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Sequential hydroaminomethylation/Pd-catalyzed hydrogenolysis as an atom efficient route to valuable primary and secondary amines

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ABSTRACT

The facile synthesis of valuable primary and secondary amines is reported using a sequential procedure of hydroaminomethylation and Pd-catalyzed hydrogenolysis. The hydroaminomethylation reaction was catalyzed by a cationic Rh(I) iminopyridyl complex and the *N*-alkylated benzylamines were produced with high chemoselectivity, albeit as mixtures of linear and branched products. Performing the hydrogenolysis reaction using 10% Pd/C, provided access to valuable primary and secondary amines which have applications in the surfactant, pharmaceutical and polymer industries.

Introduction

Amines are valuable compounds in the pharmaceutical [1], cosmetic [2] and surfactant industries [3]. Generally, amines are synthesized *via* the reduction of unsaturated nitrogen-containing compounds [4] or using processes such as Gabriel synthesis [5], Hofmann rearrangement [6] and Curtius rearrangement [7]. In addition, the direct alkylation of ammonia, as well as primary and secondary amines are also commonly used [8]. These processes generate stoichiometric amounts of waste and utilize corrosive acids and bases, while reduction reactions utilize strong reducing agents (e.g. $LiAlH_4$). Therefore, more environmentally-friendly processes are required to synthesize these amines. These processes include catalytic nucleophilic substitution of alcohols using ammonia [9], reductive amination of carbonyl containing compounds [10], hydroamination [11] and hydroaminomethylation [12].

Hydroaminomethylation, a one-pot tandem reaction combining hydroformylation with reductive amination, is a versatile reaction to produce various amines from relatively inexpensive alkene feedstocks [12]. We have previously demonstrated the hydroaminomethylation of 1-octene with piperidine, aniline and benzylamine, catalyzed by imino-pyridine rhodium catalysts [13]. Benzylamine is a masked form of ammonia and its derivatives can undergo debenzylation *via* Pd-catalyzed hydrogenolysis providing access to primary or secondary amines in a facile manner.

Vorholt and co-workers previously demonstrated the synthesis of primary amines *via* an orthogonal tandem amination reaction [14]. This entailed an initial rhodium-catalyzed hydroaminomethylation reaction to produce secondary amines, which was then followed by cleavage to primary amines using a ruthenium catalyst in the presence of ammonia.

To the best of our knowledge, the combination of hydroaminomethylation and hydrogenolysis, for the synthesis of primary and secondary amines has not been reported. Herein, we report the synthesis of primary and secondary amines using a combination of hydroaminomethylation and Pd-catalyzed debenzylation. The production of selected amines which are useful in the pharmaceutical, polymer and surfactant industries are reported to illustrate the scope of this methodology.

Results and discussion

The hydroaminomethylation of alkenes in the presence of benzylamine is shown in Scheme 1. This reaction is catalyzed by **C1**, a cationic imino-pyridine rhodium complex, the synthesis and characterization of which was reported previously. This complex was found to be an efficient catalyst precursor for the

