Oxidation and β-Alkylation of Alcohols Catalysed by Iridium(I) Complexes with Functionalized *N*-Heterocyclic Carbene Ligands

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Dedication ((optional),

Abstract:

Borrowing hydrogen methodology allows for the use of alcohols as alkylating agents for C-C bond forming processes offering significant environmental benefits over traditional approaches. Iridium(I)-cyclooctadiene complexes having a NHC ligand with a O- or N-functionalized wingtip efficiently catalysed the oxidation and β-alkylation of secondary alcohols with primary alcohols in the presence of base. The cationic complex [Ir(NCCH$_3$)(cod)(MeIm(2-methoxybenzyl))][BF$_4$] having a rigid O-functionalized wingtip shows the best catalyst performance in the dehydrogenation of benzyl alcohol in acetone, with an initial TOF$_0$ of 1283 h^{-1}, and also in β-alkylation of 2-propanol with butan-1-ol which gives a 94% of conversion in 10 h with a selectivity of 99% in heptan-2-ol. We have investigated the full reaction mechanism including the dehydrogenation, cross-aldol condensation and hydrogenation steps by DFT calculations. Interestingly, these studies reveal also the participation of the iridium catalyst in the key step leading to the formation of the new C-C bond that involves the reaction of an O-bound enolate generated in basic medium with the electrophilic aldehyde.

Introduction

Transition-metal catalysed dehydrogenative oxidation of alcohols to synthetically valuable carbonyl compounds constitutes a high atom efficiency synthetic method alternative to the use of stoichiometric oxidants. Dehydrogenation of alcohols (Oppenauer-type oxidation) can be efficiently accomplished by hydrogen transfer catalysts if suitable hydrogen acceptors, typically acetone or alkenes, are used.[1,2] On the other hand, the oxidation of alcohols based on hydrogen transfer has also been applied to the formation of C–C and C-N bonds through the borrowing hydrogen methodology.

Remarkably, the borrowing hydrogen approach is a tandem process that produces the *in situ* formation of alkenes or imines through nucleophilic addition to electrophilic carbonyl compounds derived from alcohols by hydrogen transfer oxidation. These are redox-neutral processes because the temporary removal of hydrogen by the transition metal catalyst is followed by the delivery to the unsaturated products leading to the formation of new C–C and C–N bonds by means of hydrogen transfer reactions (Scheme 1). The search for efficient hydrogen-borrowing catalysts[3] is very stimulating as these tandem strategies provide easy access to a wide range of highly valuable organic molecules while introducing environmental benefit with water as the only reaction by-product. In this context, the borrowing hydrogen methodology applied to the β-alkylation of secondary alcohol with primary alcohols involves the formation of C–C bonds by activation of two alcohols in one reaction sequence (hydrogen autotransfer reactions).[4] Related C-C bond forming processes based on the activation of alcohols using the borrowing hydrogen methodology are, for example, the α-alkylation of carbonyl and related compounds,[5] the alkylation of active methylene compounds involving Knoevenagel-type transformations[6] or the condensation of primary alcohols (Guerbet condensation).[7] In addition, other processes based on the dehydrogenative coupling of alcohols have been also reported.[8]

N-Heterocyclic carbenes (NHCs) have attracted increasing attention as ligands for homogeneous catalysis. NHCs have proven to be efficient ancillary ligands because of their strong coordination ability that imparts to the metal complexes an adequate balance between stability and activity. In addition, their remarkable tunable character allows for the control of the sterical and electronic properties of the metal centre.[9] The easy access to a variety of NHC ligands from imidazolium salts[10] in combination with well-established methodologies for coordination, has led to the preparation of a range of transition metal complexes with different geometries and potential catalytic applications.[11] Iridium and ruthenium-NHC well-defined transition metal complexes have found application in catalytic oxidation of alcohols through dehydrogenation and hydrogen transfer processes, as well as in catalytic bond-forming reactions based on borrowing hydrogen methodology. The outstanding catalytic activity of complex [Cp*IrCl$_2$]$_2$ (Cp* = η^5-C$_5$Me$_5$) in this type of processes[12] has led to the development of new Cp*Ir(III)-NHC catalyst precursors. Thus, modified Cp*-Ir(III)

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Supporting information for this article, optimized coordinates for catalytic intermediates and transition states, is given via a link at the end of the document.

catalyst systems having pentamethylcyclopentadienyl-thetered NHC ligands,[13] bidentate pyrimidine-,[14] hydroxy-, ether- and alkoxide-functionalized[15] NHC ligands for transfer hydrogenation, β-alkylation of secondary alcohols with primary alcohols, and N-alkylation of amines with primary alcohols have been recently reported.
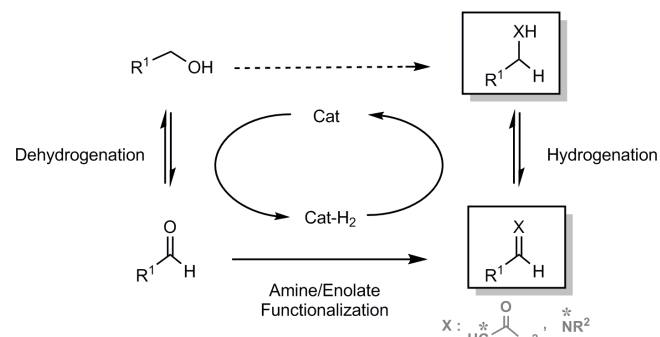
Scheme 1. Borrowing hydrogen strategy for C-C and C-N bond formation (cat-H_2 denotes the formal abstraction of two hydrogen atoms by the catalyst).

Our current interest is focused on the synthesis and catalytic applications of transition metal complexes containing heteroditopic ligands of hemilabile character. We have recently reported the high catalytic performance of (cod)-Ir(I) (cod = 1,5-cyclooctadiene) based catalyst having hemilabile O- and N-donor functionalized NHC ligands in transfer hydrogenation.[16] We have found an interesting relationship between the donor function, the flexibility of the backbone and the length of the linker in the NHC ligands with the catalytic activity in transfer hydrogenation catalysis. In particular, the catalyst precursors based on O-donor functionalized NHC ligands were found to be much more active than the corresponding N-functionalized ligands.[14,17,18]

The aim of this work is to assess the catalytic activity of selected iridium(I) catalyst precursors having a heteroditopic NHC ligand, but devoid of a cyclopendadienyl ligand, in the β-alkylation of secondary alcohol with primary alcohols. In view of the lack of mechanistic studies on this hydrogen autotransfer process,[19] the reaction mechanism has been investigated by DFT calculations. Remarkably, these studies have revealed the key role of the transition metal catalyst not only in the dehydrogenation and hydrogenation steps but also in the cross condensation step leading to the formation of the new C-C bond.

Results and Discussion

The Catalysts. We have recently reported on the catalytic activity of a series of neutral and cationic iridium(I) complexes based on hemilabile O-donor and N-donor functionalized NHC ligands in transfer hydrogenation of several unsaturated substrates as ketones, aldehydes, α,β-unsaturated ketones and imines in 2-propanol/KOH medium.[16] Interestingly, given the reversible nature of many hydrogen transfer processes, the oxidation of alcohols to carbonyl compounds might be also performed by hydrogen transfer catalysts helped by suitable hydrogen acceptors. We have observed that the donor function and flexibility of the backbone in the NHC ligands strongly influence the catalytic activity in transfer hydrogenation. Thus, a set of catalysts has been chosen in order to explore their performance in Oppenauer-type alcohol oxidation and related secondary alcohol β-alkylation reactions using the borrowing hydrogen methodology.
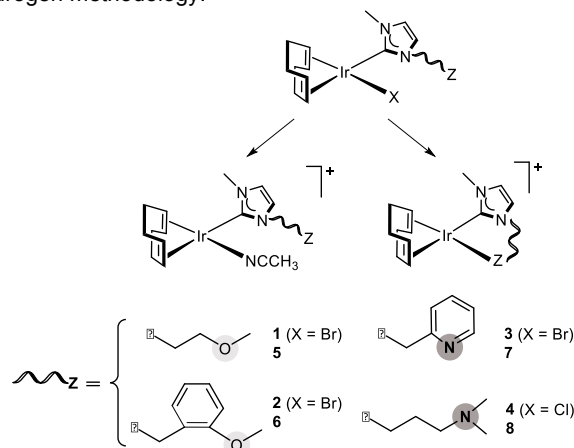

Chart 1. Neutral and cationic iridium(I) complexes with functionalized NHC ligands.

The iridium(I) complexes containing hemilabile O- and N-donor functionalized NHC ligands were synthesized using the free NHC ligands generated *in situ* by deprotonation of the functionalized imidazolium salts[16,20] by the methoxo ligands in the dinuclear complexes [{Ir(μ-OMe)(cod)}$_2$]. This synthetic route provides access to neutral mononuclear complexes [IrX(cod)(MeIm∩Z)] (**1-4**, X = Cl or Br, ∩Z = 2-methoxyethyl, 2-methoxybenzyl, pyridin-2-ylmethyl and 3-dimethylaminopropyl) having uncoordinated O- and N-donor functions with different backbone flexibility. The cationic complexes [Ir(NCCH$_3$)(cod)(MeIm∩Z)]BF$_4$ (**5-6**, ∩Z = 2-methoxyethyl and 2-methoxybenzyl) containing O-functionalized NHC ligands have uncoordinated methoxy fragments due to the coordination of a labile acetonitrile ligand. In contrast, the cationic complexes having N-functionalized NHC ligands [Ir(cod)(MeIm∩Z)]BF$_4$ (**7-8**, ∩Z = pyridin-2-ylmethyl and 3-dimethylaminopropyl) feature NHC ligands κ^2-C,N coordinated (Chart 1).

The β-alkylation of secondary alcohols with primary alcohols is a tandem reaction in which both alcohols are converted into carbonyl compounds by the temporary removal of hydrogen. For this reason, the iridium catalysts have been tested in the oxidation of primary and secondary alcohols with the aim of establishing the optimal hydrogen borrowing reaction conditions.

