Bull. Chem. Soc. Jpn., 73, 999—1014 (2000)

1,4-Addition of Diorganozincs to α,β-Unsaturated Ketones Catalyzed by a Copper(I)–Sulfonamide Combined System

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(Received November 8, 1999)

A mixture of CuCN and *N*-benzylbenzenesulfonamide catalyzes the 1,4-addition of dialkylzincs or diarylzincs (Cu : Zn = 1 : 200 to 1 : 10000) to α,β-unsaturated ketones to give, after aqueous workup, the corresponding β-substituted ketones in nearly quantitative yields. A range of cyclic enones having *s-cis* or *s-trans* geometries as well as conformationally flexible acyclic enones are usable as substrates. The ethyl group migrates more readily than the methyl and phenyl groups. CuOTf, CuO-*t*-C_4H_9, and mesitylcopper can be used in place of CuCN. The in situ-formed alkylzinc enolate, prior to aqueous workup, further undergoes an aldol reaction with aldehydes or Pd(0)-assisted coupling with allyl acetate, resulting in regio-controlled, vicinal carbacondensation products. A catalytic cycle is proposed on the basis of a kinetic study and a structural analysis of the zinc enolate product by NMR and molecular weight measurements.

1,4-Addition of organometallic reagents to α,β-unsaturated ketones is an essential method for the specific introduction of a hydrocarbon unit to the position β to a carbonyl function.[1] Furthermore, the eminent nucleophilicity of the metal enolate intermediate allows for reactions with various electrophiles, effecting the α,β-vicinal structural modification of enones and providing a powerful tool for the synthesis of complex organic molecules.[2] Organometallic compounds, however, often react with enones in both a 1,2 and 1,4 manner (Fig. 1). In addition, metal enolates may further react with a coexisting enones to give 1,2- or 1,4-addition products. Successive conjugate addition forms oligomers or polymers. Thus the development of a 1,4-selective reaction without such side products is highly desirable.

Among various organometallic compounds, homocuprates, heterocuprates, and higher-order cuprates are now the most widely used as stoichiometric reagents with a high 1,4 selectivity.[3] Their reaction systems are not simple, however. The presence of two metals in the Li/Cu or Mg/Cu system causes considerable complexity in the subsequent reaction of enolates with electrophiles, hampering the synthetic attractiveness. The utility is greatly enhanced if the 1,4-addition sequence is made catalytic in such a way as to form a well-defined, single-metal enolate. Efforts have been made along this line by the combination of a Mn,[4] Co,[5] Ni,[6] Pd,[7] Cu,[3,6f,8,9] or Zn catalyst[10] with organometallic compounds containing Li, Na, Mg, B, Al, Zn, Sn, Ti, Zr, and Mn atoms. In most cases, however, these reactions suffer from low chemical yield, low generality, or the necessity of using chlorotrimethylsilane and HMPA as additives.[6b,8f,8h,8i,9] We have therefore initiated a study that returns to the starting point of Kharasch in 1941,[11] with the objective of finding a new method of catalysis to extend the scope of the 1,4-addition process. This paper describes the current stage of our investigation.[12]

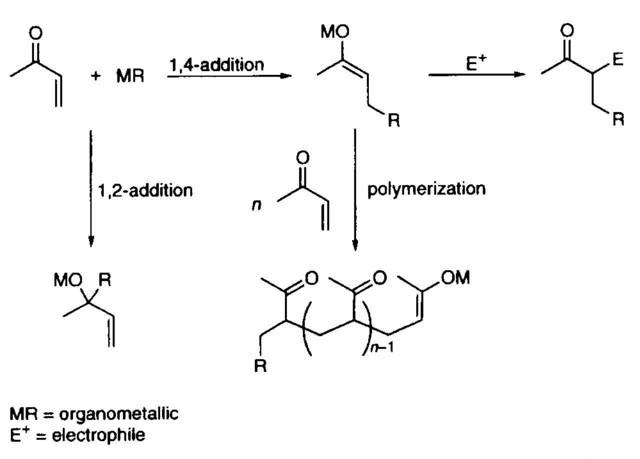


Fig. 1. Reaction of organometallic compounds and α,β-unsaturated ketones.

Results and Discussion

General Consideration. Our basic scenario is illustrated in Fig. 2, which simplifies the actual reaction occurring via more aggregated clusters. We assume that the 1,4-addition of an organometallic compound M^1R to an enone occurs in the presence of a small amount of M^2X, normally a transition metal salt. When M^1R and M^2X are mixed in solution, a metathetic anion exchange takes place under the control of the metal redox potentials, giving M^1X and M^2R. M^2R may act as a catalyst of the 1,4-addition of M^1R to the enone. However, M^2R often interacts with M^1X to form a mixed-metal cluster compound, symbolized as M^1XM^2R, where M^1 and M^2 are linked by an organic or inorganic anion X, and this complex would then catalyze the 1,4-addition. In order to accomplish this 1,4-addition with a high turnover

$$M^1R + M^2X \longrightarrow M^1X + M^2R$$

$$M^1X + M^2R \longrightarrow M^1XM^2R$$

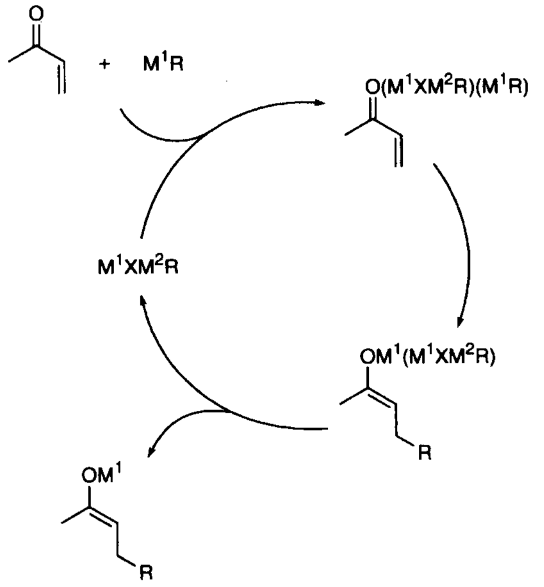


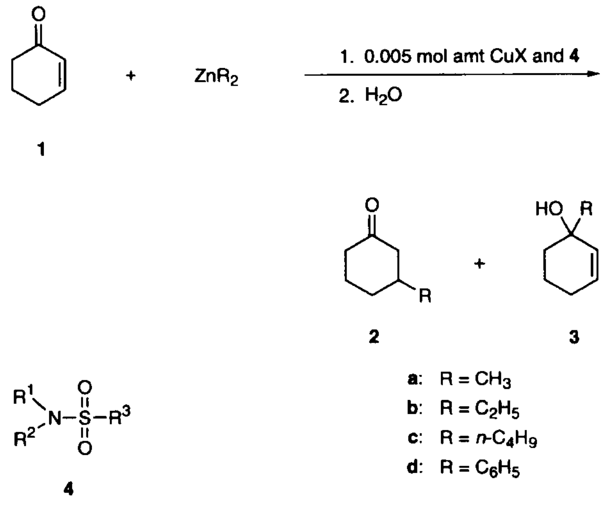
Fig. 2. 1,4-Addition of organometallic compound M^1R to an α,β-unsaturated ketone.

efficiency, inhibition of the catalytic cycle by the substrate, product, alkylating reagent, or other metallic species must be avoided. Therefore, M^1XM^2R should be readily detached from the initially formed M^1M^2 mixed-metal enolate. The resulting M^1 enolate is expected to selfassociate to form a stable aggregate, thereby preventing product inhibition of the catalytic cycle. Thus M^1, M^2, and X must be chosen suitably so as to satisfy the above requirements for the catalytic 1,4-addition.

We selected ZnR_2 as an alkyl or aryl donor and a Cu(I) compound as a catalyst precursor for the following reasons:[13] (1) diorganozincs are inert toward enones in hydrocarbon or ethereal solvents, eliminating the possible background reaction;[14] (2) the alkylzinc enolate would be stabilized by forming a dimer or a tetramer;[15] (3) empirically, Cu has taken a prominent role in conjugate addition; the Li/Cu or Mg/Cu bimetallic system shows excellent 1,4 selectivity in the stoichiometric reaction with α,β-unsaturated carbonyl compounds;[3] and (4) the oxidation potential of Zn is much higher than that of Cu.[16]

Copper-Catalyzed 1,4-Addition. The reaction of diethylzinc and 2-cyclohexenone (**1**) was chosen as a model to investigate the catalytic effects of CuX, including CuCN, CuOTf, CuO-*t*-C_4H_9, CuMes (Mes = mesityl), CuCl, CuBr, and CuI. The reaction was run on a 3.1-mmol scale in toluene at 0 °C for 1 h in the presence of a 0.005 molar amount (mol amt) of CuX. The concentrations of enone, diethylzinc, and CuX were fixed at 500, 500, and 2.5 mM (1 M = 1 mol dm^{-3}), respectively. The chemical yields of 3-ethylcyclohexanone (**2b**) and 1-ethyl-2-cyclohexen-1-ol (**3b**) were determined by GC after aqueous workup (Chart 1). Unfortunately, the above-described Cu(I) compounds were ineffective as catalyst precursors. Reaction at 0 °C for 1 h gave the adduct **2b** in < 2% yield in all cases.[17]

Apparently, initially formed ethylcopper did not catalyze the reaction of diethylzinc and 2-cyclohexenone. Furthermore, anion X in these Cu compounds did not appear to act as a suitable bridging anion in the catalytic cycle shown in Fig. 2 (M^1 = Zn, M^2 = Cu). This failure led us to test for a sulfonamide, an entirely different organic anion, which might serve as a three-atom, charge-alternating spacer bridging over Zn and Cu.[18] In fact, the effects of sulfonamides of type **4** were remarkable, as seen in Fig. 3. Thus, when enone **1** and diethylzinc were mixed in toluene containing a 0.005 mol amt of CuCN and *N*-benzylbenzenesulfonamide (**4a**) for 1 h at 0 °C, the reaction took place rapidly to give the 1,4-addition product **2b** in > 99% yield. The reaction was almost complete within 10 min at 0 °C or after 1 h even at −40 °C. Table 1 summarizes the results obtained under various reaction conditions. The reaction proceeded satisfactorily even with a 0.0001 mol amt of CuCN and a 0.001 mol amt of **4a** (Entry 7). Thus the turnover number (TON) defined as moles of product per mol of catalyst was 2600. This reaction was also rapid, with the initial turnover frequency (TOF) being 1200 h^{-1} (vide infra, kinetic study). Increasing the electronegativity of the nitrogen substituent of **4** somewhat decreased the catalytic reactivity (Entries 16 and 17). N-monosubstituted sulfonamides worked much



a: R^1 = H, R^2 = $C_6H_5CH_2$, R^3 = C_6H_5
b: R^1 = H, R^2 = $C_6H_5CH_2$, R^3 = CH_3
c: R^1 = H, R^2 = $C_6H_5CH_2$, R^3 = CF_3
d: R^1 = H, R^2 = CH_3, R^3 = C_6H_5
e: R^1 = H, R^2 = *i*-C_3H_7, R^3 = C_6H_5
f: R^1 = H, R^2 = *t*-C_4H_9, R^3 = C_6H_5
g: R^1 = H, R^2 = R^3 = C_6H_5
h: R^1 = R^2 = H, R^3 = C_6H_5
i: R^1 = R^2 = $C_6H_5CH_2$, R^3 = C_6H_5

Chart 1.

Table 1. Catalytic 1,4-Addition of Diethylzinc to 2-Cyclohexenone (**1**) in the Presence of CuX and **4**[a)]

	Catalyst system			Concentration/mM				Temp	Time	Yield of **2b**[b)]
Entry	CuX	Additive	Solvent	**1**	$Zn(C_2H_5)_2$	CuX	**4**	°C	h	%
1	CuCN	—	Toluene	500	500	2.5	0	0	1	< 2
2	CuCN	$C_6H_5CH_2NHSO_2C_6H_5$ (**4a**)	Toluene	500	500	2.5	2.5	0	1	> 99
3	CuCN	**4a**	Toluene	500[c)]	500	2.5	2.5	0	1	90[d)]
4	CuCN	**4a**	Toluene	500	500	2.5	2.5	0	0.17	99
5	CuCN	**4a**	Toluene	500	500	2.5	2.5	−40	1	97
6	CuCN	**4a**	Toluene	500	500	2.5	2.5	25	1	98
7	CuCN	**4a**	Toluene	500	500	0.05	0.5	0	48	90
8	CuCN	**4a**	Toluene	500	500	0.05	0.05	0	48	26
9	CuCN	**4a**	Toluene	2000	2000	10	10	0	2	98
10	CuCN	**4a**	Toluene	50	50	0.25	0.25	0	48	84
11	CuCN	**4a**	Ether	500	500	2.5	2.5	0	1	> 99
12	CuCN	**4a**	THF	500	500	2.5	2.5	0	1	8.8
13	CuCN	**4a**	CH_3CN	500	500	2.5	2.5	0	1	31
14	CuCN	**4a**	DMF	500	500	2.5	2.5	0	1	7.2
15	CuCN	**4a**	CH_2Cl_2	500	500	2.5	2.5	0	1	43
16	CuCN	$C_6H_5CH_2NHSO_2CH_3$ (**4b**)	Toluene	500	500	2.5	2.5	0	1	> 99
17	CuCN	$C_6H_5CH_2NHSO_2CF_3$ (**4c**)	Toluene	500	500	2.5	2.5	0	1	42
18	CuCN	$CH_3NHSO_2C_6H_5$ (**4d**)	Toluene	500	500	2.5	2.5	0	1	85
19	CuCN	$i\text{-}C_3H_7NHSO_2C_6H_5$ (**4e**)	Toluene	500	500	2.5	2.5	0	1	85
20	CuCN	$i\text{-}C_4H_9NHSO_2C_6H_5$ (**4f**)	Toluene	500	500	2.5	2.5	0	1	26
21	CuCN	$C_6H_5NHSO_2C_6H_5$ (**4g**)	Toluene	500	500	2.5	2.5	0	1	85
22	CuCN	$NH_2SO_2C_6H_5$ (**4h**)	Toluene	500	500	2.5	2.5	0	1	67
23	CuCN	$(C_6H_5CH_2)_2NSO_2C_6H_5$ (**4i**)	Toluene	500	500	2.5	2.5	0	1	< 2
24	CuOTf	—	Toluene	500	500	2.5	0	0	1	< 2
25	CuOTf	**4a**	Toluene	500	500	2.5	2.5	0	1	> 99
26	CuOTf	**4a**	Toluene	500	500	2.5	2.5	0	0.17	81
27	$CuO\text{-}t\text{-}C_4H_9$	—	Toluene	500	500	2.5	0	0	1	< 2
28	$CuO\text{-}t\text{-}C_4H_9$	**4a**	Toluene	500	500	2.5	2.5	0	1	> 99
29	$CuO\text{-}t\text{-}C_4H_9$	**4a**	Toluene	500	500	2.5	2.5	0	0.17	88
30	CuMes	—	Toluene	500	500	2.5	0	0	1	< 2
31	CuMes	**4a**	Toluene	500	500	2.5	2.5	0	1	> 99
32	CuMes	**4a**	Toluene	500[c)]	500	2.5	2.5	0	1	90[d)]
33	CuMes	**4a**	Toluene	500	500	2.5	2.5	0	0.17	92
34	CuMes	**4b**	Toluene	500	500	2.5	2.5	0	1	98
35	CuMes	**4c**	Toluene	500	500	2.5	2.5	0	1	89
36	CuCl	—	Toluene	500	500	2.5	0	0	1	< 2
37	CuCl	**4a**	Toluene	500	500	2.5	2.5	0	1	21
38	CuBr	—	Toluene	500	500	2.5	0	0	1	< 2
39	CuBr	**4a**	Toluene	500	500	2.5	2.5	0	1	96
40	CuI	—	Toluene	500	500	2.5	0	0	1	< 2
41	CuI	**4a**	Toluene	500	500	2.5	2.5	0	1	45

a) Unless otherwise noted, the reaction was carried out on a 3.1 mmol scale. b) Determined by GC analysis. c) Reaction was carried out on a 0.21 mol scale. d) Isolated yield.

better than N-unsubstituted compounds, but a bulky group on the nitrogen atom considerably lowered the reaction rate (Entries 18—22). *N*,*N*-Dibenzylbenzenesulfonamide was totally ineffective (Entry 23). Attempted reactions with other organic acids such as $HOSO_2C_6H_5$, $HOCOC_6H_5$, and $HOPO(C_6H_5)_2$ or amides including $C_6H_5CH_2NHCOC_6H_5$ and $C_6H_5CH_2NHPO(C_6H_5)_2$ did not meet with success. The highest yield of **2b** was 11% obtained with $HOSO_2C_6H_5$ and $C_6H_5CH_2NHPO(C_6H_5)_2$. The substrate concentration could be increased from 0.5 M (Entries 2—7) to 2 M without any problem (Entry 9). Toluene and ether were the solvents of choice (Entries 2 and 11), although the initial rate with ether was ca. 70% of that with toluene. Use of polar solvents such as tetrahydrofuran, acetonitrile, and *N*,*N*-dimethylformamide retarded the reaction (Entries 12—14). The reaction in dichloromethane was slow.