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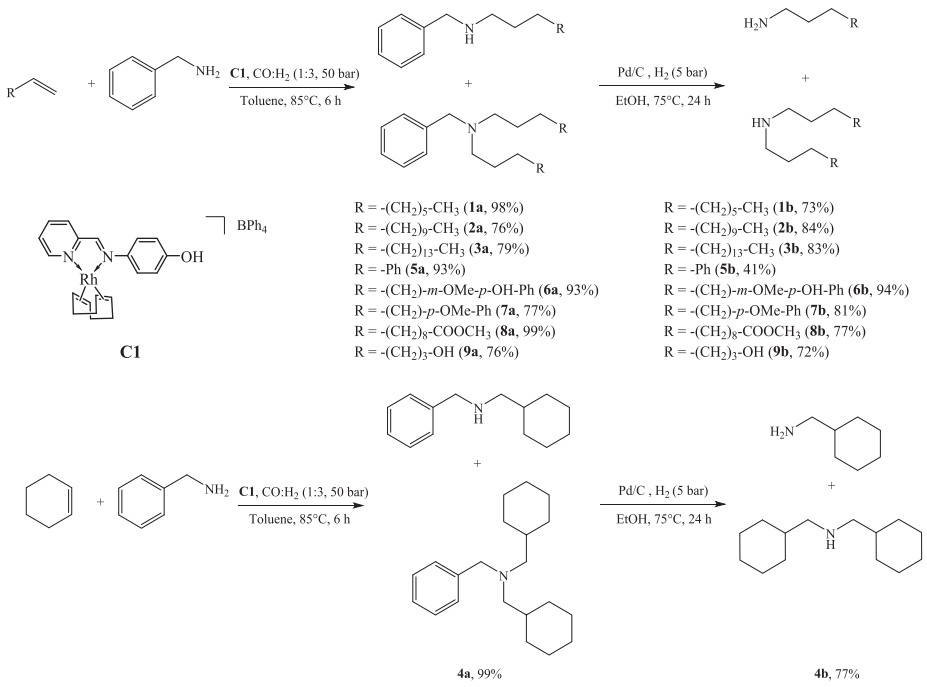


Scheme 1. General scheme for the synthesis of amines *via* hydroaminomethylation and hydrogenolysis.

hydroaminomethylation reaction, producing *N*-alkyl benzylamines chemoselectively, albeit with moderate regioselectivities [13]. Attempts to identify the active species was unfortunately not successful. In trying to probe the nature of possible reaction intermediates, the catalyst precursor was reacted with CO. This revealed the displacement of the COD ligand by CO to form a dicarbonyl species which was confirmed by solution IR spectroscopy (Fig. S46). Attempts to confirm the formation of the Rh-H active species using high pressure NMR spectroscopy was unfortunately unsuccessful. No signal was detected in the hydride region of the ^{1}H NMR spectrum when the catalyst precursor was reacted with syngas in a high pressure NMR tube (Fig. S47).

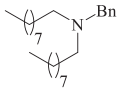
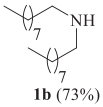
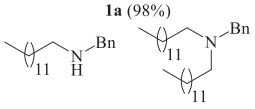
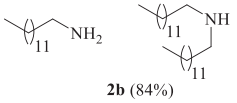
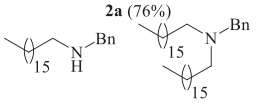
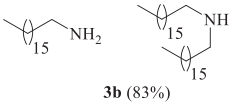
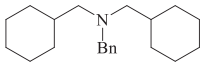
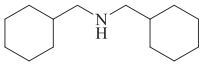
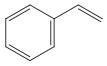
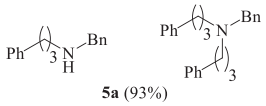
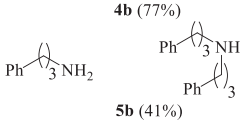
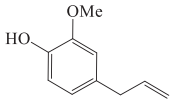
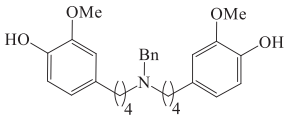
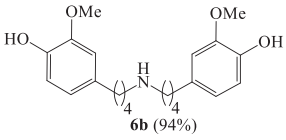
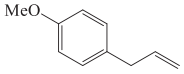
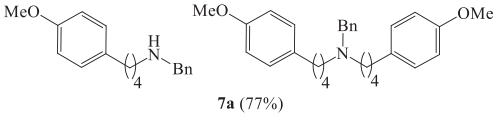
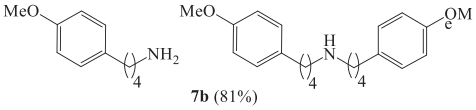
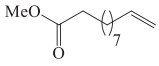
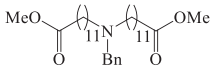
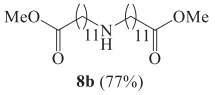
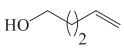
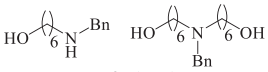
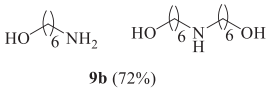
Given the ability of **C1** to mediate the hydroaminomethylation of simple alkenes, we employed the same catalyst in the hydroaminomethylation of a wider range of alkenes using benzylamine as the amine substrate. The secondary and tertiary *N*-substituted benzylamines produced were then subjected to hydrogenolysis using 10% Pd/C in the presence of hydrogen (5 bar) leading to debenzylation to form primary and secondary amines. The scope of the alkene substrates employed is illustrated in Table 1. In addition to simple aliphatic alkenes, we also explored the use of cyclic and aromatic alkenes, as well as alkenes containing ester and alcohol functionalities.

