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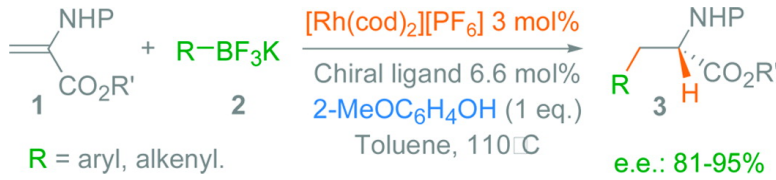


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# Access to Enantioenriched α-Amino Esters via Rhodium-Catalyzed 1,4-Addition/Enantioselective Protonation

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***Abstract:*** Conjugate addition of potassium trifluoro(organo)borates **2** to dehydroalanine derivatives **1**, mediated by a chiral rhodium catalyst and in situ enantioselective protonation, afforded straightforward access to a variety of protected α-amino esters **3** with high yields and enantiomeric excesses up to 95%. Among the tested chiral ligands and proton sources, Binap, in combination with guaiacol (2-methoxyphenol), an inexpensive and nontoxic phenol, afforded the highest asymmetric inductions. Organostannanes have also shown to participate in this reaction. By a fine-tuning of the ester moiety, and using Difluorophos as chiral ligand, increased levels of enantioselectivity, generally close to 95%, were achieved. Deuterium labeling experiments revealed, and DFT calculation supported, an unusual mechanism involving a hydride transfer from the amido substituent to the α carbon explaining the high levels of enantioselectivity attained in controlling this α chiral center.

## Introduction

Chiral α-amino acids constitute one of the most important building bocks in organic synthesis, and this structural element is encountered in many biologically active compounds. Several methods have been developed to access nonproteogenic amino acids in the past century, but approaches with stereocontrol of the α chiral center are more limited. Nevertheless, a variety of methods, which are quite general, are available for the synthesis of chiral α-amino acids.[1] These include the Strecker and Ugi condensations, the enzymatic resolution of racemic α-amino acids, glycine anion functionalization using chiral phase-transfer catalysis, and the asymmetric hydrogenation of dehydroamino esters.

An even more straightforward method would consist of a Michael type addition of an organometallic reagent to a dehydroalanine derivative with concomitant control of the α chiral center. However, such an approach has been scarcely developed in the literature. Conjugate addition of organometallics to α-amino acrylates followed by diastereoselective protonation of the resulting enolate has been described to some extent, but the reaction scope was rather limited.[2] Similar reactions, but involving radical conjugate additions, were also describe.[3,4] On the other hand, very few examples have been described concerning catalytic enantioselective conjugate additions. Sibi et al. reported in 2001 an enantioselective radical conjugate addition to α-amino acrylates[5] and α-methacrylate[6] followed by hydrogen atom transfer catalyzed by chiral Lewis acids. β-Substituted α-amino acids were also synthesized using this methodology.[7]

We recently described preliminary results concerning a new transition metal catalyzed tandem so-called 1,4-addition/enantioselective protonation of organometallics to dehydroamino esters that allowed direct preparation of α-amino acid derivatives in high yields and enantiomeric excesses up to 90%.[8] The initial idea, which initiated this research, was based on the postulated mechanism of the 1,4-addition of organometallic reagents to α,β-unsaturated substrates.[9] Several organometallic reagents and particularly organoboronic acids have been shown to participate in rhodium-catalyzed Michael additions, allowing the introduction of a chiral center in the β position of an electron-

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(8) (a) For rhodium-catalyzed tandem 1,4-addition−enantioselective protonation: Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719. For a racemic version: (b) Navarre, L.; Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2004**, 69.

(9) For an investigation of rhodium-catalyzed 1,4-addition mechanism, see: Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

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withdrawing group.[10,11] We also shown that potassium organotrifluoroborates participated efficiently in this reaction,[12] with their advantageous stability and ease of preparation compared to other boron derivatives.[13] In such reactions, it is postulated, and some intermediates have identified, that the mechanistic cycle involves the generation of an oxa-$\pi$-allylmetal intermediate.[14] Thus, one could easily imagine control of the prochiral α center of an α,α′-disubstituted alkene via a diastereoselective protonation of the putative rhodium-enolate, leading to an overall tandem 1,4-addition/enantioselective protonation.[15,16]

Other groups reported such an approach using water as a protonating agent, but enantiomeric excesses were limited to 70%. Indeed, Reetz et al.[17] were the first to show that, in the presence of an atropoisomeric binol-based diphosphonite chiral ligand, the rhodium-catalyzed 1,4-addition of phenylboronic acid to dehydroamino ester afforded α-amino ester in a modest 77% ee. Frost et al.[18] also described the use of a hindered chiral ligand in the same reaction, as well as binap ligand in the preparation of 2-substituted succinic esters,[19] but the ee values were still limited to 72%.

***Table 1.*** Phenols as Protonating Agents[a]

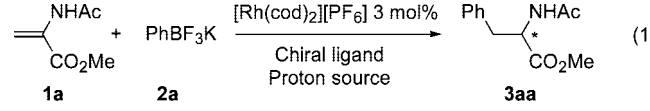
| phenol | yield | ee[c] | phenol | yield | ee[c] |
|---|---|---|---|---|---|
| $C_6H_5$ | 81 | 18 | 2-$MeOC_6H_4$ | 91 | 83 |
| 2-$MeC_6H_4$ | 63 | 37 | 2-*i*-$PrOC_6H_4$ | 91 | 63 |
| 2-*t*-$BuC_6H_4$ | 28 | 44 | 2-$HOC_6H_4$ | 4 | 7 |
| 2,6-(*t*-Bu)$_2C_6H_3$ | 63 | 54 | 3-$MeOC_6H_4$ | 84 | 51 |
| 2-$PhC_6H_4$ | 77 | 69 | 4-$MeOC_6H_4$ | 75 | 45 |
| 4-$ClC_6H_4$ | 90 | 8 | 2-MeO-6-$IC_6H_3$ | 0 | |
| 2,4-$Cl_2C_6H_3$ | 88 | −8 | 2-$FC_6H_4$ | 65 | 30 |
| 2,4,6-$Cl_3C_6H_2$ | 51 | −20 | 2-$CF_3C_6H_4$ | 45 | −4 |
| 4-$CNC_6H_4$ | 42 | 14 | 2-$MeSC_6H_4$ | 0 | |
| 2-$CNC_6H_4$ | 0 | | 3-(MeCO)$C_6H_4$ | 85 | 45 |
| 2-$NO_2C_6H_4$ | 23[b] | nd | 3,5-(MeO)$_2C_6H_3$ | 76 | 57 |
| 2-(AcNH)$C_6H_4$ | 23 | 3 | 3,4,5-(MeO)$_3C_6H_2$ | 72 | 59 |
| 2-(PhCONH)$C_6H_4$ | 18 | 18 | P1[d] | 80 | 61 |
| 2-(MeOCO)$C_6H_4$ | 36 | 26 | P2[d] | 73 | 62 |
| 2-(MeCO)$C_6H_4$ | 32 | 16 | | | |

[a] Reactions conducted using 0.5 mmol of **1a**, 2 equiv of **2a**, and 1 equiv of phenol with 3 mol% of [Rh(cod)$_2$][PF$_6$], 3.3 mol% of (*S*)-binap in toluene at 110–115 °C for 20 h. [b] Conversion determined by GC. [c] Sign plus for the (*R*) enantiomer. [d] P1 = benzo[1,3]dioxol-5-ol and P2 = 7-methoxy-naphthalen-2-ol.

From these results, it appeared that water was not the most suitable protonating agent. On the contrary, when using other proton sources such as phenol derivatives, we showed that high ee values were achieved in the 1,4-addition of organometallics to dehydroamino esters.[8a] This concept of 1,4-addition/enantioselective protonation of rhodium enolate using other proton sources than water was applied to the synthesis of $\beta^2$-amino acids using phthalimide as a protonating agent[20] and α,α′-dibenzyl esters using boric acid.[21]

We want to report here the scope and limitation of the rhodium-catalyzed 1,4-addition/enantioselective protonation of organometallic reagents to dehydroamino esters allowing direct preparation of α-amino acid derivatives in high yields and enantiomeric excesses. Moreover, mechanistic studies revealed a totally unusual reaction mechanism, explaining the efficient stereocontrol of the α chiral center on such substrates and resulting in further improvements in the efficiency of the process.

