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Reactions of $PhSCH_2Li$ and $NCCH_2Li$ with Benzaldehyde and Benzophenone: When Does the Mechanism Change from ET to Polar?

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The carbonyl-carbon kinetic isotope effect (KIE) and the substituent effect were measured for the reaction of phenylthiomethyllithium ($PhSCH_2Li$, **1**) with benzaldehyde and benzophenone, and cyanomethyllithium ($NCCH_2Li$, **2**) with benzaldehyde, and the results were compared with those for other lithium reagents such as MeLi, PhLi, $CH_2{=}CHCH_2Li$, and $CH_2{=}C(OLi)C(CH_3)_3$. It was previously shown that the reactions of MeLi, PhLi, and $CH_2{=}CHCH_2Li$ proceed via a rate-determining electron transfer (ET) process whereas the reaction of lithium pinacolone enolate goes through the polar (PL) mechanism. The reaction of **1** with benzaldehyde gave no carbonyl-carbon KIE ($^{12}k/^{13}k = 0.999 \pm 0.004$), similar to that measured previously for the MeLi reaction with benzophenone ($^{12}k/^{14}k = 1.000$). The effect of substituents of the aromatic ring of benzaldehyde and benzophenone on the reactivity gave very small Hammett ρ values of 0.17 ± 0.03 and 0.26 ± 0.05, respectively. These small ρ values are again similar to that observed for the reaction of MeLi. Likewise the reactions of **2** with benzaldehydes gave small KIE and the ρ value ($^{12}k/^{13}k = 0.996 \pm 0.004$, $\rho = 0.14 \pm 0.02$). Dehalogenation and enone-isomerization probe experiments for **2** showed no evidence for the presence of radical-ion pair of sufficient lifetime during the course of the reaction. It is concluded that the reactions of **1** and **2** with the aromatic carbonyl compounds proceed via the electron transfer-radical coupling mechanism with rate-determining ET as in the reactions of MeLi, PhLi, and $CH_2{=}CHCH_2Li$.

Introduction

Nucleophilic addition to carbonyl functions is one of the most basic organic reactions. The reaction has two possible pathways, polar addition (PL) and electron transfer (ET)-radical coupling (RC) sequence, eq 1, and the mechanism is highly nucleophile dependent. Current reaction design for synthetic purpose of additions of common nucleophiles to aldehyde and ketone is mostly based on the polar mechanism, but apparently the ET process is involved in reactions of the Grignard reagents and organolithium reagents.[1,2] In general, distinction between PL and ET mechanisms is not straightforward. Various experimental methods have been used so far to demonstrate the ET process; these include spectroscopic detection of radical intermediates,[1e,f,2a] detection of products indicative of radical intermediates,[2b,3] and measurement of secondary deuterium kinetic isotope effects (KIEs).[4,5] However, none of the methods is conclusive by itself. Gajewski's α-deuterium KIE criterion[5] can be used to distinguish the rate-determining ET mechanism from the PL mechanism, but it cannot differentiate the PL mechanism from the rate-determining RC one (vide infra). We have used the combination of several experimental methods, including KIEs, substituent effects, and chemical probe experiments, to distinguish the ET process from the PL process for the addition reactions of the Grignard,[1g,6] organolithium,[2c,d,7] and Wittig reagents.[8,9]

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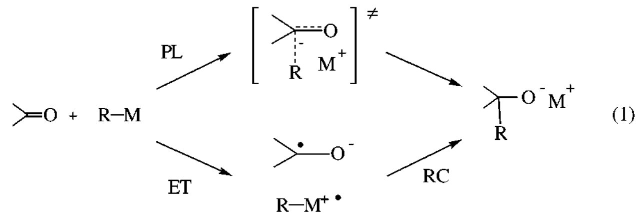

(1)

