

Oxovanadium(V)-Induced Vicinal
Dialkylation of Cyclic Enones with
Organozinc Compounds

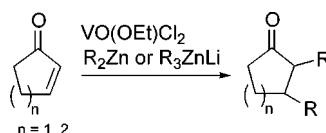
Toshikazu Hirao,* Takashi Takada, and Hidehiro Sakurai

Department of Applied Chemistry, Faculty of Engineering, Osaka University,
Yamada-oka, Suita, Osaka 565-0871, Japan

hirao@ap.chem.eng.osaka-u.ac.jp

Received September 8, 2000

ABSTRACT



Oxovanadium(V) compounds induce nucleophilic α,β -vicinal dialkylation of cyclic α,β -enones with dialkylzinc reagents. Alkylzinc enolates generated from cyclic enones and lithium trialkylzincates were also oxidized by VO(OEt)Cl₂, giving 2,3-dialkylcycloalkanones.

Oxidative transformation of main-group organometallics has been expected to develop a new type of carbon–carbon bond-forming reaction.^{1,2} Recently, we reported that oxovanadium(V) compounds induce a selective ligand coupling of two ligands on some organometallic compounds such as organoaluminum,³ boron,⁴ zirconium,⁵ and zinc compounds.⁶ As for the organozinc compound, arylalkylzinc or aryldialkylzincate is oxidized by VO(OEt)Cl₂, providing a ligand coupling product selectively (Scheme 1).⁶

(1) For chemical redox reagents of organometallic chemistry, see: Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, 96, 877 and references therein.

(2) For copper-induced oxidative ligand coupling reactions of organoborons and organozincs, see: (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K.; Sonoda, A.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1977**, 99, 5652. (b) Iyoda, M.; Kabir, S. M. H.; Vorasingha, A.; Kuwatani, Y.; Yosihda, M. *Tetrahedron Lett.* **1998**, 39, 5393. For oxidative transformation of d⁰ organometallics, see: (c) Jordan, R. F.; LaPointe, R. E.; Bajgur, C. S.; Echols, S. F.; Willet, R. *J. Am. Chem. Soc.* **1987**, 109, 4111. (d) Borkowsky, S. L.; Baenziger, N. C.; Jordan, R. F. *Organometallics* **1993**, 12, 486. (e) Burk, M. J.; Tumas, W.; Ward, M. D.; Wheeler, D. R. *J. Am. Chem. Soc.* **1990**, 112, 6133. (f) Sato, M.; Mogi, E.; Kumakura, S. *Organometallics* **1995**, 14, 3157. (g) Hayashi, Y.; Osawa, M.; Wakatsuki, Y. *J. Organomet. Chem.* **1997**, 542, 241.

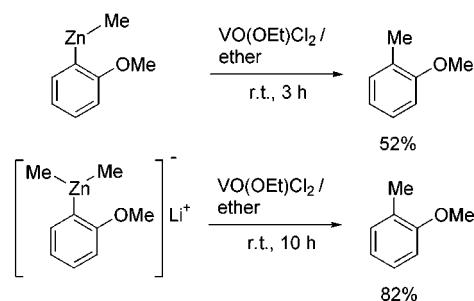
(3) Ishikawa, T.; Ogawa, A.; Hirao, T. *J. Am. Chem. Soc.* **1998**, 120, 5124.

(4) Ishikawa, T.; Nonaka, S.; Ogawa, A.; Hirao, T. *J. Chem. Soc., Chem. Commun.* **1998**, 1209.

(5) Ishikawa, T.; Ogawa, A.; Hirao, T. *J. Organomet. Chem.* **1999**, 575, 76.

(6) Hirao, T.; Takada, T.; Ogawa, A. *J. Org. Chem.* **2000**, 65, 1511.

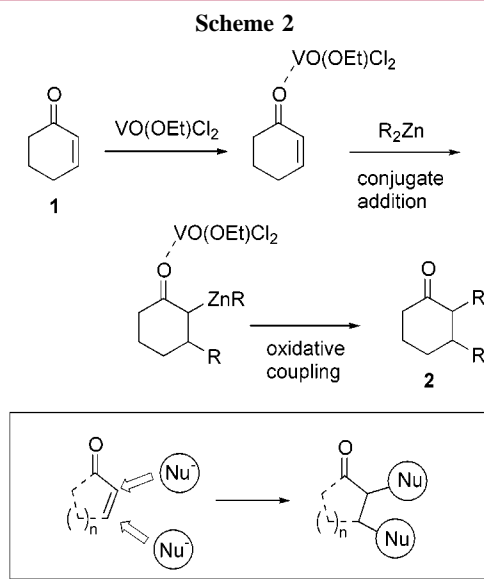
Scheme 1



On the other hand, dialkylzinc reagent (R₂Zn) is recognized as a mild nucleophile, and highly selective reactions have been developed by a combination of an additional promoter such as a Lewis acid catalyst.⁷ It is known that 1,4-addition of dialkylzinc to an α,β -unsaturated carbonyl compound also requires promotion by a Lewis acid. Judging from the characteristic features of oxovanadium(V) compounds as a Lewis acid and one-electron oxidant, they are expected to induce a novel nucleophilic vicinal dialkylation

(7) For organozinc mediated reactions, see: (a) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, 54, 8275 and references therein. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, 93, 2117 and references therein.

at both the β - and α -positions of an α,β -unsaturated carbonyl compound with a dialkylzinc reagent (Scheme 2). That is,



the oxovanadium (V) compound might promote 1,4-addition of R_2Zn to enone **1**, and the resulting zinc enolate is immediately oxidized by the adjacent oxovanadium(V) species, giving the corresponding vicinally dialkylated compound **2**.

