On the reductive amination of aldehydes and ketones catalyzed by homogeneous Rh(i) complexes

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The homogeneously catalyzed reductive amination of aldehydes and ketones under smooth conditions is reported, showing for the first time, that Rh(i) catalysts based on chelating diphosphines and diphosphinites can be advantageously employed for this reaction, even for the production of chiral amino acid derivatives.
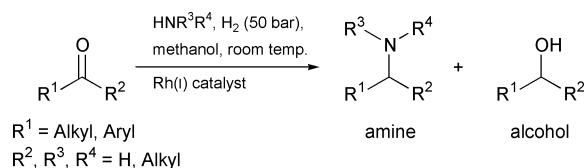
One-stage (or direct) reductive amination of aldehydes and ketones with amines affording higher alkylated amines is an interesting target in modern organic chemistry with great synthetic potential for application in academia and industry. Hitherto several chemical reducing agents, in particular borohydrides, have been shown to be valuable for this reaction giving rise to the alkylated amines in good yield.[1] However, from the ecological point of view and taking into account the demand for atom economy, more promising is the use of molecular hydrogen as a reducing agent. Indeed it was shown that reductive amination with hydrogen can be mediated by heterogeneous platinum, palladium, nickel or ruthenium metal catalysts.[2] Several amines have been prepared by this methodology even on an industrial scale.

Interestingly, only a few preliminary studies on the homogeneous version of this reaction can be found in the literature in spite of the tremendous progress which homogeneous catalysis has seen over the last decades.[3] For example, typical hydroformylation catalysts such as rhodium and cobalt carbonyls were tested, but were found to require rather severe reaction conditions (100–300 atm H_2, 100–200 °C).[4] The selectivity and efficiency of some glyoxime Rh and Co complexes were studied in the reductive amination of cyclohexanone with ammonia.[5] A related cyanocobalt catalyst afforded only moderate yields of product amines.[6] More noteworthy is the unique reaction of a sterically hindered aniline with methoxyacetone in the presence of a chiral Ir–diphosphine catalyst.[7] Tandem hydroformylation–amination reactions (hydroaminomethylation) also contain a reductive amination step, however the range of products is limited owing to the use of olefins as starting material.[8]

Recently, we reported that cationic rhodium(i) complexes [Rh(dppb)(cod)]BF_4 **1** [dppb = 1,4-bis(diphenylphosphino)butane, cod = cyclooocta-1,5-diene] and [Rh(dpoe)(cod)]BF_4 **2** [dpoe = 1,2-bis(diphenylphosphinito)ethane] are highly efficient precatalysts in the hydrogenation of imines[9] and enamines[10] under mild conditions (room temperature, 1–50 bar H_2 pressure). Usually these substrates are considered to be intermediates in some direct reductive amination reactions.[11]

Herein we demonstrate that complexes **1** and **2** are also useful for reductive amination (Scheme 1). For this reaction, besides the activity of the catalyst the selectivity for the formation of the desired amine is important. The production of the relevant alcohol by the competitive reduction of the carbonyl compound should be minimized.

Our results obtained with selected aldehydes and piperidine as the amine are listed in Table 1. Conversion with respect to the

Scheme 1 Reductive amination of aldehydes and ketones with Rh(i) catalysts.

starting carbonyl compound and selectivity in terms of produced amine/alcohol ratio in the final reaction mixtures were determined by ^{1}H NMR spectroscopy. As shown, cationic precatalysts **1** and **2** are efficient for reductive amination. It is of note that in all trials the desired amine and the corresponding alcohol were exclusively formed. Both complexes were more effective and selective than Wilkinson's complex Rh(PPh$_3$)$_3$Cl (run 1, *cf.* runs 3 and 6; run 9, *cf.* runs 11 and 14). Also the hydroformylation precatalyst Rh(PPh$_3$)$_2$(CO)Cl (run 10), frequently applied in hydroaminomethylation,[8] is inferior. Similar behavior was observed for the *in situ* prepared neutral complex [Rh(dppb)Cl]$_2$ (run 2). Although the conversion measured after 20 h was similar to that for precatalyst **1** the hydrogen uptake proceeded significantly more slowly.

Increasing concentrations of the amine had no pronounced effect on the selectivity, this applying for PhCHO (runs 3 and 4) as well as for PhCHMeCHO (runs 11 and 12) as substrate when precatalyst **1** was used. Application of precatalyst **2** in the

Table 1 Reductive amination of aldehydes with piperidine as the amine[a]

Run	Catalyst	Molar ratio piperidine/ aldehyde	Conv. aldehyde (%)[b]	Ratio produced amine/ alcohol
PhCHO				
1	Rh(PPh$_3$)$_3$Cl	1:1	94	0.1
2	[Rh(dppb)Cl]$_2$	1:1	>99	1.0
3	**1**	1:1	>99	1.5
4	**1**	2:1	>99	1.5
5	**1**[c]	1:1	>99	1.3
6	**2**	1:1	>99	1.8
7	**2**	2:1	>99	1.2
8	**2**[c]	1:1	>99	1.4
PhCHMeCHO				
9	Rh(PPh$_3$)$_3$Cl	1:1	70	0.4
10	Rh(PPh$_3$)$_2$(CO)Cl	1:1	4	n.d.
11	**1**	1:1	>99	1.7
12	**1**	2:1	>99	1.9
13	**1**[c]	1:1	>99	4.8
14	**2**	1:1	>99	6.1
15	**2**[c]	1:1	>99	3.2

[a] *Reaction conditions*: 5 mmol aldehyde, 0.2 mol% precatalyst, 10 ml MeOH, 50 bar initial pressure of H_2, room temp. [b] Measured after 20 h. [c] TsOH·xH$_2$O added (TsOH·xH$_2$O/Rh = 20).

reductive amination of benzaldehyde led to a slight decrease in selectivity (runs 6 and 7). The absence of a significant dependence of the selectivity on the amine concentration is noteworthy. Obviously, the rate limiting step in the overall process is the reduction of the corresponding intermediates but not their formation. This assumption is also confirmed by the fact that preliminary heating of a mixture of PhCHO and piperidine in methanol had no effect on the selectivity.

