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Iron-Catalyzed Reductive Ethylation of Imines Using Ethanol

Marie Vayer,[a] Sara P. Morcillo,[a] Jennifer Dupont,[a] Vincent Gandon*[a,b] and Christophe Bour*[a]

Abstract: The borrowing hydrogen strategy has been applied to the ethylation of imines, using an air-stable iron complex as precatalyst. This approach opens new perspectives in this area, as it allows the synthesis of unsymmetric tertiary amines from readily available substrates and ethanol as C2-building block. A variety of imines bearing electron-rich aromatic or alkyl groups at the nitrogen atom could be efficiently reductively alkylated, without requiring the use of molecular hydrogen. The mechanism of this reaction, which shows a complete selectivity for ethanol, has been studied experimentally and by means of DFT computations.

Tertiary amines have a wide range of applications as pharmaceuticals and in material science.[1] Among them, some mono ethyl amines show prominent biological properties and are exploited as drugs and crop protecting agents. This framework can be found in a variety of compounds, such as non-steroidal drugs for breast cancer treatment,[2] novel anti-HCV agents,[3] or synthetic plant growth regulators (Figure 1). These tertiary N-ethyl amines are also frequently encountered in molecular thermal-transfer dyes,[4] or in pigments.[5]

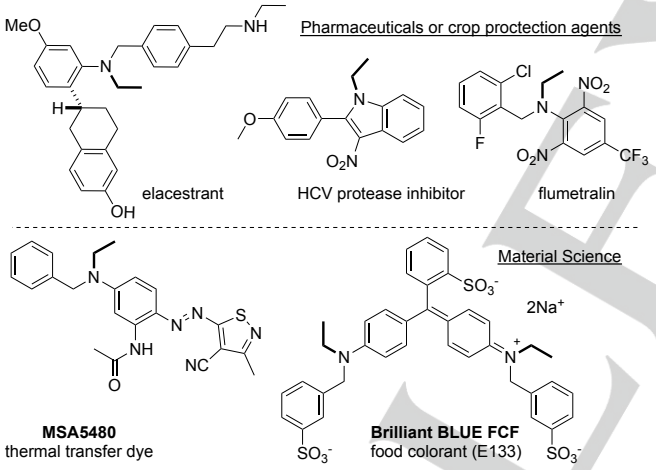
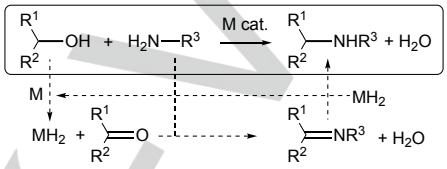


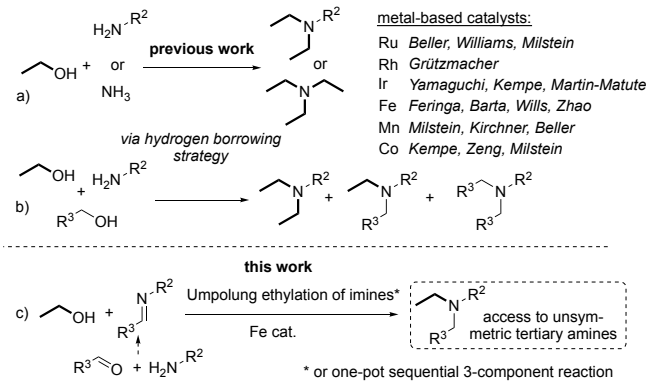
Figure 1. Selected biologically active compounds or molecular materials featuring *N*-ethyl unsymmetric tertiary amine.

Classical methods for amine ethylation rely on the use of toxic reagents such as acetaldehyde, ethyl halides or their equivalents (diethylsulfate or sulfonate).[6] Among the alternative strategies, one could think about the direct amination of alcohols through *borrowing hydrogen catalysis* (Scheme 1),[7] which has been recognized as one of the most practical methods to substitute amines by alkyl groups.[1] The broad availability of amines and alcohols, combined with the fact that water is the only by-product, are the reasons for its large-scale implementation in the industry. It was first reported with simple 2nd and 3rd row late transition metal complexes, which were rapidly followed by more elaborated well-defined species (Ru,[8] Rh,[9] Ir,[10] or Os[11]). The current trend is to replace these noble elements by more abundant 1st row transition metals. In that respect, significant improvements have been made by using Mn ,[12] Fe-[13] and Co-based catalysts.[14]



Scheme 1. Metal-catalyzed amination of alcohols.

