Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 3493–3496
Tetrahedron Letters

Chiral 5-(diphenylphosphanyl)-1,2,3,4-tetrahydroacridines: new N,P-ligands for asymmetric catalysis

Giorgio Chelucci* and Gianmauro Orrù

Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy

Received 22 February 2005; revised 15 March 2005; accepted 16 March 2005
Available online 5 April 2005

Abstract—Three chiral 5-(diphenylphosphanyl)-1,2,3,4-tetrahydroacridines, as first representative examples of a new class of chiral N,P-ligands were prepared from (+)-nopinone, (+)-camphor and 5α-androst-2-en-17-one. These ligands have been assessed in the enantioselective palladium-catalysed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. Enantioselectivity up to 74% has been obtained.

Since the design of chiral ligands plays a key role in the development of metal-catalysed asymmetric reactions, many recent studies have addressed the development of novel chiral ligands.[1]

To date, a large number of chiral ligands having hetero-donor atoms with nitrogen and phosphorus functional moieties (N,P-ligands) has been prepared and their usefulness for asymmetric reactions has been investigated.[2] In the context of N,P-ligands, those with pyridine N-donors are receiving a great deal of attention and an increasing number of reports on their synthesis and use in various catalytic processes are appearing in the literature.[3]

Recently, Kocovsky and co-workers[4] and the present authors[5] have reported the synthesis of the chiral 2-(2-diphenylphosphinophenyl)-5,6,7,8-tetrahydroquinolines **1** (Fig. 1) and their application in several type of catalytic asymmetric processes. In this class of ligands the 2-diphenylphosphinophenyl group is bonded to the 2-position of a chiral 5,6,7,8-tetrahydroquinoline ring. Pursuing our research in this field, we have now directed our interest to chiral 5-(diphenylphosphanyl)-1,2,3,4-tetrahydroacridines of type **2** (Fig. 1), in which the phenyl group of the 2-diphenylphosphinophenyl substituent is now annulated to the pyridine ring of chiral 5,6,7,8-tetrahydroquinoline framework. This structural modification makes the two nitrogen and phosphorus donor

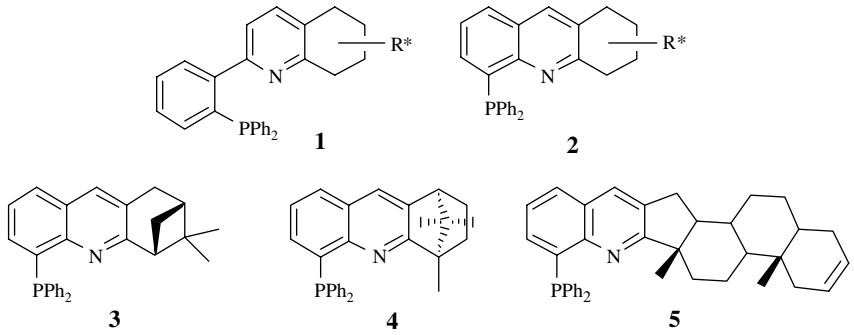


Figure 1.

Keywords: Phosphinopyridine ligands; Chiral acridines; Palladium catalysts; Enantioselective allylic substitutions.
* Corresponding author. Tel.: +39 079 229539; fax: +39 079 229559; e-mail: chelucci@ssmain.uniss.it

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.113

atoms to be arranged in rigid backbone in such a way as to provide a more rigid array of the ligand around the metal centre. Last but not least, the ligands **1** form a six-membered metal chelate while the new ligands **2** form a five-membered chelate ring.

Herein, we report the synthesis of the chiral 5-(diphenylphosphanyl)-1,2,3,4-tetrahydroacridines **3**–**5** (Fig. 1), as first representative examples of N,P-ligands of the type **2** and the preliminary results obtained with these ligands in the enantioselective palladium-catalysed allylic substitution.

For the synthesis of ligands of the type **2**, we envisaged that a convenient approach could involve the introducing of the diphenylphosphanyl group by nucleophilic substitution with lithium diphenylphosphide ($LiPPh_2$) of an electrophilic aryl fluoride on the C5 of the tetrahydroacridine **6**.[6] This could be in turn obtained by the Friedländer condensation[7] between the 3-substituted 2-aminobenzaldehyde **7** and the chiral ketone **8** (Fig. 2).

