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The synthesis of a new generation of MAP ligands containing two types of chiral elements for asymmetric catalysis

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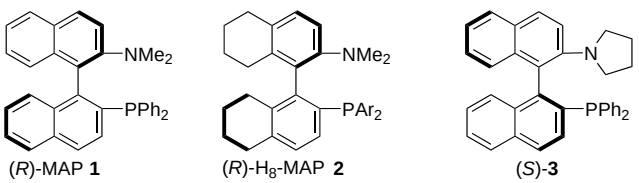
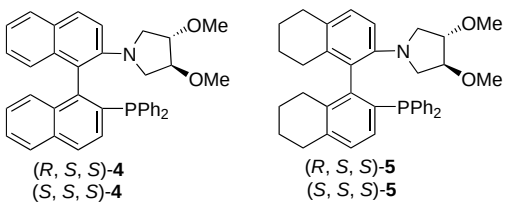
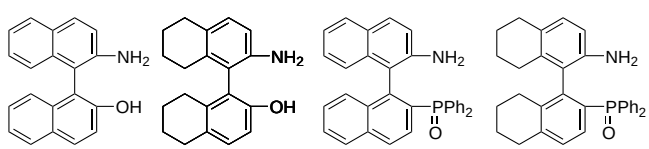
Abstract—A series of novel aminophosphine ligands containing both axial and central chirality have been synthesized for the first time from NOBIN and tartaric acid derivatives. Their capability for asymmetric induction in the Pd-catalyzed reaction of 1,3-diphenylprop-2-en-1-yl acetate and dimethyl malonate was investigated and the results clearly demonstrated that correct assembly of axial chirality in the scaffold and central chirality of the modification group was very important for achieving higher enantioselectivity in the reaction. In a matched case, the asymmetric allylation product could be obtained in 85.6% ee.

Chiral N,P ligands represent one type of important asymmetric inducers for asymmetric catalysis.[1] Recently, a new type of aminophosphine ligand (MAP) **1** has been synthesized and applied to Pd-catalyzed asymmetric allylations and Suzuki coupling reactions with moderate to good asymmetric induction.[2] Our recent work showed that improved enantioselectivity in the product (up to 90.9% ee) could be obtained in Pd-catalyzed asymmetric allylations by using H_8-MAP **2** possessing a partially reduced binaphthyl backbone as a chiral moiety.[2c] The research on the cooperative effect of multi-component chirality in single ligand compounds has received much interest because the configurational tuning in stereochemically pure ligands and metal complexes is crucial for the control of enantioselectivity in asymmetric catalysis.[3] Herein, we report the synthesis of a new generation of MAP-type ligands (**4** and **5**) containing both axial and central chirality, and their application in Pd-catalyzed enantioselective allylic substitutions.





The key intermediate, aminophosphine oxide **8**, for the synthesis of pyrrolidino derivatives could be prepared through a five-step transformation from **6**, following the literature procedure.[4] It was found that the yield for the Pd-catalyzed coupling reaction of triflate with diphenylphosphine oxide could be significantly improved by using 1,3-bis(diphenylphosphino)propane (dppp) instead of 1,4-bis(diphenylphosphino)butane (dppb) as the ligand. Accordingly, both enantiomers of **8** could be conveniently obtained from enantiopure (*R*)-**6** and (*S*)-**6**, respectively. The 5,5′,6,6′,7,7′,8,8′-octahydro analogue (**9**) of **8** could be prepared following a similar procedure to that mentioned above starting from enantiopure 5,5′,6,6′,7,7′,8,8′-octahydro-2-amino-2′-hydroxy-1,1′-binaphthyl (H_8-NOBIN) **7** which could be easily achieved by partial reduction of **6** with Ni–Al alloy in dilute aqueous alkaline solution.[5]



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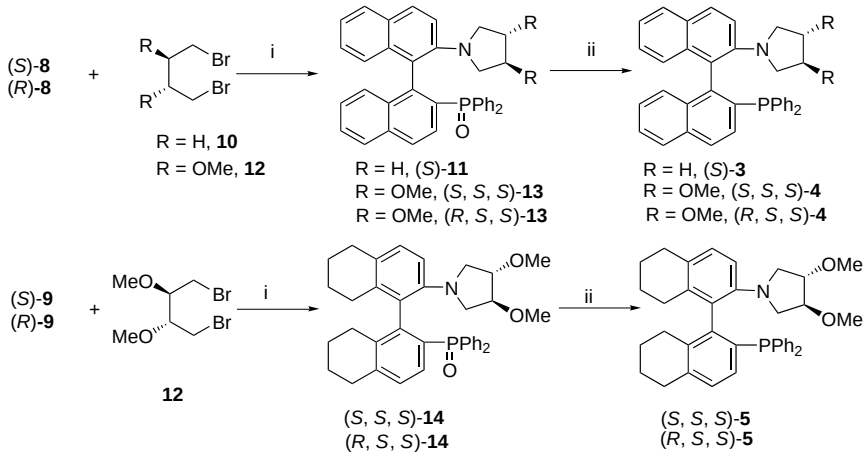
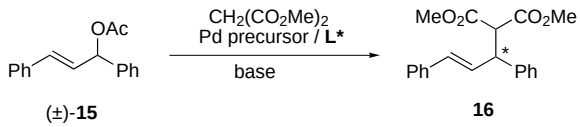
The reaction of 1,4-dibromobutane **10** with aminophosphine oxide (*S*)-**8** proceeded smoothly in toluene at 100°C in the presence of $NaHCO_3$ to give (*S*)-**11** in 63% yield. Reduction of (*S*)-**11** with trichlorosilane in the presence of *N*,*N*-dimethylaniline afforded (*S*)-**3** in 70% yield. The enantiopure chiral segment of 1,4-dibromobutane derivative **12** was prepared from L-tartaric acid according to the literature method.[6] The reaction of **12** with **8** or **9** needed much harsher conditions (150°C, in 1,3,5-trimethylbenzene), and the addition of a catalytic amount of NaI was found to be critical to achieve a practical transformation. The resulting phosphine oxide derivatives **13** and **14** were reduced smoothly by $HSiCl_3$ in toluene to furnish the corresponding aminophosphine ligands **4** and **5** (Scheme 1).

