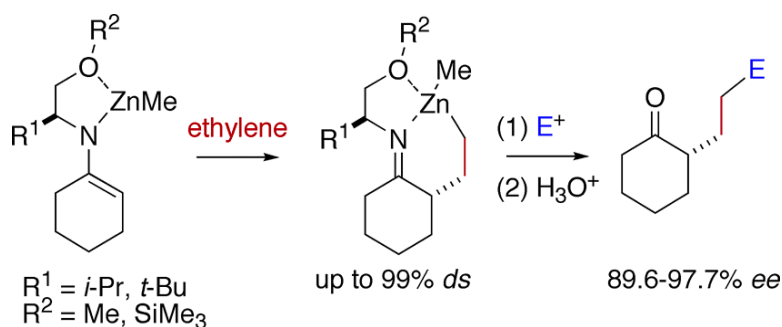


## Enantioselective Synthesis of $\alpha$ -Substituted Ketones by Asymmetric Addition of Chiral Zinc Enamides to 1-Alkenes

Masaharu Nakamura, Takuji Hatakeyama, Kenji Hara, and Eiichi Nakamura

*J. Am. Chem. Soc.*, **2003**, 125 (21), 6362-6363 • DOI: 10.1021/ja035091p • Publication Date (Web): 06 May 2003

Downloaded from <http://pubs.acs.org> on March 28, 2009



### More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 8 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)



## Enantioselective Synthesis of $\alpha$ -Substituted Ketones by Asymmetric Addition of Chiral Zinc Enamides to 1-Alkenes

Masaharu Nakamura,<sup>\*,†,‡</sup> Takuji Hatakeyama,<sup>‡</sup> Kenji Hara,<sup>§</sup> and Eiichi Nakamura<sup>\*,†</sup>

Department of Chemistry, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

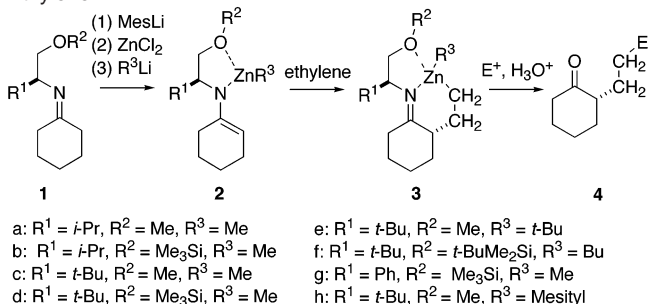
Received March 11, 2003; E-mail: masaharu@chem.s.u-tokyo.ac.jp; nakamura@chem.s.u-tokyo.ac.jp

Asymmetric  $\alpha$ -alkylation of a ketone with an alkyl halide as exemplified by an  $S_N2$  reaction of a lithiated chiral hydrazone<sup>1</sup> or imine<sup>2</sup> is a fundamental synthetic reaction, which allows for the two-component coupling synthesis of a variety of optically active  $\alpha$ -substituted ketones. In view of the reagent and environmental cost, however, the use of a simple alkene<sup>3</sup> instead of an alkyl halide may be more desirable, but has so far not been well developed.<sup>4</sup> We report here an enantioselective synthesis of  $\alpha$ -substituted ketones through three-component coupling of an optically active zinc enamide, 1-alkene, and an electrophile ( $E^+$ ) (Scheme 1). The key step involves the addition of a zinc enamide such as **2** (derived from (*S*)-valinol or (*S*)-*t*-leucinol) to an alkene, which may proceed in high yield with >99% diastereoselectivity for the coupling of a cyclohexanone imine and ethylene.

