PAPER

Diastereo- and enantioselective reductive amination of cycloaliphatic ketones by preformed chiral palladium complexes†

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An efficient preformed chiral palladium catalyzed direct diastereo- and enantioselective reductive amination of un- and substituted cycloaliphatic ketones with primary aryl amines has been developed.
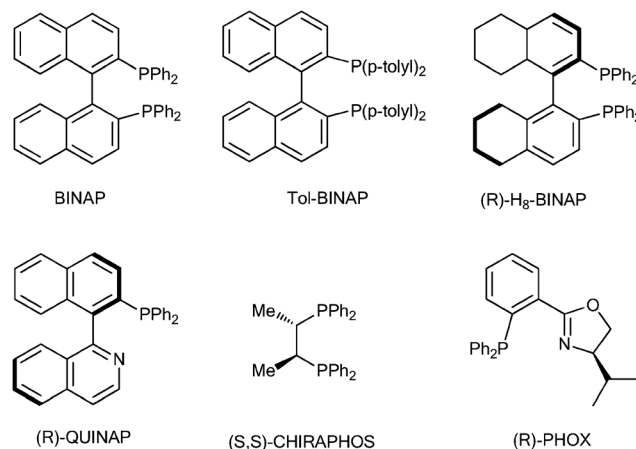
1. Introduction

Cycloaliphatic chiral amines and their analogues are useful compounds for the synthesis of natural products, pharmaceuticals, agrochemicals and material industries.[1,2] The direct asymmetric reductive amination (DARA) of carbonyl compounds with primary amines is one of the most desired strategies for the synthesis of chiral amines.[3–6] Hence, the development of an efficient enantioselective synthesis of these compounds is an important task in organic chemistry. There are only a few synthetic methods reported in the literature to access to these organic compounds from α-branched ketones.[7] The Lassaletta[8] and List[9] groups have developed the asymmetric reductive amination of α-branched ketones by dynamic kinetic resolution, employing a ruthenium catalyst and organocatalysts, respectively. Thus, efficient methods for the diastereo- and enantioselective synthesis of substituted cycloaliphatic amines are still limited. Palladium-based catalysts have been employed for the asymmetric hydrogenation of imines but have not been explored much for the reductive amination of carbonyl compounds.[10] Our group has contributed to the direct asymmetric reductive amination of alkyl and aryl ketones, and α-diketones with primary anilines catalyzed by stable chiral preformed palladium catalysts and we were able to obtain chiral amines in excellent yields and enantioselectivities (up to 99% ee).[11] Since our initial report, we have continued to explore the scope and limitations of the air-stable preformed chiral

palladium catalysts in the DARA reaction (Scheme 1). Herein, we report the general one-pot asymmetric reductive amination of cycloaliphatic ketones and α- and β-branched ketones with primary aryl amines for the non, diastereo- and enantioselective synthesis of *N*-cycloalkylamines.

2. Results and discussion

A series of unsubstituted cycloaliphatic ketones were tested for their ability to undergo direct reductive amination, using Pd[(*rac*)-BINAP]Br$_2$ as catalyst, molecular sieves (5 Å) and a hydrogen pressure of 800 psi at 80 °C for 24 h (Table 1).[12] All showed good reactivity and gave the corresponding secondary amines in 74–95% yields. Of all the ketones used in this study, small aliphatic cyclic ketones, ranging from cyclobutanone to cyclohexanone (Table 1, entries 1–4), were the most reactive. Larger cyclic ketones, such as cyclooctanone and cyclododecanone, reacted somewhat slower (Table 1, entries 9–10). Additionally, all primary aryl amines with

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Scheme 1 Structures of non- and chiral ligands used to synthesize palladium catalysts.

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Table 1 Direct reductive amination of unsubstituted cycloaliphatic ketones[a]

Reaction scheme: ketone **2** + arylamine → Pd[(rac)-BINAP]Br$_2$ (2.5 mol %), CHCl$_3$, H$_2$ (800 psi), 24 h, MS 5 Å → product **3**

