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# Breaking the Aliphatic Wall: Iridium-Catalyzed Direct Reductive Amination of Ketones and Secondary Amines

Matthieu Jouffroy,*[a] Thi-Mo Nguyen,[b] Marie Cordier,[b] Marielle Blot,[b] Thierry Roisnel,[b] and Rafael Gramage-Doria*[b]

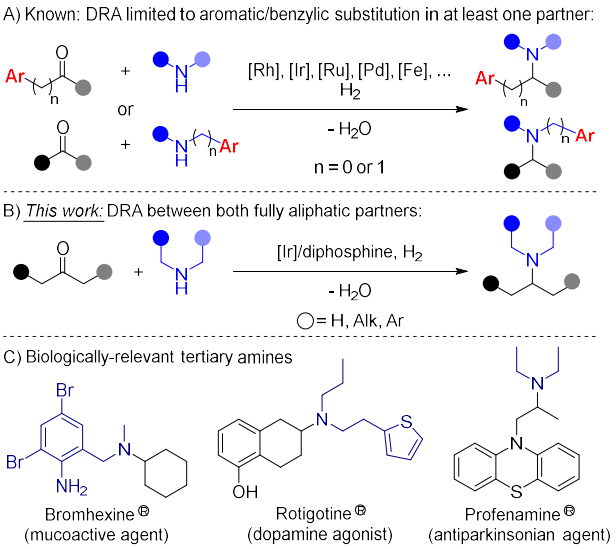
[a] Dr. M. Jouffroy
Chemical Process R&D, Discovery Process Research
Janssen Pharmaceutica N.V.
Turnhoutseweg 30, 2340 Beerse, Belgium
E-mail: mjouffro@its.jnj.com

[b] T.-M. Nguyen, M. Cordier, M. Blot, Dr. T. Roisnel, Dr. R. Gramage-Doria
Univ Rennes, CNRS, ISCR-UMR6226, Rennes F-35000, France
E-mail: rafael.gramage-doria@univ-rennes1.fr

Supporting information for this article is given via a link at the end of the document.

***Abstract:*** *Direct reductive amination (DRA) is a ubiquitous reaction in organic chemistry. This transformation between a carbonyl group and an amine is most often achieved using super stoichiometric amount of hazardous hydride reagents, thus being incompatible with many sensitive functional groups. DRA could also be achieved by means of chemo- or bio-catalysis, thereby attracting the interest of industry as well as academic laboratories due to their virtually perfect atom-economy. Although DRA are well-established for substrate pairs such as aldehydes with either 1° or 2° amines as well as ketones with 1° amines, the current methodologies are limited in the case of ketones with 2° amines. Herein, we present a general DRA protocol that overcomes this major limitation by means of iridium catalysis. The applicability of the methodology is demonstrated by accessing an unprecedented range of biologically relevant tertiary amines starting from both aliphatic ketones and aliphatic amines. The choice of a disphosphane ligand (**Josiphos A** or **Xantphos**) is essential for the success of the transformation.*

***D****irect* reductive amination (DRA) reactions allows to access highly diversified amines upon formal condensation of carbonyl- and amine-containing partners.[1] From the many existing methodologies, those based on transition metal catalysts operating under dihydrogen ($H_2$) atmosphere are particularly promising as they (1) rely on ubiquitous starting materials, (2) do not require purification/isolation of the often unstable imine, enamine or iminium intermediate and (3) generate only water as side-product due to the perfect atom-economy, being this highly relevant for scalability and applicability purposes (Scheme 1).[2] In addition, asymmetric DRA reactions have been accomplished using privileged chiral metal catalysts and substrates or by means of biocatalysis.[3] As such, transition metal-catalyzed DRA reactions are appealing to replace those reductive reactions involving the use of hazardous reagents (lithium, aluminum or boron hydrides, organosilanes, etc.) that generate over-stoichiometric amounts of dangerous waste and that typically are incompatible with many sensitive functional groups.[4] In this regard, transition metal-catalyzed DRA reactions fulfill many criteria from a sustainable point of view and they are therefore perfectly positioned for being a reaction of choice in process chemistry.[5]




**Scheme 1.** Transition metal-catalyzed direct reductive amination (DRA) reactions: state-of-the-art (**A**) *versus* present work (**B**), and relevant amines (**C**).

