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Rhodium-Catalyzed Enantioselective Addition of Boronic Acids to *N*-Benzylnicotinate Salts

Christian Nadeau ,*[†] Sara Aly,[†] and Kevin Belyk[‡]

[†]Department of Process Research, Merck Frosst Centre for Therapeutic Research, 16711 Route Trans-Canadienne, Kirkland, Québec, Canada H9H 3L1

[‡]Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065, United States

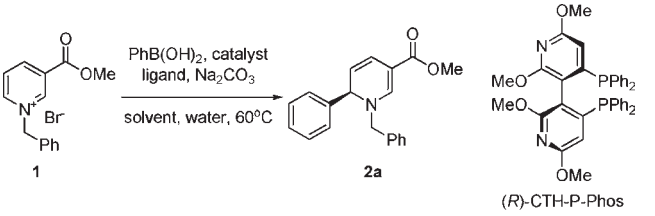
Supporting Information

ABSTRACT: The highly enantioselective catalytic asymmetric addition of aryl and alkenylboronic acids to *N*-benzylnicotinate salt **1** is described. The dihydropyridine **2** reaction products can be converted to synthetically useful piperidines. Application of the methodology to the preparation of enantioenriched quaternary chiral centers is also discussed.

Substituted piperidine motifs are found in numerous biologically active molecules and have been used for many pharmaceutical applications.[1] Recent examples of enantioenriched substituted piperidines and dihydropyridines synthesis included enantioselective reduction of pyridines,[2] organocatalytic cyclizations,[3] annulation of imines with allenes,[4] cycloisomerization of aziridinyl propargilic esters,[5] and enantioselective alkylation of piperidine.[6] Diastereoselective nucleophilic additions to pyridinium salts have successfully led to a variety of enantioenriched piperidine motifs.[7,8] However catalytic enantioselective examples of the reaction are more scarce. To date, only three reports using alkynes,[9] cyanide,[10] and dialkylzinc[11] as nucleophiles have been described. Thiourea-catalyzed enantioselective addition of silylenol ether[12] and alkenylboronic acids[13] have also been described but only for activated isoquinolines and quinolines substrates.[14] Herein, we describe the first catalytic asymmetric addition of boronic acids to *N*-benzylnicotinate salts that can be conveniently prepared by alkylation of benzyl bromide with nicotinate esters.[7c]

Rhodium-catalyzed 1,4-conjugate enantioselective addition of boronic acids to activated alkenes is an important process in organic chemistry.[15] We envisioned that activating a nicotinate ester to the corresponding *N*-benzylnicotinate salt would allow an analogous reaction to take place. We initially investigated the reaction parameters at 60 °C using (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) as ligand and were pleased to see that high % ees of dihydropyridine **2a** were obtained (Table 1). At this temperature we were able to avoid ester hydrolysis of both starting material and product and ensure optimal reaction times. Solvents had an important impact on reaction yield with dioxane providing optimal results (entry 1−3).[16] Other rhodium sources were evaluated but led to lower yields or enantioselectivity (entries 4−5). The presence of base is critical for the reaction since reaction without sodium carbonate showed no conversion (entry 6).

Table 1. Reaction Conditions Optimization for the Enantioselective Addition of Phenylboronic Acid to *N*-Benzylnicotinate salt 1[a]



entry	solvent	ligand	catalyst	% yield[b]	% ee[c]
1	2-Me-THF	(*R*)-BINAP	$Rh(COD)_2BF_4$	43	93
2	toluene	(*R*)-BINAP	$Rh(COD)_2BF_4$	78	90
3	dioxane	(*R*)-BINAP	$Rh(COD)_2BF_4$	82	93
4	dioxane	(*R*)-BINAP	$[Rh(OH)(COD)]_2$	74	93
5	dioxane	(*R*)-BINAP	$Rh(acac)(C_2H_4)_2$	6	45
6[d]	dioxane	(*R*)-BINAP	$Rh(COD)_2BF_4$	0	0
7[e]	dioxane	(*R*)-CTH-P-Phos	$Rh(COD)_2BF_4$	73[f]	99

[a] Reaction conditions: $PhB(OH)_2$ (2.5 equiv), catalyst (5 mol %), ligand (5 mol %), Na_2CO_3 (2 equiv), solvent (10 mL/g), H_2O (1 mL/g). [b] Determined by HPLC analysis. [c] Determined by chiral HPLC analysis. [d] No base was used. [e] 0.5 mL/g H_2O was used. [f] Isolated yield.

An evaluation of more than 120 ligands for this transformation showed that axial chiral bisphosphines generally gave higher enantioselectivities of dihydropyridine **2a** over P,*N*-[17] and Trost *N*,*N*-based ligands[18] with CTH-P-Phos[19] giving the best enantioselectivity (99% ee). The water content (0.5 mL/g) in the reaction was important for reproducibility. Using optimized conditions we were able to isolate **2a** in 73% yield and 99% ee (entry 7).

