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# Towards a general ruthenium-catalyzed hydrogenation of secondary and tertiary amides to amines†

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A broad range of secondary and tertiary amides has been hydrogenated to the corresponding amines under mild conditions using an *in situ* catalyst generated by combining [Ru(acac)<sub>3</sub>], 1,1,1-tris(diphenylphosphinomethyl)ethane (Triphos) and Yb(OTf)<sub>3</sub>. The presence of the metal triflate allows to mitigate reaction conditions compared to previous reports thus improving yields and selectivities in the desired amines. The excellent isolated yields of two scale-up experiments corroborate the feasibility of the reaction protocol. Control experiments indicate that, after the initial reduction of the amide carbonyl group, the reaction proceeds through the reductive amination of the alcohol with the amine arising from collapse of the intermediate hemiaminal.

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## Introduction

Amines constitute an important class of compounds which have wide industrial applications as solvents, additives, anti-foam agents, corrosion inhibitors, detergents, dyes, bactericides.<sup>1</sup> In addition, the amino group is abundantly present in agrochemicals and pharmaceuticals.<sup>1</sup> Although aliphatic amines can be prepared by numerous methodologies, reductive aminations including alcohol aminations prevail in industry on larger scale. In addition, primary aromatic and benzylic amines are most easily accessible by reduction of the corresponding nitroarenes and nitriles. For the preparation of more structurally complex bio-active compounds and natural products a preferred route for C–N bond formation combines amidation followed by reduction.<sup>2</sup> This latter reaction is usually accomplished by using (over)stoichiometric amounts of lithium aluminum hydride (LiAlH<sub>4</sub>) or borane (B<sub>2</sub>H<sub>6</sub>). Unfortunately, these reagents require complex and hazardous work-up procedures and generate stoichiometric amounts of difficult to dispose waste by-products. Therefore more efficient alternatives are highly sought after. Recently, metal-promoted catalytic hydrosilylation of amides were intensely investigated and mild operational conditions have been devised which allow for excellent functional group tolerance, yet the method suffers

from low atom efficiency because of residual siloxanes.<sup>3</sup> Another recent example of a magnesium-catalyzed deoxygenation of amides *via* hydroboration has similar limitations.<sup>4</sup> Obviously, the best option for amide reduction in terms of atom economy and waste prevention is hydrogenation with molecular hydrogen in the presence of a suitable catalyst.<sup>5</sup> However, because of the low electrophilicity of their carbonyl group, amides require elevated pressures and temperatures to be reduced. In the field of heterogeneous catalysis, copper–chromium oxide catalysts originally developed to this aim have been replaced by less toxic, more efficient bifunctional/bimetallic Ru/Mo,<sup>6a</sup> Rh/Mo,<sup>6a,b</sup> Ru/Re,<sup>6a,c</sup> and Rh/Re catalysts<sup>6a,c</sup> and more recently by bimetallic graphite-supported Pd–Re<sup>6d</sup> and TiO<sub>2</sub>-supported Pt–Re based catalysts.<sup>6e,f</sup> Improvement of heterogeneous amide hydrogenation catalysts has witnessed a mitigation of reaction conditions, yet they are incompatible with aromatic groups and multiple CC and CX bonds which are likewise reduced. Despite significant interest in developing homogeneous catalysts which should operate under milder reaction conditions, no such general methodology is available. Interestingly, depending on the type of homogeneous catalyst, the hydrogenation of amides affords either the alcohol and amine, arising from cleavage of the C–N bond in the intermediate hemiaminal, or the more desired higher amine, resulting from deoxygenation of the amide. The former type of selectivity is preferentially achieved with bifunctional catalysts, which rely on metal–ligand cooperation, and can be advantageously exploited as a mild deprotection methodology.<sup>7</sup>

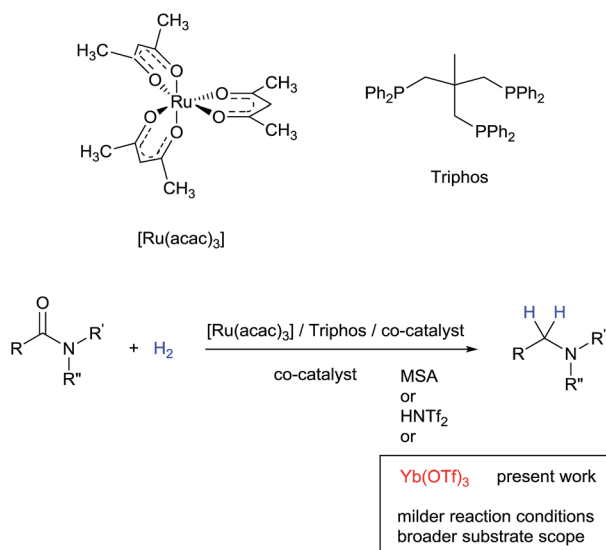
Investigations by Cole-Hamilton and co-workers, later supported by contributions from Leitner's and Klankermayer's groups, have shown that ruthenium catalysts modified by 1,1,1-tris(diphenylphosphinomethyl)ethane (Triphos) give access to

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† Electronic supplementary information (ESI) available: General procedures, additional tables and schemes, characterisation data and NMR spectra of the isolated compounds are available. See DOI: 10.1039/c5sc04671h





Scheme 1 Ru/Triphos catalytic systems competent for the homogeneous hydrogenation of amides to amines.

the higher amine (Scheme 1).<sup>8</sup> Either the catalytic system generated *in situ* from  $[\text{Ru}(\text{acac})_3]$  and Triphos<sup>8a,b</sup> or the readily accessible molecularly defined complex  $[(\text{Triphos})\text{Ru}(\text{TMM})]$  (TMM = trimethylenemethane)<sup>8c</sup> were used for this transformation at high temperature. Notably, both systems require the presence of an acid co-catalyst such as methanesulfonic acid (MSA)<sup>8a-c</sup> or bis(trifluoromethane)sulfonimide (HNTf<sub>2</sub>)<sup>8d</sup> and the catalyst performance is strongly dependent on the acid/ruthenium precursor ratio. Although the individual intermediates around the catalytic cycle have so far escaped detection, an in-depth study of the ruthenium species present in solution under catalytic conditions has allowed to shed light on the role of the acid co-catalyst: it serves to convert the catalyst precursor into an active system and it provides a weakly coordinating counter anion ( $\text{CF}_3\text{S}(\text{O})_2\text{O}^-$  or  $\text{NTf}_2^-$ ) which, while stabilizing the  $[\text{Ru}(\text{Triphos})]^{2+}$  fragment, does not prevent coordination of the incoming hydrogen molecule and substrate. Furthermore, it provides the optimal reaction medium  $\text{pK}_a$ , to promote the H-transfer and hydrolytic events which make up amide hydrogenation.<sup>8c</sup>

