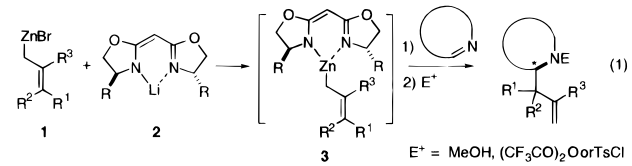
Enantioselective Allylzincation of Cyclic Aldimines in the Presence of Anionic Bis-oxazoline Ligand

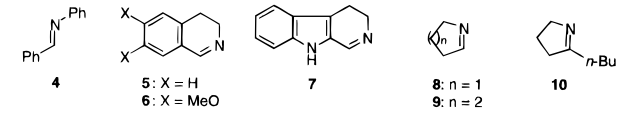
Masaharu Nakamura, Atsushi Hirai, and Eiichi Nakamura*

Department of Chemistry, The University of Tokyo Hongo, Bunkyo-ku, Tokyo 113, Japan

Received April 12, 1996

Enantioselective nucleophilic additions to C−N double bonds belong to the least developed class of asymmetric transformations.[1] We report herein that, in the presence of a lithiated bis-oxazoline (BOX) ligand[2] **2**, an allylic zinc reagent **1** reacts with a cyclic aldimine to give an allylated secondary amine with enantioselectivity of 88−99% ee (eq 1).

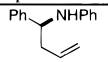
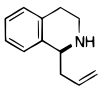
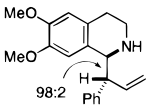
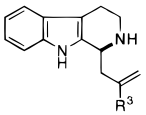
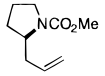
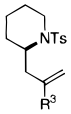
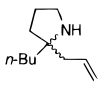




Imines of aromatic aldehydes have widely served as good substrates for enantioselective nucleophilic additions.[1g,h] Following this lead, we treated *E*-benzaldehyde *N*-phenylimine **4** with the allylic zinc reagent (**3a**, R = *i*-Pr) possessing a BOX ligand derived from L-valine. This reagent shows excellent enantioselectivity in the allylzincation of cyclopropenone acetals.[3] The organozinc reagent reacted smoothly with **4** within 4 h at −70 °C in THF/hexane to afford the allylation product **11a**, but the enantioselectivity was only 6% ee (entry 1, Table 1).

Considering the transition structures of the reactions of the zinc reagent **1** with cyclopropenone acetals,[3] we turned our attention to *Z*-aldimines. The allylzincation of cyclic aldimine proceeded smoothly at −70 °C and, upon aqueous workup, afforded a homoallylic secondary amine, which was isolated as it is or more conveniently as its *N*-trifluoroacetic (entries 2−10), *N*-methoxycarbonyl (entry 11), or *N*-*p*-toluenesulfonyl (entries 12 and 13) derivatives. The BOX ligand was recovered upon basic aqueous workup of the reaction mixture.[4]

Table 1. Enantioselective Allylation of Cyclic Imines

entry	allylZn[a] (conditions)[e]	imine	major product	yield[b] (%)	ee[c] (%)	config.[d]
1	**3a** (-70 °C, 2 h)	**4**	 **11a**	95[f]	6[g]	n.d.[h]
2	**3a**	**5**	 **12a**	72 (96)	95	(*S*)
3	**3a**[i]	**5**	**12a**	25 (100)	88	(*S*)
4	**3a**[j]	**5**	**12a**	75 (85)	59	(*S*)
5	**3a**	**6**	 **13a**(R = H)	90 (99)	95	(*S*)
6	**3b** (-70 °C, 6 h)	**6**	**13b** (R^3 = Me)	96 (100)	97.5	(*S*)
7	**3c** (-70 °C, 2 h)	**6**	**13c**(R^3 = $SiMe_3$)	74 (84)	97.5	(*S*)
8	**3d** (-70 °C, 8 h)	**6**	 98:2 **13d**	91.5 (100)[k]	77[l]	(*S*)
9	**3a** (0 °C~rt, 24 h)	**7**	 **14a**(R^3 = H)	54	90	(*S*)
10	**3b** (-40 °C, 24 h)	**7**	**14b**(R^3 = Me)	44	95[m]	(*S*)
11	**3a** (-30°C, 8 h)	**8**	 **15a**	54[f]	88[g]	(*R*)
12	**3a** (-70 °C, 12 h)	**9**	 **16a**(R^3 = H)	48[f]	89.4	(*R*)
13	**3b** (-70 °C, 12 h)	**9**	**16b**(R^3 = Me)	42[f]	99.2	(*R*)
14	**3a** (0 °C, 20 h)	**10**	 **17a**	75[f]	30	n.d.[h]