The boronic acids scope for this transformation was investigated using the optimized reaction conditions (Table 2).[20] For all examples we found that regioselectivity toward the 6-substituted **2** over the 4-substituted regioisomer was >20:1 by ^1H NMR analysis of the crude reaction mixtures. The reaction proceeded with *p*- and *o*-alkyl-substituted aryl boronic acids (entries 2 and 3). Both electron-donating and -withdrawing substituents on the

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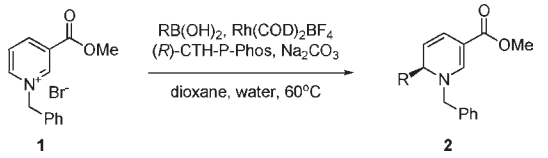
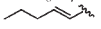
Table 2. Enantioselective Addition of Boronic Acids to *N*-Benzylnicotinate salt 1[a,b]

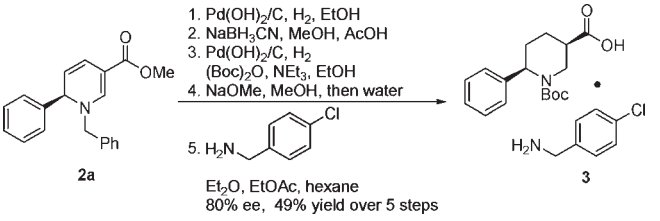


1 2

entry	R	product	% yield[c]	% ee[d,e]
1	C_6H_5	**2a**	73	99
2	4-MeC_6H_4	**2b**	83	97
3	2-MeC_6H_4	**2c**	70	84
4	4-MeOC_6H_4	**2d**	77	95
5	4-MeO_2CC_6H_4	**2e**	68	97
6	4-MeCOC_6H_4	**2f**	71	96
7	4-O_2NC_6H_4	**2g**	23	94
8	4-ClC_6H_4	**2h**	64	99
9	4-FC_6H_4	**2i**	69	99
10		**2j**	40	83

[a] Reaction conditions: $RB(OH)_2$ (2.5 equiv), $Rh(COD)_2BF_4$ (5 mol %), (*R*)-CTH-P-Phos (5 mol %), Na_2CO_3 (2 equiv), Dioxane (10 mL/g), H_2O (0.5 mL/g). [b] For all examples regioselectivity was >20: 1, as determined by ^{1}H NMR of the crude reaction mixture. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] The absolute configurations of **2** except for **2a** were assigned by analogy with entry 1.

Scheme 1. Enantioselective Synthesis of Phenyl-Substituted *N*-Boc Piperidine Acid Salt 3

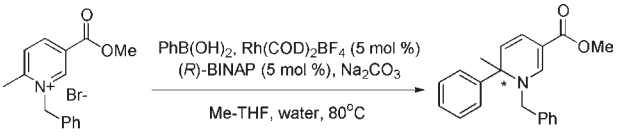


aromatic ring afforded high enantioselectivities (94−97% ee) with the nitro group leading to lower isolated yield (entries 4−7). Chloro- and fluoro-substituted aryl boronic acids afforded the corresponding dihydropyridines in 99% ee (entries 8−9). An alkenyl boronic acid also reacted under the reaction conditions and afforded the dihydropyridine in 40% yield and 83% ee (entry 10).

Dihydropyridine **2a** can be converted to the synthetically useful *N*-Boc piperidine acid salt **3** in a straightforward sequence (Scheme 1). Hydrogenation of the less substituted double bond led to the vinylogous carbamate that was converted to the *N*-benzyl piperidine ester using sodium cyanoborohydride. The benzyl protecting group was cleanly replaced by a Boc group under hydrogenolysis conditions in the presence of Boc_2O.[21] Subsequent base treatment led to epimerization of the ester group toward the equatorial position and hydrolysis to the corresponding acid. Salt formation allowed rejection of the minor diastereoisomer to afford piperidine acid salt **3**.[22] These piperidine scaffolds could be useful for the preparation of CB_1 modulators[23] and β-amyloid peptide production inhibitors.[24]

The absolute configuration of dihydropyridine **2a** was determined to be *R* by vibrational circular dichroism analysis (VCD),

Scheme 2. Enantioselective Addition of Phenylboronic Acid to 6-Methyl-*N*-benzyl Methylnicotinate Salt 4



and ^{1}H NMR NOE experiments of **3** confirmed the cis relationship of the two piperidine ring substituents.[25]

Finally, we explored the addition on 6-methyl-*N*-benzyl methylnicotinate salt **4**. In this case, the reaction proceeded in Me-THF using (*R*)-BINAP as ligand. We were pleased to find that the addition was regioselective for addition at the more sterically hindered 6-position over the less hindered 4-position of the nicotinate salt to yield **5** in 65% ee (Scheme 2).[26]

The rhodium-catalyzed construction of quaternary carbon stereocenters from the addition of boron nucleophiles to maleimides,[27] enones,[28] and unsaturated pyridylsulfones[29] has been recently reported. However, to the best of our knowledge, this is the first example of a regio- and enantioselective addition to a pyridinium salt that favors the formation of a quaternary over a tertiary chiral center.

In conclusion, we have developed the first catalytic enantioselective boronic acid addition to *N*-benzylnicotinate salts. A variety of 6-substituted dihydropyridines were isolated in 23−83% yields and 83−99% enantioselectivities. Synthetically useful piperidines can be obtained from the reaction product. Preliminary results suggest that the strategy can also be used to prepare enantioenriched quaternary chiral centers.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization, analysis of enantioselectivities, VCD spectra and computation. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
christian.nadeau01@gmail.com

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(20) Phenylboronic acid addition to *N*-benzylpyridinium bromide salt led to decomposition.

(21) No hydrogenolysis of the enantioenriched *N*-benzyl bond was observed.

(22) Erosion of enantiomeric purity from **2a** (99% ee) to **3** (80% ee) is presumably due to partial migration of the less substituted double bond into conjugation with the aromatic ring during the first hydrogenation step. Hydrogenation of the resulting conjugated trisubstituted double bond would lead to racemic material. For a discussion about double bond migration during hydrogenation reactions see: (a) Smith, G. V.; Roth, J. A.; Desai, D. S.; Kosco, J. L. *J. Catal.* **1973**, *30*, 79. (b) Mitsui, S.; Gohke, K.; Saito, H.; Nanbu, A.; Senda, Y. *Tetrahedron* **1973**, *29*, 1523. (c) Augustine, R. L.; Yaghmaie, F.; Van Peppen, J. F. *J. Org. Chem.* **1984**, *49*, 1865.

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