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Novel access to *N,N′*-diaryl-*trans*-1,2-diaminocyclohexane ligands. A cheap and easy way to prepare ligand for asymmetric transfer hydrogenation

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ABSTRACT

N,N′-diaryl-*trans*-1,2-diaminocyclohexane ligands were prepared from 1,2-diaminocyclohexane and cyclohexanone derivatives *via* a heterogeneous palladium catalysis. In one step an alkylation followed by an aromatisation is performed under air or in the presence of an hydrogen trap. The interest of the synthesized ligands were evaluated in the reduction of aromatic ketones. The alcohols were efficiently and selectively obtained with an iridium complex and a mixture of formic acid and sodium formate.

1. Introduction

Chiral molecules have found a variety of applications in pharmaceutical, agrochemical, flavor and flagrance industries. In addition, around 85% of new drugs are chiral, this can be explained by the development of asymmetric catalysis, specifically the interest for chiral ligands access and applications [1]. From the birth of asymmetric catalysis, plethora of molecules, most of them inspired by the seminal work of Knowles, Kagan, Sharpless and Noyori, have been designed and synthesized [2]. Nowadays, a wide library of ligands has been available [3]. Among them, *N,N′-trans*-1,2-diaminocyclohexane is the chiral platform of different family of diaza ligands such as SALEN, notably well-known in the epoxidation [4] or the preparation of Trost ligands [5]. *N,N′*-diaryl-*trans*-1,2-diaminocyclohexane have been less investigated [6]. From literature data, these compounds were prepared in Buchwald coupling conditions from aromatic halides [7] or *via* a Meisenheimer type nucleophilic aromatic substitution. [8] The ring-opening of *N*-phenyl aziridine with aniline allows the access to similar diarylamines [9]. Dimeric bidentated NHC were also synthezised from these intermediates [10]. Dihydroxyderivatives were prepared from 3-*N*-hydroxy-aminoprop-1-enes *via* a copper catalyzed oxidative dimerization [11]. Quinoline based ligands were studied as chaperone molecules in cycloaddition reactions [6(c)]. Nitro derivatives have shown useful application in nonlinear optics [7].

One report mentioned their evaluation as ligand in asymmetric transfer hydrogenation with isopropanol but with a poor efficiency [6(a)]. The asymmetric transfer hydrogenation has already been established as a real alternative of hydrogenation with molecular hydrogen. From the pioneer works with isopropanol, large quantity of data was collected and offer to organic chemists useful tools [12–16]. [Ruthenium, rhodium and iridium complexes are the most studied ones in this domain [17]. The most conventional hydrogen sources in ATH are 2-propanol, formic acid, and sodium format which are cheap and green reducing agents. This technology has been used notably to reduce enantioselectively ketones. In this case, preparations of chiral ligands have a determining role rendering, development of simple methodology to prepare enantioselective molecules, are still in great demand.

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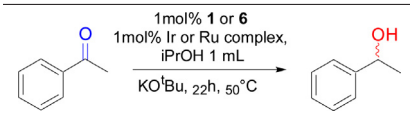
1381-1169/

Table 1
Transfer hydrogenation of acetophenone using Ru and Ir metal with ligand 1 and 6.



Entry	Metal complex	L	KO^{t}Bu(mol%)	Conv[a](%)	e.e[b] (%)
1	$[RuCl_2(p\text{-cymene})]_2$	1	5	90	Rac
2	$[RuCl_2(p\text{-cymene})]_2$	6	5	35	11 (S)
3	$[Ir(COD)_2]\,BF_4$	1	5	0	–
4	$[IrCp^*Cl_2]_2$	1	5	76	Rac

[a] % Conversion of acetophenone in alcohol was determined by GC.
[b] % Determined by GC chiral column.

In the laboratory, we previously developed the palladium catalyzed dehydrogenative alkylation of cyclohexanone derivatives to prepare aromatic ethers [18] and amines [19]. The aromatic amines were prepared by heating an amine with cyclohexanone derivatives in the presence of palladium on charcoal and 1-octene as hydrogen scavenger in a pressure tube. The formation of the imine was followed by a tautomerisation into enamine leading to the concomitant aromatization, the release of hydrogen is adsorbed on the palladium surface which hydrogenated 1-octene. With this useful tool in hand, the access to chiral aryl amine was studied.

