The use of mixtures of ligands in the Ir-catalyzed asymmetric reductive amination of 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one

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A comparative testing of complex catalysts with homo and hetero combinations of chiral and achiral monodentate phosphite- and phosphine-type ligands in the Ir-catalyzed asymmetric direct reductive amination of 2,3,4,9-tetrahydro-1*H*-carbozol-1-ones was carried out. A positive effect of the use in the reaction of a mixture of chiral and achiral ligands was demonstrated. This approach makes feasible a one-pot synthesis of valuable biologically active compounds of (tetrahydro-1*H*-carbazol-1-yl)amine series.

Key words: asymmetric direct reductive amination, iridium, phosphoramidite, biologically active compounds, mixture of ligands.

(Tetrahydro-1*H*-carbazol-1-yl)amines are an important class of organic compounds known for their biological activity. For example, these compounds exhibit activity in the inhibition of tuberculosis mycobacteria, prevention of hepatitis C, as well as in the treatment of atypical pneumonia.[1,2] There are a number of other compounds with similar structure, exhibiting high biological activity.[3] Note that until recently these compounds were used as racemic mixtures, which is considerably less efficient than the use of enantiomerically pure compounds, since the enantiomer possessing no required biological activity can have a negative effect on the patient conditions.[4] One of the promising approaches to the preparation of chiral (tetrahydro-1*H*-carbazol-1-yl)amines is a one-step asymmetric metal complex reductive amination of corresponding ketones.[5] In this case, there is no necessity in the synthesis of scaled amounts of prochiral imines by a prolonged reflux of corresponding ketones with primary amines, recrystallization of the reaction products susceptible to hydrolysis with their subsequent asymmetric reduction.[1] Recently, we reported a first successful application of synthetically available phosphite-type ligands in the reductive amination reaction of acetophenones with up to 71% *ee*, however, the use of this group of ligands in the reaction with substituted 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones gave only 34% enantioselectivity.[6] In the present work, we report the results of the use of the phosphite-type ligands in the direct enantioselective reductive amination reaction of 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones and a positive effect of the use of a mixture of chiral and achiral ligands in this catalytic reaction, which gave a considerable increase in enantioselectivity.

Results and Discussion

The phosphite-type ligands **L1**—**L3** were initially tested in the asymmetric reductive amination reaction of 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1**) with benzylamine (Scheme 1) in benzene at 50 °C, using $[Ir(COD)Cl]_2$ as an iridium precursor and $Ti(OPr^i)_4$ as a water-binding agent (Table 1, entries *1*—*3*).

Both the conversion and the selectivity in these experiments turned out to be low. Taking into account a known positive effect from the presence of iodine in the hydrogenation reaction of imines and heterocyclic compounds, we added iodine to the catalyst (see Table 1, entries *4*—*6*).[7,8] And in fact, we observed a considerable increase in the enantiomeric excess in the case of ligand **L2** (see Table 1, entry *5*). Ligand **L2**, which gave the highest enantiomeric excess in benzene, was tested in the reductive amination of 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1**) in other solvents: CH_2Cl_2, ethyl acetate, and THF. However, these changes gave either comparable, or somewhat lower values of conversion and enantioselectivity. The use of

