Nicolle, Simon M. and Lewis, William and Hayes, Christopher J. and Moody, Christopher J. (2016) Stereoselective synthesis of functionalized pyrrolidines by the diverted NH insertion reaction of metallocarbenes with β-aminoketone derivatives. Angewandte Chemie International Edition, 55 (11). pp. 3749-3753. ISSN 1433-7851

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

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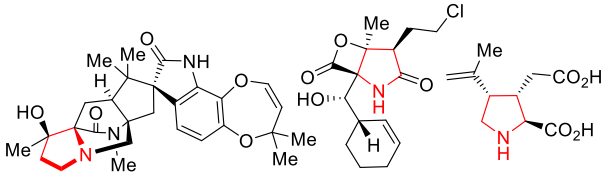
Abstract: A highly stereoselective route to functionalized pyrrolidines from the metal catalyzed diverted N-H insertion of a range of diazocarbonyl compounds with β-aminoketone derivatives is described. A number of catalysts (rhodium(II) carboxylate dimers, copper(I) triflate and an iron(III)porphyrin) are shown to promote the process under mild conditions to give a wide range of highly substituted proline derivatives. The reaction starts with a 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.[1] Examples include the mycotoxin paraherquamide **1**,[2] the potent proteasome inhibitor marine product salinosporamide A **2**[3] and the glutamate receptor agonist kainic acid **3** (Figure 1).[4]



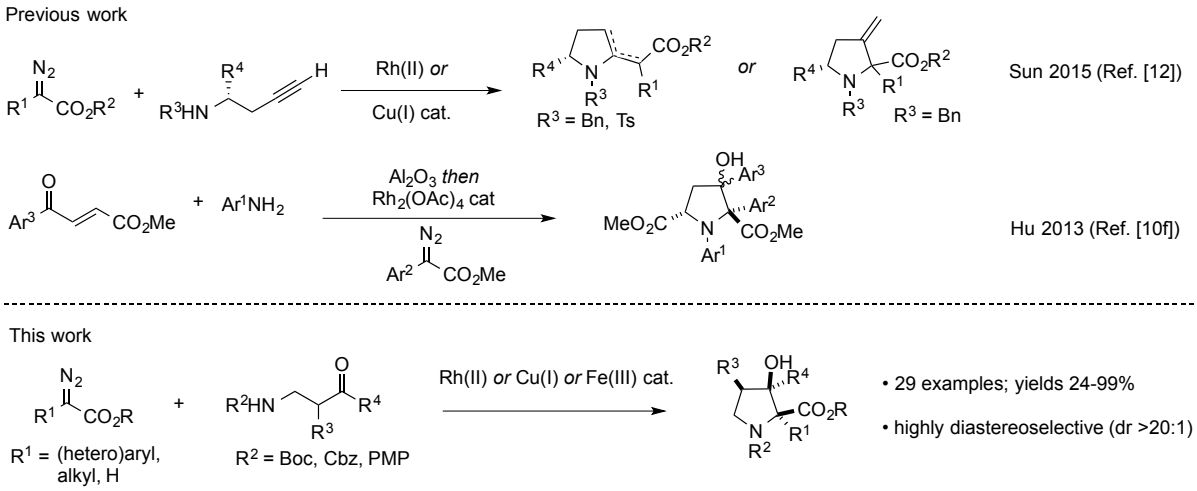
1 paraherquamide A **2** salinosporamide A **3** kainic acid

Figure 1. Some naturally occurring pyrrolidines.

Consequently, a wide range of strategies have been employed for the construction of pyrrolidines and proline derivatives,[5] with common approaches based on azomethine ylide cycloaddition,[6] hydroamination of alkenes,[7] iodocyclization,[8] and cycloisomerization.[9] 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,[10] or C-H bonds,[11] 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,[12] and Hu and co-workers have described the synthesis of pyrrolidines from the intramolecular trapping of transient ylides (Scheme 1).[10f][13] 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.[13]

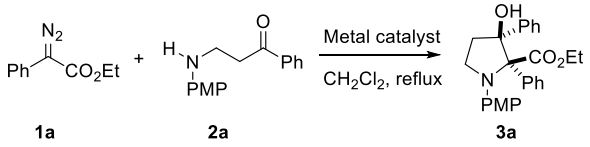
Following our interest in the use of bifunctional reagents for the preparation of heterocycles by diverted carbene insertion reactions,[14] we started investigating the use of β-aminoketone derivatives for the preparation of substituted pyrrolidines. Our initial study focused on the reaction of ethyl 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.[15] 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.[14, 16] 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[17] 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 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.*).



