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Enantioselective, Palladium-Catalyzed α-Arylation of *N*-Boc Pyrrolidine: *In Situ* React IR Spectroscopic Monitoring, Scope, and Synthetic Applications

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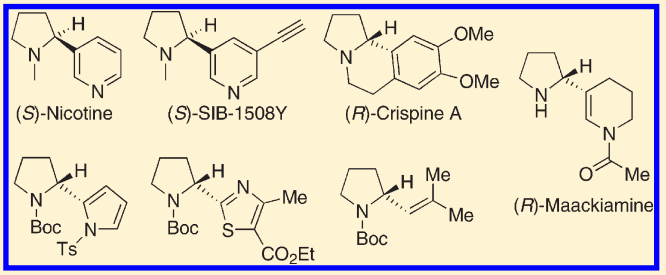
Supporting Information

ABSTRACT: A comprehensive study of the enantioselective Pd-catalyzed α-arylation of *N*-Boc pyrrolidine has been carried out. The protocol involves deprotonation of *N*-Boc pyrrolidine using *s*-BuLi/(−)-sparteine in TBME or Et_2O at −78 °C, transmetalation with $ZnCl_2$ and Negishi coupling using Pd-$(OAc)_2$, *t*-Bu_3P-HBF_4 and the aryl bromide. This paper reports several new features including *in situ* React IR spectroscopic monitoring of the process; use of (−)-sparteine and the (+)-sparteine surrogate to access products with opposite configuration; development of a catalytic asymmetric lithiation−Negishi coupling reaction; extension to a wide range of heteroaromatic bromides; total synthesis of (*R*)-crispine A, (*S*)-nicotine and (*S*)-SIB-1508Y *via* short synthetic routes; and examples of α-vinylation of *N*-Boc pyrrolidine using vinyl bromides exemplified by the total synthesis of naturally occurring (+)-maackiamine (thus establishing its configuration as (*R*)). In this way, the full scope and limitations of the methodology are delineated.



INTRODUCTION

α-Arylated nitrogen heterocycles represent an important pharmacophore in biologically active compounds. Indeed, there are three examples in the 2009 "Top 200 Pharmaceutical Products by Worldwide Sales":[1] Zetia (a cholesterol regulator), Cialis (treatment of erectile dysfunction) and Vesicare (treatment of urinary incontinence) (Figure 1). As a subset of α-arylated nitrogen heterocycles, biologically active pyrrolidines are especially prevalent, featuring in natural products and potential pharmaceuticals (Figure 2). Examples of natural products include (*S*)-nicotine, which as well as being a major constituent of tobacco exhibits important pharmacological effects on central nervous system (CNS) diseases;[2] (*R*)-crispine A, which shows cytotoxic activity against SKOV3, KB and HeLa human cancer lines;[3] and (*R*)-harmicine, which shows anti-leishmania activity.[4] The activity of (*S*)-nicotine at nicotinic acetylcholine receptors led to the synthesis and evaluation of nicotine analogues (*S*)-ABT 418 for the treatment of Alzheimer's disease[5] and (*S*)-SIB 1508Y for the treatment of Parkinson's disease.[6] Another example of an important α-arylated pyrrolidine is the non-peptide cholecystokinin (CCK) antagonist (*S*,*R*)-RP-66803.[7] In addition, α-arylated pyrrolidines are important structural motifs in chiral auxiliaries,[8] chiral catalysts for transition metals[9] and chiral organocatalysts.[10] Our interest in α-arylated pyrrolidines was initiated by the need to develop a practical and large-scale

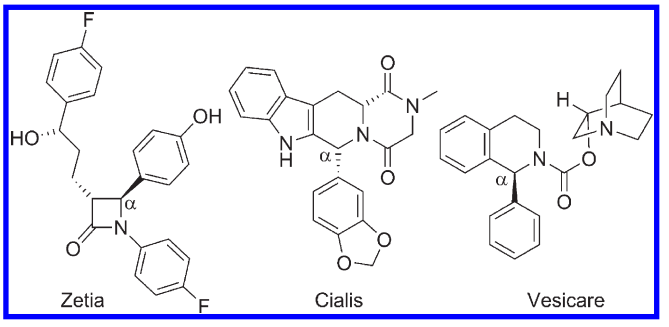


Figure 1. Examples of α-arylated nitrogen heterocycles from the "Top 200 Pharmaceutical Products by Wordwide Sales in 2009".[1]

asymmetric synthesis of the glucokinase activator (*R*)-**1**.[11] Ultimately, we developed a novel procedure for the α-arylation of *N*-Boc pyrrolidine[12] and implemented this technology in an efficient synthesis of (*R*)-**1**.[13]

Our overall aim was to develop new, general and versatile methodology for the asymmetric synthesis of structurally diverse α-arylated pyrrolidines such as those shown in Figure 2. An overview of the previous synthetic approaches to α-arylated

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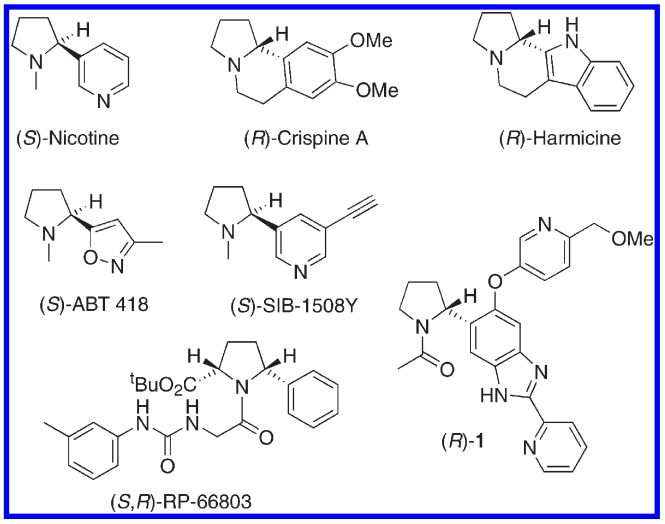
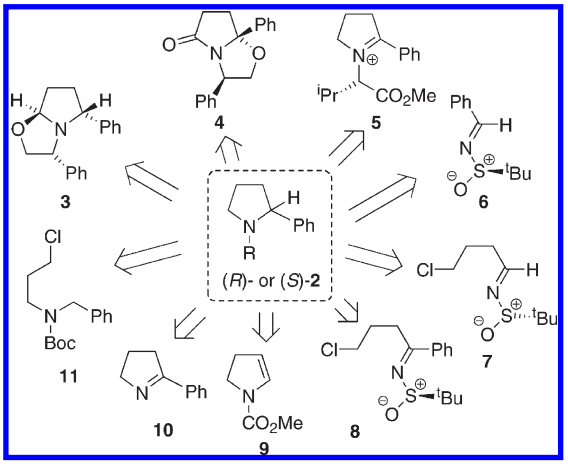


Figure 2. Examples of biologially active α-arylated pyrrolidines.

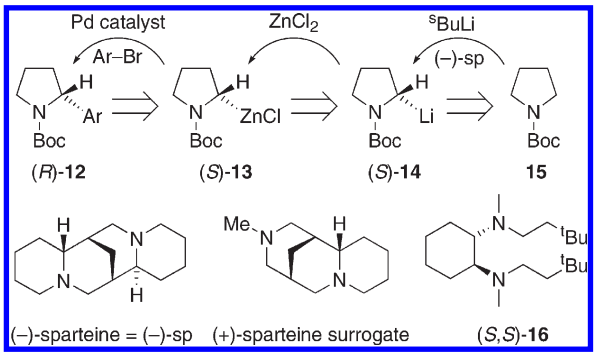
Scheme 1



pyrrolidine (*R*)- or (*S*)-**2** is summarized in Scheme 1. There have been several reports on chiral auxiliary approaches including the use of 1,3-oxazolidine **3**[14] and bicyclic lactam **4**[15] derived from phenylglycinol, reduction of a valine-derived iminium ion **5**[16] and nucleophilic addition to Ellman's *tert*-butylsulfinyl imines **6**,[17] **7**[18] and **8**.[19] Two examples of catalytic asymmetric syntheses of **2** have been described: a Pd-catalyzed Heck reaction of ene carbamate **9** followed by hydrogenation[20] and a chiral titanocene-mediated reduction of imine **10**.[21] Finally, lithiation−cyclization of *N*-Boc chloroamine **11** using *s*-BuLi and a stoichiometric amount of (−)-sparteine has also been used to prepare **2**.[22] Unfortunately, none of the methods in Scheme 1 appeared suitable for our purposes because they suffered from one or more of the following limitations: long synthetic sequences, low yields, lack of generality and modest diastereo- or enantioselectivity. Furthermore, simple variation of the aryl group and ready access to α-arylated pyrrolidines with (*R*)- or (*S*)-configuration were not facilitated by any of the routes.

Our approach to *N*-Boc protected α-arylated pyrrolidines (*R*)-**12**, shown in Scheme 2, addresses all of the aforementioned limitations. In contrast to the other routes in Scheme 1, a disconnection between the pyrrolidine ring and the aryl substituent

Scheme 2



provides the most convergent synthetic approach to (*R*)-**12**.[23] The aryl group would be installed using a Pd-catalyzed Negishi coupling[24] of an organozinc reagent such as (*S*)-**13** which could be obtained from the enantioenriched organolithium intermediate (*S*)-**14** (*via* transmetalation with $ZnCl_2$). Access to organolithium reagent (*S*)-**14** is possible using *s*-BuLi/(−)-sparteine-mediated asymmetric deprotonation of *N*-Boc pyrrolidine **15**, as pioneered by Beak et al.[25,26] Of note, the antipodal α-arylated pyrrolidines (*S*)-**12** could be accessed using the (+)-sparteine surrogate[27] or Alexakis diamine (*S,S*)-**16**.[28,29] Other aspects of the route outlined in Scheme 2 with encouraging precedent included the documented configurational stability of secondary organozinc reagents,[30] the Pd-catalyzed Negishi couplings of achiral secondary organozinc reagents with aryl halides[31] and Dieter and Li's development of a CuCN-catalyzed Pd-coupling of lithiated *N*-Boc pyrrolidine with aryl iodides as a route to racemic α-arylated pyrrolidines.[32]

The successful development and optimization of the approach outlined in Scheme 2 was the subject of our preliminary communication.[12] The optimized method involved deprotonation of *N*-Boc pyrrolidine **15** using *s*-BuLi/(−)-sparteine in TBME at −78 °C, transmetalation with 0.6 equiv of $ZnCl_2$[33] and Negishi coupling using $Pd(OAc)_2$, *t*-Bu_3P-HBF_4[34] and the aryl bromide. In this way, a wide range of arylated *N*-Boc pyrrolidines was prepared (60−87%, 96:4 er), and a number of groups have subsequently made use of this methodology. For example, Jacobsen and co-workers prepared a range of chiral α-aryl pyrrolidine organocatalysts,[10] Coldham and Leonori described the synthesis of racemic α-aryl *N*-Boc piperidines using *s*-BuLi/TMEDA-mediated lithiation,[35] Sutton et al. reported the parallel synthesis of inhibitors of heat shock protein 90,[36] Metallinos and Xu have carried out the synthesis of an α-arylated bicyclic urea[37] and Coldham et al.[38] and Beng and Gawley[39] have independently reported the synthesis of enantioenriched α-aryl *N*-Boc piperidines. Most recently, Knochel has described the diastereoselective arylation of 4-substituted *N*-Boc piperidines using a lithiation−Negishi coupling approach.[40] We have also applied the methodology to a concise formal synthesis of the CCK antagonist (*S,R*)-RP-66803 (Figure 2)[29] and an α-aryl *N*-Boc piperidine,[41] as well as developing a diamine-free lithiation−arylation of *N*-Boc pyrrolidine, a *N*-Boc imidazolidine and a *N*-Boc piperazine.[42] In this paper, we now describe important new features of the enantioselective Pd-catalyzed α-arylation of *N*-Boc pyrrolidine **15** including *in situ* React IR spectroscopic monitoring of the process, use of (−)-sparteine and the (+)-sparteine surrogate to access products with opposite configuration, development of a catalytic asymmetric lithiation−Negishi

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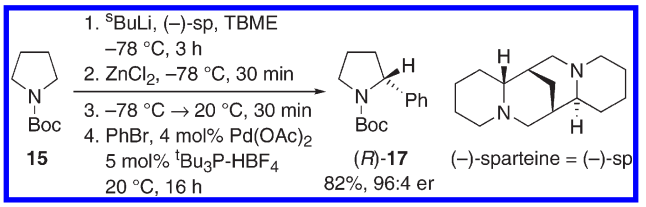
Scheme 3



coupling reaction and extension to a wide range of heteroaromatic bromides. In addition, we also report the total synthesis of (*R*)-crispine A, (*S*)-nicotine and (*S*)-SIB-1508Y and examples of α-vinylation of *N*-Boc pyrrolidine using vinyl bromides exemplified by the total synthesis of naturally occurring (+)-maackiamine (thus establishing its configuration as (*R*)).

RESULTS AND DISCUSSION

***In Situ* React IR Spectroscopic Monitoring of the Lithiation–Transmetalation–α-Arylation.** The conversion of *N*-Boc pyrrolidine **15** into (*R*)-**17** (82% yield, 96:4 er) *via* our optimized one-pot process of asymmetric deprotonation–transmetalation–Negishi coupling is shown in Scheme 3. The limiting reagent was bromobenzene, and the method utilized 1.2 equiv of *s*-BuLi/(−)-sparteine/*N*-Boc pyrrolidine **15** together with 0.6 equiv of $ZnCl_2$ relative to the lithiated *N*-Boc pyrrolidine. The high enantioselectivity indicates that transmetalation from lithium to zinc must occur below −60 °C since lithiated *N*-Boc pyrrolidine is configurationally unstable at higher temperatures.[25,43,44] Furthermore, the organozinc intermediate (which was not chraracterised but could be formulated as RZnCl, R_2Zn or R_3ZnLi) must be configurationally stable at 20 °C. The combination of $Pd(OAc)_2$ and *t*-Bu_3P-HBF_4 gave the best results for the Negishi coupling step, as previously described.[12]

As part of the optimization study, each stage of the deprotonation–transmetalation–Negishi coupling process was studied using *in situ* React IR spectroscopy. In particular, it was found that the $\nu_{C=O}$ of the Boc group was a suitable spectroscopic handle for monitoring the reaction. Thus, IR spectroscopy of a solution of (−)-sparteine and *N*-Boc pyrrolidine **15** in TBME at −70 °C gave a peak at 1697 cm^{-1} that was assigned to $\nu_{C=O}$ in *N*-Boc pyrrolidine **15**. As soon as *s*-BuLi was added, a new peak at 1644 cm^{-1} was visible in the IR spectrum (Figure 3) that was assigned to $\nu_{C=O}$ in lithiated *N*-Boc pyrrolidine (*S*)-**14** on the basis of comparison with our previous work on the React IR spectroscopic monitoring of lithiated *N*-Boc piperidine ($\nu_{C=O}$ = 1644 cm^{-1}).[41] Of note, lithiation of *N*-Boc pyrrolidine **15** using *s*-BuLi/(−)-sparteine was complete within 60 min, indicating that it is not necessary to carry out such lithiations over long time periods (typically 4–6 h[25]). On close inspection, there was evidence of a prelithiation complex formed by *s*-BuLi/(−)-sparteine complexing to the carbonyl of the Boc group ($\nu_{C=O}$ = 1675 cm^{-1}). This was, however, a fleeting intermediate presumably because lithiation from the prelithiation complex occurred readily.

Next, the transmetalation of lithium to zinc was monitored. Thus, addition of 1.0 equiv of $ZnCl_2$ led to little change to the IR spectra at −70 °C (Figure 4). However, upon warming to 20 °C, a new, broader peak was observed ($\nu_{C=O}$ = 1653 cm^{-1}) that was assigned to an organozinc species (RZnCl, R_2Zn or R_3ZnLi). Finally, it was also possible to follow the Negishi coupling step in a similar manner. After addition of bromobenzene, $Pd(OAc)_2$ and *t*-Bu_3P-HBF_4, a new peak at 1702 cm^{-1} (assigned to $\nu_{C=O}$ in the product, α-aryl pyrrolidine (*R*)-**17**) was observed (Figure 5). Thus, we have demonstrated that *in situ* React IR spectroscopy is a useful tool for monitoring and optimizing this type of

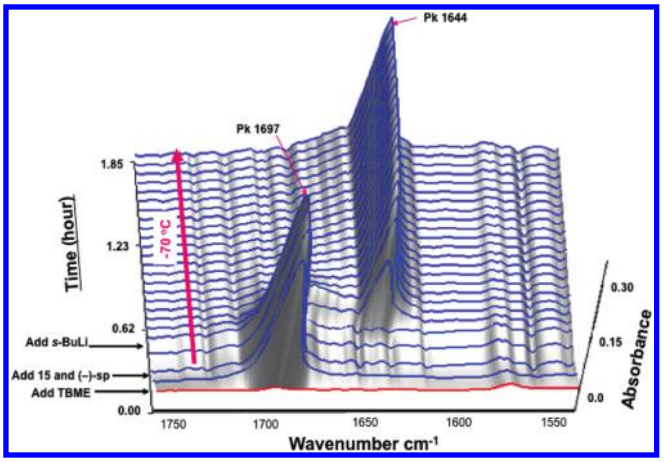


Figure 3. *In situ* React IR spectroscopic monitoring of the lithiation of *N*-Boc pyrrolidine **15**.

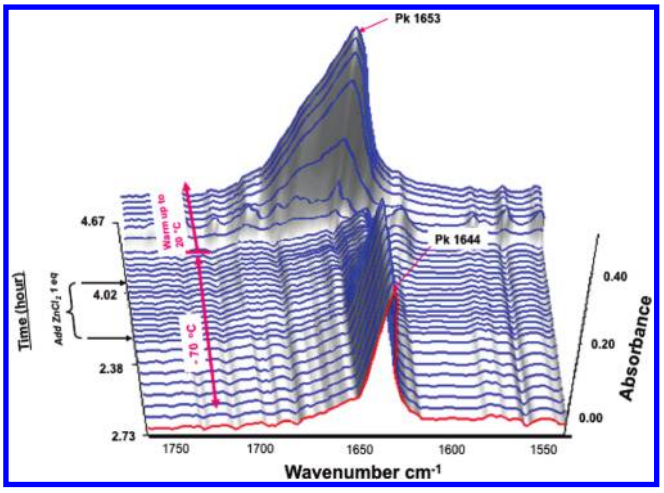


Figure 4. *In situ* React IR spectroscopic monitoring of the transmetalation step (lithium to zinc).

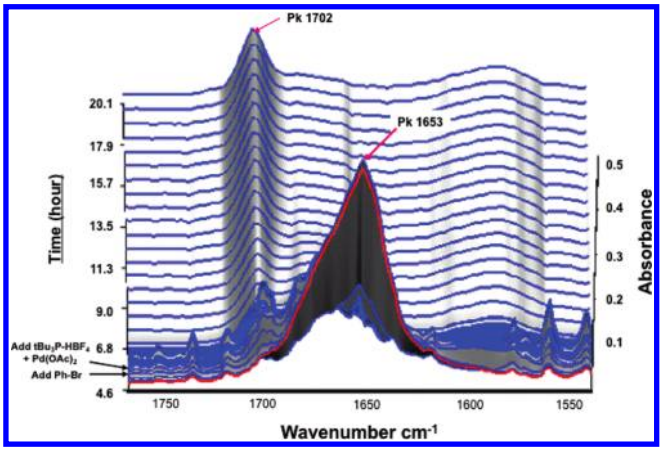


Figure 5. *In situ* React IR spectroscopic monitoring of the Negishi coupling step.

