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Design and synthesis of novel tridentate and tetradentate chiral ligands

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Abstract

A convenient and efficient synthesis of novel tridentate and tetradentate ligands featuring a key S_NAr reaction is described.

Design and synthesis of chiral catalysts for performing enantioselective transformations have attracted much attention and a number of efficient asymmetric processes have been developed.[1] Most of the powerful asymmetric catalytic reactions known to date have been discovered through trial and error and benefited from serendipitous observations. Selection or synthesis of a suitable chiral ligand followed by ligand tuning (steric and electronic properties), metal tuning and cocatalyst (achiral additive) tuning were the usual steps to be accomplished en route to uncover an ideal catalytic process. High-throughput screening strategy developed recently can shorten significantly the time span required for identifying effective chiral catalyst.[2] However, a prerequisite to such a combinatorial approach is the accessibility of different ligands, particularly the availability of new ligand prototypes if new asymmetric reactions were sought.

In connection with our ongoing project aiming at the discovery of new asymmetric catalytic processes by combination of rational ligand design and high throughput evaluation, we became interested in the synthesis of new tridentate and tetradentate ligands of type **A** and **B** (Fig. 1). Both tridentate and tetradentate ligands have found wide applications in asymmetric transformations.[1] Fig. 1 depicted some examples relevant to our ligand design.[3–6] Incorporation of an oxazoline into a ligand was thought to be beneficial because of its increased chemical stability related to the imine function found in well-known ligands **2**[4] and **4**[6]. The development of an efficient and general synthesis of these ligands featuring a key intermolecular S_NAr reaction[7] is the subject of the present communication.

Oxazoline has been demonstrated to be an effective activating group in nucleophilic aromatic substitution. Indeed, reaction of *O*-methoxyaryl oxazoline with organometallics, particularly Grignard reagents has been largely developed by Meyers' group for natural product syntheses.[8] However, reports on the same reaction with heteronucleophiles such as alcohol and amine are rare.[9] Thus, in order to find

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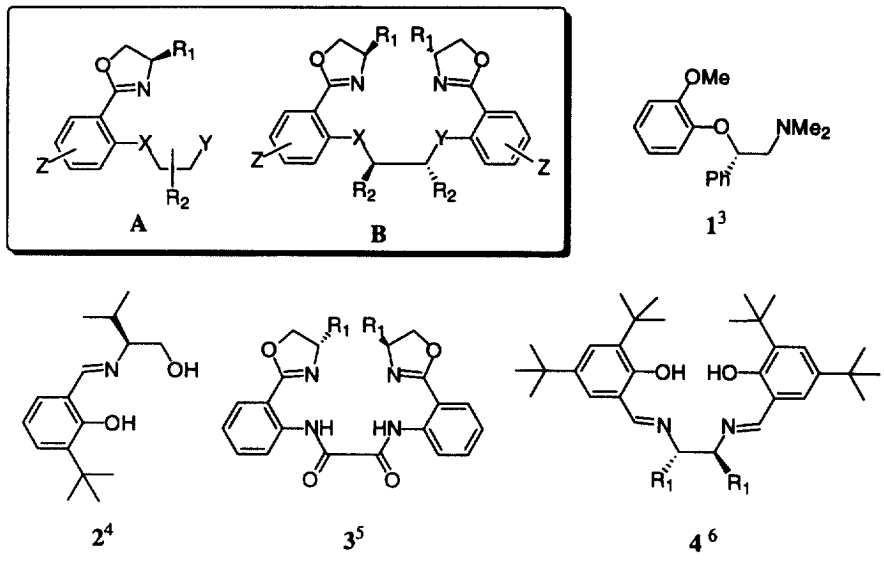
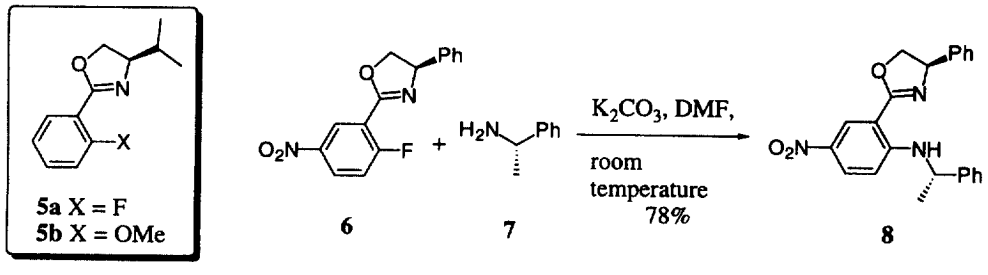


