Green Chemistry



View Article Online

COMMUNICATION



Cite this: DOI: 10.1039/c6gc00565a Received 27th February 2016, Accepted 25th April 2016 DOI: 10.1039/c6gc00565a

www.rsc.org/greenchem

Sustainable iron-catalyzed direct imine formation by acceptorless dehydrogenative coupling of alcohols with amines[†]

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The Acceptorless Dehydrogenative Coupling (ADC) of alcohols with amines is reported using a heterogeneous Fe-catalyst. The reaction operates under mild conditions with the liberation of dihydrogen and water as the byproducts. The developed ADC strategy is simple, efficient, exhibits wide functional group tolerance and can be scaled up. The present catalytic approach possesses a dual role; acting as a catalyst as well as being magnetically separable. The sustainable reuse of a heterogeneous iron catalyst is also shown.

Introduction

Imines are an exceptionally versatile functional group and are ubiquitous in pharmaceuticals, biologically active heterocycles, and natural products.1 Traditionally, imine formation was achieved by the condensation reaction of amines with highly reactive carbonyl compounds and often required dehydrating agents as well as Lewis acid catalysts.^{2,3} However, the direct formation of imines with easily accessible feedstock chemicals is very attractive and highly desirable in organic synthesis.⁴ In this context, various methods for imine synthesis have been studied based on the oxidative dehydrogenation of amines,^{5,6} and oxidative dehydrogenative coupling of alcohols with amines using various oxidants such as dioxygen, TEMPO, quinine, and iodosylbenzene.7,8 However, several drawbacks remain, for example, the intrinsic self-coupling properties of the substrates, the formation of other side products such as nitrile, amide, azo and a related compound, and the need for a stoichiometric amount of oxidants.⁶ Although the use of molecular oxygen as a mild oxidant is an attractive strategy, oxidative dehydrogenative coupling accomplished with O_2 might be problematic at higher pressures (need for special highpressure equipment) that are usually used on large scales to increase the effective concentration of the oxidant. Thus, the development of an efficient strategy for the selective construction of imine scaffolds under oxidant-free conditions is a key motivation in contemporary science.

Recently a direct coupling of alcohols with amines by the acceptorless dehydrogenative strategy has been developed as an efficient protocol to construct imine bonds (C=N) with the liberation of molecular hydrogen and water as the byproducts, which is a greener and more practical method. Despite several efficient homogeneous catalysts being well-developed for acceptorless dehydrogenation reaction under oxidant-free conditions,⁹ the major disadvantages such as the use of noble metals, extensive ligand synthesis, sensitivity, handling under practical conditions, poor recovery and competing hydrogen atom transfer reaction¹⁰ (leads to a mixture of amine and imine products) remain unaddressed. However, in a very recent report by Feringa and co-workers, imine was reported as the potential intermediate in the homogeneous Fe-catalyzed direct alkylation of amines with alcohols via hydrogen atom transfer reaction.¹¹ Indeed, heterogeneous catalysts with such activity for the straightforward synthesis of an imine by the oxidant-free, acceptorless dehydrogenative coupling of alcohols with amines are rare and very limited. Very recently, Pt nanoparticles loaded on TiO2 were shown to promote the direct synthesis of imines from alcohols and amines under UV irradiation,12 and Pd(0)-immobilized recyclable hydrotalcite catalysts (HT4) for alcohol imination via acceptorless dehydrogenation were also reported.¹³ Notably, catalysts (both homogeneous and heterogeneous) used for imine synthesis by the ADC strategy are extensively based on precious metals. In this regard, the development of novel highly active and selective non-precious metal catalysts; in particular, base metal catalysts is of pivotal importance and a focus point from the perspective of cost, abundance, and sustainable chemistry.^{14,15} To the best of our knowledge, there are no reusable heterogeneous catalysts based on earth-abundant, economical 'green' metals for

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direct imine formation by the acceptorless dehydrogenative coupling of alcohols with amines.

During the last decade, N-doped graphene materials have been shown to be an interesting commodity for sustainable catalysis.¹⁶ Inspired by these results, herein we report the preparation of a heterogeneous iron-based catalyst (Fe-Phen@C) and describe for the first time the environmentally benign dehydrogenative coupling of alcohols and amines to form imines and H₂ (Scheme 1).



Scheme 1 Overview of the present work and the reusable Fe-based heterogeneous catalyst used in this study.

