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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b02342 • Publication Date (Web): 06 Jan 2016

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Synergistic effect of the $TiCl_4$/*p*-TsOH promoter system on the Aza-Prins cyclization

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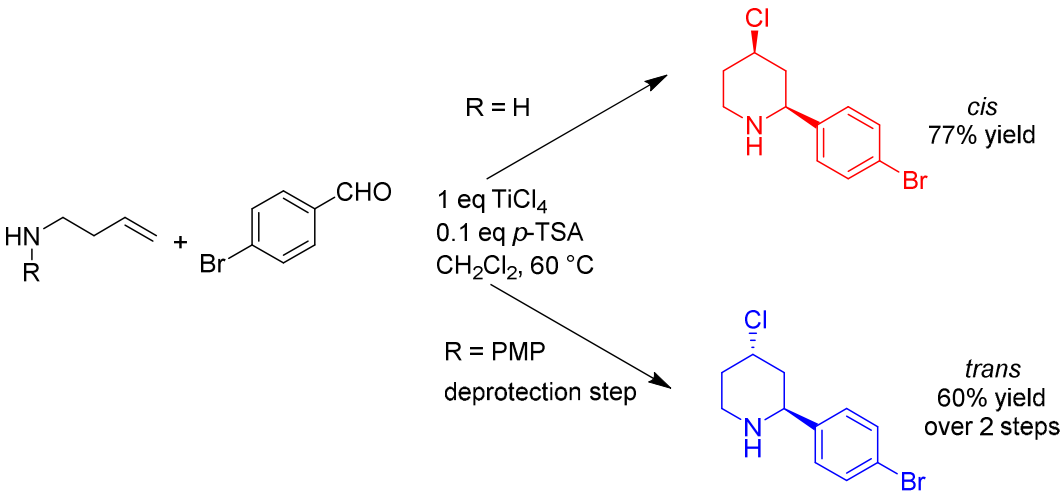


Abstract A novel aza-Prins cyclization promoted by a synergistic combination between a Lewis acid and a Brønsted acid to efficiently afford piperidines is described. Contrary to what has been previously reported in the literature, the generality of the reaction employing *N*-alkyl, *N*-aryl and non-protected homoallylamines has been demonstrated. The reaction is highly diastereoselective depending on the homoallylic amine used, *N*-PMP homoallyl amine leading preferentially to the *trans* diastereomer, and free homoallylamine affording the deprotected piperidine as single *cis* diastereomer.

Introduction

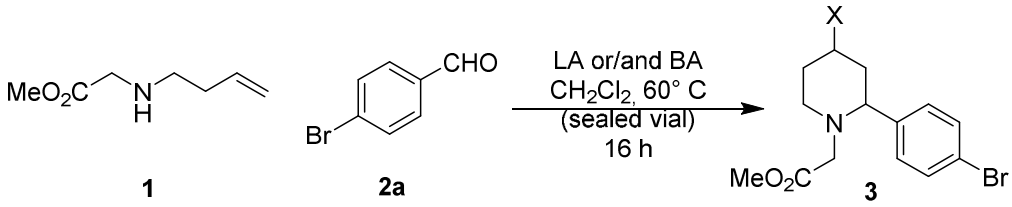
Nowadays there are many routes to prepare piperidines, among them the aza-Prins cyclization reaction involving aldehydes and homoallylic amines, appears to be a straightforward method that provides direct access to six-membered azacycles.[1] Despite the great interest and the recent advances concerning the Prins cyclization, a feasible nitrogen-based version of this reaction knows only moderate success. Indeed this reaction is restricted in most cases to *N*-sulfonyl homoallylic amines, which may limit the interest in this process and its development. Several Lewis acids are reported to promote the reaction of *N*-sulfonyl homoallylic amines with aldehydes, among them, Fe(III) halides in stoichiometric or sub-stoichiometric amount,[2] $BiCl_3$,[3] $BF_3.Et_2O$, [4] $InCl_3$[5] and TMSX.[6] Brønsted acids are also reported to catalyze the cyclization, as in the case of phosphomolybdic acid,[7] $HBF_4.Et_2O$[8] and TfOH.[9] It has to be pointed out that there are only a very few examples reported in the literature concerning aliphatic or primary amines.[10] They concern mainly the use of the aza-Prins cyclization as key step in the total synthesis of biologically active alkaloids. To the best of our knowledge to date a detailed study devoted to the development of an effective aza-Prins cyclization involving non-sulfonylated homoallylic amines has not been undertaken. We wish herein to fill this gap by reporting our results on the aza-Prins cyclization reaction with *N*-aryl, -alkyl homoallylic amines and even with non-protected ones.

Results & Discussion

We began our investigations by studying the reaction between *N*-alkyl homoallylic amine as model substrate, namely *N*-methyl but-3-en-1-ylglycinate (**1**), and *p*-bromobenzaldehyde (**2a**), in CH_2Cl_2 at 60 °C in a sealed vial overnight (table 1). In the first attempts different Lewis acids known to promote

the aza-Prins cyclization were screened, such as $FeCl_3$, $AlCl_3$ or $Bi(OTf)_3$ (entries 1-3), unfortunately without any conversion of the starting materials, in some cases only the degradation of the reagents after a prolonged reaction time was observed. Only with 3 equiv. of $MgBr_2$ or $TiCl_4$ (entry 4-5) trace amounts of the desired product were detected in the crude NMR. The use of *p*-TsOH.H_2O, TFA and *p*-nitrobenzoic acid as Brønsted acids (entries 6-8) also failed to convert the starting materials into the desired product.

Table 1. Reaction conditions optimization.[a]



Entry	Lewis Acid (equiv.)	Brønsted Acid (equiv.)	Yield (%)[b]	*Cis:trans* (d.r.)[d]	X
1	$FeCl_3$ (3)	-	n.r.[c]	-	-
2	$AlCl_3$ (3)	-	n.r.[c]	-	-
3	$Bi(OTf)_3$ (3)	-	n.r.[c]	-	-
4	$MgBr_2$ (3)	-	traces	-	Br
5	$TiCl_4$ (3)	-	traces	-	Cl
6	-	*p*-TsOH.H_2O (3)	n.r.[c]	-	-
7	-	TFA (3)	n.r.[c]	-	-
8	-	*p*-NO_2-$C_6H_4CO_2H$	n.r.[c]	-	-
9	$TiCl_4$	*p*-TsOH.H_2O (1)	98	57:43	Cl
10	$TiCl_4$(1)	*p*-TsOH.H_2O (0.1)	99	57:43	Cl
11	$MgBr_2$ (1)	*p*-TsOH.H_2O (0.1)	55	50:50	Br
12	$AlCl_3$ (1)	*p*-TsOH.H_2O (0.1)	43	45:55	Cl
13	$FeCl_3$ (1)	*p*-TsOH.H_2O (0.1)	28	50:50	Cl
14	$ZnCl_2$ (1)	*p*-TsOH.H_2O (0.1)	20	50:50	Cl

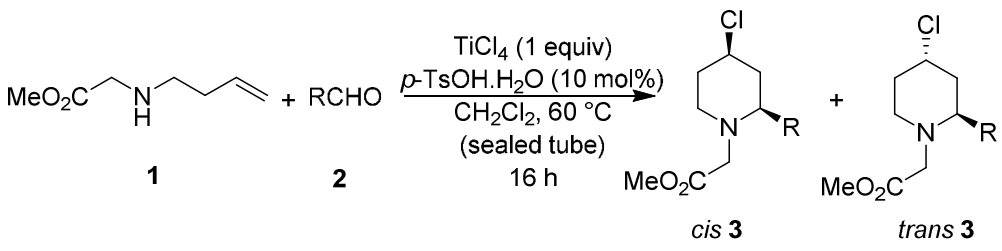
[a] General conditions: **1** (1 equiv.), **2a** (1 equiv.), CH_2Cl_2 (0.05 M) at 60 °C 16 h. [b] Yields refer to isolated products. [c] n.r.: no reaction. [d] ^{1}H NMR determination on the crude mixture.

Within our recent investigations on the Prins cyclization,[11] we reported a remarkable synergistic effect between non-reactive Brønsted and Lewis acids that lack the ability to catalyze the reaction if used alone.[11b] The benefit of this synergistic effect in the Prins cyclization was then confirmed when we disclosed the first enantioselective Prins cyclization by combining a chiral BINOL-derived bis-phosphoric acid and CuCl.[11c]

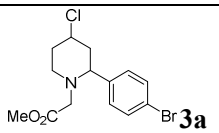
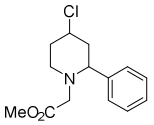
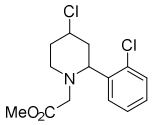
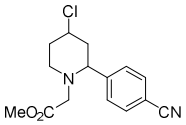
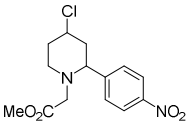
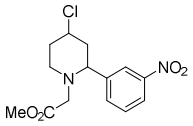
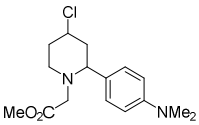
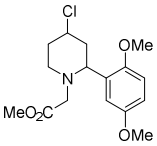
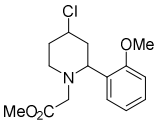
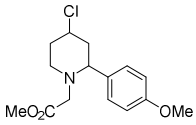
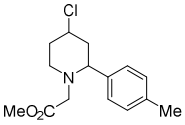
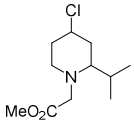
Based on our findings and on the previous observations by Aubé and coworkers,[10 a,b] we decided to combine $TiCl_4$ with *p*-TsOH.H_2O, the Lewis acid playing the role also of the nucleophile source. Thus **1**, and **2a** were reacted in the presence of 3 equiv. of $TiCl_4$ and 1 equiv. of *p*-TsOH.H_2O, in CH_2Cl_2 at 60 °C in a sealed vial overnight (table 1, entry 9). To our delight the desired product was recovered in 98% yield, as a mixture of two diastereomers (*cis:trans* = 57:43). The variation of the Lewis and Brønsted acid amounts didn't affect the reactivity (see supporting information for details) and gratifyingly the expected piperidine was recovered in quantitative yield even with only 1 equiv. of $TiCl_4$ and catalytic amount (10 mol%) of *p*-TsOH.H_2O and in the same diastereomeric ratio (table 1, entry 10). A screening of different Brønsted and Lewis acid combinations revealed $TiCl_4$ to be superior to $MgBr_2$, $AlCl_3$, $FeCl_3$ and $ZnCl_2$ (table 1, entries 11-14). On the contrary, the use of TFA, $MeSO_3H$, camphorsulfonic acid, as well as *p*-nitro benzoic acid with $TiCl_4$ didn't affect the outcome of the reaction (see Supporting Information for details). Decreasing the reaction temperature to 40 °C was detrimental for the reactivity, moreover when the reaction was performed at 60 °C in 1,2-dichloroethane a slight drop of the yield was observed.

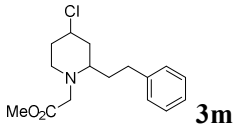
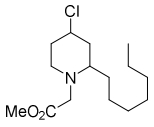
With the optimized conditions in hand we next examined the scope of the synergism between $TiCl_4$ and *p*-TsOH.H_2O with respect to different aldehydes, and the results are summarized in Table 2.

