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First practical cross-alkylation of primary alcohols with a new and recyclable impregnated iridium on magnetite catalyst[†]

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A new impregnated iridium on magnetite catalyst has been prepared, characterized, used and recycled, up to ten times with practically the same activity, for the first practical cross-alkylation of primary alcohols. The catalyst showed a wide reaction scope, is easy to prepare and handle, and it could be removed from the reaction medium just by magnetic sequestering.

Alcohols are one of the most important classes of organic compounds owing to their wide variety of uses in industrial and laboratory chemistry. Although a plethora of methods for the synthesis of alcohols are known,¹ their simple creation by carbon-carbon bond manipulation is very unusual. The Guerbet reaction, a typical hydrogen autotransfer process² (also denoted borrowing hydrogen), is the only approach to this simple process. Originally the reaction was only useful for the auto-alkylation of primary alcohols.³ However, the introduction of secondary alcohols permitted the cross-alkylation between secondary and primary alcohols,⁴ with the latter ones operating as a source of electrophiles. Besides this partial success, the trials of cross-alkylation between primary alcohols⁵ were very discouraging, since it was necessary to add an excess of one alcohol (from three to thirteen equivalents), and to use high pressure (30 atmospheres) and temperatures (from 200 to 310 °C). In these transformations, the amount of catalyst ranged from 3 to 175 mol%, affording the expected product in moderate yield (from 11 to 62%), with many other by-products.

Meanwhile, we have recently developed a new, simple and robust method to immobilize different metal oxides⁶ onto magnetite.⁷ Along this research line, we report herein the first immobilization of iridium on magnetite using an impregnation protocol and its use as a reusable heterogeneous catalyst for the cross-alkylation of primary alcohols.

The catalyst was prepared by the classical impregnation method and characterized by XPS and XRD analyses. The XPS spectra showed two peaks placed at 62.1 and 64.5 eV, which correspond to the binding energies of IrO₂ $4f_{7/2}$ and $4f_{5/2}$ levels,⁸ with the superficial incorporation (1 nm depth) being 18%. The XRD

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analysis did not provide any concluding information due to the low iridium metal loading and its high dispersion, with exception of the support diffraction peaks (Fe₃O₄). The FXR analysis revealed a total incorporation of iridium of 0.5%. The BET surface area of catalyst was 8.0 m² g⁻¹, almost the same as that of the initial magnetite, 9.6 m² g⁻¹, and the concordant results show that there was no significant sinterization process under the assayed impregnation protocol and within the error of this technique. Moreover, the TEM images showed spherical particles for the catalyst with sizes in the range 0.1 ± 0.09 µm, similar to those obtained from the initial commercial magnetite (size: 0.1 ± 0.1 µm), with a homogenous distribution of nanoparticles of iridium (size: 0.8 ± 0.2 nm; more than 95% of particles in the range of 0.5–1.5 nm).

The cross-alkylation of 2-phenylethanol (1a) and benzyl alcohol (2a) was selected as a model reaction in order to optimize the conditions (Table 1).

The influence of temperature, solvent, base, amount of KOH, alcohol **2a**, and catalyst was studied initially (see ESI[†]),

 Table 1 Optimization of catalysts^a

	HO + Catalyst KOH, PhMe, 110 °C, 4 d	OH C 3a	
Entry	Catalyst (mol%)	Yield ^{b} 3a (%)	$\text{Yield}^{b} 4 (\%)$
1	$IrO_2 - Fe_3O_4 (0.14)$	96	3
2	$Fe_{3}O_{4}(65)$	35	3
3 ^c	_	14	10
4 ^c	$IrCl_4$ (0.14)	59	7
5^c	$[IrCl(cod)]_2$ (0.07)	47	12
6 ^{<i>c</i>}	$IrO_2(0.14)$	67	9
7	$CoO-Fe_{3}O_{4}(1.4)$	0	0
8	$NiO-Fe_3O_4$ (1.0)	0	0
9	$CuO-Fe_{3}O_{4}(1.3)$	11	1
10	Ru_2O_3 -Fe ₃ O ₄ (1.4)	26	5
11	$PdO-Fe_{3}O_{4}(1.2)$	41	2
12	NiO/CuO-Fe ₃ O ₄ (0.9/1.1)	28	4
13	Pd(0,II)/CuO-Fe ₃ O ₄ (1.5/0.8)	32	8

^{*a*} Reactions were carried out using **1a** (1.0 mmol) and **2a** (2.0 mmol) in toluene (1.5 mL). ^{*b*} Isolated yield after column chromatography. ^{*c*} Reactions were performed for 5 days.

