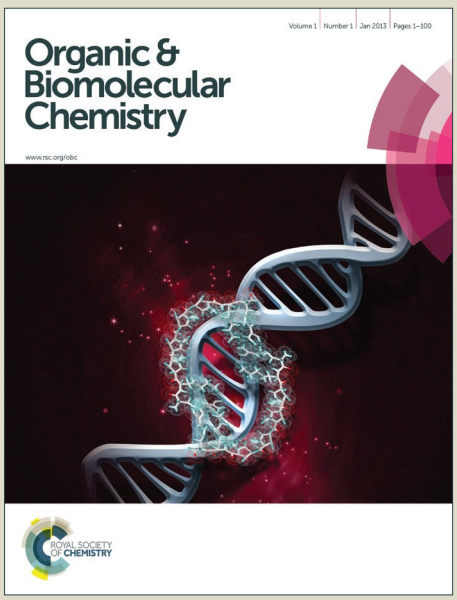
Organic & Biomolecular Chemistry

Accepted Manuscript



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ARTICLE

Optimization and Multigram Scalability of a Catalytic Enantioselective Borylative Migration for the Synthesis of Functionalized Chiral Piperidines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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You-Ri Kim[a] and Dennis G. Hall[a*]

The development of new, efficient and economical methods for the preparation of functionalized, optically enriched piperidines is important in the field of drug discovery where this class of heterocycles is often deemed a privileged structure. We have optimized a Pd-catalyzed enantioselective borylative migration of an alkenyl nonaflate derivative of the simple precursor, *N*-Boc-4-piperidone. This anomalous borylation reaction lends access to a chiral optically enriched piperidinyl allylic boronate that can be employed in carbonyl allylboration and stereoselective cross-coupling to produce substituted dehydropiperidines related to numerous pharmaceutical agents. A systematic fine-tuning of reaction conditions revealed that diethyl ether and the green solvent cyclopentyl methyl ether are suitable reaction solvents providing the highest enantioselectivity (up to 92% *ee*) under a low catalyst loading of 3 mol%. Optimization of the aldehyde allylboration step led to higher yields with further solvent economy. The gram-scalability of the entire process was demonstrated under the reaction conditions that provide optimal atom-economy and efficiency.

Introduction

The presence of functionalized piperidine rings in the structure of numerous alkaloids coupled with their prevalence as components of pharmaceutical drugs contribute to the importance of these structures in organic and medicinal chemistry.[1] It has been suggested that the piperidine ring is the most common heterocyclic unit in the structure of commercial pharmaceutical agents.[2] The compounds depicted in Figure 1A represent a few selected examples from a multitude of piperidine-containing pharmaceutical agents and clinical candidates. Moreover, a great many classes of alkaloids embed a piperidine subunit, including iminosugars (Fig. 1B). Consequently, the development of new methods that enable an efficient and economical preparation of functionalized, optically enriched piperidines is an important challenge to be addressed for the field of drug discovery. Current methods for the stereoselective preparation of polysubstituted piperidines can be classified into three general synthetic approaches (Fig. 2).[3] Cyclization of a linear precursor may be effected by *N*-alkylation[4] or through a C–C bond forming process such as ring-closing metathesis (RCM) (Fig. 2A).[5] These unimolecular approaches employ a pre-functionalized acyclic substrate whose preparation usually requires a multistep sequence. More convergent approaches include [4+2] cycloadditions, which can feature different possible disconnections (Fig. 2B).[6] With these bimolecular approaches, however, the control of regio- and diastereoselectivity can be challenging and relatively few approaches exist for the catalytic control of enantioselectivity.[6] A third option consists in using a simple piperidine precursor, which can be desymmetrized in a single step to provide enantiomerically enriched product (Fig. 2C).[7] Alternatively, prochiral pyridine derivatives can be transformed into chiral dehydropiperidines.[8] Although these direct approaches are highly advantageous on the standpoint of step- and atom-economy, it is surprising that only a few methods exist for the desymmetrization of readily available piperidine precursors.

[a] *Department of Chemistry, 4-010 Centennial Centre for Interdisciplinary Science, University of Alberta, Edmonton, Alberta, Canada, T6G 2G2; E-mail: dennis.hall@ualberta.ca*

Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra of new compounds and experimental procedures. See DOI: 10.1039/x0xx00000x

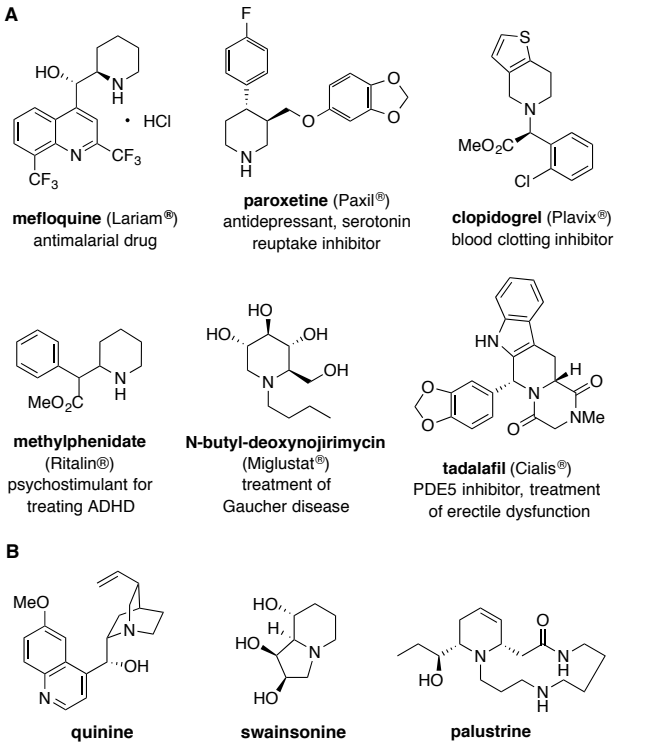


Figure 1. Examples of piperidine-containing (A) pharmaceutical drugs and (B) natural products

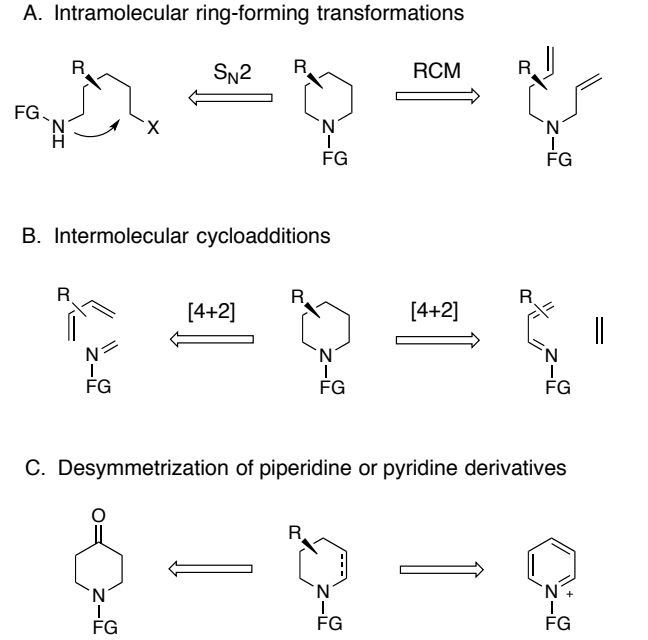
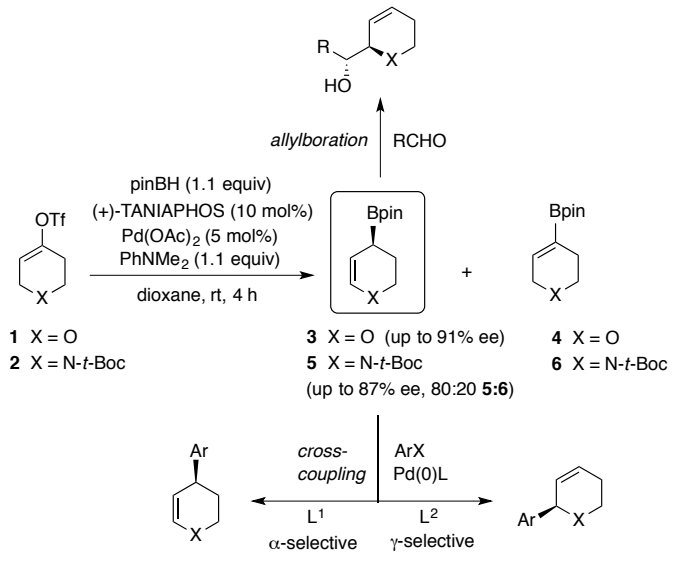