In most cases, the hydroaminomethylation step produces mixtures of secondary and tertiary *N*-alkylbenzylamines (Scheme 1). In all cases the alkene conversion is almost quantitative and the total product yield is high. The yields of the hydroaminomethylation products, which largely consisted of secondary amines were based on the amount of starting alkene. The yields of the Pd-catalyzed debenzylation products were based on the secondary *N*-alkylbenzylamine being the principal component.

Unfortunately significant challenges were encountered in trying to establish the regioselectivity of the hydroaminomethylation reaction. In the reactions investigated, complex mixtures of secondary and tertiary *N*-alkylbenzylamines were obtained during the hydroaminomethylation process (Scheme 1). In addition to this, isomerization of the alkene substrate occurs during the initial stages of the reaction, resulting in the hydroformylation step involving both 1-alkenes as well as internal alkenes as actual substrates. This leads to complex mixtures of regio-isomers for the hydroformylation products. For instance, using 1-octene as a substrate can lead to four different hydroformylation products (one linear and three branched). In the case of longer chain alkenes, such as 1-dodecene and 1-hexadecene, even more complex mixtures are possible since the extent of alkene isomerization is higher. The situation is further complicated in the case of the tertiary *N*-alkyl benzylamines which are produced in the hydroaminomethylation step. The alkyl substituents on the nitrogen atom, in addition to the benzyl group, can consist of different combinations. Thus, it is possible to have two linear alkyl chains, two branched chains or a mixture of a linear and branched chains. Even if the components can be separated, which in itself is extremely difficult, the lack of authentic standards for most of the reaction intermediates and products makes it near impossible to determine the regioselectivity quantitatively. The same complexity exists when considering the products of the Pd-catalyzed debenzylation reaction where complex mixtures of secondary and primary amines are obtained.

Hydroaminomethylation of the alkenes with benzylamine was evaluated using equimolar amounts of the two reagents, since we initially targeted the primary amines. Given the high activity of this catalyst in the hydroaminomethylation of 1-octene with benzylamine, we expanded the reaction scope to also include 1-dodecene and 1-hexadecene, under the reaction conditions that we previously reported for the hydroaminomethylation of 1-octene with benzylamine (50 bar CO:H_2 (1:3), 85 °C) [13]. However, the reaction time was extended to 6 h in order to ensure full conversion of all substrates. This produced the corresponding *N*-alkyl benzylamines (as a mixture of secondary and tertiary amines) in good to excellent isolated yields (**1a**-**3a**, 76–98%). The hydroaminomethylation of 1-dodecene has previously been investigated by Khan and Bhanage using a Rh-phosphinite catalyst system, where full conversion of 1-dodecene with 99% chemoselectivity towards the amines was obtained [15]. This was achieved under milder reaction conditions (Rh:1-dodecene 1:2500, 30 bar CO:H_2 (7:23), 80 °C, 6 h) compared to those

Table 1
Synthesis of amines *via* hydroaminomethylation and hydrogenolysis.

