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

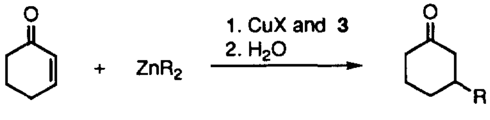
Masato Kitamura, Takashi Miki, Keiji Nakano, and Ryoji Noyori*

Department of Chemistry and Molecular Chirality Research Unit, Nagoya University,
Chikusa, Nagoya 464-01, Japan

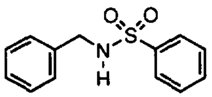
Abstract: In the presence of a Cu(I)–N-monosubstituted sulfonamide combined catalyst system, diorganozincs react with α,β-unsaturated ketones to generate Zn enolates, which may be hydrolyzed, giving the β-substituted ketones, or used for further aldol reaction or Pd(0)-catalyzed reaction with allyl acetate leading to the regiospecific α,β-vicinal condensation products. Copyright © 1996 Elsevier Science Ltd

Conjugate addition of organometallic compounds to α,β-unsaturated ketones is an important tool for specific introduction of a hydrocarbon group to the β position.[1] In addition, the resulting metal enolates may be used for further α-functionalization, effecting the α,β-vicinal skeletal modification.[2] However, the coexistence of additional metal salts and organic or inorganic compounds acting as promoters of the conjugate addition makes the reaction system complex, hampering the synthetic utility. Here we describe a catalytic addition of diorganozincs to enones with a high turnover number, cleanly generating Zn enolates which undergo regiospecific nucleophilic reactions.

$Zn(C_2H_5)_2$ is inert to 2-cyclohexenone (**1**) in toluene at room temperature.[3] We first tested the catalytic activity of Cu(I) compounds including CuCN, CuOTf, CuO-*t*-C_4H_9, CuMes (Mes = mesityl), CuCl, CuBr, and CuI at 0 °C.[4] Unfortunately, none of these showed any synthetically meaningful effects, yield of the ethylation product **2** (R = C_2H_5) being <2%, if any. However, when a small amount of *N*-benzylbenzenesulfonamide (**3**) was added to a mixture of $Zn(C_2H_5)_2$, enone **1**, and CuCN in toluene (Zn:**1**:Cu:**3** molar ratio = 200:200:1:1), a rapid reaction took place to afford desired **2** (R = C_2H_5) in >99% yield after aqueous workup.[5] This ethylation was accomplished satisfactorily on a 20-g scale even with a Zn:**1**:Cu:**3** ratio of 10 000:10 000:1:10. Cu(I) salts such as CuOTf, CuO-*t*-C_4H_9 and CuBr, or an organocopper, CuMes, could also be used as catalyst precursor. Many N-monosubstituted sulfonamides served as promoters combined with a Cu(I) salt, while *N*,*N*-



1 **2**



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dibenzylbenzenesulfonamide was totally ineffective. The best results were obtained in toluene, but ether can also be used. Polar solvents including THF, CH_3CN, and DMF are not recommended.

This catalytic method has been applied to the use of various diorganozincs and enone substrates as illustrated in Table 1. Dimethyl-, diethyl-, and di-*n*-butylzinc as well as diphenylzinc were used. In the reaction using CuCN or CuMes and **3**, methylation of the enone **1** occurred 30 and 90 times slower than ethylation. The reactivity of the ethylation decreased in the order of *s*-trans, flexible, and *s*-cis enones. 2-Cyclopentenone caused polymerization under the standard reaction conditions with the formation of 3-ethylcyclopentanone in 28% yield. Isophorone and 3-methyl-2-cyclohexenone, β-substituted enones, were not alkylated. This method does not alkylate α,β-unsaturated carboxylic esters either.