Table 2. Scope of the aza-Prins cyclization with the *N*-alkyl homoallylic amine **1**.[a]



1 **2** *cis* **3** *trans* **3**

Entry	Aldehyde **2** R=	Product **3**	Yield (%)[b]	*Cis:trans* (d.r.)[c]
1	*p*-Br-C_6H_4 **2a**	 **3a**	98	57:43
2	C_6H_5 **2b**	 **3b**	94	57:43
3	*o*-Cl-C_6H_4 **2c**	 **3c**	86	86:14
4	*p*-CN-C_6H_4 **2d**	 **3d**	96	42:58
5	*p*-NO_2-C_6H_4 **2e**	 **3e**	90	38:62
6	*m*-NO_2-C_6H_4 **2f**	 **3f**	97	45:55
7	*p*-$N(CH_3)_2$-C_6H_4 **2g**	 **3g**	60	50:50
8	2,5-$(OCH_3)_2$-C_6H_3 **2h**	 **3h**	92	87:13
9	*o*-OCH_3-C_6H_4 **2i**	 **3i**	65	85:15
10	*p*-OCH_3-C_6H_4 **2j**	 **3j**	60[d]	62:38
11	*p*-CH_3-C_6H_4 **2k**	 **3k**	74	62:38
12	$(CH_3)_2CH$ **2l**	 **3l**	86	43:57

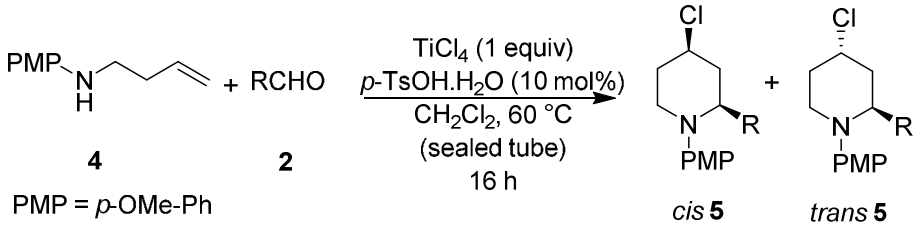
13[e]	C_6H_4-$(CH_2)_2$ **2m**	 **3m**	52	62:38
14[e]	$(CH_3)(CH_2)_6$ **2n**	 **3n**	78	62:38

[a] General conditions: **1** (1 equiv.), **2** (1 equiv.), $TiCl_4$ (1 equiv.), *p*-TsOH.H_2O (10 mol%), in CH_2Cl_2 (0.1 M) at 60 °C in a sealed vial 16 h. [b] Yields refer to isolated products. [c] ^{1}H NMR determination on the crude mixture. [d] 62% conversion. [e] Performed with **2** (1.5 equiv).

Gratifyingly benzaldehyde **2b** (entry 2) smoothly participated to the reaction leading to the desired product **3b** in 94% yield, and the same *cis:trans* selectivity (d.r. 57:43). The aromatic ring substitution in the *ortho, meta* or *para* position with electron-withdrawing groups (entries 3-6) is well tolerated as in all the cases the piperidines **3c-f** were obtained in 86-97% yields. The reaction proved to be less efficient for aromatic aldehydes substituted with an electron-donating group especially in the *para* position (entries 7, 10 and 11), leading to the products **3g**, **j** and **k** in 60%, 60% and 74% yield respectively. It's interesting to note that in the presence of an *ortho* substituent on the aromatic ring, the *cis*-product was obtained as major diastereomer (entries 3, 8 and 9) affording the desired piperidines with up to 87:13 d.r. probably because of the steric hindrance.[12] Aliphatic aldehydes undergo aza-Prins cyclization in high yields (entries 12-14), however in the case of 3-phenylpropionaldehyde (**2m**) and *n*-octanal (**2n**) a slight excess of aldehyde was needed (1.5 equiv) to have a complete conversion of **1**; these aldehydes reacting with themselves leading to small amount of the aldol-crotonization products.

The scope of the reaction was then extended to other protected homoallylic amines. Contrarily to the scarce previously reported results,[13,3,10c] our reaction conditions are not compatible with the use of carbamates as protecting group on the nitrogen atom. Both the Boc- and Cbz- are cleaved in the presence of the combination of $TiCl_4$ and *p*-TsOH.H_2O and no trace of the aza-Prins product was observed. Otherwise the aza-Prins reaction with homoallylic amine protected by the widely used *p*-methoxyphenyl (PMP) group **4** was also carried out and the results are reported in Table 3.

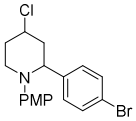
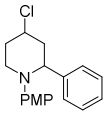
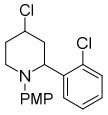
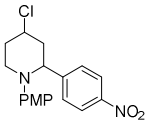
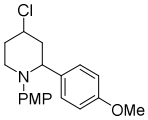
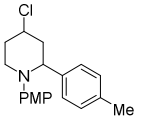
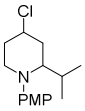
Table 3. Scope of the aza-Prins cyclization with PMP-protected homoallylic amine **4**.[a]



4 **2**

PMP = *p*-OMe-Ph

cis **5** *trans* **5**

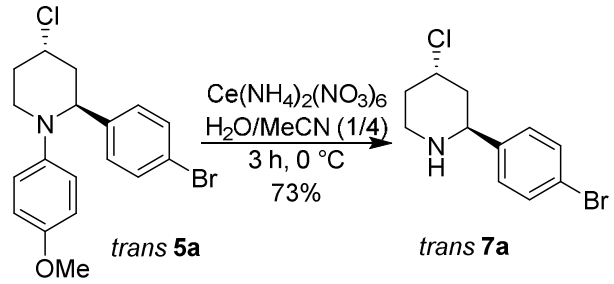
Entry	Aldehyde **2** R=	Product **5**	Yield (%)[b]	*Cis/trans* (d.r.)[c]
1	*p*-Br-C_6H_4 **2a**	 **5a**	99	12:88
2	C_6H_5 **2b**	 **5b**	93	23:77
3	*o*-Cl-C_6H_4 **2c**	 **5c**	99	28:72
4	*p*-NO_2-C_6H_4 **2e**	 **5d**	92	14:86
5	*p*-OCH_3-C_6H_4 **2j**	 **5e**	40[d]	20:80
6	*p*-CH_3-C_6H_4 **2k**	 **5f**	90	22:78
7	$(CH_3)_2CH$ **2l**	 **5g**	98	9:91

[a] General conditions: **4** (1 equiv.), **2** (1 equiv.), $TiCl_4$ (1 equiv.), *p*-TsOH.H_2O (10 mol%), in CH_2Cl_2 (0.1 M) at 60 °C in a sealed vial 16 h. [b] Yields refer to isolated products. [c] ^1H NMR determination on the crude mixture. [d] 49% conversion.

In the presence of aromatic aldehydes substituted on the *ortho* or *para* positions with electron withdrawing groups **2a-c** and **e** the aza-Prins products **5a-d**, were isolated in up to 99% yields, this time surprisingly, with a good diastereoselection in favor of the *trans* isomer (d.r. up to 86:14). Aliphatic isobutyraldehyde **2l** also provided the desired piperidine **5g** in very good yield and as single diastereomer (*trans:cis* = 91:9). The substitution on the aromatic ring with strong electron donating groups is less tolerated. Indeed, while *p*-tolualdehyde (**2k**) smoothly reacted to give the desired

piperidine in 90% yield (entry 6), *p*-anisaldehyde (**2j**) gave the product in only 40% yield (entry 5) and 2,5-dimethoxy benzaldehyde (**2h**) did not react at all. This is probably due to electronic effects, since the iminium intermediate is too electron enriched due to the donating PMP and methoxy groups. To illustrate the synthetic utility of this methodology we deprotected the PMP group in standard reaction conditions, in the presence of ceric ammonium nitrate CAN, in order to obtain the NH free piperidine as the single *trans* **7a** diastereomer in 73% yield (Scheme 1), thus with an overall yield of 66% over two steps.

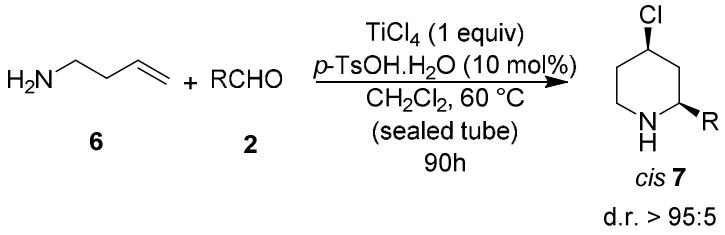
Scheme 1. Deprotection of the PMP group of the piperidine *trans* **5a**.



trans **5a** *trans* **7a**

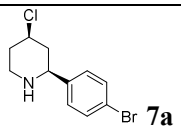
We next wondered about the possibility to carry out the aza-Prins cyclization with the but-3-en-1-amine (**6**). Indeed very few examples are reported in the literature using a free homoallyl amine or an imine. To our delight, although the reaction time was longer (90 h instead of overnight) the synergistic combination of $TiCl_4$ with *p*-TsOH.H_2O allowed isolation of the expected piperidines **7** in good yields and gratifyingly as the single *cis*-stereoisomer (d.r. > 95/5) (Table 4).

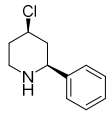
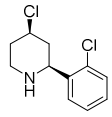
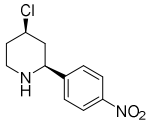
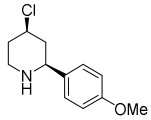
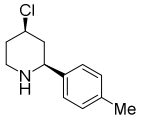
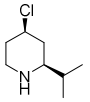
Table 4. Scope of the aza-Prins yclization with homoallyl amine **6**.[a]



6 **2** *cis* **7**

d.r. > 95:5

Entry	Aldehyde **2** R=	Product **7**	Yield (%)[b]
1	*p*-Br-C_6H_4 **2a**	 **7a**	77

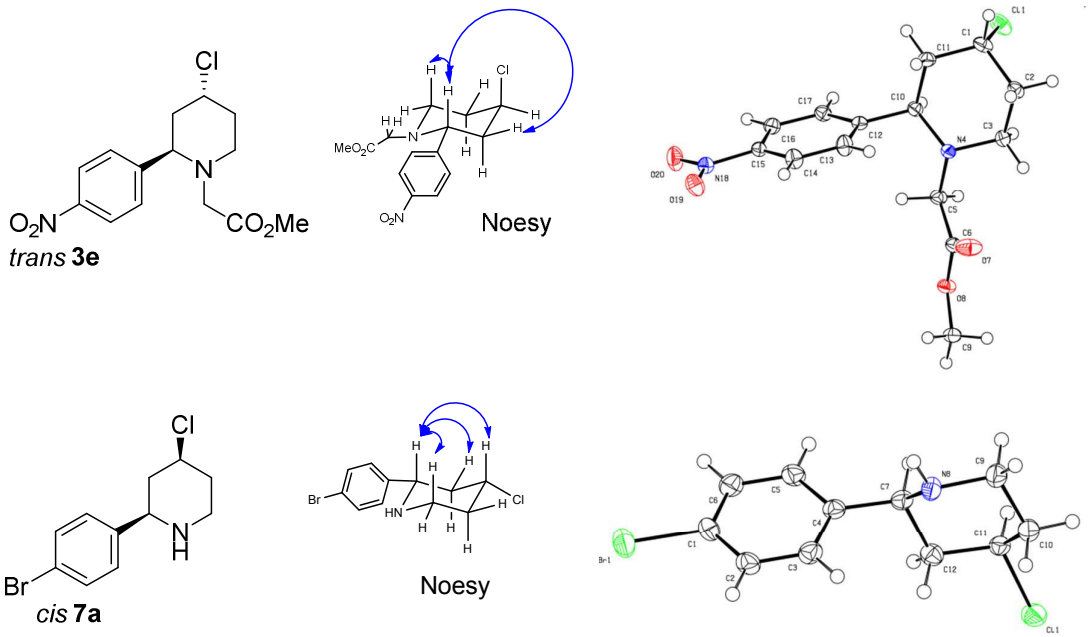
2	C_6H_5 **2b**	 **7b**	86
3	*o*-Cl-C_6H_4 **2c**	 **7c**	80
4	*p*-NO_2-C_6H_4 **2e**	 **7d**	82
5	*p*-OCH_3-C_6H_4 **2j**	 **7e**	34[c]
6	*p*-CH_3-C_6H_4 **2k**	 **7f**	70[c]
7	$(CH_3)_2CH$ **2l**	 **7g**	88

[a] General conditions: **6** (1 equiv.), **2** (1 equiv.), $TiCl_4$ (1 equiv.), *p*-$TsOH.H_2O$ (10 mol%), in CH_2Cl_2 (0.1 M) at 60 °C in a sealed vial 90 h. [b] Yields refer to isolated products. [c] Reaction time prolonged to 160 h.

Again the only exception in this trend concerns the electron rich aldehydes; the reaction with **2k** afforded the piperidine **7f** in 70% yield after a longer reaction time (160 h) and **2j** afforded **7g** in only 32% yield after 160 h.

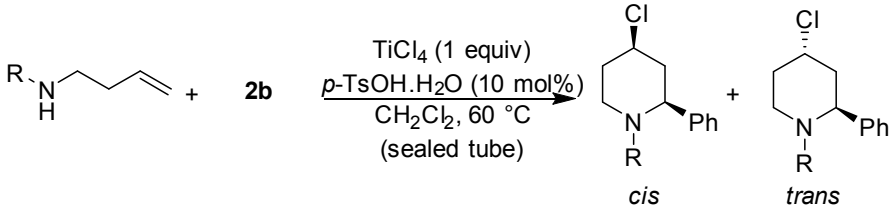
The structure of compounds *trans* **3e** and *cis* **7a** and their relative configurations were determined by NOESY experiments[14] and confirmed by single crystal X-ray analysis[14] (Figure 1).

