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Room Temperature Chemoselective Reductive Alkylation of Amines Catalyzed by a Well-Defined Iron(II) Complex using Hydrogen.

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ABSTRACT: A transition metal frustrated Lewis pair approach has been envisaged to enhance the catalytic activity of tricarbonyl phosphine-free iron complexes in reduction. A new cyclopentadienyl iron(II) tricarbonyl complex has been isolated, fully characterized and applied in hydrogenation. This phosphine-free iron complex is the first Earth-abundant metal complex able to catalyze chemoselective reductive alkylation of various functionalized amines with functionalized aldehydes. Such selectivity and functionality tolerance (alkenes, esters, ketones, acetals, unprotected hydroxyl group, phosphine) have been demonstrated also for the first time at room temperature with an Earth-abundant metal complex. This alkylation reaction was also performed without any preliminary condensation and generated only water as by-product. The resulting amines provided a rapid access to potential building blocks, metal ligands or drugs. DFT calculations highlighted first that the formation of the 16 electron species, via the activation of the tricarbonyl complex **Fe3**, was facilitated and, second, that the hydrogen cleavage did not follow the same pathway than the bond breaking usually described with the known cyclopentadienone iron tricarbonyl complexes (**Fe1** and **Fe4**). These calculations highlighted that the new complex **Fe3** does not behave as a bifunctional catalyst, in contrast to its former congeners.

INTRODUCTION

The demand for complex molecules is increasing in organic synthesis. Control of the stereoselectivity is often a key step and undoubtedly one of the case studies in homogeneous catalysis and in organic synthesis.[1] This research was mainly driven by the growing demand for optically pure compounds. But, while several new efficient catalysts and catalytic methodologies for such stereoselective control have been developed in the last two decades, these achievements were made to the detriment of the reaction scope, the regio- and/or the chemoselectivity. B. M. Trost introduced in a pioneer work, and conceptualized later in a seminal review, the importance of the chemoselectivity in synthesis.[2] Moreover, he pointed out also: "The degree of difficulty of chemoselectivity depends on the similarity of two or more functional groups. Thus, discrimination is simpler if the functional groups belong to two different classes, such as a C=O and a C=C, than if they are members of the same class, such as two different C=O groups in the same molecule." More recently, Baran stated also that chemoselectivity is a key factor in the synthesis of complex molecules.[3] Indeed, the control of the chemoselectivity may avoid some tedious protection/deprotection steps and shorten the syntheses. Regarding the "simplest" case (discrimination between C=O and C=C bonds), chemoselective reductions of carbonyl functions over alkenes or alkynes have been reported in literature in the presence of noble metals[4] or Earth-abundant metals.[5] Similarly, chemoselective reduction of alkenes over carbonyl functions has also been described.[6] As example, our group has recently disclosed a general chemoselective reduction of enones into saturated ketones in the presence of a phosphine-free bifunctional iron(0) complex.[7] However, chemoselective reduction of aldehydes in the presence of ketones has been scarcely reported.[8-12] Dupau *et al.* reported in 2015 a general base-free hydrogenation of aldehydes in the presence of ketones catalyzed by a [Ru(diamine)(diphosphine)(carboxylate)$_2$] complex.[9] More recently, a phosphine-containing iron complex,[10a] and pincer-type ligand containing Earth-abundant metal complexes (Fe,[10b-d] Co,[11] Mn[12]) were introduced for such a chemoselective hydrogenation of aldehydes. Albeit these studies demonstrated its feasability with Earth-abundant metal complexes, the scope was rather limited to some non-functionalized aromatic carbonyl derivatives.

Moreover, and quite surprisingly, no report to date has appeared on the catalytic chemoselective reductive alkylation of amines with aldehydes, while amines are important compounds in organic chemistry, chemical industry and biological processes, as well. As examples, they are present in amino acids, various biological compounds, or organic building blocks.[13-14] Synthesis of amine derivatives is widely reported in the literature. Among the different strategies to prepare alkylated amines, the reduction of imines and the reductive amination are well documented.[15-21] The use of stoichiometric reducing agent and the consequently formation of stoichiometric amount of waste led academic researchers to develop eco-friendly pathways. Recent development using molecular hydrogen,[17] formic acid,[18] hydride transfer[19] or hydrogen borrowing transfer[20] has emerged in the last decade. These reactions

were initially reported with platinum metals (rhodium, palladium, ruthenium or iridium). Due to economic pressure and sustainability concerns, the quest for efficient Earth abundant-based metals has led to the development of new complexes, and iron chemistry is at the forefront of this intensive research area.[17c-d, 19c-f, 20c-l, 21] But reductive alkylation with functionalized amines and/or carbonyl derivatives has been scarcely reported in literature.[22] We report in this work that a new phosphine-free iron(II) complex catalyzes chemoselectively the reductive alkylation of various functionalized amines with functionalized aldehydes at room temperature.

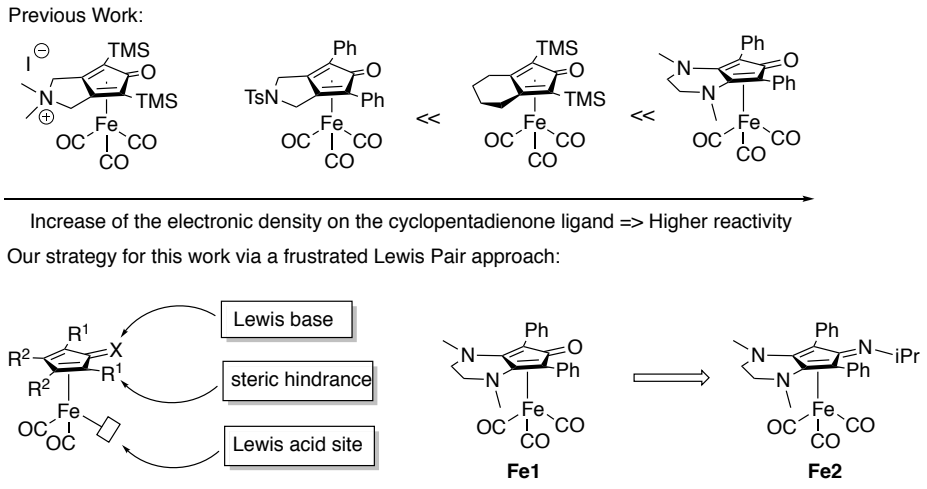
RESULTS AND DISCUSSION

Within this context, our group had described the first reductive amination between aliphatic or aromatic aldehydes, ketones and various primary and secondary amines catalyzed by cyclopentadienone iron carbonyl complexes.[23-24] A careful structural analysis highlighted that variation of the substituents on the cyclopentadienone motif controlled the reactivity of the iron catalyst. First, the steric hindrance of R^1 groups was essential to prevent dimerization of the iron complex.[23b] Second, these complexes could be seen as a transition metal frustrated Lewis pair.[25] Considering the unsaturated 16-electron intermediate and the cyclopentadienone ligand, the iron metal center would be the Lewis acid site while the carbonyl function would be the Lewis base site (Chart 1). Modifications of the electron density on both sites led to a more or less easy hydrogen cleavage.[23-24, 26] Based on these results, and in order to synthesize an iron complex exhibiting noble-metal reactivities, the replacement of the oxygen atom by a more basic atom, namely a nitrogen atom, was targeted to enhance the Lewis base character of the cyclopentadienone iron tricarbonyl complex. To achieve this goal, we conceptually designed the iron complex **Fe2** as suitable candidate (Chart 1).

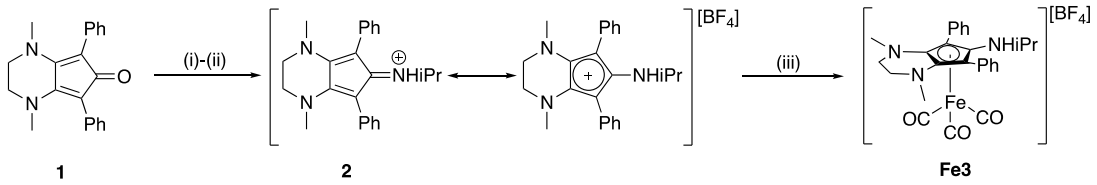
Condensation of *iso*-propylamine on the *N,N'*-dimethyl-3,4-ethylenediamino-substituted cyclopentadienone, following the Katzenellenbogen's procedure,[27] in the presence of a Lewis acid led to a complex mixture. Such reactivity might be associated to the electron-richness of the cyclopentadienone. Finally, following a procedure reported by Gompper,[28] the aminocyclopentadienylium ligand **2** was prepared in two steps from 1,4-dimethyl-5,7-diphenyl-3,4-dihydro-*1H*-cyclopenta[*b*]pyrazin-6-(2H)-one **1** in a 51 % overall yield (steps (i) and (ii), Scheme 1). A simple heating of this ligand with $[Fe_2(CO)_9]$ in toluene provided, not the expected cyclopentadienone iron(0) tricarbonyl complex **Fe2**, but the cyclopentadienyl iron(II) complex **Fe3** in 49 % yield, through a redox process (Scheme 1). To unambiguously establish the atom connectivity in complexes **Fe3**, single crystals were grown by slow diffusion of pentane in a dichloromethane solution of **Fe3**. Suitable single crystals were obtained and subjected to X-ray diffraction (XRD). Thermal ellipsoid representations are shown in Figure 1. This structure presents a slight distortion of the piperazine-type ring. The phenyl ring and the cyclopentadienyl ring are not coplanar (torsion angle = 63.28(19)°), like in complex **Fe1**, maintaining steric hindrance around the metal center.[22] The C-N bonds are also a relevant feature of this complex. The C_1-N_1 bond length was measured (1.341(6) Å) and was comparable to the Csp^2-N bond lengths of the piperazine ring (1.324(6) and 1.360(6) Å). This length is also comparable to the Csp^2-N bond length reported by Casey in an aminocyclopentadienyl ruthenium complex.[29] These observations confirm the η^5-coordination of the ancillary ligand.

To investigate the electron density on the cyclopentadienyl motif in **Fe3**, CO-bond IR stretching frequencies were investigated and compared both with the known $[(\eta^5\text{-}C_5H_5)Fe(CO)_3]^+$ and with our previous complex **Fe1**.[24, 30] The CO stretching frequencies were at 2042, 1992 and 1965 cm^{-1} in complex **Fe3**, while they were at 2120 and 2068 cm^{-1} in $[(\eta^5\text{-}C_5H_5)Fe(CO)_3]^+$ and at 2027, 1962, and 1947 cm^{-1} in **Fe1**. The experimentally measured frequencies indicated a more important back donation of the iron center to carbonyl ligand in **Fe3** compared to $[(\eta^5\text{-}C_5H_5)Fe(CO)_3]^+$, and consequently a more important electron density on the Fe(II) metal center. Furthermore, these analyses highlighted also that the electron density was similar in complexes **Fe3** and **Fe1**, albeit the oxidation numbers are not identical.

Chart 1. Cyclopentadienone iron tricarbonyl complexes: Transition Metal Frustrated Lewis Pairs.

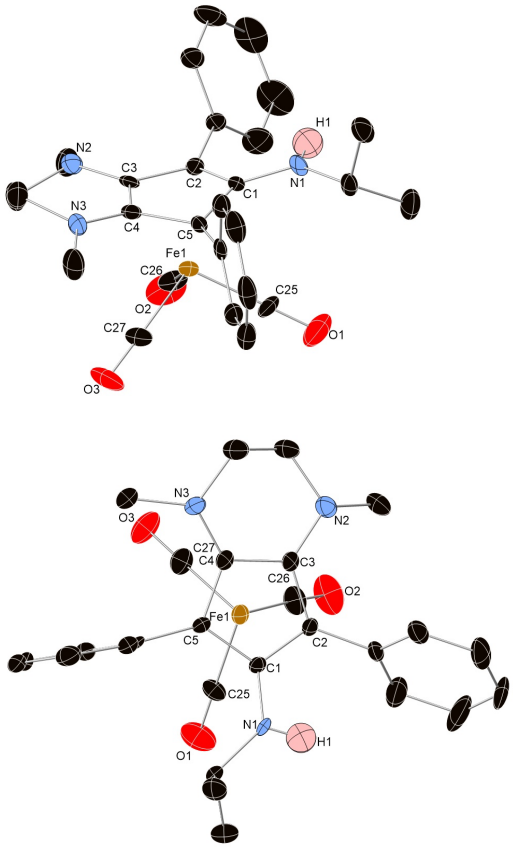


Scheme 1. Synthesis of cationic iron complex Fe3



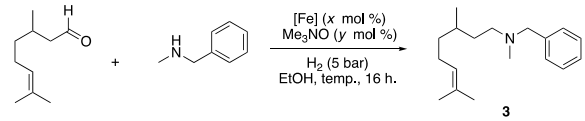
(i) $Et_3O^+BF_4^-$ (1 equiv.), CH_2Cl_2.; (ii) $iPrNH_2$ (1 equiv.), CH_2Cl_2 (overall yield: 51 %, two steps); (iii) $Fe_2(CO)_9$ (2 equiv.), toluene, Δ (yield: 45 %)

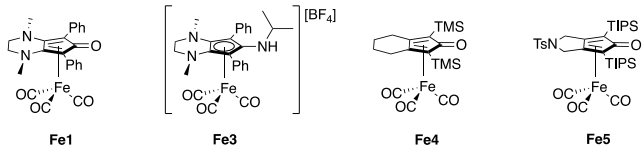
Figure 1. Thermal ellipsoid representations (50 % probability) of complex Fe3. Hydrogen atoms, except for the NH*i*Pr group, and BF_4 anion were omitted for clarity.



The catalytic activity of this new iron complex **Fe3** was initially evaluated in a model reductive amination between citronellal and *N*-methylbenzylamine and compared with previous catalysts (**Fe1**, **Fe4** and **Fe5**, see Table 1).[23-24] The Knölker's complex **Fe4** and the modified Knölker's type **Fe5** required high temperature (85 °C, entries 1-2, Table 1) while **Fe3** (under 10 bar of molecular hydrogen) was as active as our previous complex **Fe1** at 45 °C in ethanol (100 % conversion in both cases, entries 3-4, Table 1). But, to our delight, **Fe3** was also active at room temperature, unlike **Fe1** (entries 5-6, Table 1). When the catalyst loading was lowered to 1 mol %, the chemical yield in alkylated amine reduced a little from 91 to 74 % (entries 7-8, Table 1). A rapid monitoring of the conversion over time showed that the reaction started rapidly (20 % conversion after 1 h) but the reaction rate decreased in time (36 % conversion after 3 h, and 60 % conversion after 6 h). Such trend might be due to some catalyst decomposition or inhibition during the course of the reductive alkylation.

