Carbometalation of Cyclopropene. Diastereoselective *cis*-Addition of Zincated Amides, Esters, and Hydrazones

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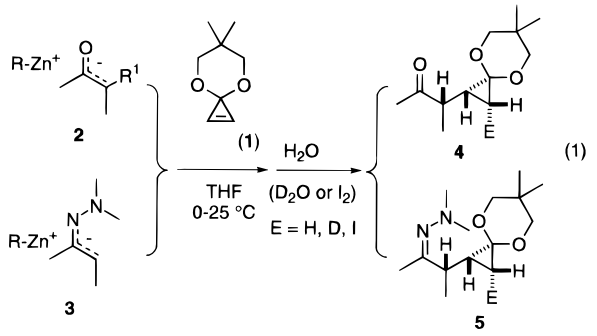
Anions of carbonyl and related compounds rarely add to isolated olefins, and hence, no information is currently available for basic issues such as reactivity profile and stereochemistry.[1,2] We report in this paper the first information on the stereochemical course of olefin carbometalation with an α-anion of amide, ester, and hydrazone, which is based on our new finding that these anions bearing a zinc(II) countercation (structures unknown and tentatively shown with structures **2** and **3**)[3] are reactive enough to add across the double bond of a cyclopropene acetal **1**.[4] This novel carbometalation reaction takes place in a *cis*-manner with a generally high level of 1,2-diastereoselectivity for the newly formed C−C bond (up to 100% ds). In the reaction of an optically active hydrazone, asymmetric induction takes place with a synthetically useful level of selectivity (87−98% ds) to provide a new synthetic entry to optically active carbonyl derivatives.

The addition of an α-anion of amides or lactams to the cyclopropene **1** takes place smoothly when the countercation is an alkylzinc cation bearing an alkyl dummy ligand[3a,5] (R in eq 1). These zinc reagents **2** and **3** were prepared by sequential treatment of a THF solution of a lithium enolate prepared by direct deprotonation with LDA or mesityllithium[6] (or from trimethylsilyl enol ether and BuLi when appropriate) with 1 equiv each of $ZnCl_2$[7] and BuLi at −78 °C. Thus, the reaction of **1** with 2 equiv



of the **2** derived from γ- and δ-lactams (Table 1, entries 1 and 2) took place smoothly at 0 °C to give the adduct in 82−100% yield with 97−98% 1,2-diastereoselectivity. Quenching the reaction of the δ-lactam with D_2O or iodine afforded an exclusively *cis*-substituted product **4** (E = D and I, entries 4 and 5). This observation indicates that the reaction took place in a *cis*-manner and that there is no exchange between the carbonyl α-proton (R^1 = H) and the zinc cation (E = Zn) during the reaction. The 1,2-diastereoselectivity did not change during the reaction course (2−18 h) and most likely reflects the kinetic preference of the addition reaction. When the amount of the enolate was reduced to 1 equiv of **1**, the reaction slowed down and afforded the desired adduct in 53−64% yield with recovery of **1**. Ester and ketone anions are not very reactive except for the zincated ($BuZn^+$) methyl isobutyrate (i.e., α,α-disubstituted ester), which reacted smoothly with **1** in good yield (entry 7). The reactions using a $ClZn^+$ countercation were either too slow to be useful for the γ-lactam or low yielding for others.

While ketone enolates do not react with **1**, we found that zincated hydrazones react smoothly with the cyclopropene. Thus, a ketone hydrazone was lithiated with *t*-BuLi, and 1 equiv each of $ZnCl_2$ and BuLi were added sequentially at 0 °C. The addition reaction of the resulting zinc reagent was complete in 10 min to 2 h at 0−25 °C, and 87−100% yields were routinely obtained by the use of 2 equiv of the reagent. With a 1:1 stoichiometry of the reactants, the consumption of **1** slowed down toward the end of the reaction period, and yields of 58−63% resulted.[3a] For the cyclohexanone hydrazone (entries 9 and 10), the reaction was 96% diastereoselective. The sense of the selectivity was found to be the same as that found for the cyclic lactam (entry 2). For linear substrates (entries 11−13), the diastereoselectivity is influenced by the nature of the lithium base (*t*-BuLi vs LDA) perhaps due to change of the stereochemistry of the hydrazone anion.[8] The observed diastereoselectivity may be interpreted with a flattened chair[5,9] six-centered transition-state model proposed for allylzincation of cyclopropene. However, with scant information on the structures of the reagent, it is premature to speculate on the detailed nature of the transition state of these reactions.[10]

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(1) Cf. Addition of transition metal enolates: Ito, Y.; Nakatsuka, M.; Kise, N.; Saegusa, T. *Tetrahedron Lett.* **1980**, *21*, 2873−2876.

(2) A rare example for main group metal enolates includes addition of a potassium enolate of an active methylene compound to 1-chlorobicyclo[4.1.0]hept-1-ene generated in situ: Arct, J.; Migaj, B. *Tetrahedron* **1980**, *36*, 953−956. Arct, J.; Migaj, B.; Leonczynski, A. *Tetrahedron* **1981**, *37*, 3689−3692.

