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Comparative Study of 1,5-Dinitrogen Schiff Bases as Potential Ligands in Palladium-Catalyzed Allylic Alkylation

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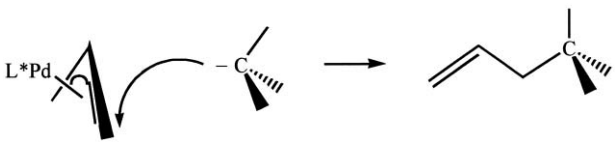
1-(2'-Pyrido and 2'-quinolino)-(1*R*)-arylethylamino)-ethylidenes (**7–12**) were prepared as potential ligands in Pd^{II} catalytic complexes for enantioselective allylic alkylation of 1,3-diphenyl-1-acetoxy-propene-2 (**15**). Alkylation with palladium complexes of **7–12** yielded 1,3-diphenyl-1-dimethylmalonyl-propene-2 (**14**) with enantioselectivity up to 55 % e.e. Enantioselectivity is discussed in view of the results recently reported for structurally related 1,5-bidentate dinitrogen ligands of C_1 symmetry. Reversal of enantioselectivity observed for the ligands **10** and **11** is attributed to the inversion of steric requirements in the second coordination sphere of their catalytic complexes.

Key words
ethylidenes
conformation
Pd^{II} complexes
allylic alkylation

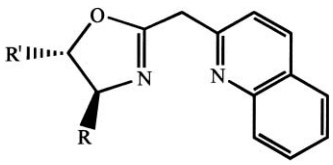
INTRODUCTION

Chiral bidentate nitrogen ligands proved highly efficient in a various homogeneous catalytic processes; such as hydrosylilation of ketones,[1] cyclopropanation of alkenes,[2] Diels-Alder reaction,[3] Heck reaction,[4] allylic aminations,[5] and allylic alkylations.[6–10] Recent papers have confirmed versatility of the asymmetric allylic alkylation, Scheme 1,[6] as the synthetic procedure for enantioselective formation of C–C bond in acyclic[11–15] and cyclic[16] substrates, or in its intramolecular variant.[17]



Scheme 1.

Despite of the large number of reports dealing with the activity and enantioselectivity of palladium catalytic systems in allylic alkylations, only a couple of studies was reported on the activity of C_1 symmetric 1,5-dinitrogen ligands.[18,19] Prompted by the results published for quinolino-oxazoline ligands **1a–1c**,[19] the representatives of C_1 symmetric 1,5-bidentate dinitrogen ligands, we report here with the results of comparative study of allylic alkylations by the palladium complexes of chiral Schiff bases, enamines of α-aryl-2-(2'-pyrido, or 2'-quinolino)-acetophenone **7–12**.



	R	R'
1a	CH_2OH	Ph
1b	$CH_3OSi(Ph)_2(t\text{-}Bu)$	Ph
1c	CH_3Ph	H

Formulae **1a–1c**.

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1-Arylmethylimines of pyridyl or quinolyl-acetophenones **7–12** are characterized by their conformational flexibility, presence of the large aromatic and heteroaromatic units, and by the imine-enamine equilibrium. We have already reported preparation of some representatives, on their CD and conformational properties,[20,21] as well as the results of enantioselective cyclopropanation with their Cu^I complexes.[22]

EXPERIMENTAL

IR: Perkin Elmer 297 spectrometer for KBr pellets, if not stated otherwise. ^1H and ^{13}C NMR: Varian Gemini XL 300 spectrometer for $CDCl_3$ solutions, δ in ppm relative to TMS as internal reference, and J in Hz. HPLC: HP 1050 chromatograph with C18 RP (Nucleosil RP-18, 250 × 4.6 mm) reverse phase column; separation was monitored by HP 1050 UV detector set up at 254 nm and connected to HP 3396A integrator. M.p.: Electrothermal Apparatus, are not corrected. Optical rotations: Optical Activity AA-10 Automatic Polarimeter in a 1 dm cell; c in g/100 ml.

$[Pd(allyl)Cl]_2$, and other commercially available compounds were purchased from Aldrich, compounds **7–10**, and **12** have been prepared as reported.[21,22] All commercial reagents were used as received.