Table 1. Fe-catalyzed reductive alkylation of *N*-methyl benzylamine with citronellal[a]



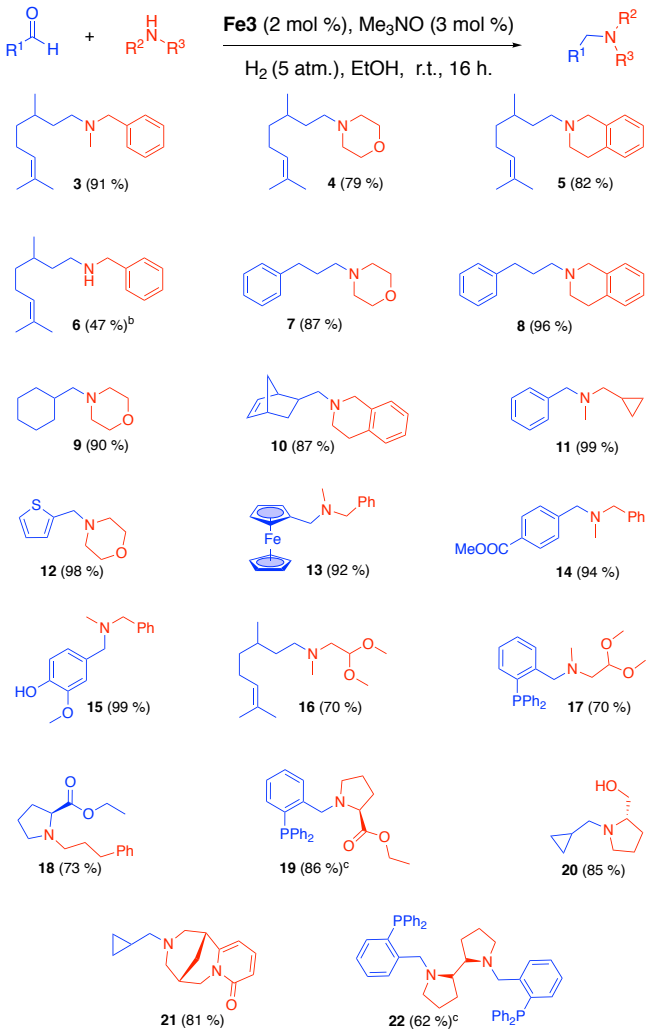


entry	catalyst (x mol %)	Me_3NO (y mol %)	temp. (°C)	yield[b] (%)
1	**Fe4** (5)	7.5	85	67
2	**Fe5** (5)	7.5	85	83
3	**Fe1** (2.5)	3.75	45	83 (100[d])
4	**Fe3** (2)	3.0	45	(100[d])
5	**Fe1** (2)	3.0	r.t.	N. R.
6[c]	**Fe3** (2)	3.0	r.t.	(100[d])
7	**Fe3** (2)	3.0	r.t.	91 (100[d])
8	**Fe3** (1)	1.5	r.t.	74

[a] General conditions: aldehyde (0.5 mmol, 1 equiv.), amine (0.6 mmol, 1.2 equiv.), under 5 bar of hydrogen in ethanol (1 mL) for 16 h. [b] Isolated yields. [c] 10 bar of hydrogen. [d] Conversion determined by ^{1}H-NMR spectroscopy.

With these conditions in hands and to validate our initial hypothesis, we decided to explore the scope and limitations of the reductive amination, initially between simple amines and aldehydes (amines **3-12**, Table 2), secondly with functionalized ones (amines **13-22**, Table 2). Reaction of citronellal, 3-phenylpropanal and cyclohexyl carboxaldehyde with various amines led to the corresponding alkylated amines **3-11** in good yields (79-99 %, Table 2). On a gram scale, as example, compound **3** was isolated in 88% yield, showing the robustness of this procedure. Neither the reduction of isolated alkene nor a cyclopropyl ring opening has been observed (amines **3-6**, **10-11** Table 2). Both secondary and primary amines could be used, albeit the latter led to lower yields (amines **3-6**, Table 2).

Table 2. Fe3-catalyzed reductive alkylation of amines[a]



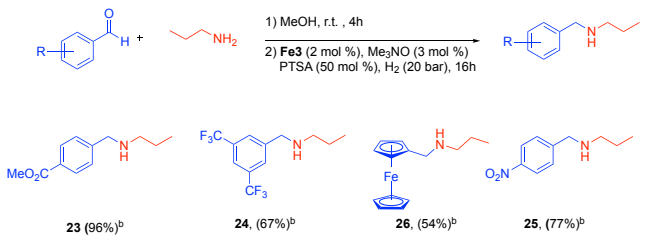
[a] General conditions: aldehyde (0.5 mmol, 1 equiv.), amine (0.6 mmol, 1.2 equiv.), **Fe3** (2 mol %), Me_3NO (3 mol %), under 5 bar of hydrogen in ethanol (1 mL) for 16 h at room temperature. Yield was based on isolated product. [b] 20 bar of hydrogen. [c] when **Fe1** (2.5 mol %) was used instead of **Fe3** with Me_3NO (3.75 mol %), under 5 bar of hydrogen in ethanol (1 mL) for 16 h at 45 °C, no reaction occured.

Aromatic aldehydes bearing either electron donating or electron withdrawing substituents could also be engaged in this reductive amination without noticeable decrease of the chemical yields (amines **12-15**, 92-99 %, Table 2). In the same reaction conditions (2 mol % of **Fe3**, 3 mol % of Me_3NO at room temperature under 5 bar of hydrogen), neither aliphatic nor aromatic ketones underwent reductive amination. Other reducible function, such as ester, remained intact and the amine **14** was isolated in 94 % yield. As mentioned above, benzylamine was used in the reductive amination but the corresponding alkylated amine was isolated in moderate yield. To extend this protocol to other primary amines, a modification of the reaction conditions has to be set up and a substoichiometric amount of an acid has to be added to generate an iminium intermediate. In these conditions, alkylated amines were isolated in moderate to excellent yields (54-96 %, Scheme 2). Other reducible functions, such as ester, nitro group or trifluoromethyl substituent, were tolerated (Scheme 2).

As limitation of the scope, unlike the reactivity observed with **Fe1**, no reductive amination occurs with pyridine carboxaldehyde in the presence of our new complex **Fe3**. As observed by ^{1}H-NMR analysis, pyridine moiety reacts with the iron centre and leads to decomposition of the complex.

Next, we turned our attention to more functionalized amines and aldehydes. Remarkably, unprotected phenol and acetal were tolerated (amines **15-16**, Table 2). Whereas phosphines are known to coordinate cyclopentadienyl iron(0) dicarbonyl complexes,[26a] the 2-diphenylphosphinebenzaldehyde could be used as alkylating agent with this new iron(II) complex and the functionalized amino-phosphine **17** was isolated in 70 % yield. No reaction occurred at 45 °C in the presence of **Fe1**, demonstrating the higher efficiency of the new catalyst over its previous congeners. It is also worth to note that a chiral aminoester such as (*S*)-proline ester could also be used with aliphatic and aromatic aldehydes and the corresponding alkylated amines **18-19** were obtained in 73-86% yield. Similarly, chiral amino-alcohols (such as (*S*)-prolinol)) or amino-amide (such as cytisine) could be alkylated in high yield and the corresponding alkylayed amines **20-21** were isolated in 81-85 %. Finally, a PNNP ligand **22** was prepared in 62 % yield in one step from the commercially available 2-diphenylphosphinebenzaldehyde and (2*R*, 2'*R*)-2,2'-bipyrrolidine.[31]

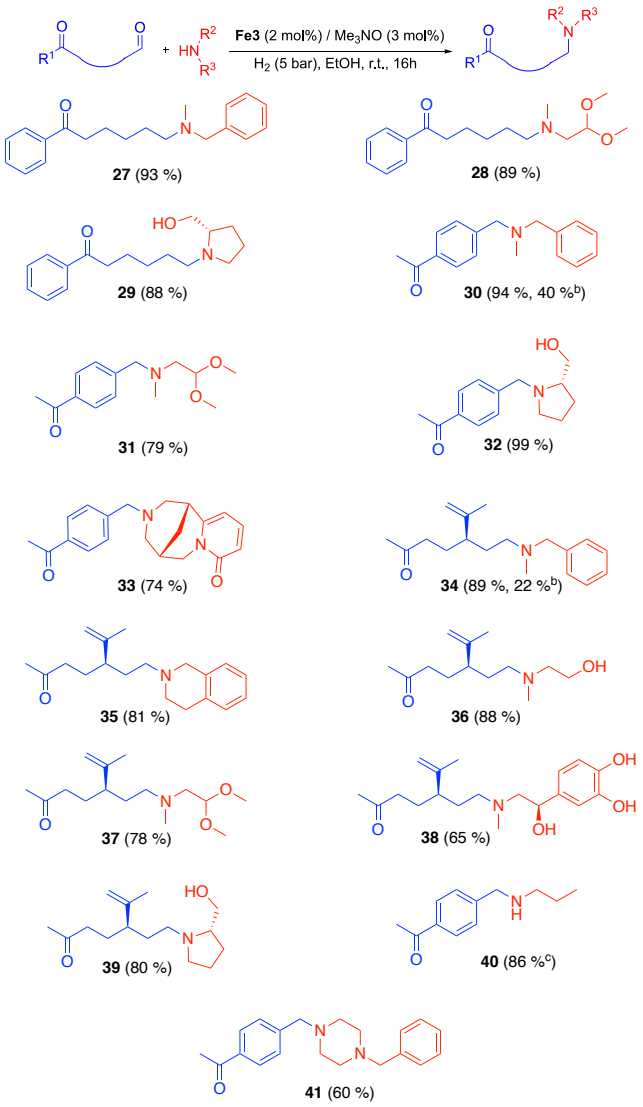
Scheme 2. Fe3-catalyzed reductive alkylation of primary amines[a]



[a] General conditions: aldehyde (0.5 mmol, 1 equiv.), amine (0.6 mmol, 1.2 equiv.), PTSA (50 mol%) under 20 bar of hydrogen in ethanol (1 mL) for 16 h. [b] Isolated yields.

As mentioned previously, selectivity is a key factor not only in organic synthesis but also for the development of sustainable chemical processes. Catalysts exhibiting complete selectivity for aldehydes over ketones are still under estimated and even rather unexplored.[8-12, 32] We showed that ketones remained non-reactive in the reaction conditions (*vide supra*), so a chemoselective reductive amination of aldehyde in the presence of a ketone function should be feasible and would bring a breakthrough not only in catalysis but also in organic synthesis. For this study, three keto-aldehydes, representing the two different classes (aliphatic and aromatic) of carbonyl functions, were engaged in the reductive amination conditions. Reductive alkylation of amines with keto-aldehydes furnished, in the presence of the new phosphine-free iron(II) complex **Fe3** under hydrogen pressure at room temperature, exclusively the aminoketones **27-41**. Neither reductive amination of the ketone functions, nor direct reduction of ketones was noticed (Table 3).

Table 3. Fe3-catalyzed chemoselective reductive alkylation of amines.[a]



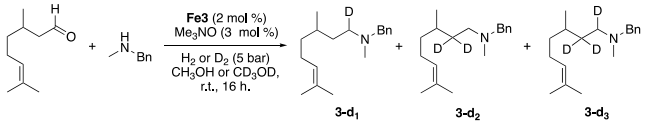
[a] General conditions: aldehyde (0.5 mmol, 1 equiv.), amine (0.6 mmol, 1.2 equiv.), **Fe3** (2 mol %), Me_3NO (3 mol %), under 5 bar of hydrogen in ethanol (1 mL) for 16 h at room temperature. Yield was based on isolated product. [b] **Fe1** (2.5 mol %) was used instead of **Fe3**, with Me_3NO (3.75 mol %), under 5 bar of hydrogen in ethanol (1 mL) for 16 h at 45 °C. [c] Reductive amination procedure as described in Scheme 2.

In more details, with the 6-phenyl-6-oxo-hexanal, alkylated amines **27-29** were isolated in 88-93 % yield. Non-protected alcohol, benzyl or acetal function, were tolerated (Table 3). With the same amines in the presence of 4-acetylbenzaldehyde, the same conclusions could be drawn and the corresponding alkylated amines **30-33** were obtained in 79-99 % yield (Table 3). Cytisine reacted with this ketoaldehyde to furnish the alkylated amine **33** in 74 % yield (Table 3). With the more challenging 3-(propen-2'-yl)-6-oxo-heptanal having both aliphatic carbonyl functions, the reductive alkylation of substituted amines provided the corresponding compounds **34-39** in high yields (65-88 %, Table 3). Again, non-protected phenol and alcohols (such as in prolinol, *N*-methylaminoethanol, adrenaline), and acetal could be introduced without any depletion of the chemical yields. As many drugs contain a piperazine framework, *N*-methylpiperazine was engaged in this alkylation as a model substrate (Table 3). The corresponding alkylated amine **41** was isolated chemoselectively in 60 % yield. Finally, the reductive amination between propylamine and 4-acetylbenzaldehyde led to compound **40** in 86% yield (Table 3). In the presence of **Fe1** instead of **Fe3**, the reductive alkylation of *N*-methylbenzylamine with 4-acetylbenzaldehyde and 3-(propen-2'-yl)-6-oxo-heptanal occurred at 45 °C albeit in much lower yields (40 and 22 %, respectively, Table 3) and no reaction was observed at room temperature. To highlight the robustness of our protocol, the reductive alkylation of *N*-methylamino acetaldehyde dimethyl acetal with 3-(propen-2'-yl)-6-oxo-heptanal was carried out on a 5 mmol scale and the corresponding alkylated amine **37** was isolated in 88 % yield.