Other Cu(I) compounds, such as CuOTf, $CuO\text{-}t\text{-}C_4H_9$, and CuMes, also acted efficiently as catalyst precursors in combination with **4a** (Entries 24—35). CuBr could be used, but CuCl and CuI were much less effective for some reason (Entries 36—41).

Generality. The reliability of this new catalytic system was affirmed by the results of large-scale reactions. The reaction of 20.2 g of enone **1** and 26.0 g of diethylzinc (1 : 1 molar ratio) in the presence of 99 mg (0.005 mol amt) of CuCN and 272 mg (0.005 mol amt) of **4a** gave, after aqueous

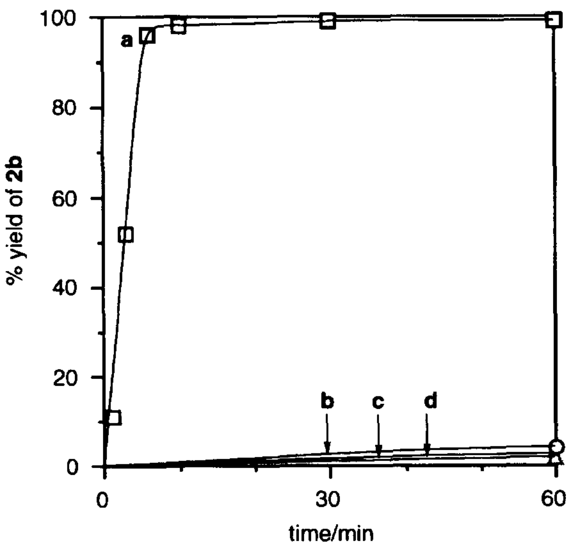
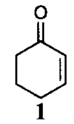
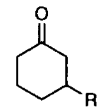
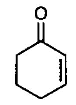
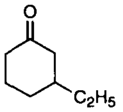
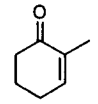
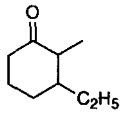
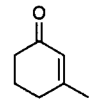
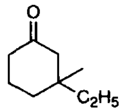
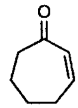
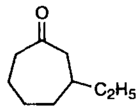
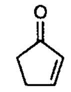
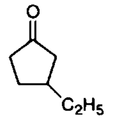
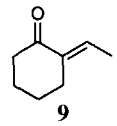
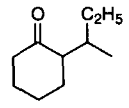
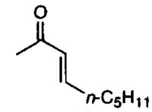
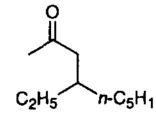


Fig. 3. Time/conversion curves in 1,4-addition of $\mathrm{Zn(C_2H_5)_2}$ to 2-cyclohexenone (**1**) in toluene at 0 °C with [**1**] = [$\mathrm{Zn(C_2H_5)_2}$] = 500 mM. **a**: 0.005 mol amt of CuCN and $\mathrm{C_6H_5CH_2NHSO_2C_6H_5}$ (**4a**). **b**: 0.005 mol amt of CuCN. **c**: 0.005 mol amt of **4a**. **d**: no additive.

workup and distillation, 23.8 g (90% yield) of 3-ethylcyclohexanone (**2b**) (Table 1, Entry 3). The use of CuMes instead of CuCN led to a similar result (Entry 32).

The catalytic 1,4-addition method has been applied to a range of organozincs and enone substrates, as illustrated in Table 2. Dimethyl-, diethyl-, and other simple dialkylzincs as well as diarylzincs can be used as hydrocarbon donors. In the presence of CuCN and **4a**, the methylation and phenylation of **1** proceeded ca. 30 times slower than the ethylation. The migratory aptitude of the phenyl group became greater with the CuMes/**4a** combined system, with the relative initial rate of methylation, phenylation, and ethylation being 1 : 30 : 90. Due to the lower reactivity of dimethylzinc and the facile exchange of Zn-alkyl groups during reaction, when the alkylation was conducted using dimethylzinc, diethylzinc, and **1** in a 0.5 : 0.5 : 1 molar ratio, 3-ethylcyclohexanone (**2b**) and 3-methylcyclohexanone (**2a**) were obtained in 86 and < 10% yield, respectively.

Table 2. Copper-Catalyzed 1,4-Addition of Organozinc Compounds to Enones$^{a)}$

Entry	Enone	$\mathrm{ZnR_2}$	1,4-Addition product Structure	 Yield/%$^{b)}$
1	 **1**	$\mathrm{Zn(CH_3)_2}$$^{c,d)}$		90
2		$\mathrm{Zn(CH_3)_2}$$^{e,f,g)}$		80
3		$\mathrm{Zn(C_2H_5)_2}$$^{c)}$		> 99
4		$\mathrm{Zn(\mathit{n}\text{-}C_4H_9)_2}$$^{e,g)}$		95
5		$\mathrm{Zn(C_6H_5)_2}$$^{e)}$		92
6	 **1**	$\mathrm{Zn(C_2H_5)_2}$+ $\mathrm{Zn(CH_3)_2}$ (1 : 1)$^{e,g,h)}$		86$^{i)}$
7	 **5**	$\mathrm{Zn(C_2H_5)_2}$$^{e,f,j)}$		50$^{k)}$
8	 **6**	$\mathrm{Zn(C_2H_5)_2}$$^{e,f,j)}$		< 2
9	 **7**	$\mathrm{Zn(C_2H_5)_2}$$^{e)}$		99
10	 **8**	$\mathrm{Zn(C_2H_5)_2}$$^{e)}$		28
11	 **9**	$\mathrm{Zn(C_2H_5)_2}$$^{d,e)}$		90$^{l)}$
12	 **10**	$\mathrm{Zn(C_2H_5)_2}$$^{c,m)}$		> 99

a) Reaction was carried out in toluene at 0 °C for 1 h using enone (500 mM) and $\mathrm{ZnR_2}$ (500 mM). b) Determined by GC analysis. c) CuCN and **4a** were used in 0.005 mol amt. d) Reaction time was 6 h. e) CuMes and **4a** were used in 0.02 mol amt. f) At 25 °C. g) Reaction time was 3 h. h) [$\mathrm{Zn(C_2H_5)_2}$] and [$\mathrm{Zn(CH_3)_2}$] = 250 mM. i) 3-Methylcyclohexanone was obtained in < 10% yield. j) Reaction time was 120 h. k) Diastereomer ratio was 1.4 : 1. l) Diastereomer ratio was 3.3 : 1. m) Reaction time was 20 h.

2-Cyclohexenone (**1**) and 2-cycloheptenone (**7**) with an *s-trans* C=C–C=O system were converted to the desired 1,4-addition products in high yields. However, with 2-cyclopentenone (**8**), a lower analogue, considerable polymerization occurred. (*E*)-2-Ethylidenecyclohexanone (**9**) with an *s-cis* geometry reacted with diethylzinc to give 2-*s*-butylcyclohexanone. (*E*)-3-Nonen-2-one (**10**), a flexible enone, was also usable. The reactivity in the ethylation increased in the order of *s-cis*, flexible, and *s-trans* enones; the relative initial rate of the reaction of **9**, **10**, and **1** catalyzed by a CuCN/**4a** system at 0 °C was 1 : 4 : 80. This alkylation reaction is sensitive toward the steric environments of enones. The yield of the 1,4-addition product of 2-methyl-2-cyclohexenone (**5**), an α-substituted enone, remained only 50%. β,β-Disubstituted enones such as isophorone and 3-methyl-2-cyclohexenone (**6**) were inactive. α,β-Unsaturated carboxylic esters were not alkylated under the standard conditions.

Three-Component Coupling. The reaction of stoichiometric amounts of a diorganozinc and enone, promoted by very small quantities of the Cu and sulfonamide additives, allows for clean generation of alkylzinc enolates. The enolates, formed by regiospecific 1,4-addition, have a high potential for further carbon–carbon bond formation by reaction with appropriate carbon electrophiles (Fig. 1, M = ZnR).^{2} The tandem condensation is directly achievable, without the isolation of any covalent organic derivatives in one pot using either a preformed enolate or an in situ-generated species.[8k,10,19]

The aldol reaction of the cyclic enolates, **11** and **12**, with aldehydes forms the β-hydroxy ketones having three consecutive stereogenic centers. In the present study, under kinetic control, only one or two stereoisomers among four possible diastereomers were formed. Thus when the reaction of cyclohexanecarbaldehyde and **11**, generated from **1** and diethylzinc in the presence of a 0.02 mol amt of CuMes and **4a**, was carried out at −78 °C in toluene, only *trans,threo*-**13a** was obtained in > 95% yield (Chart 2). In a like manner, benzaldehyde gave an 81 : 19 mixture of *trans,threo*-**13b** and *trans,erythro*-**13b** in 83% combined yield. The predominant formation of the *trans,threo* isomers can be understood in terms of a Zimmerman–Traxler transition-state model **14**.[20] When the aldol reaction was performed at 0 °C, however, the enolate equilibration occurred to afford α' aldol products in 45% yield in addition to a ca. 1 : 1 mixture of *trans,threo*- and *trans,erythro*-**13b** in < 10% yield. In addition, 2-benzylidene-5-ethylcyclohexanone and 2,6-dibenzylidene-3-ethylcyclohexanone, dehydration products, were isolated in 15 and 5% yield, respectively.

The cyclopentanone enolate behaves differently from the cyclohexanone enolate.[21] For instance, the reaction of 2-cyclopentenone (**8**) and diethylzinc aided with CuMes and **4a** under the standard catalytic conditions afforded the desired 1,4-addition product in only 28% yield (Table 2). The 1,4-addition of diethylzinc occurred efficiently as expected, but the ethylzinc enolate **12** reacted with coexisting **8** to form polymeric products. In fact, when the 1,4-addition reaction catalyzed by CuMes and **4a** was performed at 0 °C in the presence of cyclohexanecarbaldehyde, the in situ-generated enolate **12** was effectively trapped with the aldehyde to give only *trans,threo*-**15a** in > 95% yield. The reaction in the presence of benzaldehyde gave a 55 : 45 mixture of *trans,threo*-**15b** and *trans,erythro*-**15b** in a 91% combined yield. No such improvement was observed in the reaction with a CuCN/**4a** combined catalyst system;[22] the yield of the aldol was at most 53% with cyclohexanecarbaldehyde or 35% with benzaldehyde. Polymeric materials were formed in considerable amounts.

Furthermore, the alkylzinc enolates can be allylated in a stereoselective manner.[23] For example, ethylzinc enolate **11**, preformed by using a 0.02 mol amt of CuMes and **4a**, reacted with allyl acetate at 0 °C in the presence of a 0.02 mol amt of Pd[P(C_6H_5)$_3$]$_4$, giving after 2 h a 90 : 10 mixture of *trans*- and *cis*-2,3-disubstituted cyclohexanone **16** in 86% isolated yield. When all the ingredients were mixed together at the beginning, **16** was obtained with the same diastereo-

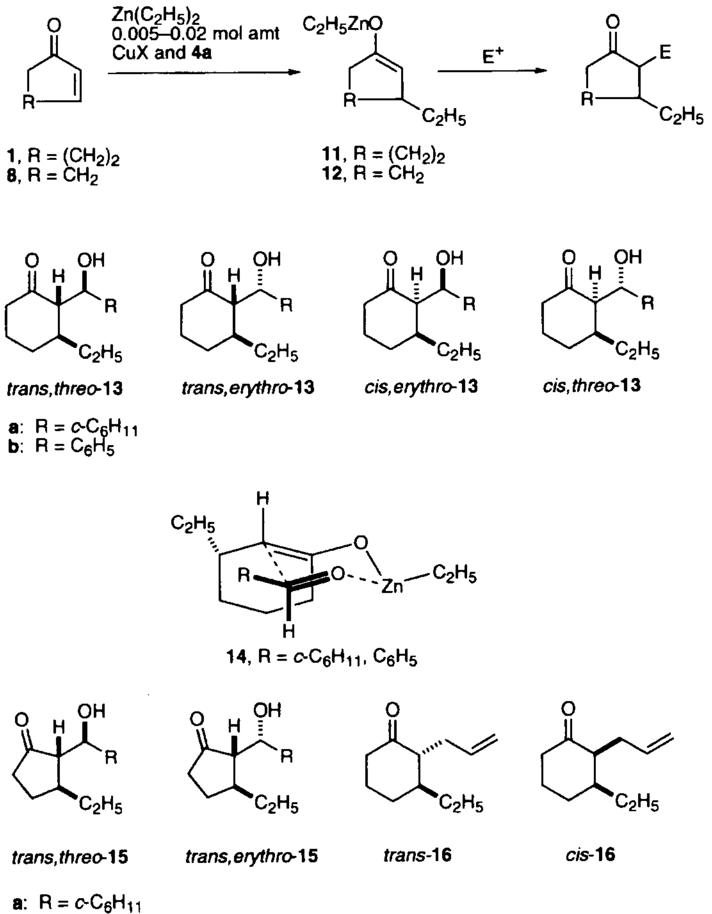


Chart 2.

selectivity in 90% yield. The CuCN/**4a** combined system was also usable. The tandem reaction using the preformed enolate **11** gave *trans*- and *cis*-**16** in an 88 : 12 ratio and in 90% yield, while a one-pot process using enone **1**, diethylzinc, allyl acetate, and Pd catalyst produced **16** as a 91 : 9 diastereomer mixture in 80% yield. Although the CuCN/**4a** catalyst system was more reactive than the CuMes/**4a** combination (Table 1), the three-component coupling reaction is better attained with the latter.[22]

Structure of the Zn Enolate. The catalytic 1,4-addition of diorganozincs to α,β-unsaturated ketones generates the corresponding zinc enolates. ^{1}H-^{1}H COSY NMR and phase-sensitive ^{13}C-^{1}H correlation NMR experiments (Fig. 4) have revealed that the product obtained from 2-cyclohexenone (**1**)