In order to investigate the cooperative effect of the chirality of the binaphthyl backbone and pyrrolidino group, the Pd(0)-catalyzed allylic substitution of racemic 1,3-diphenylprop-2-en-1-yl acetate **15** with dimethyl malonate was taken as a model reaction and N,P chiral ligands **3**–**5** were then employed for asymmetric induction. Table 1 shows the details of our results. Under the catalysis of Pd/(*S*)-**3**, a good yield and a moderate enantioselectivity of allylation product could be obtained in the *R* configuration. The introduction of central chirality at the 3- and 4-positions of the pyrrolidino group significantly influenced the enantioselectivity of the reaction (entries 2 and 3). In comparison with ligand (*R*,*S*,*S*)-**4**, (*S*,*S*,*S*)-**4** was found to possess the matched chirality of binaphthyl backbone and pyrrolidino group, giving the allylation product in up to 83% ee and 97% yield. The partially reduced binaphthyl backbone in ligands (*S*,*S*,*S*)-**5** and (*R*,*S*,*S*)-**5** did not result in a dramatic increase in the enantioselectivity of the reaction (entries 2 and 3 versus 4 and 5, respectively), which is quite different from the change we observed previously in going from **1** to partially reduced ligand **2**.[2c] It was obvious that the absolute configuration of the product was predominantly con-



Scheme 1. Synthesis of **3**–**5**. *Reagents and conditions*: (i) R = H, $NaHCO_3$, toluene, 100°C; R = OMe, NaI, $NaHCO_3$, 1,3,5-trimethylbenzene, 150°C, 63–89% yield; (ii) $HSiCl_3$, $PhNMe_2$ or Et_3N, toluene, 100°C, 70–89% yield.

Table 1. Asymmetric Pd(0)-catalyzed substitution of racemic allylic substrate **15** with malonate nucleophile[a]



Entry	Ligand	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	(*S*)-**3**	CH_2Cl_2	20	24	81	55.0 (*R*)
2	(*S*,*S*,*S*)-**4**	CH_2Cl_2	20	24	97	83.0 (*R*)
3	(*R*,*S*,*S*)-**4**	CH_2Cl_2	20	24	98	26.9 (*S*)
4	(*S*,*S*,*S*)-**5**	CH_2Cl_2	20	24	90	50.0 (*R*)
5	(*R*,*S*,*S*)-**5**	CH_2Cl_2	20	24	97	31.3 (*S*)
6	(*S*,*S*,*S*)-**4**	Toluene	20	24	93	78.4 (*R*)
7	(*S*,*S*,*S*)-**4**	$ClCH_2CH_2Cl$	20	24	92	83.4 (*R*)
8	(*S*,*S*,*S*)-**4**	$ClCH_2CH_2Cl$	0	36	23[d]	85.6 (*R*)

[a] $[Pd(C_3H_5)Cl]_2$:ligand:(±)-**15**:Cs_2CO_3:malonate = 5:7.5:100:200:200.

[b] Isolated yield.

[c] Determined by HPLC on a Chiralpak AD column, the absolute configuration of the product was assigned by comparison of the chiroptical value with that of the literature.[2c]

[d] BSA/KOAc was used as base instead of Cs_2CO_3.

trolled by the sense of backbone chirality (entries 2 and 4 versus entries 3 and 5). Alternating the reaction solvents slightly influenced the enantioselectivity of the reaction (entries 2, 6 and 7). Decreasing the reaction temperature to 0°C improved the enantiomeric excess of the product, up to 85.6% ee, but with lower yield (entry 8). Although the detailed reaction mechanism remains unknown, it is clear that the correct assembly of the chiral elements in the ligands makes the reaction more enantioselective.

In conclusion, a series of novel aminophosphine ligands containing both axial and central chirality have been successfully synthesized from NOBIN and tartaric acid derivatives. Their capacity for asymmetric induction in Pd-catalyzed reaction of 1,3-diphenylprop-2-en-1-yl acetate and dimethyl malonate was investigated and the results clearly demonstrated that the mutual match of axial chirality of the scaffold and central chirality of the modification group was very important for achieving higher enantioselectivity in the reaction. In a matched case, the asymmetric allylation product could be obtained in 85.6% ee. The investigation on the application of these ligands in other transition-metal-catalyzed asymmetric reactions is ongoing in our laboratory.

Acknowledgements

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