



# 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 by 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 as a metallocarbene N–H insertion but is diverted by an intermolecular aldol reaction.

**P**yrrolidines are among the most important N-heterocyclic compounds of biological relevance and feature in a large number of naturally occurring and unnatural compounds.<sup>[1]</sup> Examples include the mycotoxin parahequamide (**1**),<sup>[2]</sup> the potent proteasome inhibitor salinosporamide A (**2**, a marine product),<sup>[3]</sup> and the glutamate receptor agonist kainic acid (**3**; Figure 1).<sup>[4]</sup>

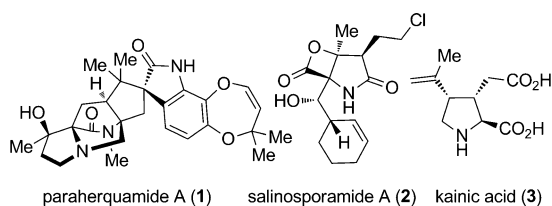


Figure 1. Some naturally occurring pyrrolidines.

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> alkene hydroamination,<sup>[7]</sup> iodocyclization,<sup>[8]</sup> and cycloisomerization.<sup>[9]</sup> Many routes for the de novo construction of these five-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. For example, Sun and co-workers have reported the stereodivergent synthesis of N-heterocycles through 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 by the intramolecular trapping of transient ylides (Scheme 1).<sup>[10f,13]</sup> Despite this recent progress, some limitations remain, including the absence of routes to C4-substituted pyrrolidines, the variable diastereoselectivity, and the preponderance of N-phenyl precursors, which 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 that is initiated by a metallocarbene N–H insertion, but is 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 *para*-methoxyphenyl (PMP) group serves 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 protected pyrrolidine **3a** exclusively as the *cis* isomer under rhodium(II) or copper(I) catalysis (Table 1, entries 1–4), with the (Cu<sup>I</sup>OTf)<sub>2</sub>-toluene complex giving the best result (entry 4).

Table 1: Catalyst screening for the preparation of N-aryl pyrrolidine **3a**.<sup>[a]</sup>

Entry	Catalyst (mol %)	Yield [%]
1	Rh <sub>2</sub> (oct) <sub>4</sub> (1)	52
2	Rh <sub>2</sub> (piv) <sub>4</sub> (1)	74
3	Rh <sub>2</sub> (esp) <sub>2</sub> (1)	62
4	(Cu <sup>I</sup> OTf) <sub>2</sub> -toluene (5)	90
5	Fe(TPP)Cl (1)	0 <sup>[b]</sup>

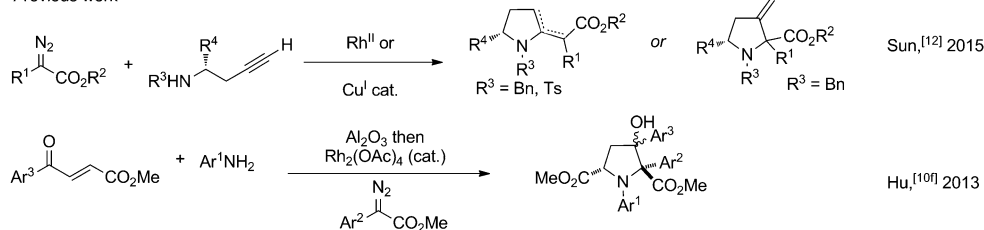
[a] Reaction conditions: **1a** (0.39 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added to a mixture of **2a** (0.3 mmol) and the catalyst in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at reflux over 30 min. **3a** was always formed with > 20:1 d.r. [b] No reaction. esp =  $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionate, oct = octanoate, piv = pivaloate, TPP = tetraphenylporphyrin.

To illustrate the utility of the process, a selection of diazo compounds (**1a–1e**) and N-PMP  $\beta$ -aminoketones (**2a–2c**) were used to access a diverse range of substituted N-PMP pyrrolidines (**3b–3g**; Scheme 2). With diazo compounds **1a** and **1c–1e**, copper triflate was found to be superior to

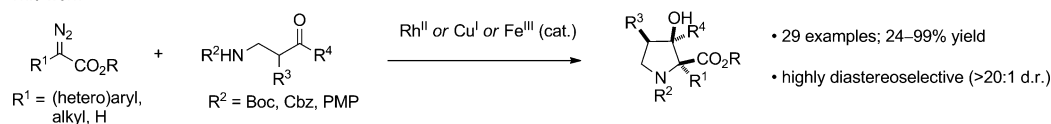
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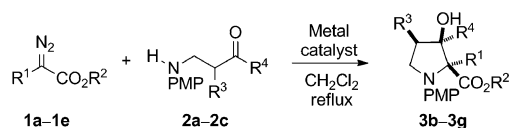
Previous work



