

# Stereoselective synthesis of functionalized pyrrolidines by the diverted N-H insertion reaction of metallocarbenes with $\beta$ -aminoketone derivatives

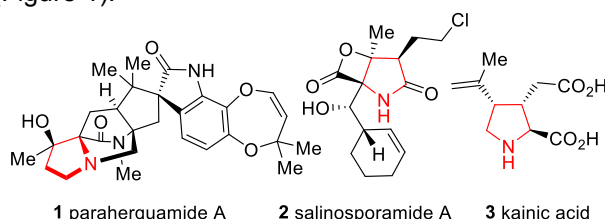
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**Abstract:** A highly stereoselective route to functionalized pyrrolidines from the metal catalyzed diverted N-H insertion of a range of diazocarbonyl compounds with  $\beta$ -aminoketone derivatives is described. A number of catalysts (rhodium(II) 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 metallocarbene 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.<sup>[1]</sup> Examples include the mycotoxin paraherquamide **1**,<sup>[2]</sup> the potent proteasome inhibitor marine product salinosporamide A **2**<sup>[3]</sup> and the glutamate receptor agonist kainic acid **3** (Figure 1).<sup>[4]</sup>

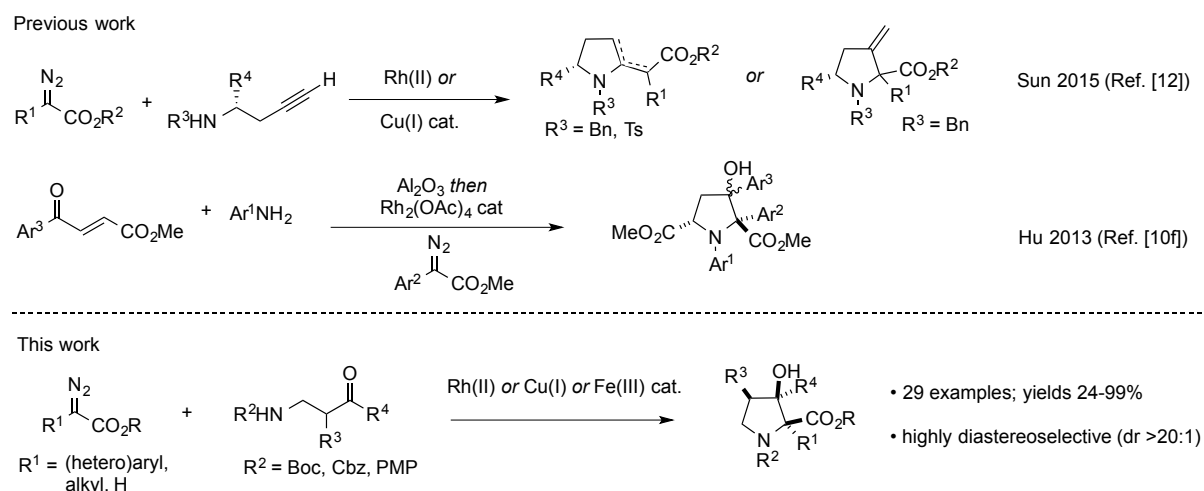


**Figure 1.** Some naturally occurring pyrrolidines.

Consequently, a wide range of strategies have been employed for the construction of pyrrolidines and proline derivatives,<sup>[5]</sup> with common approaches based on azomethine ylide cycloaddition,<sup>[6]</sup> hydroamination of alkenes,<sup>[7]</sup> iodocyclization,<sup>[8]</sup> and cycloisomerization.<sup>[9]</sup> Many routes for the *de novo* construction of these 5-membered heterocyclic rings are based on carbene and metallocarbene intermediates, and give a range of functionalized pyrrolidines through cyclization by intramolecular carbene insertion into N-H,<sup>[10]</sup> or C-H bonds,<sup>[11]</sup> and related methods continue to be developed. Thus, Sun and co-workers have reported the stereodivergent synthesis of *N*-heterocycles from the copper(I) or rhodium(II) catalyzed reaction of diazo compounds and amino alkynes,<sup>[12]</sup> and Hu and co-workers have described the synthesis of pyrrolidines from the intramolecular trapping of transient ylides (Scheme 1).<sup>[10][13]</sup> 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 metallocarbene N-H insertion, but diverted by an intramolecular aldol reaction.<sup>[13]</sup>

