1,4-Addition of Diethylzinc to Cyclohexenone Catalyzed by CuOTf-Sulfonamide Combined System. Evidence Supporting a Concerted Mechanism

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Measurement of $^{12}C/^{13}C$ isotope effect in the Cu(I)/sulfonamide-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone implies that the reaction proceeds by a concerted mechanism, different to those so far reported for the conventional stoichiometric 1,4-addition of organometallic compounds involving Cu.

A mixture of CuOTf (Tf = trifluoromethanesulfonyl) or 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 generate Zn enolates, which can be hydrolyzed, giving the corresponding β-substituted ketones in nearly quantitative yields, or used for further aldol reaction or Pd(0)-catalyzed reaction with allyl acetate leading to regiospecific α,β-vicinal condensation products.[1,2] The turnover number and turnover frequency amount to 9000 and 2000, respectively. A range of cyclic enones having s-cis or s-trans geometries as well as conformationally flexible acyclic enones can be employed substrates. The mechanism of the catalysis has been studied in the reaction of $Zn(C_2H_5)_2$ and 2-cyclohexenone (**1**) on the basis of the kinetics, rate law analysis, NMR analysis and molecluar weight measurement of the ethyl Zn enolate product **3**.[2] The picture for the transition state is, however, still unclear and arguable. In this paper, we report an evidence supporting the ethyl transfer onto the β carbon of **1** occurring in a concerted manner via the transition state **5** but not **6** and **7** which are proposed in the stoichiometric 1,4-addition of organocopper reagents or the catalytic reactions.[3]
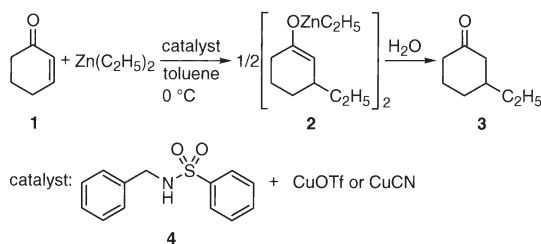
Scheme 1.
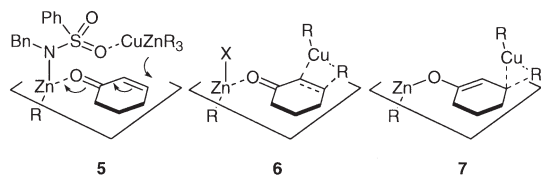
Scheme 2.

A catalytic cycle explaining the experimental observations[2] is illustrated in Figure 1. Structural information for the true catalyst and reactive intermediates in the cycle has not been obtained by NMR study.[2] Structures **A**–**C** represent only the
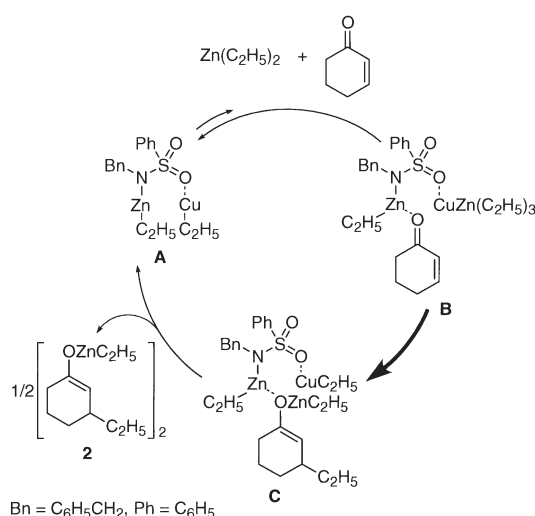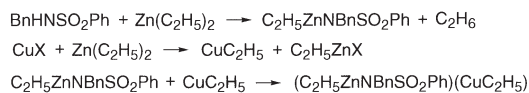

Figure 1. Supposed catalytic cycle.

chemical essentials of the actual species that would constitute more complex clusters. Protic **4** reacts with $Zn(C_2H_5)_2$ to form $C_2H_5ZnNBnSO_2Ph$ by elimination of ethane, while CuX and $Zn(C_2H_5)_2$ undergo σ-bond metathesis to form CuC_2H_5 and C_2H_5ZnX,[4] because Zn is much more electropositive than Cu (−0.76 eV vs 0.52 eV).[5] All hard anions present in the reaction system are bound to Zn. The combination of $C_2H_5ZnNBnSO_2Ph$, instead of C_2H_5ZnX, and CuC_2H_5 gives the mixed-metal complex **A**, in which the Zn center is endowed with higher Lewis acidity, and the C_2H_5 group on Cu higher electron density, in comparison to the independent entities. These effects are realized by the charge-alternating three-atom spacer, N(δ−)–S(δ+)=O(δ−), that links the Zn and Cu centers. The C_2H_5 group on Cu, however, is not sufficiently reactive to undergo nucleophilic attack to enone **1**.[6] Instead, **A** acts as a bifunctional catalyst for the reaction of $Zn(C_2H_5)_2$ and **1**. The Lewis acidic zinc atom captures the carbonyl oxygen in the substrate **1**,[7] whereas the CuC_2H_5 moiety interacts with $Zn(C_2H_5)_2$, forming a Cu/Zn cluster.[8] The formation of the catalyst/reagent/substrate complex **B** is reversible and endothermic. 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 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 **2**, and this step is facilitated by the high stability of the dimeric ethylzinc enolate **2**. The structural features of organozinc compounds prevent product inhibition, thereby making possible a very high catalytic turnover number.[9]

