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The Olefinic Aldol Reaction. Addition of Zincated Hydrazone to Vinylsilane

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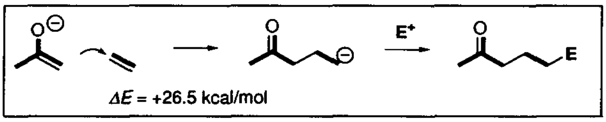
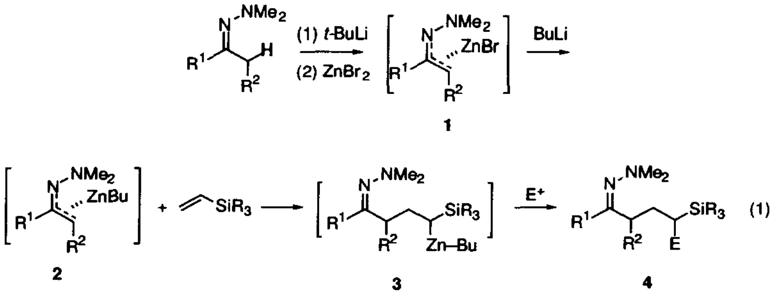
Abstract: A zincated *N,N*-dimethylhydrazone of a ketone bearing a BuZn(II) countercation undergoes intermolecular addition to a vinylsilane to afford the hydrazone of a 2-(2-silylethyl)ketone in good yield, providing a new synthetic route to functionalized carbonyl compounds. © 1997 Elsevier Science Ltd.

Several recent communications have revealed remarkable new possibilities in enolate chemistry; namely, zinc enolates cleanly add to unactivated olefins.[1,2] This apparently counter-thermodynamic reaction can be viewed as an olefinic analog of the aldol reaction and has realized multi-component coupling routes to carbonyl compounds (see below).

Olefinic aldol reaction

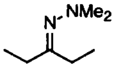
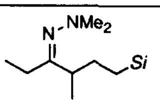
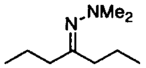
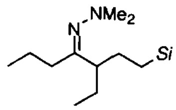
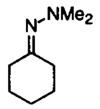
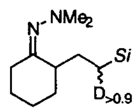
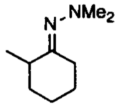
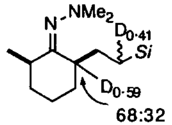
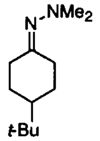
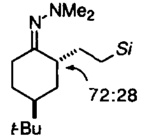
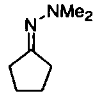
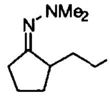


The initial reports dealt with an intermolecular addition of zincated ester, amide and hydrazone to cyclopropene,[1a] and an intramolecular cyclization of ester enolate to form proline derivatives.[2] Subsequently, the generality of the "olefinic aldol chemistry" was demonstrated in a more generalized form by the intermolecular addition of a zincated hydrazone to a simple olefin such as ethylene and styrene and by the intermolecular electrophilic trapping of the resulting hydrazone anion.[1b] Our key finding[1] for the successful "olefinic aldol reaction" is the use of a dummy ligand on the zinc atom (i.e., BuZn(II) cation),[3] with which the enolate species becomes more reactive than those with a BrZn(II) countercation.[4] A formally related (yet mechanistically different) coupling reaction of a zincated hydrazone with a vinyl Grignard reagent was recently achieved to realize a four-component synthesis of carbonyl compounds.[5] Not unexpectedly, however, unactivated olefins are rather unreactive electrophiles toward enolates,[6] and there is a pressing need to identify the factors that will enhance the reactivities of olefin toward metal enolates. We report herein that vinylsilanes[7] are highly reactive and regioselective to be used for the reaction with the zincated hydrazones.[8]



(1)

Table 1. Addition of zincated hydrazone 2 to vinylsilane.[a]