By using these methods, it has recently been shown that the reaction of benzaldehyde with lithium pinacolone enolate proceeds through the PL mechanism[7,10] (eq 1) whereas the reactions of benzaldehyde and/or benzophenone with methyllithium and allyllithium go through the ET-RC pathway.[2c,d] It was found that the mechanistic switching relates to the stability of the reagents measured by the intrinsic acidity of the conjugate acids of R anions in the gas phase. Here, the intrinsic acidity of R−H is estimated from the gas phase heat of formation (eq 2) from the data compiled in the literature:[11] 416.8 kcal/mol (R = Me), 400.8 (Ph), 390.7 ($CH_2{=}CHCH_2$), and 368.0 ($(CH_3)_3CC({=}O)CH_2$). The enolate reagent whose conjugate acid is most acidic reacts with benzaldehyde via the PL mechanism whereas the reagents whose conjugate acids are less acidic go through the ET pathway. The switching point lies between allyllithium and lithium pinacolone enolate for the reactions with benzaldehyde.

$$\mathrm{R\text{-}H} \overset{\Delta H_{\mathrm{gas}}}{\rightleftharpoons} \mathrm{R}^- + \mathrm{H}^+ \tag{2}$$

In the present study the reaction pathways for two reagents ($PhSCH_2Li$ (**1**) and $NCCH_2Li$ (**2**)), whose conjugate acids have the gas-phase heat of formation (381.6 and 372.8) between those of propene and pinacolone, were investigated experimentally by means of kinetic isotope effects (KIEs), substituent effects, and chemical probe experiments in order to determine which mechanistic scheme operates for these reagents.

Results and Discussion

Kinetic isotope effects were determined for the reactions of benzaldehyde with **1** and **2** by comparing reactivities in C_6D_5CHO/C_6H_5CHO and $C_6H_5{}^{13}CHO/C_6D_5CHO$ as reported previously,[7] and from the two values the carbonyl-carbon KIEs ($^{12}k/^{13}k$) were calculated. The indirect method was adopted in order to avoid the interference of ^{13}C natural abundance in the intensity measurement with the FT-ICR mass spectrometer. The results are listed in Table 1.

Substituent effects for the reactions of substituted benzaldehydes with **1** and **2** and for benzophenones with **1** were measured in THF at 0 °C by competition experiment as before.[7] The reaction of benzophenone with **2** was too slow to determine reliable substituent effects. Figures 1−3 illustrate the relationship between $\log(k_X/k_H)$ and the substituent constant σ. Since the σ constants of the ortho substituents were not available, the $\log(k_X/k_H)$ values for the ortho derivatives were plotted against the corresponding para-substituent constants and are indicated by closed circles, and the ρ values were calculated from the meta- and para-substituted derivatives.

Table 1. Kinetic Isotope Effects in the Reaction of 1 and 2 with Benzaldehyde in THF at 0 °C

Li reagent	k_H/k_{D5}	$k_{D5}/^{13}k$	$^{12}k/^{13}k$ [a]
$PhSCH_2Li$	1.024 ± 0.004	0.976 ± 0.002	0.999 ± 0.004
$NCCH_2Li$	1.021 ± 0.001	0.976 ± 0.004	0.996 ± 0.004

[a] Calcd from k_H/k_{D5} and $k_{D5}/^{13}k$.

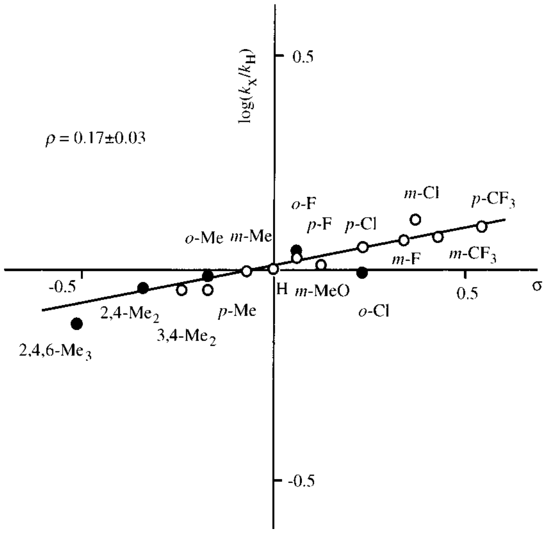

Figure 1. Variations of reactivity with σ values for the reaction of substituted benzaldehydes and **1** in THF at 0 °C.