2. Experimental

2.1. Methods and materials

All reagents were obtained from commercial sources and used as received. Cyclohexane-1, 2-diamine, cyclohexanone and tetralone derivatives were purchased from Sigma–Aldrich®. Pd/C 5 wt% on active carbon, reduced and dry (EScat™ 1431) was purchased from Strem Chemicals Inc. All reactions were performed under an inert atmosphere (argon). Silica gel (40–63 micron) was used for column chromatography. Thin layer chromatography (TLC) was performed on pre-coated silica gel 60−F 254 plates. UV light, phosphomolibdic acid and ninhydrine were used as Revelator for analysis of the TLC plates. All compounds were characterized by spectroscopic analysis. The NMR spectra were recorded with a Bruker ALS or DRX 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz), chemical shifts are expressed in ppm, J values are given in Hz; $CDCl_3$, CD_3OD and dimethyle sulfoxide DMSO-d_6, were used as solvent and internal standard ($CDCl_3$: 7.26 ppm in ^{1}H and 77.1 ppm in ^{13}C. CD_3OD: 4.87 ppm, 3.31 in ^{1}H and 49.1 ppm in ^{13}C. DMSO: 2.5 ppm in ^{1}H and 39.5 ppm in ^{13}C). The peak patterns are indicated as follows: (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br, for broad).

Chiral GC was performed on Shimadzu Gas Chromatograph GC−14A coupled with an integrator Shimadzu C−R6A Chromatopac using a Rt®−βDEXm capillary column (30.0 m × 0.25 mm × 0.25 μm) purchased from Restek Chromatography Products and an FID (flame ionisation detector). N_2 gas was used as a carrier at 1.75 kg/cm^2. Chiral HPLC was performed on a PerkinElmer Series 200 (pump, UV/VIS detector at 254 nm, Vacuum degasser) with a chiral column Chiralcel OJ−H column 0.46 × 25 cm (Daicel Chemical Ind., Ltd.).

Optical rotations were determined at 589 nm (sodium D line) at 20 °C by using a PerkinElmer−343 MC digital polarimeter. Optical rotations are reported as follows $[\alpha]^T{}_D$ (concentration c = g/100 mL of solvent) and solvent. Configurations were determined by comparison of the measured $[\alpha]^T{}_D$ with the one reported in the literature.

Melting points were recorded on a Heizbank system Kofler Type WME (Wagner & Munz).

2.2. General method for preparation of ligands

Procedure A: Dehydrogenative alkylation of functionalized α-tetralone with (1*R*, 2*R*)-cyclohexane-1, 2-diamine: In a pressure tube were successively added under inert atmosphere, 1eq of diamine (2 mmol, 0.23 g), 3eq of α-tetralone (6 mmol, 0.9 g) and 2.5 mol% of Pd/C (5%) (0.05 mmol, 107 mg). Then, the tube was sealed and placed in preheated oil bath (T = 150 °C). After 24 h of stirring at 800 rpm the crude was cooling down and diluted in a mixture (50/50) of CH_2Cl_2 and CH_3OH then filtered off on Millipore filter (Durapore filter 0.01 μm). The solvents were removed under vacuum and the crude material was purified by flash column chromatography on silica gel (Eluent cyclohexane (500 mL), then cyclohexane/ethyl acetate 90:10)

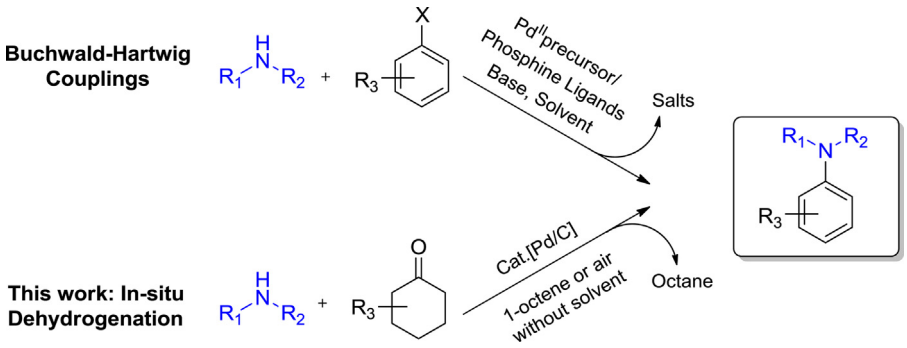
Procedure B: Dehydrogenative alkylation of functionalized β-tetralone with (1*R*, 2*R*)-cyclohexane-1, 2-diamine: In a pressure tube were successively added under inert atmosphere, 1eq of diamine (2 mmol, 0.23 g), 2.5eq of β-tetralone (5 mmol, 0.75 g) and 2 mol% of Pd/C (5%) (0.04 mmol, 85 mg). Then the tube was sealed and placed in preheated oil bath (T = 130 °C). After 24 h of stirring at 800 rpm the crude was cooling down and diluted in a mixture of (50/50) of CH_2Cl_2 and CH_3OH, then filtered off on Millipore filter (Durapore filter 0.01 μm). The solvents were removed under vacuum and the crude material was purified by flash column chromatography on silica gel (Eluent cyclohexane (500 mL) then cyclohexane/ethyl acetate 90:10).