[a] BOX ligand derived from (*S*)-valine was used unless otherwise noted. [b] NMR yield for E = H. Yields in parentheses are based on conversion of the imine. [c] Determined by chiral HPLC analysis for E = $COCF_3$, CO_2Me, or Ts. [d] Configurational assignment for **12a**,[10] **14b**,[11] **15a**,[12] and **16a**[13] made by comparison with the reported optical rotation; others made by inference. [e] The allylzincation was carried out at −70 °C for 4 h unless otherwise noted. The specified conditions are those required for the completion of the reaction. [f] Isolated yield. [g] Determined by chiral GLC analysis. [h] Not determined. [i] With BOX ligand from (*S*)-*tert*-leucine. [j] With BOX ligand from (*S*)-phenylglycine. [k] The 98:2 diastereomeric ratio for the newly formed C−C bond (by ^{1}H NMR) and the relative stereochemistry were assigned on the basis of **TS A**. [l] Determined for the major diastereomer. [m] 90% ee and 87% yield were obtained at 0 °C to rt for 24 h.

The reaction of dihydroisoquinoline **5** with the allylzinc reagent **3a** (R = *i*-Pr) gave (*S*)-1-allyl-1,2,3,4-tetrahydroisoquinoline **12a** (E = H) in 72% yield (96% based on conversion of **5**). As shown in entries 2, 3, and 4, substituents on the BOX ligand were found to affect the reactivity and the selectivity of the allylzinc reagent. The allylzinc reagent **3a** (R = *t*-Bu) possessing a bulky BOX ligand derived from (*S*)-*tert*-leucinol

(1) Review: (a) Volkmann, R. A. In *Comprehensive Organic Synthesis, Additions to C−X π-Bonds*; Schreiber, S. L. Ed.; Pergamon Press: Oxford, 1991; Part 1, Vol. 1, Chapter 1.12. (b) Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999. Additions to *N*-silyl imines: (c) Itsuno, S.; Yanaka, H.; Hachisuka, C.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1341. Watanabe, K.; Ito, K.; Itsuno, S. *Tetrahedron*: *Asymmetry* **1995**, 6, 1531. Addition to *N*-phosphinoyl imines: (d) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097. Additions to *N*-acyl imines: (e) Katrizky, A. R.; Harris, P. A. *Tetrahedron: Asymmetry* **1992**, *3*, 437. Additions to nitrones: (f) Ukaji, Y.; Hatanaka, T.; Ahmed, A.; Inomata, K. *Chem. Lett.* **1993**, 1313. Additions to *E*-aldimines: (g) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429 and references cited therein. (h) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797.

(2) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. Helmchen, G.; Krotz, A.; Ganz, K. T.; Hansen, D. *Synlett* **1991**, 257. Hall, J.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1.

(3) Nakamura, M.; Arai, M.; Nakamura, E. *J. Am. Chem. Soc.* **1995**, *117*, 1179.

S0002-7863(96)01213-9 CCC: $12.00

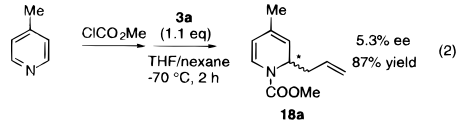
was expectedly less reactive (25% yield, 100% based on conversion) and unexpectedly[5] less selective (88% ee) than **3a** with R = *i*-Pr. The allylzinc reagent **3a** (R = Ph) bearing a BOX ligand derived from (*S*)-phenylglycinol showed only moderate selectivity (59% ee). The ligand derived from valinol (R = *i*-Pr) was therefore selected for further exploration of the asymmetric allylation reactions of cyclic imines.