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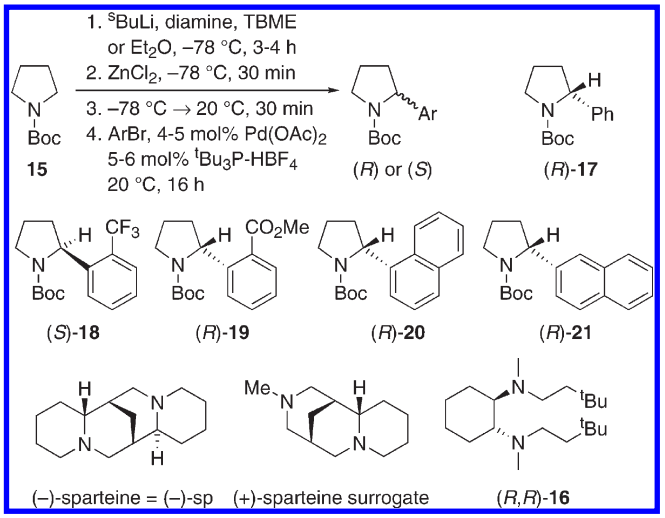
Table 1. Asymmetric Deprotonation−Transmetallation−Negishi Coupling of *N*-Boc Pyrrolidine 15



entry	Ar-Br	diamine	solvent	product	yield (%)[a]	er (*R*:*S*)[b]
1	PhBr	(−)-sp	TBME	(*R*)-**17**	82	96:4
2	PhI	(−)-sp	TBME	(*R*)-**17**	56	96:4
3	PhBr	(*R*,*R*)-**16**	Et_2O	(*R*)-**17**	35	95:5
4	PhBr	(+)-sp surrogate	Et_2O	(*S*)-**17**	71	5:95
5	*o*-$CF_3C_6H_4Br$	(−)-sp	Et_2O	(*R*)-**18**	69	95:5
6	*o*-$CF_3C_6H_4Br$	(+)-sp surrogate	Et_2O	(*S*)-**18**	69	5:95
7	*o*-$CF_3C_6H_4Br$	TMEDA	Et_2O	*rac*-**18**	12	
8	*o*-$CO_2MeC_6H_4Br$	(−)-sp	TBME	(*R*)-**19**	71	96:4
9	1-Naphthyl-Br	(−)-sp	TBME	(*R*)-**20**	79	96:4
10	2-Naphthyl-Br	(−)-sp	TBME	(*R*)-**21**	82	95:5

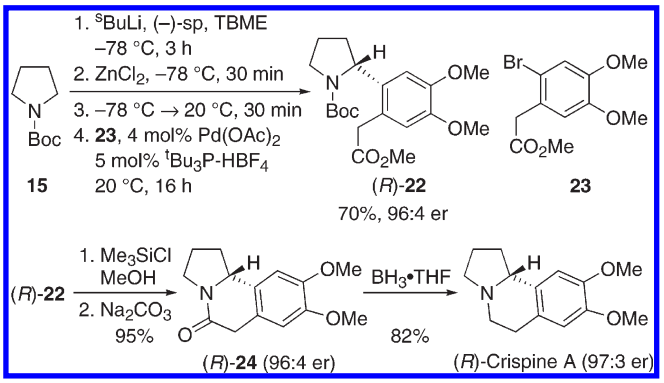
[a] Yield after purification by column chromatography. [b] Enantiomeric ratio (er) determined by CSP-HPLC.

lithiation−transmetalation−Negishi coupling process. Such an approach could prove very useful for related types of lithiation−transmetalation processes.

α-Arylation Using Simple Aryl Bromides: Synthesis of (*R*)-Crispine A. To start with, the scope of the originally reported asymmetric deprotonation−transmetalation−Negishi coupling process was explored. In Table 1, a selection of new results (entries 2−10) are compared with the result using (−)-sparteine and bromobenzene (entry 1, 82% yield, 96:4 er). Deprotonation with *s*-BuLi/(−)-sparteine and Negishi reaction with iodobenzene gave α-aryl pyrrolidine (*R*)-**17** (96:4 er) in 56% yield (Table 1, entry 2), which shows that although aryl iodides are compatible coupling partners, they are inferior to aryl bromides. We had previously shown[12] that chlorobenzene was also less efficient (48% yield, 96:4 er) and that aryl triflates and aryl tosylates gave <5% yield under the same conditions. Thus, aryl bromides are the coupling partners of choice for this process. The reaction works equally well in Et_2O or in TBME as solvent (Table 1, entries 1, 4−6 and 8−10). Four new examples using (−)-sparteine are shown in Table 1 and allowed the synthesis of CF_3-containing (*R*)-**18** (entry 5, 69%, 95:5 er), methyl ester-containing (*R*)-**19** (entry 8, 71%, 96:4 er) and naphthyl-substituted pyrrolidines (*R*)-**20** (entry 9, 79%, 96:4 er) and (*R*)-**21** (entry 10, 82%, 95:5 er).

As part of this study, we have also shown that α-aryl pyrrolidines with configuration opposite to that obtained with

Scheme 4



(−)-sparteine can be generated using the (+)-sparteine surrogate[27] and Alexakis diamine (*S*,*S*)-**16**.[28,29] Use of the "sparteine-like" (+)-sparteine surrogate was successful: α-aryl pyrrolidines (*S*)-**17** (entry 4, 71%, 95:5 er) and (*S*)-**18** (entry 6, 69%, 95:5 er) were obtained in yields and enantioselectivity comparable to those obtained using (−)-sparteine (compare with entries 1 and 5, respectively). In contrast, lithiation with *s*-BuLi/diamine (*R*,*R*)-**16** and subsequent transmetalation−Negishi coupling gave pyrrolidine (*R*)-**17** in high enantioselectivity (95:5 er) but moderate 35% yield (entry 3). Attempts to improve the yield using $Pd_2(dba)_3$ or $Pd(OAc)_2$ with Hartwig's Ru-phos[45] or Buchwald's Q-phos[46] were unsuccessful. We believe that diamine (*R*,*R*)-**16** can interfere with the Negishi coupling step (presumably by coordination to palladium) since we have also observed low yields in attempted racemic lithiation (using *s*-BuLi/TMEDA)−transmetalation−Negishi couplings with *N*-Boc pyrrolidine **15**. A 12% yield of *rac*-**18** (entry 7) is representative, and we conclude that TMEDA and "TMEDA-like" diamines such as (*R*,*R*)-**16** should be avoided. However, this effect does depend on the *N*-Boc heterocycle since high-yielding syntheses of racemic α-aryl *N*-Boc piperidines using *s*-BuLi/TMEDA-mediated lithiation have been described.[35,40]

Our deprotonation−transmetalation−Negishi coupling process is also suitable for natural product synthesis, and the cytotoxic alkaloid (*R*)-crispine A, isolated from *Carduus Crispus*,[3] was selected as an appropriate target. In recent times, (*R*)- or (*S*)-crispine A has proved to be a popular target molecule, and several asymmetric strategies have been reported.[47] The shortest route to (*R*)-crispine A is 3 steps (32% overall yield) and is also the most recently reported synthesis.[47k] For our approach, we adopted a concise route from *N*-Boc pyrrolidine **15** *via* a connective strategy that was distinct to all previous approaches; (−)-sparteine was utilized as it would provide the naturally occurring (*R*)-configuration (Scheme 4). Thus, *N*-Boc pyrrolidine **15** was deprotonated using *s*-BuLi/(−)-sparteine in TBME and subjected to transmetalation and Negishi coupling with known[48] aryl bromide **23**. This gave adduct (*R*)-**22** in 70% yield and 96:4 er. Deprotection of the Boc group using TFA in CH_2Cl_2 led to racemization. Presumably, the C−N bond of the pyrrolidine ring is readily cleaved under these acidic conditions since the resulting carbocation would be stabilized by the electron-rich aromatic ring. In contrast, use of Me_3SiCl/MeOH to cleave the Boc group gave no loss of er, and cyclization to lactam (*R*)-**24** ensued (95% yield, 96:4 er). Finally, borane reduction of the lactam delivered (*R*)-crispine A (82% yield, 97:3 er). This is an efficient synthesis of (*R*)-crispine A (54% yield over 3 steps from

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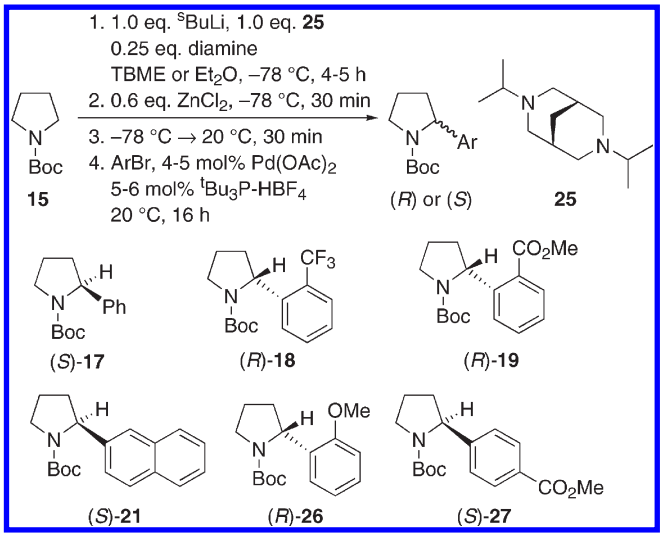
Table 2. Catalytic Asymmetric Deprotonation−Transmetallation−Negishi Coupling of *N*-Boc Pyrrolidine 15



entry	Ar-Br	diamine	solvent	product	yield (%)[a]	er (*R*:*S*)[b]
1	PhBr	(+)-sp surrogate	TBME[c]	(*S*)-**17**	80	5:95
2	*o*-$CF_3C_6H_4Br$	(−)-sp	Et_2O	(*R*)-**18**	76	80:20
3	*o*-$CF_3C_6H_4Br$	(+)-sp surrogate	Et_2O	(*S*)-**18**	75	9:91
4	*o*-$CO_2MeC_6H_4Br$	(−)-sp	Et_2O	(*R*)-**19**	50	81:19
5	2-Naphthyl-Br	(+)-sp surrogate	TBME[c]	(*S*)-**21**	77	4:96
6	*o*-$MeOC_6H_4Br$	(−)-sp	Et_2O	(*R*)-**26**	50	80:20
7	*o*-$MeOC_6H_4Br$	(+)-sp surrogate	Et_2O	(*S*)-**26**	87	4:96
8	*p*-$CO_2MeC_6H_4Br$	(+)-sp surrogate	TBME[c]	(*S*)-**27**	85	7:93

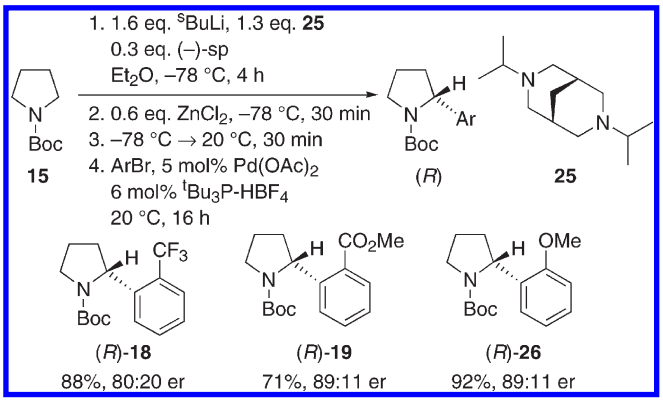
[a] Yield after purification by column chromatography. [b] Enantiomeric ratio (er) determined by CSP-HPLC. [c] 0.35 equiv of $ZnCl_2$ used for the transmetalation step.

bromide **23**) and demonstrates the synthetic potential of the methodology.

Catalytic Asymmetric Lithiation−α-Arylation of *N*-Boc Pyrrolidine. Next, we planned to determine whether the transmetalation−Negishi coupling protocol was compatible with the two-ligand catalytic asymmetric deprotonation methodology developed in our group.[49] In 2005, we disclosed that efficient asymmetric deprotonation of *N*-Boc pyrrolidine **15** could be achieved using *s*-BuLi and substoichiometric amounts (0.2−0.3 equiv) of (−)-sparteine or the (+)-sparteine surrogate provided that a second diamine, di-*i*-Pr-bispidine **25**, is present.[48a] This process is referred to as two-ligand catalysis, and the second diamine ligand was required to enable recycling of the chiral ligand. Thus, two-ligand catalytic asymmetric deprotonation−transmetalation−Negishi coupling was explored (Table 2).

The standard procedure involved deprotonation of *N*-Boc pyrrolidine **15** using 1.0 equiv of *s*-BuLi, 0.25 equiv of (−)-sparteine or the (+)-sparteine surrogate and 1.0 equiv of di-*i*-Pr-bispidine **25** in Et_2O or TBME at −78 °C for 4−5 h. Transmetalation was accomplished using 0.6 equiv of $ZnCl_2$, and Negishi coupling was carried out in the usual way (aryl bromide, $Pd(OAc)_2$ and *t*-Bu_3P-HBF_4, 20 °C, 16 h). With (−)-sparteine, these conditions gave disappointing results as α-aryl pyrrolidines (*R*)-**18**, (*R*)-**19** and (*R*)-**26** were generated in only ∼80:20 er (Table 2, entries 2, 4 and 6). In contrast, the (+)-sparteine surrogate faired much better, and a range of α-aryl pyrrolidines

Scheme 5



was prepared in 91:9−96:4 er (Table 2, entries 1, 3, 5 and 7−8) using only 0.25 equiv of the chiral diamine. The improved results of the (+)-sparteine surrogate compared to those using (−)-sparteine in two-ligand catalytic asymmetric deprotonations have been noted before and can be explained by a more efficient catalysis caused by a higher reactivity of the *s*-BuLi/(+)−sparteine surrogate complex.[49a,b]

In previous work, it has been shown that better enantioselectivity with (−)-sparteine can be observed using slightly different lithiation conditions and a higher loading of (−)-sparteine: 1.6 equiv of *s*-BuLi, 0.3 equiv of (−)-sparteine and 1.3 equiv of di-*i*-Pr-bispidine **25**.[49c] Under these conditions, we were able to prepare pyrrolidines (*R*)-**19** and (*R*)-**26** in 89:11 er, but surprisingly, there was no improvement in enantioselectivity in the formation of CF_3-substituted pyrrolidine (*R*)-**18** (80:20 er) (Scheme 5). Thus, we conclude that the Negishi protocol can be run effectively under a two-ligand catalytic asymmetric deprotonation manifold using either (−)-sparteine or the (+)-sparteine surrogate.

α-Arylation Using Heteroaryl Bromides: Synthesis of (*S*)-SIB-1508Y and (*S*)-Nicotine. Since aromatic heterocycles are key structural features of many pharmaceuticals and are present in the Alzheimer's drug (*S*)-ABT 418, the Parkinson's drug (*S*)-SIB 1508Y and glucokinase activator (*R*)-**1** (Figure 2), we carried out lithiation−transmetalation−Negishi coupling with an array of heterocyclic aryl bromides. Previously, we had reported the successful coupling with 3-bromopyridine, a Boc-protected bromoindole and even an unprotected bromoindole.[12] We extended the study to include protected pyrroles, a thiophene, thiazoles and functionalized pyridines. In all cases, α-aryl pyrrolidines (*R*)-**28**−**36** were formed in good yield (58−76%) and high enantioselectivity (94:6−97:3 er) (Scheme 6).

The results observed with the different bromopyridines are worthy of further comment. Under standard Negishi coupling conditions ($Pd(OAc)_2$ and *t*-Bu_3P-HBF_4, 20 °C, 16 h) with 3-bromopyridine, adduct (*R*)-**33** was formed in only 15% yield. By carrying out the Negishi reaction for 16 h at 60 °C, a significant improvement was observed: adduct (*R*)-**33** was isolated in 60% yield. We suspect that the nitrogen in 3-bromopyridine can coordinate to the Pd and interfere with the Pd coupling step. It appears that such interference only occurs for a pyridine with a sterically unhindered nitrogen lone pair since 2-bromopyridine (→ (*R*)-**34**, 71%) and 2-substituted 3-bromopyridines (→ (*R*)-**35**, 76%; → (*R*)-**36**, 70%) gave high yields from Negishi reactions conducted at 20 °C. Finally, a catalytic asymmetric

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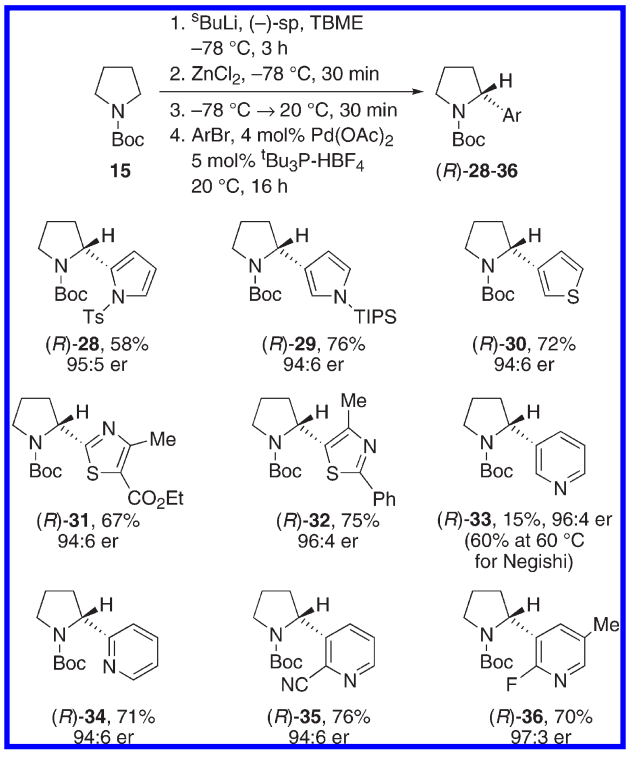
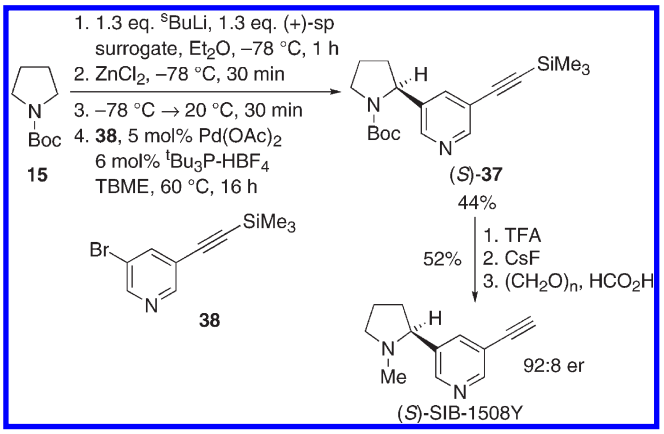
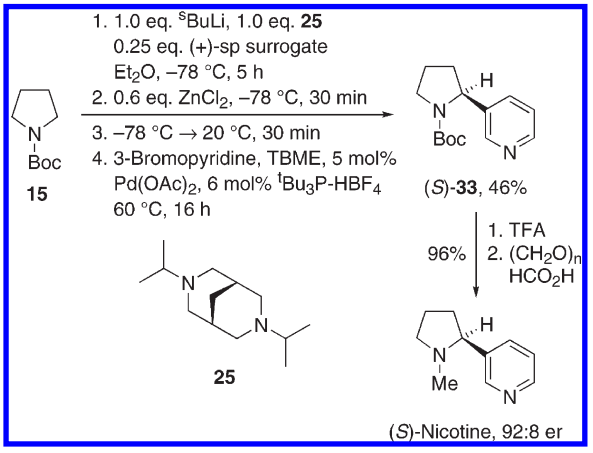
Scheme 6



Scheme 7



Scheme 8



deprotonation variant (1.0 equiv of *s*-BuLi, 0.25 equiv of (+)-sparteine surrogate and 1.0 equiv of di-*i*-Pr-bispidine **25**) was used to prepare α-aryl pyrrolidine (*S*)-**34** in 70% yield and 94:6 er.

