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Alexandre Jean, Jérôme Blanchet, Jacques Rouden, Jacques Maddaluno,
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COMMUNICATION

Stereoselective access to heteroarylmethylene-substituted pyrrolidines: fully organocatalytic Mannich–hydroamination reactions†

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Alexandre Jean,^{ab} Jérôme Blanchet,^{*a} Jacques Rouden,^a Jacques Maddaluno^b and Michaël De Paolis^{*b}

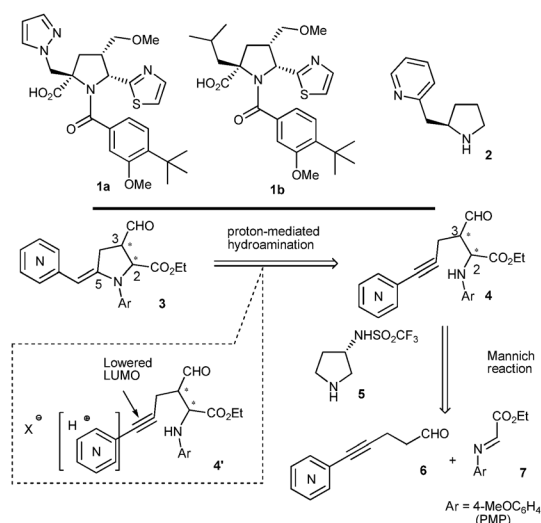
A one-pot sequence of organocatalytic transformations delivers heteroarylmethylene-substituted pyrrolidines with high stereo- and enantioselectivity. A Mannich coupling of *N*-heteroarylalkyne aldehydes with aldimine and an original metal-free hydroamination of the resulting adducts are the key transformations of the process delivering highly functionalized molecules with high potential for synthetic applications.

Due to their frequent occurrence in natural products, bioactive molecules and catalysts, the synthesis of substituted pyrrolidines is a dynamic field of investigation.¹ As illustrated by pyrrolidines **1a–b** and organocatalyst **2**, a particular class of pyrrolidines is the α -substituted *N*-heteroaryl methyl system (Scheme 1).² Interestingly, despite the known importance of *N*-heteroaromatic scaffolds in medicinal chemistry, there is a relative absence of organocatalyzed methodologies for the preparation of such pyrrolidines.³ As a possible explanation, basic or acidic *N*-heteroaromatic decorations are non-innocent groups that can interact with organocatalysts, reagents or products and alter the path and the selectivity of reactions. Thus, despite important developments in the amine-catalyzed Mannich reactions of aldimines, none were reported with aldehydes containing *N*-heteroaryl substituents.⁴

We report herein the first fully organocatalytic strategy for the stereoselective preparation of substituted α -*N*-heteroaryl methylene pyrrolidines. The key and unique features of the strategy are the highly selective Mannich coupling of *N*-heteroarylalkyne aldehydes and the metal-free hydroamination of the resulting Mannich adducts.

From a retrosynthetic perspective, we sought to obtain pyrrolidine scaffold **3** by establishing a disconnection involving the hydroamination of alkyne **4** (Scheme 1). This unprecedented transformation with *N*-heteroarylalkynes was anticipated to take place through the activation of the triple bond by a relay of proton as in **4'**.⁵ Incidentally, the enamine functional group in **3** could offer an entry point for further molecular diversity. Ideally, aminoalkyne **4** would be assembled by Mannich coupling of imine **7** and aldehyde **6** promoted by the recently introduced 3-aminopyrrolidine-based catalyst **5**.⁶ To explore such a strategy, we examined the reaction between 2-pyridyl substituted aldehyde **6a** and imine **7** (Scheme 2).

Interestingly, there is no report of the use of functionalized aldehydes such as **6**. Prepared in two steps from 2-bromopyridine and pent-4-ynol, aldehyde **6a** proved to be rather unstable.⁷ However, taking advantage of the high reactivity of catalyst **5**, the Mannich coupling was attempted at low temperature during the reaction. In line with our previous optimized conditions, the Mannich coupling was carried out



Scheme 1 Biologically relevant pyrrolidines **1a,b** and organocatalyst **2** and a retrosynthetic strategy to obtain α -*N*-heteroarylmethylene pyrrolidines.

