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Asymmetric Synthesis of Functionalized Phenylalanine Derivatives via Rh-Catalyzed Conjugate Addition and Enantioselective Protonation Cascade

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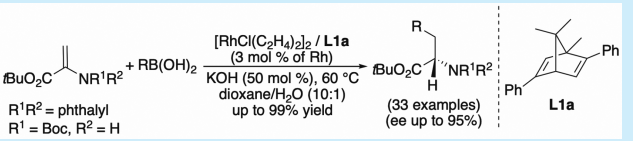
Supporting Information

ABSTRACT: The asymmetric conjugate addition of arylboronic acids to *N*-phthalimidodehydroalanine **1i** catalyzed by Rh(I)/**L1a** enables the facile preparation of chiral functionalized phenylalanines. The reaction proceeds by a conjugate addition and enantioselective protonation cascade, affording a rhodium enolate that undergoes *re*-face protonation. The reaction tolerates various arylboronic acids and can be used in the gram-scale synthesis of (*S*)-phenylalanine hydrochloride, demonstrating the reaction scope and the synthetic feasibility of the process.



Chiral α-amino acids are prominent constituents that are found in a plethora of peptides and proteins, and among these, functionalized phenylalanine derivatives (Phes) are of pharmaceutical importance.[1] For example, levodopa is a potent drug used in the treatment of Parkinson's disease (Figure 1).[2]

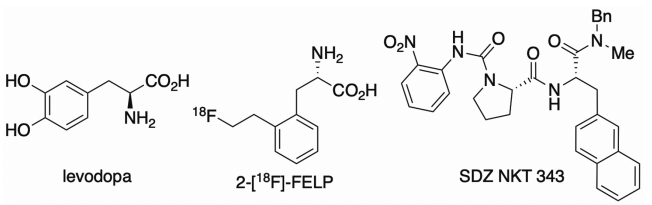


Figure 1. Biologically active phenylalanine derivatives.

SDZ NKT 343, developed by Novartis, is an orally administered preparation that is used for the treatment of neuropathic pain and chronic inflammation.[3] 2-[^{18}F]FELP, a new positron emission tomography (PET) tracer for glioma, has an enhanced in vitro cell affinity for F98 GB cells.[4]

Consequently, developing efficient and novel methods for the synthesis of α-amino acids, Phes in particular, would be of interest and highly desirable.[5] Established approaches for accomplishing this aim are asymmetric conjugate addition of organometallic nucleophiles to dehydroalanines,[6,7] enzymatic resolution of racemic α-amino acids,[8] Ugi and Strecker condensations,[9] direct functionalization of optically active α-amino acids,[10] and asymmetric hydrogenation of dehydroamino esters.[11] Among these, the asymmetric conjugate addition of organometallic nucleophiles to dehydroalanines is a straightforward and efficient method for producing chiral Phes, with features of carbon−carbon bond formation, the introduction of diverse substituents, and the generation of an α stereogenic center. In this area, Li et al. reported the Rh(I)-catalyzed conjugate addition of organotin and -bismuth compounds to ethyl *N*-phthalimidodehydroalanine to give racemic functionalized Phes in air and water,[12a] and organoboron reagents were subsequently employed in this addition reaction.[12b,c] Chiral phosphine[13a−c] and chiral phosphite[13d,e] ligands have also been used in enantioselective reactions to attain high asymmetric induction. Rh catalysts with chiral diene ligands have recently been shown to have high levels of catalytic efficiency and enantioselectivity in conjugate addition reactions involving a variety of β-substituted unsaturated substrates.[14] While the use of chiral Rh−diene catalysts has evolved into an attractive approach for producing adducts that contain a β stereogenic center, their catalytic reactivity for the in situ generation of α chirality via the enantioselective protonation of an (oxa-α-allyl)rhodium[15] species remains a challenging goal.[16,17] Herein we report the use of Rh−chiral diene catalysts for the rapid synthesis of chiral functionalized Phes via the conjugate addition of arylboronic acids to dehydroalanines.