Next, we set about applying the methodology to the total synthesis of the Parkinson's drug (*S*)-SIB 1508Y[6] and naturally occurring (*S*)-nicotine.[2] In both cases, the configuration dictated that the (+)-sparteine surrogate would be required. Our convergent synthetic approach would involve disconnection between the pyrrolidine ring and the pyridyl group and is a strategy not previously adopted in accessing the α-pyridyl pyrrolidine motif. There has been limited published work on the synthesis of (*S*)-SIB 1508Y,[50] and Comins' five-step synthesis from (*S*)-nicotine is the shortest.[50e] Our synthesis is depicted in Scheme 7. Thus, stoichiometric lithiation of *N*-Boc pyrrolidine **15** using *s*-BuLi/(+)-sparteine surrogate and subsequent transmetalation−Negishi coupling with bromopyridine **38** (prepared from 3,5-dibromopyridine, see Experimental Section) (at 60 °C) delivered α-aryl pyrrolidine (*S*)-**37** in 44% yield. The best way of converting (*S*)-**37** into (*S*)-SIB 1508Y involved Boc deprotection with TFA, fluoride-mediated removal of the trimethylsilyl group and Eschweiler−Clarke *N*-methylation. These reactions were carried out without intermediate purification, and (*S*)-SIB 1508Y was isolated in 52% yield. Analysis by ^{1}H NMR spectroscopy in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol indicated that (*S*)-SIB 1508Y was formed with 92:8 er.

A similar approach was successful for the synthesis of naturally occurring (*S*)-nicotine.[51] In this case, we adopted a catalytic asymmetric deprotonation using 1.0 equiv of *s*-BuLi, 0.25 equiv of (+)-sparteine surrogate and 1.0 equiv of di-*i*-Pr-bispidine **25**. Subsequent transmetalation and Negishi coupling with 3-bromopyridine at 60 °C gave α-aryl pyrrolidine (*S*)-**33** in 46% yield (Scheme 8). Then, the Boc group was removed using TFA, and Eschweiler−Clarke *N*-methylation afforded (*S*)-nicotine in 96% yield and 92:8 er (by ^{1}H NMR spectroscopy in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol). This two-step catalytic asymmetric synthesis of (*S*)-nicotine (44% overall yield) is the most direct approach reported to date.

α-Vinylation of *N*-Boc Pyrrolidine: Synthesis of (*R*)-(+)-Maackiamine. Finally, a preliminary study on extending the Negishi coupling methodology to vinylation was carried out. Recently, Beng and Gawley have disclosed the first examples of lithiation−transmetalation−Negishi coupling to prepare two α-vinyl piperidines.[39] In our hands, we found that changing the Pd source from $Pd(OAc)_2$ to $Pd_2(dba)_3$ gave optimal results, and four examples are summarized in Scheme 9. In all cases, good yields (67−73%) of products (*R*)-**39**−**42** were obtained. α-Vinyl pyrrolidines (*R*)-**39** and (*R*)-**40** were formed with 95:5 and 97:3 er, respectively. Although the er values of α-vinyl pyrrolidines (*R*,*E*)-**41** and (*R*,*Z*)-**42** were not determined (as suitable CSP-HPLC conditions could not be found), we were able to show that the *E*/*Z* stereochemistry in the starting vinyl bromides was maintained in the products.

The α-vinylation methodology was then applied to the total synthesis of (*R*)-maackiamine. The isolation of maackiamine from the flower of the Amur maackia tree, *Maackia amurensis*, was reported in 1989, and the absolute configuration was not determined.[52] There has been no directed synthetic efforts

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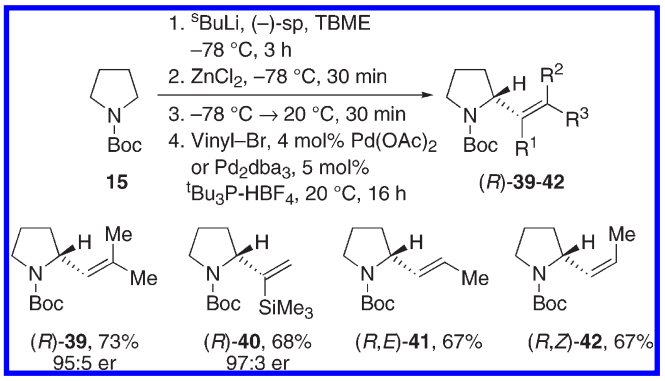
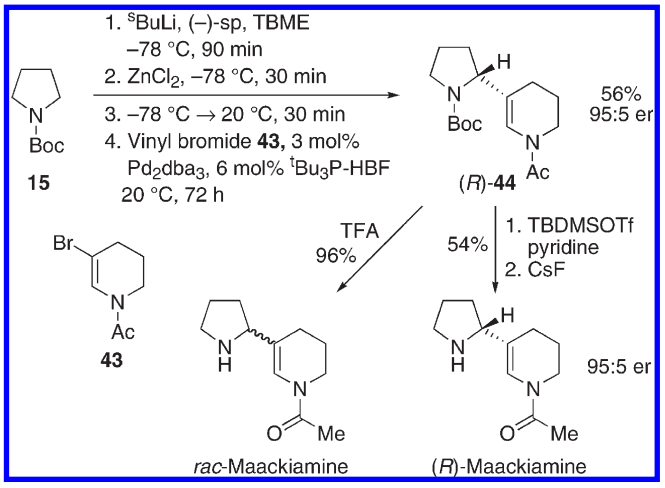
Scheme 9



Scheme 10



toward maackiamine, although Fitch and Djerassi did in fact report a synthesis of *rac*-maackiamine in 1974,[53] some 25 years *before* the isolation and characterization of natural maackiamine!

Our synthesis of (*R*)-maackiamine is shown in Scheme 10. Asymmetric deprotonation of *N*-Boc pyrrolidine **15** was accomplished using *s*-BuLi and stoichiometric (−)-sparteine in TBME (−78 °C, 90 min). Then, addition of $ZnCl_2$ was followed by Negishi coupling with vinyl bromide **43** (prepared in 3 steps from piperidine, see Experimental Section) using $Pd_2(dba)_3$ to give α-vinyl pyrrolidine (*R*)-**44** in 56% yield and 95:5 er (CSP-HPLC). Boc deprotection using TFA gave maackiamine in high yield (96%), but analysis by ^{1}H NMR spectroscopy in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol indicated that complete racemization had occurred. Presumably, cleavage of the C−N bond of the pyrrolidine ring *via* participation of the nucleophilic enamine can occur under the acidic conditions. Such an issue upon Boc deprotection may be a general problem with electron-rich α-aryl or α-vinyl substituents as racemization was also observed in the synthesis of (*R*)-crispine A. To solve this racemization problem, a non-acidic method for the removal of the Boc protecting group was required, and we turned to Ohfune's TBDMSOTf/pyridine methodology.[54] Reaction of α-vinyl pyrrolidine (*R*)-**44** with TBDMSOTf/pyridine in CH_2Cl_2 at room temperature for 16 h gave an intermediate silyloxy carbonyl compound. Treatment of this with CsF then delivered (*R*)-maackiamine of 95:5 er (by ^{1}H NMR spectroscopy in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol) in 54% yield. Our synthetic sample exhibited $[\alpha]_D$ +12.8 (*c* 1.0 in EtOH), which had the same sign as that reported for natural maackiamine ($[\alpha]_D$ +110 (*c* 0.01 in EtOH)), although we cannot explain the discrepancy in the magnitude of the two $[\alpha]_D$ values. The use of *s*-BuLi/(−)-sparteine for the asymmetric deprotonation and its well-established preference for removal of the *pro-S* proton (*vide infra*)[25] thus established the absolute configuration of natural maackiamine as (*R*).

CONCLUSION

In summary, the scope of the enantioselective Pd-catalyzed α-arylation of *N*-Boc pyrrolidine **15** has been explored. We believe that the methodology represents an important addition to the armory of synthetic chemists working in academia and in the pharmaceutical industry. Indeed, many groups have already realized the utility of the methodology for their own studies.[10,9,35−42] Of note, we have shown that (−)-sparteine and the (+)-sparteine surrogate allow access to products with opposite configuration and the approach can be coupled with two-ligand catalytic asymmetric deprotonation. Furthermore, concise syntheses of (*R*)-crispine A, (*S*)-nicotine and (*S*)-SIB-1508Y together with the first asymmetric synthesis of (*R*)-maackiamine exemplify the synthetic utility of the methodology.

EXPERIMENTAL SECTION

General. Water is distilled water. Brine refers to a saturated aqueous solution of NaCl. Et_2O and TBME were freshly distilled from sodium and benzophenone ketyl. (−)-Sparteine and *N*-Boc pyrrolidine were distilled over CaH_2 before use. Petrol refers to the fraction of petroleum ether boiling in the range 40−60 °C. All reactions were carried out under O_2-free Ar using oven-dried and/or flame-dried glassware. *s*-BuLi was titrated against *N*-benzylbenzamide[55] or *N*-pivaloyl-*o*-toluamide before use. *N*-Boc pyrrolidine **15**,[2] Alexakis' diamine (*R*,*R*)-**16**[3] and di-*i*-Pr-bispidine **25**[4] were prepared according to the published procedures.

Flash column chromatography was carried out using Chemie GmbH silica (220−440 mesh) or silica gel 60 (0.04−0.063 mm particle size). Thin layer chromatography was carried out using F_{254} aluminum-backed silica plates. ^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a −400 MHz instrument with an internal deuterium lock. Chemical shifts are quoted as parts per million and referenced to $CHCl_3$ (δ_H 7.27) and or $CDCl_3$ (δ_C 77.0, central line of triplet). ^{13}C NMR spectra were recorded with broadband proton decoupling. ^{13}C NMR spectra were assigned using DEPT experiments. Coupling constants (*J*) are quoted in hertz. IR spectra were recorded on a FTIR spectrometer. Boiling points given for compounds purified by Kugelrohr distillation correspond to the oven temperature during distillation. Electrospray high and low resolution mass spectra were recorded on a microOTOF spectrometer. Chiral stationary phase HPLC was performed with a multiple wavelength, UV−vis diode array detector; integration was performed at 210, 230, and 250 nm. Optical rotations were recorded at 20 °C (using the sodium D line; 259 nm), and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^3 g^{-1}.

An FTIR analyzer, ReactIR 4000 with a MCT detector, a KBr beam splitter and an ATR probe (DiComp) was used for all experiments. The DiComp probe was interfaced to a 250-mL glass vessel. A mechanical stirrer at 200 rpm provided adequate agitation. Nitrogen purge on the IR system was maintained throughout any experiment, and nitrogen background was used in computing the absorbance spectra. Each spectrum represents 32 co-added scans measured at a spectral resolution of 4 cm^{-1} in the 4000−650 cm^{-1} range with the Happ−Genzel apodization.

General Procedure A: Stoichiometric Lithiation−Negishi Coupling in TBME. *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane,

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5.7 mmol, 1.0 equiv) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol) and (−)-sparteine (1.3 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL) at −78 °C under N_2 (keeping the internal temperature below −68 °C). The resulting solution was stirred at −74 °C for 3 h. Then, $ZnCl_2$ (3.4 mL of a 1.0 M solution in Et_2O, 3.4 mmol, 0.6 equiv) was added dropwise (keeping the internal temperature below −68 °C), and the resulting solution was stirred at −74 °C for 30 min. Then, the solution was allowed to warm to 20 °C and stirred at 20 °C for 30 min. The aryl bromide or vinyl bromide (4.75 mmol, 0.83 equiv) was added. A mixture of $Pd(OAc)_2$ (51 mg, 0.23 mmol, 0.04 equiv) or $Pd_2(dba)_3$ (200 mg, 0.23 mmol, 0.02 equiv) and *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) was added in one portion, and the resulting solution was stirred at 20 °C for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.35 mL) was added, and the solution was stirred at rt for 1 h. The solids were removed by filtration through Celite and washed with TBME (60 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (50 mL) and water (2 × 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure B: Catalytic Lithiation−Negishi Coupling in TBME (0.25 equiv of Diamine). *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol), (+)-sparteine surrogate (291 μL, 1.4 mmol, 0.25 equiv) and di-*i*-Pr-bispidine **25** (1.23 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL) at −78 °C under N_2 (keeping the internal temperature below −68 °C). The resulting solution was stirred at −74 °C for 3 h. Then, $ZnCl_2$ (2.0 mL of a 1.0 M solution in Et_2O, 2.0 mmol, 0.35 equiv) was added dropwise (keeping the internal temperature below −68 °C), and the resulting solution was stirred at −74 °C for 30 min. Then, the solution was allowed to warm to 20 °C and stirred at 20 °C for 30 min. The aryl bromide (4.75 mmol, 0.83 equiv) was added. A mixture of $Pd(OAc)_2$ (51 mg, 0.23 mmol, 0.04 equiv) and *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) was added in one portion, and the resulting solution was stirred at 20 °C for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.35 mL) was added, and the solution was stirred at rt for 1 h. The solids were removed by filtration through Celite and washed with TBME (60 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (50 mL) and water (2 × 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General Procedure C: Catalytic Lithiation−Negishi Coupling in Et_2O (0.25 equiv of Diamine). *s*-BuLi (2.2 mL of a 1.3 M solution in cyclohexane, 2.9 mmol, 1.0 equiv) was added dropwise to a stirred solution of (−)-sparteine or (+)-sparteine surrogate (0.7 mmol, 0.25 equiv) and di-*i*-Pr-bispidine **25** (606 mg, 2.9 mmol, 1.0 equiv) in Et_2O (6 mL) at −78 °C under Ar. After stirring at −78 °C for 15 min, a solution of *N*-Boc pyrrolidine **15** (493 mg, 505 μL, 2.9 mmol) in Et_2O (1 mL) was added dropwise. The resulting solution was stirred at −78 °C for 4 h. Then, $ZnCl_2$ (1.7 mL of a 1.0 M solution in Et_2O, 1.7 mmol, 0.6 equiv) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. Then, the solution was allowed to warm to rt and stirred at rt for 30 min. The aryl bromide (2.0 mmol, 0.83 equiv) was added. A mixture of $Pd(OAc)_2$ (31 mg, 0.14 mmol, 0.05 equiv) and *t*-Bu_3PHBF_4 (32 mg, 0.18 mmol, 0.06 equiv) was added in one portion, the resulting solution was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.2 mL) was added, and the solution was stirred at rt for 1 h. The solids were removed by filtration through Celite and washed with Et_2O (2 × 10 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (20 mL) and water (2 × 20 mL), dried ($MgSO_4$) and evaporated under reducted pressure to give the crude product.

General Procedure D: Catalytic Lithiation−Negishi Coupling in Et_2O (0.3 equiv of Diamine). *s*-BuLi (1.5 mL of a 1.3 M solution in cyclohexane, 2.0 mmol, 1.6 equiv) was added dropwise to a stirred solution of (−)-sparteine (88 mg, 0.4 mmol, 0.3 equiv) and di-*i*-Pr-bispidine **25** (342 mg, 1.6 mmol, 1.3 equiv) in Et_2O (6 mL) at −78 °C under Ar. After stirring at −78 °C for 15 min, a solution of *N*-Boc pyrrolidine **15** (214 mg, 1.25 mmol) in Et_2O (1 mL) was added dropwise. The resulting solution was stirred at −78 °C for 4 h. Then, $ZnCl_2$ (750 μL of a 1.0 M solution in Et_2O, 0.75 mmol, 0.6 equiv) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. Then, the solution was allowed to warm to rt and stirred at rt for 30 min. The aryl bromide (0.9 mmol, 0.83 equiv) was added. A mixture of $Pd(OAc)_2$ (14 mg, 0.06 mmol, 0.05 equiv) and *t*-Bu_3PHBF_4 (14 mg, 0.08 mmol, 0.06 equiv) was added in one portion, and the resulting solution was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.2 mL) was added, and the solution was stirred at rt for 1 h. The solids were removed by filtration through Celite and washed with Et_2O (2 × 10 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (20 mL) and water (2 × 20 mL), dried ($MgSO_4$) and evaporated under reducted pressure to give the crude product.

React IR Spectroscopic Monitoring of the Lithiation−Transmetalation−Negishi Coupling of *N*-Boc Pyrrolidine 15 (see Figures 3, 4, and 5). TBME (63 mL) was added to a vessel equipped with a stirrer bar, thermocouple and ReactIR probe under N_2. Then *N*-Boc pyrrolidine **15** (3.0 mL, 0.017 mol) was added to the vessel followed by (−)-sparteine (3.1 mL, 0.0176 mol, 1.0 equiv). The stirred reaction was cooled to −70 °C and aged for 1 h (for stability of readout on React IR). Then, *s*-BuLi (14 mL of a 1.26 M solution in cyclohexane, 0.0176 mol, 1.0 equiv) was added at −70 °C, keeping the temperature below −65 °C, and the reaction was aged for 3 h at −70 °C. Then, $ZnCl_2$ (12 mL of a 1.0 M solution in Et_2O, 0.012 mol, 0.7 equiv) was added dropwise (keeping the internal temperature below −68 °C), and the resulting solution was stirred at −70 °C for 30 min. Then, the solution was allowed to warm to 20 °C and stirred at 20 °C for 30 min. Bromobenzene (1.5 mL, 0.0145 mol, 0.83 equiv) was added. A mixture of $Pd(OAc)_2$ (153 mg, 0.7 mmol, 0.04 equiv) and *t*-Bu_3PHBF_4 (250 mg, 0.9 mmol, 0.05 equiv) was added in one portion, and the resulting solution was stirred at 20 °C for 16 h.

