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Synthesis of Proline Analogues via Rh-Catalyzed Asymmetric Conjugate Addition

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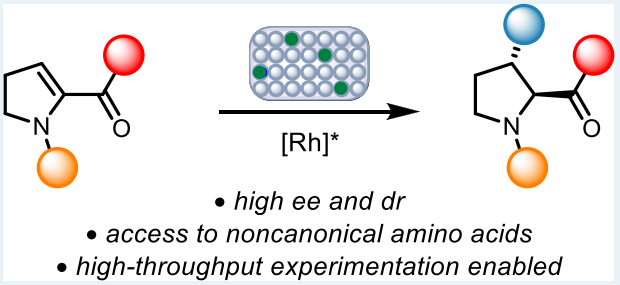
ABSTRACT: An enantio- and diastereoselective Rh-catalyzed conjugate addition reaction for the synthesis of proline analogues is reported. A high-throughput experimentation campaign was used to identify an efficient chiral catalyst which was able to afford the desired products in high yield and with high levels of diastereo- and enantioselectivity. This method was used to afford a range of 3-substituted proline derivatives from readily available dehydroproline electrophiles and boronic acid nucleophiles.



KEYWORDS: *rhodium, 1,4-addition, high-throughput experimentation, proline, unnatural amino acids*

The incorporation of noncanonical amino acids into peptides and proteins can alter a variety of physical and biochemical properties, thus influencing the structure and function of the peptide or protein itself.[1] The ability to alter these parameters has become of importance to biomedical fields in recent years with the increase of nonsmall molecule modalities including peptides, peptidomimetics, antibodies, and hybrid molecules as therapeutics.[2] Through the incorporation of non-native amino acid building blocks, one can introduce structural diversity, influence function, and introduce drug-like properties to chemical matter within these less traditional modality classes. Among the amino acids, proline offers unique utility due to its pyrrolidine backbone that is capable of forming a tertiary amide bond upon incorporation into peptides, which results in conformational rigidity that can alter secondary protein structure.[3] Consequently, analogues of proline have been used to impart changes in function and physiochemical properties of peptides and other biomolecules.[4]

Other than acting as proline replacements, pyrrolidine-based heterocycles are ubiquitous as structural constituents of natural products,[5] organocatalysts,[6] and small molecules.[7] *trans*-3-Substituted proline frameworks in particular have been utilized in the discovery and development of CDK9,[8] Rho Kinase,[9] and peptide-base HCV protease[10] inhibitors (Figure 1). Thus, the expedient, robust, and stereoselective synthesis of proline derivatives are of interest to the synthetic community and biomedical fields alike.

Whereas racemic syntheses of *trans*-3-substituted proline have been demonstrated,[11] only few enantioselective routes exist.[12] Such methods can provide reliable stereocontrol; however, multiple functional group interconversions are required to isolate the desired deprotected amino acid from a more functionalized scaffold. These sequences become prohibitively long when a large set of building blocks with

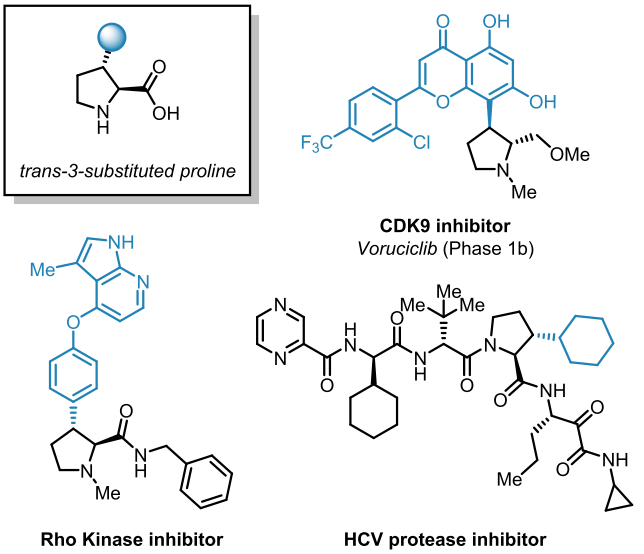


Figure 1. Inhibitors containing *trans*-3-substituted proline scaffolds.