Procedure C: In a pressure tube were successively added, under inert atmosphere, 3eq of diamine (9 mmol, 1.03 g), 1eq of α-tetralone (3 mmol, 0.4 g) and 3 mL of toluene as a solvent. The tube was sealed and placed in a preheated oil path (110 °C) for 64 h. Thereafter 2 mol% of Pd/C (5%) (0.06 mmol, 127 mg) and 2eq of Octene (6 mmol, 0.67 g) were added to the mixture under inert atmosphere, The tube was sealed again and placed in a preheated oil path (150 °C) After 24 h of stirring at 800 rpm the crude was cooling down and diluted in a mixture of (50/50) CH_2Cl_2 and CH_3OH then filtered off on Millipore filter (Durapore filter 0.01 μm). The solvents were removed under vacuum and the crude material was purified by flash column chromatography on silica gel (Eluent DCM (500 mL) then DCM/MeOH 95:5).

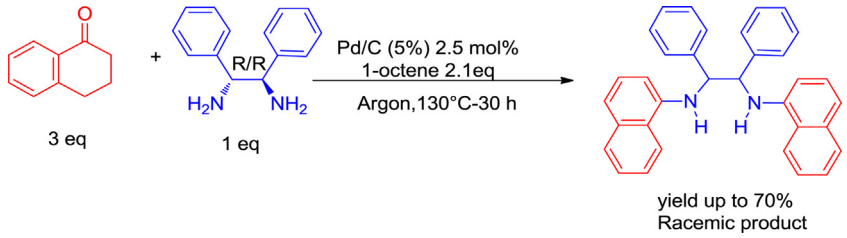
2.3. Characterization data for chiral amine ligand

(1R,2R)-N^1,N-di(naphthalen-1-yl)cyclohexane-1,2-diamine [640276–57–9]: The compound obtained by following the typical procedure A starting from (1R,2R)-cyclohexane-1, 2-diamine (0.23 g, 0.24 mL, 1eq) and α-tetralone (0.9 g, 0.8 mL, 3eq). HREIMS calculated for $C_{26}H_{26}N_2$ = 366.2096 and found m/z = 366.2081, $[a]^{20}{}_D$ = −305 (c 1.02, $CHCl_3$); Mp: 116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38–1.44 (m, 2H, CH_2), 1.54–1.60 (m, 2H, CH_2), 1.88–1.91 (m, 2H, CH_2), 2.59 (d, J = 15.0 Hz, 2H, CH_2), 3.64–3.67 (m, 2H, CH_2), 4.65 (s, 2H, NH), 6.81, (d, J = 6.0 Hz, 2H, CH_{arom}), 7.43–7.29 (m, 8H, CH_{arom}), 7.67 (d, J = 6.0 Hz, 2H, CH_{arom}), 7.78 (d, J = 9.0 Hz, 2H, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8 ($2CH_2$), 32.1 ($2CH_2$), 57.6 (2CH), 105.4 ($2CH_{arom}$), 117.9 ($2CH_{arom}$), 120.2 ($2CH_{arom}$), 124.2 ($2C_{qarom}$), 124.9 ($2CH_{arom}$), 125.9 ($2CH_{arom}$), 126.4 ($2CH_{arom}$), 128.6 ($2CH_{arom}$), 134.5 (C_{qarom}), 142.8 (C_{qarom}).

