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# Introduction

Amines are centrally important compounds in the bulk and fine chemical industry since they are frequently encountered scaffolds in agrochemicals, dyes, natural products and pharmaceutically active compounds<sup>1,2</sup> (Fig. 1a). Conventional methods to access amines include the nucleophilic substitution of halides<sup>3</sup> as well as reductive alkylation<sup>4</sup> processes. However, these methods suffer from low atom-economy and E factor due to the formation of stoichiometric amounts of waste<sup>5</sup> and may face limitations in selectivity as well as substrate cost or availability. Therefore, special attention has to be devoted to the development of novel catalytic methods<sup>6–11</sup> that would allow the selective and environmentally-friendly synthesis of amines.<sup>12</sup>

The *N*-alkylation of amines with alcohols *via* the borrowing hydrogen approach has emerged as a very attractive and waste-free alternative to provide *N*-alkylated amines.<sup>13,14</sup> More specifically, the hydrogen borrowing strategy begins with the metal-catalysed dehydrogenation of an alcohol. Further, the

# Efficient nickel-catalysed *N*-alkylation of amines with alcohols<sup>†</sup>

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The selective *N*-alkylation of amines with alcohols *via* the borrowing hydrogen strategy represents a prominent sustainable catalytic method, which produces water as the only by-product and is ideally suited for the catalytic transformation of widely available alcohol reaction partners that can be derived from renewable resources. Intensive research has been devoted to the development of novel catalysts that are mainly based on expensive noble metals. However, the availability of homogeneous or heterogeneous nonprecious metal catalysts for this transformation is very limited. Herein we present a highly active and remarkably easy-to-prepare Ni based catalyst system for the selective *N*-alkylation of amines with alcohols, that is *in situ* generated from Ni(COD)<sub>2</sub> and KOH under ligand-free conditions. This novel method is very efficient for the functionalization of aniline and derivatives with a wide range of aromatic and aliphatic alcohols as well as diols and exhibits excellent functional group tolerance including halides, benzodioxane and heteroaromatic groups. Several TEM measurements combined with elemental analysis were conducted in order to gain insight into the nature of the active catalyst and factors influencing reactivity.

> formed carbonyl compound reacts with the amine to form the corresponding imine, which is reduced to the alkylated amine by means of the metal hydride generated during the first dehydrogenation step (Fig. 1b).<sup>14</sup> This atom-economic transformation represents a prime example in green chemistry since it only produces water as by-product and uses widely available alcohol reaction partners that can also be potentially derived from renewable resources.<sup>15–17</sup>

> Following the remarkable progress in this field using precious metals,<sup>12,13,18</sup> novel methods that utilize inexpensive and widely abundant metals<sup>19</sup> such as Fe,<sup>20,21</sup> Co,<sup>22</sup> Mn<sup>23</sup> and Ni<sup>24,25</sup> have recently emerged.<sup>26</sup> Thus, there is tremendous potential for the development of novel methods using non-precious metals and great demand for improving reaction scope, substrate compatibility and catalyst stability as well as decreasing catalyst loading.

> In this context and continuing our interest in developing *N*-alkylation reactions using earth abundant metals,<sup>20,21</sup> we sought to develop an efficient catalytic system based on nickel. Searching for a catalytic system that would be convenient to prepare, and afford lower catalyst loading without the need of any organic ligand, we have turned our attention to Ni nanoparticle (NiNP) chemistry. Due to the pioneering work of Yus and others, much progress has been made in this area, especially related to transfer hydrogenation chemistry, typically using 2-pronanol.<sup>27</sup> As a specific example, 2-propanol was used as hydrogen source in the reductive amination of aldehydes and ketones catalyzed by NiNP.<sup>28</sup>

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Fig. 1 (a) Representative examples of pharmaceuticals comprising an *N*-alkyl amine moiety; (b) general mechanism of the 'borrowing hydrogen' strategy.

