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Synthesis and application of macrocyclic binaphthyl ligands with extended chiral bias

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Abstract

Two macrocyclic and one non-cyclic chiral diphosphine ligand containing a 2,2′-bridged binaphthyl unit were synthesized in six steps from (*R*)-2,2′-dimethoxy-1,1′-binaphthyl in overall yields of 25 and 17%, respectively. The new ligands showed asymmetric inductions of up to 98% e.e. if used in palladium catalyzed allylic alkylation reactions.

1. Introduction

The concepts of transition metal catalyzed asymmetric transformations have been extended to numerous reaction types.[1] Among these, carbon–carbon bond-forming reactions have attracted particular attention since the generation of a new stereogenic center and the construction of the carbon skeleton take place in a single step. The variety of C–C coupling reactions, both in view of mechanism and diversity of substrate structure make the successful modeling of catalyst reactivity and selectivity, especially in asymmetric catalysis, a challenge of central importance. According to this it was evident that groups of structurally related ligands exhibiting gradually different degrees of steric or electronic influence in suitable proximity to the co-ordinated substrate are desired.

2. Results and discussion

Searching for suitable ligand structures for allylic alkylation reactions with soft nucleophiles prompted us to investigate primarily ligands with ‘remote’ chiral interaction which are prone to envelope the substrate co-ordination sites. If co-ordinating atoms and the chiral moiety in the ligand are connected to each other through spacer groups, chiral macrocycles can be formed. Such an array seemed promising

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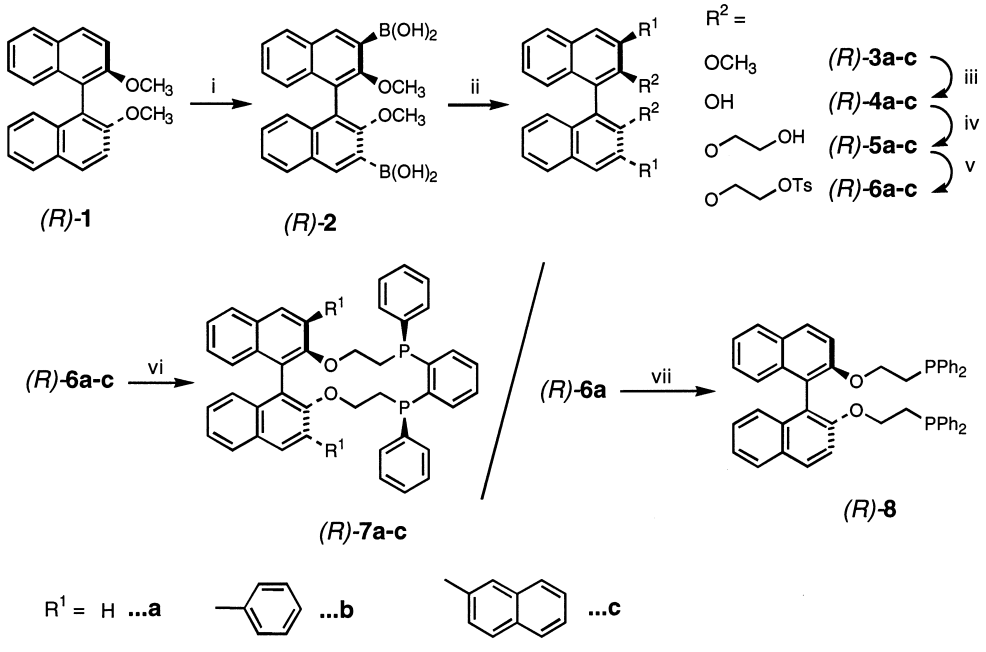
in view of the proposed mechanism which requires 'outer-sphere' chiral control of the prochiral Pd–allyl precursor.[2] The outstanding broadness of scope and efficiency of 2,2′-disubstituted 1,1′-binaphthyls in chiral auxiliaries has been amply demonstrated in a plenitude of stoichiometric and catalytic reactions.[3]

