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An Air-Stable Cationic Iridium Hydride as a Highly Active and General Catalyst for the Isomerization of Terminal Epoxides

Nicolas Humbert,[a] Devendra J. Vyas,[a] Céline Besnard[b] and Clément Mazet*[a]

We describe the use of an air-stable iridium hydride catalyst for the isomerization of terminal epoxides into aldehydes with perfect regioselectivity. The system operates at low loadings of catalyst (0.5 mol%), is highly practical, scalable, and tolerates functional groups that would not be compatible with Lewis acids typically used in stoichiometric amounts. Evidence for a rare hydride mechanism are provided.
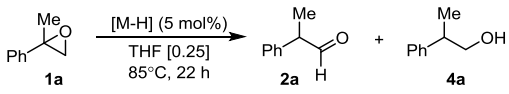
The selective isomerization of readily available epoxides into the corresponding carbonyl derivatives is a reaction of great synthetic interest.[1–5] Although it has already found several applications in the synthesis of biologically relevant (but specific) targets, numerous challenges still need to be addressed. For instance, the yield, the regioselectivity, the stereoselectivity and the stereospecificity of the reaction strongly depend on the substitution pattern of the substrate. Terminal epoxides are recognized as particularly sensitive candidates as they undergo additional rearrangements to alkenes, ketones or allylic alcohols. Moreover, from a method development point of view, most of the existing protocols rely on the use of stoichiometric or excess amounts of Lewis acids and there is yet no efficient and practical catalyst that displays wide substrate scope and high functional group tolerance.

We recently reported a [Pd−H]-catalyzed isomerization of 2,2-disubstituted epoxides **1** to aldehydes **2** (Scheme 1).[6] Experimental and theoretical investigations lent credence to a mechanism characterized by a ring-opening/hydride transfer sequence (**I→II→III**), paralleled by a concurrent metal-catalyzed tautomerization (**IV→V→IV**). Despite these hurdles, the feasibility of the kinetic resolution of terminal epoxides using chiral ligands and in situ generation of the palladium hydride was demonstrated as proof of principle and − moreover − served as a mechanistic tool. With the achiral dinuclear catalyst [(dippp)$_3$Pd$_2$(H)$_2$](OTf)$_2$ **3** (dippp = 1,3-bis(di-*iso*-propyl-phosphino)-propane), a number of terminal

and trisubstituted epoxides were selectively isomerized into the corresponding aldehydes and ketones respectively. Nonetheless, the catalyst sensitivity, the high catalyst loading (up to 6 mol%), the diversity of reaction protocols, the high reaction temperature (up to 140°C), the long reaction times and the low yields obtained for the more functionalized substrates clearly hamper use of this system in routine synthetic operations. We disclose herein the discovery of a readily accessible air-stable iridium hydride catalyst for the highly efficient isomerization of a variety of terminal epoxides into aldehydes with perfect regioselectivity. As a significant advance, the system operates according to a single set of reaction conditions at very low loadings of catalyst (0.5 mol%) and tolerates a wide number of functional groups that would not be compatible with more traditional Lewis acids.
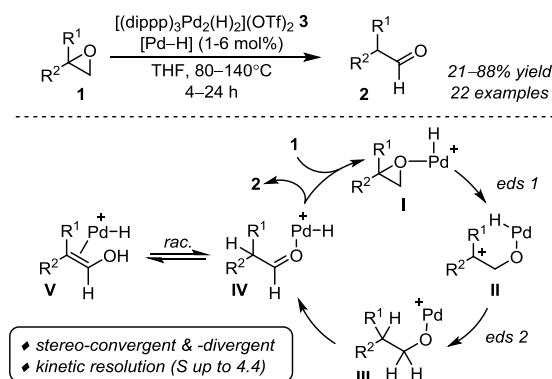
Scheme 1 Isomerization of terminal epoxides by a [Pd−H] catalyst and its mechanistic rationale (eds = enantio-determining step).

Table 1 Reaction optimization[a]

