidocinnamate (**5**) showed that a better selectivity, but still moderate, was obtained with the phosphoramidite $S_b$-**1a** ($R^1$ = *i*Bu, 62% *ee*, Table 1, Entry 7) compared to $S_b$-**1b** ($R^1$ = *i*Pr, 45% *ee*, Table 1, Entry 8). The conversion clearly depends on the amino acid moiety for this more hindered substrate, 73% of conversion was obtained with $S_b$-**1c** ($R^1$ = Bn), the enantioselectivity reaching 51% (Table 1, Entry 9), whereas $S_b$-**1a** and $S_b$-**1b** both lead to full conversion. A similar trend was observed in the hydrogenation of the rigid *N*-(3,4-dihydro-2-naphthalenyl)acetamide (**6**), a notoriously difficult substrate to hydrogenate. The conversion is most affected, as the rigidity of the substrate imposes severe constraints on the catalyst. The phosphoramidite ligands with the leucine ($S_b$-**1a**) and the valine ($S_b$-**1b**) derivatives allowed us to reach 50% and 51% conversion, respectively (Table 1, Entries 10 and 11) while using larger amino acid such as phenylalanine ($S_b$-**1c**) derivative resulted in a considerable drop of conversion to 10% (Table 1, Entry 12). The catalyst based on phosphoramidite $S_b$-**1b** is the most selective, up to 48% *ee* was reached for this difficult substrate (Table 1, Entry 11).

Table 1. Evaluation of amino acid based phosphoramidite ligands in the Rh-catalyzed hydrogenation of functionalized substrates.[a]

| Entry | Substrate | Ligand | $R^1$ | % Conversion | % *ee* (config.) |
|---|---|---|---|---|---|
| 1 | **3** | $S_b$-**1a** | *i*Bu | 100 | 80 (*S*) |
| 2 | **3** | $S_b$-**1b** | *i*Pr | 100 | 89 (*S*) |
| 3 | **3** | $S_b$-**1c** | Bn | 100 | 81 (*S*) |
| 4 | **4** | $S_b$-**1a** | *i*Bu | 100 | 67 (*R*) |
| 5 | **4** | $S_b$-**1b** | *i*Pr | 100 | 68 (*R*) |
| 6 | **4** | $S_b$-**1c** | Bn | 100 | 58 (*R*) |
| 7 | **5** | $S_b$-**1a** | *i*Bu | 100 | 62 (*R*) |
| 8 | **5** | $S_b$-**1b** | *i*Pr | 100 | 45 (*R*) |
| 9 | **5** | $S_b$-**1c** | Bn | 73 | 51 (*R*) |
| 10 | **6** | $S_b$-**1a** | *i*Bu | 50 | 38 (*R*) |
| 11 | **6** | $S_b$-**1b** | *i*Pr | 51 | 48 (*R*) |
| 12 | **6** | $S_b$-**1c** | Bn | 10 | 42 (*R*) |

[a] Ratio L/[$Rh(nbd)_2$]$BF_4$/substrate = 2.2:1:100; solvent: $CH_2Cl_2$. Reaction performed at 10 bar $H_2$ pressure at 298 K for 16 h. Conversions and enantioselectivities determined by chiral GC.