Results and discussion

The active heterogeneous iron catalyst was prepared by the pyrolysis of an *in situ* generated Fe–Phen complex (Fe(acac)₃:1,10-phenanthroline = 1:1) on an exfoliated graphene oxide support at 800 °C for 4 h under an argon atmosphere.^{17,18} The complete characterization of the active material (Fe–Phen@C) has been carried out using PXRD, TEM analysis, SEM analysis, XPS, ICP and Raman spectroscopy (see the ESI† for characterization data).

The XRD pattern of the Fe–Phen@C sample presented in Fig. 1 shows diffraction peaks confirming the presence of β'' -Fe₂O₃ (JCPDS no 40-1139), Fe₃O₄ (JCPDS no 85-1436), Fe₃N (JCPDS no 01-1236), Fe₃C (JCPDS no 85-1317) and Fe₇C₃ (JCPDS no 17-0333). The formation of Fe₃N was probably due to the decomposition of the N-containing Fe–phenanthroline complex on exfoliated graphene oxide (EGO). A peak at $2\theta = 26.6$ degrees corresponding to the (002) lattice plane of reduced graphite oxide (RGO) was also observed. The peak is broad suggesting that the carbon support was composed of a few layers of graphene sheets. In Fig. 2(a) the TEM image of the Fe–Phen@C sample is shown. In the bright field image,



Fig. 1 XRD spectra of the Fe–Phen@C material with indices of peaks with the pattern of β'' -Fe₂O₃, Fe₃O₄, Fe₃C₃, Fe₃N, Fe₃C, and graphite.



Fig. 2 (a) Microstructural characterization of the Fe–Phen@C material TEM image of Fe–Phen@C; scale bar, 50 nm. (b) FESEM image of Fe–Phen@C; scale bar, 1 μ m.

one can observe the wrinkles on the thin layers of the RGO support as dark lines and Fe-rich nanoparticles as dark spots. It can be observed that the nanoparticles are located only on the RGO sheets. The nanoparticles distributed throughout the graphene sheets varied in size from 8 to 50 nm. However, the majority of particles were in the range of 14–20 nm. The FESEM image in Fig. 2(b) shows the morphology of the as-prepared Fe–Phen@C catalyst. In the dark field, FE-SEM of Fe–Phen@C was taken using secondary electrons in which the metal which has a high surface electron density appears brighter than RGO. It can be observed that Fe-rich particles are distributed spatially apart on the graphene layers.

A recent unprecedented report from our research group on the heterogeneous iron-catalyzed acceptorless dehydrogenation of fundamentally important feedstocks such as alcohols to carbonyl compounds and cyclic amines to N-heterocycles¹⁷ prompted us to disclose our first report on a simple, efficient, reusable heterogeneous iron-catalyzed direct imine formation method by the acceptorless dehydrogenative coupling of alcohols with amines (Scheme 1, Table 1). The present ADC strategy has a broad substrate scope as well as functional group tolerance, and operates under mild conditions with the liberation of hydrogen gas and water as the by-products, thus making the protocol completely environmentally-benign. An ease of separation and reusability of the heterogeneous iron catalyst is also successfully demonstrated.

Optimization studies on iron-catalyzed direct imine formation by the ADC of alcohols with amines are summarized in Table 1. We began our investigation using (4-chlorophenyl) methanol (**1a**) and *m*-toluidine (**2a**) as benchmark substrates in the presence of a catalytic amount of Fe–Phen@C (8 mol%), and *t*-BuOK (10 mol%) in *n*-octane heated at 120 °C (bath temperature) under an open Ar atm for 24 h to yield **3aa** in 93% isolated yield with the complete conversion of **1a** (Table 1, entry 1). Indeed, the formation of molecular hydrogen was qualitatively analyzed by gas chromatography (GC). Performing the reaction under closed conditions yielded **3aa** in lower yield (40%) (Table 1, entry 2) clearly indicating that the constant removal of H₂ gas from the reaction medium is crucial.^{9,10,19} Notably, the efficiency of the reaction was