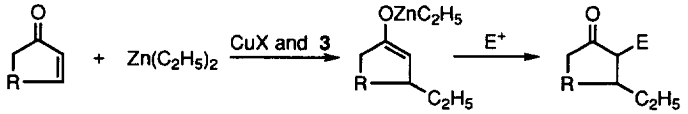
Table 1. Copper-Catalyzed Conjugate Addition of Organozinc Compounds to Enones.[a]

enone	R in ZnR_2	CuX (mol equiv)	time, h	conjugate addition product[b]	% yield[c]
2-cyclohexenone (**1**)	CH_3	CuCN (0.005)	6	**2** (R = CH_3)	90
1	CH_3	CuMes (0.02)	3[d]	**2** (R = CH_3)	80
1	C_2H_5	CuCN (0.005)	1	**2** (R = C_2H_5)	>99[e]
1	C_2H_5	CuCN (0.0001)[f]	48	**2** (R = C_2H_5)	90
1	C_2H_5	CuOTf (0.005)	1	**2** (R = C_2H_5)	>99
1	C_2H_5	CuO-*t*-C_4H_9 (0.005)	1	**2** (R = C_2H_5)	>99
1	C_2H_5	CuMes (0.005)	1	**2** (R = C_2H_5)	>99
1	C_2H_5	CuBr (0.005)	1	**2** (R = C_2H_5)	96
1	*n*-C_4H_9	CuMes (0.02)	3	**2** (R = *n*-C_4H_9)	95
1	C_6H_5	CuMes (0.02)	1	**2** (R = C_6H_5)	92
2-methyl-2-cyclohexenone	C_2H_5	CuMes (0.02)	120[d]	3-ethyl-2-methylcyclohexanone[g]	50
2-cycloheptenone	C_2H_5	CuMes (0.02)	1	3-ethylcycloheptanone[h]	99
trans-2-ethylidenecyclohexanone	C_2H_5	CuMes (0.02)	6	2-*sec*-butylcyclohexanone[i]	90
trans-3-nonen-2-one	C_2H_5	CuCN (0.005)	20	4-ethyl-2-nonanone	>99

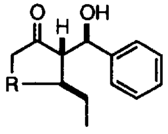
[a] Reaction was carried out in toluene at 0 °C using an enone (500 mM) and ZnR_2 (500 mM) in the presence of equimolar amounts of CuX and **3** unless otherwise stated. In all cases no 1,2-addition product was obtained. [b] Physical properties of the 1,4-addition products were consistent with those of the authentic samples or the reported values. 3-Methylcyclohexanone: commercially available (Aldrich). 3-Ethylcyclohexanone: Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242. 3-*n*-Butylcyclohexanone: Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467. 3-Phenylcyclohexanone: Cho, C. S.; Motofusa, S.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 883. 3-Ethyl-2-methylcyclohexanone: Miller, B.; Matjeka, E. R. *J. Am. Chem. Soc.* **1980**, *102*, 4772. 2-*sec*-Butylcyclohexanone: Hegedus, L. S.; Williams, R. E.; McGuire, M. A.; Hayashi, T. *J. Am. Chem. Soc.* **1980**, *102*, 4973. 4-Ethyl-2-nonanone: Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron* **1995**, *51*, 743. [c] Determined by GC analysis (capillary column, GL Science OV-1 0.25 mm x 50 m; column temp, 90–210 °C; pressure, 118–137 kPa; detection temp, 280 °C; carrier gas, He; split ratio, 100:1). *n*-Decane, *n*-undecane, or *n*-dodecane was used as an internal standard. [d] At 25 °C. [e] 99% yield after 10 min. [f] Cu:**3** = 1:10. [g] Diastereomer ratio was 1.4:1. [h] ^1H NMR (400 MHz, $CDCl_3$) δ 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) 1701; HRMS m/z (M^+) calcd 140.1202, obsd 140.1191. [i] Diastereomer ratio was 3.3:1.

The use of equimolar amounts of an alkyl donor and enone substrate, as well as the presence of very small quantities of a Cu(I) compound and a sulfonamide, allowed relatively clean formation of the Zn enolate. As a consequence, the regiospecific α,β-vicinal condensation was achieved in one pot using either a preformed or in-situ generated enolate. Condensation of cyclic Zn enolates with aldehydes leads to aldols having three consecutive stereogenic centers, where four diastereomers are possible. For example, when enolate **4**, generated from **1** and diethylzinc in the presence of 0.5 mol % of CuCN and **3** in toluene, was treated with benzaldehyde at –78 °C for 70 h, a 5.3:1 mixture of *trans,threo*-**6**[6] and *trans,erythro*-**6**[6] was obtained in >95% yield. 2-Cyclopentenone gave the ethylation product in only 28% yield *after aqueous workup* but, actually, the conjugate addition forming the enolate **5** had occurred efficiently. In fact, when $Zn(C_2H_5)_2$, 2-cyclopentenone, benzaldehyde, CuMes, and sulfonamide **3** were mixed in a 50:50:50:1:1 ratio in toluene from the beginning, after 3 h at 0 °C, *trans,threo*-**7**[6] and *trans,erythro*-**7**[6] were produced in a 1.2:1 ratio in a 91% combined yield.