Oppenauer-type Oxidation Catalysis: Preliminary Screening.
The neutral [IrBr(cod)(MeIm(2-methoxybenzyl))] (**2**) and cationic [Ir(NCCH$_3$)(cod)(MeIm(2-methoxybenzyl))][BF$_4$] (**6**) iridium complexes featuring a methoxy-functionalized NHC ligand with a rigid wingtip were found to be the most active catalysts in the transfer hydrogenation of ketones.[16] Thus, both complexes have been tested as catalyst precursors for the dehydrogenation of primary and secondary alcohols (Oppenauer-type oxidation). The oxidation of benzyl alcohol and 1-phenylethanol to benzaldehyde and acetophenone, respectively, were chosen as model reactions to optimize the reaction conditions and to establish the basis for their application in hydrogen borrowing reactions. The catalytic reactions were performed in toluene at 110 °C using different inorganic and organic bases. Standard

catalyst loading 1 mol% with a catalyst:substrate:base ratio of 1:100:100 were routinely used. The conversion attained after 24h or the reaction time to get conversions over 90% (determined by GC using mesitylene as internal standard) using **2** as catalyst precursor, and the turnover frequencies (TOF$_0$) calculated at initial time are shown in Table 1.
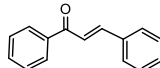
The catalytic systems with Cs$_2$CO$_3$ or KO^{t}Bu are much more efficient for the dehydrogenation of benzyl alcohol than those based on NaOMe or KOH providing up to a 70% conversion in 24 h (entries 1-5). However, the widely used and less hygroscopic Cs$_2$CO$_3$ was selected as base. The temperature has a strong influence on the catalyst performance and a sharp decrease in the catalytic activity was observed when the temperature was lowered from 110 to 80 °C (entries 1 and 2).
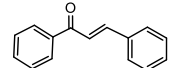
The presence of hydrogen acceptors as 3,3-dimethyl-1-butene or benzylideneacetophenone in an equimolecular amount with the alcohol displaces the equilibrium to the production of benzaldehyde almost quantitatively with initial TOF$_0$ of 350-550 h^{-1} (entries 6-8). The good conversions attained in the presence of an hydrogen acceptor allow shorter reaction times and milder reaction conditions (entry 8). Interestingly, the oxidation of benzyl alcohol in acetone as solvent at 40 °C for 8 h using KOH as base gave a 92% of conversion with the highest initial TOF$_0$ of 894 h^{-1} (entry 9). Catalyst **2** was also efficient in the dehydrogenation of 1-phenylethanol using Cs$_2$CO$_3$ as base showing similar catalytic activities (entries 10-13).

The related cationic iridium [Ir(cod)(NCCH$_3$)(MeIm(2-methoxybenzyl))][BF$_4$] (**6**), which showed a higher catalytic activity in the transfer hydrogenation of cyclohexanone, has also shown to be an efficient catalyst for the dehydrogenation of benzyl alcohol exhibiting comparable catalytic activities to those attained with **2** under the same experimental conditions. However, complex **6** showed better performance than **2** in the hydrogen transfer oxidation of benzyl alcohol in acetone using KOH as base providing a conversion of 91% in 6 h with an initial TOF$_0$ of 1283 h^{-1}.

Table 1. Catalytic dehydrogenation and hydrogen transfer oxidation of benzyl alcohol and 1-phenylethanol.[a]

entry	R	Base	Time (h)	A[b]	Yield (%)/ TOF$_0$ (h^{-1})[c]
1	H	Cs$_2$CO$_3$	24	-	68 / 283
2[d]	H	Cs$_2$CO$_3$	24	-	46 / 109
3	H	KOH	24	-	45 / 97
4	H	NaOMe	24	-	42 / 79
5	H	KO^{t}Bu	24	-	69 / 289
6	H	Cs$_2$CO$_3$	24	(3,3-dimethyl-1-butene)	95 / 349
7[d]	H	Cs$_2$CO$_3$	24	(3,3-dimethyl-1-butene)	94 / 337
8	H	Cs$_2$CO$_3$	12	(benzylideneacetophenone)	92 / 560
9[e]	H	KOH	8	(acetone)	92 / 894
10	CH$_3$	Cs$_2$CO$_3$	24	-	55 / 182
11	CH$_3$	Cs$_2$CO$_3$	24	(3,3-dimethyl-1-butene)	92 / 318
12	CH$_3$	Cs$_2$CO$_3$	17	(acetone)	91 / 411
13	CH$_3$	Cs$_2$CO$_3$	12	(benzylideneacetophenone)	95 / 573

[a] Reaction conditions: catalyst (0.03 mmol, 1 mol%), catalyst/benzylic alcohol/base ratio of 1/100/100, in toluene (0.3 mL) at 110 °C. [b] Hydrogen acceptor (3 mmol). [c] Determined by GC analysis using mesitylene as internal standard. Initial turnover frequency (mol of product/mol of catalyst per hour) determined at initial time, 60 s. [d] T = 80 °C. [e] Acetone as solvent, T = 40 °C.

Most of the reported studies on transition metal catalysed hydrogen transfer oxidation of alcohols have mainly been performed on secondary alcohols[21] and relatively few examples of the oxidation of primary alcohols affording aldehydes have been described.[22] Interestingly, the dinuclear Ir(III) complex [Cp*IrCl$_2$]$_2$ has revealed as an efficient catalyst for the oxidation of both primary and secondary benzylic alcohols, which contrast with the inactivity of the dinuclear complex [Ir(μ-Cl(cod)]$_2$.[12,23] In particular, a conversion of 86% in the oxidation of benzyl alcohol in acetone as solvent at room temperature was attained with [Cp*IrCl$_2$]$_2$ after 6 h. On the other hand, related iridium(III) complexes bearing amino-functionalized Cp* or NHC ligands are much more efficient catalyst precursors in the Oppenauer-type oxidation of alcohols reaching an average TOF of 242 in the oxidation of 1-phenylethanol without any base additive.[23a] Certainly, the electronic and steric properties of the Cp* and NHC ligands in combination with the basic properties of the substituent account for the high catalytic activities.[23]

The oxidation of 1-phenylethanol to acetophenone catalysed by [Ir(NCCH$_3$)(cod)(MeIm(2-methoxybenzyl))][BF$_4$] (**6**) was monitored by ^{1}H NMR (acetone-d_6 at 40 °C). The reaction prolife obtained from a catalytic test at 10 mol% catalyst loading using a catalyst/1-phenylethanol/Cs$_2$CO$_3$ ratio of 1/10/10 is shown in Figure 1. As can be observed, no apparent induction period was detected and quantitative conversion was attained in 2 hours. In general, the reaction profile resembles those obtained in the ketone reduction by transfer hydrogenation catalysed by **6**,[16] and in consequence, a pseudo-first-order kinetic behaviour can be inferred. The partially deuterated 2-propanol formed by reduction of the hydrogen acceptor (acetone-d_6) was observed at δ 1.17 ppm. Interestingly, when the oxidation reaction was performed in toluene-d_8 at 110 °C without any hydrogen acceptor molecular hydrogen was detected at δ 4.19 ppm.[24,25]
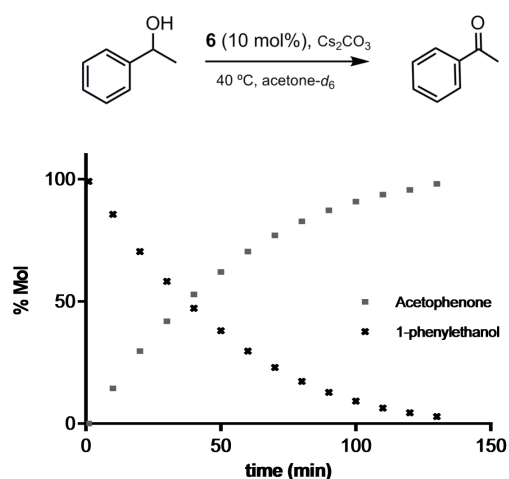
Figure 1. Time dependence of the catalytic hydrogen transfer oxidation of 1-phenylethanol catalysed by **6** (10 mol %). The reaction was performed in acetone-d_6 at 40 °C using Cs_2CO_3 as base (catalyst/1-phenylethanol/base ratio of 1/10/10).

Figure 2. Proposed mechanism for the Oppenauer-type oxidation of benzyl alcohol catalysed by **2**.

It has been proposed that key intermediates in the Oppenauer-type oxidation of alcohols are metal-alkoxide species that evolve to iridium-hydrides[12a] or ruthenium-hydrides[26] as active species. In this regard, it is worth mentioning that this transformation is also a key step in the redox isomerization of allylic alcohols and the racemization of secondary alcohols catalysed by ruthenium ciclopentadienyl complexes.[27] In fact, we have identified by NMR and MS the relevant alkoxo intermediates [Ir(OR)(cod)(MeIm∩Z)] and the unsaturated hydride species [IrH(cod)(MeIm∩Z)] (∩Z = 2-methoxybenzyl) involved in the transfer hydrogenation of unsaturated substrates in 2-propanol/KOH catalysed by iridium(I) complexes having hemilabile O- and N- donor functionalized NHC ligands.[16a] Interestingly, DFT calculations have allowed to identify an interaction between the β-H on the alkoxo ligand and the methoxy fragment of the NHC ligand, which results in a net destabilization of the alkoxo intermediate, thereby facilitating the β-H elimination step, leading to the hydride intermediate.[16a] Thus, considering the reversibility of both hydrogen transfer processes is likely that the Oppenauer-type oxidation of alcohols proceeds through the closely related mechanism shown in Figure 2.

First, an iridium alkoxo species is generated from **2** and the alcohol in the presence of the base. Then, β-H elimination yields the neutral hydride intermediate and the carbonyl compound (ketone from secondary alcohols or aldehyde from primary alcohols). At this point, in the absence of a hydrogen acceptor, alcoholysis produces $H_2(g)$ and the regeneration of the iridium alkoxo species (outer cycle in Figure 2). However, in the presence of a suitable hydrogen acceptor as acetone, the insertion into the Ir-H bond followed by alkoxide exchange proceeds to regenerate the iridium alkoxo species with release of 2-propanol, the reduced form of the acceptor (main cycle in Figure 2).
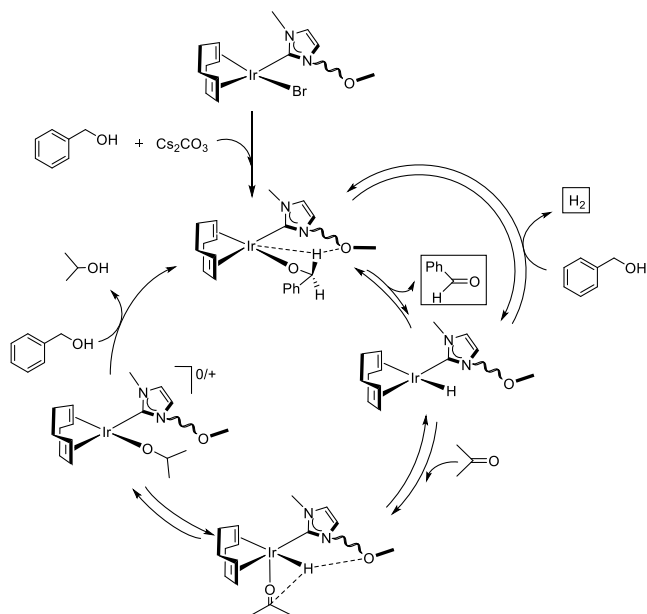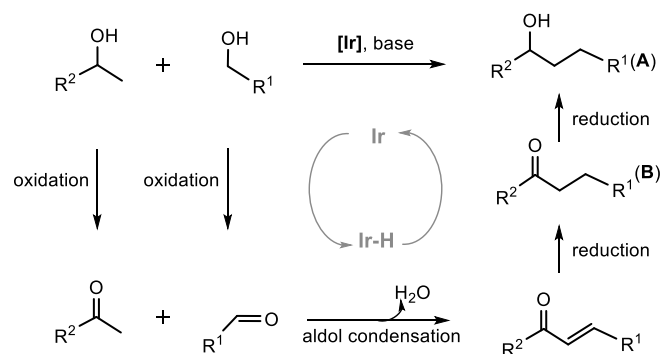
β-Alkylation of Alcohols Catalysed by Iridium Complexes with O/N-donor functionalized NHC Ligands.

