Very Important Publication

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Direct Synthesis of Primary Amines *via* Ruthenium-Catalysed Amination of Ketones with Ammonia and Hydrogen

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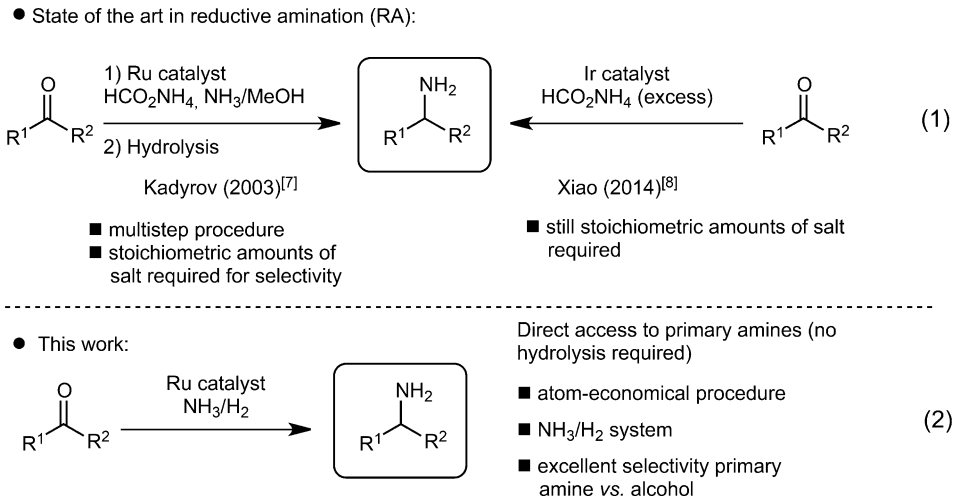
Abstract: A highly selective reductive amination of ketones to primary amines with ammonia and hydrogen using a simple ruthenium catalyst has been developed. The protocol described constitutes an efficient and direct atom-economical approach *en route* to α-methylbenzylamine derivatives in good to high yields. The presence of catalytic amounts of aluminum triflate turned out to be crucial for achieving high conversion towards primary amines.

Keywords: aluminum triflate; ammonia; hydrogen; primary amines; reductive amination; ruthenium

Primary amines are important intermediates in fine chemicals, pharmaceutical production and many valuable end products contain primary amino groups.[1] Considering ammonia as an abundant, cheap and accessible nitrogen source, several transition metal-catalysed procedures have been developed for the direct synthesis of amines such as hydroaminomethylation, hydroamination, allylic substitution, cross-coupling, alcohol amination and reductive amination.[2] Among them, alcohol amination has gained considerable importance as a greener procedure.[3] This transformation is based on the so-called "borrowing hydrogen" methodology, which constitutes an environmentally friendly process generating water as the sole by-product.[4] In this case, the hydrogen required for the final imine hydrogenation step is generated by dehydrogenation of the starting alcohol. In contrast, the synthesis of primary amines *via* reductive amination of ketones or aldehydes has not been fully developed yet.

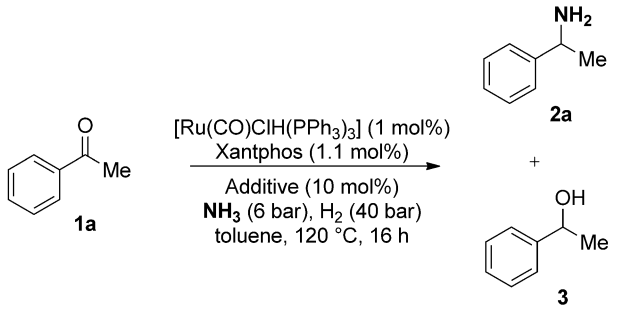
Industrially, the reductive amination with hydrogen and ammonia is carried out by heterogeneous processes under relatively forcing conditions which limits its applicability on a laboratory scale synthesis and is not suitable for sensitive substrates.[5] In order to perform the reaction under milder conditions several homogeneous catalysts were identified.[6] Pioneering work from both Beller et al. using rhodium catalysts on benzaldehydes[7] and Kadyrov et al. employing ruthenium on ketones[8] [Scheme 1, Eq. (1)] showed the feasibility for this transformation. However, with the exception of benzaldehydes as substrates,[7] the selectivity and yields for the reductive amination with H_2 and NH_3 using ketones as starting materials were relatively poor.[8] The main problem besides low conversions is usually the undesired hydrogenation of the ketone to the corresponding alcohol.[8,9] To overcome this problem, transfer hydrogenation conditions with reductants like ammonium formate, which can also act as an NH_3 surrogate, were successfully applied.[10,11] With this protocol, *N*-formyl derivatives were obtained as the main products, requiring an additional hydrolysis step to obtain the respective free primary amine. From an atom-economical standpoint, it is desirable to avoid any additional steps and to use H_2 as an inexpensive reducing agent. Therefore, we report the development of a simple catalyst to obtain primary amines directly from ketones by the use of NH_3 and H_2, where the formation of alcohols plays just a minor role compared to the known systems [Scheme 1, Eq. (2)].