Entry	Cat.	Variation from the initial conditions	Conversion of $1a^{b}$ (%)	Yield of 3aa b (%)
1	Fe-Phen@C	None	99	$97(93)^{c}$
2	Fe-Phen@C	Closed system	57	40 ^c
3	Fe-Phen@C	Without <i>t</i> -BuOK	17	8
4	Fe-Phen@C	K_2CO_3 instead of <i>t</i> -BuOK	35	19
5	Fe-Phen@C	KOH instead of <i>t</i> -BuOK	8	0
6	Fe-Phen@C	CH_3CN instead of <i>n</i> -octane	19	15
7	Fe-Phen@C	Toluene instead of <i>n</i> -octane	64	46
8	Fe-Phen@C	At 80 °C	40	$34^{c,d}$
9	Fe@C	None	5	0
10	Phen@C	None	0	0
11		Without Fe-Phen@C	0	0
12^e	Fe(acac) ₃ /Phen	Under homogeneous conditions	8	Trace
13 ^e	Fe(CO) ₅ /Phen	Under homogeneous conditions	Trace	0
14	Fe-Phen@SiO ₂	None	31	18
15	Fe-Phen@Al ₂ O ₃	None	17	8
16	Fe-Phen@TiO ₂	None	46	31^c

^{*a*} Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), cat. Fe–Phen@C (8 mol%), *t*-BuOK (10 mol%), and *n*-octane (2 mL) heated at 120 °C (oilbath temperature) for 24 h under an open argon atm. ^{*b*} Conversion of **1a** and yield of **3aa** are based on GC using anisole as the internal reference. ^{*c*} Isolated yields. ^{*d*} After 48 h. ^{*e*} Reaction under homogeneous conditions using the *in situ* generated Fe-catalyst by reacting a 1:1 mixture of Fe salt and 1,10-phenanthroline (Phen) followed by treatment with *t*-BuOK (10 mol%).

significantly affected in the absence of t-BuOK (Table 1, entry 3). Other bases like K₂CO₃ and KOH are ineffective under standard reaction conditions (Table 1, entries 4 and 5).^{20,21} The solvent dependency of the same reaction was carried out (Table 1, entries 1, 6 and 7) and we found that the reaction proceeds efficiently in *n*-octane as compared to other solvents.²² By lowering the temperature, we obtained the product in lower yield (Table 1, entry 8) and no reaction was observed in the absence of the Fe-Phen@C catalyst (Table 1, entry 11). Notably, no imine formation or hydrogen gas was observed under homogeneous conditions (Table 1, entries 12 and 13).²³ It is worth noting that under similar experimental conditions, catalysts (Fe-Phen) prepared on other conventional supports such as SiO₂, Al₂O₃ and TiO₂ showed lesser activity in the imine formation (Table 1, entries 14-16).^{18,24} These studies show that the special structure of reduced graphene oxide (RGO) may affect the reactivity in the environmentally-benign dehydrogenative coupling of alcohols and amines to form imines and H₂.

With an optimized catalytic system in hand (Table 1), we set out to probe its versatility in the direct imine synthesis of various alcohols and amines by the ADC strategy. Using (4-chlorophenyl)methanol **1a** as the benchmark substrate, a number of different anilines were tested using the Fe–Phen@C catalyst under standard conditions. As shown in Table 2, the present heterogeneous Fe-catalysis is compatible with various anilines containing electron-rich and electron-deficient substituents, affording the desired imines in good to excellent yields (up to 95%) under very mild, eco-benign conditions. Interestingly, the reaction proceeded successfully with both cyclic and acyclic secondary amines and gave the desired imines **3an** (81%), **3ao** (74%), **3ap** (73%), and **3aq** (62%) in good yields. It was noteworthy that benzylamine (**2r**) also afforded the corresponding imine in moderate yield (40%), along with the formation of (*E*)-*N*-benzyl-1-phenylmethanimine (26% by GC) by the dehydrogenative self-coupling of **2r**. The reaction of benzene-1,3-diamine (**2s**) and **1a** selectively gave the corresponding diimine (**3as**) in 75% isolated yield under our catalytic conditions.

Next, the impact of varying the substituents on the alcohol coupling partner was also assessed (Table 3). The straightforward imine formation reaction proceeded in excellent yields with either electron donating (4-methyl, 4-methoxy) or electron withdrawing (4-fluoro, 4-nitro) substituents on the benzyl alcohol. Notably, *ortho*-substituted alcohols yielded the imines (**3bi** and **3bj**) in lower yields, which could be explained by steric effects.²⁵ To our delight, biomass-derived furfuryl alcohol also gave the corresponding imine in good yield (**3bk** in 76% yield). The less reactive cinnamyl alcohol was also tested for the direct imine formation reaction and efficiently gave the corresponding imine in 45% isolated yield with 66% selectivity. However, 1-hexanol failed to convert into the corresponding aliphatic imine (**3bm**) under optimized conditions.