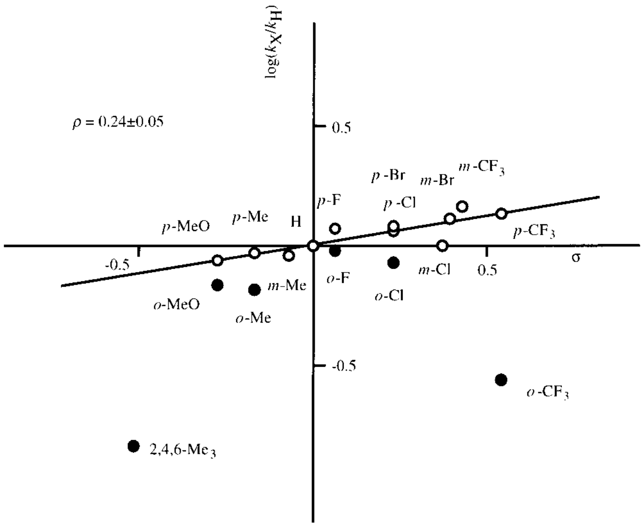

Figure 2. Variations of reactivity with σ values for the reaction of substituted benzophenones and **1** in THF at 0 °C.

Two chemical probe experiments, dehalogenation[6] and enone isomerization,[12] have been shown to be useful in estimating the possible intervention of a radical ion pair in the Grignard and Wittig reagents.[6,9,12b] In these probe experiments, o-iodobenzophenone (dehalogenation) or (Z)-2,2,6,6-tetramethylhept-4-en-3-one (enone isomerization) was mixed with a lithium reagent in THF at 0 °C, and after appropriate reaction time the reaction mixture was analyzed by GC. The results of the probe experiments are summarized in Chart 1.

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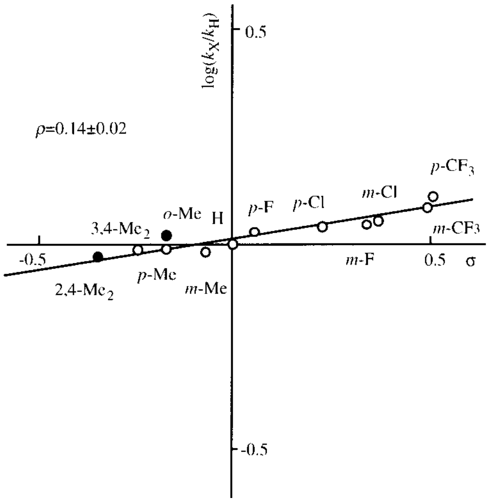

Figure 3. Variations of reactivity with σ values for the reaction of substituted benzaldehydes and **2** in THF at 0 °C.

Kinetic Isotope Effects. As is seen in Table 1 no carbonyl-carbon KIE was detected at 0 °C for both reagents. A heavy atom KIE is usually considered to be normal (larger than unity) when the total bonding at the labeled atom decreases in the TS and inverse (less than unity) when the bonding increases. In addition to the tight/loose character of the TS, however, there is an equally or even more important factor that determines the size of a primary KIE, the dynamic character of the TS;[13] KIE is larger if the labeled atom is involved to a greater extent in the reaction-coordinate motion at the TS. The importance of the reaction-coordinate contribution has well been demonstrated by calculations of primary carbon KIEs.[14] Thus, the carbonyl-carbon KIE is expected to be of considerable magnitude if the reaction proceeds via the polar mechanism or if the rate-determining step is RC in the ET-RC route since the motion of the labeled carbon is directly involved in the reaction coordinate in these cases. In contrast, the KIE would be much smaller for the rate-determining ET mechanism since there is no contribution from the reaction-coordinate motion.