(3) (a) The identity of the zinc enolate-like reagent is totally unknown as to whether the reagent bears 1 equiv each of "enolate" and butyl anion and whether the reactive species is a monomer or a dimer. The ca. 50% yield of the addition reaction under a 1:1 "enolate"/**1** stoichiometry suggests that the reactive species bears two "enolate" units. The nature of the bonding between the "enolate" unit and the zinc(II) cation is also unclear. (b) Ethylzinc enolate, which was found to be more reactive than the corresponding chlorozinc enolate, is considered to be an oxygen-bound enolate (Hansen,, M. M.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069−2074). (c) Among scant information, the zinc Reformatsky reagent is dimeric and may be viewed to possess a mixed *C*- and *O*-enolate character (Dekker, J.; Boersma, J.; van der Kerk, G. J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 553−555. Dekker, J.; Budzelaar, P. H. M.; Boersma, J.; van der Kerk, G. J. M.; Spek, A. L. *Organometallics* **1984**, *3*, 1403−1407), and lithiated ketone hydrazone has an aza-π-allylic structure (Collum, D. B.; Kahne, D.; Gut, S. A.; DePue, R. T.; Mohamadi, F.; Wanat, R. A.; Clardy, J.; Duyne, G. V. *J. Am. Chem. Soc.* **1984**, *106*, 4865−4869. Wanat, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **1985**, *107*, 2078−2082. Enders, D.; Bachstadter, G.; Kremer, K. A. M.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1522−1524).

(4) Nakamura, E. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 935−945. Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron*, **1992** *48*, 2045−2057.

(5) Kubota, K.; Nakamura, M.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1993**, *115*, 5867−5868. Nakamura, E. *Pure Appl. Chem.* **1996**, **68**, 123−130.

(6) Seebach, D.; Weller, T.; Protschuk, G.; Beck, A. K.; Hoekstra, M. S. *Helv. Chim. Acta* **1981**, *64*, 716−735.

(7) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310−3324.

(8) An α-anion of a hydrazone of aliphatic ketones may exist in its *E*-geometry (as viewed as an enolate, see ref 3): Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 5654−5659.

(9) Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1789−1798. Nakamura, M.; Nakamura, E. Computational Studies on Diastereo- and Enantioselectivities of Allylmetalation of Cyclopropenone Acetals. In Electronic Conference Heterocyclic Chemistry; Rzepa, H. S., Snyder, J., Leach, C., Eds.; Royal Society of Chemistry: London, 1997; in press (ISBN 0-85404-894-4).

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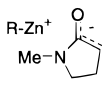
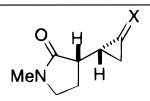
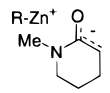
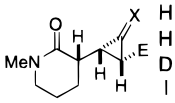
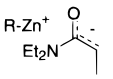
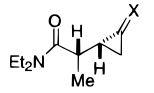
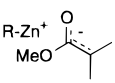
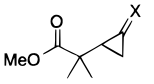
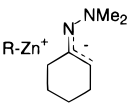
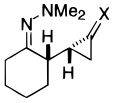
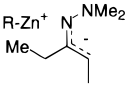
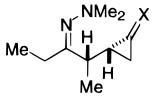
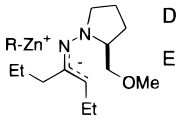
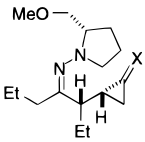
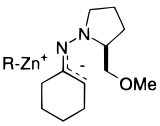
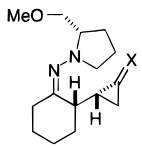
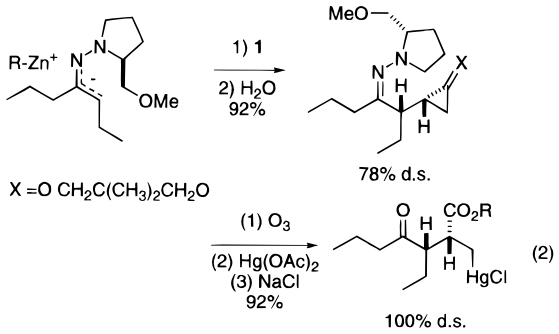
Table 1. Addition of Zincated Carbonyl Compound to Cyclopropenone Acetal 1[a]

entry	zinc reagent	method[b]	eq[c]	product	yield[d] (%)	d.s.[e] (%)
1		A	2		82	98
2		B	2		E H 100	97
3		B	1		H 53	97
4		B	1		D 53[f]	97
5		B	1		I 55[g]	97
6		C	1		64	87
7		C	2		97	–
8		C	1		58	–
9		D	2		100	96
10		D	1		63	96
11		A	2		96	96
12		D	2		96	89
13		D	1		58	83
14		D	2		92	100 (78)[h]
15		E	2		79	100 (87)[h]
16		D	2		87	96 (98)[h]