The influence of the amino acid moieties (i.e. $R^1$) on the catalytic results is significant and typically substrate-dependent. Except for the hydrogenation of the methyl α-acetamidocinnamate (**5**), the best results were obtained using ligand $S_b$-**1b** (Table 1, Entries 2, 5 and 11) having a valine moiety. Further optimization was attempted by modifications to this ligand at the $R^2$ and $R^3$ position. We examined the steric influence at the $R^2$ position (ester group) by comparing the ligand $S_b$-**1d** ($R^2$ = *t*Bu) and the ligand $S_b$-**1b** ($R^2$ = Me). The enantiomeric excess of the products is slightly higher when the methyl group was used instead of the *t*Bu, an effect that was observed for all substrates studied: 86% *ee* vs. 89% for **3** (Table 2, Entries 1 and 2), 51% *ee* vs. 68% for **4** (Table 2, Entries 5 and 6), 40% *ee* vs. 45% for **5** (Table 2, Entries 9 and 10) and 42% *ee* vs. 48% for **6** (Table 2, Entries 13 and 14). The steric hindrance brought at the position $R^2$ apparently results in lower selectivity, but also the activity is affected as is clear from the result obtained for the challenging substrate **6** that was converted to 51% using the ligand $S_b$-**1b** and 29% using the ligand $S_b$-**1d** (Table 2, Entries 13 and 14). Full conversion was obtained for the other substrates using both ligands, so differences in activity could not be noticed. Importantly, the size of the $R^2$ group, even if positioned relatively far from the coordinated phosphorus atom at the metal center, influences the catalytic performance and provides a tool for ligand fine-tuning.

We also studied the so-called match/mismatch effect by comparing the selectivity induced by catalysts based on two diasteroisomeric ligands with two sources of chirality. The corresponding diastereoisomer of $S_b$-**1b** was therefore synthesized using the same amino acid derivative in combination with (*R*)-BINOL backbone $R_b$-**1** instead of (*S*)-BINOL. By comparing the results in the asymmetric hydrogenation of various substrates we observed a mismatch effect with the ligand $R_b$-**1b** and a match effect with the ligand $S_b$-**1b** on the selectivity of the hydrogenation reaction

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Table 2. Versatility of the valine-based phosphoramidite ligands in Rh-catalyzed hydrogenation of functionalized substrates.[a]

| Entry | Substrate | Ligand | $R^2$ | $R^3$ | % Conversion | % *ee* (config.) |
|---|---|---|---|---|---|---|
| 1 | **3** | $S_b$-**1b** | Me | H | 100 | 89 (*S*) |
| 2 | **3** | $S_b$-**1d** | *t*Bu | H | 100 | 86 (*S*) |
| 3 | **3** | $R_b$-**1b** | Me | H | 100 | 84 (*R*) |
| 4 | **3** | $S_b$-**1e** | Me | Me | 43 | 3 (*S*) |
| 5 | **4** | $S_b$-**1b** | Me | H | 100 | 68 (*R*) |
| 6 | **4** | $S_b$-**1d** | *t*Bu | H | 100 | 51 (*R*) |
| 7 | **4** | $R_b$-**1b** | Me | H | 100 | 14 (*S*) |
| 8 | **4** | $S_b$-**1e** | Me | Me | 100 | 97 (*R*) |
| 9 | **5** | $S_b$-**1b** | Me | H | 100 | 45 (*R*) |
| 10 | **5** | $S_b$-**1d** | *t*Bu | H | 100 | 40 (*R*) |
| 11 | **5** | $R_b$-**1b** | Me | H | 100 | 33 (*S*) |
| 12 | **5** | $S_b$-**1e** | Me | Me | 100 | 84 (*R*) |
| 13 | **6** | $S_b$-**1b** | Me | H | 51 | 48 (*R*) |
| 14 | **6** | $S_b$-**1d** | *t*Bu | H | 29 | 42 (*R*) |
| 15 | **6** | $R_b$-**1b** | Me | H | 4 | 59 (*S*) |
| 16 | **6** | $S_b$-**1e** | Me | Me | 16 | 45 (*R*) |

[a] Ratio L/[Rh(nbd)$_2$]BF$_4$/substrate = 2.2:1:100; solvent: $CH_2Cl_2$. Reaction performed at 10 bar $H_2$ pressure at 298 K for 16 h. Conversions and enantioselectivities determined by chiral GC.

