Asymmetric Catalysis

Readily Available Biaryl P,N Ligands for Asymmetric Catalysis**

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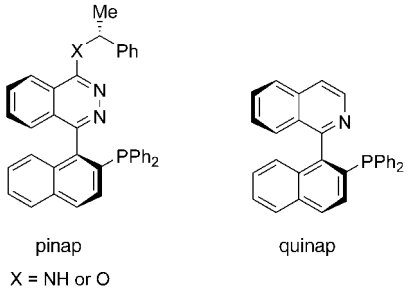
The discovery and development of new chiral ligands for transition-metal complexes is critical for expanding the scope of catalytic asymmetric synthesis.[1] The P,N ligands are a highly successful class,[2] in which quinap[3] holds a special place because it displays unique reactivity and selectivity[4] (e.g. in hydroboration,[4a] alkyne addition,[4c] diboration[4d] and azomethine cycloaddition).[4e] Herein, we present new, readily available atropisomeric P,N ligands (pinap)[5] that are structurally similar to quinap and have parallel reactivity. They



pinap
X = NH or O

quinap

have the additional advantage, however, that, unlike quinap, they are conveniently prepared and resolved as well as easily amenable to structural and electronic modifications. We describe their synthesis, as well as applications in reactions involving Rh, Ag, and Cu catalysts, which demonstrate their utility. In the Cu-catalyzed coupling of acetylenes and imines they are superior to quinap and afford products with the highest enantioselectivity reported to date.

Quinap was developed by Brown and co-workers in 1993.[6] The six-step sequence for its synthesis includes a Pd-catalyzed coupling of 2-methoxy-1-naphthylboronic acid and 1-chloroisoquinoline to generate the biaryl scaffold. After introduction of the phosphinyl group, the resolution of the enantiomeric atropisomers is carried out as the final step by treatment of (±)-quinap with a preformed chiral Pd complex prepared from (*R*)- or (*S*)-*N*,*N*-dimethyl-1-naphthalen-1-ylethylamine.[7] Quinap is commercially available, but it is rather expensive.[8] The design and synthesis of related biaryl P,N ligands has been the focus of numerous research groups.[2a,c] However, resolution of the ligands has proven difficult and has inevitably involved fractional crystallization of diastereomeric Pd complexes. This has limited the extent of structural and electronic modification that can be examined with this scaffold.

Key to our ligand design is the use of a covalently bound chiral group, which facilitates resolution at any of the various steps of the ligand synthesis. As shown in Scheme 1, the core of the ligand is easily accessed by coupling 1,4-dichlorophthalazine with 2-naphthol to give **1** in 77% yield.[9] Importantly, the use of the dichlorophthalazine allows both convenient construction of the biaryl unit and subsequent introduction of a chiral amine or an alcohol.

Treatment of **1** with (*R*)-phenylethanol afforded the diastereomeric aryl ethers (82% yield, d.r. = 1:1), which were subsequently converted into triflates **2** (91% yield). Ni-catalyzed coupling of **2** with $HPPh_2$ furnished ligands **3a** and **3b** in 70% combined yield. The two atropisomeric diastereomers were separated at this stage either by chromatography on silica gel or, alternatively, by crystallization.[10] The absolute configuration of **3a** was shown to be *R*,*M* by X-ray structure analysis.[11]

The synthesis of a related structure incorporating (*R*)-(+)-α-phenethylamine was carried out similarly (Scheme 1). Ligands **5a** and **5b** were isolated in 69% yield over three

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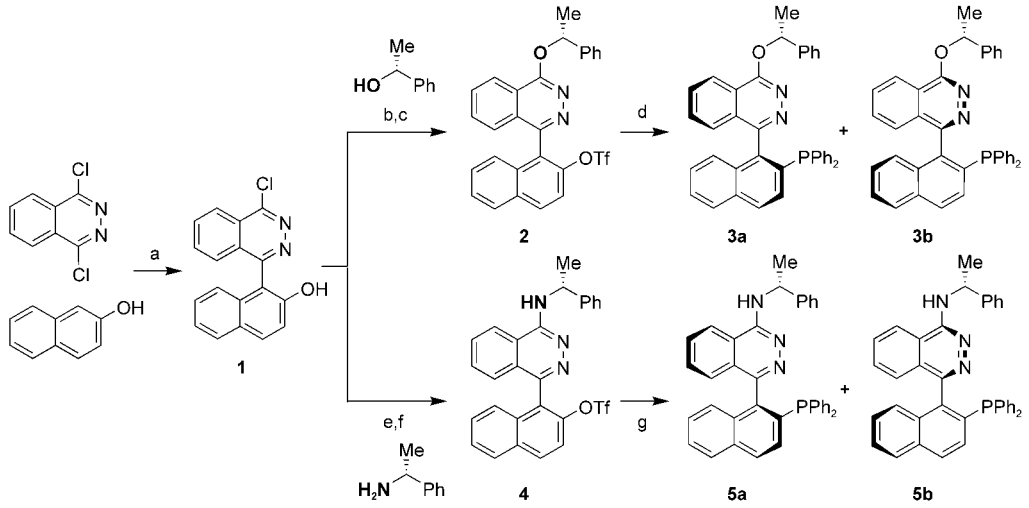
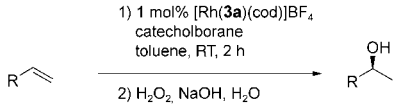