In order to have some mechanistic insights, both deuterium-labeling experiment (Table 4, Scheme 3) and DFT calculations were undertaken (Figures 2-5).[33]

Full deuterium incorporation was observed at the C1 position (the former carbonyl function, compound **3-d$_1$**) under D_2 pressure in methanol, while an incomplete incorporation was noticed at the C2 atom (compound **3-d$_2$**) under hydrogen pressure in deuterated methanol (entries 1-2, Table 4). Finally the deuterated compound **3-d$_3$** was obtained in deuterated methanol under D_2 pressure (again a full incorporation at the C1 position and a partial one at the C2, entry 3, Table 4). When 3-(propen-2'-yl)-6-oxo-heptanal and *N*-methylbenzylamine were engaged in the reduction process in deuterated methanol, the amino derivative **27-d** was isolated in 75 % yield (Scheme 3). Incorporation of deuterium occurred only at the β-position of the amino group and at the α-positon of the ketone (Scheme 3). All these deuterium-labeling experiments underline first the presence of iminium/enamine equilibrium and second the exclusive reduction of the iminium intermediate.

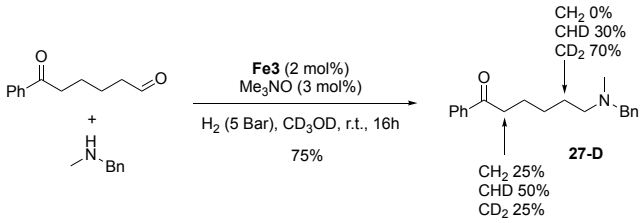
Table 4. Deuteration reaction[a]



entry	solvent	reductant	product
1	CH_3OH	D_2	**3-d$_1$** (100% at C1)
2	CD_3OD	H_2	**3-d$_2$**
3	CD_3OD	D_2	**3-d$_3$** (100% at C1)

[a] General conditions: aldehyde (0.5 mmol, 1 equiv.), amine (0.6 mmol, 1.2 equiv.), under 5 bar of a reductant gas (H_2 or D_2) in solvent (1 mL) for 16 h. Yield was based on isolated product.

Scheme 3. Deuteration reaction of ketoaldehyde[a]



[a] General conditions: aldehyde (0.5 mmol, 1 equiv.), amine (0.6 mmol, 1.2 equiv.), under 5 bar H_2 in CD_3OD (1 mL) for 16 h. Yield was based on isolated product.

To unveil how the reaction pathway is modified, switching from the relatively high temperature demanding cyclopentadienone iron tricarbonyl complexes **Fe4** or **Fe5** to the new cationic **Fe3** (see Figures 2-5), we underwent DFT calculations. The activation of catalyst **Fe3**, that generated a vacant site through the release of a carbon dioxide molecule, was more facile compared to the CO removing previously described for **Fe1** and **Fe4** (see Figure 4).[23b, 24] This step was for **Fe3** 3.3 and 6.2 kcal/mol less kinetically demanding than with **Fe1**, taking into account or not the BF_4 anion, respectively; thus, improving significantly the generation of the catalytic active species (Figure 4 and Table 5 for the energy barriers for the sake of comparison). The next step leading to intermediate **III** was the coordination of a hydrogen molecule to iron and did not require a high barrier of energy. Then, two competing pathways could be suggested. In the first one, ethanol could be involved as a proton shuttle and participate to the hydrogen bond cleavage (**III** to **IV**, Figure 2 and Figure 4). This step required an energy barrier of 23.7 and 20.6 kcal/mol, taking into account or not the BF_4 anion, respectively.

Table 5. Energy barriers for Fe1, Fe3 and Fe4.[a]

Step	**Fe1**	**Fe3** (without BF_4)	**Fe3**	**Fe4**
I-II	20.7	14.5	17.4	19.6
II-III	6.0	3.7	4.9	4.0
III-III'	7.2	8.4	27.9	13.8
III'-V	-5.8 (6.3)[a]	10.8	11.6 (13.0)[a]	0.3 (7.6)[a]
III-IV	15.2	20.6	33.7	18.9

[a] in parenthesis calculated from **III**

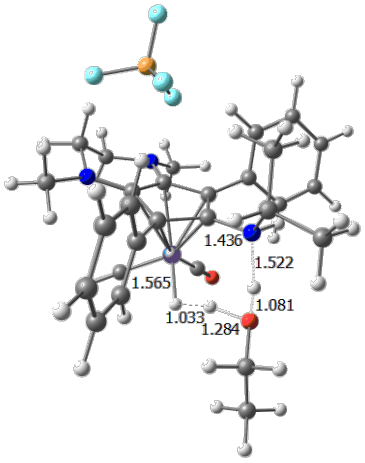


Figure 2. Transition states III-IV for Fe3 (main distances in Å).

The second possible pathway implied an external amine molecule to deprotonate one of the hydrogen atoms on the metal centre in intermediate **III** (see Figures 3 and 4). The latter step is kinetically disfavored by 5.8 kcal/mol with respect to the traditional **III-IV** step (see Figures 2-4), but the deprotonated intermediate **III'** is somewhat thermodynamically favored, especially if BF_4 anion was not included (12.5 kcal/mol).

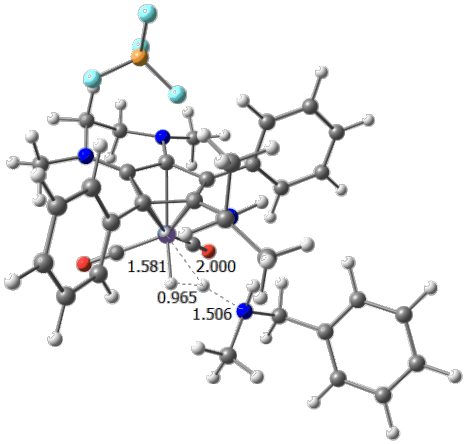


Figure 3. Transition states III-III' for Fe3 (main distances in Å).

Regarding the mechanism for **Fe1** and **Fe4**, this deprotonation mechanism is even more favored kinetically, however the equilibrium is displaced towards the previously described non-deprotonated intermediate **III**, by 12.1 and 7.2 kcal/mol, respectively (Figure 5), and **III'** is again disfavored by 19.5 and 14.8 kcal/mol, respectively, with respect to intermediate **IV**. Consequently this deprotonation mechanism might potentially only slow down the catalytic activity for both neutral complexes. Based on these calculations, the new complex **Fe3** seems also to not act as a bifunctional complex.

Finally, the last step of the reaction mechanism led to the organic product once protonated the methylidene moiety of the cationic organic moiety overcoming a rather low energy barrier for all catalysts. However this step becomes generously displaced towards the product with **Fe3** by 8.5 kcal/mol, whereas it is nearly isoenergetic for **Fe1**, and particularly rather disfavored for **Fe4** by 6.4 kcal/mol. This trend is in perfect agreement with experiments. Alternatively the other two other nitrogen atoms of the ligand in **Fe3** were also tested in the hydrogen cleavage, taking into consideration an isomer of intermediate **III**, where both carbonyls on the iron center have rotated of 120º (see SI). Thus, the H_2 moiety was placed below any of both amines of the six-member ring of the cyclopentadienyl ring. Since the homologous species **III**, **IV** and **V**, and the transition states that link them displayed close energy values to the ones in Figure 4, the potential active role of this pathway could not be ruled out.

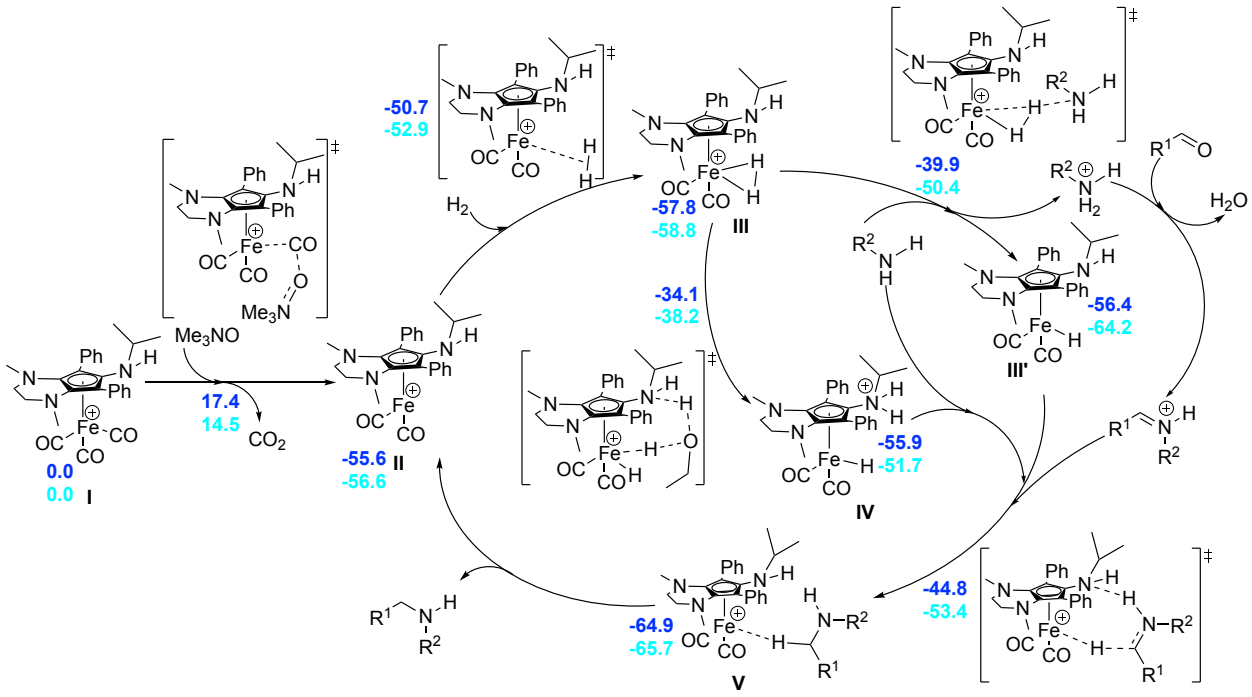


Figure 4. Energy profile for Fe3-catalyzed chemoselective reductive alkylation of amines (R^1 = CH_2CH_3, R^2 = $CH_2(Ph)$); Gibbs free energies in solvent in kcal/mol for Fe3 in blue, and BF_4 anion was omitted for clarity; in light blue without including BF_4 anion in the calculations.

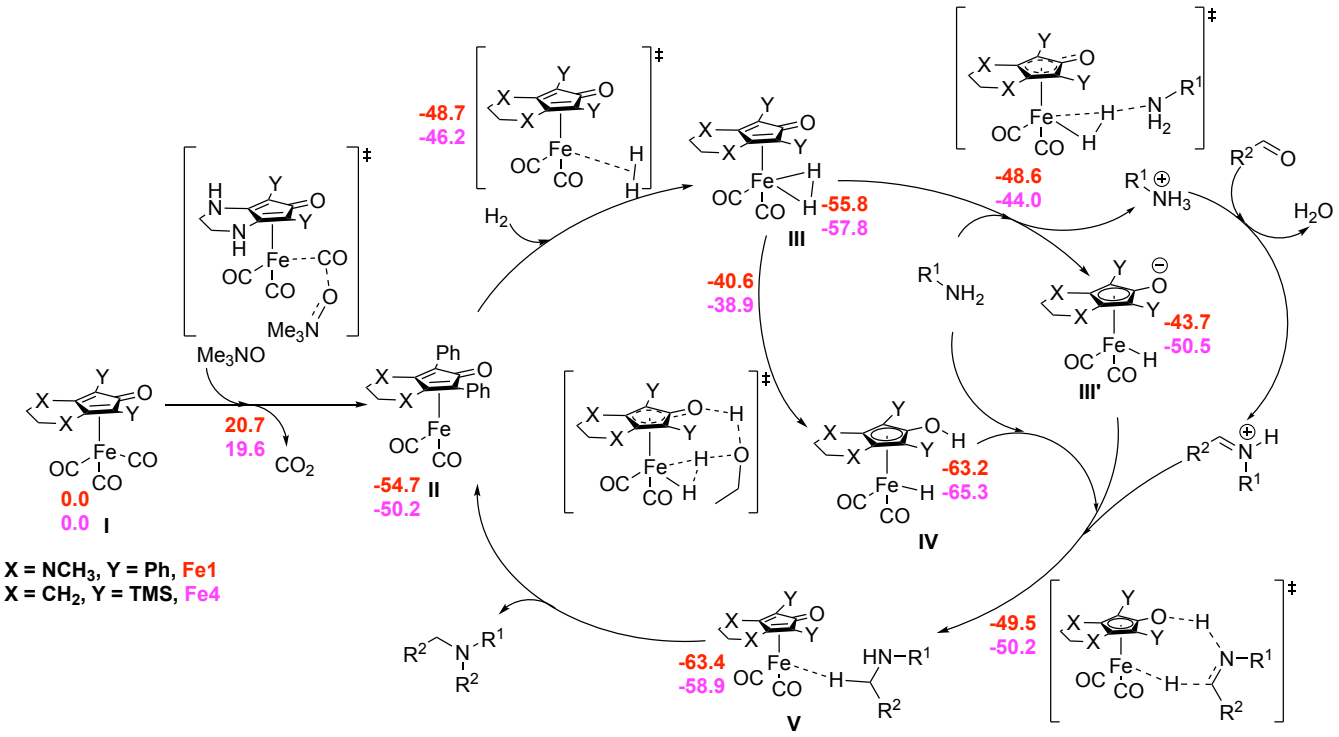


Figure 5. Energy profile for Fe1 and Fe4-catalyzed reductive alkylation of amines (R^1 = CH_2CH_3, R^2 = $CH_2(Ph)$); Gibbs free energies in solvent in kcal/mol for Fe1 and Fe4 in red and violet, respectively.