**Catalytic System Optimization.** We initially tested the feasibility of the asymmetric 1,4-addition to dehydroamino esters using methyl *N*-acetylaminoacrylate (**1a**) and potassium phenyltrifluoroborate (**2a**) as model substrates (eq 1). Despite numerous attempts, we never succeeded in achieving stereoselective control of the α center on protonation with water in the presence of various chiral ligands complexed on a rhodium catalyst. Whatever the chiral ligand tested, enantioselectivities were generally lower than 30% and the results were not always reproducible.[22]



(1)

Then, we turned out our attention to the proton source. Among the various tested proton sources, we were pleased to find that phenols were particularly suited. For example, using phenol, an 81% yield of **3aa** was obtained in 18% ee (Table 1). In order

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(15) For a first example of enantioselective protonation of a rhodium enolate intermediate (18% ee), see: Bergens, S. H.; Bosnich, B. *J. Am. Chem. Soc.* **1991**, *113*, 958.

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(22) See supporting information for some examples of the use of chiral ligands using water as a proton source.

to attain useful levels of enantioselectivities, a screening of phenols was undertaken. Among all the tested phenols, few of them allowed reaching ee values higher than 60% and the best ones generally possessed a substituent in the ortho position of the hydroxyl (Table 1).

From a general point of view, it appeared that the electronic nature and the steric hindrance of the phenol substituents does have a major influence on both yields and enantioselectivities. Phenols bearing an electron-withdrawing substituent on the aromatic ring (Cl, CN, $NO_2$, COMe, $CO_2Me$) generally afforded low enantioselectivities in the reaction of *N*-acetylaminoacrylate (**1a**) with potassium phenyltrifluoroborate (**2a**). Moreover, in the case of chlorophenol derivatives, increasing the number of substituents in the *ortho* and *para* positions resulted in a reverse, even moderate, enantioselection (from 18% ee for phenol to –20% ee for 2,4,6-trichlorophenol), suggesting a change in the reaction mechanism, and particularly the protonation step. The presence of potential complexing substituents in the *ortho* position of the phenol (NHAc, NHCOPh, $CO_2Me$, COR, F) seemed to inhibit the reaction, and a low yield and ee were observed in each case. Moreover, it appeared that increasing the steric hindrance in the *ortho* position resulted in an increase in the enantioselectivity, which reaches 54 and 69% for 2,6-di-*tert*-butylphenol and 2-phenylphenol, respectively. Generally speaking, the highest yields and enantioselectivities were obtained with electron-rich phenols, bearing an alkoxo substituent. However, with *meta*- or *para*-alkoxo-substituted phenols, moderate enantioselectivities, in the range 50–60%, were generally achieved, while the yields were acceptable (close to 80%). The highest level of enantioselectivity was attained using 2-methoxyphenol or guaiacol (83% ee).

In order to understand more closely the influence of the phenols on the enantioselectivities, we wondered if the $pK_A$ of the phenols was influencing the level of enantioselectivities. As all the $pK_A$ values given in the literature are evaluated in a protic solvent, more generally in water, and given that the reaction is conducted under aprotic conditions (toluene as solvent), we evaluated the $pK_A$ of several phenols by DFT calculation (Figure 1).[23] From these calculations it appeared that there is not a complete correlation between phenol $pK_A$'s and the measured enantioselectivities, probably because many other factors can influence the protonation step, such as steric or electronic factors. But, the general tendency is that an increase of the $pK_A$ results in an increase of the enantioselectivity; in other words, the less acidic phenols are the most suitable proton sources in the reaction. More particularly guaiacol, which gave the highest enantioselectivity, is the least acidic phenol we have evaluated, under nonprotic conditions. The influence of the phenol $pK_A$'s will be discussed in connection with the reaction mechanism (*vide infra*).

Indeed, given that guaiacol is an inexpensive and nontoxic phenol, we searched no further for a proton source and envisioned exploring the influence of the chiral ligand at the rhodium center (Table 2 and Chart 1).

Among the tested chiral ligands, only atropoisomeric ligands allowed reaching high levels of enantioselectivities. Indeed, very low or the absence of chiral induction was observed using Josiphos chiral ligand derivatives **L10**–**L13**[24] (entries 10–13), Binepine **L14**[25] (entry 14), or Duphos ligand **L15**[26] (entry 15) which have been shown to be useful ligands in asymmetric hydrogenation of dehydroamino esters. At this point, it is important to note that the amount of chiral ligand compared to rhodium does have a notable influence on the stereochemical outcome of the reaction. Indeed, by using 2.2 equiv of chiral bidentate ligand instead of 1.1 equiv (compared to Rh catalyst), we were able to increase the ee by more than 6 points and an

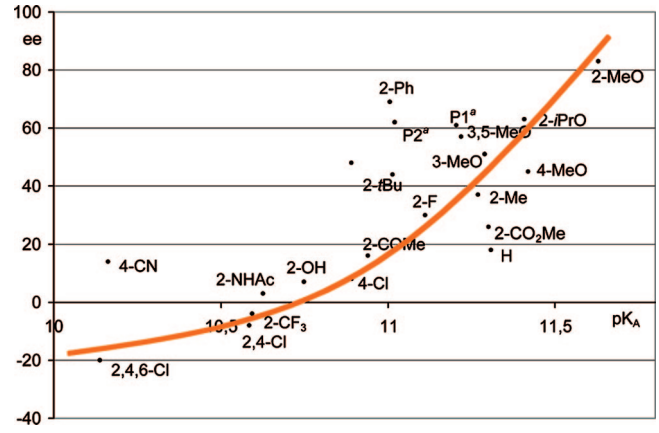


***Figure 1.*** Influence of phenols $pK_A$ on the enantioselectivities. [a] P1 = benzo[1,3]dioxol-5-ol and P2 = 7-methoxy-naphthalen-2-ol.

***Table 2.*** Ligand Screening in the 1,4-Addition/Enantioselective Protonation[a]

| entry | chiral ligand | yield[d] | ee[e] |
|---|---|---|---|
| 1 | (*S*)-Binap (**L1**) | 91 (89[b]) | 83 (89.5[b]) |
| 2 | (*S*)-TolBinap (**L2**) | 83 | 82 |
| 3 | (*S*)-MeOBiphep (**L3**) | 48 (82[b]) | 58 (84[b]) |
| 4 | (*S*)-**L4** | 32[b] | 85[b] |
| 5 | (*R*)-**L5** | 32 | −2 |
| 6 | (*S*)-**L6** | 20 | 7 |
| 7 | (*R*)-**L7** | 51[b] | −88.2[b] |
| 8 | (*R*)-**L8** | 50[b] | −88.9[b] |
| 9 | (*R*)-**L9** | 63 | 0 |
| 10 | (*R*)-(*S*)-PPF-$PCy_2$ (**L10**) | 9 | 3 |
| 11 | (*R*)-(*S*)-$Cy_2$PF-$PCy_2$ (**L11**) | 5 | nd |
| 12 | (*R*)-(*S*)-PPF-P*t*-$Bu_2$ (**L12**) | 7 | 0 |
| 13 | (*S*)-(*R*)-$Cy_2$PF-$PPh_2$ (**L13**) | 6 | nd |
| 14 | (*R*)-Binepine (**L14**) | 58[c] | 2 |
| 15 | (*R*,*R*)-MeDuphos (**L15**) | 68 | 0 |
| 16 | (*S*)-Synphos (**L16**) | 12[b] | 79[b] |

[a] Reactions conducted using 0.5 mmol of **1a**, 2 equiv of **2a**, and 1 equiv of guaiacol with 3 mol% of $[Rh(cod)_2][PF_6]$, 3.3 mol% of chiral bidentate ligand in toluene at 110–115 °C for 20 h. [b] Reactions conducted with 6.6 mol% of chiral bidentate ligand. [c] Reactions conducted with 6.6 mol% of ligand. [d] Isolated yields. [e] Determined by HPLC analysis using Daicel Chiralcel OD-H chiral column, sign plus for the (*R*) enantiomer.