The β- alkylation of secondary alcohols with primary alcohols is a tandem reaction [28] that proceeds via successive hydrogen transfer oxidation of the secondary and primary alcohols (borrowing hydrogen) to give a ketone and an aldehyde, respectively, followed by cross-aldol condensation mediated by base to afford a α,β-unsaturated ketone (and water) which is reduced by transfer hydrogenation to the β-alkylated alcohol (A) through the saturated ketone product (B) (Scheme 2). Several iridium complexes including Cp*[12,23,29], terpyridine[30] or pyrimidine[14] as ligands have been reported to catalyze this reaction.[31]

Scheme 2. β-alkylation of secondary alcohols with primary alcohols catalysed by iridium complexes.

A preliminary screening of the catalytic performance of [IrBr(cod)(MeIm(2-methoxybenzyl))] (**2**) in the β-alkylation alcohols was carried out in order to determine the influence of key reaction parameters (base, solvent and temperature) on the catalytic activity. The β-alkylation of 1-phenylethanol with benzyl alcohol was selected as model reaction. The reactions were

performed at 1 mol% catalyst loading for 3 hours under the optimized catalytic conditions of temperature (110 °C) and solvent (0.3 mL toluene) found for the catalytic system [Cp*IrCl₂]₂/NaO^{t}Bu.[12d] using a 20 mol% excess of benzyl alcohol, and the results are summarized in Table 2.[12d] It worth noting that the selectivity is not significantly affected by the benzyl alcohol/1-phenylethanol ratio, however the reactions are somewhat faster when using a moderate excess of primary alcohol.

Table 2. Influence of the base, solvent and temperature in the β-alkylation of 1-phenylethanol with benzyl alcohol catalysed by [IrBr(cod)(MeIm(2-methoxybenzyl))] (**2**).[a]

A   1,3-diphenylpropan-1-ol
B   1,3-diphenylpropan-1-one
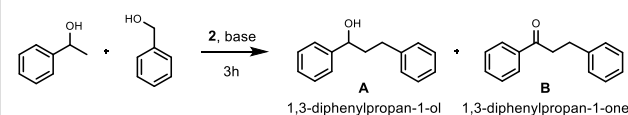
entry	Base	Solvent	Cat/Base ratio	Conv. (%)[b]	A / B ratio
1	Cs₂CO₃	toluene	1/100	68	71 / 29
2	Cs₂CO₃	toluene	1/50	31	68 / 32
3	Cs₂CO₃	toluene	1/150	69	77 / 23
4	K₂CO₃	toluene	1/100	24	51 / 49
5	KOH	toluene	1/100	45	46 / 54
6	KHMDS	toluene	1/100	60	47 / 53
7	NaHCO₃	toluene	1/100	3	- / -
8	KO^{t}Bu	toluene	1/100	69	59 / 41
9[c]	Cs₂CO₃	toluene	1/100	2	- / -
10	Cs₂CO₃	toluene (130 °C)	1/100	70	73 / 27
11	Cs₂CO₃	toluene (90 °C)	1/100	34	56 / 44
12	Cs₂CO₃	toluene (1 mL)	1/100	46	72 / 28
13	Cs₂CO₃	PhCH₂OH	1/100	64	75 / 25
14[d]	Cs₂CO₃	PhCH₂OH (1 mL)	1/100	99	- / -
15	Cs₂CO₃	-	1/100	55	70 / 30

[a] Reaction conditions: catalyst (0.03 mmol, 1 mol%), 1-phenylethanol (3 mmol), benzyl alcohol (3.6 mmol) and base (3 mmol) in toluene (0.3 mL) at 110 °C unless otherwise stated, 3 h. [b] Determined by GC analysis based on the secondary alcohol using mesitylene as internal standard.. [c] No catalyst. [d] Product = (PhCH₂)₂O, 24 h of reaction.
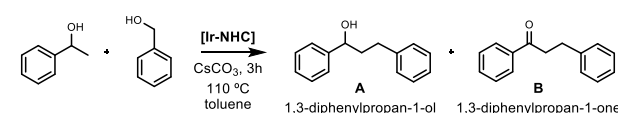
The β-alkylation of 1-phenylethanol catalysed by **2** under the standard conditions using Cs₂CO₃ as base (1:100 ratio) gave a 68% conversion of benzyl alcohol (entry 1). The conversion drastically dropped when the reaction was conducted with a catalyst/base ratio of 1:50. However, a higher ratio of 1:150 produces no significant increase of the conversion (entries 2 and 3). Thus, the optimum catalyst/base ratio of 1:100 was used in the following experiments.

The β-alkylation reaction proceeds to a much higher conversion with the base Cs₂CO₃ than with K₂CO₃ (entries 1 and 4). Stronger bases as KOH or KHMDS (entries 5 and 6) were less effective than Cs₂CO₃ while KO^{t}Bu (entry 8) gave a similar conversion. However, a weaker base as NaHCO₃ was completely inefficient (entry 7). As it could be expected, only a marginal conversion was attained without the iridium catalyst (entry 9). The β-alkylation reactions gave the β-alkylated alcohol with moderate selectivity because the half-reduced ketone product was produced to some extent. Thus, the highest 1,3-diphenylpropan-1-ol/1,3-dipheynlpropan-1-one ratio (**A/B**) was attained when using Cs₂CO₃ as base (71:29, entry 1). The temperature strongly influences the catalytic activity. Although the catalytic performance was only slightly improved at 130 °C, both conversion and selectivity dropped when the reaction was carried out at 90 °C (entries 10 and 11). Also, reducing the

concentration by increasing the volume of toluene (1 mL) gave moderate conversion while maintaining the selectivity (entry 12) which is in accordance with the observations made by Yamaguchi in the [Cp*IrCl₂]₂ catalysed alkylation of 1-phenylethanol with 1-butanol, although a selectivity decrease was also observed in this system.[23] Benzyl alcohol can also be used as solvent giving a similar conversion but with concomitant formation of a 5% dibenzylether[32] (entry 13). When the catalytic reaction was carried out in benzyl alcohol under more diluted conditions (1 mL) full conversion to dibenzylether was achieved in 24 h (entry 14). Finally, the catalytic β-alkylation reaction can be carried out without solvent although with lower conversions (entry 15).

On the basis of the above results, the iridium(I) catalysts featuring different O/N-donor functionalized N-heterocyclic carbene ligands were evaluated for the β-alkylation of 1-phenylethanol with benzyl alcohol under the optimized catalytic conditions: 1 mol% catalyst loading using Cs₂CO₃ as base (catalyst/base ratio of 1:100) in toluene (3 mL) at 110 °C. The reaction time required to reach conversions over 90% and the attained selectivities are summarized in Table 3.

Table 3. β-alkylation of 1-phenylethanol with benzyl alcohol catalysed by NHC-carbene iridium(I) catalysts having different N- and O-functionalized NHC ligands.[a,b]

A   1,3-diphenylpropan-1-ol
B   1,3-diphenylpropan-1-one

entry	Catalyst	t (h)	conv. (%)[b]	A / B ratio
1	**1**	10	93	74 / 26
2	**2**	9	92	76 / 24
3	**3**	13	91	77 / 23
4	**4**	27	93	75 / 25
5	**5**	11	96	77 / 23
6	**6**	7	93	86 / 14
7	**7**	10	92	78 / 22

8	[Ir(cod)(MeIm(N,N-dimethylaminoethyl))]⁺ structure **8**	24	91	76 / 24

8 — 24 — 91 — 76 / 24

9 — 9 — 54 — 67 / 33

10 — 9 — 12 — 43 / 57

[a] Reaction conditions: catalyst (0.03 mmol, 1 mol%), 1-phenylethanol (3 mmol), benzyl alcohol (3.6 mmol) and Cs_2CO_3 (3 mmol) in toluene (0.3 mL) at 110 °C for 3 h. [b] Determined by GC analysis based on the secondary alcohol using mesitylene as internal standard.

The iridium(I) complexes having functionalized-NHC ligands **1**-**8** were found to be moderately active in the β-alkylation of 1-phenylethanol with benzyl alcohol. In general, 1-phenylethanol conversions over 90% were attained in 7-13 h with selectivities in 1,3-diphenylpropan-1-ol higher than 75%. The cationic compound [Ir(cod)(NCCH₃)(MeIm(2-methoxybenzyl))][BF₄] (**6**), having a NHC ligand with a rigid O-functionalized wingtip, is the more active in the series, with 93% of conversions in 7 h, and also the more selective, with 86% of 1,3-diphenylpropan-1-ol (entry 6). In general, the catalyst precursors having N-functionalized NHC ligands are less active than those containing O-functionalized NHC ligands. It is worth mentioning that a similar trend had already been observed for hydrogen transfer reduction of unsaturated substrates. However, the catalytic activity of the precursors having a pyridin-2-ylmethyl wingtip, **3** and **7**, is remarkable because is only slightly lower than that of precursors **1** and **5** having a 2-methoxyethyl substituent. The neutral complex [IrBr(cod)(MeIm(2-methoxybenzyl))] (**2**) also showed notable catalytic activity reaching a 92% of conversion in 6 h, although with lower selectivity than **6**, underlining the positive effect of the rigid 2-methoxybenzyl wingtip on the catalytic activity. It is noteworthy that the catalytic performance of related iridium(I) complexes [IrCl(cod)(IMe)] (**9**) and [IrCl(cod)(IPr)] (**10**), with small and big alkyl/aryl substituents, but lacking a functionalized NHC ligand, is inferior both in terms of activity and selectivity under the same catalytic conditions (entries 9 and 10).
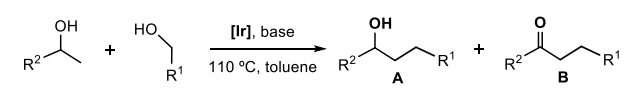
A range of secondary and primary alcohols were selected to determine the substrate scope under the optimized conditions using the more efficient catalyst precursors [IrBr(cod)(MeIm(2-methoxybenzyl))] (**2**) and [Ir(NCCH₃)(cod)(MeIm(2-methoxybenzyl))][BF₄] (**6**) both with the rigid O-functionalized wingtip in the NHC ligand (Table 4).