Transition metal-catalyzed DRA are well-established for reactions between aldehydes with either 1° or 2° amines as well as ketones with 1° amines but have scarcely met success when attempting to react 2° amines with ketones (Scheme 1). In this later case, at least one of these two partners contains an aromatic or benzylic motif directly connected to the nitrogen or the carbonyl group, respectively (Scheme 1A).[2,3] This highly restricted substrate scope could be explained by the fact that hydrogenation of the corresponding iminium intermediate is less energetically-demanding than that of a fully aliphatic version.[6] The ease of formation combined with the increased stability of the transient iminium or enamine intermediate in the case of aromatic and benzylic substituents could also explain the difference of reactivity observed.[2,3] So far, DRA between aliphatic ketones and secondary alkyl amines using metal catalyzed hydrogenation remains elusive for applicability purposes.[6j] Consequently, the quest for methodologies enabling DRA reactions using

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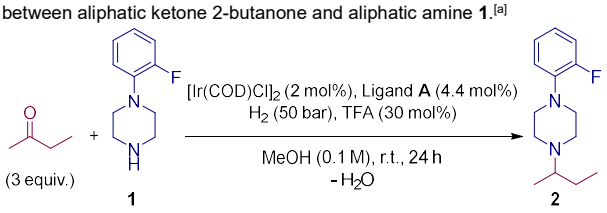
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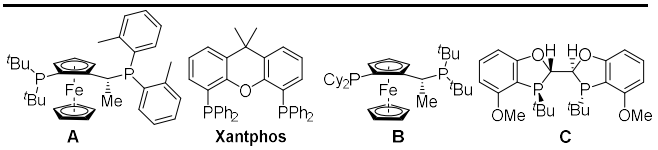

simultaneously both less reactive aliphatic amines and aliphatic ketones is of high interest (Scheme 1B). Moreover, the direct use of such building blocks might lead to access purely aliphatic tertiary amines that are fundamental motifs found in drugs, herbicides, pesticides, and active pharmaceutical ingredients, amongst other fine chemicals (Scheme 1C).[7] Herein, we report an iridium/diphosphine catalytic system operating under pressure of $H_2$ capable to reach such unprecedented transformation under mild conditions. Remarkably, this methodology displays an excellent functional group tolerance as well as scalability which makes it appealing for re-purposing current synthetic strategies as well as for application in late-stage functionalization.

Based on previous reports on DRA and more broadly on hydrogenation reactions,[8] we initiated a large screening of reaction conditions using high throughput experimentation (see the Supporting Information). We first investigated a wide range of ligands and solvents with two distinct metal precursors, namely $[Ir(COD)Cl]_2$ and $[Rh(COD)Cl]_2$ under 50 bars of $H_2$. We focused our attention on the synthesis of compound **2** starting from 2-butanone and the amine **1**, which is a key motif found in active pharmaceutical ingredients (API) such as Pefloxacin® (Table 1).[9] Interestingly, the targeted product was only obtained when combining different chelating ligands with iridium in the presence of trifluoroacetic acid (TFA) and MeOH as the solvent (Table 1 and Tables S1-S4 in the Supporting Information).[10] Extensive experimentation revealed that the optimal iridium-based catalytic system was found when using 4.4 mol% of Josiphos-type ligand **A** or Xantphos (Table 1).[10] After 24 hours at room temperature, the first catalytic system led to full conversion of **1** with an isolated yield of 74% for the corresponding tertiary amine **2**. (Table 1, entry 1). When using Xantphos as ligand, a comparable conversion of **1** was reached although the isolated yield of the final product **2** dropped to 48% (Table 1, entry 2). Other chelating ligands such **B**, **C**, dppp (1,3-bis(diphenylphosphino)propane) and dppe (1,2-bis(diphenylphosphino)ethane) featured conversions of **1** lower than 80% and isolated yields of **2** of *ca.* 30% for the best case (Table 1, entries 3-6). Consequently, the efficiency of the catalysis appears to correlate with the P-M-P bite angle that a given ligand features following the trend Xanthos > dppp > dppe.[11] Replacing diphsphanes for monophosphanes ($PPh_3$, trisfuranyl phosphine, XPhos, SPhos) under identical metal/phosphours ratio led to lower activity (see Table S4 in the Supporting Information).[10] The use of $Ti(OEt)_4$ as dehydrating agent instead of TFA was similarly efficient although purification difficulties were encountered (Table 1, entry 7). Excess or absence of TFA was not beneficial for the catalysis (Table 1, entries 8-9). Additional control experiments indicated the need of all reagents for the success of the transformation and that $[Ir(COD)(OMe)]_2$ was not an appropriate metal precursor.[10] Using 2-butanone as the limiting reagent still led to 80% conversion of **1** (Table 1, entry 10), which was increased to 93% in the presence of $Ti(OEt)_4$ instead of TFA (Table 1, entry 11), affording **2** in up to 70%. Finally, shortening the reaction time and decreasing the $H_2$ pressure, respectively, was detrimental for the catalysis.[10]