(23) Free energies of the phenols $G_{Vac}(ArOH)$ and phenates $G_{Vac}(ArO^-)$ were calculated at the B3LYP/6–31++G(d,p) level, at 298.15 K, 1 atm, and the results were converted to $pK_A$ values in water using the following linear formula: $pK_{A_{H_2O}}(ArOH) = a \times pK_{A_{vac}}(ArOH) + b$ with $a = 14/[pK_{A_{vac}}(H_2O/HO^-) - pK_{A_{vac}}(H_3O^+/H_2O)]$; $b = 14/[1 - \{pK_{A_{vac}}(H_2O/HO^-)\}/\{pK_{A_{vac}}(H_3O^+/H_2O)\}]$ and $pK_{A_{vac}}(ArOH) = -\log(\exp[\{G_{vac}(ArO^-) - G_{vac}(ArOH)\}/RT])$: see Supporting Information.

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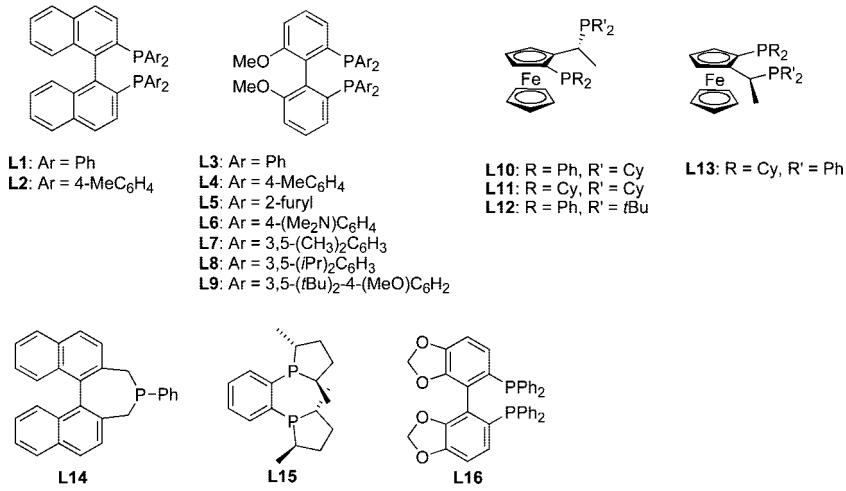
***Chart 1.*** Chiral Ligands in the 1,4-Addition/Enantioselective Protonation




**L1**: Ar = Ph
**L2**: Ar = 4-$MeC_6H_4$

**L3**: Ar = Ph
**L4**: Ar = 4-$MeC_6H_4$
**L5**: Ar = 2-furyl
**L6**: Ar = 4-$(Me_2N)C_6H_4$
**L7**: Ar = 3,5-$(CH_3)_2C_6H_3$
**L8**: Ar = 3,5-$(i\text{Pr})_2C_6H_3$
**L9**: Ar = 3,5-$(t\text{Bu})_2$-4-$(MeO)C_6H_2$

**L10**: R = Ph, R' = Cy
**L11**: R = Cy, R' = Cy
**L12**: R = Ph, R' = *t*Bu

**L13**: R = Cy, R' = Ph

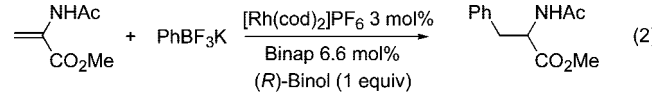
**L14** **L15** **L16**

ee of nearly 90% was obtained using Binap[27] (entry 1). The same trend was also observed with MeOBiphep ligand (**L3**)[28] (entry 2).

Various substitution patterns were evaluated either on the backbone of the atropoisomeric ligand or on the phenyl phosphorus substituents, and it appeared that ligands such as Binap (entry 1), TolBinap (entry 2), MeOBiphep derivatives[29] (entries 3–9), or Synphos[30] (entry 16) gave the highest ee on the model substrates. From these results, it is highly speculative to find any correlation between the electronic nature of the atropoisomeric ligand and the level of asymmetric induction but, in this series, ee generally decreased with increasing electron density on the chiral backbone (entries 1, 3, 16). Moreover, a study on MeOBiphep derivatives (entries 3–9) revealed an interesting steric influence of the phenyl substituents on the enantioselectivity levels: increasing steric hindrance resulted in an increase of the ee. Indeed, the 84% ee obtained with MeOBiphep (entry 3) could be improved to 88.9% when placing an isopropyl substituent in the 3,5-position (ligand **L8**, entry 8). The lowest ee obtained with ligand **L9** (entry 9), bearing high steric congestion, may be explained by electronic factors (presence of a 4-methoxy substituent) or, more probably, by too much congestion around the ligand, preventing a complete complexation of the ligand to the rhodium center. This ligand screening also revealed that electron-rich ligands like Josiphos or Duphos derivatives did not induce any asymmetric induction and conversions were generally low.

Indeed, under these conditions, addition of potassium trifluoro(phenyl)borate to methyl *N*-acetamido acrylate resulted in good yields and enantioselectivities close to 90% using Binap or MeOBiphep derivatives as the chiral ligand.

In order to further improve the enantiomeric excesses we wondered if protonation by chiral phenol derivatives would give higher levels of enantioselectivity, keeping in mind their recycling. As a model of chiral phenol, binol was chosen because of its ready availability and because it has shown to be a useful chiral inductor (eq 2).[31] Thus, we conducted the reaction using (*R*)-Binol as the proton source, in conjunction with either (*R*) or (*S*)-Binap as the chiral ligand in order to avoid match/mismatch associations. Unfortunately, on the reaction model, the same low ee values were obtained with both of the atropoisomeric chiral ligands.




(2)

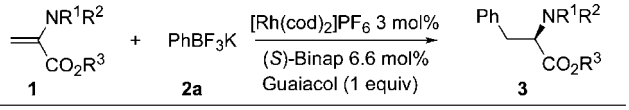
(*R*)-binap ee: 27% (*S*)
(*S*)-binap ee: 27% (*R*)

A screening of other rhodium catalyst precursors[32] and even the preformed Rh-Binap complex did not allow an increase in reaction enantioselectivities. As in the case of asymmetric 1,4-addition of potassium trifluoro(organo)borates to Michael acceptors,[12] cationic rhodium complexes were the most suitable precursors. On the contrary, the reaction medium has a great influence on either the conversion or enantioselectivity, and nonpolar solvents like dioxane or toluene were the most adapted. Finally, it is also important to note that reaction temperature has a crucial influence. The highest enantiomeric excesses were generally achieved at 110 ± 10 °C, while outside this range both yields and enantioselectivities decreased.

**Scope/Limitations of the Reaction.** With optimal conditions in hand, we evaluated the scope and limitation of this rhodium-catalyzed tandem 1,4-addition/enantioselective protonation. We first studied the extension of this reaction to diversely protected dehydroamino esters not only in order to access differently protected useful amino esters but also in order to evaluate their influence on reaction yields and enantioselectivities. All these dehydroamino esters were easily prepared in high yields from serine by selective protections and hydroxy elimination (see experimental section) without intermediate purification steps.

(27) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.
(28) Schmid, R.; Forisher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370.
(29) Schmidt, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131.
(30) (a) Duprat de Paule, S.; Champion, N.; Vidal, V.; Genet, J.-P.; Dellis, P. (Synkem), WO Patent 03029259, 2003. (b) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Deschaux, G.; Dellis, P. *Org. Process Res. Dev.* **2003**, *7*, 399.
(31) Review: (a) Brunel, J.-M. *Chem. Rev* **2005**, *105*, 857. (b) Brunel, J.-M. *Chem. Rev.* , ASAP Article (Update 1, DOI: 10.1021/cr078154l).
(32) The following catalyst precursors wee evaluated: $[Rh(CH_2CH_2)_2Cl]_2$ (8% yield, 20% ee), $[Rh(cod)_2]BF_4$ (74% yield, 84% ee), [Rh(cod)((*R*)-Binap)]$BF_4$ (51% yield, 84% ee), $[Rh(cod)OH]_2$ (15% yield, 18% ee).