The β-alkylation of 1-phenylethanol proceeds efficiently with different *para*-substituted benzyl alcohols regardless of the electronic character of the substituent. The cationic catalyst precursor **6** was somewhat more active than the neutral **2** also providing a higher selectivity to 1,3-diphenylpropan-1-ol. Conversions over 90% were typically reached after 7-9 h (entries 1-7). Interestingly, almost complete selectivity in the β-
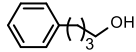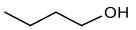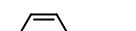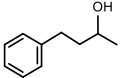
alkylated alcohol product was attained when using catalyst precursor **2** increasing the catalyst/base ratio to 1:150 (entry 2).
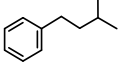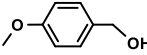
Straight chain alcohols, butan-1-ol and 3-phenylpropan-1-ol, were also efficient as alkylating agents although at slightly slower rates with lower selectivities (entries 8-12). Interestingly no self-condensation products were observed in any case. As it was observed before, catalyst precursor **2** allows increasing the selectivity in 1-phenylhexan-1-ol from 58 to 98% when using a catalyst/base ratio of 1:150 (entries 10 and 11).

Table 4. β-alkylation of secondary alcohols with primary alcohols catalysed by iridium(I) complexes **2** and **6** having a NHC ligand with a 2-methoxybenzyl substituent.[a, b]

$$R^2\text{-CH(OH)-CH}_3 + HO\text{-CH}_2\text{-}R^1 \xrightarrow[110\,°C,\ toluene]{[Ir],\ base} A\ (R^2\text{-CH(OH)-CH}_2\text{-CH}_2\text{-}R^1) + B\ (R^2\text{-CO-CH}_2\text{-CH}_2\text{-}R^1)$$
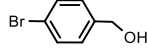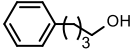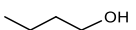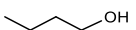
entry	R² (secondary alcohol)	R¹-OH (primary alcohol)	cat.	t (h)	conv (%)	A / B ratio
1	1-phenylethanol	benzyl alcohol	2	9	92	76 / 24
2			2[c]	9	97	99 / 1 (81 %)[d]
3			6	7	93	86 / 14
4		4-methoxybenzyl alcohol	2	9	92	74 / 26
5			6	7	93	85 / 15
6		4-bromobenzyl alcohol	2	9	91	77 / 23
7			6	7	94	83 / 17
8		3-phenylpropan-1-ol	2	12	92	72 / 28
9			6	10	91	82 / 18
10		butan-1-ol	2	11	91	58 / 42
11			2[c]	11	92	98 / 2 (78 %)[d]
12			6	10	92	64 / 36
13	1-phenylpropan-1-ol	benzyl alcohol	2	12	89	65 / 35
14	1-(4-bromophenyl)ethanol	benzyl alcohol	2	12	93	51 / 49
15	1-(4-methylphenyl)ethanol	benzyl alcohol	2	12	99	99 / 1 (83 %)[d]
16	propan-2-ol	benzyl alcohol	2	10	94	62 / 38
17			6	9	92	66 / 34
18		4-methoxybenzyl alcohol	6	9	92	69 / 31
19		4-bromobenzyl alcohol	6	9	91	68 / 32

20	(structure)	**6**	10	91	70 / 30
21	(structure)	**6**	10	92	54 / 46
22		**6**[c]	10	94	99 / 1 (69 %)[d]
23	(structure)	**2**	11	93	65 / 35
24		**6**	10	92	69 / 31
25	(structure)	**6**	10	92	65 / 35
26	(structure)	**6**	9	94	65 / 35
27	(structure)	**6**	13	91	52 / 48
28	(structure)	**6**	16	95	61 / 39
29		**6**[c]	18	92	98 / 2 (85 %)[d]

[a] Reaction conditions: catalyst (0.03 mmol, 1 mol%), catalyst/secondary alcohol/Cs_2CO_3 ratio of 1/100/100 and primary alcohol (3.6 mmol), in toluene (0.3 mL) at 110 °C for 3 h. [b] Determined by GC analysis based on the secondary alcohol using mesitylene as internal standard. [c] catalyst:base ratio of 1:150. [d] Isolated yield of the β-alkylated alcohol product A.

The β-alkylation of 1-phenyl-1-propanol with benzyl alcohol proceeds at lower rate compared to 1-phenylethanol exhibiting also lower selectivity (entries 1 and 13). The electronic effects on the secondary alcohol have been also studied. Thus, the presence of electron-withdrawing group affects negatively both at the activity and the selectivity as can be seen in the β-alkylation of 1-(4-bromophenyl)ethanol with benzyl alcohol (entries 1 and 14). However, electron-donating groups have a positive influence and 1-(4-methylphenyl)ethanol was efficiently alkylated in 12 h with complete selectivity without adding additional base (entries 1 and 15).

Propan-2-ol was also successfully alkylated by benzyl alcohol and butan-1-ol derivatives although with moderate selectivities (Table 4, entries 16-21). Again, a notable selectivity improvement was observed when the amount of Cs_2CO_3 was raised until 150 mol%. Under these conditions, the β-alkylation of 2-propanol with butan-1-ol catalysed by **6** gave a 94% of conversion in 10 h with a selectivity of 99% in heptan-2-ol (entry 22). A similar reactivity trend was observed in the β-alkylation of 4-phenylbutan-2-ol. Thus, benzyl alcohol derivatives reacted faster than straight chain alcohols with selectivities around 65% in both cases (entries 23-29). Notably, the increase of the amount of Cs_2CO_3 to 150 mol% allowed to reach a 98% of selectivity in 1-phenyloctan-3-ol (entry 29).

The β-alkylated alcohols from the catalytic runs giving a high selectivity (Table 4, entries 2, 11, 22 and 29, respectively) have been isolated as colorless oils in 70-85 % yields after purification by chromatography column (see Supporting Information).

The β-alkylation of 1-phenylethanol with benzyl alcohol catalysed by **2** in toluene-d_8 at 80 °C using KHMDS as base was monitored by ^{1}H NMR. As can be seen in the conversion *vs* time plots, both products, 1,3-diphenylpropan-1-ol (**A**) and 1,3-diphenylpropan-1-one (**B**), were formed immediately after

thermal equilibration of the reaction mixture with no apparent induction period (Figure 3). Interestingly, accumulation of the half-reduced ketone product **B** was observed during the first 2h of reaction which suggests that the reduction of **B** is slower than the reduction of the α,β-unsaturated ketone product resultant from the cross-condensation process, which was no detected under these experimental conditions (Scheme 2). On the other hand, the reaction profile also justifies the low selectivity observed in the tandem reaction at short reaction times and the positive influence of an excess of base on the selectivity, since quantitative conversion and complete selectivity to **A** was achieved in less than 6 h using a catalyst/1-phenylethanol/KHMDS ratio of 1/10/15.
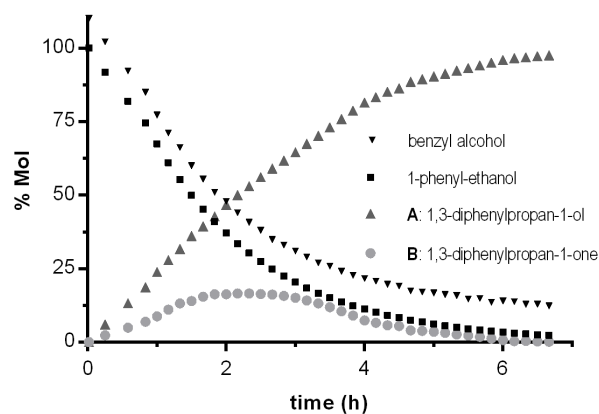

Figure 3. Time dependence of the β-alkylation of 1-phenylethanol with benzyl alcohol catalysed by **2** (10 mol %). The reaction was performed in toluene-d_8 (0.4 mL) at 80 °C using KHMDS as base (catalyst/1-phenylethanol/benzyl alcohol/base ratio of 1/10/11/15).

Mechanistic Studies. The mechanism of the transition-metal catalysed β-alkylation of secondary alcohols with primary alcohols combines the hydrogen transfer oxidation of both alcohols with the reduction of the resulting unsaturated product (Scheme 2). In the catalytic cycle, the hydrogen atom of the substrate is transferred to a metal catalyst generating a transient metal hydride species which is delivered to the unsaturated species after the C-C bond formation giving back the metal catalyst (borrowing hydrogen or hydrogen autotransfer). Thus, the metal-catalysed hydrogen transfer process plays a fundamental role in the overall catalytic cycle.

Late transition-metal catalysed transfer hydrogenation of unsaturated substrates can proceed by an inner-sphere pathway through both monohydride or dihydride intermediate species. However, in the case of Ir(I) complexes, the monohydride mechanism seems to be operative.[33] In fact, we were able to identify the hydrido intermediate [IrH(cod)(MeIm(2-methoxybenzyl))] in the transfer hydrogenation of unsaturated substrates in 2-propanol/KOH under catalytic conditions. It is thus likely that this species is also key in the borrowing hydrogen β-alkylation process. Furthermore, when solutions of complexes **2** or **6** in toluene-d_8 were heated in presence of benzyl alcohol in basic medium (KHMDS) at 110 °C for 2 min the formation of molecular hydrogen was detected at 4.48 ppm.[24] Interestingly, neither cyclooctene nor cyclooctane, the reduction products of the diene ligand, were detected which strongly support the participation "Ir(cod)" species as intermediates.

In order to ascertain the possible involvement of the transition metal catalyst also in the cross-aldol condensation step leading to the formation of the new C-C bond, some catalytic test reactions were carried out. Reaction of 1-phenylethanol and benzaldehyde in the presence of **2** under the standard catalytic conditions (1 mol% **2**, 100% Cs$_2$CO$_3$, 110 ºC, 0.3 mL toluene) for 9 h gave a mixture of products containing 13% of 1,3-diphenylpropan-1-ol (**A**), 75% of 1,3-diphenylpropan-1-one (**B**) and 12% of 1,3-diphenyl-2-propen-1-one (chalcone) (GC analysis, 95% conversion of 1-phenylethanol, Scheme 3a). Interestingly, the reaction of acetophenone with benzyl alcohol under the same experimental conditions gave a similar mixture. The large amount of the saturated ketone, 1,3-diphenylpropan-1-one, and the presence α,β-unsaturated ketone, never detected in the catalytic reactions, is in agreement with the deficit in reduction equivalents due to the presence of a carbonyl compound as partner. Both catalytic tests reinforce the participation of transfer hydrogenation processes from the alcohols to the unsaturated condensation products.
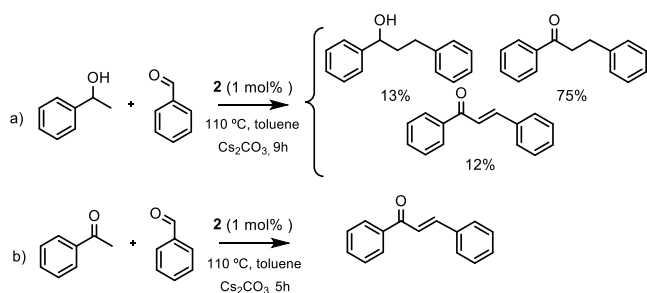
Scheme 3. β-Alkylation of alcohols: catalytic test reactions for mechanistic studies.

