New Applications of Camphor-Derived P,N-Ligands for Asymmetric Pd- and Ir-Catalyzed Reactions

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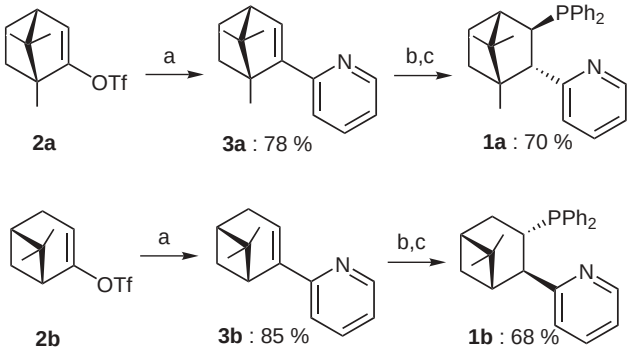
Abstract: Ir-catalyzed asymmetric hydroboration of bicyclic hydrazine **4** in the presence of chiral ligand **1a**, leads to bicyclic alcohol **5** after oxidative workup in good yield (76%) and moderate enantioselectivity (71% ee).

Key words: *meso*-bicyclic hydrazine, Ir-catalyzed hydroboration, *t*-BuOK-catalyzed addition, P,N-ligands, asymmetric catalysis

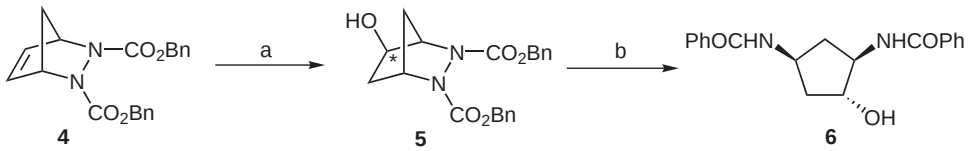
The preparation of new chiral ligands for performing of metal-catalyzed reactions is an important research field.[1] We have recently reported a new synthesis of P,N-ligands **1a**,**b** which proved to be excellent ligands to perform various iridium-catalyzed hydrogenation reactions.[2] Especially interesting were the hydrogenation of unfunctionalized stilbenes, which proceeded with up to 96% ee and the first asymmetric iridium-catalyzed asymmetric hydrogenation of dehydroamino acids with up to 96.5% ee.[2] Herein, we wish to report another application of ligands **1a**,**b** for the asymmetric hydroboration of *meso*-bicyclic hydrazines[3] as well as the use of ligand **1a**,**b** for asymmetric Pd-catalyzed allylic substitution.[4] Both ligands **1a**,**b** were readily available from the corresponding triflates **2a**,**b** which were obtained from D-(+)-camphor and (*R*)-(+)-nopinone.[5] The Pd-catalyzed Negishi cross-coupling[6] of **2a**,**b** with 2-pyridylzinc bromide furnished the unsaturated pyridines **3a**,**b** in 78–85% yield. The addition of diphenylphosphine oxide in NMP or DMSO to **3a**,**b** proceeded readily at 70 °C in the presence of *t*-BuOK (20 mol%).[7]

After the reduction of the intermediate phosphine oxides with $HSiCl_3$ and Et_3N in toluene (120 °C, 12 h),[8] the desired ligands **1a**,**b** were obtained in 70% and 68% yields, respectively (Scheme 1). We have first investigated the asymmetric hydroboration[9] of the *meso*-bicyclic hydrazine **4** with catecholborane (CatBH) in the presence of $[Ir(cod)Cl]_2$. After H_2O_2 oxidation the alcohol **5** was obtained with variable enantioselectivities (Table 1). Bicyclic alcohol **5** can be readily converted to interesting diaminocyclopentanols of type **6** by a reductive cleavage of the N–N bond and subsequent benzoylation (Scheme 2).[3b]



Scheme 1 *Reagents and conditions*: a) $Pd(dba)_2$ (2 mol%), dppf (2 mol%), 2-pyridylzinc bromide, reflux, 12 h; b) *t*-BuOK (20 mol%), DMSO, diphenylphosphine oxide, 70 °C, 16 h; c) $HSiCl_3$ (10 equiv), Et_3N (20 equiv), toluene, 120 °C, 16 h.

We found that **1a** and **1b** are effective ligands for the hydroboration of *meso*-hydrazine **4** providing high conversion in short reaction times (4–6 h). Ligand **1a** furnished alcohol **5** with a higher enantioselectivity (58% ee) whereas **1b** provided alcohol **5** with 44% ee at 25 °C (Table 1, entries 1 and 2). Performing the hydroboration at 0 °C led



Scheme 2 *Reagents and conditions*: a) i) $[Ir(cod)Cl]_2$ (1 mol%), ligands **1a** or **1b** (2.1 mol%), catecholborane (2 equiv), THF, 0 °C, ii) 30% H_2O_2, NaOH, EtOH; b) i) H_2, AcOH, Pt (cat), ii) PhCOCl, pyridine.