of substrates **3**, **4** and **5**. The increase of selectivity is moderate for the substrates **3** (from 84% *ee* to 89%, Table 2, Entries 1 and 3) and **5** [from 33% *ee* to 45% (Table 2, Entries 9 and 11)] to large for the substrate **4** (from 14% to 68%, Table 2, Entries 5 and 7). For these substrates the conversion was 100%. The match/mismatch effect in the hydrogenation of the substrate **6** is opposite as the selectivity is higher when ligand $R_b$-**1b** is used compared to $S_b$-**1b**, with 59% and 48% enantioselectivity, respectively (Table 2, Entries 13 and 15). In addition, a drop in conversion to 4% for the ligand $R_b$-**1b** compared to 51% for the ligand $S_b$-**1b** was obtained. The versatility of the amino acids allowed us to modify the $R^3$ position by using a *N*-methylated derivative to synthesize the phosphoramidite $S_b$-**1e**. The effect of that modification depends strongly on the substrate used. A dramatic decrease of both activity and selectivity is observed in the asymmetric hydrogenation of the dimethyl itaconate (**3**), only 3% enantioselectivity was obtained (Table 2, Entry 4) at a lower conversion of 43%. In contrast, in the asymmetric hydrogenation of **4** and **5** an important increase in selectivity was obtained leading to excellent *ee*, up to 97% and 84%, respectively (Table 2, Entries 8 and 12). Hydrogenation of **6** led to similar selectivity, 45% for $S_b$-**1e** (Table 2, Entry 16) and 48% for $S_b$-**1b** (Table 2, Entry 13) while a noticeable difference in conversion (16% for $S_b$-**1e** and 51% for $S_b$-**1b**) was obtained.

A new set of phosphoramidite ligands was also developed in which the stereogenic center brought by the amino acid was the only source of chiral information. Instead of the chiral BINOL backbone, the flexible biphenol backbone was used. It is known that this results in atropisomerism rendering the two diastereomers in a fast equilibrium. Gennari and co-workers demonstrated that in some particular cases these diastereoisomers are observable by $^{31}P$ NMR at low temperature.[11] Previously it also has been demonstrated that these types of flexible ligands can outperform their rigid BINOL-based analogues,[12] and as a bonus the building blocks are cheaper too. These types of ligands therefore comprise interesting analogues to study.

The enantiomeric excesses of the products formed during the hydrogenation of dimethyl itaconate (**3**) with these new ligands varied from low (8%) to moderate (up to 70%, Table 3, Entry 4). For this substrate the use of the enantiopure BINOL backbone affords higher selectivities. Also, the activity of the catalysts is strongly affected by modifications at the $R^1$ position; only 2% conversion was obtained with the phenylalanine-based phosphoramidite **2c** (Table 3, Entry 3) and 41% conversion with the tryptophan-based phosphoramidite **2f** (Table 3, Entry 4). Both these amino acid derivatives have an aromatic group. Application of the leucine- and valine-based phosphoramidites **2a** and **2b** lead to full conversion (Table 3, Entries 1 and 2), and these residues are aliphatic. The hydrogenation of methyl 2-acetamidoacrylate (**4**) appeared less sensitive to changes at the amino acid building block and the selectivities were comparable to those obtained with the rigid BINOL derivatives (Table 3, Entries 5–8). In general the enantioselectivities obtained with the *tropos* phosphoramidite ligands are good (up to 77%) and even slightly higher than the selectivities afforded by their BINOL analogues (68% *ee* obtained with $S_b$-**1b**). Ligand **2a** is an exception as its rhodium catalyst resulted in a significant lower enantioselectivity of the product that was formed (24% *ee*, Table 3, Entry 5). Similarly to the hydrogenation of the substrate **3**, the activities obtained are lower with the amino acids having an aromatic group. In the hydrogenation of the substrate **5** low to moderate conversions and selectivities were obtained (Table 3, Entries 9–12). In contrast, better conversion was obtained with the flexible backbone and the valine moiety (64%, Table 3, Entry 14) in the asymmetric hydrogenation of **6** compared to their BINOL analogues. Up to 51% *ee* was afforded

