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Chiral 3-aminopyrrolidines as a rigid diamino scaffold for organocatalysis and organometallic chemistry

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday.

ABSTRACT

Over 20 new and easily prepared diamines were screened for the asymmetric Morita–Baylis–Hillman reaction. Chiral non-racemic 3-(*N*,*N*-dimethylamino)-1-methylpyrrolidine was found to promote efficiently the reaction of methyl vinyl ketone and substituted benzaldehydes. Enantiomeric excesses up to 73% were reached with electron-deficient benzaldehyde derivatives. After a simple deprotonation, one of these diamines was transformed into a chiral mixed aggregate for the enantioselective synthesis of (*R*)-1-*o*-tolylethanol with 76% ee.

1. Introduction

The work of pioneer groups such as that of Henri Kagan in the field of asymmetric synthesis has endowed the organic chemistry community with a set of tools allowing the strict control of the newly created stereogenic centers on a routine basis. In many cases, the efforts dedicated to the understanding of the elementary mechanisms through which the stereochemical information is transferred have made these major progresses possible.[1] Because the selective formation of carbon–carbon bonds is of paramount importance to organic synthesis, a plethora of strategies based on the use of various transition metals in stoichiometric or catalytic amount has emerged. The recent renaissance of organocatalysis has come to complete this methodologic arsenal through the introduction of important developments in the aldol, Mannich, Friedel–Craft or Diels–Alder reactions.[2] Herein, results are presented suggesting that the relatively rigid diamino scaffold found in the 3-aminopyrrolidine derivatives can be successfully employed not only in the organocatalytic version of the Morita–Baylis–Hillman reaction but also, as demonstrated before,[3] in the 1,2-enantioselective addition of methylithium on *o*-tolualdehyde.

The Morita–Baylis–Hillman reaction provides probably the mildest synthesis of β-hydroxy-α-methylene carbonyl compounds and has been comprehensively reviewed.[4] The attractive character of such a methodology resides in the variety of functional groups present in the adduct, allowing further easy modification for the preparation of useful organic compounds. During the last decade, many research groups have developed intensive research programs with the aim of widening the scope of the reaction. A considerable attention has been drawn to improve the kinetics of the reaction[5] or to control the absolute configuration of the stereogenic center generated during the reaction. From the pioneering survey of Hirama[6] to Hatakeyama's milestone work,[7] many enantioselective approaches have been reported using chiral phosphines,[8] Brønsted acids,[9] peptides,[10] bicyclic amines,[11] sulfide[12] or alkaloids derivatives.[13] Recently, highly selective bifunctional catalysts combining a Brønsted acid with a Lewis base have appeared in the literature.[14]

However, the control of the stereochemistry remains a challenge for simple acceptors such as methyl vinyl ketone. Chiral tertiary amine **1a** in the presence of L-proline have been shown to catalyze the reaction between methyl vinyl ketone and 2-nitrobenzaldehyde with enantiomeric excesses (ee's) as high as 83% (Fig. 1).[15] Hayashi reported good yields and ees (up to 75%) for the enantioselective coupling of methyl vinyl ketone with various aryl aldehydes in the presence of 30 mol % of the *bis*-pyrrolidine **1b**.[16] Similarly, *N*,*N*,*N*′,*N*′-tetramethyl-propane-1,3-diamine **1c** was recently identified as an efficient promoter in the Morita–Baylis–Hillman reaction of cycloalkenones known to be poor substrates.[17] The use of chiral diamines has been neglected in this reaction despite their higher stabilities and availabilities compared to alkylphosphines.

In the course of our program on organocatalysis,[18] we anticipated that chiral diamines such as sparteine **2**, its enantiomer surogate **3**[19] derived from (−)-cytisine another lupin alkaloid or permethylated 3-aminopyrrolidine **4** could be suitable candidates to catalyze the Morita–Baylis–Hillman reaction (Fig. 1). Tertiary diamines **2** or **3** are well-known compounds to induce asymmetry in various reactions,[20] enantiopure 3-aminopyrrolidine derivatives

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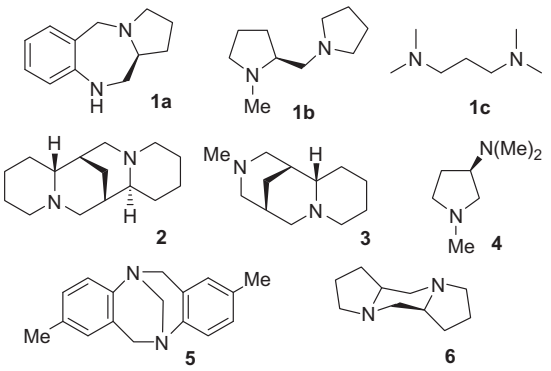
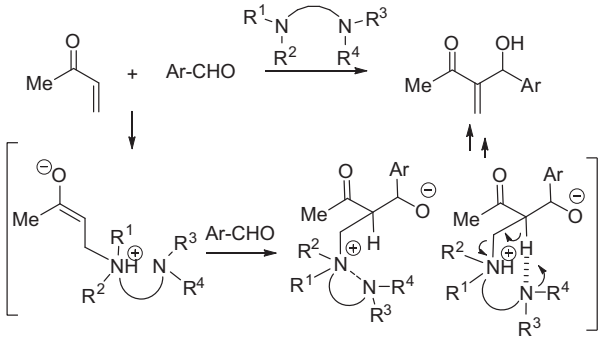


Figure 1. Known chiral amines **1a**,**b**,**c** for the Morita–Baylis–Hillman reaction and initial set of tested amines **2**–**6**.

were shown to be excellent chiral ligands in the addition of organolithium reagents to aldehydes.[3] These amines including Troger's base **5** and bisproline derivative **6** could well stabilize the enolate intermediate through an interaction between the generated ammonium and the free amine function (Scheme 1).

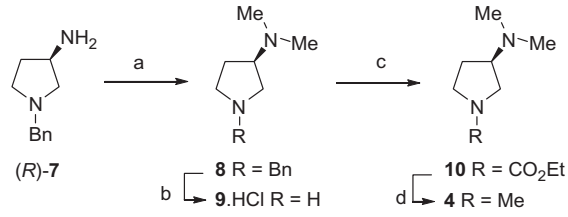


Scheme 1. Intramolecular stabilization of enolate by diamines.

Moreover, this amine could assist the deprotonation step necessary to release the catalyst. We describe herein our results on the efficiency (yields and asymmetric induction) of various chiral diamines in the Morita–Baylis–Hillman reaction.

2. Results and discussion

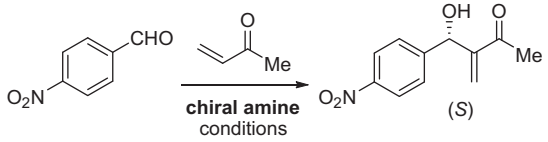
First, we chose to screen chiral amines **2**–**6** (Fig. 1) in a model reaction for the Morita–Baylis–Hillman reaction using a reactive electrophile (4-nitrobenzaldehyde) and a Michael acceptor (methyl vinyl ketone). Amines **2**–**6** were either commercially available (sparteine **2** and Troger's base **5**) or easily prepared, **3** from (−)-cytisine,[22,17] **6** from proline[23,24] and **4** in high yield from (*R*)-3-aminopyrrolidine **7** (Scheme 2). This straightforward four-step synthesis furnished pure diamine **4** in 79% overall yield and could be carried out on a multigram scale.



Scheme 2. Reagents and conditions: (a) HCHO, HCO_2H, 80 °C, 95%; (b) Pd/C, H_2, HCl 2.5 M, 92%; (c) $ClCO_2Et$, Et_3N, 100%; (d) LAH, Et_2O, 90%.

Under various conditions, we investigated the minimum requirements to promote the reaction and to observe an asymmetric induction. The Morita–Baylis–Hillman adduct was isolated by column chromatography and its enantiomeric excess measured by chiral HPLC. From this first set of experiments, the best results are reported in Table 1.

Table 1
Preliminary amine screening in the Morita–Baylis–Hillman reaction



Entry	Amine	Amine (mol %)	Solvent	*T* (°C)	Time (h)	% Yield[a] (ee)[b]
1	**2**	20	DMSO	20	48	0 (—)
2	**3**	20	DMSO	20	48	15 (0)
3	**4**	16	EtOH	0	96	71 (31)
4	**4**	16	DMSO	20	96	59 (10)
5	**5**	20	DMSO	20	48	0 (—)
6	**6**	20	DMSO	20	48	100 (7)
7	**6**	20	EtOH	20	48	86 (0)

Reaction conditions: methyl vinyl ketone (1 equiv), 4-$O_2NC_6H_4CHO$ (1.5 equiv, 2–0.5 mmol scale).
[a] Isolated yields.
[b] Determined by chiral HPLC.

The data in Table 1 show that only aminopyrrolidine **4** and proline derivative **6** were efficient in promoting the Morita–Baylis–Hillman reaction (entries 3, 4, 6, 7). Sparteine **2**, Troger's base **5**, (−)-cytisine derivatives **3** did not allow the reaction to proceed. A polar (protic or aprotic) solvent was necessary in order to achieve a high conversion (data not shown for other types of solvent). The steric hindrance around the amine functions appeared to play an important role (entries 1, 2, 5). Diamines **4** and **6** displayed similar reactivities in ethanol (entries 3 and 7) but only aminopyrrolidine **4** led to an asymmetric induction (ee 31%). This promising result led us to further investigate the parameters of the reaction with tertiary diamine **4**.

The influence of the reaction conditions (solvent, catalyst loading and temperature) on the Morita–Baylis–Hillman reaction of methyl vinyl ketone with 4-nitrobenzaldehyde in the presence of aminopyrrolidine **4** was explored. The results are summarized in Table 2. Compared to other solvents which afforded sluggish results and low selectivity (data not shown), the reaction was clean in alcohols and the Morita–Baylis–Hillman adduct was isolated in

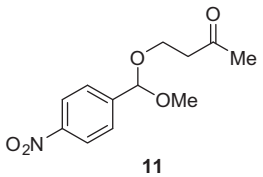
Table 2
Ees and efficiency of **4** as a function of the reaction conditions

Entry	Solvent	**4** (mol %)	*T* (°C)	Yield[a] (ee)[b] %
1	MeOH	8	0	65 (37)
2	EtOH	16	0	71 (31)
3	***i*-PrOH**	**16**	**0**	**87 (54)**
4	BuOH	8	0	81 (46)
5	*s*-BuOH	8	0	80 (46)
6	*t*-BuOH	16	20	95 (34)
7	*s*AmylOH	8	0	81 (50)
8	Dioxane/*i*-PrOH 1:1	16	0	100 (20)
9	*i*-PrOH	60	−15	91 (61)
10	*i*-PrOH	8	0	98 (37)
11	*i*-PrOH	8	20	100 (26)
12	*i*-PrOH	16	20	92 (27)

Reaction conditions: (*R*)-**4** × mol %, methyl vinyl ketone (3 equiv, 0.5 mmol scale), 96 h.
[a] Isolated yields.
[b] Determined by chiral HPLC.

good to high yields. The selectivities observed in MeOH or EtOH (Table 2, entries 1 and 2) led us to test other alcohols (entries 3–12). Propan-2-ol afforded an acceptable selectivity (54% ee, entry 3), the highest ee (61%) being obtained when 60 mol % of catalyst were used at −15 °C (entry 9). A combination of dioxane and propan-2-ol improved the solubility of reactants and preserved the reactivity, but dramatically decreased the selectivity (entry 8). The highest selectivity obtained in propan-2-ol (entries 3 and 9–12) was the result of a compromise between the temperature and the catalyst loading (0 °C and 16 mol %, entry 3).

