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Cross β-alkylation of primary alcohols catalysed by DMF-stabilized iridium nanoparticles[†]

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A simple method for the cross β -alkylation of linear alcohols with benzyl alcohols in the presence of DMF-stabilized iridium nanoparticles was developed. The nanoparticles were prepared in onestep and thoroughly characterized. Furthermore, the optimum reaction conditions have a wide substrate scope and excellent product selectivity.

Alcohols are some of the most important organic compounds in industry and research chemistry,¹ and the β -alkylation of alcohols is an important class of carbon–carbon-bond-forming reactions.² Conventionally, β -alkylated alcohols are prepared by a multi-step process involving the oxidation of alcohols, alkylation of the generated aldehydes or ketones with a halogen reagent in the presence of a strong base, and finally reduction under harsh conditions. Moreover, this approach generates halogenated waste.³

The borrowing hydrogen approach is a powerful strategy for the formation of carbon-carbon bonds.⁴ Recently, transitionmetal-catalyzed C-alkylation with alcohols as the alkyl source via the borrowing hydrogen approach has been extensively investigated using various nucleophiles, such as alcohols,⁵ ketones,⁶ amines,⁷ esters,⁸ and nitriles.⁹ The advantages of this system are the use of readily available alcohols and its environmental benignity, as water is the sole by-product. Furthermore, another carbon-carbon-bond-forming reaction, the Guerbet reaction, leads to the dimerization of primary alcohols via β -alkylation.¹⁰ Our group has reported the iridium-complex-catalyzed conversion of ethanol to butanol^{10b} linear alcohol dimerization.^{10a,c} However, cross and β-alkylation coupling reactions between primary alcohols have been scarcely reported. To the best of our knowledge, only three reports on the cross benzylation reaction between 2-arylethanol and benzyl alcohol *via* the borrowing hydrogen reaction are available (Scheme 1a). Ramón *et al.*¹¹ first investigated benzylation using a recyclable iridium-impregnated oxide on magnetite as a catalyst, while Johnson *et al.*¹² and Renaud *et al.*¹³ performed the reaction using ruthenium and iron complexes as catalysts, respectively. However, the β-benzylation of a linear alcohol starting material and the use of colloidal catalysts have not been reported.









Scheme 1 β -Alkylation of primary alcohols with benzyl alcohol *via* the borrowing hydrogen reaction: (a) cross alkylation of 2-arylethanol with benzyl alcohol, (b) cross alkylation of linear alcohols with benzyl alcohol (this work).

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Transition-metal nanoparticles (M-NPs) are highly active at low catalyst loadings owing to their large surface areas compared with those of the corresponding bulk metals.¹⁴ Typically, the synthesis of M-NPs requires a reductant and a protectant. However, our group has reported a simple method for the synthesis of DMF-stabilized M-NPs and their use in catalytic reactions.¹⁵ In this methodology, DMF is used as a reductant, protectant, and solvent.¹⁶ Among the different M-NPs, Ir-NPs show high catalytic activity for β -dimethylation of secondary alcohols with methanol *via* the borrowing hydrogen system.^{15e} However, this system does not allow catalyst recycling. Herein, we report the DMF-method solution synthesis of Ir-NPs, their structural characterization, and their use as a catalyst in the cross β -alkylation of primary alcohols with benzyl alcohol.

The oxidation state of the Ir-NPs was measured using X-ray photoelectron spectroscopy (XPS). The main peaks of Ir-NPs at 60.7 eV of $4f_{7/2}$ and 63.8 eV of $4f_{5/2}$ were comparable to those of Ir(0) (60.9 eV of $4f_{7/2}$ and 63.9 eV of $4f_{5/2}$)¹⁷ (Fig. S1, S2 and Table S1†).

