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A nanoscale iron catalyst for heterogeneous direct N- and C-alkylations of anilines and ketones using alcohols via hydrogen autotransfer conditions

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A nanoscale iron catalyst for heterogeneous direct N- and C-alkylations of anilines and ketones using alcohols via hydrogen autotransfer conditions
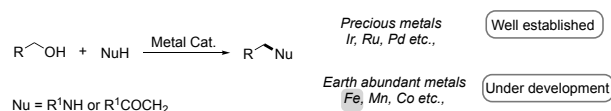
Abstract: Here, we report a commercially available nanoscale Fe catalyst for heterogeneous direct N- and C-alkylation reactions of anilines and methylketones with alcohols. A hydrogen autotransfer mechanism has been found to operate in these reactions from deuterium labelling studies. In addition, dehydrogenative quinoline synthesis is demonstrated from amino benzyl alcohols and acetophenones.

The development of efficient and sustainable methods for alkylation reactions represents an important challenge in synthetic chemistry. Among the various strategies developed so far, direct alkylations with alcohols as an alkylating source using Hydrogen Autotransfer (HAT) or borrowing hydrogen conditions[1,2] represent a straightforward and sustainable route towards higher amines[3] and ketones,[4] which are valuable compounds for the fine chemical and pharmaceutical industries (Figure 1, a). In these reactions, the starting material alcohols can easily be derived from the valorization of biomass and only water is produced as a waste/by-product, which makes this protocol highly attractive from a green chemistry perspective. The HAT mechanism starts with an initial dehydrogenation of the alcohol to the corresponding carbonyl equivalent (**I**), which then reacts with a nucleophile (either an amine or a methyl ketone enolate) to form an unsaturated intermediate (**II** or **II'**). Finally, the unsaturated intermediate is reduced in situ to an alkylated product (**III** or **III'**). In this overall redox-neutral process, hydrogen produced from the starting alcohol in the first dehydrogenation step is temporarily stored in the metal catalysts and transferred back to the product in the final step.[5,6]
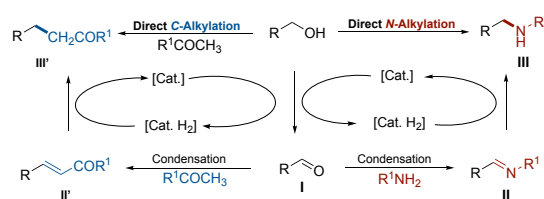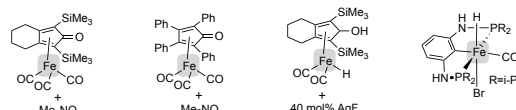

Figure 1. Direct alkylations under HAT conditions.

Recently homogeneous base metal catalyst systems[7] (Mn,[8] Fe,[9] Co,[10] and Ni[11]) for direct alkylation reactions with alcohols have been developed (Figure 1, b). Though the properties of homogeneous transition metal catalysts can be tuned by external ligands, these suffer from a number of severe drawbacks.[12] The separation of the expensive catalyst from the product for re-use is very difficult and they tend to lose their activity due to metal aggregation and precipitation. A further problem with homogeneous catalysis involves the residual metal (and ligand) impurities which remain in the final products. This is a significant issue for the pharmaceutical industry and is of particular environmental and economic concern in large-scale syntheses.
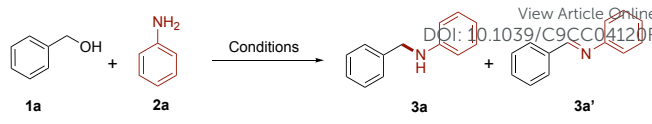
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Heterogeneous catalysts could be an attractive solution to this problem and there has been considerable interest in the development of heterogeneous catalytic systems that can be efficiently re-used whilst maintaining the original activity of the catalyst.[13] Accordingly, the development of base-metal Catalysed processes combined with the advantageous heterogeneous conditions would offer an inexpensive and industrially viable alternative to accomplish these direct alkylation reactions.

