Diastereoselective addition to *N*-acyliminium ions with aryl- and alkenyl boronic acids *via* a Petasis-type reaction†

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A highly diastereoselective synthesis of 2,3-disubstituted piperidines has been accomplished through nucleophilic additions to *N*-acyliminium ions with aryl- and alkenyl boronic acids. A reversal of stereoselectivity depending on a β-substitute on the piperidine ring was observed in the alkenylation reactions with (*E*)-styrylboronic acid. Our strategy was applied in the key step for the synthesis of the nuerokinin NK1 receptor antagonist (±)-L-733,060.

Introduction

Substituted piperidines are found in numerous alkaloids and biologically active compounds, of which 2-aryl-3-hydroxypiperidines have been prominent structural motifs. For example, (+)-L-733,060 (**1**)[1] and its *N*-analogue (+)-CP-99,994[2] are selective neurokinin-1 substance P receptor antagonist (Fig. 1).

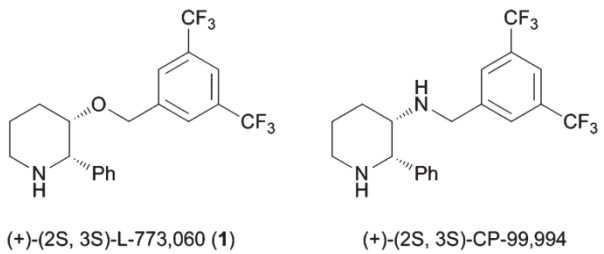
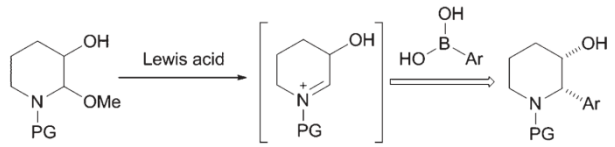


Fig. 1 Biologically active 2,3-disubstituted piperidines.

One of the most powerful methodologies to furnish the substituted piperidines is the nucleophilic addition to *N*-acyliminium ions.[3] To date, a broad range of C-based nucleophiles have been known to react with cyclic *N*-acyliminium ions. We also have achieved the asymmetric intermolecular reactions with a variety of enol derivatives.[4]

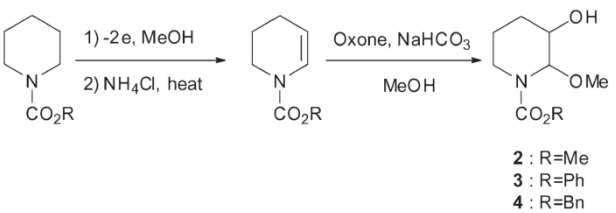
Petasis reaction,[5] which constitute efficient synthesis of allylamines and α-amino acids by the three-component coupling of an amine, an aldehydes and an organoboronic acid, is highly attractive because of the use of organoboronic acids as nucleophiles which are readily available and little sensitive toward air and water. Batey and co-workers have developed the procedure for the diastereoselective formation of functionalized *N*-heterocycles with alkenyl- and aryl boronates.[6] Moreover the asymmetric additions to chiral iminium ions derived from (*S*)-5-phenylmorpholin-2-one and aliphatic aldehydes with 2-furyl boronic acid have been reported by Harwood.[7] In spite of some examples of the arylation reactions to *N*-acyliminium ions,[8] a synthetic protocol for the asymmetric arylation onto piperidine rings with organoboronic acids as nucleophiles has not yet been reported. We herein disclose a novel approach to 2-aryl-3-hydroxypiperidines by the diastereocontrolled introduction of aromatic moieties in organoboronic acids to *N*-protected piperidinium ions mediated by a Lewis acid via a Petasis-type reaction (Scheme 1).



Scheme 1 Diastereoselective introduction of aryl moieties onto the 2-position of *N*-protected piperidinium ions.

Results and discussion

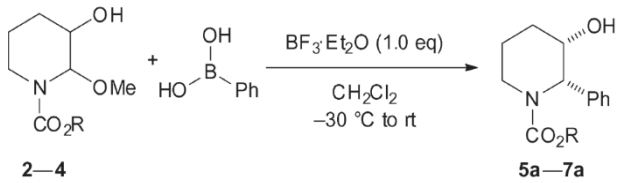
To start with, the preparation of tetrahydropyridines from the respective *N*-protected piperidines was achieved according to our previously reported method which consists of electrochemical methoxylation and elimination of methanol.[9] The tetrahydropyridines were thus treated with oxone in methanol, yielding *N*,*O*-acetals **2**−**4** as *N*-acyliminium ion precursors (eqn (1)).