For this purpose, the 2-amino-3-fluorobenzaldehyde (**7**)[8] obtained by hydrolysis of the *N*-Boc aldehyde **10**,[9] was submitted to Friedländer condensation with the (+)-nopinone (**13**) (ethanol or carbitol, saturated KOH in MeOH) to afford the 5-fluorotetrahydroacridine **12** in only 9% yield (Scheme 1). The low yield is due to the relative instability of the *o*-amino aryl aldehyde, which can readily undergo self-condensation reactions.

To overcome this drawback a different method, which avoids the isolation of the *o*-amino benzaldehyde was followed[9] (Scheme 1). Accordingly, the *N*-Boc aldehyde **10** and the ketone **13** were stirred in dioxane containing potassium *tert*-butoxide at room temperature for 2 h and then a 3 N hydrochloric acid solution was added. Heating the resulting mixture under reflux for 2 h led to **12** in good overall yield (88%). Finally, treatment of **12** with $LiPPh_2$ (THF, 0 °C, 0.5 h, then 60 °C, 2 h) afforded the desired diphenylphosphinoacridine **3**[10] in good yield (82%).

However, the extention of this procedure to the N,P-ligand **4** derived from (+)-camphor (**14**) failed (Scheme 2). In fact, no compound was obtained by reaction of **10** with **14** in the presence of *t*-BuOK as the base. The condensation product **15** was instead obtained, although in low yield (21%), when the preformed lithium enolate anion of **14** (LDA, THF, −40 °C, 2 h) was treated with the aldehyde **10**. Moreover, no azaannulation product was obtained when **15** was headed under reflux in a dioxane solution for several hours. This outcomes account for the steric hindrance of camphor carbonyl group that reduces the ability of **14** to undergo both condensation and azaannulation steps.[11] Most gratifyingly, high yield (85%) of the fluoroacridine **16** was obtained when the cyclisation reaction of **15** was carried out under rather drastic conditions (carbitol, HCl, reflux, 1 h). At last, compound **16** was converted in the usual way into the desired diphenylphosphinoacridine **4**[12] in satisfactory yield (75%).

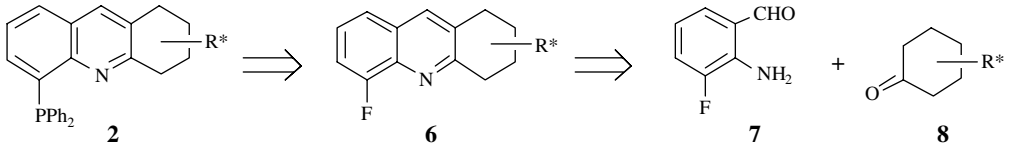
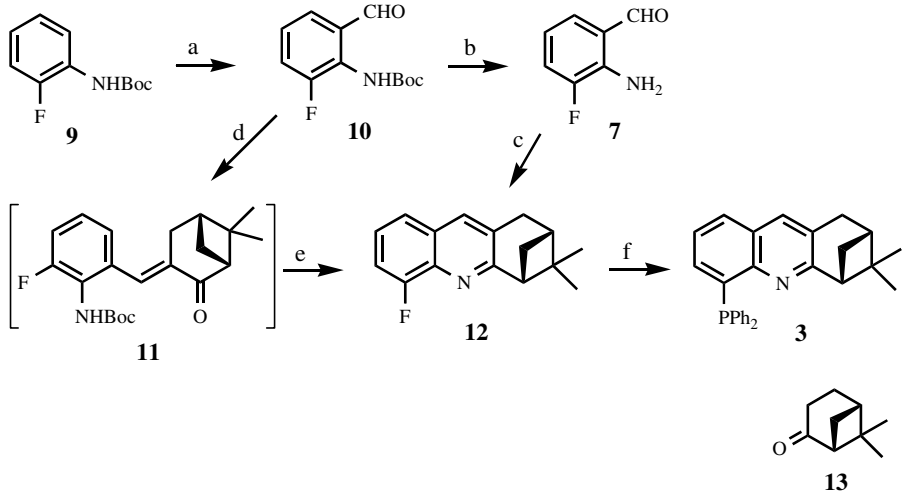
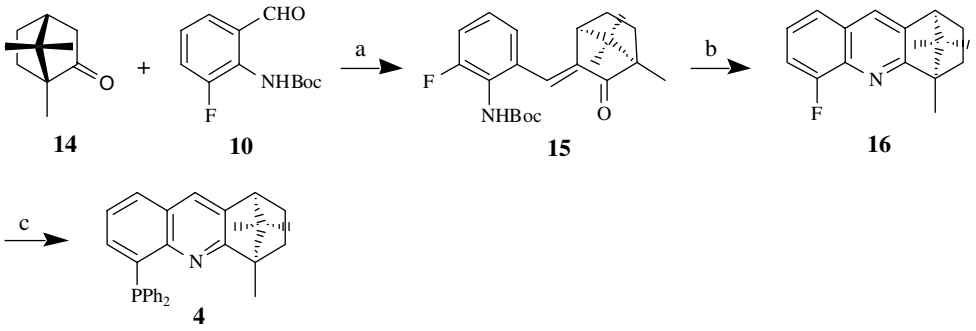


Figure 2.