Optimisation studies were conducted with acetophenone (**1a**) as the model substrate and different variables such as ruthenium precursors, ligands and additives were systematically examined. The ruthenium(II) precatalyst $[Ru(CO)ClH(PPh_3)_3]$ was selected due to its high compatibility with ammonia[12] in combination with 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) as ligand using 6 bar of NH_3 and 40 bar of H_2 in toluene at 120 °C (Table 1).[13] As judged by entry 1, reduced starting material **3** could be detected. Nevertheless, we assumed that the addi-



Scheme 1. Reductive amination for the synthesis of primary amines.

Table 1. Influence of additives to the reaction outcome.[a]



Entry	Additive	Conv. [%]	**2a** [%]	**3** [%]	**2a**:**3**
1	–	83	0	32	–
2	$In(OTf)_3$	72	7	7	1
3	$Ga(OTf)_3$	74	1	6	0.16
4	BPA	99	8	24	0.33
5	Tf_2NH	83	23	7	3.2
6	$Al(OTf)_3$	94	37	4	9.25

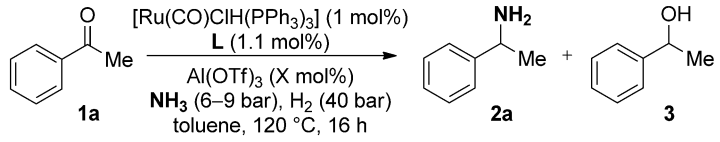
[a] *Standard reaction conditions:* 2.97 mmol of **1a**, Ru catalyst (1 mol%), ligand (1.1 mol%), additive (10 mol%), toluene (20 mL), 120 °C, $p(NH_3) = 6$ bar, $p(H_2) = 40$ bar, 16 h. Yields determined by GC using dodecane as an internal standard. Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, BPA = 1,1-binaphthyl-2,2-diyl hydrogen phosphate, Tf = trifluoromethanesulfonate.

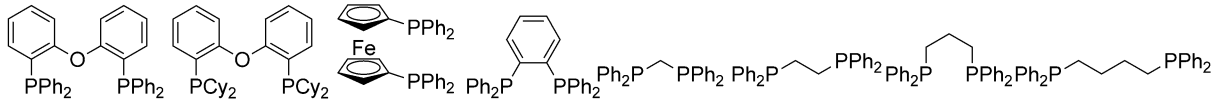
tion of an acidic co-catalyst would enhance either the rate of imine formation or imine hydrogenation thus favouring the selectivity towards **2a**. For this purpose both Lewis acidic and protic acids were examined.[14] The inclusion of $In(OTf)_3$ or 1,1′-binaphthyl-2,2'-diyl hydrogen phosphate (BPA) showed a slight increase on amine formation providing 7% and 8% yield, respectively (entries 2 and 4). However, we observed that in the presence of $Al(OTf)_3$ as an additive 37% of **2a** was obtained together with 4% of **3** (entry 6).[15] The rest of the mass balance accounted for the formation of 1-phenyl-*N*-(1-phenylethyl)ethan-1-imine detected as a major side product. Additionally, small amounts of 1,3-diphenylbutan-1-one were also detected.[16] Condensation products and the imine of **1a** were also detected as typical side products under conditions when only low selectivities of the desired primary amines were achieved.