Alkenes	Yield (Hydroaminomethylation)	Yield (Hydrogenolysis)
	 **1a** (98%)	 **1b** (73%)
	 **2a** (76%)	 **2b** (84%)
	 **3a** (79%)	 **3b** (83%)
	 **4a** (99%)	 **4b** (77%)
	 **5a** (93%)	 **5b** (41%)
	 **6a** (93%)	 **6b** (94%)
	 **7a** (77%)	 **7b** (81%)
	 **8a** (99%)	 **8b** (77%)
	 **9a** (76%)	 **9b** (72%)

Hydroaminomethylation conditions: alkene:amine (1:1), $CO:H_2$ (1:3, 50 bar), **C1** (0.5 mol%), toluene (5 mL), 85 °C, 6 h. Isolated yields.
Hydrogenolysis conditions: 10% Pd/C, EtOH (10 mL), 75 °C, 24 h. Isolated yields.

employed by us. However, it should be noted that in their case, a secondary amine (di-*n*-pentylamine) was employed, which are known to be more reactive than primary amines. To the best of our knowledge, the hydroaminomethylation of 1-hexadecene in the presence of syngas has not been previously reported. However, Karakhanov and co-workers [16] have studied the hydroaminomethylation of 1-hexadecene with dimethylamine in the presence of methylformate as a syngas surrogate using the Ru carbonyl complex $Ru_3(CO)_{12}$ as a catalyst precursor.

Hydrogenolysis of the *N*-alkyl benzylamines produced in the hydroaminomethylation step provided access to various fatty amines (Fig. 1), which were isolated in good yields (**1b**-**3b**, 73–84%). The alkene substrates can initially undergo isomerization, which leads to the formation of branched amines (only the linear products are shown in Fig. 1). ^1H NMR spectroscopy and mass spectrometry revealed that in the case of 1-octene, mostly the secondary amine (*di*-nonyl amine, **1b**) was formed as a result of bis-hydroaminomethylation, while in the case of 1-dodecene and 1-hexadecene, products **2b** and **3b** consisted of complex mixtures of primary and secondary amines (primary amines were the major product according to mass spectrometry). In these two cases, the longer alkyl chains most likely inhibit the second hydroaminomethylation reaction from taking place, while the lower reactivity of 1-dodecene and 1-hexadecene in the hydro-

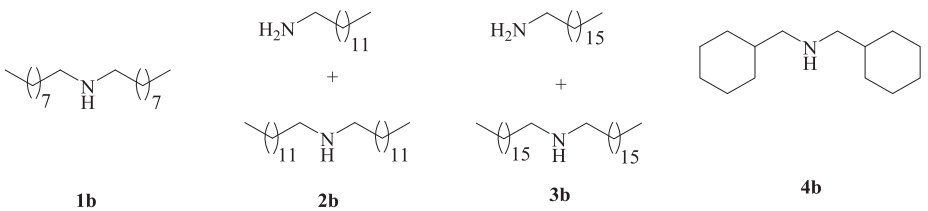


Fig. 1. Fatty amines synthesized *via* hydroaminomethylation and hydrogenolysis.

formylation step could also negatively impact the overall yield. Unfortunately, separation of the primary and secondary amines is a difficult process and we were unable to assess the selectivity of the reaction.

These fatty amines are important in industry with applications as lubricants, surfactants and corrosion inhibitors, to name just a few. In industry fatty amines are normally synthesized *via* the Nitrile process using naturally occurring fatty acids [17]. This process occurs at high temperatures (>250 °C) and usually requires long reaction times. Although our approach utilizes rhodium catalysts, it provides access to these amines under relatively mild conditions.