Figure 2. Common synthetic strategies for the preparation of chiral piperidines

In this regard, our laboratory described a catalytic enantioselective borylative migration of pyranyl and piperidinyl triflates **1** and **2** (Scheme 1).[9] This work was inspired by a report from Masuda and co-workers on the palladium-catalyzed borylation of the corresponding pyranyl alkenyl triflate **1**.[10] Instead of isolating the expected alkenyl boronate **4**, the authors observed allylic boronate **3** as the major product. Intrigued by this anomalous borylation process and encouraged by its potential as a preparative method for saturated heterocycles, we optimized this formal olefin isomerization[11] into a catalytic enantioselective formation of heterocyclic allylic boronates. The catalytic enantioselective borylative migration procedure reported by our group in 2009 employed 5 mol% of $Pd(OAc)_2$, 10 mol% of the chiral diphosphine, Taniaphos, with the base, dimethylaniline, in dioxane as the solvent.[9] Although these reaction conditions were carefully optimized for the pyranyl substrate **1**, they were transferred without any fine-tuning to the piperidinyl triflate **2**. Compared to the pyranyl analogue (90-91% *ee*), the piperidinyl triflate **2** afforded a lower level of enantioselectivity of the allylic boronate **5** (86-87% *ee*). These reaction conditions were applied to the synthesis and confirmation of absolute stereochemistry of the antimalarial piperidine drug, mefloquine, using a strategy to establish the aminoalcohol unit that took advantage of the ability of the allylic boronate **5** to undergo stereoselective aldehyde allylboration.[12] Using ultrapure $Pd(OAc)_2$ and carefully deoxygenated dioxane, we were able to obtain *ee*'s in the range of 90-99% in the allylboration of certain aldehydes.[12] In 2014, we also reported the application of optically enriched allylic boronates **3** and **5** in stereospecific, catalyst-controlled regiodivergent sp^2-sp^3 allylic Suzuki-Miyaura cross-couplings with aryl and alkenyl halides.[13] This chemistry provided a highly effective enantioselective synthesis of the piperidine drug, paroxetine.[13]



Scheme 1. Synthetic applications of heterocyclic allylic boronates, prepared by a catalytic enantioselective borylative migration

Piperidinyl allylic boronate **5** thus constitutes a very useful building block for the expedient preparation of enantiomerically enriched, functionalized piperidine products, which are of great importance in drug discovery. When using our original procedure reported in 2009, however, we occasionally encountered lower yields and enantioselectivity

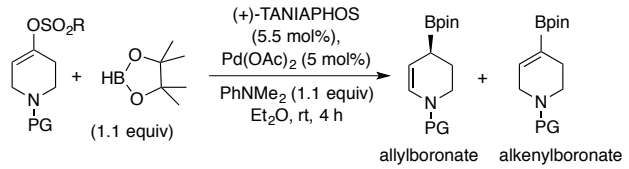
which we attributed to scale effects, insufficient optimization of reaction parameters, and other random deleterious factors such as the presence of trace peroxide in dioxane, insufficiently pure reagents, and even partially oxidized ligand. With a view to fine-tune the experimental conditions for the preparation of this useful chiral allylic boronate and exploit its applications in drug discovery, we aimed to carefully optimize the yield and enantioselectivity of the reaction by taking into account a number of practical factors such as convenience, reliability, cost, and multigram-scalability. To achieve this objective, the current study examined several parameters: the enol substrate (nature of the alkenylsulfonate group and the *N*-protecting group), the source and stoichiometry of palladium and ligand, solvent, reaction concentration, temperature, and time. Moreover, the reaction conditions for the aldehyde allylboration of **5** were briefly re-examined. Although a mechanism for this unique borylative migration was proposed in our previous report,[9] a detailed study will be reported in a subsequent account.

Results & discussion

Optimization of substrate for the catalytic enantioselective borylative migration

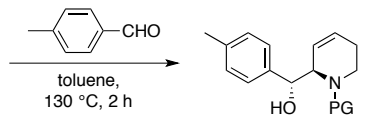
The initial study of the catalytic enantioselective borylative migration, as reported in 2009, was performed solely on the *N*-Boc-protected alkenyl triflate **2**.[9] We wondered whether another sulfonate derivative or *N*-protecting group would provide a higher yield and/or enantioselectivity, or present other advantages such as a more convenient and cost-effective preparation. Thus, with slightly modified conditions using diethyl ether as the solvent, we compared the suitability of substrates **2**, **8**, **9**, and **13** by measuring the yield of the desired allylic boronate along with that of the alkenyl boronate side-product (Table 1).

Table 1. Optimization of the reaction substrate[a]



2 R = CF_3, PG = *t*-Boc
8 R = $(CF_2)_3CF_3$, PG = *t*-Boc
9 R = $(CF_2)_3CF_3$, PG = Cbz
13 R = $(CF_2)_3CF_3$, PG = Bn

5 + **6** PG = *t*-Boc
5 + **6** PG = *t*-Boc
10 + **11** PG = Cbz
14 + **15** PG = Bn



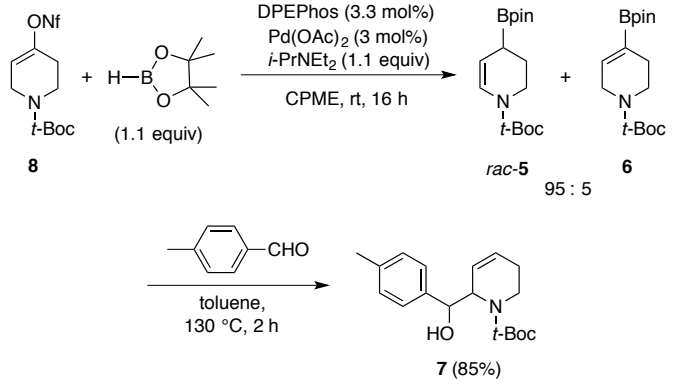
7 PG = *t*-Boc
12 PG = Cbz
16 PG = Bn

Entry	Substrate	R	PG	Proportion of 6, 11, 15 (%)[b]	Yield (%)[c]	*ee* (%)[d]
1	**2**	CF_3	*t*-Boc	10-15%	66	91
2	**8**	$(CF_2)_3CF_3$	*t*-Boc	10-15%	76	91
3	**9**	$(CF_2)_3CF_3$	Cbz	<5%	60	90
4	**13**	$(CF_2)_3CF_3$	Bn	nr[e]	0	nr[e]

[a] Scale of reactions: 0.5 mmol. [b] Separable by flash chromatography. [c] Isolated yield of **7**, **12**, or **16** after flash chromatography. [d] Determined by chiral HPLC of **7**, **12**, or **16**. [e] nr = no reaction.