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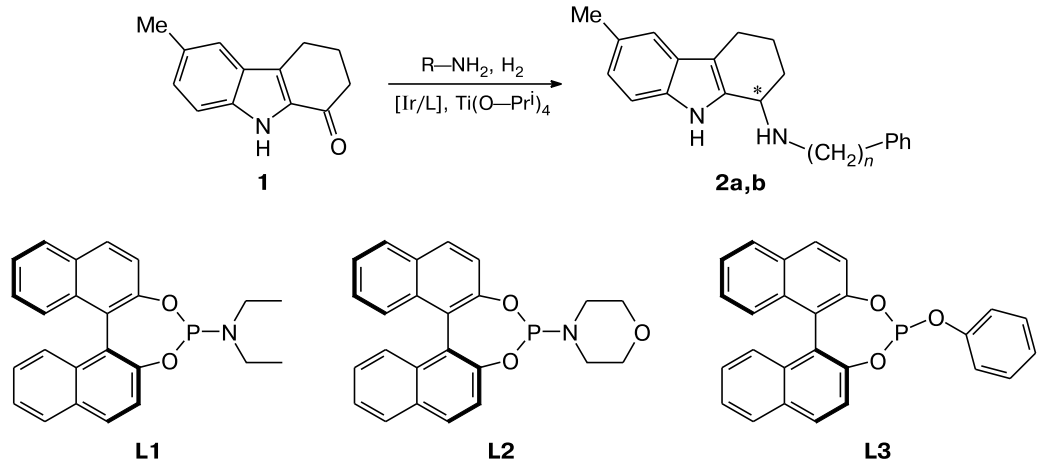
Scheme 1



n = 1 (**2a**), 2 (**2b**)

molecular sieves 3 Å as a water-binding agent, which are successfully used in the reductive amination with involvement of phosphine ligands,[5] did not lead to the expected reaction product (see Table 1, entry *10*). An increase in the reaction temperature to 60 °C with $Ti(OPr^i)_4$ as a water-binding agent led to a slight increase in the conversion, however, the enantiomeric excess decreased (see Table 1, entries *11* and *12*). Further increase in the temperature to 70 °C led to a suppression of the process selectivity (see Table 1, entries *13* and *14*).

To check a possibility of optimization of the results of this reaction, we tested an idea of the combination of two different ligands at the central metal atom in the complex-catalyst. This approach is well known in the rhodium-catalyzed hydrogenation and in a number of cases makes it possible to increase both the conversion and the enantioselectivity.[9] Apart from that, a successful example of the use of hetero combination of two different monodentate ligands in the Ir-catalyzed asymmetric hydrogenation of quinolines is known.[10,11] In fact, the co-use of monodentate ligands **L1**—**L3** with bulky triphenylphosphine made it possible to considerably increase the enantioselectivity (up to 78% *ee*) when the reaction was carried out in benzene at 50 °C (Table 2, entries *1—3*). Interestingly, the combination of "mixed" catalysts with the addition of iodine led to considerably lower values of conversion and enantioselectivity (see Table 2, entries *4—6*). Besides, in all the cases the addition of triphenylphosphine led to the

Table 1. Ir-Catalyzed direct asymmetric reductive amination of 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1**) with benzylamine (90 atm H_2, 8 h)

Entry	Catalyst	Medium	Additive	*T*/°C	Conversion (%)	*ee*[a] (%)
1	$[Ir(COD)Cl]_2$/4**L1**	Benzene	$Ti(O—Pr^i)_4$	50	21	12 (+)
2	$[Ir(COD)Cl]_2$/4**L2**	Benzene	$Ti(O—Pr^i)_4$	50	35	17 (+)
3	$[Ir(COD)Cl]_2$/4**L3**	Benzene	$Ti(O—Pr^i)_4$	50	32	26 (+)
4	$[Ir(COD)Cl]_2$/4**L1**	Benzene	$Ti(O—Pr^i)_4$, I_2	50	14	17 (+)
5	$[Ir(COD)Cl]_2$/4**L2**	Benzene	$Ti(O—Pr^i)_4$, I_2	50	18	40 (+)
6	$[Ir(COD)Cl]_2$/4**L3**	Benzene	$Ti(O—Pr^i)_4$, I_2	50	15	—
7	$[Ir(COD)Cl]_2$/4**L2**	CH_2Cl_2	$Ti(O—Pr^i)_4$, I_2	50	17	9 (+)
8	$[Ir(COD)Cl]_2$/4**L2**	EtOAc	$Ti(O—Pr^i)_4$, I_2	50	16	36 (+)
9	$[Ir(COD)Cl]_2$/4**L2**	THF	$Ti(O—Pr^i)_4$, I_2	50	20	38 (+)
10	$[Ir(COD)Cl]_2$/4**L2**	Benzene	Molecular sieves 3 Å[b]	50	0	—
11	$[Ir(COD)Cl]_2$/4**L2**	Benzene	$Ti(O—Pr^i)_4$	60	40	15 (+)
12	$[Ir(COD)Cl]_2$/4**L2**	Benzene	$Ti(O—Pr^i)_4$, I_2	60	36	25 (+)
13	$[Ir(COD)Cl]_2$/4**L2**	Benzene	$Ti(O—Pr^i)_4$	70	48	0
14	$[Ir(COD)Cl]_2$/4**L2**	Benzene	$Ti(O—Pr^i)_4$, I_2	70	42	4 (+)