(1)

As shown in Table 1, we demonstrated the Lewis acid-mediated reactions of **2**−**4** with phenylboronic acid. An initial survey using substrate **2** indicated that the reaction in the presence of $BF_3{\cdot}Et_2O$ did not proceed. The *N*,*O*-acetal **3** possessing a *N*-phenoxycarbonyl group reacted slightly with phenyboronic acid, providing the desired product **6a**. The corresponding boronate did not lead to any increase of yield.[10] In contrast, the reaction of *N*-Cbz piperidine **4** proceeded with good diastereoselectivity (*cis*:*trans*=8.3:1 by ^{1}H NMR), and gave the *cis*-adduct **7a** in 69% yield as a single isomer after purification by column chromatography. Otherwise, $TiCl_4$ was found to be a poor mediator.

Table 1 Diastereoselective nucleophilic substitution of *N*,*O*-acetals with phenylboronic acid.



2—4 5a—7a

Entry	R (Substrate)	Time (h)	Product	dr (*cis* : *trans*) [a]	Yield (%)[b]
1	Me (**2**)	18	**5a**	—	Trace
2	Ph (**3**)	18	**6a**	7.2 : 1	14
3	Bn (**4**)	24	**7a**	8.3 : 1	69
4[c]	Bn (**4**)	24	**7a**	—	0

[a] The diastereomer ratio was determined by ^{1}H NMR spectroscopy of the crude mixture. [b] Yield of isolated product after purification by column chromatography. [c] The reaction performed with 1.0 equivalent of $TiCl_4$ instead of $BF_3{\cdot}Et_2O$.

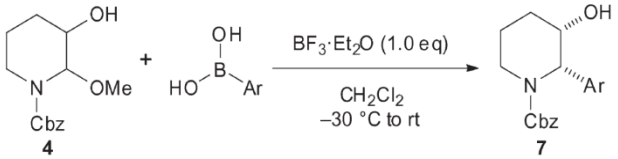
By using substrate **4**, we next examined the scope and limitation of this process with respect to substitution on the benzene ring of aryl boronic acids (Table 2, Entries 1–13). Overall adducts **7** were *cis*-formed as single diastereomers (>98:2 *cis*:*trans* by ^{1}H NMR) in moderate to high yields. When a nucleophile with a methoxy substituent was used, the 2-arylated piperidine **7b** was obtained in 86% yield. Moreover, nucleophiles bearing a methylthio, a methyl and a phenyl group provided the corresponding desired products **7c**–**g** in moderate yield. Both 1- and 2-naphthylboronic acids also were well-tolerated in this process. It should be noted that acceptable substitutions on the phenyl group are characterized by electron-neutral or –donating groups. Substrates with electron withdrawing groups are challenging for this reaction. For instance, the reaction of 4-fluoro and 4-chlorophenyl boronic acid gave adducts (**7j** and **7k**) in less than 40% yield. Additionally, (4-cyanophenyl)boronic acid was ineffective. An attempt to use disubstituted phenyl boronic acids was also successful; arylated piperidines (**7m** and **7n**) were obtained in 64% and 62% yields, respectively. The additions of other boronic acids involving an alkenyl and a heteroaryl substitute were explored (Entries 14–17). The reaction of (*E*)-2-styrylboronic acid gave *cis*-adduct **7o** in 81% yield. The electron-rich boronic acids, 3-thienylboronic acid, 2-benzothienylboronic acid and 2-benzofuranylboronic acid, were effective, providing the diastereomerically pure 2-heteroarylated piperidines (**7p**–**r**) in good to high yield.

In the case of 1-(*N*-methoxycarbonyl)indole-2-boronic acid, the reaction successfully proceeded, providing the cyclic carbamate compound **8** in 61% yield (Scheme 2).

Although we examined the temperature and solvents effect on the diastereoselectivity of **7a**, and whether the epimerization of *cis*-**7a** caused by $BF_3{\cdot}Et_2O$ was present or not in order to explain the source of lower diastereoselectivity of **7a**, we did not obtain any significant results.[11]

The synthesis of the *cis*-isomers (**7a**, **7b**, **7d**, and **7j**) has been reported[12] and the ^{1}H NMR data of compounds obtained us is consistent with literature examples. The coupling constant $J_{2,3}$ values for *cis*-isomers were 5.6–5.8 Hz, compared with <1.0 Hz for the corresponding *trans*-isomers.[8, 13] The stereochemistry of **7c**, **7e**, **7f**–**i**, **7k**, **7m**–**r** and **8** was readily determined by the examination of the coupling constant $J_{2,3}$, which was 5.2–6.1 Hz, consistent with $J_{2,3}$ values for *cis*-isomers.

Table 2 Scope of organoboronic acids in nucleophilic substitution reactions of substrate **4**.