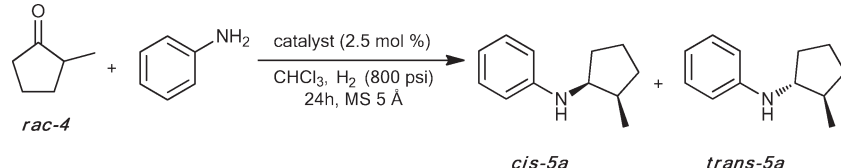| Entry	Ketone	Amine	Product	Yield[b]
1	cyclobutanone	3-(CF$_3$)aniline	**3a**	95
2	cyclopentanone	3,5-bis(CF$_3$)aniline	**3b**	93
3	cyclohexanone	aniline	**3c**	89
4	cyclohexanone	4-bromo-2-chloroaniline	**3d**	74
5	cycloheptanone	aniline	**3e**	92
6	cycloheptanone	4-Me-aniline	**3f**	91
7	cycloheptanone	2-(CF$_3$)aniline	**3g**	86
8	cycloheptanone	3-(CF$_3$)aniline	**3h**	88
9	cyclooctanone	3-(CF$_3$)aniline	**3i**	88
10	cyclododecanone	3,4-difluoroaniline	**3j**	81
11	cyclododecanone	4-nitroaniline	**3k**	0

[a] Reaction conditions: 2.5 mol% of Pd[(rac)-BINAP]Br$_2$, 1.0 mmol of **2**, 1.3 mmol of **3**, 10 mL CHCl$_3$ and H$_2$ (800 psi) at 80 °C for 24 h. [b] Isolated yield.

electron-donating or electron-withdrawing groups were used successfully in these reactions. For the same cycloaliphatic ketone, such as cyclohexanone, the direct reductive amination proceeds well with both aniline (89%, Table 1, entry 3) as the disubstituted aryl amine containing two different halogen atoms (74% yield, Table 1, entry 4). Reaction of cycloheptanone with an arylamine containing an electron-donating substituent showed similar reactivity with aniline (Table 1, entries 5 and 6). Reactions with substituted anilines either at the *ortho* or *meta* position with an electron-withdrawing group such as –CF$_3$ led to a slight decrease in

the yields (Table 1, entries 7 and 8). Interestingly, when cyclododecanone was reacted with 3,3-difluoroaniline, the desired secondary amine was isolated in good yield (81%, Table 1, entry 10). The reaction of an arylamine with a –NO$_2$ group was also considered, but no product was obtained (Table 1, entry 11).[13]

In the direct asymmetric reductive amination of substituted cycloaliphatic ketones, 2-methylcyclopentanone with aniline in the presence of hydrogen gas was chosen as the model reaction to evaluate a series of diphosphine and phosphine–nitrogen–palladium complexes (Table 2). The structures of Pd[(R)-Tol-BINAP]Br$_2$ (**1e**), Pd[(R)-PHOX]Br$_2$ (**1h**) and Pd[(R)-H$_8$-BINAP]Br$_2$ (**1i**) were confirmed by X-ray diffraction and are shown in the ESI.† In contrast to the results reported in the literature[14] for the non-diastereoselective reactions, we have obtained only the *cis*-**5a** diastereoisomer in all cases, probably this preference is due to equatorial attack of the bulky hydride-complex to the cyclic imine intermediate generated *in situ*.[14] RThe relative configuration was confirmed by NOE experiments. It is noteworthy that the heterogeneous catalyst **1a** provides **5a** with a lower selectivity (Table 2, entry 2). At room temperature, catalyst **1c** provided a low yield and enantioselectivity (Table 2, entry 4), but it was observed that an increase in temperature highly improves the yield and stereoselectivity (Table 2, entries 5–7). Therefore, this catalyst turned out to be the most effective for this transformation at 80 °C providing *cis*-**5a** in 90% yield with an enantiomeric excess of 98%. A similar result was observed with catalyst **1i** at 80 °C (Table 2, entry 13), but for availability **1c** was chosen for the next reactions. All other diphosphine–palladium catalysts used were less active. Catalysts **1h** and **1j**, containing a heterobidentate ligand gave the *cis*-**5a** with good enantioselectivities (87 and 89%, respectively) but with low yields (Table 2, entries 12 and 14).