We recently reported the synthesis of macrocyclic binaphthyl ligands[4] and their application in allylic alkylation reactions.[5] Among the structures investigated, **7a** (Scheme 1) was found to be most effective in allylic alkylation reactions with asymmetric inductions up to 86% e.e. To further improve the asymmetric induction we tried to extend the area of chiral interaction by introducing aromatic substituents of different size in positions 3 and 3′ of the binaphthyl skeleton. A Suzuki coupling was chosen to construct the biaryl moiety, using boronic acid **2** as a suitable precursor.[6] A five step synthesis applying standard procedures furnished (*R*)-**6b** and (*R*)-**6c** in an overall yield of 51 and 35%, respectively (from **2**). The final cyclization step proceeded highly stereoselectively to afford exclusively the C_1-symmetrical diastereomer. For comparative studies the non-cyclic analog **8** was also synthesized, albeit in low yield (24%).

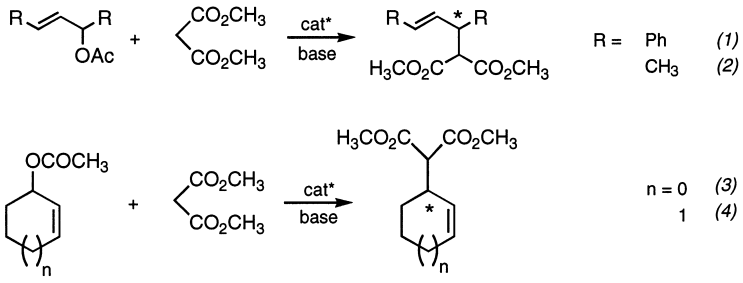


Scheme 1. *Reagents*: i: 1. n-BuLi, 2. $B(OCH_3)_3$, ii: R′X/Pd$(PPh_3)_4$/Na_2CO_3/toluene/reflux, iii: BBr_3/CH_2Cl_2/0°C→rt, iv: 1. $ClCH_2CO_2C_2H_5$/KO^{t}Bu, 2. $LiAlH_4$/THF, v: TsCl/Py/0°C, vi: 1,2-bis(phenylphosphinyl)benzene/n-BuLi/THF/reflux, vii: $LiPPh_2$/THF/0°C→rt

Macrocycles **7a**–**c** represent a set of chiral ligands with increasingly extended chiral bias which is expected to result in different chiral modeling of the reaction area.[7] Nevertheless, the degree of actual steric interaction is difficult to predict and will be governed by the preferred conformation of the macrocycle.

As test reactions we chose the Pd-catalyzed allylic alkylation reaction of 1,3-symmetrically disubstituted propenyl acetates with dimethyl malonate as the nucleophile (Scheme 2).[8]

The results are collected in Table 1. For *Reaction (1)* the presence of substituents in position 3 and 3′ of the ligand significantly improved the asymmetric induction from 86% e.e. **7a** to 98% e.e. (**7c** in CH_3CN). A solvent change from CH_2Cl_2 to THF or CH_3CN did not alter the enantioselectivity but the reaction rate reached a maximum of approximately 100 turnovers per h in CH_3CN. Generally, isolated yields are high, exceeding 90% in nearly all cases. The use of sodium hydride instead of BSA/KOAc decreased enantioselectivities to 81–91% e.e. (for **7a** and **7c**, respectively). In contrast to this, no improvement could



Scheme 2.

Table 1
Asymmetric induction in Pd-catalyzed in allylic alkylation reactions[a)]