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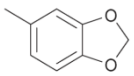
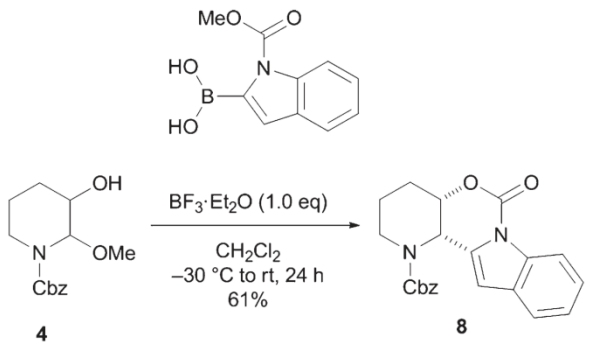
Entry	Ar	Time (h)	Product	Yield (%)[a]
1	4-$MeOC_6H_4$	5	**7b**	86
2	4-$MeSC_6H_4$	5	**7c**	71
3	4-MeC_6H_4	19	**7d**	67
4	3-MeC_6H_4	24	**7e**	66
5	2-MeC_6H_4	24	**7f**	49
6	3-Biphenyl	24	**7g**	43
7	1-Naphthyl	24	**7h**	71
8	2-Naphthyl	24	**7i**	71
9	4-FC_6H_4	24	**7j**	38
10	4-ClC_6H_4	24	**7k**	33
11	4-NCC_6H_4	24	**7l**	0
12	3,4-$(MeO)_2C_6H_3$	5	**7m**	64
13		14	**7n**	62
14	(*E*)-PhCH=CH	24	**7o**	81
15	3-Thienyl	5	**7p**	57
16	2-Benzothienyl	24	**7q**	60
17	2-Benzofuranyl	24	**7r**	90

[a] Yield of isolated product after purification by column chromatography.



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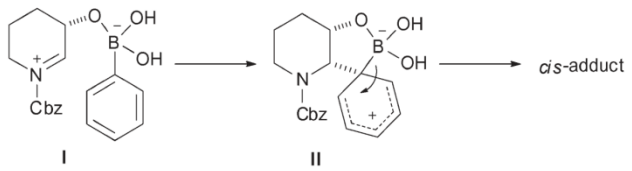
Scheme 2 Addition of 1-(*N*-methoxycarbonyl)indole-2-boronic acid to *N*,*O*-acetal **4**.

Next, we explored the scope of β-substitution with respect to the *N*-acyliminium ion partner. Indeed, neither the nucleophilic substitutions of *N*-benzyloxycarbonyl-2-methoxypiperidine nor β-halosubstituted piperidine *N*,*O*-acetals **9a**–**c** with 4-methoxyphenyl boronic acid provided the desired products. The

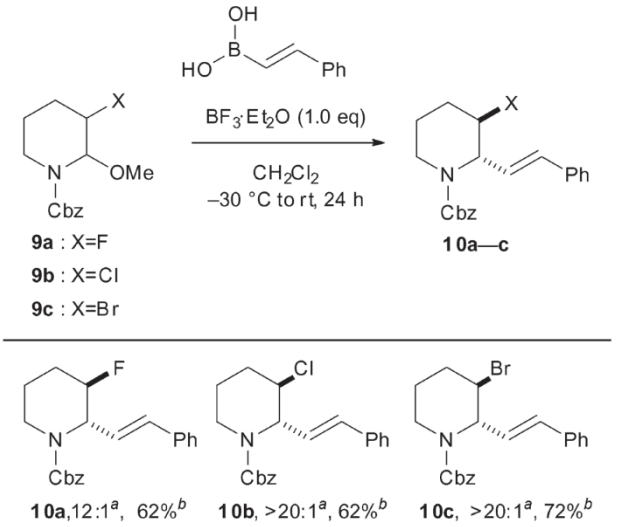
requirement for a β-hydroxyl group adjacent to the α-carbon implied the coordination to organoboronic acid. The reaction intermediates **I** and **II** which would be responsible for the reactivity and selectivity are proposed (Scheme 3). First, the *N*-acyliminium ion tetracoordinate boronic acid as an intermediate **I** would be formed by Lewis acid activation of the *N*,*O*-acetal. Next, successive intramolecular attack of boronate **I** on the *N*-acyliminium ion by the same face bearing the β-oxygen results in the diastereospecific C-C bond formation to provide the cyclic intermediate **II**. Consequently, **II** undergoes the elimination of boronic acid leading to a *cis*-2,3-disubstituted piperidine derivative with an high level of diastereoselectivity.



Scheme 3 Plausible mechanism for the diastereoselective arylation of *N*-acyliminium ions.