Based on these catalyst screening results, the applicability of catalyst **1c** to the asymmetric reductive amination of 2-methylcyclopentanone **4**, with a range of commercially available aryl amines were extended to obtain aminocyclopentane derivatives. As shown in Table 3, *rac*-**4** was reacted with functionalized anilines bearing *ortho*, *meta* and *para* substitutions on the aryl ring to give *cis*-N-(2-methylcyclopentyl)amines **5b**–**k** (Table 3, entries 1–3, 5–8 and 11) in good yields (69–91%) and good to excellent enantiomeric excesses (83–98%). The highest enantiomeric excess (98%) was achieved when *m*-trifluoromethylaniline was used (Table 3, entry 6). However, the reaction with *o*-bromo aniline gave a lower enantiomeric excess (Table 3, entry 9) contrary to *o*-trifluomethyl aniline (Table 3, entry 11). It is noteworthy that the asymmetric reductive amination reaction is influenced by the bulkiness of the substituents on the anilines. For example, when sterically congested 2,4,6-trimethylaniline and 2,3,4,5,6-pentafluoroaniline were used under the same conditions, no reaction was observed (Table 3, entries 4 and 10) only traces of the respective imine was detected by GC-MS and no reduction of the cycloaliphatic ketone was observed.

Table 2 Catalyst screening for the direct asymmetric reductive amination of **4**[a]

rac-4   *cis*-5a   *trans*-5a

Entry	Catalyst precursor	T (°C)	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	None	80	0	0	0
2	Pd/C (**1a**)	80	77	62:38	—
3	Pd[(R)-BINAP]Cl$_2$ (**1b**)	80	87	97:3	92
4	Pd[(R)-BINAP]Br$_2$ (**1c**)	rt	70	94:6	78
5		60	88	96:4	80
6		80	90	98:2	98
7		100	90	98:2	91
8	Pd[(S)-BINAP]Br$_2$ (**1d**)	80	89	98:2	95
9	Pd[(R)-Tol-BINAP]Br$_2$ (**1e**)	80	81	95:5	89
10	Pd[(S)-Tol-BINAP]Br$_2$ (**1f**)	80	82	94:6	93
11	Pd[(S,S)-CHIRAPHOS]Br$_2$ (**1g**)	80	82	92:8	96
12	Pd[(R)-PHOX] Br$_2$ (**1h**)[e]	80	63	91:9	87
13	Pd[(R)-H$_8$-BINAP]Br$_2$ (**1i**)	80	90	98:2	98
14	Pd[(R)-QUINAP]Br$_2$ (**1j**)	80	68	93:7	89

[a] Reaction conditions: 2.5 mol% of catalyst, 1.0 mmol of **2**, 1.3 mmol of **3a**, 10 mL CHCl$_3$ and H$_2$ (800 psi) at 80 °C for 24 h. [b] Isolated yield of major *cis* product. Relative stereochemistry determined by NMR. [c] Determined by NMR analysis of crude product. [d] Determined by GC-MS (EI) using a chiral column Cyclodex-β. [e] Here abbreviated as PHOX = 2-[2-(diphenylphosphino)phenyl]-4-isopropyl 1,3-oxazoline.
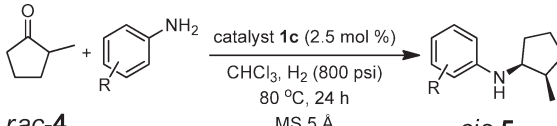
For the asymmetric reductive amination of 2-methylcyclohexanone **6**, only *cis*-N-(2-methylcyclohexyl) amines **7a–h** were obtained in good yields (Table 4, entries 1–8, 71–91%) and with good to excellent enantioselectivities (62–99%). The highest enantioselectivity was observed when *p*-methoxyaniline was used (Table 4, entry 5). From these experiments, it was concluded that the steric factor has an effect on the stereocontrol of the reaction.

On the other hand, for the reaction of (R)-(+)-3-methyl-cyclohexanone with selected anilines using catalyst **1c** (Table 5),

we achieved the formation of *trans*-3-methylcyclohexylamine derivatives **9a–d** with excellent enantioselectivity up to 99% (Table 5, entries 1–4).[15]

The potential of the palladium catalytic system was extended to other substituted cyclic ketones (Scheme 2). 2- and 4-arylsubstituted cyclohexanones (**10** and **12**) were reductively aminated with aniline to give the *cis* product in excellent yield and moderate enantioselectivity for **10**. It is also possible to transform bicyclic ketones such as norcamphor, which led to the exclusive formation of **15** with 87% ee.