Figure 1.

appropriate conditions, the reaction of oxazolines **5a** and **5b** with L-(−)-α-methylbenzylamine **7** was first examined (Scheme 1). Unfortunately, under various conditions investigated (solvents used: THF, MeCN, DMF) using either amine (in the presence of K_2CO_3) or the corresponding amide of **7** (base used: NaH, $_i$PrMgBr, BuLi, KHMDS) as nucleophile, no coupling reaction with **5a** or **5b** was observed. Heating the reaction mixture led to the degradation of oxazoline. We attributed the failure of this reaction to the insufficient electro-withdrawing ability of oxazoline. To remedy this reactivity problem, compound **6** was prepared wherein a nitro function was introduced at the *para* position of the fluorine atom.[10] As expected, reaction of **6** and **7** proceeded smoothly under mild conditions (DMF, K_2CO_3, room temperature) to give the coupling product **8** in 78% non-optimized yield.



Scheme 1.

With these results in hand, coupling of **6** with various aminoalcohols was investigated. The results are summarized in Fig. 2. It was seen that the reaction was highly chemoselective and the *N*-arylation occurred predominantly under these conditions. Only in the case of valinol, a byproduct (**11**) resulting from the concurrent *N*- and *O*-arylation (9%) was isolated. Sterically more demanding secondary amine such as (*S*)-*N*-methyl leucinol and (1*R*,2*S*)-ephedrine effectively participated in this coupling reaction to give compounds **14** and **15** in excellent yields.

Previous studies from this laboratory have shown that the reaction of aminoalcohol with 4-fluoro-3-nitro toluene can give either *N*- or *O*-arylated product depending on the base used.[11] Mild base tends to give the *N*-arylation while stronger base tends to give *O*-arylated product. In the present case, reaction of phenylglycinol with **6** using different bases such as NaH, $_i$PrMgBr, BuLi, KHMDS led only