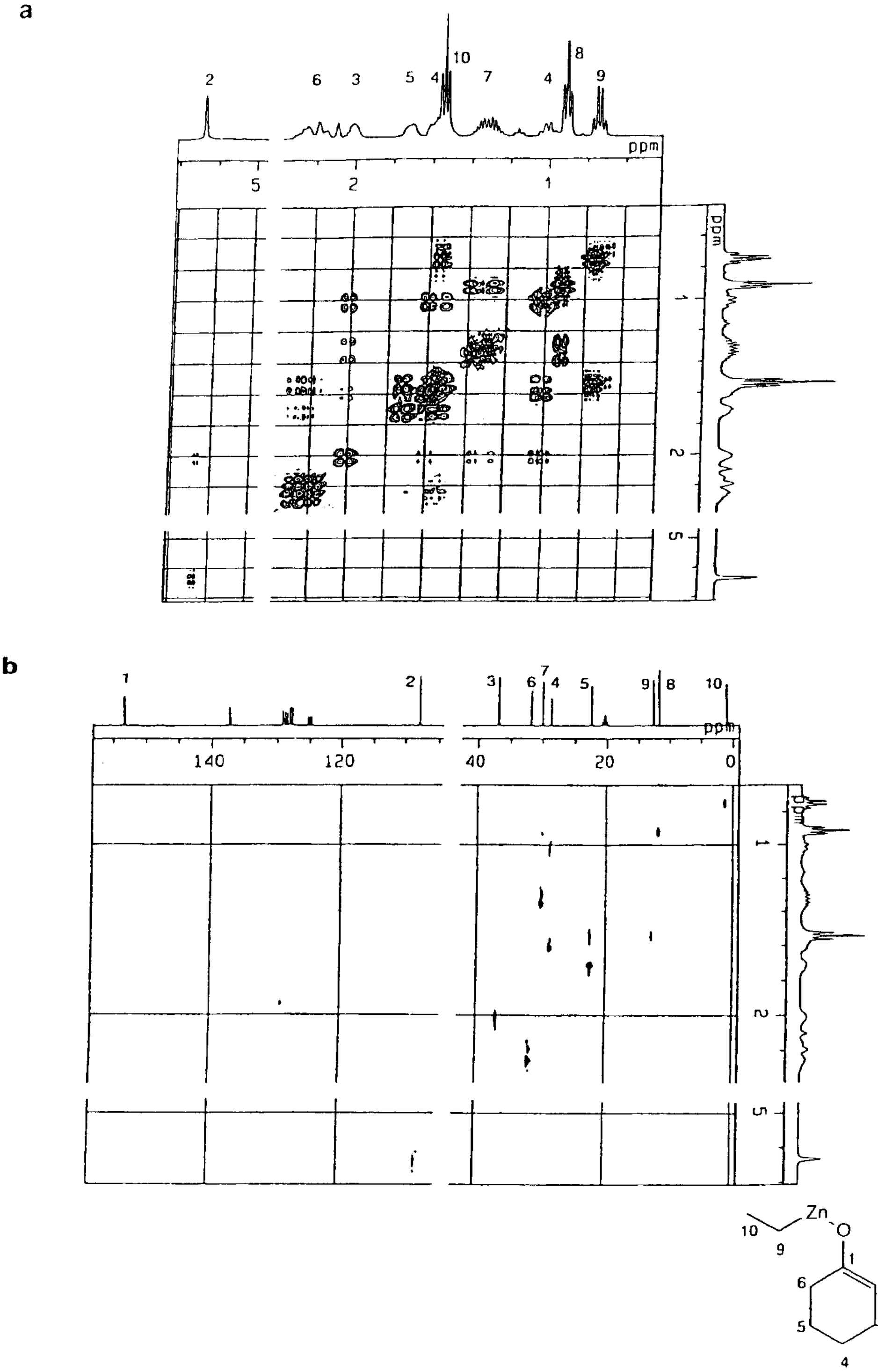
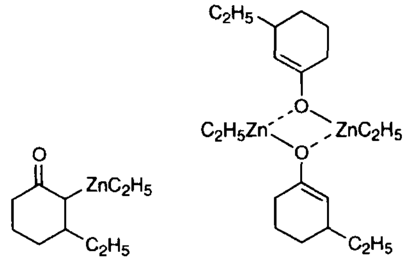


Fig. 4. The ^{1}H-^{1}H COSY spectrum (**a**) and the phase-sensitive ^{13}C-^{1}H correlation spectrum (**b**) of a 500 mM toluene-d_8 solution of ethylzinc enolate **11** at 0 °C.



17 **18**

Chart 3.

and diethylzinc in toluene-d_8 is **11** but not **17** (Chart 3).[24] The ^{13}C spectrum displayed a single set of ten nonequivalent signals. The 2D ^{1}H-^{1}H NMR spectrum exhibited two sets of cross peaks connecting the resonances of C(2)H, C(3)H, C(4)H, and C(5)H and of C(3)H and the CH_2 and CH_3 protons in the ethyl side chain. The connectivity between C(4), C(5), and C(6) was identified by the 2D ^{13}C-^{1}H NMR analysis. The low chemical shift of the C(2) proton, δ = 5.27, clearly shows that the zinc atom is connected to the oxygen atom but not C(2), since Zn-substituted methine protons are known to resonate at a higher field, δ = 1—2.[15b,15c]

The molecular weight measurement by a cryoscopic method revealed that the aggregation state of the zinc enolate in benzene was 2.17—2.26 (MW_{obsd} 477—496 vs. MW_{calcd} 219.62), indicating the dimeric structure of **18**. The NMR analysis did not define the stereochemistry, *meso* or *dl*.

Kinetics. In order to deduce the rate law and to gain insight into the catalytic cycle, the reaction rates were measured at varying temperatures and concentrations of enone **1**, diethylzinc, CuOTf or CuCN, and sulfonamide **4a**. The reaction was monitored by the observation of increases in the signal intensity of the C–O stretching band of the enolate **11** at 1145 cm^{-1} in the IR spectrum. The kinetic data are summarized in Table 3 in the Experimental Section.

(a) CuOTf. Figure 5 shows the time/conversion curve obtained under the standard conditions, $[\mathbf{1}]_0$ = $[Zn(C_2H_5)_2]_0$ = 500 mM, [CuOTf] = [**4a**] = 2.5 mM, 0 °C. An Eyring analysis of the kinetic data for the reaction at −20, −10, 0, and 10 °C (Table 3, Entries 1—4) provides the activation parameters of $\Delta G^{\neq}$ = 15.8 kcal mol^{-1}, $\Delta H^{\neq}$ = 7.94 kcal mol^{-1}, and $\Delta S^{\neq}$ = −28.8 eu at 0 °C. Arrhenius plots of v_0 vs. reciprocal temperature (T^{-1}) in a temperature range from −20 to 0 °C (Fig. 6) suggest the operation of a single mechanistic catalytic cycle. Note, however, that these are not true activation parameters but result from the combination of various kinetic and thermodynamic quantities involved in the multistep reaction.

The effects of the initial concentrations of **1** and diethylzinc on rates were examined within a range of 300 to 600 mM, and the first-order dependence in both $[\mathbf{1}]_0$ and $[Zn(C_2H_5)_2]_0$ was thus established, as shown in Figs. 7a and 7b. Figure 7c shows that the reaction follows first-order kinetics in CuOTf and sulfonamide (1 : 1) in a concentration range between 2 and 5 mM.

(b) CuCN. When CuCN was used, the time/conversion plots showed a sigmoid-type curve (Fig. 8), implying a gradual increase in the concentration of catalytically active species at an early stage of reaction. This may have been due to the low solubility of CuCN in toluene or to the high tendency to form clusters. To avoid such a complication, the reaction rates were measured after 50% completion. Therefore, 3 mmol of enone **1** was reacted under the conditions of [**1**] = 530 mM, $[Zn(C_2H_5)_2]$ = 1060 mM, [CuCN] = [**4a**] = 2.6 mM, 0 °C, and 20 min. Then 3 mmol of **1** was renewed, and the mixture was subjected to the rate measurement. As illustrated in Fig. 9, the reaction using a CuCN/**4a** combined system also obeyed first-order kinetics in $[\mathbf{1}]_0$, $[Zn(C_2H_5)_2]_0$, and [CuCN + **4a**]. Thus the CuCN/**4a** system catalyzes the reaction by the same mechanism as that for CuOTf and **4a**.

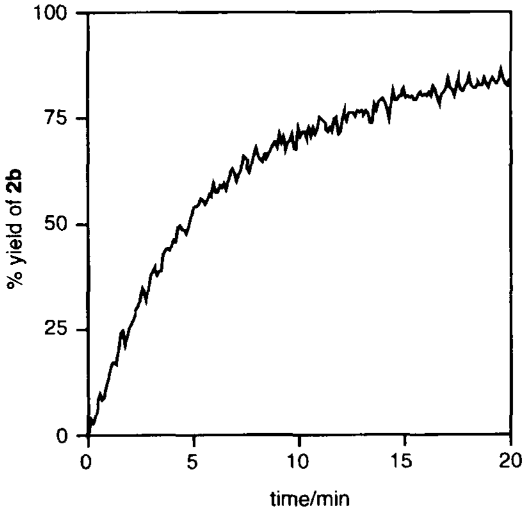


Fig. 5. Time/conversion curve in 1,4-addition of $Zn(C_2H_5)_2$ to 2-cyclohexenone (**1**) in toluene at 0 °C. [**1**] = $[Zn(C_2H_5)_2]$ = 500 mM. [CuOTf] = [**4a**] = 2.5 mM.

On the basis of this kinetic study, the present catalysis can be simply viewed as a bissubstrate-uniproduct system. The catalyst reversibly captures $Zn(C_2H_5)_2$ and enone **1** to form a catalyst/$Zn(C_2H_5)_2$/**1** complex, in which alkyl transfer occurs. The resulting catalyst/product complex releases the product by regeneration of the catalyst, completing the catalytic cycle. Because the catalysis proceeds with first-order kinetics in both $[Zn(C_2H_5)_2]_0$ and $[\mathbf{1}]_0$, the turnover rate is limited by the alkyl-transfer step but not by the product-releasing step.

Defining the equilibrium constant, K_{assoc}, for catalyst + $Zn(C_2H_5)_2 + \mathbf{1} \rightleftarrows$ catalyst/$Zn(C_2H_5)_2/\mathbf{1}$ and the rate constant, k, the rate equation is expressed by d[product]/dt = k[catalyst/$Zn(C_2H_5)_2/\mathbf{1}$]. Since the initial concentration of catalyst, $[\text{catalyst}]_0$, is approximated by the sum of [catalyst] and [catalyst/$Zn(C_2H_5)_2$/**1**], [catalyst/$Zn(C_2H_5)_2/\mathbf{1}$] = $K_{assoc}[\text{catalyst}]_0[Zn(C_2H_5)_2][\mathbf{1}](1+K_{assoc}[Zn(C_2H_5)_2][\mathbf{1}])^{-1}$ is led by using the conditional equation, K_{assoc} = [catalyst/$Zn(C_2H_5)_2/\mathbf{1}$]$[\text{catalyst}]^{-1}[Zn(C_2H_5)_2]^{-1}[\mathbf{1}]^{-1}$. Thus the rate of the catalysis is represented by Eq. 1.

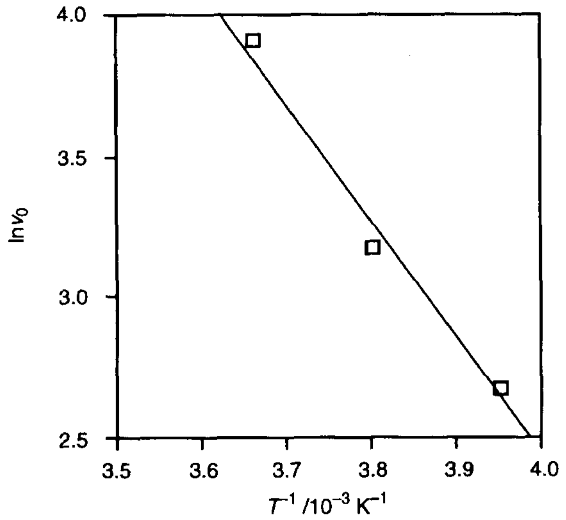


Fig. 6. Arrhenius plot of the initial rate in the 1,4-addition of $Zn(C_2H_5)_2$ to 2-cyclohexenone (**1**) in toluene. [**1**] = [$Zn(C_2H_5)_2$] = 500 mM. [CuOTf] = [**4a**] = 2.5 mM.

$$\frac{d[\text{product}]}{dt} = \frac{kK_{\text{assoc}}[\text{Zn}(\text{C}_2\text{H}_5)_2][\mathbf{1}][\text{catalyst}]_0}{1+K_{\text{assoc}}[\text{Zn}(\text{C}_2\text{H}_5)_2][\mathbf{1}]}. \qquad (1)$$

The first-order kinetics in $[\text{catalyst}]_0$, $[Zn(C_2H_5)_2]$, and [**1**] indicate that the denominator of Eq. 1 should be close to 1. When the equilibrium constants of catalyst+$Zn(C_2H_5)_2 \rightleftarrows$ catalyst/$Zn(C_2H_5)_2$ and catalyst/**1**+$Zn(C_2H_5)_2 \rightleftarrows$ catalyst/$Zn(C_2H_5)_2$/**1** as well as catalyst+**1** $\rightleftarrows$ catalyst/**1** and catalyst/$Zn(C_2H_5)_2$+**1** $\rightleftarrows$ catalyst/$Zn(C_2H_5)_2$/**1** are assumed identical, the K_{assoc} value is estimated to range from 0.05 to 0.11 M^{-2}. Thus ca. 2% of catalyst exists as a catalyst/$Zn(C_2H_5)_2$/**1** complex under the standard conditions.

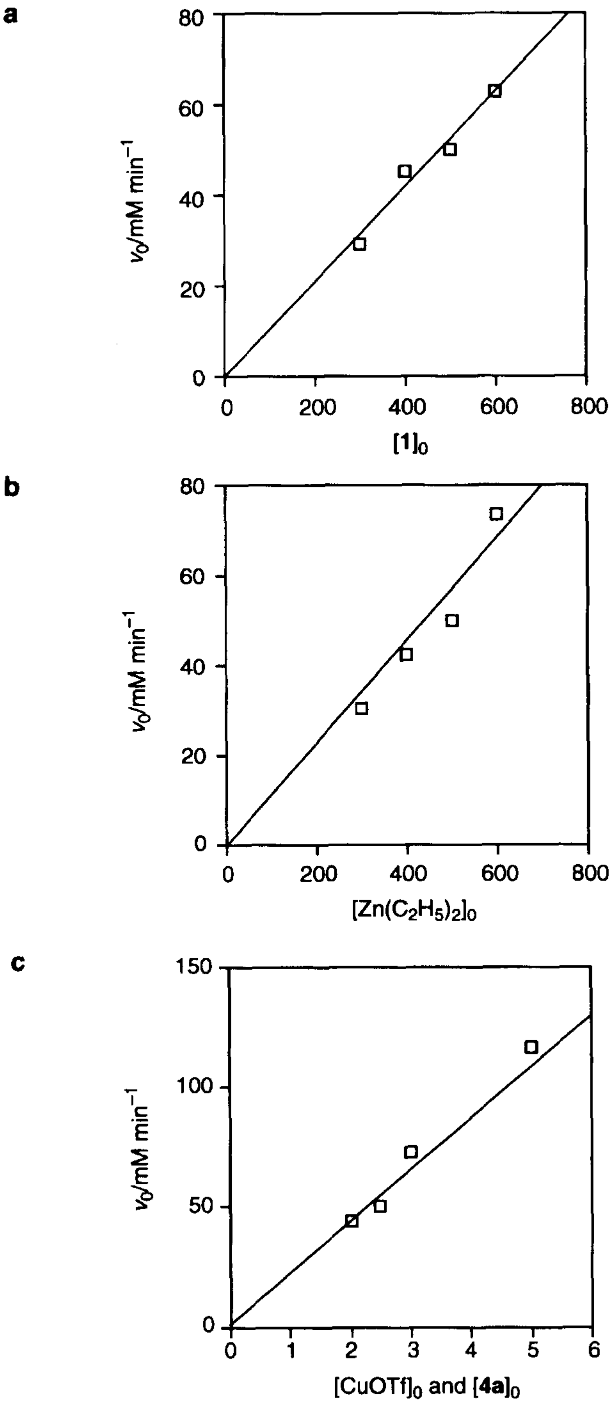


Fig. 7. The initial rates v_0 of reactions of 2-cyclohexenone (**1**) and $Zn(C_2H_5)_2$ in the presence of CuOTf and **4a** in toluene at 0 °C. **a**: Relation between v_0 and [**1**] ([$Zn(C_2H_5)_2$] = 500 mM, [CuOTf] = [**4a**] = 2.5 mM). **b**: Relation between v_0 and [$Zn(C_2H_5)_2$] ([**1**] = 500 mM, [CuOTf] = [**4a**] = 2.5 mM). **c**: Relation between v_0 and [a 1 : 1 mixture of CuOTf and **4a**] ([**1**] = [$Zn(C_2H_5)_2$] = 500 mM).