For *N*-Boc pyrrolidine **15**, a $\nu_{C=O}$ peak at 1697 cm^{-1} was observed. After addition of (−)-sparteine and then *s*-BuLi, a new peak at 1644 cm^{-1} was observed, which was assigned to $\nu_{C=O}$ in the lithiated intermediate (*S*)-**14**. On close inspection, there was evidence of a prelithiation complex formed by *s*-BuLi/(−)-sparteine complexing to the carbonyl of the Boc group ($\nu_{C=O}$ = 1675 cm^{-1}). After a lithiation time of 60 min, complete lithiation of *N*-Boc pyrrolidine **15** to give lithiated intermediate (*S*)-**14** was observed. After addition of $ZnCl_2$, there was little change to the IR spectra at −70 °C. However, upon warming to 20 °C, a new, broader peak at $\nu_{C=O}$ = 1653 cm^{-1} was observed that was assigned to an organozinc species (RZnCl, R_2ZN or R_3ZnLi). After addition of bromobenzene, $Pd(OAc)_2$ and *t*-Bu_3P-HBF_4, a new peak at 1702 cm^{-1} (assigned to $\nu_{C=O}$ in the product, α-aryl pyrrolidine (*R*)-**17**) was observed.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-phenyl Pyrrolidine (*R*)-17 (Table 1, entry 1). Using general procedure A, *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv), *N*-Boc pyrrolidine 15 (1.2 mL, 5.7 mmol) and (−)-sparteine (1.3 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL), $ZnCl_2$ (3.4 mL of a 1.0 M solution in Et_2O, 3.4 mmol, 0.6 equiv), $Pd(OAc)_2$ (51 mg, 0.23 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) and bromobenzene (746 mg, 500 μL, 4.75 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 4:1 CH_2Cl_2−hexanes and then 9:1 CH_2Cl_2−hexanes as eluent gave phenyl pyrrolidine (*R*)-**17** (962 mg, 82%, 96:4 er by CSP-HPLC) as a white solid, mp 61.9−62.7 °C; $[\alpha]_D$ +85.3 (*c* 1.9 in acetone); R_f (CH_2Cl_2) 0.4; ^1H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.35−7.25 (m, 2H), 7.25−7.08 (m, 3H), 4.97 (br s, 0.25H), 4.76 (br s, 0.75H), 3.87−3.34 (m, 2H), 2.32 (br s, 1H), 2.04−1.74 (m, 3H), 1.46 (br s, 2.25H), 1.18 (br s, 6.75H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.6 (C), 145.1 (C), 128.1 (CH), 126.4 (CH), 125.5 (CH), 125.1 (CH), 80.1 (C), 79.1 (C), 61.3 (CH), 47.2 (CH_2), 47.1 (CH_2), 36.0 (CH_2), 35.9 (CH_2), 28.4 (CH_3),

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28.1 (CH_3), 23.4 (CH_2), 23.2 (CH_2); HPLC chiralpak AD-H (99:1 heptane−*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**17** 12.2 min, (*S*)-**17** 12.9 min. Spectroscopic data consistent with those reported in the literature.[12]

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-phenyl Pyrrolidine (*R*)-17 (Table 1, entry 2). Using general procedure A, *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol) and (−)-sparteine (1.3 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL), $ZnCl_2$ (4.0 mL of a 1.0 M solution in Et_2O, 4.0 mmol, 0.7 equiv), $Pd(OAc)_2$ (51 mg, 0.23 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) and iodobenzene (530 μL, 4.75 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 4:1 CH_2Cl_2−hexane and then 9:1 CH_2Cl_2−hexane as eluent gave phenyl pyrrolidine (*R*)-**17** (657 mg, 56%, 96:4 er by CSP-HPLC) as a white solid.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-phenyl Pyrrolidine (*R*)-17 (Table 1, entry 3). *s*-BuLi (1.32 mL of a 1.3 M solution in hexanes, 1.75 mmol, 1.0 equiv) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **15** (314 mg, 307 μL, 1.75 mmol) and Alexakis' diamine (*R*,*R*)-**16** (543 mg, 1.75 mmol, 1.0 equiv) in Et_2O (3.5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 3 h. Then, $ZnCl_2$ (1.04 mL of a 1.0 M solution in Et_2O, 1.04 mmol, 0.6 equiv) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. Then, the solution was allowed to warm to rt and stirred at rt for 20 min. Bromobenzene (228 mg, 153 μL, 1.46 mmol, 0.83 equiv) was added. A mixture of $Pd(OAc)_2$ (16 mg, 0.07 mmol, 0.04 equiv) and *t*-Bu_3PHBF_4 (25 mg, 0.09 mmol, 0.05 equiv) was added in one portion, and the resulting solution was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.15 mL) was added, and the solution was stirred at rt for 1 h. The solids were removed by filtration through Celite and washed with Et_2O (20 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (15 mL) and water (2 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 as eluent gave phenyl pyrrolidine (*R*)-**17** (135 mg, 35%, 95:5 er by CSP-HPLC) as a colorless oil, $[\alpha]_D$ +81.6 (*c* 0.2 in acetone). Other Pd catalysts/ligands were explored to improve the yield: $Pd_2(dba)_3$/*t*-Bu_3PHBF_4 gave 36% yield; $Pd(OAc)_2$/CTS-Q-PHOS gave 29% yield; $Pd(OAc)_2$/Ru-PHOS gave 13% yield.

(*S*)-*N*-(*tert*-Butoxycarbonyl)-2-phenyl Pyrrolidine (*S*)-17 (Table 1, entry 4). *s*-BuLi (2.81 mL of a 1.2 M solution in hexanes, 3.4 mmol, 1.0 equiv) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **15** (591 μL, 3.4 mmol) and (+)-sparteine surrogate (656 mg, 3.4 mmol, 1.0 equiv) in Et_2O (11 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 3 h. Then, $ZnCl_2$ (2.0 mL of a 1.0 M solution in Et_2O, 2.0 mmol, 0.6 equiv) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. Then, the solution was allowed to warm to rt and stirred at rt for 20 min. Bromobenzene (356 μL, 3.4 mmol, 1.0 equiv) was added. A mixture of $Pd(OAc)_2$ (30 mg, 0.14 mmol, 0.04 equiv) and *t*-Bu_3PHBF_4 (49 mg, 0.17 mmol, 0.05 equiv) was added in one portion, and the resulting solution was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.15 mL) was added, and the solution was stirred at rt for 1 h. The solids were removed by filtration through Celite and washed with Et_2O (20 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (15 mL) and water (2 × 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 as eluent gave phenyl pyrrolidine (*S*)-**17** (595 mg, 71%, 95:5 er by CSP-HPLC) as a colorless oil, $[\alpha]_D$ −87.3 (*c* 1.4 in acetone).

(*R*)-2-(2-Trifluoromethylphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-18 (Table 1, entry 5). A solution of *N*-Boc pyrrolidine **15** (342 mg, 350 μL, 2.0 mmol) in Et_2O (1 mL) was added dropwise to a stirred solution of *s*-BuLi (1.7 mL of a 1.2 M solution in cyclohexane, 2.0 mmol, 1.0 equiv) and (−)-sparteine (469 mg, 391 μL, 2.0 mmol, 1.0 equiv) in Et_2O (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 4 h. Then, $ZnCl_2$ (1.2 mL of a 1.0 M solution in Et_2O, 1.2 mmol, 0.6 equiv) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. Then, the solution was allowed to warm to rt and stirred at rt for 30 min. *ortho*-Bromobenzotrifluoride (383 mg, 230 μL, 1.7 mmol, 0.83 equiv) was added. A mixture of $Pd(OAc)_2$ (22 mg, 0.1 mmol, 0.05 equiv) and *t*-Bu_3PHBF_4 (22 mg, 0.125 mmol, 0.06 equiv) was added in one portion, and the resulting solution was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.2 mL) was added, and the solution was stirred at rt for 1 h. The solids were removed by filtration through Celite and washed with Et_2O (20 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (20 mL) and water (2 × 20 mL), dried ($MgSO_4$) and evaporated under reducted pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2−acetone as eluent gave aryl pyrrolidine (*R*)-**18** (370 mg, 69%, 95:5 er by CSP-HPLC) as a white solid, mp 80−81 °C; $[\alpha]_D$ +51.5 (*c* 1.1 in $CHCl_3$); R_f (99:1 CH_2Cl_2−acetone) 0.8; ^1H NMR (400 MHz, $CDCl_3$) (80:20 mixture of rotamers) δ 7.68−7.58 (m, 1H), 7.57−7.43 (m, 1H), 7.38−7.26 (m, 2H), 5.38−5.30 (m, 0.2H), 5.19−5.11 (m, 0.8H), 3.80−3.64 (m, 2H), 2.48−2.39 (m, 1H), 2.05−1.84 (m, 2H), 1.83−1.72 (m, 1H), 1.47 (s, 1.8H), 1.12 (s, 7.2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.3 (C), 154.1 (C), 144.7 (C), 132.1 (CH), 131.9 (CH), 127.6 (q, *J* = 3.0 Hz, CH), 126.6 (CH) 126.5 (q, *J* = 24.0 Hz, C), 126.4 (CH), 126.0 (CH), 125.4 (q, *J* = 6.0 Hz, CH), 123.0 (C), 79.4 (C), 77.2 (C), 57.6 (CH), 47.4 (CH_2), 35.9 (CH_2), 28.4 (CH_3), 27.9 (CH_3), 23.0 (CH_2); HPLC chiralpak AD (99:1 hexane−*i*-PrOH, 0.7 mL min^{-1}) (*R*)-**18** 8.8 min, (*S*)-**18** 10.3 min. Spectroscopic data consistent with those reported in the literature.[42]

(*S*)-2-(2-Trifluoromethylphenyl)pyrrolidine-1-carboxylic acid *tert*-Butyl Ester (*S*)-18 (Table 1, entry 6). A solution of *N*-Boc pyrrolidine **15** (342 mg, 350 μL, 2.0 mmol) in Et_2O (1 mL) was added dropwise to a stirred solution of *s*-BuLi (1.7 mL of a 1.2 M solution in cyclohexane, 2.0 mmol, 1.0 equiv) and (+)-sparteine surrogate (288 mg, 2.0 mmol, 1.0 equiv) in Et_2O (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 4 h. Then, $ZnCl_2$ (1.2 mL of a 1.0 M solution in Et_2O, 1.2 mmol, 0.6 equiv) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. Then, the solution was allowed to warm to rt and stirred at rt for 30 min. *o*-Bromobenzotrifluoride (383 mg, 230 μL, 1.7 mmol, 0.83 equiv) was added. A mixture of $Pd(OAc)_2$ (22 mg, 0.1 mmol, 0.05 equiv) and *t*-Bu_3PHBF_4 (22 mg, 0.125 mmol, 0.06 equiv) was added in one portion, and the resulting solution was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.2 mL) was added, and the solution was stirred at rt for 1 h. The solids were removed by filtration through Celite and washed with Et_2O (20 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (20 mL) and water (2 × 20 mL), dried ($MgSO_4$), and evaporated under reducted pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2−acetone as eluent gave aryl pyrrolidine (*R*)-**18** (370 mg, 69%, 95:5 er by CSP-HPLC) as a white solid, mp 80−81 °C; $[\alpha]_D$ −46.5 (*c* 1.1 in $CHCl_3$).

***rac*-2-(2-Trifluoromethylphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester *rac*-18 (Table 1, entry 7).** *s*-BuLi (1.54 mL of a 1.3 M solution in hexanes, 2.0 mmol, 1.0 equiv) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **15** (342 mg, 350 μL, 2.0 mmol) and TMEDA (232 mg, 299 μL, 2.0 mmol, 1.0 equiv) in Et_2O (7 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, $ZnCl_2$ (5.2 mL of a 0.5 M solution in THF, 2.6 mmol, 1.3 equiv) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. Then, the solution was allowed to warm to rt and stirred at rt for 20 min. *o*-Bromobenzotrifluoride (593 mg, 359 μL, 2.6 mmol, 1.3 equiv) was added. A mixture of $Pd(OAc)_2$ (22 mg, 0.1 mmol, 0.05 equiv) and *t*-Bu_3PHBF_4 (22 mg, 0.125 mmol, 0.06 equiv)

was added in one portion, and the resulting solution was stirred at rt for 16 h. Then, 35% $NH_4OH_{(aq)}$ (0.2 mL) was added, and the solution was stirred at rt for 1 h. The solids were removed by filtration through Celite and washed with Et_2O (20 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2−acetone as eluent gave aryl pyrrolidine *rac*-**17** (77 mg, 12%) as a yellow oil.

(*R*)-2-(2-Methoxycarbonylphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-19 (Table 1, entry 8). Using general procedure A, *s*-BuLi (11.1 mL of a 1.3 M solution in cyclohexane, 14.4 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (2.5 mL, 14.4 mmol) and (−)-sparteine (3.3 mL, 14.4 mmol, 1.0 equiv) in TBME (30 mL), $ZnCl_2$ (7.2 mL of a 1.0 M solution in Et_2O, 7.2 mmol, 0.50 equiv), $Pd(OAc)_2$ (108 mg, 0.48 mmol, 0.033 equiv), *t*-Bu_3PHBF_4 (174 mg, 0.60 mmol, 0.042 equiv) and methyl-2-bromobenzoate (1.68 mL, 12.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 10:1 hexane−EtOAc and then 6:1 hexane−EtOAc as eluent gave aryl pyrrolidine (*R*)-**19** (2.74 g, 71%, 96:4 er by CSP-HPLC) as a colorless oil, R_f (4:1 petrol−EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.97−7.80 (m, 1H), 7.49−7.43 (m, 1H), 7.33−7.24 (m, 2H), 5.69 (br d, J = 7.5 Hz, 0.3H), 5.51 (dt, J = 7.5, 4.5 Hz, 0.7H), 3.92−3.85 (m, 3.3H), 3.68−3.61 (m, 1.7H), 2.62−2.41 (m, 1H), 1.85−1.72 (m, 3H), 1.43 (s, 2.7H), 1.12 (s, 6.3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 167.6 (C), 154.3 (C), 147.3 (C), 132.0 (CH), 130.2 (CH), 127.9 (C), 126.1 (CH), 125.8 (CH), 79.0 (C), 58.7 (CH_3), 51.9 (CH), 47.6 (CH_2), 47.3 (CH_2), 35.5 (CH_2), 34.6 (CH_2), 28.5 (CH_3), 28.0 (CH_3), 23.1 (CH_2); HPLC chiralpak AD-H (99:1 heptane−*i*-PrOH, 0.7 mL min^{-1}) (*R*)-**19** 5.7 min, (*S*)-**19** 7.1 min. Spectroscopic data consistent with those reported in the literature.[42]

(*R*)-(2-Naphthalen-1-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-20 (Table 1, entry 9). Using general procedure A, *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol) and (−)-sparteine (1.3 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL), $ZnCl_2$ (3.4 mL of a 1.0 M solution in Et_2O, 3.4 mmol, 0.6 equiv), $Pd(OAc)_2$ (51 mg, 0.23 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) and 1-naphthyl bromide (700 μL, 4.75 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 47.5:47.5:5 hexane−CH_2Cl_2−TBME as eluent gave 1-naphthyl pyrrolidine (*R*)-**20** (1.1 g, 79%, 96:4 er by CSP-HPLC) as a white solid, mp 94−95 °C; $[\alpha]_D$ +72.4 (*c* 1.2 in $CHCl_3$); IR ($CHCl_3$) 3008, 2978, 2878, 1683 (C═O), 1402, 1366, 1246, 1156, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 8.03 (br d, J = 8.0 Hz, 1H), 7.90 (br d, J = 8.0 Hz, 0.65H), 7.86 (br d, J = 8.0 Hz, 0.35H), 7.79−7.70 (m, 1H), 7.58−7.38 (m, 3H), 7.28 (br d, J = 7.0 Hz, 0.65H), 7.25 (br d, J = 7.0 Hz, 0.35H), 5.79 (br d, J = 8.5 Hz, 0.35H), 5.62 (dd, J = 8.5, 2.5 Hz, 0.65H), 3.90−3.50 (m, 2H), 2.58−2.33 (m, 1H), 2.05−1.76 (m, 3H), 1.51 (s, 3.15H), 1.11 (s, 5.85H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.9 (C), 140.2 (C), 139.0 (C), 134.3 (C), 134.0 (C), 130.4 (C), 129.0 (CH), 128.9 (CH), 127.4 (CH), 127.2 (CH), 125.9 (CH), 125.5 (CH), 125.4 (CH), 123.5 (CH), 123.1 (CH), 122.0 (CH), 121.5 (CH), 79.3 (C), 79.1 (C), 58.0 (CH), 57.8 (CH), 47.0 (CH_2), 46.7 (CH_2), 34.0 (CH_2), 33.0 (CH_2), 28.2 (CH_3), 27.8 (CH_3), 23.1 (CH_2), 22.6 (CH_2); MS (ESI) *m*/*z* 320 [(M + Na)$^+$, 100], 298 [(M + H)$^+$, 11], 242 (99), 114 (47); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{23}NO_2$ (M + Na)$^+$ 320.1621, found 320.1623 (−0.7 ppm error); HPLC chiralpak AD-H (99:1 heptane−*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**20** 5.6 min, (*S*)-**20** 7.8 min.

(*R*)-(2-Naphthalen-2-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-21 (Table 1, entry 10). Using general procedure A, *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol) and (−)-sparteine (1.3 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL), $ZnCl_2$ (3.4 mL of a 1.2 M solution in Et_2O, 3.4 mmol, 0.6 equiv), $Pd(OAc)_2$ (51 mg, 0.23 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) and 2-naphthyl bromide (1.03 g, 4.75 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 47.5:47.5:5 hexane−CH_2Cl_2−TBME as eluent gave 2-naphthyl pyrrolidine (*R*)-**21** (1.2 g, 82%, 95:5 er by CSP-HPLC) as a white solid, mp 90−92 °C; $[\alpha]_D$ +108.7 (*c* 1.1 in $CHCl_3$); IR ($CHCl_3$) 3008, 2977, 1683 (C═O), 1402, 1367, 1166, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.90−7.75 (m, 3H), 7.60 (s, 1H), 7.54−7.39 (m, 2H), 7.38−7.29 (m, 1H), 5.13 (br s, 0.25H), 4.96 (d, J = 4.0 Hz, 0.75H), 3.71 (d, J = 5.0 Hz, 1.5H), 3.60 (br s, 0.5H), 2.50−2.24 (m, 1H), 2.04−1.81 (m, 3H), 1.48 (s, 2.25H), 1.15 (m, 6.75H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.1 (C), 155.0 (C), 142.7 (C), 133.5 (C), 132.7 (C), 128.2 (CH), 127.9 (CH), 127.8 (CH), 126.2 (CH), 125.5 (CH), 124.3 (CH), 124.0 (CH), 79.2 (C), 61.2 (CH), 60.7 (CH), 47.2 (CH_2), 46.9 (CH_2), 35.5 (CH_2), 34.4 (CH_2), 28.2 (CH_3), 27.8 (CH_3), 23.2 (CH_2), 22.8 (CH_2); MS (ESI) *m*/*z* 320 [(M + Na)$^+$, 65], 298 [(M + H)$^+$, 8], 242 (100), 114 (13); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{23}NO_2$ (M + Na)$^+$ 320.1621, found 320.1622 (−0.2 ppm error); HPLC chiralpak AD-H (99:1 heptane−*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**21** 6.8 min, (*S*)-**21** 7.4 min.