The Ru–Triphos catalyst system is noteworthy in that, unlike heterogeneous catalysts, it does not promote the hydrogenation of aromatic moieties and, to the best of our knowledge, represents the only homogeneous catalytic system able to hydrogenate amides to afford the alkylated amine resulting from the hydrogenation of the carbonyl group and the formal hydrogenolysis of the ensuing C–OH bond. However, harsh conditions are still required to achieve this transformation and the substrate scope is limited as the catalyst is best suited for 1° amides and substrates which bear a phenyl ring directly attached to the nitrogen atom.<sup>8</sup>

Recently, we have shown that it is possible to extend the range of aromatic and aliphatic carboxylic acids which can be hydrogenated to the corresponding alcohols with the Ru–Triphos system by replacing the Brønsted acid co-catalyst<sup>8d,9</sup> with

either  $\text{Sn}(\text{OTf})_2$  or  $\text{Al}(\text{OTf})_3$ , affording a milder and more general method for the reduction of these challenging substrates.<sup>10a</sup> The Lewis acid is also key to the selective hydrogenation of esters to ethers promoted by the Ru–Triphos system: while no reaction occurs with methanesulfonic acid as co-catalyst, and poor selectivity is provided by trifluoromethanesulfonic acid, the combined use of Ru–Triphos and  $\text{Al}(\text{OTf})_3$  gives access to cyclic and linear ethers in good to excellent yields.<sup>10b</sup>

Inspired by these results, we envisaged that the presence of a suitable Lewis acid might be crucial for the reduction of amides as well, by activating the carbonyl group and thus allowing mitigation of the reaction conditions. Herein, we present for the first time the results of our detailed investigations which have led us to identify a superior catalyst system for the selective hydrogenation of a broad range of amides to amines. Moreover, mechanistic investigations revealed a novel pathway for the hydrogenation of amides.

## Results and discussion

In order to assess whether a Lewis acid could indeed be a beneficial co-catalyst for the transformation under investigation, preliminary experiments were performed using the hydrogenation of benzanilide **1** as benchmark reaction and the metal triflates readily available in the laboratory. The reactions were run using the catalytic system generated *in situ* from  $[\text{Ru}(\text{acac})_3]$  and Triphos in THF at 150 °C under 50 bar of H<sub>2</sub> for a standard reaction time of 15 hours in the presence of 1 equivalent of the Lewis acid as to ruthenium. The first co-catalysts to be tested were  $\text{Sn}(\text{OTf})_2$  and  $\text{Al}(\text{OTf})_3$  as these had proved effective in co-catalyzing the reduction of carboxylic acids<sup>10a</sup> and the selective hydrogenation of esters to ethers respectively.<sup>10b</sup> While  $\text{Sn}(\text{OTf})_2$  gave poor conversion with no selectivity in the desired *N*-benzylaniline **2**, the only products being benzyl alcohol **3** and aniline **4** (Table 1, entry 1),<sup>11</sup>  $\text{Al}(\text{OTf})_3$  afforded full conversion, although with a modest 27% selectivity (Table 1, entry 2). Other three metal triflates were investigated:  $\text{In}(\text{OTf})_3$ ,  $\text{Sc}(\text{OTf})_3$ ,  $\text{Hf}(\text{OTf})_4$  (Table 1, entries 3, 4, 5). Essentially quantitative conversions were achieved in all cases, with  $\text{Hf}(\text{OTf})_4$  providing the highest yield, 34%, of *N*-benzylaniline **2**. The use of a 2-fold excess of the same Lewis acid as to Ru allowed an increase in the yield of product **2** (42%, Table 1, entry 6) but larger amounts were detrimental (Table 1, entry 7 and 8).

Having established the optimal  $\text{Hf}(\text{OTf})_4/\text{Ru}$  ratio, this was applied to probe the influence of temperature and pressure on selectivity: the latter increases at higher temperature and lower pressure (Table S1†), in line with previous findings.<sup>8a,c</sup> Therefore by reducing the hydrogen pressure to 15 bar while keeping the temperature at 150 °C, the yield of *N*-benzylaniline **2** rose further to 63% (Table 1, entry 9). A control experiment was run in the presence of triflic acid (HOTf), as this might arise from the hydrolysis of the corresponding metal salt (Table 1, entry 10): while a 84% conversion was achieved, thus suggesting the possibility of a background reaction promoted by the Brønsted acid, the selectivity in **2** was lower (49%) than the one obtained with  $\text{Hf}(\text{OTf})_4$  (63%), establishing the positive influence of the metal ion.



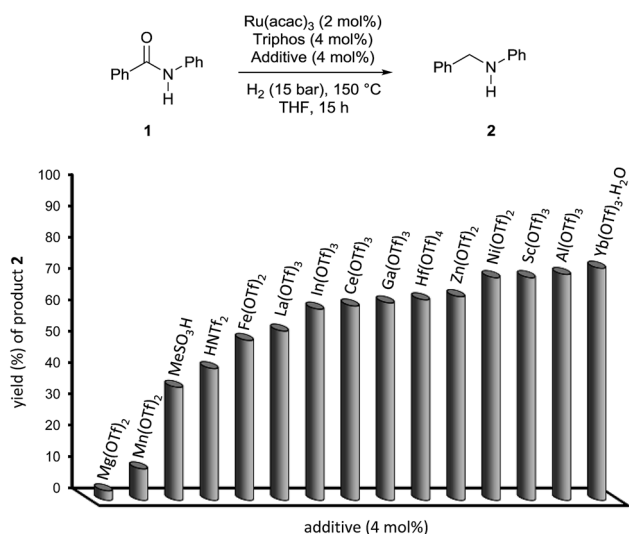
**Table 1** Hydrogenation of benzanilide **1** with the Ru/Triphos catalyst: preliminary explorative experiments into suitable additives

Entry <sup>a</sup>	Additive (mol%)	Conv. <sup>b</sup> (%)	2 <sup>b</sup> (%)	3 <sup>b</sup> (%)	4 <sup>b</sup> (%)
1	Sn(OTf) <sub>2</sub> (2)	25	—	25	25
2	Al(OTf) <sub>3</sub> (2)	>99	27	71	71
3	In(OTf) <sub>3</sub> (2)	93	23	68	67
4	Sc(OTf) <sub>3</sub> (2)	>99	29	67	66
5	Hf(OTf) <sub>4</sub> (2)	>99	34	63	60
6	Hf(OTf) <sub>4</sub> (4)	>99	42	51	37
7	Hf(OTf) <sub>4</sub> (6)	>99	40	54	39
8	Hf(OTf) <sub>4</sub> (10)	73	17	32	20
9 <sup>c</sup>	Hf(OTf) <sub>4</sub> (4)	>99	63	32	19
10 <sup>c</sup>	HOTf (16)	84	41	39	26
11 <sup>c</sup>	—	5	—	3	3

<sup>a</sup> Standard reaction conditions: benzanilide **1** (100.6 mg, 0.5 mmol), Ru(acac)<sub>3</sub> (2 mol%), Triphos (4 mol%), additive (2–16 mol%), THF (2 mL) and H<sub>2</sub> (50 bar) at 150 °C, reaction time 15 h. <sup>b</sup> Conversion of **1** and yields of **2**, **3**, and **4** were calculated by GC using hexadecane as internal standard. In some cases, variable amounts of *N*-phenylpyrrolidine (5–15%) were produced following acid promoted ring-opening of THF. <sup>c</sup> Reactions were run under 15 bar H<sub>2</sub>.

