The Reductive C^3-Functionalisation of Pyridinium and Quinolinium Salts Through Iridium-Catalysed Interrupted Transfer Hydrogenation

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Abstract: This paper describes the transformation of flat N-containing aromatic compounds (pyridines and quinolines) into complex 3-dimensional heterocycles bearing new functionality which are ideal for further manipulation. In this reaction methanol and formaldehyde are used as starting materials for the reduction and functionalisation of arenes using an iridium catalyst; thus, inexpensive and renewable feedstocks are utilised in the rapid formation of complex and high value N-heterocycles. By harnessing the in-situ formation of an enamine intermediate, the electron-deficient arene starting materials are converted into nucleophilic species and the C-C bond forming process that follows reverses the normal pattern of reactivity and allows access to the C-3 position of the arene. Mechanistic investigation reveals that formaldehyde is the ultimate source of the hydride added to the arene and further experiments using D-labelled starting materials show the reversible nature of the initial iridum-hydride addition.

Non-aromatic nitrogen-containing six membered heterocycles such as piperidines and tetrahydroquinolines are much sought after structures due to their prevalence in a wide range of pharmaceutical drug candidates and natural products;[1,2] these aza-cycles can also be found in prescription medicines such as Paroxetine and Argatroban.

The pharmaceutical industry continues to require methodologies that address key synthetic challenges such as the preparation of aliphatic aza-heterocycles and the installation of small functional handles such as CH_2OH;[3] their wide utility and importance means that considerable effort

has been expended in the synthesis of these compounds. A well-established route to access substituted piperidines is through the hydrogenation/reduction of pyridines,[4-5] using a range of different catalysts such as Pd,[6] Rh,[7] Ir,[8-13] and organocatalysis.[14] However, access to tetrahydropyridines through the partial reduction of pyridines is more synthetically interesting because the alkene-containing products can be transformed into a wide variety of functionality through well-established olefin functionalization.[15-17]

The synthesis of C-3 substituted aza-heterocycles is limited because methods starting from pyridines (for example) themselves tend to involve the formation of new carbon-hydrogen bonds and so require the synthesis of C^3 pre-functionalized arenes before reduction can be realised. Moreover, methods which do form new C-C bonds, such as the addition of organometallic reagents to pyridiniums and quinoliniums only allow the functionalization of the electrophilic 2- and 4- positions of the arene. [18-24]

Herein we show that valuable 3-substituted tetrahydropyridines and tetrahydroquinolones can be prepared in one step from the C-3 unsubstituted aromatic precursor by using a catalytic system based on iridium in the presence of methanol and formaldehyde.[25-33]

Our results reveal an iridium catalytic system that is capable of forming both new carbon-hydrogen and carbon-carbon bonds in only one synthetic operation;[34] it initiates by performing reduction of a pyridinium or quinolinium salt, forming an enamine in situ. In the presence of a suitable electrophile, the enamine intermediate then participates in nucleophilic trapping (new C-C bond formed)[35-36] and then, following a second reduction, a reductively functionalized azaheterocycle product is formed in good yield (Figure **1**, pyridine shown). The products contain an intriguing mix of saturated and unsaturated carbons with many possibilities for further functionalisation and we expect these heterocycles will have many uses as medicinal chemistry scaffolds.