A notable finding was that a 100% of conversion to chalcone, the cross-aldol condensation product, was attained in the reaction of acetophenone with benzaldehyde in the presence of **2** under the standard catalytic conditions in only 5 h, Scheme 3b. In sharp contrast, when the reaction was conducted without catalyst **2** the aldol condensation reaction proceeds at lower rate, with only a 55% of acetophenone conversion after 24h of reaction. GC/MS analysis of the reaction mixture showed the expected condensation product chalcone in 82%, but also the products of the base-induced disproportionation of benzaldehyde (Cannizzaro reaction) and traces of the product (E)-1,3-diphenylbut-2-en-1-one, resulting from self-condensation of the ketone. Both facts stongly support the participation of the iridium catalyst in the cross-aldol condensation reaction.

Enolate species are key building blocks in synthetic organic chemistry for the formation of new carbon-carbon and carbon-heteroatom bonds.[34] Nowadays, the chemistry and reaction mechanisms involving enolates have been established, specially those focused on C-C bond-formation reactions, such as aldol condensations.[35] The cross-aldol condensation is driven by the nucleophilic attack of the enolate generated under basic conditions to the electrophile aldehyde to form a β-hidroxyketone (Figure 4).
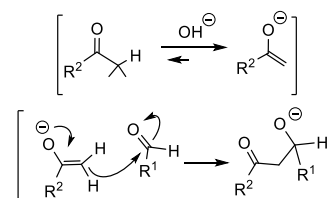

Figure 4. Base-catalysed cross-aldol reaction mechanism.

In general, it is widely accepted that the simultaneous coordination of the enolate and the electrophilic carbonyl compound to metal centre is required to enhance both the reactivity and stereoselectivity.[36] However, in the present case the participation of pentacoordinated iridium species of the type [Ir(cod)(MeImZ)(enolate)(aldehyde)] is unlikely. In this context, it is worth of noting the rich chemistry of the square planar complex [Ni(CH$_3$)(OC(=CH$_2$)Ph)(dippe)] having a acetophenone enolate ligand.[37]

Mechanism of the β-Alkylation of Alcohols Catalysed by [Ir(cod)(NHC)]$^+$ Complexes: DFT studies. The β-alkylation of phenylethanol with benzyl alcohol has been studied computationally by means of a set of DFT calculations using the fragment [Ir(cod)(IMe)] as a model of [Ir(cod)(MeIm∩Z)] (∩Z = (O- or N-functionalized wingtip) in the intermediates which take part in the catalytic cycles.

The β-alkylation model process requires the previous oxidation of benzyl alcohol to benzaldehyde and phenylethanol to acetophenone by coordination of the respective alkoxides to the NHC catalyst. The oxidation processes are almost thermoneutral (*ca.* −2 kcal/mol for the formation of acetophenone and ca. +2 kcal/mol for the formation of benzaldehyde), and they proceed with a similar activation energy of ~25 kcal/mol. (Figure 5). The resulting square planar hydrido complex **11** will react later in the hydrogenation processes of the α,β-unsaturated ketone intermediates which will lead to the final alcohol products.

As it was shown above, the experimental evidence suggests that the cross-aldol condensation process occurs in the coordination sphere of the iridium centre. Either the alkoxo complexes [Ir(OR)(cod)(IMe)] (**12**) or the starting halo-complex [IrBr(cod)(IMe)] (**13**) can coordinate acetophenone or its enolate affording **14**. Formation of the unsaturated ketone can occur via attack of benzaldehyde on the β-C atom of the O-bound enolate ligand with an activation energy of ~23 kcal/mol (**TS$_{14-15}$**, Figure 6). **TS$_{14-15}$** has been located by the study of the reverse process starting form **15**. IRC calculations show the connection of this TS with both **15** and the O-bound enolate **14**. In this context, theoretical [38] and experimental [39] studies have shown the distinctive reactivity, in the aldol reaction, of O-bound enolates compared to their possible C-bound counterparts.

Noteworthy, in this reaction both intervening O atoms switch its role as donor atom. The O atom of the benzaldehyde molecule ends as an alkoxo group coordinated to the metal atom, while the O atom of the enolate ligand is released from the coordination sphere. The resulting alkoxo-ketone ligand in complex **15** is de-coordinated via alcoholysis. The subsequent hydroxo-ketone is unstable under the reaction condition and eventually dehydrates to the α,β-unsaturated ketone.[40] The energy profile for the formation of 3-hydroxy-1,3-diphenylpropan-1-one described in the Figure 5 is presented in Figure 7.

The possible role of the substituent on the NHC ligand in this step has been further studied by including -CH$_2$-(C$_6$H$_4$)-OCH$_3$ group and re-optimizing the **TS$_{14-15}$** transition structure. Two orientations of the substituent on this full model are possible depending on its position relative to the iridium coordination plane. The two possible transition structures have been found and they differ in less than 0.4 kcal/mol (see Supporting Information). Both transition structures have confirmed by checking their connection to the reaction extrema by IRC calculations. The activation energies are 22.9 and 23.2 kcal/mol and they are almost identical to that found for the simple model used in the study of the full cycle. This suggests that the role of the substituent on the NHC ligand is almost negligible in this step and it must be involved with the alcohol oxidation process, as previously reported by us,[16a] which is in full agreement with the experimental results shown in Table 3 (entries 2 and 6 *vs* 9).
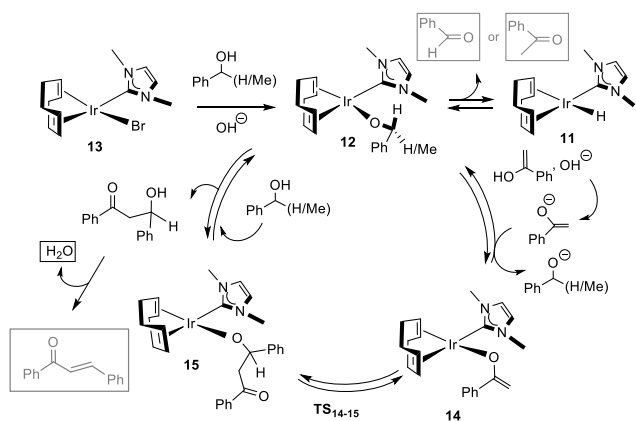

Figure 5. Proposed mechanism for the catalytic β-alkylation of secondary alcohols with primary alcohols leading to the formation of α,β-unsaturated ketones.
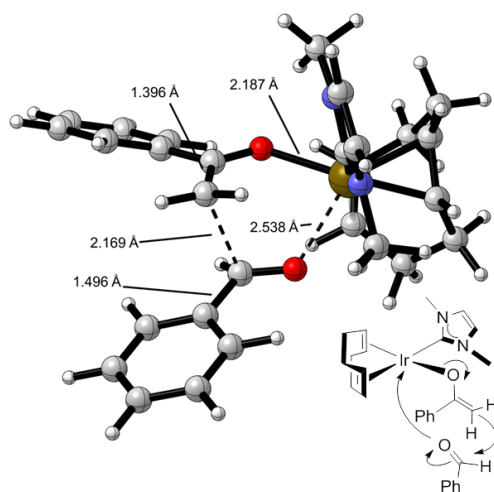

Figure 6. Transition state structure **TS$_{14-15}$** with some relevant distances.
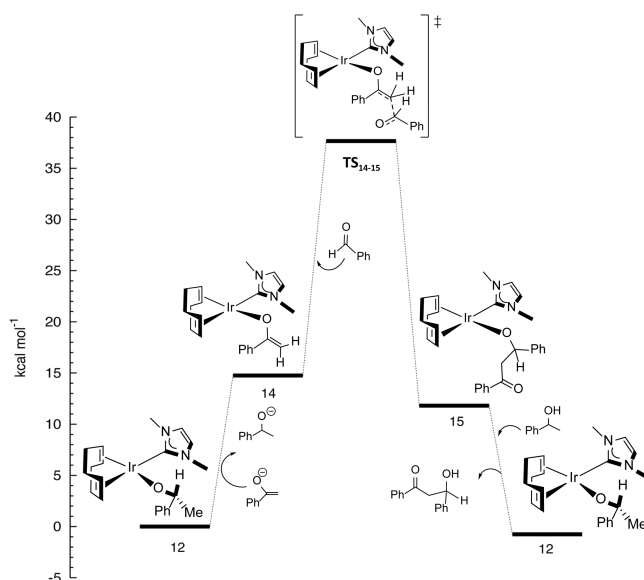

Figure 7. Energy profile for the formation of 3-hydroxy-1,3-diphenylpropan-1-one through the catalytic cycle proposed in Figure 5.

The hydrogenation of the α,β-unsaturated ketone starts by its coordination to the hydride complex **11**, which is formed in the alcohol oxidation processes (Figure 5). It is an endothermic process leading to a pentacoordinated intermediate with square pyramidal coordination geometry. Five possible isomers are possible by coordination through the keto group or the alkene bond. Coordination through the carbonyl group would result in the hydrogenation of the C=O bond leading to an alkoxo-alkene ligand. However, the η^2-ketone bound complex is 13.5 kcal/mol above the most stable isomer where the ligand is π coordinated through the C=C bond and the insertion process into the Ir-H bond requires an activation energy of 11.8 kcal/mol. This pathway represents a total energy of 25.3 kcal/mol above the most stable isomer and around 14 kcal/mol over the most accessible alternative transition state. Thus, this is a high-energy process that can be discarded as a productive pathway.