As done previously,[9] the yield and enantioselectivity were measured indirectly using a stable allylboration product (**7**, **12**, or **16**), because the desired allylic boronates tend to decompose when exposed to air or silica gel for a prolonged period of time. Optimization of the thermal carbonyl allylboration is described later in this article.

The use of alternate substrates embedding an alkenyl nonaflate or a carboxybenzyl carbamate did not lead to a significant increase of enantioselectivity; however, substrate **8** combining an alkenyl nonaflate with *N*-Boc protection led to a higher yield. Moreover, it is noteworthy that compared to that of substrate **2**, the preparation of substrate **8** is higher-yielding and more cost-effective because perfluorobutanesulfonyl fluoride is a less expensive reagent than phenyl triflimide, and the chromatographic purification is easier. Furthermore, compared to a *N*-Cbz group, which is cleaved by catalytic hydrogenation, removal of a *N*-Boc protecting group is orthogonal to the alkene of the allylboration products. Therefore, although *N*-Cbz substrate **9** provided a lower proportion of undesired alkenyl boronate **11**, it was decided to employ substrate **8** for subsequent optimization. The undesired alkenyl boronate side-product can be removed with ease, unreacted, after the subsequent aldehyde allylboration step. In the course of determining the reaction's substrate of choice, a number of important practical and experimental observations were made to help optimize success and reproducibility. It is preferable to employ a high grade (>99.95+%) of the palladium source, and pinacolborane must be employed relatively fresh, and handled and stored under nitrogen. Additionally, the base, dimethylaniline, is distilled over KOH under reduced pressure. Lastly, one must also ensure that the chiral diphosphine ligand, Taniaphos, is not partially oxidized into a phosphine oxide (which can be revealed by mass spectrometry), as we noted a detrimental impact on the reaction conversion. For the purpose of optimizing chiral HPLC separations and other situations where optically enriched allylic boronate **5** is not required, we also optimized a racemic variant of the reaction. It was best achieved with DPEPhos as the achiral diphosphine ligand and diisopropylethylamine as the base (Scheme 2).



Scheme 2. Optimal conditions for the racemic catalytic borylative migration of **8**

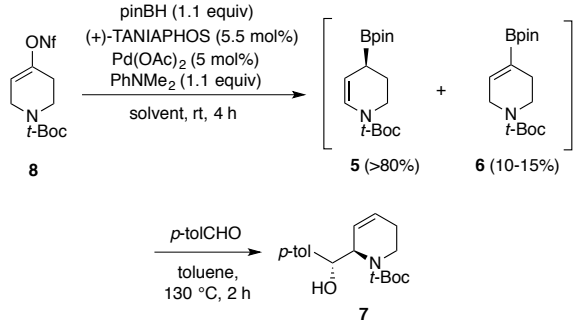
Entry	Solvent	Yield (%)[b]	*ee* (%)[c]
1	toluene	<5	-
2	chlorobenzene	<5	-
3	dioxane	78	86
4	diethyl ether	70	91
5	THF	0	-
6	2-MeTHF	0	-
7	dibutyl ether	0	-
8	diglyme	0	-
9	MTBE	60	90
10	CPME	63	90
11	CPME (0 °C)	60[d]	92
12	CPME (–10 °C)	50[d]	93

[a] Scale of reactions: 0.5 mmol. [b] Isolated yield of **7** after flash chromatography. Accompanied with 10-15% of alkenylboronate **6**, separable by flash chromatography. [c] Determined by chiral HPLC of **7**. [d] Reactions failed to reach completion even after a 16 h reaction time.

Optimization of solvent and temperature

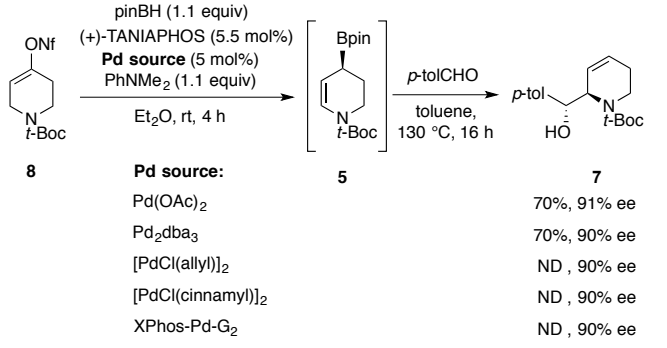
One significant concern towards the adoption of this borylative migration in larger scales or in a process setting is the reaction solvent. Specifically, we sought to identify solvents that would be safer, more efficient, and greener than dioxane. Thus, using 5 mol% of $Pd(OAc)_2$, we assessed several solvents in the exploratory scale of 0.5 mmol of substrate **8**. The results are shown in Table 2. When optimized with pyranyl alkenyl triflate **1**, our original screening of reaction conditions identified both toluene and dioxane as the optimal solvents. It was therefore surprising to find that toluene and chlorobenzene were ineffective with piperidinyl substrate **8** (entries 1-2). Many ethereal solvents, however, were found to be suitable, including diethyl ether (entry 4) and the green solvents methyl *t*-butyl ether (MTBE) and cyclopentyl methyl ether (CPME) (entries 9-10).[14] To our satisfaction, these solvents provided higher and reproducible *ee*'s of 90-91% compared to the previously optimal solvent, dioxane (entry 3). The use of lower temperatures (–10, 0 °C) did not provide significantly higher enantioselectivity and the product yields were lower due to incomplete conversion even after 16 hours. Based on these results, it was decided to continue the optimization process using ethereal solvents (e.g., diethyl ether and CPME) at ambient temperature.

Table 2. Broad evaluation of solvents in the borylative migration of **8**[a]



Optimization of palladium source

Although the source of palladium was examined in our original communication, we re-examined this important parameter with the new alkenyl nonaflate substrate **8** (Scheme 3). This short study confirmed that both Pd(0) and Pd(II) sources were suitable. Although several other Pd complexes were competent, including $Pd_2(dba)_3$, $[PdCl(allyl)]_2$, $[PdCl(cinnamyl)]_2$, and XPhos-Pd-G2, palladium diacetate was chosen for further optimization because of its stability to air and relatively lower cost.



Scheme 3. Examination of Pd source in the catalytic borylative migration of **8**

Optimization of chiral ligand

Because a new substrate, alkenyl nonaflate **8**, was being used along with new solvents other than dioxane, we re-evaluated a small number of common chiral diphosphines and other ligands in this Pd-catalyzed enantioselective borylative migration (Fig. 3). The ligands that functioned well in promoting the desired enantioselective reaction were those with a relatively wider bite angle and chelate size, like Walphos and Taniaphos. The amine-containing diphosphine, Taniaphos, remained the most effective ligand. As described above (Table 2), this ligand also provided a significant improvement of *ee* when diethyl ether, MTBE, and CPME were used as the solvents compared to dioxane.