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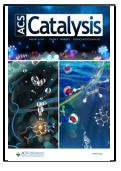
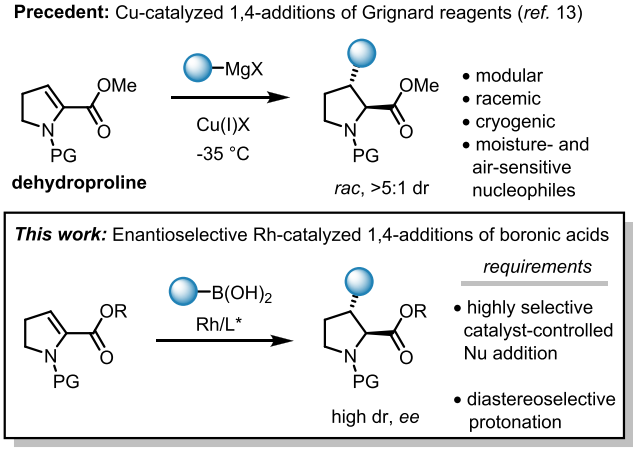


variable 3-position substitutions are desired, such as for structure activity relationship (SAR) exploration in the context of a medicinal chemistry program. It was in this vein that we sought to develop an enantioselective, direct, and modular synthesis of *trans*-3-substituted prolines.

We were encouraged by the reported Cu-catalyzed addition of Grignard reagents to dehydroproline (Scheme 1).[13] This

Scheme 1. Metal-Catalyzed Conjugate Addition Reactions with Dehydroproline Derivatives

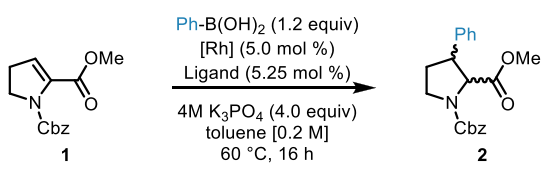


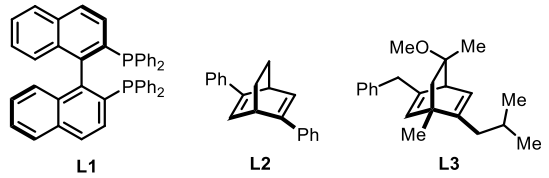
method allows for the synthesis of the desired scaffolds through the diversification of a starting material that is readily available from L-proline, albeit in racemic fashion or modest ee (70%) with chiral auxiliary. Equipped with the knowledge that dehydroproline electrophiles are reactive in metal-catalyzed 1,4-addition reactions, we sought to develop an enantioselective variation of this process to access the desired products and address the limitations of prior art. Herein we report a Rh-catalyzed asymmetric conjugate addition (Rh-ACA) of commercially available and shelf-stable organoboron reagents to prochiral electrophiles toward this effort (Scheme 1).

Rhodium complexes are commonly used as catalysts for enantioselective 1,4-addition.[14] They can undergo transmetalation under mild conditions with readily commercially available and air-stable organoboron reagents which precludes the need to use sensitive and functional group intolerant organometallic reagents. Despite Rh-ACA's application to an impressive number of substrates, to the best of our knowledge its use for the synthesis of enantioenriched α-amino acids has been limited to deyhydroalanine derivatives.[15] Dehydroproline starting materials offer additional complications as both the α and β-carbons are prochiral, and therefore, contiguous stereocenters need to be set with control upon 1,4-addition in order to achieve both a diastereo- and enantioselective transformation. Although there are some examples of Rh-ACA on 5-membered exocyclic Michael acceptors, achieving high levels of enantio- and diastereoselectivity are highly substrate dependent, and examples are limited to electron-deficient alkenes, highlighting the challenges of such an approach.[16] We began our investigations by first determining if an achiral Rh-catalyst could facilitate conjugate addition of a boronic acid to dehydroproline **1** (Table 1).

