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$NiCl_2(PPh_3)_2$-Zn Promoted Deallyloxycarbonylative Directed Aldo Reaction of Allyl β-Keto Carboxylates with Aldehydes to β-Hydroxy Ketones

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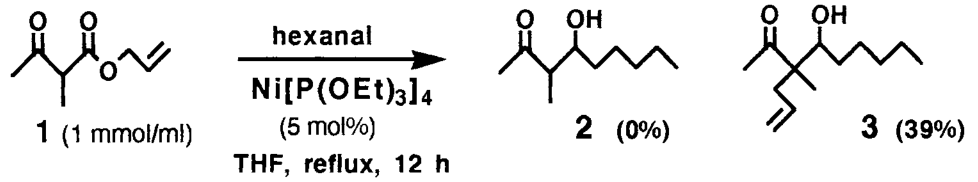
Regio- and chemospecific deallyloxycarbonylative aldol reaction of allyl(or -lic) α,α-disubstituted β-keto carboxylate with aldehyde was effectively promoted by Ni^0 ($NiCl_2(PPh_3)_2$-Zn), in which the allyloxycarbonyl group ($-COOCH_2CH{=}CH_2$) was replaced to 1-hydroxyalkyl group(-CH(OH)R, R=alkyl, vinyl, aryl) under mild reaction conditions.

β-Keto ester plays an important role in ketone synthesis especially in an elaboration of requisite molecular framework because of its high reactivity at the α-carbon atom, though the alkoxycarbonyl group must be removed via decarboxylation with hydrolysis of the ester to give the desired ketone after homologation at the α-carbon atom. However, β-keto ester is unsuitable to give β-hydroxy ketone (the aldol product) because an anion derived from β-keto ester is too stable to react with aldehyde and to give an aldol product.[1,2] In the previous report,[3] we presented a successful method for the intramolecular aldol reaction via π-allyl-palladium enolate which was generated by the palladium-catalyzed deallyloxycarbonylation of allyl β-keto carboxylates having a suitable aldehyde side chain. Application of the method to intermolecular aldol reaction gave an unsatisfactory result.[4] In the later case, the desired aldol reaction was competitive with the allylation which should take place through intramolecular ligand coupling reaction of the π-allylpalladium enolate intermediate.

Here we wish to propose new and useful method for preparation of β-hydroxy ketones by regio- and chemospecific deallyloxycarbonylative directed aldol reaction of allyl β-keto carboxylates with aldehydes under mild reaction conditions.

Nickel-catalyzed aldol reaction of allyl 2-methyl-3-oxobutanoate (**1**) with hexanal to give the desired aldol product **2** was unsuccessful, whereas the allylated aldol product **3** was obtained as a single product in 39% yield (Eq.1).[5] The fact seemed to suggest that the nickel-catalyzed(or -promoted) aldol reaction was facilitated in the case of α,α-dialkyl β-keto ester rather than that of α-monoalkyl β-keto ester.



(1)

Then, we surveyed more suitable reaction conditions of the aldol reaction using α,α-dialkyl β-keto ester **4**[6] with hexanal to give the corresponding aldol product **5** and obtained the results as shown in Table 1.

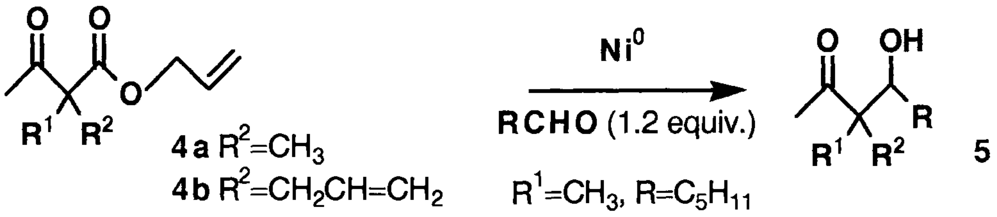


Table 1. Ni^0-Promoted Deallyloxycarbonylative Aldol Reaction of Allyl α,α-Dialkyl-β-keto Carboxylate(**4**) with Hexanal to β-Hydroxy-α,α-dialkyl Ketone(**5**)

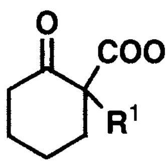
	4	Ni^0 a)	Solvent	Reaction		5	4
	-R^2	(mol%)		temp/°C	time/h	yield/%	recovery/%
4a	CH$_3$	A(20)	THF	reflux	10	33	0
4b	CH$_2$CH=CH$_2$	A(20)	THF	reflux	7	50	0
	4b	A(20)	DMF	40	18	60	20
	4b	B(50-0-50)	DMF	40	30	14	84
	4b	B(50-50-50)	DMF	40	24	67	32
	4b	C(25-25)	DMF	40	5	78	20
	4b	C(50-50)	DMF	20	26	78	22
	4b	C(50-50)	DMF	40	7	99	0

a) A: Ni[P(OEt)$_3$]$_4$; B: NiCl$_2$-PPh$_3$-Zn; C: NiCl$_2$(PPh$_3$)$_2$-Zn.