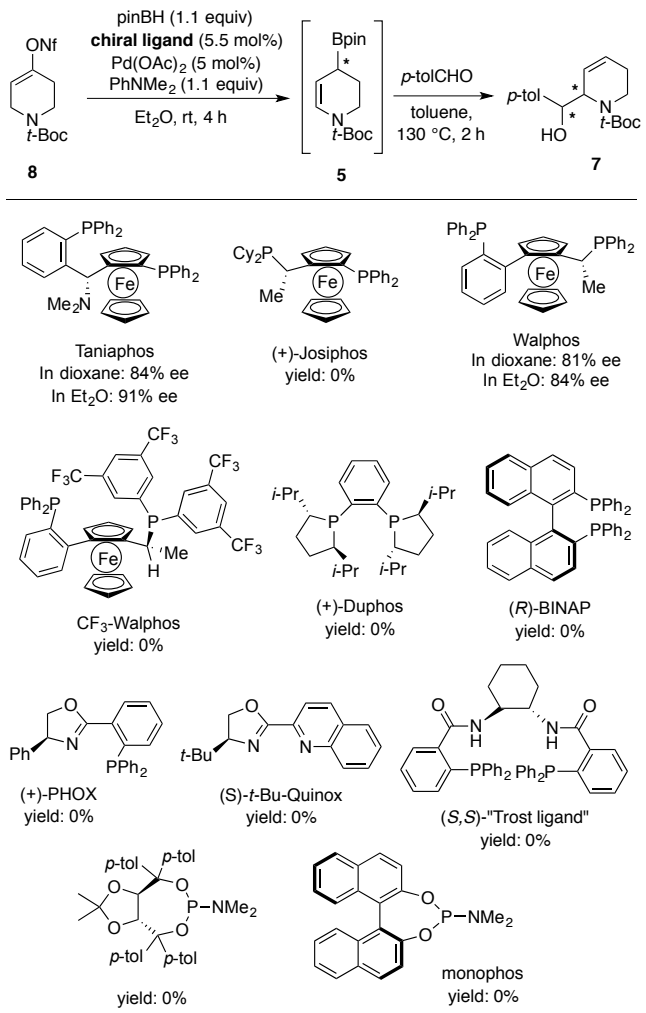
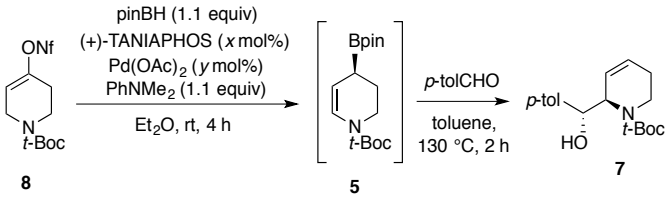


Figure 3. Selected chiral ligands evaluated in the borylative migration of **8**

Optimization of catalyst stoichiometry and concentration

Significant economies can be realized when using a lower catalyst loading, or with a higher reaction concentration to allow solvent savings. To this end, we examined the impact of varying these important parameters using diethyl ether as the model ethereal solvent (Table 3).

Table 3. Examination of catalyst loading and concentration[a]



Entry	Pd loading (mol%)	Ligand loading (mol%)	Pd conc. (mM)	Conc. of 8 (M)	Yield (%)[b]	*ee* (%)[c]
1	5	10	1.9	0.063	70	91
2	5	7	1.9	0.063	70	91
3	5	5.5	1.9	0.063	72	91
4	3	3.3	1.9	0.063	35[d]	90
5	5	5.5	3.1	0.063	70	91
6	3	3.3	3.1	0.10	50[d]	91
7	3	3.3	4.7	0.16	65[d]	90
8	3	3.3	10	0.33	66[d]	90
9	3	3.3	10	0.33[e]	73	90
10	2	2.2	3.1	0.16[f]	64[g]	90
11	2	2.2	6.7	0.33[f]	64[g]	90
12[h]	5	5.5	1.9	0.063	70	91
13[h]	3	3.3	10	0.33[e]	71	92

[a] Scale of reactions: 0.5 mmol. [b] Isolated yield of **7** after flash chromatography. Accompanied with 10-15% of alkenylboronate **6**, separable by flash chromatography. [c] Determined by chiral HPLC of **7**. [d] Reactions failed to reach completion after a 4 h reaction time. [e] Stirred for 16 h, instead of 4 h. [f] Stirred for 24 h, instead of 4 h. [g] Reactions failed to reach completion after a 24 h reaction time. [h] CPME was used as a reaction solvent.

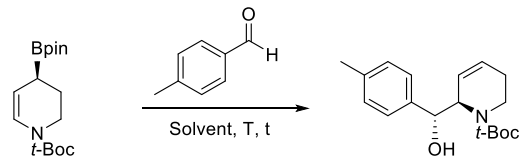
The standard conditions from our preliminary communication, optimized for pyranyl allylic boronate **3**, employed a 2:1 ligand:Pd ratio.[9] Using the same reaction conditions with diethyl ether as the solvent, a 70% yield of product **7** was obtained with 91% *ee* (entry 1). We were delighted to find that the ligand:Pd ratio can be decreased to near equimolar (entries 2-3), with a slight excess of diphosphine ligand employed to prevent Pd black out. Although decreasing the catalyst loading to 3 mol% led to a lower yield (entry 4), it was possible to make up for this loss by increasing the catalyst's concentration (entries 6-7). These optimal conditions employ only about a third of the originally reported amount of expensive chiral diphosphine, Taniaphos, however at a relatively low concentration of substrate **8**. With a view to realize further solvent economies in multigram scale applications, we attempted to increase the reaction concentration. We found it possible to run this borylative migration at a substrate concentration of 0.33 M, leading to substantial solvent savings (entries 8-9). Although a decrease in yield was observed due to a lower conversion when keeping a short reaction time of 4 hours, increasing the reaction time to 16 hours did provide the optimal yield of 73% (entry 9). Unfortunately, further attempts to decrease the catalyst loading to 2 mol% led to incomplete conversions even after an extended reaction time of 24 hours (entries 10-11). Finally, we were delighted to find that these optimal conditions with diethyl ether as the solvent are also suitable with the greener alternative, CPME, providing comparable yield and *ee* (entries 12-13).

Optimization of the aldehyde allylboration step

Compared to pyranyl allylic boronates, piperidinyl congeners react more sluggishly. The original reaction conditions for the aldehyde allylboration reported in 2009 required the use of microwave heating at 130 °C in toluene (0.2 M) for 2 hours in a

sealed vessel.[9] The resulting product yields were moderate, ranging between 50 to 65%. We suspected that these disappointing yields may be caused by an incomplete conversion of the allylboration reaction. Indeed, using continuous monitoring of the model reaction via TLC, we found that a significant proportion of the allylic boronate **5** was left unreacted after 2 hours; hence the reaction time was re-examined, using purified **5** (Table 4).

