Pergamon

Tetrahedron Letters 42 (2001) 3045–3048

TETRAHEDRON LETTERS

Modular pyridine-type *P,N*-ligands derived from monoterpenes: application in asymmetric Heck addition

Andrei V. Malkov,* Marco Bella,† Irena G. Stará‡ and Pavel Kočovský*

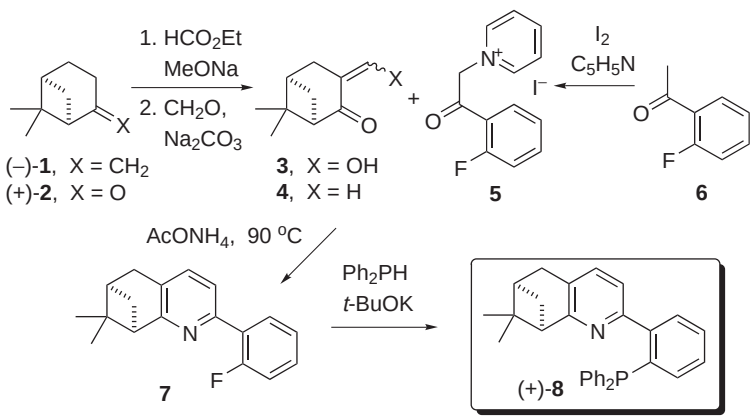
Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, UK

Received 26 January 2001; accepted 28 February 2001

Abstract—Novel (diphenylphosphinophenyl)pyridine ligands (+)-**8**, (+)-**15**, (−)-**21**, and (−)-**26** were synthesized from (−)-β-pinene, (+)-3-carene, (+)-2-carene, and (−)-α-pinene, respectively, via Kröhnke annulation as the key step, and shown to effect ≤88% ee in Heck addition (**27**→**28**). Ligands (+)-**15** and (−)-**21** are *quasi*-enantiomeric; ligands **8** and **26** can be prepared in both enantiomeric forms from (+)- and (−)-enantiomers of α- and β-pinene, respectively. © 2001 Elsevier Science Ltd. All rights reserved.

Transition metal complexes with heterobidentate ligands, such as (phosphinoaryl)oxazolines,[1] MOP,[2] QINAP,[3] and MAP,[4] are valuable catalysts for a number of asymmetric reactions, particularly in those areas where the traditional C_2-symmetrical ligands fail.[1–5] Herein, we report on the synthesis of novel (phosphinoaryl)pyridine *P,N*-ligands, where the chirality is introduced by annulation to a monoterpene segment.[6] This approach is based on our experience in the synthesis of the C_2-symmetrical bipyridine ligand PINDY, in which the pyridine units were annulated to the chiral blocks originating from (−)-β-pinene.[7,8]

In the synthesis of the first (phosphinoaryl)pyridine (+)-**8** (Scheme 1), (+)-nopinone (+)-**2**, obtained from (−)-β-pinene (−)-**1**[9a] by oxidative cleavage (cat. OsO_4, Me_3NO, Py, $NaIO_4$, *t*-BuOH–H_2O, rt, 30 min, then reflux for 2 h; 66%),[7,10] was condensed with ethyl formate (HCO_2Et, MeONa, toluene, rt, 10 h) to generate **3** (75%). Subsequent transaldolization (37% CH_2O



Scheme 1.

* Corresponding authors. E-mail: amalkov@chem.gla.ac.uk; p.kocovsky@chem.gla.ac.uk

† Exchange student from the Dipartimento di Chimica and Centro CNR di Studio per la Chimica delle Sostanze Organiche Naturali, Piazzale Aldo Moro, 5, Box No. 34, Roma 62, 00185 Rome, Italy.

‡ On leave from the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo n. 2, 166 10 Prague 6, Czech Republic.

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)00369-0

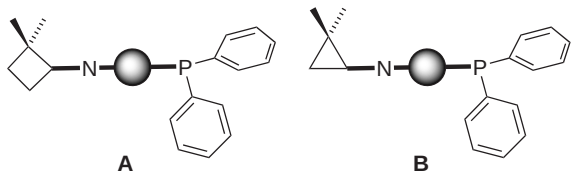


Figure 1.