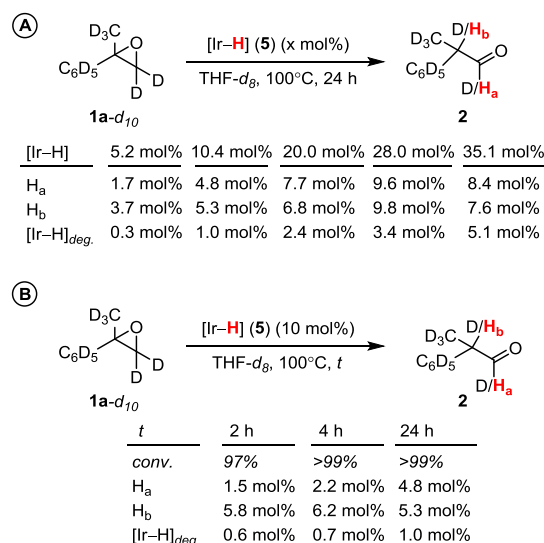| entry	catalyst	additive[b]	conv. (%)[c]	2a/4a
1	**3**	none	>99 (77)[d]	>99:1
2	[(Ph₃P)CuH]₆	none	0	nd[e]
3	[(Ph₃P)₃RhH(CO)]	none	0	nd
4	[(Ph₃P)₃RuH(Cl)]	none	49	66:34
5	[(Ph₃P)₃CuH]₆	dippp	0	nd
6	[(Ph₃P)₃RhH(CO)]	dippp	0	nd
7	[(Ph₃P)₃RuH(Cl)]	dippp	0	nd
8	[(Ph₃P)₃RuH(Cl)]	NaBArF	>99 (70)[d]	77:23
9	[Cp₂Zr(H)Cl]	none	>99	73:27
10	**5**	none	>99	>99:1
11[f]	**5**	none	>99(98)[d]	>99:1
12	**5**	dtbmp	>99	>99:1
13	**5**	TEMPO	0	nd
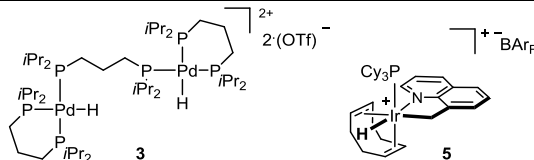
[a]Average of two independent experiments (0.15 mmol scale). [b]7.5 mol%. [c]Determined by GC or ^{1}H NMR. [d]Isolated yield of **2a**. [e]not determined. [f]0.5 mol%, 100°C, 24 h.

At the outset of our investigations, we wondered whether other well-defined transition metal hydrides would be competent catalysts for the isomerization of terminal epoxides and would hypothetically follow a productive cycle reminiscent to the one depicted on Scheme 1. Hence, a selection of commercially available candidates was subjected to prototypical reaction conditions (5 mol%; 85°C, 22 h) for the isomerization of 2-methyl-2-phenyloxirane **1a** and compared to the performances of the [Pd−H] catalyst **3** (Table 1, Entry 1−4). Both the hexameric copper hydride [(Ph₃P)CuH]₆ and the rhodium hydride [(Ph₃P)₃RhH(CO)] proved inactive. With the ruthenium hydride complex, 49% conversion into a 66:34 mixture of aldehyde **2a** and alcohol **3a** was observed.[7] Addition of a bulky, electron-rich, chelating bisphosphine ligand, which was beneficial in optimizing in situ conditions for Pd catalysis, did not result in any improvement for the [Cu−H] and [Rh−H] catalysts and even led to complete inhibition for the [Ru−H] complex (Table 1, Entry 5−7). Instead, addition of 1 equivalent of NaBArF (BArF = tetrakis-(3,5-bis-(trifluoromethyl)phenyl]borate) to generate a cationic ruthenium intermediate gave complete conversion of **1a**, though with a similar ratio between the desired aldehyde **2a** and the corresponding alcohol **4a** (Entry 8). Consistent with observations made by Wipf and co-workers, a similar outcome was observed when catalytic amounts of Schwatrz reagent [Cp₂Zr(H)Cl] (Cp = cyclopentadienyl) were employed (Entry 9).[8–9] Satisfactorily, the cyclo-metallated iridium(III) hydride complex **5** delivered exclusively and quantitatively aldehyde **2a**.[10] *This result was unexpected as 5 proved inactive in the isomerization of primary allylic alcohols, a reaction that also proceeds by an addition/elimination mechanism.*[11] Remarkably, further optimizations allowed reduction of the catalyst loading down to 0.5 mol% while maintaining excellent reactivity (100°C, 24 h, Table 1, Entry 10−11).[12]