Despite these advances, access to tertiary amines is mainly limited to products bearing two or three identical substituents (see Scheme 2a in the case of ethyl groups). Using two different alcohols usually leads to mixtures, as shown in Scheme 2b.[13d] In 2015, Shi et al reported an alcohol amination strategy for providing unsymmetric tertiary amines from primary amines via the use of aluminum oxide catalysts doped with copper.[15] Despite its flexibility, this approach requires harsh conditions and high catalyst loadings. A few unsymmetric tertiary amines have been synthesized by direct amination of readily oxidizable benzyl alcohols using secondary amines.[13d] Given the above considerations, methodologies allowing practical synthesis of unsymmetric tertiary amines remain highly desirable. Herein, we report an efficient and straightforward reductive ethylation of imines using ethanol as C_2 building block and an iron complex as catalyst (Scheme 2c).[16] An example of one-pot sequential 3-component reaction where the imine is generated in situ is also provided.



Scheme 2. N-Ethyl tertiary amine synthesis via the hydrogen borrowing strategy.

More specifically, we were attracted by (cyclopentadienone)iron

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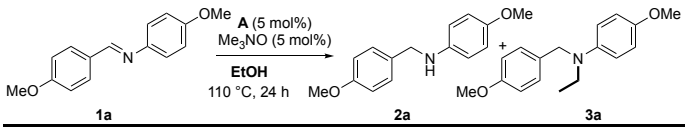
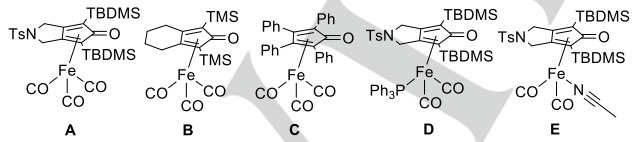
carbonyl complexes,[17] which have been used as catalysts for imines[18] or ketones hydrogenation,[19] as well as alcohol oxidation,[20] via the borrowing hydrogen mechanism. We found that the right combination of an iron carbonyl precatalyst and ethanol allowed the title reaction. To the best of our knowledge, no reports mention this type of Umpolung catalytic imine alkylation reaction.[21] Moreover, this method is complimentary to the amine methylation procedure with CO_2,[22] since ethanol can be produced sustainably.[23] After evaluation of different reaction parameters (see Tables S1-3 in the Supporting Information), we found that imine **1a** could be fully converted into ethyl amine **3a** in 99% yield in the presence of the Knölker-type iron complex **A** as precatalyst (5 mol%),[24] Me_3NO as activator (5 mol%)[19a] in EtOH (0.2 M) at 110 °C in 24 h (Table 1, entry 1).

Table 1. Catalyst screening and optimization for the N-ethylation of imine **1a**



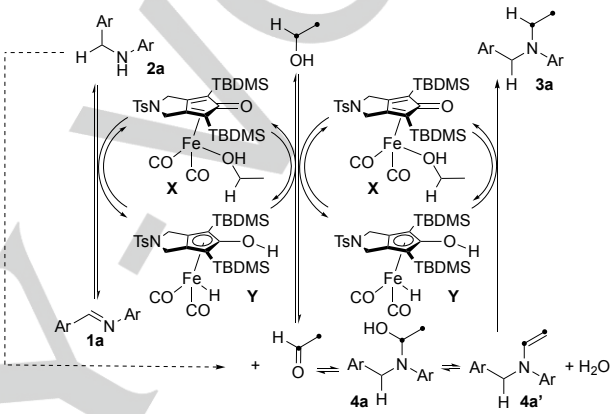
Entry	Deviation from above conditions[a]	Ratio [%][b] (**1a**/**2a**/**3a**)
1	none	0/0/100 (97)[c]
2	with 1 mol% of **A** instead of 5 mol%	91/9/-
3	K_2CO_3 instead of Me_3NO	100/-/-
4	THF/EtOH (1/1 v/v, 0.2 M) instead of EtOH	5/23/72
5	THF/EtOH (0.2 M/3 equiv) instead of EtOH	27/65/8
6	CPME/EtOH (0.2 M/3 equiv) instead of EtOH	20/80/0
7	precatalyst **B** instead of **A**	38/28/34
8	precatalyst **C** instead of **A**	43/52/5
9	precatalyst **D** instead of **A**	100/0/0
10	*precatalyst **E** instead of **A** and without Me_3NO*	*0/0/100 (99)*
11	other alcohols instead of EtOH	mostly **2a**

[a] Standard conditions: in a sealed tube, imine **1a** (0.2 M), iron complex **A** (5 mol%), Me_3NO (5 mol%) in EtOH at 110 °C for 24 h. [b] Determined by GC. [c] Isolated yield.