To accomplish this kind of vicinal alkylation, first, the reaction of 2-cyclohexenone (**1**) with dimethylzinc in THF was investigated (Table 1). Dimethylzinc was inert to **1** without an oxovanadium(V) complex (entry 1), whereas $VO(OPr^i)_3$ activated only the 1,4-addition process to give 3-methylcyclohexanone (**3a**) in 34% yield (entry 2). Use of $VO(OEt)Cl_2$, a more efficient Lewis acid and oxidant than $VO(OPr^i)_3$,⁸ led to the formation of 2,3-dimethylcyclohexanone (**2a**) in 26% yield as a diastereomeric mixture.⁹ This result encouraged us to examine the precise reaction conditions. When the reaction was carried out at -78°C for 4 h and then at -30°C for 6 h, the yield of **2a** was increased to 60% (entry 4). Next, the substituent of oxovanadium(V) compounds was screened to find that the stronger Lewis acid and oxidant gave the better results. Accordingly, the yield of **2a** decreased in the order $VO(OEt)Cl_2 > VO(OPr^i)_2Cl_2 > VO(OPr^i)_2Cl$ to 60%, 56%, and 20%, respectively (entries 4–6).⁸ Finally, the yield of **2a** was improved to 78% when 2 molar equiv of dimethylzinc and 2 molar equiv of $VO(OEt)Cl_2$ were employed at -78°C for 20 h (entry 7).¹⁰

(8) The order of the reactivity of oxovanadium(V) reagents is as follows: $VO(OR)Cl_2 - AgOTf$ or $Me_3SiOTf > VO(OR)Cl_2 > VO(OR)_2Cl > VO(OR)_3$. Hirao, T.; Mori, M.; Ohshiro, Y. *Bull. Chem. Soc. Jpn.* **1989**, 62, 2399. Hirao, T.; Mori, M.; Ohshiro, Y. *J. Org. Chem.* **1990**, 55, 358. Hirao, T.; Mori, M.; Ohshiro, Y. *Chem. Lett.* **1991**, 783.

(9) The regiochemistry of dialkylated compounds **2a–c** was determined by $^{13}\text{C}-^{13}\text{C}$ cosy using the 2D-INADEQUATE technique (CDCl_3 , 25°C) and that of **7** was determined by 1D,2D-HOHAHA. The *trans/cis* stereochemistry of **2a** and **7** was determined by NOE. The *trans/cis* stereochemistry of **2b** and **2c** was determined by $J_{\text{CH}-\text{CH}}$ coupling constant (for example, major *trans-2c*, 7.8 Hz, minor *cis-2c*, 4.9 Hz).¹²

Table 1. Vicinal Dimethylation of **1** with Dimethylzinc^a

entry	oxovanadium(V) (equiv)	solvent	conditions $^\circ\text{C}$, h	yield / % ^b of 2a (<i>trans/cis</i>)
1	—	THF	0, 6	no reaction
2	$VO(OPr^i)_3$ (1.5)	THF	0, 6	0, 3a , 34%
3	$VO(OEt)Cl_2$ (1.5)	THF	0, 6	26 (53 / 47)
4	$VO(OEt)Cl_2$ (1.5)	THF	-78°C , 4 h and -30°C , 6 h	60 (58 / 42)
5	$VO(OPr^i)_2Cl_2$ (1.5)	THF	-78°C , 4 h and -30°C , 6 h	56 (54 / 46)
6	$VO(OPr^i)_2Cl$ (1.5)	THF	-78°C , 4 h and -30°C , 6 h	20 (50 / 50)
7	$VO(OEt)Cl_2$ (2.0)	THF	-78°C , 20 h	78 (62 / 38)
8	$VO(OEt)Cl_2$ (2.0)	Et_2O	-78°C , 20 h	34 (57 / 43)
9	$VO(OEt)Cl_2$ (2.0)	CH_2Cl_2	-78°C , 20 h	52 (54 / 46)

^a1.3 equiv of Me_2Zn in entries 1–6 and 2.0 equiv in entries 7–9 were used. ^bDetermined by ^1H NMR.

When the solvent was replaced with ether or dichloromethane, the yield of **2a** decreased (entries 8 and 9).