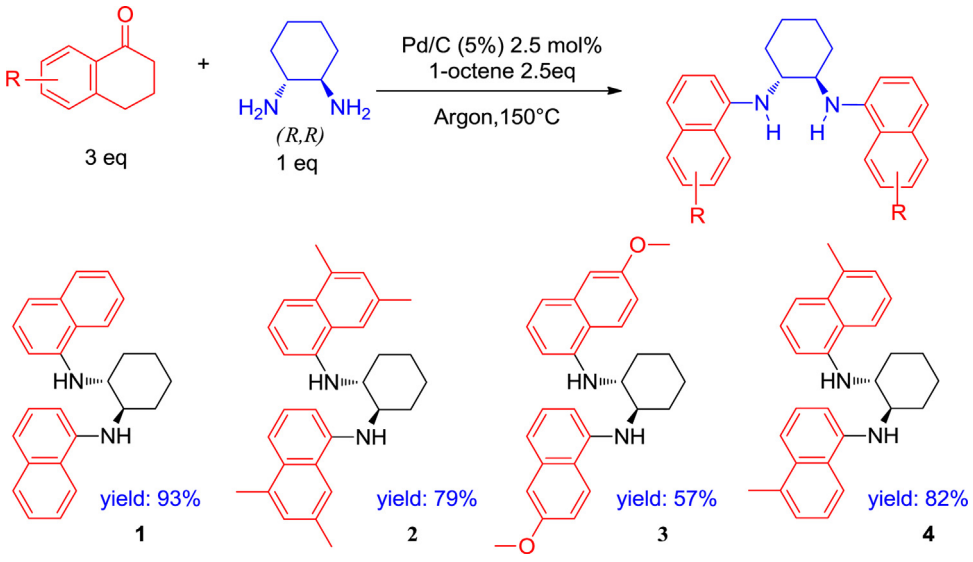
(1*R*,2*R*)-*N*^{1},*N*^{2}-bis(5-methylnaphthalen-1-yl)cyclohexane-1,2-diamine: The compound obtained by following the typical procedure A starting from (1*R*,2*R*)-cyclohexane-1, 2-diamine (0.69 g, 0.72 mL, 6eq) and 4-methyl-1-tetralone (2.9 g, 2.7 mL, 9eq). HREIMS calculated for $C_{28}H_{30}N_2$ = 394.2409 found m/z = 394.2392. $[a]^{20}{}_D$ = −201.98 (c 1.01, $CHCl_3$). Mp: 130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31–1.34 (m, 2H, CH_2), 1.45–1.52 (m, 2H, CH_2), 1.80–1.82 (m, 2H, CH_2), 2.47–2.52 (m, 2H, CH_2), 2.54 (s, 6H, $2CH_3$), 3.54–3.56 (m, 2H, CH_2), 4.3–4.76 (s, 2H, NH), 6.73 (d, J = 7.62 Hz, 2H, CH_{arom}), 7.18–7.45 (m, 8H, CH_{arom}), 7.71 (d, J = 8.34 Hz, 2H, CH_{arom}),



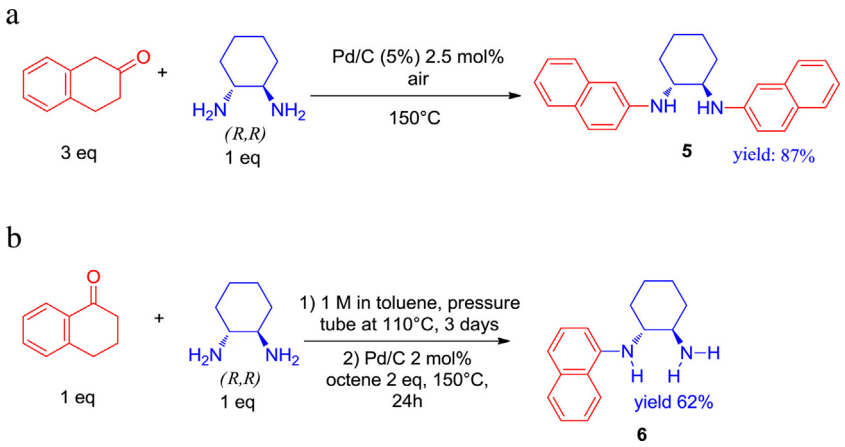
Scheme 1. Our approach compare to literature.



Scheme 2. Synthesis of aromatic amines by alkylation and dehydrogenation starting from (1*R*, 2*R*)-1,2-diphenylethanediamine.

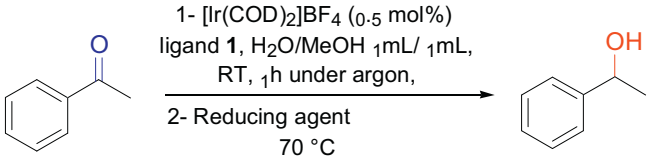


Scheme 3. Synthesis of aromatic amines by alkylation and dehydrogenation.



Scheme 4. (a) Synthesis of Ligand **5.** (b) Synthesis of monoarylated ligand **6.**

Table 2
Transfer hydrogenation of acetophenone using $[Ir(COD)_2]$ BF_4/ligand 1 system and formic acid.



Entry	Ligand **1** (mol%)	HCO_2X (equiv.)	Time (h)	Conv[a] (%)	TON	TOF[c] (h^{-1})	e.e[b] (%) (S)
1	0.5	HCO_2H, 5eq	40	30	60	1.5	77
2	1	HCO_2H, 5eq	40	65	130	3.25	78
3	1	HCO_2H, 10eq	40	24	48	1.2	70
4	1	HCO_2Na 5eq	48	49	98	2.45	50
5	1	HCO_2H 5eq	40	26	52	1.3	82
6	1	HCO_2H 2.5eq/HCO_2Na 2.5eq	23	>99	≈200	8.7	85

[a] Conversion was determined by GC.
[b] Determined by chiral GC.
[c] Minimum TOF.

Table 3
Chiral diamine ligands for transfer hydrogenation of acetophenone.

Entry	Ligand	Time (h)	Conv[a](%)	TON	TOF[c] (h^{-1})	e.e[b](%)
1	2	16	100	200	12.5	86
2	3	24	100	200	8.33	83
3	4	24	100	200	8.33	83
4	5	16	100	200	12.5	83
5	6	24	96	192	8	52

[a] Conversion was determined by GC.
[b] Determined by GC chiral column.
[c] Minimum TOF.