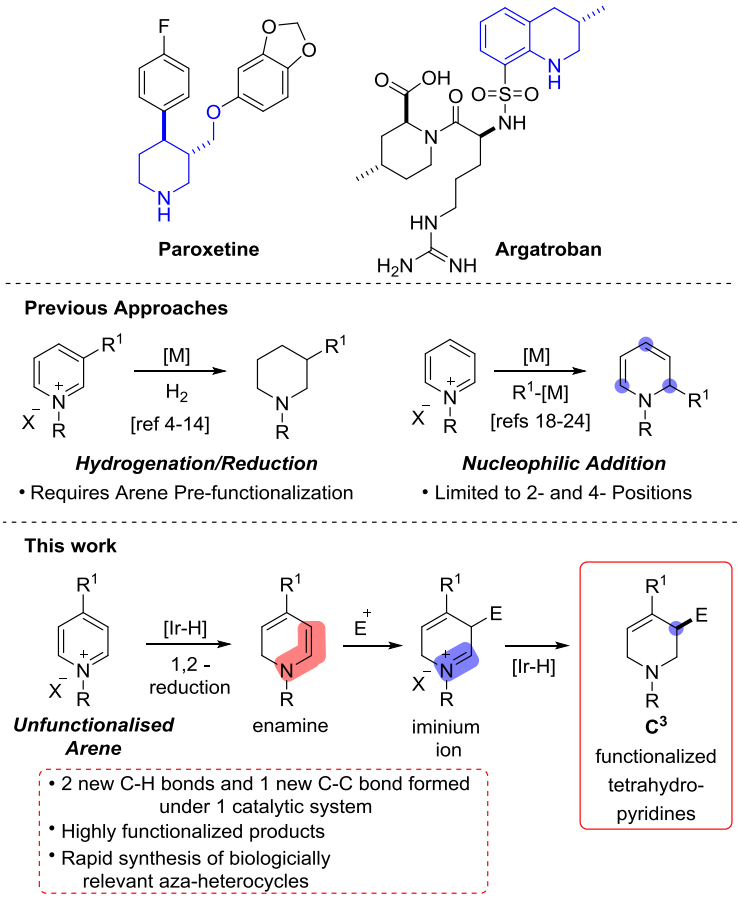


Figure 1: State-of-the-art methods used to access substituted tetrahydropyridines. (a) Active pharmaceutical ingredients that contain 3-substituted saturated aza-heterocycles; (b) Previous approaches to substituted pyridine-derived aza-heterocycles, the reduction of pre-functionalised pyridinium salts and the nucleophilic addition of organometallic reagents (c) Our new approach to preparing 3-substituted aza-heterocycles utilising an iridium-catalysed reduction, followed by trapping with formaldehyde and a final iridium-hydride reduction.

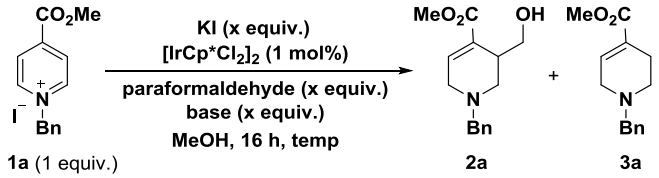
Results and Discussion

Reaction Development

We began by studying the derivatisation of pyridines which were activated towards addition, and selected *N*-benzyl methyl isonicotinium iodide (**1a**) as a model substrate. We envisaged that the oxidation of methanol with an Ir(III) species could potentially furnish both an iridium-hydride and a suitable electrophile in the form of formaldehyde, leading to the formation of a reductively hydromethylated tetrahydropyridine through an interrupted-transfer hydrogenation pathway. Our screening efforts started with $[Ir(Cp^*)Cl_2]_2$ as the catalyst and sodium methoxide at 65 °C (Table 1,

entry 1); however, only starting material **1a** was observed. In order to provide a more powerful hydride source, and electrophilic species to trap enamines formed in situ, paraformaldehyde was added to the reaction. Pleasingly, small amounts of the desired product **2a** were observed, along with several unidentified compounds, some of which were pyridinium derivatives (Table 1, entry 2). Changing the base from NaOMe to $Mg(OMe)_2$, a less aggressive base with a more Lewis acidic cation, was found to be highly beneficial, delivering the desired product **2a** in 48% yield (Table 1, entry 3) with the majority of the mass balance consisting of unidentified compounds and untrapped product **3a**. Increasing the equivalents of paraformaldehyde was then found to increase the yield of **2a** to 56% and reduce the amount of **3a** formed (Table 1, entry 4). Previous reports have indicated that the metal-catalysed reduction of pyridinium salts can be improved by the addition of potassium iodide;[16] thus the addition of 2 equivalents of KI was found to increase the yield of **2a** to 68% (Table 1, entry 5). Pleasingly, reducing the temperature to 45 °C was found to increase the yield of **2a** to 75% and the reaction was significantly cleaner (Table 1, entry 6); further reducing the temperature to room temperature had a detrimental effect on the reaction progress and yield (Table 1, entry 7). However, by increasing the equivalents of potassium iodide from 2 to 4, the reaction was found to proceed smoothly at room temperature and gave the desired product **2a** in 90% isolated yield. The beneficial increase in the amount of KI is based on work by Xiao, and is believed to maximise the number of iodides ligated to the iridium catalyst, making the iridium-hydride a better reducing agent.[16,37] Undertaking this transformation on a 3 mmol (ca. ~ 1 g) scale also worked well, giving the product **2a** in 85% yield (Table 1, entry 8). Control experiments without any iridium catalyst gave no reaction (Table 1, entry 9). To confirm the importance of both the quaternisation and the electron-withdrawing group in the 4-position, control experiments under the optimised conditions using an electron-neutral pyridinium salt (*N*-benzyl pyridinium iodide), an electron-poor pyridine (4-methyl isonicotinate), and pyridinium salts with the electron-withdrawing group in the 3-position (*N*-benzyl methylnicotinium iodide) were undertaken; in no case was product formation observed (see Supporting Information for details).