In light of the abundance of 6,7-dimethoxytetrahydroisoquinoline natural products,[6] we next examined the reaction with 6,7-dimethoxy compound **6**. The reaction of **6** with **3** (R = *i*-Pr) was slightly faster than that of the parent dihydroisoquinoline **5**. This is likely due to electron donation by the methoxy groups which will enhance the reagent/substrate complexation. The selectivity was of the same magnitude (95% ee) as that observed for the parent dihydroisoquinoline **5** (entry 5). The methallylzinc and 2-(dimethylphenylsilyl)-2-propenylzinc reagents (**3b** and **3c**, R = *i*-Pr) gave allylation products **13b** and **13c** both with 97.5% ee in 96% and 74% yield, respectively (entries 6 and 7). The reaction of cinnamylzinc reagent **3d** (R = *i*-Pr) with **6** afforded the product **13d** in 91.5% yield with exclusive S_E' selectivity (entry 8).[7] The cinnamylzincation proceeded enantio- and diastereoselectively to give the major diastereomer with 82% net selectivity.

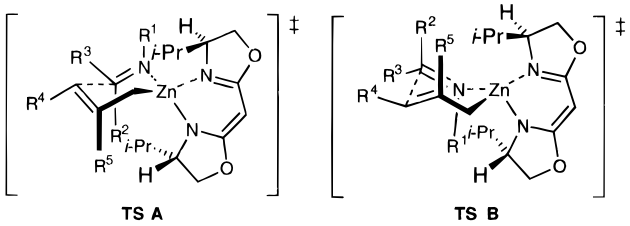
Several other cyclic imines were examined. The reactions of dihydro-*β*-carboline **7** with 2 equiv of **3a** (R = *i*-Pr) and **3b** (R = *i*-Pr) were slow but gave the allylation products **14a** and **14b** with 90% and 95% ee, respectively (entries 9 and 10).

The reaction of aliphatic cyclic imines such as 1-pyrroline **8**[8b] and Δ^1-piperideine **9**,[8c] which are enolizable and undergo competitive trimerization,[8] also took place smoothly to afford the allylation products. Thus, the addition of the allylzinc reagent **3a** (R = *i*-Pr) to **8** and **9** gave **15a** and **16a** with 88% and 89.4% ee, respectively (entries 11 and 12). The addition of methallylzinc reagent **3b** (R = *i*-Pr) to **9** gave the methallylation product **16b** with 99.2% ee (entry 13). The zinc reagents **3a** and **3b** (R = *i*-Pr) gave the allylation product as the major product beside tosylenamide (<10% yield), while the parent allylzinc bromide **1a** reacted with **9** to mainly effect enolization (71% as determined as tosylenamide) and afforded racemic **16a** in 17% yield.

Poor enantioselectivity was observed in the allylation of ketimine and acylpyridinium salt.[9] Addition of **3a** (R = *i*-Pr) to ketimine **10** took place at 0 °C to afford the secondary amine **17a** in 75% yield with 30% ee (entry 14). The addition of **3a** (R = *i*-Pr) to 4-methyl-*N*-methoxycarbonyl pyridinium salt proceeded at −70 °C smoothly to give allylation product **18a** in 87% yield with 5.3% ee (eq 2).