***Table 3.*** Scope in the Substitution Patterns on the Dehydroalanine[a]




| entry | $R^1$ | $R^2$ | $R^3$ | | yield[b] | ee[c] |
|---|---|---|---|---|---|---|
| 1 | H | Ac | Me | (**1a**) | 91 | 89.5 (*R*) |
| 2 | H | Z[d] | Me | (**1b**) | 92 | 43 |
| 3 | H | Boc[d] | Me | (**1c**) | 82 | 89.5 (*S*)[e] |
| 4 | | Phth[d] | Me | (**1d**) | 91 | 10 |
| 5 | H | $COCF_3$ | Me | (**1e**) | 100 | 15 |
| 6 | H | Ac | *i*-Pr | (**1f**) | 87 | 91 (*R*) |
| 7 | H | Boc | *i*-Pr | (**1g**) | 76 | 93 (*R*) |
| 8 | H | Boc | *t*-Bu | (**1h**) | 70 | 95 (*R*) |

[a] Reactions conducted using 0.5 mmol of **1**, 2 equiv of **2a**, and 1 equiv of guaiacol with 3 mol% of $[Rh(cod)_2][PF_6]$, 6.6 mol% of (*S*)-Binap in toluene at 110–115 °C for 20 h. [b] Isolated yields. [c] Determined by HPLC analysis using Daicel Chiralcel OD-H or Chiralpack AS-H chiral column. [d] Z: benzyloxycarbonyl. Phth: Phthalimido. Boc: *tert*-butoxycarbonyl. [e] Using (*R*)-binap.

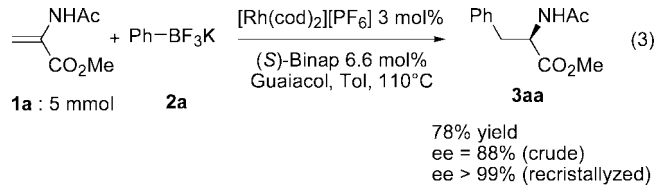
All these compounds were generally purified by simple recrystallization or distillation: no chromatographic purifications were needed.

From the tested amino protecting groups (Table 3, entries 1–5), acetyl and Boc (*tert*-butoxycarbonyl) gave good yields of phenylalanine derivatives with equally high ee values. The Z protecting group (benzyloxycarbonyl) was not compatible with the reaction conditions, giving a byproduct and low enantiomeric excess (entry 2). Concerning phthalimido or trifluoroacetyl (entries 4 and 5), despite a very efficient addition (high yields, reduced reaction time), we only obtained near racemic adducts. The influence of the ester moiety was next evaluated using different Boc and Ac protected amino esters. From these results, it appeared that increasing the steric hindrance (from methyl to *tert*-butyl ester) resulted in improved enantioselectivities. For example, using the useful Boc protecting group, an ee of 89.5% obtained with methyl ester (entry 3) was increased to 93% with an isopropyl derivative (entry 7) and even up to 95% with *tert*-butyl ester (entry 8). However, slightly lower yields were generally achieved using *tert*-butyl dehydroamino esters. Indeed a good compromise for achieving either high yields or enantioselectivities appeared with the use of isopropyl derivatives, all the more so as they are more easily accessible than the *tert*-butyl esters.

We next evaluated the scope of the reaction, by reacting different dehydroalanines with potassium aryl- and even alken-1-yl-trifluoroborates (Scheme 1) under standard conditions. From these results, it appeared that a great variety of arylalanine derivatives were readily obtained using this tandem carbometalation/enantioselective protonation process. Interesting levels of enantioselectivity ranging from 75 to 95% were generally achieved and, as previously noted, the ee increased with the steric hindrance of the ester. For example, the addition of potassium (4-fluorophenyl)trifluoroborate on acetyl and Boc dehydroalanines (**1a** and **1c**) afforded **3ab** and **3cb** in 83 and 81% ee, respectively, whereas on isopropyl esters **3f** and **3g** the ee were increased to 90 and 94%, respectively, to finally attain 95% on **3h** bearing a *tert*-butyl ester. Using potassium alkenyltrifluoroborates **2h**, it appeared that alkenyl substituted alanine derivative **3ah** is efficiently produced with good ee and yield, with some isomerization of the double bond observed, presumably via rhodium-catalyzed double-bond migration. This represents an interesting feature of this reaction since these substrates are not easily accessible, even using efficient asymmetric hydrogenation processes.[33]

From a practical point of view, dehydroalanine isopropyl esters appeared to be the most suitable substrates as good yields and enantioselectivities (ranging from 88 to 93%) were uniformly observed. Moreover the sense of the enantioselectivity is easily controlled: using (*S*)-binap, products of (*R*) configuration were obtained.

To further demonstrate the utility the present procedure for the formation of enantio-enriched arylalanine derivatives, a larger scale reaction was conducted. Reaction of dehydroamino ester **1a** (5 mmol) with potassium trifluoro(phenyl)borate **2a** furnishes **3aa** in 78% yields and 88% enantioselectivity (eq 3). After a single recrystallization, the enantiomeric excess was increased to over 99%, and **3aa** was obtained in 55% overall yield.



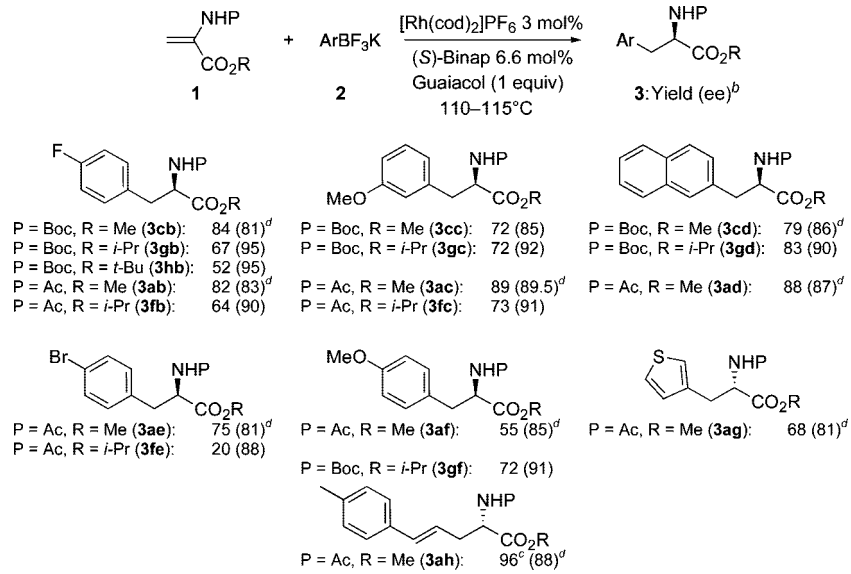

**Extension to Other Organometallic Reagents and Electron-Deficient α,α′-Disubstituted Alkenes.** The described process of 1,4-addition/enantioselective protonation is not limited to potassium trifluoro(organo)borates. We have shown previously that organosilanes and other organoboranes derivatives (boronic acids or esters) were not suitable reagents in this reaction because either no conversion or enantioselectivity was observed.[8a] On the other hand organostannanes can be successfully used in this process (Table 4). Indeed, under identical conditions, addition of trimethylphenylstannane (**4a**) to **1a** occurred in 89% yield with a moderate 71% ee.

On that substrate, the ee could be increased up to 88% using tributylphenylstannane (**4b**) instead of the trimethyl derivative. As observed in the case of potassium trifluoro(organo)borates, a phthalimido (entry 5) or benzyloxycarbonyl (Z, entry 6) protecting group is not compatible with this reaction, affording amino esters in low yields and enantiomeric excesses. On the other hand, with Boc or Ac derivatives, elevated ee values were generally observed using organostannanes (entries 2–4), whereas yields were generally slightly lower than those obtained with the corresponding trifluoroborate salts.

As reported in the introductive part, this concept of 1,4-addition/enantioselective protonation was extended to the preparation of succinic esters,[19] $\beta^2$-amino acids,[20] and α,α′-dibenzyl esters[21] using other proton sources than phenols. We wondered if our reaction conditions could be extended to other electron-deficient α,α′-disubstituted alkenes using phenols as protonating agents. Unfortunately, despite several attempts, all other tested substrates were not suitable in this reaction. Indeed,

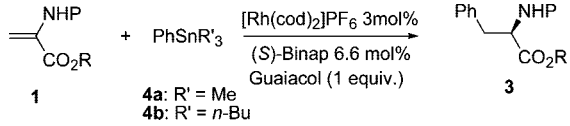
(33) (a) For reviews on asymmetric hydrogenation, see: Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; Wiley: New York, 1994. (b) Genet, J.-P. *Reductions in Organic Synthesis: Recent Advances and Practical Applications;* ACS Symposium Series 641; American Chemical Society: Washington, DC, 1996; pp 31−51. (c) Burk, M. J. *Chemtracts Org. Chem.* **1998**, *11*, 787. (d) Ohkuma, T.; Kitama, M.; Noyori, R. In *Catalytic Asymmetric Synthesis;* Ojima, I., Ed.; VCH: Weiheim, 2000; Chapter 1.4. (e) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (f) Genet, J.-P. In *Reduction of Functionalized alkenes;* Adersson, P. G., Munslow, I., Eds.; Wiley-VCH, New York, in press.

