Rhodium(I)-catalyzed hydroaminomethylation of 2-isopropenylanilines as a novel route to 1,2,3,4-tetrahydroquinolines†

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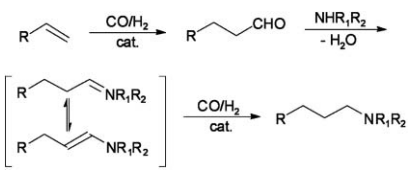
Received (in Cambridge, UK) 16th February 2007, Accepted 3rd April 2007
First published as an Advance Article on the web 19th April 2007
DOI: 10.1039/b702497e

A new atom economical approach for the preparation of 1,2,3,4-tetrahydroquinolines can be achieved by means of the intramolecular hydroaminomethylation of 2-isopropenylanilines, mediated by an ionic diamino rhodium catalyst that does not require phosphine—this reaction is highly chemo- and regioselective, and it occurs in good isolated yields.

The hydroaminomethylation reaction is an elegant approach to the synthesis of secondary and tertiary amines from olefins, due to its high atom economy.[1] It was originally discovered by Reppe and co-workers[2] in the early 1950s and consists of a tandem hydroformylation reaction followed by reductive amination (Scheme 1). Only in the last two decades has the potential of this reaction been extensively explored, and a wide range of quite efficient protocols were established for hydroaminomethylation, including alkyl (or aryl) olefins and aliphatic (or aromatic) amines.[1,3] It has also been used for the synthesis of dendrimers[4] and macroheterocycles.[5] In contrast, the intramolecular version has been demonstrated for only a few examples, and usually in low chemoselectivity.[6] The main problem resides in the first step, hydroformylation, and lactams can be formed—sometimes exclusively—*via* cleavage of the intermediate rhodium–acyl species.[1]

Tetrahydroquinolines play an important role in the fields of natural products and medicinal chemistry.[7] They are of synthetic interest for the preparation of pharmaceuticals and agrochemicals, as well as in material sciences.[8] While there are a number of methods to prepare this heterocyclic system,[9] the most convenient and direct route is still the partial hydrogenation of quinolines,[10] the preparation of which often requires harsh conditions such as high temperatures and/or strong acidic media.

We have recently reported the use of diamine rhodium catalysts for the highly regioselective hydroformylation of styrenes.[11] As a potentially different application of using **1** as a catalyst, we considered whether **1** could be valuable for hydroaminomethylation reactions. We now report a new atom economical preparation of 1,2,3,4-tetrahydroquinolines by means of a phosphine free rhodium catalyzed intramolecular hydroaminomethylation of 2-isopropenylanilines, in high chemo- and regioselectivity.

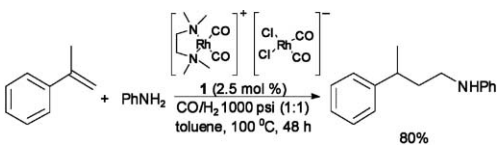


Scheme 1 Hydroaminomethylation reaction.

To test the viability of our catalytic system for the hydroaminomethylation reaction, we first performed the reaction between α-methylstyrene and aniline, catalyzed by **1** (Scheme 2). We were gratified to observe that the linear amine could be obtained as the only regioisomer in 80% isolated yield, using 2.5 mol% of catalyst. This result suggested that the catalytic system is an active and efficient one.

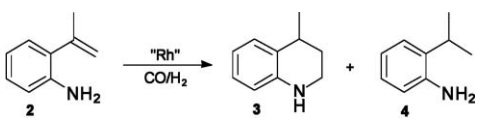
When the same conditions were investigated for 2-isopropenylaniline (**2**), only 60% conversion was achieved (Table 1, entry 1). After optimization, **3** could be obtained as the single product by using 5.0 mol% of **1** (Table 1, entry 5), under CO/H_2.

Having found the optimum conditions for our catalytic system, we extended the scope of our protocol to 2-isopropenylanilines substituted at the nitrogen and in the aromatic ring. The protocol proved to be general and the 1,2,3,4-tetrahydroquinolines were obtained in very good isolated yields (Table 2). Due to lower reactivity for the halogenated substrates, the catalyst load had to be increased to 7.5 mol%. Partial substrate hydrogenation was noticed for the electron poor fluorosubstituted derivative (entry 7).



Scheme 2 Reaction between α-methylstyrene and aniline.

Table 1 Selected screening for the hydroaminomethylation of 2-isopropenylaniline (**2**)[a]



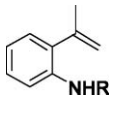
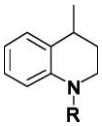
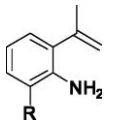
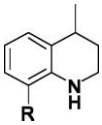
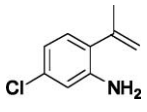
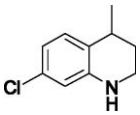
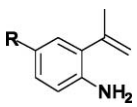
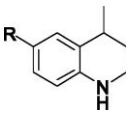
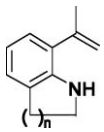
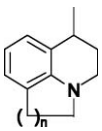
Entry	Catalyst **1** (mol%)	CO/H_2 (psi)	**3** (%)	**4** (%)
1	2.5	500/500	60	—
2	5.0	500/500	80	—
3	7.5	500/500	90	10
4	7.5	700/300	>98	Trace
5	5.0	700/300	>98	—

[a] All reactions were performed in toluene at 120 °C for 48 h. The conversion and the product ratios were determined by ^1H NMR on the crude product mixture.

Contribution from the Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5. E-mail: howard.alper@uottawa.ca; Fax: 1 613 562 5871; Tel: 1 613 562 5189

† Electronic supplementary information (ESI) available: Experimental details, full characterization of new compounds and NMR spectra. See DOI: 10.1039/b702497e

Table 2 Hydroaminomethylation of 2-isopropenylanilines[a]

Entry	Substrate	Product		Yield[b] (%)
1			R = H	89
2			R = Me	92
3			R = Bn	98
4			R = Me	85
5			R = OMe	80
6				73
7			R = F	61[c]
8			R = Br	72
9			R = Me	80
10			*n* = 1	70
11			*n* = 2	73

[a] The reactions were performed on a 1 mmol scale with 5.0 mol% (7.5 mol% for the halogenated substrates) of **1**, at 120 °C, in toluene (2 mL), for 48 h, under 1000 psi CO/H_2 (7 : 3). [b] Isolated yields. [c] 20% substrate hydrogenation.

An important feature of this novel hydroaminomethylation catalytic system is the air compatibility of **1**, and thus it is not necessary to degas the solvent prior to charging the autoclave, simplifying the manipulation.

In summary, we have found an efficient and straightforward entry to 1,2,3,4-tetrahydroquinolines through a phosphine free hydroaminomethylation of 2-isopropenylanilines, in good yields and in high chemo- and regioselectivity. We believe this new catalytic approach represents a significant advance in heterocyclic chemistry, and is promising for the synthesis of pharmaceuticals.

We are indebted to SASOL Technology for financial support of this work, and to the summer student Vikas Sikervar for the preparation of some of the substrates.

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