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Rhodium-catalyzed addition of alcohols to terminal enones

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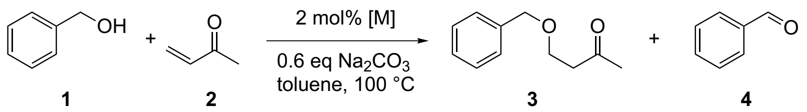
Abstract—$[Rh(COD)(OMe)]_2$ was found to catalyze the addition of aliphatic and aromatic alcohols with terminal enones to afford β-alkoxyketones in high yields.

β-Alkoxyketones serve as valuable building blocks and structural motifs in a variety of natural products.[1] Intermolecular oxa Michael additions of alcohols to enones represent an attractive method for their preparation but only a few procedures have been reported. They include UV irradiation of cycloalkenones in methanol, reactions promoted by strong base (e.g., KH or K-O-*t*-bu),[2] phosphine catalyzed reactions,[3] and acid catalyzed reactions.[4] A few transition metals (e.g., Pd, Cu, V) have also been found to induce hydroalkoxylation of α,β-unsaturated ketones.[5,6] Herein, we describe a novel Rh-catalyzed addition of alcohols with terminal enones to afford β-alkoxyketones.

The addition of benzyl alcohol (**1**) to methyl vinyl ketone (MVK, **2**) was chosen as the model reaction (see Eq. 1) and a series of transition metal complexes were screened for catalytic activity (see Table 1). MVK (2 equiv) and Na_2CO_3 (0.6 equiv) were added to toluene solutions (1 M) of benzyl alcohol. Reactions were run at 100 °C for 4 h. Various Ir, Ru, and Rh complexes predominantly afforded benzaldehyde (**4**), the oxidation product arising from transfer dehydrogenation with MVK (Table 1, entries 1–5). However, $[Rh(COD)Cl]_2$ afforded the alkoxyketone **3** as the predominant product (entry 7). Addition of a variety of ligands (phosphines, amines, and imidazolylidenes) to reactions run with $[Rh(COD)Cl]_2$ led to increased amounts of oxidation product. Importantly, control reactions confirmed that Na_2CO_3 alone did not catalyze the addition reaction (entry 8).[2]

Interestingly, $[Rh(COD)Cl]_2$ alone catalyzed the reaction but gave lower yields of **3** (Table 1, entry 9). It is known that Rh alkoxide complexes are formed from the reaction of alcohols and $[Rh(COD)Cl]_2$ in the presence of a weak base such as Na_2CO_3.[7] Thus, it seemed possible that the addition of base simply served to facilitate the generation of a key catalyst such the Rh alkoxide complex [Rh-OBn]. Indeed, $[Rh(COD)(OMe)]_2$ (**5**),[7] conveniently prepared from $[Rh(COD)Cl]_2$, MeOH, and KOH, catalyzed the addition of benzyl alcohol (**1**) to MVK in the absence of added base.



(1)

Optimization of the $[Rh(COD)(OMe)]_2$ catalyzed reaction revealed that catalyst loading, reactant ratios, and substrate concentration did not affect conversion as much as temperature and solvent. Ultimately, the best yields were observed for reactions run with 1 M BnOH

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Table 1. Catalyst screening for the addition of benzyl alcohol to MVK (Eq. 1)[a]

Entry	Catalyst	Base	%Conv. of **1**	**3/4**
1	$[Ir(COD)Cl]_2$	Na_2CO_3	100	0:1
2	$[RuCl_2(cymene)]_2$	Na_2CO_3	100	0:1
3	$Rh(PPh_3)_3Cl$	Na_2CO_3	73	0:1
4	$Rh(PPh_3)_3Me$	Na_2CO_3	84	1:0.9
5	$Rh(PPh_3)_2(CO)(Cl)$	Na_2CO_3	11	1:1
6	$Rh(CO)_2(acac)$	Na_2CO_3	53	2.2:1
7	$[Rh(COD)Cl]_2$	Na_2CO_3	56	9.6:1
8	None	Na_2CO_3	<5	N/A
9	$[Rh(COD)Cl]_2$	None	25	1:0

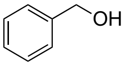
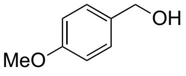
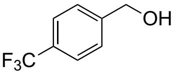
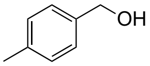
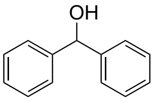
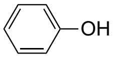
[a] Reaction conditions: 0.01 mmol catalyst, 0.6 mmol Na_2CO_3, 1 M BnOH (1 mmol) in toluene, 2 mmol MVK (**2**), 100 °C, 12 h.

Table 2. Temperature effects for the addition of BnOH (**1**) to MVK (**2**)[a]

Entry	Temperature (°C)	%Conv. of **1**
1	rt	40
2	40	53
3	50	68
4	60	72
5	70	57
6	100	38

[a] Reaction conditions: 0.01 mmol $[Rh(COD)(OMe)]_2$ (**5**), 1 M BnOH (1.1 mmol) in toluene, 1 mmol MVK (**2**), 2 h.

