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New chiral diamino ligands as sparteine analogues. Application to the palladium-catalyzed kinetic oxidative resolution of 1-phenyl ethanol

Giordano Lesma [a], Tullio Pilati [b], Alessandro Sacchetti [a,*], Alessandra Silvani [a]

[a] *Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, Via G. Venezian 21, 20133 Milano, Italy*
[b] *Istituto di Scienze e Tecnologie Molecolari—CNR, Via Golgi 19, 20133 Milano, Italy*

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ABSTRACT

Novel chiral 9-keto-bispidines were investigated as ligands in the palladium-catalyzed kinetic oxidative resolution (KOR) of 1-phenyl ethanol. The ligands were easily prepared by means of a two-step synthetic sequence starting from commercially available products.

1. Introduction

The natural alkaloid (−)-sparteine **1** (Fig. 1) has been thoroughly studied as a chiral diamino ligand, mainly in asymmetric deprotonation with alkyllithium bases.[1] In addition to organolithium reagents, (−)-sparteine has also been employed with other metals such as Mg, Cu and Zn.[2] In 2001, the use of a Pd-(−)-sparteine complex for the aerobic kinetic oxidative resolution (KOR) of racemic alcohols was also reported.[3]

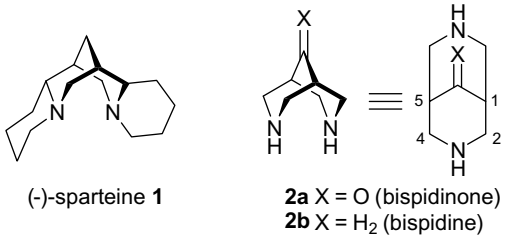

Figure 1.

The main drawback in the (−)-sparteine methodologies is that this alkaloid is readily available only as a single antipode from natural sources, and it is a difficult template to be optimized through structural variations. In 2002, O'Brien[4a] reported the synthesis of a (+)-sparteine-like tricyclic diamine, synthesized by starting from the expensive natural occurring alkaloid (−)-cytisine, which catalyzes different asymmetric transformations with good ee.[4]

In our ongoing studies on the preparation of sparteine analogues,[5] we herein report the synthesis of novel chiral C_1-symmetric diamino ligands, based on the 3,7-diaza-bicyclo[3.3.1]nonan-9-one moiety (bispidinone **2a**) and their preliminary application in the palladium-catalyzed kinetic oxidative resolution of racemic 1-phenyl ethanol. Bispidines **2b** are structurally correlated to (−)-sparteine and have been previously described as both achiral and chiral ligands in different metal-catalyzed reactions.[6]

2. Results and discussion

We planned the synthesis of the 9-keto-bispidine ligands **3a–d** (Fig. 2). These ligands could be easily prepared in enantiopure form

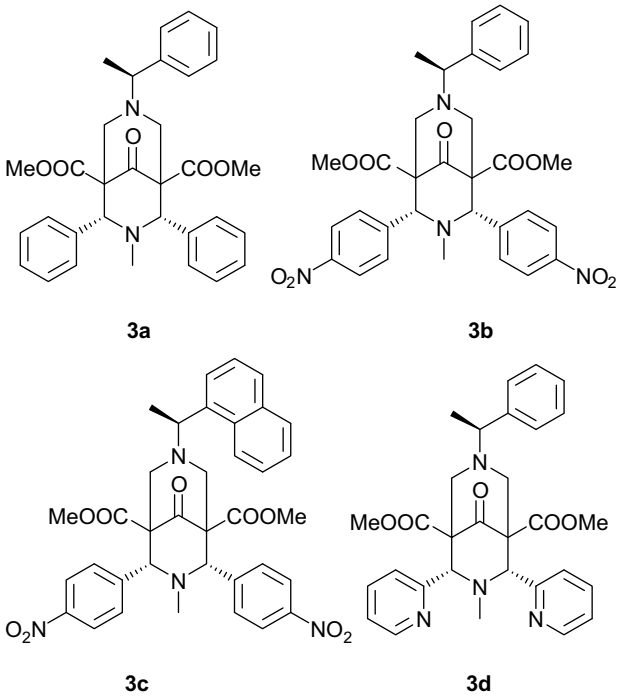

Figure 2. Ligands **3a–d**.