Table 4. Optimization of the allylboration step[a]



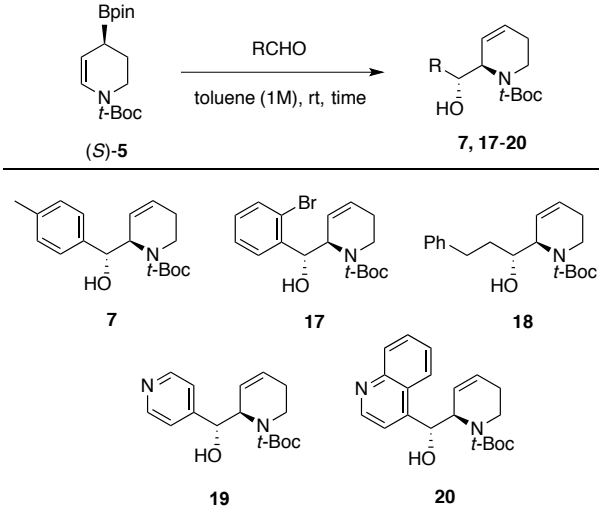
(*S*)-**5** **7**

Entry	Solvent	Heat source	Conc. (M)	T (°C)	t (h)	Yield[c] (%)	*ee*[d] (%)
1[b]	chloro-benzene	µw	0.2	160	0.5	75	-
2[b]	chloro-benzene	µw	0.2	160	2	84	-
3	toluene	µw	0.2	130	1	79	90
4	toluene	µw	0.2	130	2	80	90
5	toluene	oil bath	0.2	130	2	81	91
6	toluene	µw	0.2	130	5	86	91
7	toluene	oil bath	0.2	130	5	85	90
8	neat	N/A	N/A	rt	16	85	92

[a] Scale of reactions: 0.5 mmol. [b] Entry 1 and 2 used racemic allylboronate. [c] Isolated yield of **7** after flash chromatography. [d] Determined by chiral HPLC of **7**. [e] Allylic boronate **5** was fully purified prior to the allylboration reaction, leading to higher yields in comparison to the combined two-step yields of Table 3 utilizing quickly purified **5**.

To obtain a full conversion and a higher isolated yield of product **7**, we found it necessary to increase the reaction time to 5 hours (entry 6). No other isomer was observed in this allylboration reaction. Aside for a small standard error margin in the determination of *ee*'s by chiral HPLC, the *ee* of α-hydroxyalkylated products should mirror that of allylic boronate **5**. The allylic boronate **5** should not be prone to thermally induced epimerization or allylic migration,[15] and the highly diastereoselective allylboration step occurs from the same face as the C–B bond.[9,16] Thus, we further determined that the heat source did not affect the yield or *ee* of the allylboration reaction (entries 4-7). Our next objective was to decrease the reaction temperature. Much to our delight, the reaction underwent a full conversion at rt after 16 h, however, only under neat conditions (entry 8). Because the use of solvent is essential with solid aldehyde substrates, we investigated the scope of aldehydes at a substrate concentration of 1 M in toluene (Table 5). Under these conditions, allylboration with the model aldehyde gave a full conversion at ambient temperature after 16 h (entry 1). The same reaction conditions were successfully applied to provide product **17** (entry 2). Compared to our previous communication, allylboration with hydrocinnamaldehyde gave an improved yield and *ee* (entry 3).[9] Encouraged by this result, we examined heteroaromatic aldehydes. To our satisfaction, these reactions required a shorter time to achieve full conversion (entries 4-5). Overall, the newly optimized conditions consistently led to higher yields under lower reaction temperature and a reduced amount of solvent compared to the previous conditions.[9] All attempts to identify alternative conditions with the use of Lewis acid catalysis (e.g., BF_3, $Sc(OTf)_3$),[17] Brønsted acid catalysis (e.g., TfOH),[18] and conversion to allyldifluoroborane[19] were unsuccessful.

Table 5. Scope of allylboration of **5** with different aldehydes[a]



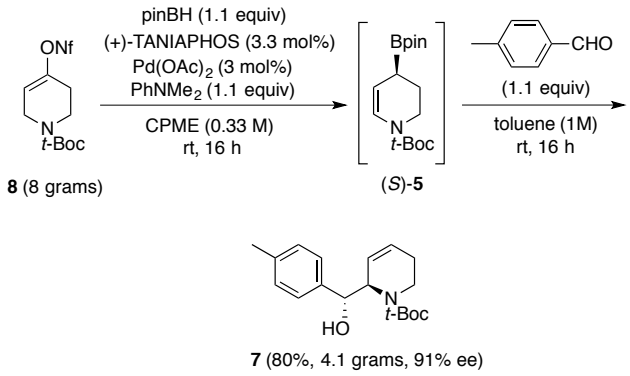
Entry	Reaction time (h)	Product	Yield[b] (%)	*ee*[c] (%)
1	16	**7**	70	92
2	16	**17**	70	90
3	16	**18**	70	90
4	3	**19**	71	94
5	3	**20**	72	91

[a] Scale of reactions: 0.5 mmol. [b] Isolated yield of **7**, **17**, **18**, **19**, or **20** after flash chromatography. [c] Determined by chiral HPLC of **7**, **17**, **18**, **19**, or **20**.

Evaluation of reaction sequence on a multigram-scale

With more robust and economical reaction conditions in hand, which feature the use of greener and safer industrially attractive ethereal solvents like CPME, we attempted a multigram scale sequence of borylative migration followed by an aldehyde allylboration (Scheme 4). Using eight grams of nonaflate **8** (17 mmol) and only 3 mol% of the catalyst, product **7** was obtained in a 80% yield with an *ee* of 91% mirroring that obtained in much smaller reaction scales of our optimization studies. The purification process of a large scale reaction was identical to that of a small scale reaction. Specifically, the allylic boronate **5** was quickly pre-purified via a

filtration through a short pad of silica gel, followed by concentration of solvent. The resulting residue was immediately subjected to the aldehyde allylboration reaction. The crude product **7** was then purified directly via silica column chromatography. During this purification, the major side-product, alkenyl boronate **6**, was easily removed to give the desired pure product **7**.



Scheme 4. Multigram-scale enantioselective borylative migration/aldehyde allylboration using the optimized procedure

Conclusions

In summary, we optimized a Pd-catalyzed enantioselective borylative migration of an alkenyl nonaflate derivative of the simple precursor *N*-Boc-4-piperidone. Compared to the previous, unoptimized process employing the corresponding triflate derivative **2**, the nonaflate substrate **8** is easier to prepare and purify. This borylative migration reaction lends access to a chiral optically enriched piperidinyl allylic boronate **5**. This reagent can be employed in carbonyl allylboration and stereoselective cross-coupling to produce functionalized dehydropiperidines related to numerous pharmaceutical agents. A systematic fine-tuning of reaction conditions revealed that diethyl ether and the green solvent CPME were suitable solvents, providing the highest enantioselectivity (up to 92% *ee*) under a low catalyst loading of 3 mol%. Optimization of the aldehyde allylboration step led to higher yields with further solvent economy. The gram-scalability of the entire process was demonstrated under the newly optimized reaction conditions that provide significantly improved atom-economy and efficiency.