In initial experiments, we investigated the asymmetric addition of phenylboronic acid (**2a**) to dehydroalanines **1** employing a catalyst prepared in situ from $[RhCl(C_2H_4)_2]_2$ and the chiral diene ligand **L1a**[18,19] (Scheme 1). Addition reactions of methyl (**1a**) and isopropyl 2-acetylamidoacrylate (**1b**) reached completion in 24 h to provide **3aa** and **3ba** in 61% yield with 39% ee and 48% yield with 63% ee, respectively. While we anticipated that increasing the bulk of the ester group would enhance asymmetric induction, the desired product was not produced when the corresponding *tert*-butyl ester substrate (**1c**) was used. An encouraging result, however, was obtained when dehydroalanine **1f** bearing a *tert*-

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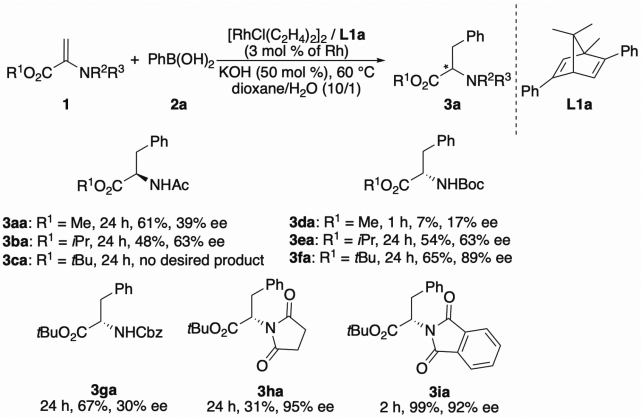
Scheme 1. Optimization of Reaction Conditions (I)[a]



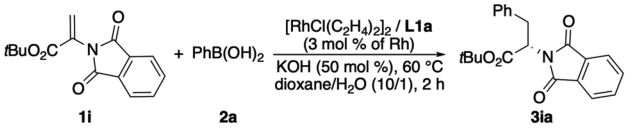
[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol, 3.0 equiv), $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), **L1a** (3.6 mol %), aqueous KOH (1.0 M, 0.1 mL, 0.5 mmol), and 1,4-dioxane (1.0 mL). Isolated yields are reported. The ee values were determined by HPLC analysis.

butyl ester and an *N*-Boc substituent was used, supplying **3fa** in 65% yield with 89% ee under identical reaction conditions. The presence of the *N*-protecting group appears to be crucial for the selectivity of the reaction, as evidenced by the formation of **3fa**, **3ga**, **3ha**, and **3ia**. Further investigation revealed that **3ia** was obtained in 99% yield with 92% ee within 2 h, leading to further optimization of the reaction parameters with the *N*-phthalimido-substituted substrate **1i**.

Varying the reaction conditions with respect to solvents, basic additives, and the proton source (Table 1, entries 1−6) in the presence of Rh/**L1a** (3 mol %) showed an effect on the enantioselectivity of **3ia**, with a combination of dioxane, with KOH, and H_2O giving the best yield and ee.[20] The corresponding α-deuterated product **3ia-*d*** (D/H > 20:1) was obtained in 97% yield with 87% ee when H_2O was replaced with D_2O in the addition of **2a** to **1i**, providing clear evidence of a tandem 1,4-addition/enantioselective protonation sequence (entry 7). Substituting the in situ-generated Rh catalyst for preformed $[RhOH(\mathbf{L1a})_2]_2$ increased the reaction rate, although it resulted in a slight decrease in ee (entry 8). Additional studies indicated that the catalysts derived from **L1a−f** had similar reactivities and selectivities, furnishing **3ia** in 90−99% yield with 88−92% ee. The use of chiral bicyclo[2.2.2]octadiene ligands **L2** and **L3** afforded **3ia** in 91% yield with −93% ee and −82% ee, respectively, although no reaction occurred when the chiral bicyclo[3.3.0]octadiene ligand **L4** and chiral sulfoxide−olefin hybrid ligand **L5** were used. The comparable catalytic reactivity and stereoselectivity of ligand **L2** relative to ligand **L1a** permitted direct access to **3ia** with the opposite chirality.