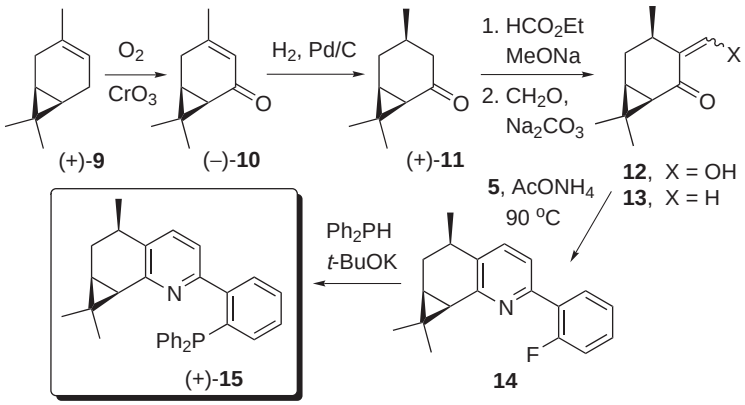
in H_2O, Na_2CO_3, ether, rt, 2 h) afforded **4** (90%),[11] whose condensation with Kröhnke reagent (**5**, $AcONH_4$, AcOH, 90°C, 3 h), obtained from **6** on iodination in pyridine (I_2, pyridine, 100°C, 2 h; 47%),[12] produced (+)-**7** (47%).[12] Treatment of (+)-**7** with Ph_2PK (Ph_2PH, *t*-BuOK, 18-crown-6, THF, rt, 48 h)[13] afforded the desired phosphine (+)-**8** (49%).

In a metal complex of (+)-**8**, the upper-left front octant will be severely hindered by the CMe_2 group (**A** in Fig. 1) but the lower-left octant will also be partly shielded by the CH_2 group of the cyclobutane ring. The latter drawback would be eliminated in the cyclopropane ligand **B**, where the CH_2 group is absent, leaving the lower-left octant free.[14]

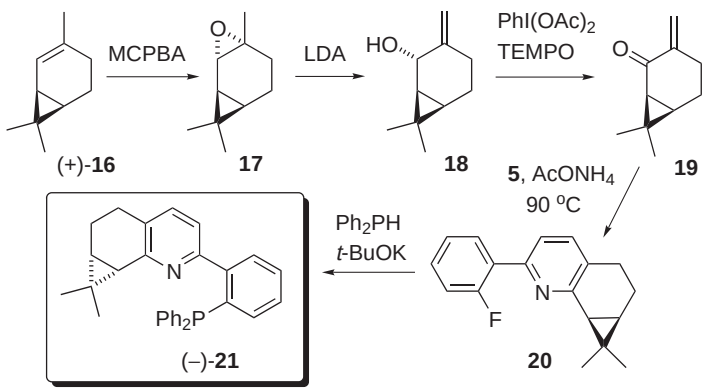
As a building block for the cyclopropane moiety, we chose (+)-3-carene (+)-**9**[9b] (Scheme 2). Allylic oxidation [O_2, CrO_3 (1 mol%), pyridine (5 mol%), rt, 24 h][15] gave (−)-**10** (20%), whose hydrogenation (H_2, 5% Pd/C, ether) produced the *cis*-derivative (+)-**11** (98%).[16] Claisen condensation of (+)-**11** (HCO_2Et, MeONa, toluene, rt, 10 h; 76%), followed by transaldolization (37% CH_2O in H_2O, Na_2CO_3, ether, rt, 2 h; 90%) gave (+)-**13**, whose treatment with Kröhnke salt (**5**, $AcONH_4$, AcOH, 90°C, 3 h) furnished (+)-**14** (60%), in which the fluorine was replaced by phosphorus (Ph_2PH, *t*-BuOK, 18-crown-6, THF, rt, 48 h) to afford ligand (+)-**15** (83%).

In a related procedure (Scheme 3), (+)-2-carene (+)-**16**[9c] was epoxidized (MCPBA, ether, rt, 12 h; 85%), and the resulting **17**[17] was isomerized (LDA, 3 equiv, THF, 0°C to rt, 6 h) to give **18** (53%),[18,19] whose oxidation [$PhI(OAc)_2$, TEMPO, CH_2Cl_2, rt, 5 h][20] afforded **19** (83%). Kröhnke annulation (**5**, $AcONH_4$, AcOH, 90°C, 3 h) produced (−)-**20** (60%), which was then converted into (−)-**21** (Ph_2PH, *t*-BuOK, 18-crown-6, THF, rt, 48 h; 74%).

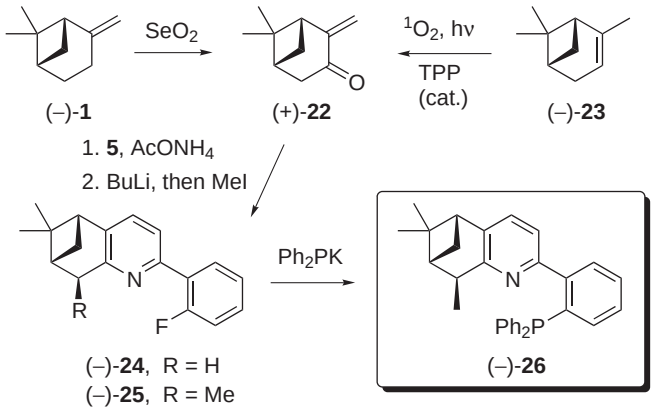
Finally, yet another ligand architecture can be envisaged for an analogue where the terpene bridge is shifted by one carbon, leaving the 'benzylic' position amenable to alkylation.[8] This ligand type, namely (−)-**26** (Scheme 4), was synthesized from (+)-pinocarvone (+)-**22**,[21] obtained either by allylic oxidation of (−)-β-pinene (−)-**1** (SeO_2, CCl_4, reflux, 24 h, 27%),[22] or via the ene-reaction of (−)-α-pinene (−)-**23** with singlet oxygen (*hv*, O_2, TPP, pyridine, DMAP, Ac_2O, CH_2Cl_2, rt, 2



