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Editors Choice Paper

Iridium-catalyzed benzylic C–H activation and functionalization of alkyl arenes

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ABSTRACT

A recyclable catalyst, Ir/C, gives C–H benzylic functionalization of simple arenes to afford aldehydes, esters, and imines. In the case of esters, an additive, Ag_2CO_3, acts as base and oxidant, while for imine formation no additive is necessary. In this latter case a double C–H activation is proposed, accompanied by loss of H_2.

1. Introduction

The development of general, catalytic and selective functionalizations of unactivated C–H bonds are highly desirable and would constitute a broadly applicable set of green transformations in organic synthesis [1]. Ever since Chatt and Davidson [2] and Shilov and Shulpin [3] established the first organometallic examples of arene and alkane C–H activation, the catalytic utility of this reaction has been widely explored [4]. Despite the fact that an arene C–H bond is stronger than that of an alkane, aromatic C–H bond activation is favored in many transition metal-mediated reactions due to the compensating higher bond strength of the resulting M–C bond for aryl over alkyl groups [5]. In the case of arenes containing benzylic C–H bonds, achieving selectivity between sp^2 and the benzylic sp^3 hybridized C–H bonds is of particular significance. Selectivity for benzylic activation may arise when (a) formation of an aryl–metal product is sufficiently sterically disfavored [6], (b) the benzylic product is stabilized by η^3 coordination [7], or (c) a radical pathway provides kinetic selectivity for the benzylic C–H [8]. While numerous metal catalyzed systems have been developed for selective aromatic and heteroaromatic C–H activation [9], fewer advances have been made in the realm of selective sp^3 C–H bond functionalization. Despite notable progress [10], most established methods for the oxidative coupling of benzylic sp^3 C–H bonds require either carbene precursors [11], directing groups, [12], stoichiometric metal reagents [10], or remain limited to benzyl halides [13–15]. General strategies for selective benzylic C–H activation without directing effects from coordinating groups would open the door to a variety of eagerly sought, useful functionalizations.

Benzylic nitrogen substituents are found in some of the major natural product classes, such as amino acids and alkaloids, as well as in a wealth of pharmaceuticals, in which their presence strongly influences their pharmacodynamic properties and bioavailability [16]. The advent of transition metal catalysis has led to the development of a few C–H activation strategies for making benzylic amines. Such reactions include hydroamination [17], but this is limited to styrene derivatives, and coupling of activated amine derivatives [18], such as secondary sulfonamides, but these require further transformations. Efficient synthesis of aromatic amines is possible with the Buchwald–Hartwig [19] C–N coupling using aryl halides and of benzylamines via nucleophilic attack of amines. These reactions require halides, however, and a similar and greener reaction for making benzylic C–N bonds directly from the alkyl arene is yet to be reported.

Likewise, forming benzylic C–O bonds to give benzylic alcohols, aldehydes, and carboxylic acids would be an important addition to the chemist's toolbox of green catalytic transformations.

Here we demonstrate an unprecedented and selective benzylic C–H activation catalyzed by a heterogeneous, commercial Ir/C catalyst. This reaction can produce functionalization of the benzylic C–H to alcohols (through ester formation), aldehydes or imines.

2. Experimental

2.1. General methods

All arene solvents were used as received unless otherwise specified. Reactions involving Ir/C were carried out in sealed

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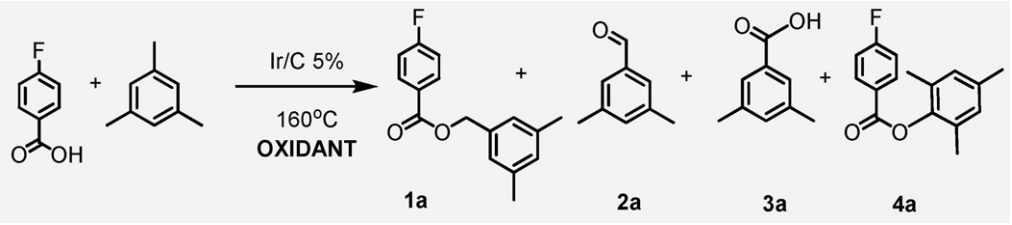
Table 1
The effect of different oxidants in Ir-catalyzed O-functionalization of mesitylene.



