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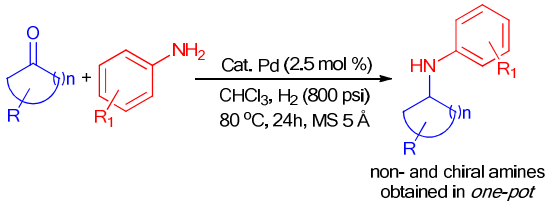

Chiral cycloaliphatic amines were obtained from direct asymmetric reductive amination of cycloaliphatic ketones using preformed chiral palladium catalyst.

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Abstract:

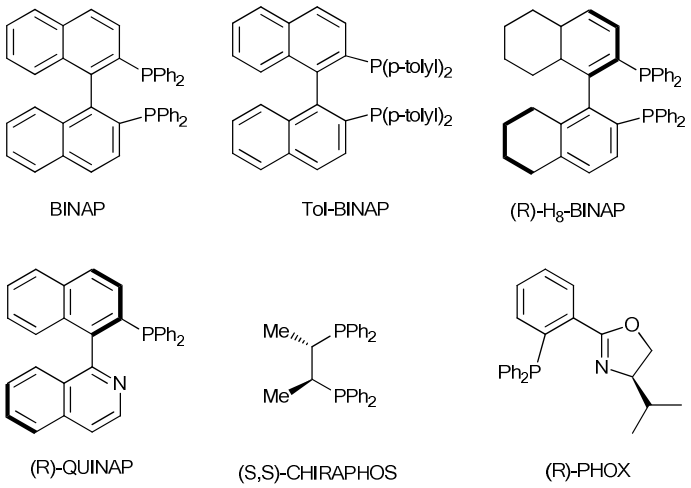
An efficient preformed chiral palladium catalyzed direct diastereo- and enantioselective reductive amination of un- and substituted cycloaliphatic ketones with primary aryl amines have been developed.

Keywords: chiral amines, diphosphine ligands, palladium catalysis, asymmetric reductive amination.

1. Introduction

Cycloaliphatic chiral amines and their analogues are useful compounds for the synthesis of natural products, pharmaceuticals, agrochemicals and material industries.[1-2] 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 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] 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 asymmetric hydrogenation of imines but have not explored much for the reductive amination of carbonyl compounds.[10] Our group has contributed in 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 a 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.

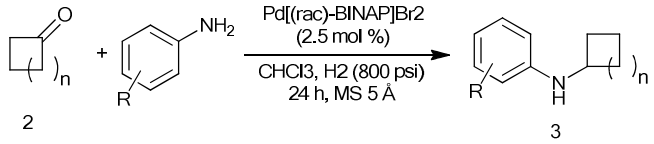


Scheme 1 Structures of non and chiral ligands used to synthesize palladium catalysts.

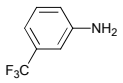
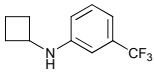
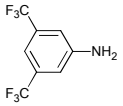
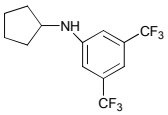
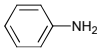
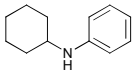
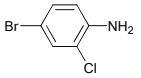
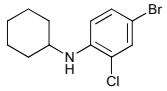
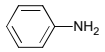
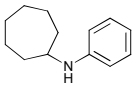
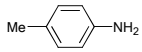
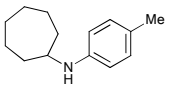
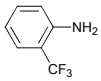
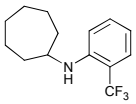
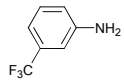
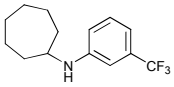
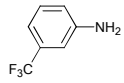
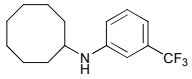
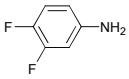
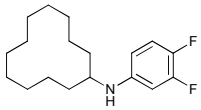
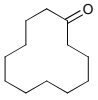
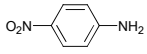
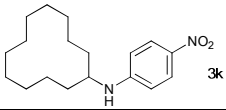
2. Results and discussion.