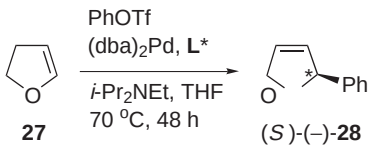
Scheme 2.



Scheme 3.



Scheme 4. TPP = tetraphenylporphine.



Scheme 5. Tf = CF_3SO_2.

days; 98%).[23] On Kröhnke annulation (**5**, $AcONH_4$, AcOH, 90°C, 5 h), (+)-**22** provided (–)-**24** (73%), whose deprotonation (*n*-BuLi, THF, −30°C, 1 h), followed by stereoselective methylation (MeI, −50°C, 4 h), afforded (–)-**25** (63%). On substitution reaction (Ph_2PH, *t*-BuOK, 18-crown-6, THF, rt, 48 h), the latter fluoro derivative afforded ligand (–)-**26** (55%).

To assess the efficacy of the new *P*,*N*-ligands **8**, **15**, **21**, and **26**, we set out to investigate Heck addition[24] of PhOTf to dihydrofuran **27** (Scheme 5).[24] Using solvent and base variation, we have identified *i*-Pr_2NEt in THF (70°C, 2 days) as the most suitable system with high enantioselectivities and minimized formation of the side products.

Ligand (+)-**8** induced the formation of (*S*)-(–)-**28** with 59% ee (45% yield); (+)-**15** proved to be more enantioselective, giving (*S*)-(–)-**28** of 70% ee, while its *quasi*-enantiomer (–)-**21** produced the opposite enantiomer (*R*)-(+)-**28** (69% ee). Reversal of product configuration was also observed for (–)-**26**, which furnished (*R*)-(+)-**28** (88% ee; 68% yield).[25] Unlike with BINAP,[24c] only slight isomerization (~1%) to the more stable 4,5-isomer was observed.

In conclusion, we have synthesized modular (phosphinoaryl)pyridine ligands (+)-**8**, (+)-**15**, (–)-**21**, and (–)-**26** from the inexpensive chiral pool, each in five steps or less. While (+)-**15** and (–)-**21** are *quasi*-enantiomers, **8** and **26** could be prepared in both enantiomeric forms. Heck addition (**27**→**28**) appears to be a promising application (88% ee)[25] and will merit further investigation.[26] For the sake of practicality, we propose the following acronyms: PINPHOS for (+)-**8**, (+)- and (–)-CANPHOS for (+)-**15** and (–)-**21**, respectively, and *iso*-PINPHOS for (–)-**26**.

Acknowledgements

The authors would like to thank the University of Glasgow for generous financial support and the Consiglio Nazionale delle Ricerche, Rome, Italy, for support to M.B. (Short Term Mobility Program).

References

1. For recent reviews, see: (a) Ghosh, A. K.; Mathiyanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1; (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325; (c) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.
2. For an overview, see: Hayashi, T. *Acta Chem. Scand.* **1996**, *50*, 259.
3. (a) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743; (b) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493.
4. (a) Vyskočil, Š.; Smrčina, M.; Hanuš, V.; Polášek, M.; Kočovský, P. *J. Org. Chem.* **1998**, *63*, 7738; (b) Kočovský, P.; Vyskočil, Š.; Císařová, I.; Sejbal, J.; Tišlerová, I.; Smrčina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714; (c) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051 and references cited therein; (d) Wang, Y.; Guo, H.; Ding, K. *Tetrahedron: Asymmetry* **2000**, *11*, 4153.
5. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, 1994.
6. For the first (phosphinoaryl)pyridine ligand, see: Ito, K.; Kashiwagi, R.; Iwasaki, K.; Katsuki, T. *Synlett* **1999**, 1563.
7. (a) Malkov, A. V.; Bella, M.; Langer, V.; Kočovský, P. *Org. Lett.* **2000**, *2*, 3047; (b) Malkov, A. V.; Baxendale, I. R.; Fawcett, J.; Russel, D. R.; Langer, V.; Mansfield, D. J.; Valko, M.; Kočovský, P. *Organometallics* **2001**, *20*, 673.
8. For an overview of the syntheses of chiral bipyridine ligands, see: (a) Knof, U.; von Zelewsky, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 303. For the most recent report, see: (b) Lötscher, D.; Rupprecht, S.; Stoeckli-Evans, H.; von Zelewsky, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4341.
9. (a) Chiral GC revealed the starting (–)-β-pinene to be of 95% ee; (b) (+)-3-Carene was of 93% ee (by GC); (c) (+)-2-Carene had $[\alpha]_D$ +81 (*c* 6.0, EtOH); Aldrich gives $[\alpha]_D$ +90±2 (*c*, 6.0, EtOH).
10. (a) Grimshaw, N.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50; (b) Brown, H. C.; Weissman, S. A.; Perumal, P. T.; Dhokte, U. P. *J. Org. Chem.* **1990**, *55*, 1217.
11. For the procedure, see Ref. 10b and: Gianini, M.; von Zelewsky, A. *Synthesis* **1996**, 702.
12. For the methodology, see: (a) Kröhnke, F. *Chem. Ber.* **1937**, *70*, 864. For an overview, see: (b) Kröhnke, F. *Synthesis* **1976**, 1.