Catalytic Cycle. Despite some NMR investigations on the reaction system, so far no useful information has been obtained for the structures of the true catalyst and reactive intermediates. Figure 10 presents the minimum mechanism that explains the experimental observations. Structures **A**—**C** represent only the chemical essentials of the actual species that would constitute more complex clusters. Because Zn is much more electropositive than Cu,[16] all hard anions present in the reaction system are bound to Zn. Protic **4** reacts with ZnR_2 to form $RZnNR'SO_2Ar$ by elimination of hydrocarbon RH, while CuX and ZnR_2 undergo metathesis to form CuR and RZnX.[25] The combination of $RZnNR'SO_2Ar$, instead of RZnX, and CuR gives the mixed-metal complex **A**. Upon the complexation, the Zn center is endowed with higher Lewis acidity, and the R group on Cu higher electron density, in comparison to the independent entities. These effects are realized by the charge-alternating three-atom spacer, N($\delta-$)-S($\delta+$)=O($\delta-$), that links the Zn and Cu centers. The R group on Cu, however, is not sufficiently reactive to undergo nucleophilic attack to enones.[26] Instead, **A** acts as a bifunctional catalyst for the reaction of ZnR_2 and enones. The Lewis acidic zinc atom captures carbonyl oxygen in an enone substrate,[27] whereas the CuR moiety interacts with ZnR_2, forming a Cu/Zn cluster.[28] The formation of the catalyst/reagent/substrate complex **B** is reversible and endothermic by ca. 1.2—1.6 kcal mol^{-1}. By forming **B**, the enone increases its acceptor ability, while the alkyl group is endowed, electronically and spatially, with the capability of undergoing a nucleophilic reaction with the

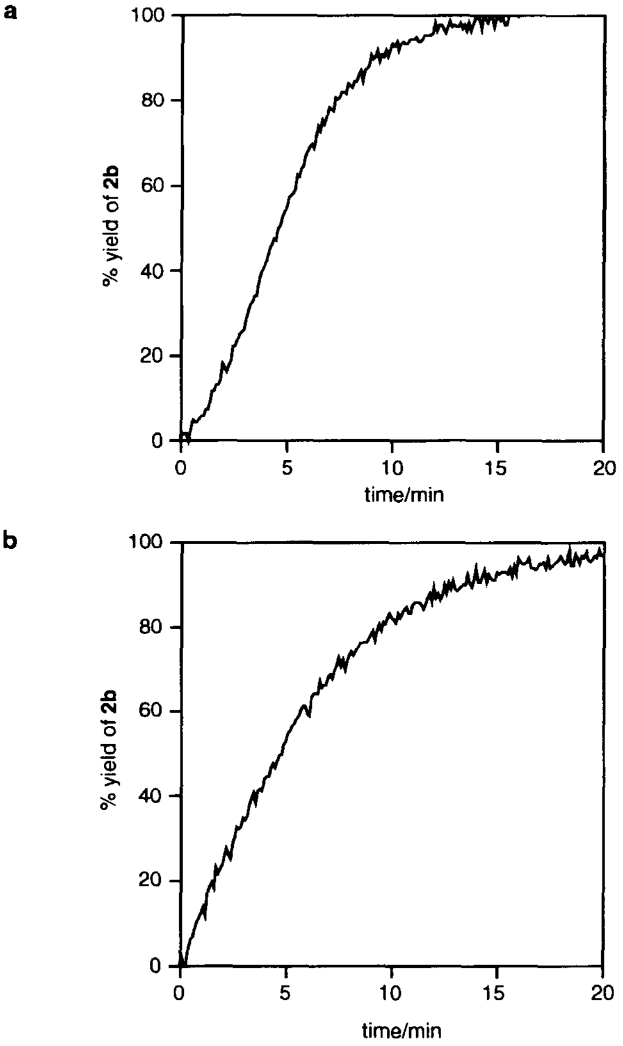


Fig. 8. Time/conversion curves in 1,4-addition of $Zn(C_2H_5)_2$ to 2-cyclohexenone (**1**) in toluene at 0 °C. **a**: [**1**] = 530 mM, $[Zn(C_2H_5)_2]$ = 1060 mM, and [CuCN] = [**4a**] = 2.6 mM. **b**: The curve obtained by addition of **1** (500 mM) to the mixture in the stage of **a**.

enone. This is not achieved by ordinary single-atom spacers such as halides or alkyls. The alkyl transfer from the metal to the β-position of the enone gives the mixed-metal enolate **C**. The turnover rate is limited by this irreversible alkyl-transfer step, whatever the detailed mechanism. **C** regenerates the catalyst **A** by releasing the Zn enolate, and this step is facilitated by the high stability of the dimeric alkylzinc enolate **D**. The structural features of organozinc compounds prevent product inhibition, thereby making possible a very high catalytic turnover number.[29]

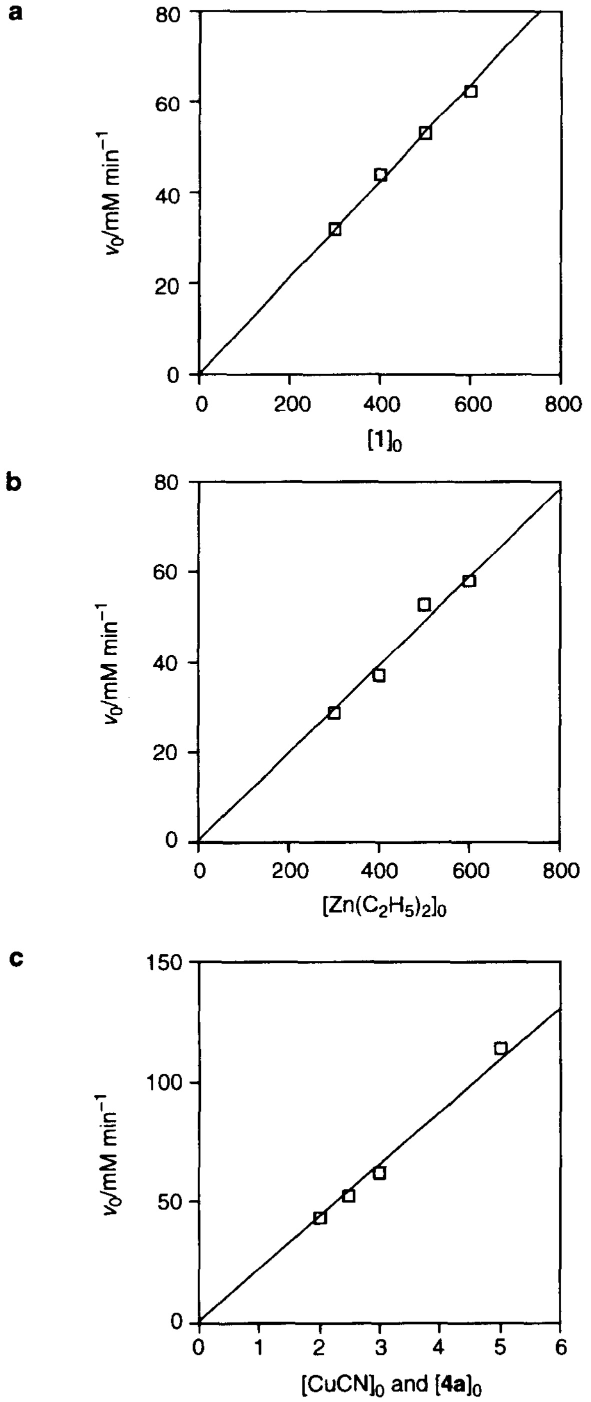


Fig. 9. The initial rates v_0 of reactions of 2-cyclohexenone (**1**) and $Zn(C_2H_5)_2$ in the presence of CuCN and **4a** in toluene at 0 °C. **a**: Relation between v_0 and [**1**] ([Zn-$(C_2H_5)_2$] = [**11**] = 500 mM, [CuCN] = [**4a**] = 2.5 mM). **b**: Relation between v_0 and $[Zn(C_2H_5)_2]$ ([**1**] = [**11**] = 500 mM, [CuCN] = [**4a**] = 2.5 mM). **c**: Relation between v_0 and [a 1 : 1 mixture of CuCN and **4a**] ([**1**] = $[Zn(C_2H_5)_2]$ = [**11**] = 500 mM).

The 1,4-addition of diorganozincs to α,β-unsaturated ketones containing sulfonamides instead of halides or alkyls as bridging anions should proceed via a Zn/Cu mixed cluster. Anion X originally present in the Cu salt is removed by the formation of RZnX. Although RZnX is probably not always an innocent spectator in the catalytic cycle, its participation is likely to be unimportant in this case. The behavior of CuOTf, CuCN, and other copper(I) compounds in the 1,4-addition is very similar. These results suggest the generation of a common species, although the structures including CuCN are more complicated, possibly due to the formation of cyanide-containing higher-order clusters.[30,31]

$$R'NHSO_2Ar + ZnR_2 \longrightarrow RZnNR'SO_2Ar + RH$$

$$CuX + ZnR_2 \longrightarrow CuR + RZnX$$

$$RZnNR'SO_2Ar + CuR \longrightarrow (RZnNR'SO_2Ar)(CuR)\ (\mathbf{A})$$

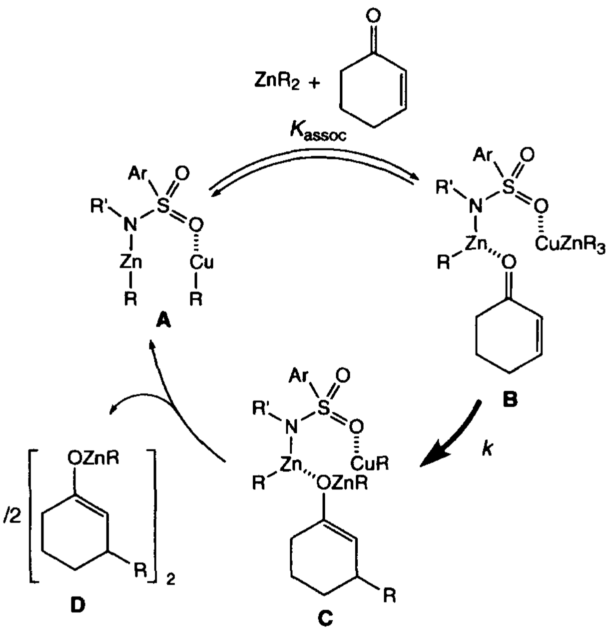


Fig. 10. Supposed catalytic cycle of the 1,4-addition of dialkylzincs to α,β-unsaturated ketones.

Conclusion

The present investigation has revealed that catalytic amounts of CuX and the sulfonamide **4** efficiently promote the 1,4-selective addition of organozinc compounds to enones. The reaction is rapid and productive. Particularly, in the presence of CuCN and **4a**, the addition of diethylzinc to the enone **1** proceeds quantitatively with a substrate to a catalyst ratio of as high as 10000. The sulfonamide ancillary plays a key role in realizing this very high efficiency. A variety of dialkyl- and diarylzincs and enone substrates can be used. The intermediary Zn enolate can be trapped regiospecifically by aldehydes, as well as by allyl acetate with the aid of a Pd(0) catalyst, to give the α,β-vicinal condensation products. Thus, the present kinetic experiments and zinc enolate structural study have afforded further insights into the catalytic cycle. The present catalytic system could open a new way to designing the asymmetric version of the catalyst.[32]

Experimental

Instruments. Melting points were measured on a Yanako micro melting point apparatus and were uncorrected. Proton and carbon magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were measured in chloroform-*d*, benzene-d_6, or toluene-d_8 on a JEOL ALPHA400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) instrument. The chemical shifts were reported in ppm downfield from TMS, and proton signal patterns were indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100M spectrophotometer and expressed by wavenumber (cm^{-1}). For kinetic studies, Perkin–Elmer FTIR-2000 was used. X-Ray crystallographic analyses were conducted on a Rigaku automated four-circle diffractometer AFC-7R with graphite-monochromated Cu $K\alpha$ radiation. Elemental analyses were performed on LECO-CHN900. HRMS were performed at an ionizing voltage of 70 eV on a JEOL JMS-LG2000. Chromatographic purification was done with 240—400 mesh silica gel (Merck 9385). Gas–liquid phase chromatography analyses were performed on a Shimadzu GC-14A instrument. The signals of GC were detected by FID. All apparatus for 1,4-addition reactions were used after drying at ca. 400 °C for 5 min under reduced pressure.

Materials. Solvents for 1,4-addition were distilled from potassium diphenylketyl (ether and THF), sodium diphenylketyl (toluene), or CaH_2 (CH_2Cl_2, CH_3CN, and DMF), and degassed. The compounds listed below are available commercially: 2-cyclohexenone (**1**) (Wako Chemicals), 3-methyl-2-cyclohexenone (**6**) (Tokyo Kasei), 2-cycloheptenone (**7**) (Aldrich, purified by silica-gel column chromatography followed by Kugelrohr distillation at 100—102 °C and 18 mmHg, 1 mmHg = 133.322 Pa), 2-cyclopentenone (**8**), (*E*)-3-nonen-2-one (**10**) (Tokyo Kasei), 3-methylcyclohexanone (**2a**) (Aldrich), 3-ethylcyclopentanone (Wiley Organics), *c*-$C_6H_{11}CHO$, C_6H_5CHO, and allyl acetate (Nacalai), $Zn(CH_3)_2$ and $Zn(C_2H_5)_2$ (Tosoh Akzo), $Zn(C_6H_5)_2$ (Strem), CuCN, CuCl, CuBr, and CuI (Aldrich), $CuOSO_2CF_3\cdot(C_6H_6)_{0.5}$ (Strem), $NH_2SO_2C_6H_5$ (Tokyo Kasei), and $Pd[P(C_6H_5)_3]_4$ (Aldrich). The following compounds were prepared according to previously reported methods: 2-methyl-2-cyclohexenone (**5**),[33] (*E*)-2-ethylidenecyclohexanone (**9**),[34] $Zn(n\text{-}C_4H_9)_2$,[35] Cu(I)-2,4,6-$(CH_3)_3C_6H_2$,[36] Cu(I)O-*t*-C_4H_9,[37] and $C_6H_5CH_2NHSO_2R$ (R = CH_3, CF_3).[38] The method reported in Ref. 38 was applied to the preparation of $RNHSO_2C_6H_5$ (R = $C_6H_5CH_2$, CH_3, *i*-C_3H_7, *t*-C_4H_9, C_6H_5) and $(C_6H_5CH_2)_2NSO_2C_6H_5$. 1,2-Addition products, 1-methyl-2-cyclohexen-1-ol (**3a**), 1-ethyl-2-cyclohexen-1-ol (**3b**), 1-butyl-2-cyclohexen-1-ol (**3c**), 1-phenyl-2-cyclohexen-1-ol (**3d**), 1-ethyl-2-cyclohepten-1-ol, 1-ethyl-2-cyclopenten-1-ol, 1-ethyl-2-methyl-2-cyclohexen-1-ol, 1-ethyl-2-ethylidenecyclohexan-1-ol, and 3-methyl-4-decen-3-ol were prepared by the reaction of the corresponding enones and organolithium or organomagnesium compounds in the presence of $CeCl_3$.[39] Substrates, protic organic compounds, $Zn(CH_3)_2$, and $Zn(C_2H_5)_2$ were purified by distillation or recrystallization before use. The structures of the aldol products were determined by single crystal X-ray analysis at 25 °C.