Under the same experimental conditions, almost no reaction took place in the absence of the Lewis acid (Table 1, entry 11).

The results of this preliminary survey were deemed encouraging and the screening of a wider range of metal triflates worthwhile: the results are summarized in Fig. 1 and Table S2.†



**Fig. 1** Hydrogenation of benzanilide **1** with the Ru/Triphos catalyst: yield of amine **2** in the presence of different Lewis and Brønsted acid co-catalysts. Reaction conditions: benzanilide **1** (100.6 mg, 0.5 mmol), Ru(acac)<sub>3</sub> (2 mol%), Triphos (4 mol%), additive (4 mol%), THF (2 mL) and H<sub>2</sub> (15 bar) at 150 °C during 15 h. Yield of **2** was calculated by GC using hexadecane as internal standard.

Triflates of several transition metals, of the third group metals and of a few of the rare-earth ones, all promoted quantitative conversion of benzanilide **1** under the applied conditions. However, the yield in *N*-benzylaniline **2** was highly affected by the type of metal going from a minimum of 3% with Mg(OTf)<sub>2</sub> up to 74% with Yb(OTf)<sub>3</sub>·H<sub>2</sub>O. Al(OTf)<sub>3</sub> afforded a comparable yield, 72%, as to Yb(OTf)<sub>3</sub>·H<sub>2</sub>O. Despite the slightly lower cost of the former,<sup>12</sup> Yb(OTf)<sub>3</sub>·H<sub>2</sub>O was selected as the co-catalyst of choice in light of the positive characteristics shown by rare-earth metal triflates such as increased stability towards moisture and air, compatibility with many Lewis bases containing nitrogen, oxygen, phosphorus and sulfur atoms (which might be beneficial for functional group tolerance) and the possibility of being recycled at the end of the reaction, for which they are regarded as environmentally friendly.<sup>13</sup> Finally, none of the tested Brønsted acids, methanesulfonic acid (MSA), bis(trifluoromethane)sulfonimide (HNTf<sub>2</sub>) and the already mentioned triflic acid outperformed Yb(OTf)<sub>3</sub>·H<sub>2</sub>O as co-catalyst under the same experimental conditions.

Having identified in Yb(OTf)<sub>3</sub>·H<sub>2</sub>O the Lewis acid of choice, more detailed investigations of the reaction conditions were carried out.

Selectivity in the amine **2** turned out to be affected by the Yb(OTf)<sub>3</sub>·H<sub>2</sub>O/ruthenium ratio and either less (Table 2, entry 1) or more (Table 2, entry 3) than **2** (Table 2, entry 2) was detrimental. This ratio was therefore applied in all subsequent experiments. When the amount of catalyst was reduced (Table 2, entry 4) activity was retained as conversion was quantitative but selectivity decreased from 74% (Table 1, entry 2) to 68%. By reducing the hydrogen pressure further from 15 to 5 bar the yield of *N*-benzylaniline **2** improved from 74% (Table 2, entry 2) to 85% (Table 2, entry 5). Carrying out the reaction in the presence of molecular sieves to remove water and shift the equilibrium towards the desired amine did not affect conversion but had a dramatic impact on selectivity affording more than 90% of benzyl alcohol **3** and aniline **4** (Table 2, entry 6). Addition of a controlled amount of water, 10% v/v as to the amount of the solvent THF, almost halved conversion but afforded the same selectivity provided by anhydrous conditions (Table 2, entry 7). Therefore the adventitious water present in the solvent and that produced by the reaction itself is required for optimal performance, either none or more again is detrimental. When the reaction was run in the absence of Triphos, with (Table 2, entry 8) or without Lewis acid (Table 2, entry 9), conversion was low and products arising from hydrogenation of the aromatic rings were observed, none of which was detected under otherwise identical experimental conditions, suggesting that the reactions are indeed homogeneous. The presence of Yb(OTf)<sub>3</sub>·H<sub>2</sub>O is essential to promote the reaction under such mild conditions, as no conversion of benzanilide **1** at all is observed with the sole Ru–Triphos catalyst (Table 2, entry 10). At such low pressure, replacing the Lewis acid with an amount of triflic acid equivalent to that expected from its complete hydrolysis reduces conversion from quantitative to 67% with an even more dramatic impact on selectivity in **2** which drops from 85 to 37% (Table 2, entry 11).



Table 2 Hydrogenation of benzanilide **1** with [Ru/Triphos/Yb(OTf)<sub>3</sub>·H<sub>2</sub>O] system: fine tuning of reaction conditions

$$\text{Ph-C(=O)-NH-Ph} \xrightarrow[\text{THF, 15 h}]{\text{H}_2, 150^\circ\text{C}, \text{Ru(acac)}_3, \text{Triphos, Additive}} \text{Ph-CH}_2\text{-NH-Ph} + \text{Ph-CH}_2\text{-OH} + \text{Ph-NH}_2$$

**1**
**2**
**3**
**4**

Entry <sup>a</sup>	H <sub>2</sub> (bar)	[Ru] (mol%)	[Yb] (mol%)	Conv. <sup>b</sup> (%)	<b>2</b> <sup>b</sup> (%)	<b>3</b> <sup>b</sup> (%)	<b>4</b> <sup>b</sup> (%)
1	15	2	2	>99	65	35	28
2	15	2	4	>99	74	24	15
3	15	2	6	>99	72	25	13
4	15	1	4	>99	68	33	24
5	5	2	4	>99	85	14	6
6 <sup>c</sup>	5	2	4	>99	5	90	94
7 <sup>d</sup>	5	2	4	59	2	54	57
8 <sup>e</sup>	5	2	4	44	—	—	—
9 <sup>e</sup>	5	2	—	32	—	—	—
10	5	2	—	—	—	—	—
11 <sup>f</sup>	5	2	—	67	25	72	75