Iron, the most abundant metal with high biocompatibility has been explored to catalyse many transformations in recent years,[14] particularly for coupling reactions.[15] For direct alkylation reactions using alcohols under HAT conditions, Feringa and Barta et.al., reported the first iron based homogeneous catalyst system in 2014.[9a] This catalyst system consists of an iron-cyclopentadiene complex and an additive, Me_3NO to catalyse the direct alkylation. Using this system, a wide range of alcohols including simple primary alcohols were utilized for the direct alkylation of anilines and benzyl amines. Following this initial report, other similar iron-cyclopentadiene complexes and pincer type complexes were also explored in these direct alkylation reactions under HAT conditions (Figure 1, c).[9b-h] However, these homogeneous methodologies involving iron organometallic complexes require tedious catalyst preparation under strict inert conditions and external additives. The two key steps in direct alkylation reactions under HAT conditions are initial dehydrogenation and final hydrogenation. Since, Fe_2O_3 has been reported to catalyse a variety of dehydrogenation[16] and hydrogenation reactions,[17] we envisaged its use in direct alkylation reactions. There are obvious advantages of such a metal oxide based catalyst systems; no ligands or inert conditions would be required for these bench stable heterogeneous catalysts. Here, we report the successful development of commercially available nano-Fe_2O_3 as an efficient heterogeneous catalyst for direct N- and C-alkylation reactions using alcohols under HAT conditions (Figure 1, d).

Our initial efforts to realize the transformation commenced with the reaction of benzyl alcohol **1a** with the aniline **2a** in the presence of iron oxide (Fe_2O_3) as a catalyst and KOH as a base under argon atmosphere in toluene at 135 °C for 24 h (Table 1, entry 1). To our delight, the reaction proceeded smoothly to give amine **3a** in a promising yield of 36%. However, efforts to increase the reaction yield with this heterogenous Fe_2O_3 were not successful (Table S1, ESI). Since nano-materials have higher surface area and more active sites compared to the bulk material, we tested nano-Fe_2O_3 (particle size < 5 nm, bought form Sigma Aldrich) as a catalyst under our reaction conditions. Excitingly, with this nano-Fe_2O_3, a much better yield of 83% was obtained (Table 1, entry 2). Other iron salts like $FeCl_3$ and $Fe(NO_3)_3$ did not yield any amine products (entries 3 and 4) under the same conditions. We then evaluated other bases like tBuOK, Cs_2CO_3 and K_2CO_3 with nano-Fe_2O_3 as a catalyst (entries 5-7). However, KOH proved to be the best under the tested conditions. Subsequently, a solvent screen was also undertaken; besides toluene, other solvents such as m-xylene, THF, DCE, and DMSO were tested (entries 8-11). No

Table 1. Optimization of reaction conditions[a]

Entry	Catalyst	Base	Solvent	3a (%)[b,c]	3a' (%)[b,c]
1	Fe_2O_3	KOH	toluene	36 (41)	-
2	nano-Fe_2O_3	KOH	toluene	83 (89)	-
3	$FeCl_3$	KOH	toluene	-	9 (19)
4	$Fe(NO_3)_3$	KOH	toluene	-	12 (21)
5	nano-Fe_2O_3	tBuOK	toluene	74 (78)	7 (15)
6	nano-Fe_2O_3	Cs_2CO_3	toluene	19 (23)	11 (20)
7	nano-Fe_2O_3	K_2CO_3	toluene	16 (20)	8 (17)
8	nano-Fe_2O_3	KOH	m-xylene	59 (65)	-
9	nano-Fe_2O_3	KOH	THF	12 (18)	14 (19)
10	nano-Fe_2O_3	KOH	DCE	15 (21)	30 (37)
11	nano-Fe_2O_3	KOH	DMSO	13 (18)	17 (25)
12[d]	nano-Fe_2O_3	KOH	toluene	-	35 (41)
13[e]	nano-Fe_2O_3	KOH	toluene	41 (45)	15 (24)

[a]Reaction Conditions: Benzyl alcohol (1 eq, 0.9 mmol), aniline (1.5 eq, 1.38 mmol), catalyst 30 mol%, base (0.3 eq, 0.27 mmol) and Solvent 1 ml, under Argon atmosphere in a pressure tube at 135 °C for 24 h. [b]Isolated yield. [c]GC yields are given in the parenthesis. [d]At air atmosphere. [e]15 mol% of catalyst was used.

significant improvement in the yields was observed. As expected, when the reaction was performed under air atmosphere, reduction becomes difficult and only imine products were obtained in lesser yields (35%, entry 12). Also, when the catalyst amount was reduced to 15 mol%, decrease in the product yield was observed (41%, entry 13). Thus, the optimal conditions were found to be heating alcohol **1a**, amine **2a**, nano-Fe_2O_3 (30 mol%) and KOH (0.3 equiv) in toluene at 135 °C for 24 h (Table 1, entry 2).