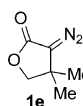
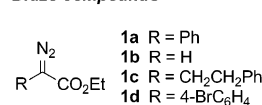
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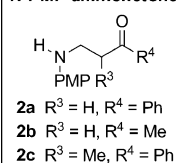
**Scheme 1.** Synthetic approaches to pyrrolidines involving metalcarbenes. Boc = *tert*-butoxycarbonyl, Cbz = benzyl-oxycarbonyl, PMP = *para*-methoxyphenyl.



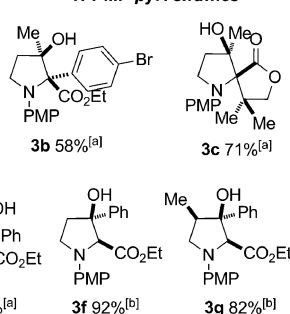
## Diazo compounds



## N-PMP aminoketones



## N-PMP pyrrolidines



**Scheme 2.** Synthesis of *N*-PMP pyrrolidines. [a]  $(CuOTf)_2$  (5 mol %) as the catalyst. [b]  $Fe(TPP)Cl$  (1 mol %) as the catalyst. All products obtained with >20:1 d.r.

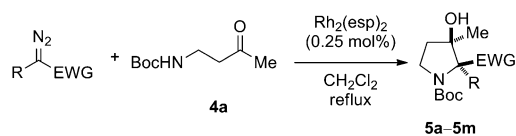
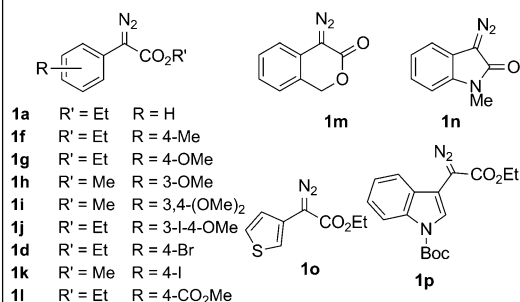
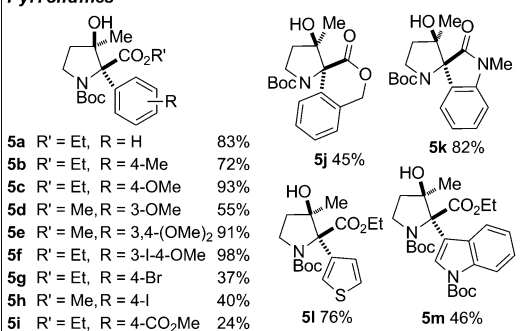
rhodium catalysts, and the corresponding pyrrolidines **3b–3e** were obtained in good yield. In particular, alkyl diazoacetate **1c** gave pyrrolidine **3d** in 55% yield under copper triflate catalysis, an important result given that diazo compounds with a  $\beta$ -hydrogen atom, such as **1b**, are prone to give alkenes by a [1,2]-H shift.<sup>[14,16]</sup> Ethyl diazoacetate (**1b**) can also be used in this reaction, and the pyrrolidines **3f** and **3g** were obtained in excellent yields provided that iron(III) tetraphenylporphyrin (TPT)<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 the diazo compounds **1a** and **1c** under the same

conditions. Moreover, when  $\alpha$ -substituted aminoketone **2c** was used, the pyrrolidine products **3e** and **3g** were obtained stereoselectively as the *cis/cis* isomers 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 (see below).

Based on the successful use of the *N*-PMP aminoketones **2a–2c**, we next investigated the use of ketocarbamate **4a** in this process. This represents a significant challenge given the decreased nitrogen nucleophilicity in **4a** compared to that of the *para*-methoxyphenyl derivatives **2a–2c**. The reaction of ketocarbamate **4a** and ethyl phenyldiazoacetate (**1a**) indeed required further optimization (see the Supporting Information). However, the use of a low loading (0.25 mol %) of Dubois’  $Rh_2(esp)_2$  catalyst<sup>[18]</sup> in dichloromethane at reflux gave the desired pyrrolidine **5a** as a single isomer (Scheme 3), the *cis* configuration 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 aryl diazoacetates to give the corresponding pyrrolidines **5b–5m** (Scheme 3). This process is particularly suited to electron-rich aryl diazoacetates (**1f–1j**), which gave the corresponding pyrrolidines **5b–5f** in high yields. The electronic nature of the aryl ring substituents was found to affect the yield of the process, and the 4-bromo-, 4-iodo-, and 4-carboxy-substituted diazo compounds **1d**, **1k**, and **1l** gave the corresponding pyrrolidines **5g–5i** in only moderate yields. Cyclic diazo compounds (**1m** and **1n**) gave the corresponding spiro products **5j** and **5k**, the structure of which was confirmed by crystallography (Figure 2), and heteroaromatic diazo compounds (**1o** and **1p**) were successfully converted into the desired pyrrolidines (**5l** and **5m**). Despite the extensive range of aryl diazo compounds that can be used in this process, ethyl diazoacetate (**1b**) and the 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.