Compared to other alcohols, methanol and ethanol afforded lower yields (Table 2, entries 1 and 2) due to the formation of an unstable side product (15–20% yield) identified as the mixed acetal **11** with methanol which has no precedent in the litterature.[25,26] Compound **11** probably resulted from the conjugate addition of the hemiacetal formed from methanol and nitrobenzaldehyde onto methyl vinyl ketone. This reaction was completely suppressed when a higher order alcohol was used as the solvent.



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In order to improve the enantioselectivity of the Morita–Baylis–Hillman reaction and in an attempt to understand the role of both nitrogens of the diamine, structural modifications of 3-aminopyrrolidine were achieved (Fig. 2). Compounds **8**, **12**–**20** were prepared using simple chemical steps (see the experimental part for details). In order to modify the electronic properties of the nitrogen (*endo*- or exocyclic) of the scaffold, hydrazine **19** and amine **20**, featuring a trifluoromethyl group in α position, were synthesized.

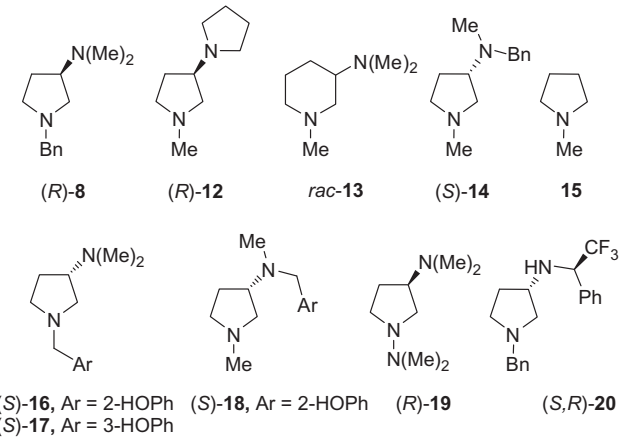
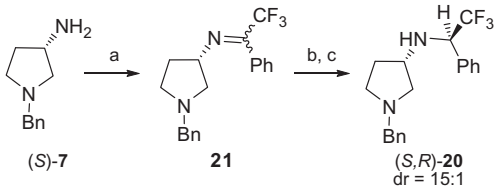


Figure 2. Chiral amines tested in the Morita–Baylis–Hillman reaction.

The stereoselective synthesis of this new kind of electrodeficient 3-aminopyrrolidine **20** is outlined in Scheme 3.[27] Condensation of (*S*)-**7** with trifluoroacetophenone afforded imine **21**. The difficult diastereoselective reduction of this imine required a screening of possible sources of hydrides.[28]

Finally, unreactive imine **21** was reduced with super-hydride ($LiEt_3BH$, 1 M in THF) at 0 °C in Et_2O to afford the best ratio of isomers (dr = 3:1).[29]

Separation of these two products turned to be complicated since **20** and its isomer were persistently coeluting. However, treatment of the crude reaction with 1 equiv of HBr (48% in H_2O) allowed the isolation and enrichment of **20**·HBr after recrystallizations. Thus, **20**·HBr can be prepared efficiently on large scale with



Scheme 3. Reagents and conditions: (a) $PhCOCF_3$, *p*-TsOH (5 mol %), PhMe, rfx, 36 h; (b) $LiEt_3BH$ (1 M in THF), Et_2O, 0 °C, 16 h, dr = 3:1; (c) HBr (48% in H_2O, 1 equiv), H_2O, 0 °C then recrystallised at 90 °C, crystallization (2–3 runs), dr = 15:1 then CH_2Cl_2/$NaHCO_3$ aq; 23% overall yield.

an overall yield of 23% from (*S*)-**7** without chromatography purification and with a dr of 15:1 (dr up to 22:1). Treatment of the mother liquors delivered additional 13% of **20**·HBr with a lower dr of 7:1. The (*R*) configuration of the second stereocenter of **20**·HBr was determined by single-crystal X-ray analysis (Fig. 3).

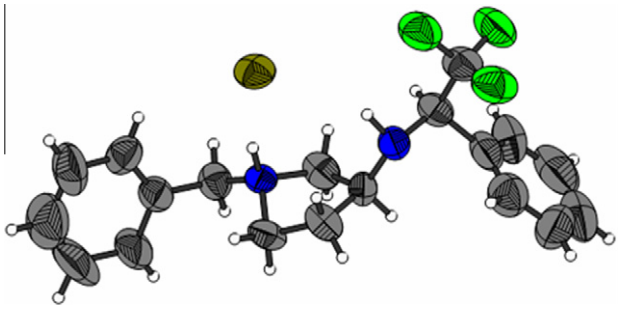


Figure 3. One of the molecules from the asymmetric unit of **20**·HBr in thermal ellipsoidal representation (50% probability).

Amines **8**, **12**–**20** were tested in the same model reaction as before and results are presented in Table 3. Compared to diamine **4**, pyrrolidine **12** afforded slightly lower enantioselective excess (30–36%, Table 3, entries 1–5), but a similar reactivity. Racemic piperidine **13**, the six-membered ring analogue of **4**, yielded the

Table 3
Catalysts screening

Entry	Amine	Conditions	Cat. load (mol %)	*T* (°C)	Yield[a] (ee)[b] (%) [Config.]
1	(***R***)-**4**	*i*-PrOH	16	0	87 (54) [*S*]
2	(***R***)-**12**	*i*-PrOH	16	0	77 (36) [*S*]
3	(***R***)-**12**	*i*-PrOH	16	20	81 (30) [*S*]
4	(***R***)-**12**	*i*-PrOH/ dioxane	16	0	84 (30) [*S*]
5	(***R***)-**12**	*s*-AmylOH	16	0	70 (33) [*S*]
6	***rac*-13**	EtOH	16	20	23 (—)
7	(***R***)-**8**	*i*-PrOH	10	0	59 (6) [*S*]
8	(***S***)-**14**	*i*-PrOH	16	0	63 (3) [*S*]
9	**15**	*i*-PrOH	16	20	0[c] (—)
10	(***S***)-**16**	EtOH	16	20[d]	41 (4) [*S*]
11	(***S***)-**16**	MeCN	16	20[d]	45 (5) [*S*]
12	(***S***)-**17**	*i*-PrOH	16	0	72 (11) [*S*]
13	(***S***)-**17**	MeCN	20	20	63 (3) [*S*]
14	(***S***)-**18**	MeCN	20	20	59 (7) [*S*]
15	(***S***)-**18**	DMSO	20	20	54 (5) [*S*]
16	(***R***)-**19**	*i*-PrOH/ dioxane	16	0[e]	30 (5) [*S*]
17	(***S,R***)-**20**	*i*-PrOH	16	20[d]	0 (—)

Reaction conditions: Amine 16 mol %, methyl vinyl ketone (3 equiv, 0.5 mmol scale), 96 h.
[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] Mixture of unidentified compounds.
[d] 168 h reaction time.
[e] 240 h reaction time.

Morita–Baylis–Hillman adduct in only 23% after four days of reaction (entry 6). Aminopyrrolidines **8** and **14** bearing a benzyl substituent either on the *endo*- or on the exocyclic nitrogen behave similarly. While affording moderate efficiencies, their enantiodiscriminations were low (entries 7 and 8). All these data showed that the 3-aminopyrrolidine structure is essential for the reactivity and that both nitrogens appeared equally involved in the reaction. The substitution of a methyl by a benzyl group was detrimental to the enantioselectivity.

Hydrogen bonding being crucial for the high enantioselectivity observed recently in Morita–Baylis–Hillman reactions,[7] we synthesized then tested aminopyrrolidines **16**–**18** bearing a phenol appendage. Disappointingly, introduction of such hydrogen donor groups failed to improve the enantioselectivity (11–3%) and the rate of the reaction (Table 3, entries 10–15). The results, similar to those obtained with diamines **8** or **14** bearing no hydroxyl function, confirmed the previous observation on the role of the benzyl group.

To the best of our knowledge few examples of catalyst improvement based on an 'alpha effect' have been reported.[30,31] In our model Morita–Baylis–Hillman reaction, hydrazine **19** afforded an adduct nearly racemic in 30% yield after 240 h (Table 3, entry 16) suggesting that the nucleophilic character of the amine and the distance between both nucleophilic centers are essential for the induction of chirality.

Alternatively, the electronic properties of the exocyclic amino group were altered on the amine **20** thanks to the trifluoromethyl group in the alpha position. The inductive effect generated by CF_3 was expected to lower the nucleophilic character of the nitrogen while acidifying the proton connected on. As a consequence, stronger hydrogen bondings to the electrophiles could take place during the course of the reaction. Additionally, it was a good opportunity to explore the advantage on the selectivity of a second stereocenter on the catalyst. Unfortunately, amine **20** did not promote the reaction between methyl vinyl ketone and 4-O_2N—C_6H_4CHO despite long reaction time (Table 3, entry 17). A screening of Michael acceptors such a acrylonitrile, methyl acrylate or the more reactive 1-naphthyl acrylate did not change the outcome of the Morita–Baylis–Hillman reaction with diamine **20** (data not shown).[32] Despite sharing a common scaffold with **4**, amine **20** was inefficient in promoting Morita–Baylis–Hillman reaction.

Control experiments involving 1-methylpyrrolidine **15** as catalyst afforded trace amounts of Morita–Baylis–Hillman adduct (Table 3, entries 9 and 17). These results underscored the importance of the structural and electronic environment of the exocyclic nitrogen of the catalyst. All these data established the need for both nitrogens to bear small methyl substituents to catalyze efficiently the reaction and to afford significant enantioselectivities.