General Procedure for the Catalytic 1,4-Addition. A 3.1-mmol scale reaction was adopted for the optimization of the conditions. The reaction scale could be increased without problems. A typical procedure for the 20-g scale ethylation of 2-cyclohexenone (**1**) was as follows: A dry 500-mL Schlenk tube containing a Teflon®-coated stirring bar was charged, under an argon stream, with CuCN (99 mg, 1.1 mmol), *N*-benzylbenzenesulfonamide (**4a**) (272 mg, 1.1 mmol), and toluene (60 mL). The mixture was cooled to 0 °C with an ice bath. $Zn(C_2H_5)_2$ (26.0 g, 0.21 mol) was added, and the mixture was stirred for 10 min. To this was added **1** (20.2 g, 0.21 mol). The resulting pale red suspension was stirred at 0 °C for 2 h, and then poured into saturated aqueous NH_4Cl solution (200 mL) cooled to 0 °C. The organic layer was removed, and the aqueous layer was extracted two times with ether (100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a ca. 3 : 1 mixture of toluene and the product. The mixture was distilled at 191—193 °C and atmospheric pressure to give 3-ethylcyclohexanone (**2b**) in 90% isolated yield (24.0 g). GC analysis of the crude reaction mixture showed that the yield of **2b** was > 99% and the 1,2-addition product, 1-ethyl-2-cyclohexen-1-ol (**3b**), was not detected under the following conditions: capillary column, GL Science OV-1 0.25 mm×50 m; column temperature, 90—130 °C; rate of temperature increase, 2 °C min^{-1}; detection temperature, 280 °C; carrier gas, He; column head pressure, 118 kPa; split ratio, 100 : 1; t_R of 2-cyclohexenone (**1**), 7.8 min (factor 1.33); t_R of 1-ethyl-2-cyclohexen-1-ol (**3b**), 10.3 min (factor 1.40); t_R of 3-ethylcyclohexanone (**2b**), 11.9 min (factor 1.44); t_R of undecane as an internal standard, 14.4 min (factor 1.00). ^{1}H- and ^{13}C NMR spectra were identical with the reported ones.[40] The reaction using CuMes was conducted in a similar manner under the following conditions: **1** (0.21 mol), $Zn(C_2H_5)_2$ (0.21 mol), CuMes (1.1 mmol), **4a** (1.1 mmol), toluene (60 mL), temperature 0 °C, time 1 h. The product **2b** (23.8 g) was isolated in 90% yield after distillation.

Listed below are the reaction conditions (amounts of substrate, ZnR_2, copper(I) compound, and *N*-benzylbenzenesulfonamide (**4a**); amount of toluene; temperature; time, h), yield of 1,4-addition product, and properties of the alkylated products. The chemical yields and 1,4/1,2 ratios were determined by GC analysis of crude reaction mixtures (capillary column, GL Science OV-1 0.25 mm×50 m; detection temperature, 280 °C; carrier gas, He; split ratio, 100 : 1). All crude products contained toluene. The structures of the 1,4-addition products were determined by comparison of NMR, IR, or mass spectra with the reported values or those of the authentic samples.

3-Methylcyclohexanone (2a). Conditions: 3.1 mmol of **1**, 3.1 mmol of $Zn(CH_3)_2$ (0.931 mL of a 3.33 M toluene solution), 0.016 mmol of CuCN, and 0.016 mmol; 5.0 mL; 0 °C; 6 h. Yield, 90%. GC conditions: column temperature, 90—120 °C; rate of temperature increase, 2 °C min^{-1}; column head pressure, 118 kPa; **1**, 7.9 min (factor 1.34); **3a**, 7.3 min (factor 1.25); **2a**, 8.4 min (factor 1.33); decane as an internal standard, 10.2 min (factor 1.00). Physical properties: consistent with the commercially available authentic sample.

3-Butylcyclohexanone (2c). Conditions: 3.1 mmol of **1**, 3.1 mmol of $Zn(n\text{-}C_4H_9)_2$ (neat), 0.062 mmol of CuMes, and 0.062 mmol; 4.7 mL; 0 °C; 3 h. Yield, 95%. GC conditions: column temperature, 90—170 °C; rate of temperature increase, 4 °C min^{-1}; column head pressure, 137 kPa; **1**, 6.3 min (factor 1.40); **3c**, 12.8 min (factor 1.58); **2c**, 14.8 min (factor 1.33); decane as an internal standard, 8.0 min (factor 1.00). Physical properties: consistent with those previously reported.[41]

3-Phenylcyclohexanone (2d). Conditions: 3.1 mmol of **1**, 3.1 mmol of $Zn(C_6H_5)_2$, 0.062 mmol of CuMes, and 0.062 mmol; 6.2 mL; 0 °C; 1 h. Yield, 92%. GC conditions: column temperature, 120 °C for 8 min and then 120—210 °C; rate of temperature increase, 6 °C min^{-1}; column head pressure, 137 kPa; **1**, 5.5 min (factor 1.35); **3d** (two signals at 16.7 and 17.2 min were observed probably due to decomposition); **2d**, 21.0 min (factor 1.24); dodecane as an internal standard, 11.5 min (factor 1.00). Physical properties: consistent with those previously reported.[7]

3-Ethyl-2-methylcyclohexanone. Conditions: 3.1 mmol of 2-methyl-2-cyclohexenone (**5**), 3.1 mmol of $Zn(C_2H_5)_2$ (0.781 mL of a 3.97 M toluene solution), 0.062 mmol of CuMes, and 0.062 mmol; 3.9 mL; 25 °C; 120 h. Yield, 50% as a 1.4 : 1 mixture of diastereomers. GC conditions: column temperature, 90—130 °C; rate of temperature increase, 2 °C min^{-1}; column head pressure, 118 kPa; **5**, 9.4 min (factor 1.31); 1-ethyl-2-methyl-2-cyclohexen-1-ol, 13.5 min (factor 1.17); 3-ethyl-2-methylcyclohexanone, 14.4 and 15.0 min (factor 1.28); dodecane as an internal standard, 19.0 min (factor 1.00). Physical properties: consistent with those previously reported.[42]

3-Ethylcycloheptanone. Conditions: 3.1 mmol of 2-cycloheptenone (**7**), 3.1 mmol of $Zn(C_2H_5)_2$ (0.781 mL of a 3.97 M toluene solution), 0.062 mmol of CuMes, and 0.062 mmol; 3.9 mL; 0 °C; 1 h. Yield, 99%. GC conditions: column temperature, 90—130 °C; rate of temperature increase, 2 °C min^{-1}; column head pressure, 137 kPa; **7**, 9.6 min (factor 1.33); 1-ethyl-2-cyclohepten-1-ol, 12.7 min (factor 1.13); 3-ethylcycloheptanone, 14.8 min (factor 1.30); dodecane as an internal standard, 17.0 min (factor 1.00). Physical properties: bp 138—140 °C at 22 mmHg (Kugelrohr distillation); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 0.90$ (t, 3, $J = 7.6$ Hz), 1.2—1.5 (m, 4), 1.5—1.7 (m, 2), 1.8—2.0 (m, 3), 2.3—2.6 (m, 4); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.32, 24.36, 28.48, 29.98, 36.40, 37.62, 43.83, 49.52, 214.51; IR (neat) 2961, 2857, 1701, 1460, 1449, 1254; HRMS *m/z* (M^+) Calcd for: M, 140.1202. Found: *m/z* 140.1191.

3-Ethylcyclopentanone. Conditions: 3.1 mmol of 2-cyclopentenone (**8**), 3.1 mmol of $Zn(C_2H_5)_2$ (0.781 mL of a 3.97 M toluene solution), 0.062 mmol of CuMes, and 0.062 mmol; 3.9 mL; 0 °C; 1 h. Yield, 28%. GC conditions: column temperature, 70 °C for 9 min and then 70—110 °C; rate of temperature increase, 4 °C min^{-1}; column head pressure, 118 kPa; **8**, 8.0 min (factor 1.57); 1-ethyl-2-cyclopenten-1-ol, 10.4 min (factor 1.85); 3-ethylcyclopentanone, 13.6 min (factor 1.33); nonane as an internal standard, 12.1 min (factor 1.00). Physical properties: consistent with the commercially available authentic sample.

2-*s*-Butylcyclohexanone. Conditions: 3.1 mmol of (*E*)-2-ethylidenecyclohexanone (**9**), 3.1 mmol of $Zn(C_2H_5)_2$ (0.781 mL of a 3.97 M toluene solution), 0.062 mmol of CuMes, and 0.062 mmol; 3.9 mL; 0 °C; 6 h. Yield, 90% as a 3.3 : 1 mixture of diastereomers. GC conditions: column temperature, 90—130 °C; rate of temperature increase, 2 °C min^{-1}; column head pressure, 118 kPa; **9**, 14.6 min (factor 1.29); 1-ethyl-2-ethylidenecyclohexan-1-ol, 17.6 min (factor 1.41); 2-*s*-butylcyclohexanone, 18.5 and 18.6 min (factor 1.24); decane as an internal standard, 10.2 min (factor 1.00). Physical properties: consistent with those previously reported.[43]

4-Ethyl-2-nonanone. Conditions: 3.1 mmol of (*E*)-3-nonen-2-one (**10**), 3.1 mmol of $Zn(C_2H_5)_2$ (0.781 mL of a 3.97 M toluene solution), 0.016 mmol of CuCN, and 0.016 mmol; 4.9 mL; 0 °C; 20 h. Yield, > 99%. GC conditions: column temperature, 90—130 °C; rate of temperature increase, 2 °C min^{-1}; column head pressure, 137 kPa; **10**, 13.1 min (factor 1.40); 3-methyl-4-decen-3-ol, 16.9 min (factor 1.44); 3-ethyl-2-nonanone, 17.5 min (factor 1.28); decane as an internal standard, 9.0 min (factor 1.00). Physical properties: consistent with those previously reported.[81]

Three-Component Coupling. Aldol Reaction: A toluene solution (6.2 mL) of the Zn enolate **11**, generated from 2-cyclohexenone (**1**) (298 mg, 3.1 mmol) and $Zn(C_2H_5)_2$ (0.781 mL of a 3.97 M toluene solution, 3.1 mmol) in the presence of CuMes (11.5 mg, 0.062 mmol) and *N*-benzylbenzenesulfonamide (**4a**) (15.3 mg, 0.062 mmol) at 0 °C for 1 h according to the procedure described above, was cooled to −78 °C. To this was added cyclohexanecarbaldehyde (348 mg, 3.1 mmol). The mixture was stirred for 18 h and then poured into saturated aqueous NH_4Cl solution (4 mL). The usual extractive workup afforded a crude oil (1.0 g), which contained > 95% of $(2R^*,3R^*)$-2-[(R^*)-cyclohexyl(hydroxy)methyl]-3-ethylcyclohexanone (*trans,threo*-**13a**). This product was judged as a single isomer based on the ^{1}H NMR analysis (1,1,2,2-tetrachloroethane as an internal standard) giving a signal at $\delta = 3.33$ (ddd). This was chromatographed on silica gel (BW300S, 30 g; eluent, a 10 : 1—3 : 1 hexane-ether mixture) to give *trans,threo*-**13a** (634 mg): Mp 68—69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 0.84$—0.97 (m, 5), 1.05—1.28 (m, 3), 1.32—1.55 (m, 3), 1.58—1.80 (m, 6), 1.88—2.15 (m, 4), 2.32—2.38 (m, 2), 2.42 (dd, 1, $J = 2.9$ and 9.8 Hz), 2.66 (d, 1, $J = 11.2$ Hz), 3.33 (ddd, 1, $J = 2.9$, 8.4, and 11.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 10.06$, 25.57, 25.87, 26.09, 26.29, 26.35, 29.28, 29.54, 30.32, 41.58, 42.47, 42.87, 55.59, 74.39, 216.56; IR (KBr) 3420, 2923, 2851, 1690. Anal. Found: C, 75.20; H, 11.38%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%. Crystallographic parameters: space group $P2_1/c$, $a = 9.456(2)$, $b = 5.989(1)$, $c = 25.338(2)$ Å, $\alpha = 90°$, $\beta = 100.40(1)°$, $\gamma = 90°$, $V = 1411.4(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.122$ g cm^{-3}; 2498 reflections obtained (1734 with $I > 3\sigma$), $R = 0.078$, $R_w = 0.089$.

Reaction of the Zn enolate **11**, generated from **1** (298 mg, 3.1 mmol) and $Zn(C_2H_5)_2$ (0.781 mL of 3.97 M toluene solution, 3.1 mmol) in the presence of CuMes (11.5 mg, 0.062 mmol) and **4a** (15.3 mg, 0.062 mmol), with benzaldehyde (329 mg, 3.1 mmol) at −78 °C for 62 h afforded, after the usual workup, a crude product (0.9 g) that contained an 81 : 19 mixture of (2*R**,3*R**)-3-ethyl-2-[(*R**)-hydroxy(phenyl)methyl]cyclohexanone (*trans,threo*-**13b**) and (2*R**,3*R**)-3-ethyl-2-[(*S**)-hydroxy(phenyl)methyl]cyclohexanone (*trans,erythro*-**13b**) in 83% yield. The yield was determined by ^{1}H NMR analysis (1,1,2,2-tetrachloroethane as an internal standard) of the benzyl signal at $\delta = 4.96$ (*trans,threo*-**13b**), and $\delta = 5.12$ (*trans,erythro*-**13b**). The mixture was subjected to silica-gel column chromatography (BW300S, 50 g; eluent, a 3 : 1—1 : 1 hexane–ether mixture) to give *trans,threo*-**13b** (350 mg) and *trans,erythro*-**13b** (43 mg).

trans,threo-**13b**: Mp 106—108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 0.87$ (t, 3, $J = 7.3$ Hz), 1.34—1.46 (m, 1), 1.50—1.62 (m, 2), 1.77—1.90 (m, 2), 1.94—2.05 (m, 2), 2.30—2.47 (m, 2), 2.67 (dd, 1, $J = 7.3$ and 5.9 Hz), 3.26 (d, 1, $J = 8.3$ Hz), 4.96 (dd, 1, $J = 8.3$ and 5.9 Hz), 7.21—7.39 (m, 5); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 10.60$, 24.84, 25.62, 27.48, 41.41, 41.59, 61.59, 72.48, 125.97, 127.36, 128.34, 143.22, 214.98; IR (KBr) 3390, 2961, 2870, 1707, 1458, 1040, 704. Anal. Found: C, 77.57; H, 8.86%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%. Crystallographic parameters: space group $P4/n$, $a = 18.217(3)$, $b = 18.217(3)$, $c = 8.387(3)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2782.3(8)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.109$ g cm^{-3}; 2404 reflections obtained (1609 with $I > 3\sigma$), $R = 0.082$, $R_w = 0.077$.

trans,erythro-**13b**: Mp 86—86.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 0.79$ (t, 3, $J = 7.3$ Hz), 1.15—1.26 (m, 1), 1.32—1.54 (m, 2), 1.65—1.74 (m, 1), 1.85—2.03 (m, 3), 2.25—2.42 (m, 2), 2.66 (dd, 1, $J = 5.9$ and 5.9 Hz), 3.17 (d, 1, $J = 5.9$ Hz), 5.12 (dd, 1, $J = 5.9$ and 5.9 Hz), 7.21—7.39 (m, 5); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 10.83$, 22.83, 26.06, 26.91, 39.16, 41.52, 61.32, 73.12, 126.49, 127.56, 128.34, 142.02, 214.69; IR (KBr) 3378, 2955, 2870, 1701, 1456, 1013, 700. Anal. Found: C, 77.28; H, 8.82%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%. Crystallographic parameters: space group Cc, $a = 22.200(7)$, $b = 11.977(4)$, $c = 10.360(7)$ Å, $\alpha = 90°$, $\beta = 102.61(4)°$, $\gamma = 90°$, $V = 2688(1)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.148$ g cm^{-3}; 1844 reflections obtained (1179 with $I > 3\sigma$), $R = 0.070$, $R_w = 0.053$. Two crystallographically independent molecules exist in the asymmetric unit.