Gram-scale synthesis

We have successfully shown the scalability and particle viability of this catalytic protocol under standard conditions. In this regard, the present iron-catalyzed direct imine synthesis was

Table 2 Iron-catalyzed direct imine synthesis: scope of amines^{a,b}



^{*a*} Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), cat. Fe-Phen@C (8 mol%), *t*-BuOK (10 mol%), and *n*-octane (2 mL) heated at 120 °C (oil-bath temperature) for 24 h under an open argon atm. ^{*b*} Yields in parentheses are based on the conversion of **1a** and selectivity of imines (3) respectively and are based on GC using anisole as the internal reference. ^{*c*} Isolated yields. ^{*d*} Self-dehydrogenative coupling of benzylamine to (*E*)-*N*-benzyl-1-phenylmethanimine was observed as the side reaction. ^{*e*} 2 equiv. of **1a**.

tested for the gram-scale synthesis of **3aa**, and it worked excellently with the expected imine obtained in 78% isolated yield after 36 h (Scheme 2). The result implies that the heterogeneous Fe-based catalytic system has a potential in the largescale production of imines under operationally simple, environmentally benign conditions.

Time-dependent experiments on direct imine formation by the ADC of alcohols with amines were conducted using a heterogeneous iron-catalyst to study the reaction kinetics (Fig. 3). Continuous sampling was undertaken with different time intervals, and the conversion of alcohol (1a) and yield of imine (3aa) were determined by gas chromatography. The formation of an aldehyde intermediate was observed during the reaction pathway, along with the desired imine as the major product.
 Table 3
 Iron-catalyzed direct imine synthesis: scope of alcohols^{a,b}



^{*a*} Reaction conditions: **1** (0.5 mmol), **2a** (0.55 mmol), cat. Fe–Phen@C (8 mol%), *t*-BuOK (10 mol%), and *n*-octane (2 mL) heated at 120 °C (oil-bath temperature) for 24 h under an open argon atm. ^{*b*} Yields in parentheses are based on the conversion of alcohol and selectivity of 3 respectively and are based on GC using anisole as the internal reference. ^{*c*} Isolated yields. ^{*d*} Based on ¹H NMR of the crude reaction mixture.



Scheme 2 Gram-scale synthesis of imine (3aa).



Fig. 3 Reaction profile for the iron-catalyzed formation of **3aa**. Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), cat. Fe–Phen@C (8 mol%), t-BuOK (10 mol%), and *n*-octane (2 mL) heated at 120 °C (oil-bath temperature) under an open argon atm.

Reusability and heterogeneity

The significant advantage of heterogeneous catalysts over soluble homogeneous catalysts is their capability for easy separation and recycling. The iron catalyst was easily separated from the reaction medium under a strong magnetic field, as shown in Fig. 4a & b. The recovered heterogeneous Fe-Phen@C was reused for direct imine synthesis in at least six cycles without a considerable loss in the yield (Fig. 4c).¹⁸ The results were within the error limits, and indeed, no deactivation of the catalyst was observed. The hot filtration test was carried out, and it was observed that no further imine formation (3aa) took place after the catalyst was filtered off at the conversion of 1a in 67% yield. Inductively coupled plasma (ICP) analysis confirmed that the iron concentration in the filtrate was less than 0.22 ppm. Notably, no imine formation was observed in the reaction under complete homogeneous conditions (Table 1, entries 12 and 13).²³ All these results clearly demonstrate that the present Fe-catalysis is truly heterogeneous in nature.

Mechanistic study

The high activity and selectivity of the Fe-catalyst in the direct imine formation by the acceptorless dehydrogenative coupling of alcohols with amines motivated us to gain an insight into the mechanistic details (Scheme 3). In this regard, we performed the acceptorless dehydrogenation of alcohol, **1a** (in the absence of amine) under identical conditions, and a quantitative yield of the corresponding aldehyde was obtained after 24 h with the liberation of hydrogen gas.¹⁷ The formation of H₂ gas in the Fe–Phen@C catalyzed direct synthesis of imines from alcohols and amines was qualitatively observed on gas chromatography. We have also endeavored to investigate the



Fig. 4 Separation of the catalyst under a strong magnetic field ((a): reaction mixture; (b): under magnetic field). (c) Recovery and reuse of the Fe–Phen@C catalyst.