CONCLUSIONS

In summary, we have synthesized and fully characterized a well-defined phosphine free iron(II) complex bearing an electron-rich cyclopentadienyl framework. Its efficiency was not only demonstrated through the reductive alkylation of functionalized amines with a broad range of carbonyl derivatives (other reducible functions, unprotected alcohols, phosphine moiety, etc… were tolerated on both partners of this reaction) but also through the chemoselectivity of this process. Amines were isolated in moderate to high yields at room temperature. To the best of our knowledge, these examples represent the

first chemoselective reductive amination of aldehydes with an Earth abundant metal complex or a FLP catalyst at room temperature under hydrogen pressure. Moreover, compared to the most recent work in reductive alkylation,[17c, 22] no molecular sieves is required. Mechanistically, DFT calculations rationalized the trend of reactivity **Fe4** < **Fe1** << **Fe3**, and highlighted the active role of the base (amine) in the activation of hydrogen in the presence of the cationic **Fe3**. This base facilitated also the protonation and release of the product, not basically by kinetics, but thermodynamics. These results open a route to environmentally acceptable atom-efficient procedure to functionalized amines. Further work will be dedicated first to extend and apply such transition metal in the activation of hydrogen, and other small molecules, in the presence of various unsaturated compounds, second to develop new chemoselective processes.

Experimental Part

General Considerations: All air- and moisture-sensitive manipulations were carried out using standard vacuum line Schlenk tubes techniques. Dry toluene was dried using a solvent purification system from Innovative Technologies, by passage through towers containing activated alumina. Xylene was purchased from Carlo Erba and was distillated over sodium and stocked over 4Å molecular sieves. Both were deglazed prior to use by bubbling argon gas directly in the solvent. Other solvents and chemicals were purchased from different suppliers and used as received. Neutral alumina was purchased from Alfa Aesar (Brockmann Grade I, 58 Angstroms, -60 Mesh Powder, S.A. 150 m^2/g) and silica from Carlo Erba (60Å 40-63µ). Deuterated solvents for NMR spectroscopy were purchased from Sigma Aldrich and used as received. NMR spectra were recorded on a 500 MHz Brücker spectrometer. Proton (^{1}H) NMR information is given in the following format: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet), coupling constant(s) (*J*) in Hertz (Hz), number of protons. The prefix *app* is occasionally applied when the true signal multiplicity was unresolved and *br* indicates the signal in question broadened. Carbon (^{13}C or DEPTQ) NMR spectra are reported in ppm (δ) relative to $CDCl_3$ unless noted otherwise. Infrared spectra were recorded over a PerkinElmer Spectrum 100 FT-IR Spectrometer using neat conditions. HRMS analyses were performed with Acquity UPLC H-Class Xevo G2-XS QTof (WATERS) by Laboratoire de Chimie Moléculaire et Thioorganique analytical Facilities Optical rotation was measured in chloroform, at 25 °C over a Jasco P-2000 polarimeter using a sodium lamp (589 nm) with a concentration of 3.5 10^{-3}g.mL^{-1}. The ligand **1** was prepared according to the previously reported procedure.[20]

N-(1,4-dimethyl-5,7-diphenyl-3,4-dihydro-1H-cyclopenta[b]pyrazine-6(2H)-ylidene)propan-2-aminium tetrafluroborate **2**: According to the procedure previously reported by Gompper,[28] starting from ligand **1** (3.13 mmol, 1 equiv, 1.0 g) in presence of triethyloxonium tetrafluoroborate (3.16 mmol, 1 equiv, 900 mg) and isopropylamine (3.16 mmol, 1 equiv, 0.27 mL), the cationic ligand **2** was obtained as a deep blue powder (647 mg, 51 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.26 (m, 8H), 7.22-7.17 (m, 2H), 5.61 (d, *J* = 9.8 Hz, 1H), 3.53 (ddd, *J* = 12.6; 8.5; 5.6 Hz, 4H), 3.29 (dhept, *J* = 9.8; 6.3 Hz, 1H), 2.65 (s, 3H), 2.64 (s, 3H), 0.78 (d, *J* = 6.3 Hz, 6H) ppm. ^{11}B-NMR ($CDCl_3$, 128 MHz) δ -0.91 ppm. ^{19}H-NMR ($CDCl_3$, 400 MHz) δ -153.7 ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz) δ 172.8, 154.6, 145.9, 133.2, 132.9 (2C), 132.4 (2C), 130.0, 129.3 (2C), 129.1 (2C), 129.0 (2C), 96.1, 90.5, 50.7, 49.3, 47.0, 41.9, 41.6, 23.3 (2C) ppm. IR (neat) 3328, 2977, 1625, 1569, 1513, 1465, 1367, 1335, 1335, 1157, 1101, 1053, 954, 732, 706, 520 cm^{-1}. HRMS (ESI+) *m/z*: $[M\text{-}BF_4]^+$ Calcd for $C_{24}H_{28}N_3$ 358.2283; Found 358.2288.

Synthesis of iron complex **Fe3**: In a 100 mL Schlenk tube, equipped with a stirring bar, under argon, cationic ligand (1.12 mmol, 1 equiv, 500 mg) and iron nonacarbonyl (2.35 mmol, 2.1 equiv, 860 mg) were suspended in dry free-O_2 toluene (20 mL). The mixture was heated at 110 °C for 18 hours. The black mixture was cooled down to room temperature and concentrated to dryness under vacuum. The dark solid was solubilized in methylene chloride (30 mL) and filtrated over a pad of Celite® and organics were evaporated. The crude product was purified by flash column chromatography on silica (ethyl acetate) and the pure complex **Fe3** was isolated as a gold orange powder (295 mg, 45 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.60-7.50 (m, 10H), 3.69 (ddd, *J* = 10.6; 6.8; 3.6 Hz, 2H), 3.03 (d, *J* = 9.2 Hz, 1H), 2.88 (ddd, *J* = 10.6; 6.8; 3.6 Hz, 2H), 3.83-2.77 (m, 1H), 2.35 (s, 6H), 0.69 (d, *J* = 6.4 Hz, 6H) ppm. ^{11}B-NMR ($CDCl_3$, 128 MHz) δ -0.85 ppm. ^{19}H-NMR ($CDCl_3$, 400 MHz) δ -152.9 ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz) δ 208.5 (3C), 138.1, 130.4 (6C), 129.8 (4C), 128.5 (2C), 118.2 (2C), 67.5 (2C), 49.7 (2C), 45.5, 40.2 (2C), 23.1 (2C) ppm. IR (neat): 3372, 2042, 1992, 1965, 1570, 1539, 1506, 1483, 1445, 1418, 1367, 1277, 1048, 1032, 754, 704 cm^{-1}. HRMS (ESI+) *m/z*: $[M\text{-}BF_4]^+$ Calcd for $C_{27}H_{28}FeN_3O_3$ 498.1480; Found 498.1492. HRMS (ESI-) *m/z* $[BF_4]$ Calcd for BF_4^- 87.0029; Found 87.0033.

Preparation of keto-aldehyde **42**:[34] In a 100 mL round bottom flask equipped with a stirring bar, (*R*)-Limonene (15 mmol, 1 equiv, 2.3 mL) was solubilized in dry methylene chloride (50 mL) and cooled down to 0 °C with an ice bath. 3-Chloroperbenzoic acid (16 mmol, 1.05 equiv, 2.76 g) was added slowly by portion over 10 minutes. The reaction was stirred 1 hour at 0 °C, then quenched by $NaHCO_3$ aqueous saturated solution (20 mL). Organic phase was separated and aqueous phase was washed twice with dichloromethane (2x20 mL). Organics were combined, dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Purification of the crude by silica flash column chromatography, afforded the pure epoxide intermediate, which was directly engaged in the next step. The crude epoxide was solubilized in a 1/1 mixture of THF/H_2O (20 mL). Sodium periodate (22.5 mmol, 1.5 equiv, 4.8 g) was added and the reaction was stirred at room temperature for 1 hour. The mixture was extracted with dichloromethane (3x20 mL) and the organic layers were dried over Na_2SO_4, filtrated and concentrated *in vacuo.* The crude product was purified by silica flash column chromatography (Pentane/Et_2O 9:1) and the pure keto-aldehyde **42** was obtained as a colorless oil (1.96 g, 78 %). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 9.67 (s, 1H), 4.84-4.81 (m, 1H), 4.77-4.76 (m, 1H), 2.70-2.64 (m, 1H), 2.45 (dd, *J* = 7.9; 2.5 Hz, 1H), 2.43 (dd, *J* = 7.9; 2.5 Hz, 1H), 2.39 (t, *J* = 7.4 Hz, 2H), 2.13 (s, 3H), 1.75-1.67 (m, 1H), 1.63 (br. s, 3H), 1.61-1.57 (m, 1H) ppm. ^{13}C{1H}-NMR ($CDCl_3$, 125 MHz) δ 208.3, 201.8, 145.1, 113.3, 47.5, 40.9, 40.8, 30.1, 26.4, 18.4 ppm. $[\alpha]_D^{25}$ = -3.2 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

Synthesis of 6-Oxo-6-phenylhexanal **43**:[35] In a 100 mL round bottom flask equipped with a stirring bar, 2-phenylcyclohexene (20 mmol, 1 equiv, 3.18 mL) was solubilized in dry methylene chloride (50 mL) and cooled down to 0 °C with an ice bath. 3-Chloroperbenzoic acid (50 % wt) (22 mmol, 1. equiv, 7.6 g) was added slowly by portion over 10 minutes. The reaction was stirred for 1 hour at 0 °C, then quenched by a saturated aqueous solution of $NaHCO_3$ (20 mL). The organic phase was separated and the aqueous phase was extracted twice with dichloromethane (2x20 mL). The organic phases were combined, dried over $MgSO_4$, filtrated and concentrated under vacuum. The crude product was purified by flash column chromatography on silica (Pentane/Et_2O 95:5), the pure epoxide intermediate was then directly engaged in the next step. The epoxide intermediate was solubilized in a 1/1 mixture of THF/H_2O (30 mL). Sodium periodate (30 mmol, 1.5 equiv, 6.41 g) was added and the reaction was stirred at room temperature for 18 hours. The mixture was extracted with dichloromethane (3x20 mL) and the organic layers were dried over Na_2SO_4, filtrated and concentrated under vacuum. The crude product was purified by flash column chromatography on silica (Pentane/Et_2O 8:2) and the pure keto-aldehyde **43** was obtained as a white solid (1.81 g, 48 %). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 9.78 (s, 1H), 7.95 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.0 Hz, 2H), 2.51 (t, *J* = 7.0 Hz, 2H), 1.82-1.69 (m, 4H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz) δ 202,0, 199.7, 136.9, 133.0, 128.6 (2C), 127.9 (2C), 43.8, 38.1, 23.6, 21.7 ppm.

Reductive amination

General Procedure A: In a 10 mL autoclave equipped with a stirring bar, under argon, aldehyde (0.5 mmol, 1 equiv), secondary amine (0.6 mmol, 1.2 equiv), **Fe3** (0.01 mmol, 2 mol %, 5.86 mg) and trimethylamine *N*-oxide (0.015 mmol, 3 mol %, 1.2 mg) were solubilized in free-O_2 ethanol (1 mL). The autoclave was sealed and pressurized

with hydrogen (5 bar), and the mixture was stirred for 16 hours at room temperature. The reaction was extracted with dichloromethane (10 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtrated and the solvent was removed under vacuum. The crude product was purified by flash column chromatography on silica.

General Procedure B: In a 10 mL autoclave equipped with a stirring bar, under argon, aldehyde (0.5 mmol, 1 equiv), benzylamine (0.6 mmol, 1.2 equiv), **Fe3** (0.01 mmol, 2 mol %, 5.86 mg) and trimethylamine *N*-oxide (0.015 mmol, 3 mol %, 1.2 mg) were solubilized in free-O_2 ethanol (1 mL). The autoclave was sealed and pressurized with hydrogen (10 bar), and the mixture was stirred for 16 hours at room temperature. The reaction was extracted with dichloromethane (10 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtrated and solvent was removed under vaccum. The crude product was purified by flash column chromatography on silica.

General Procedure C: In a 10 mL autoclave equipped with a stirring bar, under argon, aldehyde (0.5 mmol, 1 equiv), primary amine (0.6 mmol, 1.2 equiv), **Fe3** (0.01 mmol, 2 mol %, 5.86 mg) were solubilized in free-O_2 ethanol (1 mL) and stirred at room temperature for 4h. Then trimethylamine *N*-oxide (0.015 mmol, 3 mol %, 1.2 mg) and *p*-toluenesulfonic acid (0.25 mmol, 50 mol %, 43 mg) were added. The autoclave was sealed and pressurized with hydrogen (20 bar), and the mixture was stirred for 16 hours at room temperature. The reaction was extracted with dichloromethane (10 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtrated and solvent was removed under vacuum. The crude product was purified by flash column chromatography on silica gel.

N-Benzyl-N-3,7-trimethyloct-6-en-1-amine (**3**):[36] According to the general procedure A, starting from (±)-citronellal (0.5 mmol, 1 equiv, 90 µL) and *N*-benzylmethylamine (0.6 mmol, 1.2 equiv, 80 µL), **3** was obtained as a colorless oil after purification by silica flash column chromatography (Pentane/EtOAc 95/5) (118 mg, 91 %). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.29-7.17 (m, 5H), 5.04 (t, *J* = 7.1 Hz, 1H), 3.44 (q, *J* = 13.0 Hz, 1H), 2.35 (t, *J* = 7.6 Hz, 2H) ppm. $^{13}C\{^1H\}$-NMR δ 139.3, 131.1, 129.1 (2C), 128.2 (2C), 126.9, 124.9, 62.4, 55.6, 42.3, 37.3, 34.4, 30.9, 25.8, 25.5, 19.7, 17.7 ppm.

Scale up for **3**: In a 10 mL autoclave equipped with a stirring bar, under argon, (±)-citronellal (5 mmol, 1 equiv, 0.9 mL), *N*-benzylmethylamine (6 mmol, 1.2 equiv, 0.8 mL), **Fe3** (0.1 mmol, 2 mol %, 58.6 mg) and trimethylamine oxide (0.15 mmol, 3 mol %, 12 mg) were solubilized in free-O_2 ethanol (5 mL). The autoclave was sealed and pressurized with hydrogen (5 bar), and the mixture was stirred 18 hours at room temperature. The reaction was extracted with dichloromethane (30 mL) and washed twice with a saturated $NaHCO_3$ aqueous solution (2 x 20 mL), dried over $MgSO_4$, filtrated and solvent was removed *in vacuo*. The crude product was purified by silica flash column chromatography (Pentane/EtOAc 95/5) to afford the pure product **3** as a colorless oil (1.11 g, 86 %).