[a] The sign of optical rotation of the product is given in parentheses.
[b] 200 mg.

inversion of the absolute configuration in the reaction product. Most likely, this fact can be explained by the changes in the structure of metal complex because of the conversion of catalytic species Ir^{I} to Ir^{III} in the reaction with iodine, which is characteristic of the catalysts with phosphine ligands.[8] The use of THF instead of benzene practically does not affect the enantioselectivity, whereas the addition of iodine decreases both the conversion and the enantioselectivity (see Table 2, entries *7* and *8*). An increase in the reaction temperature from 50 to 70 °C led to a slight increase in the conversion, however, the selectivity of the process decreased (see Table 2, entries *9* and *10*). We also tested the equimolar additives of other achiral ligands: triphenylphosphite and triethylphosphite in a mixture with ligand **L1**. It is interesting, but in this case the products were obtained either as racemates, or with extremely low enantioselectivity (see Table 1, entries *11* and *12*). The use of the complexes containing a combination of two different chiral phosphoramidites (**L1**—**L2**) in the composition of one catalyst led to considerably lower results as compared to those obtained on the complexes with each of two ligands separately (*cf.* entry *13* in Table 2 and entries *1* and *2* in Table 1). The increase in the reaction time from 8 to 24 h using a hetero combination of **L1** and triphenylphosphine in benzene at 50 °C led to the unexpected result: the enantioselectivity increased from 78 to 90% *ee* with a simultaneous increase in the conversion (see Table 2, entry *14*). It is possible that this is due to the dynamic changes in the structure of the catalytic species in the course of the reaction, for example, the coordination of the forming reaction product, which is an *N*-ligand.

We also carried out a reductive amination of 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one **1** with 2-phenylethylamine in benzene. In this case, the reaction proceeded with high enantiomeric excess and good conversion (Table 3, entry *1*). The use of THF instead of benzene gave similar values of conversion and enantioselectivity (see Table 3, entry *2*).

In conclusion, we for the first time showed a possibility of the efficient use of a mixture of phosphite-type chiral ligands in the combination with triphenylphosphine in the Ir-catalyzed reductive amination reaction. Such a hetero combination of ligands in the complex provides a considerable increase in the enantiomeric excess of the reaction product as compared to the use of individual chiral ligands, as well as makes feasible a one-step preparation of valuable biologically active (tetrahydro-1*H*-carbazol-1-yl)amines with essential enantiomeric enrichment.

Table 2. Ir-Catalyzed direct reductive amination of 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1**) with benzylamine using mixed catalysts (90 atm H_2)