The four remaining isomers correspond to the coordination of the olefinic bond by the two faces and in two possible orientations relative to the hydrido ligand, which occupies the apical vertex of an idealized square pyramid coordination polyhedron **16**. All of them show the C=C bond coordinated at the basal plane with a disposition approximately coplanar with Ir-H bond. The four isomers are of similar energy with just a mere difference of 3.3 kcal/mol between the most stable and the one of highest energy. Those coordination modes which the olefin insertion results in the hydride transfer to the C$_\beta$ with formation of **17** with an α-alkyl ketone ligand show the lowest activation requirements either relative to the corresponding isomer (**TS$_{16-17}$** at ~11 kcal/mol *vs.* 17-18 kcal/mol for the hydride transfer to the C$_\alpha$) or relative to the most stable one. Accordingly, the olefin insertion leading to a C$_\beta$-H bond is kinetically favoured. The resulting α-alkyl ketone complex releases the ketone by alcoholysis, and the alkoxo complex formed re-enters then into the oxidation cycle, where the starting hydrido complex **11** is regenerated (Figures 8 and 9, cycle 1).

The resulting ketone is eventually hydrogenated to its alcohol by the hydrido complex **11**. Coordination of the 1,3-di-phenyl-propan-1-one to **11** is an endothermic process as the pentacoordinated intermediate **18** is 30.1 kcal/mol above the

reactants. The subsequent insertion process requires an activation energy of 6.7 kcal/mol through transition state **TS$_{18-19}$** to eventually release 1,3-di-phenyl-propan-1-ol by alcoholysis which forms an alkoxo complex which turns back into the alcohol oxidation cycle (Figures 8 and 9, cycle 2).
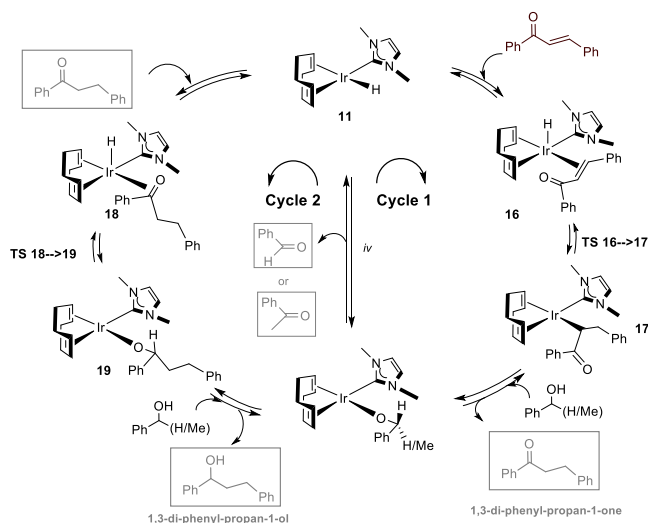

Figure 8. Proposed mechanisms for the catalytic reduction of the condensed α,β-unsaturated ketones.

The energy profile shown in Figure 9 is in full agreement with the experimental observations. The α,β-unsaturated ketone condensation product has never been observed because of the accessible energy barrier for the reduction of the C=C bond. However, the half-reduced 1,3-diphenylpropan-1-one product is accumulated due to the higher energy barrier for the reduction of the C=O bond. Interestingly, complete selectivity to 1,3-diphenylpropan-1-ol can be achieved at longer reaction times or using an excess of base. On the other hand, the involvement of the iridium catalyst in the cross-aldol condensation process results in the complete selectivity to the unsaturated ketone 1,3-diphenyl-2-propen-1-one product likely due the enhancement nucleophilic character of the enolate by coordination to the iridium centre. As a consequence, the attack of the β-C atom of the activated O-bound enolate to benzaldehyde is facilitated which results in the selective formation of the key alkoxo-ketone species (Figure 5). Finally, it should be noted that the hydrido iridium species [IrH(cod)(NHC)] (**11**), which is generated in the oxidation of both alcohols, is the responsible for the reduction of α,β-unsaturated ketone condensation product. Thus, extra addition of hydrogen donor and acceptor are not required what makes this base-dependent catalytic system a highly atom-economic process with H$_2$O as only reaction by-product.
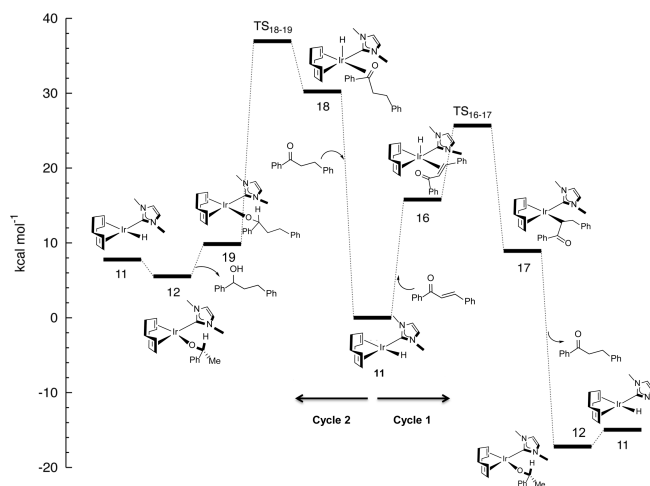

Figure 9. Formation of 1,3-diphenylpropan-1-one and 1,3-diphenylpropan-1-ol Energy profiles for cycles 1 and 2 of Figure 8.

Finally, it is worth mentioning that the results described herein are in sharp contrast with those previously reported by Grée and co-workers on the tandem isomerization–aldolization reaction between allylic alcohols and aldehydes[41] mediated by and iron catalyst. It has been shown that the role of the iron catalysts is to promote the allylic alcohol to enol isomerization affording the free enol, which adds to the aldehyde in a carbonyl-ene type reaction.[42] Thus, the aldol product is formed by reaction between the aldehyde and the free enol outside the coordination sphere of the metal centre.

Conclusions

Iridium(I)-cyclooctadiene complexes having a NHC ligand with a O- or N-functionalized wingtip have shown to be efficient precatalysts for the Oppenauer-type oxidation of alcohols and the β-alkylation of secondary alcohols with primary alcohols. The catalyst precursors having a NHC ligand with a 2-methoxybenzyl wingtip efficiently catalysed the coupling of a range of secondary alcohols with several *para*-substituted benzyl and straight chain primary alcohols, in the presence of base, to produce the corresponding β-alkylated alcohols with moderate selectivity. Interestingly, complete selectivity can be achieved if a larger excess of base is used. Experimental mechanistic studies on this hydrogen autotransfer process suggest the participation of the iridium catalyst in the cross-aldol condensation reaction leading to the α,β-unsaturated ketone product. A theoretical study of the full reaction mechanism, including both the dehydrogenation, condensation and hydrogenation steps, has been carried out. DFT calculations have revealed that the key step leading to the formation of the new C-C bond proceeds through a square-planar intermediate having an O-bound enolate, generated in basic medium, which reacts with the electrophilic aldehyde to form a β-alkoxoketone which is shifted out of the metal coordination sphere by alcoholysis and dehydrated in the reaction conditions to the α,β-unsaturated ketone. On the other hand, it has been found that the substituent on the NHC ligand has an almost negligible influence in this step

although a significant influence in the alcohol oxidation process has been identified.

Experimental Section

Scientific Equipment.

^{1}H NMR spectra were recorded on a Bruker Avance 300 (300.1276 MHz and 75.4792 MHz) or Bruker Avance 400 (400.1625 MHz and 100.6127 MHz) spectrometers. The catalytic reactions were analyzed on an Angilent 4890 D system equipped with an HP-INNOWax capillary column (0.4 μm film thickness, 25 m x 0.2 mm i. d.) using mesitylene as internal standard. Organic compounds were identified by Gas Chromatography-Mass Spectrometry (GC/MS) using an Agilent 6890 GC system with an Agilent 5973 MS detector, equipped with a polar capillary column HP-5MS (0.25 μm film thickness, 30 m x 0.25 mm i. d.).

Catalyst Synthesis:

The iridium(I) complexes containing O- and N- donor functionalized NHC ligands [IrX(cod)(MeIm∩Z)] (**1-4**, X = Cl or Br; ∩Z = 2-methoxyethyl, 2-methoxybenzyl, pyridin-2-ylmethyl and 3-dimethylaminopropyl) were synthesized by reaction of the corresponding imidazolium salts with the dinuclear complex [{Ir(μ-OMe)(cod)}$_2$] following the procedure previously described.[16] The cationic complexes [Ir(NCCH$_3$)(cod)(MeIm∩Z)]BF$_4$ (**5-6**, ∩Z = 2-methoxyethyl and 2-methoxybenzyl) were prepared by abstraction of the bromido ligand in the corresponding neutral complexes by AgBF$_4$ in the presence of acetonitrile. The cationic complexes having the coordinated N-donor set [Ir(cod)(MeIm∩Z)]BF$_4$ (**7-8**, ∩Z = pyridin-2-ylmethyl and 3-dimethylaminopropyl) were prepared following a two-step procedure involving the intermediate NHC-silver complex and the solvato complex [Ir(cod)(OCMe$_2$)$_2$]BF$_4$.[16]

Oppenauer-type oxidation of alcohols:

The catalytic oxidation reactions were carried out under an argon atmosphere in thick glass reaction tubes fitted with a greaseless high-vacuum stopcock. In a typical experiment, the reactor was charged with a solution of the substrate (3 mmol) in toluene (0.3 mL), internal standard (mesitylene, 70 μL, 0.50 mmol), hydrogen acceptor (3 mmol), base (3 mmol) and the catalyst (0.03 mmol, 1 mol%). The resulting mixture was stirred at room temperature until complete solution of the catalyst and then placed in a thermostatized oil bath at the required temperature, typically 110 ºC. Conversions were determined by Gas Chromatography analysis under the following conditions: column temperature 80 ºC (2 min) to 220 ºC at 10 ºC/min at flow rate of 1 mL/min using ultra pure He as carrier gas.

β-alkylation of secondary alcohols with primary alcohols:

The catalytic β-alkylation of alcohols reactions were carried out under an argon atmosphere in thick glass reaction tubes fitted with a greaseless high-vacuum stopcock. In a typical experiment, the reactor was charged with a solution of the primary alcohol (3.6 mmol) and the secondary alcohol (3 mmol) in toluene (0.3 mL), internal standard (mesitylene, 70 μL, 0.5 mmol), base (Cs$_2$CO$_3$, 3 mmol) and the catalyst (0.03 mmol, 1 mol%). The resulting mixture was stirred at room temperature until complete solution of the catalyst and then placed in a thermostatized oil bath at the required temperature, typically 110 ºC. Conversions were determined by Gas Chromatography analysis under the following conditions: column temperature 80 ºC (2 min) to 220 ºC at 10 ºC/min at flow rate of 1 mL/min using ultra pure He as carrier gas.

The reaction mixture was cooled to room temperature and the solution passed through a short alumina column in order to remove the catalyst. The toluene solution was concentrated to 3 ml and then eluted through a silica gel column using ethyl acetate/hexane (1:15) as eluent. NMR spectroscopic data for the β-alkylated alcohol products are given in the Supporting Information.