<sup>a</sup> Standard reaction conditions: benzanilide **1** (100.6 mg, 0.5 mmol), Ru(acac)<sub>3</sub> (1–2 mol%), Triphos (2 eq. respect to Ru), Yb(OTf)<sub>3</sub>·H<sub>2</sub>O (2–6 mol%), THF (2 mL) and H<sub>2</sub> (5 or 15 bar) at 150 °C over 15 h. In all reactions the autoclave was purged with 30 bar of hydrogen for three times. [Ru] = [Ru(acac)<sub>3</sub>] and [Yb] = [Yb(OTf)<sub>3</sub>·H<sub>2</sub>O] correspond to mol% of each species. <sup>b</sup> Conversion of **1** and yields of **2**, **3**, and **4** were calculated by GC using hexadecane as internal standard. In some cases, variable amounts of *N*-phenylpyrrolidine (5–10%) were produced following Yb(OTf)<sub>3</sub>·H<sub>2</sub>O promoted ring-opening of THF. <sup>c</sup> Run with molecular sieves (4 Å). <sup>d</sup> Run with 0.2 mL of water. <sup>e</sup> Run without Triphos. The only products observed were hydrogenation ring products. <sup>f</sup> Run in the presence of HOTf (12 mol%).

Considering the key role of the Lewis acid, the possibility that it might be as well effective in combination with other Ru-catalyst precursors was evaluated: however, only bis(2-methylallyl)(1,5-cyclooctadiene)ruthenium(II) showed a similar reactivity, although with a slightly lower selectivity (Table S3†). The steric and electronic properties of Triphos seem to be peculiar as none of the other phosphines tested in combination with [Ru(acac)<sub>3</sub>] and Yb(OTf)<sub>3</sub>·H<sub>2</sub>O afforded a system active for amide reduction (Table S4†).

Several solvents other than tetrahydrofuran were screened in order to further improve the efficiency of the [Ru(acac)<sub>3</sub>]/Triphos/Yb(OTf)<sub>3</sub>·H<sub>2</sub>O system (Table S5†). In general, ether-based solvents and alcohols, with some exceptions, provided high conversions, but ethers afforded better selectivities. With isopropanol, ethylene glycol or 1,3-propanediol the main by-product was the one arising from solvent amination with aniline **4**. Both 2-methyl-tetrahydrofuran and methyl cyclopentyl ether, which have been listed as greener substitutes for THF,<sup>14</sup> provided inferior selectivities in the desired *N*-benzylamine **2** as to THF, which remained the solvent of choice for further tests.

The substrate scope for the reduction of several amides using the [Ru(acac)<sub>3</sub>]/Triphos/Yb(OTf)<sub>3</sub>·H<sub>2</sub>O system is reported in Table 3: the reactions were run under the optimised conditions, in THF at 150 °C and 5 bar H<sub>2</sub> for a standard reaction time of 15 hours. For poorly reacting substrates, either the relative amount of catalyst was slightly increased or the reaction time was extended, thus improving both conversions and selectivities in the desired amines. Higher boiling solvents such as dioxane or ethylene glycol diethylether had to be used in such cases, instead of THF, which tended to partly condense outside

the glass vials inside the autoclave over prolonged reaction times. In general, high conversions were obtained, with a few exceptions, while yields in the desired amines were more variable, depending on the structure of the amide. In any case, the only by-products were the alcohol and amine arising from hydrogenolysis of the amide.

Initially, the hydrogenation of the bio-relevant primary amide, nicotinamide, was achieved in moderate yields (Table 3, entry 1). Next, selected benzamides were tested (Table 3, entries 2–7) with *p*-benzaniside (Table 3, entry 4) providing the highest yield, 89%. In agreement with previous reports,<sup>8c</sup> a phenyl substituent at nitrogen is beneficial and both activity and selectivity are progressively eroded going from *N*-phenyl to *N*-benzyl to *N*-Me (Table 3, entries 2, 6 and 7 respectively). Very good yields are obtained instead with the anilides of acetic (Table 3, entry 9, 80%) and phenylacetic acid (Table 3, entry 8, 65%). Several aryl-substituted acetanilides were then hydrogenated (Table 3, entries 10–20): all gave quantitative conversions and very good to excellent yields with the sole exceptions of 3-chloro- and 2-chloro acetanilide, whose amine yields were 49% and 30%, respectively. Overall, *para*-substituted acetanilides afforded a higher yield than the corresponding *meta*- and *ortho*-substituted ones and no direct correlation between the electronic nature of the substituents and amine yield became evident, although selectivity seems quite sensitive to sterics. Secondary amides containing functional groups such as ester (methyl-4-(phenylcarbamoyl)benzoate), nitro (4'-nitro-benzanilide) and alkenyl (*N*-phenyl acrylamide) were tested under optimized conditions affording low yields of the desired amine due to selectivity problems. In the case of substrates containing two amide groups the selectivity to the desired



Table 3 Substrate scope in the hydrogenation of amides catalyzed by [Ru(acac)<sub>3</sub>/Triphos/Yb(OTf)<sub>3</sub>·H<sub>2</sub>O] system

Entry <sup>a</sup>	Amide 1a	Conv. <sup>b</sup> (%)	Amine 2a	2a <sup>b</sup> (%)	Sel. <sup>b</sup> (%)
1		69		11	14
2		>99		85 [80]	85
3		80		40	50
4		>99		89 [79]	89
5		>99		45	45
6 <sup>c</sup>		78		40	52
7 <sup>d</sup>		50		14	28
8 <sup>e</sup>		>99		65	65
9		>99		80	80
10		>99		96 [82]	96
11 <sup>f</sup>		>99		59	59
12 <sup>g</sup>		>99		80 [70]	80
13 <sup>f</sup>		>99		49	49
14 <sup>g</sup>		>99		30	30
15		>99		90	90



Table 3 (Contd.)

Entry <sup>a</sup>	Amide 1a	Conv. <sup>b</sup> (%)	Amine 2a	2a <sup>b</sup> (%)	Sel. <sup>b</sup> (%)
	$  \begin{array}{ccc}  \text{R} \text{---} \text{C}(=\text{O}) \text{---} \text{N}(\text{R}') \text{R}'' & \xrightarrow[\text{THF, 15 h}]{\text{H}_2 \text{ (5 bar), 150 }^\circ\text{C}} & \text{R} \text{---} \text{CH}_2 \text{---} \text{N}(\text{R}') \text{R}'' \\  \text{1a} & & \text{2a} \\  \text{Ru(acac)}_3 \text{ (2 mol\%)} & & \\  \text{Triphos (4 mol\%)} & & \\  \text{Yb(OTf)}_3 \cdot \text{H}_2\text{O (4 mol\%)} & &   \end{array}  $				
16		>99		89 [82]	88
17 <sup>h</sup>		>99		80	80
18		>99		95 [88]	95
19 <sup>i</sup>		>99		76	76
20		94		68	72
21		>99		[86]	100
22 <sup>d</sup>		95		[84]	100
23 <sup>i</sup>		>99		61	61
24 <sup>c</sup>		>99		76	76
25 <sup>c</sup>		>99		91 [85]	91
26 <sup>i</sup>		>99		80 [70]	100
27 <sup>c</sup>		>99		53	53
28 <sup>d</sup>		89		45	51
29 <sup>c</sup>		97		30	32