The best reaction condition found out here was employed for the reaction of some other allyl(or crothyl) 3-oxocarboxylates(**4**, **6**, **8**) with aldehydes to give the corresponding aldol products as listed in Table 2.

The typical procedure is representative as follows. Methyl 3-methyl-3-allyloxycarbonyl-4-oxopentanoate (**4e**,1 mmol), prepared by the successive treatment of allyl 3-oxobutanoate with iodomethane and then with methyl bromoacetate in the presence of potassium carbonate in dry THF, was added to the mixture of NiCl$_2$(PPh$_3$)$_2$, commercially available metallic zinc(powder, technical grade), and hexanal in DMF(1 ml). The reaction mixture was stirred at 40 °C for three hours and then filtered through florisil using ethyl acetate as eluent. The filtrate was concentrated and the residue was column chromatographed on silica gel to give the aldol product (γ-butyrolactone) in 80% yield(ca. 1/1 diastereomixture).

The aldol reaction described here is characterized by the following points; (1) the allyloxycarbonyl group (-COOCH$_2$CH=CH$_2$) of allyl β-keto carboxylate is specifically replaced by 1-hydroxyalkyl group(-CH(OH)R), (2) the reaction proceeds under the mild reaction conditions (at r.t.-40 °C, in the presence of ZnCl$_2$[7] which should be formed *in situ* by the reduction of NiCl$_2$ with Zn to Ni^0), and (3) the reaction takes place smoothly on the sterically hindered carbon atom. We believe that this is the first example of chemo- and regiospecific intermolecular aldol reaction via the transition metal enolates, which are generated by the deallyloxycarbonylation of allyl(or -lic) β-keto carboxylates with M^0, with aldehydes to give the corresponding β-hydroxy ketones. The palladium-catalyzed intramolecular aldol reaction of the allyl β-keto carboxylates having an apropriate aldehyde side chain, previously reported by us,[3] is also able to be displaced by this Ni^0-promoted aldol reaction to give the same products(β-acyl cycloalkanols).[8]



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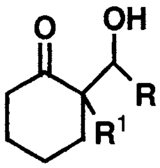

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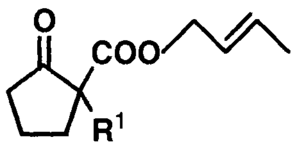

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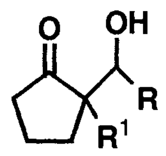

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Table 2. $NiCl_2(PPh_3)_2$-Zn Promoted Deallyloxycarbonylative Aldol Reaction of Allyl β-Keto Carboxylates (**4**, **6**, and **8**) with Aldehydes in DMF

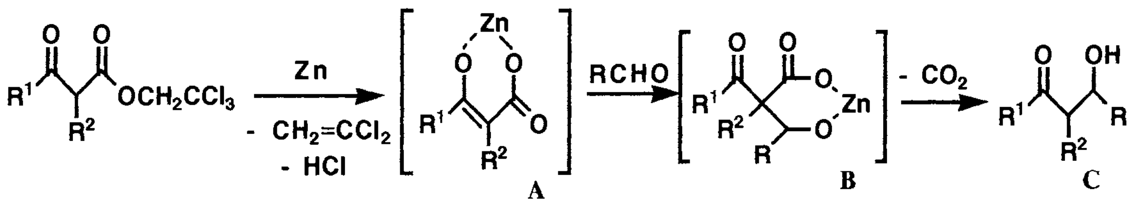
	Allyl β-keto carboxylate		Aldehyde(RCHO)	Reaction		Product	
	$-R^1$	$-R^2$	R-	temp/°C	time/h	yield/%a)	
4a	CH_3	CH_3	$CH_3CH{=}CH$	40	1.5	5	79
	4a		C_6H_5	20	3.5	5	72
4b	CH_3	$CH_2CH{=}CH_2$	$CH_3CH{=}CH$	20	4.0	5	94b)
4c	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	C_6H_5	20	5.5	5	67
4d	CH_3	$(CH_2)_4OTHP$	$CH_3(CH_2)_4$	40	3.5	5	88b)
4e	CH_3	CH_2COOMe	$CH_3(CH_2)_4$	40	3.0	5	80b) c)
4f	CH_3	$(CH_2)_2COCH_3$	$CH_3(CH_2)_4$	40	5.0	5	67b) d)
4g	$(CH_2)_4$		$CH_3(CH_2)_4$	20	4.0	5	76
6a	CH_3		$CH_3(CH_2)_4$	20	5.0	7	67b)
	6a		$CH_3CH{=}CH$	20	1.5	7	52b)
6b	CH_2COOMe		$CH_3(CH_2)_4$	20	7.0	7	61b) c)
8a	CH_3		$CH_3(CH_2)_4$	20	12	9	56b)
8b	$CH_2CH{=}CH_2$		$CH_3(CH_2)_4$	20	6.0	9	59b)

a) After isolation by columun chromatography on silica gel. b) Diastereomixture (ca. 1/1).
c) Isolated as γ-butyrolactone. d) Containing 2-hydroxy-1-oxacyclohexane (hemiacetal).