13. For the method, see, for example: Kündig, E. P.; Meier, P. *Helv. Chim. Acta* **1999**, *82*, 1360.
14. This architecture would mimic the recently reported flat structure of the bisferrocene-type bipyridine complex: Rios, R.; Liang, J.; Lo, M. M.-C.; Fu, G. C. *Chem. Commun.* **2000**, 377.
15. (a) Rothenberg, G.; Yatziv, Y.; Sasson, Y. *Tetrahedron* **1998**, *54*, 593; (b) Vyglazov, O. G.; Manukov, E. N.; Fedorishcheva, M. N.; Ariko, N. G.; Chuiko, V. A.; Bazhina, G. N. *Chem. Nat. Compd. (Engl. Transl.)* **1991**, 27; *Khim. Prir. Soedin.* **1991**, 328.
16. (a) Maas, D. D.; Blagg, M.; Wiemer, D. F. *J. Org. Chem.* **1984**, *49*, 853. For a less economical synthesis, see: (b) Cocker, W.; Shannon, P. V. R.; Staniland, P. A. *J. Chem. Soc. C* **1967**, 485.
17. Crombie, L.; Crombie, W.; Mary, L.; Jamieson, S. V.; Palmer, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1243.
18. Arbuzov, B. A.; Isaeva, Z. G.; Vil'chinskaya, A. R.; Belyaeva, M. G. *Dokl. Chem., Engl. Transl.* **1971**, *199*, 690; *Dokl. Akad. Nauk SSSR Ser. Khim.* **1971**, *199*, 1304.
19. A similar reaction with 3-carene epoxide occurred in 97% yield: Paquette, L. A.; Ross, R. J.; Shi, Y.-J. *J. Org. Chem.* **1990**, *55*, 1589.
20. For the method, see: De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.
21. Chelucci, G.; Pinna, G. A.; Saba, A. *Tetrahedron: Asymmetry* **1998**, *9*, 531.
22. Hartshorn, M. P.; Wallis, A. F. A. *J. Chem. Soc.* **1964**, 5254.
23. Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135.
24. For the application of (phosphinoaryl)oxazoline ligands in Heck addition, see Refs. 1c and 13 and: (a) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200; (b) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16. For other ligands recently employed in the arylation of **27**, see: (c) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417; (d) Hii, K. K.; Claridge, T. D. W.; Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 984; (e) Cho, S. Y.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 1773; (f) Cahill, J. P.; Bohnen, F. M.; Goddard, R.; Krueger, C.; Guiry, P. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3831; (g) Tieze, L. F.; Thede, K.; Sannicolò, F. *Chem. Commun.* **1999**, 1811; (h) Hennessy, A. J.; Malone, Y. M.; Guiry, P. J. *Tetrahedron Lett.* **1999**, *40*, 9163; (i) Tschoerner, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 670 and references cited therein; (j) Deng, W.-P.; Hou, X. L.; Dai, L.-X.; Dong, X. W. *Chem. Commun.* **2000**, 1483; (k) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161.
25. The enantioselectivity might, in fact, be slightly higher since the ligand (–)-**26** was of ~95% ee.[9]
26. Our ligands may offer an electronic tuning of the coordinating nitrogen via the γ-substituent at the pyridine ring, which can be expected to affect both the reaction rate and the enantioselectivity. For the electronic effects in asymmetric catalysis, see: (a) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 6265; (b) RajanBabu, T. V.; Radetich, B.; You, K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. *J. Org. Chem.* **1999**, *64*, 3429; (c) Neetekoven, U.; Kamer, P. C. J.; Widhalm, M.; van Leeuwen, P. W. N. M. *Organometallics* **2000**, *19*, 4596.