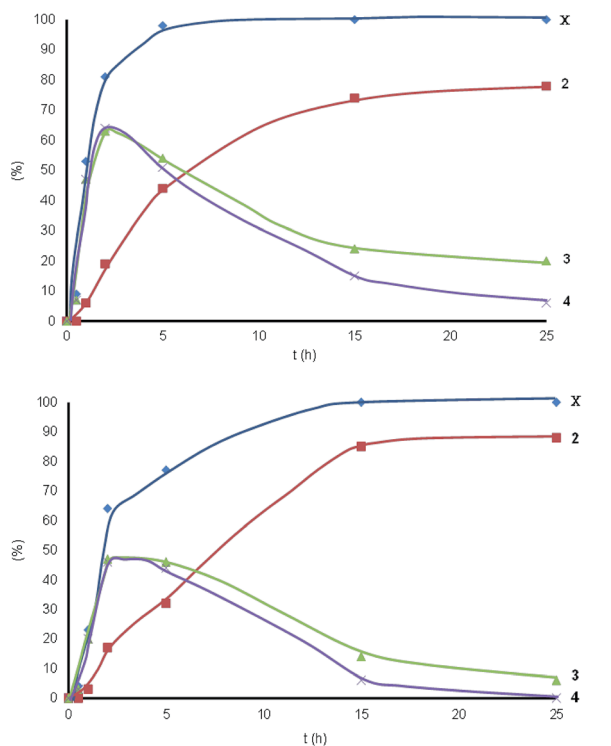
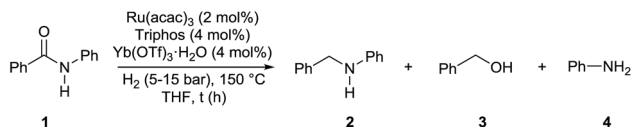


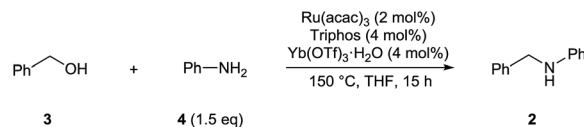
Fig. 2 Variation of the substrate conversion and product yields during the hydrogenation of benzanalide **1** with the Ru/Triphos/Yb(OTf)<sub>3</sub>·H<sub>2</sub>O catalytic system. Reaction conditions: benzanalide **1** (100.6 mg, 0.5 mmol), Ru(acac)<sub>3</sub> (2 mol%), Triphos (4 mol%), Yb(OTf)<sub>3</sub>·H<sub>2</sub>O (4 mol%), THF (2 mL) at 150 °C, H<sub>2</sub> (15 bar, top graph), (5 bar, bottom graph). Conversion (X) of **1** and yields of **2**, **3**, and **4** were calculated by GC using hexadecane as internal standard. Variable amounts of *N*-phenylpyrrolidine (5–10%) were produced following Yb(OTf)<sub>3</sub>·H<sub>2</sub>O promoted ring-opening of THF.

*N*-substituted aniline was the product of alkylation by 3,5-dimethylbenzyl alcohol. The preferential reaction with this alcohol indicates that reduction of benzanalide is slow as compared to the subsequent *N*-alkylation.

In agreement with our proposal, *N*-benzylaniline **2** is prepared in 90% yield from either the reaction of benzyl alcohol **3** (Scheme 3, eqn (1)) or benzaldehyde and aniline **4** under the previously optimized hydrogenation conditions (Scheme S2†).

As shown in Scheme 3 the synergistic combination of the [Ru(acac)<sub>3</sub>]/Triphos catalyst and Yb(OTf)<sub>3</sub>·H<sub>2</sub>O is needed for the amine alkylation as no conversion is observed otherwise (Scheme 3, eqn (2) and (3)). It is noteworthy that even without hydrogen the reaction between benzyl alcohol **3** and aniline **4** proceeded well to give *N*-benzylaniline **2** in 70% (Scheme 3, eqn (4)).

Examples have been reported in which metal triflates catalyze the direct amination of simple allylic, propargylic and benzylic alcohols through carbocation intermediates.<sup>15</sup>



	conditions	Conv. (%) <sup>a</sup>	<b>2</b> (%) <sup>a</sup>
(1) <sup>b</sup>	5 bar of H <sub>2</sub>	90	90
(2)	5 bar of H <sub>2</sub> without Yb(OTf) <sub>3</sub> ·H <sub>2</sub> O	-	-
(3)	5 bar of H <sub>2</sub> without Ru(acac) <sub>3</sub> /Triphos	1	1
(4) <sup>b</sup>	5 bar of N <sub>2</sub>	92	70
(5) <sup>b</sup>	5 bar of N <sub>2</sub> without Ru(acac) <sub>3</sub> /Triphos	6	2
(6)	5 bar of N <sub>2</sub> without Yb(OTf) <sub>3</sub> ·H <sub>2</sub> O	10	-

Scheme 3 Control experiments showing the synergistic combination of Ru(acac)<sub>3</sub>, Triphos and Yb(OTf)<sub>3</sub>·H<sub>2</sub>O in promoting the alkylation of aniline with benzyl alcohol (via hydrogen borrowing in the absence of hydrogen). <sup>a</sup> Conversion of **3** and yields of product **2** were calculated by GC using hexadecane as internal standard. <sup>b</sup> Variable amounts of *N*-phenylpyrrolidine (eqn (1) 7%, eqn (4) 4%, eqn (5) 6%) were produced following Yb(OTf)<sub>3</sub>·H<sub>2</sub>O promoted ring-opening of THF.

Therefore, the possibility that, in the absence of hydrogen, *N*-benzylaniline **2** could be formed through direct *N*-alkylation of aniline **4** with benzyl alcohol **3** was taken into account. However Yb(OTf)<sub>3</sub>·H<sub>2</sub>O alone is not able to catalyse this reaction (Scheme 3, eqn (5)), neither is the [Ru(acac)<sub>3</sub>]/Triphos catalyst (Scheme 3, eqn (6)), hence both individual catalysts are required. Furthermore, the alkylation of aniline with 1-phenylethanol, a secondary benzylic alcohol which easily generates the stabilized carbocation, in the presence of hydrogen, provided only a poor 12% yield of the alkylated amine (Scheme S3†). Although in the absence of hydrogen conversion of the alcohol was higher, the main product though (45% yield) was in this case acetophenone. Significantly, control experiments were run using a primary aliphatic alcohol, 1-octanol, under identical reaction conditions (Schemes S4 and S5†). In fact, *N*-octylaniline was obtained in 92% yield in the presence of hydrogen, 55% without! Again in this case the combination of the [Ru(acac)<sub>3</sub>]/Triphos catalyst and Yb(OTf)<sub>3</sub>·H<sub>2</sub>O is necessary. These results rule out a simple carbocation mechanism. Alkylation of aniline with benzyl alcohol is selective in that the product of double alkylation was never observed, not even when *N*-benzylaniline was reacted with extra benzyl alcohol (Scheme S7†).