(*R*)-2-(4,5-Dimethoxy-2-methoxycarbonylmethylphenyl) pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-22 (Scheme 4). Using general procedure A, *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol) and (−)-sparteine (1.3 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL), $ZnCl_2$ (3.4 mL of a 1.2 M solution in Et_2O, 3.4 mmol, 0.6 equiv), $Pd(OAc)_2$ (51 mg, 0.23 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) and aryl bromide **23**[48] (1.37 g, 4.75 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 60:40 hexane−EtOAc and then 50:50 hexane−EtOAc as eluent gave aryl pyrrolidine (*R*)-**22** (1.2 g, 70%, 96.5:3.5 er by CSP-SFC) as a brown solid, mp 45−46 °C; $[\alpha]_D$ +66.4 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2974, 1737 (C═O, CO_2Me), 1690 (C═O, Boc), 1516, 1399, 1366, 1265, 1163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 6.70 (s, 1H), 6.62 (s, 1H), 5.11−4.82 (m, 1H), 3.85 (br s, 3H), 3.80 (s, 3H), 3.67 (s, 3H), 3.76−3.44 (m, 4H), 2.39−2.17 (m, 1H), 2.03−1.77 (m, 2H), 1.77−1.61 (m, 1H), 1.41 (s, 2.25H), 1.14 (s, 6.75H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 172.4 (C), 154.8 (C), 148.6 (C), 147.7 (C), 136.5 (C), 122.7 (C), 113.6 (CH), 108.3 (CH), 79.2 (C), 57.5 (CH), 55.7 (CH_3), 51.8 (CH_3), 47.3 (CH_2), 47.2 (CH_2), 37.7 (CH_2), 35.0 (CH_2), 28.1 (CH_3), 27.8 (CH_3), 23.1 (CH_2); MS (ESI) *m*/*z* 402 [(M + Na)$^+$, 100], 380 [(M + H)$^+$], 40, 324 (42), 280 (32); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{29}NO_6$ (M + Na)$^+$ 402.1887, found 402.1884 (+0.7 ppm error); SFC chiralpak OJ-H (isocratic 4%MeOH/CO_2, 1.5 mL min^{-1}, 200 bar, 35 °C) (*R*)-**22** 3.6 min, (*S*)-**22** 3.1 min.

(*R*)-8,9-Dimethoxy-2,3,6,10b-tetrahydro-1*H*-pyrrolo[2,1-α] isoquinolin-5-one (*R*)-24 (Scheme 4). Me_3SiCl (7.1 mL, 55.8 mmol) was added dropwise (maintaining the temperature below 25 °C) to a stirred solution of aryl pyrrolidine (*R*)-**22** (5.2 g, 13.7 mmol) in MeOH (81 mL) at 20 °C. The resulting solution was stirred at 20 °C for 16 h. TBME (100 mL) was added and the organic solution was washed with 1 M $Na_2CO_{3(aq)}$ (2 × 50 mL). The combined aqueous washings were back-extracted with CH_2Cl_2 (2 × 25 mL). Then, the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 90:10 EtOAc−MeOH as eluent gave lactam (*R*)-**24** (4.2 g, 95%, 96:4 er by CSP-SFC) as a yellow solid, mp 131−132 °C; $[\alpha]_D$ +109.6 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 3005, 1639 (C═O), 1519, 1454, 1217, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.66 (s, 1H), 4.67−4.49 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.71−3.42 (m, 4H), 2.66−2.52 (m, 1H), 2.21−2.08 (m, 1H), 2.08−1.92 (m, 1H), 1.92−1.78 (m, 1H); ^{13}C NMR (100.6 MHz,

$CDCl_3$) 168.0 (C), 148.8 (C), 148.1 (C), 128.2 (C), 125.1 (C), 110.3 (CH), 107.7 (CH), 59.4 (CH), 56.0 (CH_3), 55.9 (CH_3), 44.5 (CH_2), 37.9 (CH_2), 31.5 (CH_2), 22.7 (CH_2); MS (ESI) m/z 270 [$(M + Na)^+$, 49], 248 [$(M + H)^+$, 100]; HRMS (ESI) m/z calcd for $C_{14}H_{17}NO_3$ $(M + H)^+$ 248.1281, found 248.1281 (−0.1 ppm error); SFC chiralpak AD-H column (250 × 4.6 mm, isocratic 15% MeOH/CO_2, 1.5 mL min^{-1}, 200 bar, 35 °C) (*R*)-**24** 9.6 min, (*S*)-**24** 8.9 min.

(*R*)-Crispine A (Scheme 4). Borane (4.0 mL of a 1.0 M solution in THF) was added dropwise over 15 min to a stirred suspension of lactam (*R*)-**24** (200 mg, 0.81 mmol) in THF (10 mL) at 0 °C. The resulting mixture was stirred at room temperature for 30 min and then heated at 40 °C for 7 h. After cooling to 0 °C, water (3.0 mL) was added dropwise (CAUTION − significant foaming due to hydrogen evolution). Then, 6 M $HCl_{(aq)}$ (5 mL) was added, and the resulting mixture was stirred and heated at 50 °C for 5 h (to cleave the amine-borane complex of the product). After cooling to room temperature, TBME was added and the mixture was basified by the addition of 10 M $NaOH_{(aq)}$ (3 mL). The two layers were separated and the organic layer was washed with water (2 × 20 mL). Then, the combined organic layers were evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 20:1:1 CH_2Cl_2−28% $NH_{3(aq)}$−MeOH as eluent gave (*R*)-(+)-crispine A (155 mg, 82%, 97:3 er by CSP-SFC) as an off-white solid, $[\alpha]_D$ +90.8 (*c* 0.79 in MeOH)(lit.,[47d] $[\alpha]_D$ +95.2 (*c* 1.5 in MeOH)); ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.58 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.42 (t, J = 8.3 Hz, 1H), 3.23−3.16 (m, 1H), 3.12−2.98 (m, 2H), 2.73−2.70 (m, 1H), 2.67−2.61 (m, 1H), 2.55 (q, J = 8.8 Hz, 1H), 2.37−2.27 (m, 1H), 2.10−1.81 (m, 2H), 1.78−1.67 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 147.4, 147.3, 131.2, 126.3, 111.5, 109.0, 63.0, 56.0, 55.9, 53.2, 48.4, 30.5, 28.1, 22.3; SFC chiralcel OD-H (*i*-PrOH/*i*-$BuNH_2$ modifier, 0.7 mL min^{-1}) (*R*)-**24** 9.4 min, (*S*)-**24** 9.0 min. Spectroscopic data consistent with those reported in the literature.[47d]

(*S*)-*N*-(*tert*-Butoxycarbonyl)-2-phenyl Pyrrolidine (*S*)-17 (Table 2, entry 1). Using general procedure B, *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol), (+)-sparteine surrogate (275 μL, 1.4 mmol, 0.25 equiv) and di-*i*-Pr-bispidine **25** (1.3 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL), $ZnCl_2$ (1.7 mL of a 1.2 M solution in Et_2O, 2.0 mmol, 0.35 equiv), $Pd(OAc)_2$ (51 mg, 0.23 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) and bromobenzene (746 mg, 500 μL, 4.75 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 4:1 CH_2Cl_2−hexane and then 9:1 CH_2Cl_2−hexane as eluent gave phenyl pyrrolidine (*S*)-**17** (937 mg, 80%, 95:5 er by CSP-HPLC) as a white solid.

(*R*)-2-(2-Trifluoromethylphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-18 (Table 2, entry 2). Using general procedure C, *s*-BuLi (1.3 mL of a 1.3 M solution in cyclohexane, 1.64 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (280 mg, 1.64 mmol), (−)-sparteine (96 mg, 0.4 mmol, 0.25 equiv), di-*i*-Pr-bispidine **25** (345 mg, 1.64 mmol, 1.0 equiv) in Et_2O (7 mL), $ZnCl_2$ (1.0 mL of a 1.0 M solution in Et_2O, 1.0 mmol, 0.6 equiv), $Pd(OAc)_2$ (18 mg, 0.08 mmol, 0.05 equiv), *t*-Bu_3PHBF_4 (18 mg, 0.10 mmol, 0.06 equiv) and *o*-bromobenzotrifluoride (159 μL, 1.15 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2−acetone as eluent gave aryl pyrrolidine (*R*)-**18** (278 mg, 76%, 80:20 er by CSP-HPLC) as a white solid, $[\alpha]_D$ +40.7 (*c* 1.3 in $CHCl_3$); HPLC chiralpak AD (99:1 hexane−*i*-PrOH, 0.7 mL min^{-1}) (*R*)-**18** 9.8 min, (*S*)-**18** 11.4 min.

(*S*)-2-(2-Trifluoromethylphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*S*)-18 (Table 2, entry 3). Using general procedure C, *s*-BuLi (2.2 mL of a 1.3 M solution in cyclohexane, 2.9 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (493 mg, 505 μL, 2.9 mmol), (+)-sparteine surrogate (139 mg, 0.7 mmol, 0.25 equiv), di-*i*-Pr-bispidine **25** (606 mg, 2.9 mmol, 1.0 equiv) in Et_2O (7 mL), $ZnCl_2$ (1.7 mL of a 1.0 M solution in Et_2O, 1.7 mmol, 0.6 equiv), $Pd(OAc)_2$ (31 mg, 0.14 mmol, 0.05 equiv), *t*-Bu_3PHBF_4 (32 mg, 0.18 mmol, 0.06 equiv) and *o*-bromobenzotrifluoride (434 mg, 263 μL, 2.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2−acetone as eluent gave aryl pyrrolidine (*S*)-**18** (481 mg, 75%, 91:9 er by CSP-HPLC) as a white solid, $[\alpha]_D$ −42.2 (*c* 1.4 in $CHCl_3$).

(*R*)-2-(2-Methoxycarbonylphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-19 (Table 2, entry 4). Using general procedure C, *s*-BuLi (1.55 mL of a 1.3 M solution in cyclohexane, 2.0 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (344 mg, 2.0 mmol), (−)-sparteine (118 mg, 0.5 mmol, 0.25 equiv), di-*i*-Pr-bispidine **25** (423 mg, 2.0 mmol, 1.0 equiv) in Et_2O (7 mL), $ZnCl_2$ (1.2 mL of a 1.0 M solution in Et_2O, 1.2 mmol, 0.6 equiv), $Pd(OAc)_2$ (22 mg, 0.1 mmol, 0.05 equiv), *t*-Bu_3PHBF_4 (22 mg, 0.13 mmol, 0.06 equiv) and methyl 2-bromobenzoate (198 μL, 1.4 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 4:1 petrol−Et_2O as eluent gave aryl pyrrolidine (*R*)-**19** (309 mg, 50%, 81:19 er by CSP-HPLC) as a colorless oil, $[\alpha]_D$ +14.9 (*c* 1.4 in $CHCl_3$); HPLC chiralpak AD (99:1 hexane−*i*-PrOH, 0.7 mL min^{-1}) (*R*)-**19** 5.7 min, (*S*)-**19** 7.1 min.

(*S*)-(2-Naphthalen-2-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*S*)-21 (Table 2, entry 5). Using general procedure B, *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol), (+)-sparteine surrogate (275 μL, 1.4 mmol, 0.25 equiv) and di-*i*-Pr-bispidine **25** (1.3 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL), $ZnCl_2$ (1.7 mL of a 1.2 M solution in Et_2O, 2.0 mmol, 0.35 equiv), $Pd(OAc)_2$ (51 mg, 0.23 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) and 2-naphthyl bromide (1.03 g, 4.75 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 47.5:47.5:5 hexane−CH_2Cl_2−TBME as eluent gave 2-naphthyl pyrrolidine (*S*)-**17** (1.1 g, 80%, 95:5 er by CSP-HPLC) as a white solid.

(*R*)-2-(2-Methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-26 (Table 2, entry 6). Using general procedure C, *s*-BuLi (1.55 mL of a 1.3 M solution in cyclohexane, 2.0 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (348 mg, 2.0 mmol), (−)-sparteine (119 mg, 0.5 mmol, 0.25 equiv), di-*i*-Pr-bispidine **25** (427 mg, 2.0 mmol, 1.0 equiv) in Et_2O (7 mL), $ZnCl_2$ (1.2 mL of a 1.0 M solution in Et_2O, 1.2 mmol, 0.6 equiv), $Pd(OAc)_2$ (22 mg, 0.1 mmol, 0.05 equiv), *t*-Bu_3PHBF_4 (23 mg, 0.13 mmol, 0.06 equiv) and *o*-bromoanisole (177 μL, 1.4 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 as eluent gave aryl pyrrolidine (*R*)-**26** (196 mg, 50%, 80:20 er by CSP-HPLC) as a colorless oil, $[\alpha]_D$ +23.6 (*c* 1.0 in acetone); R_f (98:2 CH_2Cl_2−acetone) 0.2; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.26−7.13 (m, 1H), 7.06 (d, J = 7.5 Hz, 0.7H), 7.01 (d, J = 7.5 Hz, 0.3H), 6.89 (t, J = 7.5 Hz, 1H), 6.85 (br d, J = 8.0 Hz, 1H), 5.25 (br d, J = 7.5 Hz, 0.3H), 5.18−5.01 (m, 0.7H), 3.83 (s, 3H), 3.69−3.40 (m, 2H), 2.38−2.12 (m, 1H), 1.94−1.71 (m, 3H), 1.47 (s, 2.7H), 1.19 (s, 6.3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 156.1 (C), 154.6 (C), 132.9 (C), 127.5 (C), 127.3 (CH), 125.9 (CH), 120.1 (CH), 110.3 (CH), 110.1 (CH), 79.0 (C), 78.8 (C), 56.1 (CH_3), 55.3 (CH), 55.2 (CH), 47.2 (CH_2), 46.8 (CH_2), 33.9 (CH_2), 32.8 (CH_2), 28.5 (CH_3), 28.1 (CH_3), 23.1 (CH_2); HPLC chiralpak AD (99:1 hexane−*i*-PrOH, 0.5 mL min^{-1}) (*S*)-**26** 19.6 min, (*R*)-**26** 22.8 min. Spectroscopic data consistent with those reported in the literature.[42]

(*S*)-2-(2-Methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*S*)-26 (Table 2, entry 7). Using general procedure C, *s*-BuLi (1.7 mL of a 1.3 M solution in cyclohexane, 2.0 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (342 mg, 350 μL, 2.0 mmol), (+)-sparteine surrogate (97 mg, 0.5 mmol, 0.25 equiv), di-*i*-Pr-bispidine **25** (421 mg, 2.0 mmol, 1.0 equiv) in Et_2O (7 mL), $ZnCl_2$ (1.2 mL of a 1.0 M solution in Et_2O, 1.2 mmol, 0.6 equiv), $Pd(OAc)_2$ (22 mg, 0.1 mmol,

0.05 equiv), *t*-Bu_3PHBF_4 (22 mg, 0.125 mmol, 0.06 equiv) and *o*-bromoanisole (318 mg, 210 μL, 1.7 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 as eluent gave aryl pyrrolidine (*S*)-**26** (410 mg, 87%, 96:4 er by CSP-HPLC) as a colorless oil, $[\alpha]_D$ −65.5 (*c* 1.2 in $CHCl_3$).

(*S*)-2-(4-Methoxycarbonylphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*S*)-27 (Table 2, entry 8). Using general procedure B, *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol), (+)-sparteine surrogate (275 μL, 1.4 mmol, 0.25 equiv) and di-*i*-Pr-bispidine **25** (1.03 g, 5.7 mmol, 1.0 equiv) in TBME (12 mL), $ZnCl_2$ (1.7 mL of a 1.2 M solution in Et_2O, 2.0 mmol, 0.35 equiv), $Pd(OAc)_2$ (51 mg, 0.23 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) and methyl 4-bromobenzoate (1.02 g, 4.75 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 80:20 hexane−EtOAc and then 75:25 hexane−EtOAc as eluent gave aryl pyrrolidine (*S*)-**27** (1.0 g, 85%, 93:7 er by CSP-HPLC) as a white solid, R_f (3:1 petrol−Et_2O) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.97 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 4.96 (br s, 0.3H), 4.79 (br s, 0.7H), 3.90 (s, 3H), 3.71−3.51 (m, 2H), 2.46−2.21 (m, 1H), 1.99−1.79 (m, 3H), 1.45 (s, 2.7H), 1.16 (s, 6.3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 166.9 (C), 154.4 (C), 150.6 (C), 129.7 (CH), 129.6 (CH), 128.4 (C), 125.4 (CH), 79.4 (C), 61.1 (CH_3), 52.0 (CH), 47.1 (CH_2), 35.9 (CH_2), 34.7 (CH_2), 28.4 (CH_3), 28.1 (CH_3), 23.5 (CH_2), 23.2 (CH_2); HPLC chiralpak AD-H (98:2 heptane−*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**27** 10.8 min, (*S*)-**27** 11.4 min. Spectroscopic data consistent with those reported in the literature.[42]

(*R*)-2-(2-Trifluoromethylphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-18 (Scheme 5). Using general procedure D, *s*-BuLi (1.5 mL of a 1.3 M solution in cyclohexane, 2.0 mmol, 1.6 equiv), *N*-Boc pyrrolidine **15** (216 mg, 1.25 mmol), (−)-sparteine (89 mg, 0.4 mmol, 0.3 equiv) and di-*i*-Pr-bispidine **25** (342 mg, 1.6 mmol, 1.3 equiv) in Et_2O (7 mL), $ZnCl_2$ (750 μL of a 1.0 M solution in Et_2O, 0.75 mmol, 0.6 equiv), $Pd(OAc)_2$ (14 mg, 0.06 mmol, 0.05 equiv), *t*-Bu_3PHBF_4 (14 mg, 0.08 mmol, 0.06 equiv) and methyl 2-bromobenzoate (123 μL, 0.9 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 4:1 petrol−Et_2O as eluent gave aryl pyrrolidine (*R*)-**19** (189 mg, 71%, 89:11 er by CSP-HPLC) as a colorless oil, $[\alpha]_D$ +16.4 (*c* 1.0 in $CHCl_3$).

(*R*)-2-(2-Methoxycarbonylphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-19 (Scheme 5). Using general procedure D, *s*-BuLi (1.5 mL of a 1.3 M solution in cyclohexane, 2.0 mmol, 1.6 equiv), *N*-Boc pyrrolidine **15** (214 mg, 1.25 mmol), (−)-sparteine (88 mg, 0.4 mmol, 0.3 equiv) and di-*i*-Pr-bispidine **25** (342 mg, 1.6 mmol, 1.3 equiv) in Et_2O (7 mL), $ZnCl_2$ (750 μL of a 1.0 M solution in Et_2O, 0.75 mmol, 0.6 equiv), $Pd(OAc)_2$ (14 mg, 0.06 mmol, 0.05 equiv), *t*-Bu_3PHBF_4 (14 mg, 0.08 mmol, 0.06 equiv) and methyl 2-bromobenzoate (123 μL, 0.9 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 4:1 petrol−Et_2O as eluent gave aryl pyrrolidine (*R*)-**19** (189 mg, 71%, 89:11 er by CSP-HPLC) as a colorless oil, $[\alpha]_D$ +16.4 (*c* 1.0 in $CHCl_3$).

