Stereoselective synthesis of functionalized pyrrolidines by the diverted N-H insertion reaction of metallocarbenes with β-aminoketone derivatives

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Abstract: A highly stereoselective route to functionalized pyrrolidines from the metal catalyzed diverted N-H insertion of a range of diazocarbonyl compounds with β-aminoketone derivatives is described. A number of catalysts (rhodium(II) carboxylate dimers, copper(I) triflate and an iron(III)porphyrin) are shown to promote the process under mild conditions to give a wide range of highly substituted proline derivatives. The reaction starts with a metallocarbone N-H insertion but is diverted by an intermolecular aldol reaction.

Amongst N-heterocyclic compounds of biological relevance, pyrrolidines are among the most important, and feature in a large number of naturally occurring and unnatural compounds. Examples include the mycotoxin paraherquamide 1, the potent proteasome inhibitor marine product salinosporamide A 2 and the glutamate receptor agonist kainic acid 3 (Figure 1).

Figure 1. Some naturally occurring pyrrolidines.

Consequently, a wide range of strategies have been employed for the construction of pyrrolidines and proline derivatives with common approaches based on azomethine ylide cycloaddition, hydroamination of alkenes, iodocyclization, and cycloisomerization. Many routes for the de novo construction of these 5-membered heterocyclic rings are based on carbene and metallocarbone intermediates, and give a range of functionalized pyrrolidines through cyclization by intramolecular carbene insertion into N-H, or C-H bonds, and related methods continue to be developed. Thus, Sun and co-workers have described the synthesis of pyrrolidines from the intramolecular trapping of transient ylides (Scheme 1). Despite this recent progress, some limitations remain, including the absence of routes to C-4 substituted pyrrolidines, the variable diastereoselectivity, and the preponderance of N-phenyl precursors that seriously limits the utility of the resulting heterocycles. We now describe a new route to highly substituted pyrrolidines that proceeds with excellent diastereoselectivity under mild conditions in a single step (Scheme 1) by a process initiated by metallocarbone N-H insertion, but diverted by an intramolecular aldol reaction.

Following our interest in the use of bifunctional reagents for the preparation of heterocycles by diverted carbene insertion reactions, we started investigating the use of β-aminoketone derivatives for the preparation of substituted pyrrolidines. Our initial study focused on the reaction of ethyl phenyldiazoacetate 1a with N-(4-methoxyphenyl)-β-aminoketone 2a, the p-methoxyphenyl (PMP) group serving both to provide a suitably nucleophilic nitrogen atom and to allow for later N-deprotection of the product. We rapidly established that diazoester 1a and β-aminoketone 2a gave N-PMP pyrrolidine 3a exclusively as the cis-isomer under rhodium(II) or copper(I) catalysis (Table 1, entries 1-4), with copper(I) triflate toluene complex giving the best result (entry 4). To illustrate the utility of the process, a selection of diazo compounds (1a-e) and N-PMP β-aminoketones (2a-c) were used to access a diverse range of substituted N-PMP pyrrolidines 3b-g (Scheme 2). Using diazo compounds 1a and 1c-e, copper triflate was found to be superior to rhodium catalysts, and the corresponding pyrrolidines 3b-e were obtained in good yield. In particular, alkyl diazoacetate 1c gave pyrrolidine 3d in 55% yield under copper triflate catalysis, an important result given that diazo compounds possessing a β-hydrogen, such as 1b, are prone to give alkenes via [1,2]-H shift. Ethyl diazoacetate 1b can also be used in this reaction, and excellent yields of pyrrolidines 3f and 3g were obtained, provided that iron(III) tetr pheny lporphyrin was used as the catalyst. In fact, iron(III) tetraphenylporphyrin was found to be an active catalyst for the hydrogenation of diazo compounds in the presence of copper triflate.
catalyst in this process only when ethyl diazoacetate 1b was used, and failed to react with diazo compounds 1a and 1c under the same conditions. Moreover, when α-substituted aminoketone 2c was used, pyrrolidine products 3e and 3g were obtained stereoselectively as the cis,cis-isomer exclusively. In all of these examples, the open chain “classical” N-H insertion product (ethyl N-(4-methoxyphenyl)-N-(3-oxo-3-phenyl)propyl phenylglycinate) was not observed, and, strikingly, the products were obtained with complete stereoselectivity. As expected, the N-PMP group could be readily removed under oxidative conditions (q.v.).

Based on the successful use of N-PMP aminoketones 2a-c, we next investigated the use of ketocarbamate 4a in this protocol. This represents a significant challenge given the decreased nitrogen nucleophilicity in 4a compared to p-methoxyphenyl derivatives 2a-c. The reaction of ketocarbamate 4a and ethyl phenyl diazoacetate 1a indeed required further optimization (see Supporting Information). However, the use of a low loading (0.25 mol%) of Dubois’ Rh2(esp)2 catalyst[18] in dichloromethane at reflux gave the desired pyrrolidine 5a as a single isomer (Scheme 3), the cis-isomer being confirmed by X-ray crystallography (Figure 2).[19] We were pleased to find that the above conditions could also be applied to a wide range of aryl diazoacetates to give the corresponding pyrrolidines 5b-m (Scheme 3). This process is particularly suited to electron-rich aryl diazoacetates 1f-j that gave high yields of the corresponding pyrrolidines 5b-f. The electronic nature of the phenyl ring substitutes was found to affect the yield of the process and the 4-bromo, 4-ido and 4-carboxy substituted diazo compounds 1d