During usual workup all organic extracts were dried over Na_2SO_4 or $MgSO_4$ and evaporated *in vacuo* on a Büchi rotavapor.

*2-(2'-Quinolino)-2,6-dimethoxy-acetophenone (**6**)*

All manipulations were performed in dry argon atmosphere. 2-Methyl-quinoline (1.0 g, 7.0 mmol) was added dropwise under stirring over 5 min period at **–**10 °C to the solution of n-BuLi (2.5 M in n-hexane; 3.1 ml, 7.7 mmol), in dry ether (10 ml). Reaction mixture was stirred for 2 h, and at the same temperature added benzoate **3** (1.51 g, 7.7. mmol). After 20 h stirring at ambient temperature i-Pr_2O (50 ml) was added and pH adjusted to 1.0 with dil. HCl. By extraction with i-Pr_2O (3 × 30 ml) hydrochloride of **6** was separated. Organic extracts were washed with dil. $NaHCO_3$, dried, evaporated and crude product crystallized from i-Pr_2O (630 mg, 29 %) m.p. 220**–**221.5 °C. IR(KBr) ν_{max}/cm^{-1}: 1635, 1585, 1555, 1540, 1470, 1415, 1330, 1250, 1110, 860, 830, 760. ^1H NMR ($CDCl_3$) δ/ppm: 3.82 (s, 6H), 5.54 (s, 1H), 6.68**–**6.54 (m, 2H), 6.72 (d, 1H, J = 9.2 Hz), 7.64**–**7.19 (m, 6H), 15.19 (s, 1H). ^{13}C NMR ($CDCl_3$) δ/ppm: 55.9, 95.4, 103.8, 117.5, 122.1, 122.9, 123.2, 127.3, 127.5, 129.2, 130.7, 135.8, 137.2, 152.6, 157.0.

Anal. Calcd. for $C_{19}H_{17}NO_3$ (M_r = 307.34): C 74.25, H 5.58, N 4.56 %; found: C 74.20, H 5.71, N 4.69 %.

*1-(R)-Methyl-1-(2,6-dimethoxyphenyl)-2-(2'-quinolino)-1-ethylidenebenzylamine (**11**)*

Compound **6** (172 mg, 0.56 mmol), (*R*)-1-phenylethylamine (80 mg, 0.67 mmol), and $Si(OEt)_4$ (208 mg, 1.0 mmol) were deaerated in toluene (2.0 ml), filtered over basic aluminum oxide, activity I, and then heated in the sealed glass tube at 160 °C over 66 h. To the cooled reaction mixture CH_2Cl_2 (20 ml) was added, and resulting mixture washed with aq. bicarbonate solution. Organic layer was separated, dried, and evaporated, and crude product crystallized on addition of small amount of MeOH. From the mother liquors second crop of **11** was obtained on evaporation and chromatography on aluminum oxide, activity II–III, with i-Pr_2O as eluent. Combined crops were crystallized from EtOH/water and collected on filter at –20 °C (53 mg, 23 %) m.p. 75–77 °C. $[\alpha]_D$ = +982 (c = 1 g/100 ml CH_2Cl_2). ^1H NMR ($CDCl_3$) δ/ppm: 1.57 (d, 3H, J = 6.9 Hz), 3.26 (s, 3H), 3.86 (s, 3H), 4.28–4.23 (m, 1H), 5.07 (s, 1H), 6.34 (d, 1H, J = 8.2 Hz), 6.60 (d, 1H, J = 8.2 Hz), 6.97 (d, 1H, J = 8.7 Hz), 7.80–7.10 (m, 11H), 11.67 (d, 1H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ/ppm: 24.9, 53.9, 55.1, 55.8, 94.7, 103.2, 103.5, 114.9, 122.5, 122.9, 124.7, 125.8, 125.9, 126.0, 126.8, 127.0, 127.8, 128.5, 129.6, 133.9, 145.8, 147.3, 149.4, 157.5, 157.7, 160.1.

Anal. Calcd. for $C_{27}H_{26}N_2O_2$ (M_r = 410.51): C 79.00, H 6.38, N 6.82 %, found: C 79.21, H 6.29, N 6.85 %.

