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SYNTHESIS OF STERICALLY HINDERED AMINES BY DIRECT REDUCTIVE AMINATION OF KETONES

Niyaz Z. Yagafarov, Pavel N. Kolesnikov, Dmitry L. Usanov, Valentin V. Novikov, Yulia V. Nelyubina, and Denis Chusov

An atom-economical methodology for the synthesis of sterically hindered tertiary amines was developed, which is based on complementary Rh- and Ru-catalyzed direct reductive amination of ketones with primary and secondary amines using carbon monoxide as a deoxygenative agent.

Reductive amination represents one of the most convenient approaches to amine synthesis due to its modular nature and the potential for rapid increase of molecular complexity. It is therefore not surprising, for instance, that in the realm of medicinal chemistry it belongs to the group of most frequently conducted transformations. Whereas a very wide variety of amines can be synthesized via reductive amination of carbonyl compounds (with hydrogen gas or complex hydrides as reductants), efficient preparation of sterically congested counterparts frequently requires substantially more complex synthetic schemes, which renders a significant proportion of this compound class poorly accessible. Yet, development of convenient ways to prepare sterically hindered amines is an important synthetic goal in light of the significance of these types of products for synthesis and catalysis (e.g. as ligands, components of frustrated Lewis pairs, etc.), as well as for numerous specialized applications, such as removal of carbon dioxide and sulfur-containing impurities from gas mixtures, controlled polymerization or stabilization of polymers against light-induced degradation. Moreover, low synthetic accessibility is responsible for the fact that sterically hindered amines remain underexplored in the contexts of spectral and structural peculiarities, reactivity, synthetic applications, and, more importantly, biomedical potential.

Previously published works heavily relied on three general synthetic approaches to sterically hindered tertiary amines, one of which involves taking advantage of the high reactivity of benzylene intermediates. Indeed, the natural problem of regioselectivity represents a substantial drawback of this pathway in addition to the burden of multi-step preparation of the corresponding benzylene precursors. The other approach employs specially designed organometallic reagents, among which the brilliant system designed by Knochel is particularly noteworthy. The third tactic is based on metal-mediated cross coupling methodology, which usually requires careful tuning of substrates, catalysts and reaction conditions and can be sensitive to small structural changes. Among this group, a marvellous system developed by Lalic et al. enables sterically hindered (aromatic and heteroaromatic) amine synthesis of high substrate tolerance. Despite all the great merits, it’s notable that the protocol requires preparation of neopentyl glycol boronic esters and O-benzoyl hydroxylamines, which inevitably limits the applicability of the protocol in the combinatorial format. Thus, in light of the dramatic shortage of simple synthetic routes towards sterically hindered amines, it was highly desirable to develop a methodology which would possess the key benefits of classical reductive amination (e.g. the possibility of one-pot versions, modular nature, availability of starting materials, scalability, etc.), yet would be able to provide access to products which are excessively sterically congested for the conventional reductive amination to be efficient.

We have recently developed a novel highly atom-economical methodology of Rh- or Ru-catalyzed reductive amination, which does not require any external hydrogen source, but rather utilizes the unique deoxygenative potential of carbon monoxide and has the potential to serve as a greener alternative to existing methods. On the grounds of this paradigm, herein we report the development of a catalytic system for direct reductive amination of ketones, which provides easy access to a broad range of sterically congested tertiary amines, many of which hitherto required substantially more complicated synthetic arrangements.

We began our studies with the model reaction between acetone and p-anisidine (Table 1). The reaction did not take place in the absence of the catalyst (entry 1), but proceeded...
well in the presence of various rhodium species (entries 2-7) with highest yield achieved with rhodium(II) acetate, rhodium(II) trifluoroacetate and rhodium(III) chloride (entries 5-7). Decreasing the temperature below 160 °C resulted in inferior yields (entries 8 and 9). Solvent screening identified a few suitable reaction media (see supporting information), and conducting the reaction without any added solvent but acetone (one of the reactants) demonstrated best results.

We noticed that more nucleophilic amines generally demonstrated higher yields under rhodium trichloride catalysis (method A), whereas less nucleophilic amines performed better when ruthenium trichloride was employed (method B, Figure 1). For instance, 3-aminobenzoic acid ethyl ester furnished the adduct with acetone more efficiently under ruthenium catalysis (1c, 75% vs. 31% observed yield) in contrast to more nucleophilic p-anisidine. Using Method A, p-anisidine (1a, 1b), benzylamine (1d) and dibenzylamine derivatives (1g-1j) were formed in 60-90% yields (50-70% isolated yields) with such ketones as acetone, 2-butanone, benzylacetone, cyclopentanone and cyclohexanone. p-Aminopyridine showed only traces of the product most likely because of the strong coordination to the catalyst. An aniline with a strong electron-withdrawing group in the para-position could be used in the reaction as well, however, the yield was lower (1e).