Table 1: Screening and optimization with a model substrate



Entry	Para-formaldehyde equiv.	Base	Base equiv.	KI equiv.	Temp (°C)	Consumption of **1a (%)**	^{1}H NMR yield of **3a**	Yield of **2a** (%)
1	0	NaOMe	1.5	0	65	<5	0	0
2	10	NaOMe	1.5	0	65	>95	2	traces
3	10	$Mg(OMe)_2$	0.75	0	65	>95	12	48
4	20	$Mg(OMe)_2$	0.75	0	65	>95	4	56
5	20	$Mg(OMe)_2$	0.75	2	65	>95	5	68
6	20	$Mg(OMe)_2$	0.75	2	45	>95	3	75
7	20	$Mg(OMe)_2$	0.75	2	22	~80	2	55
8	20	$Mg(OMe)_2$	0.75	4	22	>95	3	90 (85[b])
9[a]	20	$Mg(OMe)_2$	0.75	4	22	<5	0	0

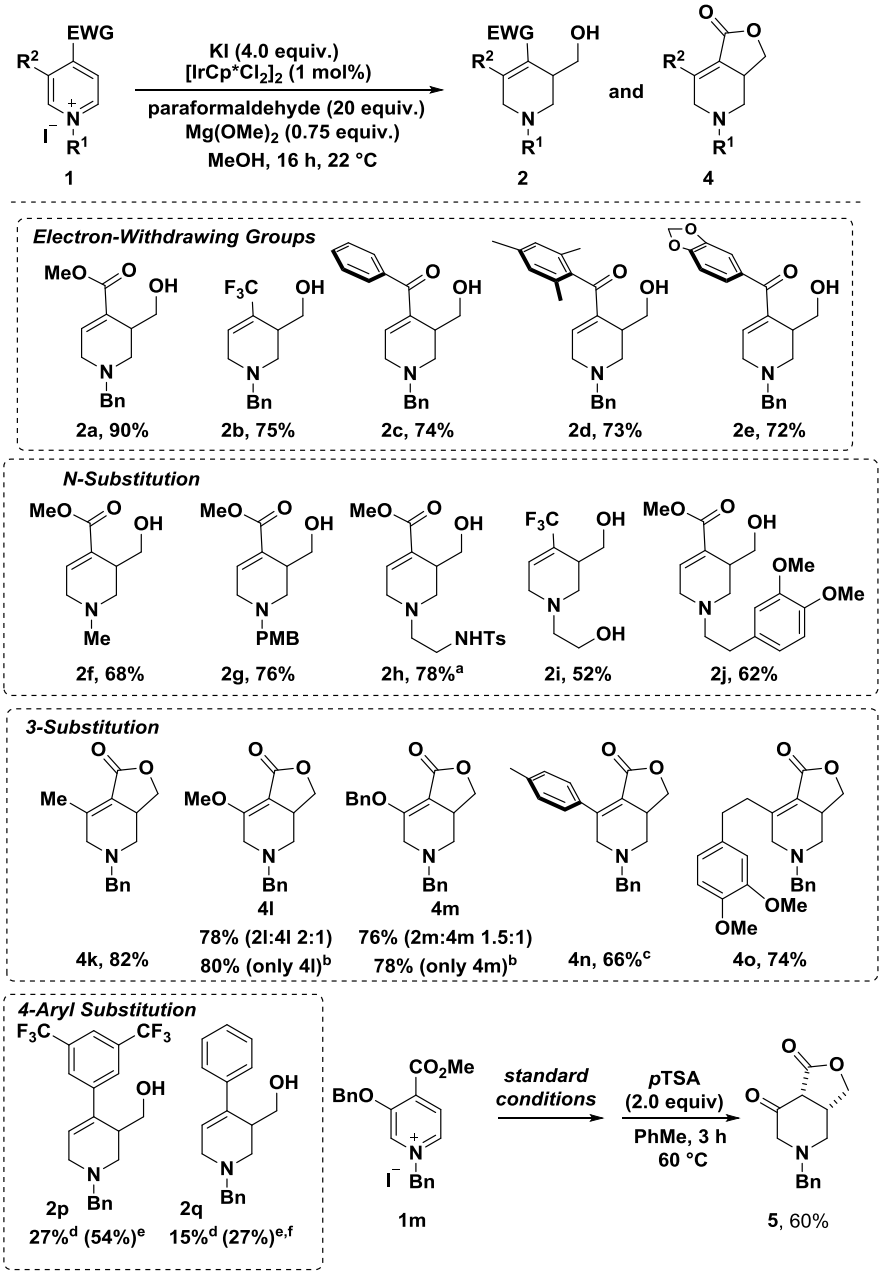
Reactions on a 0.5 mmol scale, isolated yields, [a] Reaction without Ir catalyst [b] Reaction run on a 3 mmol scale (ca, 1 g)