The scope of the reaction of methyl vinyl ketone with a variety of *ortho* and *para* substituted electron-deficient aldehydes was next examined (Table 4). The best substrates for a satisfactory enantioselectivity were those bearing a strong electronegative group NO_2 or CF_3 in *para* or *ortho* position respectively (comparisons of entries 1,2 and 4). As expected the yields were lower in the case of *ortho* substituted benzaldehydes. Switching the nitro group at the *para* position to a less electron withdrawing group preserved the reactivity but led to an important erosion of the selectivity (entries 4–6, Table 4 compared to entry 3, Table 2). Under our standard reaction conditions, benzaldehyde was found to be unreactive.

The influence of the concentration was also studied using 2-trifluoromethylbenzaldehyde. Decreasing the concentration under 1 M led to a dramatic loss of reactivity and selectivity (comparison of entries 2, 7–9 and 10–11). The best compromise to achieve both good yield and ee's requires a concentration of the aldehyde higher than 2 M (ee 65%, entries 2). Higher concentration or solventless conditions afforded comparable enantioselectivities (entries 7 and 8). A similar behavior was observed with 4-nitrobenzaldehyde (not shown).

Table 4
Morita–Baylis–Hillman reaction of methyl vinyl ketone with aldehydes catalyzed by diamine **4**

Entry	Aldehyde	Concn (M)	Yield[a] (%)	ee[b]
1	2-O_2N–C_6H_4CHO	2	75	36
2	2-F_3C–C_6H_4CHO	2	77	73
3	2,4-Cl–C_6H_3CHO	2	99	56
4	4-F_3C–C_6H_4CHO	2	94	8
5	4-MeO_2C–C_6H_4CHO	2	94	30
6	4-NC–C_6H_4CHO	2	81	29
7	2-F_3C–C_6H_4CHO	Neat	60	65
8	2-F_3C–C_6H_4CHO	4	73	63
9	2-F_3C–C_6H_4CHO	1	49	61
10	2-F_3C–C_6H_4CHO	0.5	31	49
11	2-F_3C–C_6H_4CHO	0.25	0	–

Reaction conditions: Amine **4** (16 mol %), methyl vinyl ketone (3 equiv) *i*PrOH, rt, 96 h.
[a] Isolated yields.
[b] Determined by chiral HPLC (*S* enantiomer is the major product in all entries).

Racemization during the course of the reaction is documented for the phosphine-catalyzed aza-Morita–Baylis–Hillman in the presence of protic additives.[33] In order to check the configurational stability of the Morita–Baylis–Hillman adduct under the reaction conditions, the ee of the adduct of methyl vinyl ketone with 2-trifluoromethylbenzaldehyde was measured after various reaction times. Figure 4 suggests that no racemization took place, even after 120 h, despite the strong basic character of the catalyst **4** since an average ee of 59% is measured all along.

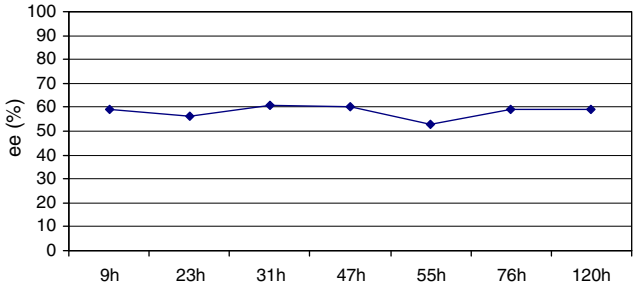
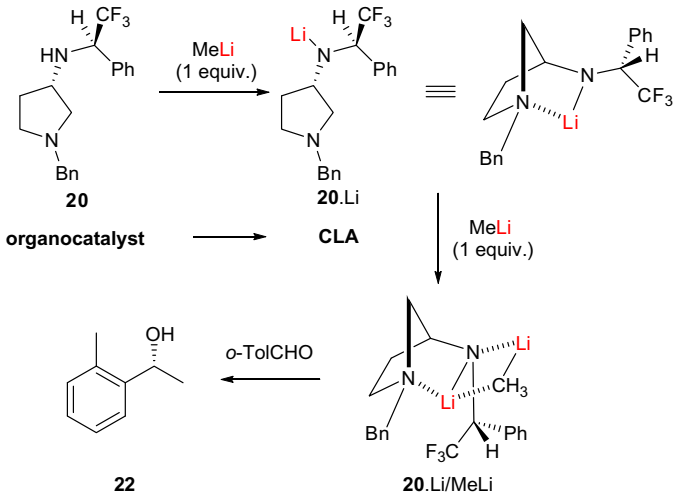


Figure 4. Reaction conditions: Amine **4** (16 mol %), 2-F_3C–C_6H_4CHO (1 equiv), methyl vinyl ketone (3 equiv), *i*PrOH, 0 °C. The ees were determined by chiral HPLC.

Chiral organocatalysts that have been designed originally as potential ligands for Lewis acidic metals are numerous.[34] Transforming a chiral organocatalyst into a promoter for asymmetric organometallic reactions—the reverse journey—can also be a good way of discovering new systems for enantioselective synthesis.

Thus, and within the frame of our works on lithium amides of 3-aminopyrrolidines (3-APLi) as chiral ligands for 1,2-addition of alkyl-[21,35] vinyl-[36] and aryllithiums[37] on aldehydes, we decided to evaluate the potential of the secondary amine **20** in this type of organometallic chemistry. The formation of non-covalent mixed aggregates between the 3-APLi and the organolithium reagent has been well documented in several cases and these species have been proposed as being at the origin of good to high level of asymmetric induction in the 1,2-addition on aldehydes.[38] The model reaction we have been working on consists in the addition of an alkyllithium, complexed by a chiral 3-APLi, on *o*-tolualdehyde. The formation of 1:1 mixed aggregates 3-APLi/RLi in donor solvent such as THF has been evidenced in several cases by ^6Li–^1H NOESY, COSY and HOESY experiments. The resulting complex displays N–Li–C–Li quadrilateral aggregate directly connected to the

stereogenic centers of the amide. Therefore, the transformation of amine **20** into chiral lithium amides by a simple deprotonation in the presence of 2 equiv of MeLi should lead to a similar mixed aggregate featuring a lithium amide stabilized by inductive effect (Scheme 4). The Lewis acidity of the lithium cation of amide **20**·Li is supposed to be increased because of the inductive effect of the vicinal CF_3 group. As a consequence, the shape and the lengths of the bonds (N–Li–C–Li) of **20**·Li and the aggregate **20**·Li/MeLi are expected to be slightly affected allowing a possible improvement of enantioselectivity during the reaction of hydroxyalkylation. The influence of fluorine or fluorinated groups on the chemical and stereochemical properties of lithium amides is not well known, but interesting results were obtained with fluorinated lithium amides, in particular by Koga.[39]



Scheme 4. Structure and model reaction of 3APLi **20**·Li mixed aggregates.

The enantioselective hydroxyalkylation of *o*-tolualdehyde with MeLi in the presence of a stoechiometric amount of the chiral lithium amide was investigated. Following our previously published procedure,[3] we added 2 equiv of MeLi on **20** at −78 °C in THF. The reaction was next warmed up to −20 °C then cooled back to −78 °C before addition of *o*-tolualdehyde. This protocol afforded alcohol **22** with a good enantioselectivity (76% ee, 90% yield) but without obvious improvement over our previous results with electron rich 3-aminopyrrolidines (up to 85% ee).

Therefore, altering the electronic properties of the lithium amide through inductive effect does not seem to play a significant role in the model reaction. Nevertheless, we are currently pursuing this strategy of dual use of these amines **4**–**20** for both organocatalysis and the promotion of enantioselective transformations involving organometallic reagents. In particular, the efficiency of the di-tertiary diamines **4**, **8**, **12**–**19** in the enantioselective hydroxyalkylation illustrated in Scheme 4 is currently being evaluated.

3. Conclusions

With the aim of finding simple and stable organocatalysts for the Morita–Baylis–Hillman reaction, monocyclic and bicyclic diamines derived from (+)- and (−)-3-aminopyrrolidine and from (−)-cytisine were synthesized and tested in the reaction of methyl vinyl ketone and aromatic aldehydes. The most efficient catalyst was found to be dimethyl-((*R*)-1-methylpyrrolidin-3-yl)amine **4**. This organocatalyst presents the major advantages of being easily prepared on multigram scale and to be simply removed from the reaction mixture due to its volatility. The results presented above suggest that both nucleophilic nitrogens of the aminopyrrolidines are involved in the reaction. Compared to the previously proline derived diamine **1b**[16] and *N*,*N*,*N*′,*N*′-tetramethylpropane-1,3-diamine **1c**[17] which were used in large amounts (30 mol % or 1 equiv), 8 mol % of pyrrolidine **4** are sufficient for high conversion and chiral induction. Additionally, the synthesis of a new class of 3-aminopyrrolidine bearing a chiral 2,2,2-trifluoroethyl group has been designed. If synthetic applications of this substrate are still to be found, amine **20** may constitute a scaffold with interesting biological activities.[40] Further investigations concerning the mechanism and optimization of all these catalysts will be reported in due course. Finally, this study highlights the potential of the aminopyrrolidine skeleton, compared to piperidines, in organocatalytic reactions.

4. Experimental

4.1. General method

Proton NMR spectra were recorded on Bruker Avance DPX 250, 300 and 400 spectrometers. Default solvent for NMR spectra recording was $CDCl_3$. ^1H chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane (TMS, 0.0 ppm), or with the solvent reference. ^{13}C NMR spectra were recorded on Bruker 400 (100 MHz), 300 (125 MHz) or 250 (62 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in parts per million (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, 77.0 ppm). Thin layer chromatography was performed on Silica Gel 60 F-254 plates (0.1 mm, Merck). Detection was accomplished by irradiation with a UV lamp or staining with $KMnO_4$ or ninhydrin solutions. Chromatographic separations were achieved on silica gel columns (Kieselgel 60, 40–63 μm, Merck). Analytical high performance liquid chromatography (HPLC) was carried out with a Waters instrument [detector M996 (200–400 nm) and pump 600], respectively. Mass and high resolution mass spectra (HRMS) were obtained on a Waters-Micromass Q-Tof micro instrument. IR spectra were recorded on a Perkin–Elmer 16 PC FTIR spectrometer. Optical rotations were measured, at room temperature, on a Perkin–Elmer 241 LC polarimeter in a 10 cm cell. Specific rotation {$[\alpha]_D$} values are given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Solvents (THF, CH_2Cl_2, MeCN, Et_2O) were dried and purified from PureSolv™ 400 Solvent Purification System. All aldehydes and methyl vinyl ketone were used as received. (−)-Sparteine **2**, (+)-Troger's base **5**, (*R*) or (*S*)-1-benzyl-3-aminopyrrolidine **7** are commercially available. Piperazine **6**[41,42] and alcohol **22** [42070-90-6] are known compounds.

