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Ir-catalysed formation of C–F bonds. From allylic alcohols to α -fluoroketones†

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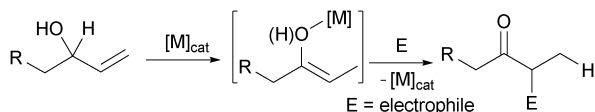
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A novel iridium-catalysed tandem isomerisation/C–F bond formation from allylic alcohols and Selectfluor® to prepare α -fluorinated ketones as single constitutional isomers is reported.

The introduction of fluorine into organic compounds has become a widely applied strategy to modulate the steric, electronic and lipophilic properties of a molecule. In this way, fluorine atoms can be used to modify the pharmacokinetic properties of pharmaceuticals.¹ Electrophilic fluorination of carbonyl compounds,^{2–5} including asymmetric versions,^{2b–d,6} has emerged as a powerful tool for aliphatic C–F bond formation.⁷ Still, few methods for highly regioselective fluorination of unsymmetrical ketones have been reported, and sufficient steric differentiation at the α -carbons is usually a requirement for obtaining high selectivity. Alternatively, enones,⁸ epoxides⁹ or other non-carbonyl precursors^{10,11} can be used to introduce a handle for regiocontrol.

Allylic alcohols can be isomerised into carbonyl compounds in the presence of a transition metal catalyst.¹² The isomerisation may occur *via* formation of transition metal enolates,¹³ and, if electrophiles are present in the reaction media, α -functionalised carbonyl compounds are formed regioselectively (Scheme 1). Although previously reported for aldehydes and imines,^{14,15} heteroatomic electrophiles have never been used in this fashion. To some extent, the reason for this has been the incompatibility of many transition metal complexes with strongly electrophilic reagents.

Here, we present a novel one-pot method to synthesise α -fluoro ketones in a regioselective manner by combining an iridium-catalysed isomerisation of allylic alcohols with an electrophilic fluorination.



Scheme 1 Tandem isomerisation/ α -functionalisation of allylic alcohols.

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Catalysts such as $\text{RhCl}(\text{PPh}_3)_3$, $[\text{Rh}(\text{COD})\text{Cl}]_2$, $[\text{Rh}(\text{COD})(\text{MeCN})_2]\text{BF}_4$, $[\eta^5\text{-(Ph}_5\text{C}_5)\text{Ru}(\text{CO})_2\text{Cl}]$ or $\text{Cp RuCl}(\text{PPh}_3)_2$ are known to isomerise allylic alcohols into ketones.^{14,16} Attempts to obtain fluorination by combining them with reagents such as *N*-fluorobenzenesulfonimide (NFSI) or Selectfluor® (SelectF) were unproductive due to deactivation of the catalyst. To overcome this, we evaluated complexes of a higher oxidation state, such as $[\text{RhCp}^*\text{Cl}_2]_2$ and $[\text{IrCp}^*\text{Cl}_2]_2$ (Table 1). When combined with NFSI, these two complexes catalysed the isomerisation/fluorination of 1-octen-3-ol (**1a**) in 43 and 70% yield, respectively (Table 1, entries 1 and 2). Unexpectedly, the product was a mixture of isomeric α -fluoroketones **2a** and **2a'**. In an attempt to explain the formation of **2a'**, we performed a control experiment and confirmed that octan-3-one (**3a**) was unreactive under the reaction conditions used in Table 1, entry 2. Therefore, this fluorination (entry 2) did not proceed from base- (the reactions were run in the presence of Na_2CO_3) or Lewis acid-catalysed enolisation of **3a**, but rather *via* an alternative (unselective) mechanism to that of Scheme 1.¹⁷ When SelectF was used as the fluorine source and water was used as a co-solvent, only the desired constitutional isomer (**2a**) was formed in 40% yield, together with 60% of non-fluorinated ketone (**3a**) (Table 1, entry 3). Under the

Table 1 Catalyst and fluorine source screening^a

Entry	[M]	F source	Solvent	Conv. ^b (%)	2a/2a'/3a ^b (%)
1 ^c	$[\text{RhCp}^*\text{Cl}_2]_2$	NFSI	THF	47	28/15/4
2 ^c	$[\text{IrCp}^*\text{Cl}_2]_2$	NFSI	THF	100	52/18/16 ^d
3	$[\text{IrCp}^*\text{Cl}_2]_2$	SelectF	THF/H ₂ O ^e	100	40/—/60
4	$[\text{IrCp}^*\text{Cl}_2]_2$	NFPY	THF/H ₂ O ^e	100	—/—/100
5	$[\text{IrCp}^*\text{Cl}_2]_2$	NFSI	THF/H ₂ O ^e	—	—/—/—

^a Unless otherwise noted, the reactions were run with 2.5 mol% of metal dimer (5 mol% metal), allylic alcohol **1a** (0.2 mmol), fluorine source (0.2 mmol) and Na_2CO_3 (0.1 mmol) in the solvent indicated (1 mL), and analysed after 2 h. ^b Determined by ¹H NMR with respect to consumption of **1a**. ^c After 18 h. ^d 14% 1-octene-3-one formed. ^e THF/H₂O 2 : 1.