Reaction Scope

With the optimal conditions in hand, we investigated the range of pyridinium salts that were amenable to the transformation (Table **2**). First, we investigated the scope of the electron-withdrawing group in the 4-position of the pyridinium salt; in addition to the methyl ester group (**1a**), pyridinium salts that feature both trifluoromethyl (**1b**) and ketones (**1c-1e**) at the 4-position were found to be compatible, giving the hydroxymethylated products (**2a-e**) in good yields. Additionally, substitution on the nitrogen atom is not limited to a benzyl group and other protecting groups such as methyl (**1f**) and *para*-methoxybenzyl (**1g**) gave the desired product in high yields. Furthermore, substitution at the nitrogen atom is tolerated, including alkyl chains bearing sulphonamide (**2h**), unprotected alcohol (**2i**), and electron-rich aromatic (**2j**) functionality. These entries illustrate the excellent functional group tolerance of this interrupted transfer hydrogenation methodology. Interestingly, substitution was well tolerated in the 3-position of the pyridine, giving

hydromethylation at the opposite side of the pyridine to the initial substitution, allowing access to tetrahydropyridines with substitution in the 3,4, and 5-positions, a class of products which can be difficult to access using current methodologies. Various substrates (**1k-1o**) showed that methyl (**1k**), alkyl (**1o**), aryl (**1n**), and ether (**1l + 1m**) substitution were well tolerated at this position. Notably, when substitution was present in the 3-position, the resulting products were found to lactonize under the reaction conditions, forming the corresponding [6,5] bicycle. Substrates bearing alkyl groups (**4k** and **4o**) were found to completely lactonize under the reaction conditions, while substrates bearing either ether (**4l + 4m**) or aryl (**4n**) groups were found to give a mixture between "open" and lactonized products. However, an additional work-up was found to convert all the "open" product to the lactone, allowing high yields of the lactone to be gathered. Finally, a pyridinium salt bearing a 4-(3,5-(trifluoromethyl)aryl) group (**1p**) was found to perform disappointingly at room temperature and only slightly better at 65 °C (27% yield). However, the use of an analogous rhodium-catalyst ($[RhCp^*Cl]_2$) gave **1p** in 54% yield, although it was not possible to hydroxymethylate 4-phenylpyridinium iodide **1q** in good yields (currently ca. 30%) under any of the catalytic systems we have developed so far. Interestingly, the rhodium catalyst was less competent than iridium in every system examined except for the less electron-deficient 4-aryl pyridinium compounds.