References

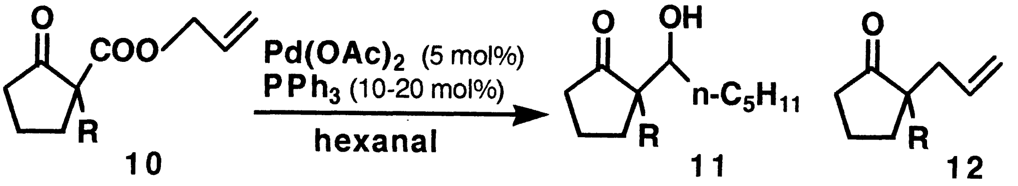
1) It is well known that the β-keto carboxylate which has an active methylene reacts with aldehyde smoothly in the presence of piperidine to give the α-alkylidene-β-keto carboxylate (the Knoevenagel reaction). However, there is no text described on the aldol reaction of the α-alkyl β-keto carboxylate (an active methyne) with aldehyde to give the corresponding β-hydroxy-α-alkoxycarbonyl ketone.

2) Mukaiyama et al. reported the regiospecific aldol reaction; the active zinc enolate(A) was generated by the reduction of 2,2,2-trichloroethyl α-substituted β-keto carboxylate with Zn and the aldol product C was obtained via the decarboxylation of chelate intermediate **B**, formed by the reaction of A with aldehyde, after hydrolytic work-up. T. Mukaiyama, T. Sato, S. Suzuki, T. Inoue, and H. Nakamura, *Chem. Lett.*, **1976**, 95.



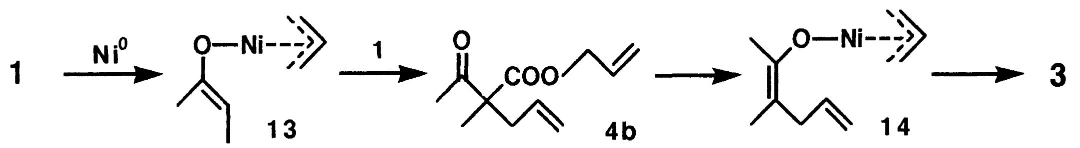
3) J. Nokami, T. Mandai, H. Watanabe, H. Ohyama, and J. Tsuji, *J. Am. Chem. Soc.*, **111**, 4126 (1989).

4) 2-Allyloxycarbonylcyclopentanone(**10a**, 1 mmol) was treated with hexanal(excess) in the presence of $Pd(OAc)_2$ (5 mol%) and triphenylphosphine (10-20 mol%) in acetonitrile at room temperature to give 2-(1-hydroxyhexyl)cyclopentanone(**11a**). The yield seemed to depend on the concentration of aldehyde. However, an aldol product(**11b**) was not obtained by the palladium-catalyzed reaction of 2-methyl-2-allyloxycarbonylcyclopentanone(**10b**) with hexanal.



10		Solvent (CH_3CN)	Hexanal	PPh_3	Reaction	Yield /%	
	R	(ml)	(mmol)	(mol%)	time/h	11	12
a	H	2.5	1.7	20	1	29	62
a	H	3.5	1.7	10	5	42	56
a	H	1.0	3.0	10	2	53	41
b	CH_3	1.0	3.0	10	5	0	<20

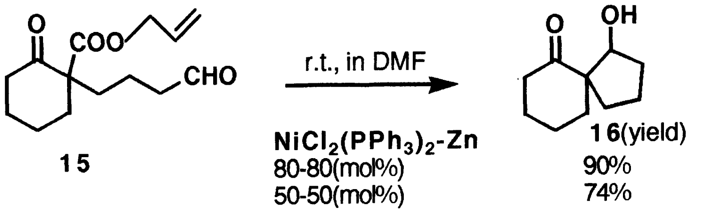
5) For the reaction of allyl β-keto carboxylate which has an active methyne protone, it is assumed that *the active methyne* of **1** was deprotonated and allylated by initially formed π-allylnickelenolate (**13**) to allyl 2-allyl-2-methyl-3-oxobutanoate (**4b**), which was also converted to π-allylnickel enolate (**14**) and then reacted with aldehyde to give the aldol product **3**.



6) The alkylation of the active methylene and methyne of allyl β-keto carboxylate was carried out by the treatment with the corresponding alkylhalide and excess amount of potassium carbonate in dry hot THF in satisfactory yield.

7) It seems resonable to appreciate the effect of $ZnCl_2$ which should be formed *in situ* and activate the aldehyde to react with the nucleophile, though the reaction mechanisum is not clear as well as a reason of the low diastereoselectivity.

8) The allyl β-keto carboxylate derivatives (**15**) gave the corresponding intramolecular aldol product (**16**) in a good yield under the reaction conditions as described in the text.



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