With the optimized reaction conditions in hand, the scope of the heterogeneous nano-Fe_2O_3 catalysed direct N-alkylation of amines with alcohols was studied, as illustrated in Figure 2. Generally, the reaction efficiency was not sensitive to the electronic properties of the substituents on the aryl ring of the aniline moiety, as the substrates bearing both electron-donating (**3b–g**, 79%– 86%) and electron-withdrawing groups (**3h–k**, 77%–87%) worked very well with good yields. Interestingly, heteroaromatic amines such as aminopyridines and aminopyrazines also proceeded smoothly to give the desired amine products (**3l–n**, 86-90%). When a 1,3-benzodioxole derived amine was used, the amine product **3o** was isolated in 80% yield. The scope of the reaction with respect to benzyl alcohols was also examined and a variety of substituents were well tolerated in the reactions. Amines(**3p-3t**) were isolated in 84-90% yields. In addition to benzyl alcohols, our methodology was also extended to comparatively lesser reactive straight chain aliphatic alcohols. Two straight chain alcohols were tested under slightly modified conditions (2 equiv of alcohols were taken with respect to the aniline) to give amines **3u** and **3v** in 73% and 67% isolated yields, respectively. However, methanol failed to produce the desired coupling products under our conditions.
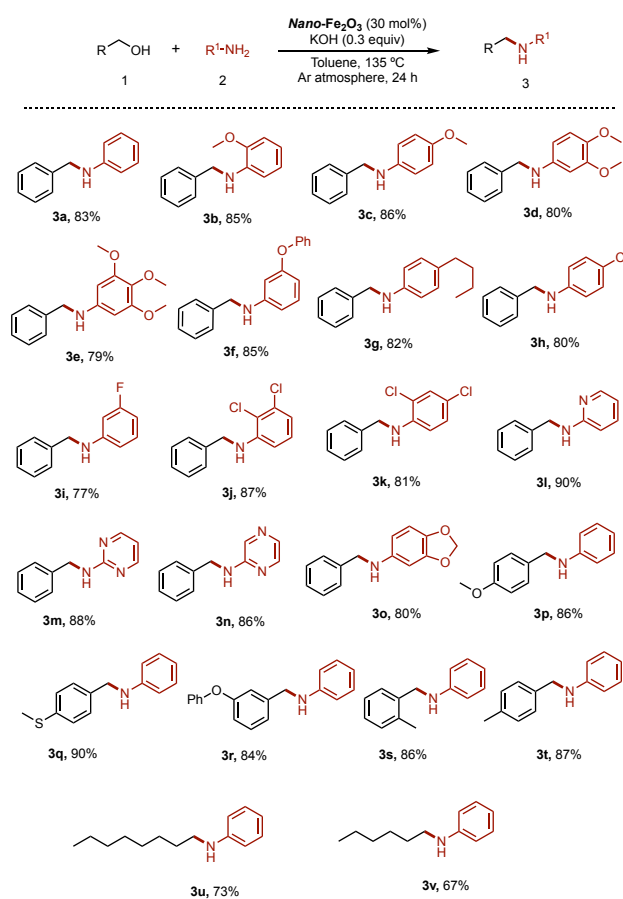
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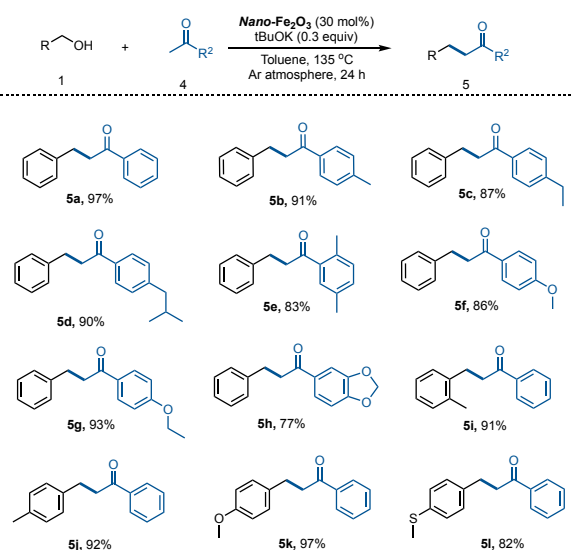
Figure 2. N-alkylation substrate scope