Table 2: Scope of pyridinium salts



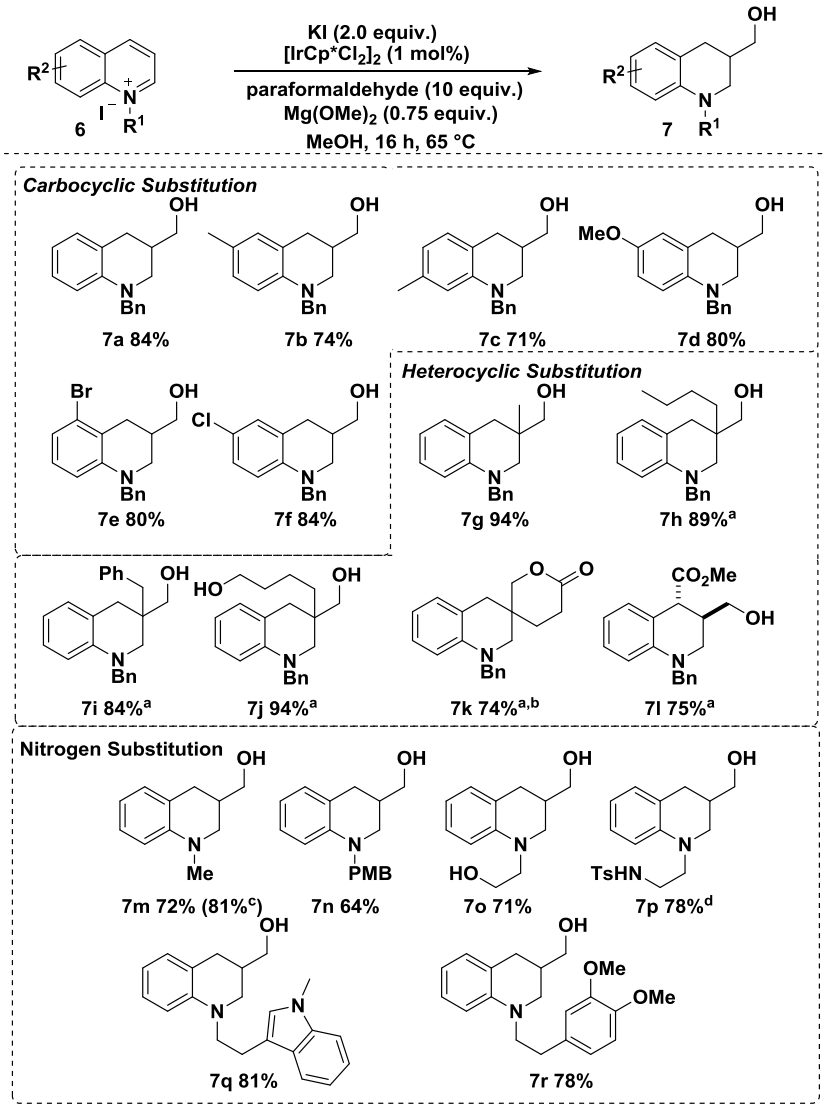
Reactions on 0.5 mmol scale, isolated yields [a] Using the tosylate salt, [b] yield after treatment of crude material with $Ti(OiPr)_4$ (1.0 equiv.), [c] yield after treatment of crude material with *p*TSA (1.1 equiv.), [d] reaction at 65 °C with 2 equiv. of KI, [e] using $[Rh(Cp^*)Cl_2]_2$ (1 mol%) and no KI at 65 °C, [f] NMR yield

In addition to generating products bearing 4 distinctly different functional groups (protected amine, electron-poor olefin, ester, and primary alcohol), the product bearing enol ether functionality (**4m**) contains a protected ketone and under treatment of the crude reaction mixture with acid, the bicyclic *β*-ketolactone **5** was isolated in good yield further illustrating that this methodology is an excellent approach to these desirable and biologically relevant small molecules.

