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Reaction Pathway and Transition State of the Zn-Promoted Barbier-Type Reactions of Benzaldehyde and Benzophenone with Allylic Iodides

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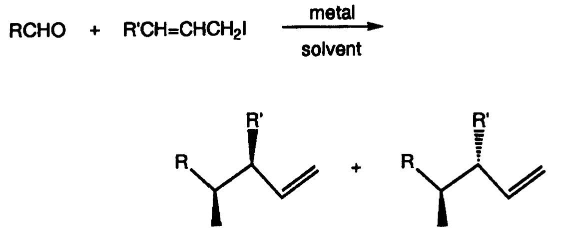
The carbonyl-^{14}C kinetic isotope effects and the substituent effects on the reactivity of the Zn-promoted Barbier-type reaction of allyl iodide (3-iodo-1-propene) with benzaldehyde and benzophenone were determined in THF at 25 °C. The observed normal carbon isotope effects as well as positive Hammett ρ values suggest that the reactions go through a direct nucleophilic addition mechanism. No indication of the occurrence of electron transfer was obtained by enone isomerization and dehalogenation probe experiments. Diastereoselectivity in the reaction of crotyl iodide (1-iodo-2-butene) with benzaldehyde was low and independent of the substituent on aldehyde, consistent with the six-membered cyclic transition state.

Nucleophilic alkylation of carbonyl compounds with organometallics is one of the most useful reactions in organic synthesis. The use of alkyl halide and metal (often called Barbier-type) is a convenient method to achieve the carbonyl addition especially of allyl halide. Because of the high reactivity of allyl halide in the Barbier-type reaction, a variety of metal can be used and the difference in reactivity and diastereoselectivity has been investigated (Eq. 1).[1—5]

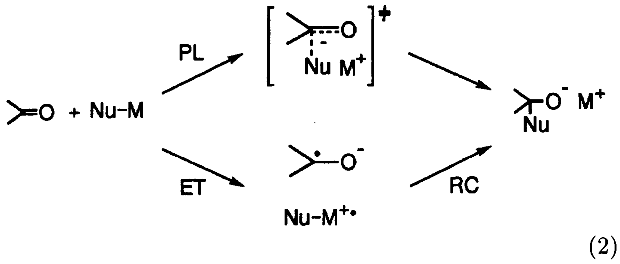


(1)

Mechanistically there remain several points to be clarified in the Barbier-type reaction; (1) does the reaction occur on the metal surface or in solution; (2) does electron transfer occur from the metal or an organometallic reagent formed in situ to a carbonyl compound; and (3) what does the transition state look like? We have previously investigated the Barbier-type reaction of allyl iodide with benzaldehyde in the presence of Sn or Pb, and concluded that the reaction does not occur on the metal surface but in solution and goes through a polar cyclic transition state.[6] We now wish to report the results of mechanistic study of the Zn-promoted Barbier-type reaction and to see whether there are any mechanistic difference for different metals besides in reactivity.

Results and Discussion

In general, the nucleophilic addition to carbonyl functions has two possible reaction pathways, the polar (PL) route and the electron transfer-radical coupling (ET-RC) sequence (Eq. 2). Whether a reaction goes through the PL or the ET-RC route depends on the nature of the nucleophile as well as the strctuture of the carbonyl compounds, and the determination of the reaction route is quite difficult in some cases.



(2)

We have recently demonstrated that the mechanistic criteria shown in Chart 1 are useful in determining the reaction route of the nucleophilic additions.[7] Here, three mechanistic possibilities, the PL mechanism, the ET-RC mechanism with rate-determining ET, and the ET-RC mechanism with rate-determining RC, can be distinguished by the combination of the criteria. By this technique, it has been shown that the reactions of allyllithium and allylmagnesium bromide go through the ET-RC pathway with rate-determing ET[8—10] while the reactions of allyltin and allyllead reagents proceed via the PL route.[6,10]

The carbonyl-^{14}C kinetic isotope effects in the Zn-promoted Barbier-type reactions of allyl iodide with benzaldehyde and benzophenone were determined in THF at 25.0±0.1°C as described previously.[8,9] The relative reactivities in the Barbier-type reactions with substituted benzaldehydes or benzophenones were determined by the competition experiemts.[6] In Figs. 1 and 2 are shown the results of kinetic isotope effects and the Hammett plots for benzaldehyde and benzophenone, respectively. Since the σ constants of the ortho substituents were not determined, the $\log(k_X/k_H)$ values for the ortho derivatives were plotted against the corresponding para substituent constants and indicated by closed circles. The points for the *o*-substituted derivatives are not on the correlation line especially for the benzophenone case, but meta and para substituents

Chart 1.