***Scheme 1.*** Scope of the 1,4-Addition/Enantioselective Protonation[a]




[a] Reactions conducted using 0.5 mmol of **1**, 2 equiv of **2**, and 1 equiv of guaiacol with 3 mol % of $[Rh(cod)_2][PF_6]$, 6.6 mol% of (*S*)-binap in toluene at 110–115°C for 20 h. [b] Determined by HPLC analysis using chiral column (see Supporting Information). [c] Isolated as an inseparable mixture containing 30% of the 3,4-isomer. [d] (*S*) isomer obtained using (*R*)-binap as ligand.

***Table 4.*** 1,4-Addition/Enantioselective Protonation Using Phenylstannanes[a]

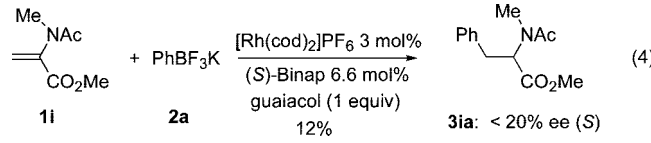



| entry | dehydroalanine | $PhSnR'_3$ | yield[b] | ee[c] |
|---|---|---|---|---|
| 1 | **1a** | **4a** | 89 | 71 (*R*) |
| 2 | **1a** | **4b** | 82 | 88 (*R*) |
| 3 | **1c** | **4a** | 80 | 88 (*R*) |
| 4 | **1g** | **4b** | 45 | 91 (*R*) |
| 5 | **1d** | **4a** | 61 | 17 (*S*) |
| 6 | **1b** | **4a** | 0 | |

[a] Reactions conducted using 0.5 mmol of **1**, 2 equiv of **4a** or **4b**, and 1 equiv of guaiacol with 3 mol% of $[Rh(cod)_2][PF_6]$, 6.6 mol% of (*S*)-Binap in toluene at 110–115 °C for 20 h. [b] Isolated yields. [c] Determined by HPLC analysis using Daicel Chiralcel OD-H or Chiralpack AS-H chiral column.

itaconic acid derivatives afforded quasi-racemic 1,4-addition adducts while yields were still elevated. In the same way, on reaction with potassium trifluoro(phenyl)borate, 5-exomethylenefuran-2-one gave racemic 1,4-adduct in 90% yield. Indeed, it appeared that our optimized conditions, involving binap (or other atropoisomeric bidentate phosphanes) as the ligand for rhodium and guaiacol as the proton source, were only adapted for dehydroamino ester derivatives. Intrigued by the specificity of this reaction, we conducted complementary experiments in order to obtain some insights into the reaction mechanism.

**Discussion on the Reaction Pathway. On the Importance of the N−H Amido Substituent.** From the results obtained with a large variety of substrates (vide supra), it appeared that the presence of a free N−H bond in the α-position of the Michael acceptor was essential in order to achieve ahigh level of enantioselectivity: substrates lacking this NH substituent (itaconic esters derivatives) or diprotected dehydroamino esters (phthalimido) all gave quasi-racemic products. The crucial role played by the presence of this free N−H substituent was confirmed by the fact that the reaction with **1i**, where the hydrogen has been substituted by a methyl, afforded phenyl alanine **3ia** in low and even reversed enantiomeric excess (eq 4).




(4)

Such low asymmetric induction was generally observed upon protonation with water. For example, methyl *N*-acetylaminoacrylate (**1a**), under identical conditions, but using water instead of guaiacol afforded a maximum of 18% ee of opposite sign compared to phenol protonation.

Even more intriguing, it appeared that the reaction course was influenced by the acidity, not only of the phenol (vide supra) but also of the substrate: reaction of trifluoroacetyl derivative **1e** with potassium trifluoro(phenyl)borate afforded phenylalanine in low ee (Table 3, entry 5). However, the calculated $pK_A$ of this dehydroamino ester (8.05, ACD)[34,35] or of the resulting amino ester (9.7, ACD) are lower by more than one unity than those of acetamido or Boc derivative (Table 5). The $pK_A$ of this trifluoroacetyl derivative is to compare with acidic phenols that always resulted in low enantioselectivity: one can guess that this dehydroamino ester is itself acting as a nonselective proton source. Indeed, it does seem that the acidity of the reacting substrate (and even the product) has a great influence on the stereochemical outcome of the reaction.

To obtain further evidence on the reaction pathway, we initiated deuterium labeling experiments in order to find the origin of the incoming proton (substrate or phenol). Cross-experiments were conducted, using either deuterated dehydroamino esters or deuterated guaiacol (Scheme 2).

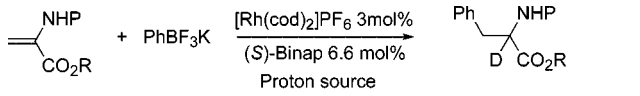
(34) *ACDpKa, V. 8.03*; Advanced Chemistry Development: Toronto, Canada, 2007.
(35) The predicted values of $pK_a$ were obtained using the ACD/I-Lab Webservice (ACD/pKa 8.03).

***Table 5.*** Calculated p$K_A$ of Alanine Derivatives[a]

| P | NHP / $CO_2Me$ | Ph, NHP / $CO_2Me$ |
|---|---|---|
| Ac | 13.1 | 14.7 |
| Boc | 9.6 | 11.2 |
| Z | 9.4 | 11.0 |
| $COCF_3$ | 8.05 | 9.67 |

[a] p$K_A$ values determined at 25 °C and zero ionic strength in aqueous solution: see ref 35.

***Scheme 2.*** Deuterium Labeling Studies: Origin of the Protonation




| | | |
|---|---|---|
| **1a** | $D_2O$ | 100[a] (ee ≈ 10%, 96% yield) |
| | guaiacol-$d_1$[b] | 28[a] (ee = 90%, 81% yield) |
| **1g** | guaiacol-$d_1$[b] | 43[a] (ee = 92%, 86% yield) |
| **1a**-$d$[c] | guaiacol | 41[a] (ee = 90%, 93% yield) |

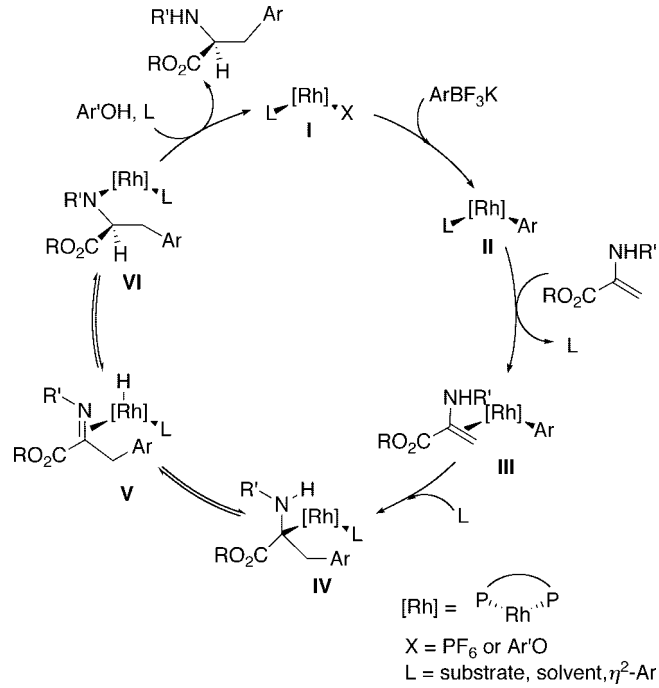
[a] % of deuterium incorporation in the α position determined by $^1$H NMR. [b] 2-Methoxyphenol-$d_1$. [c] Methyl 2-(acetyldeuterioamino)acrylate.