Entry	Hydrazone	CH_2=CHSi (Si =)	Conditions (temp, time)	Product	% Yield[b]
1		EtOMe$_2$Si	ether rt, 2 h		73
2		tBuOMe$_2$Si	ether rt, 6 h		85
3		EtOMe$_2$Si	DME rt, 4 d		97
4		EtOMe$_2$Si	THF rt, 4 d		30
5		Ph$_3$Si	DME rt, 9 d		58
6		Me$_3$Si	ether rt, 2 d		87
7		EtOMe$_2$Si	DME rt, 4 d		77
8		EtOMe$_2$Si	DME rt, 4 d		95[c,d]
9		EtOMe$_2$Si	DME rt, 4 d		73[e]
10		EtOMe$_2$Si	DME rt, 2 d		64[e]
11		EtOMe$_2$Si	DME rt, 4 d		45

[a] All reactions were carried out at 25-30 °C under nitrogen atmosphere. Deprotonation was carried out with *t*-BuLi except entries 12 and 14 (with BuLi and *s*-BuLi, respectively). [b] Isolated yield. [c] Reaction was quenched with deuterium oxide. [d] A 1:1 mixture of diastereomers as to the carbon bearing the deuterium atom. [e] The assignment of the diastereomers was made in analogy to the selectivity for *Si* = SiMe$_3$ (data not shown), which in turn was assigned by base-equilibration of the ketone obtained by oxidative removal of the hydrazone moiety.

The experimental procedure is straightforward (eq 1).[9] The mixed hydrazone/alkyl zinc reagent **1** was prepared as reported previously[1] by sequential treatment of a solution of lithiated hydrazone prepared by direct deprotonation of the corresponding hydrazone with *tert*-butyllithium or *sec*-butyllithium[10] followed by sequential addition of one equivalent each of $ZnBr_2$ and alkyllithium. The exact structures of the reagents **1** and **2** are currently unknown and those shown above represent only the formal stoichiometry. As examined for several cases related to the reaction in entry 1 of Table 1, the BrZn(II) enolate **1** is unreactive to vinylsilanes, and the BuZn(II) cation is superior to MeZn(II) and *tert*-BuZn(II) cations. The solvent plays an important role both in terms of the reaction rate and the product yield. The reaction is fastest in ether, slower in 1,2-dimethoxyethane (DME), the slowest in THF. For the vinylsilane part, we found a variety of vinylsilanes can be employed successfully, but also found significant effects of the substituents on the silicon atom.

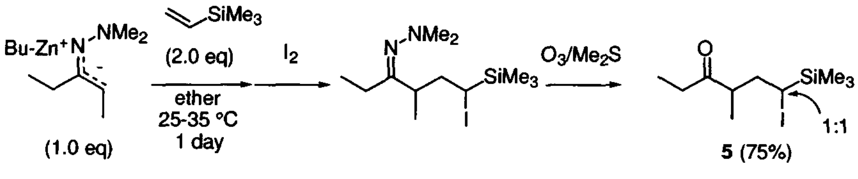
Trialkylvinylsilanes and triphenylvinylsilane are the least reactive, and alkoxyvinylsilanes are much more reactive, while (diethylamino)dimethylvinylsilane does not react smoothly with the zincated hydrazones. We have so far not been able to employ vinylsilanes bearing substituents on the vinyl moiety. The details are described below and the data summarized in Table 1.