Table 3. Rhodium-catalyzed addition of alcohols to terminal enones[a]

Entry	Alcohol	Enone	%Yield[b]
1a		MVK	72
1b		PVK	61
2a		MVK	50
2b		PVK	92
3a		MVK	37
3b		PVK	82
4a		MVK	69
4b		PVK	95
5a		MVK	82
5b		PVK	84
6a	MeOH	MVK	74
6b		PVK	99
7a	EtOH	MVK	88
7b		PVK	87
8a	*i*-PrOH	MVK	35
8b		PVK	64
9a		MVK	0
9b		PVK	34

[a] Reaction conditions: 0.01 mmol $[Rh(COD)(OMe)]_2$ (**5**), 1 M alcohol (1.1 mmol) in benzene-d_6, 1 mmol enone, 2–10 h at 60 °C.

[b] ^1H NMR yield (average of two runs).

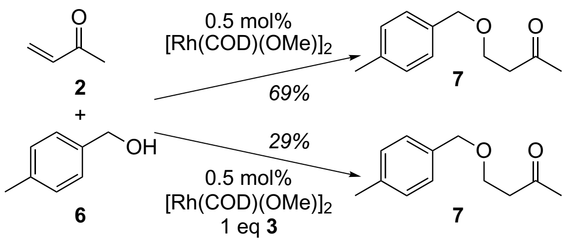
(1:1.1 BnOH–MVK) in toluene using 1 mol% $[Rh(COD)(OMe)]_2$ at 60 °C for 2 h (see Table 2). Similar results were obtained when the reaction was run in tetrahydrofuran, benzene, hexanes, and dichloroethylene. Reactions performed in *tert*-butyl alcohol displayed lower conversions and lower yields. No reaction was observed in polar solvents such as DMSO and acetonitrile.

A variety of alcohols were reacted with MVK under the optimized reaction conditions and are summarized in Table 3. Both electron withdrawing and donating substituted benzyl alcohols seemed to moderately attenuate the reaction (entries 2a and 3a). However, diphenylmethanol reacted cleanly with MVK to afford the β-alkoxyketone product in good yield (entry 5a). Relatively small primary alcohols, such as methanol and ethanol, reacted smoothly with MVK (entries 6a and 7a) whereas alcohols with increased steric bulk led to decreased yields. For example, only 35% of the β-alkoxyketone was obtained from the reaction of *iso*-propanol with MVK (entry 8a).

The reaction of phenyl vinyl ketone (PVK) was also explored (see Table 3). In general, higher yields were obtained for all alcohols studied. Notably, reactions of aryl alcohols afforded the corresponding β-alkoxyketones in yields ranging from 61% to 95% (entries 1b–5b). Similarly, reactions with alkyl alcohols also displayed increased activities. For example, high yields of product were observed for MeOH and EtOH (99% and 87%, respectively; entries 6b and 7b). In addition, *i*-PrOH gave the corresponding β-alkoxyketone in 64% yield (as compared to 35% with MVK). It is interesting to note that the reaction of phenol and PVK afforded the β-alkoxyketone in 34% (entry 9b) whereas no reaction was observed with MVK (entry 9a).

In general, bulky alcohols (e.g., *tert*-butyl alcohol, triethylsilanol) did not readily react with either MVK or PVK and afforded only trace amounts of product. Furthermore, the use of substituted alkenes completely inhibited the reaction. For example, no product was observed with cyclohexenone or pentenone and catalyst decomposition was observed. Acrylates also proved to be unsuccessful coupling partners.

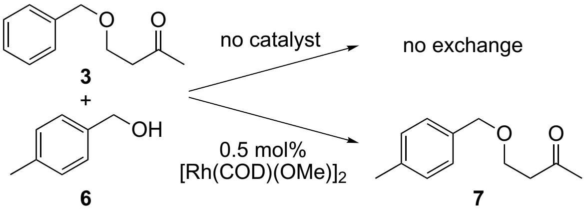
The reaction also displayed moderate product inhibition. For example, as shown in Scheme 1, addition of alkoxyketone **3** to the reaction mixtures resulted in



Scheme 1. Product inhibition.

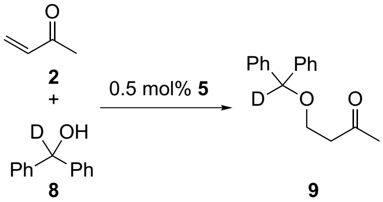
depressed yields of **7** (29% vs 69%), which is believed to be due to chelation effects.

The reversibility of the reaction was also explored. 4-Methyl benzyl alcohol (**6**) readily underwent exchange with **3** in the presence of Rh to afford a 1:1 mixture of **3** and **7**, suggesting that the reaction is reversible (Scheme 2). No exchange was observed in the absence of catalyst.



Scheme 2. Reversibility of the Rh-catalyzed oxa Michael reaction.

Labelling experiments were also performed to provide insight into the mechanism of the reaction. Deuterated benzhydrol (**8**), prepared from $NaBD_4$ reduction of benzophenone, was added to MVK under our optimized reaction conditions (Eq. 2). Deuterium scrambling was not observed in the β-alkoxyketone product (**9**), which indicated that β-hydride elimination does not lie on the catalytic pathway.



(2)

In summary, $[Rh(COD)(OMe)]_2$ serves as a catalyst for the addition of alcohols to terminal enones under mild conditions. The catalyst may be generated in situ through the addition of Na_2CO_3 to an alcoholic solution of $[Rh(COD)Cl]_2$.

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