Entry	Oxidant	Additive	Product & yield
1	Ag_2CO_3	–	**1a** (56%)[a], **2a** (17%)[b]
2	AgOAc	–	**1a** (43%)[a], **2a** (12%)[b]
3	$^tBu_4N^+$ oxone	K_2CO_3	**2a** (4%)[b], **3a** (9%)[b]
4	$Cu(OAc)_2$	–	**1a** (45%)[a]
5	Iodosobenzene	K_2CO_3	**1a** (35%)[a], **4** (44%)[a]
6	$CuCO_3$	–	**1a** (24%), **2a** (7%)[b]
7	CuO	–	**2a** (5%)[b]
8	None	K_2CO_3	**2a** (4%)[b]

[a] Isolated yields.
[b] Estimated yield based on mass.

pressure-safe vials under an inert atmosphere and without exclusion of air, and both sets of conditions were found to give comparable yields. Reactions and manipulations involving $[IrCp^*Cl_2]_2$ and other organometallic compounds were carried out under dry nitrogen and in oven-dried glassware. 4-Fluorobenzoic acid, silver carbonate, and oxidants in Table 1 were obtained from commercial sources and were used without further purification. 5% Ir/C was obtained from Strem Chemicals. Aniline was distilled prior to use. ^1H and ^{13}C NMR spectra were recorded on Bruker 400 or 500 MHz spectrometers. A Biotage Initiator microwave unit equipped with Biotage reactor tubes was used for all microwave work.

2.2. General catalytic protocol for coupling of benzoic acids with arenes

A Pyrex pressure-safe vial was loaded with a stir bar, 0.05 eq. 5% Ir/C (0.135 g), 1 eq. 4-fluorobenzoic acid (0.100 g, 0.704 mmol), 1 eq. Ag_2CO_3 (0.194 g, 0.705 mmol) and 2.00 mL arene solvent. The vial was sealed and immersed in a 160 °C oil bath for 16 h, unless otherwise specified. The reaction was then cooled, diluted with 20 mL EtOAc and filtered. The catalyst was washed with 2 mL × 20 mL EtOAc and 10 mL hexanes and dried for re-use. The filtrate was concentrated *in-vacuo* and was purified by flash chromatography using a mixture of 80:20 hexanes:diethyl ether to give compounds **1** and **2**.

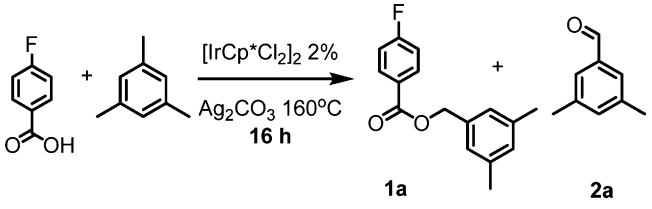
2.3. General catalytic protocol for coupling of anilne with arenes

A Pyrex pressure-safe vial was loaded with a stir bar, 0.05 eq. 5% Ir/C (0.135 g), 1 eq. aniline (0.100 mL, 1.08 mmol), and 2.00 mL arene solvent. The vial was sealed and immersed in a 160 °C oil bath for 16 h, unless otherwise specified. To obtain the crude imine, the reaction was then cooled to room temperature, diluted with 20 mL EtOAc, filtered and dried *in-vacuo* to give crude **3**. The imine could alternatively be hydrogenated to the amine by cooling the reaction mixture to room temperature, then introducing a hydrogen atmosphere via a septum to an H_2 balloon fitted with a long needle. The mixture was then allowed to stir for 12 h, after which 20 mL of EtOAc were added, and the mixture filtered. The filtrate was concentrated *in-vacuo* and purified by flash chromatography using a mixture of 80:20 hexanes:diethyl ether to give the amine. Products were identified by spectral comparison with authentic materials.