Rate-determining step	Carbonyl-^{14}C KIE	Hammett ρ value	Enone isomerization	Dehalogenation probe
PL	Large	Large	No	No
RC	Large	Large	Yes	Yes
ET	Small	Small	Yes[a)]	Yes[a)]

a) These may be "no" in cases that the RC step is fast compared to isomerization or dehalogenation.

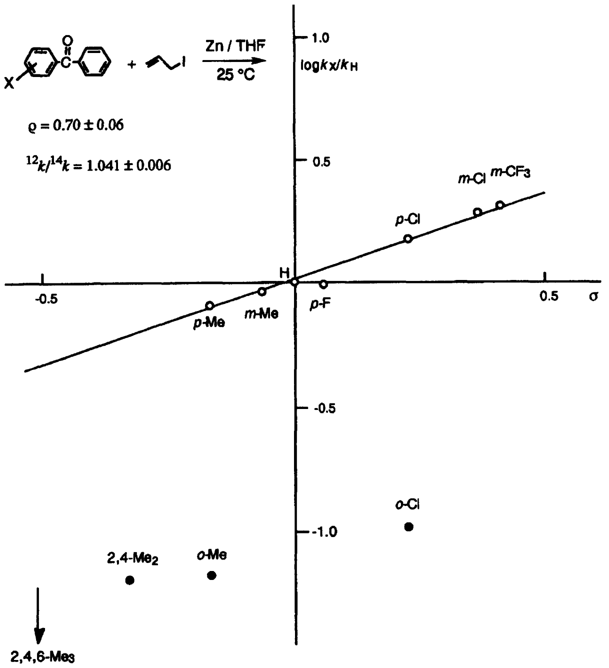


Fig. 1. The subsituent effects and the carbonyl-^{14}C kinetic isotope effect for the Zn-promoted Barbier-type reaction of benzophenone with allyl iodide at 25 °C in THF. Filled circles refer to the *o*-substituted derivatives.

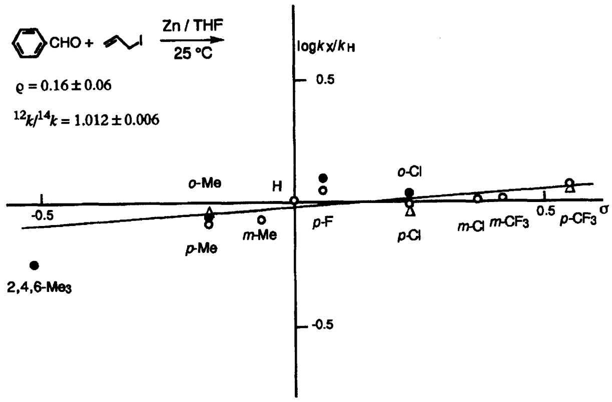


Fig. 2. The substituent effects and the carbonyl-^{14}C kinetic isotope effect for the Zn-promoted Barbier-type reaction of benzaldehyde with allyl iodide at 25 °C in THF. Filled circles refer to the *o*-substituted derivatives and triangles denote the reactivities of the *p*-substituted derivatives under the conditions that excess Zn powder was eliminated from the reaction mixture.

gave reasonably good straight lines, from which the ρ values were calculated.

The Zn-promoted Barbier-type reaction of benzophenone gave fairly large carbonyl-^{14}C kinetic isotope effect of 1.041, which clearly indicates that the bonding to the carbonyl carbon is changing at the rate-determining transition state. The Hammett plot of the reaction in Fig. 1 shows a positive ρ value (0.70±0.06) as well as large rate retardation effects ($k_{o\text{-Me}}/k_{p\text{-Me}}$=0.08) of the ortho substituents. The steric ortho substituent effects suggest that the C–C bond formation is involved in the transtion state. These results are consistent with the polar mechanism and the ET-RC mechanism with rate-determining RC.