Furthermore, NiNP catalyst enabled the activation of primary alcohols for reductive aza-Wittig reaction.<sup>29</sup> Interestingly, NiNP chemistry has recently found application in the chemistry of renewable resources. Hartwig and coworkers discovered that *in situ* generated NiNP are highly active for the scission of phenyl ether bonds in simple lignin model compounds,<sup>30</sup> while Luque and coworkers have reported on microwave assisted preparation of Ni nanoparticles stabilized by ethylene glycol for the hydrogenolysis of benzyl-phenyl ether.<sup>31</sup>

Surprisingly, the efficient *N*-alkylation of amines has not yet been realized with any NiNP system.

Herein, we describe the *N*-alkylation of amines *via* the hydrogen borrowing mechanism, to the best of our knowledge, yet unprecedented by Ni nanoparticles generated *in situ*. This catalyst is conveniently prepared from  $Ni(COD)_2$  in the presence of sub-stoichiometric amount of base and shows versatility in the selective monoalkylation of various aniline derivatives with a broad range of alcohols.

# Experimental

# Representative procedure for catalytic *N*-alkylation of aniline with benzyl alcohol

An oven-dried 20 mL Schlenk tube, equipped with a stirring bar, was charged with aniline (0.5 mmol, 1 equiv.), benzyl alcohol (0.75 mmol, 1.5 equiv.), Ni(COD)<sub>2</sub> (0.015 mmol, 3 mol%), KOH (0.15 mmol, 0.3 equiv., 30 mol%) and cyclopentyl methyl ether (solvent, 2 mL). The solid materials were weighed into the Schlenk tube under air, Ni(COD)<sub>2</sub> was weighed in the glovebox; then the Schlenk tube was removed from the glovebox, subsequently connected to an argon line and vacuum–argon exchange was performed three times. Liquid starting materials and solvent were charged under an argon stream. The Schlenk tube was capped and the mixture was rapidly stirred at room temperature for 1 min, then was placed into a pre-heated oil bath at the appropriate temperature (typically 140 °C) and stirred for a given time (typically 18 hours). The reaction mixture was cooled down to room temperature. After taking a sample (app. 0.5 mL) for GC analysis, the crude mixture was filtered through silica gel, eluted with ethyl-acetate, and concentrated *in vacuo*. The residue was purified by flash column chromatography to provide the pure amine product.

#### Representative procedure for generating TEM specimens

After reaction, according to the *Representative Procedure* above indicated, the Schlenk vessel was cooled to room temperature and the solvent was evaporated under vacuum for at least 1 h. Then, the concentrated solution was taken by means of a 1 mL glass syringe and resuspended into 1 mL of toluene by discharging two droplets through the septum of the polypropylene screw-thread cap of a 2 mL Amber vial. After sonication for 15 min, two drops from the solution were sequentially placed onto a TEM grid, which was allowed to dry in the glovebox for 1 h prior to analysis.

# **Results and discussions**

# Establishing an active NiNP catalyst system for *N*-alkylation of amines

In order to establish the desired full hydrogen borrowing cycle (Fig. 1b) that involves alcohol dehydrogenation, as well as imine hydrogenation, we selected benzyl alcohol and aniline as model substrates. Initially, the reaction was conducted with various Ni precursors (Table 1, entries 1–4, Table S1†) in the range of 120–140 °C under an argon atmosphere. While relatively low conversion was obtained with precursors Ni(OTf)<sub>2</sub> and NiBr<sub>2</sub>, a high conversion value was detected with Ni(COD)<sub>2</sub>, which can be attributed to the ease of NiNP generation from this Ni(0) precursor at 140 °C even in the absence of hydrogen gas. Selecting Ni(COD)<sub>2</sub> for further study, the effect of various bases was evaluated (Table 1, entries 1, 5–8, Table S2†) with significant variation in substrate conversion and product selectivity. Interestingly, with KOH a perfect