4.2. Synthesis of catalysts

4.2.1. Dimethyl-((*R*)-1-methylpyrrolidin-3-yl)amine 4 and ((*R*)-1-benzylpyrrolidin-3-yl)dimethylamine 8

To (*R*)-1-benzyl-3-aminopyrrolidine **7** (1.0 g, 5.7 mmol) was added a mixture of formaldehyde (8.0 mL, 37 w/v%, 100 mmol) and formic acid (7.3 mL, 194 mmol). The solution was refluxed for 4 h. After cooling, aqueous ammonia (28%) was added until pH >10. The aqueous layer was extracted with Et_2O and the organic layers were combined and dried over Na_2SO_4. The volatile compounds were evaporated and (*R*)-1-benzyl-*N*,*N*-dimethylpyrrolidine **8** was obtained as a colorless oil which did not require any purification (1.1 g, 95%). $[\alpha]_D^{20} = +2.8$ (*c* 0.5, $CHCl_3$). ^1H NMR δ 1.64–1.77 (m, 1H), 1.87–2.07 (m, 2H), 2.19 (s, 6H), 2.29 (dd, *J* = 8.4 Hz, *J* = 6.8 Hz, 1H), 2.48 (dt, *J* = 8.9 Hz, *J* = 6.8 Hz, 1H), 2.69–2.88 (m, 2H), 3.53 and 3.62 (AB, *J* = 12.8 Hz, 2H), 7.24–7.35 (m, 5H). ^{13}C NMR δ 29.0, 43.7, 53.2, 58.4, 60.4, 65.3, 126.7, 128.0, 128.5, 138.9. IR (neat, ν cm^{-1}) 2948, 2862, 2778, 1660, 1494, 1454, 1152, 1042, 910, 698 cm^{-1}. MS (EI) *m*/*z* = 204 ($M^{+\cdot}$, 3), 159

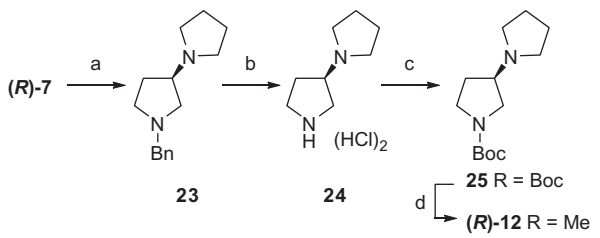
(42), 132 (60), 113 (62), 91 (72), 84 (42), 65 (31), 42 (100). HRMS (MH^+) Calcd for $C_{13}H_{21}N_2$: 205.1705. Found: 205.1700.

Pyrrolidine **8** (1.0 g, 4.9 mmol) and Pd–C (10%, 260 mg, 0.25 mmol) were added to a solution of methanol and 2.5 M aqueous HCl (16:4, 20 mL). The mixture was stirred at 40 °C under a atmosphere of hydrogen (40 bars) for 24 h. The solids were filtered over Celite and washed with MeOH (50 mL). The filtrate was evaporated under reduced pressure to give the crude dihydrochloride **10** as a pale yellow oil which was used directly in the next step (843 mg, 92%). ^{1}H NMR (D_2O) δ 1.80 (dq, J = 12.6 Hz, J = 8.3 Hz, 1H), 1.98–2.11 (m, 1H), 2.26 (s, 6H), 2.79 (quint, J = 7.3 Hz, 1H), 2.94 (dd, J = 11.1 Hz, J = 7.7 Hz, 1H), 3.08–3.20 (m, 1H), 3.20–3.32 (m, 2H). ^{13}C NMR (D_2O) δ 29.0, 44.4, 44.9, 48.3, 64.9.

To the bis-hydrochloride **9** (187 mg, 1 mmol) in CH_2Cl_2 (20 mL) were added triethylamine (2.24 mL, 16 mmol) and ethyl chloroformate (1.6 mL, 1.6 mmol). The mixture was stirred at room temperature for 24 h. The solvent was removed and the residue treated with an aqueous solution of ammonia (10 mL). The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 93:7) to give **10** as a colorless oil (186 mg, 100%). $[\alpha]_D^{20} = -11.4$ (c 0.25, $CHCl_3$). ^{1}H NMR δ 1.25 (t, J = 7.1 Hz, 3H), 1.70–1.89 (m, 1H), 2.02–2.18 (m, 1H), 2.27 (s, 6H), 2.57–2.75 (m, 1H), 3.05–3.21 (m, 1H), 3.25–3.42 (m, 1H), 3.50–3.76 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H). ^{13}C NMR δ (2 conformers) 14.9, 29.8 *30.7*, 44.3, 44.9 *45.2*, 50.2 *50.5*, 60.9 *61.0*, 64.9 *65.7*, 155.1. IR (neat, ν cm^{-1}) 1698, 1426, 1381, 1275, 1210, 1124. MS (EI) (m/z) 186 (83), 171 (25), 157 (52), 141 (20), 113 (70), 99 (10), 84 (100), 70 (65). HRMS (MH^+) Calcd for $C_9H_{19}N_2O_2$: 187.1447. Found: 187.1460.

To the carbamate **10** (145 mg, 0.78 mmol) in Et_2O (20 mL) at 0 °C under argon was added $LiAlH_4$ (140 mg, 3.47 mmol) in one portion. The suspension was heated under reflux for 24 h. After cooling at 0 °C, the grey suspension was treated successively with water (140 μL), aqueous NaOH (15%, 140 μL) and water (420 μL). The solids were filtered over Celite and washed with Et_2O (100 mL). The filtrate was evaporated under reduced pressure to give the title compound **4** as a pale yellow and volatile oil (90 mg, 90%) which required no purification. $[\alpha]_D = -0.4$ (c 0.8, $CHCl_3$). ^{1}H NMR δ 1.67–1.80 (m, 1H), 1.89–2.09 (m, 1H), 2.22 (s, 6H), 2.29 (dd, J = 8.0 Hz, J = 6.5 Hz, 1H), 2.34 (s, 3H), 2.45 (dt, J = 9.0 Hz, J = 6.8 Hz, 1H), 2.69–2.88 (m, 3H). ^{13}C NMR δ 29.7, 42.4, 43.9, 55.6, 60.9, 66.0. IR (NaCl, ν cm^{-1}) 2967, 2783, 1452, 1362, 1347, 1270, 1238, 1202, 1154, 1021. GC/MS (m/z) 129 (7), 113 (2), 97 (2), 83 (58), 70 (23), 57 (79), 42 (100). HRMS (MH^+) Calcd for $C_7H_{17}N_2$: 129.1392. Found: 129.1387.

4.2.2. (*R*)-1′-Methyl-[1,3′]bipyrrolidine 12



Reagents and conditions: (a) dibromobutane, K_2CO_3, EtOH, 54%; (b) Pd/C, MeOH, aq HCl, 100%; (c) Boc_2O, K_2CO_3, THF/H_2O, 56%; (d) Et_2O, reflux, 91%.

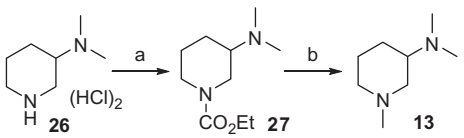
Dibromobutane (864 mg, 4.0 mmol) was added to *N*-benzyl-3-aminopyrrolidine **7** (704 mg, 4.0 mmol), K_2CO_3 (552 mg, 4.0 mmol) and EtOH (20 mL). The mixture was heated at 60 °C for 24 h. After cooling at room temperature, water was added (20 mL) and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to afford the diamine **23** as a colorless oil (500 mg, 54%). $[\alpha]_D^{20} = +2.3$ (c 0.5, $CHCl_3$). ^{1}H NMR δ 1.70–1.86 (m, 5H), 1.96–2.11 (m, 1H), 2.33 (dd, J = 7.9 Hz, J = 6.9 Hz, 1H), 2.42–2.58 (m, 5H), 2.72–2.93 (m, 3H), 3.59 and 3.62 (AB, J = 12.9 Hz, 2H), 7.20–7.36 (m, 5H). ^{13}C NMR δ 23.3, 30.2, 53.1, 53.3, 59.6, 60.7, 64.1, 127.0, 128.3, 128.9, 139.1. IR (neat, ν cm^{-1}) 2960, 2785, 1603, 1585, 1495, 1454, 1380, 1256, 1205, 1136. GC/MS (m/z) 231 (100, MH^+), 160 (32), 139 (83), 132 (41), 120 (43), 110 (60), 96 (36), 91 (70), 65 (25), 42 (53). HRMS (MH^+) Calcd for $C_{15}H_{23}N_2$: 231.1861. Found: 231.1862.

The diamine **23** (500 mg, 2.17 mmol) and Pd/C (166 mg, 10% Pd, 0.16 mmol) was added to a solution of methanol and 2.5 M aqueous HCl (4:1, 20 mL). The mixture was stirred at 40 °C under an hydrogen atmosphere (P = 40 bars) for 24 h. The solids were filtered over Celite and washed with MeOH (50 mL). The filtrate was evaporated under reduced pressure to give the crude dihydrochloride **24** as a colorless solid (462 mg, 100%). $[\alpha]_D^{20} = +1.2$ (c 0.3, H_2O). ^{1}H NMR (D_2O) δ 1.80–2.00 (m, 2H), 2.00–2.24 (m, 3H), 2.46–2.61 (m, 1H), 3.02–3.19 (m, 2H), 3.26–3.73 (m, 5H), 3.78 (dd, J = 13.0 Hz, J = 8.2 Hz, 1H), 4.05 (quint, J = 7.9 Hz, 1H). ^{13}C NMR (D_2O) δ 22.6, 27.5, 44.5, 45.9, 54.0, 61.9. IR (NaCl, ν cm^{-1}) 3371, 2965, 2479, 1635, 1449, 1040.

Boc_2O (710 mg, 3.26 mmol) was added to a stirred solution of the crude dihydrochloride **24** (460 mg, 2.17 mmol) and K_2CO_3 (1.05 g, 7.6 mmol) in THF/H_2O (1:1, 70 mL). The mixture was stirred at room temperature for 12 h and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to afford the aminocarbamate **25** as a colorless oil (290 mg, 56%). $[\alpha]_D^{20} = +11.2$ (c 0.2, $CHCl_3$). ^{1}H NMR δ 1.45 (s, 9H), 1.72–1.89 (m, 5H), 1.99–2.11 (m, 1H), 2.44–2.61 (m, 4H), 2.69 (sext, J = 7.5 Hz, 1H), 3.13 (q, J = 9.3 Hz, 1H), 3.21–3.34 (m, 1H), 3.42–3.69 (m, 2H). ^{13}C NMR δ (2 conformers) 23.4, 28.6, 30.9 *31.7*, 44.6 *44.9*, 50.6 *51.1*, 53.2, 63.6 *64.2*, 79.2, 154.6. IR (NaCl, ν cm^{-1}) 2970, 2875, 2788, 1694, 1479, 1455, 1400, 1364, 1249, 1166, 1148, 1120. GC/MS (m/z) 241 (22, MH^+), 185 (100), 141 (4). HRMS (MH^+) Calcd for $C_{13}H_{25}N_2O_2$: 241.1907. Found: 241.1916.