(*R*)-2-(2-Methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-26 (Table 2, entry 6). Using general procedure D, *s*-BuLi (1.75 mL of a 1.3 M solution in cyclohexane, 2.3 mmol, 1.6 equiv), *N*-Boc pyrrolidine **15** (243 mg, 1.4 mmol), (−)-sparteine (100 mg, 0.43 mmol, 0.3 equiv) and di-*i*-Pr-bispidine **25** (388 mg, 1.85 mmol, 1.3 equiv) in Et_2O (7 mL), $ZnCl_2$ (852 μL of a 1.0 M solution in Et_2O, 0.85 mmol, 0.6 equiv), $Pd(OAc)_2$ (16 mg, 0.07 mmol, 0.05 equiv), *t*-Bu_3PHBF_4 (16 mg, 0.09 mmol, 0.06 equiv) and *o*-bromoanisole (124 μL, 1.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 as eluent gave aryl pyrrolidine (*R*)-**26** (253 mg, 92%, 89:11 er by CSP-HPLC) as a colorless oil, $[\alpha]_D$ +59.8 (*c* 1.0 in acetone); HPLC chiralpak AD (99:1 hexane−*i*-PrOH, 0.5 mL min^{-1}) (*S*)-**26** 18.9 min, (*R*)-**26** 21.5 min.

(*R*)-1′-(Toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1′*H*-[2,2′] bipyrrolyl-1-carboxylic Acid *tert*-Butyl Ester (*R*)-28 (Scheme 6). Using general procedure A, *s*-BuLi (1.0 mL of a 1.2 M solution in cyclohexane, 1.2 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (250 μL, 1.2 mmol) and (−)-sparteine (260 μL, 1.2 mmol, 1.0 equiv) in TBME (3 mL), $ZnCl_2$ (710 μL of a 1.0 M solution in Et_2O, 0.7 mmol, 0.6 equiv), $Pd(OAc)_2$ (8 mg, 0.05 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (12 mg, 0.06 mmol, 0.05 equiv) and the appropriate aryl bromide (250 mg, 1.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 70:30 hexane−EtOAc as eluent gave aryl pyrrolidine (*R*)-**28** (140 mg, 58%, 95:5 er by CSP-HPLC) as an orange solid, mp 104−105 °C; $[\alpha]_D$ +27.4 (*c* 1.2 in $CHCl_3$); IR ($CHCl_3$) 3008, 2979, 1683 (C═O), 1401, 1368, 1172, 1061, 749, 675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.71 (d, *J* = 7.5 Hz, 2H), 7.26 (d, *J* = 7.5 Hz, 2H), 7.09 (br s, 0.7H), 7.04 (br s, 0.3H), 6.94 (br s, 0.3H), 6.90 (s, 0.7H), 6.15 (br s, 1H), 4.83 (br s, 0.3H), 4.66 (d, *J* = 3.5 Hz, 0.7H), 3.44 (br s, 1.4H), 3.34 (br s, 0.6H), 2.38 (s, 3H), 2.10 (br s, 1H), 1.94−1.68 (m, 3H), 1.43 (s, 2.7H), 1.16 (s, 6.3H,); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.8 (C), 145.1 (C), 136.4 (C), 133.1 (C), 130.1 (CH), 127.0 (CH), 121.1 (CH), 116.9 (CH), 113.1 (CH), 112.3 (CH), 79.0 (C), 54.2 (CH), 54.1 (CH), 46.05 (CH_2), 45.98 (CH_2), 33.8 (CH_2), 27.9 (CH_3), 26.7 (CH_2), 21.2 (CH_3); MS (ESI) *m*/*z* 413 [(M + Na)$^+$, 100], 391 [(M + H)$^+$, 11], 335 (63), 207 (14), 114 (44); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{26}N_2SO_4$ (M + Na)$^+$ 413.1505, found 413.1495 (+2.6 ppm error); HPLC chiralpak AD-H (90:10 hexane−*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**28** 10.3 min, (*S*)-**28** 8.1 min.

(*R*)-1′-Triisopropylsilanyl-2,3,4,5-tetrahydro-1′*H*-[2,3′] bipyrrolyl-1-carboxylic Acid *tert*-Butyl Ester (*R*)-29 (Scheme 6). Using general procedure A, *s*-BuLi (1.0 mL of a 1.2 M solution in cyclohexane, 1.2 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (250 μL, 1.2 mmol) and (−)-sparteine (260 μL, 1.2 mmol, 1.0 equiv) in TBME (3 mL), $ZnCl_2$ (710 μL of a 1.0 M solution in Et_2O, 0.7 mmol, 0.6 equiv), $Pd(OAc)_2$ (8 mg, 0.05 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (12 mg, 0.06 mmol, 0.05 equiv) and the appropriate aryl bromide (252 mg, 1.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 90:10 hexane−EtOAc as eluent gave aryl pyrrolidine (*R*)-**29** (250 mg, 76%, 94:6 er by CSP-HPLC) as a colorless oil, R_f 0.8 (6:4 petrol−Et_2O); $[\alpha]_D$ +51.6 (*c* 1.0 in $CHCl_3$); IR (film) 2946, 2867, 1694 (C═O), 1464, 1393, 1365, 1169, 1099, 884, 659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (85:15 mixture of rotamers) δ 6.66 (t, *J* = 2.0 Hz, 1H), 6.53 (br s, 1H), 6.12 (br s, 1H), 4.99 (br s, 0.15H), 4.87 (br s, 0.85H), 3.46 (br s, 2H), 2.18−2.02 (m, 1H), 2.02−1.74 (m, 3H), 1.38 (septet, *J* = 7.5 Hz, 3H), 1.35 (br s, 1.35H), 1.07 (br s, 15.3H), 1.05 (br s, 2.7H), 1.04 (s, 7.65H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.2 (C), 124.1 (CH), 121.5 (C), 120.7 (CH), 108.8 (CH), 78.7 (C), 54.9 (CH), 45.7 (CH_2), 34.1 (CH_2), 28.2 (CH_3), 22.8 (CH_2), 17.5 (CH_3), 17.4 (CH_3), 11.9 (CH), 11.3 (CH); MS (ESI) *m*/*z* 415 [(M + Na)$^+$, 100], 393 [(M + H)$^+$, 58], 337 (85), 224 (39), 209 (11), 114 (25); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{40}N_2O_2Si$ (M + H)$^+$ 393.2932, found 393.2925 (+1.6 ppm error); HPLC chiralpak AD-H (98:2 hexane−*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**29** 2.1 min, (*S*)-**29** 2.7 min.

(*R*)-2-Thiophen-3-ylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-30 (Scheme 6). Using general procedure A, *s*-BuLi (1.0 mL of a 1.2 M solution in cyclohexane, 1.2 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (250 μL, 1.2 mmol) and (−)-sparteine (260 μL, 1.2 mmol, 1.0 equiv) in TBME (3 mL), $ZnCl_2$ (710 μL of a 1.0 M solution in Et_2O, 0.7 mmol, 0.6 equiv), $Pd(OAc)_2$ (8 mg, 0.05 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (12 mg, 0.06 mmol, 0.05 equiv) and the appropriate aryl bromide (163 mg, 1.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 85:15 hexane−EtOAc as eluent gave aryl pyrrolidine (*R*)-**30** (140 mg, 72%, 94:6 er by CSP-HPLC) as a colorless oil, R_f 0.4 (6:4 petrol−EtOAc); $[\alpha]_D$ +114.8 (*c* 1.0 in $CHCl_3$); IR (film) 2974, 2877, 1692 (C═O),

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1392, 1366, 1169, 1112, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 7.23 (dd, J = 5.0, 3.0 Hz, 1H), 6.96 (br s, 1H), 6.92 (br s, 1H), 5.03 (br s, 0.35H), 4.87 (br d, J = 5.0 Hz, 0.65H), 3.53 (br s, 1.3H), 3.43 (br s, 0.7H), 2.35−2.08 (m, 1H), 2.03−1.77 (m, 3H), 1.45 (s, 3.25H), 1.25 (s, 5.85H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.9 (C), 146.2 (C), 126.0 (CH), 125.8 (CH), 125.6 (CH), 119.7 (CH), 79.1 (C), 57.0 (CH), 56.6 (CH), 46.4 (CH_2), 46.1 (CH_2), 34.2 (CH_2), 33.0 (CH_2), 28.1 (CH_3), 27.9 (CH_3), 23.3 (CH_2), 22.8 (CH_2); MS (ESI) m/z 276 [$(M + Na)^+$, 73], 254 [$(M + H)^+$, 12], 198 (100), 114 (40); HRMS (ESI) m/z calcd for $C_{13}H_{19}NO_2S$ $(M + Na)^+$ 276.1029, found 276.1033 (−1.6 ppm error); HPLC chiralpak AD-H (95:5 hexane−*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**30** 6.5 min, (*S*)-**30** 7.0 min.

2-((*R*)-1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-4-methylthiazole-5-carboxylic Acid Ethyl Ester (*R*)-31 (Scheme 6). Using general procedure A, *s*-BuLi (1.0 mL of a 1.2 M solution in cyclohexane, 1.2 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (250 μL, 1.2 mmol) and (−)-sparteine (260 μL, 1.2 mmol, 1.0 equiv) in TBME (3 mL), $ZnCl_2$ (710 μL of a 1.0 M solution in Et_2O, 0.7 mmol, 0.6 equiv), $Pd(OAc)_2$ (8 mg, 0.05 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (12 mg, 0.06 mmol, 0.05 equiv) and the appropriate aryl bromide (208 mg, 1.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 70:30 hexane−EtOAc as eluent gave aryl pyrrolidine (*R*)-**31** (150 mg, 67%, 94:6 er by CSP-HPLC) as a colorless oil, R_f 0.3 in (6:4 petrol−EtOAc); $[\alpha]_D$ +8.9 (*c* 1.0 in $CHCl_3$); IR (film) 2977, 2933, 1703 (C═O, CO_2Et + Boc), 1385, 1320, 1261, 1167, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 5.14 (d, J = 7.5 Hz, 0.4H), 5.03 (d, J = 7.0 Hz, 0.6H), 4.29 (q, J = 7.0 Hz, 2H), 3.69−3.33 (m, 2H), 2.67 (s, 3H), 2.43−2.21 (m, 1H), 2.21−2.06 (m, 1H), 2.00−1.82 (m, 2H), 1.46 (s, 3.6H), 1.32 (br s, 8.4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 179.2 (C), 178.4 (C), 162.7 (C), 160.8 (C), 160.6 (C), 155.0 (C), 154.5 (C), 121.7 (C), 121.5 (C), 80.4 (CMe_3), 80.2 (C), 61.0 (CH_2), 59.5 (CH), 59.2 (CH), 46.8 (CH_2), 46.3 (CH_2), 33.7 (CH_2), 32.6 (CH_2), 28.1 (CH_3), 27.9 (CH_3), 23.6 (CH_2), 22.7 (CH_2), 17.1 (CH_3), 13.9 (CH_3); MS (ESI) m/z 363 [$(M + Na)^+$, 19], 341 [$(M + H)^+$, 100], 285 (59); HRMS (ESI) m/z calcd for $C_{16}H_{24}N_2O_4S$ $(M + H)^+$ 341.1530, found 341.1529 (+0.1 ppm error); HPLC chiralpak AD-H (95:5 hexane−*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**31** 6.7 min, (*S*)-**31** 6.3 min.

(*R*)-2-(4-Methyl-2-Phenylthiazol-5-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-32 (Scheme 6). Using general procedure A, *s*-BuLi (1.0 mL of a 1.2 M solution in cyclohexane, 1.2 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (250 μL, 1.2 mmol) and (−)-sparteine (260 μL, 1.2 mmol, 1.0 equiv) in TBME (3 mL), $ZnCl_2$ (710 μL of a 1.0 M solution in Et_2O, 0.7 mmol, 0.6 equiv), $Pd(OAc)_2$ (8 mg, 0.05 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (12 mg, 0.06 mmol, 0.05 equiv) and the appropriate aryl bromide (254 mg, 1.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 70:30 hexane−EtOAc as eluent gave aryl pyrrolidine (*R*)-**32** (127 mg, 75%, 96:4 er by CSP-HPLC) as a colorless oil, R_f 0.3 (6:4 petrol−EtOAc); $[\alpha]_D$ + 34.2 (*c* 1.0 in $CHCl_3$); IR (film) 2974, 1692 (C═O), 1458, 1398, 1249, 1165, 1115, 763, 733, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.87 (d, J = 6.5 Hz, 2H), 7.45−7.33 (m, 3H), 5.17 (br s, 0.3H), 5.02 (br s, 0.7H), 3.69−3.32 (m, 2H), 2.43 (s, 3H), 2.32 (br s, 1H), 2.16−2.01 (m, 1H), 2.00−1.80 (m, 2H), 1.42 (s, 2.7H), 1.28 (s, 6.3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 164.3 (C), 154.6 (C), 147.83 (C), 147.82 (C), 134.1 (C), 129.8 (C), 129.3 (C), 129.0 (CH), 127.1 (CH), 126.3 (CH), 79.7 (C), 54.3 (CH), 46.2 (CH_2), 34.8 (CH_2), 34.7 (CH_2), 28.1 (CH_3), 23.6 (CH_2), 23.0 (CH_2), 15.0 (CH_3); MS (ESI) m/z 345 [$(M + H)^+$, 100]; HRMS (ESI) m/z calcd for $C_{19}H_{24}N_2O_2S$ $(M + H)^+$ 345.1631, found 345.1631 (+0.2 ppm error); HPLC chiralpak AD-H (95:5 hexane−*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**32** 3.9 min, (*S*)-**32** 3.5 min.

(*R*)-2-Pyridin-3-ylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-33 (Scheme 6). Using general procedure A, *s*-BuLi (1.0 mL of a 1.2 M solution in cyclohexane, 1.2 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (250 μL, 1.2 mmol) and (−)-sparteine (260 μL, 1.2 mmol, 1.0 equiv) in TBME (3 mL), $ZnCl_2$ (710 μL of a 1.0 M solution in Et_2O, 0.7 mmol, 0.6 equiv), $Pd(OAc)_2$ (8 mg, 0.05 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (12 mg, 0.06 mmol, 0.05 equiv) and the appropriate aryl bromide (80 μL, 1.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 40:60 hexane−EtOAc as eluent gave aryl pyrrolidine (*R*)-**33** (37 mg, 15%, 96:4 er by CSP-HPLC) as a colorless oil, HPLC chiralpak AD-H (isocratic 80:20 heptane−*i*-PrOH, 0.7 mL min^{-1}) (*R*)-**33** 3.77 min, (*S*)-**33** 3.45 min. Carrying out the Negishi coupling at 60 °C gave a 60% yield of (*R*)-**33**, as previously reported.[12]

(*R*)-2-Pyridin-2-ylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-34 (Scheme 6). Using general procedure A, *s*-BuLi (1.0 mL of a 1.2 M solution in cyclohexane, 1.2 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (250 μL, 1.2 mmol) and (−)-sparteine (260 μL, 1.2 mmol, 1.0 equiv) in TBME (3 mL), $ZnCl_2$ (710 μL of a 1.0 M solution in Et_2O, 0.7 mmol, 0.6 equiv), $Pd(OAc)_2$ (8 mg, 0.05 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (12 mg, 0.06 mmol, 0.05 equiv) and the appropriate aryl bromide (80 μL, 1.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 30:70 hexane−EtOAc as eluent gave aryl pyrrolidine (*R*)-**34** (165 mg, 71%, 94:6 er by CSP-HPLC) as a colorless oil, R_f 0.2 (6:4 petrol−EtOAc); $[\alpha]_D$ +67.6 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2978, 1686 (C═O), 1456, 1399 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 8.49 (d, J = 4.0 Hz, 1H), 7.64−7.53 (m, 1H), 7.23−6.98 (m, 2H), 4.95 (br d, J = 5.0 Hz, 0.35H), 4.82 (dd, J = 8.0, 4.5 Hz, 0.65H), 3.69−3.37 (m, 2H), 2.48−2.16 (m, 1H), 2.10−1.72 (m, 3H), 1.40 (s, 3.15H), 1.13 (s, 5.85H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 164.1 (C), 162.9 (C), 154.9 (C), 154.8 (C), 149.5 (CH), 149.1 (CH), 136.6 (CH), 136.5 (CH), 121.9 (CH), 121.7 (CH), 120.2 (CH), 119.7 (CH), 79.2 (C), 62.6 (CH), 61.9 (CH), 47.1 (CH_2), 46.8 (CH_2), 33.9 (CH_2), 33.6 (CH_2), 28.1 (CH_3), 27.7 (CH_3), 23.6 (CH_2), 22.8 (CH_2); MS (ESI) m/z 271 [$(M + Na)^+$, 13], 249 [$(M + H)^+$, 100], 193 (56), 149 (37); HRMS (ESI) m/z calcd for $C_{14}H_{20}N_2O_2$ $(M + H)^+$ 249.1598, found 249.1597 (+0.4 ppm error); HPLC chiralpak AD-H (90:10 hexane−*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**34** 3.5 min, (*S*)-**34** 5.3 min.

(*R*)-2-(2-Cyanopyridin-3-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-35 (Scheme 6). Using general procedure A, *s*-BuLi (1.0 mL of a 1.2 M solution in cyclohexane, 1.2 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (250 μL, 1.2 mmol) and (−)-sparteine (260 μL, 1.2 mmol, 1.0 equiv) in TBME (3 mL), $ZnCl_2$ (710 μL of a 1.0 M solution in Et_2O, 0.7 mmol, 0.6 equiv), $Pd(OAc)_2$ (8 mg, 0.05 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (12 mg, 0.06 mmol, 0.05 equiv) and the appropriate aryl bromide (184 mg, 1.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 30:70 hexane−EtOAc and then EtOAc as eluent gave aryl pyrrolidine (*R*)-**35** (202 mg, 76%, 94:6 er by CSP-HPLC) as a white solid, mp 118−119 °C; $[\alpha]_D$ +35.8 (*c* 0.9 in $CHCl_3$); IR ($CHCl_3$) 3018, 1980 (C≡N), 1691 (C═O), 1386, 1368, 1217, 1158, 1124, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 8.60 (br d, J = 4.0 Hz, 0.7H), 8.57 (br s, 0.3H), 7.69 (br d, J = 7.5 Hz, 0.7H), 7.62 (br d, J = 7.5 Hz, 0.3H), 7.57−7.30 (m, 1H), 5.17 (br s, 0.3H), 5.12 (t, J = 7.0 Hz, 0.7H), 3.79−3.68 (m, 0.6H), 3.68−3.55 (m, 1.4H), 2.65−2.43 (m, 1H), 2.05−1.75 (m, 3H), 1.43 (s, 2.7H), 1.17 (s, 6.3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.4 (C), 154.2 (C), 149.6 (CH), 149.4 (C), 146.4 (C), 134.1 (CH), 132.0 (C), 127.0 (CH), 116.0 (C), 80.2 (C), 58.4 (CH), 58.1 (CH), 47.5 (CH_2), 47.2 (CH_2), 35.2 (CH_2), 34.1 (CH_2), 28.1 (CH_3), 27.7 (CH_3), 23.7 (CH_2), 23.4 (CH_2); MS (ESI) m/z 296 [$(M + Na)^+$, 100], 274 [$(M + H)^+$, 96], 218 (24), 174 (20); HRMS (ESI) m/z calcd for $C_{15}H_{19}N_3O_2$ $(M + H)^+$ 274.1550,

found 274.1551 (−0.2 ppm error); HPLC chiralpak AD-H (90:10 hexane−*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**35** 4.4 min, (*S*)-**35** 5.1 min.