Scheme 1. Reagents and conditions: (a) *t*-BuLi, −78 to −50 °C, 3 h, then DMF, −78 °C to slowly rt, 71%; (b) HCl (3 N), dioxane, 60 °C, 1 h, 55%; (c) **13**, carbitol, saturated KOH in MeOH, 9%; (d) **13**, *t*-BuOK, 1,4-dioxane, rt, 2 h, then 3 N HCl, reflux, 2 h, 88%; (e) $LiPPh_2$, THF, −10 °C, 0.5 h, then 60 °C, 2 h, 82%.



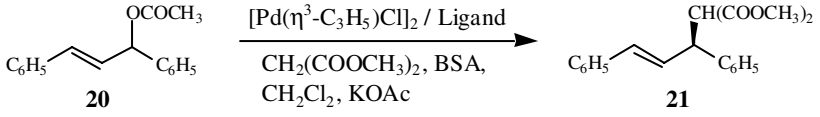
14 10 15 16 4

Scheme 2. Reagents and conditions: (a) **14**, LDA, THF, −40 °C, 2 h, then **10**, 15 min then slowly rt, 21%; (b) carbitol, catalytic HCl, reflux, 1 h, 85%; (c) $LiPPh_2$, THF, −10 °C, 0.5 h, then 60 °C, 2 h, 75%.

Finally, following the protocol established for **4**, the N,P-ligand **5**[13] was obtained in 51% overall yield starting from 5α-androst-2-en-17-one **17**[14] (Scheme 3).

As a model for the evaluation of the ability of the new P–N ligands to provide asymmetric induction in catalytic processes we selected the palladium-catalysed allylic substitutions and in particular the alkylation of 1,3-diphenylprop-2-enyl acetate (**20**) with dimethyl malonate, which serves as a model substrate to compare the outcome of different ligands.[15] Allylic substitutions were carried out employing $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as procatalyst and a mixture of dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in methylene chloride.[16]

analogue ligands **1** bearing the same chiral tetrahydroquinoline unit. Thus, ligand **3a** induced in 2 h the formation of (*S*)-**21** with 74% ee, whereas **1a** [(6*R*,8*R*)-(+)-5,6,7,8-tetrahydro-7,7-dimethyl-2-(2-diphenylphosphinophenyl)-6,8-methanoquinoline] required 70 h to give (*S*)-**21** with 70% ee.[5] More evident is the difference between ligands **4** and **1b** [(5*S*,8*R*)-(−)-5,6,7,8-tetrahydro-8,9,9-trimethyl-2-(2-diphenylphosphinophenyl)-7,8-methanoquinoline]. In fact, ligand **4** led in less than 3 h to the reaction product with 69% ee, whilst **1b** needed 12 h to afford (*S*)-**21** with 50% ee.[5] Both ligands **3**,**4** and **1a**,**b** afforded the product with the same prevailing (*S*)-configuration indicating that the reactive transition state, which determines the stereochemical outcome is likely the same.

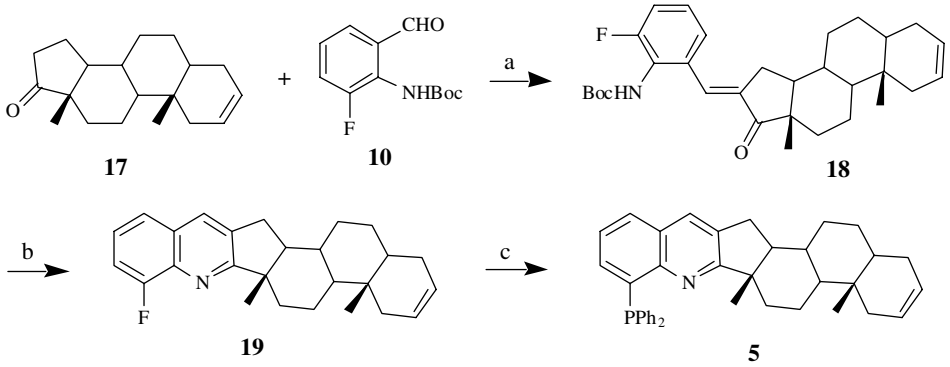


20 21

Ligands **3**–**5** were able to provide effective palladium catalysts to give the dimethyl 1,3-diphenylprop-2-enyl malonate (**21**) in good yields (90–95%) within 3 h. In all cases the (*S*)-enantiomer of the product in moderate enantiomeric excess (69–74%) was obtained.

