Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 1159–1167

TETRAHEDRON

Macrocyclic vs acyclic derivatives of chiral bis(oxazolines); ligand distortion and enantioselectivity of Pd(II) complexes in catalytic allylic alkylation

Dragan Šepac, Željko Marinić, Tomislav Portada, Mladen Žinić and Vitomir Šunjić*

Ruđer Bošković Institute, Bijenička c. 54, P.O.B. 180, 10002 Zagreb, Croatia

Received 2 October 2002; revised 2 December 2002; accepted 2 January 2003

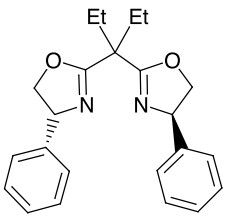
Abstract—Pd(II) complexes of acyclic (**1**,**2**;**4**,**5**) and macrocyclic (**3**,**6**–**10**) derivatives of 1,5-bis(oxazolines), are tested in the enantioselective allylic alkylation of racemic 1,3-diphenyl-3-acetoxyprop-2-ene (**14**) by dimethylmalonate anion to allyl malonate derivative **15**. Conformation in solution of representative allyl Pd(II) complexes **12** and **13** is studied by 2D NMR and CD spectroscopy. 2D NMR data reveal loss of C_2 symmetry of the ligands in Pd(II)allyl-bis(oxazoline) complexes. CD spectra indicate distortion of the bidentate ligand in the complex and a conformationally forced larger twist between two chromophores in the macrocyclic complex. Only moderate variation of enantioselectivity with the length and ring size of the ligand is observed, and a rationale offered.

1. Introduction

Recently we reported the first example of Cu(I) complexes with chiral macrocyclic ligands, derivatives of 1,5-bis(oxazolines), as catalysts for enantioselective cyclopropanation,[1] and provided a detailed study of the structure, stoichiometry and conformation in solution of Cu(I) and Ag(I) complexes of these ligands and their cyclic counterparts.[2] The Cu(I) complexes of some macrocyclic ligands have shown the highest cumulative (dia- and enantio-) selectivity obtained as yet with C_2 symmetric dinitrogen ligands.[1] Continuing this work on supramolecular macrocyclic catalysts with a chiral cleft, here we report the results of the conformational study of a couple of acyclic and macrocyclic bis(oxazoline) ligands and their Pd(II) catalytic complexes, and on their enantioselectivity in the standard allylic alkylation of 1,3-diphenyl-3-acetoxyprop-2-ene by dimethylmalonate (DMM) anion.[3–6] Though it cannot be expected that Pd(II) complexes of the cyclic ligands accommodate both allyl cation and DMM anion in the chiral cavity, topological distortion of the Pd(II) allyl complex by the macrocycle is expected to be reflected, at least in part, in higher enantioselectivity. The coordination of bis(oxazoline) ligands containing four or five spacer atoms to allyl palladium fragment in macrocyclic complex has recently been reported, and the catalytic behaviour of these complexes was rationalized in terms of the coordination mode of the ligands in the macrocyclic complex.[7] The first probing of the conformation in solution of C_2-symmetric macrocyclic, flexible catalysts based on bis(sulfonamido) ligands, used in asymmetric alkylation of benzaldehyde has also been reported.[8]

2. Results and discussion

Compounds **2**,**3** and **5**–**10** are prepared according to the reported method,[9] compounds **1** and **4** are commercially available. Pd(II) complexes of the ligands **5** and **10** with 1,3-diphenylallylic cation (**12** and **13**) were prepared from **11** according to the protocol of Pfaltz et al.[5] (Scheme 1) and isolated in the crystalline form.