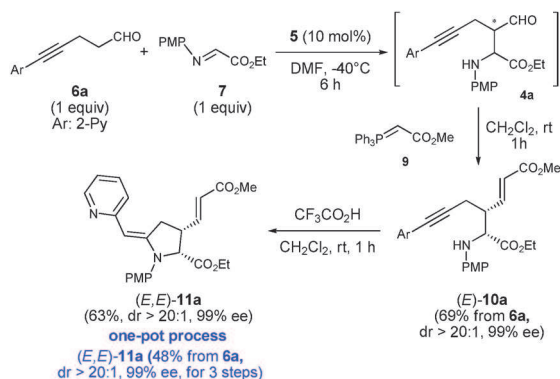
^a Laboratoire de Chimie Moléculaire et Thio-organique, ENSICAEN, Université de Caen, CNRS UMR, 6 boulevard du Marechal Juin, 14050 Caen, France.

E-mail: jerome.blanchet@ensicaen.fr

^b Laboratoire des Fonctions Azotées et Oxygénées Complexes de l'IRCOF, CNRS UMR 6014 & FR 3038, Université et INSA de Rouen, Mont Saint-Aignan, France.

E-mail: michael.depaolis@univ-rouen.fr

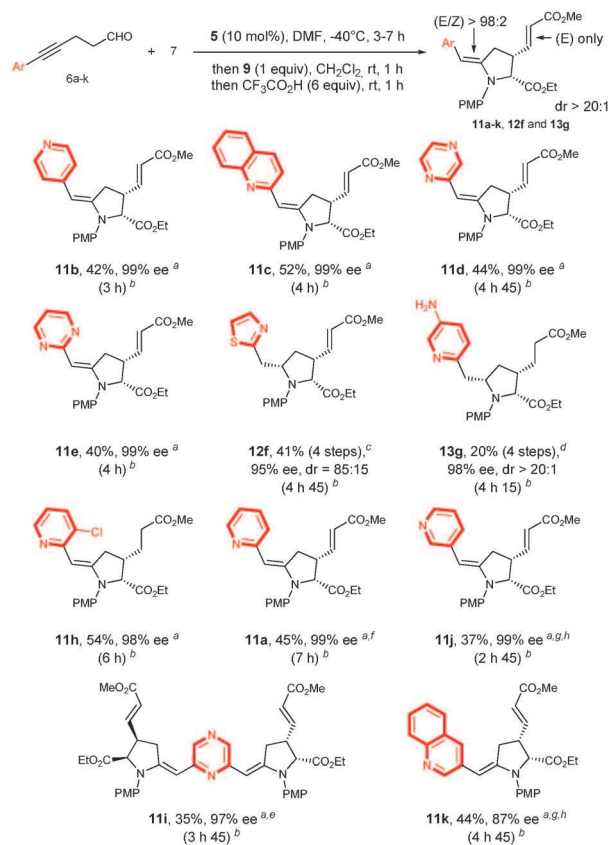
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data, NMR spectra of all products and HPLC traces. CCDC 891357. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc38954a



Scheme 2 Stepwise and one-pot preparation of **11a**.

in DMF at $-40\text{ }^{\circ}\text{C}$ in the presence of 10 mol% of **5**. Notably, a stoichiometric amount of imine **7** and freshly prepared aldehyde **6a** were used. Pleasingly, the reaction proceeded without noticeable degradation or homoaldolisation but the instability of the resulting aldehyde **4a** precluded any isolation of the Mannich product despite attempts to stabilize **4a**. Eventually, we found that one-pot stereoselective Wittig–Horner olefination of **4a** led to the stable acrylate **10a** ($E/Z > 20 : 1$). Hence, despite the sensitivity of aldehydes **6a** and **4a**, the highly functionalized Mannich adduct **10a** was isolated in 69% yield over 2 steps as a single diastereomer ($dr > 20 : 1$, as determined by ^1H NMR analysis of the crude product) and with very high enantioselectivity (99% ee, as determined by chiral HPLC).⁸