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E-mail: djramon@ua.es; Fax: + 34-965903549; Tel: + 34-965903986† Electronic supplementary information (ESI) available: General procedure for the preparation of catalyst and products, XPS, TEM, EDS, and XRD analyses, particle size distribution, and ¹H and ¹³C NMR spectra. See DOI: 10.1039/c2cc33101b



Fig. 1 Recycling of IrO₂-Fe₃O₄ catalyst.

with the conditions presented in entry 1 of Table 1 showing the maximum yield of product **3a**. (*E*)-Prop-1-ene-1,3-diyldibenzene (**4**), which formed from the dehydrogenation of the starting alcohol **1a**, an auto-condensation process and final decarbonylation,⁹ was also detected as a by-product. The effect of the commercial micro-magnetite support was also tested (entry 2), which gave a modest yield in the cross-alkylation process. The reaction using 200 mol% of magnetite rendered compound **3a** in 70% yield, after 7 days. Even some amount of product **3a** could be detected when the reaction was performed in the absence of any transition salt (entry 3). Then, other sources of iridium catalyst were checked and both soluble and insoluble catalysts gave similar results (entries 4–6). Finally, other impregnated metals on magnetite were used as catalyst, but in all trials the yields were appreciably lower (entries 7–13).

Once the optimal reaction conditions were established, the problem of recycling was examined. The catalyst recovered from the reaction by using a magnet (entry 1, Table 1) was washed with toluene and re-used under the same reaction conditions, which resulted in the expected product 3a (Fig. 1). The iridium catalyst could be re-used up to ten times without practically losing its activity, with the lower yield obtained being 71%. The phenomenon of leaching was studied by ICP-MS analysis of the resulting reaction solution mixture, and 3.3% of the initial amount of iridium was detected (0.4% for iron). All these data demonstrate the possible structural integrity of the catalyst. Moreover, the TEM images of the ten-times recycled catalyst showed a homogenous distribution of nano-particles of iridium (size: 1.0 ± 0.4 nm; more than 90% of particles in the range of 0.5-1.5 nm), which is similar to the initial one, with the BET surface area being 7.5 $\text{m}^2 \text{g}^{-1}$ and the XPS spectra being exactly the same as those obtained from the fresh catalyst.

To know whether the reaction was carried out by the iridium leached into the organic medium, we performed the standard reaction between compounds 1a and 2a (Table 1, entry 1). After that, the catalyst was removed by a magnet and washed with toluene. The solvents of the above solution, without catalyst, were removed under low pressure and 2-(4-methoxyphenyl)ethanol (1f), benzyl alcohol (2a), KOH and toluene were added to the above residue. The resulting mixture was heated again at 110 °C for 5 days. The analysis of the crude mixture, after hydrolysis, revealed the formation of compound 3a in 91% (catalyzed process) and product **3m** in only 32% yield (compare with entry 13 in Table 2). Therefore, we could exclude that the final leached iridium was responsible for the reaction results. The three-phase test¹⁰ was performed in order to exclude a possible dynamic metal leach and return process. So, a benzylic alcohol moiety was attached to a NovaSyn-amino resin by reaction with phthalide.