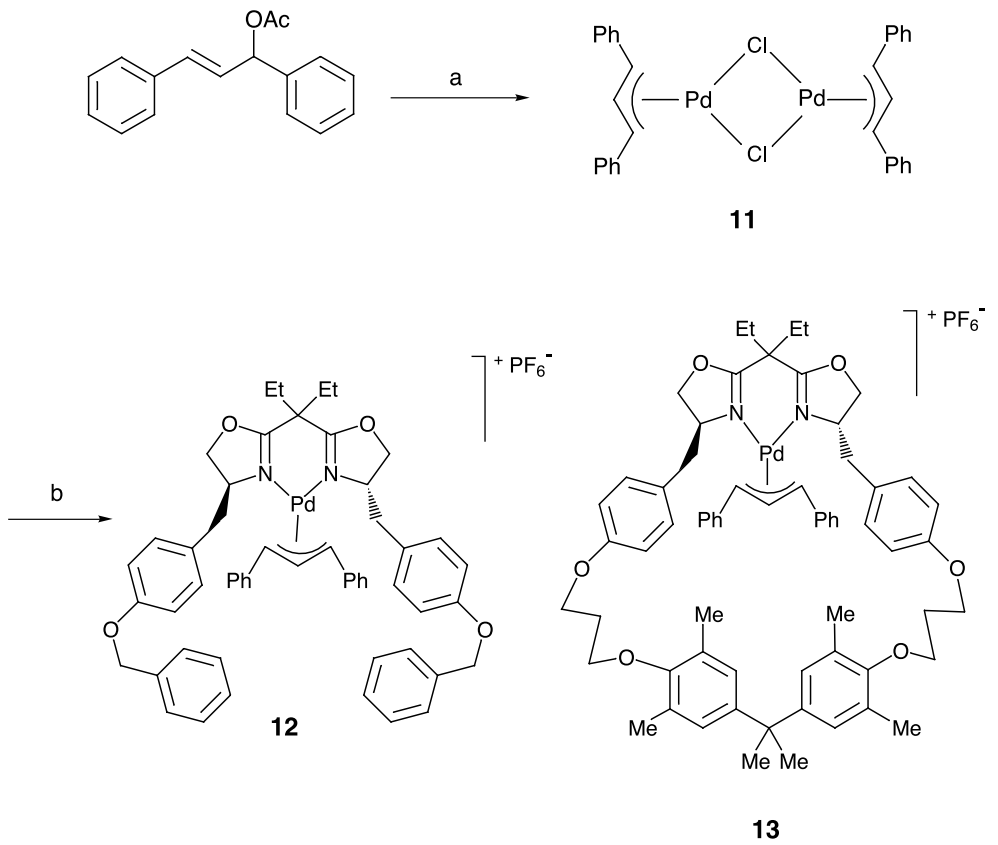


1

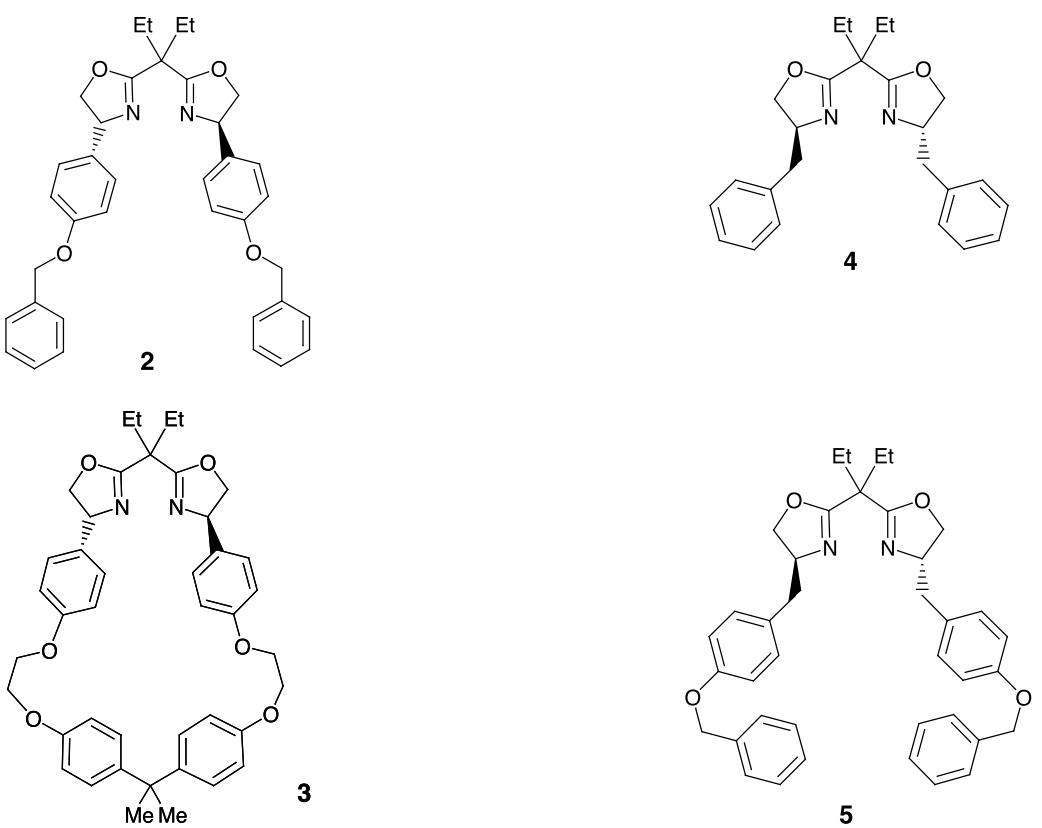
Keywords: macrocycles; oxazolines; catalysts; alkylation; palladium.

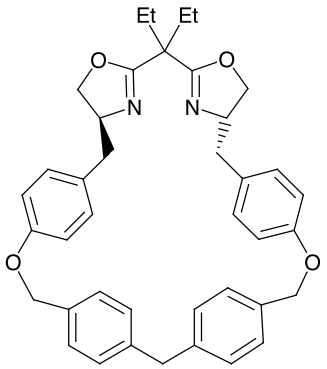
* Corresponding author. Tel.: +385-1-4680-108; fax: +385-1-4680-195; e-mail: sunjic@rudjer.irb.hr

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00043-7

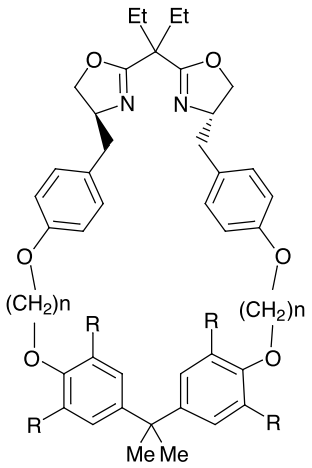


Scheme 1. (a) PdCl/LiCl/CO; HCl, EtOH, (b) $AgPF_6$, **5** or **10**; THF/CH_2Cl_2/MeOH.





6



	R	n
7	H	2
8	H	3
9	Me	2
10	Me	3

Acyclic and cyclic ligands **5** and **10** and their respective Pd(II) complexes **12** and **13** were selected for detailed spectroscopic and conformational study. Free ligands **5** and **10** show in the IR spectra characteristic strong C═N band at 1655 cm^{-1}; for their complexes **12** and **13** the same strong C═N band appears at 1644 cm^{-1}, revealing depletion of the π-electron density on coordination to Pd(II).

Ligands **5** and **10** lose C_2 symmetry in their allyl Pd(II) complexes **12** and **13**, as already observed by Pfaltz et al. for the reference ligand **4**.[5] The twist of the two bis(oxazoline) rings brings one of the two formerly enantiotopic substituents into a more perpendicular orientation with respect to the bis(oxazoline) chromophore, and the other into a more in-plane position. This is reflected in the doubling of the characteristic diastereotopic ^{1}H and ^{13}C signals indicated for the complex **12** in Figure 1.