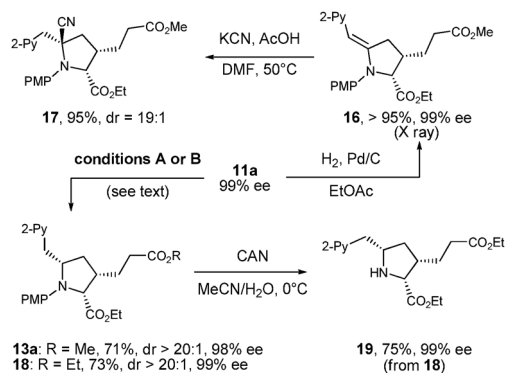
Our efforts next turned to the hydroamination step. To our knowledge, scarce examples of metal-free promoted 5-*exo-dig* hydroamination of alkynes were reported, specifically by Jacobi^{9a} and Cossy.¹⁰ While Jacobi described the 5-*exo-dig* cyclization of amide to alkynes promoted by ammonium salts, the proton-mediated hydroamination of phenylalkyne demonstrated by Cossy required harsh conditions (neat at $150\text{ }^{\circ}\text{C}$) and it is only with β -dialkyl amino compounds exhibiting Thorp–Ingold effects that the 5-*exo-dig* cyclization occurred. In view of the sensitivity toward oxidation or epimerization of our substrates, it was therefore important to assess the feasibility under milder conditions of such a transformation. Hence, alkyne **10a** was treated with trifluoroacetic acid (TFA, 1.1 equiv.) and after 1 h of reaction at rt, we were pleased to isolate the enamine **11a** in 63% yield. Clearly, the protonation of the pyridine ring positively influences the cyclization rate. Two points are worth mentioning: the (*E*)-enamine was formed stereoselectively ($E/Z > 20 : 1$, as determined by ^1H NMR) and no spontaneous oxidation to the corresponding pyrrole was observed. Having demonstrated the stepwise formation of substituted pyrrolidine **11a**, the one-pot process was attempted from **6a** and **7**.¹¹ Hence, after 6 h of reaction, ylide **9** was added to the mixture. After 1 h, TFA was introduced to promote the cyclization furnishing the pyrrolidine **11a** in 48% yield and in similar selectivity to the stepwise process ($dr > 20 : 1$, 99% ee). The scope of the methodology was examined with prepared aldehydes **6a–k** containing various *N*-heteroaromatic groups (Scheme 3, see ESI† for their preparation). Gratifyingly, **6b** decorated with *para*-substituted pyridine provided efficiently **11b** (46%, 99% ee) and **6c**, containing the 2-quinoline scaffold, was converted into **11c** (52%, 98% ee).



Scheme 3 Preparation of pyrrolidines **11a–k**, **12f** and **13g**.^a Isolated yields after 3 steps unless otherwise mentioned. ^b Experiment time for the Mannich coupling. ^c Treatment of the crude with HSiEt_3 , $\text{BF}_3 \cdot \text{OEt}_2$, MeNO_2 , $30\text{ }^{\circ}\text{C}$, 9 d. ^d Hydrogenation of the crude with H_2 , Pd/C, K_2CO_3 , AcOEt , rt, 62 h. ^e Using 20 mol% of **5**. ^f Using 5 mol% of **5**. ^g Obtained from isolated **10j** and **10k** by treatment with $4\text{-MeC}_6\text{H}_4\text{-SO}_3\text{H}$, MeNO_2 , $80\text{ }^{\circ}\text{C}$, 3 h. ^h ee of the corresponding **10j** and **10k**.

To demonstrate that 2-pyrazine and 2-pyrimidine scaffolds are compatible with this chemistry, we next surveyed aldehydes **6d,e** furnishing **11d** (44%, 99% ee) and **11e** (40%, 99% ee). The strategy was also applied to **6f** substituted with a thiazole group. Again, the whole sequence proceeded smoothly furnishing enamine **11f** (not shown) that could not be isolated without degradation. In order to stabilize this adduct, ionic reduction of the enamine was carried out on **11f** (HSiEt_3 , $\text{BF}_3 \cdot \text{OEt}_2$, MeNO_2 , $30\text{ }^{\circ}\text{C}$, 9 d, $dr = 85 : 15$), providing *cis*-**12f** (41%, 95% ee) as the major isomer. The sequence was next explored with electron deficient pyridines **6g** (Ar = 3- NO_2 -2- $\text{C}_5\text{H}_3\text{N}$) and **6h** (Ar = 3- Cl -2- $\text{C}_5\text{H}_3\text{N}$) for which the proton mediated cyclization could have been more challenging. With **6g**, the process occurred smoothly delivering **11g** (not shown) for which the reduction (H_2 , Pd/C, K_2CO_3 , AcOEt , $dr > 20 : 1$) was also required to isolate pyrrolidine **13g** (20% for 4 steps, 98% ee) as the only isomer while 3-chloro-2-pyridine pyrrolidine **11h** was efficiently obtained from **6h** in 54% yield and 98% ee.

We then wished to investigate the methodology on C_2 -symmetrical dialdehyde **6i** containing the 2,6-pyrazine core. Remarkably, bis-pyrrolidine **11i** was obtained as the only isomer in 35% yield and 97% ee (20 mol% of **5** were used). Moreover, the Mannich reaction of aldehyde **6a** was conducted



Scheme 4 Synthetic transformations of **11a**.

in the presence of 5 mol% of catalyst **5** without altering the enantioselectivity (99% ee).