Figure 1 ORTEP representation of the piperidines products *trans*-**3e** and *cis*-**7a**. The thermal ellipsoids are shown at 50% probability.



It is worth noting that the *cis*/*trans* ratio is strongly dependent on the feature of the nitrogen atom substituent, as depicted in Table 5. To determine the trend of the selectivity dependence, the reactions between benzaldehyde (**2b**) and different substituted homoallylic amines were performed.

Table 5. Selectivity dependence.



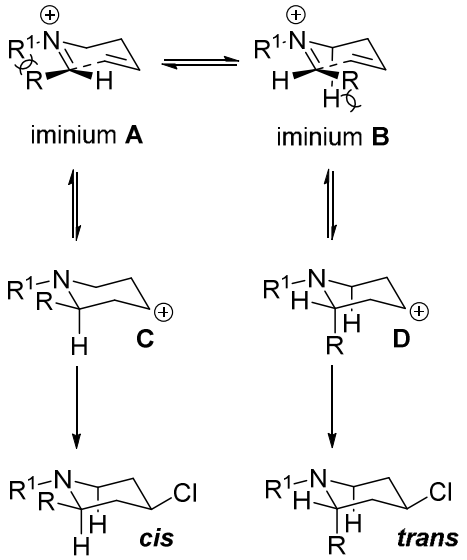
Entry	R=	Product (Yield %)[a]	*Cis/trans* (d.r.)[b]
1	CH_2CO_2Me (**1**)	**3b** (94)	57:43
2	PMP (**4**)	**5b** (93)	23:77
3	H (**6**)	**7b** (86)	>95:5
4	Ts (**8**)	**11** (93)	>5:95
5	Bn (**9**)	**12** (66)	50:50
6	*n*-Pr (**10**)	**13** (90)	50:50

[a] Yields refer to isolated products. [b] ^{1}H NMR determination on the crude mixture.

With *N*-tosyl homoallyl amine (**8**) only the product *trans* **11** was recovered in 95% yield (entry 4). Next we employed *N*-alkyl homoallylic amines such as *N*-benzyl (**9**) and *N*-propyl (**10**) (entries 5 and 6): both delivered an equimolar mixture of *cis* and *trans* isomers **12** and **13** in good yield. We can therefore conclude that whereas the free amine **6** led to the piperidine *cis* **7b** as unique stereoisomer (entry 3), the arylamine **4** and the tosylamine **8** gave the *trans* isomer as major product (entries 2 and 4), finally no selectivity was observed with the alkylamines **1**, **9** and **10** (entries 1, 5 and 6).

These results could be explained as follow (Figure 2). According to the common reaction mechanism of the aza-Prins cyclization, the reaction starts by the formation of an iminium whose **A** and **B** forms are in equilibrium and then the nucleophilic attack (here the chloride anion) occurs on the equatorial position. As mentioned by Padrón et al.,[2a] in the case of R^1=Ts, *ab-initio* calculations showed that the iminium **B** is more stable than the isomer **A**. This is probably due to the strong steric repulsion between the groups R^1 and R in comparison to the lower energy cost of the allylic strain between R and H. Obviously, this comment can also explain the *trans*- selectivity with R^1=PMP. When R^1=H, only the allylic strain remains,[15] favoring thus the formation of the iminium **A** and consequently the formation of the *cis*-piperidine. The observed lack of selectivity when the amine bears an alkyl chain (homoallylic amine **1**) is certainly due to an equivalent energy cost between the steric repulsion for the iminium **A** and the allylic strain for **B**. This last case helps us to better understand the high *cis*-selectivity when the reaction was carried out with *ortho*-substituted aryl aldehydes (Table 2, entries 3-8-9). These *ortho*-substituents could contribute to increase the steric hindrance detrimental to the iminium **B** by reinforcing the negative contribution of the allylic strain versus the steric repulsion between the residue CH_2CO_2Me (R^1) and the aryl group (R).

Figure 2. Comparison of possible transition structures for the cyclization reaction.



In conclusion, we have demonstrated that the synergism between $TiCl_4$ and *p*-TsOH.H_2O can promote the aza-Prins cyclization with *N*-aryl, -alkyl and even non protected homoallylic amines. The piperidine derivatives are obtained in good yields and with a *cis*/*trans* ratio dependent on the group borne by the nitrogen atom. The *trans*-isomer was obtained as major compound when tosyl and PMP are used as protecting groups, while the *cis*-isomer was formed in the absence of protecting group. This methodology can be useful for preparing either *cis*- or *trans*- piperidines and could be later used for the synthesis of valuable piperidine scaffolds found in natural and bioactive products.

Experimental section

General information

All the reactions were performed in dried glassware, under argon atmosphere and with dry solvents. Reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. TLC analyses were performed using precoated Merck TLC Silica Gel 60 F254 plates. Purifications by column chromatography on silica gel were performed using Merck Silica Gel 60 (70-230 mesh) and purifications by preparative thin layer chromatography on silica gel using Merck Silica Gel 60 PF254. Petroleum ether (PE) used for purifications was the low boiling point fraction (40-60 °C). ^{1}H NMR and ^{13}C spectra were recorded on a 300 Mhz instrument using TMS and $CDCl_3$ respectively as internal standards. Chemical shifts (δ) are reported in parts per million (ppm). The

following abbreviations are used for multiplicities: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; q, quadruplet; quint, quintuplet; td, triplet of doublets; dt, doublet of triplets; tt, triplet of triplets, m, multiplet. Carbon multiplicities were determined by Jmod experiments. Coupling constants (*J*) are reported in Hertz (Hz). - HRMS analyses were obtained using MaXis 4G or a TOF Q for ESI. X-ray crystallographic data were collected on a crystal diffractometer. Melting points were obtained on a hot bench.

Preparation of *N*-methyl but-3-en-1-ylglycinate (1): To a solution of methyl glycinate hydrochloride (11.12 g, 2 equiv., 88.6 mmol) in acetonitrile (220 mL) was added K_2CO_3 (18.36 g, 3 equiv., 133 mmol). The mixture was stirred 1 h at room temperature, then 4-bromo-1-butene (4.5 mL, 1 equiv., 44.9 mmol) was added and the stirring continued at 45 °C for 48 h. The insoluble material was filtered off and the filtrate concentrated under reduced pressure. CH_2Cl_2 (60 mL) and H_2O were added, the two-phase mixture was separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and evaporated in vacuo. Compound 1 was isolated as colorless oil (6.01 g, 90% yield) after distillation (70 °C, to reduced pressure). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.85-5.75 (m, 1 H), 5.14-5.04 (m, 2 H), 3.73 (s, 3 H), 3.43 (s, 2 H), 2.68 (t, *J* = 6.7 Hz, 2 H), 2.26 (q, *J* = 6.7 Hz, 2 H), 1.66 (bs, NH). ^{13}**C** NMR ($CDCl_3$, 75 MHz): δ = 173.0 (C=O), 136.2 (=CH), 116.7 (=CH_2), 51.9 (CH_3), 50.8 (CH_2), 48.6 (CH_2), 34.4 (CH_2). ESI-HRMS calculated for $C_7H_{14}NO_2$ $[M+H]^+$ 144.1024, found 144.1022.

Preparation of *N*-(but-3-en-1-yl)-4-methoxyaniline (4): To a solution of *p*-anisidine (6.16 g, 5 equiv., 49.2 mmol) and 4-bromo-1-butene (1.33 g, 1 equiv., 9.85 mmol) in EtOH (20 mL) was added NaI (147 mg, 0.1 equiv., 0.98 mmol). The mixture was stirred to reflux for 4 h, and then the solvent was removed in vacuo. CH_2Cl_2 (20 mL) followed by KOH (1 M, 20 mL) were added. The two-phase mixture was separated, and the organic phase was washed with water (2 × 20 mL) and brine (2 × 20 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The compound 4 was isolated as brown oil (1.58 g, 90% yield) after purification by flash chromatography (10% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.78 (d, *J* = 8.8 Hz 2 H), 6.58 (d, *J* = 8.8 Hz, 2 H), 5.86-5.75 (m, 1 H), 5.16-5.08 (m, 2 H), 3.73 (s, 3 H), 3.27 (bs, NH), 3.13 (t, *J* = 6.7 Hz, 2 H), 2.36 (q, *J* = 6.7 Hz, 2 H).

^{13}**C** NMR ($CDCl_3$, 75 MHz): δ = 152.2 (C), 142.6 (C), 136.0 (=CH), 117.1 (=CH_2), 115.0 (2 × CH), 114.4 (2 × CH), 55.9 (CH_3), 43.9 (CH_2), 33.8 (CH_2). ESI-HRMS calculated for $C_{11}H_{16}NO$ $[M+H]^+$ 178.1232, found 178.1232.

Preparation of *N*-but-3-en-1-yl-4-methylbenzenesulfonamide (8): This substrate was synthesized according to a described procedure.[16] To a solution of 3-buten-1-amine (662 mg, 1 equiv., 9.3 mmol), NEt_3 (1.9 mL, 1.5 equiv., 13.9 mmol) and dimethylaminopyridine (341 mg, 0.3 equiv., 2.79 mmol) in CH_2Cl_2 (30 mL), at 0 °C tosyl chloride (2.13 g, 11.2 mmol, 1.2 eq) was added. The reaction was warmed to r.t., stirred for 3 h, quenched with water and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography (EP/EtOAc 4:1) to afford the corresponding tosylamine 15 (2.08 g, 99% yield) as colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.75 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz 2 H), 5.69-5.56 (m, 1 H), 5.09-5.01 (m, 2 H), 4.42 (s, NH), 3.02 (q *J* = 6.6 Hz, 2 H), 2.43 (s, 3 H), 2.20 (q, *J* = 6.6 Hz, 2 H). ^{13}**C** NMR ($CDCl_3$, 75 MHz) : δ = 143.6 (C), 137.1 (C), 134.3 (=CH), 129.9 (2 × CH), 127.3 (2 × CH),118.4 (=CH_2), 42.2 (CH_2), 33.7 (CH_2) 21.7 (CH_3).

Preparation of *N*-benzylbut-3-en-1-amine (9): This substrate was synthesized according to a described procedure.[17] To a solution of benzylamine (5.25 g, 5 equiv., 49.0 mmol) and 4-bromo-1-butene (1 mL, 1 equiv., 9.85 mmol) in EtOH (20 mL), NaI (150 mg, 0.1 equiv., 0.98 mmol) was added. The mixture was stirred to reflux for 4 h. Then the solvent was removed in vacuo, CH_2Cl_2 (20 mL) followed by KOH (1 M, 20 mL) were added and the two-phase mixture was separated. The organic phase was washed with water (2 × 20 mL) and brine (2 × 20 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography (10 % EtOAc in petroleum ether) to give pure product 17 (*N*-benzylbut-3-en-1-amine) as a yellow oil (1.51 g, 95% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.33–7.22 (m, 5 H), 5.85-5.72 (m, 1 H), 5.12–5.02 (m, 2 H), 3.81 (s, 2 H), 2.71 (t, *J* = 6.8 Hz, 2 H), 2.31 (qt, *J* = 6.8, 1.3 Hz, 2 H), 1.84 (br s, 1 H). ^{13}**C** NMR ($CDCl_3$, 75 MHz): δ = 140.1 (C), 136.5 (=CH), 128.6 (2 × CH), 128.3 (2 × CH), 127.1 (CH), 116.6 (=CH_2), 53.9 (CH_2), 48.3 (CH_2), 34.3 (CH_2).

Preparation of *N*-propylbut-3-en-1-amine (10): To a solution of but-3-en-1-amine (0.77 mL, 1.0 equiv., 8.4 mmol) in MeOH (10 mL) was added propanal (0.74 mL, 1.2 equiv., 10.1 mmol). The mixture was stirred at room temperature for 2 h. Solid $NaBH_4$ (794 mg, 2.5 equiv., 21 mmol) was then added portionwise over 1 h. The reaction was stirred at room temperature overnight, quenched with 2.0 M aq. NaOH (10 mL) and extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by distillation (70 °C under reduce pressure) to give compound 19 (900 mg, 95% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.86-5.72 (m, 1 H), 5.12–5.02 (m, 2 H), 2.67 (t, *J* = 6.8 Hz, 2 H), 2.57 (t, *J* = 7.3 Hz, 2 H), 2.28 (qt, *J* = 6.8, 1.2 Hz, 2 H), 1.51 (q, *J* = 7.3 Hz, 2 H), 0.91 (t, *J* = 7.3 Hz, 3 H). **^{13}C** NMR ($CDCl_3$, 75 MHz): δ = 136.7 (=CH), 116.4 (=CH_2), 51.9 (CH_2), 48.9 (CH_2), 34.5 (CH_2), 23.3 (CH_2), 11.9 (CH_3).