After investigating several achiral Rh-catalysts and reaction conditions, we found that 5 mol % $Rh(nbd)_2BF_4$ in toluene with aqueous base at 60 °C could catalyze the conjugate addition of phenylboronic acid to **1** to provide **2** as a 14:1 dr *trans:cis* mixture (Table 1, entry 1). We then turned to investigate chiral ligands commonly used in Rh-ACA to afford the enantioenriched product. Attempts to use (*R*)-BINAP (**L1**) with different rhodium catalysts resulted in 1:1 dr, and moderate enantioinduction was observed (entries 2 and 4).[3,17,18] Chiral diene ligands could be used to afford a stereoselective reaction but required the use of a Rh-catalyst that did not give a background reaction (Table 1, entry 3). Using Ph-bod (**L2**)[19] resulted in improved yield and enantioselectivities, however, low diastereoselectivity slightly favoring the desired *trans*-isomer was observed (entry 5). DOLEFIN[20] (**L3**) gave slightly improved dr in low yield and low enantioselectivity (entry 6). Since these initial results showed that catalyst and ligand choice can have a dramatic effect on the diastereo- and enantiomeric outcome of the transformation, we aimed to survey a broader scope of ligands. Because of the abundance of bisphosphine ligands with vastly different steric and electronic properties, many of which have been applied to other Rh-catalyzed transformations,[21] we began our study with different classes of these ligands. In order to examine a large array of ligands as quickly and efficiently as possible, we pursued a high throughput experimentation (HTE) campaign assessing 96 chiral bidentate phosphine ligands in parallel.[22] Analysis of the crude reaction mixtures with SFC informed on relative amounts, diastereomeric ratio,

Table 1. Preliminary Results[a]





entry	[Rh]	ligand	LCAP of **2** (%)	dr (*trans:cis*)	*ee* (%) (*trans*)	*ee* (%) (*cis*)
1	$Rh(nbd)_2BF_4$	-	94	14:1	-	-
2	$Rh(nbd)_2BF_4$	**L1**	52	1:1	66	96
3	$[Rh(C_2H_4)_2Cl]_2$	-	<5	-	-	-
4	$[Rh(C_2H_4)_2Cl]_2$	**L1**	54	1:1	69	96
5	$[Rh(C_2H_4)_2Cl]_2$	**L2**	78	2.2:1	89	91
6	$[Rh(C_2H_4)_2Cl]_2$	**L3**	17	3:1	47	nd

[a]Reactions were performed on 0.3 mmol scale. Liquid chromatography area percent (LCAP) determined by UPLC. dr and *ee* determined by SFC.