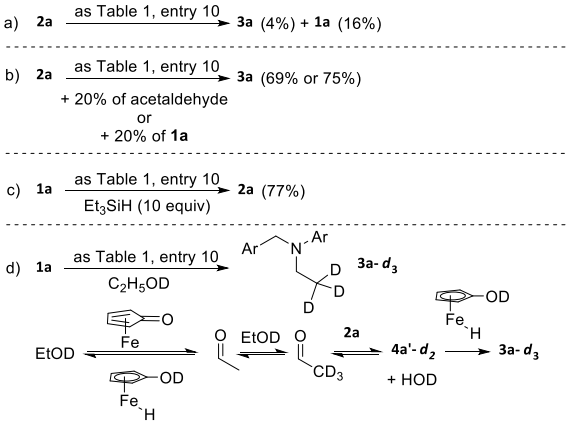
Remarkably, the hydrogenation product **2a** was not observed. Decreasing the catalyst loading to 1 mol%, or treating **A** with K_2CO_3 instead of Me_3NO inhibited the reaction (entries 2 and 3). Adding THF or CPME in the reaction mixture strongly encouraged the formation of **2a** (entries 4-6).[25] Precatalysts **B**-**D** proved poorly efficient (entries 7-9). Gratifyingly, when the air-stable iron-dicarbonyl-nitrile complexes **E** was used,[18b,26] **3a** was isolated in 99% yield, without activation with Me_3NO (entry 10). As noted previously, the TBDMS groups can enhance the reactivity by preventing iron dimers formation.[19b, 20c] Importantly, whatever the precatalyst used, the alkylation was not oberved with other primary alcohols which mostly led to the hydrogenation product **2a** (entry 11, see Table S4 for details).[18f]

The complete selectivity for EtOH in this alkylative process raised questions regarding its mechanism. A tentative one is shown in Scheme 3. The reaction to form **3a** starts with the coordination of EtOH to iron to give complex **X** and then concerted oxidation of EtOH generates the Fe(II) hydride **Y** and acetaldehyde.[19a-b] Hydrogen transfer from **Y** to imine **1a** leads to amine **2a**, while regenerating the unsaturated Fe(0) complex **X**. Amine **2a** then reacts with acetaldehyde to give hemiaminal **4a**[27] and then enamine **4a'**. Hydrogen transfer from **Y** to **4a'** delivers the final product **3a**. Apart from the last one, all steps are presumably equilibrated.



Scheme 3. Mechanistic proposal (Ar = 4-$MeOC_6H_4$).

This rationale is supported by previous contributions,[7,18] and by the following experiments. The reaction progress was monitored by GC (see Figure S1), which revealed that **2a** is the precursor of **3a**. However, when the reaction was carried out with amine **2a** as starting material, only traces of **3a** were formed (Scheme 4a).



Scheme 4. Mechanistic investigations (Ar = 4-$MeOC_6H_4$).

A low amount of imine **1a** was also detected, indicating the reversibility of the process. Interestingly, after adding a catalytic amount of acetaldehyde or imine **1a**, full conversion into **3a** was reached (Scheme 4b). This result clearly reveals the

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interdependence of the two catalytic cycles and that acetaldehyde is a likely intermediate. When Et_3SiH was used as competitive reducing agent, only the hydrogenation product **2a** was observed, thus confirming that ethanol is both the hydrogen transfer and the alkylating agent (Scheme 4c).[28] Using C_2D_5OD, only a low amount of hydrogenated imine was isolated. The formation of the Fe(II) complex seems to be severely slowed down,[19a] as well as the capture of acetaldehyde-d_4 and the reduction of the corresponding adducts. On the other hand, using EtOD led to **3a-d_3** as major product, showing complete deuterium incorporation at the β-ethyl position (Scheme 4d). This suggests that the produced acetaldehyde undergoes rapid H/D exchange[29] in C_2H_5OD to become D_3CCHO prior to be trapped by **2a**. Thus, the combination of a rapid trapping of the formed aldehyde (which rules out larger alcohols)[30] and of the reduction of resulting enamine (which rules out MeOH), might be at the origin of the complete selectivity for EtOH.[31] We decided to investigate the ability of a complex such as **Y** to transfer its two hydrogen atoms to a model enamine by DFT computations (Figure 2, see the Supporting Information for details). The hydrogenation was predicted as straightforward, requiring only 8.0 kcal/mol of free energy of activation. It is moderately exergonic, but the dissociation of the complex and its reoxidation should ensure an overall irreversibility. Of note, with an additional methyl group at the double bond terminus, the hydrogenation is slower but still very reasonable in energy ($\Delta G^{\ddagger}_{298}$ 10.1 kcal/mol). Thus, it is not only this step that would account for the absence of alkylation when *n*-PrOH is used, but also the rate of the trapping of propanal and that of the formation of the enamine.