Following our interest in the use of bifunctional reagents for the preparation of heterocycles by diverted carbene insertion reactions,<sup>[14]</sup> we started investigating the use of  $\beta$ -aminoketone derivatives for the preparation of substituted pyrrolidines. Our initial study focused on the reaction of ethyl phenyldiazoacetate **1a** with *N*-(4-methoxyphenyl)- $\beta$ -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.<sup>[15]</sup> We rapidly established that diazoester **1a** and  $\beta$ -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  $\beta$ -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  $\beta$ -hydrogen, such as **1b**, are prone to give alkenes via [1,2]-H shift.<sup>[14, 16]</sup> Ethyl diazoacetate **1b** can also be used in this reaction, and excellent yields of pyrrolidines **3f** and **3g** were obtained, provided that iron(III) tetraphenylporphyrin<sup>[17]</sup> was used as the catalyst. In fact, iron(III) tetraphenylporphyrin was found to be an active

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  $\alpha$ -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.*).



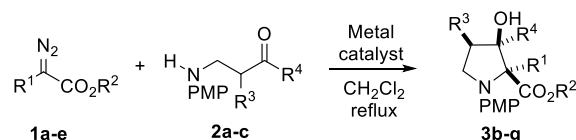
**Scheme 1.** Synthetic approaches to pyrrolidines involving metallocarbenes.

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

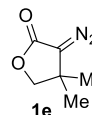
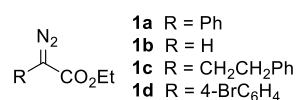
Entry	Catalyst <sup>[a]</sup>	Yield <b>3a</b> %	dr
1	Rh <sub>2</sub> (oct) <sub>4</sub> (1 mol%)	52	>20:1
2	Rh <sub>2</sub> (piv) <sub>4</sub> (1 mol%)	74	>20:1
3	Rh <sub>2</sub> (esp) <sub>2</sub> (1 mol%)	62	>20:1
4	(CuOTf) <sub>2</sub> .Tol (5 mol%)	90	>20:1
5	Fe(TPP)Cl (1 mol%)	0 <sup>[b]</sup>	-

[a] oct = octanoate, piv = pivaloate, esp =  $\alpha$ ,  $\alpha$ ,  $\alpha'$ ,  $\alpha'$ -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.

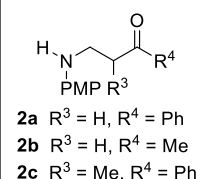
Based on the successful use of *N*-PMP aminoketones **2a-c**, we next investigated the use of ketocarbamate **4a** in this protocol. This represents a significant challenge given the decreased nitrogen nucleophilicity in **4a** compared to *p*-methoxyphenyl derivatives **2a-c**. The reaction of ketocarbamate **4a** and ethyl phenyldiazoacetate **1a** indeed required further optimization (see Supporting Information). However, the use of a low loading (0.25 mol%) of Dubois' Rh<sub>2</sub>(esp)<sub>2</sub> catalyst<sup>[18]</sup> 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).<sup>[19]</sup> We were pleased to find that the above conditions could also be applied to a wide range of aryldiazoacetates to give the corresponding pyrrolidines **5b-m** (Scheme 3). This process is particularly suited to electron-rich aryldiazoacetates **1f-j** that gave high yields of the corresponding pyrrolidines **5b-f**. The electronic nature of the phenyl ring substituents was found to affect the yield of the process and the 4-bromo, 4-iodo and 4-carboxy substituted diazo compounds **1d**



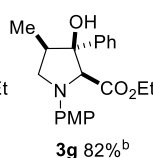
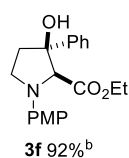
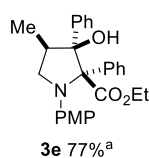
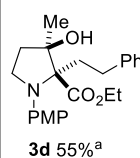
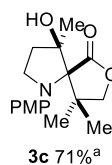
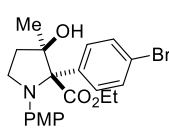
**Diazo compounds**