Table 2 Isomerisation/fluorination of 1-octen-3-ol (**1a**) in THF/H₂O mixtures^d

Entry	Solvent	T/°C	Conv. ^b (%)	2a/2a'/3a ^b (%)
1 ^c	THF/H ₂ O (5:1)	30	100	82/0/18
2 ^d	THF/H ₂ O (5:1)	30	100	67/0/33
3	THF/buffer ^e (5:1)	30	100	82/0/18
4 ^f	THF/buffer ^e (5:1)	30	100	84/0/16
5	THF/buffer ^e (5:1)	50	100	70/0/30
6	THF/buffer ^e (5:1)	10	100	82/0/18

^a **1a** (0.2 mmol) was added to a mixture of [IrCp*Cl₂]₂ (1 mol%) and SelectF (0.25 mmol) in the solvent mixture indicated (1 mL), and analysed after 1 h. ^b Determined by ¹H NMR with respect to consumption of **1a**. ^c With Na₂CO₃ (10 mol%). ^d At pH 3 after 15 min. ^e K/NaPO₄²⁻ buffer (pH 7) was used. ^f With 2.5 equiv. SelectF.

same reaction conditions, NFSI or *N*-fluoropyridinium tetrafluoroborate (NFPY) failed to give any fluorinated products (Table 1, entries 4 and 5). Only monofluorinated products were obtained (*i.e.* no difluorinated ketones), under any of the reaction conditions.

Since SelectF in THF/water mixtures successfully produced only one constitutional isomer of the product (*i.e.* **2a'** was not formed), further screening on this system was performed (Table 2). The best results were obtained using a THF/water mixture of 5:1. Less water failed to dissolve SelectF, and more water increased by-product (**3a**) formation. The catalyst loading could be lowered to 1 mol% (Table 2, entry 1). At acidic pH, higher amounts of unwanted ketone **3a** are obtained and the reaction is complete in a shorter time (15 min) (Table 2, entry 2). The best selectivities (**2a/3a** ratio) are obtained in the presence of Na₂CO₃ or at neutral conditions (using a phosphate buffer, pH 7) (Table 2, entries 1 and 3 vs. 2). Increasing the amount of SelectF had little effect on the product distribution (Table 2, entry 4). At higher temperatures than 30 °C, more of **3a** was formed (Table 2, entry 5). Neither did the amount of **2a** increase when the temperature was lowered to 10 °C, due to decreased solubility of SelectF (Table 2, entry 6). The fluorination did not proceed in the absence of the iridium catalyst. The reactions are operationally simple, run at, or close to room temperature, and under an atmosphere of air.

We examined a variety of allylic alcohols (Table 3) and observed that for substrates requiring longer reaction times basic conditions promoted catalyst decomposition. Thus, we used a phosphate buffer (pH 7) or deionised water in combination with THF. All allylic alcohols tested (**1a–h**) afforded α -fluorinated ketones (**2a–h**) as single isomers. Non-fluorinated ketones (**3a–3h**) were formed as by-products (5–19%). Both terminal (Table 3, entries 1–4) and 1,2-disubstituted alkenes (Table 3, entries 5 and 6) afforded α -fluoroketones in good yields. Also **1g** underwent isomerisation/fluorination to give **2g** with a fluorine substituent on a tetrasubstituted carbon (Table 3, entry 7). Aromatic allylic alcohols (**1h**) can also be fluorinated using this procedure in high yields, and fluorination of the aromatic ring was not detected (Table 3, entry 8).

The C–F bond is formed exclusively at the alkenic carbon of the starting allylic alcohol. To further support this, **1c** (1 equiv.) was treated with [IrCp*Cl₂]₂ (1 mol%) and SelectF (4 equiv.) in the presence of 3-octanone (**3a**, 1 equiv.). After 2 h,

Table 3 Isomerisation/fluorination of allylic alcohols **1a–h**^d

Entry	Allylic alcohol	Product	Time/h	2a–h ^g /3a–h ^b (%)
1 ^c			1	82/13
2 ^{c,d}			4	78/19
3			2	91 (77)/5
4			8	92 (74)/5
5			1	69/15
6 ^d			2	78 (67)/15
7 ^e			15	60/11
8 ^{d,f}			15	82 (67)/8