Table 3. *tropos* phosphoramidite ligands in Rh-catalyzed hydrogenation of functionalized substrates.[a]

| Entry | Substrate | Ligand | $R^1$ | % Conversion | % *ee* (config.) |
|---|---|---|---|---|---|
| 1 | **3** | **2a** | *i*Bu | 100 | 8 (*S*) |
| 2 | **3** | **2b** | *i*Pr | 100 | 16 (*S*) |
| 3 | **3** | **2c** | Bn | 2 | 26 (*S*) |
| 4 | **3** | **2f** | 3-Me-1*H*-indole | 41 | 70 (*S*) |
| 5 | **4** | **2a** | *i*Bu | 90 | 24 (*R*) |
| 6 | **4** | **2b** | *i*Pr | 100 | 70 (*R*) |
| 7 | **4** | **2c** | Bn | 57 | 77 (*R*) |
| 8 | **4** | **2f** | 3-Me-1*H*-indole | 78 | 70 (*R*) |
| 9 | **5** | **2a** | *i*Bu | 24 | 16 (*R*) |
| 10 | **5** | **2b** | *i*Pr | 27 | 7 (*R*) |
| 11 | **5** | **2c** | Bn | 22 | 21 (*R*) |
| 12 | **5** | **2f** | 3-Me-1*H*-indole | 41 | 19 (*R*) |
| 13 | **6** | **2a** | *i*Bu | 18 | 34 (*R*) |
| 14 | **6** | **2b** | *i*Pr | 64 | 40 (*R*) |
| 15 | **6** | **2c** | Bn | 28 | 51 (*R*) |
| 16 | **6** | **2f** | 3-Me-1*H*-indole | 45 | 41 (*R*) |

[a] Ratio L/[Rh(nbd)$_2$]BF$_4$/substrate = 2.2:1:100; solvent: $CH_2Cl_2$. Reaction performed at 10 bar $H_2$ pressure at 298 K for 16 h. Conversions and enantioselectivities determined by chiral GC.

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(Table 3, Entry 15), competing with the best result obtained with the BINOL-derived phosphoramidite ligands (59%, Table 2, Entry 15).

In general, good conversions were obtained with the ligands using amino acid building blocks with an alkyl residue, whereas phosphoramidite **2c**, having an aromatic group at the $R^1$ position (Table 3, Entries 3, 7, 11 and 15), gives rise to much lower conversions. The same phenomenon is observed when comparing the BINOL-based ligands $S_b$-**1a**, $S_b$-**1b** and $S_b$-**1c**. A plausible explanation for the low activities is the effect of the *tert*-butyl groups attached to the biphenol ring that bring steric bulk close to the metal center. Indeed the substitution of the 3,3′ positions of the BINOL or biphenol backbone is often used to enhance the selectivity of a catalyst, but too bulky ligands are generally less effective.[13] In the present case, the accessibility of the substrate to the metal center can be hindered affording lower activities.

## Conclusions

Two sets of phosphoramidite ligands were synthesized and evaluated in the rhodium-catalyzed hydrogenation of different functionalized alkenes. The new ligands are made from simple amino acid building blocks, giving new handles to fine tune catalyst performance. Modification of the amino acid residue ($R^1$ position) was effective and resulted in better performance for the current substrate alkyl chains than aromatic side chains. The ligand $S_b$-**1b**, based on the amino acid valine, was identified as most efficient in the series, leading to the conclusion that for the current asymmetric hydrogenation reactions the bulkiness should be close to the ligand donor atom. Modifications of the valine derivative led us to observe a substrate-dependent match/mismatch effect, the diastereoisomer (*S*,*S*)-$S_b$-**1b** being more selective than (*R*,*S*)-$R_b$-**1b** for three out of four substrates. This ligand was further tuned by varying the ester moiety, positioning additional steric bulk remote from the phosphorus donor. Nevertheless, this also affects the catalytic outcome, although to a reduced extent. At this position a small alkyl group ($R^2$ = Me) is preferred, because it results in higher selectivities than a large one ($R^2$ = *t*Bu). The final position that was modified was the NH next to the phosphorus donor atom ($R^3$). Having a methyl group instead of a proton strongly affects the catalytic results. The *N*-methylated valine-based phosphoramidite $S_b$-**1e** outperformed all the others, achieving excellent enantioselectivity, with up to 97% for the methyl 2-acetamidoacrylate (**4**) and up to 84% for the methyl α-acetamidocinnamate (**5**).