4-Methoxyphenyl deprotection: To a solution of *trans* 5a (114.2 mg, 1.0 equiv., 0.3 mmol) in MeCN-H_2O (4:1, 6 mL) was added ceric ammonium nitrate $Ce(NH_4)_2(NO_3)_6$ (987 mg, 6 equiv., 1.8 mmol) at 0 °C. The mixture was stirred at the same temperature for 3 h. Solid $NaBH_4$ (794 mg, 2.5 equiv., 21 mmol) was then added portionwise over 1 h. Then water (12 mL) was added and extracted with EtOAc (90 mL). The aqueous layer was basified with K_2CO_3, filtered through a pad of celite and extracted with EtOAc (2 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography (100% EtOAc) to give pure product *trans* 7a (60 mg, 73% yield) as a black solid. Black solid, M.p. 78-80 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45 (d, *J* = 8.3 Hz, 2 H), 7.26 (d, *J* = 8.3 Hz, 2 H), 4.60 (quint, *J* = 3.0 Hz, 1 H), 4.15 (dd, *J* = 10.7, 3.0 Hz, 1 H), 3.31 (td, *J* = 12.1, 3.0 Hz, 1 H), 3.08 (bs, NH), 3.01(ddd, *J* = 12.1, 4.4, 2.6 Hz, 1 H), 2.13-1.91 (m, 4 H). **^{13}C** NMR ($CDCl_3$, 75 MHz): δ = 142.7 (C), 131.7 (2 × CH), 128.7 (2 × CH), 121.3 (C), 57.9 (CH), 54.8 (CH), 42.0 (CH_2), 41.2 (CH_2), 33.2 (CH_2). ESI-HRMS calculated for $C_{11}H_{14}NClBr$ $[M+H]^+$ 273.9993, found 273.9993.

General procedure

To a solution of homoallylic amine (1 equiv., 0.4 mmol) and aldehyde (1 equiv*., 0.4 mmol) in CH_2Cl_2 (4 mL) *p*-TSA.H_2O (0.1 equiv., 0.04 mmol) was added. The mixture was stirred for 15 min

then a solution of $TiCl_4$ (1 M in CH_2Cl_2, 1 equiv., 0.4 mmol) was added. The solution was stirred at 60 °C for 16 h (with amine **1**, **4**, **15**, **17** and **19**), 90 h (with amine **6****) or 160 h (with amine **8**, **10** and **12**), quenched with $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, solvent was removed, and the residue was purified by flash chromatography on silica gel (10% EtOAc in petroleum ether) to give the pure piperidine products.

* 1.5 eq for aldehyde **2m** and **2n**

** For amine **6** reaction with **2j** and **2k** has been extended for 160 h

*Methyl 2-(2-(4-bromophenyl)-4-chloropiperidin-1-yl)acetate **3a*** (98%, 136 mg, dr: 57:43)

Cis **3a**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 3.94 (tt, *J* = 11.7, 4.3 Hz, 1 H), 3.63 (dd, *J* = 12.1, 2.2 Hz, 1 H), 3.61 (s, 3 H), 3.08 (ddd, *J* = 12.1, 4.1, 2.8 Hz, 1 H), 3.07 (ABq, 2 H), 2.66 (td, *J* = 12.1, 2.2 Hz, 1 H), 2.24-2.15 (m, 2 H), 2.06 (qd, *J* = 12.1, 4.1 Hz, 1 H), 1.89 (q, *J* = 12.1 Hz, 1 H). ^{13}**C** NMR ($CDCl_3$, 75 MHz): δ = 171.1 (C), 141.1 (C), 132.1 (2 × C), 129.5 (2 × C), 121.7 (C), 64.9 (C), 56.5 (C), 54.9 (C), 52.4 (C), 51.5 (C), 45.9 (C), 36.8 (C). ESI-HRMS calculated for $C_{14}H_{17}NO_2ClBrNa$ $[M+Na]^+$ 368.0029, found 368.0032. *Trans* **3a**: Yellow oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 4.53 (quint, *J* = 3.0 Hz, 1 H), 3.95 (dd, *J* = 10, 3.8 Hz, 1 H), 3.64 (s, 3 H), 3.11 (ABq, 2 H), 3.05-2.92 (m, 2 H-H), 2.32-2.21 (m, 1 H), 2.10-1.95 (m, 3 H). ^{13}**C** NMR ($CDCl_3$, 75 MHz): δ = 171.3 (C), 141.6 (C), 132.1 (2 × C), 129.7(2 × C), 121.5 (C), 60.0 (C), 57.0 (C), 56.0 (C), 51.6 (C), 47.4 (C), 43.1 (C), 33.4 (C). ESI-HRMS calculated for $C_{14}H_{17}NO_2ClBrNa$ $[M+Na]^+$ 368.0028, found 368.0028.

*Methyl 2-(4-chloro-2-phenylpiperidin-1-yl)acetate **3b*** (94%, 100 mg, dr: 57:43)

Cis **3b**: Yellow oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.33-7.26 (m, 5 H), 3.96 (tt, *J* = 11.7, 4.3 Hz, 1 H), 3.62 (dd, *J* = 10.9, 2.6 Hz, 1 H), 3.60 (s, 3 H), 3.10 (ddd, *J* = 11.9, 4.1, 2.9 Hz, 1 H), 3.08 (ABq, 2 H), 2.66 (td, *J* = 12.0, 2.6 Hz, 1 H), 2.21 (m, 2 H), 2.07 (qd, *J* = 12.0, 4.2 Hz, 1 H), 1.96 (q, *J* = 12.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.3 (C), 142.0 (C), 128.9 (2 × CH), 128.0 (CH), 127.7 (2 × CH), 65.7 (CH), 56.9 (CH), 55.0 (CH_2), 52.5 (CH_2), 51.4 (CH_3), 46.0 (CH_2), 36.9 (CH_2). ESI-HRMS calculated for $C_{14}H_{18}NO_2ClNa$ $[M+Na]^+$ 290.0924, found 290.0922. *Trans* **3b**: Yellow oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.38-7.25 (m, 5 H), 4.54 (quint, *J* = 2.9 Hz, 1 H), 3.94 (dd, *J* = 10.8, 3.0 Hz, 1

H), 3.63 (s, 3 H), 3.11 (ABq, 2 H), 3.01-2.91 (m, 2 H), 2.30-2.28 (m, 1 H), 2.17-1.96 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.4 (C), 142.4 (C), 128.9 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 60.7 (CH), 57.3 (CH), 56.1 (CH_2), 51.5(CH_3), 47.5 (CH_2), 43.1(CH_2), 33.5 (CH_2). ESI-HRMS calculated for $C_{14}H_{18}NO_2ClNa$ $[M+Na]^+$ 290.0924, found 290.0926.

Methyl 2-(4-chloro-2-(2-chlorophenyl)piperidin-1-yl)acetate ***3c*** (86%, 103 mg, dr: 86:14)

Cis **3c***:* Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.61 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.33 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.28 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.18 (td, *J* = 7.9, 1.7 Hz, 1 H), 4.10 (dd, *J* = 11.2, 3.1 Hz, 1 H), 3.97 (tt, *J* = 11.7, 4.3 Hz, 1 H), 3.63 (s, 3 H), 3.18 (dt, *J* = 11.8, 3.5 Hz, 1 H), 3.08 (ABq, 2 H), 2.60 (td, *J* = 12.0, 2.5 Hz, 1 H), 2.32-2.19 (m, 2 H), 2.06 (qd, *J* = 12.1, 4.1 Hz, 1 H), 1.79 (q, *J* = 12.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.1 (C), 139.2 (C), 133.2 (C), 129.8(CH), 128.8 (CH), 128.6 (CH), 127.7 (CH), 61.2 (CH), 56.4 (CH), 55.3 (CH_2), 52.8 (CH_2), 51.6 (CH_3), 44.5 (CH_2), 36.7 (CH_2). ESI-HRMS calculated for $C_{14}H_{17}NO_2Cl_2Na$ $[M+Na]^+$ 324.0534, found 324.0536. *Trans* **3c***:* Yellow oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.62 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.33 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.26 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.17 (td, *J* = 7.9, 1.7 Hz, 1 H), 4.53 (quint, *J* = 4.5 Hz, 1 H), 4.46 (dd, *J* = 11.0, 2.9 Hz, 1 H), 3.66 (s, 3 H), 3.09 (ABq, 2 H), 3.01-2.96 (m, 2 H), 2.29-2.22 (m, 1 H), 2.13-2.08 (m, 1 H), 2.02-1.87 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.4 (C), 139.9 (C), 133.6 (C), 129.9 (CH), 128.9 (CH), 128.5 (CH), 127.6 (CH), 56.8 (CH), 56.4 (CH), 56.4 (CH_2), 51.7 (CH_3), 47.7 (CH_2), 41.7 (CH_2), 33.4 (CH_2). ESI-HRMS calculated for $C_{14}H_{17}NO_2Cl_2Na$ $[M+Na]^+$ 324.0534, found 324.0535.

Methyl 2-(4-chloro-2-(4-cyanophenyl)piperidin-1-yl)acetate ***3d*** (96%, 112 mg, dr: 42:58)

Cis **3d***:* Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.64 (d, *J* = 8.3 Hz, 2 H), 7.47 (d, *J* = 8.3 Hz, 2 H), 3.95 (tt, *J* = 11.7, 4.2 Hz, 1 H), 3.78 (dd, *J* = 12.1, 2.4 Hz, 1 H), 3.62 (s, 3 H), 3.10 (ddd, *J* = 11.9, 3.9, 2.9 Hz, 1 H), 3.06 (ABq, 2 H), 2.70 (td, *J* = 12.1, 2.3 Hz, 1 H), 2.26-2.16 (m, 2 H), 2.04 (qd, *J* = 12.1, 4.2 Hz, 1 H), 1.86 (q, *J* = 11.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.8 (C), 147.6 (C), 132.8 (2 × CH), 128.5 (2 × CH), 118.7 (C), 111.8 (C), 65.0 (CH), 56.2 (CH), 54.8 (CH_2), 52.2 (CH_2), 51.5 (CH_3), 45.7 (CH_2), 36.6 (CH_2). ESI-HRMS calculated for $C_{15}H_{17}N_2O_2ClNa$ $[M+Na]^+$ 315.0876, found 315.0877. *Trans* **3d***:* Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.64 (d, *J* = 8.6 Hz, 2 H), 7.51

(d, *J* = 8.6 Hz, 2 H), 4.53 (quint, *J* = 2.9 Hz, 1 H), 4.07 (t, *J* = 6.8 Hz, 1 H), 3.65 (s, 3 H), 3.07 (ABq, 2 H), 3.02 (td, *J* = 11.6, 3.0 Hz, 1 H), 2.98-2.93 (m, 1 H), 2.27-2.22 (m, 1 H), 2.02-1.98 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.0 (C), 148.3 (C), 132.7 (2 × CH), 128.6 (2 × CH), 117.7 (C), 111.6 (C), 60.1 (CH), 56.5 (CH), 56.0 (CH_2), 51.6 (CH_3), 47.1 (CH_2), 43.0 (CH_2), 33.2 (CH_2). ESI-HRMS calculated for $C_{15}H_{17}N_2O_2ClNa$ $[M+Na]^+$ 315.0876, found 315.0876.