NMR and CD spectra of **12** and **13** suggest a larger distortion of these complexes compared to that of **4**. In the 1D-^{13}C-APT spectrum of **12**, signals for C-atoms of the

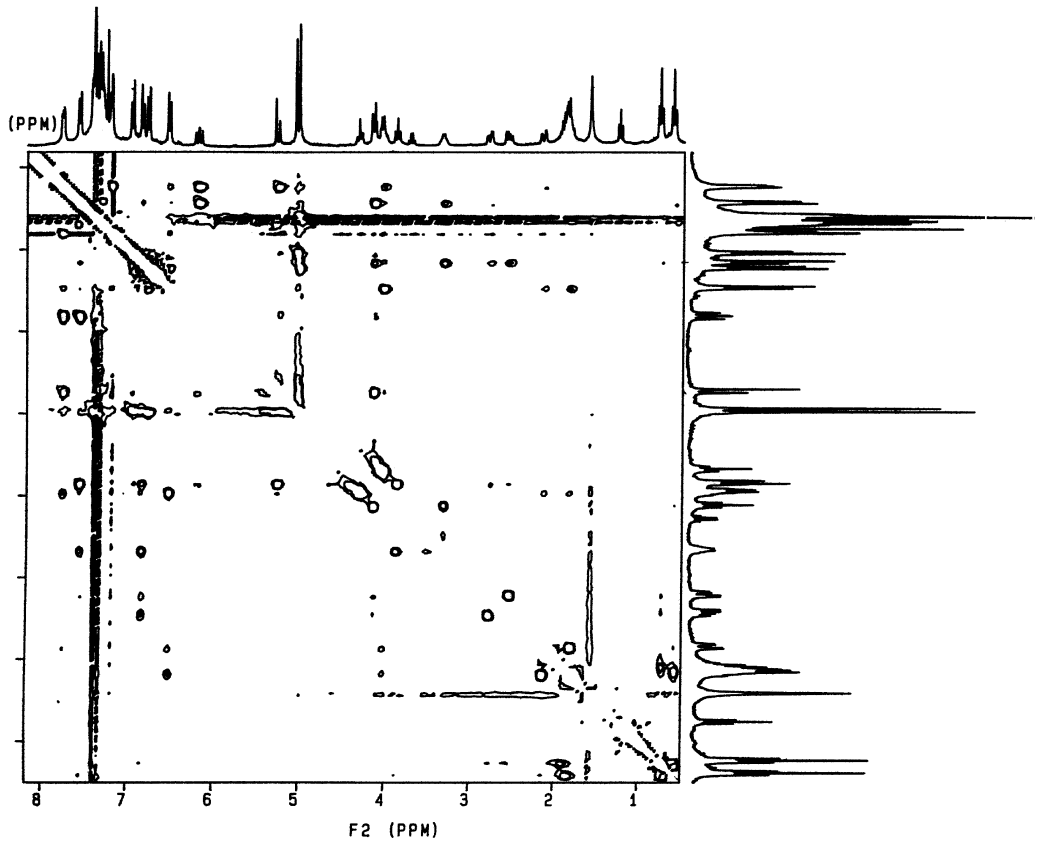
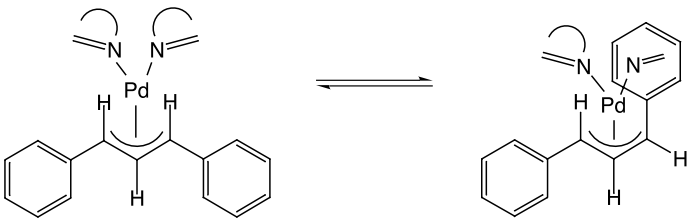


Figure 1. NOESY spectrum of the complex **12**.



Scheme 2.

allylic unit, C(40) and C(42) (numbered according to Ref. 5, see Section 3) are observed at 83.94 and 71.82 ppm, respectively. Analogous C-atoms in the complex of bis(oxazoline) **4** are found at 81.80 and 74.17 ppm.[5] Thus, $\Delta\delta$ for terminal allylic ^{13}C signals is ca. 1.6 times larger in **12** than in **4**, suggesting a larger distortion of one Pd–C. 2D-Spectra of **12** and **13** were run using COSY, NOESY, ROESY; and HMBC techniques; the most useful information was obtained from NOESY spectra. The diastereotopicity of specific C and H atoms in the complex **12** is particalarly evidenced in the NOESY spectrum (Fig. 1).

Contacts between *ortho*-aromatic protons of the first aromatic (ex-tyrosine) ring with benzylic protons on C(10) and C(26), connected to the stereogenic centers, can be traced though in part superimposed to the signals of methylenic protons of one ethyl group of the bridge. This interaction reveals the spatial proximity of methylenic protons on C(10) to the *ortho*-protons at C(32) and C(36) of the second phenyl group. Pfaltz et al. have observed in the complex of **4** the inversion of the chair conformation of the six-membered Pd(II) chelate ring, as evidenced in the NOESY spectrun of **4** by the contacts between *trans*-H atoms of the allylic cation with *ortho* and *meta*-H atoms in one of the two benzyl groups. Fast equilibrium is suggested for two allylic conformers (Scheme 2).[5]

Complex **12**, instead, seems to undergo slow interconversion between two allyl conformers in solution. Slow equilibrium between two *trans*-conformers of **12** can be traced by the coupling between central and any one of the two terminal protons on C(40) and C(42) allylic atoms (Fig. 1). Relative intensities of NOE interactions indicate the prevalence of one conformer in the solution.

Stronger steric perturbation by the substituents on C(9) and C(25) on the oxazole rings in **12** cause a larger electronic non-equivalence of the terminal allylic carbons and protons as compared to complex of **4**. Although this non-equivalence was suggested as one of the origins of enantioselection in allylic alkylation,[6] the complex of acyclic ligand **12** exhibited nearly the same enantioselectivity as the complex of the reference ligand **4** (vide infra).

UV and CD spectra of ligand **5** and its Pd(II) allyl complex **12**, as well as ligand **10** and its complex **13**, are presented in Figures 2, 4 and 3, 5, respectively.

The strongest UV band in the spectra of both ligands **5** and **10** and their respective complexes **12** and **13** is the short-wavelength band found around 190–200 nm, which belongs to $\pi-\pi^*$ ($^{\pi}C{=}N-{}^{\pi*}C{=}N$) transition.[2,10,11] This UV band in **5** and its complex **12** is less intense and shifted by ca. 5 nm to shorter wavelengths as compared to their cyclic counterparts. The intensity of this band remains nearly unchanged upon complexation of ligands with Pd(II), however, a new broad band appears around 270 nm.