7.90 (d, J = 8.34 Hz, 2H, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9 ($2CH_3$), 24.8 ($2CH_2$), 32.0 ($2CH_2$), 57.7 (2CH), 106.0 ($2CH_{arom}$), 120.8 ($2CH_{arom}$), 124.0 ($2CH_{arom}$), 124.70 ($2CH_{arom}$), 124.78 ($2CH_{arom}$), 124.9 ($2C_{qarom}$), 125.7 ($2CH_{arom}$), 126.8 ($2CH_{arom}$), 133.3 (C_{qarom}), 141.1 (C_{qarom}).

The compound obtained by following the typical procedure A starting from (1*R*,2*R*)-cyclohexane-1,2-diamine (0.69 g, 0.72 mL, 6eq) and 5,7-dimethyl-1-tetralone (3.14 g, 9eq). HREIMS calucated for $C_{30}H_{35}N_2$ = 423.2722 found m/z = 423.2786. [a]$^{20}_D$ = −262.94 (*c* 0.976, CH_2Cl_2). Mp: 134 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36–1.39 (m, 2H, CH_2), 1.52–1.58 (m, 2H, CH_2), 1.86–1.89 (m, 2H, CH_2), 2.32 (s, 6H, $2CH_3$), 2.6 (s, 6H, $2CH_3$), 3.63–3.66 (m, 2H, CH_2), 4.63 (s, 2H, NH), 6.68–6.81 (m, 2H, CH_{arom}), 7.10 (s, 2H, CH_{arom}), 7.30 (s, 2H, CH_{arom}), 738 (d, J = 4.5 Hz, 2H, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0 ($2CH_3$), 221.9 ($2CH_3$), 24.9 ($2CH_2$), 32.2 ($2CH_2$), 57.7 (2CH), 105.7 ($2CH_{arom}$), 114.8 ($2CH_{arom}$), 117.0 ($2CH_{arom}$), 124.4 ($2C_{qarom}$), 125.2 ($2CH_{arom}$), 129.9 ($2CH_{arom}$), 131.8 ($2C_{qarom}$), 134.11 ($2C_{qarom}$), 134.7 ($2C_{qarom}$), 142.8 ($2C_{qarom}$).

(1R,2R)-N^1N^2-bis(6-methoxynaphthalen-1-yl)cyclohexane-1,2-diamine: The compound obtained by following the typical procedure A starting from (1R,2R) -cyclohexane-1, 2-diamine (0.23 g, 0.24 mL 1eq) and 6-methoxy-1-tetralone (1.06 g, 3eq). HREIMS calculated for $C_{28}H_{30}N_2O_2$ = 426.2307 found m/z = 426.2289. [a]$^{20}_D$ =279.5 (c 1.03, $CHCl_3$). Mp: decomposed at 72 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.40 (m, 2H, CH_2), 1.49–1.53 (m, 2H, CH_2), 1.85–1.86 (m, 2H, CH_2), 2.52–2.56 (s, H, CH_2), 3.61–3.64 (m, 2H, CH_2), 3.88 (s, 2-O-CH_3), 4.98 (s, 2H, NH), 6.73 (d, J = 6.0 Hz, 2H, CH_{arom}), 7.95–7.98 (m, 2H, CH_{arom}), 7.01 (s, 2H, CH_{arom}), 7.15–7.30 (m, 4H, CH_{arom}), 7.61 (d, J = 6.0 Hz, 2H, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7 ($2CH_2$), 26.9 ($2CH_2$), 55.2 ($2CH_3$), 57.8 (2CH), 106.8 ($2CH_f$), 117.1 ($2CH_{arom}$), 119.4 ($2C_q$), 121.9 ($2CH_{arom}$), 127.1 ($2C_q$), 135.9 (2Cq), 157.9 ($2C_{qarom}$).