Less nucleophilic diphenylamine showed by far better performance with RuCl₃ rather than RhCl₃ as a catalyst; products 1k-1n were obtained via method B in 70-93% yields (54-75% isolated yields). Likewise, ruthenium catalysis generally remained superior for the reactions of N-isopropyl-p-anisidine with cyclic ketones, which furnished unsymmetrical products 1o-1r. Notably, as sterically congested compound as 2-adamantanone derivative 1r could be isolated with moderate yield. Lowered isolated yield of aminophenol derivative 1f (versus 53% yield observed by NMR) is most likely associated with relative easiness of oxidation. The structure of compound 1f has been elucidated by X-ray diffraction analysis of the trifluoroacetate salt (see Supporting Information). Compatibility of our methodology with the hydroxyl moiety (1f) is a noteworthy advantage with respect to many of the existing approaches to the synthesis of sterically hindered amines. One-step conversion of phenolic products into the corresponding triflates enables metal-mediated cross-coupling reactions; such a synthetic tandem would constitute a powerful approach for the rapid and highly modular generation of hitherto poorly accessible libraries of sterically hindered amines, which can be interesting in the context of bioactive small-molecule discovery.

Table 1 Catalyst and temperature screening.

<table>
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<tr>
<th>Entry</th>
<th>T, °C</th>
<th>Catalyst</th>
<th>Catalyst, mol%</th>
<th>Yield %</th>
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<tr>
<td>1</td>
<td>160</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>160</td>
<td>CpRh(CO)I₂</td>
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<tr>
<td>3</td>
<td>160</td>
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<td>[Rh(CO)Cl]₂</td>
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<td>9</td>
<td>140</td>
<td>RhCl₃</td>
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*10 eq of acetone was used. *Yields were determined by NMR with internal standard.

Figure 1 Substrate scope of direct reductive amination of ketones.
by eliminating the necessity to use unsymmetrical secondary amines as substrates. Thus, we carried out a one-pot protocol starting with a simple and accessible primary amine instead (p-anisidine), which underwent sequential Ru-catalysed reductive amination reactions with two different ketones, namely acetone and cyclohexanone (Scheme 1). To our delight, we observed formation of product 1p in 60% yield (30% isolated yield), which was comparable with the efficiency of a one-step reaction employing N-isopropyl-p-anisidine as a substrate.

Scheme 1  One-pot synthesis of unsymmetrical tertiary amines.

When Rh-catalyzed reaction of p-anisidine with acetone was conducted in hydrogen atmosphere instead of carbon monoxide under otherwise identical conditions, formation of the desired product was not detected at all (Scheme 2). In fact, the reaction yielded a mixture of exhaustively reduced mono-condensation products and starting materials with no aromatic compounds remaining. Together with our previous studies, these results exclude the possibility that the reaction proceeds via water-gash shift reaction and emphasize the unique selectivity and synthetic value of the developed methodology for the synthesis of tertiary amines. A plausible mechanism is depicted in Scheme 3.

Scheme 3  Plausible mechanism of reductive amination.

In summary, we developed a methodology for one-step preparation of sterically hindered tertiary amines from cyclic and acyclic ketones and primary or secondary amines. The system is based on complementary rhodium and ruthenium catalysts and is notable for simplicity (e.g., no ligands are needed) and highly atom-economical nature. In order to alleviate the necessity to use unsymmetrical secondary amines as substrates for the preparation of unsymmetrical tertiary amines, we developed a one-pot two-step protocol which allows the use of much more readily accessible primary substrates with identical efficiency. In combination with the established methods of rapid build-up of molecular complexity, our methodology has a great potential to provide easy access to libraries of novel compounds which can be of interest in the biomedical context. We hope that the simplicity of the developed protocols will render sterically hindered tertiary amines, hitherto difficult to prepare, much more accessible to the scientific community, which might stimulate efforts in exploration of their properties in the contexts of chemistry, material science and drug discovery.

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Notes and references


5 For cross-coupling methods of preparation of tertiary amines see: (a) M. Prashad, X. Y. Mak, Y. Liu, O. Repič, J. Org. Chem., 2003, 68, 1163; (b) L. Ackermann, R. Sandmann, M. Schinkel, M. V. Kondrashov,