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Efficient and chemoselective direct reductive amination of aromatic aldehydes catalyzed by oxo–rhenium complexes containing heterocyclic ligands

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ABSTRACT

This work describes the catalytic activity of 17 oxo–rhenium complexes containing heterocyclic ligands in the direct reductive amination of 4-nitrobenzaldehyde with 4-chloroaniline, using phenylsilane as reducing agent. In general, all of the catalysts tested gave excellent yields of the secondary amine, although, the best result was obtained with the catalytic system $PhSiH_3$/$ReOBr_2$(Hhmpbta)(PPh_3) (2.5 mol %). This system was also applied to the synthesis of a large variety of secondary amines in good to excellent yields and tertiary amines in moderate yields, with tolerance of different functional groups.

1. Introduction

Reductive amination of carbonyl compounds with amines remains one of the most versatile and useful synthetic route for the preparation of amines and their derivatives, which are synthetically useful organic intermediates in pharmaceuticals and agrochemicals.[1] This reaction involves the formation of an imine or iminium as intermediate, followed by *in situ* reduction. The importance of reductive amination procedures is exemplified by the enormous number of its synthetic uses.

There are two types of reducing agents employed for direct reductive amination of aldehydes with amines. These two strategies are mainly based on metal catalyzed hydrogenation,[1] and hydride reducing agents, such as $NaBH_4$,[2] $NaBH_3CN$,[3] $NaBH(OAc)_3$,[4] and pyridine–BH_3.[5] However, in terms of functional group tolerance and side reactions, most of these reagents may have one or more drawbacks. For example, catalytic hydrogenation is incompatible with compounds containing other reducible functional groups, such as double and triple bonds, nitro, and cyano groups. $NaBH_4$ sometimes requires harsh reaction conditions, cyanoborohydride is highly toxic and generate toxic by-products, such as HCN or NaCN, and pyridine–BH_3 is unstable to heat and must be handled with extreme care.

With increasing environmental concerns and constraints, there exists a tremendous potential for development of new reductive amination methodologies. Organosilanes are mild and environmentally benign reducing agents, and in recent years, several reagent systems containing silanes, such as Et_3SiH/$InCl_3$,[6] Et_3SiH/[IrCl(cod)]$_2$,[7] $PhSiH_3$/Bu_2SnCl_2,[8] $PhSiH_3$/MoO_2Cl_2,[9] polymethylhydrosiloxane (PMHS)/Ti(O^iPr)$_4$,[10] $FeCl_3$/PMHS[11] have also been employed in reductive amination.

Previously, our group have demonstrated that several oxo–rhenium complexes were good catalysts for the direct reductive amination of aldehydes using silanes as reducing agents.[12] The results obtained demonstrate that the catalytic system $PhSiH_3$/$ReIO_2(PPh_3)_2$ (2.5 mol %) was very efficient for the synthesis of secondary amines in high yields and good chemoselectivity, and also for the synthesis of tertiary amines in moderate yields. Later, Ghorai and Das[13] developed an efficient method for direct reductive amination of aldehydes with electron-deficient protected amines, such as Cbz–, Boc–, EtOCO–, Fmoc–, Bz–, $ArSO_2$–, Ar_2PO–, etc., using Re_2O_7 as catalyst and silanes as reducing agent.

Due to the biological and chemical importance of amines, the search for novel catalyst systems, leading to efficient and highly chemoselective methods for their preparation, remains an important target in organic synthesis. The rhenium complexes containing heterocyclic moieties constantly attract the interest of chemists and pharmacists on account of their versatile biological activity and

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industrial applications. Surprisingly, catalytic studies using rhenium complexes incorporating such ligands have been relatively rare. In continuation of our work about the use of oxo-complexes as efficient catalysis in organic chemistry,[14] herein we report the catalytic activity of 17 oxo–rhenium complexes containing heterocyclic ligands in direct reductive amination of aldehydes.