The distinction between the two possibilities can be made by the probe experiments shown in Chart 1. Enone-isomerization[11,12)] and dehalogenation experiments[13,14)] are the probes that measure whether a reagent has enough ability to transfer an electron to the carbonyl compounds, and therefore if the two probes are positive there will be a good possibility that the reaction proceeds via the ET-RC sequence. In the former experiment, isomerization of the starting cis enone to trans enone upon mixing with a reagent is taken as indication of occurrence of ET from the reagent to enone. Since the reduction potential of (*Z*)-2,2,6,6,-tetramethyl-4-hepten-3-one is more negative (−2.28 V vs. SCE) than those of benzaldehyde (−1.84 V) and benzophenone (−1.82 V),[14)] a positive result of the enone isomerization experiment then indicates the possible occurrence of ET to the aromatic aldehyde and ketone. In the dehalogenation experiment, *o*-bromo- or *o*-iodobenzophenone is treated with a reagent. If the electron transfer occurs and the lifetime of the halobenzopheone ketyl thus formed is long enough, the halobenzophenone ketyl will undergo dehalogenation to yield benzophenone and other dehalogenation products, and therefore the detection of such products can be evidence for the occurrence of electron transfer. We have so far observed several positive response in the probe experiments for reactions which could be considered to go through the ET mechanism.[7,13—15)]

The two probe experiments were carried out as described previously[7,13,14)] and found negative for the present Barbier-type reaction; thus, neither enone isomerization nor dehalogenation was observed in all cases. From these, coupled with the isotope effect and the substituent effect results, we conclude that the Zn-promoted Barbier-type reaction of allyl iodide with benzophenone proceeds through the polar nucleophilic mechanism.

The reaction with benzaldehyde is also likely to go through the polar mechanism, since nucleophilic attack is much feasible for aldehyde than for ketone for the steric reason while electron accepting ability of benzaldehyde is similar to benzophenone. The small but significant positive carbonyl-^{14}C kinetic iostope effect observed for the benzaldehyde reaction supports this conclusion. The Hammett plot in Fig. 2 shows that the ρ value for the benzalehyde reaction is small, which may be attributable to an early transition state. Another evidence that suggests the polar mechanism for both benzaldehyde and benzopheneone is the relative reactivity of these two substrate. The relative reactivity of benzophenone vs. benzaldehyde was determined by the usual competition experiment, and was found to be 8.9±2.2 for the present Barbier-type reaction. The higher reactivity of benzaldehyde over benzophenone is due to the steric effect and characteristic of the polar nucleophilic addition mechanism. On the other hand, the reactivity ratio of 1.3±0.1 was obtained for the reactions of allylmagnesium bromide, which has been shown to react via the rate-determining electron transfer mechanism with these aromatic carbonyl compounds.[9,10] This rather similar reactivity is consistent with the similar reduction potentials of these compounds.

It has been documented in the literature that the Sn-promoted Barbier-type reaction of allyl iodide proceeds by the nucleophilic addition of an organotin reagent, $I_2Sn(CH_2CH{=}CH_2)_2$, formed in situ to carbonyl compounds.[6,16] It is likely that the Zn-mediated reaction also proceeds through the prior formation of an organozinc reagent before the addition takes place. In order to confirm this, competititon experiments were carried out by adding a supernatant solution prepared from allyl iodide and Zn powder to a pair of benzaldehydes of different substituents. It was found that the supernatant solution has similar reactivity to the mixture of allyl iodide and Zn. Furthermore, the relative reactivitites obtained for the reactions without Zn in the reaction mixture are similar to those under the normal Barbier conditions as shown in the triangles in Fig. 2. The results indicate that the reaction does not occur on the metal surface and are consistent with the formation of an organozinc reagent prior to the addition reaction.

The *erythro*: *threo* ratios in the Zn-promoted Bariertype reactions of substituted benzaldehydes with crotyl iodide were measured and listed in Table 1 together with those determined previously for the Sn-promoted reactions. It can be seen that the selectivity in the Zn-promoted reaction is low and essentially indepenendent of the substituents as in the Sn-promoted one. These results can be rationalized by considering a cyclic six-membered transition state as usually assumed for the Barbier-type reactions.[17,18] In such a transition state, the *erythro*: *threo* ratio should basically be governed by the E: Z ratio of the butenyl unit of the in situ formed reagent[19] and the ratio would be independent of the substituent.