Because of the lack of polarity, ethylene is entirely unreactive to a metal enolate or enamide of cyclohexanone (metal = Li, Mg, and Zn). A zincated *N,N*-dimethylhydrazone is reasonably reactive to ethylene, but when a chiral hydrazone bearing an additional Lewis basic group (e.g., methoxy group in the SAMP-hydrazone) is used, the corresponding zinc enamide is rather unreactive (and poorly stereoselective).<sup>4</sup> After extensive experimentation, we found the best compounds and conditions to achieve the desired asymmetric transformation in high yield and with high stereoselectivity. Thus, an optically active cyclohexanone imine **1a** ( $R^1 = i$ -Pr,  $R^2 = Me$ ; >99% ee) was prepared by condensation of cyclohexanone and methyl ether of (*S*)-valinol (94% yield),<sup>2</sup> and the purified imine was then deprotonated with 1 equiv of mesityllithium at 0 °C in ether. The zinc enamide **2a** ( $R^1 = i$ -Pr,  $R^2 = Me$ ,  $R^3 = Me$ ) was generated in situ by transmetalation with  $ZnCl_2$  followed by treatment with methyl lithium ( $R_3Li$ ). The methyl lithium treatment was necessary to obtain high reactivity as reported previously for related reactions.<sup>5</sup> Diethyl ether was replaced with hexane, and the reaction mixture was stirred under ethylene atmosphere (20 atm) at 40 °C for 24 h. The desired 2-ethylcyclohexanone **4** ( $E = H$ ) was obtained in good yield after hydrolysis (see Supporting Information for details). As shown in entry 1 in Table 1, (*R*)-2-ethylcyclohexanone was obtained with 96.0% ee in 24% yield when the hydrolysis was stopped after 5 min, and with 92.0% ee in 85% after 1 h.<sup>6</sup> When we used more expensive but more selective imine substrate **1d** derived from a silyl ether of (*S*)-*t*-leucinol (>99.5% ee), virtually complete stereoselectivity of >99.3% was achieved (entry 1). The synthetic operation can be carried out easily on a gram scale.<sup>7</sup>

Studies on substituent effects and some representative examples of the reactions with ethylene, propene, and styrene showed the versatility of the present reaction as summarized in Table 1. In entry 1 are shown the product yields and selectivity when the  $R^1$ ,  $R^2$ , and  $R^3$  groups are changed. The selectivity with the *t*-leucinol

**Scheme 1.** Stereoselective Addition of Chiral Zinc Enamides to Ethylene



is better than that of the valinol derivatives. Too bulky  $R^2$  and  $R^3$  groups (e.g., enamides **2e** and **2f**) tend to slow the reaction and to lower the selectivity. The overall enantioselectivity for the cyclohexanone imines shown in entries 1–3 depends more on the rate of racemization during imine hydrolysis rather than on the selectivity of the addition reaction.<sup>6</sup> For instance, the reaction of zinc enamide **5d** (entry 2, 97.7% ee, 92% yield) was more enantioselective than that of **7d** (90.0% ee, 89% yield), because the racemization was slower than that in the latter case. The zinc enamide of cycloheptanone **9d** reacted with ethylene at 60 °C to give an  $\alpha$ -ethylated ketone **10d** in 82% yield with 95.6% ee (entry 4). Similarly, the zinc enamide **11d** gave **12d** in 93% yield with 96.2% ee (entry 5). For reasons yet unknown, zinc enamides derived from cyclopentanone and cyclooctanone were very unreactive to ethylene under the same conditions.

The stereoselectivity of the acyclic enamide may depend on the *E/Z* geometry of the olefinic bond (entry 6). Thus, the zinc enamide **13d** of 3-pentanone that bears a methyl dummy ligand on the zinc atom gave **14** of only 18% ee (entry 6). Considering that *E/Z* enamide isomers can interconvert with each other via a metal enamide/ $\alpha$ -metalloimine equilibrium,<sup>2,8</sup> we changed the  $R^3$  group from a methyl group to a bulky mesityl group. Thus, the zinc enamide **13h** gave the corresponding ethylated product with improved enantioselectivity of 58.0% ee in 81% yield (entry 6). On the basis of the *S* stereochemistry of the product (the same sense of stereoselectivity obtained for the cyclic enamides), we assume that the bulky dummy ligand allowed either selective formation or participation of an *E*-enamide in the reaction.

Propene and styrene also took part in the reaction.<sup>9</sup> The zinc enamide **2d** added to propene to give (*S*)-2-isopropylcyclohexanone **15** in 47% yield with 93.2% ee after 48 h (entry 7). The formation of the branched product indicates that the addition took place to generate a primary alkyl zinc intermediate. The reaction with styrene gave **16** (71% yield, 77.6% ee) with reversed regioselectivity in such a manner to generate a benzylic zinc intermediate. Note that the corresponding zincated hydrazone adds to styrene to give a mixture of the regioisomers.<sup>4</sup>

<sup>†</sup> PRESTO, Japan Science and Technology Corporation (JST).