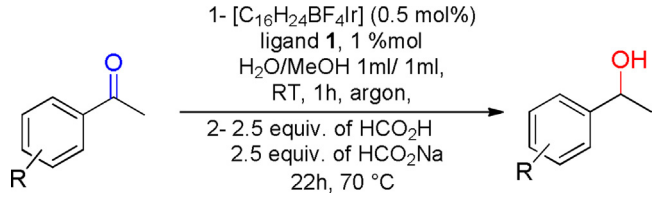
(1R,2R)-N^1,N^2-di(naphthalen-2-yl) cyclohexane-1,2-diamine: The compound obtained by following the typical procedure B starting from (1R,2R)-cyclohexane-1, 2-diamine (0.7 g, 0.72 mL, 3eq) and 2-tetralone (2.19 g, 1.98 mL, 3eq). HREIMS calculated for $C_{26}H_{26}N_2$ 366,2096 found m/z = 366.2077. [α]$^{20}_D$ = +348.36 (c 1.018, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30–1.35 (m, 2H, CH_2), 1.53–1.56 (m, 2H, CH_2), 1.85–1.89 (m, 2H, CH_2), 2.47–2.52 (m, 2H, CH_2), 3.42–3.45 (m, 2H, CH_2), 4.16 (s, 2H, NH), 6.85–6.91 (m, 4H, CH_{arom}), 7.21–7.71 (m, 10H, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6 ($2CH_2$), 32.2 ($2CH_2$), 57.2 (2CH), 105.2 ($2CH_{arom}$), 118.6 ($2CH_{arom}$), 122.2 ($2CH_{arom}$), 125.9 ($2CH_{arom}$), 126.4 ($2CH_{arom}$), 129.1 ($2CH_{arom}$), 130.0 ($2C_{qarom}$), 135.1 (C_{qarom}), 145.1 (C_{qarom}).

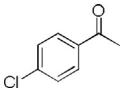
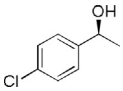
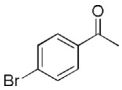
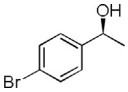
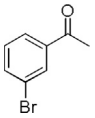
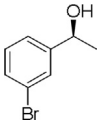
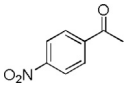
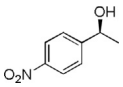
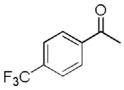
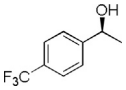
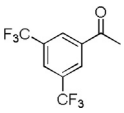
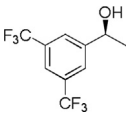
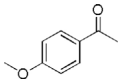
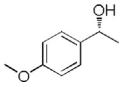
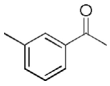
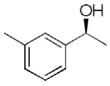
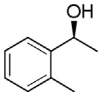
(1R,2R)-N^1-(naphthalen-1-yl) cyclohexane-1, 2-diamine [847901–48–8]: The compound obtained by following the typical procedure C starting from (1R, 2R)-cyclohexane-1,2-diamine (1.027 g, 1.08 mL, 3eq) and 2-tetralone (0.44 g, 0.4 mL, 1eq). HREIMS calculated for $C_{16}H_{20}N_2$ 240,1626 found m/z = 240.1624. [a]$^{20}_D$ = −126.35 (c 0.2, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.97–1.01 (m, 1H), 1.29 (m, 3H), 1.71 (m, 2H), 1.99 (m, 1H), 2.22–2.27 (m, 1H), 2.54 (m, 1H), 2.77 (br. s, 2H), 3.32 (m, 1H), 4.21 (br. s, 1H), 6.72 (d, J = 9.0 Hz, 1H), 7.22 (m, 4H), 7.78 (d, J = 7.32 Hz, 1H), 7.90–7.92 (d, J = 7.98 Hz, 1H) ppm. ^{13}C NMR (75 MHz,CD_3OD): δ = 25.8 (CH_2), 26.1 (CH_2), 32.2 (CH_2), 33.9 (CH_2), 55.8 (CH), 59.1 (CH), 106.1 (CH_{arom}), 118.2 (CH_{arom}), 122.14 (CH_{arom}), 125.4 (CH_{arom}), 126.6 (C_{qarom}), 126.6 (CH_{arom}), 127.58 (CH_{arom}), 129.4 (CH_{arom}), 136.1 (C_{qarom}), 144.6 (C_{qarom}).

2.4. Procedure for the reduction of ketone with [$C_{16}H_{24}BF_4Ir$] and chiral amine ligand

In a pressure tube, 0.5 mol% of metal precursor [$C_{16}H_{24}BF_4Ir$] (2.48 mg, 0.005 mol) and 1 mol% of chiral amine ligand (3.66 mg, 0.01 mmol) were dissolved in 2 mL of water and methanol (ratio 1:1) and stirred at room temperature for 1 h under argon atmosphere. Then formic acid (2.5eq, 0.1 mL), sodium formate (2.5eq, 170 mg) and 1eq of ketone substrate (1 mmol) were introduced. The reaction mixture was stirred at 500 rpm and heated at 70 °C for

Tables 4
Reduction of ketones derivatives.



Entry	Ketone	Product	Isolated yield	TON	TOF[a] (h^{-1})	e.e%
1			86	172	7.2	(*S*)-85
2			70	140	6.37	(*S*)-85
3			80	160	7.27	(*S*)-80
4			79	168	7.63	(*S*)-84
5			87	174	7.91	(*S*)-52
6			86	172	7.2	(*S*)-86
7			71	142	6.45	(*S*)-63
8			31	62	2.82	(*R*)-25
9			66	132	6	(*S*)-86
10			81	162	7.36	(*S*)-93

e.e determined by GC chiral column or OD HPLC chiral column.