For the reaction of the hydrazone derived from 3-pentanone (entries 1-6), we examined the basic reactivity profile. The reaction toward two equivalents of ethoxybis(trimethyl)vinylsilane in ether was very fast and completed in 2 h (entry 1). The yield remained moderate because of a C-silylating side reaction of the hydrazone anion by the alkoxysilane. This side reaction could be suppressed by the use of *tert*-butoxyvinylsilane at the expense of a slight decrease of the reaction rate (entry 2). DME was the best compromise of the reaction rate and the suppression of the side reaction. In DME, the reaction at 25-30 °C gave the 4-silylated hydrazone **4** (E = H) in 97% isolated yield (entry 3). The use of a methyl group as a dummy ligand on the zinc atom instead of the butyl group as in **2** slowed down the reaction to afford the adduct in 50% under the same conditions as in entry 1, and so did a *tert*-butyl dummy ligand (not listed in the table). The reaction in THF was clean but very slow (entry 4). As shown by comparison of entry 5 with entry 3, triphenylvinylsilane is less reactive than the alkoxysilane. The low reactivity of trialkylvinylsilane can be compensated by the use of ether as solvent as shown in entry 6 for the high-yield addition to trimethylvinylsilane.

In entries 7-11 of Table 1 are listed other examples of hydrazones. *N,N*-dimethylhydrazone acyclic and cyclic ketones which served as a nucleophile. The reaction, however, appears to be rather sensitive to structural effects. Thus, cyclopentanone hydrazone and substituted cyclohexanone hydrazones are less reactive and gave lower yield. We also found that *N,N*-diphenylhydrazones are unreactive (data not shown).

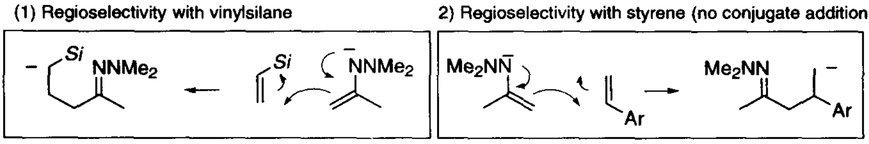
Deuterium quenching of the reaction of the cyclohexanone hydrazone adduct shown in entry 8 indicated that the intermediary 4-zinciohydrazone **3** retains its regiochemical integrity during the 4-day reaction time as indicated by >90% deuterium incorporation in the product **4** (E = D). There was no selectivity as to the chiral center generated in the deuteration. It is curious, however, that the stability of **3** is dependent on the subtle structural change as found in entry 9. While the alkylation of 2-methylcyclohexanone hydrazone resulted in complete regioselectivity at the 6-position,[11] D_2O-quenching of the intermediate resulted in deuterium incorporation at two positions, α- and γ from the hydrazone, which suggests that there occurred prototropic equilibration in the product **3**. Such prototropic equilibrium of γ-zincio hydrazone to its α-isomer was not observed in the olefinic aldol reaction with ethylene.[1b]

Trapping of the metal-carbon bond in intermediate **4** with a carbon electrophile has so far been unsuccessful. We may reason that the silicon group reduces the anionic reactivities of **4** through electronic and steric influences.[12] Electrophilic trapping did take place, however, when a highly electrophilic iodine was employed (eq 2), and the iodinated product **5** was isolated in good yield after removal of the hydrazone moiety, whose presence destabilized the γ-iodohydrazone intermediate. Elaboration of the silyl group will provide a variety of useful compounds based on the rich chemistry of organosilicon compounds.



(2)

In summary, we have shown that vinylsilane serves as a good acceptor of zincated hydrazone in the intermolecular olefinic aldol reaction. The regioselectivity of the addition reaction is such that a silicon-stabilized anion forms as the only product, which is opposite to the one observed in the addition of the same zincated hydrazone to styrene[1b] as shown in the equation below. Such a profile of *the regioselectivity does not conform to that expected for a simple "conjugate" addition of an anionic species to electron-deficient olefins*, and is consistent with the one expected for carbometalation of olefin with an alkyl metal reagent (where the metal is a soft atom).[13,14]



(1) Regioselectivity with vinylsilane

2) Regioselectivity with styrene (no conjugate addition)