Morpholino-4-(3,7-dimethyl-6-octen-1-yl) (**4**):[37] According to the general procedure A, starting from (±)-citronellal (0.5 mmol, 1 equiv, 90 µL) and morpholine (0.6 mmol, 1.2 equiv, 55 µL) **4** was isolated, after filtration with pentane over a pad of Celite®, as a yellowish oil (89 mg, 79 %). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.02 (t, *J* = 7.0 Hz, 1H), 3.65 (t, *J* = 4.0 Hz, 4H), 2.42-2.32 (br. s, 4H), 2.32-2.22 (m, 2H), 1.98-1.83 (m, 2H), 1.61 (s, 3H), 1.53 (s, 3H), 1.50-1.42 (m, 1H), 1.40-1.35 (m, 1H), 1.29-1.17 (m, 2H), 1.14-1.06 (m, 1H), 0.82 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz) δ 131.2, 124.9, 67.1, 57.3, 52.9, 37.2, 33.6, 31.1, 25.9, 25.8, 19.7, 17.7 ppm.

2-(3,7-dimethyloct-6-en-1-yl)-1,2,3,4-tetrahydroisoquinoline (**5**):[38] According to the general procedure A, starting from (±)-citronellal (0.5 mmol, 1 equiv, 90 µL) and 1,2,3,4-tetrahydroisoquinoline (0.6 mmol, 1.2 equiv, 76 µL), **5** was isolated after purification by silica flash column chromatography (Pentane/Et_2O 9/1), as a yellowish oil (111 mg, 82 %). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.14-7.07 (m, 3H), 7.04-6.99 (m, 1H), 5.11 (t, *J* = 7.5 Hz, 1H), 3.63 (s, 2H) 2.91 (t, *J* = 6.0 Hz, 2H), 2.76-2.70 (m, 2H), 2.57-2.47 (m, 2H), 2.07-1.93 (m, 2H), 1.69 (s, 3H), 1.68-1.62 (m, 1H), 1.61 (s, 3H), 1.56-1.47 (m, 1H), 1.46-1.16 (m, 4H), 0.92 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz) δ 135.0, 134.4, 131.2, 128.7, 126.6, 126.1, 125.6, 124.8, 56.7, 56.4, 51.2, 37.3, 34.3, 31.1, 29.2, 25.8, 25.6, 19.8, 17.7 ppm.

N-Benzyl-3,7-dimethyl-6-octenylamine (**6**):[39] According to general procedure B, starting from (±)-citronellal (0.5 mmol, 1 equiv, 90 µL) and *N*-benzylamine (0.75 mmol, 1.5 equiv, 90 µL), **6** was isolated, after purification by silica flash column chromatography (Dichloromethane/MeOH 97/3), as a yellowish oil (58 mg, 47 %). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.34-7.31 (m, 4H), 7.28-7.23 (m, 1H), 5.08 (tt, *J* = 7.2; 1.4 Hz, 1H), 3.82-3.77 (m, 2H), 2.71-2.60 (m, 2H), 2.09-1.89 (m, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.59-1.51 (m, 1H), 1.50-1.44 (m, 1H), 1.38-1.27 (m, 2H), 1.19-1.11 (m, 1H), 0.87 (d, *J* = 6.8 Hz, 3H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz) δ 140.1, 131.2, 128.4 (2C), 128.3 (2C), 127.0, 124.9, 54.0, 47.3, 37.2, 37.1, 30.6, 25.7, 25.5, 19.6, 17.7 ppm.

1-(3-Phenylpropyl)morpholine (**7**):[40] According to the general procedure A, starting from 3-phenylpropionaldehyde (0.5 mmol, 1 equiv, 70 µL) and morpholine (0.6 mmol, 1.2 equiv, 55 µL), **7** was isolated, after filtration with pentane over a pad of Celite® , as a yellowish oil (89 mg, 87 %). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.31-7.25 (m, 2H), 7.21-7.16 (m, 3H), 3.72 (q, *J* = 4.6 Hz, 4H), 2.65 (t, *J* = 7.7 Hz, 2H), 2.47-2.40 (br. s, 4H), 2.37 (t, *J* = 7.7 Hz, 2H), 1.82 (quint, *J* = 7.7 Hz, 2H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz) δ 142.1, 128.4 (2C), 128.4 (2C), 125.8, 67.1 (2C), 58.4, 53.8 (2C), 33.7, 28.3 ppm.

1,2,3,4-tetrahydro-2-(3-phenylpropyl)-isoquinoline (**8**):[41] According to the general procedure A, starting from 3-phenylpropionaldehyde (0.5 mmol, 1 equiv, 70 µL) and morpholine (0.6 mmol, 1.2 equiv, 55 µL), **8** was isolated, after purification by silica flash column chromatography (Pentane/Et_2O 9/1), as a colorless oil (120 mg, 96 %). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.29-7.25 (m, 2H), 7.22-7.15 (m, 3H), 7.13-7.06 (m, 3H), 7.02-6.98 (m, 1H), 3.61 (s, 2H), 2.89 (t, *J* = 5.5 Hz, 2H), 2.73-2.65 (m, 4H), 2.53 (t, *J* = 7.5 Hz, 2H), 1.92 (quint, *J* = 7.5 Hz, 2H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz) δ 142.3, 134.9, 134.4, 128.7 (2C), 128.5, 128.4, 126.7, 126.1, 125.9, 125.8, 125.6, 57.9, 56.2, 51.0, 33.8, 29.2, 28.9ppm.

4-(Cyclohexylmethyl)morpholine (**9**):[42] According to the general procedure A, starting from cyclohexanecarboxaldehyde (0.5 mmol, 1 equiv, 60 µL) and morpholine (0.6 mmol, 1.2 equiv, 55 µL), **9** was isolated, after filtration with pentane over a pad of Celite®, as a yellowish oil (83 mg, 90 %). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.69 (t, *J* = 4.0 Hz, 4H), 2.41-2.33 (br. s, 4H), 2.11 (d, *J* = 7.0 Hz, 2H), 1.84-1.63 (m, 4H), 1.52-1.43 (m, 1H), 1.27-1.10 (m, 4H), 0.91-0.81 (m, 2H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz) δ 67.1 (2C), 66.2, 54.2 (2C), 34.7, 31.8 (2C), 26.8, 26.2 (2C) ppm.

2-({bicyclo[2.2.1]hept-5-en-2-yl}methyl)-1,2,3,4-tetrahydroisoquinoline (**10**): According to general procedure A starting from (0.5 mmol, 60 µL) and 1,2,3,4-tetrahydroisoquinoline (0.6 mmol, 1.2 equiv, 76 µL), **10** was isolated, after purification by flash column chromatography on silica gel (Pentane/Et_2O: 9/1), as a mixture of two diastereoisomers endo and exo in a 1:1 ratio (103 mg, 87 %). Diastereoisomer 1 ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.14-7.07 (m, 3H), 7.04-6.99 (m, 1H), 6.14-6.10 (m, 1H), 6.09-6.05 (m, 1H), 3.64 (q, *J* = 14.8 Hz, 2H), 2.90 (t, *J* = 5.8 Hz, 2H), 2.83 (s, 1H), 2.80-2.69 (m, 3H), 2.58-2.48 (m, 2H), 1.76-1.69 (m, 1H), 1.35 (s, 2H), 1.34-1.24 (m, 2H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ 136.8, 136.7, 135.1, 134.5, 128.7, 126.6, 126.0, 125.5, 64.5, 56.5, 51.3, 45.3, 45.2, 41.9, 36.5, 31.9, 29.0 ppm. IR (neat): ν 3059, 2959, 2757, 2760, 1498, 1455, 1378, 1334, 1127, 1097, 936, 740, 708 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{22}N$ 240.1752; Found 240.1753. $[\alpha]_D^{25}$= -280.2 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$). Diastereoisomer 2 ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.14-7.07 (m, 3H), 7.04-6.98 (m, 1H), 6.17-6.11 (m, 1H), 5.99-5.95 (m, 1H), 3.62 (q, *J* = 11.9 Hz, 2H), 2.97-2.86 (m, 3H), 2.79-2.77 (m, 1H), 2.77-2.72 (m, 1H), 2.70-2.63 (m, 1H), 2.32-2.25 (m, 1H), 2.19-2.13 (m, 1H), 1.89 (td, *J* = 10.0; 4.4 Hz, 1H), 1.42 (d, *J* = 8.1 Hz, 1H), 0.66-0.60 (m, 1H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$: 125 MHz) δ 137.0, 135.2, 134.5, 132.7, 128.6, 126.6, 126.0, 125.5, 63.0, 56.6, 51.1, 49.5, 45.2, 42.5, 36.6, 31.6, 29.0 ppm. IR (neat): ν 2957, 2935, 2865, 2763, 1498, 1453, 1340, 1265, 1095, 936, 739, 718 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$: calcd for $C_{17}H_{22}N$ 240.1752; Found 240.1751. $[\alpha]_D^{25}$ = +267.3 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

Benzyl(cyclopropylmethyl)methylamine (**11**): According to general procedure A starting from cyclopropane carboxaldehyde (0.5 mmol,

37 µL) and *N*-benzylmethylamine (0.6 mmol, 1.2 equiv, 80 µL), **11** was isolated, after purification by flash column chromatography on silica (Dichloromethane/MeOH 9:1), as an oil (88 mg, 99 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.29-7.22 (m, 4H), 7.20-7.15 (m, 2H), 3.48 (s, 3H), 2.22 (s, 3H), 2.21 (d, *J* = 6.7 Hz, 2H), 0.90-0.81 (m, 1H), 0.48-0.42 (m, 2H), 0.03 (q, *J* = 4.8 Hz, 2H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$: 125 MHz) δ 139.2, 129.1 (2C), 128.2 (2C), 126.8, 62.4, 62.3, 42.4, 8.9, 3.9 (2C) ppm. IR (neat): ν 3077, 3002, 2941, 2775, 1495, 1453, 1365, 1026, 737, 698 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$: Calcd for $C_{12}H_{18}N$ 176.1439; Found 176.1440.

4-(2-thienylmethyl)-morpholine (**12**):[43] According to the general procedure A, starting from 2-thiophene carboxaldehyde (0.5 mmol, 1 equiv, 47 µL) and morpholine (0.6 mmol, 1.2 equiv, 55 µL), **12** was isolated, after filtration with pentane over a pad of Celite®, as a yellowish oil (89 mg, 98 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.53-8.50 (m, 1H), 7.61 (td, *J* = 7.6; 1.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.14-7.10 (m, 1H), 3.69 (t, *J* = 4.9 Hz, 4H), 3.61 (s, 2H), 2.46 (t, *J* = 4.9 Hz, 4H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 159.6, 149.3, 136.6, 123.3, 122.2, 66.9 (2C), 64.9, 55.8 (2C) ppm.

(N,N-Benzylmethylaminomethyl)ferrocene (**13**): According to general procedure A, starting from ferrocene carboxaldehyde (0.5 mmol, 1 equiv, 107 mg) and N-benzylmethylamine (0.6 mmol, 1 equiv, 90 µL), **13** was isolated, after purification by flash column chromatography on silica (pentane/Et_2O 8/2), as a yellow oil (146 mg, 92 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.29-7.18 (m, 5H), 4.14 (t, *J* = 1.9 Hz, 2H), 4.08 (t, *J* = 1.9 Hz, 2H), 4.04 (s, 4H), 3.39 (s, 4H), 2.10 (s, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 139.3, 129.1 (2C), 128.3 (2C), 126.9, 83.2, 70.3 (2C), 68.6 (5C), 67.9 (2C), 61.0, 56.9, 41.8 ppm. IR (neat): ν 3086, 3027, 2930, 2835, 2780, 1494, 1453, 1105, 1022, 1000, 858, 818, 734, 698, 520, 481 cm^{-1}. HRMS (ESI+) *m/z*: [M+H] Calcd for $C_{19}H_{21}NFe$ 319.1023; found 319.1023.

Methyl 4-(benzyl(methyl)amino)methyl)benzoate (**14**): According to the general procedure A, starting from methyl 4-formylbenzoate (0.5 mmol, 1 equiv, 82 mg) and *N*-benzylmethylamine (0.6 mmol, 1.2 equiv, 80 µL), **14** was isolated, after purification by flash column chromatography on silica (Pentane/Et_2O 8/2), as a colorless oil (127 mg, 95 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.30-7.22 (m, 4H), 7.19-7.15 (m, 1H), 3.83 (s, 3H), 3.48 (s, 2H), 3.45 (s, 2H), 2.11 (s, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 167.1, 145.0, 139.1, 129.6 (2C), 128.9 (2C), 128.7 (2C), 128.3 (2C), 127.1, 62.0, 61.5, 52.1, 42.4 ppm. IR (neat): ν 2819, 2840, 2787, 1719, 1616, 1453, 1434, 1274, 1191, 1173, 1108, 1099, 1018, 757, 749, 698 cm^{-1}. HRMS (ESI+) *m/z* $[M+H]^+$ Calcd for $C_{17}H_{20}NO_2$ 270.1494; Found 270.1497.

4-((benzyl(methyl)amino)methyl)-2-methoxyphenol (**15**): According to the general procedure A, starting from vanillin (0.5 mmol, 1 equiv, 75 mg) and *N*-benzylmethylamine (0.6 mmol, 1.2 equiv, 80 µL), **15** was isolated, after purification by flash column chromatography on silica (Dichloromethane/MeOH 98/2), as a yellowish solid (127 mg, 99 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.28-7.20 (m, 4H), 7.18-7.13 (m, 1H), 6.85-6.83 (m, 1H), 6.78-6.70 (m, 2H), 6.18-5.29 (br. s, 1H), 3.79 (s, 3H), 3.42 (s, 2H), 3.38 (s, 2H), 2.09 (s, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 146.6, 144.7, 139.2, 131.1, 129.1 (2C), 128.3 (2C), 127.0, 121.9, 113.9, 111.4, 61.9, 61.6, 55.9, 42.2 ppm. IR (neat): ν 3526, 3398, 3027, 2938, 2835, 2784, 1601, 1512, 1495, 1463, 1451, 1430, 1364, 1271, 1234, 1206, 1152, 1118, 1033, 870, 816, 796, 739, 698, 568 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{20}NO_2$ 258.1494; Found 258.1497.