2. Results and discussion

Initially, we studied the catalytic activity of the 17 oxo–rhenium complexes containing the heterocyclic ligands namely 2-(2′-hydroxy-5′-methylphenyl)benzotriazole (Hhmpbta),[15] 2-(2-hydroxyphenyl)-2-benzothiazole (Hhpbt),[16] 2-(2-hydroxyphenyl)-2-benzoxazole (Hhpbo),[17] 2-(2-hydroxyphenyl)-1*H*-benzimidazole (Hhpbi)[18] (Fig. 1) in the direct reductive amination of 4-nitrobenzaldehyde with 4-chloroaniline, using $PhSiH_3$ as reducing agent (Table 1). In general, all the oxo–rhenium complexes were very efficient, affording high yields of the secondary amine. The reaction catalyzed by 2.5 mol % of $ReOBr_2$(Hhmpbta)(PPh_3) at refluxing THF gave the best result, producing the amine in 98% yield after only 13 min (Table 1, entry 1). The results obtained also demonstrate that in general the catalysts with Br ligands (Table 1, entries 1, 2, 6, 7, 10, 11, and 14) are more reactive than the complexes containing Cl ligands. Comparison between the oxo–rhenium complexes containing the heterocyclic ligands with the similar complexes without the heterocyclic ligands shows that the catalysts $ReOBr_2(L)(PPh_3)$ (Table 1, entries 1, 7, 10, and 14) are more efficient than $ReOBr_3(PPh_3)_2$ (Table 1, entry 18), in contrast, the reactions with the catalysts $ReOCl_2(L)(PPh_3)$ (Table 1, entries 3, 9, 13, and 16) or $ReOCl_2(L)(AsPh_3)$ (Table 1, entries 4, 8, 12, and 15) required more time than the reactions with the complexes $ReOCl_3(PPh_3)_2$ or $ReOCl_3(AsPh_3)_2$ (Table 1, entries 19 and 20). Finally, no reductive amination was observed with phenylsilane in the absence of catalyst (Table 1, entry 21), demonstrating the catalytic role of the oxo–rhenium complex.

Direct reductive amination of 4-nitrobenzaldehyde with aniline was studied using several silanes namely phenylsilane, dimethylphenylsilane (DMPSH), triethylsilane, triphenylsilane, and polymethylhydrosiloxane (PMHS). The reductions carried out with $PhSiH_3$, DMPSH, Et_3SiH, and PMHS produced the amine in excellent yields (Table 2, entries 1–4), although, the reaction with $PhSiH_3$ is the faster (13 min) (Table 2, entry 1) in contrast to the reduction with PMHS that required 24 h (Table 2, entry 4). No reaction was observed using Ph_3SiH (Table 2, entry 5) or without silane (Table 2, entry 6).

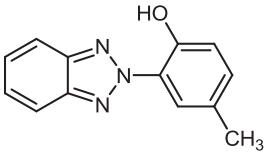
In Table 3 are summarized the results of the search for the appropriate solvent. We found that THF was the best solvent for this reaction at reflux temperature, affording the amine in 98% conversion after only 13 min (Table 3, entry 1). At room temperature, this reaction required 24 h and only moderate conversion of the amine was obtained (Table 3, entry 2). Chloroform, toluene, and benzene also gave good to excellent conversions of the product, but these reductions required 24 h (Table 3, entries 3–5). Finally, the reductions performed in acetonitrile and dichloromethane produced the amine in moderate conversions after 24 h (Table 3, entries 6 and 7).

In order to study the scope and the limitations of the catalytic system $PhSiH_3/ReOBr_2$(Hhmpbta)(PPh_3) (2.5 mol %), the direct reductive amination was explored with a variety of aldehydes and aniline (Table 4). In general, all the secondary amines were obtained in good to excellent yields within short reaction times, including the amines prepared from aldehydes bearing electron-withdrawing or electron-donating groups. This reaction showed broad substrate scope, tolerating several functional groups, such as $-NO_2$, $-CF_3$, $-SO_2R$, $-Br$, $-CO_2R$, $-OCH_3$, $-SCH_3$, $-NCOR$, and furfuryl ring.

Another interesting result was the chemoselective reductive amination of cinnamaldehyde with aniline in 81% yield without affecting the double bond (Table 4, entry 11). Heteroaromatic aldehyde 2-furaldehyde also reacted with aniline affording the corresponding secondary amine in excellent yield (Table 4, entry 2).

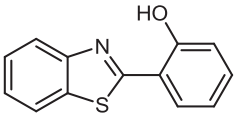
In this work, we have also studied the reductive amination of 4-methoxybenzaldehyde with different anilines (Table 5). All the reactions afforded the corresponding secondary amines in good to excellent yields. The reactions carried out with anilines containing electron-withdrawing groups were much faster (Table 5, entries 1–3) than the reactions with anilines containing electron-donating groups (Table 5, entries 4 and 5).

The catalytic activity of the system $PhSiH_3/ReOBr_2$(Hhmpbta)(PPh_3) (2.5 mol %) was also explored for the synthesis of tertiary amines in the reactions between *N*-methylaniline and several aldehydes (Table 6). These reductions were carried out with heteroaromatic aldehydes



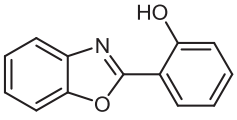
2-(2'-hydroxy-5'-methylphenyl)benzotriazole

(Hhmpbta)



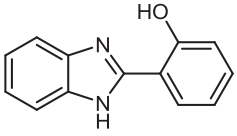
2-(2-hydroxyphenyl)-2-benzothiazole

(Hhpbt)



2-(2-hydroxyphenyl)-2-benzoxazole

(Hhpbo)



2-(2-hydroxyphenyl)-1H-benzimidazole

(Hhpbi)

Fig. 1. Structure of heterocyclic ligands.