The same dialkylation takes place with diethylzinc as shown in Table 2. Furthermore, this method could be applied to trialkylaluminum (R_3Al)³ and trialkylborane (R_3B)⁴ compounds. Diethylation of **1** with diethylzinc, triethylaluminum,

Table 2. Dialkylation of **1** with Organometallic Reagent^a

entry	R_nM	yield / % ^b		
		2 (<i>trans/cis</i>)		3
1	Et_2Zn	74 ^c (77 / 23)		10
2	Et_3Al	84 ^d (74 / 26)		—
3 ^e	Et_3B	50 (68 / 32)		8
4	Me_2CuLi	—		quant

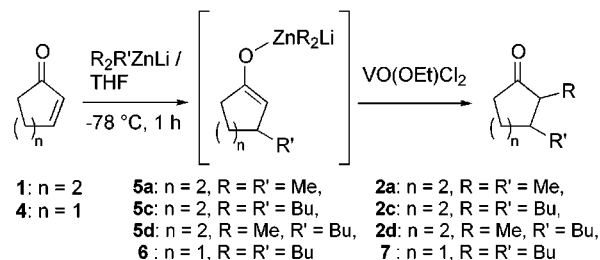
^a Me_2CuLi was prepared from CuI and 2.0 equiv of MeLi *in situ*. ^bDetermined by GC analysis. ^cIsolated yield was 72%. ^dIsolated yield was 75%. ^e**1** (18%) was recovered.

and triethylborane proceeded smoothly to afford the 2,3-diethylcyclohexanone **2b** in 74%, 84%, and 50% yields, respectively (Table 2, entries 1–3). In contrast, an organocuprate reagent exhibited no reactivity toward the oxidative coupling at the α -position and gave only conjugate addition product **3a** quantitatively (entry 4).

Contrary to dialkylzinc, lithium trialkylzincate (R_3ZnLi) has enough nucleophilicity for conjugate addition to an α,β -unsaturated carbonyl compound without the aid of a Lewis acid.⁷ Moreover, the oxovanadium(V)-induced ligand coupling of aryldialkylzincates proceeds more effectively than that of alkylarylzinc compounds as reported.⁶ In fact, Me_3ZnLi (1.2 equiv) added to 2-cyclohexenone to afford the zinc enolate, which underwent oxovanadium(V)-induced oxidation, giving **2a** in 78% yield (Table 3, entry 1). This two-step procedure can be applied to various lithium trialkylzincates, affording the corresponding vicinally dialkylated cycloalkanones in good yields (Table 3). Butylzinc enolate **5c** generated from **1** and Bu_3ZnLi was oxidized by $VO(OEt)Cl_2$, giving dibutylcyclohexanone **2c** in 75% yield (entry 2). When Bu_3ZnLi –TMEDA,¹¹ prepared from a $ZnCl_2$ –TMEDA complex and $BuLi$, was used as a reagent for vicinal alkylation of **1**, **2c** was obtained in 98% yield (entry 3). 2-Cyclopentenone similarly underwent oxidative vicinal alkylation with Bu_3ZnLi –TMEDA to give 2,3-dibutylcyclopentanone (**7**) in 56% yield (entry 4). It is noteworthy that two different alkyl groups can be introduced regioselectively, giving 2-methyl-3-butylcyclohexanone **2d**, when $Me_2BuZnLi$ ¹¹ was employed (entry 5).

In summary, a novel nucleophilic vicinal dialkylation at both the α - and β -positions of cyclic α,β -enones with an

Table 3. Oxidative Coupling Reaction with Zincate^a



entry	substrate	zincate	yield / % ^b (<i>trans/cis</i>)
1	1	Me_3ZnLi	2a 78 [72] (54 / 46)
2	1	Bu_3ZnLi	2c 75 [68] (78 / 22)
3	1	Bu_3ZnLi ·TMEDA	2c 98 [72] (72 / 28)
4	4	Bu_3ZnLi ·TMEDA	7 56 [38] (74 / 26)
5	1	$Me_2BuZnLi$	2d 60 [51] (71 / 29)

^a $R_2R'ZnLi$, 1.2 equiv. Reaction conditions for the oxidation with $VO(OEt)Cl_2$: 0 °C – r.t., 20 h in entries 1–2 and 5, –78 °C, 8 h in entries 3–4. ^bDetermined by GC. Isolated yields are shown in parentheses.

organozinc compound is induced by an oxovanadium(V) compound. This method permits selective 1,4-addition and oxidative ligand coupling in a one- or two-step procedure.

Acknowledgment. The use of the facilities of the Analytical Center, Faculty of Engineering, Osaka University, is acknowledged. This work was partly supported by a Grant-in-Aid for Scientific Research (No. 11450341) from the Ministry of Education, Science, and Culture, Japan.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL006564P

(10) **Typical procedure for vicinal dialkylation:** To a solution of **1** (1.0 mmol) in THF (2.0 mL) under argon at –78 °C was added Me_2Zn (2.0 mmol, 2.0 mL, 1.0 M in Hexane) followed by $VO(OEt)Cl_2$ (2.0 mmol), and the mixture was stirred for 20 h at –78 °C. Workup gave the desired dialkylated product **2**.

(11) Tückmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581.

(12) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141.