To the aminocarbamate **25** (290 mg, 1.21 mmol) in Et_2O (20 mL) at 0 °C under an atmosphere of argon was added $LiAlH_4$ (180 mg, 4.82 mmol) in one portion. The suspension was heated under reflux for 24 h. After cooling to 0 °C, water (180 μL) and aqueous NaOH (15%, 180 μL) were added followed by water (540 μL). The solids were filtered over Celite and washed with Et_2O (50 mL). The filtrate was evaporated under reduced pressure to give the volatile crude diamine (*R*)-**12** as a colorless oil (170 mg, 91%) which required no purification. $[\alpha]_D^{20} = -6.5$ (c 1.2, $CHCl_3$). ^{1}H NMR δ 1.71–1.86 (m, 5H), 1.95–2.12 (m, 1H), 2.14–2.30 (m, 1H), 2.33 (s, 3H), 2.38–2.57 (m, 5H), 2.69–2.79 (m, 3H). ^{13}C NMR δ 23.3, 30.8, 42.3, 53.9, 55.5, 62.0, 64.6. IR (NaCl, ν cm^{-1}) 2963, 2778, 1477, 1448, 1377, 1346, 1312, 1239, 1140, 1029. GC/MS (m/z) 155 (100, MH^+), 127 (81), 112 (5), 96 (16), 84 (79). HRMS (MH^+) Calcd for $C_9H_{19}N_2$: 155.1535. Found: 155.1524.

4.2.3. Dimethyl-(1-methylpiperidin-3-yl)amine 13

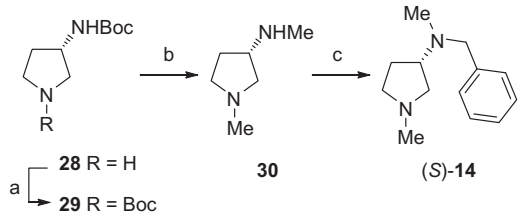


Reagents and conditions: (a) $ClCO_2Et$, Et_3N, CH_2Cl_2, 63%; (b) $LiAlH_4$, THF, 58%.

Commercially available 3-dimethylaminopiperidine dihydrochloride **26** (400 mg, 2.0 mmol) was dissolved in CH_2Cl_2 (50 mL). Triethylamine (3.8 mL, 27.1 mmol) and ethyl chloroformate (3.2 mL, 32.0 mmol) were added and the mixture was stirred at room temperature for 24 h. The solvent was removed and aqueous ammonia was added. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 98:2) to afford **27** as a yellow pale oil (250 mg, 63%). ^{1}H NMR δ 1.28 (t, J = 7.1 Hz, 3H), 1.34–1.52 (m, 2H), 1.72–1.80 (m, 1H), 1.96–2.04 (m, 1H), 2.15–2.24 (m, 1H), 2.35 (s, 6H), 2.65–2.80 (m, 2H), 3.91–4.10 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.17–4.32 (m, 1H). ^{13}C NMR δ (2 conformers) 14.8 *14.9*, 24.4, 28.8, 42.4, 44.3, 46.8 *47.1*, 60.9 *61.0*, 61.4, 155.7. IR (NaCl, ν cm^{-1}) 1698, 1434, 1276, 1260, 1159. GC/MS (*m/z*) 200 (15), 155 (3), 127 (3), 98 (5), 84 (100), 71 (8), 56 (9), 42 (22). HRMS (MH^+) Calcd for $C_{10}H_{21}N_2O_2$: 201.1603. Found: 201.1604.

To the piperidine **27** (220 mg, 1.1 mmol) in Et_2O (30 mL) at 0 °C under Ar was added $LiAlH_4$ (200 mg, 4.79 mmol) in one portion. The suspension was heated under reflux for 24 h. After cooling to 0 °C, water (200 μL) and aqueous NaOH (15%, 200 μL) were added followed by water (600 μL).The solids were removed by filtration through Celite and the filter cake was washed with Et_2O (100 mL). The filtrate was evaporated under reduced pressure to give **13** as a pale yellow oil (90 mg, 58%). ^{1}H NMR δ 1.15 (dq, J = 12.0 Hz, J = 4.1 Hz, 1H), 1.51–1.70 (tt, J = 13.1 Hz, J = 3.8 Hz, 1H), 1.73–1.95 (m, 4H), 2.29 (s, 3H), 2.31 (s, 6H), 2.32–2.44 (m, 1H), 2.75 (br d, 1H), 2.97 (br dt, 1H). ^{13}C NMR δ 24.6, 26.6, 42.2, 46.7, 55.9, 58.7, 61.5. IR (NaCl, ν cm^{-1}) 1449, 1371, 1253, 1160, 1017. GC/MS (*m/z*) 142 (26), 97 (22), 84 (100), 71 (20), 58 (72), 42 (58). HRMS (MH^+) Calcd for $C_8H_{19}N_2$: 143.1548. Found: 143.1538.

4.2.4. (*S*)-*N*-Benzyl-*N*-methyl-*N*-(1-methylpyrrolidin-3-yl)amine 14



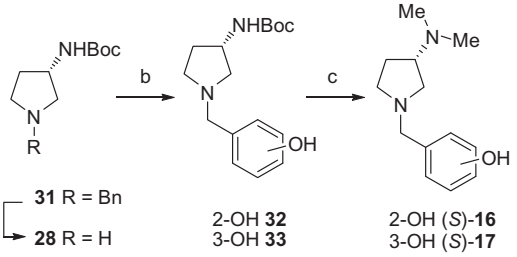
Reagents and conditions: (a) Boc_2O, THF/H_2O, K_2CO_3, 77%; (b) $LiAlH_4$, Et_2O, reflux, 90%; (c) PhCHO, $NaBH(OAc)_3$, THF, 72%.

Boc_2O (262 mg, 1.2 mmol) was added to pyrrolidine **28** (185 mg, 1 mmol), K_2CO_3 (166 mg, 1.2 mmol) and THF/H_2O (1:1, 8 mL). The mixture was stirred at room temperature for 12 h, then water (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to afford **29** as a colorless oil (220 mg, 77%). $[\alpha]_D^{20} = +6.8$ (c 2.0, $CHCl_3$). ^{1}H NMR δ 1.44 (s, 9H), 1.45 (s, 9H), 1.75–1.90 (m, 1H), 2.05–2.16 (m, 1H), 3.16 (br dd, 1H), 3.32–3.47 (m, 2H), 3.58 (dd, J = 11.3 Hz, J = 6.2 Hz, 1H), 4.17 (br s, 1H), 4.60 (br s, 1H). ^{13}C NMR δ (2 conformers) 28.4, 28.5, 31.2 *32.1*, 43.7 *44.0*, 49.9 *50.6*, 51.4 *51.9*, 79.5, 79.7, 154.5, 155.3. IR (NaCl, ν cm^{-1}) 3326, 2977, 1675, 1526, 1478, 1455, 1406, 1365, 1250, 1161, 1130. GC/MS (ESI) (*m/z*) 309 (55, M+Na$^+$), 253 (62), 209 (100), 197 (31), 109 (77). HRMS (M+Na$^+$) Calcd for $C_{14}H_{26}N_2O_4Na$: 309.1790. Found: 309.1780.

To a solution of pyrrolidine **29** (195 mg, 0.68 mmol) in Et_2O (15 mL) at 0 °C under an atmosphere of argon was added $LiAlH_4$ (155 mg, 4.08 mmol). The suspension was heated under reflux for 24 h. After cooling to 0 °C, water (155 μL) was added followed by aqueous NaOH (15%, 155 μL) and by water (465 μL). The solids were filtered over Celite and washed with Et_2O (50 mL). The filtrate was evaporated under reduced pressure to give the volatile crude diamine **30** as a colorless oil (70 mg, 90%) which required no purification. $[\alpha]_D^{20} = -0.8$ (c 1.0, $CHCl_3$). ^{1}H NMR δ 1.50–1.64 (m, 2H), 2.04–2.25 (m, 2H), 2.33 (s, 3H), 2.38 (s, 3H), 2.35–2.49 (m, 1H), 2.63 (dt, J = 9.3 Hz, J = 6.5 Hz, 2H), 3.14–3.25 (m, 1H). ^{13}C NMR δ 32.5, 34.7, 42.2, 55.3, 59.6, 69.2. IR (NaCl, ν cm^{-1}) 3297, 2923, 2853, 2796, 1452, 1365, 1239, 1172, 1147. GC/MS (EI) (*m/z*) 115 (11, MH^+), 99 (4), 83 (53), 82 (23), 70 (22), 58 (28), 57 (88), 42 (100). HRMS (MH^+) Calcd for $C_6H_{15}N_2$: 115.1235. Found: 115.1239.

To a solution of benzaldehyde (71 μL, 0.7 mmol) and the pyrrolidine **30** (50 mg, 0.44 mmol) in THF (5 mL) was added sodium triacetoxyborohydride (279 mg, 1.32 mmol). The mixture was stirred at room temperature under an atmosphere of argon for 24 h and then treated with aqueous ammonia. The aqueous layer was extracted with CH_2Cl_2 and the organic layers were combined and dried over Na_2SO_4. The solvent was removed under vacuum and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH, 92:8:1) to afford the diamine (*S*)-**14** as a colorless oil (65 mg, 72%). $[\alpha]_D^{20} = +5.5$ (c 1.0, $CHCl_3$). ^{1}H NMR δ 1.81–1.90 (m, 1H), 2.00–2.09 (m, 1H), 2.12 (s, 3H), 2.36 (s, 3H), 2.47 (dd, J = 9.2 Hz, J = 6.9 Hz, 1H), 2.53 (dt, J = 8.8 Hz, J = 6.2 Hz, 1H), 2.64–2.71 (m, 1H), 2.80 (dd, J = 9.2 Hz, J = 7.4 Hz, 1H), 3.16 (dq, J = 8.8 Hz, J = 6.9 Hz, 1H), 3.43 and 3.54 (AB, J = 13.1 Hz, 2H), 7.20–7.32 (m, 5H). ^{13}C NMR δ 29.1, 39.6, 42.5, 55.7, 60.0, 60.3, 64.4, 126.9, 128.2, 129.1, 139.1. IR (NaCl, ν cm^{-1}) 2964, 2939, 2837, 2777, 1532, 1495, 1479, 1452, 1364, 1245, 1169. GC/MS (EI) (*m/z*) 205 (92, MH^+), 177 (37), 146 (15), 134 (93), 120 (15), 113 (38), 91 (100). HRMS (MH^+) Calcd for $C_{13}H_{21}N_2$: 205.1705. Found: 205.1695.