A set of preliminary mechanistic experiments was conducted to assess whether, a hydride-type mechanism analogous to the one described on Scheme 1 would be operating with complex **5**. While no reactivity was observed when a hydride trap such as TEMPO (TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy) was employed,[13] the use of a non-coordinating base such as dtbmp (dtbmp = 2,6-di-*tert*-butyl-4-methylpyridine) did not inhibit the catalytic process (Table 1, Entry 12−13).[14] These control experiments suggest that a discrete [Ir−H] intermediate derived from **5** might indeed be responsible for the catalytic activity in the isomerization of **1a**. To substantiate these observations further, labelling NMR experiments were conducted using a fully deuterated version of our model substrate **1a**-d_{10} (Scheme 2). At various catalyst loadings, H−incorporation was systematically detected in the benzylic (H$_b$) and aldehydic (H$_a$) positions of the product, while no incorporation was detected either in the aromatic ring or in the methyl position (Scheme 2; A). At the end of these NMR experiments (t = 24 h), two new signals that accounted for most of the remaining non-incorporated hydrogen content, were detected in the hydride region. These were attributed to degraded forms of the catalyst. Attempts to isolate and characterize these new species proved unsuccessful (See Supplementary Data). At very high catalyst loading, the loss of hydrogen content was more pronounced. The extent of incorporation of hydrogen in the aldehydic region was found to increase over time, even after completion of the reaction (Scheme 2; B). This suggests the existence of a hydride-catalyzed enolization process in which both the catalyst and the two new hydride species might be involved.[6,15] Although additional experiments are needed to elucidate the exact reaction mechanism fully, collectively our observations suggest that a hydride-type mechanism is the dominant reaction pathway. Partial contribution from a Lewis acid-type mechanism cannot be ruled out, in particular at very high catalyst loading.

To further emphasize the practical aspect of the present catalytic system, the iridium hydride precatalyst **5** was prepared on a large scale (0.45 mmol) using commercially available reagents (Scheme 3). A net improvement in yield was observed with respect to the original procedure and complex **5** was isolated in quantitative yield

[Ir–H]	5.2 mol%	10.4 mol%	20.0 mol%	28.0 mol%	35.1 mol%
H$_a$	1.7 mol%	4.8 mol%	7.7 mol%	9.6 mol%	8.4 mol%
H$_b$	3.7 mol%	5.3 mol%	6.8 mol%	9.8 mol%	7.6 mol%
[Ir–H]$_{deg.}$	0.3 mol%	1.0 mol%	2.4 mol%	3.4 mol%	5.1 mol%

t	2 h	4 h	24 h
conv.	97%	>99%	>99%
H$_a$	1.5 mol%	2.2 mol%	4.8 mol%
H$_b$	5.8 mol%	6.2 mol%	5.3 mol%
[Ir–H]$_{deg.}$	0.6 mol%	0.7 mol%	1.0 mol%

Scheme 2 Labelling experiments using **1a**-d_{10} (A: at various catalyst loadings; B: at mol% and various temperature). [Ir–H]$_{deg.}$ denotes degraded hydride catalyst. Conversion measured by ^{2}H NMR spectroscopy. The slight imperfect balance for some measurements is attributed to experimental error.
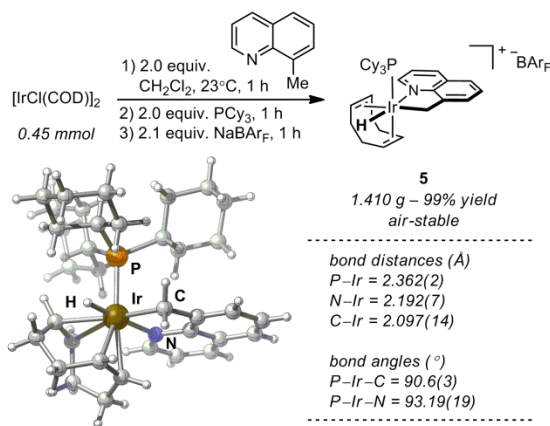
Scheme 3 Large scale preparation of complex **5** and Cylview representation of its molecular structure. Selected bond lengths (Å) and angles (°). The anion is omitted for clarity.

(1.410 g) as an air-stable beige solid after simple filtration over a short pad of silica. Single crystals of suitable quality were obtained and an X-ray diffraction study enabled to confirm the molecular structure, which had been initially established on the sole basis of multidimensional NMR studies.[16]

Finally, a collection of 22 different terminal epoxides was evaluated with catalyst **5** (Scheme 4). For sake of practicality, the conditions identified for **1a** were systematically applied as a uniform isomerization protocol (0.5 mol%, 100°C, 24 h), with only 1 exception (**2i**; 2.0 mol%, 100°C, 24 h). Scheme 4 provides a comparative evaluation of the performances of the Pd and Ir hydride complexes with emphasis being placed on the loading of the precatalyst.[17] All reactions were essentially quantitative and the products were isolated in pure form after removal of the degraded iridium complex by a simple filtration. This corresponds in most cases to an eight to twelve-fold decrease in catalyst loading (22 examples). In one case (**2t**), the loading was even reduced from 10 mol% to 0.5 mol% while the yield was improved from 21% to 97%. Substrates with primary (**2a-c**), secondary (**2d-e**, **2h**) and tertiary (**2f**) alkyl substituents were all isomerized effectively. Sensitive functional groups such as aryl halides (**2j-m**, **2o**), methoxy (**2p**), benzyloxy (**2q**), cyano (**2r**), ester (**2s**), alkyne (**2t**) and alkene (**2u**) were all tolerated. Remarkably, many of these synthetically useful functions would not be compatible with the Lewis acids traditionally employed for the rearrangement of epoxides. Last, isomerization of epoxide **1v**, which proved particularly challenging with palladium catalyst **3**, was performed on a 1.0 gram scale using only 49 mg of **4**. Again, the analytically pure aldehyde **2v** was isolated quantitatively after filtration.