Experimental

General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. THF and toluene were purified using a MBraun MB SPS* solvent system. Dioxane was distilled over sodium. Diethyl ether (Et_2O) was distilled over sodium/benzophenone ketyl. Anhydrous chlorobenzene, cyclopentyl methyl ether (CPME), methyl *tert*-butyl ether (MTBE), dibutyl ether, 2-methyltetrahydrofuran (2-MeTHF), and diglyme were purchased from Sigma-Aldrich and used as received. *N,N*-Diisopropylethylamine (DIPEA) and *N,N*-dimethylaniline (DMA) were purchased from Sigma-Aldrich and distilled over potassium hydroxide prior to use. Pinacolborane and 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) were purchased from Oakwood Products and Sigma-Aldrich, respectively, and were used without further purification. 1-*tert*-Butoxycarbonyl-4-piperidone, 1-carbobenzoxy-4-piperidone, 1-benzyl-4-piperidone, and perfluorobutanesulfonyl fluoride were purchased from Combi-Blocks Inc. and were used without further purification. All aldehydes were purified by a bulb-to-bulb distillation under reduced pressure. Taniaphos, DPEPhos, Walphos, palladium(II) acetate, allylpalladium(II) chloride dimer, and tris(dibenzylideneacetone)dipalladium(0) were purchased from Strem Chemicals. All other palladium catalysts and ligands were purchased from Sigma-Aldrich. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} plates and visualized with UV light, p-anisaldehyde stain, and $KMnO_4$ stain. Flash column chromatography was performed on ultra-pure silica gel 230-400 mesh. Nuclear magnetic resonance (NMR) spectra were recorded on INOVA-400 or INOVA-500 instruments. The residual solvent protons (^1H) and the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; app s, apparent singlet; t, triplet; app t, apparent triplet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet. Reported *J*-values are deemed accurate within ± 0.3 Hz. NMR data were processed either using VnmrJ from Agilent Technologies or MestReNova from Mestrelab Research. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using electrospray ionization (ESI) method. Infrared spectra were obtained from a Nicolet Magna-IR machine with frequencies expressed in cm^{-1}. Optical rotations were measured using a 1 mL cell with a 1 dm length on a P.E. 241 polarimeter. Regioselectivity of alkenyl to allyl boronate and the diastereomeric ratios for chiral compounds were determined by integration of relevant signals on the crude ^1H NMR spectra. The enantiomeric excess ratios for optically enriched compounds were determined using a HPLC Agilent instrument with a Chiralcel-OD or IB or IC column as specified in the following individual procedures.

Experimental details

Pinacolborane received in a bottle was transferred to a round bottom flask under a nitrogen atmosphere and stored in a freezer. DIPEA and DMA were distilled over potassium hydroxide under a nitrogen atmosphere and stored in a refrigerator. Synthesized alkenyl nonaflates were transferred

to vials after purification and stored in a refrigerator. Prior to the borylative migration reaction, pinacolborane, the base, and the alkenyl nonaflate were allowed to warm up to room temperature (ca. 20 min). Ultrapure (99.95+%) $Pd(OAc)_2$ was used. All the phosphine ligands were checked for oxidation via ESI-ToF technique prior to use. Palladium and ligand were weighed out carefully and transferred to a reaction flask, which was evacuated and back-filled with nitrogen three times. Due to its instability to a prolonged exposure to air and silica gel, freshly-made crude allylic boronate **5** was filtered through a silica plug(silica gel to crude product, 100/1, w/w) very quickly (ca. 30 seconds) and subjected to the allylboration reaction directly after concentration of solvent. The major side product, alkenyl boronate, was removed during the purification of final products, *α*-hydroxyalkyl dehydropiperidines.

General procedure for the synthesis of alkenyl nonaflates (Table 1)

N-Protected piperidone (10 mmol, 1.0 equiv) was dissolved in THF (50 mL) under a nitrogen atmosphere. The mixture was cooled in an ice-water bath (0 °C) and stirred for 5 min. DBU (1.8 mL, 12 mmol, 1.2 equiv) and perfluorobutanesulfonyl fluoride (2.2 mL, 12 mmol, 1.2 equiv) were added respectively and the resulting solution was stirred for 10 min. The reaction was then allowed to warm up to rt and stirred for 16 h. The reaction was quenched with a slow addition of water (50 mL) and extracted with Et_2O (3 × 60 mL). The organic layers were combined and washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The brown oil was then purified by flash column chromatography (25% Et_2O/pentane).

tert-Butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (8)

A colorless oil (4.6 g, 95% yield) was obtained according to the general procedure using 1-(*tert*-butoxycarbonyl)-4-piperidone (2.0 g, 10 mmol, 1.0 equiv) as a substrate. Spectral data correspond to that reported.[20] $\mathbf{R_f}$ = 0.61 (15% EtOAc/hextane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 5.76 (app s, 1 H), 4.04 (app s, 2 H), 3.62 (app s, 2 H), 2.43 (app s, 2 H), 1.46 (s, 9 H).

Benzyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (9)

A light-yellow oil (4.6 g, 89% yield) was obtained according to the general procedure using 1-carbobenzoxy-4-piperidone (2.3 g, 10 mmol, 1.0 equiv) as a substrate. $\mathbf{R_f}$ = 0.41 (15% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.39 – 7.32 (m, 5 H), 5.82 – 5.75 (m, 1 H), 5.16 (s, 2 H), 4.14 (app s, 2 H), 3.72 (app s, 2 H), 2.47 (app s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$, ^{19}F decoupled, 60 °C) δ (ppm) 155.1, 147.0, 136.5, 128.7, 128.3, 128.1, 115.8, 115.4, 114.5, 110.1, 108.7, 67.8, 42.1, 40.8, 28.2; **^{19}F NMR** (376 MHz, $CDCl_3$, ^{1}H decoupled, 60 °C) –80.8, –109.4, –120.6, –125.5; **IR** (Microscope, cm^{-1}) 3035, 2957, 1711, 1423, 1353, 1280; **HRMS** (ESI-ToF) for $C_{17}H_{14}F_9NNaO_5S$ ($M + Na^+$): calcd. 538.0341; found 538.0337.

1-(Benzyl)-4-[(nonafluorobutanesulfonyl)oxy]-1,2,3,6-tetrahydropyridine (13)

A yellow oil (4.3 g, 91% yield) was obtained according to the general procedure using 1-benzyl-4-piperidone (1.9 mL, 10 mmol, 1.0 equiv) as a substrate. $\mathbf{R_f}$ = 0.56 (15% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.35 – 7.27 (m, 5 H), 5.75 – 5.73 (m, 1 H), 3.64 (s, 2 H), 3.15 – 3.13 (m, 2 H), 2.73 (t, J = 5.7 Hz, 2 H), 2.46 – 2.45 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$, ^{19}F Dec) δ (ppm) 147.5, 137.7, 129.0, 128.5, 127.4, 117.1, 116.3, 114.2, 109.9, 108.5, 61.3, 50.5, 49.1, 28.4; **^{19}F NMR** (376 MHz, $CDCl_3$, ^{1}H decoupled) –80.8, –110.1, –121.1, –126.0; **IR** (Microscope, cm^{-1}) 3031, 2926, 2806, 1699, 1454, 1421; **HRMS** (ESI-ToF) for $C_{16}H_{15}F_9NO_3S$ ($M + H)^+$: calcd. 472.0623; found 472.0618.

General procedure for the synthesis of optically enriched allylic boronate (Table 1)

Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and (+)-TANIAPHOS (23 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with nitrogen three times. Et_2O (3 mL) was added and the mixture was stirred for 30 min. DMA (140 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated *in vacuo*, followed by a quick filtration through a silica plug (100% Et_2O). The resulting mixture was concentrated *in vacuo* and purified by flash column chromatography (25% Et_2O/pentane).

(4S)-tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2H)-carboxylate (5)

A colorless oil (155 mg, 50% yield) was obtained according to the general procedure. Spectral data correspond to that reported.[9] Regioselectivity of alkenyl to allyl boronic ester determined by integration of relevant signals on the crude ^{1}H NMR spectrum was 1:4. $\mathbf{R_f}$ = 0.35 (25% Et_2O/pentane); **^{1}H NMR** (500 MHz, $CDCl_3$) rotamers are present: δ (ppm) 6.84 – 6.71 (m, 1 H), 4.94 – 4.82 (m, 1 H), 3.58 – 3.53 (m, 2 H), 1.87 – 1.83 (m, 3 H), 1.47 (s, 9 H), 1.23 (s, 12 H).