4.2.5. 2-[(*S*)-3-Dimethylaminopyrrolydin-1-ylmethyl]phenol 16



Reagents and conditions: (a) Pd/C, H_2, MeOH, 100%; (b) salicylaldehyde, $NaBH(OAc)_3$, THF, 100% for **32**; 3-hydroxybenzaldehyde, $NaBH(OAc)_3$, THF, 89% for **33**; (c) HCHO, HCO_2H, reflux, 79% for (*S*)-**16**, 71% for (*S*)-**17**.

A solution of the known (*S*)-Boc pyrrolidine **31**[43] (430 mg, 1.56 mmol) and Pd/C (170 mg, 10% Pd, 0.16 mmol) in degassed MeOH (10 mL) was stirred at room temperature under an atmosphere of hydrogen (balloon) for 24 h. The solids were removed by filtration through Celite and the filter cake was washed with MeOH (50 mL). The filtrate was evaporated under reduced pressure to give **28**[44] as a colorless solid (285 mg, 100%) which was directly used for the next step. Mp 74 °C. ^{1}H NMR δ 1.45 (s, 9H), 1.65–1.72 (m, 1H), 2.10–2.20 (m, 1H), 2.79–3.15 (m, 5H), 4.11 (br s, 1H), 4.95 (br s, 1H). ^{13}C NMR δ 28.6, 33.4, 45.6, 51.7, 53.8, 79.7, 155.8.

To salicylaldehyde (140 μL, 1.35 mmol) and aminocarbamate **28** (279 mg, 1.5 mmol) in THF (10 mL) was added sodium triacetoxyborohydride (475 mg, 2.25 mmol). The mixture was stirred at room temperature under an atmosphere of argon for 12 h and then treated with aqueous NaOH (3 N). The aqueous layer was extracted with Et_2O and the organic layers were combined and dried over

Na_2SO_4. Solvent was removed under vacuum and the crude product was purified on silica gel chromatography (CH_2Cl_2/MeOH, 97:3) to afford amine **32** as a colorless oil (370 mg, 100%). $[\alpha]_D^{20} = +18.1$ (*c* 1.1, $CHCl_3$). ^1H NMR δ 1.43 (s, 9H), 1.45–1.50 (m, 1H), 1.62–1.72 (m, 1H), 2.25–2.36 (m, 1H), 2.41–2.50 (m, 1H), 2.63–2.70 (m, 1H), 2.72–2.81 (m, 1H), 2.83–2.93 (m, 1H), 3.79 (AB, *J* = 19.5 Hz, 2H), 4.22 (br s, 1H), 4.90 (br s, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H). ^{13}C NMR δ 28.3, 32.3, 49.7, 52.3, 58.7, 60.3, 79.5, 115.9, 119.1, 121.9, 128.0, 128.7, 155.3, 157.5. IR (neat, ν cm^{-1}) 3334, 2976, 2817, 1689, 1591, 1490, 1471, 1365, 1250, 1165. GC/MS (*m/z*) 293 (15, MH^+), 238 (5), 237 (100), 131 (17), 107 (2). HRMS (MH^+) Calcd for $C_{16}H_{25}N_2O_3$: 293.1865. Found: 293.1855.

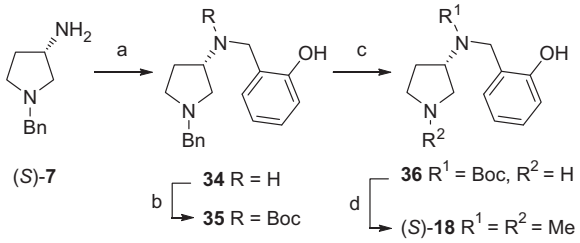
To an aqueous solution of formol (1.84 mL, 37% w/v, 22 mmol) was added formic acid (1.76 mL, 45.1 mmol) and the amine **32** (320 mg, 1.1 mmol). The mixture was heated under reflux for 4 h. After cooling, the solution was treated with aqueous ammonia and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 96:4) to afford diamine (*S*)-**16** as a colorless oil (190 mg, 79%). $[\alpha]_D^{20} = +16.6$ (*c* 2.5, $CHCl_3$). ^1H NMR δ 1.75–1.87 (m, 1H), 1.98–2.14 (m, 1H), 2.22 (s, 6H), 2.43–2.50 (m, 1H), 2.63 (dt, *J* = 9.2 Hz, *J* = 6.1 Hz, 1H), 2.75–2.95 (m, 3H), 3.79 and 3.80 (AB, *J* = 14 Hz, 2H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 7.0 Hz, 1H), 7.17 (dt, *J* = 7.7 Hz, *J* = 1.4 Hz, 1H). ^{13}C NMR δ 29.2, 43.8, 52.9, 57.8, 59.2, 65.3, 116.0, 119.1, 122.2, 128.1, 128.8, 157.9. IR (neat, ν cm^{-1}) 2950, 2866, 2817, 1614, 1591, 1468, 1404, 1254, 1135, 1035. GC/MS (ESI) (*m/z*) 221 (25, MH^+), 193 (9), 176 (16), 136 (5), 115 (88), 107 (100). HRMS (MH^+) Calcd for $C_{18}H_{23}N_2O$: 221.1630. Found: 221.1640.

4.2.6. 3-[(*S*)-3-Dimethylaminopyrrolydin-1-ylmethyl]phenol 17

To a solution of 3-hydroxybenzaldehyde (122 mg, 1 mmol) and aminocarbamate **28** (185 mg, 1 mmol) in dichloromethane (10 mL) was added sodium triacetoxyborohydride (300 mg, 1.4 mmol). The mixture was stirred at room temperature under an atmosphere of argon for 24 h and then treated with $NaHCO_3$. The aqueous layer was extracted with Et_2O and the organic layers were combined and dried over Na_2SO_4. The solvent was removed under vacuum and the crude product was purified on silica gel chromatography (CH_2Cl_2/MeOH, 98:2) to afford amine **33** as a colorless oil (260 mg, 89%). $[\alpha]_D^{20} = -4.8$ (*c* 0.5, $CHCl_3$). ^1H NMR δ 1.42 (s, 9H), 1.52–1.70 (m, 1H), 2.20–2.40 (m, 2H), 2.62 (d, *J* = 4.8 Hz, 2H), 2.80–2.95 (m, 1H), 3.55 (s, 2H), 4.21 (br s, 1H), 5.16 (br d, 1H), 6.72–6.82 (m, 3H), 7.11–7.20 (m, 1H). ^{13}C NMR δ 28.5, 32.5, 52.9, 53.5, 60.0, 60.9, 79.5, 115.1, 116.4, 121.1, 129.6, 139.2, 155.7, 156.4. IR (NaCl, ν cm^{-1}) 3325, 2976, 2807, 1678, 1589, 1486, 1455, 1392, 1366, 1249, 1160, 1078. GC/MS (*m/z*) 293 (40, MH^+), 237 (100). HRMS (MH^+) Calcd for $C_{16}H_{25}N_2O_3$: 293.1865. Found: 293.1875.

To a solution of formol (37% w/v in water) (1.37 mL, 16.4 mmol) and formic acid (1.32 mL, 33.6 mmol) was added the amine **33** (240 mg, 0.82 mmol). The mixture was heated under reflux for 4 h. After cooling, the solution was treated with aqueous ammonia and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 93:7) to afford the diamine (*S*)-**17** as a colorless oil (120 mg, 71%). $[\alpha]_D^{20} = +1.2$ (*c* 0.9, $CHCl_3$). ^1H NMR δ 1.72–1.81 (m, 1H), 1.94–2.03 (m, 1H), 2.23 (s, 6H), 2.34–2.41 (m, 1H), 2.52 (dt, *J* = 9.0 Hz, *J* = 6.7 Hz, 1H), 2.73 (m, 1H), 2.80–2.89 (m, 2H), 3.52 and 3.57 (AB, *J* = 12.8 Hz, 2H), 6.68 (ddd, *J* = 7.8 Hz, *J* = 2.4 Hz, *J* = 0.8 Hz, 1H), 6.71–6.74 (m, 1H), 6.77–6.81 (d, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR δ 28.7, 43.7, 53.3, 58.2, 60.5, 65.4, 114.8, 116.4, 120.5, 129.5, 140.0, 156.9. IR (NaCl, ν cm^{-1}) 2957, 2786, 1586, 1484, 1456, 1379, 1280, 1234, 1155, 1038. GC/MS (*m/z*) 221 (100, MH^+), 193 (59), 176 (100), 136 (22), 107 (95).

4.2.7. 2-{[Methyl-((*S*)-1-methylpyrrolidin-3-yl)amino)]methyl}phenol 18



Reagents and conditions: (a) salicylaldehyde, $NaBH(OAc)_3$, THF, 64%; (b) Boc_2O, CH_2Cl_2, 67%; (c) Pd/C, H_2, MeOH, 97%; (d) HCHO, HCO_2H, reflux, 81%.

To a solution of salicylaldehyde (380 μL, 3.6 mmol) and *N*-benzyl-3-aminopyrrolidine (*S*)-**7** (708 mg, 4 mmol) in THF (20 mL) was added sodium triacetoxyborohydride (1.27 mg, 6 mmol). The mixture was stirred at room temperature under an atmosphere of argon for 12 h and then quenched with an aqueous solution of NaOH (3 N). The aqueous layer was extracted with Et_2O. The organic layers were combined and dried over Na_2SO_4. The solvent was removed under vacuum and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to afford diamine **34** as a colorless oil (720 mg, 64%). $[\alpha]_D^{20} = +8.9$ (*c* 0.75, $CHCl_3$). ^1H NMR δ 1.60–1.74 (m, 1H), 2.07–2.22 (m, 1H), 2.38 (dt, *J* = 8.7 Hz, *J* = 6.8 Hz, 1H), 2.58 (d, *J* = 5.0 Hz, 2H), 2.74 (dt, *J* = 8.7 Hz, *J* = 5.0 Hz, 1H), 3.31 (sext, *J* = 4.5 Hz, 1H), 3.60 (s, 2H), 3.92 (s, 2H), 6.75 (dt, *J* = 7.3 Hz, *J* = 0.8 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.95 (d, *J* = 7.3 Hz, 1H), 7.15 (dt, *J* = 7.7 Hz, *J* = 1.4 Hz, 1H), 7.21–7.33 (m, 5H). ^{13}C NMR δ 31.5, 50.8, 52.7, 56.1, 59.7, 60.2, 116.5, 119.0, 122.5, 127.1, 128.3, 128.4, 128.8, 138.9, 158.4. IR (neat, ν cm^{-1}) 3291, 1589, 1492, 1474, 1454, 1409, 1378, 1348, 1255, 1185, 1149, 1104, 907. MS (ESI) (*m/z*) 283 (100, MH^+), 177 (95). HRMS (MH^+) Calcd for $C_{18}H_{23}N_2O$: 283.1810. Found: 283.1799.