*Dicarbomethoxy-4-phenyl-1,3-butadiene (**13**)*

All operations were performed in argon atmosphere; CH_2Cl_2 was dried over aluminum oxide (activity I).

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). Reaction mixture was stirred for 24 h at ambient temperature, solvent evaporated, and yellow oil crystallized on addition of MeOH (8.0 ml). On standing overnight in refrigerator 1.89 g (61.6 %) of **13** was obtained, m.p. 66–68 °C (lit. m.p. 67 °C).[23] IR(KBr) ν_{max}/cm^{-1}: 2950, 1720, 1610, 1590, 1430, 1285, 1240, 1225, 1210, 1060, 750. ^1H NMR ($CDCl_3$) δ/ppm: 3.81 (s, 3H), 3.89 (s, 3H), 7.04 (d, 1H, J=15.4 Hz), 7.22–7,58 (m, 7H). ^{13}C NMR ($CDCl_3$) δ/ppm: 52.1, 52.15, 123.1, 123.9, 127.8, 128.7, 129.8, 135.4, 145.1, 153.1, 155.1, 165.6.

*1,3-Diphenyl-1-dimethylmalonylprop-2-ene (**14**)*

Et_2O (10.0 ml) was added on the Mg-powder (100 mg, 4.1 mmol), then bromobenzene (319 mg, 2.0 mmol) and catalytic quantity of bromine were added. Reaction mixture was heated 2.5 h under reflux in argon atmosphere, then cooled to ambient temperature, and solution of diene **13** (227 mg, 0.9 mmol) was added dropwise until yellow precipitate was dissolved. Then heating under reflux was continued for 1 h, reaction solution cooled and decanted from the solid residue, washed with std. solution of NH_4Cl (10 ml), and worked-up as usual. Crude product was purified on silica gel column (15 silica gel), with n-hexane/i-Pr_2O (5:2) as eluent; on crystallization from i-Pr_2O were obtained 230 mg (77 %) of **14**, colourless crystalls, m.p. 94–96 °C (lit. m.p. 94 °C).[24] IR (KBr) ν_{max}/cm^{-1} 2950, 1760, 1495, 1435, 1320, 1265, 1145, 745, 705, 690. ^1H NMR ($CDCl_3$) δ/ppm: 3.52 (s, 3H), 3.70 (s, 3H), 3.96 (d, 1H, J = 10.9 Hz, 4.24–4.27 (m, 1H), 6.34–6.37 (m, 1H), 6.49 (d, 1H), 7.20–7.32 (m 10H).

^{13}C NMR ($CDCl_3$) δ/ppm: 49.0, 52.2, 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.