Table 1	Optimization of	f the reaction	conditions for	amination of	f benzyl	alcohol ( <b>1a</b> )	with aniline	(2a′
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	OH + NH2 -		[Ni], base				
	1a	2a'		3a		3a'	
Entry	Alcohol (equiv.)	Base (equiv.)	Precatalyst (mol%)	Temp [°C]	Conv. [%]	Sel. of 3a [%]	Sel. of 3a' [%]
1	2	КОН (0.5)	$Ni(COD)_2$ (5)	140	>99	99	1
2	2	KOH (0.5)	NiCl <sub>2</sub> (dme) (5)	140	86	79	7
3	2	KOH (0.5)	$Ni(OTf)_2(5)$	140	73	63	10
4	2	KOH (0.5)	$NiBr_{2}(5)$	140	78	70	5
5	2	LiOH (0.5)	$Ni(COD)_2(5)$	140	>99	7	74
6	2	NaOH (0.5)	$Ni(COD)_2(5)$	140	>99	10	90
7	2	$KO^tBu$ (0.5)	$Ni(COD)_2(5)$	140	90	87	3
8	2	$K_2 CO_3 (0.5)$	$Ni(COD)_2(5)$	140	10	0	7
9	2	KOH (0.5)	$Ni(COD)_2(5)$	100	23	16	7
10	2	KOH (0.5)	$Ni(COD)_2(5)$	120	31	19	9
11	2	KOH (0.1)	$Ni(COD)_2$ (3)	140	67	30	30
12	1.2	KOH (0.3)	$Ni(COD)_2$ (3)	140	94	92	2
13	2	_	$Ni(COD)_2(5)$	140	73	48	22
14	2	KOH (0.5)	_	140	7	1	6
$15^a$	1.5	KOH (0.3)	$Ni(COD)_2$ (3)	140	>99	91	5
16	1.5	KOH (0.3)	$Ni(COD)_2$ (3)	140	>99	>99	<1
$17^b$	1.5	KOH (0.3)	$Ni(COD)_2$ (3)	140	>99	95	5
$18^c$	1.5	KOH (0.3)	$Ni(COD)_2$ (3)	140	>99	93	7
19	1.5	KOH(0.3) + Hg(30)	$Ni(COD)_2$ (3)	140	25	20	5
$20^d$	1.5	КОН (0.3)	$Ni(COD)_2$ (3)	140	16	0	16

General reaction conditions: general procedure (see ESI, page S5–S9), 0.6–1 mmol of 1a, 0.5 mmol of 2a', Ni(COD)<sub>2</sub> (0.015–0.025 mmol, 3–5 mol%), KOH (0.05–0.25 mmol, 10–50 mol%), 100–140 °C, 2 mL CPME, 18 h. Conversion and selectivity were determined by GC-FID using decane as an internal standard. <sup>*a*</sup> At the beginning of the reaction NiNP were generated from Ni(COD)<sub>2</sub> (0.015 mmol, 3 mol%) and 2 mL CPME (as a solvent) at 140 °C during 30 min, later KOH (0.15 mmol, 30 mol%), 1a (0.75 mmol), 2a' (0.5 mmol) were added and the reaction mixture was stirred and heated at 140 °C for 18 h. <sup>*b*</sup> Reaction performed with freshly distilled benzyl alcohol. <sup>*c*</sup> Reaction performed under non-inert conditions. <sup>*d*</sup> Used pentylamine (0.5 mmol) instead of aniline (2a').

selectivity and conversion was achieved at 140 °C, while the use of K<sub>2</sub>CO<sub>3</sub> gave much poorer results. The optimum reaction temperature was found to be 140 °C as shown by the lower conversion values in experiments conducted at lower temperature range (Table 1, entries 9 and 10, Table S4<sup>+</sup>). Without Ni precursor, only traces of product were observed in the presence of base (Table 1, entry 14). Importantly, the catalyst loading could be lowered to 3 mol% and loading of base to 0.3 equivalents (Table 1, entry 16). Further, in order to exclude the possibility for small amounts of aldehyde or other impurities in the alcohol starting material to exhibit catalytic activity,32 we have conducted an experiment with freshly distilled benzyl alcohol, with unchanged results (entry 17 versus entry 16; see also ESI,† Note 3). Importantly, we also successfully carried out an experiment under non-inert conditions during which all starting materials were handled under air (entry 18, see also ESI,† Note 4).