Methyl 2-(4-chloro-2-(4-nitrophenyl)piperidin-1-yl)acetate ***3e*** (90%, 111 mg, dr: 38:62)

Cis **3e***:* Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.20 (d, *J* = 8.8 Hz, 2 H), 7.53 (d, *J* = 8.6 Hz, 2 H), 3.96 (tt, *J* = 11.7, 4.3 Hz, 1 H), 3.86 (dd, *J* = 11.4, 2.5 Hz, 1 H), 3.62 (s, 3 H), 3.11 (ddd, *J* = 11.9, 4.1, 3.0 Hz, 1 H), 3.07 (ABq, 2 H), 2.72 (td, *J* = 12.2, 2.5 Hz, 1 H), 2.28-2.17 (m, 2 H), 2.07 (qd, *J* = 12.2, 4.1 Hz, 1 H), 1.88 (q, *J* = 11.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.8 (C), 149.6 (C), 147.7 (C), 128.6 (2 × CH), 124.3 (2 × CH), 64.7 (CH), 56.1 (CH), 54.8 (CH_2), 52.2 (CH_2), 51.6 (CH_3), 45.8 (CH_2), 36.7 (CH_2). ESI-HRMS calculated for $C_{14}H_{17}N_2O_4ClNa$ $[M+Na]^+$ 335.0775, found 335.0775. *Trans* **3e***:* Orange solid M.p. 112-114 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.20 (d, *J* = 8.8 Hz, 2 H), 7.59 (d, *J* = 8.6 Hz, 2 H), 4.54 (quint, *J* = 3.0 Hz, 1 H), 4.15 (t, *J* = 7.0 Hz, 1 H), 3.65 (s, 3 H), 3.08 (ABq, 2 H), 3.05-2.94 (m, 2 H), 2.28-2.22 (m, 1 H), 2.04-2.00 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.0 (C), 150.4 (C), 147.6 (C), 128.7 (2 × CH), 124.2 (2 × CH), 59.9 (CH), 56.5 (CH), 56.0 (CH_2), 51.6 (CH_3), 47.1 (CH_2), 43.1 (CH_2), 33.2 (CH_2). ESI-HRMS calculated for $C_{14}H_{17}N_2O_4ClNa$ $[M+Na]^+$ 335.0775, found 335.0775.

Methyl 2-(4-chloro-2-(3-nitrophenyl)piperidin-1-yl)acetate ***3f*** (97%, 122 mg, dr: 45:55)

Cis **3f***:* Yellow solid M.p. 98-100 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.21 (s, 1 H), 8.15 (d, *J* = 8.1 Hz, 1 H), 7.71 (d, *J* = 7.6 Hz, 1 H), 7.53 (t, *J* = 7.9 Hz, 1 H), 3.97 (tt, *J* = 11.7, 4.3 Hz, 1 H), 3.86 (dd, *J* = 11.4, 2.3 Hz, 1 H), 3.62 (s, 3 H), 3.11 (ddd, *J* = 11.7, 3.9, 2.6 Hz, 1 H), 3.09 (ABq, 2 H), 2.72 (td, *J* = 12.2, 2.3 Hz, 1 H), 2.26-2.22 (m, 2 H), 2.06 (qd, *J* = 12.2, 4.1 Hz, 1 H), 1.90 (q, *J* = 11.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.8 (C), 148.7 (C), 144.4 (C), 133.8 (CH), 130.0 (CH), 123.1 (CH), 122.8 (CH), 64.5 (CH), 56.1 (CH), 54.8 (CH_2), 52.2 (CH_2), 51.5 (CH_3), 46.0 (CH_2), 36.7 (CH_2). ESI-HRMS calculated for $C_{14}H_{17}N_2O_4ClNa$ $[M+Na]^+$ 335.0775, found 335.0777. *Trans* **3f**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.26 (t, *J* = 1.1 Hz, 1 H), 8.14 (qd, *J* = 8.1 , 1.1 Hz, 1 H), 7.75 (d, *J* = 7.7

Hz, 1 H), 7.52 (d, *J* = 7.9 Hz, 1 H), 4.55 (quint, *J* = 2.9 Hz, 1 H), 4.17 (t, *J* = 7.0 Hz, 1 H), 3.65 (s, 3 H), 3.09 (dt, *J* = 11.9, 2.5 Hz, 1 H), 3.08 (ABq, 2 H), 2.98-2.92 (m, 1 H), 2.33-2.23(m, 1 H), 2.07-2.03 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.9 (C), 148.7 (C), 145.0 (C), 134.1 (CH), 129.9 (CH), 129.9 (CH), 122.9 (CH), 59.7 (CH), 56.6 (CH), 56.0 (CH_2), 51.6 (CH_3), 47.1 (CH_2), 43.2 (CH_2), 33.3 (CH_2). ESI-HRMS calculated for $C_{14}H_{17}N_2O_4ClNa$ $[M+Na]^+$ 335.0775, found 335.0775.

Methyl 2-(4-chloro-2-(4-(dimethylamino)phenyl)piperidin-1-yl)acetate ***3g*** (60%, 75 mg, dr: 50:50)

Cis **3g***:* White solid M.p. 88-90 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.17 (d, *J* = 8.7 Hz, 2 H), 6.68 (d, *J* = 8.7 Hz, 2 H), 3.95 (tt, *J* = 11.7, 4.4 Hz, 1 H), 3.60 (s, 3 H), 3.48 (dd, *J* = 11.4, 2.4 Hz, 1 H), 3.10 (ABq, 2 H), 3.09 (dt, *J* = 11.8, 3.4 Hz, 1 H), 2.94 (s, 6 H), 2.61 (td, *J* = 12.0, 2.4 Hz, 1 H), 2.22-2.17 (m, 2 H), 2.12-1.93 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.5 (C), 150.3 (C), 129.5 (C), 128.5 (2 × CH), 112.7 (2 × CH), 65.2 (CH), 57.2 (CH), 54.9 (CH_2), 52.5 (CH_2), 51.3 (CH_3), 45.8 (CH_2), 40.7 (2 × CH_3), 36.9 (CH_2). ESI-HRMS calculated for $C_{16}H_{23}N_2O_2ClNa$ $[M+Na]^+$ 333.1346, found 333.1345. *Trans* **3g***:* Brown solid M.p. 60-62 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.20 (d, *J* = 8.8 Hz, 2 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 4.54 (quint, *J* = 2.9 Hz, 1 H), 3.80 (dd, *J* = 10.9, 2.8 Hz, 1 H), 3.62 (s, 3 H), 3.11 (ABq, 2 H), 2.94-2.89 (m, 8 H), 2.32-2.22 (m, 1 H), 2.17-2.08 (m, 1 H), 2.02-1.93 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.7 (C), 150.2 (C), 129.9 (C), 128.7 (2 × CH), 112.7 (2 × CH), 60.0 (CH), 57.8 (CH), 56.1 (CH_2), 51.4 (CH_3), 47.6 (CH_2), 42.9 (CH_2), 40.7 (2 × CH_3), 33.6 (CH_2). ESI-HRMS calculated for $C_{16}H_{23}N_2O_2ClNa$ $[M+Na]^+$ 333.1346, found 333.1348.

Methyl 2-(4-chloro-2-(2,5-dimethoxyphenyl)piperidin-1-yl)acetate ***3h*** (92%, 120 mg, dr: 87:13)

Cis **3h**: Yellow solid M.p. 78-80 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.10 (d, *J* = 2.85 Hz, 1 H), 6.81-6.73 (m, 2 H), 3.98-3.92 (m, 2 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.62 (s, 3 H), 3.16 (dt, *J* = 11.7, 3.5 Hz, 1 H), 3.07 (ABq, 2 H), 2.52 (td, *J* = 12.0, 2.0 Hz, 1 H), 2.26-2.17 (m, 2 H), 2.08 (qd, *J* = 12.0, 4.0 Hz, 1 H), 1.87 (q, *J* = 12.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.4 (C), 154.3 (C), 151.0 (C), 130.9 (C), 113.9 (CH), 112.9 (CH), 112.2 (CH), 58.1 (CH), 56.9 (CH), 56.1(CH_3), 55.8 (CH_3), 55.6 (CH_2), 53.2 (CH_2), 51.5 (CH_3), 44.6 (CH), 36.7 (CH). ESI-HRMS calculated for $C_{16}H_{22}NO_4ClNa$ $[M+Na]^+$ 350.1135, found 350.1139. *Trans* **3h**: Yellow solid M.p. 72-74 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.11 (d, *J* = 3.00 Hz, 1 H), 6.81-6.75 (m, 2 H), 4.53 (quint, *J* = 2.9 Hz, 1 H), 4.32 (dd, *J* =

7.7, 5.9 Hz, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.64 (s, 3 H), 3.10 (ABq, 2 H), 2.99-2.86 (m, 2 H), 2.29-2.24 (m, 1 H), 2.03-2.01 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.8 (C), 154.3 (C), 151.5 (C), 131.6 (C), 113.7 (CH), 113.1 (CH), 112.5 (CH), 57.5 (CH), 56.6 (CH_2), 56.5 (CH), 55.9 (CH_3), 53.0 (CH_3), 51.6 (CH_3), 48.1 (CH_2), 41.7 (CH_2), 33.5 (CH_2). ESI-HRMS calculated for $C_{16}H_{22}NO_4ClNa$ $[M+Na]^+$ 350.1135, found 350.1144.

Methyl 2-(4-chloro-2-(2-methoxyphenyl)piperidin-1-yl)acetate ***3i*** (65%, 78 mg, dr: 85:15)

Cis **3i***:* Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.50 (dd, *J* = 7.5, 1.7 Hz, 1 H), 7.22 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1 H), 6.97 (td, *J* = 8.2, 1.0 Hz, 1 H), 6.85 (dd, *J* = 8.2, 1.0 Hz, 1 H), 4.00-3.95 (m, 2 H), 3.80 (s, 3 H), 3.61 (s, 3 H), 3.18 (dt, *J* = 11.8, 3.4 Hz, 1 H), 3.06 (Abq, 2 H), 2.52 (td, *J* = 12.0, 2.5 Hz, 1 H), 2.23-2.13 (m, 2 H), 2.08 (qd, *J* = 12.1, 4.0 Hz, 1 H), 1.89 (q, *J* = 12.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.5 (C), 156.8 (C), 129.8 (C), 128.4 (CH), 128.0 (CH), 121.2 (CH), 110.7 (CH), 57.9 (CH), 57.0 (CH), 55.6 (CH_2), 55.5 (CH_3), 53.2 (CH_2), 51.5 (CH_3), 44.6 (CH_2), 36.8 (CH_2). ESI-HRMS calculated for $C_{15}H_{21}NO_3Cl$ $[M+H]^+$ 298.1210 , found 298.1211. *Trans* **3i***:* Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.50 (dd, *J* = 7.5, 1.7 Hz, 1 H), 7.22 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1 H), 6.95 (td, *J* = 8.2, 1.0 Hz, 1 H), 6.86 (dd, *J* = 8.2, 1.0 Hz, 1 H), 4.54 (quint, *J* = 2.8 Hz, 1 H), 4.35 (m, 1 H), 3.82 (s, 3 H), 3.63 (s, 3 H), 3.09 (ABq, 2 H), 3.02-2.86 (m, 2 H), 2.34-2.26 (m, 1 H), 2.06-1.95 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.7 (C), 157.3 (C), 130.3 (C), 128.3 (CH), 128.3 (CH), 121.2 (CH), 110.8 (CH), 57.5 (CH), 56.5 (CH_2), 55.7 (CH_3), 52.8 (CH), 51.6 (CH_3), 48.2 (CH_2), 41.5 (CH_2), 33.5 (CH_2). ESI-HRMS calculated for $C_{15}H_{21}NO_3Cl$ $[M+H]^+$ 298.1210 , found 298.1209.

Methyl 2-(4-chloro-2-(4-methoxyphenyl)piperidin-1-yl)acetate ***3j*** (60%, 71 mg, dr: 62:38)

Cis **3j**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.23 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 3.95 (tt, *J* = 11.8, 4.3 Hz, 1 H), 3.80 (s, 3 H), 3.60 (s, 3 H), 3.56 (dd, *J* = 11.3, 2.3 Hz, 1 H), 3.09 (dt, *J* = 11.7, 3.4 Hz, 1 H), 3.08 (ABq, 2 H), 2.67 (td, *J* = 12.1, 2.4 Hz, 1 H), 2.22-2.17 (m, 2 H), 2.05 (qd, *J* = 12.1, 4.2 Hz, 1 H), 1.95 (q, *J* = 12.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.4 (C), 159.3 (C), 134.0 (C), 128.8 (2 × CH), 114.2 (2 × CH), 65.0 (CH), 57.0 (CH), 55.4 (CH_3), 54.9 (CH_2), 52.5 (CH_2), 51.4 (CH_3), 46.0 (CH_2), 36.9 (CH_2). ESI-HRMS calculated for $C_{15}H_{20}NO_3ClNa$ $[M+Na]^+$ 320.1029, found 320.1028. *Trans* **3j**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.27 (d, *J* = 8.7 Hz,

2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 4.54 (quint, *J* = 3.0 Hz, 1 H), 3.87 (dd, *J* = 11.0, 2.4 Hz, 1 H), 3.79 (s, 3 H), 3.63 (s, 3 H), 3.10 (ABq, 2 H), 2.98-2.94 (m, 2 H), 2.32-2.21 (m, 1 H), 2.15-1.94 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.6 (C), 159.2 (C), 134.4 (C), 129.0 (2 × CH), 114.2 (2 × CH), 59.9 (CH), 57.6 (CH), 56.1 (CH_2), 55.4 (CH_3), 51.5 (CH_3), 47.6 (CH_2), 43.1 (CH_2), 33.6 (CH_2). ESI-HRMS calculated for $C_{15}H_{20}NO_3ClNa$ $[M+Na]^+$ 320.1029, found 320.1027.