The carbonyl-carbon KIEs of unity observed for **1** and **2** eliminate the possibility that these reactions proceed through the polar mechanism or the rate-determining RC mechanism of the ET-RC scheme. It should be noted that these KIE results are similar to those observed for other lithium reagents such as MeLi, PhLi, and $CH_2{=}CHCH_2Li$, for which no carbonyl-carbon KIE was detected,[2c,d] but different from the observation for lithium pinacolone enolate for which a normal carbon KIE was observed.[7]

Substituent Effects. The reaction of **1** gave small ρ values both with substituted benzaldehydes (0.17 ± 0.03) and benzophenones (0.24 ± 0.05). The ρ value for the reaction of **2** with benzaldehyde is also small (0.14 ± 0.02). These small ρ values are again similar to those observed previously for reactions of MeLi, PhLi, and $CH_2{=}CHCH_2Li$.[2c,d] A large substituent effect is reasonably expected for the polar mechanism, and the ρ value would also be large for the rate-determining RC mechanism because this mechanism involves ET preequilibrium, for which the Hammett ρ value is quite large.[15] Thus, the PL and the rate-determining RC mechanism would show similar kinetic behavior. In contrast to the above two cases, the magnitude of the ρ value for the rate-determining ET mechanism is not easily predictable because the character of the ET TS is not clear. However, previous results suggested that the ρ value could be rather small,[1g,2c,2d] which was rationalized in terms of predominant contribution of solvent reorganization in the activation process of the charge-separation type ET step.[2c]

The present results clearly indicate that the addition reactions with **1** and **2** proceed via the same mechanism as with other reactive Li reagents, namely rate-determining ET. It is noticeable in Figure 2 that the points of the benzophenone derivatives with bulky ortho-substituents (2,4,6-Me_3 and *o*-CF_3) deviate downward from the correlation line. The results resemble the Hammett plots for the reactions of benzophenone with MeLi.[2c] In the latter case the point for 2,4,6-Me_3 benzophenone deviated downward from the correlation line, and this substrate gave normal carbonyl-carbon KIE of 1.023 ($^{12}k/^{14}k$), indicative of the change of the rate-determining step from ET (for meta- and para-substituted benzophenone) to RC (for 2,4,6-Me_3 benzophenone) due to the steric retardation of the RC step for 2,4,6-Me_3 benzophenone.

Probe Experiments. Enone isomerization[12] and dehalogenation[6] experiments are the probes that measure whether a reagent has enough ability to transfer electron to enone and halobenzophenone, respectively. The enone isomerization was previously used by House and Ashby for RLi and RMgX.[12] Here, isomerization of the starting cis enone to trans upon mixing with a reagent is taken as indication of occurrence of ET from the reagent to the enone. Since *Z*-2,2,6,6-tetramethylhept-4-en-3-one has more negative reduction potential (−2.28 V vs SCE) than benzaldehyde (−1.84 V) and benzophenone (−1.82 V),[16] a positive response in the enone-isomerization experiment then indicates the possible occurrence of ET to the aromatic aldehyde and ketone. Dehalogenation experiment measures the occurrence of ET from a reagent to halobenzophenone.[6] As indicated by Savéant[17] and Tanner,[18] halobenzophenone radical anion undergoes dehalogenation with rate constants ranging 10^2−10^6 when the halogen is Br or I, and this reaction can compete with the RC step when a radical ion-pair intermediate was formed by ET. Although the dehalogenation rate for the actual reaction intermediate would be much slower than reported because of strong interaction between the ketyl and the counter radical cation of the nucleophile, there would be good possibility for dehalogenation to occur if one uses *o*-halobenzophenones, for which the RC step is slowed by the steric reason.[1g] If these two probes were positive there would be a good possibility that the reaction proceeds via the ketyl intermediate of sufficient lifetime.

The probe experiments were applied for **2**, which may lie in a borderline region between PL and ET pathways.