(*R*)-2-(2-Fluoro-5-methylpyridin-3-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-36 (Scheme 6). Using general procedure A, *s*-BuLi (1.0 mL of a 1.2 M solution in cyclohexane, 1.2 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (250 μL, 1.2 mmol) and (−)-sparteine (260 μL, 1.2 mmol, 1.0 equiv) in TBME (3 mL), $ZnCl_2$ (710 μL of a 1.0 M solution in Et_2O, 0.7 mmol, 0.6 equiv), $Pd(OAc)_2$ (8 mg, 0.05 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (12 mg, 0.06 mmol, 0.05 equiv) and the appropriate aryl bromide (190 mg, 1.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 70:30 hexane−EtOAc as eluent gave aryl pyrrolidine (*R*)-**36** (190 mg, 70%, 97:3 er by CSP-HPLC) as a white solid, mp 63−64 °C; $[\alpha]_D$ +101.4 (*c* = 1.1 in $CHCl_3$); IR ($CHCl_3$) 2981, 1688 (C═O), 1455, 1400, 1367, 1163, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.87 (s, 0.7H), 7.84 (s, 0.3H), 7.35 (d, *J* = 9.0 Hz, 0.7H), 7.28 (d, *J* = 9.0 Hz, 0.3H), 5.04 (d, *J* = 7.0 Hz, 0.3H), 4.99−4.86 (m, 0.7H), 3.71−3.39 (m, 2H), 2.43−2.20 (m, 1H), 2.28 (s, 3H), 1.98−1.72 (m, 3H), 1.45 (s, 2.7H), 1.21 (s, 6.3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 159.4 (d, *J* = 238.0 Hz, C), 154.6 (C), 145.3 (d, *J* = 14.5 Hz, CH), 138.3 (d, *J* = 5.0 Hz, CH), 130.9 (d, *J* = 4.5 Hz, C), 125.7 (C), 79.7 (C), 55.4 (CH), 54.9 (CH), 47.0 (CH_2), 46.7 (CH_2), 33.7 (CH_2), 32.4 (CH_2), 28.1 (CH_3), 27.8 (CH_3), 23.3 (CH_2), 22.9 (CH_2), 17.2 (CH_3), 17.1 (CH_3); MS (ESI) *m*/*z* 303 [(M + Na)$^+$, 61], 281 [(M + H)$^+$, 100], 225 (11); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}N_2O_2F$ (M + Na)$^+$ 303.1479, found 303.1481 (−0.5 ppm error); HPLC chiralpak AD-H (98:2 heptane−*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**36** 7.2 min, (*S*)-**36** 8.0 min.

3-Bromo-5-trimethylsilylethynylpyridine 38 (Scheme 7). Trimethylsilylacetylene (622 μL, 4.40 mmol) was added dropwise to a stirred solution of 3,5-dibromopyridine (947 mg, 4.00 mmol), CuI (76 mg, 0.40 mmol) and $Pd(PPh_3)_2Cl_2$ (281 mg, 0.40 mmol) in Et_3N (1.4 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, water (6 mL) was added, and the resulting solution was extacted with Et_2O (3 × 6 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol−CH_2Cl_2 as eluent gave bromopyridine **38** (666 mg, 72%) as a brown oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (br s, 2H), 7.90 (s, 1H), 0.27 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.0 (CH), 150.3 (CH), 141.5 (CH), 122.0 (C), 120.2 (C), 100.3 (C), 99.7 (C), −0.7 (CH_3). Spectroscopic data consistent with those reported in the literature.[56]

(*S*)-2-(5-Trimethylsilylethynylpyridin-3-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*S*)-37 (Scheme 7). *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 equiv) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **15** (171 mg, 175 μL, 1.0 mmol) and (+)-sparteine surrogate (213 mg, 1.3 mmol, 1.3 equiv) in Et_2O (7 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, $ZnCl_2$ (0.6 mL of a 1.0 M solution in Et_2O, 0.6 mmol, 0.6 equiv) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. Then, the solution was allowed to warm to rt and stirred for 30 min. A solution of bromopyridine **38** (178 mg, 0.7 mmol, 0.7 equiv) in TBME (5 mL) was added. A mixture of $Pd(OAc)_2$ (11 mg, 0.05 mmol, 0.05 equiv) and *t*-Bu_3PBHF_4 (11 mg, 0.06 mmol, 0.06 equiv) was added in one portion. The reaction flask was transferred to a preheated oil bath and the solution was stirred and heated at reflux for 16 h. After cooling to rt, 35% $NH_4OH_{(aq)}$ (0.3 mL) was added, and the resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite and washed with Et_2O (20 mL). The filtrate was washed with water (10 mL) and saturated brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 93:7 CH_2Cl_2−MeOH as eluent gave pyridylpyrrolidine (*S*)-**37** (75 mg, 44%, 92:8 er by NMR spectroscopy of a derivative in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol) as a yellow oil, R_f (93:7 CH_2Cl_2−MeOH) 0.4; $[\alpha]_D$ −57.3 (*c* 1.0 in $CHCl_3$); IR (film) 2973, 2880, 2159, 1697 (C═O), 1448, 1392, 1366, 1250, 1164, 1115, 846, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 8.56 (br s, 1H), 8.40 (br s, 1H), 7.54 (s, 1H), 4.91 (br s, 0.3H), 4.75 (br s, 0.7H), 3.62 (br s, 2H), 2.34 (br s, 1H), 1.98−1.69 (m, 3H), 1.45 (br s, 2.7H), 1.21 (br s, 6.3H), 0.25 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 154.1 (C), 150.1 (CH), 146.6 (CH), 139.4 (C) 137.0 (C), 135.7 (CH), 101.3 (C), 98.1 (C), 79.7 (C), 58.7 (CH), 58.5 (CH), 47.0 (CH_2), 35.6 (CH_2), 34.3 (CH_2), 28.3 (CH_3), 28.0 (CH_3), 23.2 (CH_2), −0.3 (CH_3); MS (ESI) *m*/*z* 345 [(M + H)$^+$, 100]; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{28}N_2O_2Si$ (M + H)$^+$ 345.1993, found 345.1995 (−0.7 ppm error).

(*S*)-3-Ethynyl-5-pyrrolidin-2-ylpyridine (Scheme 7). TFA (466 mg, 304 μL, 4.09 mmol) was added dropwise to a stirred solution of pyridylpyrrolidine (50 mg, 0.2 mmol) in CH_2Cl_2 (4 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h. Then, the solvent and excess TFA were evaporated under reduced pressure. Water (5 mL) was added to the residue and 5 M $NaOH_{(aq)}$ was added dropwise until pH 14. CsF (310 mg, 2.04 mmol) was added, and the resulting solution was stirred at rt under air for 1 h. The solution was adjusted to pH 1 by addition of 5 M $HCl_{(aq)}$, and the resulting solution was extracted with CH_2Cl_2 (3 × 6 mL). The aqueous layer was adjusted to pH 14 by addition of 5 M $NaOH_{(aq)}$ and extracted with Et_2O (8 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give (*S*)-3-ethynyl-5-pyrrolidin-2-ylpyridine (26 mg, 76%) as a yellow oil, $[\alpha]_D$ −100.8 (*c* 0.5 in $CHCl_3$); IR ($CHCl_3$) 3292 (NH), 2964, 2871, 1444, 1416, 892, 711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.0 Hz, 1H), 8.54 (d, *J* = 2.0 Hz, 1H), 7.82 (t, *J* = 2.0 Hz), 4.16 (t, *J* = 7.5 Hz, 1H), 3.19 (s, 1H), 3.22−3.14 (m, 1H), 3.09−3.02 (m, 1H), 2.27−2.17 (m, 1H), 2.12 (br s, 1H), 2.00−1.80 (m, 2H), 1.70−1.60 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.0 (CH), 148.1 (CH), 140.1 (C), 137.2 (CH), 118.8 (C), 80.6 (CH), 80.2 (C), 59.4 (CH), 46.9 (CH_2), 34.4 (CH_2), 25.5 (CH_2); MS (ESI) *m*/*z* 173 [(M + H)$^+$, 100], 156 (13); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{12}N_2$ (M + H)$^+$ 173.1073, found 173.1077 (−1.9 ppm error).

(*S*)-(+)-5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine (*S*)-SIB1508Y (Scheme 7). Formic acid (34 mg, 22 μL, 0.75 mmol) was added to a stirred solution of (*S*)-3-ethynyl-5-pyrrolidin-2-ylpyridine (26 mg, 0.15 mmol) and parafomaldehyde (22 mg, 0.75 mmol) in water (3 mL) at rt. The resulting solution was stirred and heated at reflux for 16 h. Then, 5 M $NaOH_{(aq)}$ (2 mL) was added and the aqueous solution was extracted with Et_2O (8 × 8 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give (*S*)-SIB1508Y (19 mg, 68%, 92:8 er by NMR spectroscopy in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol) as a colorless oil, $[\alpha]_D$ −78.7 (*c* 0.7 in EtOH) (lit.,[57] $[\alpha]_D$ −162.0 (*c* 0.8 in EtOH)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.0 Hz, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 7.81 (t, *J* = 2.0 Hz, 1H), 3.24 (ddd, *J* = 9.5, 7.5, 2.0 Hz, 1H), 3.20 (s, 1H), 3.10 (t, *J* = 8.0 Hz, 1H), 2.32 (q, *J* = 9.5 Hz, 1H), 2.27−2.18 (m, 1H), 2.17 (s, 3H), 2.04−1.90 (m, 1H), 1.89−1.76 (m, 1H), 1.75−1.63 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.5 (CH), 149.0 (CH), 138.5 (C), 138.0 (CH), 119.1 (C), 80.5 (C), 80.3 (CH), 68.4 (CH), 56.9 (CH_2), 40.4 (CH_3), 35.2 (CH_2), 22.7 (CH_2). Spectroscopic data consistent with those reported in the literature.[57]

Determination of the Enantiomeric Ratio of (*S*)-(+)-5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine (*S*)-SIB1508Y (Scheme 7). Enantiomeric ratio was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equiv of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. A 0.036 M solution of SIB1508Y was prepared by dissolving SIB1508Y (4 mg, 0.021 mmol) in $CDCl_3$ (0.6 mL). Then, (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol

(24 mg, 0.087 mmol) was added. Diagnostic signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (NMe, major), 1.98 (NMe, minor). Integration of the major and minor NMe signals in the ^{1}H NMR spectra indicated that (*S*)-SIB1508Y was present in 92:8 er. Enantiomeric ratio was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. A 0.031 M solution of SIB1508Y was prepared by dissolving SIB1508Y (4 mg, 0.021 mmol) in $CDCl_3$ (0.7 mL). Then, (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ehtanol (24 mg, 0.087 mmol) was added. Diagnostic signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (NMe, minor), 1.99 (NMe, major). Integration of the major and minor NMR signals in the ^{1}H NMR spectra indicated that (*S*)-SIB1508Y was present in 92:8 er.

(*S*)-2-Pyridin-3-ylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*S*)-33 (Scheme 8). *s*-BuLi (1.7 mL of a 1.3 M solution in hexanes, 2.2 mmol, 1.0 equiv) was added dropwise to a stirred solution of (+)-sparteine surrogate (97 mg, 0.5 mmol, 0.25 equiv) and di-*i*-Pr-bispidine **25** (467 mg, 2.2 mmol, 1.0 equiv) in Et_2O (6 mL) at −78 °C under Ar. After stirring at −78 °C for 15 min, a solution of *N*-Boc pyrrolidine **15** (380 mg, 390 μL, 2.2 mmol) in Et_2O (1 mL) was added dropwise. The resulting solution was stirred at −78 °C for 5 h. Then, $ZnCl_2$ (1.3 mL of a 1.0 M solution in Et_2O, 1.3 mmol, 0.6 equiv) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. Then, the solution was allowed to warm to rt and stirred for 30 min. A solution of 3-bromopyridine (246 mg, 153 μL, 1.6 mmol, 0.7 equiv) in TBME (5 mL) was added. A mixture of $Pd(OAc)_2$ (25 mg, 0.11 mmol, 0.05 equiv) and *t*-Bu_3PBHF_4 (25 mg, 0.11 mmol, 0.06 equiv) was added in one portion. The reaction flask was transferred to a preheated oil bath and the solution was stirred and heated at reflux for 16 h. After cooling to rt, 35% $NH_4OH_{(aq)}$ (0.3 mL) was added, and the resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite and washed with Et_2O (20 mL). The filtrate was washed with water (10 mL) and saturated brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 petrol−EtOAc as eluent gave pyridylpyrrolidine (*S*)-**33** (179 mg, 46%, 92:8 er by NMR spectroscopy of a derivative in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol) as a colorless oil, $[\alpha]_D$ +80.0 (*c* 1.0 in CH_2Cl_2) (lit.,[12] $[\alpha]_D$ −83.6 (*c* 1.55 in CH_2Cl_2) for (*R*)-**33** of 94:6 er); ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 8.45−8.43 (m, 2H), 7.50−7.43 (m, 1H), 7.25−7.16 (m, 1H), 4.93 (br s, 0.4H), 4.75 (br s, 0.6H), 3.64−3.46 (m, 2H), 2.40−2.25 (m, 1H), 1.95−1.77 (m, 3H), 1.42 (s, 3.6H), 1.17 (s, 5.4H). Spectroscopic data consistent with those reported in the literature.[12]

(*S*)-Nicotine (Scheme 8). TFA (1.01 g, 658 μL, 8.86 mmol) was added dropwise to a stirred solution of aryl pyrrolidine (*S*)-**33** (110 mg, 0.44 mmol, 92:8 er) in CH_2Cl_2 (6 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h. Then, the solvent was evaporated under reduced pressure. Et_2O and 5 M $NaOH_{(aq)}$ (6 mL) were added to the residue. The two layers were separated, and the aqueous layer was extracted with Et_2O (7 × 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Then, water (7 mL), paraformaldehyde (80 mg, 2.66 mmol) and formic acid (123 mg, 80 μL, 2.66 mmol) were added. The resulting solution was stirred and heated at reflux for 16 h. The solvent was evaporated under reduced pressure, and 5 M $NaOH_{(aq)}$ (5 mL) and Et_2O (25 mL) were added to the residue. The two layers were separated, and the aqueous layer was extracted with Et_2O (7 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give (*S*)-nicotine (68 mg, 96%, 92:8 er by NMR spectroscopy in the presence of 1-(9-anthryl)-2,2,2-trifluoroethanol) as a colorless oil, $[\alpha]_D$ −81.0 (*c* 1.0 in EtOH) (lit.,[51a] $[\alpha]_D$ −145.0 (*c* 1.0 in EtOH) for (*S*)-nicotine of 99% ee); ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.52 (s, 1H), 8.47 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.70−7.65 (m, 1H), 7.24 (dd, *J* = 8.0, 5.0 Hz), 3.22 (t, *J* = 7.5 Hz, 1H), 3.06 (t, *J* = 8.5 Hz, 1H), 2.34−2.25 (m, 1H), 2.24−2.07 (m, 4H), 2.01−1.88 (m, 1H), 1.86−1.65 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.4 (CH), 148.5 (CH), 138.6 (C), 134.7 (CH), 123.4 (CH), 68.7 (CH), 56.9 (CH_2), 40.2 (CH_3), 35.1 (CH_2), 22.5 (CH_2). Spectroscopic data consistent with those reported in the literature.[51a]

Determination of the Enantiomeric Ratio of (*S*)-Nicotine (Scheme 8). Enantiomeric ratio was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equiv of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. A 0.052 M solution of nicotine was prepared by dissolving nicotine (5 mg, 0.031 mmol) in $CDCl_3$ (0.6 mL). Then, (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (34 mg, 0.12 mmol) was added. Diagnostic signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (NMe, major), 1.89 (NMe, minor). Integration of the major and minor NMe signals in the ^{1}H NMR spectra indicated that (*S*)-nicotine was present in 92:8 er. Enantiomeric ratio was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. A 0.026 M solution of nicotine was prepared by dissolving nicotine (3 mg, 0.018 mmol) in $CDCl_3$ (0.7 mL). Then, (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (20 mg, 0.072 mmol) was added. Diagnostic signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (NMe, minor), 1.95 (NMe, major). Integration of the major and minor NMe signals in the ^{1}H NMR spectra indicated that (*S*)-nicotine was present in 92:8 er.

(*R*)-2-(2-Methylpropenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-39 (Scheme 9). Using general procedure A, *s*-BuLi (3.7 mL of a 1.3 M solution in cyclohexane, 4.8 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (0.84 mL, 4.8 mmol) and (−)-sparteine (1.1 mL, 4.8 mmol, 1.0 equiv) in TBME (10 mL), $ZnCl_2$ (2.4 mL of a 1.0 M solution in Et_2O, 2.4 mmol, 0.5 equiv), $Pd(OAc)_2$ (36 mg, 0.16 mmol, 0.03 equiv), *t*-Bu_3PHBF_4 (58 mg, 0.20 mmol, 0.04 equiv) and the appropriate vinyl bromide (410 μL, 4.0 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 15:1 hexane−EtOAc as eluent gave vinyl pyrrolidine (*R*)-**39** (659 mg, 73%, 95:5 er by CSP-HPLC) as a colorless oil, R_f 0.3 (5:1 petrol−Et_2O); $[\alpha]_D$−28.0 (*c* 1.0 in $CHCl_3$); IR ($CHCl_3$) 2974, 2930, 2875, 1693 (C═O), 1453, 1394, 1366, 1169, 1107 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (br d, *J* = 7.0 Hz, 1H), 4.39 (br s, 1H), 3.53−3.22 (m, 2H), 2.07−1.95 (m, 1H), 1.92−1.74 (m, 2H), 1.673 (s, 3H), 1.670 (s, 3H), 1.61−1.48 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.2 (C), 131.2 (C), 127.2 (CH), 78.7 (C), 55.1 (CH), 46.1 (CH_2), 33.0 (CH_2), 28.3 (CH_3), 25.4 (CH_3), 23.5 (CH_3), 23.4 (CH_2); MS (ESI) *m*/*z* 248 [$(M + Na)^+$, 100], 170 (58), 114 (54); HRMS (ESI) *m*/*z* calcd for $C_{13}H_{23}NO_2$ $(M + Na)^+$ 248.1621, found 248.1619 (+0.9 ppm error); chiralcel OD-H (97:3 heptane−*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**39** 7.0 min, (*S*)-**39** 7.6 min.