On the other hand, in our research, we found that (*E*)-2-styrylboronic acid as a nucleophile was suitable for nucleophilic additions to *N*-acyliminium ions derived from *N*,*O*-acetals **9a**–**c**. The reaction of **9a** in the presence of $BF_3{\cdot}Et_2O$ gave the desired product **10a** with good diastereoselectivity (dr=12:1) in 62% yield. Interestingly, the reactions of 3-chloro- and 4-bromopiperidine *N*,*O*-acetals **9b** and **9c** provided exclusively a single isomer in good yield, respectively. The major isomers **10a**–**c** were confirmed to be *trans*-formed by the examination of their coupling constant $J_{2,3}$= <1.0 Hz, consistent with literature examples for *trans*-2-aryl-3-hydroxypiperidines.

Further investigation will be required to elucidate the mechanism on the alkenylation reaction. We envisage that transient iminium ions (**III**–**V**) would be formed due to the high conformational control (Figure 2). Organofluorine compounds tend to stabilize the conformations by hyperconjugative and electrostatic interactions.[14] For instance, the [NH-FC] dipole effect in 3-fluoropiperidine derivatives has been observed by Snyder and Lankin.[15] In addition, Gilmour and co-workers developed a glycosylation stereocontrolled by the polarized C-F bond which would orient towards the electropositive center in a *gluco*-configured 2-fluoro-oxonium ion.[16] We postulated that an electrostatic interaction between the partially negatively charged C-F bond and the *N*-acyliminium cation would lead to conformational rigidification of 3-fluoropiperidinium ion **III** because they are positioned closer together in a pseudoaxial conformer than in a pseudoequatorial conformer. On the other hand, 3-chloro and 3-bromopiperidinium ion intermediates should be indicated by the two proposed conformational states (**IV** and **V**). The alkenylations of **9b** and **9c** with



Scheme 4 Scope of β-position substitutes of *N*,*O*-acetals in the diastereoselective reaction with (*E*)-2-styrylboronic acid. [a] The diastereomer ratio was determined by ^{1}H NMR spectroscopy of the crude mixture. [b] Yield of isolated product after purification by column chromatography.

(*E*)-2-styrylboronic acid would proceed via a pseudoaxial conformer **V** providing *trans*-products, and not via the pseudoequatorial conformer **IV** which might cause a steric repulsion between a halogen substitute and a nucleophile.

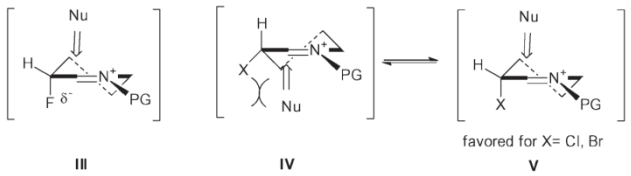
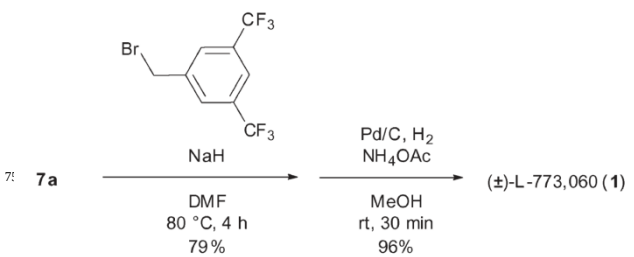


Fig. 2 Conformational control in 3-halopiperidinium ions.

Finally, we aimed at the synthesis of (±)-L-773,060 (**1**).[17] With diastereomerically pure **7a** in hand, the treatment with NaH for the deprotonation of β-hydroxyl group to form the alkoxyl anion which reacted with 3,5-bis(trifluoromethyl)benzyl bromide afforded the *O*-benzyl ether product. The subsequent hydrogenolysis of *N*-Cbz with ammonium acetate and Pd/C according to Sajiki's condition[18] afforded the desired product (±)-L-773,060 (**1**) in excellent yield (Scheme 5).



Scheme 5 Preparation of **1** from **7a**.

Conclusions

In conclusion, we disclosed a versatile approach to *cis*-2-aryl-3-hydroxypiperidine derivatives through highly diastereoselective α-arylations of piperidinium ions with a broad range of readily available arylboronic acids involving heteroaryl- and alkenyl boronic acids. In the alkenylation of *N*,*O*-acetals with (*E*)-styrylboronic acid, a reversal of stereoselectivity was observed depending on whether a hydroxyl group or a halogen as β-substitute was present. A concise synthesis of (±)-L-773,060 was realised using our method. Further investigation on the scope of substrates and the detailed mechanism is currently on-going.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data. NMR Spectra for all novel compounds. See DOI: 10.1039/b000000x/

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