Next, we turned our attention to examine the ligand effect on our reductive amination protocol. The most significant results are summarised in Table 2. When moving from xantphos to a more flexible ligand backbone with a narrower bite angle such as DPEphos, the yield of **2a** increased to 56% (entry 1).[13] Employing a more bulky and electron-donating diphosphine ligand such as **L1** was detrimental for the reaction outcome (entry 2). The use of the ferrocenyl-based ligand dppf or alkyl bisphosphine dppm was also inefficient for this transformation (entries 3 and 5). Interestingly, simple dppe provided a significant enhancement in yield, furnishing the desired product **2a** in 74% yield, albeit with a moderate selectivity (entry 6). Further studies revealed that increasing the pressure of NH_3 to 9 bar provided 95% isolated yield of **2a** with only trace amounts of **3** (entry 7). To the best of our knowledge, this is the highest selectivity reported to date for a homogeneously catalysed reductive amination of ketones using NH_3 and H_2 gas.

The catalyst loading could be decreased to 0.5 mol% and the amount of $Al(OTf)_3$ to 1 mol% without a significant loss in conversion or selectivity (entry 8). It is worth mentioning that dppp (entry 11) provided similar results as dppe. However, a considerable decrease in selectivity was found when employing dppb (entry 12). Finally, control experiments suggested the importance of the ligand and additive for

Table 2. Ligand screening.[a]





Entry	Ligand	$Al(OTf)_3$ (X mol%)	Conv. [%]	**2a** [%]	**3** [%]	**2a**:**3**
1	DPEphos	10	95	56	4	14
2	**L1**	10	64	0	1	–
3	dppf	10	62	0	0	–
4	**L2**	10	92	43	4	11
5	dppm	10	60	0	0	–
6	dppe	10	95	74	5	15
7[b]	dppe	10	100	99 (95)[c]	1	99
8[d]	dppe	1	97	92	6	18.4
9	dppe	–	70	21	32	0.7
10	–	10	40	0	11	–
11	dppp	10	95	68	5	14
12	dppb	10	86	51	18	2.8

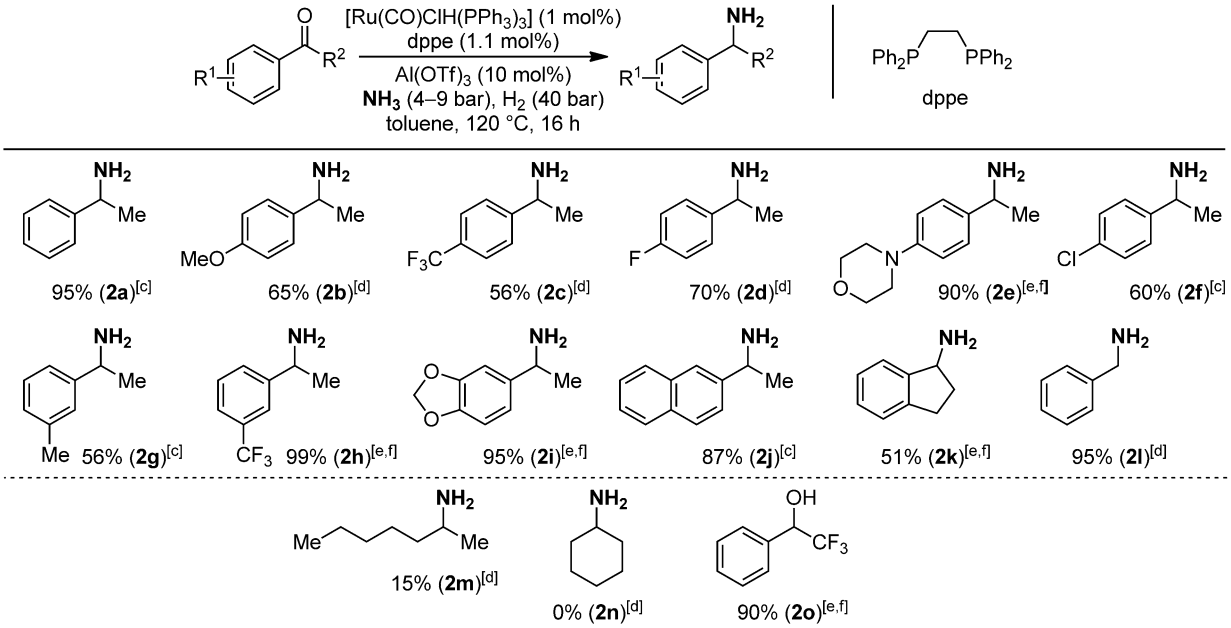
[a] *Standard reaction conditions:* 2.97 mmol of **1a**, Ru catalyst (1 mol%), ligand (1.1 mol%), additive (10 mol%), toluene (20 mL), 120 °C, $p(NH_3) = 6$ bar, $p(H_2) = 40$ bar, 16 h. Yields determined by GC using dodecane as an internal standard.
[b] Using $p(NH_3) = 9$ bar.
[c] Isolated yield.
[d] Using 0.5 mol% of $[Ru(CO)ClH(PPh_3)_3]$ and 1 mol% of $Al(OTf)_3$.