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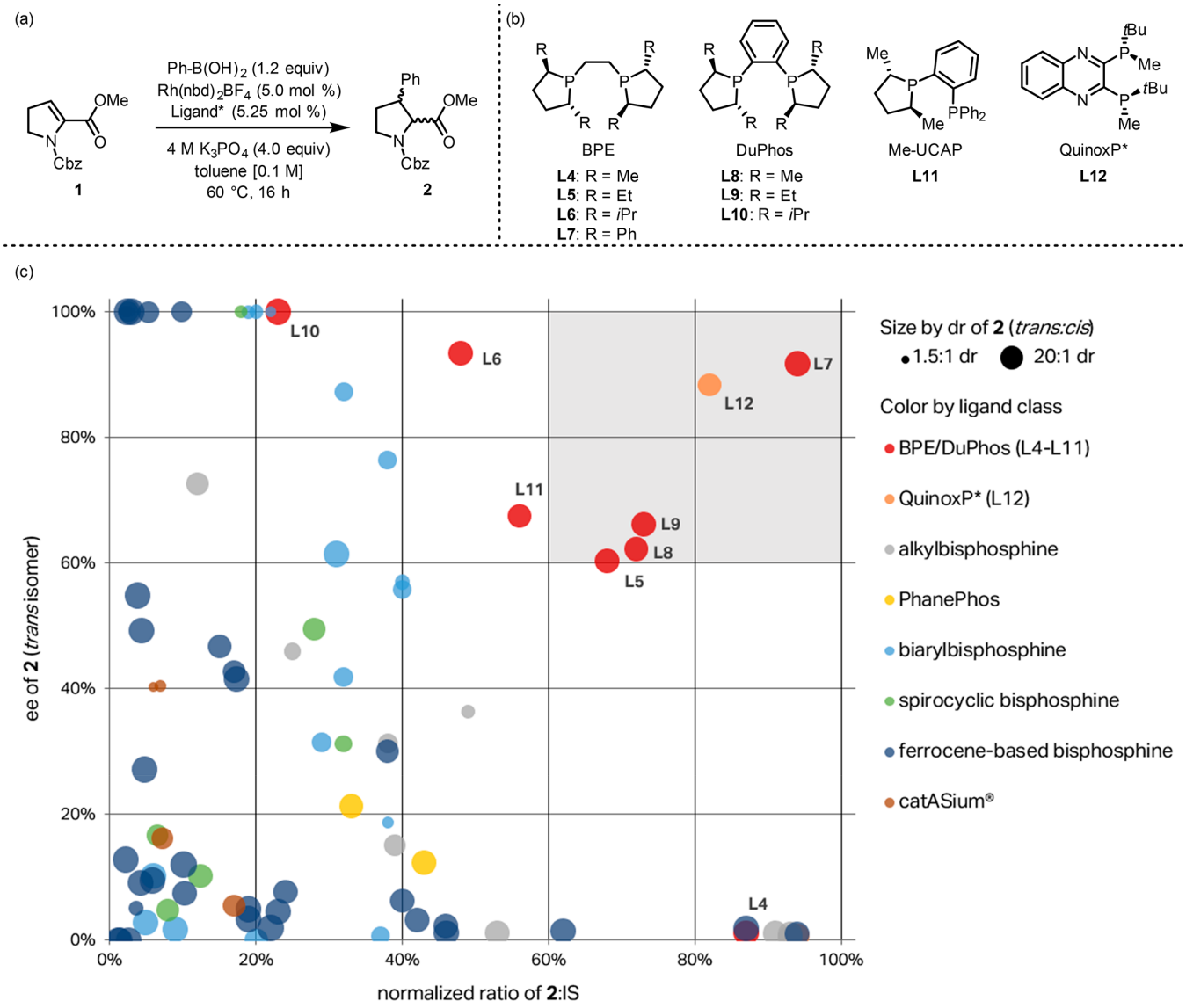

Figure 2. HTE screen of chiral bidentate phosphine ligands. (a) conditions used. (b) Hits from HTE screen. (c) results from HTE screen. Reactions were performed on 8 μmol scale. Ratio of **2**:internal standard (IS) was determined by integration of SFC peaks and normalized. ee and dr were determined by SFC. Alkylbisphosphines include ligands from the DIPAMP, BisP*, and miniPhos classes. Biarylbisphosphines include ligands from the BINAP, BIPHEP, Segphos, Garphos, and BINAM classes. Spirocyclic bisphosphines include ligands from the SDP and SKP classes. Ferrocene-based bisphosphines include ligands from the Josiphos, ferrolane, Walphos, JAFAphos, and Twinphos classes. See Supporting Information for details.

and enantioenrichment of the desired product. A summary of the HTE campaign is shown in Figure 2.

Ligands from several classes gave appreciable conversion to the desired product in varying levels of diastereo- and enantioselectivity, although only a few ligands were able to afford the desired product in >60% yield and >60% *ee* (shaded region). With the bisphosphine ligands surveyed, the *trans* isomer was consistently observed to be the major diastereomer. Of the 96 ligands screened, the best performing ligands were from the BPE/DuPhos ligand class (Figure 2, **L4**–**L11**, shown in red).[23] P-Chiral ligand QuinoxP* (**L12**, shown in orange) also performed well, although it gave slightly diminished dr (13:1) compared with the BPE/DuPhos ligands (all >15:1 dr).[24] Within the BPE and Duphos class, increasing enantioselectivities were observed with increased steric bulk of the alkyl-R group at the expense of product yield. This trend is seen with Me-BPE (**L4**), Et-BPE (**L5**), and iPr-BPE (**L6**), as well as Me-Duphos (**L8**), Et-Duphos (**L9**), and iPr-Duphos (**L10**). Ph-BPE (**L7**)[25] was the best performing ligand overall, affording the *trans*-diastereomer of product **2** in high yield and >95% *ee*. Both enantiomers of this ligand are readily available, allowing for the synthesis of both D- and L-proline analogues depending on the enantiomer of ligand used. Moving forward, we used the commercially available Ph-BPE-Rh complex, which gave comparable results to that observed in our screen and precludes the need to complex metal and ligand, simplifying the reaction setup.[26] With the optimal catalyst in hand, we sought to optimize the reaction conditions (see Supporting Information) and explore the substrate scope (Table 2).