Monitoring of the oxidation of 1-phenylethanol catalysed by 6:

To a solution of [Ir(NCCH$_3$)(cod)(MeIm∩Z)]BF$_4$ (**6**, ∩Z = 2-methoxybenzyl) (18 mg, 0.030 mmol) and Cs$_2$CO$_3$ (98 mg, 0.30 mmol) in acetone-d_6 (0.5 mL, NMR tube) was added 1-phenylethanol (36 μL, 0.30 mmol). The solution was monitored by NMR at 40 ºC. The conversion of 1-phenylethanol to acetophenone was quantified by integration of the ^{1}H NMR spectrum.

Monitoring of the β-alkylation of 1-phenylethanol with benzyl alcohol catalysed by 2:

To a solution of [[IrBr(cod)(MeImR)] (**2**, R = 2-methoxybenzyl) (17 mg, 0.030 mmol) and potassium hexamethyldisilazide (KHMDS) (89 mg, 0.45 mmol) in toluene-d_8 (0.5 mL, NMR tube) were added sequentially 1-phenylethanol (36 μL, 0.30 mmol) and benzyl alcohol (37 μL, 0.36 mmol). The solution was monitored by NMR at 80 ºC. The conversion of 1-phenylethanol to 1,3-diphenyl-1-propanol and 1,3-diphenyl-1-propanone was quantified by integration of the ^{1}H NMR spectrum.

Calculation details:

DFT calculations have been carried out with Gaussian 09[43] using the B3PW91 functional with a 6-31G** basis set for all atoms but Ir where the LANL2DZ basis set and pseudopotential has been used supplemented with an additional f function.[44] All the minima have been characterized by frequency calculation. Additionally the transition structures have been checked by examining visually the imaginary frequency and by IRC calculations. The structure in Figure 6 has been depicted using CYLview. 1.0b.[45]

[1]   a) *Iridium Catalysis*, in Top Organomet Chem, *Vol. 34* (Ed.P. G. Andersson), Springer-Verlag, Berlin-Heidelberg, **2011**; b) *Iridium Complexes in Organic Synthesis. (*Eds.: L. A. Oro, C. Claver), Wiley-VCH, Weinheim, **2009**; c) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226–236.

[2]   a) O. Prakash, K. N. Sharma, H. Joshi, P. L. Gupta, A. K. Singh, *Organometallics* **2014**, *33*, 983–993; b) R. Levy, CAzerraf, D. Gelman, K. Rueck-Braun, P. N. Kapoor, Catal. Commun. *2009*, *11*, 298–301; c) F. Hanasaka, K.-I. Fujita, R. Yamaguchi, *Organometallics* **2006**, *25*, 4643–4647; d) A. N. Ajjou, *Tetrahedron Lett.* **2001**, *42*, 13–15.

[3]   a) Q. Yang, Q. Wang, Z. Yu, *Chem. Soc. Rev.* **2015**, 14, 2305–2329; b) C. Gunanathan D. Milstein, *Science* **2013**, *341*, 249–251; c) S. Pan, T.i Shibata, *ACS Catal.* **2013**, *3*, 704–712; d) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010**, *110*, 1611–1641; e) X. Cui, F. Shi, M. Tse, D.

Goerdes, K. Thurow, M. Beller, Y. Deng, *Adv. Synth. Catal.* **2009***, 351,* 2949–2958; f) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555–1575.

[4] a) W. Bai, G. Jia, *Inorg. Chim. Acta* **2015**, *431*, 234–241; b) D. Wang, K. Zhao, X. Yu, H. Miao, Y. Ding, *RSC Adv.*, **2014**, *4*, 42924–42929; c) X. Chang, L. W. Chuan, S. Yongxin, S. A. Pullarkat, *Tetrahedron Lett.* **2012**, *53*, 1450–1455; d) C. Xu, L.Y. Goh, S. A. Pullarkat, *Organometallics* **2011**, *30*, 6499–6502; e) D. Gnanamgari, C. H. Leung, N. D. Schley, S. T. Hilton, R. H. Crabtree, *Org. Biomol. Chem.* **2008**, *6*, 4442–4445; f) H. W. Cheung, T. Y. Lee, H. Y. Lui, C. H. Yeung, C. P. Lau, *Adv. Synth. Catal.* **2008**, *350*, 2975–2983; g) R. Martínez, D. J. Ramón, M. Yus, *Tetrahedron* **2006**, *62*, 8982–8987; h) C. S. Cho, B. T. Kim, H.-S. Kim, T.-J. Kim, S. C. Shim, *Organometallics* **2003**, *22*, 3608–3610.

[5] a) Y. Obora, *ACS Catalysis* **2014**, *4*, 3972–398; b) S. Bhat, V. Sridharan, *Chem. Commun.* **2012**, *48*, 4701–4703; c) B. Anxionnat, D. G. Pardo, G. Ricci, J. Cossy, *Org Lett.* **2011**, 13, 4084–4087; d) Y. Iuchi, Y. Obora, Y. Ishii, *J. Am. Chem. Soc.* **2010**,*132*, 2536–2537; e) T. Jensen, R. Madsen, *J. Org. Chem.* **2009**, *74*, 3990–3992; f) Y. M. A. Yamada, Y. Uozumi, *Org. Lett.* **2006**, *8*, 1375–1378; g) C. Löfberg, R. Grigg, M. A. Whittaker, A. Keep, A. Derrick, *J. Org. Chem.* **2006**, *71*, 8023–8027; h) M. S. Kwon, N. Kim, S. H. Seo, I. S. Park, R. K. Cheedrala, J. Park, *Angew. Chem. Int. Ed.* **2005**, *44*, 6913–6915; i) K. I. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka, R. Yamaguchi, *Org. Lett.,* **2005**, *7*, 4017–4019; j) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2004**, *126*, 72–73.

[6] a) Y. Iuchi, M. Hyotanishi, B. E. Miller, K. Maeda, Y. Obora, Y. Ishi, *J. Org. Chem.* **2010**, *75*, 1803–1806; b) A. E. W. Ledger, P. A. Slatford, J. P.Lowe, M. F. Mahon, M. K. Whittlesey, J. M. J. Williams, *Dalton. Trans.* **2009**, 716-722; c) R. Grigg, C. Lofberg, S. Whitney, V. Sridharan, A. Keep, A. Derrick, *Tetrahedron* **2009**, *65*, 849–854; d) S. J. Pridmore, J. M. J. Williams, *Tetrahedron Lett.* **2008**, *49*, 7413–7415; e) M. I. Hall, S. J. Pridmore, J. M. J. Williams, *Adv. Synth. Catal.* **2008**, *350*, 1975–1978; f) M. Morita, Y. Obora, Y. Ishii, *Chem. Commun.* **2007**, 2850–2852; g) P. A. Slatford, M. K. Whittlesey, J. M. J. Williams, *Tetrahedron Lett.* **2006**, *47*, 678–6789.

[7] a) T. Matsuura, S. Sakaguchi, Y. Obora, Y. Ishii, *J. Org. Chem.* **2006**, *71,* 8306–8308; b) C. Carlini, A. Macinai, A. M. Raspolli Galletti, G. Sbrana, *J. Mol. Catal. A: Chem.* **2004**, *212,* 65–70; c) C. Carlini, M. Di Girolamo, A. Macinai, M. Marchionna, M. Noviello, A. M. Raspolli Galletti, G. Sbrana, *J. Mol. Catal. A: Chem.* **2003**, *204*, 721-728.

[8] a) S. Musa, L. Ackermann, D. Gelman, *Adv. Synth. Catal.* **2013**, *355*, 3077–3080; b) I. S. Makarov, R. Madsen, *J. Org. Chem.* **2013**, *78*, 6593–6598; c) D. Srimani, E. Balaraman, B. Gnanaprakasam, Y. Ben-David, D. Milstein, *Adv. Synth. Catal.* **2012**, *354*, 2403–2406; d) D. Spasyuk, S. Smith, D. G. Gusev, *Angew. Chem. Int. Ed.* **2012**, *51*, 2772–2775; e) D. Spasyuk, D. G. Gusev, *Organometallics* **2012**, *31*, 5239–5242; f) M. Nielsen, H. Junge, A. Kammer, M. Beller, *Angew. Chem. Int. Ed.* **2012**, *51*, 5711–5713; g) C. Gunanathan, D. Milstein, *Acc. Chem. Res.* **2011**, *44*, 588–602; h) S. Musa, I. Shaposhnikov, S. Cohen, D. Gelman, *Angew. Chem. Int. Ed.* **2011**, *50*, 3533–3537.

[9] a) F. E. Hahn, M. C. Jahnke, *Angew. Chem. Int. Ed.* **2008**, *47*, 3122–3172; b) C. M. Crudden, D. P. Allen, *Coord. Chem. Rev.* **2004**, *248*, 2247–2273; c) W. A. Herrmann, *Angew. Chem. Int. Ed.* **2002**, 41, 1290–1309.

[10] a) L. Benhamou, E. Chardon, G. S. Lavigne Bellemin-Laponnaz, V. César, *Chem. Rev.* **2011**, *111*, 2705–2733; b) E. Peris *Top. Organomet. Chem* **2007**, *21*, 83–116.

[11] a) G. Lázaro, V. Polo, F. J. Fernández-Álvarez, P. García-Orduña, F. J. Lahoz, M. Iglesias, J. J. Pérez-Torrente, L. A. Oro, ChemSusChem **2015**, 8, 495–503; b) Q. Zhou, Y.-N. Wang, X.-Q. Guo, X.-H. Zhu, Z.-M. Li, X.-F. Hou, *Organometallics* **2015**, *34*, 1021–1028; c) E. L. Kolychev, S. Kronig, K. Brandhorst, M. Freytag, P. G. Jones, M. Tamm, *J. Am. Chem. Soc.* **2013**, *135*, 12448–12459; d) G. Guisado-Barrios, J Hiller, E. Peris, *Chem. Eur. J.* **2013**, *19*, 10405–10411; e) L. Wu, L. Falivene, E. Drinkel, S. Grant, A. Linden, L. Cavallo, R. Dorta, *Angew. Chem. Int. Ed.* **2012**, *51*, 2870–2873; f) E. Peris, R. H. Crabtree in *Iridium Complexes Organic Synthesis* (Eds.: L. A. Oro, C. Claver), Wiley-VCH-Verlag: Weinheim, Germany, **2009**; pp 39–54; g) I. E.

Markò, S. Stèrin, O. Buisine, G. Mignani, P. Branlard, B. Tinant, J. P. Declercq, *Science* **2002**, *298*, 204–206; h) M. S. Sanford, J. A. Love, R. H. Grubbs, *Organometallics* **2001**, *20*, 5314–5318.