### Table 1. Catalyst screening for the preparation of N-aryl pyrrolidine 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst[a]</th>
<th>Yield 3a %</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh2(oct)4 (1 mol%)</td>
<td>52</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>2</td>
<td>Rh2(piv)4 (1 mol%)</td>
<td>74</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>3</td>
<td>Rh2(esp)2 (1 mol%)</td>
<td>62</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>4</td>
<td>(CuOTf)2.Tol (5 mol%)</td>
<td>90</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td>Fe(TPP)Cl (1 mol%)</td>
<td>0 [b]</td>
<td>-</td>
</tr>
</tbody>
</table>

[a] oct = octanoate, piv = pivaloate, esp = α, α’, α’-tetramethyl-1,3-benzenedipropionate; [b] no reaction. **Conditions:** the diazo compound (0.39 mmol) in dichloromethane (2 mL) was added over 30 min to a mixture of aminoketone (0.3 mmol) and catalyst in dichloromethane (1 mL) at reflux.
Scheme 2. Synthesis of N-PMP pyrrolidines (PMP = 4-methoxyphenyl). a: copper(I) triflate toluene complex (5 mol%) as catalyst; b: iron(III) tetraphenylporphyrin (1 mol%) as catalyst; pyrrolidines 3b-g obtained with dr >20:1.

and 1 k-l gave pyrrolidines 5g-i in only moderate yields. Cyclic diazo compounds 1m and 1n gave the corresponding spiro-compounds 5j and 5k, the structure of which was confirmed by crystallography (Figure 2), and heteroaromatic diazo compounds 1o and 1p were successfully used to give pyrrolidines 5l and 5m. Despite the extensive range of aryldiazo compounds that can be used in this process, ethyl diazoacetate 1b, alkyl diazo compounds 1c and 1d did not give the corresponding pyrrolidines. Nevertheless, these minor limitations can be overcome through the use of N-PMP aminoketones, as described above.
Scheme 3. Rhodium catalyzed synthesis of C-2 and C-3 functionalized pyrrolidines (EWG = electron withdrawing group).

Turning our attention to variation in the ketocarbamate component of the reaction (Scheme 4), we observed that the N-H insertion – cyclization event occurred with a range of substrates of varying reactivity such as vinyl ketone 4b, ketoester 4c, aryl ketones 4d-f, and hydroxyketone derivative 4g to give the corresponding pyrrolidines 5n-s. With α-substituted ketones 4h-i, pyrrolidines 5t-u were obtained stereoselectively in high yields and in both cases as the cis,cis-isomer, as determined on the basis of NOESY-experiments. These results are in line with those previously obtained with N-PMP aminoketones 3i-j. Finally, the reaction was not limited to tert-butyl carbamates and Cbz-pyrrolidine 5v was obtained from benzoxycarbonyl aminoketone 4j in high yield.
In all examples presented in Schemes 3 and 4, the pyrrolidines 5a-v were obtained as a single diastereoisomer, and no products of classical N-H insertion, for example compound 6, were identified. In the case of pyrrolidine 5a, ring opening was observed to occur in high yield via retro-aldol in presence of a base such as DMAP to give N-H insertion product 6 (Scheme 5). Importantly, the products 5a and 6 were found not to interconvert under the pyrrolidine forming reaction conditions, suggesting that the open chain product 6 is not the precursor to pyrrolidine 5a.
Scheme 4. Rhodium(II) catalyzed synthesis of highly substituted pyrrolidines.

Scheme 5. Control reactions and retro-aldol ring opening reaction of pyrrolidine 5a to aminoketone 6.

In line with previous reports from our group$^{14}$ and others$^{10f, 10i}$ we propose that the formation of pyrrolidine products from the metal catalyzed reaction of $\beta$-aminoketone derivatives with diazo compounds results from the intramolecular trapping of an intermediate ylide species (Scheme 6). Ammonium ylide B is proposed to arise from the attack of the carbamate/aniline N-H of 4d/2a onto the electrophilic metallocarbene A, as generally accepted in N-H insertion reactions processes.$^{20}$ We additionally propose that cyclization occurs via a highly ordered transition state C involving a proton transfer from the carbamate/aniline nitrogen to the ketone carbonyl assisted by the ester carbonyl group, thus explaining the full selectivity for the cis-product 5p/3a. Importantly, these results support the view that the N-H insertion of rhodium metallocarbene into carbamates occurs via a stepwise mechanism$^{21}$ rather than a concerted process, as previously proposed.$^{10b}$
Finally, pyrrolidines 5a and 5v were deprotected under standard conditions to give N-H pyrrolidines 7 and 8, respectively (Scheme 7). Additionally, the PMP-group of pyrrolidine 3f was cleaved under oxidative conditions to give cis-3-hydroxyproline derivative 9, the structure of which was confirmed by X-ray crystallography (Figure 2). These results show the advantages of the present strategy for the construction of pyrrolidines as it allows for facile further N-functionalization of products 7-9.

In conclusion, we have presented a strategy for the preparation of a wide range of functionalized pyrrolidines (29 examples) by a diverted carbene insertion strategy based on the complementary use of N-PMP aminoketones and ketocarbamates. Overall, this protocol allows for the highly stereoselective construction of pyrrolidines bearing removable protecting groups on nitrogen, under rhodium(II), copper(I) or iron(III) catalysis, and using a range of diazo compounds, including ethyl diazoacetate and alkyl diazoesters.

Experimental Section

For full experimental details and copies of NMR spectra, see Supporting Information.

Acknowledgements
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**Keywords:** nitrogen heterocycles • diazo compounds • aldol reaction • transition-metal catalysis • carbenes


[19] A rotameric mixture was observed by HMNR in deuterated chloroform at room temperature. Partial coalescence was observed in DMSO at 90 °C. The identification of the cis-pyrydine was initially deduced from NOESY experiments.