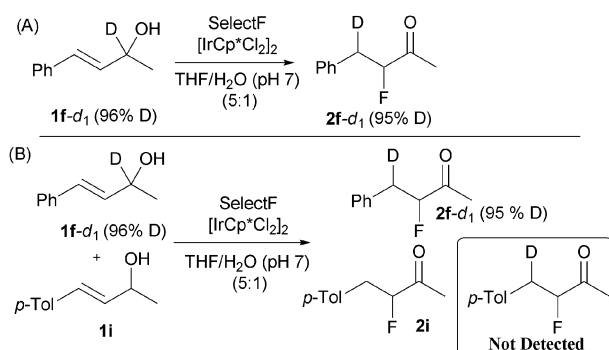
^a Unless otherwise noted, reactions were run with [IrCp*Cl₂]₂ (1 mol%), allylic alcohol **1a–h** (1 mmol), SelectF (1.25 mmol) in THF (5 mL)/deionised H₂O (1 mL) at 30 °C. ^b Determined by ¹H NMR with 1,4-dimethoxybenzene or fluorobenzene as internal standard. Isolated yields in parentheses. ^c Phosphate buffer pH 7. ^d 2 equiv. SelectF. ^e 3 mol% of [IrCp*Cl₂]₂. ^f THF/H₂O = 10:1. ^g Formed as single constitutional isomers.

2c was the only fluorinated product produced (88%), and **3a** remained unconverted (see ESI[†]). This demonstrates that the reaction occurs *via* an Ir-catalysed isomerisation/fluorination sequence from allylic alcohols and that non-fluorinated ketones are not reaction intermediates (*i.e.* Scheme 1).

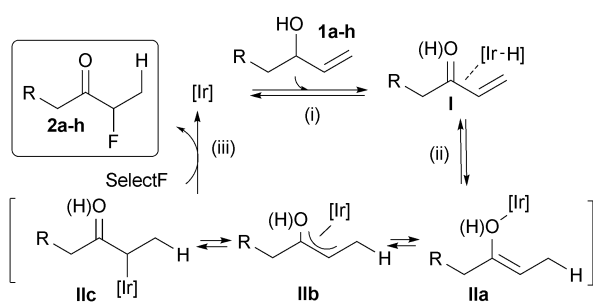
When deuterated allylic alcohol **1f-d**₁ (96% D) was subjected to the reaction conditions, **2f-d**₁ (95% D) was formed *via* a 1,3-hydrogen (deuterium) shift, with the deuterium label exclusively at the benzylic position (Scheme 2A). The high conservation of deuterium in **2f-d**₁ (95% D) confirms that there is no hydride exchange with water and also excludes a mechanism *via* iridium dihydrides.¹⁴ The crossover experiment shown in Scheme 2B established that the 1,3-hydrogen shift occurs intramolecularly, since no traces of deuterium were detected upon analysis of **2i**.^{18†}

We propose the mechanism outlined in Scheme 3. Step (i) involves an oxidation of the allylic alcohol to α,β -unsaturated ketone **I** with concomitant formation of an [Ir–H] species. Based on the deuterium labelling results, in step (ii) hydride addition to the double bond occurs before the unsaturated ketone leaves the coordination sphere of the metal centre forming intermediate **II**. The enol(ate) may bind to the Ir in





Scheme 2 Deuterium labelling studies.



Scheme 3 Proposed catalytic cycle.

a η^1 -mode through the oxygen atom (**IIa**) or through the methylenic carbon (**IIc**), or in a η^3 -mode as an oxoallyl (**IIb**).^{15b,19} In step (iii), the C–F bond is formed upon reaction with the electrophilic SelectF. Step (iii) can occur directly from **II**, or *via* formation of the free enol.§

In conclusion, we have shown that α -fluorinated ketones can be prepared as single constitutional isomers by combining a tandem iridium-catalysed isomerisation of allylic alcohols with an electrophilic fluorination. The choice of the Ir complex was essential to successfully combine both steps. The reaction is easy to perform and is run under an atmosphere of air. To the best of our knowledge, this is the first report on the use of iridium catalysts to form C–F bonds,⁶ and it is also the first example on the construction of a C–heteroatom bond in the transition metal-catalysed coupled isomerisation/bond-forming reactions from allylic alcohols. The reaction works for substrates with different degrees of substitution and C–F bonds on a tetrasubstituted C can also be formed. We are currently investigating the participation of the Ir center in the C–F bond formation, and whether Ir–F species are involved in the mechanism.

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Notes and references

‡ We have confirmed that **1f-d**₁ and **1i** convert at similar rates.

§ In a control experiment using KF (1 equiv.) instead of SelectF, we ruled out the formation of the C–F bond *via* nucleophilic attack of fluoride to the enolate intermediate **II**.²⁰

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