THE PIONEERING WORK OF SECONDARY ALCOHOL WITH AMMONIA

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ABSTRACT

we have presented a new and scalable procedure for the direct amination of cyanohydrins with the partnerofammoniaviatitanium-catalyzedcyano-borrowing reaction. an atom-efficient and very selective catalytic route for the direct synthesis of primary amines from secondary alcohols and ammonia without the need for protecting groups. The scope of the reaction includes cyclic and acyclic aliphatic substrates, as well as unsaturated and aryl-substituted alcohols

KEYWORDS: Cp*Ir-catalyst, aldehydecyanohydrins, TBME, Ru/PNP complex

palladium-catalyzed telomerization of butadiene and ammonia giving primary alkylamines, rhodium- and iridium-catalyzed reductive aminations of carbonyl compounds with ammonium formate and ammonia affording primary alkylamines, and copper- and palladium-catalyzed coupling reactions of ammonia with arylhailides producing arylamines.The efficient selective synthesis of secondary and tertiary amines has been achieved by means of Cp*Ir-catalyzed multialkylation of ammonium salts with alcohols without solvent: the reactions of ammonium acetate with alcohols gave tertiary amines exclusively, while those of ammonium tetrafluoroborate afforded secondary amines selectively. Using this method, secondary 5- and 6-membered cyclic amines were synthesized from ammonium tetrafluoroborate and diols in one pot. We have reported an atom-economical catalytic system for the synthesis of secondary and tertiary amines by the N-alkylation of primary and secondary amines with alcohols catalyzed by a Cp*Ir complex,6 in which the high catalytic performance of Cp*Ir complexes for hydrogen transfer reactions is essential.7 S Homogeneously catalyzed aminations of alcohols using primary and secondary amines have been known, the heterogeneously catalyzed amination of alcohols using ammonia is performed on an industrial scale.[1]Using the Ru/PNP complex for secondary alcohols under identical reaction conditions yielded neither the amine nor the corresponding ketone..Beller and co-workers reported that [Ru3(CO)12] in combination with bulky phosphorus-based s-donor ligands give high conversions and selectivity for secondary or tertiary amines; they reported up to 100% conversion and 99% selectivity under mild conditions. Amines were alkylated with various alcohols to give secondary and tertiary amines with high conversions and yields. Williams and co-workers refer to this process as the “borrowing hydrogen methodology”. So far, no catalytic systems that are able to aminate secondary alcohols with NH3 to solely form primary amines have been described. a homogeneous ruthenium-catalyzed direct amination of

secondary alcohols. with NH3 to obtain primary amines with high selectivity, and forming water as the only by-product. In searching for an efficient catalyst for the conversion of secondary alcohols using NH3 we chose cyclohexanol as a model substrate. A number of ruthenium complexes were

tested as catalyst precursors in combination with phosphorus ligands. cyclohexylamine was delivered with high selectivity (over 75%), even at high conversion (up to 90%). The best results were obtained when using cyclohexane as the solvent at a reaction temperature of 1408C in a stainless-steel autoclave. The ligands were systematically varied to study and optimize the reaction. The catalysts derived from bulky triarylphosphines 1 and 2 showed very poor activities, although promising selectivities towards cyclohexylamine were already observed for Ru/1. Next, the bulky s-donating PCy3 (3) was used, and showed complete selectivity in combination with Ru towards the primary amine, although with low activity. Consequently, one of the cyclohexyl groups in 3 was replaced by a phenyl group, giving rise to ligand
4 and the Buchwald ligand 5, and the corresponding catalysts showed increased activity and good selectivity towards the primary amine., the scope of the reaction was investigated by subjecting a range of secondary alcohols to amination reactions with ammonia.
Table 2 shows that the conversions are satisfying for all substrates. Conversions are slightly lower for acyclic substrates (Table 2, entries 4–8). Aryl-substituted and also unsaturated alcohols are converted equally well (Table 2, entries 10–11). The primary amine selectivity is good to excellent for all substrates and for menthol complete selectivity is observed (Table 2, entry 12). These examples demonstrate the potential of this new transformation. In all cases, the corresponding secondary imine was formed as the major by-product. For acyclic alcohols, more intermediate ketone was observed. In general, as a result of the higher nucleophilicity of the primary amine product, compared to that of NH3, the secondary imine is formed. Only very little of the secondary amine (typically below 2%) was observed. Remarkably, upon using longer reaction times the amount of secondary imines decreased in favor of the primary amine selectivity. Apparently, under the given reaction conditions, the formation of the secondary imine seems to be reversible. This effect was investigated by analyzing the reaction mixture during the course of the catalytic reaction (Figure 2). It was found that the selectivity towards the primary amines increases over time for all secondary alcohol substrates tested (Figure 3). In this process, the secondary imine can Scheme 3. Ruthenium-catalyzed direct amination of cyclohexanol with ammonia.wenoticethatthehydrogenborrowing reaction just aminates the primaryandsecondaryalcohols with ammonia, α-Aminonitrilesareimportantstructuralbuilding blocksofpharmacy and drugs.[10]thealdehydecyanohydrins(2°alcohols) couldbeaminatedbyammoniaundermild reaction conditions aswell.