1,4-Addition reaction of diethylzinc to 2-cyclopentenone (**8**) in the presence of aldehydes was carried out as follows. *N*-Benzylbenzenesulfonamide (**4a**) (15.3 mg, 0.062 mmol) and toluene (3.9 mL) were charged in a dry argon-filled 20-mL Schlenk tube. To this was added a 0.040 M toluene solution of CuMes (1.5 mL, 0.062 mmol). The mixture was cooled to 0 °C with an ice bath. To this was added a 3.97 M toluene solution of diethylzinc (0.781 mL, 3.1 mmol) and the mixture was stirred for 10 min. Cyclohexanecarbaldehyde (348 mg, 3.1 mmol) and **8** (255 mg, 3.1 mmol) were added simultaneously at 0 °C. The resulting light brown suspension was stirred at 0 °C for 3 h, and then poured into saturated aqueous NH_4Cl solution (4 mL) cooled to 0 °C. A workup similar to that described in the above procedure gave a crude solid (1.0 g) that contained (2*R**, 3*R**)-2-[(*R**)-cyclohexyl(hydroxy)methyl]-3-ethylcyclopentanone (*trans,threo*-**15a**) as a single isomer. The yield was determined to be > 95% on the basis of ^{1}H NMR analysis (1,1,2,2-tetrachloroethane as an internal standard) of a signal at $\delta = 3.36$ (ddd). The mixture was chromatographed on silica gel (BW300S, 50 g; eluent, a 2 : 1 hexane–ether mixture) to give *trans,threo*-**15a** (625 mg): Mp 64—67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 0.93$—1.45 (m, 10), 1.57—1.80 (m, 6), 1.82—1.90 (m, 1), 1.95—2.38 (m, 5), 2.63 (d, 1, $J = 6.3$ Hz), 3.36 (ddd, 1, $J = 4.0$, 6.3, and 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 11.38$, 25.77, 26.14, 26.30, 26.46, 27.37, 28.20, 30.00, 38.77, 40.96, 41.24, 56.03, 75.69, 221.97; IR (KBr) 3505, 2923, 2851, 1721. Anal. Found: C, 74.84; H, 11.18%. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78%. Crystallographic parameters: space group $P2_1/a$, $a = 9.249(6)$, $b = 14.702(7)$, $c = 10.628(6)$ Å, $\alpha = 90°$, $\beta = 110.08(4)°$, $\gamma = 90°$, $V = 1357(1)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.098$ g cm^{-3}; 2261 reflections obtained (1158 with $I > 3\sigma$), $R = 0.065$, $R_w = 0.074$.

Under the same conditions, use of benzaldehyde afforded a 55 : 45 mixture of (2*R**,3*R**)-3-ethyl-2-[(*R**)-hydroxy(phenyl)methyl]cyclopentanone (*trans,threo*-**15b**) and (2*R**,3*R**)-3-ethyl-2-[(*S**)-hydroxy(phenyl)methyl]cyclopentanone (*trans,erythro*-**15b**) in 91% combined yield based on the ^{1}H NMR analysis (1,1,2,2-tetrachloroethane as an internal standard) of the benzyl signals at $\delta = 4.74$ (*trans,threo*-**15b**) and $\delta = 5.19$ (*trans,erythro*-**15b**). The mixture (1.1 g) was chromatographed on silica gel (BW300S, 100 g; eluent, a 20 : 1 benzene–acetone mixture) to give *trans,threo*-**15b** (275 mg) and *trans,erythro*-**15b** (238 mg). *trans,threo*-**15b**: Bp 150—152 °C at 0.05 mmHg (Kugelrohr distillation); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 0.67$ (t, 3, $J = 7.3$ Hz), 0.75—0.93 (m, 2), 1.34—1.45 (m, 1), 1.63—1.84 (m, 1), 2.07—2.26 (m, 3), 2.36—2.45 (m, 1), 4.30 (d, 1, $J = 1.5$ Hz), 4.74 (dd, 1, $J = 1.5$ and 7.8 Hz), 7.20—7.38 (m, 5); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 10.87$, 26.32, 26.93, 38.07, 40.59, 59.79, 74.97, 126.67, 127.91, 128.26, 141.26, 223.01; IR (neat) 3461, 2963, 2932, 2876, 1721, 1456, 1159, 702. The aldol compound *trans,threo*-**15b** was converted to the *p*-bromobenzoate for elemental analysis as well as X-ray crystallographic analysis: Mp 90—91 °C. Anal. Found: C, 62.84; H, 5.36%. Calcd for $C_{21}H_{21}O_3Br$: C, 62.85; H, 5.28%. Crystallographic parameters: space group $P2_1/n$, $a = 10.083(2)$, $b = 14.058(1)$, $c = 13.804(2)$ Å, $\alpha = 90°$, $\beta = 98.99(1)°$, $\gamma = 90°$, $V = 1932.7(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.379$ g cm^{-3}; 2317 reflections obtained (2292 with $I > 3\sigma$), $R = 0.125$, $R_w = 0.134$. *trans,erythro*-**15b**: Mp 84—86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 0.76$ (t, 3, $J = 7.3$ Hz), 0.98—1.09 (m, 1), 1.18—1.39 (m, 2), 1.97—2.13 (m, 3), 2.24 (dd, 1, $J = 4.4$ and 8.5 Hz), 2.28—2.35 (m, 1), 3.41 (d, 1, $J = 6.8$ Hz), 5.19 (dd, 1, $J = 4.4$ and 6.8 Hz), 7.20—7.38 (m, 5); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 11.15$, 26.62, 27.47, 38.46, 38.98, 60.20, 72.84, 125.78, 127.38, 128.30, 142.17, 222.13; IR (KBr) 3424, 2961, 2890, 1718, 1165, 1024, 702. Anal. Found: C, 76.74; H, 8.50%. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%. Crystallographic parameters: space group $Pbca$, $a = 23.425(4)$, $b = 14.245(3)$, $c = 7.318(2)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2442(1)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.187$ g cm^{-3}; 2126 reflections obtained (1300 with $I > 3\sigma$), $R = 0.068$, $R_w = 0.066$.

Allylation: A toluene solution (2.0 mL) of the Zn enolate **11** was obtained by reaction of 2-cyclohexenone (**1**) (96.1 mg, 1.0 mmol) and $Zn(C_2H_5)_2$ (0.252 mL of a 3.97 M toluene solution, 1.0 mmol) in the presence of CuMes (3.7 mg, 0.02 mmol) and **4a** (4.9 mg, 0.02 mmol) at 0 °C for 30 min according to the procedure described above. To this were added $Pd[P(C_6H_5)_3]_4$ (23 mg, 0.02

mmol) and allyl acetate (100 mg, 1.0 mmol) successively. The mixture was stirred at 0 °C for 2 h and then poured into saturated aqueous $\mathrm{NH_4Cl}$ solution (2 mL). The usual extractive workup afforded a crude product (300 mg), which was chromatographed on silica gel (BW300S, 10 g; eluent, a 10 : 1 pentane–ether mixture) to give a 90 : 10 mixture of *trans*- and *cis*-2,3-disubstituted cyclohexanones **16** (148 mg, 86% yield). The *trans*/*cis* ratio was determined by comparison of the intensity of the $^{13}\mathrm{C}$ NMR signals at $\delta = 136.54$ (*trans*-**16**) and $\delta = 136.26$ (*cis*-**16**). A 90 : 10 mixture of *trans*- and *cis*-**16**: Bp 147—150 °C at 24 mmHg (Kugelrohr distillation); $^{1}\mathrm{H}$ NMR of *trans*-**16** (400 MHz, $\mathrm{CDCl_3}$) $\delta = 0.90$ (t, 3, $J = 7.6$ Hz, $\mathrm{CH_2C}\mathit{H}_3$), 1.32 (m, 1, $\mathrm{C}\mathit{H}\mathrm{HCH_3}$), 1.5 (m, 1, $\mathrm{C(4)}\mathit{H}\mathrm{H}$), 1.55—1.75 (m, 3, $\mathrm{CH}\mathit{H}\mathrm{CH_3}$, C(3)H, $\mathrm{C(5)}\mathit{H}\mathrm{H}$), 1.8 (m, 1, $\mathrm{C(4)H}\mathit{H}$), 2.0 (m, 1, $\mathrm{C(5)H}\mathit{H}$), 2.2—2.5 (m, 5, C(2)H, $\mathrm{C(6)H_2}$, $\mathrm{C}\mathit{H}_2\mathrm{CH{=}CH_2}$), 4.98 (dd, 1, $J = 2.8$ and 10.4 Hz, $\mathrm{CH_2CH{=}C}\mathit{H}\mathrm{H}$), 5.03 (ddd, 1, $J = 1.6$, 2.8, and 17.2 Hz, $\mathrm{CH_2CH{=}CH}\mathit{H}$), 5.79 (m, 1, $\mathrm{CH_2C}\mathit{H}\mathrm{{=}CH_2}$). $^{1}\mathrm{H}$ NMR of *cis*-**16** (400 MHz, $\mathrm{CDCl_3}$) $\delta = 0.86$ (t, 3, $J = 8.0$ Hz, $\mathrm{CH_2C}\mathit{H}_3$), 1.08 (m, 1, $\mathrm{C}\mathit{H}\mathrm{HCH_3}$), 1.80 (m, 1), 2.10 (m, 1, $\mathrm{C}\mathit{H}\mathrm{HCH{=}CH_2}$), 2.58 (m, 1, C(2)H), 5.70 (m, 1, $\mathrm{CH_2C}\mathit{H}\mathrm{{=}CH_2}$). $^{13}\mathrm{C}$ NMR of *trans*-**16** (100 MHz, $\mathrm{CDCl_3}$) $\delta = 10.51$ ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$), 24.98 (C(5)), 25.82 ($\mathit{C}\mathrm{H_2CH_3}$), 28.46 (C(4)), 31.50 ($\mathit{C}\mathrm{H_2CH{=}CH_2}$), 41.27 (C(6)), 43.28 (C(3)), 54.61 (C(2)), 116.00 ($\mathrm{CH_2CH{=}}\mathit{C}\mathrm{H_2}$), 136.54 ($\mathrm{CH_2}\mathit{C}\mathrm{H{=}CH_2}$), 212.97 (C(1)). $^{13}\mathrm{C}$ NMR of *cis*-**16** (100 MHz, $\mathrm{CDCl_3}$) $\delta = 11.58$ ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$), 20.86 ($\mathit{C}\mathrm{H_2CH_3}$), 23.68, 27.01, 30.36 ($\mathit{C}\mathrm{H_2CH{=}CH_2}$), 40.93, 42.74 (C(3)), 54.70 (C(2)), 116.09 ($\mathrm{CH_2CH{=}}\mathit{C}\mathrm{H_2}$), 136.26 ($\mathrm{CH_2}\mathit{C}\mathrm{H{=}CH_2}$), 213.16 (C(1)). IR (neat) 3075, 2963, 2938, 2874, 1711, 1640, 1458, 912; HRMS *m*/*z* ($\mathrm{M^+}$) Calcd for: M, 166.1358. Found: *m*/*z* 166.1348. The reaction was conducted using CuCN in a similar manner under the following conditions: **1** (1.0 mmol), $\mathrm{Zn(C_2H_5)_2}$ (1.0 mmol), CuCN (0.005 mmol), **4a** (0.005 mmol), allyl acetate (1.0 mmol), $\mathrm{Pd[P(C_6H_5)_3]_4}$ (0.02 mmol), toluene (1.5 mL), temperature 0 °C, time 2 h after adding allyl acetate and Pd catalyst. The three-component coupling products, *trans*- and *cis*-**16**, were obtained in an 88 : 12 ratio and in 90% combined yield.

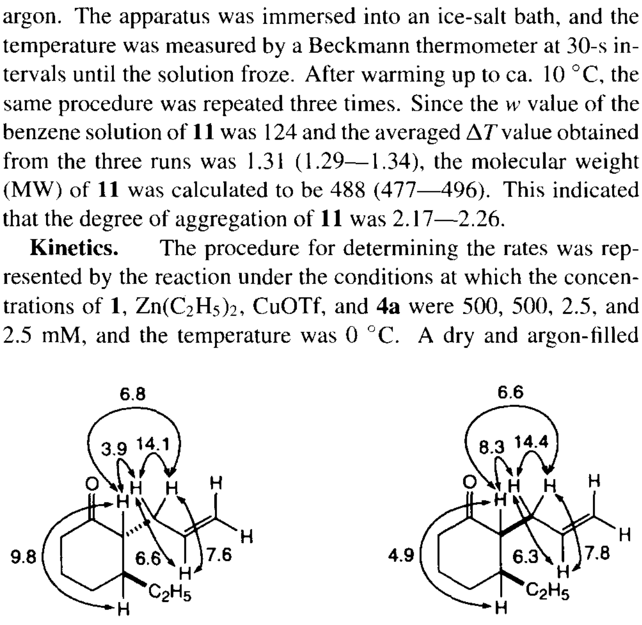
The regiochemistry of 2-allyl-3-ethylcyclohexanone (**16**) was determined by analysis of the $^{13}\mathrm{C}$-$^{13}\mathrm{C}$ COSY spectrum of a 90 : 10 mixture of *trans*- and *cis*-**16** (141 mg) in $\mathrm{CDCl_3}$ (0.65 mL) at 25 °C by using the 2D-INADEQUATE technique. The cross signals of the major isomer were observed between $\delta = 136.54$ ($\mathrm{CH_2}\mathit{C}\mathrm{H{=}CH_2}$), 31.50 ($\mathit{C}\mathrm{H_2CH{=}CH_2}$), 54.61 ($\mathit{C}\mathrm{(2)HCH_2CH{=}CH_2}$), 43.28 (C(2)-$\mathrm{H}\mathit{C}\mathrm{(3)HCH_2CH_3}$), and 25.82 ($\mathrm{C(3)H}\mathit{C}\mathrm{H_2CH_3}$) in this order, indicating the α,β-disubstituted structure. The major/minor ratio was shifted from 90 : 10 to the thermodynamic ratio of 67 : 33[44] by treatment with sodium methoxide in methanol at 70 °C for 2 h, showing that the minor **16** has the same connectivity as the major isomer.

The *trans*/*cis* stereochemistry of **16** was elucidated by $^{1}\mathrm{H}$ NMR analysis of a 67 : 33 mixture of **16** (20 mg) in $\mathrm{C_6D_6}$ (0.65 mL) at 25 °C. The 1D-homonuclear Hartmann–Hahn (HOHAHA) subspectra were developed with a mixing time of 113 ms from vinylic methine proton resonances at $\delta = 6.01$ for the major isomer and at $\delta = 5.75$ for the minor isomer to extract the relayed proton signals of $\mathrm{C}\mathit{H}_2\mathrm{CH{=}CH_2}$ and C(2)H. By the combination of the HOHAHA experiments with the decoupling experiments, in which the signals at $\delta = 6.01$ and 5.75 were irradiated respectively, the coupling constants between C(2)H and C(3)H of the major and minor isomers were deduced to be 9.8 and 4.9 Hz, respectively. This indicated that the major isomer had the *trans* structure. Selected coupling constants are shown in Fig. 11.