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Table 1 Enantioselective Ir-Catalyzed Hydroboration of the *meso*-Hydrazine **4** in the Presence of Ligands **1a**,**b**

Entry	L*	Molarity	Solvent	Temp (°C)	Yield (%)[a]	%ee[b,c]
1	**1a**	0.25	THF	25	57	58
2	**1b**	0.25	THF	25	67	44
3	**1a**	0.25	THF	25	61 (54)[c]	71 (52)[d]
4	**1a**	0.25	THF	–20	–	–
5	**1a**	0.25	toluene	25	30	65
6	**1a**	0.25	DME	0	63	67
7	**1a**	0.1	THF	0	56	62
8	**1a**	0.6	THF	0	76	71
9	(*R*,*S*)-Josiphos	0.6	THF	0	61	64[e]

[a] Yield of analytically pure products.
[b] The enantioselectivity was determined by chiral HPLC (Chiracel AD: *i*-PrOH:*n*-hexane, 20:80, flow: 0.8 mL/min).
[c] The absolute configuration of the major enantiomer with **1a** has been established to be (1*S*,4*R*,5*R*).
[d] Results in parentheses were obtained using 1 equivalent of CatBH.
[e] The absolute configuration of the major enantiomer has been established to be (1*S*,4*R*,5*R*).[3a]

to a further improvement of the enantioselectivity providing alcohol **5** with 71% ee and 61% yield (entry 3). On lowering the reaction temperature further (–20 °C), no significant reaction occurred (entry 4). Using toluene as solvent led to a lower conversion (30% yield) and 65% ee (entry 5) whereas change to DME provided alcohol **5** in 63% yield and 67% ee (entry 6). In order to improve the reaction yield we increased the concentration (compare entries 3, 7 and 8) and obtained our best result with a 0.6 M solution of bicycle **4** (76% yield, 71% ee, entry 8). Lowering the amount of CatBH from 2 equivalents to 1 equivalent in order to avoid an eventual uncatalyzed racemic hydroboration did not succeed and resulted in 54% yield and 52% ee (entry 3). Compared to previous studies using (*R*,*S*)-Josiphos,[3a] the use of the new ligand **1a** represents an improvement of yield and a slight improvement in enantioselectivity (from 68% ee to 71% ee).

Next, we have used ligands **1a**,**b** to perform palladium-catalyzed allylation reactions. We examined the Pd(0)-catalyzed amination of 1,3-diphenylallyl acetate **7** with benzylamine as well as the reaction of **7** with dimethyl malonate in the presence of $[Pd(C_3H_5)Cl]_2$ (1–2.5 mol%) and the new P,N-ligands **1a**,**b** under standard conditions. We found that both ligands gave good enantioselectivities. Thus, the reaction with benzylamine under standard conditions provided the desired allylic amine **8** in 95% yield and 87% ee using the ligand **1b** (2 mol%). Similarly, substitution with dimethylmalonate provided the expected product **9** in the presence of ligand **1a** (5 mol%) in 75% yield and 96% ee (Scheme 3).

In summary, we have reported the use of the new modular ligands **1a**,**b** for Ir-catalyzed asymmetric hydroboration and Pd(0)-catalyzed allylation. Further applications of this new family of ligands are currently underway in our laboratories.[11]

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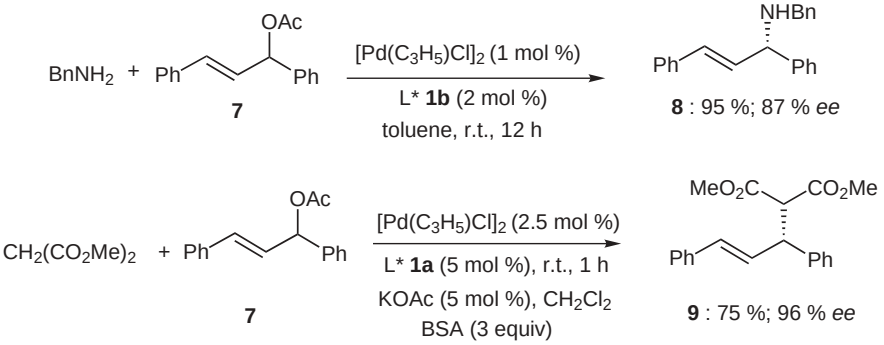

Scheme 3

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(11) $[Ir(COD)Cl]_2$ (3.4 mg, 5 mol, 1 mol%), ligand **1a** (4.2 mg, 11 mol, 2.1 mol%) and **4** (182 mg, 0.5 mmol) were placed under Ar in a flame-dried Schlenk tube. THF (0.85 mL) was degassed at –50 °C and added to the mixture at this temperature. The reaction was stirred at r.t. for 30 min and cooled to 0 °C. Catecholborane (0.11 mL, 1 mmol) was added at 0 °C and stirred for 4 h. EtOH (0.5 mL), 3 M NaOH (0.85 mL) and 30% H_2O_2 (0.5 mL) were added and stirred at 25 °C for 16 h. The reaction mixture was extracted with EtOAc (3 × 10 mL). The organic phase was washed with 1 M NaOH (5 × 10 mL), brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (50% EtOAc in cyclohexane), affording (1*S*,4*R*,5*R*)-**5** (145 mg, 76%, 71% ee) as a colorless liquid. The ee value was determined by HPLC [Chiralcel AD, *n*-hexane–*i*-PrOH, 80:20, 0.8 mL/min, 220 nm): t_r (min) = 14.6 (1*S*,4*R*,5*R*), 16.4 (1*R*, 4*S*,5*S*)].