We investigated the Ir-NP-catalyzed cross β -alkylation of 1-decanol (1a) with benzyl alcohol (2a) as model substrates under different conditions (Table 1). The reaction of 1a (1 mmol) with 2a (5 mmol) was performed in the presence of

Table 1	Ir-NP-catalyzed	β -alkylation	of	1-decanol	(1a)	with	benzyl
alcohol	(2a) ^a						

-	1 mmol 5 mmol 1a 2a	Cat. [Ir] Base 1,4-Dioxane 150 °C, 24 h 3a	он + Н7 он Н ₈ 4а
Entry	[Ir]	Base	Total yield ^{b,c} [%] Selectivity (3a : 4a)
1	Ir-NPs	KO ^t Bu	92 (98:2) [76]
2	IrCl ₃ ·nH ₂ O	KO ^t Bu	25 (84:16)
3^e	IrCl ₃ ·nH ₂ O	KO ^t Bu	35 (92:8)
4	$[Cp*IrCl_2]_2$	KO ^t Bu	86 (90:10)
5	$[IrCl(cod)]_2$	KO ^t Bu	62 (85:15)
6	$[Ir(OMe)(cod)]_2$	KO ^t Bu	63 (87:13)
7	None	KO ^t Bu	Trace
8	Ir-NPs	None	n.d.
9	Ir-NPs	K_2CO_3	Trace
10	Ir-NPs	Cs_2CO_3	33 (91:9)
11	Ir-NPs	KOH	57 (88:12)
12^{J}_{σ}	Ir-NPs	KO'Bu	93 (53:47)
13^{g}_{h}	Ir-NPs	KO'Bu	49 (86:14)
$14''_{i}$	Ir-NPs	KOʻBu	76 (88:12)
$15'_{i}$	Ir-NPs	KO'Bu	45 (80:20)
16^{j}_{k}	Ir-NPs	KO'Bu	88 (89:11)
17^	Ir-NPs	KO'Bu	>99 (89:11)

^{*a*} Reaction conditions: **1a** (1 mmol) was allowed to react with **2a** (5 mmol) in the presence of an Ir catalyst (0.1 mol%) and base (0.5 mmol) in 1,4-dioxane (1 mL) at 150 °C for 24 h. ^{*b*} GC yield based on **1a**. ^{*c*} Numbers in square brackets show the isolated yields. ^{*d*} Numbers in parentheses show the selectivity for **3a** and **4a**. ^{*e*} Ir catalyst (5 mol%) was used. ^{*f*} **1a** (1 mmol) and **2a** (1 mmol) were used. ^{*g*} At 130 °C. ^{*h*} Toluene was used instead of 1,4-dioxane. ^{*i*} Ir-NPs (0.001 mol%) for 48 h. ^{*j*} One drop (10.7 mg) of water was added under standard conditions. ^{*k*} Under an air atmosphere.

Ir-NPs (0.1 mol%) and KO^tBu (0.5 mmol) as the base at 150 °C for 24 h under Ar, giving the main product 3a with 4a as the homoalkylation by-product in 92% total yield and 98:2 selectivity (entry 1). The use of IrCl₃·nH₂O as the catalyst resulted in low yields (entries 2 and 3). Other iridium complexes known to be good catalysts for hydrogen autotransfer reactions gave the desired products in moderate yields (entries 4-6). Furthermore, we investigated whether the reaction proceeds without a catalyst or a base (entries 7 and 8), confirming that both are essential for this reaction to proceed. Other weak and strong bases (K₂CO₃, Cs₂CO₃, and KOH) gave the desired product in lower yields than that achieved using KO^tBu (entries 9-11). The base (0.5 mmol) is sufficient enough for the reaction under these conditions. When 1 mmol of benzyl alcohol instead of 5 mmol was used, the total yield was similar, but the selectivity was poor (entry 12). The reaction temperature was demonstrated to be an important factor (entry 13), and when the slightly polar solvent toluene was used, the main product was obtained in moderate yield (entry 14). Furthermore, the cross β -alkylation reaction proceeded with very low catalyst loading, with the desired product being obtained in 36% yield when 0.001 mol% of Ir-NPs was used as the catalyst (entry 15). The reaction proceeded smoothly both in the presence of a small amount of water (entry 16) and under an air atmosphere (entry 17).

