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Chiral vicinal diamines as promising ligands in Pd-catalyzed reductive Heck type cyclizations

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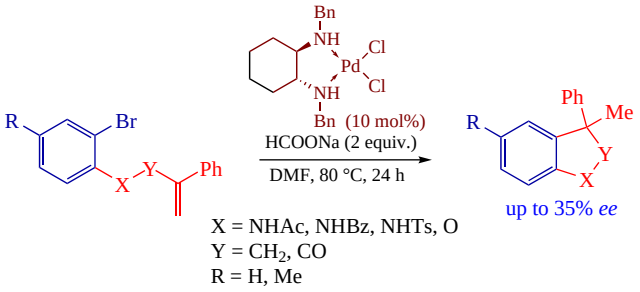
Palladium complexes with inexpensive and available vicinal diamines can serve as catalysts for the reductive Heck-type cyclization. *o*-Bromo-*N*-(2-phenylallyl)anilides are converted into the corresponding 3-methyl-3-phenylindolines, the analogous cyclization occurred for 2-bromo-4-methylphenyl 2-phenylallyl ether and *N*-(2-bromophenyl)-2-phenylacrylamides. The use of (1*R*,2*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine provides up to 35% *ee* of the indolines; this is the first case of asymmetric induction during the reductive Heck reaction involving diamine complexes.



Keywords: reductive Heck reaction, chiral vicinal diamines, palladium complexes, enantioselectivity, indolines, dihydrobenzofurans.

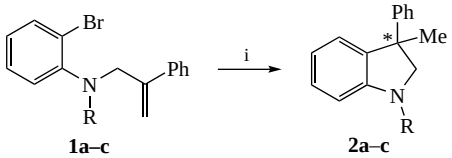
Chiral indoline and 2,3-dihydrobenzofuran key structural motifs are encountered in natural products, drugs, and other biologically active compounds. Molecules with an indoline moiety exhibit multi-target anticancer activity (kinase, histone deacetylase inhibitors, microtubule protein inhibitors, apoptosis inducers), some of them are antibacterial agents. Substituted indolines are also considered as prospective drugs for cardiovascular diseases treatment, anti-inflammatory and analgesic agents.[1–5] On the other hand, some 3,3-disubstituted 2,3-dihydrobenzofuran derivatives are potent and selective cannabinoid receptor 2 (CB_2) agonists and promising for drug development for neuropathic pain.[6] A number of polysubstituted natural and synthetic 2,3-dihydrobenzofurans also exhibit antitumor activity (see Online Supplementary Materials, Figure S1).[7,8]

After the studies by Larock,[9] Grigg[10] and Diaz,[11] the intramolecular reductive Heck reaction has been regarded as a convenient and atom-economical one-step route to form pyrrolidine, dihydrofuran and similar heterocyclic moieties. The Heck reaction can be successfully used for the synthesis of complex polycyclic systems.[12,13] Although numerous chiral ligands and catalysts have been developed so far, only a handful of them was successful in the reductive Heck type cyclizations.[12,14–17] Catalysis by complexes containing bisphosphine, phosphine-oxazoline, and phosphoramidite ligands provided the most significant results in terms of the potential for achieving high enantioselectivity. The use of complexes with NHC ligands can be complicated by the formation of palladium nanoparticles and imidazolium salts.[18]

Chiral vicinal diamines can be a good alternative to expensive and easily oxidizable phosphorus-containing ligands. Apparently, the main limiting factor preventing their implementation in practice is the destabilization of low-valence states of metals by strongly donor ligands.[19,20] However, some studies have demonstrated the ability of diamine palladium complexes to form fairly stable oxidative addition products with iodoarenes.[21] Subsequently, the authors carried out insertion reactions of such diamine aryl palladium complexes with a number of unsaturated compounds.[22] These data raise hope that palladium diamine complexes can be suitable catalysts for the reductive Heck reaction. To date, there is only one report on the use of bis-imine Pd complexes as catalysts for this purpose.[23] In this work, we report the successful catalysis of an intramolecular reductive Heck reaction by a palladium complex with a chiral vicinal diamine. The possibility of asymmetric induction in this reaction was shown for the first time.