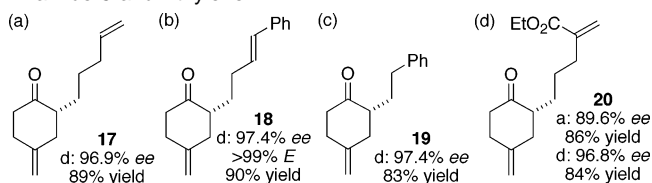
<sup>‡</sup> The University of Tokyo.

<sup>§</sup> Present address: Hokkaido University.

**Table 1.** Enantioselective  $\alpha$ -Alkylation of Ketones with Ethylene, Propene, and Styrene<sup>a</sup>

entry	zinc enamide <sup>a</sup>	product <sup>b</sup>	ee(%) <sup>c</sup> , yield(%)
1			<b>4 (R)</b> (E = H) a: 92.0, 85 <sup>d</sup> (96.0, 24) <sup>h</sup> b: 93.8, 81 <sup>d</sup> (97.8, 32) <sup>h</sup> c: 93.6, 87 <sup>d</sup> (98.1, 16) <sup>h</sup> d: 95.0, 91 <sup>d</sup> (99.3, 29) <sup>h</sup> e: 88.2, 73 <sup>d</sup> f: 55.2, 14 <sup>d</sup> g: 76.6, 86 <sup>d</sup>
2			<b>6 (R)</b> a: 90.9, 93 <sup>e</sup> (94.1, 38) <sup>h</sup> d: 97.7, 92 <sup>e</sup> (99.1, 33) <sup>h</sup>
3			<b>8 (R)</b> d: 90.0, 89 <sup>g</sup> (95.1, 33) <sup>h</sup>
4			<b>10 (R)</b> d: 95.6, 82 <sup>g</sup> (98.8, 34) <sup>h</sup>
5			<b>12 (R)</b> d: 96.2, 93 <sup>e</sup>
6			<b>14 (S)</b> d: 18, 84 <sup>d</sup> h: 58.0, 81 <sup>d</sup>
7			<b>15 (S)<sup>ij</sup></b> a: 84.2, 45 <sup>f</sup> d: 93.3, 47 <sup>f</sup> (98.0, 15) <sup>h</sup>
8			<b>16 (S)<sup>ik</sup></b> c: 77.6, 71 <sup>g</sup>

<sup>a</sup> N denotes an amino-alcohol group specified by the coding in Scheme 1. <sup>b</sup> Addition reaction was carried out in an autoclave under an ethylene atmosphere (20–30 atm) at 40–60 °C for 24 h. <sup>c</sup> ee values were determined by GC analysis. <sup>d–f</sup> Based on the starting imine and determined by GC analysis by using decane,<sup>d</sup> undecane,<sup>e</sup> and tridecane<sup>f</sup> as an internal standard. <sup>g</sup> Isolated yield. <sup>h</sup> The data in parentheses refer to the yield and selectivity determined for the ketone product obtained after 5–10 min of hydrolysis. <sup>i</sup> Regioselectivity was >99:1. <sup>j</sup> Propene atmosphere (8 atm), 60 °C for 48 h. <sup>k</sup> 1.5 equiv of styrene, 70 °C for 48 h.

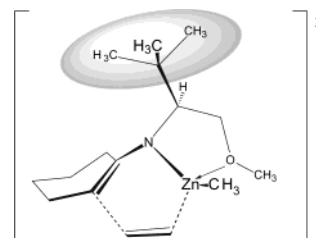
**Chart 1.** Products (17–20) of the Electrophilic Trapping of the  $\gamma$ -Zincioimine Intermediate In-Situ Generated by Coupling of Enamide **5** and Ethylene<sup>a</sup>

<sup>a</sup> (a) Allyl bromide (2 equiv)/CuBr·SMe<sub>2</sub> (20 mol %), (b)  $\beta$ -bromostyrene (2 equiv, >99.9% E)/Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol %), (c) iodobenzene (2 equiv)/Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol %), (d) ethyl 2-(bromomethyl)acrylate (2 equiv)/CuBr·SMe<sub>2</sub> (1 equiv).