The asymmetric induction may be explained by the fact that the substituent on the cycloaliphatic imine must be
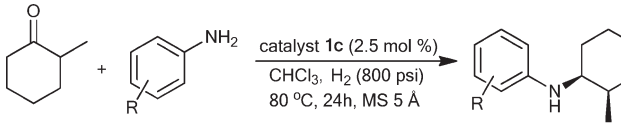
Table 3 Asymmetric reductive amination of 2-methyl cyclopentanone with anilines[a]

rac-4   *cis* 5

Entry	R	Product	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	*m*-CH$_3$	**5b**	90	97:3	93
2	*p*-CH$_3$	**5c**	91	97:3	95
3	*p*-C$_2$H$_5$	**5d**	86	98:2	83
4	2,4,6-CH$_3$	**5e**	0	—	—
5	*p*-CH$_3$O	**5f**	78	99:1	96
6	*m*-CF$_3$	**5g**	80	96:4	98
7	*m*-Cl	**5h**	86	98:2	91
8	*p*-Cl	**5i**	88	97:3	84
9	*o*-Br	**5j**	75	93:7	18
10	2,3,4,5,6-F	**5k**	0	—	—
11	*o*-CF$_3$	**5l**	69	92:8	95

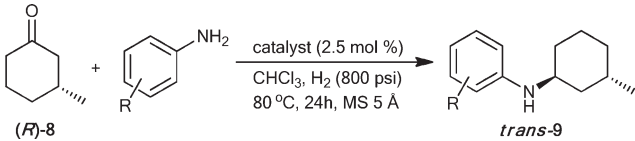[a] The reaction conditions were the same as those in Table 2. [b] Isolated yield of major diastereomer. [c] Determined by NMR analysis. [d] Determined by GC-MS (EI) using a chiral column Cyclodex-β.

Table 4 Asymmetric reductive amination of 2-methyl cyclohexanone with anilines[a]

rac-6   *cis*-7

Entry	R	Product	Yield[b]	d.r.[c] (%)	ee[d] (%)
1	H	**7a**	91	91:9	79
2	*p*-CH$_3$	**7b**	91	94:6	75[d]
3	*p*-C$_2$H$_5$	**7c**	74	90:10	62
4	*o*-CH$_3$O	**7d**	83	92:8	98
5	*p*-CH$_3$O	**7e**	85	93:7	>99
6	*m*-Cl	**7f**	90	91:9	93
7	*p*-Cl	**7g**	82	91:9	89
8	*p*-Br	**7h**	71	89:11	83[e]

[a] The reaction conditions were the same as those in Table 2. [b] Isolated yield of major diastereomer. [c] Determined by NMR analysis. [d] Determined by GC-MS (EI) using a chiral column Cyclodex-β. [e] Realized with catalyst **1d**.

Table 5 Asymmetric reductive amination of (R)-3-methylcyclohexanone with selected anilines[a]

Entry	R	Product	Yield[b] (%)	d.r.	ee[c] (%)
1	H	9a	87	98:2	91
2	p-C$_2$H$_5$	9b	90	98:2	95
3	m-CF$_3$	9c	84	99:1	>99
4	m-Cl	9d	89	96:4	>99

[a] The reaction conditions were the same as those in Table 2. [b] Isolated yield. [c] Determined by GC-MS (EI) using a chiral column Cyclodex-β.

Fig. 1 Suggested arrangement of the palladium–hydride complex for the obtained stereochemistry in the products.
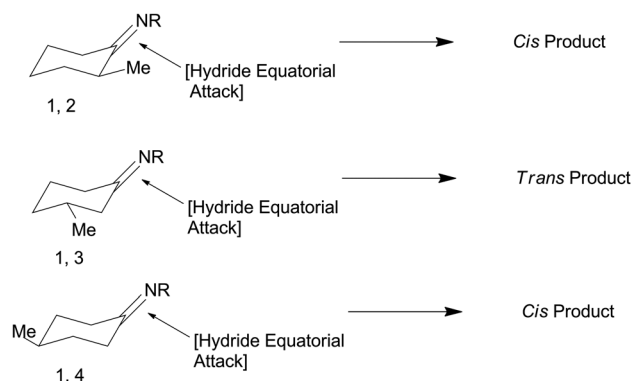
Fig. 2 Preferential hydride attack on the iminic bond.

oriented far from the equatorial phosphinic phenyl groups of the BINAP ligand in order to avoid steric hindrance.[16] This promotes the preferential hydride attack on the Si face of the substrate. In the case when the Re face is attacked by the hydride, the R$_1$ group on the cyclic imine would present a greater repulsion from the equatorial phenyl (Eq) group. Fig. 1 shows the favored arrangement.

The suggested arrangement shown in Fig. 1 also explains the increment in ee due to higher fluxionality. Thus, there will be more steric congestion in the hydride species at higher temperatures.