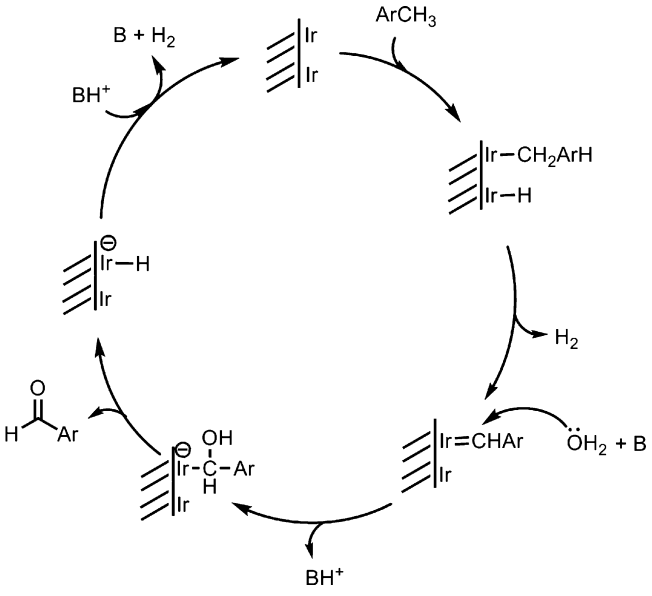
3. Results and discussion

3.1. O-functionalization

In an attempt to study Ir-catalyzed decarboxylations [21] in mesitylene using $[IrCp^*Cl_2]_2$, we observed products derived from the C–H activation of the arene solvent. A reaction with *p*-fluorobenzoic acid and Ag_2CO_3 as base and oxidant in mesitylene resulted in formation of 42% 3,5-dimethylbenzyl-4-fluorobenzoate (**1a**) and 3,5-dimethylbenzaldehyde (**2a**, Scheme 1).



Scheme 1.



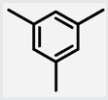
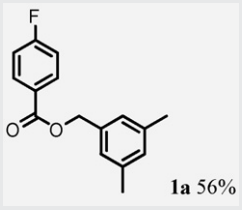
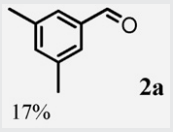
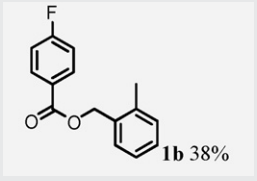
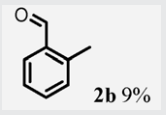
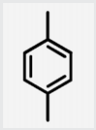
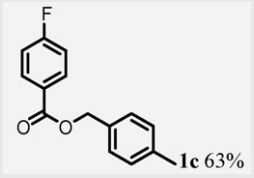
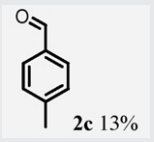
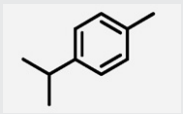
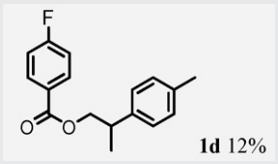
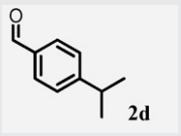
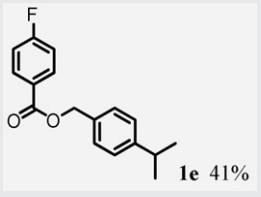
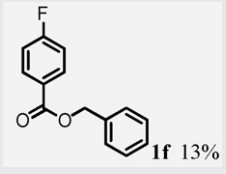
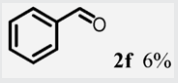
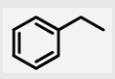
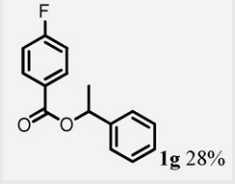
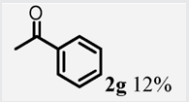
Scheme 2.

Screening other complexes identified a series of active iridium complexes for this reaction. The best homogeneous catalyst was ([Ir(cod)(pyr)PCy_3]PF_6), which gave 48% yield of ester **1a**. We always observed decomposition of the successful catalysts to iridium black, however, so this prompted us to try an authentic heterogeneous iridium catalyst, 5% Ir/C. This indeed produced comparable yields (52%) of **1a**. We thus assume that the catalysts were operating heterogeneously and transferred our attention to the Ir/C catalyzed reactions.

Further study showed that the formation of **1a** is strongly dependent on the nature of the oxidant (Table 1). Whereas both Ag^+ salts give comparable yields of **1a** (entries 1–2), only $Cu(OAc)_2$ of the Cu^{2+} sources tested gave similar results. Notably, iodosobenzene gave a 1:1 mixture of the benzylic C–H activated product **1a** and the aromatic C–H activation product **4a**. This was the only instance in which any aromatic C–H activation was encountered. In all cases some amount of **2a** was also formed.