Pd-allylation, General Method

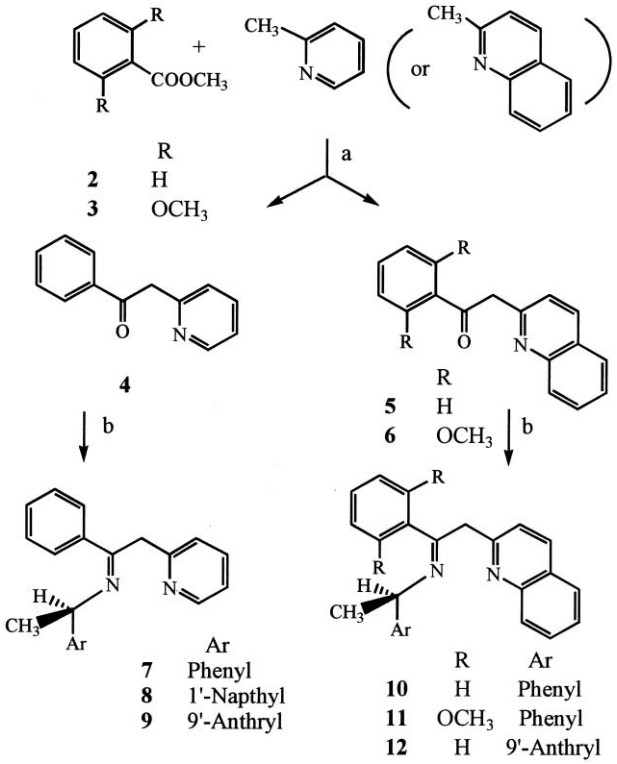
All reactions are performed in the flame-dried vials under argon atmosphere, using standard Schlenk technique. To $[Pd(allyl)Cl]_2$ (2.9 mg, 7.9 μmol) dissolved in MeCN (1.0 ml, freshly distilled over CaH_2), was added ligand (25 μmol). Resulting solution was deaerated under argon by repeated evacuation under water-pump, then heated at 50 °C for 2 h. On cooling to ambient temperature compound **15** (126 mg, 0.5 mmol) was added, Schlenk tube was spilled with MeCN (0.8 ml), then DMM (370 mg, 2.8 mmol), BSA (570 mg, 2.8 mmol) and KOAc (2.0 mg) were added. The reaction went to completeness at 50 °C overnight. On cooling CH_2Cl_2 (5.0 ml) was added, and reaction solution washed with std. aqueous NH_4Cl solution (5.0 ml). Organic phase was dried, solvent removed and crude product purified by flash chromatography on 30 g silica gel, with n-hexane/i-Pr_2O (5:2) as eluent. Fractions with pure **14** were collected and evaporated to dryness; determination of yield and e.e. was performed on such chromatographically pure material; HPLC conditions; Chiralcel OD-H column, 25 × 0.46 cm, pre-column Chiralcel OD, 5.0 cm, eluens n-hexane/i-PrOH (99:1).

RESULTS AND DISCUSSION

To prepare final ketimines **7–12** in the satisfactory yields, (*R*)-1-arylethylamines and ketones **4–6** were heated in the presence of tetraethoxysilane at 160 °C under inert atmosphere, Scheme 2. According to the ^{13}C and ^{1}H NMR data, newly prepared bulky ketone **6** is present in the solution completely in the enamino-enolic form, as we already observed for similar quinolino-ketones.[20,21] The signals for the enolic C-atom at 157 ppm, and for the N-H proton at 15.19 ppm, hydrogen bonded to the carbonyl O-atom, can be observed. Besides, the signals for the methylenic (CH_2) group protons and carbon are absent from the ATP spectra of **6**.

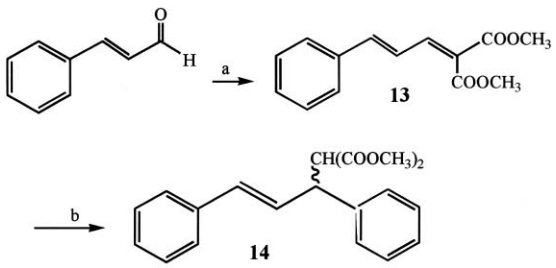
Improving reported procedures,[23,24] racemic **14** was prepared as HPLC standard in *ca*. 50 % overall yield according to sequence of reactions outlined in the Scheme 3, and resolved on a Chiralcel OD-H column. Compound **15** was prepared according to the method reported in literature.[25] Its enantioselective alkylation to the enantiomerically enreached **14** was performed by the catalytic complexes of **7–12** formed from $[Pd(\eta^3\text{-}C_3H_5)Cl_2]$, and using a mixture of dimethylmalonate (DMM), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate to generate malonate anion according to the protocol of Pfaltz *et al*.,[26] Scheme 4.

After having established general procedure, allylic alkylation was performed with *in situ* prepared Pd^{II} complexes of **7–12**. The results presented in the Table I reveal the variation of e.e. up to 55 % e.e., comparable with e.e.s obtained with ligands **1a–c** (44–69 %).[19] Large variation of the chemical yield was regularly observed, and is attributed to the sensitivy of the catalytic complex to the trace impurities in the solvent or substrate.



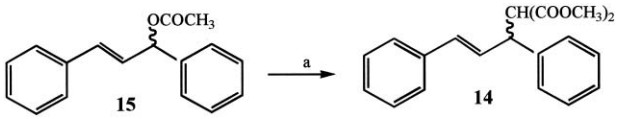
a) n-BuLi/Et_2O/–10 °C,
b) α-(*R*)-arylethylamine/$Si(OEt)_4$/*p*-TsOH/160 °C

Scheme 2.



a) $CH_2(COOCH_3)_2$/pyperidine/CH_2Cl_2/r.t.,
b) PhMgBr/Et_2O/Δ

Scheme 3.



a) $[Pd(allyl)C]_2$/**7-12**, DMM, BSA, KOH/MeCN

Scheme 4.

