ENHANCED REACTIVITY OF ZINC ENOLATES OVER LITHIUM ENOLATES IN ASYMMETRIC NITROOLEFINATION

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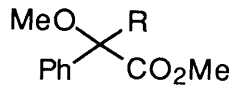
Zinc enolates derived from an ester and a lactone, **1** and **4**, were found to have enhanced reactivity over the corresponding lithium enolates in asymmetric nitroolefination.

KEYWORDS zinc enolate; enantioselective reaction; nitroolefin; asymmetric synthesis

Zinc enolates have been often utilized to control chemo- and stereo-selectivity in carbon-carbon bond forming reactions.[1] The reactivity of zinc enolates appears to be relatively low out of various metal enolates, as exemplified by Reformatsky reaction.[2] Recent studies have revealed the generally lower reactivity of zinc enolates than the corresponding lithium enolates.[3] However, in the course of our study on asymmetric nitroolefination,[4] we have found that zinc enolates of **1** and **4** have much enhanced reactivity over that of the lithium enolates toward a nitroenamine **3**.

A reaction of the lithium enolate of **1** with a chiral nitroenamine **3** at -78 °C took place smoothly to afford (*S*)-**2** in 88% yield with only 6% ee. Surveying metal halides as additives for the reactions,[5] it was found that an addition of zinc chloride afforded (*R*)-**2** in 96% yield with 69% ee.[6, 7] To investigate the property of the zinc enolates, we carried out asymmetric nitroolefination of the lithium enolate of **1** in the presence of various amounts of zinc chloride (Table I). Chemical yields of the reactions were high irrespective of the amount of zinc chloride. The maximum enantioselectivity (69% ee) was obtained when 1.0 eq of zinc chloride was used. Surprisingly, use of only 0.1 eq afforded 59% ee. This indicates that the zinc enolate dominated the reaction path in the presence of the lithium enolate which exists by nine times of zinc enolate, even though the lithium enolate is reactive toward **3** by itself.[8] Assuming that the *pure* zinc enolate (1.0 eq of $ZnCl_2$) affords 69% ee of the *R*-enantiomer and the *pure* lithium enolate (0 eq of $ZnCl_2$) affords 6% ee of the *S*-enantiomer, the production of the *R*-enantiomer of 59% ee implies that 87% of the product **2** was originated from the zinc enolate and 13% from the lithium enolate. Rough calculations show that the zinc enolate of **1** reacts with **3** approximately 60 times faster than the lithium enolate. Similarly, zinc enolate of **4** reacts with **3** faster than the corresponding lithium enolate. The results are shown in Table II. In



1 : R=H
2 : R=CH=CH-NO_2

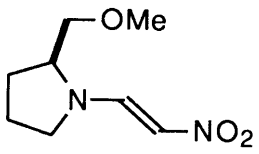


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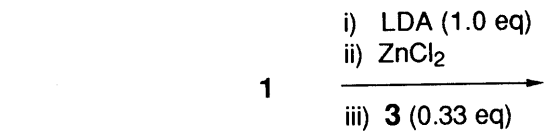
Table I. Effect of $ZnCl_2$ on Enantioselectivity of Nitroolefination of **1**[a)]



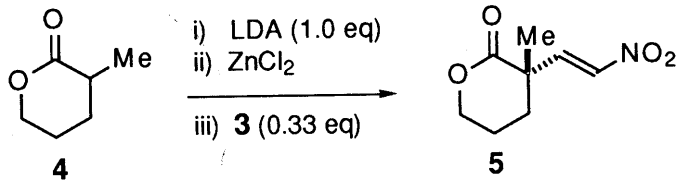
mol eq of $ZnCl_2$[b)]	0	0.1	0.4	0.7	0.9	1.0	1.4	2.0
Yield of **2**[c)](%)	88	88	99	96	95	96	87	98
ee of **2**[d)](%)	6	59	60	65	67	69	43	37
Config[e)]	*S*	*R*	*R*	*R*	*R*	*R*	*R*	*R*

a) Reactions were run in THF at -78 °C; see reference 6. *b*) 0.49-0.97 M solution of zinc chloride[3b] in THF was used. Concentration of zinc chloride was determined by a titration with EDTA in dil NH_4OH using Eriochrome Black T as an indicator. *c*) Yield based on **3**. *d*) Determined by 400 MHz ^{1}H-NMR with $Eu(hfc)_3$ or by $[\alpha]_D$. *e*) Determined by chemical correlations, see reference 7.

the absence of zinc chloride, nitroolefin **5** was obtained in 30% ee, while 94% ee was achieved when one eq of zinc chloride was employed. Addition of 0.1 eq of zinc chloride gave **5** of 72% ee. Calculations as above indicate that the zinc enolate is roughly 15 times more reactive than the lithium one. We assume that higher reactivity of the zinc enolates are ascribed to the the stronger Lewis acidity of Zn^{2+} toward the nitroenamine **3** than that of Li^+. Another intriguing point is that the zinc enolate is expected to be a catalytically active species in the asymmetric nitroolefination of **1**. A hypothetical catalytic cycle is shown in Chart I. The zinc enolate **6** generated from **1** reacts with **3** preferentially in the presence of lithium enolate **7**. A metal-metal exchange between **7** and **8** takes place to regenerate the zinc enolate **6**. Interestingly, increasing the amount of zinc chloride more than one eq decreased the ee of the products. We suppose that the excess zinc chloride may destroy the tight cyclic transition state consisting of the zinc enolate and **3** that is crucial for the high asymmetric induction[4)].