**Table 1.** Selected optimization data of the iridium-catalyzed DRA reaction between aliphatic ketone 2-butanone and aliphatic amine **1**.[a]




| Entry | Deviations from above | Conv.[b] | Yield of **2**[c] |
|---|---|---|---|
| 1 | none | >99 | 74 |
| 2 | Xantphos instead of **A** | >97 | 48 |
| 3 | **B** instead of **A** | 67 | 29 |
| 4 | **C** instead of **A** and 64 h | 78 | 31 |
| 5 | dppp instead of **A** | 74 | 60[d] |
| 6 | dppe instead of **A** | 48 | 30[d] |
| 7 | $Ti(OEt)_4$ (1 equiv.) instead of TFA | 86 | 52 |
| 8 | TFA (100 mol%) | 77 | n.d. |
| 9 | without TFA | 6 | n.d. |
| 10 | 2-butanone (1 equiv.) and **1** (3 equiv.) | 80 | 65[d] |
| 11 | as entry 10 but with $Ti(OEt)_4$ (1 equiv.) | 93 | 70[d] |




[a] Reaction conditions: **1** (0.1 mmol), 2-butanone (0.3 mmol), TFA (30 mol%), **A** (4.4 mol%), $[Ir(COD)Cl]_2$ (2 mol%), $H_2$ (50 bar), MeOH (1 mL), r.t., 24 hours. [b] Conversion calculated by GC-FID analysis and confirmed by $^1H$ NMR spectroscopy studies using 1,3,5-trimethylbenzene as internal standard. [c] Isolated yield on 0.5 mmol scale (**1**) after purification by column chromatography. [d] Yields determined by GC-FID analysis. n.d. = not determined.