[12] a) R. Kawahara, K. Fujita, R. Yamaguchi, *J. Am. Chem. Soc.* **2012**, *134*, 3643–3646; b) T. Matsu-ura, S. Sakaguchi, Y. Obora, Y. Ishii, *J. Org. Chem.* **2006**, *71*, 8306–8308; c) G. Onodera, Y. Nishibayashi, S. Uemura, *Angew. Chem. Int. Ed.* **2006**, *45*, 3819–3822; d) K. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka, R. Yamaguchi, *Org. Lett.* **2005** *7*, 4017–4019.

[13] A. P. da Costa, M. Viciano, M. Sanaú, S. Merino, J. Tejada, E. Peris, B. Royo, *Organometallilcs* **2008**, *27*, 1305–1309.

[14] D. Gnanamgari, E. L. O. Sauer, N. D. Schley, C. Butler, C. D. Incarvito, R. H. Crabtree, *Organometallics* **2009**, *28,* 1–325.

[15] A. Bartoszewicz, R. Marcos, S. Sahoo, A. K. Inge, X. Zou, B. Martín-Matute, *Chem. Eur. J.* **2012**, *18*, 14510–14519.

[16] a) M. V. Jiménez, J. Fernández-Tornos, J. J. Pérez-Torrente, F. J. Modrego, S. Winterle, C. Cunchillos, F. J. Lahoz, L. A. Oro, *Organometallics* **2011**, *30*, 5493–5508; b) M. V. Jiménez, J. Fernández-Tornos, J. J. Pérez-Torrente, F. J. Modrego, P. García-Orduña, L. A. Oro, *Organometallics* **2015**, *34*, 926–940.

[17] H. Türkmen, T. Pape, F. E. Hahn, B. Çetinkaya, *Eur. J. Inorg. Chem.* **2008**, 5418–5423.

[18] A. Binobaid, M. Iglesias, D. Beetstra, A. Dervisi, I. Fallis, K. J. Cavell, *Eur. J. Inorg. Chem.* **2010**, 5426–5431.

[19] For related mechanistic studies on the alkylation of amines with alcohols see: a) A. Bartoszewicz, G. González Miera, R. Marcos, P.-O. Norrby, B. Martín-Matute, *ACS Catal.* **2015**, *5*, 3704–3716; b) D. Weickmann, W. Frey, B. Plietker*, Chem. Eur. J.* **2013**, *19*, 2741–2748; c) P. Fristrup, M. Tursky, R. Madsen, *Org. Biomol. Chem.* **2012**, *10*, 2569–2577; d) D. Bacells, A. Nova, E. Clot, D. Gnanamgari, R. H. Crabtree, O. Eisenstein, *Organometallics* **2008**, *27*, 2529–2535.

[20] a) M. C. Jahnke, T. Pape, E. F. Hahn, *Eur. J. Inorg. Chem.* **2009**, 1960–1969; b) M. V. Jiménez, J. J. Pérez-Torrente, M. I. Bartolomé, V. Gierz, F. J. Lahoz, L. A. Oro, *Organometallics*, **2008**, *27*, 224–234; c) Z. Fei, W. H. Ang, D. Zhao, R. Scopelliti, E. E. Zvereva, S. A. Katsyuba, P. J. Dyson, *J. Phys. Chem. B* **2007**, *111*, 10095–10108; d) P. Wasserscheid, T. Welton, in *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, Germany, 2003; e) D. S. McGuinness, K. J. Cavell, *Organometallics* **2000**, *19*, 741–748.

[21] a) D. Xu, S. Wang, Z. Shen, C. Xia, W. Sun *Org. Biomol. Chem.* **2012**, *10*, 2730–2732; b) M. K. Brown, M. M. Blewett, J. R. Colombe, E. J. Corey*, J. Am. Chem. Soc.* **2010**, *132*, 11165–11170; c) G. Maayan, R. Neumann, *Catal. Lett.* **2008**, *123*, 41–45; d) A. N. Ajjou, J.-L. Pinet, *Can. J. Chem.* **2005**, *83*, 702–710.

[22] a) K. Fujita, T. Uejima, R. Yamaguchi, *Chem. Lett.* **2013**, *42*, 1496–1498; b) A. Miyata, M. Murakami, R. Irie, T. Katsuki, *Tetrahedron Lett.* **2001**, *42*, 7067–7070.

[23] a) F. Hanasaka, K. Fujita, R. Yamaguchi, *Organometallics* **2006**, *25*, 4643–4647; b) F. Hanasaka, K. Fujita, R. Yamaguchi, *Organometallics* **2005**, *24*, 3422–3433; c) F. Hanasaka, K. Fujita, R. Yamaguchi, *Organometallics* **2004**, *23*, 1490–1492; d) K. Fujita, S. Furukawa, R. Yamaguchi, *J. Organomet. Chem.* **2002**, *649*, 289–292.

[24] X.-Y. Yu, B. O. Patrick, B. R. James, *Organometallics* **2006**, *25*, 4870–4877.

[25] T. Suzuki, *Chem. Rev.* **2011**, *111*, 1825-1845.

[26] M. L. S. Almeida, M. Beller, G.-Z. Wang, J.-E. Backvall, *Chem. Eur. J.* **1996**, 2, 1533–1536.

[27] a) M. C. Warner, J.-E. Bäckvall. *Acc. Chem. Res.* **2013**, *46*, 2545-2555. b) B. Martín-Matute, J. B. Åberg, M. Edin, J.-E. Bäckvall. *Chem. Eur. J.* **2005**, *13*, 6063–6072. c) B. Martín-Matute, K. Bogár, M. Edin, F. B. Kaynak, J.-E. Bäckvall. *Chem. Eur. J.* **2005**, *11*, 5832–5842.

[28] G. Guillena, D. J. Ramón, M. Yus *Angew. Chem. Int. Ed.* **2007**, *46*, 2358–2364.

[29] R. Yamaguchi, K. Fujita in *Ligand Platforms in Homogenous Catalytic Reactions with Metals Chapter 2*, John Wiley and Sons, New Jersey, **2015**.

[30] D. Gnanamgari, C. H. Leung, N. D. Schley, S. T. Hilton, R. H. Crabtree, *Org. Biomol. Chem.* **2008**, *6*, 4442-4445.

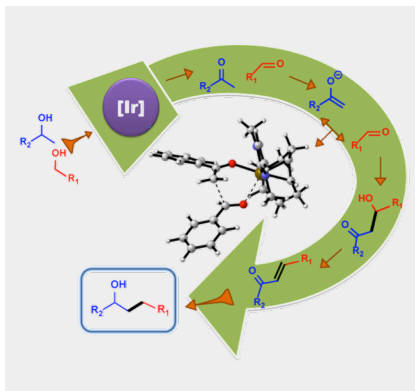[31] Ken-ichi Shimizu *Catal. Sci. Technol.*, **2015**, *5*, 1412–1427.

[32] A. Prades, R. Corberán, M. Poyatos, E. Peris, *Chem. Eur. J.* **2008**, *14*, 11474–11479.

[33] a) M. Albrecht, J. R. Miecznikowski, A. Samuel, J. W. Faller, R. H. Crabtree Organometallics **2002**, 21, 3596–3604; b) Pàmies, J.-E. Bäckvall, *Chem. Eur. J.* **2001**, 7, 5052–5058.

[34] a) N. Ahlsten, A. Bartoszewicza, B. Martín-Matute, *Dalton Trans.* **2012**, *41*, 1660–1670; b) T. D. Sheppard, *Synlett* **2011**, 1340–1344.

[35] A. Marrone, A. Renzetti, P. De Maria, S. Gérard, J. Sapi, A. Fontana, N. Re, *Chem. Eur. J.* **2009**, *15*, 11537–11550.

[36] a) M. Sodeoka, Y. Hamashima *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941–956; b) J. Nokami , T. Mandai , H. Watanabe , H. Ohyama , J. Tsuji *J. Am. Chem. Soc.* **1989**, *111*, 4126–4127.

[37] J. Cámpora, I. Matas, P. Palma, E. Álvarez, C. Graiff, A. Tiripicchio, *Organometallics* **2007**, *26*, 5712–5721.

[38] Y.-F. Yang, T. Shi, X.-H. Zhang, Z.-X. Tang, Z.-Y. Wen, J.-M. Quan, Y.-D. Wu, *Org. Biomol. Chem.* **2011**, *9*, 5845–5855.

[39] a) J. Cámpora, C. M. Maya, P. Palma, E. Carmona, E. Gutiérrez-Puebla, C. Ruiz, *J. Am. Chem. Soc.* **2003**, *125*, 1482–1483. b) R.-H. Hsu, J.-T. Chen, G.-H. Lee, Y. Wang, *Organometallics* **1997**, *16*, 1159–1166. c) G. A. Slough, R. G. Bergman, C. H. Heathcock, ***J. Am. Chem. Soc.*** **1989**, *111*, 938–949.

[40] L. A. Paquette, J. E. Hofferberth, *Org. React.* **2004**, 477–567.

[41] a) A. Bartoszewicz, M. Livendahl, B. Martín-Matute, *Chem. Eur. J.* **2008**, 1*4*, 10547–10550; b) D. Cuperly, J. Petrignet, C. Crévisy, R. Grée, *Chem. Eur. J.* **2006**, *12*, 3261–3274; c) D. Cuperly, C. Crévisy, R. Grée*, Synlett* **2004**, 93– 96; d) M. Uma, M. Davies, C. Crévisy, R. Grée, *Tetrahedron Lett.* **2001**, *42*, 3069–3172; e) C. Crévisy, M. Wietrich, V. Le Boulaire, M. Uma, R. Grée, *Tetrahedron Lett.* **2001**, *42*, 395 –398.

[42] D. Cuperly, C. Crévisy, R. Grée*, Synlett* **2004**, 93–96.

[43] Gaussian 09, Revision D.01 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, et al., 2009.

[44] A. Ehlers, M. Böhme, S. Dapprich, A. Gobbi, A. Höllwarth, V. Jonas, K. Köhler, R. Stegmann, A. Veldkamp, G. Frenking, *Chemical Physics Letters* **1993**, *208*, 111–114.

[45] Legault, C. Y. CYLview, 1.0b, (http://www.*cylview*.org), Université de Sherbrooke, **2009**.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

An active role: Iridium(I)-cyclooctadiene complexes having a O/N-functionalized NHC ligand efficiently catalysed the oxidation and β-alkylation of secondary alcohol with primary alcohols. DFT calculations about the full reaction mechanism, including both the dehydrogenation, cross condensation and hydrogenation steps, reveal also the active participation of the iridium catalyst in the key step leading to the formation of the new C-C bond.

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Oxidation and β-Alkylation of Alcohols Catalysed by Iridium(I) Complexes with Functionalized *N*-Heterocyclic Carbene Ligands