#### Characterization and nature of the catalyst

To gain additional proof of the heterogeneous nature of the Ni catalyst *in situ* obtained from Ni(COD)<sub>2</sub>, we conducted several experiments. When we subjected Ni(COD)<sub>2</sub> to thermal decomposition in CPME, in the absence of the substrates, followed by the addition of all reactants and base, we obtained 99% of conversion and 91% of product (Table 1, en-

try 15), comparable to a regular reaction when typically, solvent and all substrates were added at the same time. Furthermore, when the reaction was conducted in the presence of mercury (Table 1, entry 19), which is a well-known poison for heterogeneous catalysts, inhibition of the catalysis took place.35,36 When the poisoning test was repeated in a different fashion, namely initially the reaction was conducted for 1 h and analysed, after mercury was added and the reaction was continued for 1 h and analysed again, the two samples taken showed practically identical results, indicating an inhibition of catalytic activity upon addition of mercury (see ESI<sup>†</sup> Table S7). At this point it is worth to mention that although the mercury poisoning test is indicative for a reaction operating with heterogeneous catalyst, it does not exclude processes related to catalyst modification in situ such as leaching of soluble monometallic species, or formation of smaller set of clusters of metal particles in solution during catalysis. As described in the excellent review of Ananikov and co-workers,<sup>34</sup> several catalytic systems using metal nanoparticles<sup>33</sup> rely on dynamic processes involving a homogeneous or heterogeneous pre-catalyst.

Recycling experiments were successfully conducted, albeit the results showed gradually declining substrate conversion over four consecutive runs (Fig. S1 and Table S8†).

Next, a series of TEM measurements were conducted in order to determine the nature and size distribution of the *in* 



**Fig. 2** TEM micrographs of the *in situ* generated Ni-NPs under various reaction conditions and particle size distribution of the investigated samples: a) Ni precursor only; b) Ni precursor in presence of KOH; c) Ni precursor in presence of  $K_2CO_3$ ; d) Ni precursor in presence of benzyl alcohol; e) Ni precursor in presence of KOH and benzyl alcohol; f) Ni precursor in presence of KOH, benzyl alcohol and aniline.





General reaction conditions: general procedure (see ESI, page S13–S15), 1.5 mmol of 1a–v, 1 mmol of aniline, Ni(COD)<sub>2</sub> (0.03 mmol, 3 mol%), KOH (0.3 mmol, 30 mol%), 140 °C, 2 mL CPME, 18 h. <sup>*a*</sup> Yield was calculated based on GC-FID. <sup>*b*</sup> 1 mL of methanol or ethanol, 1 mmol of aniline, Ni(COD)<sub>2</sub> (0.1 mmol, 10 mol%), KOH (1 mmol), 150 °C, 2 mL CPME, 48 h. For details see ESI, Table S9.

*situ* generated NiNP. To gain more insight into the possible structural changes imparted by the various components of this peculiar system, a number of experiments were carried out by systematic variation of the base, alcohol and amine and the corresponding TEM images were recorded (Fig. 2).

The first sample (Fig. 2a), prepared by heating Ni(COD)<sub>2</sub> in CPME showed Ni oxide clusters of *ca.* 20 nm in large regions with agglomerated particles sized in the range of 2–5 nm, as expected in the absence of the base and any substrates present. The same sample, however in the presence of KOH (30 mol%) (Fig. 2b), displayed larger Ni oxide clusters (50–100 nm) formed by nanoparticles still of 2–5 nm (Fig. 2b) surrounded by potassium. Caubère,<sup>37,38</sup> and Hartwig<sup>30</sup> have previously indicated that base can stabilize nickel nanoparticles and this phenomenon is observed in our system as well. In contrast to KOH, the specimen obtained using  $K_2CO_3$  showed particles with mark-

edly different morphology, with more agglomeration and poor dispersion ( $\approx 2\%$ ) of Ni nanoparticles (Fig. 2c). This is a likely explanation for the lower catalytic activity of this system (Table 1 entry 1 versus entry 8 and ESI† Table S2 entry 1 versus entry 5). Next, the influence of the benzyl alcohol was investigated. Isolated Ni oxide clusters of ca. 25 nm (Fig. 2d) with well dispersed nanoparticles (average size 4 nm) were obtained in presence of 1.5 equivalents of benzyl alcohol that confirmed our assumption of a possible stabilization of metal particles by benzyl alcohol, supporting the alcohol-Ni interaction that is necessary for the dehydrogenation reaction. This effect was even more pronounced in the presence of KOH. The mixture containing benzyl alcohol and KOH after 20 min (Fig. 2e) showed no visible nickel particles at low magnification. However, at higher magnification, very regularly and finely distributed metal Ni nanoparticles of ca. 2 nm were observed,

