

Direct β -Alkylation of Secondary Alcohols with Primary Alcohols Catalyzed by a Cp^*Ir Complex

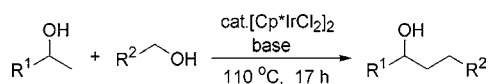
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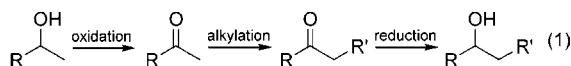
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ABSTRACT



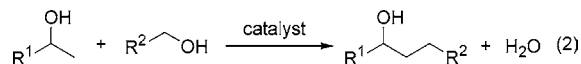
A new catalytic system for β -alkylation of secondary alcohols has been developed. In the presence of $[\text{Cp}^*\text{IrCl}_2]_2$ (Cp^* = pentamethylcyclopentadienyl) catalyst and base, the reactions of various secondary alcohols with primary alcohols give β -alkylated higher alcohols in good to excellent yields without any hydrogen acceptor or hydrogen donor. This reaction proceeds via successive hydrogen-transfer reactions and aldol condensation.

Alcohols are one of the most basic and important classes of organic compounds because they have a wide variety of uses in industrial and laboratory chemistry. Although a huge number of methods for the synthesis of alcohols are known,^{1,2} the synthesis of a variety of alcohols having intricate structures through alkylation of simple alcohols usually requires tedious processes using many reagents. For example, β -alkylation of a secondary alcohol can usually be accomplished via three-step transformations (oxidation,³ alkylation,⁴ and reduction^{2,5}) (eq 1).



Taking into account increasing demands for environmentally benign and economical synthetic methods, a direct

catalytic process for β -alkylation of a secondary alcohol with another alcohol to give a higher alcohol along with H_2O as a coproduct would be highly desirable (eq 2). Only one report on this subject using a Ru catalyst has appeared;⁶ however, it is necessary in this system to add both a large amount of a sacrificial hydrogen acceptor (5 equiv of 1-dodecene) and a hydrogen donor (dioxane solvent).⁷ From the viewpoint of atom economy, it is most preferable to avoid these additives.



We have recently found an extremely high catalytic activity of $[\text{Cp}^*\text{IrCl}_2]_2$ toward both oxidative and reductive hydrogen-transfer reactions,⁸ demonstrating that the electronic and steric effects of the Cp^* ligand are essential in high performance as a hydrogen transfer catalyst. In this paper, we report a new and atom economical catalytic system using $[\text{Cp}^*\text{IrCl}_2]_2$ as a catalyst for β -alkylation of secondary alcohols with primary alcohols *without any sacrificial additives*.

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(7) In the system reported in ref 6, employment of 2 equiv of primary alcohols is also required.

At first, we investigated the iridium-catalyzed β -alkylation of 1-phenylethanol (**1a**) with 1-butanol (**2a**) under various conditions (Table 1). When the reaction of almost equimolar

Table 1. β -Alkylation of 1-Phenylethanol (**1a**) with 1-Butanol (**2a**) under Various Conditions^a

				yield ^b (%)	
entry	catalyst (% metal)	base	solvent (mL)	3a	4a
1	[Cp*IrCl ₂] ₂ (1.0)	NaO ^t Bu	toluene (0.3)	90	6
2	[Cp*IrCl ₂] ₂ (0.5)	NaO ^t Bu	toluene (0.3)	82	7
3	[Cp*IrCl ₂] ₂ (0.5)	NaOH	toluene (0.3)	77	4
4	[Cp*IrCl ₂] ₂ (1.0)	Na ₂ CO ₃	toluene (0.3)	0	0
5 ^c	[Cp*IrCl ₂] ₂ (0.5)	NaO ^t Bu	toluene (0.3)	52	3
6	[Cp*IrCl ₂] ₂ (0.5)	NaO ^t Bu	toluene (3.0)	60	20
7	[Cp*IrCl ₂] ₂ (0.5)	NaO ^t Bu	none	52	7
8 ^d	[Cp*IrCl ₂] ₂ (0.5)	NaO ^t Bu	THF (3.0)	12	1
9 ^e	[Cp*IrCl ₂] ₂ (0.5)	NaO ^t Bu	dioxane (3.0)	23	2
10	Cp*IrCl ₂ (PPh ₃) (1.0)	NaO ^t Bu	toluene (0.3)	10	2
11	[IrCl(cod)] ₂ (1.0)	NaO ^t Bu	toluene (0.3)	30	5
12	[Cp*RhCl ₂] ₂ (1.0)	NaO ^t Bu	toluene (0.3)	26	2