References and Notes

1. (a) Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, *62*, 792-793; (b) Kubota, K.; Nakamura, E. *Angew. Chem.*, in press.
2. Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **1997**, *38*, 85-88; Lorthiois, E.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1997**, *38*, 89-92.
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4. While the intramolecular reaction in ref 2 took place with a BuZn(II) cation, we found that the BuZn(II) cation also serves well for intramolecular reactions (to be published).
5. Nakamura, E.; Kubota, K.; Sakata, G. *J. Am. Chem. Soc.* **1997**, *119*, 5457-5458.
6. Thus, the reaction of ethylene with zincated hydrazone at room temperature takes 4 days for completion, and that of styrene is halfway to completion even after 1 week.
7. For the ability of vinylsilane to accept nucleophiles, see: Seyferth, D.; Wada, T. *Inorg. Chem.* **1962**, *1*, 78-83. Stober, M.; Michael, K. W.; Speier, J. L. *J. Org. Chem.* **1967**, *32*, 2740-2744. Tamao, K.; Kanatani, R.; Kumada, M. *Tetrahedron Lett.* **1984**, *25*, 1913-1916.
8. For utility of hydrazones, see: Bergbreiter, D. E.; Momongan, M. in *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Eds.; Pergamon press: Oxford, **1991**; *Vol.* 2, pp. 503-526.
9. Procedure for the reactions in entry 6 and eq 2: To a solution of *N*,*N*-dimethyl hydrazone of 3-pentanone (1.60 mL, 10 mmol) in Et_2O (10 mL) was added *t*-BuLi (1.54 M in pentane, 6.6 mL, 10 mmol) at -70 °C, and the mixture was warmed to 0 °C. After 4 h, $ZnBr_2$ (0.338 M in Et_2O, 30 mL, 10 mmol) was added to the lithium aza-enolate. After 30 min, BuLi (1.55 M in hexane, 6.5 mL, 10 mmol) was added to the zinc reagent at -70 °C, and the mixture was warmed to 0 °C. After 30 min, trimethylvinylsilane (3.1 mL, 20 mmol) was added, and the mixture was warmed to room temperature. The reaction mixture was stirred for 2 days at room temperature and quenched with a 1/15 *M* phosphate buffer solution, 3-methyl-1-trimethylsilyl-4-hexanone *N*,*N*-dimethylhydrazone was obtained in 87% yield after chromatographic purification.

   Alternatively, when the mixture was quenched with I_2 (7.6 g, 30 mmol) in THF (30 mL) at 0 °C, an unstable iodinated hydrazone product formed and was isolated as the corresponding 2-(2-iodo-2-trimethylsilyl)ethylated ketone after oxidative removal of the hydrazone group. Thus, 5 min after the addition of I_2, the reaction mixture was cooled to -70 °C, MeOH (30 mL) was added, and O_3 was bubbled for 10 h. Me_2S (2.2 mL, 30 mmol) was added to the reaction mixture, and the mixture was warmed to room temperature. Extractive workup and purification on silica gel (30 g, eluent: 10% Et_2O in hexane) afforded 2.66 g of 1-iodo-3-methyl-1-trimethylsilyl-4-hexanone (75% yield) as a 3:2 mixture of diastereomers.
10. Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 4687-4690. Hosomi, A.; Araki, Y.; Sakurai, H. *J. Am. Chem. Soc.* **1982**, *104*, 2081-2083, and references cited therein.
11. This is due to regioselective lithiation known for a 2-methylcyclohexanone hydrazone (cf. ref. 8).
12. Electrophilic trapping was successful for the ethylene adducts (ref 1b), wherein the intermediate corresponding to **3** is a primary zinc reagent lacking the silyl group.
13. Nakamura, E.; Miyachi, Y.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1992**, *114*, 6686-6692. Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Chem. Soc., Faraday Trans.* **1994**, *29*, 1789-1798.
14. This work was supported by Grant-in-Aid for Scientific Research on Priority Areas (No. 283 , "Innovative Synthetic Reactions") from the Monbusho.

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