Scheme 1. Synthetic approaches to pyrrolidines involving metallocarbenes.

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

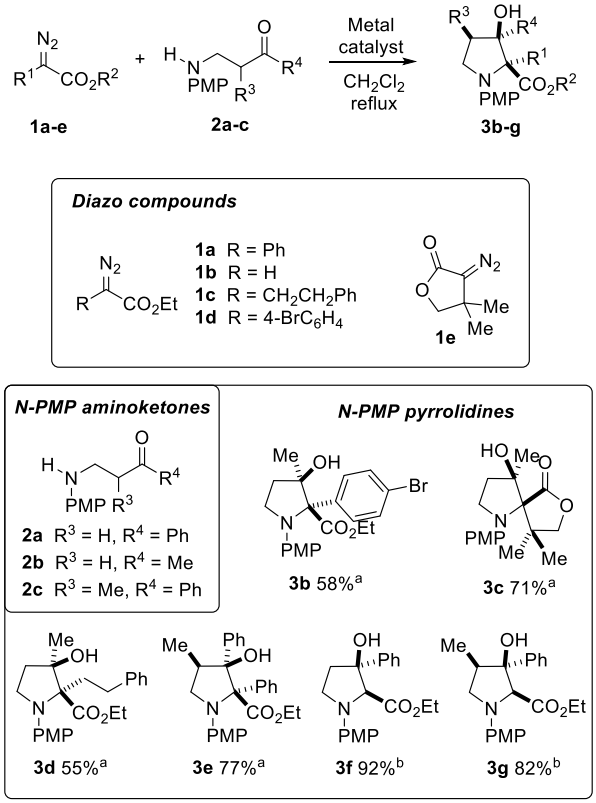


1a **2a** **3a**

Entry	Catalyst [a]	Yield **3a** %	dr
1	$Rh_2(oct)_4$ (1 mol%)	52	>20:1
2	$Rh_2(piv)_4$ (1 mol%)	74	>20:1
3	$Rh_2(esp)_2$ (1 mol%)	62	>20:1
4	$(CuOTf)_2$.Tol (5 mol%)	90	>20:1
5	Fe(TPP)Cl (1 mol%)	0 [b]	-

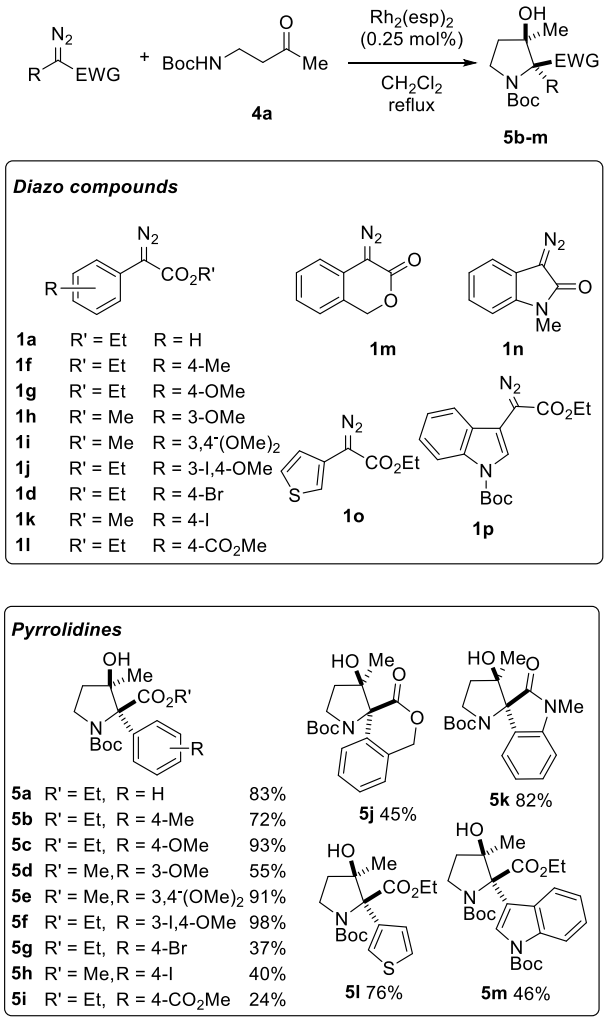
[a] oct = octanoate, piv = pivaloate, esp = α, α, α', α'-tetramethyl-1,3-benzenedipropionate; [b] no reaction. *Conditions*: the diazo compound (0.39 mmol) in dichloromethane (2 mL) was added over 30 min to a mixture of aminoketone (0.3 mmol) and catalyst in dichloromethane (1mL) at reflux.