We found the reaction to be general, and a variety of aromatic boronic acid nucleophiles were reactive under the reaction conditions to give the desired products in good yield with high dr and *ee*. The reaction could also be performed on

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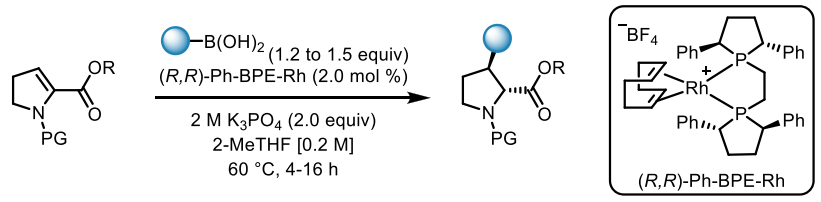
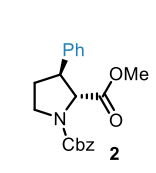
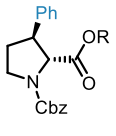
Table 2. Substrate Scope[g]

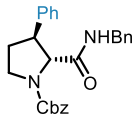




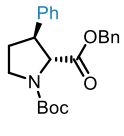
2
83%, 20:1 dr, 95% *ee*[a]
75%, 20:1 dr, 96% *ee*[b]
81%, 20:1 dr, 96% *ee*[c]
80%, 20:1 dr, 96% *ee*[d]



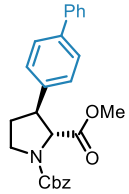
3 R = Et: 83%, 12:1 dr, 97% *ee*
4 R = *t*Bu: 65%[e] (46%)[f], 10:1 dr, >98% *ee*
5 R = Bn: 87%[e] (64%)[f], 17:1 dr, 96% *ee*



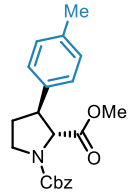
6, 94%
1.8:1 dr
>98% *ee* (*trans*)
>98% *ee* (*cis*)