Figure 3. C-alkylation substrate scope

Most of the catalysts developed for N-alkylation of amines using alcohols under HAT conditions have been seamlessly integrated into protocols for the C-alkylation of ketones. Therefore, we examined C-alkylation of ketones under our optimized conditions for the alkylation of amines. The reaction of acetophenone with benzyl alcohol under our optimized conditions gave 76% yields of the expected ketone
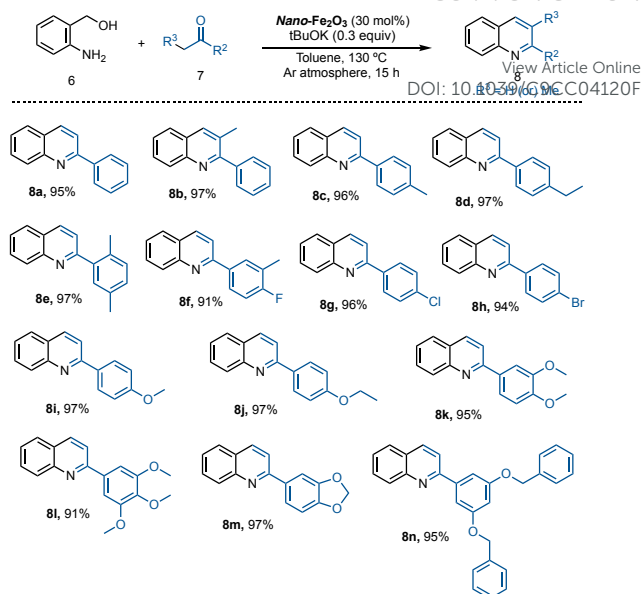
Figure 4. Quinoline synthesis substrate scope

5a. Interestingly switching the base from KOH to tBuOK gave a better yield of 97%. A screening of acetophenones with various substitutions under our reaction conditions revealed that the alkylation of ketones catalysed by nano-Fe_2O_3 also worked well and provides higher ketones in good to excellent yields (Figure 3). Acetophenones and benzylalcohols with electron-donating groups like 4-methoxy, 4-thiomethoxy, 4-ethoxy and alkyl substituents worked well under our conditions (**5b-5h**). However, When acetophenones or benzylalcohols containing electron-withdrawing groups like 4-nitro, 3-CF_3, 4-Cl and 4-Br were tested, though the good conversion of starting materials was found, the reaction was not clean and multiple unidentified products were observed along with low amounts of the desired product by crude NMR. Also, when straight chain alcohols were tested under the standard conditions, no desired products were observed. The acetophenone containing the benzodioxole moiety was tolerated as well, affording the ketone **5h** in 77% yield.

Inspired by the efficient catalysis of HAT protocols by nano-Fe_2O_3 we decided to explore the catalyst for heterocycle synthesis through dehydrogenative annulation reactions. As a model system we tried a modified Friedlander synthesis of quinolines from 2-amino benzyl alcohols and methyl ketones To our delight, these substrates reacted smoothly under the present reaction conditions, providing the desired quinoline products with excellent yields of up to 97% in an optimized time of 16 h.(Figure 4, **8a-n**).

Next, to support our proposed HAT mechanism involving dehydrogenation, imine formation and hydrogenation (Figure 1a), deuterium labelling studies were performed (Scheme 1). When the standard N-alkylation reaction was performed with deuterated benzyl alcohol **[D2]-1a**, along with 91.5% of fully benzylic deuterated product (**[D2]-3a**), 8% of H/D product(**[D1]-3a**) and 0.5% **3a** was observed in ^{1}H NMR analysis (Scheme 1a). In addition, a competitive reaction of benzyl alcohol **1a**, deuterated benzyl alcohol **[D2]-1a** and aniline **2a** was also investigated (Scheme 1b). As expected, the crossover product **[D1]-3a** was obtained with 32% yield on the basis of ^{1}H NMR analysis (pages S7-S12, ESI). This

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observation is consistent with the necessary D-H exchange and micro reversible nature of the proposed HAT/borrowing hydrogen mechanism. The intermolecular competitive reactions between **1a**, **[D2]-1a** and **2a** gave kCHH/kCDH = 1.72 on the basis of ^{1}H NMR analysis. These experimental findings further confirm that benzylic C–H bond cleavage taking part in the rate determining step.
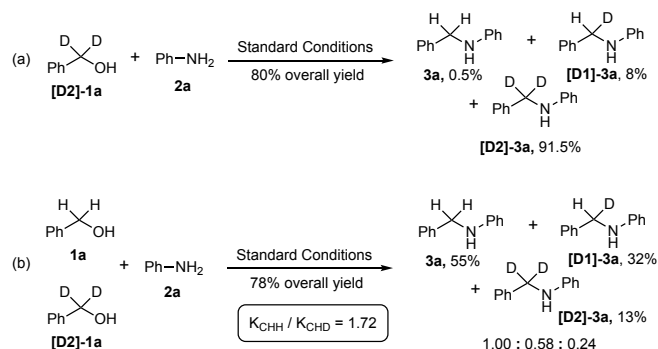
Scheme 1. Deuterium labelling Studies

