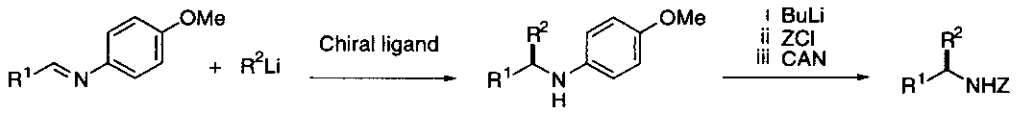
ENANTIOSELECTIVE ADDITION OF METHYLLITHIUM TO 2-FURALDEHYDE IMINE WITH THE AID OF CHIRAL LIGAND[1]

Daisuke Taniyama, Motomu Kanai,[‡] Akira Iida, and Kiyoshi Tomioka*

Faculty of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-01, Japan
[‡]ISIR, Osaka University, Ibaraki, Osaka 567, Japan

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 carbonucleophiles 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]

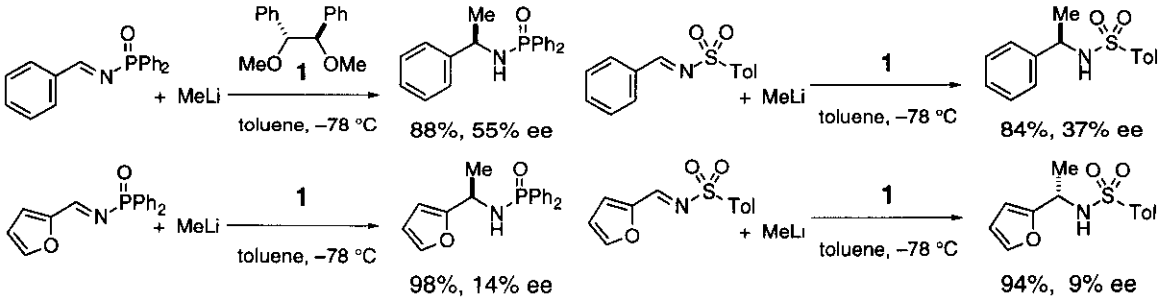


External chiral ligand mediated enantioselective addition of organometallic reagents to imines has a high potential in the production of optically active amines. The use of a stoichiometric and catalytic amount of a chiral ether and amines has been reported as an external chiral ligand that forms a chiral, 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

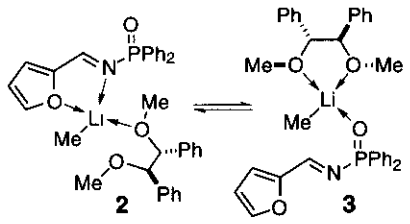
with the reaction through coordination to the lithium atom of the organolithium, and results in destruction of the binary complex of organolithium–chiral ligand. We studied the reaction of the furylimine with organolithium in the presence of the chiral ligand that is the subject of the present report.

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.

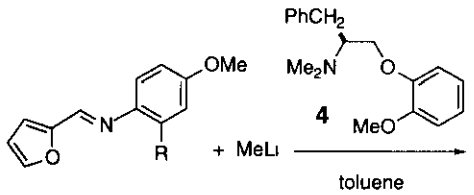
First, we examined the reaction of methyllithium with benzaldehyde imines bearing a P=O or S=O group. The reactions in the presence of a stoichiometric amount of **1** gave the product (*R*)-amides of 55 and 37% ees in high yields, respectively,[9] whereas the corresponding furylimines unfortunately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

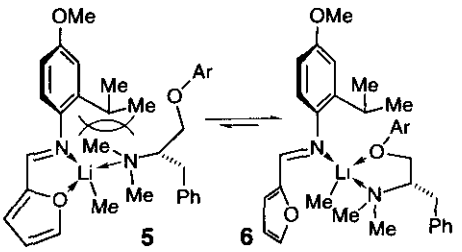


	–78 °C		–95 °C	
R	yield%	ee%	yield%	ee%
H	98	57		
Me	92	77		
iPr	96	83	85	91

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

We gratefully acknowledge financial support from the Ministry of Education, Science, Sports and Culture, JSPS (RFTF-96P00302), and the Science and Technology Agency, Japan.