In this process ligands **3**–**5** showed a general better catalytic activity and stereodifferentiating ability than the

In summary, we have prepared a new class of chelating ligands of the type N–P from naturally occurring natural compounds. The preliminary results obtained in enantioselective palladium-catalysed allylic substitutions indicate that they are worthy of attention for their applications in the field of asymmetric catalysis. Further studies aimed at the modification to the ligand design and the application to other catalytic asymmetric reactions are in progress.



17 10 18 19 5

Scheme 3. Reagents and conditions: (a) **17**, LDA, THF, −40 °C, 2 h, then **10**, 15 min, then slowly rt, 74%; (b) carbitol, catalytic HCl, reflux, 1 h, 69%; (c) $LiPPh_2$, THF, −10 °C, 0.5 h, then 60 °C, 2 h, 50%.

Acknowledgements

Financial support from MIUR (PRIN 2003033857-Chiral ligands with nitrogen donors in asymmetric catalysis by transition metal complexes. Novel tools for the synthesis of fine chemicals) and from the University of Sassari is gratefully acknowledged by G.C.

References and notes

1. (a) Ojiama, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley: New York, 2000; (b) *Stereoselective Synthesis*; Nogradi, M., Ed.; VCH: New York, 1995; (c) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; John Wiley: New York, 1994.
2. (a) Sutcliffe, O. B.; Bryce, M. R. *Tetrahedron: Asymmetry* **2003**, *14*, 2297, and references cited therein; (b) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159; (c) Tonks, L.; Williams, J. M. J. *Contemp. Org. Synth.* **1997**, *4*, 353; (d) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497.
3. For a review, see: Chelucci, G.; Orrù, G.; Pinna, G. A. *Tetrahedron* **2003**, *59*, 9471; For recent works in this area, see: (a) Bunlaksananusorn, T.; Knochel, P. *J. Org. Chem.* **2004**, *69*, 4595; (b) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3941; (c) Bunlaksananusorn, T.; Luna, A. P.; Bonin, M.; Micouin, L.; Knochel, P. *Synlett* **2003**, 2240; (d) Rahm, F.; Fischer, A.; Moberg, C. *Eur. J. Org. Chem.* **2003**, 4205.
4. Malkov, A. V.; Bella, M.; Stará, G.; Kocovsky, P. *Tetrahedron Lett.* **2001**, *42*, 3045.
5. Chelucci, G.; Saba, A.; Soccolini, F. *Tetrahedron* **2001**, *57*, 9989.
6. (a) Coote, S. J.; Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Synlett* **1993**, 509; (b) Allen, D. G.; McLaughlin, G. M.; Robertson, G. B.; Steffen, W. L.; Salem, G.; Wild, S. B. *Inorg. Chem.* **1982**, *21*, 1007.
7. For the newest review, see: Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37–200; For recent works in this area, see: (a) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765; (b) Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467–477; (c) Gladiali, S.; Chelucci, G.; Madadu, M. S.; Gastaut, M.-A.; Thummel, R. P. *J. Org. Chem.* **2001**, *66*, 400; (d) Lindsay, D. M.; Dohle, W.; Jensen, A. E.; Kopp, F.; Knochel, P. *Org. Lett.* **2002**, *4*, 1819–1822; (e) Matsugi, M.; Tabusa, F.; Minamikawa, J. *Tetrahedron Lett.* **2000**, 8523–8525.