As expected, reaction of dehydroalanine **1a** with potassium phenyltrifluoroborate (**2a**), in the presence of 3 mol% [Rh(cod)$_2$]BF$_6$ and 6.6 mol% (*S*)-Binap, using $D_2O$ as the proton source in toluene at 110 °C afforded 100% of α-deuterated near racemic amino ester **3aa**-*d* in quantitative yield. It is also important to note that the reaction using water as the proton source is more than 10 times faster than that using guaiacol. Using 1 equiv of deuterated guaiacol[36] under identical conditions, we were surprised to observe only 28% deuterium incorporation in the purified product **3aa**, with an enantiomeric excess of 90% as observed before. Low but higher deuterium incorporation was also observed using **1g** as starting material. Indeed, at this point, it seems that the percentage of deuteration is dependent on the starting dehydroalanine substrate. We were all the more surprised by the results obtained starting with amino-deuterated dehydroalanine **1a**-*d*.

The reaction conducted with **1a**-*d*, but using phenol as the proton source, afforded **3aa** with 41% deuterium incorporation, a proportion that was even higher than those observed in the reaction of **1a** with guaiacol-$d_1$. In light of these results, it became clear that the reaction did not involve a direct protonation of a putative rhodium enolate, which should have resulted in the clean formation of α-deuterated adducts, as observed using $D_2O$ as theproton source.[37] On the contrary, it seemed that the N−H proton of the starting substrate **1** is involved in the reaction mechanism, all the more so when this proton is absent, as is substrate **1i** (*vide supra*), very low yield and enantioselectivity were achieved.

Indeed, we proposed a new reaction mechanism to account for these experimental results, which is supported by computational modeling studies (*vide infra*). After transmetalation of potassium organotrifluoroborate to the rhodium(I) complex **I** and complexation of the dehydroalanine, an alkyl-rhodium

***Scheme 3.*** Proposed Reaction Mechanism

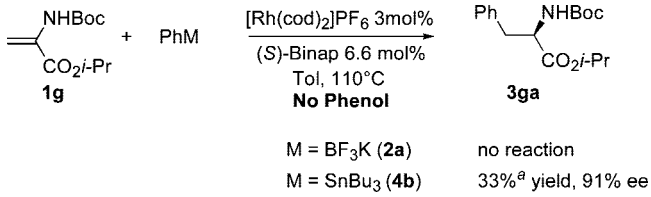



species **IV** is formed (Scheme 3). This $\eta^1$-carbon-bounded rhodium complex is certainly in equilibrium with $\eta^1$-oxygen-bounded rhodium enolate species or oxa-$\pi$-allyl[9] type enolate.[38]

This rhodium complex **IV** can undergo a $\beta$-hydride elimination to generate a rhodium hydride species **V** complexed to the formed imidoester. Generation of such species has also been evoked in rhodium-catalyzed enantioselective hydrogenation of α-acetamidocinnamate substrates.[39] Hydride transfer to the imido will generate an amido-rhodium complex **VI** with concomitant control of the α center. The first implication of such a hydride intramolecular transfer and the generation of an imido species is that the imido must remain complexed to the rhodium center before the hydride transfer occurs in order to achieve high enantioselectivity. The amido-rhodium bond is then protonated by the guaiacol to generate an aryloxo-rhodium complex **I** liberating the arylalanine product **3**. This aryloxo-rhodium species is suited for transmetalation with the boron reagent. Transmetalation of organoboron compounds to an alkoxo or a hydroxo complex of palladium,[40] rhodium,[9] or ruthenium[41] has been described, allowing the regeneration of organo-rhodium species. Indeed, in the absence of phenol, no reaction occurs using potassium aryltrifluoroborates as an organometallic partner (Scheme 4). On the other hand, a reaction using organostannanes occurs even in the absence of added

(36) Mafumé, F.; Hashimoto, Y.; Hashimoto, M.; Kondow, T. *J. Phys. Chem.* **1995**, *99*, 13814.
(37) To a certain extent, some deuterium scrambling is occurring between dehydroalanine substrate and guaiacol, but this process is slow compared to the reaction kinetic.
(38) For references concerning the structure of rhodium-enolates, see: (a) Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938. (b) Wu, J.; Bergman, R. G *J. Am. Chem. Soc.* **1989**, *111*, 7628. (c) Slough, G. A.; Hayashi, R.; Ashbaugh, J. R.; Shamblin, S. L.; Aukamp, A. M. *Organometallics* **1994**, *13*, 890. (d) Reference 9.
(39) (a) Wiles, J. A.; Bergens, S. H. *Organometallics* **1998**, *17*, 2228. (b) Detllier, C.; Gelbard, G.; Kagan, H. B. *J. Am. Chem. Soc.* **1978**, *100*, 7556.
(40) Review: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(41) (a) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (b) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706. (c) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516.

***Scheme 4.*** 1,4-Addition/Enantioselective Protonation in the Absence of Proton Source




[a] Isolated yield after hydrolysis of the reaction mixture.

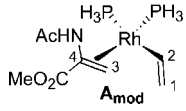



***Figure 2.*** Model system $\mathbf{A_{mod}}$ for DFT calculations.

phenol, proving that the organotin compound can directly transmetalate imido-rhodium species **VI**, while it is not the case with trifluoroborate species.[42]

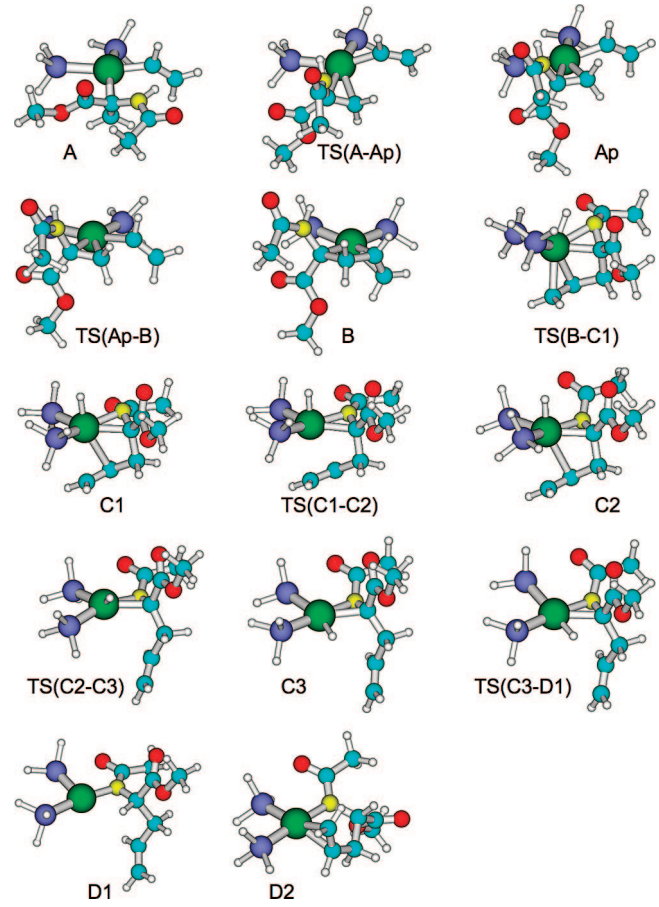
Indeed, reaction of phenyltributylstannane (**4b**) with dehydroalanine **1g** under optimized conditions, but in the absence of guaiacol, afforded the expected product **1ga** in a 33% yield and an enantioselectivity of 91%, which is comparable to those obtained in the presence of guaiacol (Table 4, entry 4). Apparently, phenol is only useful in the reactions with potassium organotrifluoroborates, and its role would be the regeneration of a rhodium species suited for transmetalation with borane reagents. The overall mechanism implies a 1,4-addition type reaction of the organometallic reagent followed by an intramolecular hydride transfer from nitrogen to the adjacent carbon. It is believed that, using more acidic phenols or water as proton sources, a rhodium enolate species is protonated before the hydride transfer has occurred and that this protonation is not diastereoselective.

In order to support this postulated mechanism, computational modeling studies were conducted.

**Computational Modeling Studies on the Reaction Mechanism.** DFT calculations of the catalytic reaction potential energy surface were undertaken for a simple achiral model at the B3LYP/BII level. The transmetalation step will not be addressed as well as complexation of the starting substrate and decomplexation of the final product. Model complex $\mathbf{A_{mod}}$ (Figure 2) was chosen to mimic the structural and electronic features while minimizing computational time. Model $\mathbf{A_{mod}}$, which corresponds to the starting dehydroalanine-catalyst adduct **III** (Scheme 3), consists of a neutral rhodium complex with two *cis* ligated $PH_3$ ligands, coordinated substrate **1a** and a vinyl substituent to mimic the aromatic ring of the potassium aryltrifluoroborate precursor.