**N-PMP aminoketones**

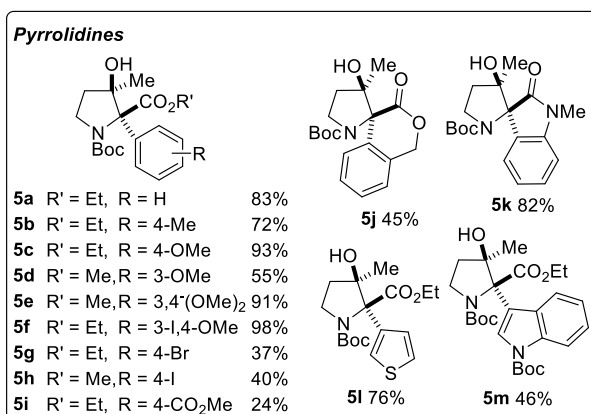
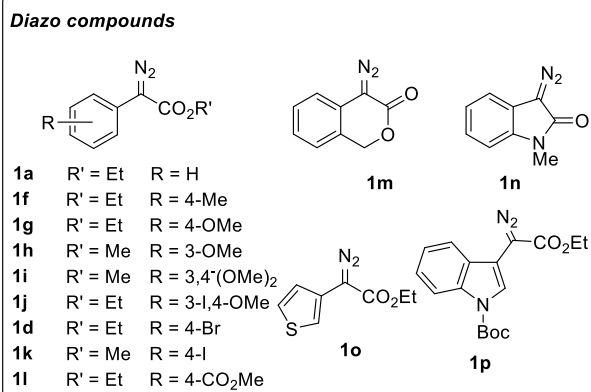
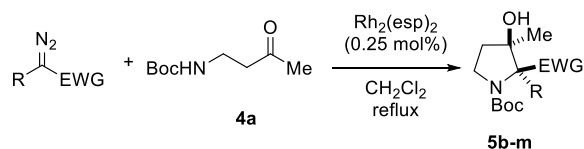


**N-PMP pyrrolidines**



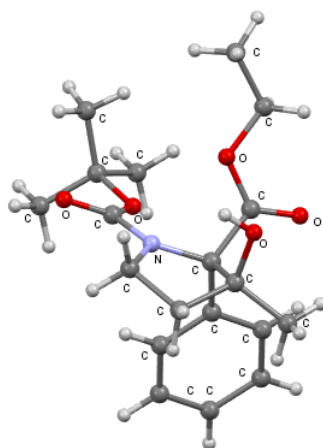
**Scheme 2.** Synthesis of *N*-PMP pyrrolidines (PMP = 4-methoxyphenyl). a: copper(I) triflate toluene complex (5 mol%) as catalyst; b: iron(III) tetraphenylporphyrin (1 mol%) as catalyst; pyrrolidines **3b-g** obtained with dr >20:1.

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.

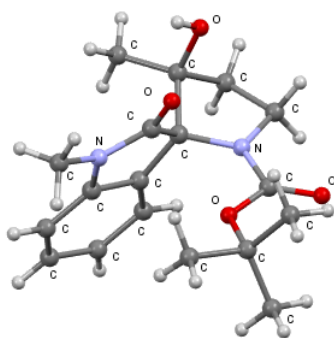


**Scheme 3.** Rhodium catalyzed synthesis of C-2 and C-3 functionalized pyrrolidines (EWG = electron withdrawing group).

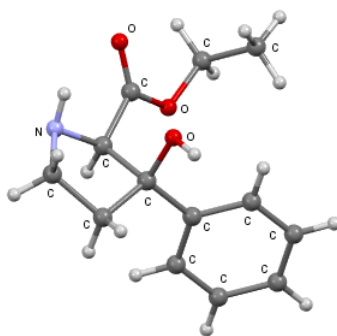
Turning our attention to variation in the ketocarbamate component of the reaction (Scheme 4), we observed that the N-H insertion – cyclization event occurred with a range of substrates of varying reactivity such as vinyl ketone **4b**, ketoester **4c**, aryl ketones **4d-f**, and hydroxyketone derivative **4g** to give the corresponding pyrrolidines **5n-s**. With  $\alpha$ -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 benzyloxycarbonyl aminoketone **4j** in high yield.