Turning our attention to variations 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 different reactivity, such as vinyl ketone **4b**, ketoester **4c**, aryl ketones **4d–4f**, and hydroxyketone derivative **4g** to give the corresponding pyrrolidines **5n–5s**. With

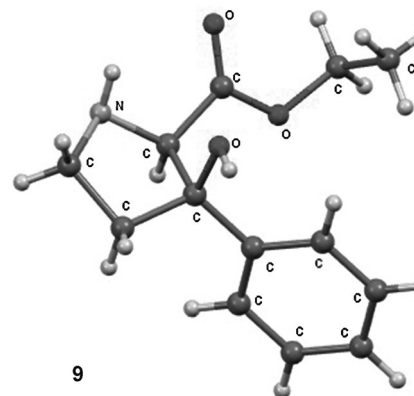
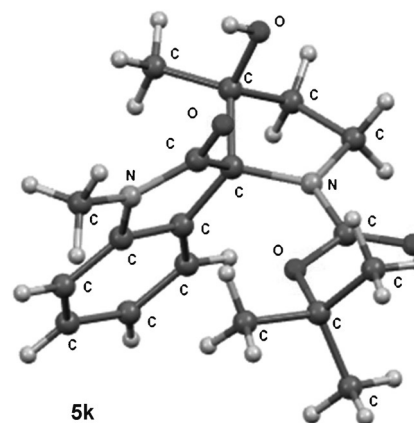
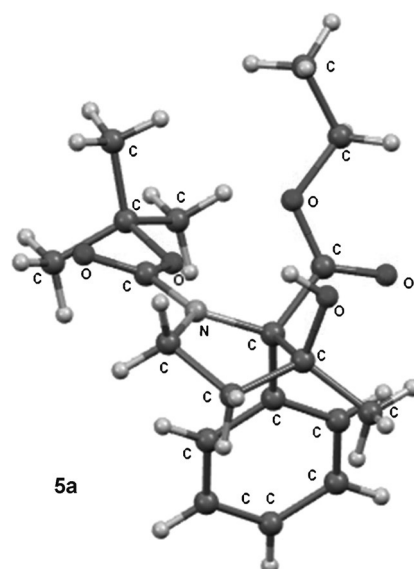
**Diazo compounds****Pyrrolidines**

**Scheme 3.** Rhodium-catalyzed synthesis of C2- and C3-functionalized pyrrolidines (EWG = electron-withdrawing group).

the  $\alpha$ -substituted ketones **4h** and **4i**, the pyrrolidines **5t** and **5u** were obtained stereoselectively in high yields as the *cis/cis* isomers (determined by NOESY). These results are in line with those previously obtained with the *N*-PMP amino-ketones **3i** and **3j**. Finally, the reaction was not limited to *tert*-butyl carbamates, and CBz pyrrolidine **5v** was obtained from the benzyloxycarbonyl-substituted aminoketone **4j** in high yield.

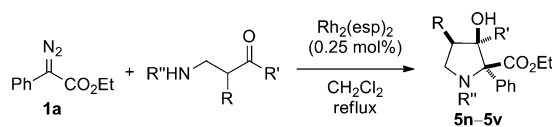
In all examples presented in Schemes 3 and 4, pyrrolidines **5a–5v** were obtained as single diastereoisomers, and no products of classical N–H insertion, for example, compound **6**, were identified. In the case of pyrrolidine **5a**, ring opening was observed to occur in high yield through a retro-aldol process in the presence of a base, such as DMAP, to give N–H insertion product **6** (Scheme 5). Importantly, products **5a** and **6** were found not to interconvert under the pyrrolidine-forming reaction conditions, suggesting that open-chain product **6** is not a precursor to pyrrolidine **5a**.