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Chart 1

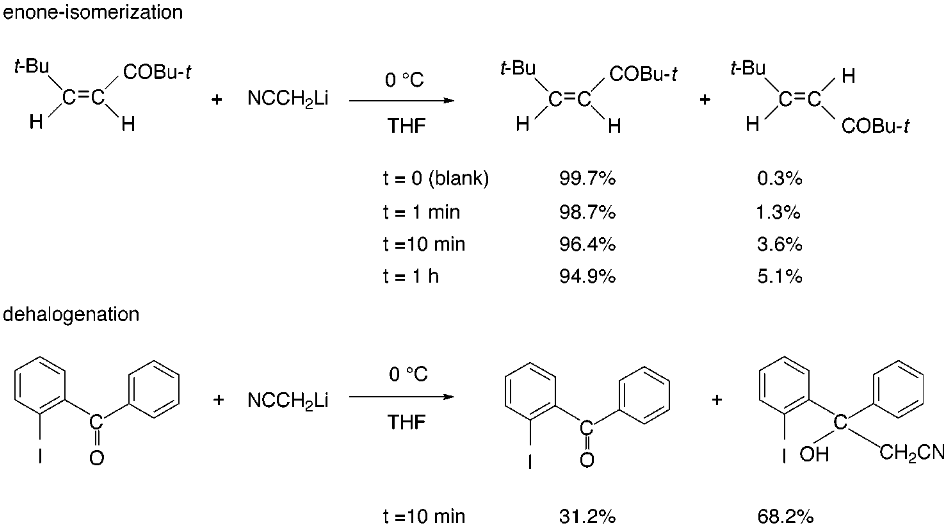

Table 2. Summary of Carbon Kinetic Isotope Effects and Hammett ρ Values for Reactions of a Series of Lithium Reagents with Aromatic Carbonyl Compounds[a]

Li reagent/solvent	substrate	KIE[b]	ρ value	rate-determining step	ΔH_{gas}[e]
MeLi/Et$_2$O	BP	1.000 ± 0.002	0.23 ± 0.09	ET	416.8
PhLi/c-Hex−Et$_2$O	BP	1.003 ± 0.001	0.19 ± 0.08	ET	400.8
	BA	0.998 ± 0.003	0.13 ± 0.07	ET	
AllylLi/Et$_2$O	BP	0.994 ± 0.003	0.21 ± 0.09	ET	390.7
PhSCH$_2$Li/THF	BA	0.998 ± 0.008[c]	0.17 ± 0.03	ET	381.6
	BP	nd[d]	0.24 ± 0.05	ET	
NCCH$_2$Li/THF	BA	0.992 ± 0.008[c]	0.14 ± 0.02	ET	372.8
Li enolate/THF	BA	1.039 ± 0.009[c]	1.16 ± 0.31	PL	368.0

[a] At 0 °C. BP: benzophenone, BA: benzaldehyde. Data for MeLi, PhLi, and AllyLi were taken from ref 2c,d, and for Li enolate from ref 7. [b] $^{12}k/^{14}k$. [c] Corrected to $^{12}k/^{14}k$. [d] Not determined. [e] Calculated from the data compiled in ref 11, in kcal/mol.

Chart 1 illustrates the results of the probe experiments. The near absence of enone isomerization suggests that the ability is low for **2** to transfer electron to the enone of relatively low electron-accepting ability. The point of mechanistic changeover from ET to PL in the reaction of aromatic carbonyl compounds is likely to exist just beyond NCCH$_2$Li to the lithium pinacolone enolate side. The dehalogenation experiment gave no evidence for the presence of a radical ion-pair intermediate of sufficient lifetime, consistent with the rate-determining ET mechanism

Mechanistic Consideration. Table 2 summarizes the results of the KIEs and the Hammett ρ values on the addition reactions of several organolithium reagents with benzaldehyde and benzophenone, together with the gas phase heat of formation of the conjugated carbon acids defined in eq 2. The reactions of organolithium reagents with benzaldehyde proceed via either a polar addition mechanism (PL, in eq 1) or an electron transfer (ET)−radical coupling (RC) mechanism depending on the structure of the reagents. The present results indicate that the mechanistic switching from the rate-determining ET to PL occurs within a very narrow range between **2** and lithium pinacolone enolate.