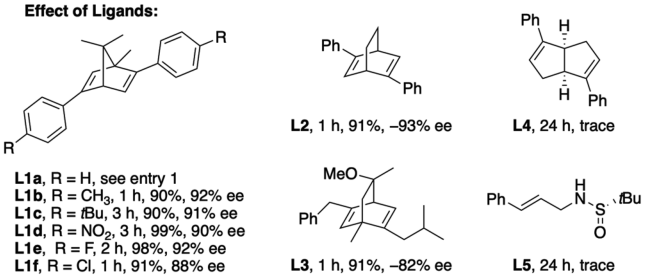
The scope of arylboronic acids **2** was subsequently investigated under the optimized conditions as indicated in Table 1, entry 1 in the addition reaction with dehydroalanine **1i** (Scheme 2). Arylboronic acids containing electron-rich (**2b−d**), electron-neutral (**2e−h**), and extended π or conjugated substituents (**2i−k**) were typically well-tolerated, providing adducts **3ib−ik** in 45−99% yield with 63−95% ee. The presence of an *ortho* substituent, however, in the cases of 2-tolylboronic acid (**2g**) and 1-naphthylboronic acid (**2j**) had an adverse effect on the formation of adducts **3ig** and **3ij**. Arylboronic acids substituted with electron-withdrawing groups participated successfully in the addition reaction to

Table 1. Optimization of Reaction Conditions (II)[a]



entry	variation from the standard conditions	yield (%)	ee (%)
1	none	99	92
2	THF instead of dioxane	97	86
3[b]	toluene instead of dioxane	88	90
4	MeOH instead of dioxane	80	75
5[b,c]	Et_3N instead of KOH	68	88
6[b]	Et_3N instead of KOH, guaiacol instead of H_2O	trace	N.D.[d]
7[f]	D_2O instead of H_2O	97	87
8[c,e]	$[Rh(OH)\mathbf{L1a}]_2$ instead of $[RhCl(C_2H_4)_2]_2$/ **L1a**	99[c]	90

[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol, 3.0 equiv), $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), **L1a** (3.6 mol %), aqueous KOH (1.0 M, 0.1 mL, 0.5 equiv), and 1,4-dioxane (1.0 mL). Isolated yields are reported. The ee values were determined by HPLC analysis. [b]24 h. [c]H_2O (0.1 mL) was added. [d]Not determined. [f]**3ia-*d*** was obtained with D/H > 20:1. [e]0.5 h.



form optically active Phes (**3il−it**) in 79−99% yield with 84−92% ee. The newly formed chiral center was unambiguously determined to have the *S* configuration by single-crystal X-ray crystallography analysis of the adduct **3ip**. Alkenylboronic acids (**2u** and **2v**) were also found to be good reaction partners in this enantioselective approach to access the corresponding adducts (**3iu** and **3iv**). In addition to *N*-phthalimidodehydroalanine **1i**, the scope of the reaction for the *N*-Boc counterpart **1f** as a substrate with various arylboronic acids was also evaluated (Scheme 3). Even though the corresponding adducts were smoothly produced, the resulting yields and selectivities were somewhat lower.

On the basis of the observed results, a plausible reaction pathway is proposed (Scheme 4). The initial step in the reaction is the generation of the active **L1a**Rh(OH) complex **A** by treatment of **L1a**RhCl with aqueous KOH. Complex **A** activates phenylboronic acid **2a** to yield the putative phenylrhodium complex **B** (Scheme 4). As illustrated in Figure 2, the results of DFT calculations on complex **C** formed from complex **B** and **1i** revealed that the phenyl addition proceeds preferentially through the *si* face (**4b**). While the conjugate addition step yields no chiral C−C bond, the presence of the bulky *tert*-butyl ester group in transition structure **4b** leads to the selective formation of the transient (*Z*)-rhodium enolate **D**, which undergoes *re*-face protonation to yield (*S*)-**3ia** with the regeneration of complex **A**. A primary kinetic isotope effect (KIE) of 1.5 was determined when H_2O was replaced with a 1:1 mixture of H_2O and D_2O, suggesting