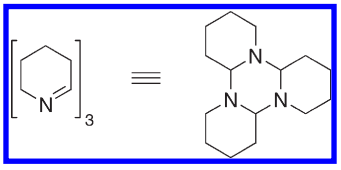
(*R*)-2-(1-Trimethylsilylvinyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-40 (Scheme 9). Using general procedure A, *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol) and (−)-sparteine (1.3 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL), $ZnCl_2$ (3.4 mL of a 1.0 M solution in Et_2O, 3.4 mmol, 0.6 equiv), $Pd_2(dba)_3$ (105 mg, 0.23 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) and the appropriate vinyl bromide (740 μL, 4.75 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane−EtOAc as eluent gave vinyl pyrrolidine (*R*)-**40** (870 mg, 68%, 97:3 er by CSP-HPLC) as a colorless oil, R_f 0.2 (9:1 petrol−Et_2O); $[\alpha]_D$ +111.6 (*c* 0.7 in $CHCl_3$); IR ($CHCl_3$) 2957, 1694 (C═O), 1400, 1365, 1248, 1170, 1122, 863, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 5.89 (br s, 0.5H), 5.85 (br s, 0.5H), 5.64 (d, *J* = 1.0 Hz, 0.5H), 5.60 (d, *J* = 1.0 Hz, 0.5H), 4.20 (br s, 1H), 3.40 (br s, 2H), 2.12−1.90 (m, 1H), 1.84−1.66 (m, 3H), 1.40 (br s, 9H), 0.04 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.1 (C), 146.6 (CH_2), 128.3 (C), 79.0 (C), 61.0 (CH), 46.1 (CH_2), 31.8 (CH_2), 28.2 (CH_3), 22.5 (CH_2), −1.6 (CH_3); MS (ESI) *m*/*z* 292 [$M + Na)^+$, 78], 214 (100), 198 (11), HRMS (ESI) *m*/*z* calcd for

$C_{14}H_{27}NO_2Si$ $(M + Na)^+$ 292.1703, found 292.1703 (+0.2 ppm error); chiralpak AD-H (99:1 heptane−*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**40** 8.2 min, (*S*)-**40** 10.2 min.

(*R*)-((*E*)-2-Propenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R,E*)-41 (Scheme 9). Using general procedure A, *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol) and (−)-sparteine (1.3 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL), $ZnCl_2$ (3.4 mL of a 1.0 M solution in Et_2O, 3.4 mmol, 0.6 equiv), $Pd_2(dba)_3$ (105 mg, 0.23 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) and the appropriate (*E*)-vinyl bromide (410 μL, 4.75 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane−EtOAc as eluent gave vinyl pyrrolidine (*R,E*)-**41** (670 mg, 67%) as a colorless oil, R_f 0.2 (5:1 petrol−Et_2O); $[\alpha]_D$−4.5 (*c* 1.1 in $CHCl_3$); IR ($CHCl_3$) 2976, 1682 (C═O), 1404, 1366, 1169, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 5.47 (br s, 1H), 5.34 (br s, 1H), 4.53 (br s, 0.5 H), 4.16 (br s, 0.5H), 3.36 (br s, 2H), 2.08−1.90 (m, 1H), 1.85−1.76 (m, 2H), 1.660 (dd, *J* = 6.5, 1.0 Hz, 1.5H,), 1.657 (dd, *J* = 6.5, 1.0 Hz, 1.5H), 1.59−1.51 (m, 1H), 1.43 (br s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.4 (C), 132.0 (CH), 125.2 (CH), 78.9 (C), 58.6 (CH), 53.8 (CH_3), 45.9 (CH_2), 32.2 (CH_2), 28.2 (CH_3), 22.6 (CH_2); MS (ESI) *m/z* 234 [$(M + Na)^+$, 83], 156 (100), 114 (21); HRMS (ESI) *m/z* calcd for $C_{12}H_{21}NO_2$ $(M + Na)^+$ 234.1465, found 234.1462 (+1.3 ppm error). Spectroscopic data consistent with those reported in the literature.[58]

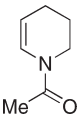
(*R*)-((*Z*)-2-Propenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R,Z*)-42 (Scheme 9). Using general procedure A, *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.7 mmol, 1.0 equiv), *N*-Boc pyrrolidine **15** (1.2 mL, 5.7 mmol) and (−)-sparteine (1.3 mL, 5.7 mmol, 1.0 equiv) in TBME (12 mL), $ZnCl_2$ (3.4 mL of a 1.0 M solution in Et_2O, 3.4 mmol, 0.6 equiv), $Pd_2(dba)_3$ (105 mg, 0.23 mmol, 0.04 equiv), *t*-Bu_3PHBF_4 (83 mg, 0.285 mmol, 0.05 equiv) and the appropriate (*Z*)-vinyl bromide (400 μL, 4.75 mmol, 0.83 equiv) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane−EtOAc as eluent gave vinyl pyrrolidine (*R,Z*)-**42** (670 mg, 67%) as a colorless oil, R_f 0.2 (5:1 petrol−Et_2O); $[\alpha]_D$−46.2 (*c* 0.6 in $CHCl_3$); IR ($CHCl_3$) 2978, 1681 (C═O), 1401, 1367, 1167, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 (br s, 1H), 5.32 (br s, 1H), 4.52 (br s, 1H), 3.39 (br s, 2H), 2.14−1.98 (m, 1H), 1.91−1.76 (m, 2H), 1.67 (br s, 3H), 1.63−1.54 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.1 (C), 133.0 (CH), 129.3 (CH), 79.0 (C), 59.2 (CH), 53.8 (CH_3), 46.1 (CH_2), 32.9 (CH_2), 28.3 (CH_3), 28.1 (CH_2); MS (ESI) *m/z* 234 [$(M + Na)^+$, 100], 156 (94), 114 (22); HRMS (ESI) *m/z* calcd for $C_{12}H_{21}NO_2$ $(M + Na)^+$ 234.1465, found 234.1462 (+0.9 ppm error).

Dodecahydro-4a,8a,12a-triazatriphenylene.



Piperidine (5.0 g, 5.9 mL, 58.7 mmol) was added dropwise to a stirred solution of *N*-chlorosuccinimide (8.34 g, 62.5 mmol) in Et_2O (60 mL) at rt under Ar. The resulting mixture was stirred at rt for 2 h, and the solids were removed by filtration. The filtrate was washed with water (2 × 35 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give an oily residue. A solution of NaOMe in MeOH [freshly prepared by dissolving Na (1.53 g, 66.7 mmol) in MeOH (35 mL)] was added to the oily residue at rt under Ar. The resulting solution was stirred and heated at reflux for 45 min. After cooling to rt, water was added until all the solids had dissolved. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 125 mL). The combined organic layers were evaporated under reduced pressure until a sticky residue remained. Et_2O (100 mL) was added to the residue, and the solution was dried ($MgSO_4$) and evaporated under reduced pressure to give dodecahydro-4a,8a,12a-triazatriphenylene (2.72 g, 56%) as a colorless oil, ^1H NMR (400 MHz, $CDCl_3$) δ 3.08 (dt, *J* = 11.0, 5.0 Hz, 3H, NCH), 2.76 (br d, *J* = 5.5 Hz, 3H, NCH), 2.04−1.91 (m, 3H, NCH), 1.76−1.58 (m, 9H, CH_2), 1.57−1.46 (m, 6H, CH_2), 1.31−1.18 (m, 3H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 81.8 (CH), 46.0 (CH_2), 28.7 (CH_2), 25.3 (CH_2), 21.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[59]

1-(3,4-Dihydro-2*H*-pyridin-1-yl)ethanone.



A solution of dodecahydro-4a,8a,12a-triazatriphenylene (2.72 g, 10.91 mmol) in acetic anhydride (48 mL) was stirred and heated at 50 °C under Ar for 16 h. After cooling to rt, EtOAc (55 mL) was added, and the solution was washed with 1 M $NaOH_{(aq)}$ (3 × 30 mL) and water (2 × 30 mL) and evaporated under reduced pressure. Saturated $Na_2CO_{3(aq)}$ (40 mL) was added to the residue, and the resulting aqueous solution was extracted with EtOAc (10 × 60 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give 1-(3,4-dihydro-2*H*-pyridin-1-yl)ethanone (2.66 g, 65%) as a brown oil, ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.07 (dt, *J* = 8.5, 2.0 Hz, 0.3H, NCH═), 6.47 (dt, *J* = 8.5, 2.0 Hz, 0.7H, NCH═), 4.96 (dt, *J* = 8.5, 4.0 Hz, 0.3H, NCH═C*H*), 4.86 (dt, *J* = 8.5, 4.0 Hz, 0.7H, NCH═C*H*), 3.58 (t, *J* = 6.0 Hz, 1.4H, NCH_2), 3.48 (t, *J* = 6.0 Hz, 0.6H, NCH_2), 2.05 (s, 2.1H, Me), 2.04 (s, 0.9H, Me), 2.01−1.94 (m, 2H, CH_2), 1.81−1.67 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 174.0 (C), 168.5 (C), 125.8 (CH), 123.8 (CH), 108.7 (CH), 108.4 (CH), 44.0 (CH_2), 39.8 (CH_2), 21.6 (CH_2), 21.3 (CH_3), 21.2 (CH_2), 21.0 (CH_2), 20.9 (CH_3), 20.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[60]

1-(4-Bromo-3,4-dihydro-2*H*-pyridin-1-yl)ethanone 43. Bromine (356 mg, 115 μL, 2.23 mmol) was added dropwise to a stirred solution of 1-(3,4-dihydro-2*H*-pyridin-1-yl)ethanone (250 mg, 2.00 mmol) in CH_2Cl_2 (8 mL) at −78 °C under Ar until an orange color persisted. Then, *i*-Pr_2NEt (283 mg, 381 μL, 2.19 mmol) was added, and the resulting solution was allowed to warm to rt and stirred for 45 min. Saturated $Na_2S_2O_{3(aq)}$ (8 mL) was added, and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 18 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 petrol−EtOAc as eluent gave vinyl bromide **43** (534 mg, 91%) as a colorless oil, R_f (7:3 petrol−EtOAc) 0.3; IR (film) 2931, 1640 (C═O), 1392, 1349, 1296, 1257, 986, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.55 (t, *J* = 1.5 Hz, 0.3H), 6.91 (t, *J* = 1.5 Hz, 0.7H), 3.69−3.63 (m, 1.4H), 3.58−3.53 (m, 0.6H), 2.51−2.42 (m, 2H), 2.15 (s, 2.1H), 2.13 (s, 0.9H), 2.03−1.06 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 168.4 (C), 167.8 (C), 126.7 (CH), 124.9 (CH), 108.2 (C), 42.8 (CH_2), 38.5 (CH_2), 31.2 (CH_2), 31.0 (CH_2), 21.6 (CH_3), 21.3 (CH_3); MS (ESI) *m/z* 204 [$(M + H)^+$, 11], 148 (33), 126 (100); HRMS (ESI) *m/z* calcd for $C_7H_{10}NO^{79}Br$ $(M + H)^+$ 204.0019, found 204.0019 (−0.4 ppm error).

(*R*)-2-(1-Acetyl-1,4,5,6-tetrahydropyridin-3-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (*R*)-44 (Scheme 10). *s*-BuLi (2.3 mL of a 1.3 M solution in hexanes, 3.0 mmol, 1.3 equiv) was added dropwise to a stirred solution of (−)-sparteine (690 μL, 3.0 mmol, 1.3 equiv) in TBME (6 mL) at −78 °C under Ar. After stirring at −78 °C for 15 min, a solution of *N*-Boc pyrrolidine **15** (395 mg, 405 μL, 2.3 mmol) in TBME (1 mL) was added dropwise. The resulting solution was stirred at −78 °C for 90 min. Then, $ZnCl_2$ (1.39 mL of a 1.0 M solution in Et_2O,

1.39 mmol, 0.6 equiv) was added dropwise, and the resulting solution was stirred at −78 °C for 30 min. Then, the solution was allowed to warm to rt and stirred for 30 min. A solution of vinyl bromide **43** (330 mg, 1.62 mmol, 0.7 equiv) in TBME (2 mL) was added. A mixture of Pd_2dba_3 (52 mg, 0.06 mmol, 0.03 equiv) and *t*-Bu_3PHBF_4 (26 mg, 0.14 mmol, 0.06 equiv) was added in one portion, and the resulting mixture was stirred at rt for 72 h. Then, 35% $NH_4OH_{(aq)}$ (0.4 mL) was added, and the resulting mixture was stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite and washed with Et_2O (2 × 10 mL). The filtrate was washed with 10% $NH_4Cl_{(aq)}$ (2 × 25 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 EtOAc−petrol as eluent gave *N*-Boc maackiamine (*R*)-**44** (266 mg, 56%, 95:5 er by CSP-HPLC) as a colorless oil, R_f (8:2 EtOAc−petrol) 0.3; $[\alpha]_D$ +40.9 (*c* 1.0 in $CHCl_3$); IR(film) 2972, 2930, 1692 (C═O), 1649 (C═O), 1394, 1366, 1331, 1258, 1165, 1113, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.13−7.02 (m, 0.3H), 6.39 (s, 0.7H), 4.32−4.05 (m, 1H), 3.69−3.44 (m, 4H), 2.12 (s, 3H), 1.99−1.93 (m, 4H), 1.90−1.68 (m, 4H), 1.41 (br s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 168.8 (C), 167.3 (C), 154.3 (br, CH), 121.0 (C), 79.0 (C), 61.0 (CH), 46.8 (CH_2), 44.1 (CH_2), 40.1 (CH_2), 31.7 (CH_2), 30.7 (CH_2), 28.3 (CH_3), 23.4 (CH_2), 21.9 (CH_3), 21.7 (CH_2), 21.3 (CH_3), 21.1 (CH_2); MS (ESI) *m*/*z* 317 [(M + Na)$^+$, 100], 295 [(M + H)$^+$, 60], 239 (18); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{26}N_2O_3$ (M + Na)$^+$ 317.1836, found 317.1836 (0.0 ppm error); HPLC Chiralpak AD (90:10 hexane−*i*-PrOH, 1.0 mL min^{-1}) (*R*)-**44** 8.1 min, (*S*)-**44** 9.8 min. Other Pd catalysts/conditions were explored to improve the yield: $Pd(OAc)_2$/*t*-Bu_3PHBF_4 (Et_2O), rt, 16 h gave 29% yield, 94:6 er; $Pd(OAc)_2$/*t*-Bu_3PHBF_4 (TBME), rt, 16 h gave 37% yield, 80:20 er; $Pd(OAc)_2$/*t*-Bu_3PHBF_4 (TBME), reflux, 16 h gave 43% yield, 93:7 er; $Pd_2(dba)_3$/*t*-Bu_3PHBF_4 (TBME), rt, 16 h gave 40% yield, 92:8 er

1-((*R*)-5-Pyrrolidin-2-yl-3,4-dihydro-2*H*-pyridin-1-yl)ethanone (*R*)-Maackiamine (Scheme 10). *tert*-Butyldimethylsilyl triflate (170 μL, 0.8 mmol) was added dropwise to a stirred solution of *N*-Boc maackiamine (*R*)-**44** (200 mg, 0.68 mmol, 95:5 er) and pyridine (80 μL, 1.0 mmol) in CH_2Cl_2 (10 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The solvent was evaporated under reduced pressure, and the residue was dried thoroughly under high vacuum. The residue was dissolved in saturated $NH_4Cl_{(aq)}$ (10 mL), and the aqueous solution was extracted with Et_2O (5 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. THF (7.5 mL) was added to the residue, and the resulting solution was added dropwise to a stirred suspension of CsF (152 mg, 1.0 mmol) in THF (7.5 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. The solvent was evaporated under reduced pressure, and 1 M $NaOH_{(aq)}$ (15 mL) was added to the residue. The resulting aqueous solution was extracted with Et_2O (5 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by preparative TLC on silica with 7:7:2 EtOAc−hexane−Et_2NH as eluent gave (*R*)-maackiamine (71 mg, 54%, 95:5 er by NMR spectroscopy in the presence of (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol)) as a colorless oil, R_f (7:7:2 EtOAc−hexane−Et_2NH) 0.3; $[\alpha]_D$ +12.8 (*c* 1.0 in EtOH) (lit.,[52] $[\alpha]_D$ +110 (*c* 0.01 in EtOH)); ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.21 (s, 0.3H), 6.62 (s, 0.7H), 3.71−3.45 (m, 3H), 3.09−3.02 (m, 1H), 2.97−2.87 (m, 1H), 2.17−2.01 (m, 3H,), 2.16 (s, 2.1H), 2.15 (s, 0.9H), 1.94−1.71 (m, 5H), 1.63−1.47 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 168.6 (C), 168.2 (C), 122.1 (C), 121.7 (C), 121.5 (CH), 119.9 (CH), 62.4 (CH), 62.3 (CH), 46.4 (CH_2), 46.3 (CH_2), 44.2 (CH_2), 40.1 (CH_2), 30.1 (CH_2), 29.5 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 22.1 (CH_2), 21.8 (CH_2), 21.7 (CH_3), 21.5 (CH_2), 21.2 (CH_3), 21.0 (CH_2). Spectroscopic data consistent with those reported in the literature.[52]

***rac*-1-(5-Pyrrolidin-2-yl-3,4-dihydro-2*H*-pyridin-1-yl)ethanone *rac*-Maackiamine (Scheme 10).** TFA (95 μL, 1.31 mmol) was added dropwise to a stirred solution of *N*-Boc maackiamine (*R*)-**44** (77 mg, 0.26 mmol, 95:5 er) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 4 h. Then, the solvent and excess TFA were evaporated under reduced pressure. 1 M $NaOH_{(aq)}$ (5 mL) was added to the residue, and the resulting aqueous solution was extracted with CH_2Cl_2 (8 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give *rac*-maackiamine (448 mg, 96%, 50:50 er by NMR spectroscopy in the presence of (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol) as a brown oil, R_f (7:7:2 EtOAc−hexane−Et_2NH) 0.3.

Determination of the Enantiomeric Ratio of 1-((*R*)-5-Pyrrolidin-2-yl-3,4-dihydro-2*H*-pyridin-1-yl)ethanone (*R*)-Maackiamine (Scheme 10). Enantiomeric ratio was determined by high resolution ^1H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. A 0.043 M solution of maackiamine was prepared by dissolving maackiamine (5 mg, 0.026 mmol) in $CDCl_3$ (0.6 mL). Then, (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (28 mg, 0.10 mmol) was added. Diagnostic signals: ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (AcNCH═, major), 6.19 (AcNCH═, minor). Integration of the major and minor AcNCH singals of each rotamer in the ^1H NMR spectra indicated that (*R*)-maackiamine was present in 95:5 er. Enantiomeric ratio was determined by high resolution ^1H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equiv of (*R*)- or (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. A 0.043 M solution of *rac*-maackiamine was prepared by dissolving maackiamine (5 mg, 0.026 mmol) in $CDCl_3$ (0.6 mL). Then, (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (28 mg, 0.10 mmol) was added. Diagnostic signals: ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (AcNCH═), 6.12 (AcNCH═). In a similar fashion, a 0.043 M solution of maackiamine was prepared by dissolving *rac*-maackiamine (5 mg, 0.026 mmol) in $CDCl_3$ (0.6 mL). Then, (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (28 mg, 0.10 mmol) was added. Diagnostic signals: ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (AcNCH═), 6.12 (AcNCH═). Integration of the major and minor AcNCH signals of each rotamer in each of the ^1H NMR spectra indicated that the sample of maackiamine was racemic.

■ ASSOCIATED CONTENT

Supporting Information. $^1H/^{13}C$ NMR spectra of all compounds and CSP-HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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