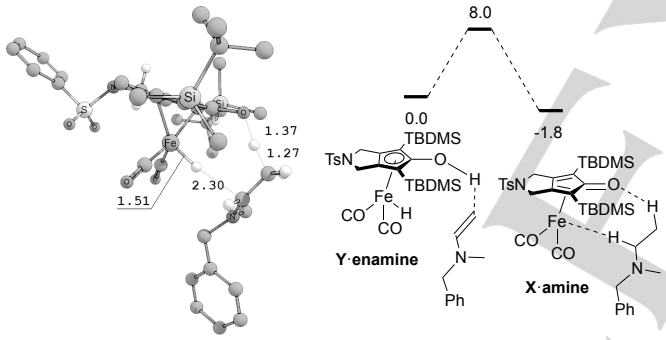
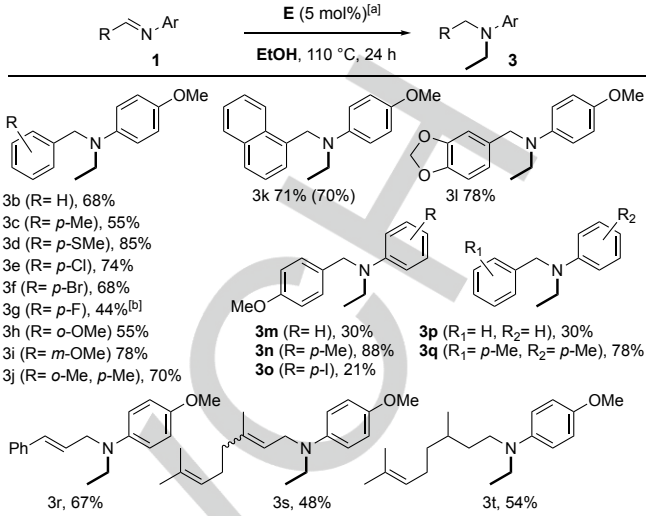
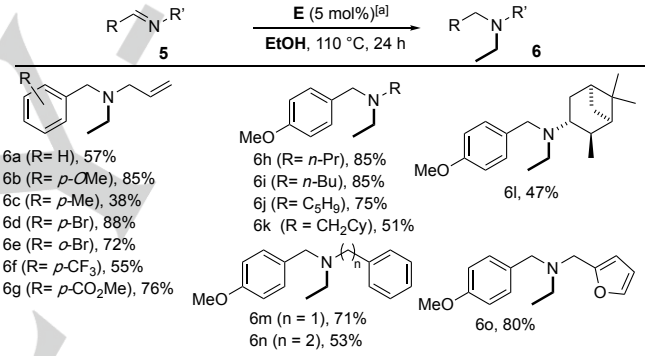


Figure 2. Computed transition state for the hydrogenation of a model enamine (left, some hydrogen atoms have been ommited for clarity, distances in Å) and corresponding free energy profile (right, ΔG_{298}, kcal/mol).

To demonstrate the effectiveness of this novel catalytic ethylation, various aromatic imines were tested (Scheme 5). Yields are mostly good to high, provided the aromatic group at the nitrogen atom is electron-rich. Interestingly, while iron hydrides are known to promote the isomerization of alkenes, no C=C bond migration was observed with **1r-t**.[16a] We next explored the applicability of the reductive N-ethylation reaction with a series of alkyl imines (Scheme 6). Such substrates proved also compatible with the title reaction and provided the desired unsymmetric tertiary amines with high chemoselectivity. Imines exhibiting short chains (C_3, C_4) or cycloalkanes at the nitrogen were also successfully ethylated to give unsymmetric tertiary benzylamines, which are of major interest to the industry of surfactants, flotation agents, gasoline detergents, rubber processing additives, etc.[32] The fact that electron-rich aryl imines (Scheme 5) and alkyl imines (Scheme 6) work well in this chemistry is consistent with the proposed trapping of acetaldehyde (Scheme 3), which requires the most nucleophilic amines to displace the equilibrium.