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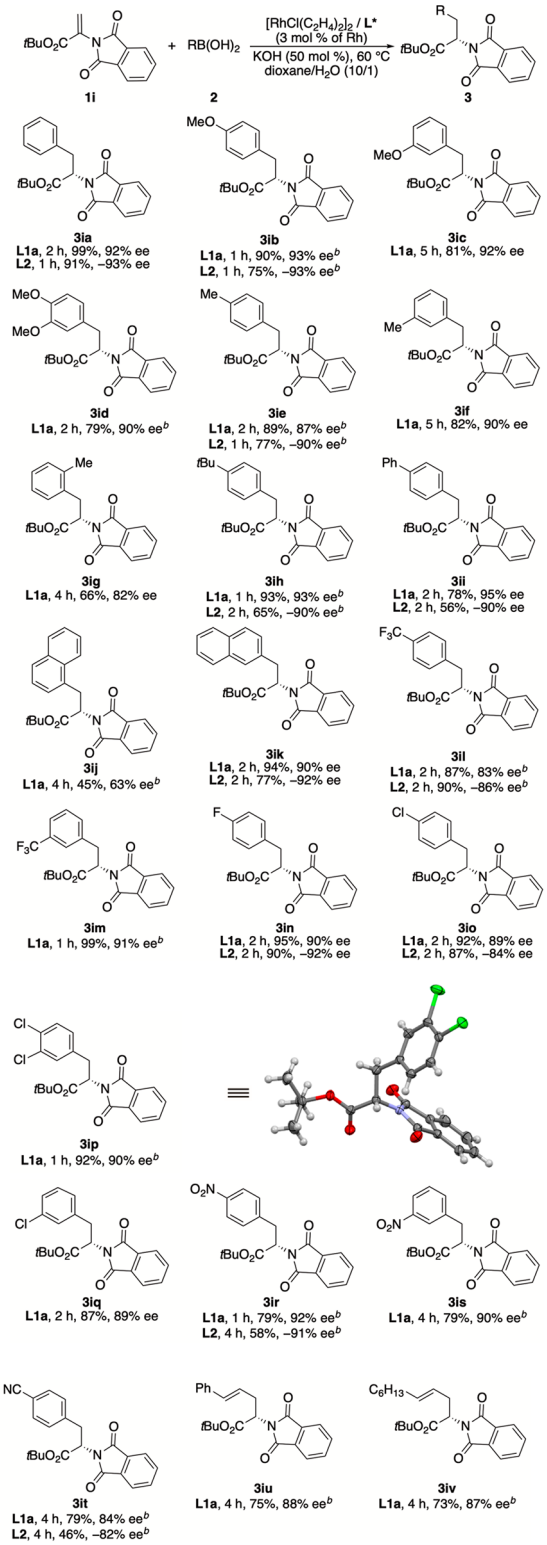
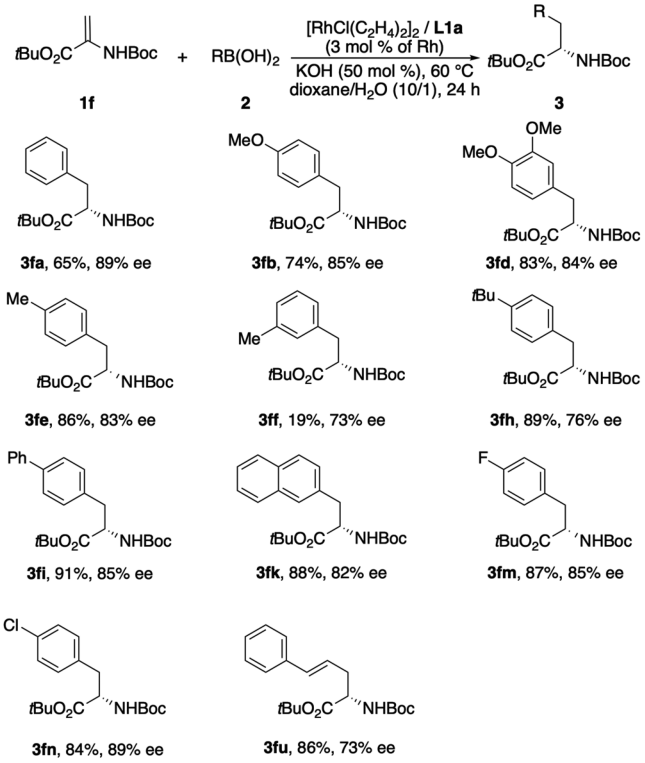
Scheme 2. Scope of Boronic Acid Nucleophiles[a]



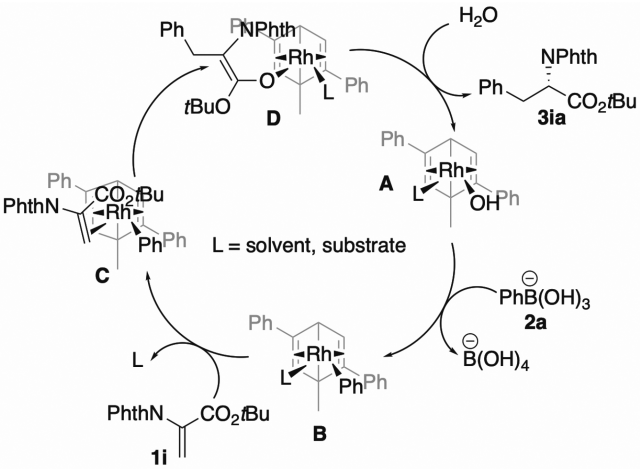
[a]Reaction conditions: **1i** (0.2 mmol), **2** (0.6 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), ligand **L** (3.6 mol %), and KOH (0.5 equiv) in dioxane (1.0 mL). Isolated yields are reported. The ee values were determined by chiral HPLC analysis. [b]0.4 M.