Entry	Catalyst	Medium	Additive	*T*/°C	τ/h	Conversion (%)	*ee** (%)
1	$[Ir(COD)Cl]_2$/2**L1**, $2PPh_3$	Benzene	$Ti(O—Pr^i)_4$	50	8	45	78 (–)
2	$[Ir(COD)Cl]_2$/2**L2**, $2PPh_3$	Benzene	$Ti(O—Pr^i)_4$	50	8	32	58 (–)
3	$[Ir(COD)Cl]_2$/2**L3**, $2PPh_3$	Benzene	$Ti(O—Pr^i)_4$	50	8	30	63 (–)
4	$[Ir(COD)Cl]_2$/2**L1**, $2PPh_3$	Benzene	$Ti(O—Pr^i)_4$, I_2	50	8	16	10 (+)
5	$[Ir(COD)Cl]_2$/2**L2**, $2PPh_3$	Benzene	$Ti(O—Pr^i)_4$, I_2	50	8	24	29 (+)
6	$[Ir(COD)Cl]_2$/2**L3**, $2PPh_3$	Benzene	$Ti(O—Pr^i)_4$, I_2	50	8	28	5 (+)
7	$[Ir(COD)Cl]_2$/2**L1**, $2PPh_3$	THF	$Ti(O—Pr^i)_4$	50	8	35	78 (–)
8	$[Ir(COD)Cl]_2$/2**L1**, $2PPh_3$	THF	$Ti(O—Pr^i)_4$, I_2	50	8	22	6 (–)
9	$[Ir(COD)Cl]_2$/2**L1**, $2PPh_3$	Benzene	$Ti(O—Pr^i)_4$	70	8	55	70 (–)
10	$[Ir(COD)Cl]_2$/2**L1**, $2PPh_3$	Benzene	$Ti(O—Pr^i)_4$, I_2	70	8	49	4 (–)
11	$[Ir(COD)Cl]_2$/2**L1**, $2P(OPh)_3$	Benzene	$Ti(O—Pr^i)_4$	50	8	30	0
12	$[Ir(COD)Cl]_2$/2**L1**, $2P(OEt)_3$	Benzene	$Ti(O—Pr^i)_4$	50	8	15	5 (+)
13	$[Ir(COD)Cl]_2$/2**L1**, 2L2	Benzene	$Ti(O—Pr^i)_4$	50	8	7	0
14	$[Ir(COD)Cl]_2$/2**L1**, $2PPh_3$	Benzene	$Ti(O—Pr^i)_4$	50	24	75	90 (–)

* The sign of optical rotation of the product is given in parentheses.

Table 3. Ir-Catalyzed direct reductive amination of 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1**) with 2-phenylethylamine (50 °C, 90 atm H_2, 24 h)

Entry	Catalyst	Medium	Additive	Conversion (%)	*ee** (%)
1	$[Ir(COD)Cl]_2$/2**L1**, $2PPh_3$	Benzene	$Ti(O—Pr^i)_4$	55	81 (–)
2	$[Ir(COD)Cl]_2$/2**L1**, $2PPh_3$	THF	$Ti(O—Pr^i)_4$	50	79 (–)

* The sign of optical rotation of the product is given in parentheses.

Experimental

NMR spectra were recorded on a Bruker Avance 600 spectrometer (600.15 MHz). Chemical shifts in ^{1}H and ^{13}C spectra were determined relative to the residual signals of chloroform-d. 2D homonuclear correlation spectra COSY were recorded to obtain information about homonuclear proton-proton interaction. Direct proton-carbon correlations were recorded using a pulse procedure HSQC. Remote proton-carbon interactions were registered using a pulse procedure HMBC. Optical rotation for the catalysis products was measured on a Perkin—Elmer 341 polarimeter. Hydrogenation was carried out in 10-mL stainless steel autoclaves. (S_a)-2-(Diethylamino)dinaphtho[2,1-*d*:1′,2′-*f*]-[1,3,2]dioxaphosphepine (**L1**),[12] (S_a)-2-(morpholino)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine (**L2**),[12] (S_a)-2-(phenoxy)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine (**L3**),[13] $[Ir(COD)Cl]_2$,[14] 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1**)[15] were obtained according to the procedures described in the literature. Conversion was measured using ^{1}H NMR data. Spectral characteristics of 1-benzylamino-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (**2a**) agree with the literature data.[6] Optical yields were determined by HPLC on an Agilent HP-1100 chromatograph. Compound **2a** was isolated under the following conditions: a Chiralcel AS-H column (UV, λ = 219 nm, hexane—isopropyl alcohol—diethylamine = 98 : 2 : 0.1, 1 mL min^{-1}). The retention times for enantiomers of **2a** are 10.0 min for (+)-isomer and 11.0 min for (−)-isomer. Compound **2b** was isolated under the following conditions: a Chiralcel OD-H column (UV, λ = 219 nm, hexane—isopropyl alcohol—diethylamine = 90 : 10 : 0.1, 1 mL min^{-1}). The retention times for enantiomers of **2b** are 9.4 min ((+)-isomer) and 11.0 min ((−)-isomer).