Initially, we studied the reductive cyclization of *N*-(2-bromophenyl)-*N*-(2-phenylallyl)acetamide **1a** (Scheme 1, Table 1) in the presence of palladium complexes with various phosphorus- and nitrogen-containing ligands. DMF and methanol/toluene were used as solvents, since polar medium may contribute to the cationic reaction pathway. As shown by previous studies,[24] this pathway favors asymmetric induction in the Heck reaction when using bidentate chiral ligands. Sodium formate was used as a reducing agent.

The attempted use of the catalytic system $Pd(dba)_2$/(*R*)-BINAP did not lead to a positive result (see Table 1, entry 1). However, the use of sodium acetate as an additive provided a 30% yield of 1-acetyl-3-methyl-3-phenylindoline **2a** with slight enantiomeric excess (entry 2). For this reason, sodium acetate



1a–c **2a–c**

a R = Ac (max. 35% *ee*, *R*)
b R = Bz (max. 30% *ee*, *R*)
c R = Ts (*rac*)

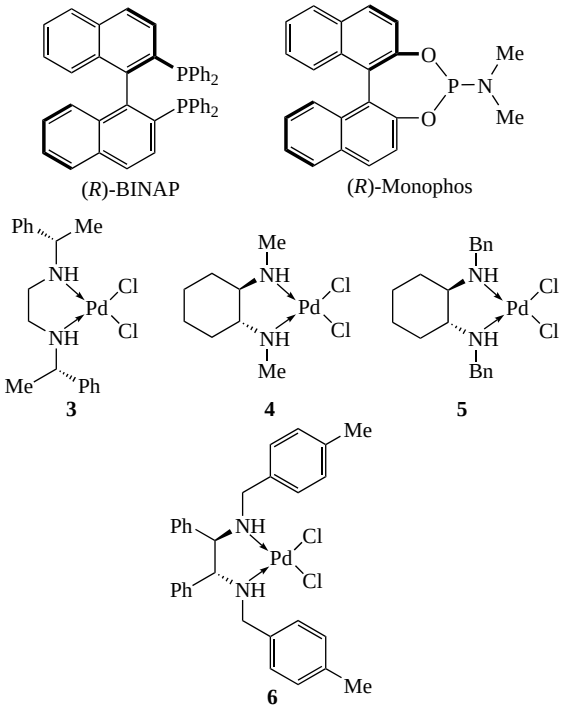
Scheme 1 *Reagents and conditions*: i, [Pd] (10 mol%), HCOONa (2 equiv.), solvent, 80 °C, 24 h (for details, see Table 1).

Table 1 Reductive Heck reaction of compounds **1a–c** in the presence of palladium complexes with phosphorus containing and diamine ligands.[a]

Entry	Substrate	Catalyst (mol%)	Additive[b]	Conversion[c] (%)	Yield[d] (%)	*ee*[e] (%)
1	**1a**	$Pd(dba)_2$ (*R*)-BINAP[g]	–	0[f]	0[f]	–
2	**1a**	$Pd(dba)_2$ (*R*)-BINAP[g]	AcONa	100	30	5
3	**1a**	$Pd(dba)_2$ (*R*)-Monophos[h]	AcONa	100	59	4
4	**1a**	**3**	AcONa	100	55	0
5	**1a**	**4**	AcONa/15-crown-5	100	43	0
6	**1a**	**5**	AcONa/15-crown-5	100 (25[i])	66 (0[i])	35
7	**1a**	**6**	AcONa/15-crown-5	100	36	0
8	**1b**	**5**	AcONa/15-crown-5	100	50	30
9	**1c**	**5**	AcONa/15-crown-5	100	61	5.6

[a] Reaction conditions: compounds **1a–c** (0.6 mmol), HCOONa (1.2 mmol), [Pd] (0.06 mmol, *i.e.* 10 mol%), DMF (4 ml), 80 °C, 24 h. [b] If applied, 2.5 equiv. of AcONa and 10 mol% of 15-crown-5. [c] Determined by GC. [d] After column chromatography. [e] Determined by chiral HPLC. [f] The same result was in 1 : 1 MeOH/PhMe mixture. [g] BINAP 20 mol%. [h] Monophos 40 mol%. [i] In the absence of 15-crown-5.

was used as an additive in further studies. An attempt to use monodentate (*R*)-Monophos as a ligand led to some increase in the yield of indoline **2a**, however the enantiomeric excess of the product remained negligible (entry 3). Having failed to achieve asymmetric induction with mono- and bidentate phosphorus-containing ligands, we decided to investigate the catalytic properties of palladium complexes **3**–**6** with chiral vicinal diamines.