Following our exploration of the pyridinium scope, we were intrigued as to whether this methodology could be extended to related heterocyclic arenes, in particular quinolinium salts. Pleasingly, subjecting *N*-benzyl quinolinium iodide **6a** to the optimal reaction conditions gave the corresponding hydroxymethylated tetrahydroquinoline **7a**, with similar reductive functionalisation. However, we found that the reaction was far more sluggish with the quinolinium salts and a reaction time of 7 days was required for complete conversion (75% isolated yield). The benzannulation of the heterocycle in quinoline leads to a lower penalty due to loss of aromaticity in the initial reduction; thus an electron-withdrawing substituent in the 4-position is not required. After an optimization study, we found that the reaction proceeded more rapidly at 65 °C, required less paraformaldehyde and potassium iodide and furnished product **7a** in 84% yield after 16 hours. Following these optimization studies, a study of the scope of the quinolinium salts was also undertaken (Table **3**). Substitution of the carbocyclic aromatic ring of the quinoline was well tolerated, with good yields for substrates with both electron-rich substituents (**6b**-**6d**) and electron-poor substituents (**6e**-**6f**); furthermore these substitutions are well tolerated in a range of positions including the 5- (**6e**), 6- (**6b**, **6d, + 6f**), and 7- (**6c**) position. Additionally, substitution on the heteroatom-containing ring was also well tolerated, of particular note are examples **6g-6k** where substitution lies at the 3-position of the quinoline, resulting in the formation of a quaternary centre; such products are not accessible through the reduction of pre-functionalized quinolines. Note that substrates (**6g-6k**) were found to work better with conditions involving KOH and MgI_2 rather than $Mg(OMe)_2$ and KI. If the alkyl chain in the 3-position features a pendent ester (**6k**), a mixture of "open" and lactonized products were observed and treatment of the crude mixture with acid delivered the lactone product **7k** exclusively. Notably when substitution is present in the 4-position the reaction proceeds smoothly, giving the product (**7l**) as a single (*trans*) diastereomer. Variations on the nitrogen atom are also tolerated, including protecting groups such as methyl (**6m**) and PMB (**6n**) along with a selection of functionalized alkyl chains (**6o-6r**), these results again demonstrate a wide range of functional group tolerance including halogens, esters, unprotected alcohols, sulfonamides, electron-rich aromatic,

and other heterocycles. While the prospect of an enantioselective version of this reaction will be examined in the future, preliminary experiments regarding the formation of **7l** using a chiral ligand for iridium gave a 45:55 enantiomeric ratio; proving that the concept of an enantioselective Ir-H addition to an arene is feasible in this system.

Table 3: Scope of the quinolinium salts



Reactions on 0.5 mmol scale, isolated yields. [a] Using KOH (2.0 equiv.) and MgI_2 (1.0 equiv.), [b] Yield after treatment of crude material with *p*TSA (0.1 equiv.), [c] Using KOH (1.5 equiv.) and KI (2.0 equiv.), [d] Using tosylate salt.

Mechanistic Considerations

Having explored the substrate scopes of both salts, we were interested in probing the mechanistic details of the reaction to enable us to understand the process better, account for the observed regioselectivity, and propose a feasible catalytic cycle. Preliminary experimentation using the 3-methylpyridinium salt **1k** in conjunction with d^4-MeOD and CH_2O revealed that no deuterium incorporation was observed at either the C^2 or C^6 position of the tetrahydropyridine, nor the installed CH_2OH moiety of **2k**, indicating it is unlikely that the Ir-H species is generated from the oxidation of methanol itself; this in turn does not generate any d^2-formaldehyde. Conversely, using d^2-paraformaldehyde in conjuction with CH_3OH resulted in deuterium incorporation at both the C^2 and C^6-position and the installed CH_2OH handle (full incorporation), indicating that the Ir-H arises from the iridium-catalysed oxidation of formaldehyde (full details can be found in the Supporting Information). Re-isolation and analysis of the remaining starting material (**d-1k**) showed that appreciable quantities of deuterium had been incorporated in both the C^2 and C^6 positions of the pyridinium salt (Figure 2). These intriguing results not only show that the reduction of the pyridinium salt is reversible, but can also account for the regioselectivity observed in product **4k**; they allow us to propose the following mechanism (Figure 2). The iridium hydride species **9** is formed through addition of methanol to formaldehyde to generate intermediate **8** which is oxidized by the iridium, forming methyl formate and an iridium-hydride (indeed ^{1}H NMR analysis of the crude reaction mixture shows the presence of methyl formate). Following the formation of the iridium hydride, reduction can occur at the C^6 position or C^2 position. However, reduction at the C^6 position gives rise to sterically encumbered enamine **10**; trapping formaldehyde to form a quaternary centre is slow and unfavourable, and thus enamine **10** is re-oxidized back to **1k**. Conversely, when enamine **11** is formed it can trap formaldehyde, leading to iminium ion **12**, which is then reduced by a second equivalent of irdium-hydride generating product **2k** (this spontaneously lactonises *in situ* to form **4k**). The reversible nature of the initial Ir-H reduction accounts for the regioselectivity observed in **4k**, deriving from reduction at the more hindered carbon centre.