(2,2-dimethoxyethyl)(3,7-dimethyloct-6-en-1-yl)methylamine (**16**): According to the general procedure A, starting from (±)-citronellal (0.5 mmol, 1 equiv, 90 µL) and *N*-methylaminoacetaldehyde dimethyl acetal (0.6 mmol, 1.2 equiv, 65 µL), **7** was isolated, after purification by flash column chromatography on silica (Pentane/Et_2O 9/1) as a yellowish oil (90 mg, 70 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 5.09 (t, *J* = 6.8 Hz, 1H), 4.49 (t, *J* = 5.2 Hz, 1H), 3.36 (s, 6H), 2.55-2.47 (m, 2H), 2.47-2.37 (m, 2H), 3.07 (s, 3H), 2.01-1.95 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.56-1.47 (m, 1H), 1.45-1.39 (m, 1H), 1.36-1.23 (m, 2H), 1.19-1.11 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 131.1, 124.8, 102.8, 58.9, 56.6, 53.3 (2C), 43.2, 37.2, 33.9, 30.9, 25.7, 19.6, 17.6 ppm. IR (neat): ν 2953, 2916, 2848, 2784, 1456, 1377, 1194, 1128, 1076, 968 cm^{-1}. HRMS (ESI+) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{32}NO_2$ 258.2433; Found 258.2434.

(2,2-dimethoxyethyl)({[2-(diphenylphosphanyl)phenyl]methyl})methyl amine (**17**): According to general procedure A starting from 2-(diphenylphosphino)benzaldehyde (0.5 mmol, 145 mg) and *N*-methylaminoacetaldehyde dimethyl acetal (0.6 mmol, 1.2 equiv, 65 µL), **17** was isolated, after purification by flash column chromatography on silica (Pentane/Et_2O 9/1), as a white solid (136 mg, 70 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.50-7.46 (m, 1H), 7.28-7.23 (m, 7H), 7.22-7.16 (m, 4H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.85-6.81 (m, 1H), 4.22 (t, *J* = 5.0 Hz, 1H), 3.72 (d, *J* = 2.0 Hz, 2H), 3.20 (s, 6H), 2.45 (d, *J* = 5.0 Hz, 2H), 2.07 (s, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 144.0 (d, *J* = 22.8 Hz, 1C), 137.5 (d, *J* = 10.3 Hz, 2C), 136.4 (d, *J* = 14.9, 1C), 138.8, 133.7 (d, *J* = 19.7 Hz, 2C), 129.2 (d, *J* = 5.1 Hz, 1C), 128.6 (2C), 128.4 (2C), 128.3 (d, *J* = 5.1 Hz, 2C), 127.1, 103.1, 60.6 (d, *J* = 20 Hz, 1C), 58.1, 53.2 (2C), 42.2 ppm. ^{31}P-NMR ($CDCl_3$, 203 MHz): δ -15.6 ppm. IR (neat): ν 3052, 2927, 2829, 1585, 1433, 1364, 1192, 1122, 1067, 1026, 965, 743, 695, 502 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{29}NO_2P$ 394.1936; Found 394.1937.

Ethyl-(2S)-1-(3-phenylpropyl)pyrrolidine-2-carboxylate (**18**): According to general procedure A starting from 3-phenylpropionaldehyde (0.5 mmol, 85 mg) and *(S)*-proline methyl ester 5 (0.6 mmol, 1.2 equiv, 90 mg), **18** was isolated, after purification by flash column chromatography on silica (Pentane/Et_2O 8/2), as yellowish oil (95 mg, 73 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 4.23-4.12 (m, 2H), 3.22-3.17 (m, 1H), 3.13-3.09 (m, 1H), 2.75-2.98 (m, 3H), 2.45-2.39 (m, 1H), 2.32 (q, *J* = 8.5 Hz, 1H), 2.14-2.07 (m, 1H), 1.96-1.88 (m, 2H), 1.87-1.77 (m, 3H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 174.9, 142.1, 128.4 (2C), 128.3 (2C), 125.9, 66.3, 60.6, 54.7, 53.6, 51.8, 33.7, 30.2, 23.2, 14.3 ppm. IR (neat): ν 2940, 1728, 1496, 1454, 1371, 1174, 1128, 1030, 746, 699 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{24}NO_2$ 262.1807; Found 262.1813. $[\alpha]_D^{25}$ = -47.3 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

Ethyl(2S)-1-[2-(diphenylphosphanyl)phenyl]pyrrolidine-2-carboxylat e (**19**): According to general procedure A starting from 2-(diphenylphosphino)benzaldehyde (0.5 mmol, 145 mg) and *(S)*-proline methyl ester (0.6 mmol, 1.2 equiv, 90 mg), **19** was isolated, after purification by flash column chromatography on silica (Pentane/Et_2O 95/5), as white solid (180 mg, 86 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.51-7.47 (m, 1H), 7.33-7.26 (m, 6H), 7.23-7.18 (m, 4H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.90-6.86 (m, 1H), 4.11 (q, *J* =7.1 Hz, 2H), 4.02 (s, 2H), 3.35-3.30 (m, 1H), 2.84-2.78 (m, 1H), 2.42 (q, *J* = 7.0 Hz, 1H), 1.73-1.50 (m, 4H), 1.35-1.27 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 174.4, 144.4 (d, J^{C-P}= 23.8 Hz), 137.9 (d, J^{C-P}= 13.9 Hz), 137.8 (d, J^{C-P}= 13.9 Hz), 136.2 (d, J^{C-P}= 15.3 Hz), 134.2, 133.7 (d, J^{C-P}= 5.8 Hz, 2C), 133.5 (d, J^{C-P}= 5.8 Hz, 2C), 129.3 (d, J^{C-P}= 5.5 Hz), 128.7 (2C), 128.4, 128.3, 128.2, 127.2 ppm. ^{31}P-NMR ($CDCl_3$, 203 MHz): δ -15.8 ppm. IR (neat): ν 3053, 2977, 2833, 1729, 1586, 1434, 1177, 1144, 1027, 744, 697, 905 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{29}NO_2P$ 418.1936; Found 418.1938. $[\alpha]_D^{25}$ = + 56.7 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

[(2S)-1-(cyclopropylmethyl)pyrrolidin-2-yl]methanol (**20**): According to general procedure A starting from cyclopropane carboxaldehyde (0.5 mmol, 37 µL) and L-prolinol (0.6 mmol, 1.2 equiv, 60 µL), **20** was isolated, after purification by flash column chromatography on silica (Dichloromethane/Methanol 95/5), as a yellowish oil (67 mg, 86 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 3.62 (dd, *J* = 10.3; 3.8 Hz, 1H), 3.38 (dd, *J* = 10.3; 2.6 Hz, 1H), 3.34-3.28 (m, 1H), 2.64 (dd, *J* = 12.5; 6.4 Hz, 1H), 2.60-2.54 (m, 1H), 2.31 (q, *J* = 8.5 Hz, 1H), 2.06 (dd, *J* = 12.5 Hz; 7.1 Hz, 1H), 1.91-1.81 (m, 1H), 1.80-1.69 (m, 3H), 0.93-0.84 (m, 1H), 0.57-0.43 (m, 2H), 0.16-0.06 (m, 2H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz) :δ 64.3, 61.9, 59.2, 54.7, 27.7, 23.7, 10.2, 4.7, 3.1 ppm. IR (neat): ν 3370, 3077, 2960, 2874, 2806, 1657, 1461, 1399, 1200, 1092, 1046, 1020, 829 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_9H_{18}NO$ 156.1388; Found 156.1394. $[\alpha]_D^{25}$ = + 35.1 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

(-)-N-cyclopropylmethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2α][1,5]diazocin-8-one (**21**):[44] According to general procedure A starting from cyclopropane carboxaldehyde (0.5 mmol, 37 µL)

and cytisine (0.6 mmol, 1.2 equiv, 115 mg), **21** was isolated, after evaporation of the solvent and filtration with diethyl ether over a pad of Celite®, as a white solid (99 mg, 81 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.24 (dd, *J* = 9.1; 6.8 Hz, 1H), 6.40 (dd, *J* = 9.1; 1.3 Hz, 1H), 5.96 (dd, *J* = 6.8; 1.3 Hz, 1H), 3.87 (dd, *J* = 15.1; 6.6 Hz, 1H), 3.08-3.03 (m, 1H), 2.99-2.95 (m, 1H), 2.93-2.89 (m, 1H), 2.42-2.37 (m, 1H), 2.30 (dd, *J* = 10.7; 2.1 Hz, 1H), 2.27-2.23 (m, 1H), 2.13 (dd, *J* = 12.7; 6.3 Hz, 1H), 2.08-2.02 (m, 1H), 1.86-1.82 (m, 1H), 1.75-1.70 (m, 1H), 0.66-0.57 (m, 1H), 0.39-0.34 (m, 2H), -0.06 (qd, *J* = 4.9; 0.7 Hz, 2H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 166.6, 151.8, 138.5, 116.4, 104.5, 62.8, 60.4, 59.8, 49.9, 35.5, 27.9, 25.9, 7.9, 3.7, 3.5 ppm.

(2R,2'R)-1,1'-bis({[2-(diphenylphosphanyl)phenyl]methyl})-2,2'-bipyrrolidine (**22**):[45] According to general procedure A starting from 2-(diphenylphosphino)benzaldehyde (0.34 mmol, 1.2 equiv, 100 mg) and (2*R*,2'*R*)-2,2'-bipyrrolidine (0.14 mmol, 20mg), **22** was isolated, after purification by flash column chromatography on silica (Dichloromethane/MeOH 99/1), as white solid (60mg, 62 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.52-7.50 (m, 2H), 7.31-7.27 (m, 14H), 7.25-7.19 (m, 8H), 7.10 (t, *J* = 7.3 Hz, 2H), 6.83-6.81 (m, 2H), 4.06 (d, *J* = 13.6 Hz, 2H), 3.53(dd, *J* = 2.2, 13.8 Hz, 2H), 2.73-2.68 (m, 4H), 1.97-1.91 (m, 2H), 1.73-1.26 (m, 8H) ppm. ^{31}P-NMR ($CDCl_3$, 200 MHz): δ -16.4 ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 145.2 (d, *J* = 23.2 Hz, 2C), 137.7 (d, *J* = 11.6 Hz, 2C), 137.0 (d, *J* = 10.4 Hz, 2C), 135.4 (d, *J* = 14.7 Hz, 2C), 133.9 (d, *J* = 19.9 Hz, 6C), 133.7 (d, *J* = 19.3 Hz, 6C), 133.5 (2C), 128.9 (d, *J* = 5.7 Hz, 2C), 128.7 (2C), 128.4 (d, *J* = 6.7 Hz, 6C), 128.3 (d, *J* = 6.8 Hz, 4C), 126.7 (2C), 65.0 (2C), 57.4 (d, *J* = 20.5 Hz, 2C), 54.7 (2C), 25.8 (d, *J* = 1.7 Hz, 2C), 23.57 (2C) ppm. $[\alpha]_D^{25}$ = + 44.1 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

Methyl 4-(Propylaminomethyl)benzoate (**23**):[46] According to the general procedure C, starting from methyl 4-formylbenzoate (0.5mmol, 1 equiv, 80 mg) and propylamine (0.6 mmol, 1.2 equiv, 49 µL), **23** was isolated, after filtration with pentane over a pad of Celite, as yellow oil (100 mg, 96 %).^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 3.9 (s, 3H), 3.84 (s, 2H), 2.58 (t, *J* = 7.1 Hz, 2H), 1.52 (sext, *J* = 7.3 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 167.1, 146.0, 129.7 (2C), 128.7, 126.8 (2C), 53.7, 52.0, 51.4, 23.2, 11.8 ppm.

N-[[3,5-bis(trifluoromethyl)phenyl]methyl]propan-1-amine (**24**): According to the general procedure C, starting from 3,5-bis(trifluoromethyl)benzaldehyde (0.5mmol, 1 equiv, 121 mg) and propylamine (0.6 mmol, 1.2 equiv, 49 µL), **24** was isolated, after filtration with pentane over a pad of Celite, as yellow oil (96 mg, 67 %).^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.81 (s, 2H), 7.75 (s, 1H), 3.91 (s, 2H), 2.60 (t, *J* = 7.1 Hz, 2H), 1.54 (sext., *J* = 7.2 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 143.4, 131.5 (q, *J* = 33.2 Hz, 2C), 128.0 (dd, *J* = 1.1, 3.6 Hz, 2C), 124.3, 122.5, 120.9 (quint, *J* = 3.9 Hz, 1C), 53.0, 51.4, 23.2, 11.7 ppm. ^{19}F-NMR ($CDCl_3$, 500 MHz): δ -62.8 ppm. IR (neat): ν 2964, 2936, 2879, 1623, 1461, 1376, 1275, 1168, 1123, 898, 843, 706, 682 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{14}NF_6$ 286.1030 Found 286.1034.

N-(4-Nitrobenzyl)propylamine (**25**):[47] According to the general procedure C, starting from 4-nitrobenzaldehyde (0.5mmol, 1 equiv, 76 mg) and propylamine (0.6 mmol, 1.2 equiv, 49 µL), **25** was isolated, after a purification by flash column chromatography on silica (CH_2Cl_2/MeOH 98/2), as yellow oil (75 mg, 77 %).^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.17 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5Hz, 2H), 3.01 (s, 2H), 2.59 (t, *J* = 7.1 Hz, 2H), 1.54 (sext, *J* = 7.2 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 148.2, 147.0, 128.7 (2C), 123.6 (2C), 53.1, 51.4, 23.1, 11.7 ppm.

(N-Propylaminomethyl)ferrocene (**26**):[48] According to the general procedure C, starting from ferrocene carboxaldehyde (0.5mmol, 1 equiv, 107mg) and propylamine (0.6 mmol, 1.2 equiv, 49 µL), **26** was isolated, after a purification by flash column chromatography on silica (CH_2Cl_2/MeOH 98/2), as yellow powder (70 mg, 54 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 4.24 (app. t, *J*= 1.7Hz, 2H), 4.12 (s, 7H), 3.60 (s, 2H), 2.61 (t, *J* = 7.3 Hz, 2H), 1.56 (sext, *J* = 7.2 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 67.0 (2C), 68.5 (6C), 68.1 (2C), 50.7, 48.6, 22.4, 11.7 ppm.