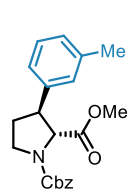
7, 78%[e] (62%)[f]
17:1 dr
96% *ee*



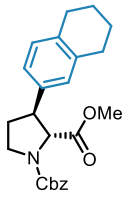
8, 81%
19:1 dr
95% *ee*



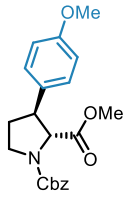
9, 84%
>20:1 dr
95% *ee*



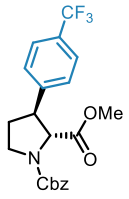
10, 79%
18:1 dr
95% *ee*



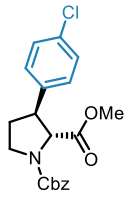
11, 79%
>20:1 dr
95% *ee*



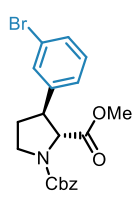
12, 50%
19:1 dr
96% *ee*



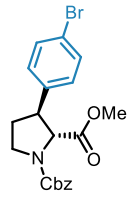
13, 81%
17:1 dr
92% *ee*



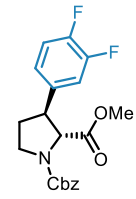
14, 73%
18:1 dr
96% *ee*



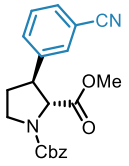
15, 66%[f]
19:1 dr
95% *ee*



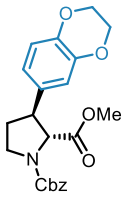
16, 74%
17:1 dr
96% *ee*



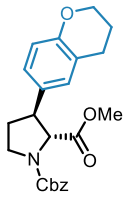
17, 57%[e] (49%)[f]
>20:1 dr
96% *ee*



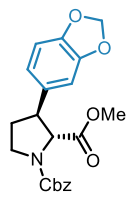
18, 48%
15:1 dr
93% *ee*



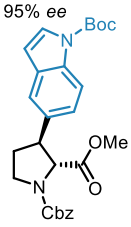
19, 59%
>20:1 dr
94% *ee*



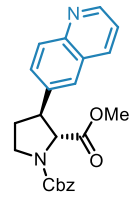
20, 56%
19:1 dr
95% *ee*



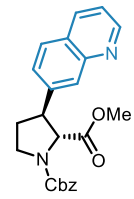
21, 50%
>20:1 dr
95% *ee*



22, 71%
>20:1 dr
96% *ee*

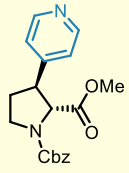


23, 37%
>20:1 dr
64% *ee*

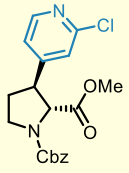


24, 32%
6:1 dr
70% *ee*

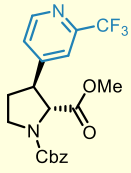
with pyridyl nucleophiles[g]



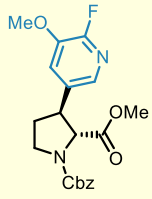
25, 34%
2:1 dr
4% ee (*trans*)
81% *ee* (*cis*)



26, 41%
1.5:1 dr
2% ee (*trans*)
83% *ee* (*cis*)

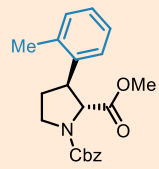


27, 44%
2.5:1 dr
53% *ee* (*trans*)
72% *ee* (*cis*)

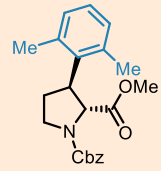


28, 22%
10:1 dr
90% *ee*

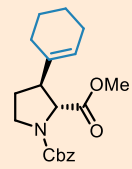
with $Rh(nbd)_2BF_4$[h]



rac-**29**, 85%
19:1 dr



rac-**30**, 67%
>20:1 dr



rac-**31**, 76%
10:1 dr

[g]Isolated yields of the diastereomeric mixtures are reported. dr determined by crude ^{1}H NMR (reported as *trans*:*cis* ratio). *ee* determined by SFC after purification. *ee* of only the major diastereomer is reported unless otherwise shown. Reactions were performed on 0.3−0.5 mmol scale. [a]4.0 mmol (1 g scale) with 0.5 mol % catalyst. [b]R-BF_3K used instead of R-$B(OH)_2$. [c]R-B(pin) used instead of R-$B(OH)_2$. [d]R-B(neo) used instead of R-$B(OH)_2$. [e]Collected as mixture of product and remaining starting material. [f]Yield after HPLC purification. [g]Cs_2CO_3 (2.0 equiv), dioxane [0.2 M], H_2O (10.0 equiv), 100 °C. [h]Achiral catalyst conditions: $Rh(nbd)_2BF_4$ (3.0 mol %), 2 M K_3PO_4 (2.0 equiv), dioxane [0.2 M], 60 °C.

gram-scale with 0.5 mol % catalyst while still maintaining high efficiency. Under optimized conditions, different organoboron reagents such as the boronic acid, potassium trifluoroborate salt, and pinacol and neopentyl esters were all competent nucleophiles to afford **2** in high yield and selectivity. The reaction was tolerant to substitution on the ester, although slight variations in yield, dr, and ee were observed to give products **3**, **4**, and **5**. Replacing the ester for a benzylamide was also tolerated to afford **6**, indicating the potential for this method to be used toward the late stage-functionalization (LSF) of peptides.[27]

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Nitrogen protecting groups such as CBz and Boc (**7**) are tolerated; however, a *N*-nosylate-protected substrate did not afford product (not shown). Simple carbon-substituted benzene rings afforded products **8**, **9**, **10**, and **11** all with good selectivity. The reaction was successful with functionalized boronic acids as well. Using *p*-OMe and *p*-CF_3-substituted phenylboronic acids yielded **12** and **13**. Organoboron nucleophiles bearing functional group handles such as halides or nitriles, allowing for further elaboration, were also tolerated in the reaction to afford products **14**, **15**, **16**, **17**, and **18**. Heterocyclic boronic acids also performed well in the reaction to afford compounds **19**, **20**, **21**, and **22**, although using quinolinyl nucleophiles resulted in lower yields and products with lower ee (**23** and **24**).