#### Table 3 N-alkylation of various aniline with n-butanol



General reaction conditions: general procedure (see ESI, page S15–S18), 1.5 mmol of *n*-butanol (4a), 1 mmol of 2a–r, Ni(COD)<sub>2</sub> (0.03 mmol, 3 mol%), KOH (0.3 mmol, 30 mol%), 140 °C, 2 mL CPME, 18 h. <sup>*a*</sup> Yield was calculated based on GC-FID. <sup>*b*</sup> 3 mmol of *n*-butanol, 1.5 mmol of corresponding amine, Ni(COD)<sub>2</sub> (0.03 mmol, 3 mol%), KOH (0.3 mmol, 30 mol%), 140 °C, 2 mL CPME, 48 h. <sup>*c*</sup> 3 mmol of *n*-butanol, 1.5 mmol of corresponding amine, Ni(COD)<sub>2</sub> (0.05 mmol, 5 mol%), KOH (0.5 mmol, 50 mol%), 140 °C, 2 mL CPME, 72 h. For details see ESI, Table S10.

accounting for a metal dispersion as high as 50% (for EDX analysis of this sample see ESI† Fig. S4) – signifying the active system prior to the addition of aniline. The actual reaction mixture, after 20 minutes reaction time showed similar finely dispersed particles (see ESI† Fig. S3a), while the reaction mixture imaged after 18 hours (Fig. 2f) still showed well dispersed Ni° nanoparticles, although slightly larger than those observed in the initial phase of the reaction. Interestingly, when the Ni particles were generated in presence of pentylamine (see ESI† Fig. S3c) the TEM images showed that the particles were completely besieged by the amine, whereas in the presence of aniline (see ESI† Fig. S3b) they were well dispersed. A reaction mixture comprising benzyl alcohol and pentylamine showed similar be-

haviour (Fig. S3d†). This can be explained by a stronger coordination of the more basic (aliphatic) amines to the nickel particles and likely the cause of the poor conversion values obtained in the presence of pentylamine (Table 1, entry 20) and similar substrates (ESI† Table S10, entries 28–31).

#### N-Alkylation of aniline with a wide range of alcohols

To demonstrate the general applicability of the catalytic system, various (hetero)aromatic and aliphatic alcohols, including diols, were evaluated in the catalytic *N*-alkylation of aniline under optimized conditions (Table 2). Electron-donating and electron-withdrawing substituted benzyl alcohols were successfully used in the selective mono-alkylation of aniline (Table 2). Notably, benzyl alcohols (1a-1e) with electrondonating substituents, including the sterically more hindered 2-methoxy benzyl alcohol (1c) reacted smoothly with aniline, resulting in very good to excellent (84-98%) isolated yields of 3a-e (Table 2). When benzyl alcohols bearing the electronwithdrawing groups -NO2, -CN, -CH3COOCH3, -CF3 were employed, much lower reactivity was observed (Table S9, entries 23-26, in the ESI<sup>†</sup>). Furthermore, the important building block piperonyl alcohol (1g) was transformed to the desired product 3g with 62% isolated yield. Interestingly, heteroaromatic alcohols such as the biomass-derived furfuryl alcohol and 2-(hydroxymethyl)pyridine were alkylated selectively, albeit with moderate yields (Table 2, 3h and i, respectively). Next, aliphatic alcohols as reaction partners in the N-alkylation of aniline were investigated. Gratifyingly, short and long chain aliphatic alcohols (1k-s) readily afforded the corresponding desired amine product (3k-s, 69-90%) under optimized conditions. It was even possible to achieve N-alkylation with methanol, but only 38% GC yield of N-methylated product was seen even at high catalyst/base loading. Notably, when 1,5- and 1,6-diols were examined, the mono-alkylated amino alcohols (3ua) and (3va) were obtained in 63% and 67% isolated yield, respectively, and minor amounts of cyclic products were observed (Table 2).