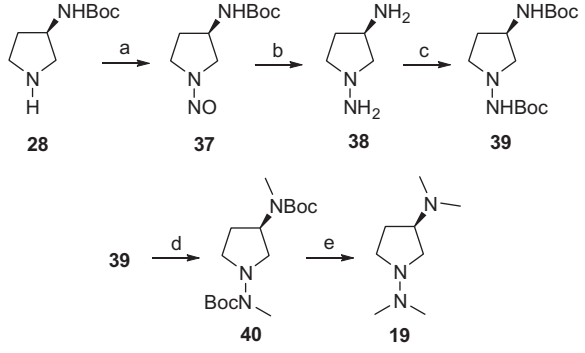
Boc_2O (636 mg, 2.92 mmol) was added to a solution of diamine **34** (690 mg, 2.43 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at room temperature for 36 h and quenched with water. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to afford the aminocarbamate **35** as a colorless oil (620 mg, 67%). $[\alpha]_D^{20} = +4.6$ (*c* 1.05, $CHCl_3$). ^1H NMR δ 1.50 (s, 9H), 1.72–1.83 (m, 1H), 2.11–2.20 (m, 1H), 2.29 (q, *J* = 8.4 Hz, 1H), 2.45 (dd, *J* = 10.3 Hz, *J* = 8.3 Hz, 1H), 2.90 (dd, *J* = 10.4 Hz, *J* = 3.4 Hz, 1H), 2.91–3.00 (m, 1H), 3.51 (d, *J* = 12.5 Hz, 1H), 3.78 (d, *J* = 12.2 Hz, 1H), 4.40 (d, *J* = 15.2 Hz, 1H), 4.55 (d, *J* = 15.3 Hz, 1H), 4.66 (br s, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.91 (dd, *J* = 8.1 Hz, *J* = 1.1 Hz, 1H), 7.18 (dt, *J* = 7.7 Hz, *J* = 1.6 Hz, 1H), 7.23–7.43 (m, 6H). ^{13}C NMR δ 28.6, 30.1, 44.4, 53.5, 55.6, 57.2, 60.3, 81.5, 117.7, 119.6, 125.1, 127.5, 128.5, 129.2, 129.5, 131.4, 137.9, 156.2, 157.4. IR (neat, ν cm^{-1}) 3281, 3064, 1759, 1652, 1605, 1486, 1454, 1419, 1367, 1345, 1241, 1120, 909. GC/MS (ESI) (*m/z*) 383 (9, MH^+), 327 (100), 283 (26), 177 (11). HRMS (MH^+) Calcd for $C_{23}H_{31}N_2O_3$: 383.2335. Found: 383.2327.

A suspension of aminocarbamate **35** (220 mg, 0.58 mmol) and Pd/C (31 mg, 10% Pd, 0.029 mmol) in degassed MeOH (10 mL) was stirred at room temperature under an atmosphere of hydrogen (balloon) for 24 h. The solids were filtered through Celite and washed with MeOH (50 mL). The filtrate was evaporated under

reduced pressure to give the crude **36** as a colorless solid (165 mg, 97%). Mp 82 °C. $[\alpha]_D^{20} = -4.4$ (*c* 1.5, $CHCl_3$). ^1H NMR δ 1.48 (s, 9H), 2.02–2.12 (m, 1H), 2.13–2.25 (m, 1H), 3.11 (q, *J* = 8.8 Hz, 1H), 3.20–3.33 (m, 2H), 3.38–3.48 (m, 2H), 4.36 and 4.44 (AB, *J* = 15.4 Hz, 2H), 6.69 (br s, 2H), 6.80 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR δ 28.5, 28.7, 45.5, 47.4, 50.6, 57.1, 81.9, 116.7, 119.8, 124.2, 129.2, 130.3, 155.2, 156.2. IR (neat, ν cm^{-1}) 3186, 1674, 1598, 1456, 1419, 1367, 1239, 1160, 1124, 908. GC/MS (*m/z*) 293 (11, MH^+), 237 (100), 193 (44). HRMS (MH^+) Calcd for $C_{16}H_{25}N_2O_3$: 293.1865. Found: 293.1856.

A solution of formol (0.92 mL, 37% in water, 11.28 mmol) and formic acid (0.88 mL, 22.75 mmol) was added to the amine **36** (165 mg, 0.56 mmol). The mixture was heated under reflux for 4 h. After cooling, the solution was treated with aqueous ammonia and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 96:4) to afford the diamine (*S*)-**18** as a colorless oil (100 mg, 81%). $[\alpha]_D^{20} = -9.5$ (*c* 1.0, $CHCl_3$). ^1H NMR δ 1.83–1.98 (m, 1H), 2.00–2.16 (m, 1H), 2.25 (s, 3H), 2.36 (s, 3H), 2.51–2.69 (m, 3H), 2.79 (t, *J* = 8.4 Hz, 1H), 3.26 (dq, *J* = 8.8 Hz, *J* = 6.8 Hz, 1H), 3.66 (d, *J* = 14.0 Hz, 1H), 3.78 (d, *J* = 14 Hz, 1H), 6.77 (dt, *J* = 7.5 Hz, *J* = 0.9 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.95 (d, *J* = 6.5 Hz, 1H), 7.16 (dt, *J* = 7.7 Hz, *J* = 1.5 Hz, 1H). ^{13}C NMR δ 28.3, 38.9, 42.4, 55.5, 58.9, 59.6, 63.7, 116.2, 119.1, 121.7, 128.5, 128.7, 158.0. IR (neat, ν cm^{-1}) 3362, 1589, 1475, 1455, 1423, 1347, 1254, 1150, 1017. GC/MS (ESI) (*m/z*) 221 (26, MH^+), 193 (4), 115 (100), 107 (2). HRMS (MH^+) Calcd for $C_{13}H_{21}N_2O$: 221.1638. Found: 221.1630.

4.2.8. (*R*)-N^2,N^2,N^3,N^3-Tetramethylpyrrolidine-1,3-diamine 19



Reagents and conditions: (a) $NaNO_2$, HCl, THF, 70% (b) $TiCl_3$, NH_4OAc, 81%; (c) Boc_2O, CH_2Cl_2, 70%; (d) NaH, MeI, THF, 76%; (e) LAH, Et_2O, 96%.

To the pyrrolidine **28** (185 mg, 1 mmol), were added a solution of THF (6 mL)/HCl (0.5 M, 2 mL, 5 mmol) and $NaNO_2$ (89 mg, 1.3 mmol). The mixture was stirred at room temperature for 48 h. The aqueous layer was extracted with Et_2O. The combined organic extracts were washed with a saturated aqueous solution of NaCl and were dried ($MgSO_4$) before evaporation under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to afford the nitrosopyrrolidine **37** as a colorless solid (150 mg, 70%). Mp 103 °C. $[\alpha]_D^{20} = +6.6$ (*c* 0.4, $CHCl_3$). ^1H NMR δ (2 conformers) 1.41 (s, 4.5H) *1.42* (s, 4.5H), 1.87–2.10 (m, 1H), 2.19–2.38 (m, 1H), 3.43 (m, 0.5 H), 3.51–3.74 (m, 1H), 3.80 (dd, *J* = 15.0 Hz, *J* = 7.0 Hz, 0.5 H), 4.16–4.55 (m, 3H), 5.0 (br s, 1H). ^{13}C NMR δ (2 conformers) 28.0, 30.5, 43.6, 47.9, 55.2, 80.2, 155.2 *155.3*. IR (neat, ν cm^{-1}) 3671, 3368, 2980, 1678, 1519, 1459, 1416, 1366, 1303, 1249, 1159. MS (ESI) (*m/z*) 216 (14, MH^+), 160 (100), 130 (10).

This nitrosopyrrolidine **37** (200 mg, 0.93 mmol) was diluted in water (6 mL). NH_4OAc (4 M, 12 mL) and $TiCl_3$ (15% w/v in 10% aqueous HCl, 6 mL), were added and the mixture was stirred for 1 h. Aqueous solution of ammonia was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) before evaporation under reduced pressure to give the aminopyrrolidine **38** which did not require any purification (151 mg, 81%). $[\alpha]_D^{20} = -13.2$ (*c* 0.4, $CHCl_3$). ^1H NMR δ 1.45 (s, 9H), 1.55–1.65 (m, 1H), 2.20–2.41 (m, 2H), 2.66–2.72 (m, 1H), 2.74–2.90 (m, 2H), 3.00–3.11 (m, 2H), 4.15 (br s, 1H), 4.95 (br s, 1H). ^{13}C NMR δ 28.5, 32.0, 53.5, 58.6, 61.9, 79.4, 155.4. IR (NaCl, ν cm^{-1}) 3322, 2976, 2932, 1688, 1513, 1456, 1391, 1365, 1246, 1162, 1047. MS (ESI) (*m/z*) 202 (30, MH^+), 146 (100), 102 (7). HRMS (MH^+) Calcd for $C_9H_{19}N_3O_2$: 202.1556. Found: 202.1552.

Boc_2O (518 mg, 2.38 mmol) was added to a stirred solution of the aforementioned aminopyrrolidine **38** (95 mg, 0.475 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 24 h, and then evaporated under reduced pressure. The residue was purified by flash chromatography (pentane/EtOAc, 70:30) to afford bis-Boc-aminopyrrolidine **39** as a colorless oil (100 mg, 70%). $[\alpha]_D^{20} = +9.6$ (*c* 0.45, $CHCl_3$). ^1H NMR δ 1.43 (s, 9H), 1.45 (s, 9H), 1.65–1.75 (m, 1H), 2.11–2.19 (m, 1H), 2.68–2.80 (m, 1H), 2.88–2.97 (m, 1H), 2.98–3.08 (m, 1H), 3.15–3.25 (m, 1H), 4.15 (br s, 1H), 5.21 (br s, 1H), 5.58 (br s, 1H). ^{13}C NMR δ 28.1, 28.2, 31.2, 48.5, 52.6, 60.3, 78.9, 79.9, 154.7, 155.2. IR (NaCl, ν cm^{-1}) 3290, 2977, 2933, 1685, 1514, 1456, 1391, 1365, 1248, 1157, 1076. MS (ESI) (*m/z*) 324 (51, MNa^+), 268 (100), 224 (45), 212 (18), 168 (6), 124 (5). HRMS (MNa^+) Calcd for $C_{14}H_{27}N_3O_4Na$: 324.1899. Found: 324.1883.