both reactivity and selectivity (entries 9 and 10). In the absence of $Al(OTf)_3$ in the reaction media, alcohol **3** was obtained as the major product featuring the crucial role of the additive for achieving high selectivity.

With the optimised conditions in hand, we explored the scope of our reductive amination protocol. As shown in Table 3, a series of acetophenone derivatives undergo reductive amination in good to excellent yields. Both electron-donating (**2b**) and electron-withdrawing groups (**2c**) were tolerated (65% and 56% yield, respectively). Considering the importance of fluorinated compounds in pharmaceuticals and agrochemicals, we were pleased to access **2c**, **2d** and **2h** in moderate to excellent yields (56–99%). Even *p*-chloro-substituted acetophenone could be aminated in 60% yield as shown by **2f**,[17] thus leaving ample opportunities for further functionalisation *via* standard cross-croupling techniques. When placing a substituent at the *meta*-position of the aromatic ring, **2g** could be obtained in 56% yield (30% of ketone recovered). The naphthyl moiety also reacted well providing high yields (87%), as shown by **2j**. As expected, the reaction with benzaldehyde proceeded very smoothly towards benzylamine **2l** (95% yield). Interestingly, the reaction is not only limited to acetophenone reagents as exemplified by 1-indanone, providing **2k** in 53% yield, with 45% of unreacted starting material. Unfortunately, dialkyl substrates such as **2m** or **2n** showed poor reactivity using our protocol (15% and 0% yield, respectively). For both substrates mostly starting ketone was recovered. Besides, the more activated substrate **2o** was fully hydrogenated to the undesired alcohol.

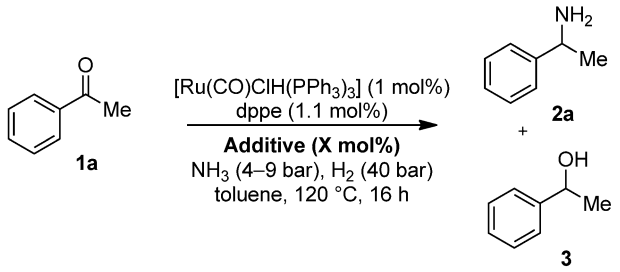
In order to evaluate the impact of $Al(OTf)_3$ on this reductive amination reaction, the series of experiments given in Table 4 was conducted. As judged by entry 2, using 30 mol% of NH_4OTf as an additive turned out to be less effective compared to $Al(OTf)_3$. However, decreasing the amount of NH_4OTf to 10 mol% resulted in the complete loss of reactivity, even at a higher ammonia pressure (entry 3). In that particular case, high amounts of imine were observed hence suggesting the inability of our catalyst to hydrogenate the imine in the absence of aluminium. As shown in entry 5, NH_4Cl had no impact on the reaction outcome as similar results were obtained when no additive was added (see Table 2, entry 7). Other aluminium sources like anhydrous aluminium trichloride were equally effective, reinforcing the important role of aluminium for obtaining high selectivity towards **2a**.

Table 3. Reductive amination – scope.[a,b]



[a] *Standard reaction conditions:* 2.97 mmol of ketone, Ru catalyst (1 mol%), ligand (1.1 mol%), additive (10 mol%), toluene (20 mL), 120 °C, $p(NH_3) = 4$ bar, $p(H_2) = 40$ bar, 16 h.
[b] Isolated yields.
[c] Reaction conducted at $p(NH_3) = 9$ bar.
[d] Reaction conducted at $p(NH_3) = 4$ bar.
[e] Reaction conducted at $p(NH_3) = 6$ bar.
[f] Reaction conducted at 140 °C.