Reaction	solvent	(*R*)-**7a**[d)]	(*R*)-**7b**[d)]	(*R*)-**7c**[d)]	(*R*)-**8**[d)]
(1)	CH_2Cl_2	86 *S* (93)	96 (*S*) (93)	97 (*S*) (94)	66 (*S*) (91)
(1)	THF	87 *S* (94)	96 (*S*) (94)	97 (*S*) (93)	73 (*S*) (94)
(1)	CH_3CN	86 *S* (95)	97 (*S*) (97)	**98 (*S*) (95)**	70 (*S*) (96)
(1)[b)]	CH_2Cl_2	81 *S* (89)	86 (*S*) (99)	91 (*S*) (82)	n.e.
(2)	CH_2Cl_2	19 (-) (81)	4 (+) (98)	20 (-) (83)	28 (-) (87)
(2′)[c)]	CH_2Cl_2	18 (-) (74)	21 (-) (55)	24 (-) (79)	25 (-) (89)
(3)	CH_2Cl_2	n.e.	13 (S) (90)	10 (*S*) (70)	10 (*R*) (87)
(4)	CH_2Cl_2	n.e.	17 (S) (83)	1 (*R*) (58)	9 (*S*) (66)

(a) Experiments were run in 1 ml of solvent with 1 mmol of substrate and 3 mmol of dimethylmalonate and N,O-bis(trimethylsilyl)acetamide (BSA) each, a trace of KOAc, and the catalyst prepared in situ from 0.5 mol% of $[Pd(C_3H_5)Cl]_2$ and 2 mol% of ligand; for experimental details see the literature.[5]
(b) NaH was used instead of BSA/KOAc.
(c) Instead of pentenyl acetate the corresponding carbonate was used as substrate.
(d) Figures refer to: e.e./configuration of product/isolated yield (in parentheses); e.e was determined by HPLC (*Reaction (1)*: Chiralcel-ODH, 250×4.6 mm, 2-PrOH/n-hexane, 2:98), GC (*Reaction (2)*: 50% of octakis(6-O-methyl-2,3-di-O-pentyl)-ɣ-cyclodextrin, 0.25 mm×25 m, 0.5 bar H_2, 55°C) or on the basis of specific rotation:[9] *Reaction (3)*: (*S*)-dimethyl 2-(cyclopent-2-ene-1-yl)malonate $[\alpha]_D^{20}=-98.7$ (c=2.27, $CHCl_3$); *Reaction (4):* (*S*)-dimethyl 2-(cyclohex-2-ene-1-yl)malonate $[\alpha]_D^{20}=-46.1$ (c=2.85, $CHCl_3$).

be attained for *Reaction (2)*. Only 24% e.e. in the case of ligand **7c** was observed using the corresponding pentenyl carbonate as substrate, which is a lower selectivity than that obtained with the non-cyclic ligand **8** (28% e.e.). The asymmetric induction was also found to be low for cyclic substrates (*Reactions (3)* and *(4)*) and did not show any dependence upon the steric bulk of the ligands.

3. Conclusions

New ligands **7b** and **7c** with extended chiral bias (compared with **7a**) allow excellent enantioselectivity in the allylic alkylation reactions of 1,3-diphenylpropenyl acetate but failed to induce considerable asymmetric induction with aliphatic cyclic and non-cyclic substrates, a behavior frequently observed with

other ligands. From our findings we conclude that for alkyl-substituted substrates a more carefully tuned steric interaction between substrate and ligand is required. In view of the so far incomplete understanding of the mechanism[10] the 'tailoring' of ligands will be an empirical procedure, preferably by varying steric interaction in proximity to the P-co-ordination sites. Appropriate structural modifications of the ligand are presently under progress.