A relatively strong CD band ($\Delta\varepsilon$ 15–30) can be observed in

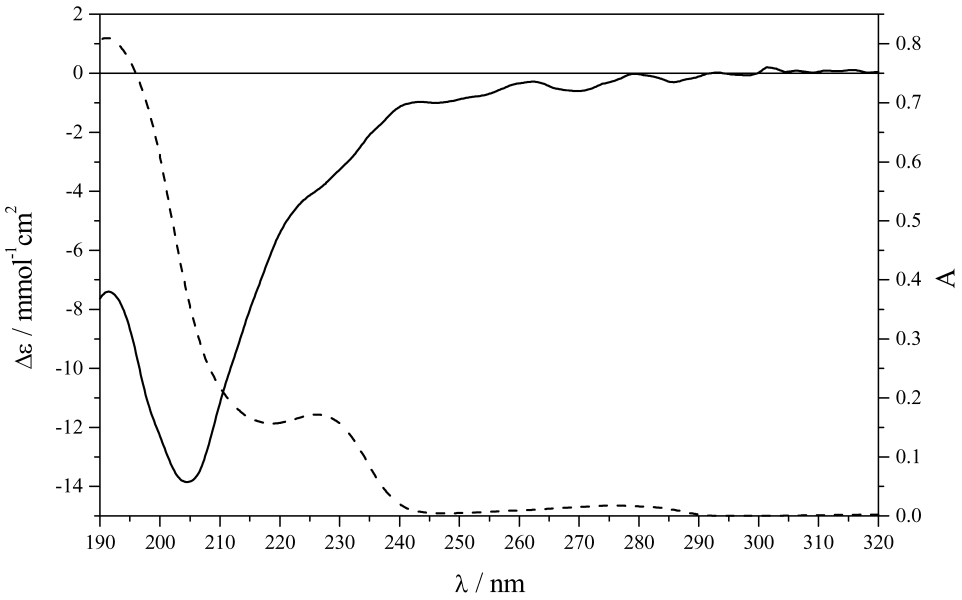


Figure 2. The CD spectrum (—) and absorption spectrum (- - -) of **5** in MeCN (c=7.80×10^{-4} mol dm^{-3}, l=0.01 cm).

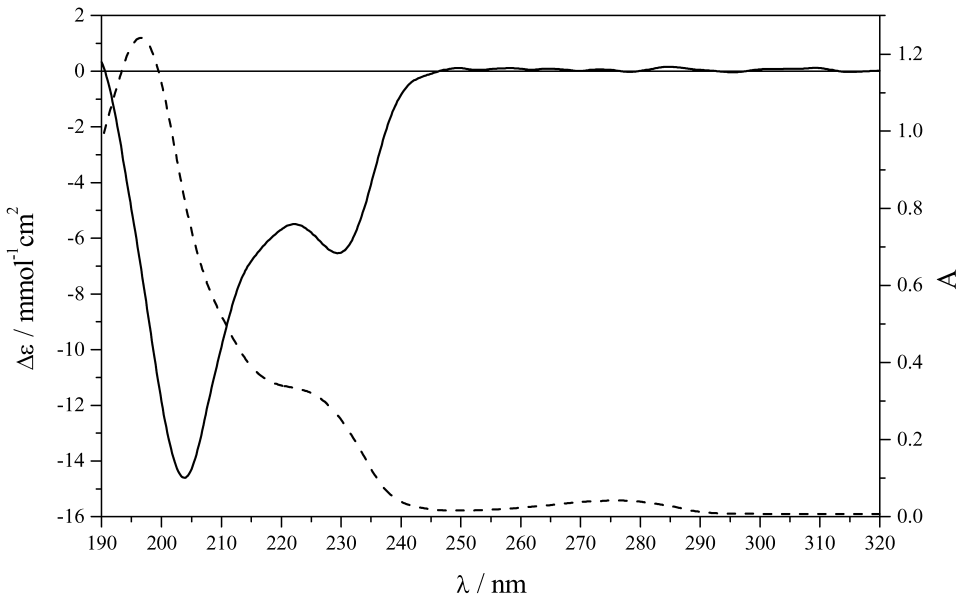


Figure 3. The CD spectrum (—) and absorption spectrum (- - -) of **10** in MeCN (c=1.59×10^{-3} mol dm^{-3}, l=0.01 cm).

the short-wavelength region of ligands and complexes. This band is nearly two times more intense for the cyclic complex **13**, as for the acyclic counterpart **12**. In both complexes two exciton-type bands appear at 210–220 nm, the first one (at longer wavelength) being negative, and the second one positive. They cannot be interpreted as coupled excitons of two $\pi-\pi^*$ transitions, however. In our recent study, the aromatic ^1B_b band for C(4) benzyl and phenyl-bis(oxazolines) is analyzed, and only for C(4)-phenyl analogs was this type of coupling observed; exciton coupling between C=N $\pi-\pi^*$ bands is excluded.[2] It can be suggested that the twist between two C=N bonds is larger in **12** than in **13**, impaired by the conformational restrictions to the macrocycle, causing a stronger CD effect.

Racemic reference compound **15** was prepared by the improved method of Meerwein[12] (Scheme 3). To validate the allylic alkylation method, enantioselective alkylation of **14** to **15** was repeated with bis(oxazoline) ligand **4**, using [Pd(η^3-C_3H_5)Cl]$_2$ as precatalyst and a mixture of dimethylmalonate (DMM), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate (Scheme 4).[13] This method serves to generate a catalytic base, which produces low concentration of $^-CH(CO_2Me)_2$ in situ, thus allowing the diastereomeric intermediates to equilibrate and destroy any potential memory effect.[14]

When we repeated catalytic allylation of **14** in dichloromethane (dried over Al_2O_3, then over CaH_2, and distilled under the argon atmosphere), according to the reported protocol,[13] enantiomerically enriched **15** was obtained after 68 h in 25% yield and 84% e.e. as compared to the reported