On the other hand, the diastereomeric excess found in this reaction can be explained by the steric influence exerted by the large hydride palladium species, which in turn facilitates the equatorial attack[14] preferentially on the iminic bond (Fig. 2). This results in a 1,2- or 1,4-cis-amino methyl product, as the methyl group is in the β-equatorial position on the ring. In the case of 1,3-di substitution, the methyl group at the α-equatorial position generates the trans-1,3-reduced product.
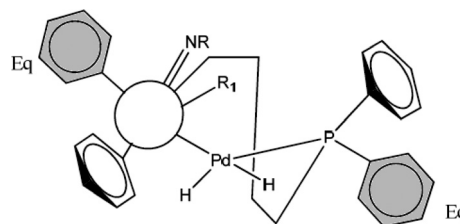
3. Conclusion

In summary, the preformed chiral palladium catalysts provides a direct and efficient route towards the diastereo- and enantioselective synthesis of N-cycloalkylamines from substituted cycloaliphatic ketones in good yields with good to excellent enantiomeric excess. This catalytic system shows versatility with different substituents on the aniline derivatives. The steric bulkiness of the aniline derivatives has an important effect on the stereocontrol of the process. The
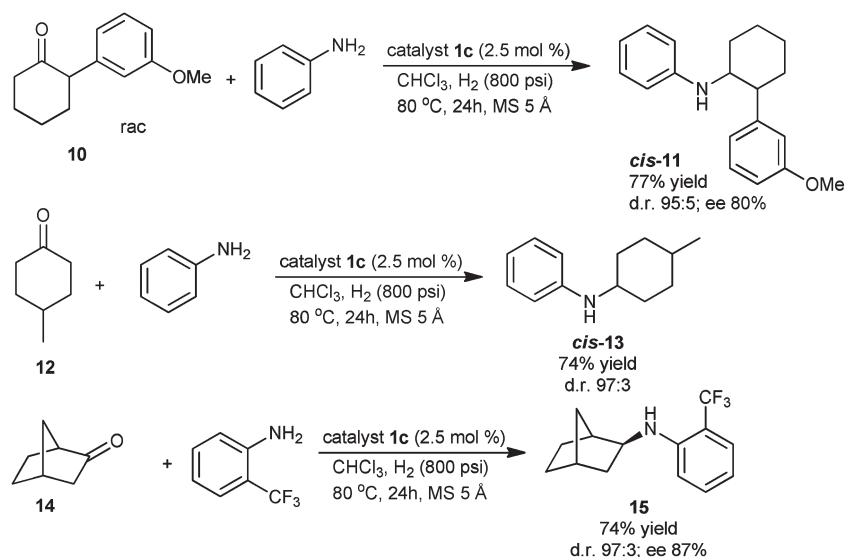
Scheme 2 Other ring sizes for asymmetric reductive amination.

diastereoselective preparation of either of the two possible chiral diastereomers represents a significant challenge for organic synthesis. Further investigations to expand the scope of other substrates and to further understand the mechanism of this reaction are in progress.

Acknowledgements

Notes and references

1 For a general review on the reductive amination reaction, see: (a) R. P. Triphathi, S. S. Verma, J. Pandey and V. K. Tiwari, *Curr. Org. Chem.*, 2008, **12**, 1093–1115; (b) V. I. Tararov and A. Börner, *Synlett*, 2005, 203–205; (c) H. Gröger, O. May, H. Werner, A. Menzel and J. Altenbuchner, *Org. Process Res. Dev.*, 2006, **10**, 666–669; (d) R. O. Hutchins and M. K. Hutchins, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991.

2 (a) B. G. Main and H. Tucker, in *Medicinal Chemistry*, ed. C. R. Genellin and S. M. Roberts, Academic Press, New York, 1993, p. 187; (b) V. A. Tarasevich and N. G. Kozlov, *Russ. Chem. Rev.*, 1999, **68**, 55–72.

3 For organocatalytic reductive amination using Brønsted acids in combination with a Hantzsch ester, see. (a) R. I. Storer, D. E. Carrera, Y. Ni and D. W. C. Macmillan, *J. Am. Chem. Soc.*, 2006, **128**, 84–86; (b) J. Zhou and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 7498–7499.

4 For biocatalytic reductive amination, see: D. Koszelewski, I. Lavandera, D. Clay, G. M. Guebitz, D. Rozzell and W. Kroutil, *Angew. Chem., Int. Ed.*, 2008, **47**, 9337–9340.