^a The reaction was carried out with **1a** (3.0 mmol), **2a** (3.6 mmol), catalyst, and base (3.0 mmol) at 110 °C for 17 h. ^b GC yield based on **1a**. ^c At 90 °C. ^d At 65 °C. ^e At 100 °C.

amounts of **1a** (3.0 mmol) and **2a** (3.6 mmol) was carried out in the presence of [Cp*IrCl₂]₂ (1.0%Ir) catalyst and NaO^tBu (3.0 mmol) at 110 °C for 17 h in toluene (0.3 mL),⁷ 1-phenylhexan-1-ol (**3a**) was formed in a yield of 90% along with a small amount of 1-phenylhexan-1-one (**4a**, 6%) (entry 1). The reaction proceeded in a high yield of **3a** (82%) with a reduced amount of catalyst (0.5%Ir) (entry 2). NaOH was also effective as a base comparable to NaO^tBu (entry 3), while the use of a weaker base (Na₂CO₃) gave no product (entry 4). The reaction at 90 °C resulted in a lower yield (entry 5). The amount of toluene was important to obtain the desired product **3a** selectively; when the reaction was carried out in an increased amount of toluene (3.0 mL), the formation of a considerable amount of **4a** (20%) in addition to **3a** (60%) was observed (entry 6). The reaction without solvent, in THF, or in dioxane resulted in a lower yield (entries 7–9). Other catalysts such as Cp*IrCl₂(PPh₃), [IrCl(cod)]₂, or [Cp*RhCl₂]₂ showed lower activity than [Cp*IrCl₂]₂ (entries 10–12).

On the basis of the above results, we next examined the reactions of various secondary alcohols with primary alcohols under the optimized conditions (Table 2). The reactions of **1a** with aliphatic primary alcohols gave the corresponding

Table 2. Cp*Ir Complex Catalyzed β -Alkylation of Various Secondary Alcohols with Primary Alcohols^a

entry	secondary alcohol	primary alcohol	catalyst [%Ir]	base	product yield [%] ^b
1	1a Ar = Ph	2a R ² = Pr	1.0	NaO ^t Bu	3a 88 ^c
2	1a	2b R ² = heptyl	2.0	NaOH	3b 77 ^c
3	1a	2c R ² = ⁱ Pr	2.0	NaOH	3c 75 (8)
4	1a	2d R ² = ⁱ Bu	2.0	NaOH	3d 82 ^d (12)
5 ^e	1a	2e R ² = Ph	2.0	NaO ^t Bu	3e 75 ^c
6	1a	2f R ² = 4-MeC ₆ H ₄	4.0	NaO ^t Bu	3f 80 ^c
7 ^e	1a	2g R ² = 4-MeOC ₆ H ₄	4.0	NaO ^t Bu	3g 81 ^c
8 ^e	1a	2h R ² = 4-ClC ₆ H ₄	4.0	NaO ^t Bu	3h 80 ^c
9 ^e	1a	2i R ² = 4-CF ₃ C ₆ H ₄	4.0	NaO ^t Bu	3i 87 ^c
10	1a	2j R ² = benzyl	2.0	NaO ^t Bu	3j 74
11	1a	2k R ² = phenethyl	2.0	NaOH	3k 83
12	1b Ar = 4-MeC ₆ H ₄	2a	4.0	NaOH	3l 80 (14)
13	1c Ar = 4-MeOC ₆ H ₄	2a	4.0	NaOH	3m 69 (22)
14	1d Ar = 4-ClC ₆ H ₄	2a	2.0	NaOH	3n 78 (14)
15	1e Ar = 4-CF ₃ C ₆ H ₄	2a	1.0	NaO ^t Bu	3o 77
16	1f	2a	4.0	NaO ^t Bu	3p 58
17	1g	2e	2.0	NaO ^t Bu	3q 78
18	1h	2a	4.0	NaO ^t Bu	3r 65 ^f (34)

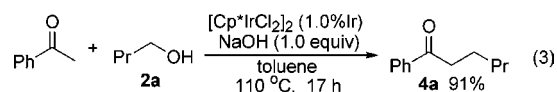
^a The reaction was carried out with secondary alcohol (3.0 mmol), primary alcohol (3.6 mmol), catalyst, and base (3.0 mmol) in toluene (0.3 mL) at 110 °C for 17 h. ^b Isolated yield based on secondary alcohol. Values in parentheses indicate the isolated yield of corresponding ketone. ^c Formation of a small amount of the corresponding ketone which was not isolated was observed by GC analysis (5–10%). ^d Mixture of diastereomers (1:1). ^e Reaction was carried out in 3.0 mL of toluene. ^f Mixture of diastereomers (cis/trans = 54:46).