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' $Rh_2(esp)_2$ 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 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 substit-uents was found to affect the yield of the process and the 4-bromo, 4-iodo and 4-carboxy substituted diazo compounds **1d**



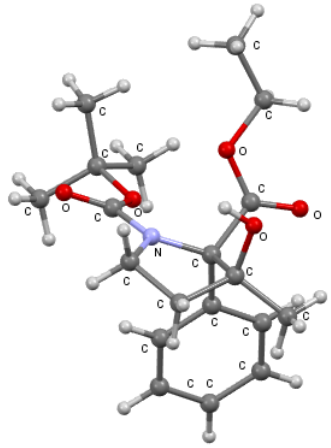
Scheme 2. Synthesis of *N*-PMP pyrrolidines (PMP = 4-methoxyphenyl). a: copper(I) triflate toluene complex (5 mol%) as catalyst; b: iron(III) tetraphenylporphyrin (1 mol%) as catalyst; pyrrolidines **3b-g** obtained with dr >20:1.

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.

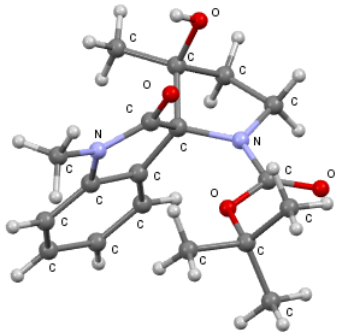


Scheme 3. Rhodium catalyzed synthesis of C-2 and C-3 functionalized pyrrolidines (EWG = electron withdrawing group).

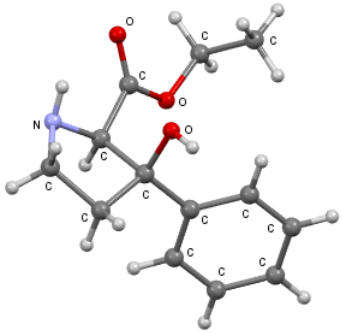
Turning our attention to variation in the ketocarbamate component of the reaction (Scheme 4), we observed that the N-H insertion – cyclization event occurred with a range of substrates of varying reactivity such as vinyl ketone **4b**, ketoester **4c**, aryl ketones **4d-f**, and hydroxyketone derivative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