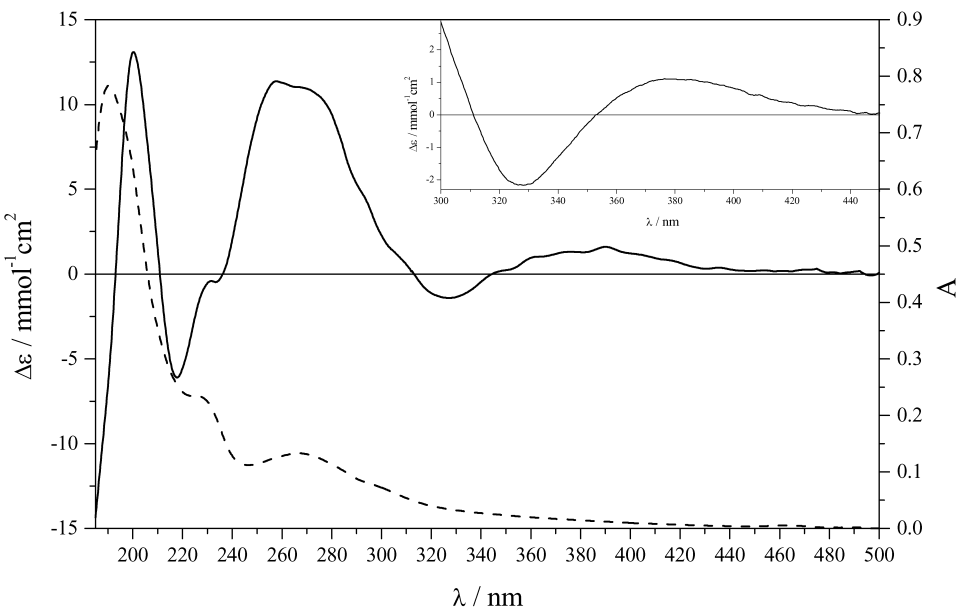


Figure 4. The CD spectrum (—) and absorption spectrum (- - -) of **12** in MeCN (c=7.00×10^{-4} mol dm^{-3}, l=0.01 cm). Insert: long-wavelength region of the CD spectrum (c=6.21×10^{-4} mol dm^{-3}, l=0.2 cm).

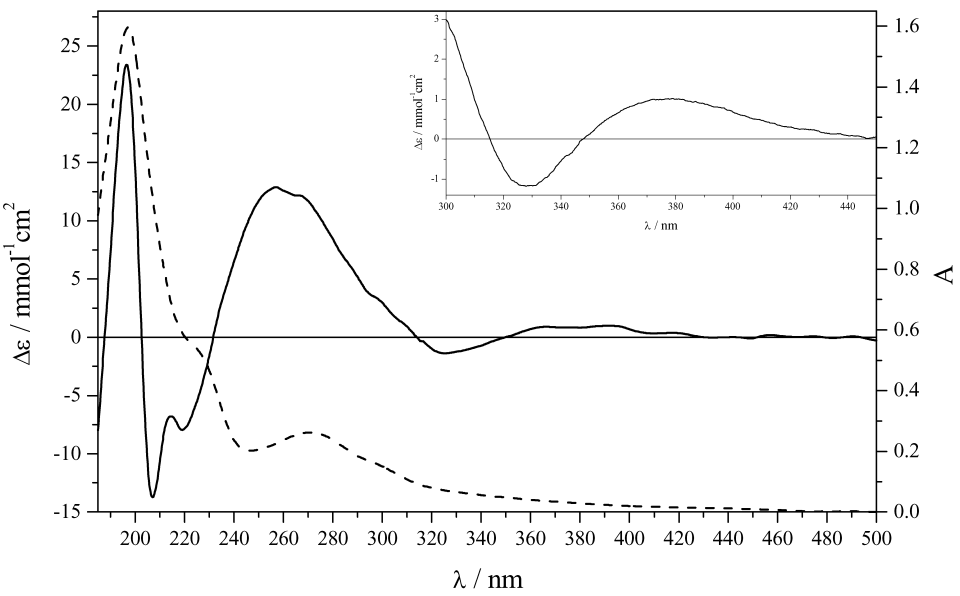
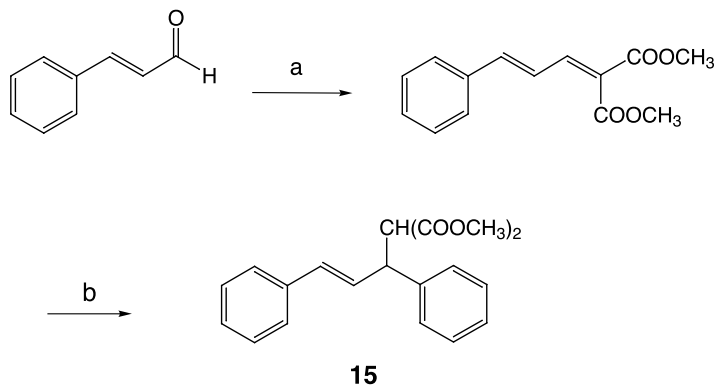
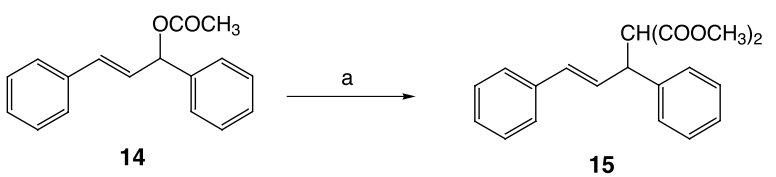


Figure 5. The CD spectrum (—) and absorption spectrum (- - -) of **13** in MeCN (c=1.24×10^{-3} mol dm^{-3}, l=0.01 cm). Insert: long-wavelength region of the CD spectrum (c=6.17×10^{-4} mol dm^{-3}, l=0.2 cm).



Scheme 3. (a) $CH_2(COOCH_3)_2$/piperidine/CH_2Cl_2/rt; (b) PhMgBr/Et_2O/△, 77%.



Scheme 4. (a) [Pd(allyl)Cl]$_2$/**1**–**10**, DMM, BSA, KOAc/MeCN, 14–>98%.

97% yield and 87% e.e. Screening of the solvents revealed acetonitrile as the solvent of choice in which **15** was obtained in 95% yield and 87% e.e. To reduce the long reaction time needed for reaction in dichloromethane at ambient temperature,[13] the catalytic reaction was repeated in acetonitrile at 50°C and 100°C. At 50°C the reaction was complete within 16 h (96% yield, 88% e.e.), whereas at 100°C the reaction took only 15 min and **15** was isolated in 90% yield and 78% e.e.