Recently two groups have published papers, which directly or indirectly relate to the mechanism of the reactions of the aromatic carbonyl compounds with organolithium reagents.[5,19] One is a caution for the use of competition experiments as a mechanistic diagnostic for ultrafast reactions.[19] An answer to the alarm of using competition experiments should be provided by direct rate measurements, and we are measuring rate constants of reactions of benzaldehyde and benzophenone with various RLi and RMgX reagents by use of the stopped-flow method. Preliminary results indicated that the relative reactivities determined by competition were essentially reproduced by the direct rate measurements for reaction of benzophenone with MeLi and MeMgBr and that the reactions of MeLi with benzophenone and **2** with benzaldehyde are not too fast to be deteriorated by diffusion.[20] We will report full results in due course.

In a recent paper, Gajewski and co-workers used the secondary α-deuterium KIE as a mechanistic probe to elucidate the rate-determining step of the addition reaction of various nucleophiles with benzaldehyde.[5] The basis idea is that the rate-determining formation of a ketyl radical anion results in a normal deuterium KIE, whereas the polar addition leads to an inverse KIE. The rate-determining RC mechanism was not explicitly considered, but this and the PL mechanism should give similar results because the C−C bond formation is rate determining in both mechanisms. Three different classes of reagents were examined: complex metal hydrides, RMgX, and RLi. The measured secondary α-deuterium KIEs were in most cases consistent with our previous conclusions based on the carbonyl-carbon KIE and the Hammett substituent effects for the reactions of ben-

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[20] Direct rate measurements by means of the stopped-flow method gave the pseudo-first-order rate constant $k = 16.4\ s^{-1}$ ([MeLi] = 4.2 mmol L^{-1}, [Ph$_2$C=O] = 1.0 mol L^{-1}) and 11.1 s^{-1} ([**2**] = 5.0 mmol L^{-1}, [PhCHO] = 1.0 mmol L^{-1}).

zophenone at 0 °C.[1g,2c,d,21] For example, the inverse α-deuterium KIEs for $LiAlH_4$ ($k_H/k_D = 0.975$), $LiBH_4$ (0.885), and $NaBH_4$ (0.82) at −78 °C suggested the PL mechanism, the inverse KIEs for MeMgBr (0.87 at −78 °C) were compatible with the RC mechanism,[1g] and the normal KIEs observed for allylMgBr (1.04) and allyllithium (1.095) at −78 °C could be taken as evidence for the rate-determining SET mechanism, all these agreeing with our previous mechanistic assignment.[1g,2c,d,21]

By contrast, the reactions of MeLi and BuLi with benzaldehyde were reported to give an inverse (0.88) and null (0.99) deuterium KIEs, respectively, at −78 °C, which were taken as the indication of rate-determining C−C bond formation. The assigned mechanism apparently disagrees with the rate-determining ET mechanism previously concluded for the reaction of MeLi and BuLi with benzophenone.[2c,d] We, at present, have no explanation for the discrepancy. The apparent difference might have arisen from the temperature effect (−78 vs 0 °C) or from the difference between benzaldehyde and benzophenone. Clearly the mechanism of these apparently simple reactions is not fully understood, and further thorough and careful experiments are needed.

Experimental Section

Materials. THF was dried over sodium/benzophenone and distilled immediately before use. All substituted benzaldehydes were commercially available and purified either by distillation or recrystallization. Substituted benzophenones were obtained as described in the literature.[8] Benzaldehyde-carbonyl-^{13}C was synthesized by the pyridinium dichromate oxidation of benzyl alcohol-7-^{13}C, which was prepared by carbonylation of phenylmagnesium bromide with $^{13}CO_2$ gas (99%, Aldrich) and the borane reduction of the resultant benzoic acid-7-^{13}C. Benzaldehyde-d_5 was prepared according to the same sequence of reactions starting with bromobenzene-d_5.