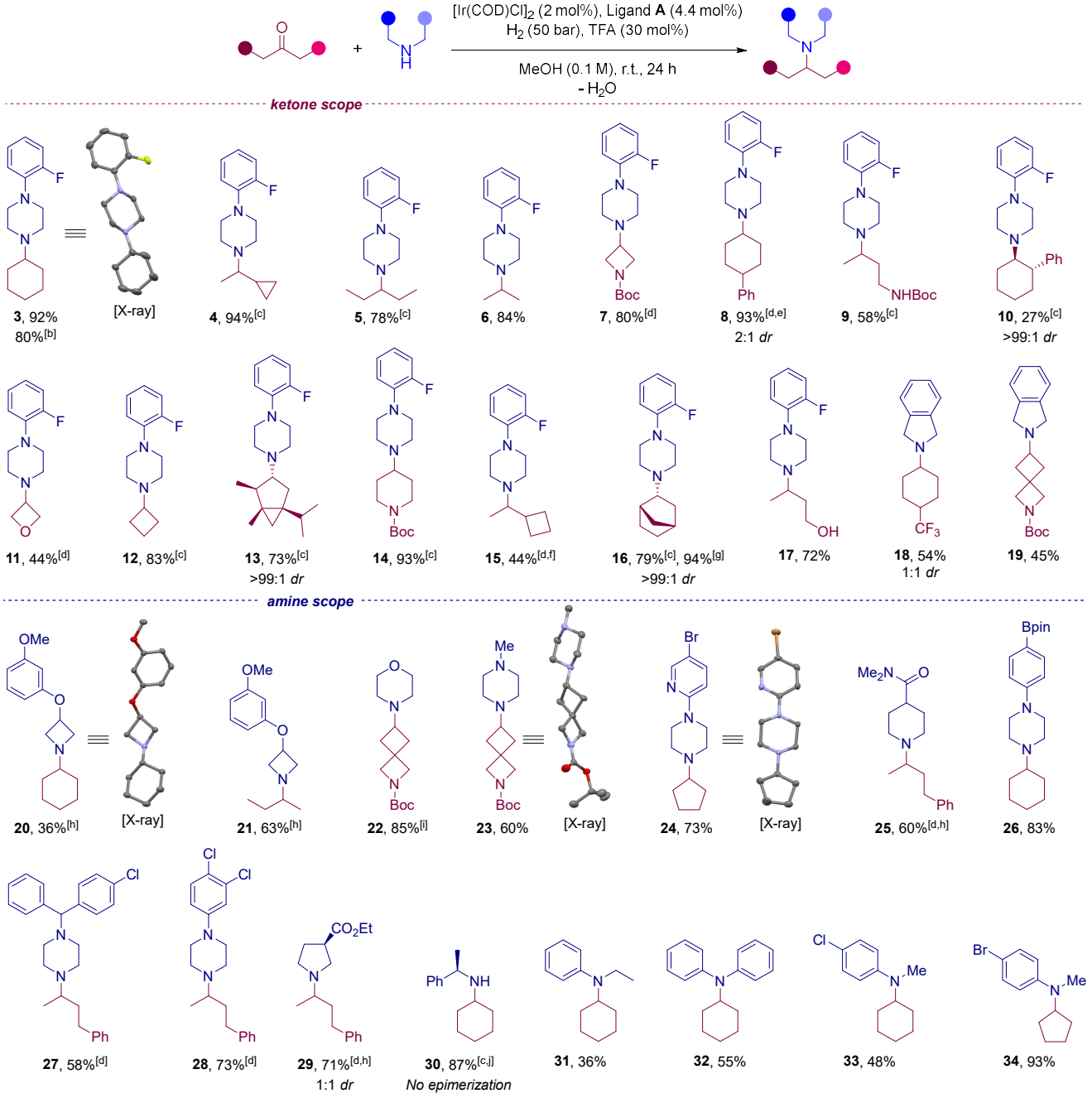
With the optimal reaction conditions in hand, we studied the functional group tolerance of the methodology using a wide variety of amines and ketones (Table 2). The catalytic system was found to be compatible with an exceptionally large array of functional groups such as aryl halides, ethers, unprotected alcohols, esters, tertiary amides, carbamates and even boronic esters. Alkyl chains and cycles of different sizes and shapes were found to be perfectly compatible with this methodology, even strained systems such as cyclobutane and other bicyclic aliphatic groups. We were very pleased to observe that all tested heterocycles (e.g., piperazine, azetidine, morpholine, isoindoline, pyridine, pyrrolidine, piperidine, oxetane) performed well in this transformation and that enantiomerically pure ketones and amines did not epimerize under the developed reaction conditions. All compounds were obtained in synthetically useful yields after standard purification by column chromatography and highlight the compatibility of the methodology with functional groups typically found in active pharmaceutical ingredients and agrochemicals.

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**Table 2.** Substrate scope of the iridium-catalyzed DRA reaction between aliphatic amines and aliphatic ketones.[a]




[a] Reaction conditions: amine (0.5 mmol), ketone (1.5 mmol), TFA (30 mol%), **A** (4.4 mol%), $[Ir(COD)Cl]_2$ (2 mol%), $H_2$ (50 bar), MeOH (5 mL), r.t., 24 hours. Percentage numbers refer to isolated yields of products after purification by column chromatography. [b] Reaction performed with Xantphos instead of **A**. [c] MeOH was replaced by $^t$AmOH and the reaction temperature was 80 °C at 80 bar of $H_2$. [d] Reaction performed at 50 °C. [e] Reaction performed with $H_2$ at 80 bar. [f] 5 equivalents of ketone were used. [g] Reaction performed on gram scale under $H_2$ at 80 bar in $^t$AmOH at 80 °C. [h] The corresponding ammonium chloride salt was used instead of the amine. [i] The amine/ketone ratio was reversed. [j] 1 equivalent of ketone was used.