Compound **5a**



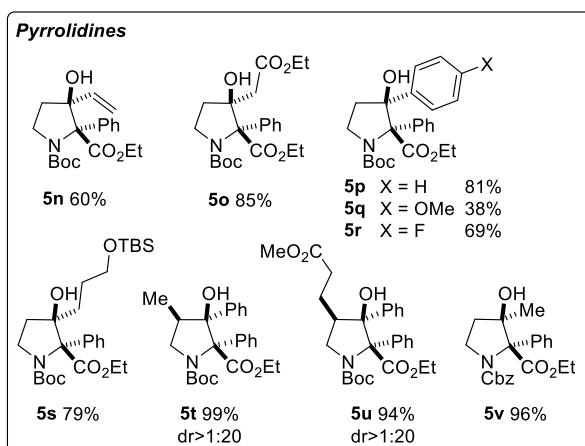
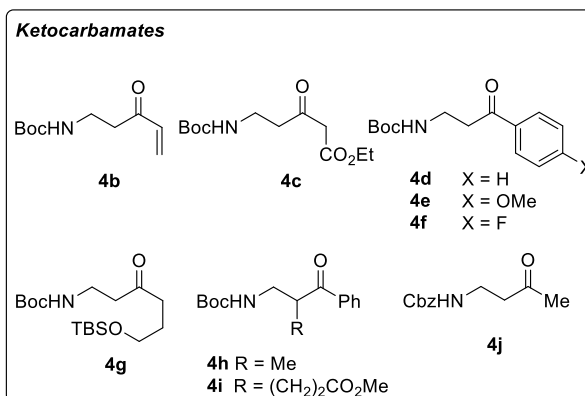
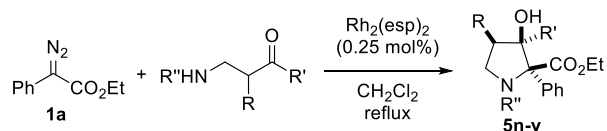
Compound **5k**



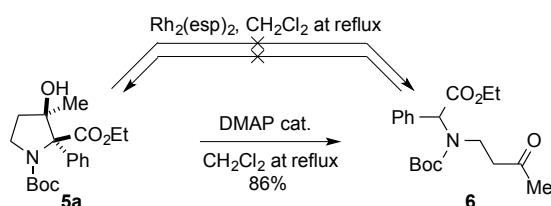
Compound **9**

**Figure 2.** X-Ray crystal structures of pyrrolidines **5a**, **5k** and **9**.

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**.

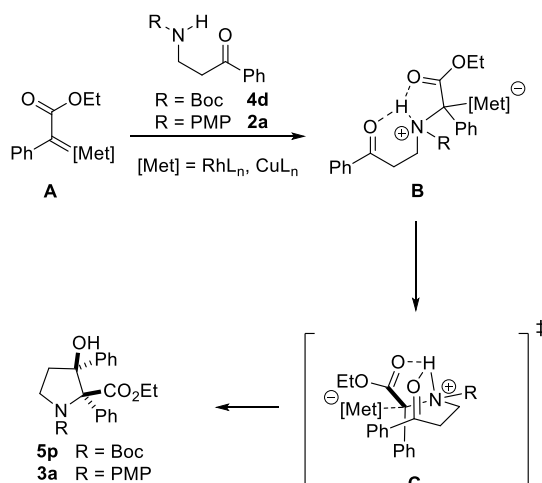


**Scheme 4.** Rhodium(II) catalyzed synthesis of highly substituted pyrrolidines.



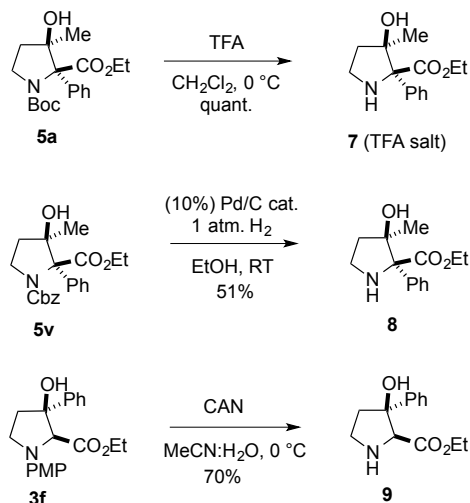
**Scheme 5.** Control reactions and retro-aldol ring opening reaction of pyrrolidine **5a** to aminoketone **6**.

In line with previous reports from our group<sup>[14]</sup> and others,<sup>[10f, 10i]</sup> 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.<sup>[20]</sup> 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<sup>[21]</sup> rather than a concerted process, as previously proposed.<sup>[10b]</sup>



**Scheme 6.** Proposed mechanism for the diverted N-H insertion reaction of aminoketones and diazo compounds.

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**.



**Scheme 7.** Deprotection of pyrrolidines **5a**, **5v** and **3f**.

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

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