Nitrogen Heterocycles Hot Paper

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

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

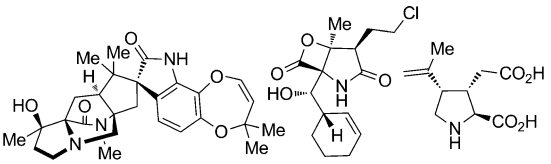
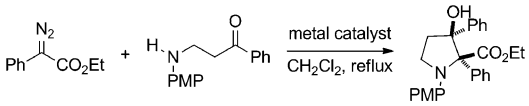


Figure 1. Some naturally occurring pyrrolidines.

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] alkene hydroamination,[7] iodocyclization,[8] and cycloisomerization.[9] 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[10] or C–H bonds,[11] 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,[12] and Hu and co-workers have described the synthesis of pyrrolidines by the intramolecular trapping of transient ylides (Scheme 1).[10f,13] 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.[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 *para*-methoxyphenyl (PMP) group serves 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 protected pyrrolidine **3a** exclusively as the *cis* isomer under rhodium(II) or copper(I) catalysis (Table 1, entries 1–4), with the $(Cu^{I}OTf)_2$·toluene complex giving the best result (entry 4).

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



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

Entry	Catalyst (mol%)	Yield [%]
1	$Rh_2(oct)_4$ (1)	52
2	$Rh_2(piv)_4$ (1)	74
3	$Rh_2(esp)_2$ (1)	62
4	$(CuOTf)_2$·toluene (5)	90
5	Fe(TPP)Cl (1)	0[b]

[a] Reaction conditions: **1a** (0.39 mmol) in CH_2Cl_2 (2 mL) was added to a mixture of **2a** (0.3 mmol) and the catalyst in CH_2Cl_2 (1 mL) at reflux over 30 min. **3a** was always formed with >20:1 d.r. [b] No reaction. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate, oct = octanoate, piv = pivaloate, TPT = tetraphenylporphyrin.

To illustrate the utility of the process, a selection of diazo compounds (**1a**–**1e**) and *N*-PMP β-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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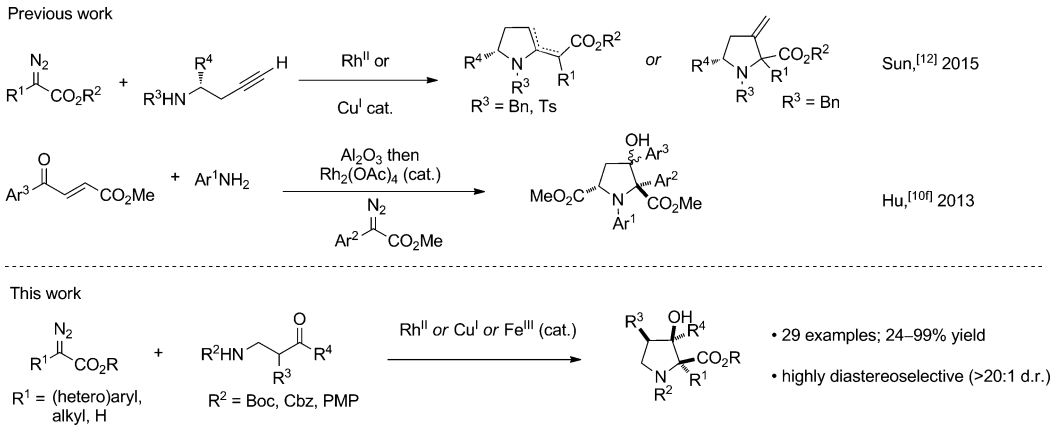
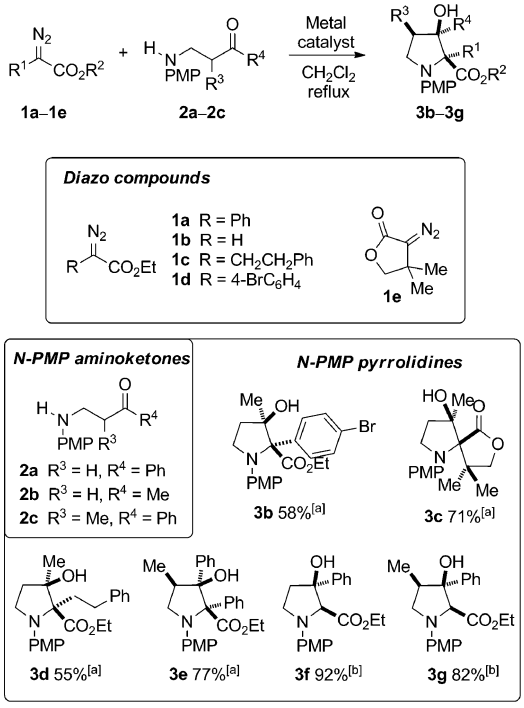