Scheme 3 Mechanistic studies.

effect of the catalyst in the consequent condensation step. It was clearly observed that the rate of condensation of aldehydes and amines was accelerated in the presence of the Fe–Phen@C catalyst, which implies the presence of Lewis acid sites on the catalyst.

To determine if any radical intermediates (e.g. superoxide radical anion, O_{2}^{-} ; due to the presence of residual oxygen/air or use of t-BuOK) were involved in the reaction, we performed the reaction in the presence of a radical scavenger (2,6-di-tertbutyl-4-methylphenol). The scavenger had no effect on the reaction rate in the formation of 3aa, and thus the effect of residual oxygen or air as an oxidant, and the involvement of a radical mechanism can be completely ruled out.²⁶ Indeed, t-BuOK is required to activate alcohols for the initial dehydrogenation reaction. A deuterium labeling experiment unambiguously illustrated that the initial alcohol dehydrogenation step is irreversible. Thus, upon treatment of a 1:1 mixture of 4-methylbenzyl alcohol and $\alpha, \alpha - d_2$ -(4-chlorophenyl)methanol with *m*-toluidine 2a (1.1 equiv.) at 120 °C in *n*-octane for 22 h with a catalytic amount of Fe-Phen@C catalyst (8 mol%) and t-BuOK (10 mol%), 69% of (E)-1-(4-chlorophenyl)-N-(m-tolyl) methanimine-d (3aa-d) and 37% of (E)-N-m-tolyl-1-(p-tolyl) methanimine (3bd) were obtained as reaction products (Scheme 3d). H/D scrambling was not detected in both of the imine products, suggesting that the initial alcohol dehydrogenation step is irreversible.

Conclusions

In summary, a more sustainable iron-catalyzed direct imine formation by the acceptorless dehydrogenative coupling of alcohols with amines under oxidant-free conditions is reported for the first time. The reaction operates under very mild and environmentally benign conditions with the liberation of

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dihydrogen and water as the byproducts. The present catalytic approach possesses a dual role; acting as a catalyst as well as being magnetically separable. The recyclability experiments showed that the catalytic activity for imination can be retained for at least six cycles. The present strategy has great potential for the straightforward synthesis of imines from feedstock chemicals because it tolerates a wide range of substrates with high yields. Mechanistic studies showed that the reaction proceeds in a tandem manner (*via* aldehyde formation), and deuterium labeling experiments unambiguously illustrated that the initial alcohol dehydrogenation step is irreversible.

Acknowledgements

This research is supported by the SERB (SB/FT/CS-065/2013) and EMR/2015/30 (under Green Chemistry program) and CSIR-NCL. GJ thanks UGC and VGL thanks CSIR for fellowships and DJ acknowledges the financial support of DST-Ramanujan Fellowship (RJN-112/2012) and BRNS (37(2) 14/21/2015/BRNS). We thank Dr P. R. Rajamohanan for the NMR facility and Dr S. P. Borikar for GC-MS analysis. EB thanks Dr Abhishek Dey, IACS, Kolkata for providing Fe(CO)₅.

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- 19 Interestingly we did not observe any imine hydrogenated product (*via* borrowing hydrogen strategy), probably Fe-Phen@C does not act as a hydrogenating catalyst under these conditions.
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- 21 The role of the base (*t*-BuOK) is unclear in the present Fecatalysis. However, we believe that a catalytic amount of the base is required to activate the alcoholic substrates.
- 22 Further screening using a representative set of common solvents, including apolar arenes (*o*-xylene, PhCl, anisole), or polar DMF, DMSO, DMA, and DCE proved ineffective.
- 23 The reaction was performed under an *in situ* generated soluble Fe–Phen complex by reacting a 1:1 mixture of either the readily available Fe(m)-acetylacetonate or $Fe(CO)_5$ as the iron precursor and 1,10-phenanthroline as a ligand followed by treatment with a catalytic amount of a base (10 mol% of *t*-BuOK).
- 24 Formation of molecular hydrogen was not observed on GC.
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