* Corresponding author. Tel.: +39 02 50314081; fax: +39 02 50314078.
E-mail address: alessandro.sacchetti@unimi.it (A. Sacchetti).

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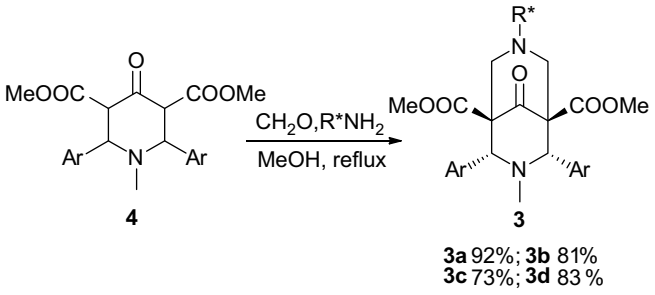
by means of a two-step synthetic sequence relying on double Mannich reactions, starting from commercially available products on a gram scale. Different substituents can be easily introduced onto the diaza-bicyclo[3.3.1]nonan-9-one framework, thus allowing, in principle, the preparation of a library of ligands. Ligands **3a–d** are characterized by the presence of two aromatic groups on C2 and C4, which increase the steric hindrance at the coordinating nitrogen atom, and two carbomethoxy groups on C1 and C5. The source of chirality is a chiral primary amine [(*S*)-1-phenyl-ethylamine or (*S*)-1-naphthalen-1-yl-ethylamine] introduced in the last synthetic step. Whilst ligands **3a–c** can act as bidentate diamino ligands, for ligand **3d**, further coordination capabilities can be predicted due to the presence of pyridine donor substituents.

Ligands **3a–d** were synthesized according to Scheme 1. Piperidine-4-ones **4** were prepared in a single step following a reported procedure.[7] A double Mannich reaction of **4** with either (*S*)-1-phenyl-ethylamine or (*S*)-1-naphthalen-1-yl-ethylamine and 2.5 equiv of formaldehyde in refluxing methanol gave the desired products in high yields (73–92%).



Scheme 1. Synthesis of ligands **3a–d**.

All bispidinones **3a–d** could be easily purified by crystallization from methanol and have been characterized by NMR spectroscopy and MS. A 2-D NMR analysis allowed us to confirm a *cis* diequatorial relative disposition of the aryl substituents on the C2 and C4 of the bispidinone framework. This observation is in agreement with previous literature reports on the conformational and configurational behaviour of substituted bispidinones.[8] For ligand **3d**, we were able to perform an X-ray diffraction analysis on a single crystal, isolated after crystallization from *i*-PrOH (Fig. 3). The structure confirms the chair–chair conformation for the bispidine core, with the two pyridyl residues in a *cis* diequatorial relative disposition.

We tested ligands **3a–d** in the kinetic oxidative resolution of racemic 1-phenyl ethanol. Reactions were carried out in toluene at 80 °C under an oxygen atmosphere in the presence of 3 Å molecular sieves. The catalytic system was realized using 20 mol % of ligand and 5 mol % of $Pd(nbd)Cl_2$. Chiral HPLC was used to determine both conversions and enantiomeric excesses. Reactions were stopped after 72 h. In these conditions (−)-sparteine gave, in our hands, 55% conversion and 96% ee [(*S*)-enantiomer] and a selectivity factor (k_{rel}) of 31.9, completely in agreement with literature.[3] Results are reported in Table 1.

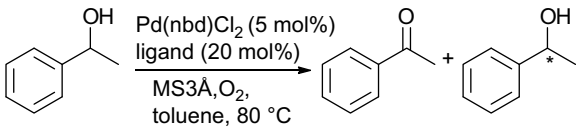


Figure 3. Plot of the structure of ligand **3d** as determined by X-ray crystallography (hydrogen atoms omitted: see Section 4).