The hydroaminomethylation of a cyclic alkene, *viz.* cyclohexene, with benzylamine gave the corresponding *N*-di-cyclohexyl benzylamine **4a** in 99% yield. Similar results (94% yield) were previously obtained by Khan and co-workers for the hydroaminomethylation of cyclohexene with morpholine as an amine source, using a rhodium polyether diphosphinite complex [18]. Although their reaction was performed at lower pressures in comparison to our approach (~28 bar), higher temperatures were used (100 °C) in combination with a more reactive secondary amine [18].

1-Cyclohexyl-*N*-(cyclohexylmethyl)methanamine **4b** was also synthesized in good yield (77%) *via* the debenzylation of **4a**. This amine has found use in the synthesis of rotaxanes which are commonly used in the production of molecular motors as well as ultra-stable dyes [19–21]. This compound is typically synthesized *via* the hydrogenation of cyclohexanecarbonitrile (70% conversion), as reported by Wang and co-workers [22]. However, our approach is more facile and uses cyclohexene as a less expensive substrate.

The hydroaminomethylation of aryl-based alkenes can provide access to pharmacologically-active amines, examples of which are shown in Fig. 2.

In this regard, the hydroaminomethylation of styrene produced **5a** in 93% yield as a complex mixture of linear and branched products (only the linear products are shown in Fig. 2) and as a complex mixture of secondary and tertiary *N*-alkyl benzylamines. As previously mentioned, this makes determining the regioselectivity very challenging.

This yield is superior to that obtained by Zhang and co-workers (54%) in their study of the hydroaminomethylation of styrene with benzylamine, using a rhodium tetraphosphine-based catalyst system [23]. In addition to this, they used a higher reaction temperature of 125 °C and a longer reaction time of 16 h.

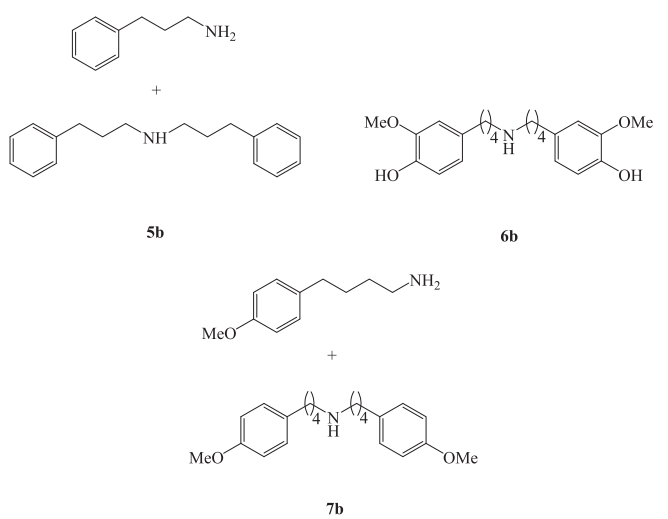


Fig. 2. Aryl-based primary and secondary amines synthesized *via* hydroaminomethylation and hydrogenolysis.

Subsequent debenzylation of **5a** provided **5b** in 41% yield, which was also obtained as a complex mixture of primary and secondary amines. Once again as previously mentioned, we were not able to determine the selectivity for the primary and secondary amines. Synthesis of the primary amine was previously demonstrated by the groups of Beller, Ohkuma, and Togo [24–26]. In these reports, the primary amine was isolated in high yields by both Beller [24] and Ohkuma [25] (99% and 87%, respectively) using direct methods in which the corresponding nitrile and azides were employed as substrates, respectively. In our case, the synthesis of **5b** was achieved *via* hydroaminomethylation using styrene, followed by hydrogenolysis. In contrast to our one-pot protocol, Togo and co-workers [26] obtained primary amine **5b** in high yield (~83%) over multiple synthetic steps, which involved conversion of 4-phenylbutanoic acid to the corresponding *N*-alkylsuccinimide over three steps, followed by deprotection of the protected amine using hydrazine. The corresponding secondary amine is commonly synthesized *via* the hydrogenation of cinnamonitrile which also requires prior synthesis [27].