Scheme 1. Synthetic approaches to pyrrolidines involving metallocarbenes. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, PMP = *para*-methoxyphenyl.

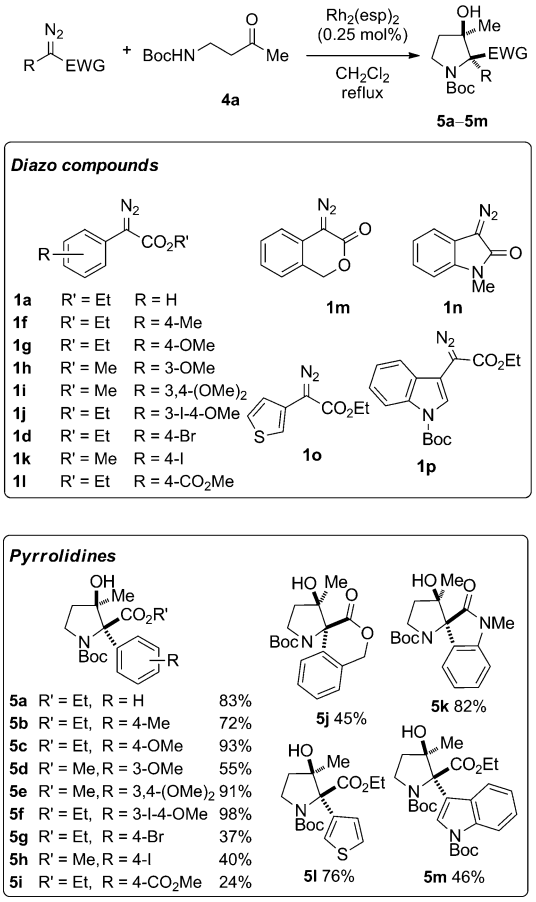


Scheme 2. Synthesis of *N*-PMP pyrrolidines. [a] $(CuOTf)_2$·toluene (5 mol%) as the catalyst. [b] Fe(TPP)Cl (1 mol%) as the catalyst. All products obtained with > 20:1 d.r.

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 β-hydrogen atom, such as **1b**, are prone to give alkenes by a [1,2]-H shift.[14,16] 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)[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 the diazo compounds **1a** and **1c** under the same conditions. Moreover, when α-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[18] 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).[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**–**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



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

the α-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 aminoketones **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[14] and others,[10f,i] we propose that the formation of pyrrolidine products by 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