5 For hydrogen transfer in reductive amination, see: (a) G. D. Williams, R. A. Pike, C. E. Wade and M. Wills, *Org. Lett.*, 2003, **5**, 4227–4230; (b) R. Kadyrov and T. H. Riermeier, *Angew. Chem., Int. Ed.*, 2003, **42**, 5472–5474.

6 For asymmetric reductive aminations catalyzed by transition metals, see. (a) Y. Chi, Y. G. Zhou and X. Zhang, *J. Org. Chem.*, 2003, **68**, 4120–4122; (b) H.-U. Blaser, H.-P. Buser, H.-P. Jalett, B. Pugin and F. Spindler, *Synlett*, 1999, 867–868; (c) V. I. Tararov, R. Kadyrov, T. H. Riermeier and A. Börner, *Chem. Commun.*, 2000, 1867–1868; (d) R. Kadyrov, T. H. Riermeier, U. Dingerdissen, V. Tararov and A. Börner, *J. Org. Chem.*, 2003, **68**, 4067–4070; (e) T. C. Nugent,

V. N. Wakchaure, A. K. Ghosh and R. R. Mohanty, *Org. Lett.*, 2005, **7**, 4967–4970; (f) C. Salmi, Y. Letourneux and J. M. Brunel, *Lett. Org. Chem.*, 2006, **3**, 384–389; (g) M. Chang, S. Liu, K. Huang and X. Zhang, *Org. Lett.*, 2013, **15**, 4354–4357; (h) A. Pagnoux-Ozherelyeva, N. Pannetier, D. Mbaye, S. Gaillard and J. L. Renaud, *Angew. Chem., Int. Ed.*, 2012, **51**, 4976–4980.

7 For diastereoselective reductive amination of alkyl, aryl and cyclic ketones by transition metals, see: (a) T. C. Nugent, A. K. Ghosh, V. N. Wakchaure and R. R. Mohanty, *Adv. Synth. Catal.*, 2006, **348**, 1289–1299; (b) T. C. Nugent, M. El-Shazly and V. N. Wakchaure, *J. Org. Chem.*, 2008, **73**, 1297–1305; (c) M. Breuer, K. Ditrich, B. Hauer, M. Keßeler, R. Stürmer and T. Zelinsky, *Angew. Chem.*, 2004, **116**, 806.

8 A. Ros, A. Magriz, H. Dietrich, M. Ford, R. Fernandez and J. M. Lassaletta, *Adv. Synth. Catal.*, 2005, **347**, 1917–1920.

9 (a) S. Hoffman, M. Nicoletti and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 13074–13075; (b) J. Zhou and B. List, *Synlett*, 2007, 2037–2040.

10 Q. A. Chen, Z. S. Ye, Y. Duan and Y. G. Zhou, *Chem. Soc. Rev.*, 2013, **42**, 497–511.

11 (a) L. Rubio-Pérez, F. J. Pérez-Flores, P. Sharma, L. Velasco and A. Cabrera, *Org. Lett.*, 2009, **11**, 265–268; (b) A. Cabrera, P. Sharma, M. Ayala, L. Rubio-Pérez and M. Amézquita-Valencia, *Tetrahedron Lett.*, 2011, **52**, 6758–6762.

12 The starting primary aromatic amine was used in 30% excess in order to control the selectivity toward alkylation. The addition of molecular sieves (MS 5 Å) was necessary to absorb water molecules, which are generated by the condensation between the cycloaliphatic ketone and aniline derivatives. Without MS 5 Å, the reaction proceeds with low yield.

13 Only reduction of the –NO_2 group on aniline to –NH_2 was detected by GC-MS.

14 Conformational studies over stereoselective reduction of cyclopentyl and cyclohexyl imines by hydride reagents, see: (a) R. O. Hutchins, W. Y. Su, S. Ramachandran, F. Cistone and Y. P. Stercho, *J. Org. Chem.*, 1983, **48**, 3412–3422; (b) R. O. Hutchins, J. Adams and M. C. Rutledge, *J. Org. Chem.*, 1995, **60**, 7396–7405.

15 The synthesis of 3-substituted cyclohexylamines with chiral phosphoric acids gives the corresponding *cis*-diastereomers, see ref. 3b.

16 T. Ohkuma, M. Kitamura and R. Noyori, *New Frontiers in Asymmetric Catalysis*, ed. K. Mikami and M. Lautens J. Wiley & Sons Inc., 2007, ch. I.