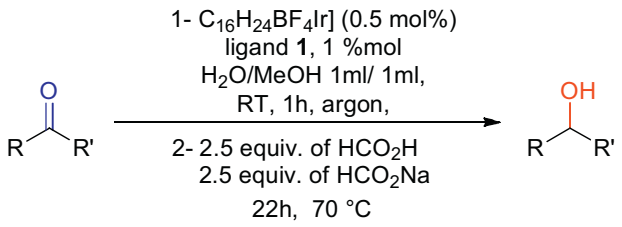
22 h. After that, the tube was cooled to room temperature; and the organic compound was extracted with either with ethyl acetate or CH_2Cl_2, then the solution was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel using cyclohexane/ethyl acetate as gradient eluent (90:10–7:3). After evaporation, alcohols were obtained as oil or solid. The products were identified by NMR. The conversion and the enantioselectivity were determined by chiral GC or chiral HPLC analysis (Scheme 1).

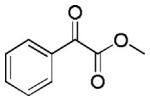
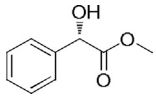
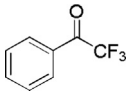
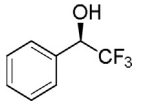
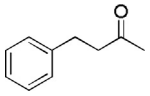
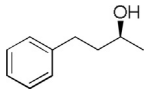
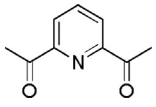
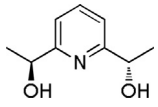
3. Results and discussions

At first, one reaction was performed with enantiopure α-methylbenzylamine and α-tetralone at 130 °C in the presence of palladium on charcoal and octene in a pressure tube. 46% of the desired product was isolated but unfortunately the HLPC analysis showed that a complete racemisation was observed. (1R, 2R)-1,2-Diphenylethane-1,2-diamine was also engaged in the reaction with α-tetralone (Scheme 2). Even though a better isolated yield was obtained in this case (up to 70%) a complete racemization has been observed. In both cases the acidity of the benzylic proton could be responsible of the chirality loss as the non rigidity of the structure (Scheme 3).

Based on these observations, (1R,2R)-cyclohexanediamine which is a rigide diamine was then considered. The dehydrogenative alkylation was occurred with α-tetralone in the presence of 2.5 mol% of Pd/C and 1-octene in a pressure tube at 150 °C. The enantioselective dinaphtyl derivative was isolated in 93% yield showing only one peak in HPLC analysis. To confirm the retention of configuration, both racemic 1,2-cyclohexanediamine and (1S,2S) cyclohexanediamine were arylated and isolated in 95% yields. The HPLC analysis reveals for the racemic mixture two peaks within 10 min between each. This very large difference of retention time supposes that enantiomers are well differenciated by the cyclodextrines. As a result we were curious to evaluate their utilization in asymmetric transformation (Scheme 4).

Table 5
Reduction of ketone derivatives.



Entry	Ketone	Product	Isolated yield	TON	TOF[a] (h^{-1})	e.e%
1			71	144	6.55	(*S*)-43
2			86	172	7.82	(*R*)-59
3			41	82	3.73	(*R*)-15
4			47	92	4.18	>99 d.e: 67%

e.e determined by GC chiral column or OD HPLC chiral column.
[a] Minimum TOF.

Following the same procedure, substituted napthyl from α-tetralone derivatives were synthesized with good isolated yields. In each case, only one enantiomer was observed. The conditions were adapted for the dehydrogenative alkylation with β-tetralone to reach ligand 5 high yield, with the successful preparation of the diaryl ligands, we were curious to selectively prepare the monoaryl derivative. In the above conditions, the desired monoarylated product was obtained with the diarylated one as well as some of starting materials. Therefore, the reaction was realized stepwise with at first the formation of the imine followed by the aromatization in the presence of palladium. By this way, 62% of the monoarylated molecule **6** was isolated and no racemization of the chiral center was detected through HPLC analysis.

The convenient synthesis of these ligands prompts us to evaluate their interest in asymmetric transformation. Inspired by the literature data, transfer hydrogenation of ketones was considered and Ru or Ir complexes was associated to isopropanol in the presence of potassium tert-butoxide [20,21].