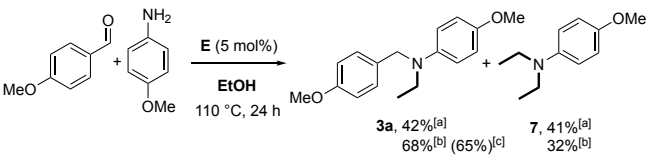


Scheme 5. Reductive N-ethylation of aromatic imines with ethanol. [a] Reaction conditions: in a sealed tube, imine (0.1-0.2 mmol, 0.2 M), **E** (5 mol%) in EtOH, 110 °C, 24 h. Yields of isolated products are given. [b] At 130 °C.



Scheme 6. Reductive N-ethylation of alkyl imines with ethanol. [a] Reaction conditions: in a sealed tube, imine (0.1-0.2 mmol, 0.2 M), **E** (5 mol%) in EtOH, 110 °C, 24 h. Yields of isolated products are given.

A multi-component approach where the imine is generated in situ was also briefly investigated (Scheme 7). A mixture of *p*-anisaldehyde and *p*-anisidine was converted into the desired product **3a**, accompanied in equal amount by the diethylation product **7**. Since this product results from the ethylation of the starting aniline, we decided to wait for the imine to be formed prior to adding the iron catalyst. Although the imine formation proved to be complete within 1 h, the presence of water in the reaction medium disrupted the equilibria and the diethylation product **7** was again observed by GC analysis. The hydrolysis of the imine is probably encouraged by the fast ethylation of the resulting primary amine and of the subsequent secondary one.[33] Nevertheless, the desired product could be isolated in 65% yield, showing the feasibility of a one-pot process.



Scheme 7. One-pot synthesis of an unsymmetric tertiary amine. [a] Reaction conditions: aldehyde (0.37 mmol), amine (0.40 mmol), **E** (5 mol%) in EtOH

(2 mL) at 110 °C, 24 h. GC conversion. [b] Same as [a] but **E** is added after 1 h of stiring at 110 °C. GC conversion [c] Isolated yield.

In conclusion, we have disclosed a general catalytic approach for the reductive ethylation of imines, using ethanol as a sustainable C_2 building block. This transformation proceeds with good chemoselectivity with an air-stable iron complex as precatalyst. This straightforward method eases the synthesis of unsymmetric ethylated tertiary amines and is complemetary to the aforementioned methylation procedure.[22]

Acknowledgements

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Keywords: amines • borrowing hydrogen • ethylation • catalysis • iron

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[30] When the reaction was carried out with amine **2a** (0.2 M) in the presence of propanal (20 mol%) in *n*PrOH, no alkylation was observed.

[31] The volatility of methanal at high temperature could also prevent methylation.

[32] *Global Tertiary Amines Market to 2022: Production, Consumption, Revenue, Gross margin and more*, DOI 10.1787/100111226661.

[33] The use of $MgSO_4$ or molecular sieves considerably reduced the activity of the catalyst.

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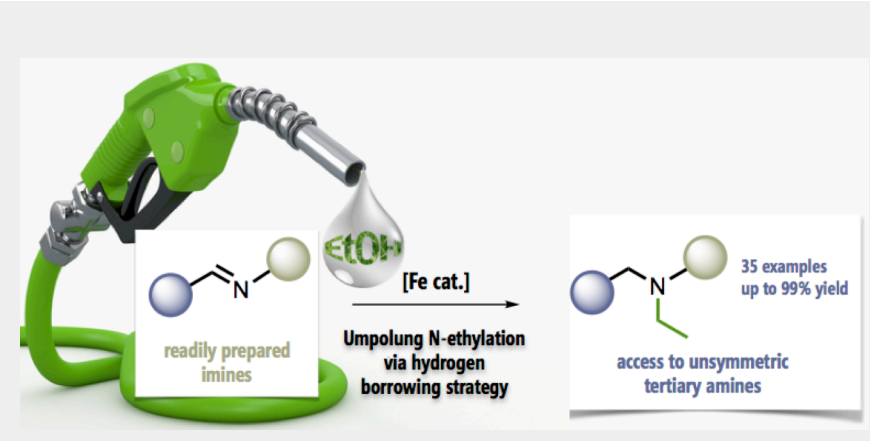

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