weselectedacetophenonecyanohydrin 1a as the starting material with the partner of ammonia (7Minmethanol).InthepresenceofTi(O^{i}-Pr)$_4$,theaminationwas carriedoutinthemediaoftoluene,was obtained with 25% yield (Table 2, entry 1). We used TBME instead and delivered the product with 41% yield (Table2,entry2),andothersolvents,suchasTHF,CH_3CN, DCM, CPME, and MeOH, did not improve the reactivity of this transformation (Table 2, entries 3−7 vs 2). Benzoicacid wasaddedastheadditive,and64%of2awaso

btained.Other carbonylacids,suchas*p*-nitrobenzoicacid,*p*-methoxylbenzoicacid,andaceticacid,gavemoderateyields(40−54%)(Table2, entries 9−11). When the reaction temperature wasincreased to80°C,thereactivityofthiscyano-borrowingreactionwas almost the same as at 60 °C (Table 2, entry 12), and a lower yieldwasobtainedwhilethereactionwascarriedoutat40°C

Scheme 1.Amination of Alcohols Using Ammonia

Cp*Ir-Catalyzed Trialkylation of Ammonium Salts with Benzyl Alcohol

Entry	[1a]catalyst	ammonium salt[2a]	yield b (%)
Benzyl Alcohol	[Cp*IrCl2]2	NH4OAc	72
Benzyl Alcohol	RuCl2(PPh3)3	NH4OAc	0
Benzyl Alcohol	[Cp*IrCl2]2	NH4HCO3	43
Benzyl Alcohol	[Cp*IrCl2]2	(NH4)2CO3	66

The reactions were carried out with ammonium salt (1.0 mmol) and benzyl alcohol (3.0 mmol). b GC yield. c The yield of the reaction conducted at 140 °C is in parentheses. d The reaction was carried out with NH4OAc (1.0 mmol), PhCH2OH (3.6 mmol), [Cp*IrCl2]2 (0.5 mol % Ir), and NaHCO3 (1.0 mol %) at 130 °C for 17 h.

Entry	solvent	additives	yield (%)
1	toluene		25
2	TBME		41
3	THF		Trace
4	CH_3CN		30
5	DCM		21
6	CPME		Trace
7	MeOH		Trace
8	TBME	$PhCO_2H$	64
9	TBME	*p*-$NO_2C_6H_4CO_2H$	45
10	TBME	*p*-$MeOC_6H_4CO_2H$	51
11	TBME	AcOH	40
12[b]	TBME	$PhCO_2H$	63
13[c]	TBME	$PhCO_2H$	42

[a]Reactionwascarriedoutwith0.4mmolof1,0.2mLofammonia(7 Minmethol),and10mol%Ti(O^{i}-Pr)$_4$,in0.8mLofsolventat60°C for18h.Theyieldsareisolatedyields.[b]Reactionwascarriedoutat80 °C. [c]Reaction was carried out at 40 °C.

yanohydrins reacted with 3.5 equipment of ammonia in methanol in the presence of 10 mol % of Ti(O^{i}-Pr)$_4$ and 40 mol%of benzoicacidwithTBMEasthereactionmedia at60 °C.