For the practical applications of heterogeneous catalysts, the lifetime of the catalyst and its level of reusability are key factors. To examine this, the recyclability of nano-Fe_2O_3 was investigated under the standard reaction conditions (Table S2, ESI). The cycle was repeated five times and the isolated yields of the amine products were determined by column chromatography. Even after five cycles, the recovered catalyst maintained its catalytic reactivity and the amine product was obtained above 75% yield (Table S2, entry 5). Thus, the nano-Fe_2O_3 catalyst could be used at least 5 times without significant changes in its activity. Also, a Hot filtration test for catalyst leaching was performed for a standard N-alkylation (Table S3, ESI). The catalyst was filtered off at 14 h when the product **3a** was observed in 43% yield by gas chromatography. Continuing the reaction in the absence of the catalyst for the full optimized reaction time, 24 h yielded no significant increase in the yield of the product (44%). This confirms the true heterogeneous nature of this catalyst and rules out any catalyst leaching. Furthermore, we found that this methodology is scalable as demonstrated by the gram scale synthesis of **3a**, **5a** and **8a** with 67%, 91% and 92% yields respectively (Table S4, ESI).

In conclusion, by using a commercially available nano-Fe_2O_3, we have developed efficient heterogeneous iron catalysed direct N- and C-alkylation reactions with alcohols via hydrogen autotransfer for the synthesis of aniline and ketone derivatives. We have also demonstrated the utility of this transformation in the synthesis of highly valuable quinoline systems. Deuterium labeling studies have confirmed that the present reaction proceeds through hydrogen autotransfer pathway. Further studies for extending the use of this nano-Fe_2O_3 catalyst to other HAT methodologies is currently underway.
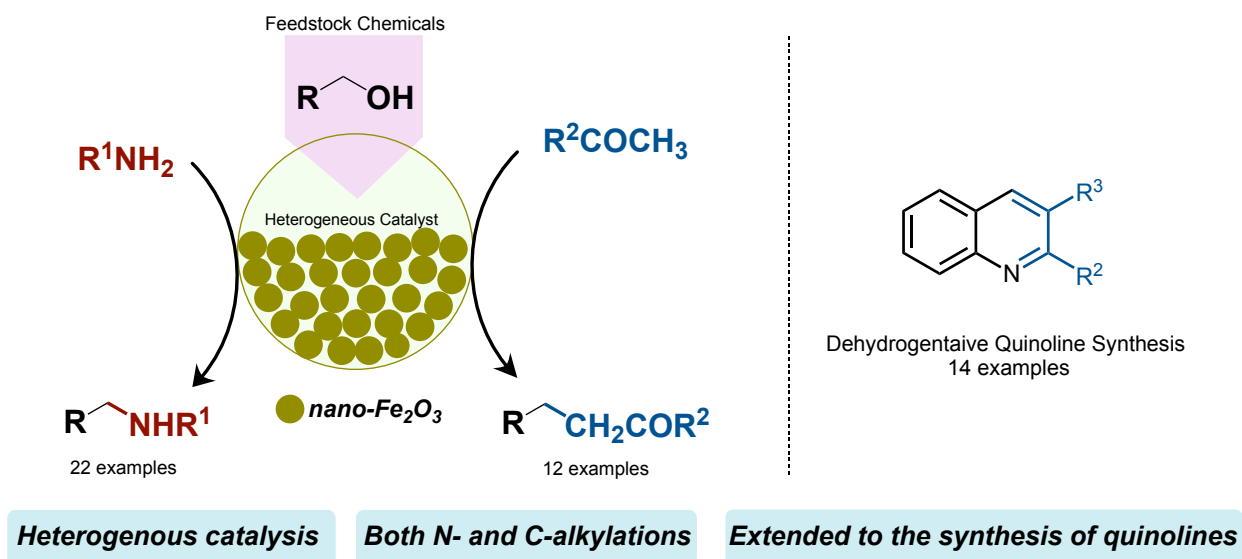
Conflicts of interest

There are no conflicts to declare.

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Table of Contents

Feedstock Chemicals

R—OH

R^1NH_2

R^2COCH_3

Heterogeneous Catalyst

nano-Fe_2O_3

R—NHR^1

22 examples

R—CH_2COR^2

12 examples

R^3

R^2

Dehydrogentaive Quinoline Synthesis
14 examples

Heterogenous catalysis   **Both N- and C-alkylations**   **Extended to the synthesis of quinolines**

Heterogeneous and commercially available nanoscale iron catalyst for direct N- and C-alkylation reactions of anilines and methylketones with alcohols under hydrogen autotransfer conditions.