Previously, we demonstrated the high catalytic activity of complex **3** in the intramolecular reductive Heck reaction with sterically hindered unsaturated substrates.[25] In this work, we synthesized complexes with (1*R*,2*R*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine **4**, (1*R*,2*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine **5** and (1*R*,2*R*)-*N*,*N*′-bis(4-methylbenzyl)-1,2-diphenylethane-1,2-diamine **6** *via* displacement of cycloocta-1,5-diene in $[PdCl_2(COD)]$ by the corresponding diamines (see Online Supplementary Materials). The structure of complex **5** was determined by X-ray diffraction analysis (Figure 1).† The unusual orientation of the benzyl substituents in this complex is noteworthy. Both substituents are spatially close to each other occupying pseudoaxial positions in the chelate ring. Thus, in this complex the (*R*,*S*)-configuration is realized at the nitrogen atoms (see Figure 1).

The use of complexes **3**, **4** and **6** as catalysts for the reductive cyclization of substituted acetamide **1a** gave racemic indoline **2a** in moderate yields (see Table 1, entries 4, 5 and 7). A somewhat higher yield of indoline was achieved in the presence of 15-crown-5 (entry 6). In addition, it was found that the catalysis by complex **5** with (1*R*,2*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine led to scalemic product with 35% *ee* (entry 6). It should be noted that, contrary to fears, even traces of palladium black were not found in experiments with diamines, and discoloration of the reaction mixture was observed in the course of the reaction. A scalemic sample compound **2a** with 70% *ee* was obtained from the mother liquor after precipitation of racemic crystals of **2a** from cyclohexane at room temperature. The absolute (*R*)-configuration of the predominant enantiomer in compound **2a** was assumed based on correlation of the sign of the computed specific rotation with experimental data (Table S3). The optimization of geometry and calculation of specific rotation were performed using the B3LYP functional and the 6-311++G(2d,2p) basis set.

Subsequently, we examined the reductive Heck type cyclization of other amides **1b**,**c** in the presence of complex **5** (see Scheme 1). Reaction of benzoyl derivative **1b** afforded indoline **2b** with 30% *ee* (see Table 1, entry 8). The structure of the resulting indolines was confirmed, among other things, by X-ray diffraction analysis data (Figure 2).† Racemic crystals of

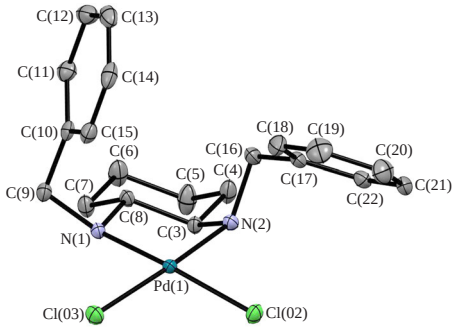


Figure 1 ORTEP diagram of complex **5**; atoms are shown as thermal ellipsoids at 50% probability level. Selected bond lengths (Å) and angles (°): N^1–Pd 2.0513(18), N^2–Pd 2.0360(19), Cl^{02}–Pd 2.3007(6), Cl^{03}–Pd 2.3137(6); N^2–Pd–N^1 84.18(7), Cl^{02}–Pd–Cl^{03} 91.25(2).

† *Crystal data for* **5**. (*R*,*R*)-**5** ($C_{20}H_{26}Cl_2N_2Pd$, M = 471.73), orthorhombic, space group $P2_12_12_1$, at 102 K, a = 10.3396(12), b = 10.8284(11) and c = 18.9391(19) Å, $\alpha = \beta = \gamma = 90°$, V = 2120.4(4) Å^3, Z = 4, d_{calc} = 1.478 g cm^{-3}, μ = 1.132 mm^{-1}, $F(000)$ = 960, $-14 \leqslant h \leqslant 14$, $-15 \leqslant k \leqslant 15$, $-27 \leqslant l \leqslant 27$. Intensities of 69147 reflections were measured with a Bruker D8 QUEST diffractometer [λ(MoKα) = 0.71073 Å], and 6287 independent reflections (R_{int} = 0.0208) were used in further refinement.

