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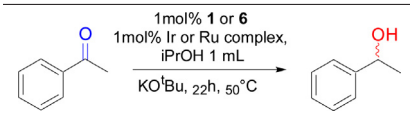
Table 1
Transfer hydrogenation of acetophenone using Ru and Ir metal with ligand 1 and 6.



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}),