

ENANTIOSELECTIVE ADDITION OF METHYLLITHIUM TO 2-FURALDEHYDE IMINE WITH THE AID OF CHIRAL LIGAND¹

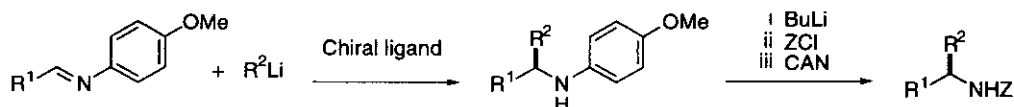
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Abstract-The chiral ligand mediated enantioselective reaction of methyllithium with furylimines was investigated in the presumed 1,4- and 1,2-addition manners. The imines bearing a phosphinoyl or sulfonyl group on the imine nitrogen atom gave rather poor enantioselectivity. On the other hand, the imines bearing a 2-substituted anisidine moiety were found to be the appropriate substrate, giving the corresponding amines with up to 91% ee.

Organolithium is among the established, powerful carbonnucleophiles in the formation of carbon-carbon bonds. The extended application of the reagent into asymmetric reactions with imines has been a considerable challenge in synthetic organic chemistry. Indeed, there have been significant achievements in the development of the chiral imines even though these require at least a stoichiometric amount of a chiral auxiliary bounded covalently to the imine.² Another promising approach relies on a chiral external ligand, which opens a catalytic way to an asymmetric reaction.³

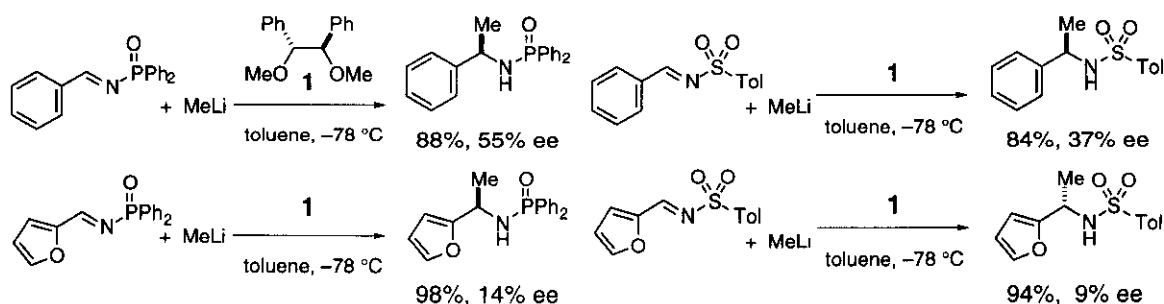


External chiral ligand mediated enantioselective addition of organometallic reagents to imines has a high potential in the production of optically active amines. The use of a stoichiometric and catalytic amount of a chiral ether and amines has been reported as an external chiral ligand that forms a chiral, binary complex with an organolithium.⁴ As a research program aimed at the development of asymmetric reactions mediated by external chiral ligands,⁵ we have already reported the first asymmetric addition of organolithiums to imines derived from aldehydes and 4-anisidine, giving the product amines in high ee.^{6,7} However, the imines reported so far are the relatively simple molecules not bearing synthetically and medicinally useful heterocycles.⁸ The coexistence of a heteroatom in the imine molecule may interfere

with the reaction through coordination to the lithium atom of the organolithium, and results in destruction of the binary complex of organolithium–chiral ligand. We studied the reaction of the furylimine with organolithium in the presence of the chiral ligand that is the subject of the present report.

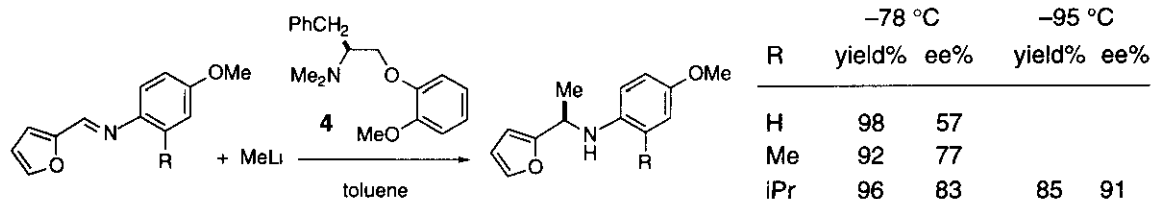
It is probable to expect that the reaction of the imine bearing a X=O group on the imine nitrogen atom proceeds in a 1,4- addition manner without interference of coordination by the furan oxygen atom.

First, we examined the reaction of methyllithium with benzaldehyde imines bearing a P=O or S=O group. The reactions in the presence of a stoichiometric amount of **1** gave the product (*R*)-amides of **55** and **37%** ees in high yields, respectively,⁹ whereas the corresponding furylimines unfortunately resulted in the production of the amides in poorer 14 and 9% ees, respectively.¹⁰



These data suggest the concomitant occurrence of 1,2- and 1,4-additions from **2** and **3**, respectively. Probably, **2** loses rigidity and gives the product in poor ee. The corresponding chelation is absent in the reaction of benzaldehyde imine.⁶

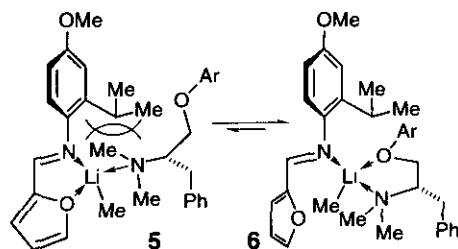
Second, we investigated the reaction of imines bearing a substituted anisidine moiety on the basis of our previous observation that a bulky 2-substitution of anisidine ring provided the significant improvement of the enantioselectivity in the reaction of simple imines with **4**.⁶ As we expected, the reaction of anisidine imine by the aid of **4** gave the corresponding amine with higher ee. The bulkier the substituent at the 2-position is, the higher the enantioselectivity is. The 2-isopropyl substituent gave 83% ee at -78°C and 91% ee at -95°C .¹¹



There is a steric repulsion between the 2-substituent of anisidine and the ligand moiety in the chelated complex (**5**) which leads to formation of the sterically favored complex (**6**). The complex (**6**) is much

more sterically ordered than **5** and gives rise to higher stereoselectivity.

In summary, steric tuning was found to be a useful way in realizing efficient enantioselective addition reaction of the heterocycle-involving imine. Further application of the present process into an asymmetric synthesis of a biologically potent compound is in progress in our laboratories.



ACKNOWLEDGMENT

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11. The absolute configuration was tentatively assigned to be *R* based on the previous observation.⁶

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