β -alkylated products in high yields (entries 1–4). The reactions of **1a** with benzyl alcohols bearing an electron-donating or an electron-withdrawing substituent also proceeded efficiently (entries 5–9). In these cases, optimum results were obtained by the reactions in 3.0 mL of toluene. The reactions of 1-arylethanol (**1b–e**) with **2a** also gave the β -alkylated products (entries 12–15). In these reactions a considerable amount of the corresponding ketone products were also isolated in addition to the desired alcohol product. Other secondary alcohols such as **1f–h** were also applicable to the present catalytic system to give moderate to good yields (entries 16–18). The reaction of 1,2,3,4-tetrahydro-1-naphthol (**1h**) with **2a** gave a diastereomeric mixture (cis/trans = 54:46) of 2-butyl-1,2,3,4-tetrahydronaphthalen-1-ol (**3r**, 65%) in addition to 3,4-dihydro-2-butylnaphthalen-1(2H)-one (**4r**, 34%) (entry 18).

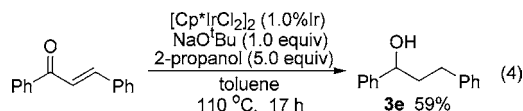
To obtain information concerning the reaction mechanism, the α -alkylation of ketone with a primary alcohol⁹ and

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transfer hydrogenation of an α,β -unsaturated ketone¹⁰ under the present catalytic conditions was undertaken. The reaction of acetophenone with 1-butanol (**2a**) in the presence of $[\text{Cp}^*\text{IrCl}_2]_2$ (1.0%Ir) and NaOH (1.0 equiv) at 110 °C for 17 h in toluene gave 1-phenylhexan-1-one (**4a**) in 91% yield (eq 3).

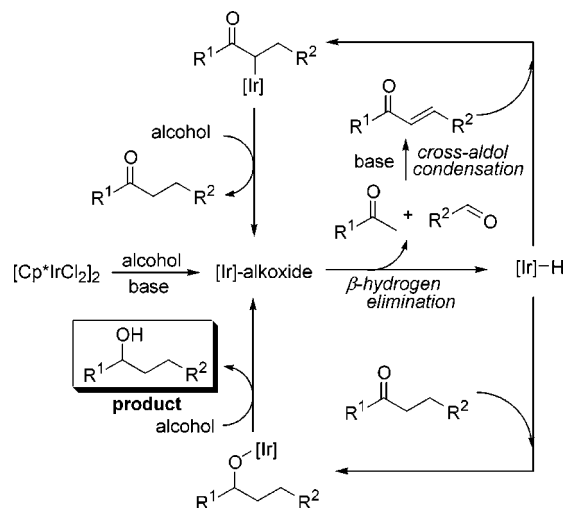


When the transfer hydrogenation of benzylideneacetophenone using 2-propanol (5.0 equiv) as a hydrogen donor was carried out in the presence of $[\text{Cp}^*\text{IrCl}_2]_2$ (1.0%Ir) and NaO^tBu (1.0 equiv) at 110 °C for 17 h in toluene, 1,3-diphenylpropan-1-ol (**3e**) was formed in 59% yield (eq 4).^{11,12}



A possible mechanism for Cp*Ir complex-catalyzed β -alkylation of secondary alcohols with primary alcohols is described in Scheme 1. The first step of the reaction would involve the oxidation of primary and secondary alcohols to aldehyde and ketone accompanied by the generation of a hydrido iridium species.⁸ Then, base-mediated cross-aldol condensation between aldehyde and ketone would occur to

Scheme 1. Possible Mechanism for Cp*Ir Complex Catalyzed β -Alkylation of Secondary Alcohols with Primary Alcohols



give an α,β -unsaturated ketone. Successive transfer hydrogenation of C=C and C=O double bonds of the α,β -unsaturated ketone by the hydrido iridium species would occur to give the product. It should be noted that, in this catalytic system, the hydrido iridium species generated at the stage of the oxidation of alcohols are consumed at the stage of the reduction of α,β -unsaturated ketone. Thus, additions of hydrogen donor and acceptor are not required, making this catalytic system a highly atom economical process.

In summary, we have shown a new efficient system for the β -alkylation of secondary alcohols with primary alcohols catalyzed by a Cp*Ir complex. It should be noted that the coproduct in these reactions is only H₂O. Moreover, the present system requires an extra addition of neither hydrogen acceptor nor donor. In addition, almost equimolar amount of substrates are sufficient to obtain good yields of products.

Supporting Information Available: Full experimental details and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) 1,3-Diphenylpropan-1-one (**4e**) was also formed in 14% yield as a byproduct.

(12) Similar transfer hydrogenation of benzylideneacetophenone using 1.0 equiv of 2-propanol as a hydrogen donor gave 1,3-diphenylpropan-1-one (**4e**) in 73% yield.