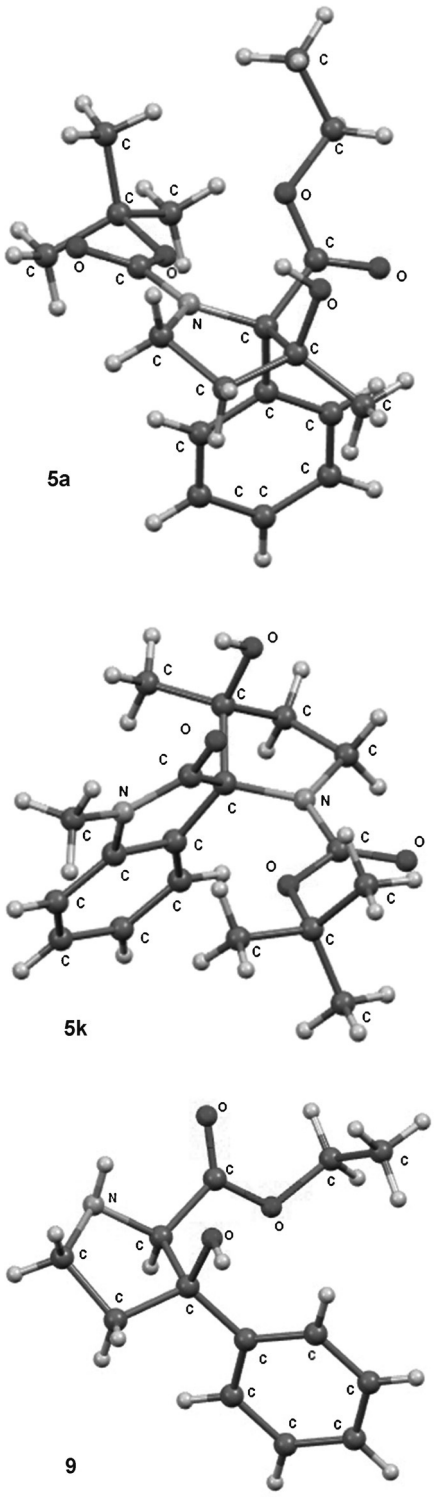
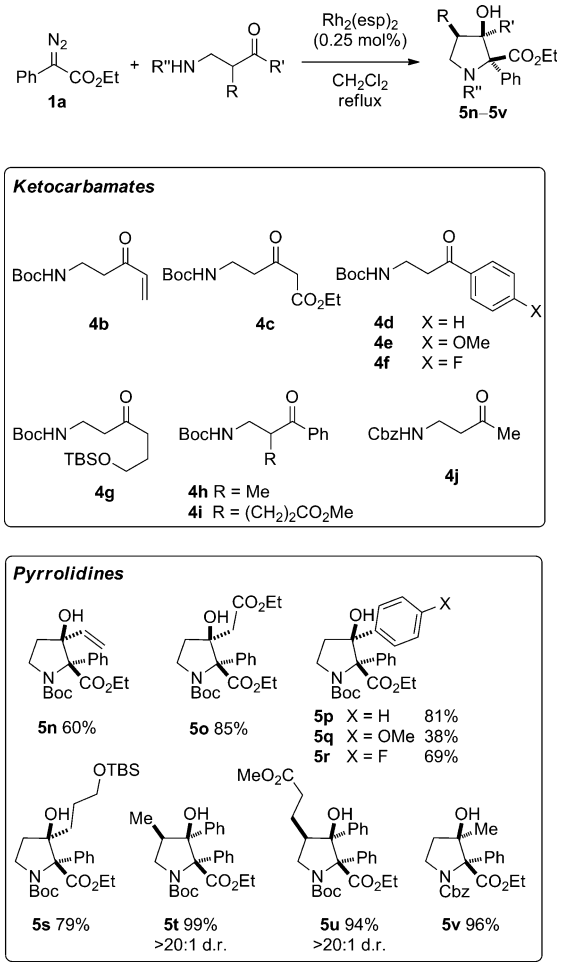
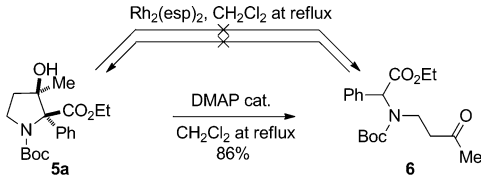


Figure 2. X-ray crystal structures of pyrrolidines **5a**, **5k**, and **9**.

electrophilic metallocarbene **A**, as generally accepted in N–H insertion processes.[20] 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