Scheme 1. a) $AlCl_3$, DCE, 80 °C, 77%; b) (*R*)-phenylethanol, NaH (2 equiv), THF, 23 °C, 82%; c) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 91%; d) [$NiCl_2$(dppe)] (10 mol%), $HPPh_2$, DABCO, DMF, 100 °C, 70%; e) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 93%; f) (*R*)-phenylethylamine (5 equiv), neat, 120 °C, 93%, g) [$NiCl_2$(dppe)] (10 mol%), $HPPh_2$, DABCO, DMF, 130 °C, 80%. DABCO = 1,4-diazabicyclo[2.2.2]octane, DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl.

steps (d.r. = 1:1.2). These ligands are conveniently separated by crystallization or chromatography on silica gel.[10] The stereochemistry of **5a** was assigned unambiguously by X-ray structure analysis.[11]

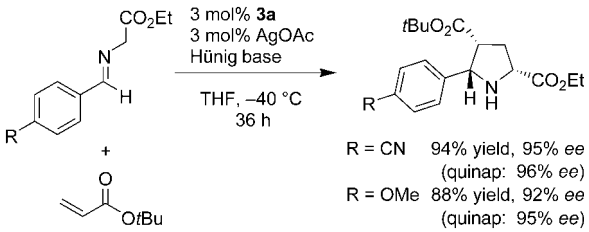
We tested these ligands in three different reactions. In the Rh-catalyzed hydroboration[12] the cationic Rh^I complex formed with **3a** proved to be optimal,[13] leading to optically active alcohols in 2 h using 1 mol% catalyst (room temperature). The regio- (86:14 to >99:1) and enantioselectivity (84–92% *ee*; Table 1) are comparable to those reported for quinap, which is the ligand that demonstrates the broadest scope for this reaction.[4a] Interestingly, an important difference in reactivity was observed for the Rh^I complex of **3a** when compared to previous work. Thus, in contrast to reactions with quinap, the electronics of the aryl substrate exerted little influence on the *ee* value of the product (Table 1, entries 5 and 6), indicating an unanticipated advantage of the complex derived from **3a**.

Table 1: Rh-catalyzed hydroboration.



Entry	R	Yield [%]	*ee* [%]	Quinap [% *ee*][4a]
1	Ph	73	92	92
2	*p*-Tol	94	92	89
3	*m*-Tol	85	84	86
4	*o*-Tol	81	91	92
5	*p*-MeO-C_6H_4	80	90	94
6	*p*-Cl-C_6H_4	87	87	78

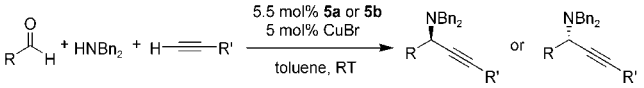
The asymmetric, Ag-catalyzed azomethine cycloaddition reaction with acrylates first reported by Zhang et al.[14] was examined next. Its substrate scope has been recently expanded by using a Ag–quinap catalyst.[4e] We have observed that 3 mol% of the putative Ag^I complex of **3a** catalyzes the reaction, affording adducts with high yields and enantioselectivities (Scheme 2).[15]



Scheme 2. Ag-catalyzed azomethine cycloaddition reaction with acrylates.

Our interest in the chemistry of terminal acetylenes[16] compelled us to examine the ligands in the Cu-catalyzed reaction of alkynes and imines. First reported in 1963,[17] these additions have been recently investigated by Knochel et al. with the complex formed by quinap and CuBr.[4c] We have observed that the Cu^I complexes of **5a** and **5b** catalyze the formation of the propargylic amines in 90–99% *ee*,[18] which are the best values obtained to date (Table 2).

Table 2: Cu-catalyzed addition of alkynes to imines.



R	R′	Ligand	Yield [%]	*ee* [%]	Quinap [% *ee*][4c]
*i*Pr	Me_3Si	**5a**	84	98 (*R*)	92
		5b	82	99 (*S*)	
*i*Pr	Ph	**5a**	88	90 (*R*)	84
		5b	82	95 (*S*)	
*i*Bu	*n*Bu	**5a**	74	91 (*R*)	82
		5b	72	94 (*S*)	

In the examined reactions, the configuration of the biaryl moiety dictates stereoinduction. It is noteworthy that in this process subtle remote effects are observed with respect to the stereogenic center in the phenethyl group. Thus, when compared to **5a**, the use of the diastereomeric ligand **5b** can lead to a measurable and consistent increase (up to 5%) in the *ee* value of the product (Table 2). Interestingly, in these additions it is the *R,P*-configured ligand that affords the higher selectivities, whereas in the hydroboration and cycloaddition reactions the *R,M*-configured ligands proved superior.

In conclusion, we have presented a new class of P,N ligands and demonstrated their utility in three different asymmetric reactions with three different metals. The efficiency (four steps from commercially available material) and modular nature of the synthesis should permit fine tuning of the ligand to accommodate a broad scope of asymmetric transformations. Further studies aimed at diversifying the structure of the ligands and their application in new reactions are underway in our laboratories.

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