A control experiment, entry 8 in Table 1, using only K_2CO_3 base and no oxidant gave no ester product (**1a)**, but unexpectedly still produced aldehyde **2a**. Despite distillation of the solvent, exclusion of peroxides by passing the solvent though basic alumina and strict exclusion of oxygen by carrying out the reaction under an

Table 2
Substrate scope for Ir/C catalyzed benzylic acylation.[a] Isolated aldehydes are also reported as side products of this reaction.

Entry	Substrate	Product 1	TON	Product 2
1		 **1a** 56%	11	 **2a** 17%
2		 **1b** 38%	8	 **2b** 9%
3		 **1c** 63%	13	 **2c** 13%
4		 **1d** 12%	2	 **2d**
		 **1e** 41%	8	
5		 **1f** 13%	3	 **2f** 6%
6		 **1g** 28%	6	 **2g** 12%

[a] Conditions: 0.05 eq. 5% Ir/C, 1 eq. Ag_2CO_3, 1 eq. 4-fluorobenzoic acid, 2.00 mL arene substrate, 160 °C, 16 h. Entry 5: 130 °C, 16 h.

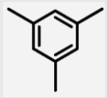
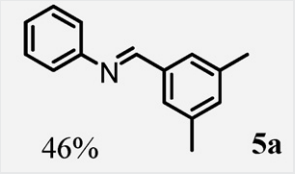
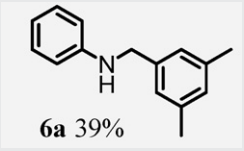
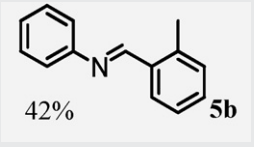
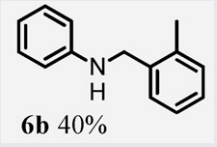
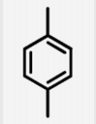
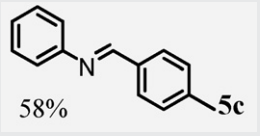
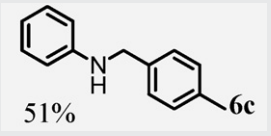
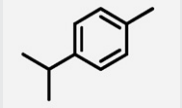
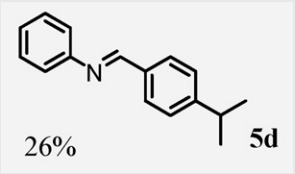
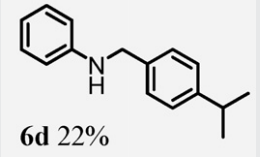
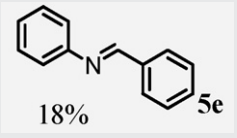
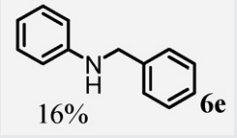
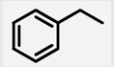
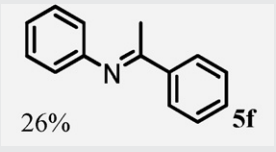
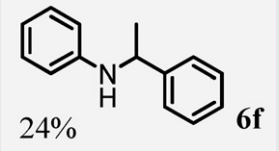
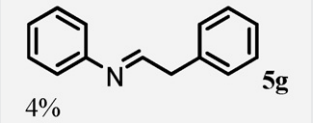
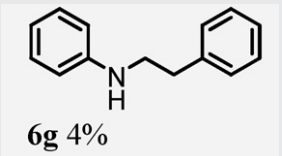
inert atmosphere, similar amounts of **2a** were still formed in all control reactions. Only the mono-aldehyde was observed in each case, the high selectivity no doubt arising from the low conversion. Aldehyde formation occurred independent of the presence of the carboxylate, which was a mere spectator. In an additional control, exclusion of the base and 4-flurobenzoic acid yielded only trace amounts of aldehyde. A control excluding both the oxidant and base also yielded no product detectable by NMR or GC–MS.