TABLE I. Enantioselective allylic alkylation of **15** with dimethyl malonate according to Scheme 4

Entry	Ligand	Yield of **14** / %	e.e. / %	Config.[a]
1	**7**	100	49.0	(*R*)
2	**8**	81	55.0	(*R*)
3	**9**	14	5.5	(*R*)
4	**10**	26	6.7	(*S*)
5	**11**	97	18.0	(*S*)
6	**12**	17	26.0	(*R*)

[a]According to the HPLC data and optical rotation reported in Ref. 26.

Remarkably, in the series **7–12** ligands **10** and **11** afford (*S*)**-14**, whereas other ligands give (*R*)**-14**. Reversal of enantioselectivity observed for **10** and **11** results from the inversion of the larger and smaller group close to the stereogenic center. In the ligands **7–9** and **12** aryl group bound to stereogenic center is larger than the heteroaromatic unit, while in the compounds **10** and **11** it is smaller then the quinoline moiety. In the recent studies of Moberg *et al*.[27,28] such inversion of the enantioselective bias has been reported for 6-substituted pyrido-oxazolines, and explained by the formation of palladium complexes with different conformations. We have therefore compared stable conformations of the previously reported ligands **I** with those of the ligands **7–12**, creating 3D structures optimized by MM2, Figure 1.

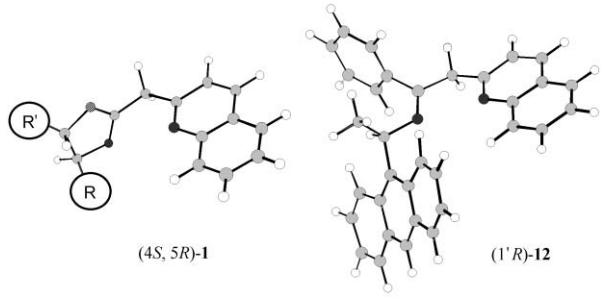


Figure 1. Ball and stick presentation of the lowest energy conformers of (4*S*)-**1a**, and (1'*R*)-**12**.

Substantial conformational difference resides in the position of the larger group R; in the ligands **1a–c;** it is *psudoaxial* while in the ligands **7–12** it can adopt various conformations.

In conclusion, we have shown for 1,5-dinitrogen ligands **7–12** that the reactivity and enantioselectivity in allylic alkylation catalyzed by their Pd^{II} complexes resambles to those obtained with some structurally related 1,5-dinitrogen ligands. Chiral second sphere around metal atom is invoked to explain the inversion of enantioselectivity with complexes of **10** and **11** as compared to the complexes of **7–9** and **12**.

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SAŽETAK

Uporedni studij 1,5-didušikovih Schiffovih baza kao potencijalnih liganada u paladijem kataliziranoj alilnoj alkilaciji

Dragan Šepac, Marin Roje, Zdenko Hameršak i Vitomir Šunjić

Pripravljeni su 1-(2'-pirido i 2'-kinolino)-(1*R*)-ariletilamino)-etilideni (**7–12**) kao potencijalni ligandi u Pd^{II} katalitičkim kompleksima za enantioselektivnu alilnu alkilaciju 1,3-difenil-1-acetoksi-propena-2 (**15**). Alkilacijom uz paladijeve komplekse liganada **7–12** dobiven je 1,3-difenil-dimetilmalonil-propen-2 (**14**) s enantioselektivnošću do 55% e.v. Enantioselektivnost je razmatrana u svjetlu nedavno objavljenih rezultata sa strukturno sličnim 1,5-bidentatnim ligandima C_1 simetrije. Inverzija enantioselektivnosti opažena za ligande **10** i **11** objašnjena je inverzijom steričkih zahtjeva u drugoj koordinacijskoj sferi njihovih katalitičkih kompleksa.