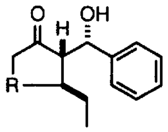
The alkylzinc enolates can be allylated in a stereoselective fashion.[7] When ethylzinc enolate **4**, preformed from $Zn(C_2H_5)_2$, enone **1**, CuCN, and **3** (1:1:0.005:0.005), was reacted with one mol equivalent of allyl acetate and 0.02 mol equivalent of $Pd[P(C_6H_5)_3]_4$ at 0 °C for 2 h, a 9:1 mixture of *trans*- and *cis*-**8**[8] was produced in a 90% combined yield.



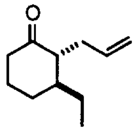
4, R = $(CH_2)_2$
5, R = CH_2



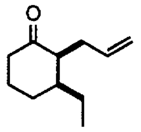
trans,threo-**6**: R = $(CH_2)_2$
trans,threo-**7**: R = CH_2



trans,erythro-**6**: R = $(CH_2)_2$
trans,erythro-**7**: R = CH_2



trans-**8**



cis-**8**

The conjugate addition of ZnR_2 (R = alkyl or aryl) in the presence of a Cu(I) compound is remarkably accelerated by the addition of an N-monosubstituted sulfonamide, $R'NHSO_2Ar$. Although the reaction would occur via a mixed-metal cluster, the structure may be simplified as $RZn(NR'SO_2Ar)CuR$. The three-atom, charge-alternating sufonamide spacer linking the two metals at N and O[9] could provide a Lewis acidic property to the Zn center, interacting with the enone oxygen, and polarize the Cu–R bond through coordination of the sulfonyl oxygen to the Cu center, facilitating the conjugate delivery of the R group. In addition, the tendency of Zn enolates to form the stable dimers or tetramers[10,11] contributes to the creation of a smooth catalytic cycle.

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5. A typical procedure for 20-g scale reaction is as follows: A dry 500-mL Schlenk tube containing a Teflon-coated stirring bar was charged, under argon stream, with CuCN (99 mg, 1.1 mmol), **3** (272 mg, 1.1 mmol), and toluene (60 mL), and 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). The organic layer was removed, and the aqueous layer was extracted twice 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. 25% toluene solution of the product. The mixture was distilled at 191–193 °C and atmospheric pressure to give **2** ($R = C_2H_5$) in 90% isolated yield (24.0 g). GC analysis of the reaction mixture showed the yield to be >99%; 1-ethyl-2-cyclohexen-1-ol was not detected (capillary column, GL Science OV-1 0.25 mm x 50 m; column temperature, 90–130 °C; rate of temperature increase, 2 °C/min; detection temperature, 280 °C; carrier gas, He; column head pressure, 118 kPa; split ratio, 100:1; t_R of **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 **2** ($R = C_2H_5$), 11.9 min (factor 1.44); t_R of *n*-undecane as an internal standard, 14.4 min (factor 1.00)).
6. The stereochemistry was determined by single crystal X-ray analysis.
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8. The regiochemistry and trans/cis stereochemistry of **8** were elucidated by NMR analysis. The order of the cross signals of major *trans*-**8** in ^{13}C–^{13}C COSY using 2D-INADEQUATE technique ($CDCl_3$, 25 °C): δ 136.54 ($CH_2CH{=}CH_2$), δ 31.50 ($\mathit{C}H_2CH{=}CH_2$), δ 54.61 ($\mathit{C}(2)HCH_2CH{=}CH_2$), δ 43.28 ($C(2)H\mathit{C}(3)HCH_2CH_3$), and δ 25.82 ($C(3)H\mathit{C}H_2CH_3$). The major/minor ratio was shifted from 9:1 to 2:1 by $NaOCH_3$ treatment, indicating that minor *cis*-**8** has the same connectivity as major **8**. $J_{C(2)H\text{–}C(3)H}$ of *trans*- and *cis*-**8** based on 1D-HOHAHA and decoupling experiments (C_6D_6, 25 °C): 9.8 and 4.9 Hz.
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11. The enolate **4** exists as a dimer in benzene: molecular weight determined by cryoscopy, 424–440.

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