Crystal data for rac-**2b**. $C_{22}H_{19}NO$, M = 313.38, orthorhombic, space group *Pbca*, at 102 K, a = 8.3006(9), b = 18.1475(19) and c = 21.510(2) Å, $\alpha = \beta = \gamma = 90°$, V = 3240.2(6) Å^3, Z = 8, d_{calc} = 1.285 g cm^{-3}, μ = 0.078 mm^{-1}, $F(000)$ = 1328, $-11 \leqslant h \leqslant 11$, $-24 \leqslant k \leqslant 24$, $-29 \leqslant l \leqslant 29$. Intensities of 83254 reflections were measured with a Bruker D8 QUEST diffractometer [λ(MoKα) = 0.71073 Å], and 3209 independent reflections (R_{int} = 0.0414) were used in further refinement.

CCDC 2307155 and 2307152 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

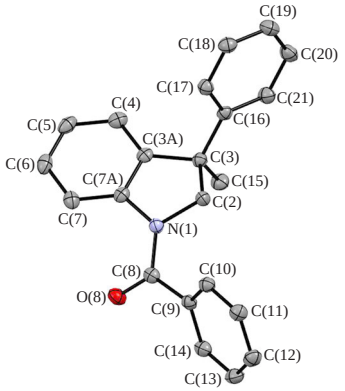
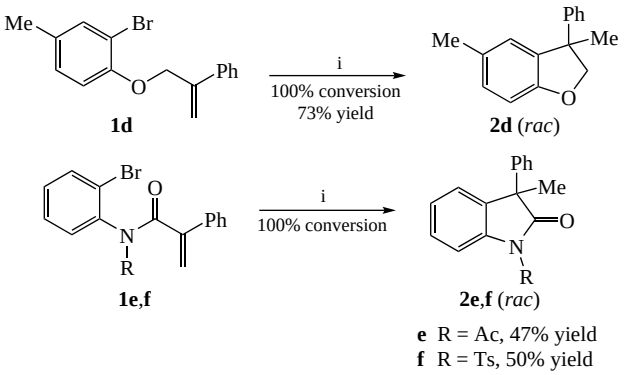


Figure 2 ORTEP diagram of *rac*-**2b**; atoms are shown as thermal ellipsoids at 50% probability level.

2b suitable for analysis were obtained from a cyclohexane solution.

On the other hand, the reductive cyclization of tosylamide **1c** results in indoline **2c** with slight enantiomeric excess (see Scheme 1 and Table 1, entry 9). Thus, the predominant formation of one enantiomer was observed only for unsaturated derivatives **1a**,**b** containing acyl substituents at nitrogen. The addition of 15-crown-5 to the reaction mixture leads to a significant increase in the yield and enantiomeric excess of the reaction product. Under similar conditions, cyclization of ether **1d** gives racemic 2,3-dihydrobenzofuran **2d** with good yield (Scheme 2). Having obtained positive results with non-activated olefins bearing *o*-bromoaryl substituent, we investigated the catalytic activity of complex **5** in the reaction with 2-phenylacrylamides **1e**,**f**. Oxindoles **2e**,**f** were obtained in moderate yields in racemic form (see Scheme 2).



Scheme 2 *Reagents and conditions*: i, HCOONa (2 equiv.), complex **5** (10 mol%), AcONa (2.5 equiv.), 15-crown-5 (10 mol%), DMF, 80 °C, 24 h.

In conclusion, palladium complexes with available and inexpensive vicinal diamines were first proposed as catalysts for the reductive Heck type cyclization. The possibility of asymmetric induction during catalysis by these complexes was shown for the first time. Although the achieved enantioselectivity is not high, the obtained unexpected results point to the prospect of further developments in this field through the molecular design of chiral vicinal diamines.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.04.024.

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