#### N-Alkylation of a variety of amines with 1-butanol

Further expanding the scope of the reaction, n-butanol was chosen as coupling partner to a series of diversely substituted aniline derivatives, bearing electron-donating (2a-e) and electron-withdrawing (2i-I) groups as well as sterically hindered amines (2f-g), and diamines (2m, 2o-q), which were selectively alkylated. More specifically, there was no significant difference in the reactivity of p-methoxy-aniline (2a) compared to p-methyl-aniline (2b), however a gradual decrease of product yield was observed (77% for 5b, 53% for 5c, 32% for 5d) when the substrate was changed to the meta- and ortho-substituted analogues. A similar behavior was observed for fluoro-anilines 2i, 2j and 2k. Interestingly, pyrrole substituted aniline furnished 57% isolated yield of 5r. Aromatic amines bearing the electron-withdrawing groups -CN, -CH<sub>3</sub>COOCH<sub>3</sub> and -CF<sub>3</sub> showed low reactivity with 1-butanol, namely only minor amounts of products were observed (Table S10, entries 19-21, in the ESI<sup>†</sup>). Next, when aromatic diamines were used as a substrate, the corresponding mono and di-N-alkylated amines were isolated (Table 3, 50a-50b and 5pa-5pb). When aliphatic amine cyclohexylamine was used, it gave 32% GC yield of desired product 5n and 67% of imine (5n'). Other aliphatic amines (benzylamine, pentylamine and morpholine) did not afford any products under the optimized reaction conditions (Table S10, entries 28-30, in the ESI<sup>†</sup>), in accordance with previous TEM investigation that shows stronger coordination of aliphatic amines to the Ni particles likely leading to diminished activity.

Examples of heterogeneous catalysts comprising nickel on alumina<sup>39,40</sup> or silica,<sup>41</sup> γ-Al<sub>2</sub>O<sub>3</sub> supported Ni and Cu bimetal-

lic nanoparticles<sup>42</sup> and RANEY®-nickel<sup>43</sup> are known for the amination of alcohols. Besides this, a few homogeneous catalytic systems using nickel for alkylation of amines<sup>24,25</sup> and N-alkylation of hydrazides and arylamines with racemic alcohols<sup>44</sup> were very recently reported, but to the best of our knowledge, the system described above is the first example where in situ generated Ni nanoparticles act as highly efficient catalysts for the attractive N-alkylation of amines. Clear advantages are the Ni loading being as low as 3%, and there is no catalyst preparation or any ligand required. Therefore, we believe our system to be a valuable addition to these examples of Ni catalysts that are either homogeneous or supported heterogeneous in nature. This is an excellent starting point for establishing robust, highly active and recyclable Ni catalyst in the future, for example by using polyethylene glycol (PEG)<sup>45</sup> or ionic liquids.<sup>46</sup>

### Conclusion

In summary, we have developed a simple and highly active catalytic system for efficient and selective N-alkylation of amines with alcohols that can be conveniently prepared using a catalytic amount (as low as 3 mol%) of Ni(COD)<sub>2</sub> and sub-stoichiometric amount of KOH under ligand-free conditions. The described system is tolerant to a variety of functional groups such as halides, benzodioxane and heteroaromatic groups present in either the alcohol or the amine substrate. In order to gain further insight into the nature of the active catalytic system and influence of reaction parameters on catalyst morphology, a series of TEM measurements combined with elemental analysis were performed that found finely dispersed in situ generated metal particles in the catalysed reaction. Additional studies revealed that potassium hydroxide is uniquely suited for the stabilization of Ni nanoparticles and that the alcohol substrate also has a stabilizing role. Furthermore, clear differences in the morphology of the particles were seen in the presence of aromatic versus aliphatic amine, the latter leading to poor reactivity due to stronger amine coordination. The substrate scope was well in line with these findings, where the nature of the alcohol reaction partner could be broadly varied (benzyl alcohol, short or long chain aliphatic alcohol, diol) while aniline derivatives were better suited substrates than aliphatic amines. To the best of our knowledge this is the first, very simple yet highly active and selective NiNP catalyst system for the N-alkylation of amines with alcohols that operates via the hydrogen borrowing strategy.

# Conflicts of interest

There are no conflicts to declare.

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