The organozinc intermediate containing an imine functionality such as **3** was found to be very stable under the reaction condition of 40–60 °C in terms of its chemical and stereochemical integrity likely because of its chelate structure. On the other hand, such an intermediate still shows the chemical reactivities characteristic of an organozinc species (Chart 1). For instance, the intermediate

generated by the reaction of **5** and ethylene undergoes copper- and palladium-catalyzed C–C bond forming reactions in high overall yield and with high stereoselectivity. We previously noted also for an  $\alpha$ -substituted zinc homoenolate such stereochemical stability of a stereogenic center next to a carbonyl group.<sup>10</sup>

The zinc enamide **3c** reacts with ethylene to generate (*R*)-2-ethylcyclohexanone (93.6% ee), and this selectivity is opposite to that obtained in the alkylation of its lithium enamide with ethyl iodide in THF at –78 °C, which gave (*S*)-2-ethylcyclohexanone with 79.4% ee.<sup>2</sup> The sense of the selectivity in the former reaction may be explained by a six-centered transition state shown below,<sup>11</sup> and that of the latter reaction needs a different way of reasoning.



**Supporting Information Available:** Details of the experimental procedure, and characterization and physical data of products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.
- (2) (a) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. J. *J. Am. Chem. Soc.* **1981**, *103*, 3081. (b) Meyers, A. I.; Williams, D. R.; White, S.; Erickson, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 3088.
- (3) Rodriguez, A. L.; Bunlalsanansorn, T.; Knochel, P. *Org. Lett.* **2000**, *2*, 3285.
- (4) (a) Kubota, K.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2491. (b) Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, *62*, 792. (c) Nakamura, E.; Kubota, K.; Sakata, G. *J. Am. Chem. Soc.* **1997**, *119*, 5457. (d) Nakamura, E.; Kubota, K. *Tetrahedron Lett.* **1997**, *38*, 7099.
- (5) (a) Nakamura, M.; Hara, K.; Hatakeyama, T.; Nakamura, E. *Org. Lett.* **2001**, *3*, 3137. (b) Nakamura, M.; Hara, K.; Sakata, G.; Nakamura, E. *Org. Lett.* **1999**, *1*, 1505. (c) Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* **1998**, *39*, 2157. (d) Kubota, K.; Isaka, M.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **1993**, *115*, 5867. (e) Lorthiois, E.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1998**, *63*, 2442.
- (6) Racemization of the chiral center took place even under the best current hydrolysis conditions, which is not due to epimerization of the final ketone product but due to that of an imine intermediate.
- (7) Enantioselective three-component coupling of 4-methylenecyclohexanone enamide **5**, ethylene, and ethyl 2-(bromomethyl)acrylate: An imine precursor to **5a** (2.09 g, 10.0 mmol) was added slowly to an ethereal solution of mesityllithium (10.0 mmol) at 0 °C. Zinc chloride (ether solution, 10.0 mmol) at 0 °C and then methyl lithium (ether solution, 10.0 mmol) at –78 °C were added. Hexane (20 mL) was added, and the reaction mixture was heated at 45 °C for 30 min to remove ether under dry nitrogen stream. The reaction mixture was pressurized with ethylene (30 atm) and stirred for 24 h at 60 °C. After release of excess ethylene, tetrahydrofuran (20 mL), CuBr·SMe<sub>2</sub> (2.06 g, 10.0 mmol), and ethyl 2-(bromomethyl)acrylate (2.42 mL, 20.0 mmol) were added at –78 °C. The reaction mixture was stirred at 0 °C for 6 h and then hydrolyzed with acetic acid buffer (20 mL). Purification by silica gel chromatography gave the desired  $\alpha$ -alkylated ketone (2.15 g, 86% yield, 89.6% ee). The amino ether chiral auxiliary can be recovered in >70% yield.
- (8) Both isomers may be of nearly equal energies, but only the zinc enamide can take part in the addition reaction.
- (9) The reaction is general for 1-alkenes but produces a mixture of diastereomers as to the newly formed C–C bond. The stereochemical issue still remains to be resolved to make this extension synthetically useful.
- (10) Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *1*, 155.
- (11) Hirai, A.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 11791.

JA035091P