The reactivity pattern of the alcohols, primary or secondary, benzylic or aliphatic, disproves a direct alkylation pathway. Instead, the control experiments in the absence of hydrogen indicate that the [Ru(acac)<sub>3</sub>]/Triphos/Yb(OTf)<sub>3</sub>·H<sub>2</sub>O system shows activity in the alkylation of aniline with an alcohol<sup>16</sup> which occurs through a borrowing hydrogen pathway.<sup>17</sup> The latter comprises the initial (i) oxidation (dehydrogenation) of the alcohol to form the corresponding aldehyde through hydrogen transfer to the metal catalyst,<sup>18</sup> (ii) condensation of the aldehyde with the amine substrate to give an imine intermediate, and (iii) reduction of the imine by transfer of the



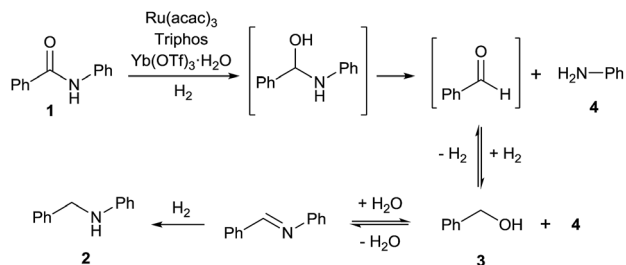


Fig. 3 Proposed mechanism for the formation of the higher amine 2 from amide 1.

hydrogen termini temporarily stored in the catalyst. The poor yields obtained with secondary alcohols reflects the inferior reactivity of ketones as to aldehydes in the reductive amination.<sup>19</sup>

Based on the experiments described above, a mechanism for the formation of amine 2 from amide 1 is proposed in Fig. 3. We believe that amide hydrogenation under the here described conditions initially leads to hydrogenolysis of the amide. Then, a borrowing hydrogen-type alkylation of the amine with the produced alcohol takes place. This new mechanistic insight opens the door for further catalyst improvements as well as new transformations, *e.g.* the reductive alkylation of amides as shown in Scheme S1.†

Although numerous ruthenium-based catalytic systems have been developed to date which promote the atom-economical and environmentally benign alkylation of amines with alcohols (water is the only by-product), the present system is quite different.<sup>20,21</sup> In fact, the results of our control experiments, the recently reported Ru–Triphos catalyzed amination of alcohols with ammonia<sup>22</sup> and the methylation of aromatic amines with formic acid as the sole carbon and hydrogen source<sup>23</sup> add to the toolbox of useful synthetic transformation promoted by the Ru–Triphos system for the synthesis of amines, which includes their methylation with H<sub>2</sub> and CO<sub>2</sub> (ref. 24) and alkylation with carboxylic acids and hydrogen.<sup>25</sup>

It is clear that the possibility to achieve selective alkylation of amines with an alcohol by combining the Ru/Triphos system and Yb(OTf)<sub>3</sub>·H<sub>2</sub>O, as highlighted by the control experiments, deserves further investigations as these results represent the first examples of a reaction of this type which proceeds under acid catalysis and is currently being explored in our laboratories.

## Conclusions

The [Ru(acac)<sub>3</sub>]/Triphos catalytic system with Yb(OTf)<sub>3</sub> constitutes an improved catalyst system for the hydrogenation of aliphatic and aromatic secondary and tertiary amides. Compared to previous work a significantly broader range of amides can be hydrogenated to the corresponding amines under milder conditions. No special care is needed and the reactions can be simply set in air. Control experiments indicate a different mechanism for this important transformation: after the initial reduction of the amide carbonyl group to the

hemiaminal this intermediate collapses to give the alcohol and the non-alkylated amine. These compounds slowly produce the desired product *via* a hydrogen borrowing mechanism. The synergistic combination of Ru/Triphos and the metal triflate is necessary for both steps. Quantitative conversions were achieved with most of the tested substrates while selectivities still need to be improved for some of them. Further work is aimed to allow for hydrogenation under milder conditions in the presence of more demanding functionalized substrates, *e.g.* peptides. In the latter instance, because the only by-products are the alcohol and lower amine, investigations into the reductive amination step might serve to improve the system further on. Finally, it should be recognized that the [Ru(acac)<sub>3</sub>]/Triphos/Yb(OTf)<sub>3</sub> system is competent for alcohol amination through hydrogen auto-transfer under acidic conditions.

## Experimental details

### General procedure for the hydrogenation of benzanilide (1)

A 8 mL glass vial containing a stirring bar was sequentially charged with benzanilide 1 (100.6 mg, 0.5 mmol), Ru(acac)<sub>3</sub> (4.0 mg, 0.01 mmol), Triphos (12.5 mg, 0.02 mmol), Yb(OTf)<sub>3</sub>·H<sub>2</sub>O (12.8 mg, 0.02 mmol), *n*-hexadecane (50 mg) as an internal standard and THF (2 mL) as solvent. Afterwards, the reaction vial was capped with a septum equipped with a syringe needle and set in the alloy plate, which was then placed into a 300 mL autoclave. Once sealed, the autoclave was purged three times with 30 bar of hydrogen, then pressurized to 5–50 bar and placed into an aluminium block, which was preheated at 130–170 °C. After the desired reaction time (0.5–25 h), the autoclave was cooled in an ice bath, and the remaining gas was carefully released. Finally, the reaction mixture was diluted with ethyl acetate and analysed by GC.