The reaction also performed well using Xantphos as the ligand (**3**). In cases in which the ketone is significantly costly when compared to the amine, it is possible to employ the ketone substrate as the limiting reagent with excellent efficiency (**22**). Interestingly, ammonium chloride salt in place of the free amine were also suitable substrates for this catalysis and did not require the use of exogeneous TFA (**20**, **21**, **25, 29**). This finding is particularly relevant as many aliphatic amines are typically commercialized and stored as the corresponding ammonium salts due to their high benchmark chemical stability and ease of isolation. In few cases a poor reactivity at room temperature was encountered. This issue was circumvented by either simply raising the temperature to 50 °C or using *tert*-amyl alcohol as the solvent at 80 °C and increasing the pressure of $H_2$ to 80 bar. These alternative conditions successfully afforded the targeted compounds (**4-5, 7-16, 25, 27-30**) and are adequately compatible with standard laboratory equipment and most industrial processes. It is worthy to note that these reaction conditions are also compatible with primary amines and that no epimerization took place (**30**). In addition, the molecular structure of compounds **3**,

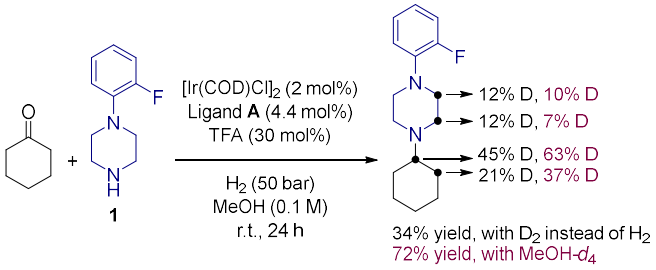




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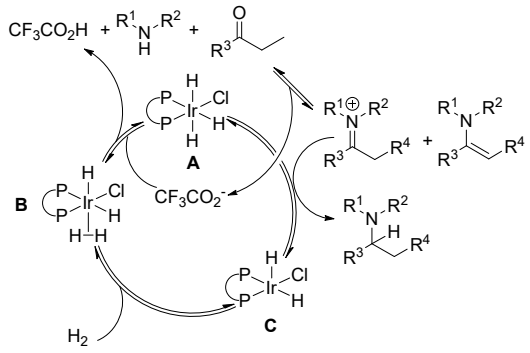
**20**, **23** and **24** was unambiguously established by single crystal X-ray diffraction studies (Table 2).[12]

The applicability of the reaction was further demonstrated by performing a gram scale experiment in which the product was not only obtained, but in increased yield compared to the standard 0.5 mmol scale (**16**, 94% *vs* 79%), highlighting the robustness and efficiency of the reported transformation. Importantly, most of the compounds featured in Table 2 might be regarded as analogues of API such as Levofloxacin® (**3-17**),[9] Mecamylamine® (**13**),[13a] Elayta® (**18**,**19**),[13b] PF-03635659® (**20**,**21**),[13c] Buclizine® (**27**),[7d] and Aripiprazole® (**28**),[13d] among others. As an expected limitation, we noted that ketone derivatives prone to undergo hydrogenation prior to imine formation (e.g., acetophenone, α,β-unsatured ketones) as well as extremely bulky ones (e.g., *tert*-butyl methyl ketone, diisopropyl ketone) were not tolerated (see extended substrate scope in the Supporting Information).[10]




**Scheme 2.** Deuteration experiments in the iridium-catalyzed DRA reaction between aliphatic ketone cyclohexanone and aliphatic amine **1**.[a]