Methyl 2-(4-chloro-2-p-tolylpiperidin-1-yl)acetate ***3k*** (74%, 83 mg, dr: 62:38)

Cis **3k**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.23 (d, *J* = 7.9 Hz, 2 H), 7.15 (d, *J* = 7.9 Hz, 2 H), 3.94 (tt, *J* = 11.7, 4.4 Hz, 1 H), 3.61 (s, 3 H), 3.60 (d, *J* = 7.7 Hz, 1 H), 3.12 (dt, *J* = 11.8, 3.4 Hz, 1 H), 3.10 (ABq, 2 H), 2.67 (td, *J* = 12.0, 2.1 Hz, 1 H), 2.34 (s, 3 H), 2.25-2.18 (m, 2 H), 2.09 (qd, *J* = 11.9, 4.0 Hz, 1 H), 2.00 (q, *J* = 12.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.3 (C), 138.8 (C), 137.7 (C), 129.6 (2 × CH), 127.6 (2 × CH), 65.4 (CH), 56.9 (CH), 54.9 (CH_2), 52.5 (CH_2), 51.4 (CH_3), 45.9 (CH_2), 36.8 (CH_2), 21.2 (CH_3). ESI-HRMS calculated for $C_{15}H_{21}NO_2Cl$ $[M+H]^+$ 282.1261 , found 282.1264. *Trans* **3k**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.24 (d, *J* = 7.9 Hz, 2 H), 7.13 (d, *J* = 7.9 Hz, 2 H), 4.54 (quint, *J* = 2.9 Hz, 1 H), 3.87 (dd, *J* = 10.8, 2.9 Hz, 1 H), 3.63 (s, 3 H), 3.11 (ABq, 2 H), 2.95-2.90 (m, 2 H), 2.32 (s, 3 H), 2.29-2.21 (m, 1 H), 2.15-2.06 (m, 1 H), 2.02-1.95 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.6 (C), 139.5 (C), 137.4 (C), 129.5 (2 × CH), 127.8 (2 × CH), 60.3 (CH), 57.5 (CH), 56.2 (CH_2), 51.5 (CH_3), 47.5 (CH_2), 43.1 (CH_2), 33.5 (CH_2), 21.2 (CH_3). ESI-HRMS calculated for $C_{15}H_{21}NO_2Cl$ $[M+H]^+$ 282.1261 , found 282.1264.

Methyl 2-(4-chloro-2-isopropylpiperidin-1-yl)acetate ***3l*** (86%, 80 mg, dr: 43:57)

Cis **3l**: Yellow oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.87 (tt, *J* = 11.8, 4.3 Hz, 1 H), 3.69 (s, 3 H), 3.41 (ABq, 2 H), 2.91 (ddd, *J* = 12.0, 4.6, 2.5 Hz, 1 H), 2.77 (td, *J* = 12.1, 2.6 Hz, 1 H), 2.55 (ddd, *J* = 11.4, 3.9, 2.0 Hz, 1H), 2.11-2.01 (m, 2 H), 1.96-1.79 (m, 2 H), 1.50 (q, *J* = 11.9 Hz, 1 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.6 (C), 63.4 (CH), 58.4 (CH), 53.1 (CH_2), 52.9 (CH_2), 51.5 (CH_3), 36.6 (CH_2), 35.5 (CH_2), 27.9 (CH), 20.0 (CH_3), 15.2 (CH_3). ESI-HRMS calculated for $C_{11}H_{21}NO_2Cl$ $[M+H]^+$ 234.1261, found 234.1263. *Trans* **3l**: Yellow oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.50 (quint, *J* = 3.6 Hz, 1 H), 3.72 (s, 3 H), 3.42 (ABq, 2 H), 3.09 (td, *J* = 11.8, 2.8 Hz, 1 H), 2.85 (ddd, *J* = 9.8, 4.9, 3.0 Hz, 1 H), 2.76 (dt, *J* = 12.0, 4.1 Hz, 1 H), 2.05-1.97 (m,

2 H), 1.87-1.81 (m, 2 H), 1.76 (qd, *J* = 9.8, 3.4 Hz, 1 H), 0.90 (d, *J* = 6.8 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.9 (C), 58.9 (CH), 57.9 (CH), 54.3 (CH_2), 51.6 (CH_3), 47.9 (CH_2), 33.1 (CH_2), 32.1 (CH_2), 27.3 (CH), 19.9 (CH_3), 15.9 (CH_3). ESI-HRMS calculated for $C_{11}H_{21}NO_2Cl$ $[M+H]^+$ 234.1261, found 234.1259.

Methyl 2-(4-chloro-2-phenethylpiperidin-1-yl)acetate ***3m*** (52%, 61 mg, dr: 62:38)

Cis **3m**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.31-7.26 (m, 2 H), 7.21-7.16 (m, 3 H) 3.89 (tt, *J* = 11.7, 4.4 Hz, 1 H), 3.68 (s, 3 H), 3.42 (ABq, 2 H), 2.96 (ddd, *J* = 12.2, 4.2, 2.9 Hz, 1 H), 2.77-2.52 (m, 4 H), 2.22 (dquint, *J* = 12.6, 2.2 Hz, 1 H), 2.09 (dsex, *J* = 12.6, 2.2 Hz, 1 H), 1.93-1.86 (m, 2 H), 1.77-1.65 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.4 (C), 142.0 (C), 128.6 (2 × CH), 128.4 (2 × CH), 126.1 (CH), 58.5 (CH), 57.5 (CH), 53.2 (CH_2), 52.9 (CH_2), 51.6 (CH_3), 41.3 (CH_2), 36.2 (CH_2), 34.9 (CH_2), 31.0 (CH_2). ESI-HRMS calculated for $C_{16}H_{23}NO_2Cl$ $[M+H]^+$ 296.1417 , found 296.1425.

Trans **3m**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.31-7.26 (m, 2 H), 7.21-7.16 (m, 3 H), 4.43 (quint, *J* = 4.2 Hz, 1 H), 3.70 (s, 3 H), 3.40 (ABq, 2 H), 3.06-2.95 (m, 2 H), 2.80-2.56 (m, 3 H), 2.09-2.02 (m, 2 H), 1.97-1.89 (m, 3 H), 1.77-1.70 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.6 (C), 142.1 (C), 128.6 (2 × CH), 128.5 (2 × CH), 126.0 (CH), 57.0 (CH), 54.8 (CH), 54.8 (CH_2), 51.8 (CH_3), 47.8 (CH_2), 38.1 (CH_2), 33.5 (CH_2), 33.0 (CH_2), 31.6 (CH_2). ESI-HRMS calculated for $C_{16}H_{23}NO_2Cl$ $[M+H]^+$ 296.1417 , found 296.1414.

Methyl 2-(4-chloro-2-heptylpiperidin-1-yl)acetate ***3n*** (78%, 90 mg, dr: 62:38)

Cis **3n**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.88 (tt, *J* = 11.7, 4.3 Hz, 1 H), 3.70 (s, 3 H), 3.41 (s, 2 H), 2.94 (dt, *J* = 12.1, 3.0 Hz, 1 H), 2.69 (ddd, *J* = 12.1, 4.2, 2.8 Hz, 1 H), 2.66-2.62 (m, 1 H), 2.18-2.04 (m, 2 H), 1.89 (qd, *J* = 12.2, 4.3 Hz, 1 H), 1.60 (q, *J* = 11.9 Hz, 1 H), 1.26 (s, 12 H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.5 (C), 59.1 (CH), 57.7 (CH), 53.4 (CH_2), 53.0 (CH_2), 51.6 (CH_3), 41.4 (CH_2), 36.3 (CH_2), 33.2 (CH_2), 31.9 (CH_2), 30.0 (CH_2), 29.3 (CH_2), 24.9 (CH_2), 22.8 (CH_2), 14.2 (CH_3). ESI-HRMS calculated for $C_{15}H_{28}NO_2ClNa$ $[M+Na]^+$ 312.1706, found 312.1714. *Trans* **3n**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.42 (quint, *J* = 4.0 Hz, 1 H), 3.73 (s, 3 H), 3.42 (ABq, 2 H), 3.05-2.98 (m, 2 H), 2.77 (dt, *J* = 11.9, 4.3 Hz, 1H), 2.11-2.07 (m, 1 H), 1.96-1.85 (m, 3 H), 1.26 (s, 12 H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.5 (C), 57.1

(CH), 55.1 (CH), 54.8 (CH_2), 51.8 (CH_3), 47.8 (CH_2), 38.2 (CH_2), 33.6 (CH_2), 31.9 (CH_2), 31.2 (CH_2), 30.0 (CH_2), 29.4 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 14.2 (CH_3). ESI-HRMS calculated for $C_{15}H_{28}NO_2ClNa$ $[M+Na]^+$ 312.1706, found 312.1706.

2-(4-bromophenyl)-4-chloro-1-(4-methoxyphenyl)piperidine ***5a*** (99%, 151 mg, dr: 12:88)

Cis **5a**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.27 (d, *J* = 8.9 Hz, 2 H), 7.10 (d, *J* = 8.9 Hz, 2 H), 6.86 (d, *J* = 8.3 Hz, 2 H), 6.64 (d, *J* = 8.3 Hz, 2 H), 4.02 (tt, *J* = 11.7, 4.3 Hz, 1 H), 3.91 (dd, *J* = 11.1, 2.6 Hz, 1 H), 3.67 (s, 3 H), 3.36 (dt, *J* = 12.4, 3.6 Hz, 1 H), 2.79 (td, *J* = 12.1, 3.0 Hz, 1 H), 2.37-2.18 (m, 2 H), 2.17 (qd, *J* = 12.1, 4.1 Hz, 1 H), 1.96 (q, *J* = 12.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.0 (C), 144.5 (C), 142.2 (C), 131.5 (2 × CH), 129.3 (2 × CH), 125.7 (2 × CH), 120.5 (C), 114.0 (2 × CH), 64.6 (CH), 57.5 (CH_2), 56.8 (CH), 55.3 (CH_3), 46.9 (CH_2), 37.5 (CH_2). ESI-HRMS calculated for $C_{18}H_{20}NOClBr$ $[M+H]^+$ 380.0417 , found 380.0418. *Trans* **5a**: Black solid M.p. 106-108 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.29 (d, *J* = 8.5 Hz, 2 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 6.92 (d, *J* = 9.0 Hz, 2 H), 6.68 (d, *J* = 9.0 Hz, 2 H), 4.51-4.47 (m, 2 H), 3.70 (s, 3 H), 3.35 (td, *J* = 10.9, 2.8 Hz, 1 H), 3.16 (dt, *J* = 12.3, 4.1 Hz, 1 H), 2.36-2.26 (m, 1 H), 2.17-2.14 (m, 2 H), 2.03 (dd, *J* = 14.0, 3.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.4 (C), 145.2 (C), 142.3 (C), 131.5 (2 × CH), 129.4 (2 × CH), 124.4 (2 × CH), 120.4 (C), 114.1 (2 × CH), 58.7 (CH), 56.9 (CH), 55.4 (CH_3), 50.7 (CH_2), 43.4 (CH_2), 34.5 (CH_2). ESI-HRMS calculated for $C_{18}H_{20}NOClBr$ $[M+H]^+$ 380.0417 , found 380.0416.