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## Notes and references

- (a) K. Eller, E. Henkes, R. Rossbacher and H. Hoke, *Ullman's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, 2000, Amines, Aliphatic, DOI: 10.1002/14356007.a02\_001; (b) *Amines: Synthesis, Properties and Applications*, ed. S. A. Lawrence, Cambridge University, Cambridge, 2006.
- (a) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, 4, 2337–2347; (b) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, 54, 3451–3479.
- For selected recent examples, see: (a) S. Zhou, K. Junge, D. Addis, S. Das and M. Beller, *Angew. Chem., Int. Ed.*,



- 2009, **48**, 9507–9510; (b) S. Das, D. Addis, S. Zhou, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 1770–1771; (c) S. Das, D. Addis, K. Junge and M. Beller, *Chem.–Eur. J.*, 2011, **17**, 12186–12192; (d) S. Das, B. Wendt, K. Möller, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2012, **51**, 1662–1666; (e) S. Park and M. Brookhart, *J. Am. Chem. Soc.*, 2012, **134**, 640–653; (f) C. Cheng and M. Brookhart, *J. Am. Chem. Soc.*, 2012, **134**, 11304–11307; (g) J. T. Reeves, Z. Tan, M. A. Marsini, Z. S. Han, Y. Xu, D. C. Reeves, H. Lee, B. Z. Lu and C. H. Senanayake, *Adv. Synth. Catal.*, 2013, **355**, 47–52; (h) T. Dombay, C. Helleu, C. Darcel and J.-B. Sortais, *Adv. Synth. Catal.*, 2013, **355**, 3358–3362. For a recent example of organo-catalytic promoted hydrosilylation of amides to amines, see: (i) E. Blondiaux and T. Cantat, *Chem. Commun.*, 2014, **50**, 9349–9352.
- 4 N. L. Lampland, M. Hovey, D. Mukherjee and A. D. Sadow, *ACS Catal.*, 2015, **5**, 4219–4226.
- 5 (a) D. Dodds and D. J. Cole-Hamilton, in *Sustainable Catalysis: Challenges and Practices for the Pharmaceutical and Fine Chemical Industries*, ed. P. J. Dunn, K. K. Hii, M. J. Krische and M. T. Williams, John Wiley and Sons, Inc., Hoboken, New Jersey, 2013, pp. 1–36; (b) A. M. Smith and R. Whyman, *Chem. Rev.*, 2014, **114**, 5477–5510.
- 6 (a) C. Hirose, N. Wakasa and T. Fuchikami, *Tetrahedron Lett.*, 1996, **37**, 6749–6752; (b) G. Beamson, A. J. Papworth, C. Philipps, A. M. Smith and R. Whyman, *J. Catal.*, 2010, **269**, 93–102; (c) G. Beamson, A. J. Papworth, C. Philipps, A. M. Smith and R. Whyman, *J. Catal.*, 2011, **278**, 228–238; (d) M. Stein and B. Breit, *Angew. Chem., Int. Ed.*, 2013, **52**, 2231–2234; (e) R. Burch, C. Paun, X.-M. Cao, P. Crawford, P. Goodrich, C. Hardacre, P. Hu, L. McLaughlin, J. Sá and J. M. Thompson, *J. Catal.*, 2011, **283**, 89–97; (f) J. Coetzee, H. G. Manyar, C. Hardacre and D. J. Cole-Hamilton, *ChemCatChem*, 2013, **5**, 2843–2847.
- 7 (a) E. Balaraman, B. Gnanaprakasam, L. J. W. Shimon and D. Milstein, *J. Am. Chem. Soc.*, 2010, **132**, 16756–16758; (b) J. M. John and S. H. Bergens, *Angew. Chem., Int. Ed.*, 2011, **50**, 10377–10380; (c) M. Ito, T. Ootsuka, R. Watari, A. Shiibashi, A. Himizu and T. Ikariya, *J. Am. Chem. Soc.*, 2011, **133**, 4240–4242; (d) T. Miura, I. E. Held, S. Oishi, M. Naruto and S. Saito, *Tetrahedron Lett.*, 2013, **54**, 2674–2678; (e) R. Barrios-Francisco, E. Balaraman, Y. Diskin-Posner, G. Leitner, L. J. W. Shimon and D. Milstein, *Organometallics*, 2013, **32**, 2973–2982; (f) J. M. John, S. Takebayashi, N. Dabral, M. Miskolzie and S. H. Bergens, *J. Am. Chem. Soc.*, 2013, **135**, 8578–8584; (g) Y. Kita, T. Higuchi and K. Mashima, *Chem. Commun.*, 2014, **50**, 11211–11213; (h) J. M. John, R. Loorthuraja, E. Antoniuk and S. H. Bergens, *Catal. Sci. Technol.*, 2015, **5**, 1181–1186; (i) J. R. Cabrero-Antonino, E. Alberico, H.-J. Drexler, W. Baumann, K. Junge, H. Junge and M. Beller, *ACS Catal.*, 2016, **6**, 47–54.
- 8 (a) A. A. Núñez Magro, G. R. Eastham and D. J. Cole-Hamilton, *Chem. Commun.*, 2007, 3154–3156; (b) D. L. Dodds, J. Coetzee, J. Klankermayer, S. Brosinski, W. Leitner and D. J. Cole-Hamilton, *Chem. Commun.*, 2012, **48**, 12249–12262; (c) J. Coetzee, D. L. Dodds, J. Klankermayer, S. Brosinsky, W. Leitner, A. M. Z. Slawin and D. J. Cole-Hamilton, *Chem.–Eur. J.*, 2013, **19**, 11039–11050; (d) T. vom Stein, M. Meuresch, D. Limper, M. Schmitz, M. Hölscher, J. Coetzee, D. J. Cole-Hamilton, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2014, **136**, 13217–13225.
- 9 (a) F. M. A. Geilen, B. Engendahl, A. Harwardt, W. Marquardt, J. Klankermayer and W. Leitner, *Angew. Chem., Int. Ed.*, 2010, **49**, 5510–5514; (b) F. M. A. Geilen, B. Engendahl, M. Hölscher, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2011, **133**, 14349–14358; (c) A report has recently appeared concerning the use of an *in situ* Co–Triphos catalytic system which is able to hydrogenate carboxylic acids to the corresponding alcohols with no additives T. J. Korstanje, J. I. van der Vlugt, C. J. Elsevier and B. de Bruin, *Science*, 2015, **350**, 298–301.
- 10 (a) X. Cui, Y. Li, C. Topf, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2015, **54**, 10596–10599; (b) Y. Li, C. Topf, X. Cui, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2015, **54**, 2231–2234.
- 11 Unless otherwise stated, benzyl alcohol **3** and aniline **4** were the only by-products in the reduction of benzanilide **1**.
- 12 The cost of Al(OTf)<sub>3</sub> (99.99% metal basis) is 5.5 € per mmol, that of Yb(OTf)<sub>3</sub>·H<sub>2</sub>O (Yb 25–28%) is 6.5€ per mmol (by Sigma Aldrich).
- 13 S. Kobayashi, M. Sugiura, H. Kitagawa and W. W.-L. Lam, *Chem. Rev.*, 2002, **102**, 2227–2302.
- 14 (a) K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31–36; (b) R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binksa and A. D. Curzons, *Green Chem.*, 2011, **13**, 854–862; (c) D. Prat, O. Pardigon, H.-W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani and P. Hosek, *Org. Process Res. Dev.*, 2013, **17**, 1517–1525; (d) H. E. Eastman, C. Jamieson and A. J. B. Watson, *Aldrichimica Acta*, 2015, **40**, 51–55.
- 15 (a) W. Huang, Q.-S. Shen, J.-L. Wang and X.-G. Zhou, *Chin. J. Chem.*, 2008, **26**, 729–735; (b) T. Takashi Ohshima, J. Ipposhi, Y. Nakahara, R. Shibuya and K. Mashima, *Adv. Synth. Catal.*, 2012, **354**, 2447–2452.
- 16 (a) G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2010, **110**, 1611–1641; (b) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853–1864; (c) Q. Yang, W. Qingfu and Z. Yu, *Chem. Soc. Rev.*, 2015, **44**, 2305–2329.
- 17 (a) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555–1575; (b) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, **38**, 753–762; (c) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681–703; (d) A. J. A. Watson and J. M. J. Williams, *Science*, 2010, **329**, 635–636; (e) S. Pan and T. Shibata, *ACS Catal.*, 2013, **3**, 704–712; (f) C. Gunanathan and D. Milstein, *Science*, 2013, **341**, 249–261; (g) J. M. J. Williams, in *Sustainable Catalysis*:



- Challenges and Practices for the Pharmaceutical and Fine Chemical Industries*, ed. P. J. Dunn, K. K. Hii, M. J. Krische and M. T. Williams, John Wiley and Sons, Inc., Hoboken, New Jersey, 2013, pp. 121–137; (h) D. Hollmann, *ChemSusChem*, 2014, 7, 2411–2413; heterogeneous catalysis: K. Shimizu, *Catal. Sci. Technol.*, 2015, 5, 1412–1427; (j) For a recent survey of the Borrowing hydrogen approach to the synthesis of some pharmaceutically relevant intermediates, see: J. J. Leonard, A. J. Blacker, S. P. Marsden, M. F. Jones, K. R. Mulholland and R. Newton, *Org. Process Res. Dev.*, 2015, 19, 1400–1410.
- 18 (a) S. Gladiali and E. Alberico, *Transferhydrogenations in Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, 2004, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2nd edn, pp. 145–166; (b) J. S. M. Samec, J.-E. Backvall, P. G. Andersson and P. Brandt, *Chem. Soc. Rev.*, 2006, 35, 237–248; (c) D. Wang and D. Astruc, *Chem. Rev.*, 2015, 115, 6621–6686.
- 19 M. B. Smith, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, John Wiley & Sons, Inc., Hoboken, New Jersey 7th edn, 2013.
- 20 Recent reports: (a) D. Hollmann, A. Tillack, D. Michalik, R. Jackstell and M. Beller, *Chem.–Asian J.*, 2007, 2, 403–410; (b) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, 131, 1766–1774; (c) S. Imm, S. Bhn, M. Zhang, L. Neubert, H. Neumann, F. Klasovsky, J. Pfeffer, T. Haas and M. Beller, *Angew. Chem., Int. Ed.*, 2011, 50, 7599–7603; (d) Y. Liu, W. Chen, C. Feng and G. Deng, *Chem.–Asian J.*, 2011, 6, 1142–1146; (e) D. Pingen, O. Diebolt and D. Vogt, *ChemCatChem*, 2013, 5, 2905–2912; (f) A. B. Enyong and B. Moasser, *J. Org. Chem.*, 2014, 79, 7553–7563; (g) S. P. Shan, T. T. Dang, A. M. Seayad and B. Ramalingam, *ChemCatChem*, 2014, 6, 808–814; (h) D. Pingen, M. Lutz and D. Vogt, *Organometallics*, 2014, 33, 1623–1629; (i) D. Pingen and V. Dieter, *Catal. Sci.*, 2014, 4, 47–52; (j) N. J. Oldenhuis, V. M. Dong and Z. Guan, *J. Am. Chem. Soc.*, 2014, 136, 12548–12551; (k) X. Xie and V. Huynh, *ACS Catal.*, 2015, 5, 4143–4151; (l) T. T. Dang, B. Ramalingam and A. M. Seayad, *ACS Catal.*, 2015, 5, 4082–4088; (m) E. Balaraman, D. Srimani, Y. Diskin-Posner and D. Milstein, *Catal. Lett.*, 2015, 145, 139–144; (n) R. Ramachandran, G. Prakash, M. Nirmala, P. Viswanathamurthi and J. G. J. Malecki, *Organomet. Chem.*, 2015, 791, 130–140; (o) S. P. Shan, X. Xiaoke, B. Boopathy Gnanaprakasam, T. T. Dang, B. Ramalingam, H. V. Huynh and A. M. Seayad, *RSC Adv.*, 2015, 5, 4434–4442.
- 21 For selected reports on Ru-catalysed alcohol amination with NH<sub>3</sub>, see: (a) C. Gunanathan and D. Milstein, *Angew. Chem., Int. Ed.*, 2008, 47, 8661–8664; (b) S. Imm, S. Bähn, L. Neubert, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2010, 49, 8126–8129; (c) D. Pingen, C. Muller and D. Vogt, *Angew. Chem., Int. Ed.*, 2010, 49, 8130–8133; (d) W. Baumann, A. Spannenberg, J. Pfeffer, T. Haas, A. Köckritz, A. Martin and J. Deutsch, *Chem.–Eur. J.*, 2013, 19, 17702–17706; (e) X. Ye, P. N. Plessow, M. K. Brinks, M. Schelwies, T. Schaub, F. Rominger, R. Paciello, M. Limbach and P. Hofmann, *J. Am. Chem. Soc.*, 2014, 136, 5923–5929; (f) D. Pingen, T. Lebl, M. Lutz, G. S. M. Nicho, P. C. J. Kamer and D. Vogt, *Organometallics*, 2014, 33, 2798–2805.
- 22 E. J. Derrah, M. Hanauer, P. N. Plessow, M. Schelwies, M. K. da Silva and T. Schaub, *Organometallics*, 2015, 34, 1872–1881.
- 23 S. Savourey, G. Lefèvre, J.-C. Berthet and T. Cantat, *Chem. Commun.*, 2014, 50, 14033–14036.
- 24 (a) K. Beydoun, T. von Stein, J. Klankermayer and W. Leitner, *Angew. Chem., Int. Ed.*, 2013, 52, 9554–9557; (b) Y. Li, I. Sorribes, T. Yan, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2013, 52, 12156–12160; (c) K. Beydoun, G. Ghattas, J. Klankermayer and W. Leitner, *Angew. Chem., Int. Ed.*, 2014, 53, 11010–11014.
- 25 I. Sorribes, J. R. Cabrero-Antonino, C. Vicent, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2015, 137, 13580–13587.