Having established a general procedure, allylic alkylation was performed with in situ prepared Pd(II) complexes of **1**–**10**. Table 1 shows the results of allylic alkylation according to the Scheme 4. Comparison of ligands **1**–**3** with

Table 1. Results of asymmetric alkylation of *rac*-1,3-diphenyl-3-acetoxy-prop-1-ene with dimethyl malonate (Scheme 4)

Ligand	*T* (°C)	Time (h)	Yield	e.e. (%)	Config.[a]
1	50	20	49	84.9	*R*
2	50	20	>98	92.0	*R*
3	50	20	14	79.9	*R*
4	50	20	93	86.0	*R*
5	50	20	>98	87.5	*S*
6	50	20	>98	65.0	*S*
7	50	20	74	80.8	*S*
8	50	20	39	83.8	*S*
9	50	20	41	79.9	*S*
10	50	20	22	84.0	*S*

[a] According to HPLC data and optical rotation reported in Ref. 13.

a phenyl group on the stereogenic centers reveals that an elongated side chain in the acyclic ligand **2**, or macrocyclization to its cyclic counterpart **3**, led to either slightly enhanced (92% e.e.) or diminished (80% e.e.) enantioselectivity, as compared to the reference ligand **1** (84% e.e.).

A somewhat less consistent picture is seen for **4**–**10** with a benzyl group on the stereogenic centers. Acyclic ligand **5** with a *para*-substituted (benzyloxy)benzyl group on the stereogenic center exhibit nearly the same e.e. (87.5%) as the reference ligand **4** (86% e.e.), whereas their cyclic counterpart **6** was less effective (64% e.e.). Although the cumulative number of methylenic groups in cyclic ligands **3** and **6** are the same (four), the enantioselectivity with the former is nearly 30% higher than with the latter. When the number of methylenic groups in the macrocyclic ligands **7** and **8** is increased to six and eight, respectively, enantioselectivity is enhanced to 81–84%. Ligands **9** and **10**, as analogs of **7** and **8** containing 'crowded lower part' to the macrocycle, exhibited similar enantioselectivity as for **7** and **8**. This result, and the higher efficacy of **3** than that of **6**, indicates that steric perturbation in the 'upper part' of the macrocyclic ligand mainly contributes to enantioselection.

In conclusion, the 1,3-diphenyl moiety seems equally well accommodated by the Pd(II) complexes of acyclic and macrocyclic ligands. The approach of the malonate anion to one face of the π-allyl unit[15–17] is not controlled as well by the macrocyclic counterparts. It can be concluded that complexes of the macrocyclic ligands reported herewith could potentially be more effective in an intramolecular variant of enantioselective allylation. Application of catalytic complexes of macrocyclic ligands in specific intramolecular C–C bond forming reactions is envisaged, that are expected to offer a new approach to the carbon skeleton of biologically active compounds.

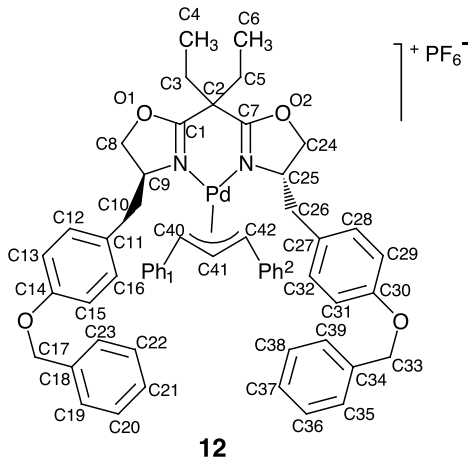
3. Experimental

3.1. General

IR spectra were run on a Perkin–Elmer 297 spectrometer for KBr pallets. ^{1}H and ^{13}C NMR spectra were obtained with a Varian Gemini XL 300 spectrometer in $CDCl_3$ solutions, δ in ppm is relative to TMS as internal reference, with *J* values quoted in Hz. HPLC chromatography was performed on a HP 1050 chromatograph, separation was monitored by a HP 1050 UV detector set up at 254 nm and connected to a HP 3396A integrator. Mps were determined on Electrothermal Apparatus, and are not corrected. Optical rotations were obtained with an Optical Activity AA-10 Automatic Polarimeter in a 1 dm cell; *c* in g/100 mL. CD spectra were run on a JASCO J-810 spectropolarimeter, in quartz cuvettes (*l*=1 dm) for MeCN solutions at ambient temperature. HR/MS spectra were obtained on Extrel-FTMS 2001DD instrument, HPLC purity of the analytical samples was ≥99.5%.

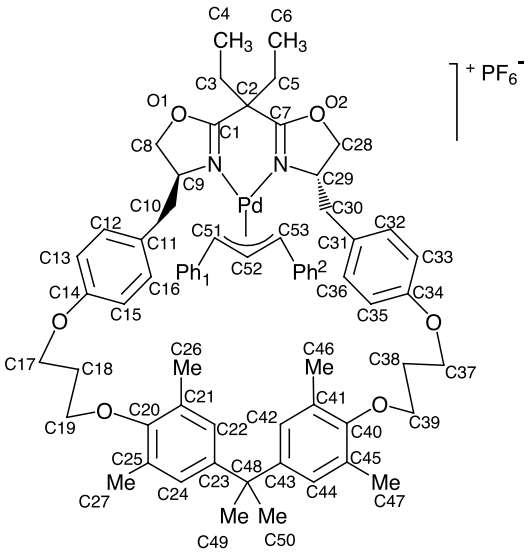
All commercial reagents were used as received. Ligands **2**, **3**, **5**–**10**, are prepared according to the reported method.[9] Di-μ-chlorobis[η^3-1,3-diphenylallyl palladium (II)] (**11**) was prepared from commercial $PdCl_2$ according to the method of Pfaltz et al.[5]