In line with previous reports from our group<sup>[14]</sup> and others,<sup>[10,11]</sup> we propose that the formation of pyrrolidine products by 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

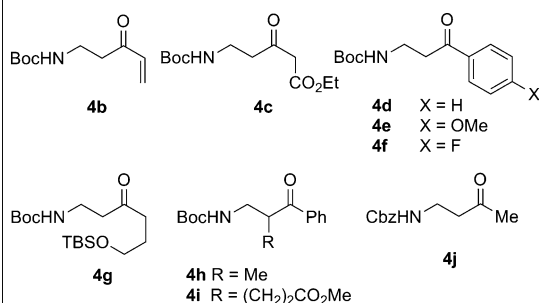


**Figure 2.** X-ray crystal structures of pyrrolidines **5a**, **5k**, and **9**.

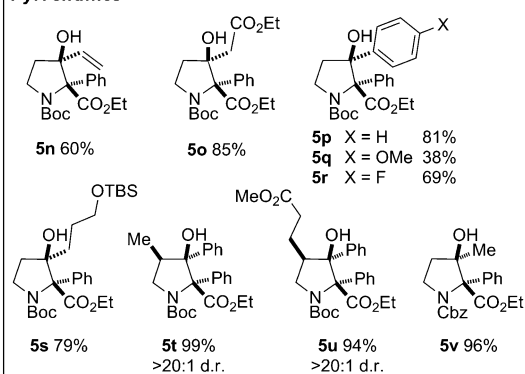
electrophilic metalcarbene **A**, as generally accepted in N–H insertion processes.<sup>[20]</sup> We additionally propose that cyclization occurs via a highly ordered transition state **C**, which involves a proton transfer from the carbamate/aniline nitrogen atom to the ketone carbonyl group that is assisted by the ester carbonyl group, thus explaining the full selectivity for the *cis* product **5p/3a**. Importantly, these results support the



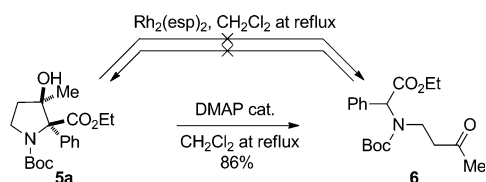
## Ketocarbamates



## Pyrrolidines



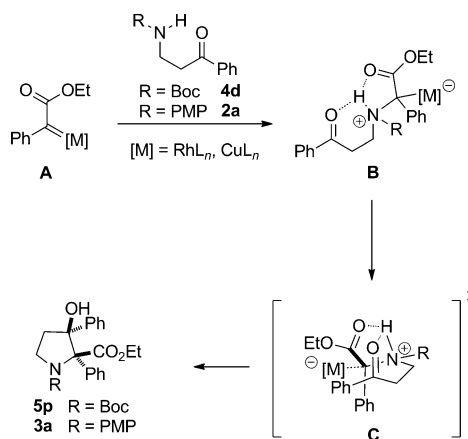
**Scheme 4.** Rhodium(II)-catalyzed synthesis of highly substituted pyrrolidines.



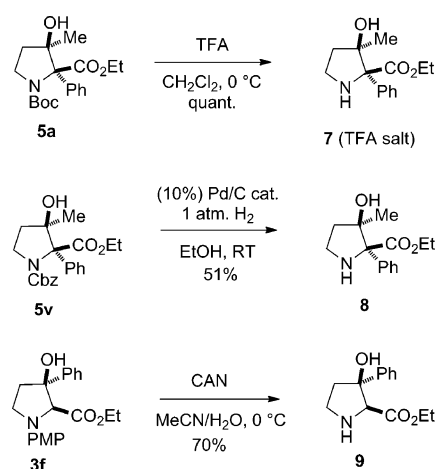
**Scheme 5.** Control reactions and retro-aldol ring-opening reaction of pyrrolidine **5a** to aminoketone **6**.

view that the N–H insertion of rhodium metalcarbenes into carbamates occurs by a stepwise mechanism<sup>[21]</sup> rather than a concerted process, as previously proposed.<sup>[10b]</sup>

Finally, pyrrolidines **5a** and **5v** were deprotected under standard conditions to give the NH pyrrolidines **7** and **8**, respectively (Scheme 7). Furthermore, 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 enables the facile further N functionalization of products **7–9**.



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



**Scheme 7.** Deprotection of pyrrolidines **5a**, **5v**, and **3f**. CAN = cerium(IV) ammonium nitrate, TFA = trifluoroacetic acid.

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 keto-carbamates. Overall, this method enables the highly stereo-selective construction of pyrrolidines bearing removable protecting groups on the nitrogen atom from a range of diazo compounds, including ethyl diazoacetate and alkyl diazoesters, under rhodium(II), copper(I), or iron(III) catalysis.

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

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