6-[benzyl(methyl)amino]-1-phenylhexan-1-one (**27**): According to general procedure A starting from **42** (0.5 mmol, 95 mg) and *N*-benzylmethylamine (0.6 mmol, 1.2 equiv, 80 µL), **27** was isolated, after purification by flash column chromatography on silica (Dichloromethane/MeOH 9/1), as a yellowish oil (137 mg, 93 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.90 (d, *J* = 7.9 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.29-7.23 (m, 4H), 7.21-7.16 (m, 1H), 3.46 (s, 3H), 2.91 (t, *J* = 7.3 Hz, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.16 (s, 3H), 1.70 (quint, *J* = 7.6 Hz, 2H), 1.54 (quint, *J* = 7.3 Hz, 2H), 1.36 (quint, *J* = 7.6 Hz, 2H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 200.3, 138.6, 137.0, 129.1 (2C), 128.5 (2C), 128.2 (2C), 127.9 (2C), 126.9, 62.2, 57.1, 42.0, 38.4, 27.1, 24.1 ppm. IR (neat): ν 2936, 2786, 1683, 1597, 1449, 1363, 1213, 1074, 1027, 796, 690 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{26}NO$ 296.2014 Found 296.2018.

6-[(2,2-dimethoxyethyl)(methyl)amino]-1-phenylhexan-1-one (**28**): According to general procedure A starting from **42** (0.5 mmol, 95 mg) and *N*-methylaminoacetaldehyde dimethyl acetal (0.6 mmol, 1.2 equiv, 65 µL), **28** was isolated, after purification by flash column chromatography on silica (Dichloromethane/MeOH 9/1), as a colorless oil (130 mg, 89 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.93 (d, *J* = 7.9 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 4.46 (t, *J* = 5.1 Hz, 1H), 3.34 (s, 6H), 2.95 (t, *J* = 7.3 Hz, 2H), 2.49 (d, *J* = 5.1, 2H), 2.39 (t, *J* = 7.2 Hz, 2H), 2.27 (s, 3H), 1.74 (quint, *J* = 7.5 Hz, 2H), 1.51 (quint, *J* = 7.5 Hz, 2H), 1.37 (quint, *J* = 7.7 Hz, 2H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 200.3, 136.9, 132.8, 128.5 (2C), 127.9 (2C), 102.7, 58.8, 58.3, 53.2 (2C), 43.2, 38.4, 27.1, 26.9, 24.1 ppm. IR (neat): ν 2935, 2830, 1683, 1448, 1368, 1125, 1065, 968, 749, 691 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{28}NO_3$ 294.2069 Found 294.2072.

6-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-1-phenylhexan-1-one (**29**): According to general procedure A starting from ketoaldehyde **42** (0.5 mmol, 95 mg) and L-prolinol (0.6 mmol, 1.2 equiv, 60 µL), **29** was isolated, after purification by flash column chromatography on silica (Dichloromethane/Methanol 95/5), as a yellowish oil (120 mg, 88 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.97-7.93 (m, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 3.61 (dd, *J* = 10.5; 3.6 Hz, 1H), 3.37 (d, *J* = 10.5 Hz, 1H), 3.18-3.13 (m, 1H), 2.97 (t, *J* = 7.3 Hz, 2H), 2.84 (br. s, 1H), 2.71 (dt, *J* = 12.0; 8.0 Hz, 1H), 2.57-2.52 (m, 1H), 2.28-2.17 (m, 2H), 1.91-1.81 (m, 1H), 1.80-1.65 (m, 6H), 1.54 (quint, *J* = 6.9 Hz, 2H), 1.49-1.33 (m, 2H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 200.3, 137.0, 132.9, 128.5 (2C), 128.0 (2C), 64.9, 61.7, 54.2, 54.1, 38.5, 28.8, 27.6, 27.1, 24.1, 23.6 ppm. IR (neat): ν 3357, 2936, 2863, 2801, 1682, 1597, 1580, 1448, 1358, 1225, 1203, 1044, 751, 691 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{26}NO_2$ 276.1964 Found 276.1967. $[\alpha]_D^{25}$ = +27.2 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

4-(N-Benzyl-N-methylaminomethyl)acetophenone (**30**):[49] According to the general procedure A, starting from 4-acetylbenzaldehyde (0.5 mmol, 1 equiv, 75 mg) and *N*-benzylmethylamine (0.6 mmol, 1.2 equiv, 80 µL), **30** was isolated, after purification by flash column chromatography on silica (Pentane/Et_2O 8/2), as a colorless oil (119 mg, 94 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.81 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.29-7.14 (m, 5H), 3.49 (s, 2H), 3.45 (s, 2H), 2.51 (s, 3H), 2.08 (s, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 197.9, 145.3, 139.0, 136.1, 128.9 (2C), 128.8 (2C), 128.4 (2C), 128.3 (2C), 127.2, 62.1, 61.4, 42.4, 26.7 ppm.

1-(4-{[(2,2-dimethoxyethyl)(methyl)amino]methyl}phenyl)ethan-1-one (**31**): According to general procedure A starting from 4-acetylbenzaldehyde (0.5 mmol, 1 equiv, 75 mg) and *N*-methylaminoacetaldehyde dimethyl acetal (0.6 mmol, 1.2 equiv, 65 µL), **31** was isolated, after purification by flash column chromatography on silica (Pentane/Et_2O 1/1), as an oil (99 mg, 79 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 4.51 (t, *J* = 5.0 Hz, 1H), 3.61 (s, 2H), 3.32 (s, 6H), 2.58 (s, 3H), 2.54 (d, *J* = 5.0 Hz, 2H), 2.28 (s, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 197.9, 136.0, 128.9 (2C), 128.5 (2C), 126.5, 102.8, 62.4, 58.5, 53.3 (2C), 43.2, 26.6 ppm. IR (neat): ν 2930, 2831, 1681, 1507, 1412, 1359, 1267, 1125, 1073, 1015, 967, 815 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{22}NO_3$ 252.1600; found 252.1602.

1-(4-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl}phenyl)ethan-1-one (**32**): According to general procedure A starting from 4-acetylbenzaldehyde (0.5 mmol, 1 equiv, 75 mg) and L-prolinol (0.6

mmol, 1.2 equiv, 60 µL), **32** was isolated, after purification by flash column chromatography on silica (Dichloromethane/MeOH 98/2), as an oil (117 mg, 99 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 4.08 (d, *J* = 13.8 Hz, 1H), 3.66 (dd, *J* = 10.5; 3.1 Hz, 1H), 3.44 (t, *J* = 13.2 Hz, 2H), 2.99-2.94 (m, 1H), 2.79-2.73 (m, 1H), 2.69-2.61 (m, 1H), 2.60 (s, 3H), 2.28 (q, *J* = 8.0 Hz, 1H), 1.99-1.90 (m, 1H), 1.89-1.81 (m, 1H), 1.77-1.67 (m, 2H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 197.8, 145.1, 136.1 (2C), 128.7 (2C), 128.5, 64.5, 61.8, 58.3, 54.6, 27.6, 26.6, 23.5 ppm. IR (neat): ν 3419, 2949, 2806, 1681, 1607, 1413, 1358, 1267, 1017, 819, 732 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{20}NO_2$ 234.1494; found 234.1500. $[\alpha]_D^{25}$ = + 31.5 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

(1R,9S)-11-[(4-acetylphenyl)methyl]-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-6-one (**33**) : According to general procedure A starting from 4-acetylbenzaldehyde (0.5 mmol, 74 mg) and cytisine (0.6 mmol, 1.2 equiv 100mg), **33** was isolated, after purification by flash column chromatography on silica (Dichloromethane/MeOH 99/1), as yellowish oil (120mg, 74 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.77 (d, *J* = 6.2 Hz, 2H), 7.31-7.29 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.51 (d, *J* = 8.8 Hz, 1H), 5.91 (d, *J* = 6.7 Hz, 1H), 4.13 (d, *J* = 15.3 Hz, 1H), 3.89 (dd, *J* = 6.3, 15.3, 1H), 3.52 (d, *J* = 14.3 Hz, 1H), 3.43 (d, *J* = 14.3 Hz, 1H), 2.95-2.92 (m, 2H), 2.81 (d, *J* = 10.5 Hz, 1H), 2.55 (s, 3H), 2.47-2.42 (m, 2H), 2.33 (d, *J* = 10.6 Hz, 1H), 1.95-1.91 (m, 1H), 1.83-1.79 (m, 1H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 198.0, 163.7, 151.2, 143.9, 138.7, 136.1, 128.4 (2C), 128.2 (2C), 116.7, 104.8, 61.6, 60.2, 60.1, 50.0, 35.5, 28.2, 26.6, 25.9 ppm. IR (neat): ν 2937, 2792, 1678, 1648, 1606, 1585, 1546, 1358, 1266, 1140, 1102, 1060, 909, 729, 644, 582, 552, 507. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{22}N_2O_2$ 323.1760, found 323.1766. $[\alpha]_D^{25}$ = +43.42 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

(5R)-5-{2-[benzyl(methyl)amino]ethyl}-6-methylhept-6-en-2-one (**34**): According to general procedure A starting from ketoaldehyde **42** (0.5 mmol, 85 mg) and *N*-benzylmethylamine (0.6 mmol, 1.2 equiv, 80 µL), **34** was isolated, after purification by flash column chromatography on silica (Pentane/Et_2O 1/1), as yellowish oil (112 mg, 89 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.32-7.27 (m, 4H), 7.26-7.21 (m, 1H), 4.75-4.73 (m, 1H), 4.66-4.64 (m, 1H), 3.45 (s, 2H), 2.36-2.26 (m, 4H), 2.16 (s, 3H), 2.11 (s, 3H), 2.10-2.04 (m, 1H), 1.69-1.61 (m, 1H), 1.56 ‘s, 3H), 1.59-1.50 (m, 4H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 209.1, 146.5, 129.1 (2C), 128.2 (2C), 126.9, 112.6, 62.5, 55.7, 44.9, 42.6, 41.6, 31.1, 30.4, 30.1, 26.9, 17.2 ppm. IR (neat): ν 3026, 2937, 2789, 1717, 1644, 1453, 1365, 1161, 1027, 890, 738, 699 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$: calculated $C_{18}H_{28}NO$ 274.2171; Found 274.2176. $[\alpha]_D^{25}$ = -5.5 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

(5R)-6-methyl-5-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]hept-6-en-2-one (**35**): According to general procedure A starting from ketoaldehyde **43** (0.5 mmol, 85 mg) and 1,2,3,4-tetrahydroisoquinoline (0.6 mmol, 1.2 equiv, 80 µL) **35** was isolated, after purification by flash column chromatography on silica (Dichloromethane/Methanol 99/1), as light purple oil (116 mg, 81 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.13-7.07 (m, 3H), 7.03-6.99 (m, 1H), 4.79-4.78 (m, 1H), 4.71-4.69 (m, 1H), 3.67-3.59 (m, 1H), 2.90 (t, *J* = 5.8 Hz, 2H), 2.73 (t, *J* = 5.8 Hz, 2H), 2.44 (t, *J* = 8.3 Hz, 2H), 2.36 (t, *J* = 8.3 Hz, 2H), 2.12 (s, 3H), 2.16-2.07 (m, 1H), 1.75-1.54 (m, 5H), 1.61 (s, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 208.1, 145.2, 133.5, 133.1, 127.6, 125.7, 125.1, 124.6, 11.8, 55.5, 55.1, 50.1, 43.9, 40.4, 29.6, 29.1, 27.9, 25.9 ppm. IR (neat): ν 2932, 2804, 1714, 1643, 1453, 1368, 1192, 1161, 1097, 890, 711 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{28}NO$ 286.2171; Found 286.2177. $[\alpha]_D^{25}$ = -7.3 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

(5R)-5-{2-[(2-hydroxyethyl)(methyl)amino]ethyl}-6-methylhept-6-en-2-one (**36**): According to general procedure A starting from ketoaldehyde **43** (0.5 mmol, 85 mg) and *N*-methylaminoethanol (0.6 mmol, 1.2 equiv, 60 µL), **36** was isolated, after purification by flash column chromatography on silica (Dichloromethane/Methanol 9/1), as a colorless oil (100 mg, 88 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 4.78 (s, 1H), 4.67 (s, 1H), 3.93-3.74 (br. s, 1H), 3.63 (t, *J* = 4.7 Hz, 2H), 2.68-2.58 (m, 2H), 2.49-2.38 (m, 2H), 2.37-2.31 (m, 2H), 2.34 (s, 3H), 2.10 (s, 3H), 2.08-2.03 (m, 1H), 1.71-1.62 (m, 1H), 1.57 (s, 3H), 1.59-1.49 (m, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 208.8, 145.8, 113.2, 59.0, 57.9, 55.8, 44.5, 41.5, 41.2, 30.1, 29.9, 26.7, 17.4 IR (neat): ν 3386, 2939, 2876, 2801, 1711, 1644, 1450, 1412, 1366, 1163, 1063, 1037, 890 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{26}NO_2$ 228.1964; Found 228.1966. $[\alpha]_D^{25}$ = -25.2 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

(5R)-5-{2-[(2,2-dimethoxyethyl)(methyl)amino]ethyl}-6-methylhept-6-en-2-one (**37**): According to general procedure A starting from ketoaldehyde **43** (0.5 mmol, 85 mg) and *N*-methylaminoacetaldehyde dimethyl acetal (0.6 mmol, 1.2 equiv, 65 µL), **37** was isolated, after purification by flash column chromatography on silica (Dichloromethane/Methanol 98/2), as a colorless oil (106 mg, 78 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 4.76 (s, 1H), 4.67 (s, 1H), 4.47 (t, *J* = 5.0 Hz, 1H), 3.35 (s, 6H), 2.49 (d, *J* = 5.0 Hz, 2H), 2.33 (q, *J* = 7.3 Hz, 4H), 2.28 (s, 3H), 2.10 (s, 3H), 2.05-1.98 (m, 1H), 1.70-1.61 (m, 1H), 1.56 (s, 3H), 1.55-1.47 (m, 3H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ 208.9, 146.2, 112.7, 102.7, 58.9, 56.6, 53.3, 44.8, 43.2, 41.5, 30.4, 30.0, 26.9, 17.5 cm^{-1}. IR (neat): ν 2937, 2831, 1715, 1644, 1448, 1366, 1191, 1124, 1064, 968, 889 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{30}NO_3$ 272.2226 Found 272.2226 . $[\alpha]_D^{25}$ = -21.2 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

Scale up for **37**: In a 10 mL autoclave equipped with a stirring bar, under argon, ketoaldehyde **43** (5 mmol, 1 equiv, 0.85 mL), *N*-methylaminoacetaldehyde dimethyl acetal (6 mmol, 1.2 equiv, 0.65 mL), **Fe3** (0.1 mmol, 2 mol %, 58.6 mg) and trimethylamine *N*-oxide (0.15 mmol, 3 mol %, 12 mg) were solubilized in free-O_2 ethanol (5 mL). The autoclave was sealed and pressurized with hydrogen (5 bar), and the mixture was stirred for 18 hours at room temperature. The reaction was extracted with dichloromethane (30 mL) and washed twice with a saturated $NaHCO_3$ aqueous solution (2 x 20 mL). The organic phases were dried over $MgSO_4$, filtrated and the solvent was removed *in vacuum*. Crude product was purified by flash column chromatography on silica (Dichloromethane/Methanol 98/2) to afford the pure product **37** as a colorless oil (1.2 g, 88 %).