Table 1
Palladium-catalyzed kinetic oxidative resolution of racemic 1-phenyl ethanol

Entry	Ligand	Conversion[a] (%)	ee[a] (%)	k_{rel}[b]
1	**3a**	53	20 (*R*)	1.7
2	**3b**	42	31 (*R*)	3.3
3	**3c**	45	42 (*R*)	4.6
4	**3d**	10	4 (*R*)	2.2
5	(−)-Sparteine	55	96 (*S*)	31.9

[a] Determined by HPLC analysis on a chiral column. See Section 4 for details.
[b] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$.

For ligands **3a**,**c** good conversions were achieved, as result of an efficient LAC (ligand accelerated catalysis) effect. Unfortunately the ee proved to be modest. Comparisons between **3a** and **3b** indicated that the presence of electron poor aromatic residues seems to be favourable. By changing the phenyl group of **3b** with the more sterically hindered naphthalen-1-yl substituent in ligand **3c**, we could obtain the highest ee (42%) and selectivity (k_{rel} = 4.6). In contrast, the presence of the two pyridine substituents in **3d** caused a dramatic lowering of both yield and ee. A possible reason for the low activity of ligand **3d** could be the formation of stabilized highly coordinated palladium complexes, in which **3d** acts as a tetra-coordinating agent.[9] In this way, the palladium would be prevented from coordinating the substrate, thus resulting in an inhibition of the first step of the catalytic cycle.

In order to improve these results, we performed the reaction in different solvents, such as dichloromethane, chloroform and *tert*-butanol,[10] without any success. The addition of exogenous inorganic bases such as caesium carbonate or sodium carbonate did not affect the results.[11] Changing the palladium source from $Pd(nbd)Cl_2$ to $PdCl_2$ only resulted in a slight shortening of the reaction time, without any influence on the enantiomeric excess.

3. Conclusions

In conclusion, we have developed a new class of bispidinone-based chiral ligands. All compounds could be easily obtained by a two-step synthesis, starting from commercially available and low cost products on gram scale. Ligands with electron poor aromatic substituents catalyzed the kinetic oxidative resolution (KOR) with good conversion and moderate enantioselectivity. These ligands represent the first example of simple diamino chiral ligands applied in the palladium-catalyzed kinetic oxidative resolution of racemic alcohols.

4. Experimental

4.1. General

All solvents were distilled and properly dried, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. During the

usual workup, all organic extracts were dried (Na_2SO_4 or $MgSO_4$) and evaporated. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (Merck); spots were visualized with UV light or by treatment with 1% aqueous $KMnO_4$ solution. ^1H and ^{13}C NMR spectra were recorded with Bruker AC 300 (^1H, 300 MHz; ^{13}C, 75.4 MHz) and 400 MHz Avance (^1H, 400 MHz; ^{13}C, 100 MHz) NMR spectrometers. Chemical shifts are reported in parts per million downfield from $SiMe_4$ ($\delta = 0.0$). HPLC analyses were performed on a Jasco LC2000 Series System equipped with a UV detector and a Chiralcell OD HPLC column. HR FAB mass spectra in the positive mode were measured on VG 70–70 EQ-HF instrument equipped with its standard sources. Optical rotations were measured with a Perkin–Elmer 241 polarimeter.

4.2. Synthesis

4.2.1. Typical procedure for the synthesis of the bispidinones 3a–d

To a suspension of paraformaldehyde (7.5 mmol) in 20 ml of methanol, the piperidinone **4** (3 mmol) and (*S*)-1-phenyl-ethylamine or (*S*)-1-naphthalen-1-yl-ethylamine (3 mmol) were added. The mixture was heated at reflux for 24 h. On cooling to room temperature the product precipitated and was collected by filtration. The crude was purified by crystallization with methanol, affording the pure bispidinones as a solid.