REFERENCES AND NOTES

1. We dedicate this paper to the Memory of the late Professor Shun-ichi Yamada.
2. P. G. Cozzi, B. D. Simone, and A. Umani-Ronchi, *Tetrahedron Lett.*, 1996, **37**, 1691; D. J. Hallett and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, **1995**, 657; Y. Hashimoto, N. Kobayashi, A. Kai, and K. Saigo, *Synlett*, **1995**, 961; Y. Gao and F. Sato, *J. Org. Chem.*, 1995, **60**, 8136; H. Hioki, T. Izawa, M. Yoshizuka, R. Kunitake, and S. Ito, *Tetrahedron Lett.*, 1995, **36**, 2289; K. Bambridge, M. J. Begley, and N. S. Simpkins, *Tetrahedron Lett.*, 1994, **35**, 3391; D. Enders and J. Schankat, *Helv. Chim. Acta*, 1993, **76**, 402; Y. A. Dembélé, C. Belaud, P. Hitchcock, and J. Villiéras, *Tetrahedron: Asymmetry*, 1992, **3**, 351; W. L. Neumann, M. M. Rogic, and T. J. Dunn, *Tetrahedron Lett.*, 1991, **32**, 5865; Z.-Y. Chang and R. M. Coates, *J. Org. Chem.*, 1990, **55**, 3475; T. Weber, J. P. Edwards, and S. E. Denmark, *Synlett*, **1990**, 20; R. P. Polniaszek and L. W. Dillard, *Tetrahedron Lett.*, 1990, **31**, 797; H. Kunz and W. Pfrengle, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1067; S. G. Pyne and B. Dikic, *J. Chem. Soc., Chem. Commun.*, **1989**, 826; P. Ermert, J. Meyer, C. Stucki, J. Schneebeli, and J.-P. Obrecht, *Tetrahedron Lett.*, 1988, **29**, 1265; G. Cainelli, M. Panunzio, D. Giacomini, G. Martelli, and G. Spunta, *J. Am. Chem. Soc.*, 1988, **110**, 6879; T. Yamada, K. Suzuki, and T. Mukaiyama, *Chem. Lett.*, **1987**, 293; D. Enders, H. Schbert, and C. Nübling, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1109; D. A. Claremon, P. K. Lumma, and B. T. Phillips, *J. Am. Chem. Soc.*, 1986, **108**, 8265; Y. Yamamoto, S. Nishii, K. Maruyama, T. Komatsu, and W. Ito, *J. Am. Chem. Soc.*, 1986, **108**, 7778; T. Iimori and M. Shibasaki, *Tetrahedron Lett.*, 1985, **26**, 1523; T. Chiba, M. Nagatsuma, and T. Nakai, *Chem. Lett.*, **1984**, 1927; C. Fuganti, P. Crasselli, and G. Pedrocchi-Fantoni, *J. Org. Chem.*, 1983, **48**, 909; H. Takahashi and H. Suzuki, *Chem. Pharm. Bull.*, 1983, **31**, 4295.
3. Situation of the external chiral ligand controlled-asymmetric reaction of organolithiums with imines has been summarized: S. E. Denmark and O. J.-C. Nicaise, *Chem. Commun.*, **1996**, 999.
4. M. Nakamura, A. Hirai, and E. Nakamura, *J. Am. Chem. Soc.*, 1996, **118**, 8489; S. E. Denmark, N. Nakajima, and O. J.-C. Nicaise, *J. Am. Chem. Soc.*, 1994, **116**, 8979; Y. Ukaji, T. Hatanaka, A. Ahmed, and K. Inomata, *Chem. Lett.*, **1993**, 1313; A. R. Katritzky and P. A. Harris, *Tetrahedron:*

Asymmetry, 1992, **3**, 437; K. Soai, T. Hatanaka, and T. Miyazawa, *J. Chem. Soc., Chem. Commun.*, **1992**, 1097; S. Itsuno, H. Yanaka, C. Hachisuka, and K. Ito, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1341.

5. M. Mizuno, M. Kanai, A. Iida, and K. Tomioka, *Tetrahedron: Asymmetry*, 1996, **7**, 2483; Y. Nakagawa, M. Kanai, Y. Nagaoka, and K. Tomioka, *Tetrahedron Lett.*, 1996, **37**, 7805.
6. Asymmetric 1,2-addition reaction of organolithium with imine: I. Inoue, M. Shindo, K. Koga, M. Kanai, and K. Tomioka, *Tetrahedron: Asymmetry*, 1995, **6**, 2527; I. Inoue, M. Shindo, K. Koga, and K. Tomioka, *Tetrahedron*, 1994, **50**, 4429; K. Tomioka, I. Inoue, M. Shindo, and K. Koga, *Tetrahedron: Asymmetry*, 1993, **4**, 1603; *Idem, Tetrahedron Lett.*, 1991, **32**, 3095; *Idem, ibid.*, 1990, **31**, 6681.
7. Asymmetric reaction of lithium ester enolate with imine: H. Fujieda, M. Kanai, T. Kambara, A. Iida, and K. Tomioka, *J. Am. Chem. Soc.*, 1997, **119**, 2060.
8. J. C. P. Hopman, E. van den Berg, L. O. Ollero, H. Hiemstra, and W. N. Speckamp, *Tetrahedron Lett.*, 1995, **36**, 4315.
9. The reaction was carried out according to the standard procedure described in reference 6. The ee was determined by chiral HPLC as has been described.
10. W.-S. Zhou, Z.-H. Lu, and Z.-M. Wang, *Tetrahedron*, 1993, **49**, 2641.
11. The absolute configuration was tentatively assigned to be *R* based on the previous observation.[6]

Received, 24th March, 1997