[a] All reactions (0.2−20 mmol) were carried out at 0 °C for 0.2−18 h, except in entries 7, 8, and 15 (at rt). Y = $-OCH_2C(CH_3)_2CH_2O-$. Stereochemistry of the product was determined by X-ray crystallographic analysis[14] (entry 2), chemical correlation shown in Supporting Information (entry 14), and analogy based on transition state analysis (others). R is a butyl group, except in entry 15 where it is Cl. [b] Zinc reagent preparation: (Method A) deprotonation with LDA, followed by sequential treatment with 1 equiv each of $ZnCl_2$ and BuLi; (Method B) same as method A except for deprotonation with mesityllithium; (Method C) same as method A with the lithium enolate prepared by BuLi treatment of the corresponding ketene silyl acetal or ketene silyl aminal; (Method D) same as method A except for deprotonation with *tert*-BuLi; (Method E) same as method D except that the final BuLi treatment was omitted. [c] The amount of zinc reagent against **1**. [d] Based on pure isolated material. [e] The numbers refer to the diastereoselectivity for the newly formed C−C bond. [f] Quenched with D_2O. [g] Quenched with I_2. [h] The numbers refer to the diastereoselectivity for the cyclopropane chirality relative to the chiral hydrazone chirality.

Finally, the reaction of optically active hydrazones provided access to optically active ketone derivatives.[11] Thus, the zincated 4-heptanone SAMP hydrazone reacted with 100% 1,2-diastereoselectivity and 78% stereoselectivity as to the chirality induction from the SAMP hydrazone (entry 14).[12] The latter selectivity improved to 87% by the use of the ZnCl reagent at the expense of slight decrease of reactivity and yield (entry 15). Chemical correlation established the indicated absolute stereochemistry for the newly form chiral centers. The sense of the chirality induction on the hydrazone α-chiral center is the same as the one previously proposed for alkylation and allylation of SAMP/RAMP hydrazone.[11] The reaction of cyclohexanone SAMP hydrazone afforded a 94:2:4 mixture of diastereomers (entry 16). The 1,2-diastereoselectivity was 96% as determined after removal of the SAMP group, and therefore, the SAMP-induced stereoselectivity was 98%.[13]

The chemistry available specifically for the cyclopropenone acetal is also noteworthy. For instance, conversion of the adduct in entry 15 of Table 1 to an optically active functionalized γ-keto ester was achieved by the three-stage procedure shown in eq 2, wherein the cyclopropenone acetal serves formally as a "reversed polarity" Michael acceptor of an enolate anion. Both the removal of the hydrazone moiety and the cyclopropane ring cleavage were achieved without loss of the relative stereochemistry for the two chiral centers in the product as examined for each step. The mercury group in the final ketoester product can be readily removed (cf. Supporting Information) under reductive conditions.



In summary, the present studies elucidated for the first time the basic stereochemical issues of olefin carbometalation with metalated carbonyl derivatives, concerning the diastereoselectivity as to the olefinic partner, the newly formed C−C bond, and the stereochemistry relative to a neighboring chiral center. These findings suggest new possibilities of enolate chemistry, which will merit further studies from synthetic and mechanistic points of view.

Acknowledgment. We thank H. Mukai for some experimental data and I. Iikura for the X-ray crystal structure analysis. A research grant from the Ministry of Education, Science, Sports and Culture is gratefully acknowledged. K.K. thanks JSPS for predoctoral fellowship.

Supporting Information Available: Experimental data for Table 1 and structure determination (21 pages).

JO962140Q

(10) **Experimental Procedure.** The *N*,*N*-dimethylhydrazone of 3-pentanone (3.1 mL, 20 mmol) was added to a solution (0 °C) of LDA [from BuLi (1.58 M in hexane, 21 mmol) and diisopropylamine (2.75 mL, 21 mmol) in THF (21 mL)]. Freshly fused $ZnCl_2$ in THF (1.01 M, 20 mL, 20 mmol, at 0 °C) and then BuLi (1.58 M in hexane, 12.6 mL, 20 mmol, at −70 °C) were added. After 30 min at 0 °C, **1** (1.4 mL, 10 mmol) was added, and the mixture was stirred for 10 min. A 1/15 N phosphate buffer solution was added, and after extractive workup, an oily crude product (3.28 g) was obtained. Purification on silica gel (10% and then 20% EtOAc in hexane) afforded the desired adduct (2.52 g, 94%) as a 94:6 mixture of diastereomers.

(11) Enders, D. *Asymmetric Synthesis*; Morrison, J. M., Ed.; Academic Press: New York, 1984; Vol. 3, pp 275−339.

(12) For the determination of stereochemistry, see footnote a in Table 1.

(13) Attempts to achieve enantioselective carbometalation with enolates bearing a chiral metal ligand so far failed (low ee's). Cf.: Nakamura, M.; Arai, M.; Nakamura, E. *J. Am. Chem. Soc.* **1995**, *117*, 1179−1180. Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489−8490.

(14) The author has deposited atomic coordinates for (1′*R**,2*S**)-2-(3-aza-3-methyl-2-oxocyclohexyl)cyclopropanone 1,3-(2,2-dimethylpropanediyl acetal) with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.