To the carbamate **39** (265 mg, 0.88 mmol), in THF (10 mL), were added NaH (60% in oil, 345 mg, 8.8 mmol) and MeI (560 μL, 8.8 mmol). The mixture was stirred at room temperature for 24 h. Water was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and then evaporated under reduced pressure. The residue was purified by flash chromatography (pentane/EtOAc, 80:20) to afford the compound **40** as a colorless oil (220 mg, 76%). $[\alpha]_D^{20} = +3.2$ (*c* 0.5, $CHCl_3$). ^1H NMR δ 1.45 (s, 9H), 1.47 (s, 9H), 1.61–1.66 (m, 1H), 1.74–1.84 (m, 1H), 2.03–2.12 (m, 1H), 2.85 (s, 3H), 2.92 (s, 3H), 2.93–3.20 (m, 3H), 4.16–4.36 (m, 1H). ^{13}C NMR δ 27.4, 28.5, 28.6, 28.9, 29.8, 48.4, 51.2, 52.0, 79.6, 80.1, 155.8. IR (NaCl, ν cm^{-1}) 2974, 2931, 2873, 1689, 1479, 1455, 1405, 1390, 1365, 1339, 1251, 1139. GC/MS (ESI) (*m/z*) 330 (41, MH^+), 274 (100), 218 (50), 174 (10). HRMS (MH^+) Calcd for $C_{16}H_{33}N_3O_4$: 330.2393. Found: 330.2411.

To the biscarbamate **40** (220 mg, 0.67 mmol) in Et_2O (15 mL) at 0 °C under an atmosphere of argon was added $LiAlH_4$ (150 mg, 3.95 mmol). The suspension was heated under reflux for 24 h. After cooling to 0 °C, water (150 μL) and NaOH (15%, 150 μL) were added followed by water (450 μL). The solids were filtered over Celite and washed with Et_2O (30 mL). The filtrate was evaporated under reduced pressure to give pyrrolidine **19** as a colorless oil (100 mg, 96%) which did not require any purification. $[\alpha]_D^{20} = +7.1$ (*c* 0.5, $CHCl_3$). ^1H NMR δ 1.55–1.70 (m, 1H), 1.80–2.02 (m, 1H), 2.22 (s, 6H), 2.40 (s, 6H), 2.48–2.69 (m, 2H), 2.76–2.86 (m, 2H), 2.97 (dd, *J* = 7.5 Hz, *J* = 6.5 Hz, 1H) ^{13}C NMR δ 27.6, 40.3, 43.9, 45.3, 50.1, 63.4. IR (NaCl, ν cm^{-1}) 2933, 2857, 1614, 1455, 1391, 1366, 1348, 1251, 1143. MS (EI) (*m/z*) 157 (12), 113 (78), 84 (100), 70 (14), 58 (8), 42 (54). HRMS (MH^+) Calcd for $C_8H_{20}N_3$: 158.1657. Found: 158.1662.

4.2.9. (*S*)-1-Benzylpyrrolidin-3-yl-((*R*)-2,2,2-trifluoro-1-phenylethyl)amine 20

To a solution of (*S*)-**7** (7.65 g, 0.043 mmol) in freshly distilled PhMe (50 mL) were added 2,2,2-trifluoroacetophenone (6.07 mL, 0.043 mmol) and APTS (150 mg). The system is fitted with a Dean

Stark apparatus and heated to 140 °C for 36 h. The crude reaction was diluted with Et_2O and washed with a solution of $NaHCO_3$ (10%), brine and dried on Na_2SO_4. The organic layer was concentrated under vacuum to deliver imine **21** as brown oil. To a solution of **21** in freshly distillated Et_2O (100 mL) cooled to 0 °C was slowly added $LiEt_3BH$ (1.1 equiv, 1 M in THF). The mixture was stirred 16 h at this temperature before quenching with a solution of aqueous $NaHCO_3$ (10%) and extractions with Et_2O. The organic layers were pooled, washed with brine and dried with Na_2SO_4. After concentration by rotary evaporation, the ratio of isomers of diamine **20** was estimated by ^1H NMR spectroscopy of the crude reaction (dr = 3:1). The crude was taken up in MeOH (20 mL) and 1 equiv of HBr (48% in H_2O) was added at 0 °C. The resulting mixture was concentrated to dryness and 200 mL of demineralized water was added, the heterogenous system was heated to 90 °C and filtrated while still hot. The brown pale filtrate was separated from oily solids remaining. The filtrate was once more heated and the hot solution obtained was poured into a beaker to let the system cool to rt. The crystallization is rapidly occurring and the crystals were let growing during 1 h. The solids were then filtrated and sucked to dryness. The crystals were taken into water -the minimum amount- and heated to 90 °C. Additional water was added to ensure the full solubility at this temperature and the operation of recrystallisation was repeated as described above until high dr of **20** was obtained (4.17 g, 23%, dr = 15:1, according to ^1H and ^{19}F NMR of the amine). This operation was usually repeated 2–3 times before obtaining this ratio of isomers. Aqueous filtrates were pooled and concentrated until half of the volume of water is removed. The operations of crystallization were repeated on this material to yield a second batch of additional **20**·HBr (2.70 g, 13%, dr = 7:1). The ratio of isomers can be increased to 22:1 from 15:1 by further recrystallisation. Suitable crystals for X-ray characterization were obtained by slow evaporation of a solution of **20**·HBr in CH_2Cl_2. Dissolving the salt **20**·HBr in CH_2Cl_2 and treating this with a $NaHCO_3$ saturated aqueous solution delivered **20** as pale yellow oil after removal of the solvent. $[\alpha]_D^{20} = -67$ (*c* 7.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.98–7.09 (m, 10H), 4.30–4.12 (m, 1H), 3.72 (q, *J* = 13.0 Hz, 2H), 3.35 (s, 1H), 2.84–2.76 (m, 1H), 2.67–2.61 (m, 2H), 2.49 (m, 1H), 2.18 (m, 1H), 1.71–1.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 134.7, 134.7, 129.1, 128.8, 128.8, 128.7, 128.4, 127.1, 125.6 (q, *J* = 281 Hz), 63.4 (q, *J* = 28 Hz), 60.4, 59.8, 55.0, 52.8, 32.5; ^{19}F NMR (282 MHz) δ −73.9. MS (EI, M^+): 334 (50%), 314 (100%).

4.3. Crystallographic study of 20·HBr

A colorless prism monoclinic, space group $P2_1$ (No. 4), a = 9.631(2) Å, b = 7.4178(17) Å, c = 27.787(6) Å, β = 94.044(4)°, V = 1980.2(8) Å^3, Z = 8, dcalcd = 1.393, μ = 2.106 mm^{-1} was used for data collection. Diffraction intensities were measured using a Bruker SMART APEX diffractometer equipped with a CCD area Detector using Mo Kalpha radiation at ambient temperature. Unit cell parameters and orientation matrix were determined by using the SMART software.[45] Intensities were integrated, corrected for Lorentz polarization. Absorption and unit cell parameters were refined by using SAINT plus and SADABS Softwares.[46] The SHELX 97 Software package[47] was used to solve and to refine the structural model. The final cycle of full-matrix least-squares refinement was based on 3656 observed reflections (for $I > 2\sigma(I)$) and 460 variable parameters and gave R_1 = 0.0772, wR_2 = 0.1711. The value of the goodness of fit indicator was 1.009 (Summary of Data CCDC 767786).

4.4. Typical procedure for Morita–Baylis–Hillman reactions

To the 4-nitrobenzaldehyde (0.5 mmol), was added successively the aminopyrrolidine **4** (10 mg, 0.08 mmol, 0.16 equiv), *i*-PrOH (0.5 mL) and methyl vinyl ketone (120 μL, 1.5 mmol, 3 equiv). The mixture was stirred for four days at 0 °C. The solvent was evaporated under reduced pressure and the residue purified via flash chromatography (pentane/EtOAc, 80:20) to afford 3-(hydroxy(4-nitrophenyl)methyl)but-3-en-2-one. Enantiomeric excess was determined using a Daicel Chiralpak AD-H column [1 mL min^{-1} *n*-heptane (95%), MeOH/EtOH (v:v: 1:1, 5%, 20 °C, room temperature (*R:* 60 min; *S:* 90 min)]. Absolute configurations were determined by comparison with the signs of the optical rotations of previously reported compounds: X-Ar-CH(OH)C(=CH_2)COMe: X = 4-NO_2 (column AD-H, 20 °C, 1 mL min^{-1}, 95% heptane—5% (50% MeOH + 50% EtOH): t_1 = 58.5 min, t_2 = 87.6 min),[48] X = 2-NO_2 (AD-H, 20 °C, 1 mL min^{-1}, 95% heptane—5% *i*PrOH: t_1 = 50.0, t_2 = 55.2.),[10] X = 2-CF_3 (AD-H, 20 °C, 1 mL min^{-1}, 95% heptane—5% *i*PrOH: t_1 = 11.9, t_2 = 14.7).[49] The *S* configurations of the major enantiomers of the Morita–Baylis–Hillman adducts with X = CN (AD-H, 20 °C, 1 mL min^{-1}, 95% heptane—5% (50% MeOH + 50% EtOH): t_1 = 51.7 min, t_2 = 98.9 min), 2,4-Cl_2 (OD-H, 20 °C, 0.8 mL min^{-1}, 90% heptane—10% *i*PrOH: t_1 = 8.2, t_2 = 12.2), 4-CF_3 (AD-H, 20 °C, 1 mL min^{-1}, 95% heptane—5% (50% MeOH + 50% EtOH): t_1 = 25.0, t_2 = 26.6),[50] 4-CO_2Me (AD-H, 20 °C, 1 mL min^{-1}, 90% heptane—10% *i*PrOH: t_1 = 15.6 min, t_2 = 17.2 min) were assigned by comparing their retention times with those of the closest known structures.

4.5. Typical procedure for hydroxyalkylations of *o*-tolualdehyde

Under an argon atmosphere, MeLi (1 equiv, 1.6 M solution in Et_2O) was added to a solution of **20** (1 equiv) in anhydrous THF (C = 0.2 M) at −20 °C. After stirring 20 min, a second portion of MeLi (1.2 equiv, 1.6 M solution in Et_2O) was added dropwise to the preformed solution of lithium amide (**20**·Li) and the resulting mixture was stirred for 30 min at −20 °C. Then, the mixture was cooled to −78 °C and aged 30 min at this temperature. A solution of *o*-tolualdehyde (1 equiv) in THF (2 mL) was added at −78 °C over a 5-min period and the mixture was stirred at −78 °C for 90 min. The medium was quenched at −78 °C with a 3 M aqueous HCl solution and was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduce pressure. Purification of the residue by column chromatography (AcOEt/cyclohexane 30:70) gave **22**. The enantiomeric excess was measured by GC with a chiral permethylated β-cyclodextrin column (*R*-isomer 6.80 min and *S*-isomer 8.15 min).

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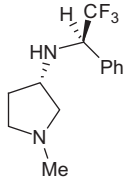

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