Scheme 2.Ru/PNP pincer complex for primary alcohol amination

Using the Ru/PNP complex for secondary alcohols under identical reaction conditions

yielded neither the amine nor the corresponding ketone. Furthermore, for primary alcohols considerable amounts of by-products such as secondary amines and imines were formed at higher conversions. Closely related to the direct amination of alcohols with NH3 is the alkylation of amines with alcohols. [Ru3(CO)12] in combination with bulky phosphorus-based s-donor ligands give high conversions and selectivity for secondary or tertiary amines; they reported up to 100% conversion and 99% selectivity under mild conditions.[6] With these systems, amines could be alkylated by primary alcohols, even if the alcohol bears a second, secondary alcohol .Another elegant method was published by Williams and co-workers for the alkylation of amines with alcohols in the presence of ruthenium arene complexes . Amines were alkylated with various alcohols to give secondary and tertiary amines with high conversions and yields. One example of an iridium-catalyzed amine alkylation has been reported wherein no additives are required, and it proceeds in water .Williams and co-workers refer to this process as the "borrowing hydrogen methodology".[14] So far, no catalytic systems that are able to aminate secondary alcohols with NH3 to solely form primary amines have been described .Herein we report the first examples of a homogeneous ruthenium-catalyzed direct amination of secondary alcoholswith NH3 to obtain primary amines with high selectivity, and forming water as the only by-product (Scheme 3). In searching for an efficient catalyst for the conversion of secondary alcohols using NH3 we chose cyclohexanol as a model substrate.A number of ruthenium complexes were tested as catalyst precursors in combination with phosphorus ligands. The best results were obtained with the combination of [Ru3(CO)12] and simple phosphine ligands (Figure 1 and Table 1); cyclohexylamine was delivered with high selectivity (over 75%), even at high conversion (up to 90%). The best results were obtained when using cyclohexane as the solvent at a reaction temperature of 1408C in a stainless-steel autoclave. The ligands were systematically varied to study and optimize the reaction. The catalysts derived from bulky triarylphosphines 1 and 2 showed very poor activities, although promising selectivities towards cyclohexylamine were already observed for Ru/1. Notably, 1 gave good results in the ruthenium-catalyzed amine alkylation with primary alcohols as reported by Beller.[6] Next, the bulky s-donating PCy3 (3) was used, and showed complete selectivity in combination with Ru towards the primary amine, although with low activity. Consequently, one of the cyclohexyl groups in 3 was replaced by a phenyl group, giving rise to ligand 4 and the Buchwald ligand 5, and the corresponding catalysts showed increased activity and good selectivity towards the primary amine. The catalyst derived from the pyrrole phosphine 6, successfully used by Beller for the alkylation of amines with primary alcohols,[6] gave the best results in terms of activity and selectivity. The results obtained with catalysts derived from the N-alkyl derivative 8 and the pyridine phosphine 9 demonstrated some activity, but good selectivity. On the basis of the results

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Reaction conditions: cyclohexanol (10 mmol), [Ru3(CO)12] (0.1 mmol), ligand (0.6 mmol), cyclohexane (6 mL), NH3 (l) (6 mL), 1408C, 21 h ([Ru3(CO)12]/L/substrate=1:6:100). [a] Conversions were determined by GC analysis and based on the alcohol consumption and amine production [b] S(primary + secondary amine + secondary imine), the remainder is the intermediate ketone. [c] Percentage of the primary amine present within the total amount of amine products.

In conclusion, an atom-efficient and very selective catalytic route for the direct synthesis of primary amines from secondary alcohols and ammonia without the need for protecting groups. The scope of the reaction includes cyclic and acyclic aliphatic substrates, as well as unsaturated and aryl-substituted alcohols. This reaction may open up new pathways to the conversion of bio-based feedstocks into intermediates and fine chemicals. Mechanistic studies concerning the structure and properties of the catalyst are underway. Furthermore, detailed investigations into the equilibria involved in this reaction are in progress

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