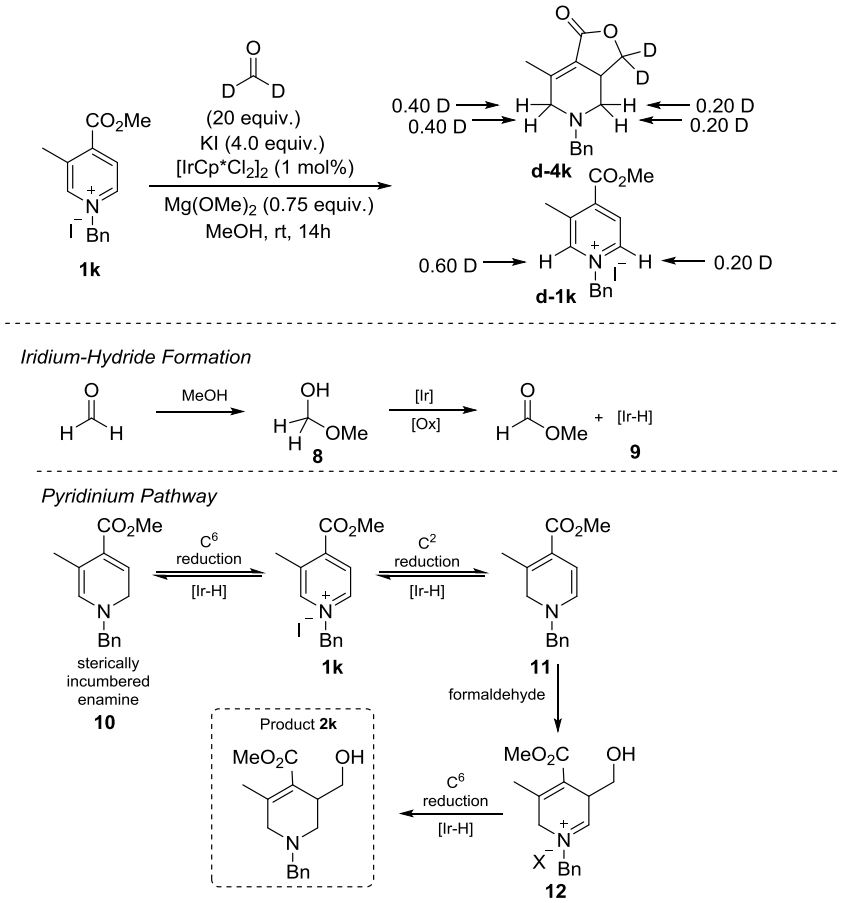


Figure 2: **Deuterium labelling studies and proposed mechanism for the pyridinium salts** (a) Labelling studies with d_2-paraformaldehyde show incorporation of deuterium in both the product and unreacted starting material, indicating a reversible reduction. (b) Iridium-hydride is formed through the oxidation of the hemiacetal to give methyl formate. (c) The mechanism proceeds through an initial iridium-hydride reduction, followed by trapping of the formaldehyde and then a second iridium-hydride reduction.

In the case of the quinolinium salts, experiments using deuterated methanol and paraformaldehyde gave similar results (full details can be found in the Supporting Information). As an additional mechanistic probe both 2-deutero and 4-deutero quinolinium salts (**2-D 1a + 4-D 1a**) were prepared and subjected to the optimal reaction conditions, along with 1 equivalent of the 6-methoxyquinolinium salt **6d**. Analysis of the products illustrates that in both cases, deuterium incorporation could be observed in the 2- and 4- positions of the standard product **d-7a** and in the 2- and 4- positions of the methoxy product **d-7d**. Given that the only source of deuterium in these reactions is the starting quinolinium salts, it confirms that hydride addition at both the 2- and 4-