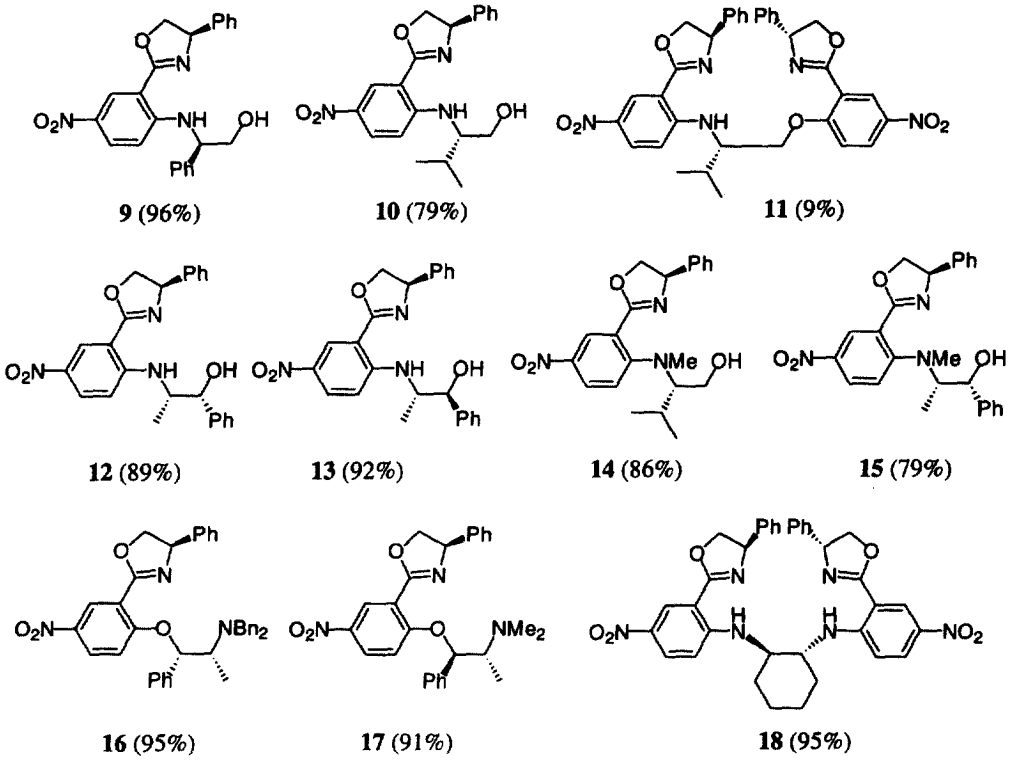
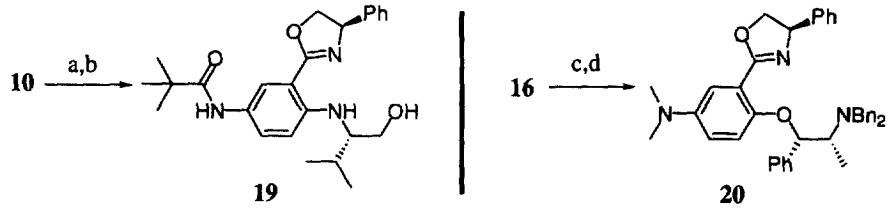


Figure 2.

to the decomposition of oxazoline function. After numerous unsuccessful essays, appropriate reaction conditions were finally found to promote the coupling of *N,N*-dialkylated aminoalcohol with **6**. Thus, treatment of (1*S*,2*R*)-*N,N*-dibenzyl norephedrine with KHMDS followed by addition of **6** gave coupling product **16** in 95% yield. Compound **17** was prepared in similar fashion in 91% yield (Fig. 2).[12]

A tetradentate C_2-symmetrical ligand (**18**, Fig. 2) was prepared in excellent yield by reaction of (1*R*,2*R*)-1,2-diaminocyclohexane[13] with 2 equivalents of oxazoline **6**. Since *p*-nitrobromobenzene failed to couple with 1,2-diphenylethylenediamine under the palladium catalyzed *N*-arylation conditions,[14] this synthesis was thus complementary to that developed recently by Mangeney[15] and Denmark's group.[16]

Finally, the possibility of post-manipulation of nitro group was briefly examined. Hydrogenolysis of **10** followed by acylation gave the corresponding pivaloyl amide **19** in excellent overall yield. On the other hand, reduction of **16** with $SnCl_2$ followed by reductive alkylation gave the *N,N*-dimethylamino derivative **20** (Scheme 2). Although ligands **10**, **19** and **16**, **20** shared similar steric environment, their electronic property were considerably different, which would allow us to evaluate the electronic effect of a given ligand.[17]



Scheme 2. Reagents and conditions: (a) Pd/C, H_2, EtOH. (b) Pivaloyl chloride, Et_3N, CH_2Cl_2, 97%. (c) $SnCl_2$, DMF or Pd/C, EtOAc, H_2. (d) $NaBH_3CN$, aqueous HCHO, MeCN, 74%

In conclusion, a series of new tridentate and tetradentate ligands have been designed and synthesized in a highly efficient manner. Application of these ligands in asymmetric transformation is pursuing.

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