The reduction of acetophenone was studied firstly. When $[RuCl_2(pcymene)]_2$ was used as metal precursor with ligand **1** (Table 1, entry 1), 1-phenyl-ethanol was formed with 90% conversion in a racemic mixture, while with ligand **6** the conversion was much lower (34%) with a poor enantiomeric excess (11%) (Table 1, entry 2). With $[Ir(COD)_2]BF_4$ and ligand 1 no transformation was observed (Table 1, entry 3). On the other hand, when the $[IrCp^*Cl_2]_2$ was used, a good conversion was obtained but unfortunately without enantioselectivity (Table 1, entry 4). In view of these results, the nature of the reductant was modified following Carreira conditions: [22] the reduction of acetophenone was carried out with $[(COD)_2Ir]BF_4$ and ligand **1** in water/methanol (1:1) at room temperature under argon atmosphere for one hour, before adding formic acid as a reducing agent.

Initially, for 1:1 ratio metal:ligand **1** a low conversion was measured with a relatively good enantiomeric excess (e.e 77%), while using 1:2 ratio metal-ligand the conversion reached 65% with 78% e.e Table 2 entry 1 and 2). The configuration of the alcohol was identified as S isomer by comparison with the literature. An addition of formic acid 10equiv. (instead of 5) was not beneficial for the reduction since the conversion was lower (Table 2, entry 3) this maybe due to the dilution effect and a modification of the pH. Sodium formate was also examined and no improvement was observed for both conversion and enantiomeric excess (Table 2, entry 4). Furthermore, the reaction was investigated under air and gave low conversion (26%) with a good improvement of the e.e (82%) (Table 2, entry 5). Then a mixture of formic acid and sodium formate of ratio 1:1 was used and showed a complete conversion with 85% e.e in 22 h (entry 6). The $[(COD)_2Ir]BF_4$/ligand **1** system using a mixture of formic acid and sodium formate (with pH 3.5 at the beginning of the reaction) as a reductant gave the best results for this reduction (conversion >99%). This pH-dependant reactivity with formic derivatives was previously observed by Ogo [23].

The other derived ligands were evaluated in the same conditions.

The substituent on the aromatic ring has no influence on the reduction since complete conversion was observed for ligand **2**, **3**, **4** with similar enantiomeric excess (Table 3, entries 1,2,3). In addition, similar results were also observed with the derivative coming from β-tetralone (Table 3, entry 4), while a loss of the enantiomeric excess was noticed with the monoarylated ligand (Table 3, entry 5).

With the optimized condition, a range of ketones has been reduced into corresponding alcohols with high to moderate isolated yields and good e.e using catalytic system $[C_{16}H_{24}BF_4Ir]$/ligand **1** as shown in Table 4.

The substitution of acetophenone with halogen did not affect the reaction since ketones were efficiently and enantioselectively reduced whatever the position (Table 4, entries 2–4). The reduction of acetophenone bearing a EWG nitro group afforded the corresponding alcohol with a good yield but with a poor enantiomeric excess (Table 4, entry 5), but EWG like trifluoromethyl in the same position, the reduction occurred with a similar conversion and enantioselectivity compared to acetophenone (Table 4, entry 6). Nevertheless, the meta-substitution with two CF_3 groups was dele-

terious for the enantiomeric excess (Table 4, entry 7). The acidity of the benzylic proton for the nitro and the di-trifluoromethyl derivatives might be responsible for the decrease of enantiomeric excess. Acetophenone bearing p-methoxy group was reduced with a low yield as well as a low enantioselectivity (Table 4, entry 8). In this particular case, the configuration of the carbon is inverted compared to other, may is due to the coordination or EDG character of methoxy group. Electron donating group as a methyl in meta give a lower isolated yield of alcohol with only the starting material but with similar ee. And the same group in ortho position has a positive effect on the enantiomeric excess (Table 4, entries 9 and 10).

The reduction of more functionalized ketones was also investigated (Table 5).

With activated ketone, the corresponding hydroxy ester (Table 5, entry 1) was obtained with a modest induction 43 % (-e.e and 71% isolated yields. Close results were observed with the trifluoromethyl derivative (Table 5, entry 12) which was obtained with a good isolated yield 86% in 59% ee with the opposite configuration. This change is linked to the CF_3 group which inverts the priority order of the group as already well described. Dialkyl ketones (Table 5, entry 3), gave low e.e 15% of S configuration with moderate isolated yield. The reaction of 2,6-diacetylpyridine afforded the corresponding diol (entry 4) in 67% d.e and >99% e.e of S,S configuration.

4. Conclusions

From a very simple procedure to prepare aryl amine, conditions were optimized to prepare aryl dicyclohexandiamine ligands with retention of the configuration in good yields. The interest of these ligands was evaluated on the asymmetric transfer hydrogenation with a homogeneous iridium catalyst associated to formic acid and its sodium salt. Best conditions are obtained using a mixture of sodium formate and formic acid as a hydrogen source, improving the efficiency of the catalyst at pH 3.5 at the beginning of the reaction. These achievements demonstrated the interest of this type of ligands. As a result, further studies on the development of diverse of chiral amine ligands and their application in other reactions of asymmetric catalysis are ongoing.

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