4-chloro-1-(4-methoxyphenyl)-2-phenylpiperidine ***5b*** (93%, 113 mg, dr: 23:77)

Cis **5b**: Yellow solid M.p. 78-80 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.26-7.06 (m, 5 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 6.63 (d, *J* = 9.0 Hz, 2 H), 4.01 (tt, *J* = 11.4, 4.5 Hz, 1 H), 3.93 (dd, *J* = 11.1, 2.7 Hz, 1 H), 3.65 (s, 3 H), 3.39 (dt, *J* = 12.4, 3.5 Hz, 1 H), 2.81 (td, *J* = 12.1, 3.1 Hz, 1 H), 2.40-2.34 (m, 1 H), 2.25-2.16 (m, 2 H), 2.02 (q, *J* = 11.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.8 (C), 144.9 (C), 143.1 (C), 128.3 (2 × CH), 127.6 (2 × CH), 126.9 (CH), 125.7 (2 × CH), 113.9 (2 × CH), 65.3 (CH), 57.6 (CH_2), 57.1 (CH), 55.3 (CH_3), 47.1 (CH_2), 37.6 (CH_2). ESI-HRMS calculated for $C_{18}H_{21}NOCl$ $[M+H]^+$ 302.1306, found 302.1305. *Trans* **5b**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.27-7.08 (m, 5 H), 6.92 (d, *J* = 9.0 Hz, 2 H), 6.67 (d, *J* = 9.0 Hz, 2 H), 4.57 (dd, *J* = 8.5, 3.9 Hz , 1 H), 4.46 (quint, *J* = 4.1 Hz , 1 H), 3.66 (s, 3 H), 3.39 (td, *J* = 11.3, 2.9 Hz, 1 H), 3.18 (dt, *J* = 12.6, 4.4 Hz, 1 H),

2.35-2.14 (m, 3 H), 2.06-1.99 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 154.9 (C), 145.4 (C), 142.8 (C), 128.4 (2 × CH), 127.6 (2 × CH), 126.7 (C), 123.6 (2 × CH), 114.1 (2 × CH), 59.2 (CH), 57.0 (CH), 55.4 (CH_3), 50.1 (CH_2), 43.1 (CH_2), 34.6 (CH_2). ESI-HRMS calculated for $C_{18}H_{21}NOCl$ $[M+H]^+$ 302.1306, found 302.1306.

4-chloro-2-(2-chlorophenyl)-1-(4-methoxyphenyl)piperidine ***5c*** (99%, 130 mg, dr: 28:72)

Cis **5c**: Yellow oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45-7.41 (m, 1 H), 7.23-7.20 (m, 1 H), 7.04-6.95 (m, 2 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 6.65 (d, *J* = 9.0 Hz, 2 H), 4.50 (dd, *J* = 11.0, 2.7 Hz, 1 H), 4.06 (tt, *J* = 11.6, 4.5 Hz, 1 H), 3.67 (s, 3 H), 3.45 (dt, *J* = 12.4, 3.6 Hz, 1 H), 2.79 (td, *J* = 12.2, 3.0 Hz, 1 H), 2.48-2.43 (m, 1 H), 2.27-2.24 (m, 1 H), 2.19 (qd, *J* = 12.0, 4.2 Hz, 1 H), 1.85 (q, *J* = 12.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.8 (C), 144.8 (C), 140.1 (C), 132.2 (C), 129.3 (CH), 129.2 (CH), 127.9 (CH), 127.2 (CH), 124.9 (2 × CH), 114.1 (2 × CH), 59.7 (CH), 58.0 (CH_2), 56.8 (CH), 55.3 (CH_3), 44.8 (CH_2), 37.6 (CH_2). ESI-HRMS calculated for $C_{18}H_{20}NOCl_2$ $[M+H]^+$ 336.0922 , found 336.0923. *Trans* **5c**: Yellow solid M.p. 96-98 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.42-7.38 (m, 1 H), 7.23-7.20 (m, 1 H), 7.01-6.97 (m, 2 H), 6.92 (d, *J* = 9.0 Hz, 2 H), 6.66 (d, *J* = 9.0 Hz, 2 H), 5.00 (dd, *J* = 10.4, 2.9 Hz, 1 H), 4.55 (quint, *J* = 3.2 Hz, 1 H), 3.65 (s, 3 H), 3.32-3.26 (m, 2 H), 2.37-2.23 (m, 2 H), 2.08-1.92 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.5 (C), 145.5 (C), 140.7 (C), 132.5 (C), 129.3 (CH), 129.3 (CH), 127.7 (CH), 127.0 (CH), 124.5 (2 × CH), 114.1 (2 × CH), 56.9 (CH), 55.3 (CH_3), 54.3 (CH), 52.1 (CH_2), 41.9 (CH_2), 34.4 (CH_2). ESI-HRMS calculated for $C_{18}H_{20}NOCl_2$ $[M+H]^+$ 336.0922 ,found 336.0919.

4-chloro-1-(4-methoxyphenyl)-2-(4-nitrophenyl)piperidine ***5d*** (92%, 131 mg, dr: 14:86)

Trans **5d**: Black solid M.p. 106-108 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.02 (d, *J* = 8.7 Hz, 2 H), 7.45 (d, *J* = 8.7 Hz, 2 H), 6.94 (d, *J* = 8.9 Hz, 2 H), 6.68 (d, *J* = 8.9 Hz, 2 H), 4.62 (dd, *J* = 9.6, 3.7 Hz, 1 H), 4.56 (quint, *J* = 3.3 Hz, 1 H), 3.68 (s, 3 H), 3.34 (td, *J* = 11.9, 2.7 Hz, 1 H), 3.19 (dt, *J* = 12.3, 3.9 Hz, 1 H), 2.39-2.30 (m, 1 H), 2.18-2.05 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.9 (C), 151.3 (C), 146.8 (C), 144.9 (C), 128.5 (2 × CH), 125.0 (2 × CH), 123.7 (2 × CH), 114.2 (2 × CH), 58.8 (CH), 56.6 (CH), 55.4 (CH_3), 51.2 (CH_2), 43.5 (CH_2), 34.2 (CH_2). ESI-HRMS calculated for $C_{18}H_{20}N_2O_3Cl$ $[M+H]^+$ 347.1157, found 347.1160.

4-chloro-1,2-bis(4-methoxyphenyl)piperidine ***5e*** (40%, 52 mg, dr: 20:80)

Trans **5e**: Orange solid M.p. 98-100 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.16 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.72 (d, *J* = 8.8 Hz, 2 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 4.53-4.46 (m, 2 H), 3.71 (s, 3 H), 3.68 (s, 3 H), 3.38 (td, *J* = 10.5, 2.7 Hz, 1 H), 3.17 (dt, *J* = 12.5, 4.4 Hz, 1 H), 2.29-2.17 (m, 3 H), 2.05-1.99 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.3 (C), 155.0 (C), 145.5 (C), 134.8 (C), 128.7 (2 × CH), 123.7 (2 × CH), 114.0 (2 × CH), 113.7 (2 × CH), 58.6 (CH), 57.1 (CH), 55.4 (CH_3), 55.2 (CH_3), 50.0 (CH_2), 43.1 (CH_2), 34.7 (CH_2). ESI-HRMS calculated for $C_{19}H_{23}NO_2Cl$ $[M+H]^+$ 332.1417, found 332.1417.

4-chloro-1-(4-methoxyphenyl)-2-p-tolylpiperidine ***5f*** (90%, 113 mg, dr: 22:78)

Cis **5f**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.10 (d, *J* = 7.9 Hz, 2 H), 6.95 (d, *J* = 7.9 Hz, 2 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 6.63 (d, *J* = 9.0 Hz, 2 H), 4.03 (tt, *J* = 11.4, 4.7 Hz, 1 H), 3.89 (dd, *J* = 11.1, 2.7 Hz, 1 H), 3.66 (s, 3 H), 3.38 (dt, *J* = 12.3, 3.5 Hz, 1 H), 2.79 (td, *J* = 12.0, 3.1 Hz, 1 H), 2.38-2.32 (m, 1 H), 2.24-2.15 (m, 5 H), 2.01 (q, *J* = 12.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.8 (C), 145.0 (C), 140.1 (C), 136.4 (C), 129.1 (2 × CH), 127.4 (2 × CH), 125.7 (2 × CH), 113.8 (2 × CH), 64.9 (CH), 57.6 (CH_2), 57.2 (CH), 55.3 (CH_3), 47.2 (CH_2), 37.6 (CH_2), 21.2(CH_3). ESI-HRMS calculated for $C_{19}H_{23}NOCl$ $[M+H]^+$ 316.1468, found 316.1465. *Trans* **5f**: Orange solid M.p. 102-104 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.14 (d, *J* = 7.9 Hz, 2 H), 6.98 (d, *J* = 7.9 Hz, 2 H), 6.92 (d, *J* = 9.0 Hz, 2 H), 6.68 (d, *J* = 9.0 Hz, 2 H), 4.55 (dd, *J* = 8.5, 3.7 Hz, 1 H), 4.44 (quint, *J* = 4.7 Hz, 1 H), 3.66 (s, 3 H), 3.38 (td, *J* = 10.0, 3.0 Hz, 1 H), 3.18 (dt, *J* = 12.6, 4.6 Hz, 1 H), 2.29-2.13 (m, 6 H), 2.04-2.00 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.8 (C), 145.5 (C), 139.7 (C), 136.2 (C), 129.1 (2 × CH), 127.5 (2 × CH), 123.4 (2 × CH), 114.1 (2 × CH), 58.9 (CH), 57.0 (CH), 55.4 (CH_3), 49.9 (CH_2), 43.1 (CH_2), 34.7 (CH_2), 21.1 (CH_3). ESI-HRMS calculated for $C_{19}H_{23}NOCl$ $[M+H]^+$ 316.1468, found 316.1468.

4-chloro-2-isopropyl-1-(4-methoxyphenyl)piperidine ***5g*** (98%, 105 mg, dr: 9:91)

Cis **5g**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.07 (d, *J* = 8.9 Hz, 2 H), 6.84 (d, *J* = 8.9 Hz, 2 H), 3.99 (tt, *J* = 11.5, 4.3 Hz, 1 H), 3.79 (s, 3 H), 3.07 (dt, *J* = 12.2, 3.6 Hz, 1 H), 2.75-2.67 (m, 2 H), 2.15-2.13 (m, 2 H), 1.99 (qd, *J* = 12.0, 4.3 Hz, 1 H), 1.71 (q, *J* = 11.5 Hz, 1 H), 1-70-1.65 (m, 1 H),

0.78 (t, *J* = 7.2 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.9 (C), 144.8 (C), 126.5 (2 × CH), 114.4 (2 × CH), 65.0 (CH), 58.7 (CH), 56.9 (CH_2), 55.5 (CH_3), 37.5 (CH_2), 35.7 (CH_2), 28.2 (CH), 19.7 (CH_3), 15.1 (CH_3). ESI-HRMS calculated for $C_{15}H_{23}NOCl$ $[M+H]^+$ 268.1468, found 268.1465. *Trans* **5g**: Orange oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.93 (d, *J* = 9.1 Hz, 2 H), 6.82 (d, *J* = 9.1 Hz, 2 H), 4.37 (sp, *J* = 4.1 Hz 1 H), 3.76 (s, 3 H), 3.44 (dt, *J* = 13.8, 4.7 Hz, 1 H), 3.30 (m, 1 H), 3.03 (m, 1 H), 2.13-2.07 (m, 2 H), 1.96-1.86 (m, 3 H), 0.89 (d, *J* = 6.7 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.8 (C), 145.3 (C), 120.4 (2 × CH), 114.6 (2 × CH), 62.5 (CH), 56.7 (CH), 55.7 (CH_3), 46.0 (CH_2), 34.7 (CH_2), 34.5 (CH_2), 27.5 (CH), 20.4 (CH_3), 18.6 (CH_3). ESI-HRMS calculated for $C_{15}H_{23}NOCl$ $[M+H]^+$ 268.1468, found 268.1466.

2-(4-bromophenyl)-4-chloropiperidine ***cis*** **7a** Yellow solid (77%, 84 mg)

M.p. 64-66 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 3.99 (tt, *J* = 11.7, 4.3 Hz, 1 H), 3.61 (dd, *J* = 11.4, 2.5 Hz, 1 H), 3.23 (ddd, *J* = 12.2, 2.5, 1.7 Hz, 1 H), 2.79 (td, *J* = 12.2, 2.5 Hz, 1 H), 2.30-2.17 (m, 2 H), 1.84 (ddd, *J* = 12.2, 4.6, 2.3 Hz, 1 H), 1.82 (s, NH), 1.76 (q, *J* = 12.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 142.4 (C), 131.8 (2 × CH), 128.5 (2 × CH), 121.4 (C), 61.0 (CH), 57.4 (CH), 46.4 (CH_2), 45.3 (CH_2), 36.8 (CH_2). ESI-HRMS calculated for $C_{11}H_{14}NClBr$ $[M+H]^+$ 273.9998, found 273.9998.