Among the different structures of type **A** found on the potential energy surface (minima), two of them **A** and **Ap**, which are in rapid equilibrium, were susceptible to further involvement in carbon−carbon bond formation (Chart 2 and Figure 3). In the more stable complex **A**, the carbon−carbon double bond is perpendicular to the rhodium-phosphanes plane whereas in **Ap** the double bong is parallel. These two minima are interconnected *via* the transition state **TS(A-Ap)**, corresponding to the rotation of the dehydroalanine moiety along the $C_4$−Rh bond. The $C_3$

***Chart 2.*** Optimized Structures at the B3LYP/BII Level




and $C_2$ carbons are closer in complex **Ap** compared to structure **A** (3.047 and 2.583 Å, respectively), which is favorable for the carbon−carbon bond formation (Table 6). Thanks to this favorable rearrangement, the bond formation can occur, with a comparatively low free activation energy of +8.4 kcal/mol (**TS(Ap-B)**), resulting in the formation of a $\sigma$-alkyl-rhodium complex **B** of type **IV** (Scheme 3), where the double bond of the model organometallic part is still complexed to the rhodium center.[43] The carbon−carbon bound formation is a highly exergonic process ($\Delta G = -22.8$ kcal/mol).

In complex **B**, the N−H bond of the amide is above the plane, with a Rh−H distance of 2.911 Å. From this minimum, we

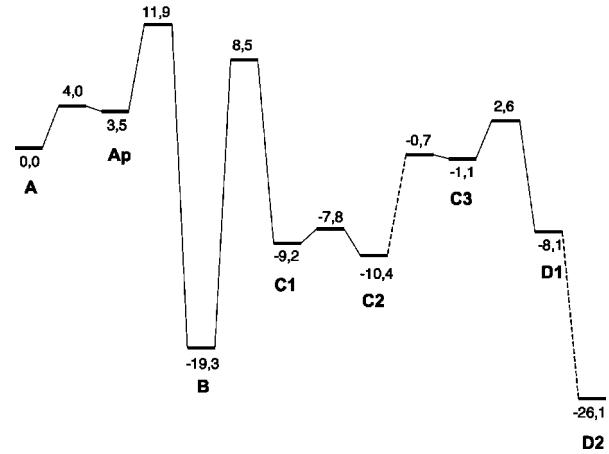



***Figure 3.*** Free energy (kcal/mol) surface for the 1,4-addition/protonation at the B3LYP/BII level.

(42) Transmetalation of organoboronic acids to silylamido-rhodium species have been described: Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 1876.

***Table 6.*** Selected Bond Length (in Å) of the Optimized Rhodium Structures

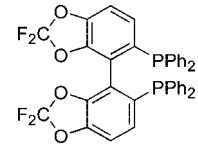
| | Rh−$C_2$ | Rh−$C_3$ | Rh−$C_4$ | Rh−N | Rh−H | $C_2$−$C_3$ | $C_4$−N | N−H | $C_4$−H |
|---|---|---|---|---|---|---|---|---|---|
| **A** | 2.030 | 2.155 | 2.304 | 3.131 | 3.028 | 3.047 | | | |
| **TS(A-Ap)** | 2.054 | 2.218 | 2.280 | 3.025 | 2.925 | 2.693 | | | |
| **Ap** | 2.095 | 2.226 | 2.281 | 3.051 | 2.916 | 2.583 | | | |
| **TS(Ap-B)** | 2.160 | 2.313 | 2.152 | 2.984 | 2.933 | 1.970 | | | |
| **B** | 2.249 | 2.795 | 2.172 | 2.985 | 2.911 | 1.519 | | | |
| **TS(B-C1)** | 2.239 | 2.763 | 2.162 | 2.151 | 1.638 | | | 1.488 | |
| **C1** | 2.491 | 2.887 | 2.187 | 2.065 | 1.538 1.364 | 2.426 | 2.812 | | |
| **TS(C1-C2)** | | | | | | | | | |
| **C2** | 2.529 | 2.878 | 2.174 | 2.070 | 1.529 | | 1.368 | 2.485 | 2.744 |
| **TS(C2-C3)** | 3.374 | 3.156 | 2.178 | 2.053 | 1.563 | | 1.358 | 2.994 | 2.390 |
| **C3** | | 3.188 | 2.175 | 2.082 | 1.585 | | 1.351 | 2.978 | 2.283 |
| **TS(C3-D1)** | | | 2.212 | 2.083 | 1.598 | | 1.353 | 2.634 | 1.839 |
| **D1** | 3.042 | 2.557 | 2.676 | 2.011 | 2.281 | | 1.437 | | 1.123 |
| **D2** | 2.160 | 2.944 | 3.027 | 2.061 | 3.652 | | 1.477 | | 1.101 |

found a transition state **TS(B-C1)** associated with the $\beta$-hydride elimination of the amide hydrogen resulting in the formation of a rhodium hydride species **C1** of type **V** (Scheme 3). The imaginary frequency of this transition state is associated with the hydride migration from the nitrogen to the rhodium atom, starting from an $\eta^3$-(C−N−H)Rh complex whose structure is very close to **TS(B-C1)**. However, at this level of theory, we could not find, despite several attempts, any intermediate between **B** and **TS(B-C1)**. The overall activation energy of this $\beta$-elimination process is $\Delta G^{\ddagger} = +27.8$ kcal/mol, representing the rate-determining step of the reaction, but this energy is compatible with the reaction temperature (110–115 °C). Rhodium hydride **C1** has a distorted trigonal bipyramidal structure, the hydride ligand and the C═C bond being in pseudoequatorial positions. After a series of favorable isomerizations, the hydride, complexed at the rhodium center in **C1**, is transferred to carbon $C_4$ leading to the formation of the amido-rhodium **D1**.

The rhodium hydride **C1** is first isomerized to the slightly more stable complex **C2** *via* a transition state **TS(C1-C2)** of low activation energy (1.4 kcal/mol). In this process the acetyl substituent on the nitrogen is moving from below the rhodium-phosphane plane in **C1** to above the plane in **C2**, facilitating the following hydride migration from the equatorial to axial position, adapted to the hydride transfer. The hydride movement takes place *via* the transition state **TS(C2-C3)** ($\Delta G^{\ddagger} = +9.7$ kcal/mol) to give the square planar complex **C3**. This process is endergonic by 9.3 kcal/mol, but in this complex the hydride is in close contact with the $C_4$ carbon atom (the distance between $C_4$ and H is 2.283 Å). The imaginary frequency of this transition state **TS(C2-C3)** only corresponds to the movement of the hydride from the axial to equatorial position. Indeed, at this level of theory, the transformation of **C2** to **C3** first involves a decomplexation of the carbon−carbon double bound followed by the hydride transfer. But once again, we did not localize any other intermediate between **C2** and **C3**.

Starting from the rhodium-hydride complex **C3**, we were able to localize a transition state **TS(C3-D1)** connecting **C3** to the amido-rhodium **D1**. In this step, the hydride is transferred from the rhodium to the carbon atom $C_4$ giving **D1** presenting an agostic bond with the newly formed C−H bond. Overall, at this stage the hydride transfer process is reversible, but a more stable amido-rhodium species **D2** (type **VI**, Scheme 3) was found in the potential energy surface. We did not try to localize any transition state or intermediate connecting **D1** to **D2** since they did not involve any bound transformation, but simple ligand exchange at the rhodium center.

***Chart 3.*** Difluorphos Ligand




Difluorphos (**L17**)

Indeed, the DFT calculations, on this simple model, support our proposed reaction mechanism involving a $\beta$-hydride elimination and, thus, an overall process involving an hydride transfer from the nitrogen atom of the amido substituent to the adjacent carbon $C_4$. The high activation energy of the rate-determining $\beta$-hydride elimination step is compatible with a reaction temperature of 110–115 °C necessary for the reaction to proceed.