The absolute stereochemistry determined for allylated tetrahydroisoquinoline **12a**,[10] methallylated tetrahydrocarboline **14b**,[11] 2-allylpyrrolidine **15a**,[12] and 2-allylpiperidine **16a**[13] indicated that the above reactions have occurred in a single stereochemical sense. On the basis of the stereochemical data in this and our previous studies,[3] we constructed a working model **TS A** which qualitatively accounts for the experimental results. Under the assumption of a chair transition state with all equatorial disposition of the substituents, the reaction of *Z*-aldimines (R^2 = H) will favor **TS A** over the alternative **TS B** (note R^1/*i*-Pr interaction). The low enantioselectivities[5] in the reactions of *E*-aldimine **4** and ketimine **10** (entries 1 and 14) are also consistent with this model, since, with these imines, both **TS A** and **TS B** suffer steric hindrance (R^2/*i*-Pr interaction in **TS A** and R^1/*i*-Pr interaction in **TS B**). The R^5 substituent may destabilize **TS B** (interaction with *i*-Pr) and hence increase the enantioselectivity, as observed for the reagents **3b** (R^5 = Me) and **3c** (R^5 = $SiMe_2Ph$) (entries 6, 7, 10, and 13). The lack of enantioselectivity in eq 2 may rather suggest that the reaction does not involve such cyclic transition states.



In summary, the allylic zinc reagents bearing an anionic BOX ligand are useful for stereoselective introduction of an allylic group to a cyclic aldimine and for the increase of nucleophilicity of the allylation reagent. The proposed working model accounts for the observed selectivities and appears to be worthy of further theoretical verification.

Supporting Information Available: Procedures for the enantioselective allylzincation reactions and electrophilic quenches and spectroscopic data for compounds **12a**, **13a**−**d**, **14a,b**, **15a**, and **16a,b** (14 pages). See any current masthead page for ordering and Internet access instructions.

JA961213K

(4) Experimental procedure: The lithio bis-oxazoline **2** (R = *i*-Pr) was prepared in THF by the treatment of the protio compound (1.45 g, 6.08 mmol) in THF (7.0 mL) with *n*-BuLi (1.61 M, hexane) at 0 °C. A 1.06 M THF solution of methallylzinc bromide **1b** (5.35 mL, 5.67 mmol) was then added. After 30 min, 6,7-dimethoxy-3,4-dihydroisoquinoline **6** (0.96 g, 5.01 mmol) was added at −70 °C. After 6 h, the reaction mixture was quenched with 0.5 mL of MeOH and then diluted with Et_2O. The organic layer was washed with 0.2 N NaOH and dried (Na_2SO_4) and filtered. Concentration of the filtrate afforded a mixture (2.92 g) of **13b** (E = H, 95.5% NMR yield) and a 2:1 complex of bis-oxazoline and zinc (BOX_2-Zn). A 2.62 g portion of the crude product was purified by silica gel chromatography to obtain the desired amine **13b** (E = H, 1.09 g, 4.39 mmol, 88% yield) as well as **3** (30% recovery) and BOX_2-Zn (40% recovery), which can be quantitatively converted to **3** without racemization (*cf.* ref 3).

(5) We speculate that the lower ee is due to a competing nonselective pathway. Note that, in the reaction of **3** with cyclopropenone acetals (ref 3), the ligand with R = *t*-Bu gave higher enantioselectivity than those with R = *i*-Pr and Ph.

(6) Mann, J. In *Natural Products;* Longman Scientific & Technical: Harlow, 1994; Chapter 7.

(7) The reaction of benzyl Grignard and benzylzinc reagents in the presence of **2** (R = *i*-Pr) showed poor enantioselectivity.

(8) (a) Grisar, J. M.; Claxton, G. P.; Stewart, K. T. *Synthesis* **1974**, 284. (b) Poisel, H. *Monatsh. Chem.* **1978**, *109*, 925. (c) Scully, F. E., Jr. *J. Org. Chem.* **1980**, *45*, 1515.

(9) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656. Comins, D. L.; Chung, G.; Foley, M. A. *Heterocycles* **1994**, *37*, 1121 and references cited therein.

(10) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095.

(11) Kawate, T.; Yamada, H.; Soe, T.; Nakagawa, M. *Tetrahedron*: *Asymmetry* **1996**, 7, 1249. We thank Prof. M. Nakagawa for provision of experimental data before publication.

(12) Ukaji, Y.; Tsukamoto, K.; Nasada, Y.; Shimizu, M.; Fujisawa, T. *Chem. Lett.* **1993**, 221.

(13) Aketa, K.-I.; Terashima, S.; Yamada, S.-I. *Chem. Pharm. Bull.* **1976**, *24*, 621.