We have disclosed the enhanced reactivity of zinc enolates as well as the catalytic property in the asymmetric nitroolefination. This may open a new avenue for catalytic asymmetric induction utilizing zinc as a counter cation. Studies toward this end are currently in progress.

Table II. Effect of $ZnCl_2$ on Enantioselectivity of Nitroolefination of **4**[a)]



mol eq of $ZnCl_2$[b)]	0	0.03	0.1	0.3	0.7	1.0	1.2	1.4
Yield of **5**[c)](%)	81	69	43	59	67	60	64	54
ee of **5**[d,e)](%)	30	46	72	78	90	94	65	41

a) Reactions were run in DME at -78 ~ -40 °C. *b*) 0.53 M solution of zinc chloride in ether was used. *c*, *d*) Same as footnotes *c* and *d* in Table I, respectively. *e*) Product **5** has *S*-configuration[4)] in every run.

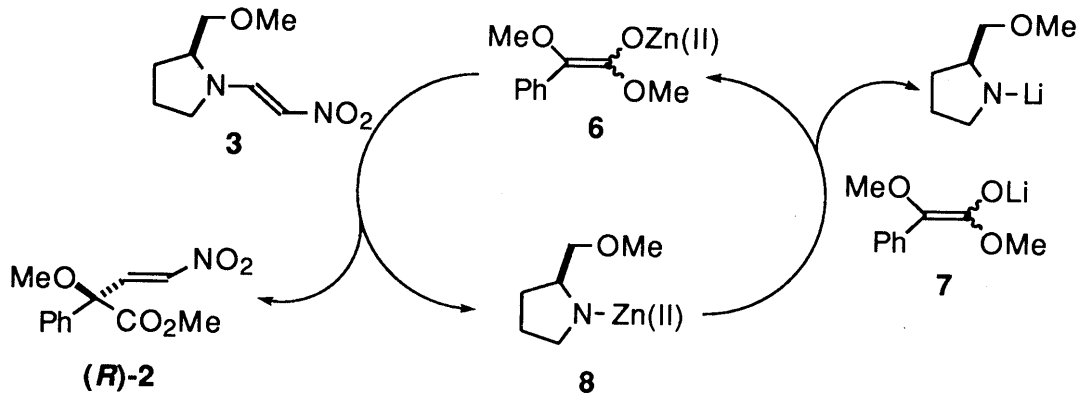


Chart I. Possible Catalytic Cycle of Zn(II) Enolate in Asymmetric Nitroolefination

REFERENCES AND NOTES

1) For examples, see: a) W. J. Thompson, R. G. Ball, P. L. Darke, J. A. Zugay, J. E. Thies, *Tetrahedron Lett.*, **33**, 2957 (1992); b) G. Pattenden, N. Pegg, A. G. Smith, *Tetrahedron Lett.*, **27**, 403 (1986).

2) For an example, see: H. O. House, *Modern Synthetic Reactions 2nd Ed.*, W. A. Benjamin, Inc., California, **1972**, pp. 671-678.

3) a) M. M. Hansen, P. A. Bartlett, C. H. Heathcock, *Organometallics*, **6**, 2069 (1987); b) H. O. House, D. S. Crumrine, A. Y. Teranishi, H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).

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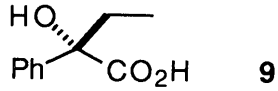
5) Ph_3SnCl, $TiCl_4$, $ZrCl_4$, and Cp_2ZrCl_2 were examined. The results are as follows; Ph_3SnCl : 57% ee (*R*) (96% yield), $TiCl_4$: 29% ee (*R*) (31% yield), $ZrCl_4$: 10% ee (*R*) (12% yield), Cp_2ZrCl_2 : no reaction.

6) A typical experimental procedure: A solution of **1** (281 mg, 1.56 mmol) in THF (2.0 mL) was added to an LDA (1.62 mmol) solution in THF (2.0 mL) at -78 °C. After stirring for 30 min, zinc chloride solution in ether (0.49 M, 3.2 mL) was added, and the mixture was warmed to -20 °C and stirred for 1 h. The resulting mixture was added to a solution of **3** (89 mg, 0.52 mmol) in THF (2.0 mL) at -78 °C and stirred for 1 h. The reaction mixture was poured into 3% HCl at 0 °C, then neutralized with saturated aq $NaHCO_3$. Extractive workup followed by silica gel column chromatography afforded **2** (125 mg, 96% yield).

7) The absolute configurations of **2** was determined by a chemical correlation with **9**; see: S. Mitsui, S. Imaizumi, Y. Senda, K. Konno, *Chem. Ind.*, 233 (1964).

8) Recently, it has been reported that a lithium enolate could be activated by an addition of a catalytic amount of zinc chloride, only in the case when the lithium enolate was unreactive toward the electrophile; see: F. H. van der Steen, H. Kleijn, J. T. B. H. Jastrzebski, G. van Koten, *J. Org. Chem.*, **56**, 5147 (1991).



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