Compound **5a**



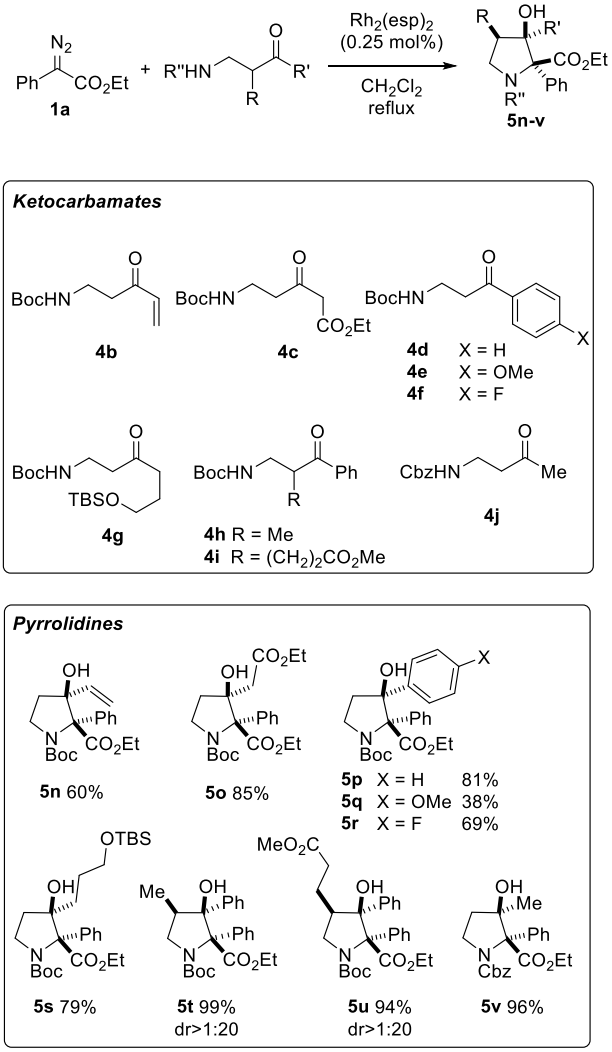
Compound **5k**



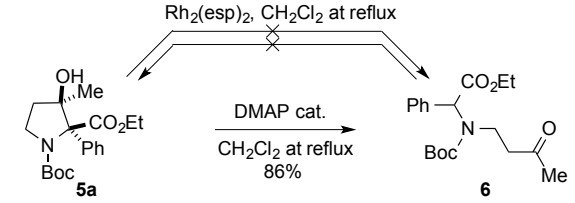
Compound **9**

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**.

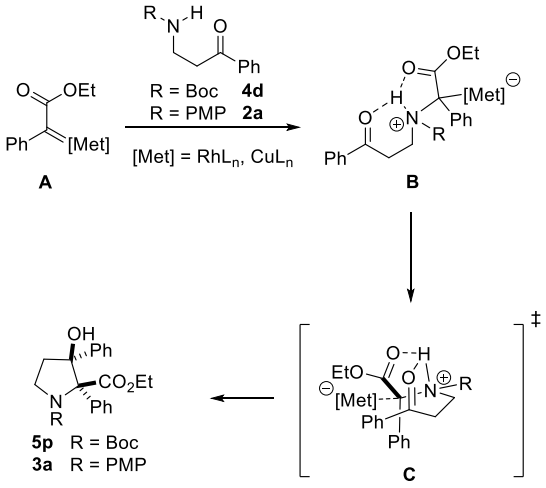


Scheme 4. Rhodium(II) catalyzed synthesis of highly substituted pyrrolidines.



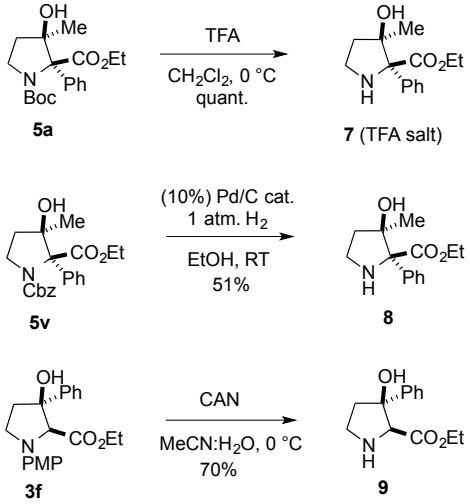
Scheme 5. Control reactions and retro-aldol ring opening reaction of pyrrolidine **5a** to aminoketone **6**.

In line with previous reports from our group[14] and others,[10f, 10i] we propose that the formation of pyrrolidine products from the metal catalyzed reaction of β-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]



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

We thank the University of Nottingham for support.

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

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