Reactions. All reactions were carried out in THF at 0 °C under dry nitrogen using the Schlenk tube technique.[22] A THF solution of **1** was prepared by mixing an equimolar amount of thioanisol and butyllithium in THF at −78 °C. A THF solution of **2** was prepared from acetonitrile and LiHMDS (1.0 M, Aldrich). The reactions of these reagents with substituted benzaldehydes and of **1** with benzophenones gave the corresponding carbonyl adducts as the only product. The products were isolated by TLC and characterized by ^1H NMR (JEOL JNM-EX 400, $CDCl_3$). Material balance of the reaction was confirmed for the parent compounds to be excellent (99.9 ± 0.9%).

Relative Reactivity Measurement. A pair of benzaldehydes (normally the parent and a substituted one, 0.5 mmol each) and 1-methylnaphthalene (ca 0.1 mmol, internal standard) were placed in a dry, serum-capped test tube and dissolved in 3.0 mL of dry THF. The solution was divided to two parts; thus, each test tube contained two kinds of benzaldehydes, 0.25 mmol each. To one test tube out of the two was added 1.0 mL of a lithium reagent (0.33 M in THF, 0.33 mmol) at 0 °C by means of hypodermic syringe. The solution was then allowed to react for 1 min for **1** and 20 s for **2**. The reaction mixture was treated with aq NH_4Cl, extracted with ether, dried over $MgSO_4$, and subjected to HPLC analysis (RP-18, $CH_3CN:H_2O = 7:3$, detected at 250 nm). The relative intensity of each reactant to that of the internal standard was compared to the corresponding relative intensity from the solution to which the lithium enolate solution was not added. The fractions of reaction (f) were calculated for both reactants, and the reactivity ratio was computed according to equation

$$k_A/k_B = \log(1 - f_A)/\log(1 - f_B)$$

The reactions of substituted benzophenone with **1** were carried out in a similar manner except that the fraction of reaction were determined by GC (2-m glass column packed with 3% PEG-HT) with dibenzyl ether as an internal standard.

Carbon-13 KIE Measurement. The isotope effects were determined for C_6D_5CHO vs C_6H_5CHO and $C_6H_5{}^{13}CHO$ vs C_6D_5CHO in order to avoid the interference of ^{13}C natural abundance in intensity measurement. Isotopically labeled and unlabeled benzaldehyde (2.0 mmol each) and 1-methylnaphthalene (0.14 mmol) were dissolved dry THF (7.6 mL), and the solution was divided into eight parts. To each solution was added at 0 °C a preset amount of reagent (0.33 M in THF) in such a manner that the fraction of reaction varies from 20% to 80%. After 1 min for **1** and 20 s for **2**, the reaction solution was hydrolyzed with NH_4Cl, and the organic layer was subjected to HPLC in order to determine the fraction of reaction. The organic layer was then transferred to a sample inlet tube, and the volatile materials were removed under reduced pressure. The isotopic ratio of the remaining recovered benzaldehyde was analyzed with Extrel FTMS 2001 Fourier transform mass spectrometer as described previously.[7]

Probe Experiments. Enone isomerization and dehalogenation probe experiments were done in a similar manner as reported previously.[6,9] *Z*-2,2,6,6-Tetramethylhepta-4-en-3-one (0.12 mmol) and 1-methylnaphthalene (0.25 mmol) were dissolved in dry THF (1.0 mL), to which was added **2** in THF (0.32 M, 0.5 mL) at 0 °C. The solution was allowed to react for preset time (1 min, 10 min, and 1 h), and the degree of isomerization was analyzed by GLC (PEG 2 m, 180 °C). Dehalogenation experiment was carried out similarly using *o*-iodobenzophenone as a probe substrate instead of enone. The addition product was isolated by TLC and characterized by NMR (δ 3.37−3.45, 2H, m; δ 3.50, 1H, s; δ 7.04−7.94, 9H, m) and MS ($m/z = 348.998$), and the product ratio was determined by HPLC (RP-18, $CH_3CN:H_2O = 7:3$, 250 nm).

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