4-chloro-2-phenylpiperidine ***cis*** **7b**[10a] Yellow solid (86%, 68 mg)

M.p. 60-62 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.37-7.29 (m, 5 H), 4.04 (tt, *J* = 11.8, 4.4 Hz, 1 H), 3.66 (dd, *J* = 11.4, 2.4 Hz, 1 H), 3.26 (ddd, *J* = 12.2, 4.4, 2.4 Hz, 1 H), 2.66 (td, *J* = 12.2, 2.4 Hz, 1 H), 2.34 (dquint, *J* = 12.6, 2.3 Hz, 1 H), 2.22 (dsex, *J* = 12.6, 2.3 Hz, 1 H), 1.90-1.88 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 143.4 (C), 128.7 (2 × CH), 127.7 (CH), 126.7 (2 × CH), 61.6 (CH), 57.7 (CH), 46.5 (CH_2), 45.4 (CH_2), 37.0 (CH_2). ESI-HRMS calculated for $C_{11}H_{15}NCl$ $[M+H]^+$ 196.0893 , found 196.0897.

4-chloro-2-(2-chlorophenyl)piperidine ***cis*** **7c** Orange oil (80%, 74 mg)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.62 (dd, *J* = 7.7, 1.7 Hz, 1 H), 7.36-7.17 (m, 3 H), 4.14 (dd, *J* = 11.3, 2.0 Hz, 1 H), 4.03 (tt, *J* = 11.7, 4.3 Hz, 1 H), 3.41 (bs, NH), 3.26 (ddd, *J* = 12.2, 4.1, 2.5 Hz, 1 H), 2.85 (td, *J* = 12.2, 2.5 Hz, 1 H), 2.40 (dquint, *J* = 12.6, 2.1 Hz, 1 H), 2.22 (dsex, *J* = 12.6, 2.1 Hz, 1

H), 1.93 (qd, *J* = 12.1, 4.3 Hz, 1 H), 1.76 (q, *J* = 12.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.7 (C), 132.7 (C), 129.7(CH), 128.8 (CH), 127.7 (CH), 127.5 (CH), 57.3 (CH), 56.9 (CH), 46.3 (CH_2), 43.1 (CH_2), 36.4 (CH_2). ESI-HRMS calculated for $C_{11}H_{14}NCl_2$ $[M+H]^+$ 230.0503 , found 230.0503.

4-chloro-2-(4-nitrophenyl)piperidine ***cis*** **7d**[10a] Orange solid (82%, 79 mg)

M.p. 100-102 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.20 (d, *J* = 8.6 Hz, 2 H), 7.56 (d, *J* = 8.6 Hz, 2 H), 4.02 (tt, *J* = 11.8, 4.4 Hz, 1 H), 3.79 (dd, *J* = 11.3, 2.4 Hz, 1 H), 3.28 (ddd, *J* = 12.2, 4.3, 2.6 Hz, 1 H), 2.84 (td, *J* = 12.2, 2.6 Hz, 1 H), 2.35-2.20 (m, 2 H), 1.94 (bs, NH), 1.87 (qd, *J* = 12.2, 4.5 Hz, 1 H), 1.77 (q, *J* = 12.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 150.8 (C), 147.5 (C),127.6 (2 × CH), 124.0 (2 × CH), 61.0 (CH), 57.0 (CH), 46.3 (CH_2), 45.3 (CH_2), 36.7 (CH_2). ESI-HRMS calculated for $C_{11}H_{14}N_2O_2Cl$ $[M+H]^+$ 241.0744 , found 241.0747.

4-chloro-2-(4-methoxyphenyl)piperidine ***cis*** **7e**[10a] White solid (34%, 31 mg)

M.p. 74-76 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.26 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 3.99 (tt, *J* = 11.7, 4.4 Hz, 1 H), 3.79 (s, 3 H), 3.59 (dd, *J* = 11.2, 2.3 Hz, 1 H), 3.22 (ddd, *J* = 12.2, 4.4, 2.6 Hz, 1 H), 2.79 (td, *J* = 12.3, 2.5 Hz, 1 H), 2.28 (dquint, *J* = 12.5, 2.3 Hz, 1 H), 2.19 (dsex, *J* = 12.6, 2.3 Hz, 1 H), 1.91-1.74 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.1 (C), 135.6 (C), 127.8 (2 × CH), 114.0 (2 × CH), 61.1 (CH), 57.8 (CH), 55.4 (CH_3), 46.5 (CH_2), 45.5 (CH_2), 37.0 (CH_2). ESI-HRMS calculated for $C_{12}H_{17}NOCl$ $[M+H]^+$ 226.0998, found 226.0998.

4-chloro-2-p-tolylpiperidine ***cis*** **7f** White solid (70%, 58 mg)

M.p. 78-80 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.23 (d, *J* = 8.0 Hz, 2 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 3.98 (tt, *J* = 11.7, 4.4 Hz, 1 H), 3.58 (dd, *J* = 11.3, 2.3 Hz, 1 H), 3.21 (ddd, *J* = 12.2, 4.3, 2.6 Hz, 1 H), 2.77 (td, *J* = 12.3, 2.5 Hz, 1 H), 2.32 (s, 3 H), 2.27 (dquint, *J* = 12.5, 2.2 Hz, 1 H), 2.17 (dsex, *J* = 12.5, 2.3 Hz, 1 H), 1.90-1.74 (m, 2 H), 1.67 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.5 (C), 137.2 (C), 129.3 (2 × CH), 126.5 (2 × CH), 61.3 (CH), 57.8 (CH), 46.5 (CH_2), 45.5 (CH_2), 37.0 (CH_2), 21.1 (CH_3). ESI-HRMS calculated for $C_{12}H_{17}NCl$ $[M+H]^+$ 210.1049, 210.1051.

4-chloro-2-isopropylpiperidine ***cis*** **7g** Orange oil (88%, 57 mg)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.90 (tt, *J* = 11.7, 4.3 Hz, 1 H), 3.17 (ddd, *J* = 12.6, 4.5, 2.5 Hz, 1 H), 2.64 (td, *J* = 12.6, 2.5 Hz, 1 H), 2.30 (ddd, *J* = 11.3, 5.8, 2.2 Hz, 1H), 2.21-2.10 (m, 2 H), 1.82 (bs,

NH), 1.70 (qd, *J* = 11.9, 4.5 Hz, 1 H), 1.64-1.58 (m, 1 H), 1.42 (q, *J* = 11.9 Hz, 1 H), 0.94 (d, *J* = 2.6 Hz, 3 H), 0.92 (d, *J* = 2.6 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 62.6 (CH), 58.6 (CH), 46.3 (CH_2), 40.6 (CH_2), 37.7 (CH_2), 33.1 (CH), 19.0 (CH_3), 18.8 (CH_3). ESI-HRMS calculated for $C_8H_{17}NCl$ $[M+H]^+$ 162.1049 , found 162.1049.

4-chloro-2-phenyl-1-tosylpiperidine ***trans*** **11**[2a] Yellow solid (93%, 130 mg)

M.p. 104-106 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.78 (d, *J* = 8.2 Hz, 2 H), 7.35-7.26 (m, 7 H), 5.40 (d, *J* = 5.0 Hz, 1 H), 3.99-3.86 (m, 2 H), 3.09-2.99 (m, 1 H), 2.73 (dquint, *J* = 13.6, 1.9 Hz, 1 H), 2.46 (s, 3 H), 1.94-1.83 (m, 2 H), 1.64-1.50 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 143.7 (C), 138.1 (C), 137.4 (C), 130.1 (2 × CH), 129.1 (2 × CH), 127.5 (C), 127.0 (2 × CH), 126.6 (2 × CH), 56.1 (CH), 52.9 (CH), 41.5 (CH_2), 37.7 (CH_2), 35.3 (CH_2), 21.7 (CH_2). ESI-HRMS calculated for $C_{18}H_{20}NO_2ClNaS$ $[M+Na]^+$ 372.0801 , found 372.0802.

1-benzyl-4-chloro-2-phenylpiperidine **12** (64%, 73 mg, dr: 52:48)

Cis **12**: White solid M.p. 134-136 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.44 (d, *J* = 7.1 Hz, 2 H), 7.36-7.19 (m, 8 H), 3.92 (tt, *J* = 11.6, 4.2 Hz, 1 H), 3.26 (ABq, 2 H), 3.20 (dd, *J* = 11.3, 2.7 Hz, 1 H), 3.00 (dd, *J* = 11.2, 3.0 Hz, 1 H), 2.30-2.23 (m, 1 H), 2.12-1.87 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 143.5 (C), 139.2 (C), 128.9 (2 × CH), 128.7 (2 × CH), 128.3 (2 × CH), 127.6 (CH), 127.5 (2 × CH), 126.9 (CH), 68.5 (CH), 58.8 (CH_2), 57.3 (CH), 52.1 (CH_2), 46.7 (CH_2), 36.8 (CH_2). ESI-HRMS calculated for $C_{18}H_{21}NCl$ $[M+H]^+$ 286.1362, found 286.1361. *Trans* **12**: White solid M.p. 126-128 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.47 (d, *J* = 7.1 Hz, 2 H), 7.35-7.19 (m, 8 H), 4.51 (t, *J* = 2.9 Hz, 1 H), 3.70 (dd, *J* = 8.5, 5.5 Hz, 1 H), 3.34 (ABq, 2 H), 2.78 (dt, *J* = 11.9, 3.5 Hz, 1 H), 2.54 (td, *J* = 12.1, 2.6 Hz, 1 H), 2.10-2.06 (m, 3 H), 1.88 (d, *J* = 14.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 144.2 (C), 139.6 (C), 128.8 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 127.7 (2 × CH), 127.4 (CH), 126.8 (CH), 62.5 (CH), 59.4 (CH_2), 57.8 (CH), 46.3 (CH_2), 43.8 (CH_2), 33.6 (CH_2). ESI-HRMS calculated for $C_{18}H_{21}NCl$ $[M+H]^+$ 286.1362, found 286.1361.

4-chloro-2-phenyl-1-propylpiperidine **13** (90%, 85 mg, dr: 57:43)

Cis **13**: Yellow oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.32-7.24 (m, 5 H), 3.92 (tt, *J* = 11.7, 4.3 Hz, 1 H), 3.20 (dt, *J* = 11,3, 3.2 Hz, 1 H), 3.08 (dd, *J* = 11.3, 2.5 Hz, 1 H), 2.37-2.30 (m, 1 H), 2.24-2.16 (m,

2 H), 2.10-1.79 (m, 4 H), 1.36 (q, *J* = 7.6 Hz, 2 H), 0.71 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 143.6 (C), 128.7 (2 × CH), 127.6 (2 × CH), 127.4 (CH), 68.5 (CH), 57.4 (CH), 56.2 (CH_2), 52.0 (CH_2), 46.6 (CH_2), 37.0 (CH_2), 19.5 (CH_2), 11.8 (CH_3). ESI-HRMS calculated for $C_{14}H_{21}NCl$ $[M+H]^+$ 238.1362, found 238.1359. *Trans* **13**: Yellow oil ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.35-7.23 (m, 5 H), 4.51 (quint, *J* = 2.9 Hz, 1 H), 3.59 (dd, *J* = 8.9, 4.7 Hz, 1 H), 2.97 (dt, *J* = 11.9, 3.2 Hz, 1 H), 2.64 (td, *J* = 12.0, 2.1 Hz, 1 H), 2.44-2.34 (m, 1 H), 2.18 (t, *J* = 13.1 Hz 1 H), 2.01-1.97 (m, 4 H), 1.44-1.37 (m, 2 H), 0.72 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 144.1 (C), 128.6 (2 × CH), 127.8 (2 × CH), 127.2 (CH), 62.2 (CH), 57.9 (CH), 56.8 (CH_2), 46.3 (CH_2), 43.6 (CH_2), 33.7 (CH_2), 19.4 (CH_2), 11.9 (CH_3). ESI-HRMS calculated for $C_{14}H_{21}NCl$ $[M+H]^+$ 238.1362, found 238.1362.

Supporting Information

Copies of 1H NMR and 13C NMR spectra for products **1-4-8-9-10**, for all piperidines **3-5-7-11-12-13** and X-ray crystallographic data, and crystal structure of compounds *trans* **3e** and *cis* **7a** are provided. The Supporting Information is available free of charge on the ACS Publications website at DOI:

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The authors declare no competing financial interest.

Acknowledgments

We thank Université de Rennes 1, CNRS, Rennes Métropole and Région Bretagne for financial support. The CRMPO de l'Institut des Sciences Chimiques de Rennes is gratefully acknowledged for mass measurement.

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