Table 4. Effect of Al^{3+} and triflate.[a]



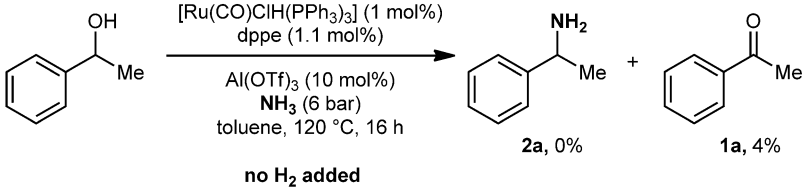
Entry	Additive	**2a** [%]	**3** [%]
1	$Al(OTf)_3$ (10 mol%)	74	5
2	NH_4OTf (30 mol%)	50	0
3[b]	NH_4OTf (10 mol%)	0	0
4	NaOTf (30 mol%)	9	1
5	NH_4Cl (10 mol%)	20	29
6	$AlCl_3$ (10 mol%)	76	4

[a] *Standard reaction conditions:* 2.97 mmol of **1a**, Ru catalyst (1 mol%), ligand (1.1 mol%), additive (10 mol%), toluene (20 mL), 120 °C, $p(NH_3) = 4$ bar, $p(H_2) = 40$ bar, 16 h. Yields determined by GC using dodecane as an internal standard.
[b] Using $p(NH_3) = 9$ bar.

At that point we speculate that the role of aluminium triflate could be to activate the imine towards hydrogenation rather than assisting in imine formation.[19] In order to support this idea, acetophenone **1a** was charged into a 100-mL autoclave, pressurised with NH_3 (4 bar) and stirred for 1 h at 120 °C (Supporting Information, Scheme S1).[13] After analysis of the crude reaction mixture, only 6% of imine was detected. Interestingly, a similar result was obtained when adding $Al(OTf)_3$ hence suggesting that the aluminium aids in imine hydrogenation or catalyst activation rather than imine formation.

Finally, we also excluded a mechanism involving ketone reduction followed by a "borrowing hydrogen" type mechanism (Scheme 2).[3,4] When 1-phenylethan-1-ol was subjected under our reaction conditions in the absence of hydrogen pressure, no amine **2a** was detected with only 4% of **1a**.

In summary, we have developed a direct atom-economical reductive amination for the synthesis of primary amines from acetophenone derivatives. This protocol overcomes the necessity of adding stoichiometric amounts of salts such as ammonium formate, providing excellent selectivity towards imine reduction *versus* the more facile ketone reduction. Catalytic amounts of $Al(OTf)_3$ were responsible for such a high



Scheme 2. Possible alcohol amination pathway for the synthesis of primary amines.

selectivity, presumably by imine activation. Moreover, our precatalyst and ligand are both commercially available and inexpensive. Further mechanistic studies and the development of an enantioselective version are currently underway.

Experimental Section

General Procedure for the Reductive Amination of Acetophenone Derivatives

Inside the glove box, carbonylchlorohydridotris(triphenylphosphine)ruthenium(II) 28.3 mg (0.0298 mmol) catalyst, ethylenebis(diphenylphosphine) 12.6 mg (0.0326 mmol), $Al(OTf)_3$ 141 mg (0.297 mmol), freshly distilled and degassed acetophenone **2** 0.35 mL (2.97 mmol), degassed and dried dodecane (674 μL) together with dried and degassed anhydrous toluene (20 mL) were added to a 100-mL autoclave. The autoclave was taken out of the glove box and pressurised up to 6 bar of NH_3 (2 g, 40 equiv.). Then the autoclave was pressurised with 40 bar of H_2 (total pressure 45–46 bars). The reaction mixture was stirred for 16 h at 120 °C. Then, the mixture was allowed to cool to room temperature and an aliquot of the crude reaction mixture (1,5 mL) was filtered through a plug of celite and analysed by GC and GC-MS.

Acknowledgements

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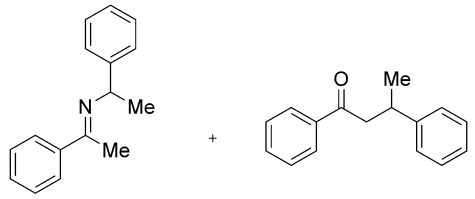
[16] The following side products were detected together with alcohol **3**.



imine dimer (major by-product) aldol-type product (traces)

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