Conclusions

In conclusion, we have discovered and characterized a well-defined air-stable iridium hydride catalyst for the selective isomerization of a vast array of structurally and electronically diversified terminal epoxides in aldehydes. The catalyst was optimized according to a single experimental protocol which requires a loading of only 0.5 mol%. More importantly, several sensitive functional groups are compatible with the method, delivering the products in essentially quantitative yield. Preliminary mechanistic investigations point to a hydride mechanism similar to the one recently elucidated for a palladium hydride complex. Current efforts are directed toward the synthesis of enantiopure variants of the iridium complex for application in enantioselective reactions.
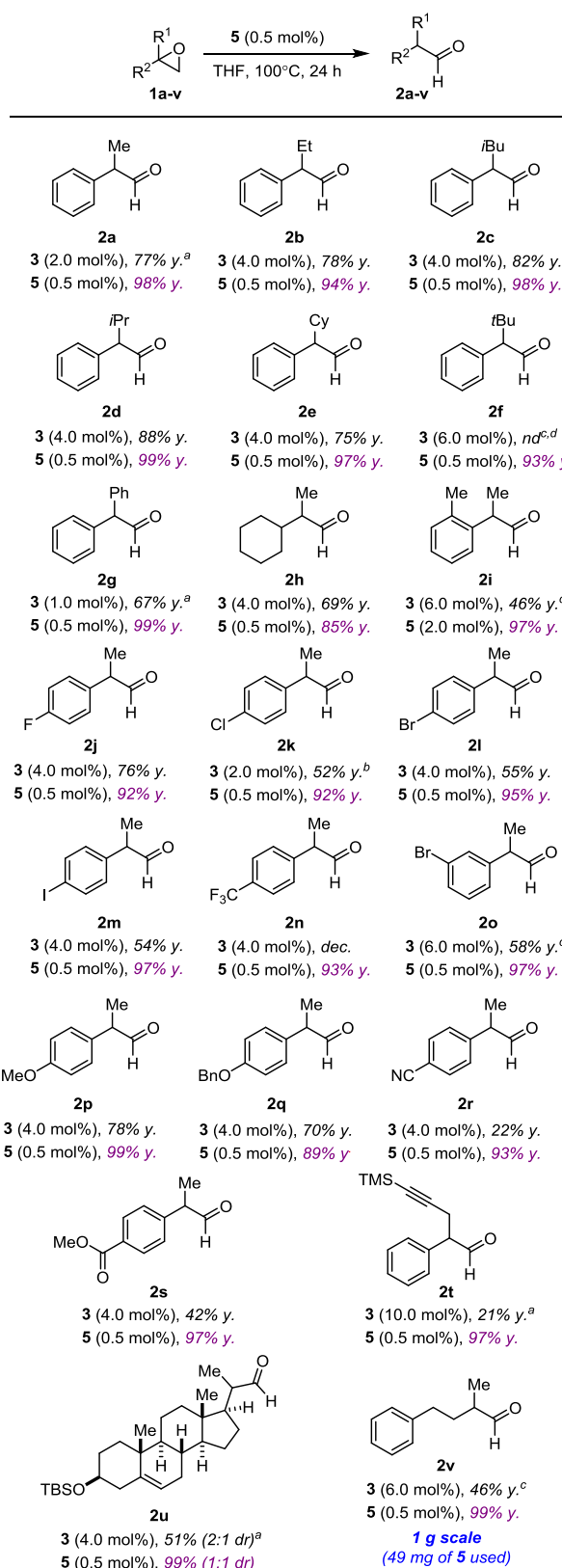
Average of two experiments. All reactions with **3** were run at 100°C unless otherwise noted. [a]At 85°C. [b]At 120°C. [c]At 140°C. [d]Not determined. Substrate and product were not separable (Conv. = 46%).

Scheme 4 Comparative performances of catalysts **3** and **5**.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, NMR spectra and crystallographic data. See DOI: 10.1039/c000000x/

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12 Although the catalyst is air-stable and the reaction can be set on a benchtop, at these very low loadings the use of perfectly anhydrous substrates and solvent is preferable. The iridium complexes with BArF anion are usually hygroscopic and are best kept in a desiccator.

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17 For additional experimental details, see ref. 6.