A series of unsubstituted cycloaliphatic ketones were tested for the direct reductive amination using Pd[(*rac*)-BINAP]Br_2 as catalyst, molecular sieves (5Å) and hydrogen pressure (800 psi) at 80 ^oC for 24 h (Table 1).[12] All, showed good reactivity and the corresponding secondary amines in 74-95% yield were obtained. Of all the ketones used in this study, small aliphatic cyclic ketones, ranging from cyclobutanone to cyclohexanone (entries 1-4), were most reactive. Larger cyclic ketones such as cyclooctanone and cyclododecanone reacted somewhat slower (entries 9-10). Additionally, all primary aryl amines with 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%, entry 3) as disubstituted aryl amine containing two different halogen atoms (74% yield, entry 4). Reaction of cycloheptanone with an arylamine containing electron-donating substituent showed similar reactivity with aniline (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 (entries 7 and 8). Interestingly, when cyclododecanone was reacted with 3,3-difluoroaniline, the desired secondary amine was isolated in good yield (81%, entry 10). The reaction with -NO_2 group on arylamine was also considered, but no product was obtained (entry 11).[13]

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



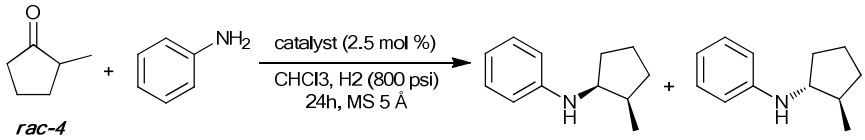
2 3

Entry	Ketone	Amine	Product		Yield[b] (%)
1				3a	95
2				3b	93
3				3c	89
4				3d	74
5				3e	92
6				3f	91
7				3g	86
8				3h	88
9				3i	88
10				3j	81
11				3k	0

[a] 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 ºC for 24 h. [b] Isolated yield.

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). 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 Supporting Information. 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] Relative configuration was confirmed by NOE experiments. It is noteworthy that heterogeneous catalyst **1a** provides **5a** with a lower selectivity (entry 2). At room temperature, catalyst **1c** provided low yield and enantioselectivity (entry 4), but it was observed that with an increase in temperature, highly improves the yield and stereoselectivity (entries 5-7). Therefore, this catalyst turned out to be the most effective for this transformation at 80 ^{o}C providing *cis*-**5a** in 90% yield with an enantiomeric excess of 98%. A similar result was observed with catalyst **1i** at 80 ^{o}C (entry 13), but for available **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 (entries 12 and 14).

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



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

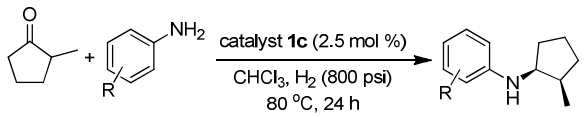
Entry	Catalyst precursor	T (°C)	Yield (%)[b]	d.r.[c]	ee (%)[d]
1	none	80	0	0	0
2	Pd/C (**1a**)	80	77	62:38	--
3	Pd[(*R*)-BINAP]Cl_2 (**1b**)	80	87	97:3	92
4	Pd[(*R*)-BINAP]Br_2 (**1c**)	rt	70	94:6	78
5		60	88	96:4	80
6		80	90	98:2	98
7		100	90	98:2	91
8	Pd[(*S*)-BINAP]Br_2 (**1d**)	80	89	98:2	95
9	Pd[(*R*)-Tol-BINAP]Br_2 (**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] 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 Ciclodex-β. [d] Here abbreviated as PHOX = 2-[2-(diphenylphosphino)phenyl]-4-isopropyl1,3-oxazoline

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 c*is*-*N*-(2-methylcyclopentyl)amines **5b-k** (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 (entry 6). However, the reaction with *o*-bromo aniline gave lower enantiomeric excess (entry 9) contrary to a *o*-trifluomethyl aniline (entry 11). It is noteworthy that the reductive asymmetric reductive amination reaction is influenced by bulkiness of the substituents on 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 (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 3. Asymmetric reductive amination of 2-methyl cyclopentanone with anilines.[a]



