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The Olefinic Aldol Reaction. Intramolecular Cyclization Forming Five- and Six-membered Rings

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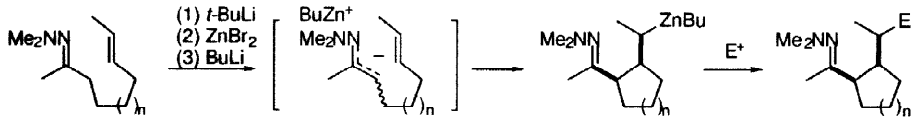
Abstract: An enolate anion undergoes intramolecular addition to a neighboring olefinic bond suitable for cyclization, when the countercation of the enolate is a BuZn(II) cation. Thus, zinc enolates of olefinic *N,N*-dimethylhydrazone and lactam undergo a 5-exo and 6-exo trigonal cyclization reaction in good to high yield to afford 1,2-substituted cyclopentane and cyclohexane derivatives bearing a hydrazone or lactam side chain.

The olefinic version of the aldol reaction, i.e., enolate addition to olefin,[1,2] was recently discovered for inter- and intramolecular additions; however, the latter has been illustrated for essentially a single example of a 5-exo cyclization of an ester enolate to form a proline skeleton.3 We demonstrate, in this communication, further synthetic potential of the intramolecular olefinic aldol reaction by describing the 5-exo and 6-exo trigonal cyclization of zincated ketone hydrazones and lactam. It was confirmed, as in our previous studies[1], that a BuZn(II) cation serves as a better countercation than a BrZn(II) cation.



1 2 3

As detailed in note 4 , the experimental procedure is simple and the reaction takes place under mild room temperature conditions. Thus, an *N,N*-dimethylhydrazone of an olefinic ketone was deprotonated with *tert*-BuLi and, after 4 h at 0 ℃, treated with one equivalent of $ZnBr_2$ at 0 ℃ for 1 h. The azaenolate bearing a ZnBr counter cation cyclizes very slowly (for the case equivalent to entry 1 in Table 1, 15% in 25 h to give a trans product). When one equivalent of BuLi was added, the cyclization reaction proceeded faster, and after one day to several days at room temperature, the desired cyclization product formed in good to excellent yield. The results of intramolecular reaction are summarized in Table 1. The cyclization reaction took place smoothly both in a 5-exo and 6-exo manner (entries 1-4). No products arising from 6-endo and 7-endo mode cyclizations were detected. We could not effect 7-exo cyclization for the homolog of the compound in entry 2. The reactions took place in such a manner that the hydrazone and the cyclization terminus are placed cis to each other.

The cyclization onto a disubstituted double bond (entry 4) was much slower than that onto a terminal olefin (e.g., entry 1). For reasons yet unknown, the presence of a bulky *tert*-butyl group in the substrate significantly slowed down the cyclization reaction (entry 3). The case with the lactam in entry 5 indicates that *both azaenolate and ordinary oxygen enolates take part in the olefinic aldol reaction.* The 5-exo cyclization reactions of a γ-lactam and an open chain amide of structures similar to the case in entry 5 were extremely slow.

All reactions shown in Table 1 took place with high levels of diastereoselectivity. The 5-exo trigonal cyclization afforded a 1,2-cis-substituted cyclopentane with >85% selectivity. The 6-exo cyclization reaction also took place smoothly and with >91% cis-selectivity. The stereochemical assignment of the cyclopentane

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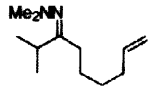
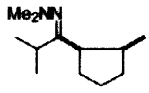
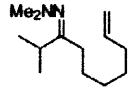
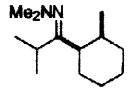
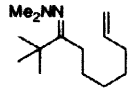
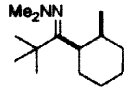
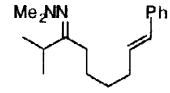
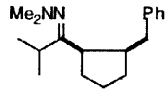
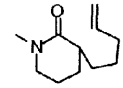
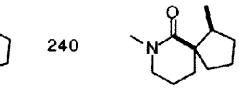
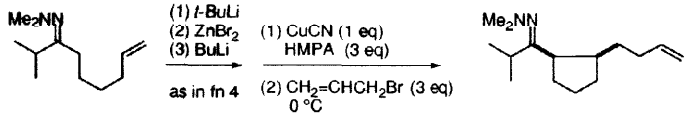
Table 1. Intramolecular cyclization of zincated hydrazone and amide.[a]

Entry	Substrate	Time (h)	Major product	%Yield[b]	%d.s
1		25		90	88
2		25		83	91
3		240		42	~100
4		25		40	95
5		240		70	~100

[a] The reaction was carried out as in note 4 except for the reaction time. [b] Isolated yield. The uncyclized and cyclized hydrazones accounted for >90% of the material balance.

product rests on the NOE studies on both cis and trans isomers combined with Monte-Carlo conformational analysis, and that of the cyclohexane product on the coupling constant analysis.

The organozinc reagent **2** can be further functionalized by the reaction with an electrophile. For example, trapping with allyl bromide produces the corresponding allylated product in 78% overall yield by taking advantage of a beneficial combination of Cu and Zn.[5]



78%

In summary, we have shown that intramolecular olefinic aldol reactions of both zinc enolate and azaenolate have considerable synthetic potential as a ring-forming process. Successful 6-exo cyclization, mild reaction conditions, and the formation of a stable yet reactive "bishomoenolate" species represent significant advantages of the process over the classical thermal Conia ene cyclization reaction of olefinic carbonyl compounds.[6,7]

References and Notes

1 Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, *62*, 792-793; Kubota, K.; Nakamura, E. *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2491-2493; Nakamura, E.; Kubota, K. *Tetrahedron Lett.* **1997**, *38*, 7099-7102.

2 Nakamura, E.; Kubota, K.; Sakata, G. *J. Am. Chem. Soc.* **1997**, *119*, 5457-5458

3 Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **1997**, 38, 85-88; Lorthiois, E.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1997**, *38*, 89-92.

4 Typical experiments as illustrated for entry 1: To a solution of 8-methyl-1-nonen-7-one *N,N*-dimethylhydrazone (9.51 mL, 40.0 mmol) in Et_2O (60.0 mL) was added t-BuLi (1.76 M in pentane, 22.7 mL, 40.0 mmol) at -78 °C, and the mixture was warmed to 0 °C. After 4 h at 0 °C, $ZnBr_2$ (0.33 M in Et_2O, 120.0 mL, 40.0 mmol), and, then after 1 h at -78 °C, BuLi (1.60 M in hexane, 25.0 mL, 40.0 mmol) was added to the solution at -78 °C. After 25 h at 20-25 °C, the cyclization was almost complete. Addition of a 1/15 N phosphate buffer solution followed by extractive workup and chromatography (350 g, first treated with N,N-dimethylaniline (70 mL), eluent: 2% Et_2O in pentane) afforded the 5-exo cyclization product in entry 1 (7.10 g, 90%, as a yellow oil) as an 88:12 mixture of cis- and trans-isomers as determined by capillary GC analysis (HR-1).

5 Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, *J. Am. Chem. Soc.* **1987**, *109*, 8056-8066. See also: Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390-2392.

6 Conia, J. M.: Perchec, P. Le. *Synthesis* **1975**, 1-19.

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