(5R)-5-(2-{[(2R)-2-(3,4-dihydroxyphenyl)-2-hydroxyethyl](methyl)amino}ethyl)-6-methylhept-6-en-2-one (**38**): According to general procedure A starting from ketoaldehyde **43** (0.5 mmol, 80 mg) and adrenaline (0.6 mmol, 1.2 equiv, 110 mg), **38** was isolated, after purification by flash column chromatography on silica (Dichloromethane/MeOH 8/2), as an oil (110 mg, 65 %). ^{1}H-NMR (CD_3OD, 500 MHz): δ 6.82 (s, 2H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 4.68 (d, *J* = 7.1 Hz, 1H), 2.77 (t, *J* = 9.7 Hz, 1H), 2.68-2.57 (m, 2H), 2.57-2.49 (m, 1H), 2.48 (s, 3H), 2.44-2.35 (m, 2H), 2.10 (s, 3H), 2.11-2.03 (m, 1H), 1.69-1.51 (m, 5H), 1.61 (s, 3H) ppm. ^{13}C{^{1}H}-NMR (CD_3OD, 125 MHz): δ 211.9, 147.3, 146.4, 146.0, 135.3, 118.6, 116.2, 114.3, 113.7, 70.9, 65.6, 56.9, 46.0, 42.5, 30.2, 29.9, 29.6, 27.9, 17.3 ppm. IR (neat): ν 3355, 2938, 1698, 1447, 1275, 1204, 114, 1067, 887, 815, 759 cm^{-1}. HRMS (ESI-) *m/z*: $[M-H]^-$ Calcd for $C_{19}H_{28}NO_4$ 334.2018 Found 334.2011. $[\alpha]_D^{25}$ = -15.1 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

(5R)-5-[2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]ethyl]-6-methylhept-6-en-2-one (**39**): According to general procedure A starting from ketoaldehyde **43** (0.5 mmol, 85 mg) and L-prolinol (0.6 mmol, 1.2 equiv, 60 µL), **39** was isolated, after purification by flash column chromatography on silica (Dichloromethane/MeOH 99/1), as yellowish oil (100mg, 79 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): d 4.79 (s, 1H), 4.70 (d, *J* = 1.6 Hz, 1H), 3.59 (dd, *J* = 2.9, 10.6 Hz, 1H), 3.36 (d, *J* = 10.6, 1H), 3.21-3.15 (br. s, 1H), 2.68-2.63 (m, 1H), 2.60-2.55 (m, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.21-2.12 (m, 2H), 2.11 (s, 3H), 1.89-1.81 (m, 1H), 1.80-1.71 (m, 4H), 1.68-1.61 (m, 2H), 1.59-1.51 (m, 6H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): d 209.0, 146.1, 113.2, 65.1, 61.8, 54.1, 52.5, 44.8, 41.5, 32.80, 30.1, 27.5, 27.1, 23.6, 17.2 ppm. IR (neat): ν 3386, 2938, 2873, 1712, 1644, 1447, 1365, 1162, 1044, 891, 539 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{27}NO_2$ 254.2120 Found 254.2122. [a]$_D^{25}$ = +25.14 (C = 3.5 10^{-3}g.mL^{-1} $CHCl_3$).

4-(propylaminomethyl)acetophenone (**40**): According to the general procedure C, starting from 4-acetylbenzaldehyde (0.5mmol, 1 equiv, 75 mg) and propylamine (0.6 mmol, 1.2 equiv, 49 µL), **40** was isolated, after filtration with pentane over a pad of Celite, as yellow oil (82 mg, 86 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 3.84 (s, 2H), 2.59-2.57 (m, 5H), 1.52

(sext, J = 7.3 Hz, 2H), 0.91 (t, J = 7.5 Hz, 3H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ 197.9, 146.3, 135.9, 128.5 (2C), 128.1 (2C), 53.6, 51.4, 26.7, 23.2, 11.8 ppm. IR (neat): ν 3345, 2958, 2930, 2873, 2814, 1678, 1607, 1357, 1265, 1122, 1017, 955, 816, 597 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{18}NO$ 192.1388 Found 192.1383.

1-{4-[(4-benzylpiperazin-1-yl)methyl]phenyl}ethan-1-one (**41**): According to general procedure A starting from 4-acetylbenzaldehyde (0.5 mmol, 1 equiv., 75 mg) and benzylpiperazine (0.6 mmol, 1.2 equiv., 105 µL), **41** was isolated, after purification by silica flash column chromatography (Dichloromethane/MeOH 98:2), as a yellow solid (92 mg, 60 %). ^1H-NMR ($CDCl_3$, 500 MHz) δ 7.90 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.31-7.28 (m, 5H), 3.55 (s, 2H), 3.52 (s, 2H), 2.58 (s, 3H), 2.56 – 2.41 (*br*. s, 8H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz) δ 197.9, 136.1, 129.26 (2C), 129.2 (2C), 128.4 (2C), 128.2 (2C), 127.1, 126.7, 63.1, 62.6, 53.2, 53.0 (2C), 26.7 (2C) ppm. IR (neat) ν 3064, 3029, 3005, 2948, 2908, 2797, 2762, 1678, 1605, 1267, 1160, 1129, 1010, 836, 727, 696, 591 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{25}N_2O$ 309.1967; Found 309.1971.

Deuterium Labeling:

Benzyl[3,7-dimethyl(2-deuterium)oct-6-en-1-yl]methylamine (**3-D$_2$**): In a 10 mL autoclave equipped with a stirring bar, under argon, (±)-citronellal (0.5 mmol, 1 equiv, 90 µL), *N*-benzylmethylamine (0.6 mmol, 1.2 equiv, 80 µL), **Fe3** (0.01 mmol, 2 mol %, 5.86 mg) and trimethylamine *N*-oxide (0.015 mmol, 3 mol %, 1.2 mg) were solubilized in free-O_2 deuterated methanol (CD_3OD; 1 mL). The autoclave was sealed and pressurized with hydrogen (5 bar), and the mixture was stirred for 16 hours at room temperature. The solvent was removed under vacuum and the crude product was purified by flash column chromatography on silica (Penatne/Et_2O 9/1). **3-D$_2$** was obtained as a colorless oil (105 mg, 81 %). ^1H-NMR ($CDCl_3$, 500 MHz): δ 7.32-7.29 (m, 4H), 7.26-7.21 (m, 1H), 5.09 (tt, J = 7.1; 1.3 Hz, 1H), 3.52-3.46 (q, J = 12.0 Hz, 2H), 2.39-2.35 (m, 2H), 2.17 (s, 3H), 2.04-1.89 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.46 (sextuplet, J = 6.6 Hz, 1H), 1.36-1.27 (m, 1H), 1.19-1.10 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ 139.3, 131.1, 129.1 (2C), 128.1 (2C), 126.8, 124.9, 62.4, 55.4, 42.3, 37.2, 34.1-33.5 (m, 1C), 30.7, 25.7, 25.5, 19.7, 17.6 ppm. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{28}D_2N$ 262.2504 ; found 262.2502.

Benzyl[3,7-dimethyl(1-deuterium)oct-6-en-1-yl]methylamine (**3-D$_1$**): In a 10 mL autoclave equipped with a stirring bar, under argon, (±)-citronellal (0.5 mmol, 1 equiv, 90 µL), *N*-benzylmethylamine (0.6 mmol, 1.2 equiv, 80 µL), **Fe3** (0.01 mmol, 2 mol %, 5.86 mg) and trimethylamine *N*-oxide (0.015 mmol, 3 mol %, 1.2 mg) were solubilized in free-O_2 methanol (1 mL). The autoclave was sealed and pressurized with deuterium (5 bar), and the mixture was stirred for 16 hours at room temperature. The solvent was removed under vacuum and the crude product was purified by flash column chromatography on silica (Penatne/Et_2O 9/1). **3-D$_1$** was obtained as a colorless oil (121 mg, 93 %). ^1H-NMR ($CDCl_3$, 500 MHz): δ 7.32-7.29 (m, 4H), 7.26-7.21 (m, 1H), 5.09 (tt, J = 7.1; 1.3 Hz, 1H), 3.52-3.42 (m, 2H), 2.37-2.31 (m, 1H), 2.17 (s, 3H), 2.04-1.89 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.58-1.52 (m, 1H), 1.46 (sextuplet, J = 6.6 Hz, 1H), 1.36-1.27 (m, 2H), 1.19-1.10 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ 139.3, 131.1, 129.1 (2C), 128.1 (2C), 126.8, 124.9, 62.4, 55.2 (t, J = 20 Hz, 1C), 42.2, 37.2, 34.3, 30.8, 25.7, 25.5, 19.7, 17.6 ppm. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{28}DN$ 261.2441; found 261.2444.

Benzyl[3,7-dimethyl(1,2,2-deuterium)oct-6-en-1-yl]methylamine (**3-D$_3$**): In a 10 mL autoclave equipped with a stirring bar, under argon, (±)-citronellal (0.5 mmol, 1 equiv, 90 µL), *N*-benzylmethylamine (0.6 mmol, 1.2 equiv, 80 µL), **Fe3** (0.01 mmol, 2 mol %, 5.86 mg) and trimethylamine *N*-oxide (0.015 mmol, 3 mol %, 1.2 mg) were solubilized in free-O_2 deuterated methanol (CD_3OD; 1 mL). The autoclave was sealed and pressurized with deuterium (5 bar), and the mixture was stirred for 16 hours at room temperature. Solvent was removed under vacuum and the crude product was purified by flash column chromatography on silica (Penatne/Et_2O 9/1). **3-D$_3$** was obtained as a colorless oil (107 mg, 82 %). ^1H-NMR ($CDCl_3$, 500 MHz): δ 7.32-7.29 (m, 4H), 7.26-7.21 (m, 1H), 5.09 (tt, J = 7.1; 1.3 Hz, 1H), 3.52-3.42 (m, 2H), 2.37-2.31 (m, 1H), 2.17 (s, 3H), 2.04-1.89 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.46 (sextuplet, J = 6.6 Hz, 1H), 1.36-1.27 (m, 1H), 1.19-1.10 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ 139.3, 131.1, 129.1 (2C), 128.1 (2C), 126.8, 124.9, 62.4, 55.2 (t, J = 20 Hz, 1C), 42.2, 37.2, 34.1-33.5 (m, 1C), 30.8, 25.7, 25.5, 19.7, 17.6 ppm. HRMS (ESI+) *m/z*: $[M+H]^+$ Cacld for $C_{18}H_{26}D_3N$ 263.2567; found 263.2565.

6-[benzyl(methyl)amino]-1-phenylhexan-1-one (**27-D**): In a 10mL autoclave equipped with a stirring bar, under argon ketoaldehyde **41** (0.5 mmol, 95 mg) and *N*-benzylmethylamine (0.6 mmol, 1.2 equiv, 80 µL), **Fe3** (0.01 mmol, 2 mol%, 5.86 mg) and trimethylamine *N*-oxide (0.015 mmol, 3 mol%, 1.2 mg) were solubilized in free-O_2 deuterated methanol (CD_3OD; 1 mL). The autoclave was sealed and pressurized with hydrogen (5 bar), and the mixture was stirred for 16 hours at room temperature. The reaction mixture was extracted with dichloromethane (10 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtrated and concentrated under vacuum. The pure product was isolated after purification by flash column chromatography on silica (Dichloromethane/MeOH 9/1) as a yellowish oil (110 mg, 75 %). ^1H-NMR ($CDCl_3$, 500 MHz): δ 7.88 (d, J = 7.9 Hz, 2H), 7.49 (tt, J = 7.2, 1.4 Hz, 1H), 7.39 (t, J = 7.9 Hz, 2H), 7.26-7.23 (m, 4H), 7.20-7.18 (m, 1H), 3.46 (s, 3H), 2.90 (t, J = 7.3 Hz, 0.5 H), 2.87 (tt, J = 7.0, 2.0 Hz, CDH), 2.35 (s, 2H), 2.16 (s, 3H), 1.70-1.66 (m, 2H), 1.50 (m, 0.3H), 1.36-132 (m, 2H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ 200.6, 200.5, 200.4, 137, 133, 129.2, 128.6, 128.3, 128.0, 127.2, 62.2, 57.0, 42.1, 38.5, 38.2 (t, J = 19.2 Hz), 37.8 (quint, J = 18.4 Hz), 27.0-26.9 (m), 26.7 (t, J = 19.6 Hz), 26.3 (quint, J = 18.6 Hz), 24.2-24.1 (m) ppm. IR (neat): ν 3061, 3027, 2932, 2839, 2784, 1682, 1448, 1267, 1025, 736, 690 cm^{-1}. HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{25}DNO$ 297.2077 Found 297.2073, $C_{20}H_{24}D_2NO$ calculated 298.2140 Found 298.2134, $C_{20}H_{23}D_3NO$ calculated 299.2203 Found 299.2193, $C_{20}H_{22}D_4NO$ calculated 300.2265 Found 300.2248.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Spectroscopic details of the catalytic reactions; DFT calculations

Data for $C_{27}H_{28}BF_4N_3O_3Fe$ (CIF) - CCDC: 1857379

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