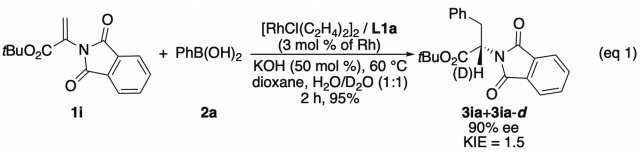
Scheme 3. Reaction of Arylboronic Acids with Dehydroalanine 1f[a]



[a]Reaction conditions: **1f** (0.2 mmol), **2** (0.6 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), ligand **L1a** (3.6 mol %), and KOH (0.5 equiv) in dioxane (1.0 mL). Isolated yields are reported. The ee values were determined by chiral HPLC analysis.

Scheme 4. Proposed Reaction Pathway





that the rate-determining step involves a C−H or C−D bond-forming/breaking process[21] (eq 1).

No reduction in catalytic reactivity and selectivity was observed when the asymmetric reaction of **3ia** was carried out on a gram scale (Scheme 5). The ensuing hydrolysis in aqueous HCl furnished (*S*)-phenylalanine hydrochloride (**5**) in

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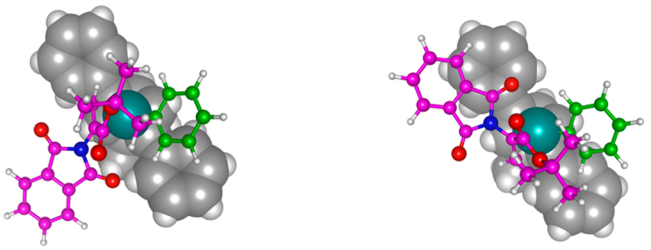
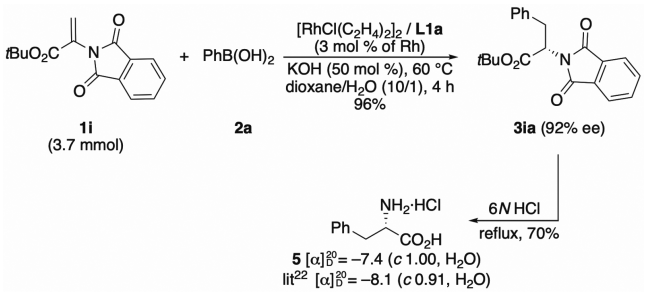


4a +2.1 kcal mol^{-1} **4b** +0.0 kcal mol^{-1}

Figure 2. DFT-optimized transition structures for the phenylation step with **1i**.

Scheme 5. Gram-Scale Synthesis of α-Amino Acid Salt 5



70% yield.[22] This approach was also useful for the preparation of known precursors for the synthesis of levodopa[23] and the SDZ NKT 343[3] from adducts **3id** and **3ik**, respectively.

In summary, the facile synthesis of highly enantioselective functionalized phenylalanine derivatives via the Rh(I)-catalyzed asymmetric arylation of dehydroalanine is reported. This method tolerates a variety of aryl- and alkenylboronic acids as prenucleophiles and *N*-phthalimido (**1i**) and *N*-Boc (**1f**) substituted dehydroalanines as electrophiles, affording addition products in up to 99% yield with 95% ee in the presence of a 3 mol % loading of a Rh(I) catalyst under mild reaction conditions. The two catalysts derived from **L1a** and **L2** exhibited similar levels of catalytic activity and stereoselectivity to allow access to *R*- and *S*-configured functionalized Phe derivatives, respectively. The synthetic application of this method was exemplified in a gram-scale synthesis of (*S*)-phenylalanine hydrochloride.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03666.

Experimental procedures, additional reaction condition screening tables, complete characterization data, HPLC chromatograms and NMR spectra (PDF)

Accession Codes

CCDC 1959338 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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