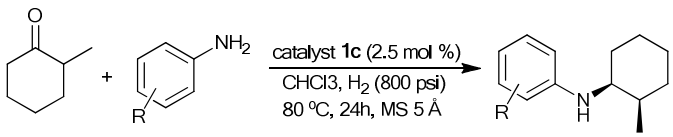
rac-**4** *cis* **5**

Entry	R	Product	Yield (%)[b]	d.r.	ee (%)[d]
1	*m*-CH_3	**5b**	90	97:3	93
2	*p*-CH_3	**5c**	91	97:3	95
3	*p*-C_2H_5	**5d**	86	98:2	83
4	2,4,6-CH_3	**5e**	0	--	--
5	*p*-CH_3O	**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 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 Ciclodex-β.

The asymmetric reductive amination of 2-methylcyclohexanone **6**, only *cis*-*N*-(2-methylcyclohexyl) amines **7a**-**h** were obtained in good yields (entries 1-8, 71-91%) and with good to excellent enantioselectivities (62-99%). Highest enantioselectivity was observed when *p*-methoxyaniline was used (entry 5). From these experiments, it was concluded that steric factor has an edge on the stereocontrol of the reaction.

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



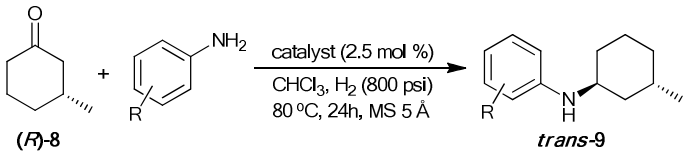
rac-**6** *cis*-**7**

Entry	R	Product	Yield	d.r.[b] (%)	ee (%)[c]
1	H	**7a**	91	91:9	79
2	*p*-CH_3	**7b**	91	94:6	75[a]
3	*p*-C_2H_5	**7c**	74	90:10	62
4	*o*- CH_3O	**7d**	83	92:8	98
5	*p*- CH_3O	**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 conditions reaction 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 Ciclodex-β. [e] Realized with catalyst **1d**.

On the other hand, reaction of (*R*)-(+)-3-methylcyclohexanone with selected anilines using catalyst **1c** (Table 5), we found the formation of *trans*-3-methylcyclohexylamine derivatives **9a-d** with excellent enantioselectivity up to 99% (entries 1-4).[15]

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

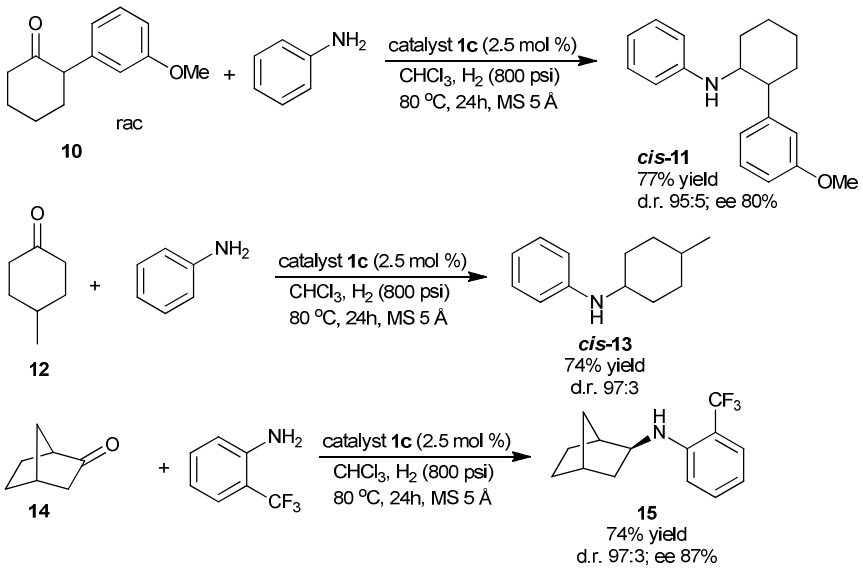


(*R*)-8 *trans*-9

Entry	R	Product	Yield (%)[b]	d.r.	ee (%)[c]
1	H	**9a**	87	98:2	91
2	*p*-C_2H_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 conditions reaction were the same as those in Table 2. [b] Isolated yield. [c] Determined by GC-MS (EI) using a chiral column Ciclodex-β.