Structural Analysis of the Zn Enolate. **Connectivity:** CuCN (0.5 mg, 6 µmol) and a 0.03 M toluene-d_8 solution of **4a** (200 µL, 6 µmol) were placed into a 5-mm NMR tube equipped with a Young's tap. To the resulting white suspension, a 1.7 M toluene-d_8 solution of diethylzinc (170 µL, 0.3 mmol) was added at 0 °C under an argon stream and the mixture was vigorously shaken. After 10 min, 2-cyclohexenone (**1**) (1.7 M toluene-d_8 solution 170 µL, 0.3 mmol) was added at 0 °C. The whole mixture was shaken and kept at 0 °C for 30 min followed by measurement of the $^{1}\mathrm{H}$-$^{1}\mathrm{H}$ COSY NMR and phase-sensitive $^{13}\mathrm{C}$-$^{1}\mathrm{H}$ correlation NMR spectrum at 0 °C: $^{1}\mathrm{H}$ NMR (400 MHz, toluene-d_8) $\delta = 0.75$ (q, 2, $J = 8.1$ Hz), 0.92 (t, 3, $J = 7.3$ Hz), 1.01 (dd, 1, $J = 11.7$ and 21.5 Hz), 1.32 (m, 2) 1.54 (t, 3, $J = 8.1$ Hz), 1.47—1.64 (m, 2), 1.71 (m, 1), 2.01 (m, 1), 2.13—2.33 (m, 2), 5.27 (s, 1); $^{13}\mathrm{C}$ NMR (100 MHz, toluene-d_8) $\delta = 1.04$, 11.76, 12.65, 22.51, 28.61, 29.99, 31.80, 36.83, 107.92, 153.36. The cross signals in $^{1}\mathrm{H}$-$^{1}\mathrm{H}$ COSY NMR $\delta = 0.75$—1.55, 0.92—1.32, 1.01—1.55, 1.01—1.60, 1.32—2.01, 1.55—1.71, 1.55—2.13, 1.55—2.33, 1.71—2.13, 1.71—2.33, 2.01—5.27. The cross signals between $^{1}\mathrm{H}$- and $^{13}\mathrm{C}$ NMR $\delta = 0.75$—1.04, 0.92—11.76, 1.01—28.61, 1.32—29.99, 1.54—12.65, 1.55—22.51, 1.60—28.61, 1.71—22.51, 2.01—36.83, (2.13—2.33)—31.80, 5.27—107.92.

Aggregation State: Cryoscopic measurement was performed using a freezing-point depression apparatus modified for this air- and moisture-sensitive compound.[45] The number-average molecular weights were calculated from: $\Delta T = K_\mathrm{f} \cdot w/\mathrm{MW}$, where ΔT = depression (degrees), K_f = molal depression of the solvent, w = weight (g) of solute in 1000 g of solvent, and MW = molecular weight. The K_f value of this apparatus was calculated to be 5.16 on the basis of the depression of a benzene (10.53 g) solution of naphthalene (118.6—566.6 mg). The procedure for the molecular-weight determination of the ethylzinc enolate **11** was as follows: A dry Schlenk-type cryoscopy cell containing a Teflon®-coated stirring bar was evacuated and filled with argon that was then replaced with CuCN (2.9 mg, 0.0325 mmol), **4a** (8.0 mg, 0.0325 mmol), and benzene (11.57 g). The mixture was cooled to 7 °C. To this was added diethylzinc (807 mg, 6.5 mmol). After 10-min stirring at 7 °C, 2-cyclohexenone (**1**) (626 mg, 6.5 mmol) was added, and the mixture was stirred for 2 h at the same temperature. The whole mixture was degassed by three freeze-thaw cycles and filled with argon. The apparatus was immersed into an ice-salt bath, and the temperature was measured by a Beckmann thermometer at 30-s intervals until the solution froze. After warming up to ca. 10 °C, the same procedure was repeated three times. Since the w value of the benzene solution of **11** was 124 and the averaged ΔT value obtained from the three runs was 1.31 (1.29—1.34), the molecular weight (MW) of **11** was calculated to be 488 (477—496). This indicated that the degree of aggregation of **11** was 2.17—2.26.

Kinetics. The procedure for determining the rates was represented by the reaction under the conditions at which the concentrations of **1**, $\mathrm{Zn(C_2H_5)_2}$, CuOTf, and **4a** were 500, 500, 2.5, and 2.5 mM, and the temperature was 0 °C. A dry and argon-filled



trans-**16** *cis*-**16**

Fig. 11. Selected coupling constants (Hz) of $^{1}\mathrm{H}$ NMR (in $\mathrm{C_6D_6}$ at 25 °C).

Table 3. Kinetic Data of 1,4-Addition of $Zn(C_2H_5)_2$ to 2-Cyclohexenone (**1**) in Toluene Using CuOTf or CuCN and *N*-Benzylbenzenesulfonamide (**4a**)

		Concentration/mM				Temp	v_0
Entry	CuX	**1**	$Zn(C_2H_5)_2$	CuX	**4a**	T/°C	mM min^{-1}
1	CuOTf	500	500	2.5	2.5	0	50.0
2	CuOTf	500	500	2.5	2.5	−20	14.5
3	CuOTf	500	500	2.5	2.5	−10	24.0
4	CuOTf	500	500	2.5	2.5	10	43.0
5	CuOTf	300	500	2.5	2.5	0	29.1
6	CuOTf	400	500	2.5	2.5	0	45.2
7	CuOTf	600	500	2.5	2.5	0	63.0
8	CuOTf	500	300	2.5	2.5	0	30.3
9	CuOTf	500	400	2.5	2.5	0	42.4
10	CuOTf	500	600	2.5	2.5	0	73.5
11	CuOTf	500	500	2.0	2.0	0	44.0
12	CuOTf	500	500	3.0	3.0	0	72.5
13	CuOTf	500	500	5.0	5.0	0	116.0
14	CuCN	500	500	2.5	2.5	0	52.7
15	CuCN	300	500	2.5	2.5	0	32.0
16	CuCN	400	500	2.5	2.5	0	44.0
17	CuCN	600	500	2.5	2.5	0	62.4
18	CuCN	500	300	2.5	2.5	0	28.8
19	CuCN	500	400	2.5	2.5	0	37.3
20	CuCN	500	600	2.5	2.5	0	57.9
21	CuCN	500	500	2.0	2.0	0	43.3
22	CuCN	500	500	3.0	3.0	0	62.0
23	CuCN	500	500	5.0	5.0	0	114.0

20-mL Schlenk tube containing a Teflon®-coated stirring bar was equipped with a Zn–Se Attenuated Total Reflectance (ATR) accessory from Remspec, and the whole system was vacuumed and filled with argon gas three times. To this was added, at 23 °C and under an argon stream, **4a** (3.7 mg, 0.015 mmol), toluene (4.6 mL), and 30 mM toluene solution of CuOTf (0.5 mL, 0.015 mmol). After being stirred for 5 min at the same temperature, the mixture was cooled to 0 °C with an ice bath. A 5.02 M toluene solution of $Zn(C_2H_5)_2$ (0.6 mL, 3.0 mmol) was added. The mixture was stirred at 600 rpm for 10 min and the spectrum was collected as blank data. The substrate **1** (0.29 mL, 3 mmol) was added and the monitoring was started within the range from 910 to 2100 cm^{-1}. The measurement interval was 6 s. The reaction rate was calculated to be 50.0 mM min^{-1} based on the increase of absorbance at 1145 cm^{-1}.

The conditions for determination of the rates with CuCN were the same as those for CuOTf except for the amount of a 5.02 M toluene solution of $Zn(C_2H_5)_2$ (1.2 mL, 6.0 mmol). After addition of the substrate **1** (0.29 mL, 3 mmol) and taking of blank data, the mixture was stirred for 18 min and then the spectrum was again collected as blank data. Another 3 mmol of **1** was added to the mixture and the internal IR reflectance was measured.

All the kinetics data are listed in Table 3.

This work was supported by a Grant-in-Aid for COE Research No. 07CE2004 from the Ministry of Education, Science, Sports and Culture.

References

1 Reviews: P. Perlmutter, "Conjugate Addition Reactions in Organic Synthesis," Pergamon Press, Oxford (1992); V. J. Lee, "Conjugate Additions of Reactive Carbanions to Activated Alkenes and Alkynes," in "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 4, p. 69; V. J. Lee, "Conjugate Additions of Carbon Ligands to Activated Alkenes and Alkynes Mediated by Lewis Acids," in "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 4, p. 139.

2 M. J. Chapdelaine and M. Hulce, "Tandem Vicinal Difunctionalization: β-Addition to α,β-Unsaturated Carbonyl Substrates Followed by α-Functionalization," in "Organic Reactions," ed by L. A. Paquette, John Wiley & Sons, New York (1990), Vol. 38, p. 225.

3 Reviews: a) Y. Yamamoto, "Formation of C–C Bonds by Addition to α,β-Unsaturated Carbonyl Compounds," in "Houben–Weyl, Methods of Organic Chemistry," ed by G. Helmchen, R. W. Hoffmann, J. Mulzer, and E. Schaumann, Thieme, Stuttgart (1995), Vol. E 21b, p. 2041. b) R. J. K. Taylor, "Organocopper Chemistry: An Overview," in "Organocopper Reagents," ed by R. J. K. Taylor, Oxford University Press, Oxford (1994), Chap. 1. c) R. J. K. Taylor and G. Casy, "General Procedures: Starting Materials and Reaction Guidelines," in "Organocopper Reagents," ed by R. J. K. Taylor, Oxford University Press, Oxford (1994), Chap. 2 . d) R. D. Rieke and W. R. Klein, "Preparation of Organocopper Reagents Using Active Copper," in "Organocopper Reagents," ed by R. J. K. Taylor, Oxford University Press, Oxford (1994), Chap. 3, . e) P. Knochel M. J. Rozema, and C. E. Tucker, "Preparation of Highly Functionalized Reagents," in "Organocopper Reagents," ed by R. J. K. Taylor, Oxford University Press, Oxford (1994), Chap. 4. f) B. H. Lipshutz, "Higher Order Cyanocuprates," in "Organocopper Reagents," ed by R. J. K. Taylor, Oxford University Press, Oxford (1994), Chap. 5. g) E. Nakamura, "Me_3SiCl-Accelerated Conjugate Addition Reactions of Organocopper Reagents," in "Organocopper Reagents," ed by R. J. K. Taylor, Oxford University Press, Oxford (1994), Chap. 6. h) T. Ibuka and Y. Yamamoto, "Boron Trifluoride/Aluminum Trichloride-Mediated Conjugate Addition and Substitution Reactions," in "Organocopper Reagents," ed by R. J. K. Taylor, Oxford University Press, Oxford (1994), Chap. 7. i) M. Suzuki and R. Noyori, "Conjugate Addition-Enolate-Trapping Reactions," in "Organocopper Reagents," ed by R. J. K. Taylor, Oxford University Press, Oxford (1994), Chap. 9. j) J.-F. Normant, "Alkyne Carbocupration and Polyene Synthesis," in "Organocopper Reagents," ed by R. J. K. Taylor, Oxford University Press, Oxford (1994), Chap. 11. k) J. A. Kozlowski, "Organocuprates in the Conjugate Addition Reaction," in "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 4, p. 169. l) E. Nakamura, *Synlett*, **1991**, 539. m) S. H. Bertz and G. Dabbagh, *Tetrahedron*, **45**, 425 (1989). n) G. H. Posner, "An Introduction to Synthesis Using Organocopper Reagents," John Wiley & Sons, New York (1980). See also: o) S. H. Bertz, M. Eriksson, G. Miao, and J. P. Snyder, *J. Am. Chem. Soc.*, **118**, 10906 (1996). p) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966). q) H. Gilman, R. G. Jones, and L. A. Woods, *J. Org. Chem.*, **17**, 1630 (1952).

4 G. Cahiez and M. Alami, *Tetrahedron Lett.*, **27**, 569 (1986).

5 R. Scheffold, G. Rytz, and L. Walder, "Vitamin B_{12} and Related Co-Complexes as Catalysts in Organic Synthesis," in "Modern Synthetic Methods," ed by R. Scheffold, Salle/ Frankfurt, Sauerländer/ Aarau, John Wiley & Sons/ Chichester (1983), Vol. 3, p. 355.

6 a) S. Flemming, J. Kabbara, K. Nickish, H. Neh, and J. Westermann, *Tetrahedron Lett.*, **35**, 6075 (1994). b) B. A. Grisso, J. R. Johnson, and P. B. Mackenzie, *J. Am. Chem. Soc.*, **114**, 5160

(1992). c) R. C. Sun, M. Okabe, D. L. Coffen, and J. Schwartz, *Org. Synth.*, **71**, 83 (1992). d) C. Petrier, J. C. de Souza Barbosa, C. Dupuy, and J.-L. Luche, *J. Org. Chem.*, **50**, 5761 (1985). e) R. T. Hansen, D. B. Carr, and J. Schwartz, *J. Am. Chem. Soc.*, **100**, 2244 (1978). f) E. C. Ashby and G. Heinsohn, *J. Org. Chem.*, **39**, 3297 (1974). g) E. A. Jeffery, A. Meisters, and T. Mole, *J. Organomet. Chem.*, **74**, 365 (1974).

7 C. S. Cho, S. Motofusa, K. Ohe, and S. Uemura, *J. Org. Chem.*, **60**, 883 (1995).

8 Cu(I)-catalyzed 1,4-addition of organometallics. Li: a) J. Green and S. Woodward, *Synlett*, **1995**, 155. Mg: b) M. T. Reetz and A. Kindler, *J. Organomet. Chem.*, **502**, C5 (1995). c) H. O. House, R. A. Latham, and C. D. Slater, *J. Org. Chem.*, **31**, 2667 (1966). d) F. S. Prout and M. M. E. Abdulslam, *J. Chem. Eng. Data*, **11**, 616 (1966). e) A. J. Birch and M. Smith, *Proc. Chem. Soc.*, **1962**, 356. Al: f) J. Kabbara, S. Flemming, K. Nickisch, H. Neh, and J. Westermann, *Tetrahedron*, **51**, 743 (1995). g) P. Wipf, J. H. Smitrovich, and C.-W. Moon, *J. Org. Chem.*, **57**, 3178 (1992). Zn: h) A. Alexakis, J. Vestra, and P. Mangeney, *Tetrahedron Lett.*, **38**, 7745 (1997). Ti: i) M. Arai, E. Nakamura, and B. H. Lipshutz, *J. Org. Chem.*, **56**, 5489 (1991). Zr: j) B. H. Lipshutz and M. Segi, *Tetrahedron*, **51**, 4407 (1995); k) P. Wipf, W. Xu, J. H. Smitrovich, R. Lehmann, and L. M. Venanzi, *Tetrahedron*, **50**, 1935 (1994). Mn: l) G. Cahiez and M. Alami, *Tetrahedron Lett.*, **30**, 3541 (1989). For Cu(II)-catalyzed reaction, see: m) H. Sakata, Y. Aoki, and I. Kuwajima, *Tetrahedron Lett.*, **31**, 1161 (1990).

9 Chlorotrimethylsilane-assisted, Cu-catalyzed 1,4-addition of organozinc compounds: B. H. Lipshutz, M. R. Wood, and R. Tirado, *J. Am. Chem. Soc.*, **117**, 6126 (1995); S. Sibille, V. Ratovelomanana, and J. Périchon, *J. Chem. Soc., Chem. Commun.*, **1992**, 283; Y. Tamaru, H. Tanigawa, T. Yamamoto, and Z. Yoshida, *Angew. Chem., Int. Ed. Engl.*, **28**, 351 (1989); E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, **106**, 3368 (1984). $LiCu(CH_3)_2$-catalyzed 1,4-addition of alkenylzirconium compounds in the presence of $LiCH_3$ and $LiZn(CH_3)_3$: B. H. Lipshutz and M. R. Wood, *J. Am. Chem. Soc.*, **116**, 11689 (1994). Conjugate addition of alkyl halides in the presence of Zn/Cu couple: C. Petrier, C. Dupuy, and J. L. Luche, *Tetrahedron Lett.*, **27**, 3149 (1986). For the stoichiometric reaction using Li/Zn/Cu mixed reagents: M. J. Rozema, A. Sidduri, and P. Knochel, *J. Org. Chem.*, **57**, 1956 (1992); L. Zhu, R. M. Wehmeyer, and R. D. Rieke, *J. Org. Chem.*, **56**, 1445 (1991). For the acceleration effect of chlorotrimethylsilane on the 1, 4-addition reaction of lithium diorganocuprates, see: C. R. Johnson and T. Marren, *Tetrahedron Lett.*, **28**, 27 (1987); E. Nakamura, S. Matsuzawa, Y. Horiguchi, and I. Kuwajima, *Tetrahedron Lett.*, **27**, 4029 (1986); A. Alexakis, J. Berlan, and Y. Besace, *Tetrahedron Lett.*, **27**, 1047 (1986); E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **26**, 6019 (1985); C. Chuit, J. P. Foulon, and J. F. Normant, *Tetrahedron*, **36**, 2305 (1980).