**Difluorphos Ligand in 1,4-Addition/Enantioselective Protonation.** Thanks to a better understanding of the reaction mechanism, we wondered if the 1,4-addition/enantioselective protonation reaction could not be further improved in terms of catalytic activity and/or enantioselectivity based on simple propositions. First in order to achieve high enantioselectivity, and because of this internal hydride transfer, it is important that the generated imide in complex **C1** remains complexed to the rhodium center until the formation of the carbon−hydrogen bond in **D1**. Second, based on the putative mechanism, the overall process could be favored by facilitating the $\beta$-hydride elimination step. We simply reasoned that employing a more electron-deficient chiral ligand would create a more electron-deficient rhodium center, not only favoring the $\beta$-elimination step[44] but also preventing decomplexation of the intermediate imide.

Among the atropoisomeric ligands described in the literature, difluorphos[45] (**L17**, Chart 3) appeared to fulfill the previous requirement: the presence of a difluoromethylene on the biaryl backbone resulting in a slight, but measurable, increase in $\pi$-accepting properties of the ligand.[46] Moreover, as mentioned earlier, in a related process, Sibi et al. have shown that the

(43) On related DFT calculations of other rhodium-catalyzed processes, starting from an aryl-rhodium complex, the structure of type **B** is also presenting an $\eta^2$-complexation to the arene moiety: Darses, S. Unpublished results.

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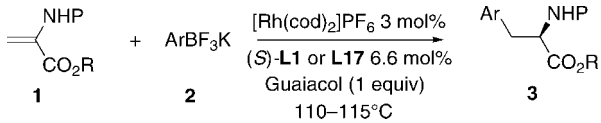
***Table 7.*** Binap *versus* Difluorphos in 1,4-Addition/Enantioselective Protonation[a]




1 2 3

| entry | product **3** | yield[b] (ee) **L1** | yield[b] (ee) **L17** |
|---|---|---|---|
| 1 | **3aa** | 89 (89.5) | 86 (92) |
| 2 | **3cb** | 84 (81)[c] | 97 (94)[c] |
| 3 | **3cc** | 72 (85) | 77 (95) |
| 4 | **3cd** | 79 (86)[c] | 97 (94)[c] |
| 5 | **3ga** | 76 (93) | 97 (95) |
| 6 | **3gb** | 44 (95) | 97 (95) |
| 7 | **3fc** | 73 (91) | 99 (91) |

[a] Reactions conducted using 0.5 mmol of **1**, 2 equiv of **2**, and 1 equiv of guaiacol with 3 mol% of $[Rh(cod)_2][PF_6]$, 6.6 mol% of (*S*)-**L1** or (*S*)-**L17** in toluene at 110–115 °C for 20 h. [b] Isolated yields. [c] (*S*) isomer obtained using (*R*)-**L1** or (*R*)-**L17**.

difluorphos ligand was the most suitable in the synthesis of $\beta^2$-amino acids *via* 1,4-addition, enantioselective protonation.[20]

Indeed, we envisioned evaluating this ligand in the rhodium-catalyzed addition of potassium organotrifluoroborates to dehydroalanine derivatives. As a test ligand for comparison, we also evaluated the Binap ligand on the same substrates. Under previously optimized conditions, e.g., using $[Rh(cod)_2]BF_6$ as a catalyst precursor, 2 equiv of an atropoisomeric ligand compared to rhodium, and guaiacol as the proton source, some potassium aryltrifluoroborates were allowed to react with dehydroalanine derivatives (Table 7).

We were pleased to find that the difluorphos ligand compared favorably and even surpassed the Binap ligand, not only in terms of reactivity but also in terms of enantioselectivity. In the reactions conducted with dehydroalanines possessing a methyl ester (entries 1–4), comparable or higher yields were generally observed, but, and more importantly, the enantiomeric excesses obtained were always higher than those using binap ligand (up to 10 point were gained in the formation of **3cc**, entry 3). We also evaluated the benefit of the difluorphos ligand on isopropyl ester dehydroalanine derivatives (entries 5–7). As noted previously, and because of steric hindrance, higher enantioselectivities were generally achieved with these substrates compared to the methyl esters. As expected, the enantioselectivities observed with this ligand were in the same range as those obtained with binap ligand. However, higher yields (and generally quantitative yields) were achieved with difluorphos (entries 5–7). More particularly, phenylalanine **3gb** was obtained in 97% yield, whereas by using the binap ligand only a moderate yield of 44% was achieved.

Indeed, from these preliminary results, it appeared that difluorphos is a highly suitable ligand in this reaction, allowing production of phenylalanines in quantitative yields and with enantioselectivities close to 95%.

## Conclusion

We have shown that the concept of rhodium-catalyzed tandem carbometalation/enantioselective protonation was highly suited for introduction of an organic substituent in the $\beta$-position of an electron-deficient alkene with concomitant control of the chirality of the α center. In this tandem process, the use of phenol derivatives, and particularly nontoxic and inexpensive guaiacol, as the proton source was crucial in order to achieve good levels of enantioselectivity and for the reproducibility of the reaction. This proton source may be easily recovered and have completely suppressed competitive reduction of the organometallic reagent that is usually observed in these rhodium-catalyzed reactions. Applied to dehydroamino esters, this reaction allowed access to diversely substituted α-amino esters in high yields and good enantiomeric excesses. By fine-tuning of the ester moiety, and using difluorophos as a chiral ligand, increased levels of enantioselectivity, generally close to 95%, were achieved. Deuterium labeling experiments revealed, and DFT calculation supported, an unusual mechanism involving a hydride transfer from the amido substituent to the α carbon explaining the high levels of enantioselectivity achieved in controlling this α chiral center.

## Experimental Section

**Computational Details.** All calculations were performed with Gaussian 03.[47] All intermediate and transition-state geometries were optimized using density functional theory (DFT), with Becke's three-parameter functional (B3)[48] and Lee, Yang, and Parr (LYP) correlation energies.[49] The double-ζ quality, Hay and Wadt LANL2DZ basis set for the valence and penultimate shells, with effective core potentials at rhodium[50] and phosphorus,[51] and a Dunning/Huzinaga full double-ζ basis[52] on C, H, N, and O, was used for initial studies. This set of basis functions and effective core potentials is referred to as BI. From these optimized structures, geometry optimizations were performed using the more sophisticated basis sets and effective core potentials from the Stuttgart group: these computations used effective core potentials for rhodium[53] replacing 28 core–electrons and a valence basis set with the following contraction scheme: (311111/22111/411). For all other atoms a 6-31G(d,p) basis set was utilized.[54] This basis set will be referred to as BII throughout this work.

Vibration frequency calculations were performed on all of the optimized structures with the same method to provide free energies at 298.15 K. The optimized minima and the transition structures have been confirmed by harmonic vibration frequency calculations as well as with IRC calculations for some transitions states. The calculated relative electronic energies have been corrected with zero-point energies (ZPEs).

**Typical Procedure for the Asymmetric 1,4-Addition to Dehydroalanine Derivatives.** A septum-capped vial equipped with a magnetic stirring bar was charged with dehydroamino ester **1a** (0.5 mmol, 71.6 mg), potassium (4-bromophenyl)trifluoroborate **2e** (2 equiv, 1 mmol, 263 mg), $[Rh(cod)_2][PF_6]$ (3 mol%, 6.9 mg), and (*R*)-binap (6.6 mol%, 20.6 mg). The vial was closed and evacuated under vacuum and placed under an argon atmosphere. Degassed toluene (2 mL) and distilled guaiacol (1 equiv, 0.5 mmol, 55 $\mu$L) were added, and the mixture was stirred in a preheated oil bath at 110–115 °C for 20 h. After cooling the vessel to room temperature, the reaction mixture was purified by silica gel chromatography

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(ethyl acetate/cyclohexane 3:2) to afford **3ae** as a white solid (113 mg, 75% yield). $[\alpha]_D^{25} = +79$ ($c = 1.03$, $CHCl_3$). HPLC (Daicel Chiralcel OJ, hexane/propan-2-ol 90/10, 0.5 mL/min, 215 nm): $t_R = 25.3$ (*S*) and 29.2 min (*R*).

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**Note Added after ASAP Publication.** The graphics for Chart 2 and Table 7 were incorrect due to a production error in the version published on the Web April 9, 2008. The corrected version was reposted on April 12, 2008.

**Supporting Information Available:** Experimental section for the preparation and the description of the compounds, and the optimized structures (phenols and rhodium) with total energies of the species in the proposed pathways. This information is available free of charge via the Internet at http://pubs.acs.org.

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