8. The 2-amino-3-fluorobenzaldehyde has been obtained in 55% yield by hydrolysis of *tert*-butyl *N*-(2-formyl-6-fluorophenyl)carbamate (1,4-dioxane, 3 N HCl, 60 °C, 3 h).
9. Chelucci, G.; Manca, I.; Pinna, G. A. *Tetrahedron Lett.* **2005**, *46*, 767.
10. (2*R*,4*R*)-5-(Diphenylphosphino)-2,4-methano-3,3-dimethyl-1,2,3,4-tetrahydroacridine (**3**): mp 160–161 °C; $[\alpha]_D^{25}$ −31.3 (*c* 3.77, $CHCl_3$); ^{1}H NMR δ 7.79 (s, 1H), 7.66 (d, 1H, *J* = 8.1 Hz), 7.40–7.20 (m, 11H), 7.02–6.93 (m, 1H), 3.07 (s, 2H), 3.02 (t, 1H, *J* = 5.7 Hz), 2.70–2.63 (m, 1H), 1.34 (s, 3H), 1.27 (d, 1H, *J* = 9.6 Hz), 0.53 (s, 3H). ^{13}C NMR δ 166.5, 146.9, 138.1, 137.9, 137.8, 134.3, 134.1, 134.0, 133.8, 133.5, 132.6, 129.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.1, 127.0, 125.2, 50.8, 39.7, 39.2, 31.1, 30.5, 25.8, 21.1. ^{31}P NMR δ −13.08. Anal. Calcd for $C_{28}H_{26}NP$: C, 82.53; H, 6.43; N, 3.44. Found: C, 82.98; H, 6.66; N, 3.23.
11. (1*S*,4*R*)-5-(Diphenylphosphino)-1,4-methano-4,11,11-trimethyl-1,2,3,4-tetrahydroacridine (**4**): mp 173–174 °C; $[\alpha]_D^{25}$ −71.93 (*c* 1.48, $CHCl_3$); ^{1}H NMR δ 7.63 (d, 1H, *J* = 8.1 Hz), 7.45–7.17 (m, 11H), 7.0–6.95 (m, 2H), 2.87 (d, 1H, *J* = 3.9 Hz), 2.2–2.0 (m, 2H), 1.85–1.7 (m, 2H), 1.00 (s, 3H), 0.94 (s, 3H), 0.37 (s, 3H). ^{13}C NMR δ 170.5, 139.9, 138.2, 138.0, 137.9, 134.5, 134.2, 134.1, 133.8, 133.7, 131.2, 128.1, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.0, 125.5, 124.9, 55.2, 53.9, 51.1, 31.3, 26.2, 19.9, 18.7, 9.7. ^{31}P NMR δ −10.23. Anal. Calcd for $C_{29}H_{28}NP$: C, 82.63; H, 6.70; N, 3.32. Found: C, 82.33; H, 6.85; N, 3.37.
12. 5′α-2′-Androstadieno-[17′,16′-*b*]-5-(diphenylphosphino)-quinoline (**5**): mp 174–175 °C; $[\alpha]_D^{25}$ +110.78 (*c* 1.38, $CHCl_3$); ^{1}H NMR δ 7.80 (s, 1H), 7.66 (d, 2H, *J* = 8.1 Hz), 7.87–7.40 (m, 10H), 6.99 (dd, 1H, *J* = 4.0, 7.0 Hz), 5.59 (s, 2H), 2.83 (dd, 1H, *J* = 6.0, 14.0 Hz), 2.54 (t, 1H, *J* = 12.0 Hz), 2.08–0.90 (m, 16H), 0.80 (s, 3H), 0.74 (s, 3H). ^{13}C NMR δ 173.20, 138.42, 138.31, 138.02, 137.88, 137.08, 135.16, 137.51, 134.38, 134.24, 134.12, 131.94, 130.48, 128.13, 128.09, 128.05, 128.03, 127.95, 126.85, 125.86, 125.73, 125.18, 88.23, 55.25, 54.48, 45.61, 41.56, 39.56, 34.88, 34.66, 33.21, 31.44, 30.27, 30.15, 28.54, 20.41, 17.29, 11.65. ^{31}P NMR δ −10.78. Anal. Calcd for $C_{38}H_{40}NP$: C, 84.25; H, 7.44; N, 2.59. Found: C, 84.50; H, 7.64; N, 2.39.
13. Kang, S.-K.; Kim, W.-S.; Moon, B.-O. *Synthesis* **1985**, 1161.
14. Chelucci, G.; Delogu, G.; Gladiali, S.; Soccolini, F. *J. Heterocycl. Chem.* **1986**, *23*, 1395.
15. (a) Trost, M. B.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921; (b) Graening, T.; Schmalz, H.-G. *Angew. Chem.* **2003**, *115*, 2685; *Angew. Chem., Int. Ed.* **2003**, *42*, 2580.
16. Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.