4.2.2. (1*R*,2*R*,4*S*,5*S*)-3-Methyl-9-oxo-2,4-diphenyl-7-((*S*)-1-phenyl-ethyl)-3,7-diaza-bicyclo[3.3.1]nonane-1,5-dicarboxylic acid dimethyl ester 3a

2.53 g, 92% yield. Mp 134 °C. $[\alpha]_D^{25} = +6.5$ (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.04 (m, 2H), 7.48–7.04 (m, 13H), 4.42 (s, 1H), 4.38 (s, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.61 (q, $J = 6.7$ Hz, 1H), 3.40 (dd, $J = 11.6$, 1.8 Hz, 1H), 3.20 (d, $J = 12.1$, 1.8 Hz, 1H), 2.70 (m, 2H), 1.82 (s, 3H), 1.53 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.3, 169.3, 169.1, 142.0, 139.1, 138.9, 130.1–128.2 (15C), 73.7, 73.6, 65.4, 64.2, 64.1, 56.4, 55.7, 52.8, 52.7, 43.8, 17.7. HRMS-FAB *m*/*z* calcd 526.2468, found 526.2471. Anal. Calcd for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32; O, 15.19. Found: C, 73.00; H, 6.38; N, 4.86.

4.2.3. (1*R*,2*R*,4*S*,5*S*)-3-Methyl-2,4-bis-(4-nitro-phenyl)-9-oxo-7-((*S*)-1-phenyl-ethyl)-3,7-diaza-bicyclo[3.3.1]nonane-1,5-dicarboxylic acid dimethyl ester 3b

1.86 g, 81% yield. Mp 196 °C. $[\alpha]_D^{25} = +4.9$ (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.25–8.00 (m, 4H), 7.55–7.15 (m, 9H), 4.60 (s, 1H), 4.55 (s, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.60 (q, $J = 7.1$ Hz, 1H), 3.25 (d, $J = 13.1$ Hz, 1H), 3.20 (d, $J = 13.1$, Hz, 1H), 2.75 (m, 2H), 2.20 (s, 3H), 1.45 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.8, 167.7, 167.5, 147.8 (2C), 145.3 (2C), 140.9, 129.7–123.5 (13C), 72.0, 71.9, 62.9, 62.8, 58.5, 56.9, 53.5, 52.7, 52.6, 43.3, 15.1. HRMS-FAB *m*/*z* calcd 616.2169, found 616.2165. Anal. Calcd for $C_{32}H_{32}N_4O_9$: C, 62.33; H, 5.23; N, 9.09; O, 23.35. Found: C, 62.28; H, 5.30; N, 9.17.

4.2.4. (1*R*,2*R*,4*S*,5*S*)-3-Methyl-7-((*S*)-1-naphthalen-1-yl-ethyl)-2,4-bis-(4-nitro-phenyl)-9-oxo-3,7-diaza-bicyclo[3.3.1]nonane-1,5-dicarboxylic acid dimethyl ester 3c

1.12 g, 73% yield. Mp 115 °C. $[\alpha]_D^{25} = +12.9$ (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.45 (d, $J = 8.5$ Hz, 1H), 8.25 (d, $J = 8.5$ Hz, 1H), 8.15–7.95 (m, 3H), 7.80–7.45 (m, 8H), 7.25 (m, 2H), 4.65 (q, $J = 7$ Hz, 1H), 4.55 (s, 1H), 4.50 (s, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.35 (d, $J = 13$ Hz, 1H), 3.25 (d, $J = 13$ Hz, 1H), 3.15 (d, $J = 13$ Hz, 1H), 3.00 (d, $J = 13$ Hz, 1H), 1.70 (s, 3H), 1.55 (d, $J = 7$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.9, 167.8, 167.5, 147.9, 147.7, 145.1, 145.0, 137.6, 134.3, 131.7, 130.4, 130.1, 129.9, 129.4, 128.6, 128.2, 126.2–123.2 (9C), 72.0, 71.9, 62.9, 62.8, 58.5, 56.9, 53.5, 52.7, 52.6, 43.3, 15.1. HRMS-FAB *m*/*z* calcd 666.2326, found 666.2321. Anal. Calcd for $C_{36}H_{34}N_4O_9$: C, 64.86; H, 5.14; N, 8.40; O, 21.60. Found: C, 64.80; H, 5.16; N, 8.37.