3.1.1. (η^3-1,3-Diphenyl) (*S*,*S*)-2,2′-(1-ethylpropylidene) bis-(4-(oxobenzyl)benzyl)-4,5-dihydro-oxazol) [palladium (II) hexafluorophosphate] (12). All reactions were performed under argon atmosphere in abs. dry solvents. Di-μ-chlorobis[η^3-1,3-diphenylallyl palladium (II)] (**11**; 45.0 mg, 0.06 mmol) and bis(oxazoline) derivative **5** (0.13 mmol) were dissolved in a solvent mixture THF/MeOH/CH_2Cl_2 (1.0:1.0:1.0; 6.0 mL), and heated in a sealed vial at 50°C for 3 h, then left for 20 h at ambient temperature. To the reaction mixture was added the solution of $AgPF_6$ (33 mg, 0.013 mmol) in THF (1.0 mL), and stirred in the dark at ambient temperature for 1 h. The solution was filtered through a Millipore filter (5 μm), the filtrate was evaporated to dryness, the crude material dissolved in CH_2Cl_2 (3.0 mL), washed with satd aqueous NaCl solution (3.0 mL), aqueous phase extracted with CH_2Cl_2 (3×3 mL), combined extracts are dried (Na_2SO_4) and evaporated. The oily residue was dissolved in CH_2Cl_2 (1.0 mL), solution covered with Et_2O (1.0 mL) and left for precipitation. The supernatant was pipetted off, and chromatographically pure product (132 mg, quantitative) was crystallized from CH_2Cl_2/EtOH at −15 °C. On standing in an open vial over 10 days pale-yellow crystals of **12** were collected; mp 93–94°C. IR (KBr): 3447, 1644, 1611, 1511, 1456, 1243, 1179, 839, 759, 697, 558 cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.79 (d, *J*=3.9 Hz, 2H, C(19)H; C(23)H), 7.59 (d, *J*=7.1 Hz, 2H, C(35)H; C(39)H), 7.44–7.21 (m, 16H), 6.93 (d, *J*=8.5 Hz, 2H, C(13)H; C(15)H), 6.85 (d, *J*=8.5 Hz, 2H, C(12)H; C(16)H), 6.79 (d, *J*=8, 5 Hz, 2H, C(29)H; C(31)H), 6.54 (d, *J*=8.3 Hz, 2H, C(32)H; C(36)H), 6.20 (t, *J*=6.6 Hz, C(40)2H), 5.30 (d, *J*=12.6 Hz, C(42)H), 5.07 (s, 2H, C(17)2H), 5.03 (s, 2H, C(33)2H), 4.34 (t, *J*=6.4 Hz, C(24)H), 4.21–4.14 (m, 2H, C(8)H; C(42)H), 4.08–4.06 (m, 2H, C(24)H; C(8)H), 3.89 (t, *J*=8.8 Hz, C(8)H), 3.36 (m, C(9)H), 2.82 (dd, J_1=14.5 Hz; J_2=5.5 Hz, C(10)H_b), 2.58 (dd, J_1=14.8 Hz, J_2=8.5 Hz, 1H, C(10)H_a), 2.19–2.14 (m, 1H, C(26)H_b), 1.95–1.81 (m, 5H, C(3)2H; C(5)2H+C(6)H), 0.78 (t, *J*=7.4 Hz, C(4)3H), 0.62 (t, *J*=7.4 Hz, C(6)3H) ppm. ^{13}C NMR ($CDCl_3$): 171.4, 171.0, 157.7, 157.4, 138.0, 136.4, 135.9, 130.2, 129.7; 129.5, 129.3, 129.0, 128.0, 127.5, 127.4, 127.0, 126.7, 126.1, 114.6, 114.2, 106.9, 102.3, 83.9, 71.8, 71.6, 69.4, 64.8, 64.1, 49.7, 38.8, 38.3, 31.2, 30.8 ppm. ESMS, M^+ calcd for $C_{54}H_{56}N_2O_4PF_6Pd$ 901.3191; found; 901.3259.



12

3.1.2. (η^3-1,3-Diphenyl) (*S*,*S*)-2,2′-(1-ethylpropylidene) bis-(4-(4-(3-(4-(1-methyliden)-2,6-dimethylphenoxy)-propoxy)-benzyl)-4,5-dihydro-oxazol) [palladium (II) hexafluorophosphate] (13). This complex was prepared as described for complex **12** starting from bis(oxazoline) **10** (100 mg, 0.13 mmol), compound **11** (45 mg, 0.06 mmol) and $AgPF_6$ (32 mg, 0.13 mmol). On extraction and evaporation the crude complex was purified by chromatography on the thick-layer alox-plate with methyl-*tert*-butylether/CH_2Cl_2 (4.0:1.5) as eluent. The amorphous product (106 mg, 71%) was purified by crystallization from CH_2Cl_2/EtOH at −15°C, pale-yellow crystals, m.p. 164–165°C (dec). IR (KBr): 3434, 1644, 1610, 1511, 1243, 1179, 1128, 1026, 1002, 840, 759, 740, 697, 558 cm^{-1}. ^1H NMR ($CDCl_3$): 7.78–7.76 (m, 2H, *o*-Ph_1), 7.67 (d, *J*=7.14 Hz, 2H, *o*-Ph_2, 7.47–7.38 (m), 6.83–6.67 (m), 6.26 (t, *J*=12.1 Hz, C(52)H), 5.28 (d, *J*=13.5 Hz, C(51)H), 4.41 (d, *J*=10.7 Hz, C(53)H), 4.27–3.73 (m, C(8)H; C(28)H; C(10)H; C(30); C(52)H), 2.14 (s, C(26)3H; C(27)3H), 2.05 (s, C(46)3H; C(47)3H), 1.89–1.82 (m, C(3)2H; C(5)3H; C(52)H), 1.57 (C(49)3H; C(59)3H), 0.65 (m, C(17)H; C(19)H; C(37)H; C(39)H), 0.42 (t, *J*=7.1 Hz C(18)H; C(38)H) ppm. ^{13}C NMR ($CDCl_3$): 172.3, 171.9, 158.5, 158.1, 153.6, 153.4, 146.0, 138.9, 137.1, 137.0, 131.0, 130.7, 129.9, 129.7, 129.6, 128.8, 128.4, 128.0, 127.2, 127.1, 127.0, 126.7, 114.7, 114.5, 107.8, 83.2, 73.8, 72.1, 71.9, 68.4, 68.0, 65.0, 64.6, 64.3, 49.4, 41.7, 38.7, 38.2, 31.0, 30.6, 30.5, 30.1, 16.7, 16.5, 9.2, 9.1 ppm. ESMS, M^+ calcd for $C_{65}H_{76}N_2O_6PF_6Pd$ 1085.4665; found; 1085.4616.