Asymmetric direct reductive amination of 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (general procedure). Dimeric $[Ir(COD)Cl]_2$ (2.5 mg, 0.0037 mmol) and a corresponding ligand (0.0149 mmol) (see Table 1) or two ligands (0.0074 mmol each) (see Tables 2 and 3) were dissolved in CH_2Cl_2 (0.4 mL) and the mixture was magnetically stirred for 5 min in an autoclave (10 mL). If necessary (see Tables), I_2 (19 mg, 0.074 mmol) was added, and the mixture was stirred for another 10 min. The solvent was evaporated *in vacuo*, 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1**) (147 mg, 0.74 mmol), amine (0.89 mol), $Ti(O—Pr^i)_4$ (0.33 mL, 1.11 mmol), and a corresponding solvent (3 mL) (see Tables 1—3) were added to the catalyst obtained. The reaction mixture was stirred in an autoclave filled with hydrogen, at the pressure and the temperature listed in Tables 1—3. The reaction mixture was diluted with ethyl acetate (3 mL), followed by the addition of water (4 mL) and centrifuging the precipitate of titanium oxide at the rate of 3000 rpm for 15 min. The organic phase was passed through a short layer of silica gel with subsequent evaporation of the solvent *in vacuo*. The composition of the reductive amination products were analyzed by ^{1}H NMR and HPLC.

1-(2-Phenylethylamino)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (2b). ^{1}H NMR ($CDCl_3$), δ: 1.64—1.71 (m, 1 H, H_a(2), cyclohexyl); 1.71—1.80 (m, 1 H, H_a(3), cyclohexyl); 1.97—2.03 (m, 1 H, H_b(3), cyclohexyl); 2.15—2.21 (m, 1 H, H_b(2), cyclohexyl); 2.42 (s, 3 H, Me); 2.62—2.68 (m, 2 H, H(4), cyclohexyl); 2.79—2.85 (m, 1 H, H_a, CH_2); 2.90—2.95 (m, 1 H, H_b, CH_2); 2.97—3.03 (m, 2 H, N—CH_2); 4.03—4.07 (m, 1 H, N—CH); 6.94 (d, 1 H, H(6); indole, $J_{H,H}$ = 8.0 Hz); 7.14 (d, 1 H, H(7), indole, $J_{H,H}$ = 8.0 Hz); 7.21—7.25 (m, 3 H, *o*-H, *p*-H); 7.26 (s, 1 H, H(4), indole); 7.31 (t, 2 H, *m*-H, $J_{H,H}$ = 7.4 Hz); 8.28 (s, 1 H, NH). ^{13}C{^{1}H} NMR ($CDCl_3$), δ: 21.00 (C(4), cyclohexyl); 21.60 (Me); 21.85 (C(3), cyclohexyl); 29.76 (C(2), cyclohexyl); 36.56 CH_2); 46.92 (N—CH_2); 52.42 (N—CH); 110.71 (C(7), indole); 111.48 (C(3), indole); 118.14 (C(4), indole); 123.26 (C(6), indole); 126.48 (*m*-C); 127.65 (C); 128.37 (C(5), indole); 128.65 (*o*-C); 128.96 (*p*-C); 134.22 (N—C); 139.79 (*ipso*-C); 140.70 (C(2), indole). Found (%): C, 82.94; H, 7.88; N, 9.11. $C_{21}H_{24}N_2$. Calculated (%): C, 82.85; H, 7.95; N, 9.20.

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