General procedure for the synthesis of optically enriched *α*-hydroxyalkyl dehydropiperidines (Table 5)

Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and (+)-TANIAPHOS (23 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with nitrogen three times. Et_2O (3 mL) was added and the mixture was stirred for 30 min. DMA (140 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and alkenyl nonaflate (1.0 mmol, 1.0 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated *in vacuo*, followed by a quick filtration through a silica plug (100% Et_2O). The resulting mixture was concentrated *in vacuo* and transferred to a pre-dried 5 mL

round bottom flask using dry toluene (1 mL). The flask was flushed with nitrogen and aldehyde (1.1 mmol, 1.1 equiv) was added. The solution was stirred at rt under nitrogen for 3 or 16 h. The mixture was purified directly by flash column chromatography.

(R)-tert-Butyl 2-[(R)-hydroxy(p-tolyl)methyl]-5,6-dihydropyridine-1(2H)-carboxylate (7)

The title compound (**7**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and *p*-tolualdehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a colorless oil (213 mg, 70% yield) after flash column chromatography (50% Et_2O/pentane). $\mathbf{R_f}$ = 0.50 (20% EtOAc/hexane); $\mathbf{[\alpha]^{20}_D}$ + 135.0 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) rotamers are present: δ (ppm) 7.25 – 7.23 (m, 2 H), 7.17 – 7.15 (m, 2 H), 5.89 – 5.81 (m, 1 H), 5.34 – 5.17 (m, 1 H), 4.63 – 4.53 (m, 2 H), 4.18 – 3.85 (m, 1 H), 3.04 – 2.78 (m, 1 H), 2.34 (s, 3 H), 2.22 – 2.17 (m, 1 H), 1.95 – 1.90 (m, 1 H), 1.49 (s, 9 H); **^{1}H NMR** (400 MHz, $CDCl_3$, 65 °C) δ (ppm) 7.24 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 5.85 – 5.81 (m, 1 H), 5.30 – 5.28 (m, 1 H), 4.63 – 4.62 (m, 2 H), 4.13 – 4.09 (m, 1 H), 2.92 – 2.86 (m, 1 H), 2.34 (s, 3 H), 2.18 – 2.14 (m, 1 H), 1.95 – 1.89 (m, 1 H), 1.49 (s, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$, 60 °C) δ (ppm) 156.8, 138.6, 137.6, 129.1, 127.1, 125.1, 80.5, 76.4, 58.5, 37.9, 28.5, 24.8, 21.1; **IR** (Microscope, cm^{-1}) 3060, 2975, 2930, 1644, 1611, 1512, 1250; **HRMS** (ESI-ToF) for $C_{18}H_{25}NNaO_3$ $(M + Na)^+$: calcd. 326.1727; found 326.1724; **HPLC** (Chiralcel OD): 3.8% *i*-PrOH/hexane, 6 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 19.6 min, T_{minor} = 17.3 min; 92% *ee*; >96% *de*.

(R)-tert-Butyl 2-[(R)-hydroxy(o-bromophenyl)methyl]-5,6-dihydropyridine-1(2H)-carboxylate (17)

The title compound (**17**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and 2-bromobenzaldehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a colorless oil (258 mg, 70% yield) after flash column chromatography (50% Et_2O/pentane). $\mathbf{R_f}$ = 0.49 (20% EtOAc/hexane); $\mathbf{[\alpha]^{20}_D}$ + 50.5 (*c* 1.42, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$, 65 °C) δ (ppm) 7.57 (app d, *J* = 7.7 Hz, 1 H), 7.51 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.33 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.13 (app td, *J* = 7.7, 1.8 Hz, 1 H), 5.97 – 5.91 (m, 1 H), 5.41 – 5.35 (m, 1 H), 5.25 (d, *J* = 6.7 Hz, 1 H), 4.73 – 4.72 (m, 1 H), 4.21 – 4.14 (m, 1 H), 3.16 – 3.09 (m, 1 H), 2.21 – 2.19 (m, 1 H), 2.01 – 1.94 (m, 1 H), 1.39 (s, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$, 60 °C) δ (ppm) 156.0, 140.7, 132.7, 129.1, 129.0, 128.0, 127.7, 124.7, 123.3, 80.3, 75.1, 57.5, 38.2, 28.4, 24.8; **IR** (Microscope, cm^{-1}) 3427, 3028, 2976, 2929, 1670, 1592, 1454; **HRMS** (ESI-ToF) for $C_{17}H_{23}BrNO_3$ $(M + H)^+$: calcd. 368.0856; found 368.0850; **HPLC** (Chiralcel OD): 3.8% *i*-PrOH/hexane, 6 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 26.5 min, T_{minor} = 19.3 min; 90% *ee*; >96% *de*.

(R)-tert-Butyl 2-[(R)-1-hydroxy-3-phenylpropyl]-5,6-dihydropyridine-1(2H)-carboxylate (18)

The title compound (**18**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and hydrocinnamaldehyde (145 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a yellow oil (222 mg, 70% yield) after flash column chromatography (25% Et_2O/pentane). Spectral data correspond to that reported.[9] $\mathbf{R_f}$ = 0.65 (50% EtOAc/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$, 60 °C) δ (ppm) 7.28 – 7.15 (m, 5 H), 5.96 – 5.93 (m, 1 H), 5.68 – 5.66 (m, 1 H), 4.41 – 4.37 (m, 1 H), 4.16 – 4.06 (m, 1 H), 3.72 – 3.68 (m, 1 H), 3.02 – 2.97 (m, 1 H), 2.93 – 2.88 (m, 1 H), 2.80 – 2.76 (m, 1 H), 2.21 – 2.17 (m, 1 H), 1.98 – 1.85 (m, 2 H), 1.84 – 1.78 (m, 1 H), 1.48 (s, 9 H); **HPLC** (Chiralcel OD): 10% *i*-PrOH/hexane, 25 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 12.2 min, T_{minor} = 9.4 min; 90% *ee*, >96% *de*.

(R)-tert-Butyl 2-[(R)-hydroxy(4-pyridyl)methyl]-5,6-dihydropyridine-1(2H)-carboxylate (19)