Table 2	Cross-alkylation of primary alcohols ^a				
	R + 1	OH Ar 2 IrO2-Fe3O4 (0.14 mol%) KOH, PhMe, 110 °C, 4 d	Ar R 3	ЭН	
Entry	R	Ar	Alcohol	$\operatorname{Yield}^{b}(\%)$	
1	Ph	Ph	3a	96	
2^c	Ph	$4-ClC_6H_4$	3b	72	
3 ^c	Ph	4-MeC ₆ H ₄	3c	73	
4^c	Ph	$4-tBuC_6H_4$	3d	71	
5 ^c	Ph	4-MeOC ₆ H ₄	3e	75	
6 ^{<i>c</i>}	Ph	3,5-(MeO) ₂ C ₆ H ₃	3f	72	
7^c	$4-BrC_6H_4$	Ph	3g	79	
8 ^c	$4-ClC_6H_4$	Ph	3h	68	
9^c	$4-ClC_6H_4$	$4-ClC_6H_4$	3i	80	
10^{c}	$4-ClC_6H_4$	4-MeOC ₆ H ₄	3j	89	
11	$2-ClC_6H_4$	Ph	3k	98	
12^c	3-ClC ₆ H ₄	Ph	31	87	
13^{c}	4-MeOC ₆ H ₄	Ph	3m	83	
14^c	$4-MeOC_6H_4$	$4-ClC_6H_4$	3n	93	
15 ^c	$4-MeOC_6H_4$	4-MeOC ₆ H ₄	30	97	
16 ^c	Et	Ph	3р	88	
17	Et	$4-ClC_6H_4$	3q	90	
18	Et	4-MeOC ₆ H ₄	3r	86	
19 ^c	Me(CH ₂) ₉	Ph	3s	82	

^{*a*} Reactions were carried out using **1** (1.0 mmol) and **2** (2.0 mmol), KOH (1 mmol) in toluene (1.5 mL). ^{*b*} Isolated yield after column chromatography. ^{*c*} Reactions were performed for 5 days.

The usual cross-alkylation process using alcohol **1a** and IrO_2 -Fe₃O₄, after seven days and final treatment with trifluoroacetic acid, did not produce the expected compound **3**. Moreover, the standard reaction mixture was filtered off at 110 °C after one-day reaction (21% of compound **3a**), and the resulting solution was kept at this temperature for three more days, which resulted in only a 26% yield of compound **3a**. In a similar experiment, after the hot-filtration, magnetite (65 mol%), compound **1f**, benzyl alcohol (**2a**), and KOH were added and after 4-day reaction only compound **3a** (29%) was detected, and compound **3m** was not formed.

The optimized protocol was applied to other substrates in order to study the scope of the reaction (Table 2). The protocol gave homogenous results in the case of using functionalized benzyl alcohols (2) independent of electron-withdrawing or electrondonating groups (Table 2, entries 1–6). The methodology could be applied to different 1-arylethanol reagents (1) with practically the same yields (entries 7–15), even it was possible to carry out the reaction with an aliphatic alcohol (1), which gave the expected product with similar results (entries 16–19). The reaction failed when two different aliphatic alcohols were used, resulting in the recovery of the starting materials.

The last part of this study was focused on the possible catalytic pathway of the reaction, for the standard reaction between 2-phenylethanol and benzyl alcohol. The same reaction was performed with different combinations of labelled reagents, in all cases, it was found that the product 3'a was labelled in different ratios but always at the same positions. Thus, the reaction using only deuterated alcohol 1'a gave the expected product 3'a with a poor incorporation of deuterium at the α -position (19%) and at the γ -position (40%), with respect to the hydroxy group. When the alcohol 2'a was obtained with an incorporation of deuterium of



Scheme 1 Indirect evidence for the reduction of the condensation intermediate by a Michael-type hydride addition.



Fig. 2 Hypothetic mechanism pathway.

63 and 37% at α - and γ -positions, respectively. Finally when both reagents used were labelled (Scheme 1) the product obtained was **3'a** with nearly 100% incorporation of deuterium. In none of the occasions, the related alcohol labelled at the β -position was observed.

These experiments seem to show that after the dehydrogenation process by the iridium catalytic species, both aldehydes condense to give the α , β -unsaturated aldehyde, which suffers a reduction of the C–C double bond by the *in situ* generated iridium hydride in a Michael-type fashion, generating an enolate, and not following a typical hydrogenation process. The protonation of this intermediate by water renders the corresponding aldehyde, which finally is reduced by the iridium hydride (Fig. 2).

In conclusion, impregnated iridium on magnetite is an excellent heterogeneous and recyclable catalyst for the first real cross-alkylation of primary alcohols. The catalyst is very robust, easy to prepare, handle and store, and the general process shows a reasonable scope. All these facts, together with the simple recovery of catalyst by sequestering it with a simple magnet, without losing its activity, permit us to anticipate a good future for the process shown in this study not only in the laboratory but also in the industry.

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