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 reductive aminated with aniline to give the *cis* product with excellent yields and moderate enantioselectivity for 10. It is also possible to transform bicyclic ketones such as norcamphor which led to the exclusive formation of the **15** with 87% ee.



Scheme 2. Other rings size for asymmetric reductive amination

The asymmetric induction may be explained by the fact that the substituent on cycloaliphatic imine must be oriented far from the equatorial phosphinic phenyl groups of BINAP ligand in order to avoid steric hindrance[16]. This last promotes the preferential hydride attack on *Si* face of the substrate. In case if *Re* face is attacked by the hydride, R_1 group on cyclic imine would present a greater repulsion from the equatorial phenyl (Eq) group. Figure 1 shows the favored arrangement:

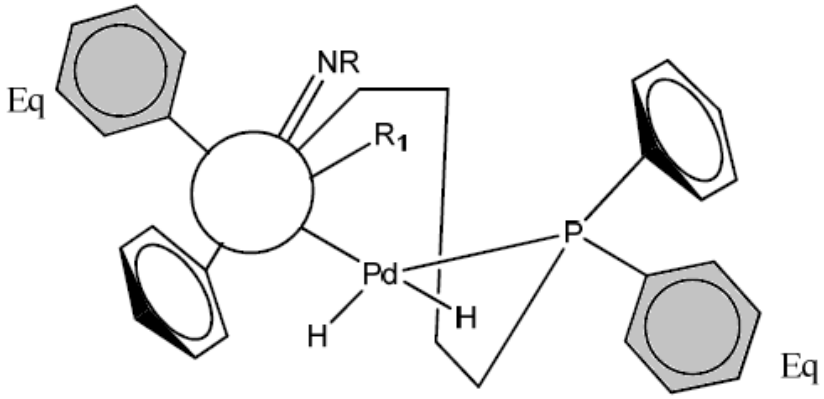


Figure 1. Suggested arrangement of palladium –hydride complex for obtained stereochemistry in the products

The suggested arrangement shown in Figure 1 also explains the increment in ee due to higher fluxionality, thus more steric congestion at higher temperature in the hydride species.

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

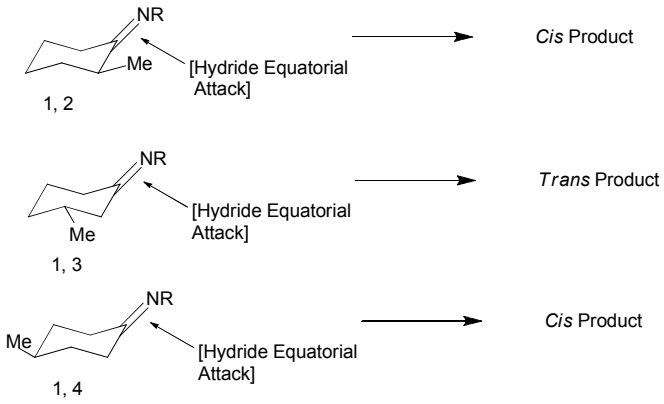


Figure 2. Preferential Hydride attack on the iminic bond

3. Conclusion

In summary, the preformed chiral palladium catalysts provide a direct and efficient route for 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 aniline derivatives. Steric bulkiness of aniline derivatives has an important effect on the stereocontrol in the process. The 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.

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Supplementary data

Electronic supplementary information (ESI) available: Experimental, spectroscopy data, scanned spectra and X-ray of **1e**, **1h** and **1i**. See DOI:

Notes and references.

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