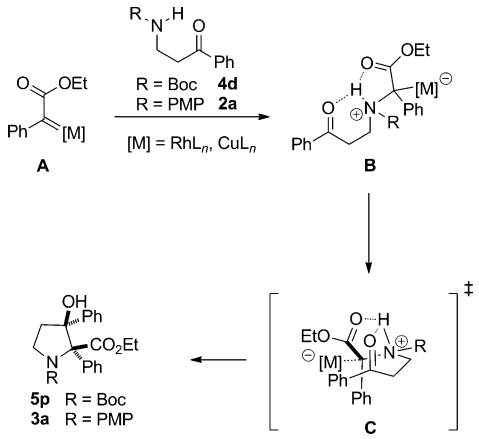
Scheme 4. Rhodium(II)-catalyzed synthesis of highly substituted pyrrolidines.



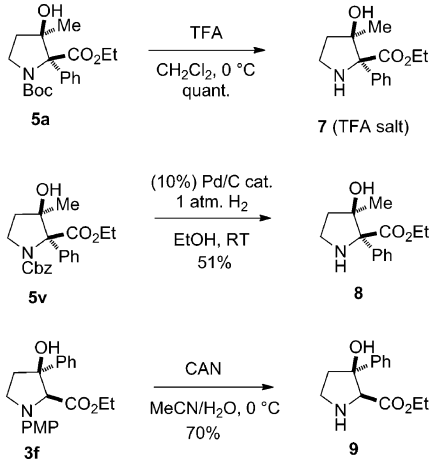
Scheme 5. Control reactions and retro-aldol ring-opening reaction of pyrrolidine **5a** to aminoketone **6**.

view that the N–H insertion of rhodium metallocarbenes into carbamates occurs by 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 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 ketocarbamates. Overall, this method enables the highly stereoselective 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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[1] a) C. Bhat, S. G. Tilve, *RSC Adv.* **2014**, *4*, 5405 – 5452; b) J. P. Michael, *Nat. Prod. Rep.* **1999**, *16*, 675 – 696.

[2] M. Yamazaki, E. Okuyama, M. Kobayashi, H. Inoue, *Tetrahedron Lett.* **1981**, *22*, 135 – 136.

[3] R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed.* **2003**, *42*, 355 – 357; *Angew. Chem.* **2003**, *115*, 369 – 371.

[4] M. G. Moloney, *Nat. Prod. Rep.* **2002**, *19*, 597 – 616.

[5] M.-Y. Han, J.-Y. Jia, W. Wang, *Tetrahedron Lett.* **2014**, *55*, 784 – 794.

[6] G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484 – 4517.

[7] a) X. Han, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2006**, *45*, 1747 – 1749; *Angew. Chem.* **2006**, *118*, 1779 – 1781; b) K. D. Hesp, M. Stradiotto, *Org. Lett.* **2009**, *11*, 1449 – 1452; c) Z. Liu, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 1570 – 1571.

[8] a) A. Feula, S. S. Dhillon, R. Byravan, M. Sangha, R. Ebanks, M. A. Hama Salih, N. Spencer, L. Male, I. Magyary, W.-P. Deng, F. Muller, J. S. Fossey, *Org. Biomol. Chem.* **2013**, *11*, 5083 – 5093; b) M. C. Marcotullio, V. Campagna, S. Sternativo, F. Costantino, M. Curini, *Synthesis* **2006**, 2760 – 2766.

[9] a) Y. Terada, M. Arisawa, A. Nishida, *Angew. Chem. Int. Ed.* **2004**, *43*, 4063 – 4067; *Angew. Chem.* **2004**, *116*, 4155 – 4159; b) W. Rao, S. N. Berry, P. W. H. Chan, *Chem. Eur. J.* **2014**, *20*, 13174 – 13180.