It was suspected that loss of H_2 might account for the oxidation. Double gem C–H activation of $ArCH_3$ to give a surface bound ArCH= Schrock carbene could occur. Hydrolysis might then allow water to provide the oxygen source for the aldehyde ArCH=O as shown in Scheme 2, where the aldehyde is formed by α-hydride elimination, followed by reductive elimination of the product. The involvement of water was tested experimentally by adding 1 eq. of water to a reaction of 1 eq. mesitylene and 0.05 eq. Ir/C under air. This gave 24% aldehyde, while an identical control experiment without deliberately added water provided only 14% aldehyde. The latter may come from adventitious water, always hard to remove completely. Water is thus suspected to act as the oxygen source. The carboxylic acid observed may come from subsequent oxidation of the aldehyde by a similar mechanism. Isotopic labeling experiments using $H_2{}^{18}O$ were considered, but due to the known fast isotopic ^{18}O exchange of aldehydes [20], this approach was abandoned. Trapping of the proposed iridium carbene with other reagents, such as nobornene, was attempted, but was unsuccessful.

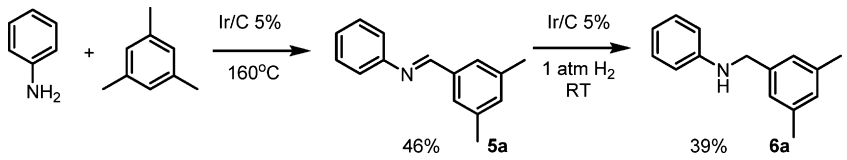
The mechanism for ester formation may well be distinct from that for the aldehyde, since ester is only formed when oxidants, such as Ag^+ or Cu^{2+} salts, are present.

Screening of solvents for the reaction in Scheme 1 showed that polar solvents strongly disfavored both aldehyde and ester formation, and the best yields were obtained in neat alkyl arene.

Table 3
Substrate scope of Ir/C catalyzed benzylic imination[a] and amination[b].

Entry	Substrate	Product 5	TON	Product 6
1		 46% **5a**	9	 **6a** 39%
2		 42% **5b**	8	 **6b** 40%
3		 58% **5c**	12	 51% **6c**
4		 26% **5d**	5	 **6d** 22%
5		 18% **5e**	4	 16% **6e**
6		 26% **5f**	5	 24% **6f**
		 4% **5g**		 **6g** 4%

[a] Conditions: 0.05 eq. 5% Ir/C, 1 eq. aniline, 2.00 mL arene substrate, 160 °C, 16 h.
[b] Conditions: Mixture was cooled to RT, then put under 1 atm H_2 for 12 h while stirring. Entry 5: 130 °C, 16 h.



Scheme 3.

Although the full mechanism of this reaction is still under investigation, the selectivity and substrate scope can provide some mechanistic insights (Table 2).

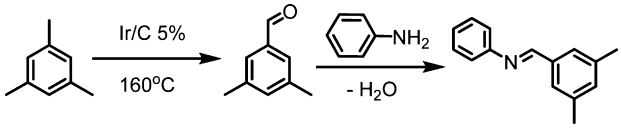
Under our conditions a benzylic C–H of the substrate is attacked preferentially to the aromatic C–H. In the case of substrates with two benzylic protons, such as *p*-cymene (entry 4), we observe reaction at the primary benzylic C–H but no product from the tertiary. This suggests that a free radical mechanism is unlikely, as the tertiary benzylic radical would be strongly stabilized relative to the primary benzylic one. An unusual feature of this reaction is the minor product, **1d**, formed from attack at the primary position of the isopropyl group, a CH bond that is not benzylic and is therefore not activated.

Since refluxing substrate acts as the solvent and the reaction is strongly temperature-dependent, using low-boiling substrates like toluene (entry 5) significantly reduced the yield of the ester and aldehyde. To overcome this, two strategies were developed – one was to use a sealed vial and carry out the reaction at elevated temperature and pressure (130 °C), and the other was to use microwave irradiation in sealed reaction tubes with a teflon insert that allows the reaction to be carried out at 150 °C. At this temperature the ester yield is comparable (43%) to that of mesitylene (52%).

For entries 1 and 2 the esters were hydrolyzed by addition of methanol and 1 eq. KOH, 10 min prior to the end of the reaction. The corresponding alcohols were thus isolated.