We then turned our attention to investigating the enantiocontrol of this metal-catalyzed DRA, aiming to develop an asymmetric variant to this transformation. Despite the consequent number of chiral ligands tested for the formation of **2**, the enantiocontrol observed remained low (e.g., 15-20% *ee* using ligands **B** and **C**).[10] This observation pushed us to wonder whether several mechanisms were involved in this transformation, which would explain the difficulty we encountered in finding a suitable chiral catalytic system for this transformation. To get an insight on the reaction mechanism, a catalytic experiment was performed replacing $H_2$ by $D_2$ while performing the reaction in deuterated and non-deuterated methanol. Although the isolated yields significantly decreased, incorporation of deuterium in the final product was clearly observed (Scheme 2).[14] The isolated products consist of a mixture of mono-, bis-, and other poly-deuterated species in which deuterium was incorporated at the alpha and beta positions of the newly formed C-N bond.[10] The formation of these species suggests the presence of two distinct reaction mechanism for the hydrogenation, one going through the direct hydrogenation of the iminium species, the other *via* the hydrogenation of the corresponding enamine. As such, and based on previous results from the literature,[2,3,8,15] a simplified reaction mechanism is proposed in Scheme 3. First, the ketone and the amine *in situ* form the iminium intermediate present in equilibrium with the corresponding enamine, releasing trifluoroacetate.[16] In parallel, the active hydride-containing iridium(III) species **A** forms from **B** in the presence of the former anion.[15,17] Hydrogenation of the imine or enamine to amine as the last step might regenerate the active catalytic species **C**. The likely presence of two distinct species prone to hydrogenation could explain the low enantiomeric excess observed for the asymmetric direct reductive amination between secondary alkyl amines and ketones.[18]




**Scheme 3.** Postulated, simplified reaction mechanism. P⌒P= diphosphine ligand.

In conclusion, we have disclosed the first highly chemoselective DRA protocol enabling the formation of purely aliphatic tertiary amines starting from readily available ketones and secondary amines. Thanks to an iridium catalyst formed *in situ* with privileged ligands such as Josiphos-type **A** or Xantphos, the reaction tolerates a large number of functional groups (up to 34 examples) that impose reactivity and selectivity issues with other reductive amination methodologies. Overall, since this methodology is compatible with substructures of pharmaceutical interest (i.e., API), we expect to stimulate its implementation in research campaigns devoted to the discovery of novel active pharmaceutical ingredients.[19] Further investigations aiming to understand the mechanism of this transformation and ultimately bring an asymmetric variant to this DRA are currently ongoing.

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**Keywords:** amines • ketones • hydrogenation • iridium • reductive amination • high throughput experimentation

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[12] Deposition Numbers 2129684 (**1**·**TFA**), 2129685 (**3**), 2129686 (**20**), 2129687 (**23**) and 2129688 (**24**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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[14] Incorporation of deuterium in the final product was also observed when using $H_2$ in deuterated MeOH but with a different product distribution, see details in the Supporting Information.

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[16] Treatment of amine **1** with TFA in the presence of cyclohexanone in methanol solvent afforded single crystals suitable for X-ray diffraction studies, indicating formation of (**1**·**TFA**), see reference [10] and [12]. This supports the initial steps of the catalytic cycle proposed in **Scheme 3**.

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[18] The experiments presented in Scheme 2 cannot, however; explain the absence of epimerization of compounds such as **30** (Table 2), which will require further specific studies.

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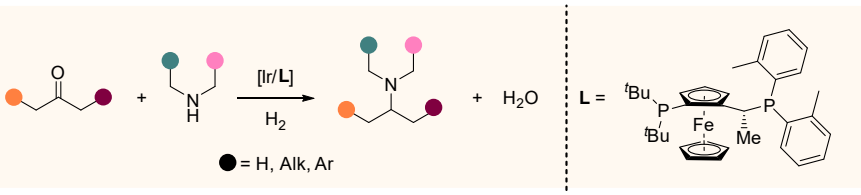
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The so-far elusive direct reductive amination between both aliphatic amines and aliphatic ketones is reported. This has been achieved using a diphosphine-coordinated iridium catalyst. The applicability and functional group tolerance are demonstrated by the synthesis of a panel of tertiary amines relevant for medicinal chemistry research. This methodology is promising for implementation on late-stage functionalization and repurposing current retrosynthetic schemes.

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