13

3.1.3. 1,3-Diphenyl-1-dimethylmalonylprop-2-ene (15). To the ice-cold solution of cinnamaldehyde (freshly distilled, 1.65 g, 13 mmol) in CH_2Cl_2 (20 mL), dimethylmalonate (DMM, 3.2 g, 2.6 mmol) was added over 15 min under stirring, then piperidine (3 drops) and Na_2SO_4 (5.0 g). The reaction mixture was stirred for 24 h at ambient temperature, the solvent evaporated, and the yellow oil crystallized on addition of MeOH (8 mL). On standing overnight in refrigerator 1.89 g (61.6%) of intermediary malonyl diene was obtained (mp 66–68°C). Et_2O (10 mL) was added to Mg (100 mg, 4.1 mmol), then bromobenzene (320 mg, 2.0 mmol) and a catalytic quantity of Br_2 were added. The reaction mixture was heated 2.5 h under reflux in argon atmosphere, then cooled to ambient temperature, and a solution of diene (227 mg, 0.9 mmol) in Et_2O (10 mL) was added dropwise until the yellow precipitate was dissolved. Heating under reflux was continued for 1 h, the reaction solution was cooled, supernatant decanted from the solid residue, washed with satd. solution of NH_4Cl (10 mL), organic solution dried (Na_2SO_4). The crude product was purified on silica gel column (15 silica gel), with *n*-hexane/*i*-Pr_2O (5:2) as eluent; crystallization from *i*-Pr_2O afforded 230 mg (77%) of **15**, colourless crystals, mp 94–96°C (lit., mp 94°C).[12] IR (KBr): 2950, 1760, 1495, 1435, 1320, 1265, 1145, 745, 705, 690. ^1H NMR ($CDCl_3$): 3.52 (s, C*H*3), 3.70 (s, C*H*3), 3.96 (d, C*H*, *J*=10.9 Hz, 4.24–4.27 (m, Ar–C*H*═), 6.34–6.37 (m, CH═C*H*), 6.49 (d, Ph–C*H*═CH), 7.20–7.32 (m, 10H) ppm. ^{13}C NMR: 49.0, 52.20, 52.4, 57.4, 126.3, 127.1, 127.5, 127.8, 128.4, 128.6, 130.1, 131.7, 140.1, 167.7, 168.2 ppm.

3.2. Pd-Catalyzed allylic alkylation—general procedure

All compounds were prepared under a dry argon atmosphere using standard Schlenk and vacuum-line techniques. To the solution of $[Pd(allyl)Cl]_2$ (3.0 mg, 8 μmol) in MeCN (1.0 mL) ligand (25 μmol) was added, the reaction mixture was deaerated in vacuo, then heated at 50°C for 2 h. On cooling to ambient temperature 1,3-diphenyl-1-acetoxy-propen-2-ene (125 mg, 0.5 mmol) was added, and then DMM (370 mg, 2.8 mmol), BSA (570 mg, 2.8 mmol) and KOAc (2 mg) were added. The reaction mixture was heated at 50°C for 20 h, then diluted with CH_2Cl_2 (5.0 mL), washed with satd. NH_4Cl solution (5 mL), and the separated organic solution dried over Na_2SO_4. On evaporation crude product was purified by flash-chromatography (10 g silica gel column), with *n*-hexane/*i*-Pr_2O (5.0:2.5) as eluent. Fractions with pure compound **14** were evaporated and the product dried in vacuo. The yield and e.e. were calculated on chromatographically pure material, which exhibited the same chromatographic and spectroscopic properties as reported. HPLC conditions: Chirlacel ODH column 25×0.46 cm, Chiralcel OD precolumn 5.0 cm, eluents

n-hexane/*i*-PrOH (99:1), UV detector at 254 nm. The retention times: faster running enantiomer 19.1 min, slower running enantiomer 21.6 min.

Acknowledgements

The authors are indebted to Mr D. Žiher, R & D Institute, PLIVA d.d for running CD spectra. This work was supported by Croatian Ministry of Science and Technology (Projects 980701 and 980702).

References

1. Portada, T.; Roje, M.; Raza, Z.; Čaplar, V.; Žinić, M.; Šunjić, V. *Chem. Commun.* **2000**, 1993–1994.
2. Hollosi, M.; Majer, Z.; Vass, E.; Raza, Z.; Tomašić, V.; Portada, T.; Piantanida, I.; Žinić, M.; Šunjić, V. *Eur. J. Inorg. Chem.* **2002**, 1738–1748.
3. Ghosh, A. K.; Mathiavanan, P.; Cappiello, J. *Tetrahedron Asymmetry* **1998**, *9*, 1–45.
4. Fache, F.; Schewucz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159–2231.
5. von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Ruegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265–284.
6. Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.
7. Gomez, M.; Jansat, S.; Muller, G.; Meastro, M. A.; Mahia, J. *Organometallics* **2002**, *21*, 1077–1087.
8. Balsells, J.; Betancort, J. M.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 3428–3430.
9. Čaplar, V.; Raza, Z.; Katalenić, D.; Žinić, M. *Croat. Chem. Acta* **2003**, *76*, in press.
10. Bosnich, B. *J. Am. Chem. Soc.* **1968**, *90*, 627–632.
11. Kovač, B.; Klasinc, L.; Raza, Z.; Šunjić, V. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2455–2459.
12. Meerwein, H. *Liebigs Ann. Chem.* **1908**, 323–347.
13. Fahrni, C.; Matt, P. V.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143–2156.
14. Fairlamb, I. J. S.; Lloyd-Jones, G. C.; Vyskičil, Š.; Kočovsky, P. *Chem. Eur. J.* **2002**, *8*, 4443–4453, The authors are indebted to the referee for drawing their attention to this paper.
15. Pfaltz, A. *Acta Chim. Scand.* **1996**, *56*, 189–194.
16. Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727–10737.
17. Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 9374–9380.