Table 1. *Erythro*: *Threo* Ratios in the Barbier-Type Reactions of Substituted Benzaldehydes with Crotyl Iodide[a]

Substituent	Zn/THF	Sn/THF[b]
H	55 : 45	52 : 48
o-Cl	54 : 46	54 : 46
p-Cl	56 : 44	54 : 46
o-Me	54 : 46	56 : 44
p-Me	57 : 43	55 : 45
2,4,6-Me_3	57 : 43	51 : 49

a) Reactions were carried out at 25 °C. Figures are the averages of more than two runs, and the reproducibility is ±2%. b) Ref. 6.

In summary, the present results lead us to conclude as follows. (1) The Zn-promoted Barbier-type reaction does not occur on the metal surface but in solution. (2) The reaction goes through the direct polar addition mechanism. No evidence was obtained for the occurrence of electron transfer during the reaction. (3) The transition state is most likely to have a cyclic six-membered geometry at least for the reaction benzaldehyde.

Experimental

Materials. Substituted benzaldehydes were commercially available and purified by distillation. THF was distilled from $LiAlH_4$ and benzopheone/Na successively. Crotyl iodide was prepared from the reaction of crotyl bromide and NaI in acetone. Commercial zinc powder (nacalai, Guaranteed Reagent) was purified according to the literature.[20] Carbonyl-^{14}C-labeled benzaldehyde and benzophenone were prepared as mentioned before.[8,9] Allymagnesium bromide was prepared from allyl bromide and doubly sublimed Mg (Ventron) and standardized.[21]

Reactions. The Barbier-type reaction was carried out under stirring at 25 °C in THF under the dry nitrogen atmosphere. The reaction with allylmagnesium bromide was run as described previously.[9] All reactions gave the expected addititon products exclusively, which were isolated and characterized by ^{1}H NMR (Bruker-360, $CDCl_3$) and IR. The material balance was confirmed for the unsubstituted benzaldehyde and benzophenone, and found excellent (100±2%, and 99±2%, respectively). The general procedures of the relative reactivity measurement,[6,7] the reaction with supernatant solution,[6] the enone isomerization probe experiment,[7,14] the dehalogenation probe experiment,[6,7] and the measurement of the diastereomer ratio[6] were described previosly.

Determination of Carbon-14 Kinetic Isotope Effects. The procedures are basically the same as before.[8,9] A THF solution of benzaldehyde-*carbonyl*-^{14}C (25 mL, 50 mmol) containing naphthalene (internal standared for GC analysis, 10 mmol) was divided into several parts and transferred to flame-dried test tubes. To each test tube were added preset amounts of Zn powder (0.2—0.8 equiv) and allyl iodide (0.4—1.6 equiv), and the mixture was stirred at 25.0±0.1°C for 1 h. The solution was hydrolyzed, extracted with ether, dried over $MgSO_4$, and subjected to GC analysis (2-m glass column packed with 3% PEG-HT) to measure the fraction of reaction (f). The ethereal solution, which contains the product alcohol and the unreacted benzaldehyde, was treated with excess amount of PhLi; the reaction of benzaldehyde with PhLi is known to give diphenylmethanol quantitatively with the carbonyl-^{14}C kinetic isotope effect of unity.[8)] The resulting diphenylmethanol was isolated by TLC, purified by bulb-to-bulb distillation and recrystallization (hexane). The molar radioactivity of diphenylmethanol was measured by a liquid scintillation counter (Beckman LS-9000), and the isotope effect was calculated by the least-squares method according to Eq. 3,[22)] where R_r and R_0 stand for the molar radioactivity of the starting and the recovered benzaldehyde (measured as diphenylmethanol), respectively. The method of determining the kinetic isotope effect of the benzophenone reaction was the same as above except that no reaction with PhLi was required since benzophenone is easy to handle and readily purified by recrystallization from hexane.

$$\log R_r = \log R_0 - \left[1 - \left({}^{14}k/{}^{12}k\right)\right] \log (1 - f) . \quad (3)$$

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