It is interesting that both precatalysts exhibited approximately the same selectivity with PhCHO as carbonyl component (runs 3 and 6) while the selectivity observed in the reductive amination of PhCHMeCHO with **1** as a precatalyst was lower than with **2** (runs 11 and 14).

The effect of TsOH·xH$_2$O as additive is less clear. Thus, this additive slightly diminished the selectivity of precatalysts **1** and **2** in the reaction of benzaldehyde with piperidine (runs 3/5, 6/8). However, in the reaction with PhCHMeCHO the effect of the additive was dependent upon the precatalyst used (runs 11/13, 14/15). In general, in the presence of TsOH·xH$_2$O, the rate of the hydrogen uptake was lowered.

We next investigated the reductive amination of aldehydes with a two-fold excess of piperidine as a function of the substitution pattern of the aldehyde using precatalyst **1** (Table 2). In the series of substituted benzaldehydes (runs 1–5) the beneficial effect of electron-withdrawing groups upon the selectivity is evident. The presence of a methyl group in an *ortho* position exhibited no steric effect on the selectivity (run 3). Unfortunately, NO$_2$- and CN-groups did not survive under the reaction conditions. An alkyl substituent α to the carbonyl group strongly affected the selectivity of amination (runs 6–8). The highest selectivity was observed with *n*-octanal (run 8).

Table 2 Comparison of the selectivity and the rate of amination of various aldehydes with piperidine using [Rh(dppb)(cod)]BF$_4$ **1** as a precatalyst[a]

| Run	Aldehyde	Ratio produced amine/alcohol[b]
1	4-HOC$_6$H$_4$CHO	0.8
2	4-MeOC$_6$H$_4$CHO	0.9
3	2-MeC$_6$H$_4$CHO	1.0
4	PhCHO	1.5
5	4-ClC$_6$H$_4$CHO	1.9
6	PhCHMeCHO	1.9
7	EtCHMeCHO	2.4
8	*n*-C$_7$H$_{15}$CHO	12.0

[a] For reaction conditions see Table 1. [b] After 20 h full conversion was observed in all reactions.

The results of reductive amination of PhCHO with various amines are summarized in Table 3. In general, good correlation between the selectivity of the reaction and the basicity of the amine was observed (runs 1–4). Apparently, steric effects can exert a strong influence. Thus, with 2-methylpiperidine as substrate, which has approximately the same basicity as

Table 3 Comparison of reductive amination of PhCHO with various amines employing [Rh(dppb)(cod)]BF$_4$ **1** as a precatalyst[a]

Run	Amine	pK_a (amine)	Ratio produced amine/alcohol[b]
1	Pyrrolidine	11.27	2.30
2	Piperidine	11.02	1.50
3	Me$_2$NH	10.73	0.43
4	Et$_2$NH	10.49	0.07
5	2-Methylpiperidine	10.99	< 0.05

[a] *Reaction conditions*: 5 mmol aldehyde, 10 mmol amine, for other conditions see Table 1. [b] After 20 h full conversion was observed in all reactions.
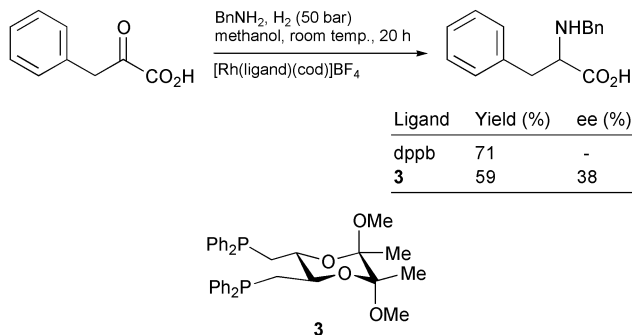
Scheme 2 Preparation of racemic and enantiomerically enriched *N*-benzylphenylalanine.

piperidine but is sterically more hindered, only traces of the desired amine were formed (run 5).

In contrast to the reductive amination of PhCHO with piperidine, the reaction with PhCH$_2$NH$_2$ using precatalyst **1** was slow. After 20 h only 39% conversion was observed. However the high observed amine/alcohol ratio of 11 is remarkable.

Unexpectedly, reductive alkylation with α-keto acid derivatives afforded good yields of the desired amino acids. Thus, the industrially relevant reductive amination of PhCH$_2$COCOH with benzyl amine gave *N*-benzylphenylalanine in a yield of 71% (Scheme 2). The product precipitated from the reaction mixture and the analytically pure compound could simply be isolated by filtration and subsequent washing with ethanol. In a preliminary investigation the reaction was also run with a catalyst bearing the chiral diphosphine **3**.[12] (*R*)-*N*-Benzylphenylalanine was obtained in 59% isolated yield and 38% ee.

In conclusion, Rh(I) complexes represent efficient homogeneous catalysts for reductive amination of aldehydes and ketones. The successful employment of chelating phosphorus ligands for this reaction opens up a broad field of modifications, whereby asymmetric reductive amination is one of the most challenging goals.

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