Analysis of $^{12}C/^{13}C$ isotope effect would give important information for discriminating the possible transition state structures **5**, **6**, and **7** at the rate-determining step.[3c–e,10,11] If the transition state **5** is involved in the above catalytic cycle, the $^{12}C/^{13}C$ isotope effect should be observed at the C(1), C(2), and C(3) of the enone substrate **1** which is recovered at the very late stage of the reaction, or observed at the C(1), C(2), C(3), and the methylene carbon of the ethyl group at C(3) of the product **3** at the initial stage of the reaction. In the case where the reaction proceeds in the carbocupration mechanisms via **6**, the C(2) and C(3) of the recovered substrate **1** are enriched with ^{13}C. When the reductive elimination mechanisms via **7** is operating, only C(3) of **1** is to show the significant $^{12}C/^{13}C$ isotope effect.[12]

Thus, the catalytic 1,4-addition of $Zn(C_2H_5)_2$ to enone **1** was conducted in a 0.1 mol scale in toluene under the following conditions ([CuOTf] = 2.5 mM, [**4**] = 2.5 mM, [$Zn(C2H5)_2$] = 450 mM, [**1**] = 500 mM, 0 °C),[13] and the reaction was stopped at 90.6(2)% conversion (GC 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, 10.3 min (factor 1.40); t_R of 3-ethylcyclohexanone (**3**), 11.9 min (factor 1.44); t_R of undecane as an internal standard, 14.4 min (factor 1.00)). Usual aqueous workup followed by separation of **1** by column chromatography (silica gel 1 kg; eluent, a 5:1 hexane–ethyl acetate mixture) and simple molecular distillation (70–80 °C/15 mmHg) gave 198 mg of unreacted **1**. The sample was subjected to 125 MHz ^{13}C NMR measurement (flip angle, 45°; points, 524288; acquisition time, 5.973 sec; pulse delay, 120 s; sample concentration, 185 mg/0.36 mL (CDCl$_3$), measurement time, 2000 scans (70 h).[10] ^1H decoupling was effected only during acquisition time. The condition satisfied PD > 5 × T1 of protons and AT + PD > 5 × T1 of carbons. Before collecting data, the 250-scan dummy measurements were conducted under the above conditions to stabilize the probe. The measurements were done 3 times for the sample. The ^{13}C signal intensities of C(1), C(2), and C(3) were compared by using the $^{13}CH_2$ signal at C(6) (not involved in the reaction), as an internal standard. As shown in Figure 2, the relative proportions of the ^{13}C isotopic composition at C(1), C(2), and C(3) were increased by 4.4%, 2.9%, and 3.3%, respectively. No other signals showed significant changes in the ^{13}C isotopic composition. Using the equations of Biegeleisen,[14] the $^{12}C/^{13}C$ isotope effects are calculated to be 1.018 at C(1), 1.012 at C(2),

and 1.014 at C(3), respectively. If the rate-determining ethyl transfer proceeds via **6** or **7**, an isotope effect is expected to be seen at C(2) and C(3) or at C(3). The observed isotope effects at all of three sp^2 carbon are in accord with the above concerted mechanism via **5** although the transferring atom can not be determined.[15]

In summary the present $^{12}C/^{13}C$ isotope effect experiments imply that the 1,4-addition of diethylzinc to 2-cyclohexenone (**1**) catalyzed by a mixture of CuOTf and *N*-benzylbenzenesulfonamide (**4**) in toluene may proceed in neither a carbocupration nor reductive elimination mechanism but in a concerted mechanism.

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12   The equilibrium isotope effect is also observable, but the degree of contribution is supposed not to become significant due to little change of the zero-point vibration pattern at C(1) and C(2) at the ground state.
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15   The present result is also consistent with the view of the concerted transfer of Cu atom via **5** followed by low energy reductive elimination of **7**. For more information, a detailed analysis of the product at the initial stage is required.
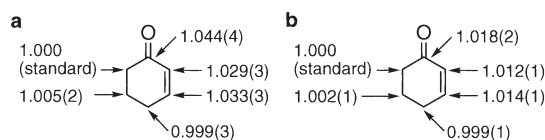
Figure 2. The ^{13}C isotopic composition of enone **1** obtained at 90.6(2)% conversion (**a**) and the $^{12}C/^{13}C$ kinetic isotope effects (**b**).