Given the success in converting the aforementioned alkene substrates into amino-functionalized products, we further examined the substrate scope by employing hydroxy and methoxy containing aryl alkenes. For example, eugenol underwent bis-hydroaminomethylation with benzylamine, forming the corresponding amine (**6a**) (only the linear products are shown in Fig. 2) in high yield (93%). Debenzylation of **6a** gave **6b** in 94% yield as a complex mixture of linear and branched isomers.

Estragole was also successfully converted to the corresponding product **7a** in good yield (77%) as a complex mixture of secondary and tertiary *N*-alkylbenzylamines. Similar yields were previously obtained by Gusevskaya and co-workers [28] for the hydroaminomethylation of estragole with di-*n*-butylamine (75%), albeit at a slightly higher pressure (60 bar) and using a longer reaction times (24 h), making our system better in this regard. Subsequent debenzylation of **7a** gave **7b** as a complex mixture of primary and secondary amines. The primary amine is a tyramine-analogue and this approach represents an improvement on the previously reported synthetic approaches for this compound [29].

We further studied the hydroaminomethylation of ester and alcohol functionalized alkenes, such as methyl 10-undecenoate and pent-4-en-1-ol to produce ester and alcohol containing amines (Fig. 3).

Methyl 10-undecenoate, a bio-renewable substrate derived from castor oil, was converted into the corresponding amine **8a** in 99% yield *via* hydroaminomethylation. This yield is superior to that obtained by Vorholt and co-workers for the hydroaminomethylation of methyl 10-undecenoate (70%) [30]. However, in their case the reaction was performed with piperazine, which undergoes bis-hydroaminomethylation. In our system, the hydrogenolysis of **8a** produced **8b** (complex mixture of linear and branched products), an α,ω-diester, in 77% yield. This com-

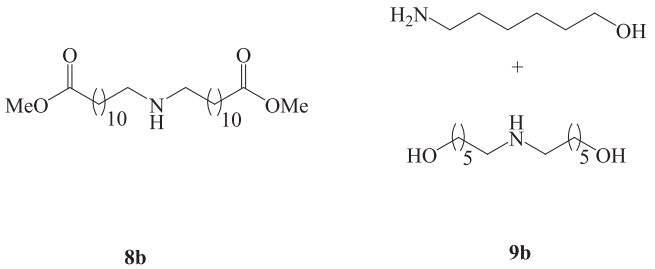


Fig. 3. α,ω-Diester and amino-alcohol synthesized *via* hydroaminomethylation and hydrogenolysis.

pound can potentially be used in the synthesis of polyamide polymers, resembling well-known Nylon-type polymers [31].

The hydroaminomethylation of pent-4-en-1-ol with benzylamine produced **9a** in 76% yield as a complex mixture of secondary and tertiary *N*-alkyl benzylamines. To the best of our knowledge, this is the first example of the hydroaminomethylation of pent-4-en-1-ol however, similar substrates have previously been evaluated in hydroaminomethylation [32–34]. Subsequent debenzylation of **9a** gave amino alcohol **9b** as a mixture of linear and branched isomers (only the linear product is shown in Fig. 3) and consisting of a mixture of primary and secondary amine products. Amino alcohols are of interest in the surfactant industry and can also be used in the synthesis of polymers *via* their reaction with bifunctional carboxylic acids derivatives [35,36]. Polyester-based polymers would be produced if the reaction occurs exclusively at the alcohol functionalities of the amino alcohol **9b**. However, poly(ester amide)s could also be formed due to the presence of both hydroxy and amino functionalities [37].

Conclusion

The facile synthesis of primary and secondary amines were demonstrated *via* the hydroaminomethylation of alkenes with benzylamine followed by hydrogenolysis using Pd/C to provide the corresponding primary and secondary amines. Work is currently underway in order to separate the primary and secondary amine mixtures and also to evaluate different ammonia surrogates.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153018.

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