10 Y. Morita, M. Suzuki, and R. Noyori, *J. Org. Chem.*, **54**, 1785 (1989); J. F. G. A. Jansen and B. L. Feringa, *J. Chem. Soc., Chem. Commun.*, **1989**, 741. For the 1,4-addition of Li/Zn or Mg/Zn mixed reagents, see: M. Suzuki, Y. Morita, H. Koyano, M. Koga, and R. Noyori, *Tetrahedron*, **46**, 4809 (1990); T. Takahashi, M. Nakazawa, M. Kanoh, and K. Yamamoto, *Tetrahedron Lett.*, **31**, 7349 (1990); M. Suzuki, H. Koyano, Y. Morita, and R. Noyori, *Synlett*, **1989**, 22; R. A. Kjonaas and R. K. Hoffer, *J. Org. Chem.*, **53**, 4133 (1988); W. Tückmantel, K. Oshima, and H. Nozaki, *Chem. Ber.*, **119**, 1581 (1986); M. Isobe, S. Kondo, N. Nagasawa, and T. Goto, *Chem. Lett.*, **1977**, 679. Application to the prostaglandins synthesis: R. Noyori, "Asymmetric Catalysis in Organic Synthesis," John Wiley & Sons, New York (1994), Chap. 6; M. Suzuki, A. Yanagisawa, and R. Noyori, *J. Am. Chem. Soc.*, **110**, 4718 (1988).

11 M. S. Kharasch and P. O. Tawney, *J. Am. Chem. Soc.*, **63**, 2308 (1941).

12 Preliminary communication: M. Kitamura, T. Miki, K. Nakano, and R. Noyori, *Tetrahedron Lett.*, **37**, 5141 (1996).

13 For the mechanistic studies on Cu-based 1,4-addition, see: D. E. Frantz, D. A. Singleton, and J. P. Snyder, *J. Am. Chem. Soc.*, **119**, 3383 (1997); M. Eriksson, A. Johansson, M. Nilsson, and T. Olsson, *J. Am. Chem. Soc.*, **118**, 10904 (1996); S. H. Bertz, G. Miao, B. E. Rossiter, and J. P. Snyder, *J. Am. Chem. Soc.*, **117**, 11023 (1995); A. S. Vellekoop and R. A. J. Smith, *J. Am. Chem. Soc.*, **116**, 2902 (1994); N. Krause, R. Wagner, and A. Gerold, *J. Am. Chem. Soc.*, **116**, 381 (1994); B. H. Lipshutz, S. H. Dimock, and B. James, *J. Am. Chem. Soc.*, **115**, 9283 (1993); E. J. Corey, F. J. Hannon, and N. W. Boaz, *Tetrahedron*, **45**, 545 (1989); Y. Horiguchi, M. Kamatsu, and I. Kuwajima, *Tetrahedron Lett.*, **30**, 7087 (1989); C. Ullenius and B. Christenson, *Pure Appl. Chem.*, **60**, 57 (1988); S. R. Krauss and S. G. Smith, *J. Am. Chem. Soc.*, **103**, 141 (1981); J. Berlan, J.-P. Battioni, and K. Koosha, *Bull. Soc. Chim. Fr. II*, **1979**, 183; H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976); C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, **95**, 7783 (1973). Molecular orbital calculation on the transition structures for the conjugate addition of organocopper reagents: S. Mori and K. Morokuma, *Chem. Eur. J.*, **5**, 1534 (1999); E. Nakamura, S. Mori, and K. Morokuma, *J. Am. Chem. Soc.*, **119**, 4900 (1997); B. H. Lipshutz, D. H. Aue, and B. James, *Tetrahedron Lett.*, **37**, 8471 (1996); J. P. Snyder, *J. Am. Chem. Soc.*, **117**, 11025 (1995); A. E. Dorigo and K. Morokuma, *J. Am. Chem. Soc.*, **111**, 6524 (1989).

14 J. Boersma, "Zinc and Cadmium," in "Comprehensive Organometallic Chemistry," ed by G. Wilkinson, F. G. A. Stone, and E. W. Abel, Pergamon Press, New York (1982), Vol. 2, Chap. 16.

15 a) F. H. van der Steen, J. Boersma, A. L. Spek, and G. van Koten, *Organometallics*, **10**, 2467 (1991). b) M. M. Hansen, P. A. Bartlett, and C. H. Heathcock, *Organometallics*, **6**, 2069 (1987). c) J. Dekker, P. H. M. Budzelaar, J. Boersma, and G. J. M. van der Kerk, *Organometallics*, **3**, 1403 (1984).

16 "Handbook of Chemistry and Physics," 70th ed, **1989—1990**, ed by R. C. Weast, CRC Press, Boca Raton (1989), p. D-151.

17 The result obtained with CuCN was reproducible in our laboratories. However, Alexakis et al. reported that 0.005 mol amt of CuCN catalyzes the conjugate addition of diethylzinc to 2-cyclohexenone in toluene, giving 3-ethylcyclohexanone in 21% yield after 1 h at 0 °C.[8h] The discrepancy may be due to the purity of diethylzinc, CuCN, or 2-cyclohexenone. The purity of diethylzinc profoundly influences the reactivity.

18 M. F. N. N. Carvalho, A. C. Consiglieri, M. T. Duarte, A. M. Galvão, A. J. L. Pombeiro, and R. Herrmann, *Inorg. Chem.*, **32**, 5160 (1993); E. J. Corey, S. Sarshar, and J. Bordner, *J. Am. Chem. Soc.*, **114**, 7938 (1992); F. A. Cotton and P. F. Stokely, *J. Am. Chem. Soc.*, **92**, 294 (1970); J. Moréno and M. Alléaume, *Compt. Rend.*, **C267**, 64 (1968).

19 T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date, and M. Shibasaki, *Angew. Chem., Int. Ed. Engl.*, **35**, 104 (1996); N. Shida, T. Uyehara, and Y. Yamamoto, *J. Org. Chem.*, **57**, 5049 (1992); T. Shono, I. Nishiguchi, and M. Sasaki, *J. Am. Chem. Soc.*, **100**, 4314 (1978).

20 H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957).

21 H. O. House, "Modern Synthetic Reactions," 2nd ed, Benjamin, Menlo Park, CA (1972), Chaps. 9—11; R. L. Augustine,

"Carbon–Carbon Bond Formation," Marcel Dekker, New York (1979), Vol. 1.

22 The mixed-metal enolate might induce side reactions facilely.

23 Some metal or mixed-metal enolates can be allylated in high yield by using Pd complexes as catalysts. Si: J. Tsuji, I. Minami, and I. Shimizu, *Chem. Lett.*, **1983**, 1325. Sn: B. M. Trost and E. Keinan, *Tetrahedron Lett.*, **21**, 2591 (1980). B/Li: F.-T. Luo and E. Negishi, *Tetrahedron Lett.*, **26**, 2177 (1985). B/K: E. Negishi, H. Matsushita, S. Chatterjee, and R. A. John, *J. Org. Chem.*, **47**, 3188 (1982). Zn/Li: E. Negishi and R. A. John, *J. Org. Chem.*, **48**, 4098 (1983).

24 R. Tsushima and T. Tsuruta, *J. Polym. Sci.*, **12**, 183 (1974).

25 H. K. Hofstee, J. Boersma, and G. J. M. van der Kerk, *J. Organomet. Chem.*, **144**, 255 (1978); K.-H. Thiele and J. Köhler, *J. Organomet. Chem.*, **12**, 225 (1968).

26 Methylcopper formed from equimolar amounts of CH_3Li and CuI does not undergo conjugate addition, whereas the 2 : 1 adduct is an excellent methylating agent.[3p]

27 S. Shambayati and S. L. Schreiber, "Lewis Acid Carbonyl Complexation," in "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 1, p. 283.

28 P. R. Markies, G. Schat, O. S. Akkerman, F. Bikelhaupt, W. J. J. Smeeta, and A. L. Spek, *Organometallics*, **9**, 2243 (1990); E. Weiss and R. Wolfrum, *Chem. Ber.*, **101**, 35 (1968).

29 R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, **30**, 49 (1991); M. Kitamura, S. Okada, S. Suga, and R. Noyori, *J. Am. Chem. Soc.*, **111**, 4028 (1989); M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, **108**, 6071 (1986). Theoretical support: M. Yamakawa and R. Noyori, *Organometallics*, **18**, 128 (1999); M. Yamakawa and R. Noyori, *J. Am. Chem. Soc.*, **117**, 6327 (1995).

30 I. G. Dance, P. A. W. Dean, and K. J. Fisher, *Inorg. Chem.*, **33**, 6261 (1994); B. F. Hoskins and R. Robson, *J. Am. Chem. Soc.*, **112**, 1546 (1990); C. Kappenstein and U. Schubert, *J. Chem. Soc., Chem. Commun.*, **1980**, 1116; D. T. Cromer, A. C. Larson, and R. B. Roof, Jr., *Acta Crystallogr.*, **19**, 192 (1965).

31 C. M. P. Kronenburg, J. T. B. H. Jastrzebski, A. L. Spek, and G. van Koten, *J. Am. Chem. Soc.*, **120**, 9688 (1998), and references cited therein. See also: S. H. Bertz, K. Nilsson, Ö. Davidsson, and J. P. Snyder, *Angew. Chem., Int. Ed. Engl.*, **37**, 314 (1998); J. A. Cabezas and A. C. Oehlschlager, *J. Am. Chem. Soc.*, **119**, 3878 (1997); S. H. Bertz, G. Miao, and M. Eriksson, *Chem. Commun.*, **1996**, 815; T. L. Stemmler, T. M. Barnhart, J. E. Penner-Hahn, C. E. Tucker, P. Knochel, M. Böhme, and G. Frenking, *J. Am. Chem. Soc.*, **117**, 12489 (1995); B. H. Lipshutz and B. James, *J. Org. Chem.*, **59**, 7585 (1994).

32 Reviews: B. L. Feringa and A. H. M. de Vries, "Advances in Catalytic Process," ed by M. D. Doyle, JAI Press, Connecticut (1995), Vol. 1, p. 151; R. Noyori, "Asymmetric Catalysis in Organic Synthesis," John Wiley & Sons, New York (1994), Chap. 4; A. Alexakis, "Asymmetric Conjugate Addition," in "Organocopper Reagents," ed by R. J. K. Taylor, Oxford University Press, Oxford (1994), Chap. 8; B. E. Rossiter and N. M. Swingle, *Chem. Rev.*, **92**, 771 (1992); H.-G. Schmalz, "Asymmetric Nucleophilic Addition to Electron Deficient Alkenes," in "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 4, p. 199. Co-catalyzed asymmetric 1,4-addition: A. H. M. de Vries and B. L Feringa, *Tetrahedron: Asymmetry*, **8**, 1377 (1997). Rh-catalyzed asymmetric 1,4-addition: Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, and N. Miyaura, *J. Am. Chem. Soc.*, **120**, 5579 (1998). Ni-catalyzed asymmetric 1,4-addition: A. H. M. de Vries, R. Imbos, and B. L Feringa, *Tetrahedron: Asymmetry*, **8**, 1467 (1997); C. L. Gibson, *Tetrahedron: Asymmetry*, **7**, 3357 (1996); M. Asami, K. Usui, S. Higuchi, and S. Inoue, *Chem. Lett.*, **1994**, 297; A. Corma, M. Iglesias, M. V. Martín, J. Rubio, and F. Sánchez, *Tetrahedron: Asymmetry*, **3**, 845 (1992); M. Uemura, R. Miyake, K. Nakayama, and Y. Hayashi, *Tetrahedron: Asymmetry*, **3**, 713 (1992); C. Bolm and M. Ewald, *Tetrahedron Lett.*, **31**, 5011 (1990); K. Soai, T. Hayasaka, and S. Ugajin, *J. Chem. Soc., Chem. Commun.*, **1989**, 516. Cu-catalyzed asymmetric 1,4-addition: O. Pàmies, G. Net, A. Ruiz, and C. Claver, *Tetrahedron: Asymmetry*, **10**, 2007 (1999); M. Yan, L.-W. Yang, K.-Y. Wong, and A. S. C. Chan, *Chem. Commun.*, **1999**, 11; Y. Nakagawa, M. Kanai, Y. Nagaoka, and K. Tomioka, *Tetrahedron*, **54**, 10295 (1998); B. L Feringa, M. Pineschi, L. A. Arnold, R. Imbos, and A. H. M. de Vries, *Angew. Chem., Int. Ed. Engl.*, **36**, 2620 (1997); A. K. H. Knöbel, I. H. Escher, and A. Pfaltz, *Synlett*, **1997**, 1429; A. Alexakis, J. Vestra, J. Burton, and P. Mangeney, *Tetrahedron: Asymmetry*, **8**, 3193 (1997); V. Wendisch and N. Sewald, *Tetrahedron: Asymmetry*, **8**, 1253 (1997); M. Kanai and K. Tomioka, *Tetrahedron Lett.*, **36**, 4275 (1995); M. Spescha and G. Rihs, *Helv. Chim. Acta*, **76**, 1219 (1993); D. M. Knotter, D. M. Grove, W. J. J. Smeets, A. L. Spek, and G. van Koten, *J. Am. Chem. Soc.*, **114**, 3400 (1992); K.-H. Ahn, R. B. Klassen, and S. J. Lippard, *Organometallics*, **9**, 3178 (1990). Zn-catalyzed asymmetric 1,4-addition: J. F. G. A. Jansen and B. L. Feringa, *J. Org. Chem.*, **55**, 4168 (1990).

33 E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Synth.*, Coll. Vol. 4, 162 (1963).

34 T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).

35 C. R. Noller, *Org. Synth.*, Coll. Vol. 2, 184 (1943).

36 E. M. Meyer, S. Gambarotta, C. Floriani, A. Chiesi-Villa, and C. Guastini, *Organometallics*, **8**, 1067 (1989).

37 T. Tsuda, T. Hashimoto, and T. Saegusa, *J. Am. Chem. Soc.*, **94**, 658 (1972).

38 R. D. Trepka, J. K. Harrington, and J. W. Belisle, *J. Org. Chem.*, **39**, 1094 (1974).

39 T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima, and Y. Kamiya, *J. Am. Chem. Soc.*, **111**, 4392 (1989).

40 E. Wenkert, L. L. Davis, B. L. Mylari, M. F. Solomon, R. R. da Silva, S. Shulman, R. J. Warnet, P. Ceccherelli, M. Curini, and R. Pellicciari, *J. Org. Chem.*, **47**, 3242 (1982).

41 Q.-L. Zhou and A. Pfaltz, *Tetrahedron*, **50**, 4467 (1994).

42 B. Miller and E. R. Matjeka, *J. Am. Chem. Soc.*, **102**, 4772 (1980).

43 G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 7788 (1973); L. S. Hegedus, R. E. Williams, M. A. McGuire, and T. Hayashi, *J. Am. Chem. Soc.*, **102**, 4973 (1980).

44 D. Caine, S. T. Chao, and H. A. Smith, *Org. Synth.*, **56**, 52 (1977).

45 M. Kitamura, S. Suga, M. Niwa, and R. Noyori, *J. Am. Chem. Soc.*, **117**, 4832 (1995).