[10] a) A. C. B. Burtoloso, R. M. P. Dias, B. Bernardim, *Acc. Chem. Res.* **2015**, *48*, 921 – 934; b) F. A. Davis, B. Yang, J. Deng, *J. Org. Chem.* **2003**, *68*, 5147 – 5152; c) F. A. Davis, T. Fang, R. Goswami, *Org. Lett.* **2002**, *4*, 1599 – 1602; d) I. Rodríguez, M. I. Calaza, A. I. Jiménez, C. Cativiela, *New J. Chem.* **2015**, *39*, 3310 – 3318; e) Q.-H. Deng, H.-W. Xu, A. W.-H. Yuen, Z.-J. Xu, C.-M. Che, *Org. Lett.* **2008**, *10*, 1529 – 1532; f) C. Jing, D. Xing, Y. Qian, T. Shi, Y. Zhao, W. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 9289 – 9292; *Angew. Chem.* **2013**, *125*, 9459 – 9462; g) C. Jing, D. Xing, W. Hu, *Chem. Commun.* **2014**, *50*, 951 – 953; h) L. Jiang, R. Xu, Z. Kang, Y. Feng, F. Sun, W. Hu, *J. Org. Chem.* **2014**, *79*, 8440 – 8446; i) J. J. Medvedev, O. S. Galkina, A. A. Klinkova, D. S. Giera, L. Hennig, C. Schneider, V. A. Nikolaev, *Org. Biomol. Chem.* **2015**, *13*, 2640 – 2651.

[11] a) A. R. Reddy, C.-Y. Zhou, Z. Guo, J. Wei, C.-M. Che, *Angew. Chem. Int. Ed.* **2014**, *53*, 14175 – 14180; *Angew. Chem.* **2014**, *126*, 14399 – 14404; b) C. J. Hayes, A. E. Sherlock, M. P. Green, C. Wilson, A. J. Blake, M. D. Selby, J. C. Prodger, *J. Org. Chem.* **2008**, *73*, 2041 – 2051.

[12] K. Liu, C. Zhu, J. Min, S. Peng, G. Xu, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 12962 – 12967; *Angew. Chem.* **2015**, *127*, 13154 – 13159.

[13] During the preparation of this manuscript, the following report was published: C. Jing, D. Xing, L. Gao, J. Li, W. Hu, *Chem. Eur. J.* **2015**, *21*, 19202 – 19207.

[14] S. M. Nicolle, W. Lewis, C. J. Hayes, C. J. Moody, *Angew. Chem. Int. Ed.* **2015**, *54*, 8485 – 8489; *Angew. Chem.* **2015**, *127*, 8605 – 8609.

[15] For examples of *N*-PMP cleavage under oxidative conditions, see: a) D. R. Kronenthal, C. Y. Han, M. K. Taylor, *J. Org. Chem.* **1982**, *47*, 2765 – 2768; b) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, P. L. Alsters, F. L. van Delft, F. P. J. T. Rutjes, *Tetrahedron Lett.* **2006**, *47*, 8109 – 8113.

[16] a) N. Ikota, N. Takamura, S. D. Young, B. Ganem, *Tetrahedron Lett.* **1981**, *22*, 4163 – 4166; b) D. F. Taber, R. J. Herr, S. K. Pack, J. M. Geremia, *J. Org. Chem.* **1996**, *61*, 2908 – 2910.

[17] a) I. Aviv, Z. Gross, *Synlett* **2006**, 951 – 953; b) I. Aviv, Z. Gross, *Chem. Eur. J.* **2008**, *14*, 3995 – 4005; c) L. K. Baumann, H. M. Mbuvi, G. Du, L. K. Woo, *Organometallics* **2007**, *26*, 3995 – 4002.

[18] C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378 – 15379.

[19] A rotameric mixture was observed by ^{1}H NMR spectroscopy of the compound in deuterated chloroform at room temperature. Partial coalescence was observed in DMSO at 90 °C. Confirmation of the *cis* pyrrolidine configuration was initially obtained from NOESY experiments.

[20] a) D. Gillingham, N. Fei, *Chem. Soc. Rev.* **2013**, *42*, 4918 – 4931; b) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981 – 10080.

[21] J. Jiang, H.-D. Xu, J.-B. Xi, B.-Y. Ren, F.-P. Lv, X. Guo, L.-Q. Jiang, Z.-Y. Zhang, W. Hu, *J. Am. Chem. Soc.* **2011**, *133*, 8428 – 8431.

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