Under standard reaction conditions, however, reactivity was not observed with pyridyl organoboron reagents. Because these are important structural motifs in the context of pharmaceutically relevant chemical matter, we felt it was important to attempt to engage these nucleophiles in the reaction. We found more forcing conditions (dioxane as solvent, heating to 100 °C) were necessary for product formation. Increased yield was observed with increasing the boronic acid loadings to 3 equiv, using Cs_2CO_3 as base, and lowering the H_2O loading to 10 equiv. With these modifications to the reaction protocol, we were able to obtain products **25**−**28** in synthetically useful yields. In certain cases, with the 4-pyridyl substituted nucleophiles, low levels of diastereo- and enantioinduction were observed (**25**, **26**, and **27**).[28] Despite the diminished selectivity, these products are challenging to prepare otherwise.

Sterically encumbered substrates (**29** and **30**) gave low yields under our standard reaction conditions because of consumption of the organoboron reagent in an undesired protodeboronation pathway.[14a] Whereas background reactions can cause protodeboronation, a competing protonation of a Rh(I)-aryl intermediate after transmetalation may contribute to the composition as well. With simple hydrocarbon boronic acid nucleophiles, we observed that protodeboronation only occurred in the presence of the Ph-BPE-Rh catalyst. This Rh-catalyzed protodeboration pathway becomes more competitive with sterically bulky substrates, likely because of the substrate (**1**) being unable to bind to a more hindered Rh-center. Higher yields of racemic mixtures of product were observed with these substrates with $Rh(nbd)_2BF_4$ to give the results shown. The reaction with cyclohexenyl boronic acid to give **31** was also low yielding under the optimized reaction conditions, but good yield of the racemate was obtained with the achiral catalyst.[29]

To gain a better understanding of the high diastereoselectivities observed in the reaction, several additional experiments were performed. When single stereoisomer *cis*-**2** is subjected to the standard reaction conditions, *trans*-**2** is not detected, indicating that epimerization is not responsible for the observed diastereomeric ratios. DFT calculations show the difference between the ground state energies of *trans*-**2** and *cis*-**2** (ΔG) is approximately 0.18 kcal/mol, equating to a 1.3:1 dr at 60 °C (see Supporting Information). Furthermore, when single stereoisomer *trans*-**2** is subjected to basic conditions, erosion of the diastereomeric ratio is observed, indicating that the diastereoselectivity seen in the catalytic transformation is kinetically driven.[30]

We have developed a highly stereoselective Rh-ACA for the modular synthesis of *trans*-3-aryl proline derivatives, a chemical space which is difficult to access efficiently with current methods. High-throughput experimentation was used to screen a large array of chiral ligands that identified a highly efficient and selective catalyst, and the optimized conditions were general, achieving good to excellent ee and drs for a variety of substrates. This transformation was suitable for the modification of a variety of dehydroamino ester derivatives, showcasing the robustness of the reaction and its potential for late-stage functionalization of complex biological targets, which is currently under further exploration. This method can be used as a reliable synthetic tool for the synthesis of analogues of both L- and D-amino acids and other substituted pyrrolidine scaffolds to enable the exploration of novel chemical matter.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c04648.

Instrumental information, optimization details, detailed experimental procedures, absolute stereochemistry determination, and product characterization (PDF)

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(29) Use of chiral diene ligand **L2** for the synthesis of **30** and **31** resulted in lower conversions and products with low dr.

(30) When single stereoisomer *trans*-**2** is subjected to 1 equiv of LiOMe in MeOH/THF at 60 °C for 5 h, approximately 35% saponification is observed, and the resulting 65% of material has epimerized to give 4.2:1 *trans*-**2**:*cis*-**2**.

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