Acknowledgements

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References

1. (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH: Weinheim, 1993. (b) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods 1989;* Scheffold, R., Ed.; Springer Verlag: Berlin, 1989; pp. 115.
2. Trost, B. M.; Van Vranken, D. L. *Chem. Rev*. **1996**, *96*, 395.
3. Noyori, R.; Takaya, H. *Acc. Chem. Res*. **1990**, *23*, 345.
4. (a) Widhalm, M.; Kalchhauser, H.; Kählig, H. *Helv. Chim. Acta* **1994**, *77*, 409. (b) Widhalm, M.; Klintschar, G. *Chem. Ber*. **1994**, *127*, 1411. (c) Wimmer, P.; Widhalm, M. *Phosphorus, Sulfur Silicon* **1995**, *106*, 105. (d) Wimmer, P.; Klintschar, G.; Widhalm, M. *Heterocycles* **1995**, *41*, 2745.
5. Widhalm, M.; Wimmer, P.; Klintschar, G. *J. Organomet. Chem*. **1996**, *523*, 167.
6. Wimmer, P.; Haslinger, U.; Widhalm, M. *Monatsh. Chem*. in press.
7. All new compounds gave analyses and spectroscopic data in agreement with the proposed structures; selected data: (*R*)-**7b**: yield: 88%; white powder; mp: 143–146°C, $[\alpha]_D^{20}$=+419 (c=1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 1.93–2.01 (m, 1H); 2.07–2.30 (m, 3H); 3.52–3.66 (m, 2H); 3.73–3.81 (m, 1H); 3.85–3.93 (m, 1H); 6.68–6.73 (m, 1H); 6.78–6.82 (m, 1H); 6.95–6.99 (m, 2H); 7.03–7.23 (m, 15H); 7.29–7.41 (m, 9H); 7.82 (s, 1H); 7.82 (d, *J*=7.8 Hz, 1H); 7.88 (d, *J*=7.3 Hz, 2H); 7.91 (d, *J*=7.8 Hz, 1H); 8.00 (s, 1H). ^{31}P NMR δ: −27.13 (d, *J*=149.2 Hz); −28.93 (d, *J*=149.2 Hz). MS (FD, 230°C): 784.9 (M^+, 100%). (*R*)-**7c**: Yield: 76%; white powder; mp: 149–152°C; $[\alpha]_D^{20}$=+190 (c=1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 2.00–2.16 (m, 3H); 2.30–2.38 (m, 1H); 3.58–3.72 (m, 2H); 3.74–3.82 (m, 1H); 4.02–4.10 (m, 1H); 6.46–6.50 (m, 1H); 6.80–6.84 (m, 7H); 6.99 (t, *J*=7.5 Hz, 3H); 7.04–7.11 (m, 2H); 7.18 (d, *J*=8.5 Hz, 2H); 7.25–7.31 (m, 2H); 7.34–7.45 (m, 5H); 7.54–7.58 (m, 3H); 7.68–7.70 (m, 1H); 7.77 (d×d, *J*=2.0, 8.5 Hz, 2H); 7.86–7.94 (m, 4H); 7.97 (t, *J*=4.0 Hz, 2H); 8.06 (brs, 1H); 8.09 (d×d, *J*=1.5, 8.5 Hz, 1H); 8.14 (s, 1H); 8.38 (s, 1H). ^{31}P NMR δ: −26.00 (d, *J*=152.1 Hz); −29.85 (d, *J*=152.1 Hz). MS (FD, 280°C): 884 (M^+, 100%).
8. High asymmetric inductions have been reported for *Reaction (1)*, cf.: Andersson, P. G.; Harden, A.; Tanner, D.; Norby, P. O. *Chem. Eur. J*. **1995**, *1*, 12; von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 566; Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coates, S. W. *Tetrahedron Lett*. **1993**, *34*, 3149; *Reaction (2)* cf.: Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc*. **1996**, *118*, 6520; *Reactions (3) and (4)*: Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc*. **1994**, *116*, 4089; Helmchen, G.; Kudis, S.; Sennhenn, P.; Steinhagen, H. *Pure Appl. Chem*. **1997**, *69*, 513.
9. Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett*. **1994**, *35*, 8595.
10. Although palladium catalyzed allylic substitution reactions have been the subject of numerous mechanistic investigations the origin of enantioselection is not completely understood; different mechanistic models have been presented and arguments for both early and late transition states have been proposed for the nucleophile attack, the rate- and configuration-determining step. In this context the role of an equilibrium between preceding diastereomeric π-allyl-palladium(II) complexes was also discussed. See: Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc*. **1985**, *107*, 2033; Mackenzie, P. B.; Wehlan, J.; Bosnich, B. *J. Am. Chem. Soc*. **1985**, *107*, 2046; Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493; see also Helmchen, G. et al. in Ref. 8.