The title compound (**19**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and 4-pyridinecarboxaldehyde (104 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 3 h. The product was obtained as a colorless oil (206 mg, 71% yield) after flash column chromatography (100% EtOAc). $\mathbf{R_f}$ = 0.27 (100% EtOAc); $\mathbf{[\alpha]^{20}_D}$ + 131.6 (*c* 1.07, $CHCl_3$); **^{1}H NMR** (400 MHz, DMSO-d_6) rotamers are present: δ (ppm) 8.48 – 8.47 (m, 2 H), 7.25 – 7.23 (m, 2 H), 5.91 – 5.88 (m, 1 H), 5.71 – 5.66 (m, 2 H), 4.77 (app t, *J* = 4.8 Hz, 1 H), 4.52 – 4.41 (m, 1 H), 3.94 – 3.68 (m, 1 H), 2.71 – 2.62 (m, 1 H), 1.94 – 1.83 (m, 2 H), 1.33 – 1.21 (m, 9 H); **^{1}H NMR** (400 MHz, DMSO-d_6, 80 °C) δ (ppm) 8.48 (d, *J* = 5.8 Hz, 2 H), 7.25 (d, *J* = 5.8 Hz, 2 H), 5.89 – 5.88 (m, 1 H), 5.71 – 5.68 (m, 1 H), 5.45 – 5.43 (m, 1 H), 4.78 (app t, *J* = 4.8 Hz, 1 H), 4.51 (app s, 1 H), 3.87 – 3.83 (m, 1 H), 2.64 – 2.57 (m, 1 H), 1.96 – 1.91 (m, 1 H), 1.83 – 1.78 (m, 1 H), 1.32 (s, 9 H); **^{13}C NMR** (100 MHz, DMSO-d_6, 80 °C) δ (ppm) 153.6, 151.0, 148.6, 126.7, 124.6, 121.8, 78.3, 72.5, 56.3, 37.2, 27.6, 23.7; **IR** (Microscope, cm^{-1}) 3402, 3189, 2976, 2929, 1691, 1603, 1477, 1455; **HRMS** (ESI-ToF) for $C_{16}H_{23}N_2O_3$ $(M + H)^+$: calcd. 291.1703; found 291.1707; **HPLC** (Chiralcel IC): 50% *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 6.3 min, T_{minor} = 14.2 min; 94% *ee*; >96% *de*.

(R)-tert-Butyl 2-[(R)-hydroxy(4-quinolinyl)methyl]-5,6-dihydropyridine-1(2H)-carboxylate (20)

The title compound (**20**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and 4-quinolinecarboxaldehyde (173 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 3 h. The product was obtained as a colorless oil (245 mg, 72% yield) after flash column chromatography (100% EtOAc). $\mathbf{R_f}$ = 0.44 (100% EtOAc); $\mathbf{[\alpha]^{20}_D}$ + 51.4 (*c* 1.56, $CHCl_3$); **^{1}H NMR** (500 MHz, DMSO-d_6) rotamers are present: δ (ppm) 8.85 – 8.82 (m, 1 H), 8.26 – 8.11 (m, 1 H), 8.04 – 7.98 (m, 1 H), 7.74 – 7.71 (m, 1 H), 7.59 – 7.50 (m, 2 H), 5.98 – 5.80 (m, 2 H), 5.69 – 5.60 (m, 2 H), 4.71 – 4.59 (m, 1 H), 3.99 – 3.95 (m, 1 H), 3.18 – 3.12 (m, 1 H), 1.93 – 1.86 (m, 2

H), 1.30 – 0.67 (m, 9 H); **^{1}H NMR** (500 MHz, DMSO-d_6, 115 °C) δ (ppm) 8.83 (d, J = 4.4 Hz, 1 H), 8.21 (d, J = 8.4 Hz, 1 H), 8.02 (d, J = 8.4 Hz, 1 H), 7.70 (dt, J = 7.6, 0.91 Hz, 1 H), 7.56 – 7.51 (m, 2 H), 5.92 – 5.89 (m, 1 H), 5.75 – 5.72 (m, 1 H), 5.59 (app t, J = 4.5 Hz, 1 H), 5.39 (app s, 1 H), 4.74 (app s, 1 H), 3.85 – 3.84 (m, 1 H), 2.73 (br s, 1 H), 2.01 – 1.93 (m, 1 H), 1.83 – 1.80 (m, 1 H), 1.12 (s, 9 H); **^{13}C NMR** (125 MHz, DMSO-d_6, 115 °C) δ (ppm) 153.5, 149.0, 147.5, 147.4, 129.1, 127.9. 126.5, 125.7, 125.2, 125.0, 123.1, 119.0, 77.9, 69.4, 56.0, 36.9, 27.2, 23.5; **IR** (Microscope, cm^{-1}) 3405, 3180, 3041, 2976, 2930, 1687, 1477; **HRMS** (ESI-ToF) for $C_{20}H_{25}N_2O_3$ $(M + H)^+$: calcd. 341.1860; found 341.1863; **HPLC** (Chiralcel IC): 50% *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 280 nm, T_{major} = 6.1 min, T_{minor} = 13.2 min; 90% *ee*; >96% *de*.

(R)-Benzyl 2-[(R)-hydroxy(p-tolyl)methyl]-5,6-dihydropyridine-1(2H)-carboxylate (12)

The title compound (**12**) was synthesized by the general procedure (modification: use of (−)-TANIAPHOS instead of (+)-TANIAPHOS) using benzyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**9**) (515 mg, 1.00 mmol, 1.00 equiv) and *p*-tolualdehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a colorless oil (202 mg, 60% yield) after flash column chromatography (50% Et_2O/pentane). $\mathbf{R_f}$ = 0.41 (20% EtOAc/hexane); $[\alpha]^{20}_D$ −109.1 (*c* 0.32, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.38 – 7.31 (m, 5 H), 7.31 – 7.12 (m, 4 H), 5.89 – 5.82 (m, 1 H), 5.41 – 5.38 (m, 1 H), 5.23 – 5.11 (m, 2 H), 4.70 – 4.67 (m, 2 H), 4.22 – 3.46 (m, 1 H), 3.03 – 2.83 (m, 1 H), 2.34 (s, 3 H), 2.23 – 2.20 (m, 1 H), 1.97 – 1.93 (m, 1 H); **^{1}H NMR** (400 MHz, $CDCl_3$, 65 °C) δ (ppm) 7.39 – 7.29 (m, 5 H), 7.23 (app d, J = 7.9 Hz, 2 H), 7.14 (app d, J = 7.9 Hz, 2 H), 5.89 – 5.84 (m, 1 H), 5.36 – 5.34 (m, 1 H), 5.18 (s, 2 H), 4.68 – 4.66 (m, 2 H), 4.21 – 4.16 (m, 1 H), 2.98 – 2.90 (m, 1 H), 2.35 (s, 3 H), 2.27 – 2.17 (m, 1 H), 1.97 – 1.90 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$, 65 °C) δ (ppm) 156.8, 138.3, 137.8, 136.9, 129.2, 128.6, 128.1, 128.0, 127.1, 124.9, 76.2, 67.6, 58.7, 38.0, 24.8, 21.2; **IR** (Microscope, cm^{-1}) 3438, 3031, 2921, 1697, 1515, 1431, 1391; **HRMS** (ESI-ToF) for $C_{21}H_{23}NNaO_3$ $(M + Na)^+$: calcd. 360.1570; found 360.1567; **HPLC** (Chiralcel IB): 5% *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 15.8 min, T_{minor} = 18.9 min; 90% *ee*; >96% *de*.

Acknowledgements

This research was supported by the Natural Science and Engineering Research Council (NSERC, Discovery Grant No. 203287-2012) of Canada and the University of Alberta. The authors thank Mr. Hao Fu for help with chiral HPLC measurements and Dr. Ryan McKay and Mark Miskolzie for help with NMR spectrometry.

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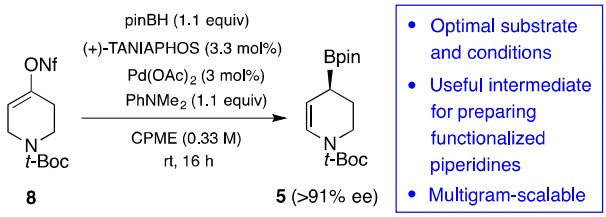

A systematic optimization of a Pd-catalyzed enantioselective borylative migration of an alkenyl nonaflate derivative of the simple precursor, *N*-Boc-4-piperidone, was achieved.