We also explored the substrate scope of the reaction (Table 2). The o-, m-, and p-methylated benzyl alcohols gave the corresponding desired products in good yields (3b-d). The methoxy- and tert-butyl-substituted benzyl alcohol derivatives 3e and 3f were obtained in 65% and 74% yields, respectively. Electron-withdrawing groups (Cl and CF₃) led to the formation of the corresponding alcohols in poor yields (3g and 3h). Cyclopropanemethanol (2i) and 2-naphthalenemethanol (2j) as alkyl reagents reacted smoothly. Interestingly, heterocyclic compounds were obtained in good yields (3k and 3l), and aliphatic alcohols with different alkyl chain lengths reacted successfully under the optimized conditions (3m-p). Furthermore, a methoxy-terminated linear alcohol gave the corresponding alkyl product 3q in 64% yield. However, a branched alcohol exhibited low reactivity in this reaction (3r). 2-Phenylethanol, the model substrate used in a previous study, was found to be applicable to this catalyst system (3s). Under the optimized reaction conditions, γ -phenyl and -cyclohexyl propanol reacted with benzyl alcohol to give the desired products in good yields (3t and 3u). We also investigated the substrate scope using 1,6-hexanediol (1v). As a result, the dibenzyl product was obtained in 20% yield.

The recyclability of the DMF-stabilized Ir-NPs in this system was also investigated. After performing the reaction with 1-butanol **1m** and benzyl alcohol **2a**, the base was removed by a cotton filter from the reaction mixture. Next, substrates **1m**, **2a**, the desired product **3m**, and solvent were removed by vacuum distillation at 110 °C for 1 h under 0.3 mm Hg (Scheme S1†) then reused. In the first and second cycles, product **3m** was obtained in 77% and 68% yields, respectively (Fig. S3†). Thus, the Ir-NPs can be reused. A slight increase in

Table 2 Ir-NP-catalyzed β-alkylation^a



^{*a*} Condition: the same as entry 1, Table 1. ^{*b*} Yields of the isolated product after purification. ^{*c*} 1a (10 mmol) reacted with 2a (50 mmol) in the presence of Ir-NPs (0.05 mol%) and base (5 mmol) in 1,4-dioxane (5 mL) at 150 °C for 48 h. ^{*d*} KOH was used instead of KO'Bu at 48 h. ^{*e*} Reaction time, 48 h. ^{*f*} KO'Bu (1 mmol) was used.

the size of the nanoparticles resulted in a decrease in the yield of **3m** during the recycling steps.

Annular dark-field (ADF) scanning transmission electron microscopy (STEM) and dynamic light scattering (DLS) analyses were used, which was performed using **1m** (1 mmol) and **2a** (5 mmol) in the presence of Ir-NPs (0.1 mol%) and KOH (0.5 mmol) as the base at 150 °C for 48 h under Ar. The results of the analyses show that, before the reaction, the Ir-NPs are mostly 1–5 nm in size (Fig. 1a, b, and S4a†). After the reaction, the Ir-NP sizes are mostly 10–12 nm (Fig. 1c, d, and S4b†). The DLS analyses show that the size of the nanoparticles slightly increased during the course of the reaction (Fig. S4†).

To investigate the mechanism of the cross β -alkylation of linear alcohols with benzyl alcohols catalyzed by Ir-NPs, we carried out monitoring of the reaction intermediates and labeling studies. When 1-decanal was allowed to react with benzaldehyde under the optimal conditions determined above, the reaction gave an α , β -unsaturated aldehyde in 22% yield (Scheme S2†). We attempted a deuterium-labeling experiment

Fig. 1 (a) ADF-STEM image (scale bar = 20 nm) of the Ir-NPs before the reaction; (b) particle-size distribution of the Ir-NPs before the reaction; (c) ADF-STEM image (scale bar = 20 nm) of the Ir-NPs after the reaction; (d) particle size distribution of the Ir-NPs after the reaction.

using benzyl alcohol- d_7 . A deuterated product was obtained in 74% yield. These results indicate that 1-decanal and benzaldehyde are the reaction intermediates in this system and that the benzyl alcohol acts as the hydrogen source (Scheme S3†). Based on these results, we propose the catalytic cycle shown in Scheme 2. Briefly, the transformation begins with the dehydrogenation of alcohols to aldehydes with the generation of an Ir-NP-hydride. Then, the aldehydes react through a base-catalyzed aldol-type condensation to produce an α,β -unsaturated aldehyde and water. Subsequently, the double bond and aldehyde group are hydrogenated by the Ir-NP-hydride.

In conclusion, Ir-NPs catalyze the cross β -alkylation reaction of linear alcohols with benzyl alcohols. This reaction exhibits high product selectivity without the use of ligands and a broad substrate scope. The catalyst shows high catalytic activity and can be recycled two times.

Scheme 2 A plausible reaction mechanism.

Conflicts of interest

There are no conflicts to declare.

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