We prepared and studied also a set of amino acid based phosphoramidite ligands having a flexible biphenol backbone. These *tropos* phosphoramidite ligands proved to be effective ligands in rhodium-catalyzed hydrogenation, and in some cases they compete with the rigid BINOL-based ligands. In the selective hydrogenation of the methyl 2-acetamidoacrylate (**4**) they even surpassed their BINOL-based analogues (77% *ee* obtained relative to 68%), proving that ligands with the amino acids as the sole source of chirality are able to steer enantioselectivity in the rhodium-catalyzed hydrogenation. Although the current library is rather small, it is evident that the amino acid components in these ligands have added value, as these building blocks can be varied tremendously and are very accessible. We anticipate that these new ligand structures will be widely used for the screening of catalysts for asymmetric conversions, and rhodium-catalyzed asymmetric hydrogenation in particular.

## Experimental Section

### General Procedure for the Preparation of Ligands $S_b$-1a-e and $R_b$-1b

**Method A:** $PCl_3$ (2.5 mL) was added to a Schlenk containing (*S*)- or (*R*)-2,2′-bisnaphthol (1.0 mmol). The solution was refluxed overnight. The excess of $PCl_3$ was removed in vacuo. Anhydrous toluene (3 × 3 mL) was added and co-evaporated to remove the remaining $PCl_3$ to obtain the phosphochloridite as a white foam. The phosphochloridite was dissolved in 5 mL of dry toluene and the solution was cooled to 0 °C. The amino acid derivative (1.1 mmol) and $NEt_3$ (2.1 mmol) were added and the solution was stirred for 1 h at 0 °C. After allowing the solution to warm to room temperature, the medium was stirred for 3 additional hours. The solution was then filtered to remove the salt and the solvent evaporated. Purification by flash chromatography (hexane/ethyl acetate, 8:2) afforded the corresponding ligand as a white powder.

**Method B:** (*S*)-(+)-(3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]dinaphthalen-4-yl)diethylamine (1.0 mmol) was dissolved in 5 mL of dry toluene in a Schlenk. To this solution the amino acid derivative (1.2 mmol) and 1*H*-tetrazole (2.0 mmol) were added. The solution was refluxed for 3 h. After filtration of the salt, the solvent was evaporated. Purification by flash chromatography (hexane/ethyl acetate, 8:2) afforded the corresponding ligand as a white powder.

**General Procedure for Rhodium-Catalyzed Hydrogenation Reactions:** The hydrogenation experiments were carried out in a stainless steel autoclave (150 mL) charged with an insert suitable for 8 reaction vessels (including Teflon® mini stirring bars) for conducting parallel reactions. In a typical experiment, to a solution of $Rh(nbd)_2BF_4$ (1 μmol, 1 equiv.) in 0.4 mL of dry $CH_2Cl_2$ was added a solution of ligand (2.2 μmol, 2.2 equiv.) in 0.6 mL of dry $CH_2Cl_2$. The solution was stirred for 30 min. The mixture was then added to the reaction vessels charged with 0.10 mmol of alkene substrate. Before starting the catalytic reactions, the charged autoclave was purged three times with 5 bar of $H_2$ and then pressurized at 10 bar $H_2$. The reaction mixtures were stirred at 25 °C for 16 h. After catalysis the pressure was released. The conversion and enantiomeric purity were determined by chiral GC.

**Supporting Information** (see also the footnote on the first page of this article): Experimental procedures, spectroscopic and analytical data of ligands, substrate synthesis and chiral GC separations.

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