position of the quinolinium salts are reversible and the presence of cross-over deuterium incorporation shows that this process occurs through a formal oxidation, back to the quinolinium salt,[38] rather than a potential intramolecular hydride shift (Figure 3). The proposed mechanism for the quinolinium salts proceeds as shown (Figure 3). The iridium hydride species is formed through the oxidation of formaldehyde; the resulting reduction can either occur at the C^2 or C^4 positions. Reduction at the C^2 position generates dihydroquinoline **13** which does not easily trap formaldehyde and re-oxidizes to reform **6a**. Reduction at the C^4-position forms enamine **14**, which then traps formaldehyde to form iminium ion **15** which is reduced by a second equivalent of iridium-hydride to form product **7a**. Not only is this proposed mechanistic pathway consistent with observed regioselectivity and the deuterium labelling studies, subjecting dihydroquinoline **13** (prepared separately) to the reaction conditions results in a high level of formation of the product **7a**, further supporting our mechanistic proposal. Compound **13** was not converted into product **7a** in the absence of iridium catalyst. Supplementary experiments (see ESI) did reveal that **13** was capable of transferring a hydride to a quinolinium salt in the absence of iridium catalyst. However, this process was slow relative to the metal catalysed reaction and was not able to produce product **7a** without iridium.

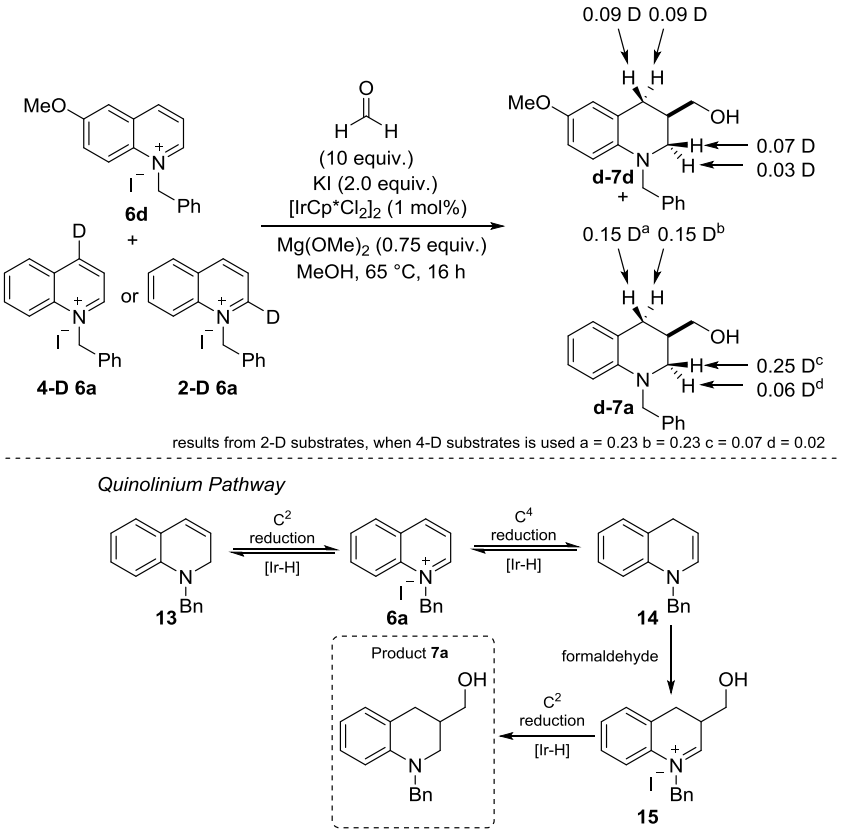


Figure 3: **Deuterium labelling studies and proposed mechanism for the quinolinium salts** (a) Doubly labelled cross-over experiments show intermolecular transfer of deuterium and a reversible initial reduction step (b) The mechanism is proposed to proceed through an initial iridium-hydride reduction, followed by enamine trapping of formaldehyde, before a final iridium-hydride reduction.

Conclusions

In conclusion we have developed the reductive-hydroxymethylation of pyridinium and quinolinium salts through an interrupted transfer hydrogenation process. This methodology leads to the synthesis of highly functionalized and useful tetrahydropyridine and tetrahydroquinoline products, bearing multiple functional handles and substitution patterns that are not possible to prepare using current state of the art methods. Isotope labelling studies have shed light on the mechanism, allowing greater understanding of the processes in play. Work is ongoing within our laboratories to extend this methodology to other heterocycles and apply it to the synthesis of natural products and pharmaceutical targets.

Data Availability

Supplementary information, chemical compound information and copies of spectra are available in the online version of the paper.

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Additional Information

Competing Financial Information

The authors declare no competing financial information