4.2.5. (1*R*,2*S*,4*R*,5*S*)-3-Methyl-9-oxo-7-((*S*)-1-phenyl-ethyl)-2,4-di-pyridin-2-yl-3,7-diaza-bicyclo[3.3.1]nonane-1,5-dicarboxylic acid dimethyl ester 3d

2.84 g, 83% yield. Mp 174 °C (decomp.). $[\alpha]_D^{25} = +8.0$ (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): 8.43 (t, 1H, $J = 3.7$ Hz), 7.92 (d, 1H, $J = 7.9$ Hz), 7.84 (d, 1H, $J = 7.9$ Hz), 7.60 (td, 1H, $J = 7.7$, 1.8 Hz), 7.53 (td, 1H, $J = 7.7$, 1.8 Hz), 7.29 (m, 3H), 7.13 (m, 1H), 4.65 (s, 1H), 4.64 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.47 (q, 1H, $J = 6.9$ Hz), 3.05 (m, 2H), 2.58 (m, 2H), 1.96 (s, 3H), 1.31 (d, 3H, $J = 6.9$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.4, 169.4, 169.3, 159.0, 158.9, 149.7 (2C), 141.7, 136.8, 136.7, 129.0 (2C), 128.9 (2C), 128.0, 124.2, 124.0, 123.5, 123.4, 72.0, 71.9, 64.7, 62.9, 62.8, 56.1, 53.8, 52.7, 52.6, 43.3, 15.9. HRMS-FAB *m*/*z* calcd 528.2373, found 528.2379. Anal. Calcd for $C_{30}H_{32}N_4O_5$: C, 68.17; H, 6.10; N, 10.60; O, 15.13. Found: C, 68.22; H, 6.18; N, 10.55.

4.3. Procedure for the kinetic oxidative resolution of 1-phenyl ethanol

At first 0.25 g of 3 Å molecular sieves was placed in a 25 mL reaction flask and flame-dried under vacuum. After cooling under nitrogen, 5 mL of dry toluene was added followed by 7 mg of $Pd(nbd)Cl_2$ (0.025 mmol, 0.05 equiv) and by the ligand (0.10 mmol, 0.2 equiv). Nitrogen was removed under reduced pressure and the flask filled with O_2. The reaction mixture was heated to 80 °C for 30 min, then 60 μL of 1-phenyl ethanol (0.5 mmol, 1 equiv) was added. The reaction was monitored by HPLC analysis for 72 h (HPLC analysis conditions: column, Chiralcel OD; eluant 95:5 *n*-hexane/*i*-PrOH; flow rate, 0.8 mL/min; UV detector, 230 nm. Commercially available (*R*)-1-phenyl ethanol and (*S*)-1-phenyl ethanol were used as an analytical standard. Retention time of (*R*)-1-phenyl ethanol: 11 min. Retention time of (*S*)-1-phenyl ethanol: 13 min). Aliquots of the reaction mixture were collected, filtered through a small plug of silica gel (EtOAc eluant), evaporated and analyzed.

4.4. Crystal data for 3d

$M_r = 528.60$, trigonal, $P3_1$, $a = 14.3904(12)$, $c = 11.5091(10)$ Å, $V = 2064.0(2)$ Å^3, $Z = 3$, $T = 123$ K, $D_c = 1.276$ g cm^{-3}, μ(Mo Kα) = 0.088 cm^{-1}, $F(000) = 840$; block, $0.48 \times 0.32 \times 0.22$ mm, Bruker *APEX*2000 diffractometer; 28,606 data collected, 3982 unique, $R_{int} = 0.0459$, 3386 with $I_o > 2\sigma(I_o)$. The structure was solved by direct method,[12] and refined anisotropically by matrix least-squares based on F^2,[13] to give $R_1 = 0.0405$, $wR_2 = 0.0641$ for all 3982 reflections and 480 parameters and 1 restraint. The absolute configuration was chosen on the known chirality of the (*S*)-1-phenyl-ethylamine group, unchanged by the chemical synthesis. Supplementary crystallographic data were deposited as CCDC 635829 with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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