3.2. *N*-functionalization

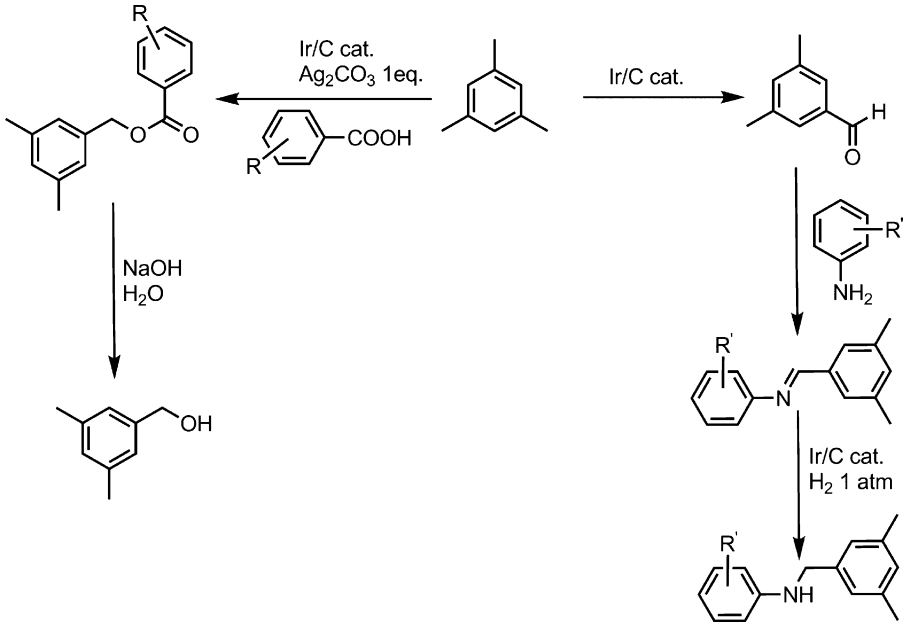
We next considered the possibility of taking advantage of the aldehyde formation by trapping it with an amine to form an imine. When the reaction of Scheme 3 was carried out without deliberate water or oxidant addition and in the presence of aniline, imine formation was indeed observed. Addition of 1 eq. Ag_2CO_3 did increase the imine yield, but also gave rise to several side products. Thus working in the absence of added oxidant was preferred. Once formed, the imines were readily hydrogenated to the corresponding amines with the same Ir/C catalyst on cooling the reaction to room temperature and introducing 1 atm H_2.



Scheme 4.

This reaction proved possible for a series of arenes. For those where multiple products are possible due to the presence of multiple benzylic C–H bonds, only the imine product corresponding to the aldehyde observed previously (Table 3) was isolated. For example, for *p*-cymene (entry 4), only *N*-(4-isopropylbenzylidene)aniline (**5d**) was observed, plausibly arising from the 4-isopropylbenzaldehyde (**2d**). This suggests that the main mechanistic pathway to the imine involves aldehyde formation followed by condensation (Scheme 4).

In order to probe whether the system first produces the amine, then dehydrogenates it with release of H_2 to form the imine, we treated the isolated amine with 5% Ir/C at 160 °C. After 12 h only 12% of the amine was converted to imine, which suggests this mechanism is unlikely. Finally we tested whether deliberate addition of water can increase the yield of amine. Adding 1 eq. H_2O per equivalent of aniline only resulted in the presence of aldehyde in the reaction mixture, presumably due to imine hydrolysis. When 1 eq. H_2O was added to the mesitylene and catalyst mixture and allowed to react for 6 h before adding the aniline, the expected increase of the yield of imine was indeed observed (58% vs 46%). This modest



Scheme 5.

increase was consistent with the corresponding increase in aldehyde yield upon addition of water. Some oxidation of the aldehyde to acid was also noted. The higher yield of imine formation in this reaction vs aldehyde formation in the earlier reaction could be rationalized by assuming the consumption of aldehyde by reaction with the amine displaces the equilibrium towards aldehyde by mass action. Finally, the Ir/C catalyst was recycled twice with retention of activity.

4. Conclusion

A novel primary benzylic C–H functionalization reaction catalyzed by a recyclable, commercially available Ir/C is reported. Two distinct reactions are indicated – one uses an oxidant to give O-acylation of benzylic C–H bonds, and the second produces an aldehyde, presumably with H_2 loss to account for the oxidation and using adventitious or added water as the O-atom source (Scheme 5). The aldehyde can also be trapped with an amine to give the imine, which can in turn be hydrogenated in a subsequent step using the same Ir/C catalyst in a "one pot" procedure under 1 atm H_2.

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