Finally, aldehyde containing a *meta*-substituted pyridine scaffold such as **6j** was evaluated. While the Mannich–Wittig sequence proceeded as usual enabling the preparation of alkyne **10j** (69%, 99% ee), the proton-mediated cyclization required harsher reaction parameters (4-MeC₆H₄SO₃H, MeNO₂, 80 °C, 3 h) than the *ortho*- or the *para*-pyridine substrates and was therefore carried out in a stepwise fashion to furnish **11j** (54%). Similarly, the 3-quinoline substituted aldehyde **6k** was converted to **10k** (65%, 87% ee) which was cyclized into **11k** (68%) according to the same procedure. Despite being much less stable than **11a**, pyrrolidines **11j** and **11k** were isolated and characterized. The cyclization of substrates containing *meta*-*N*-heteroaromatic groups was then demonstrated, broadening further the scope of the strategy.

In summary, the methodology provided pyrrolidines **11a–k**, **12f** and **13g** with excellent ee's (87–99%) and dr (>20 : 1) values. In every case, the (*E*)-configuration of the enamine was exclusively observed. The overall yields (20–54%) remain synthetically useful considering that at least three steps are taking place in the same flask from readily available reagents.

As illustrated in Scheme 4, the versatility of the molecular scaffold **11a** was demonstrated through synthetic transformations. On the one hand, the selective reduction of the α,β -unsaturated ester (H₂, Pd/C, AcOEt) furnished enamine **16** (>95%, 99% ee) on which X-ray crystallographic analysis was performed.¹² Next, diastereoselective Strecker reaction of **16** delivered amino nitrile **17** (95%, dr = 19 : 1). On the other hand, the simultaneous hydrogenation of α,β -unsaturated ester and enamine moieties was carried out in AcOEt to provide **13a** (H₂, Pd/C, K₂CO₃, 18 d, conditions A) in good yield (71%, 98% ee) or in EtOH for shorter reaction time (23 h). Under these conditions (H₂, Pd/C, K₂CO₃, conditions B), the transesterification of the methyl ester occurred simultaneously to yield **18** (74%, 99% ee) as the sole isomer. Then, removal of the PMP group proceeded by treatment with CAN ((NH₄)₂Ce(NO₃)₆) furnishing **19** (75%, 99% ee).

In conclusion, the first one-pot process for the highly selective preparation of *N*-heteroarylmethylene-substituted pyrrolidines, for numerous applications both in medicinal chemistry and asymmetric catalysis, is presented. One of the pivotal features of the strategy is the highly selective Mannich coupling of functionalized aldehydes containing various basic *N*-heteroaromatic groups

which adds a new piece to the organocatalytic puzzle. The second synthetic input is the proton-mediated hydroamination of aminoalkyne connected to *ortho*-, *para*- and *meta*-substituted *N*-heteroaromatic substrates, unveiling an original approach to pyrrolidines containing these versatile scaffolds. Importantly, the whole sequence takes place sequentially in a single flask, is metal-free, employs readily available catalysts and reagents, and proceeds with excellent ee values.

Notes and references

- For recent catalytic enantioselective synthesis of pyrrolidines, see: (a) J. E. Redford, R. I. McDonald, M. L. Rigby, J. D. Wiensch and S. S. Stahl, *Org. Lett.*, 2012, **14**, 1242; (b) R. Jana, T. P. Pathak, K. H. Jensen and M. S. Sigman, *Org. Lett.*, 2012, **14**, 4074; (c) J. Hernández-Toribio, S. Padilla, J. Adrio and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2012, **51**, 8854; (d) N. T. Jui, J. A. O. Garber, F. G. Finelli and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2012, **134**, 11400; (e) S. Reborado, E. Reyes, J. L. Vicario, D. Badía, L. Carrillo, A. de Cózar and F. P. Cossío, *Chem.–Eur. J.*, 2012, **18**, 7179; (f) B. M. Trost and S. M. Silverman, *J. Am. Chem. Soc.*, 2012, **134**, 4941; (g) X. Zhang, T. J. Emge and K. C. Hultsch, *Angew. Chem., Int. Ed.*, 2012, **51**, 394; (h) I. Kumar, N. A. Mir, V. K. Gupta and Rajnikant, *Chem. Commun.*, 2012, **48**, 6975.
- (a) M. J. Slater, E. M. Amphlett, D. M. Andrews, G. Bravi, G. Burton, A. G. Cheasty, J. A. Corfield, M. R. Ellis, R. H. Fenwick, S. Fernandes, R. Guidetti, D. Haigh, C. D. Hartley, P. D. Howes, D. L. Jackson, R. L. Jarvest, V. L. H. Lovegrove, K. J. Medhurst, N. R. Parry, H. Price, P. Shah, O. M. P. Singh, R. Stocker, P. Thommes, C. Wilkinson and A. Wonacott, *J. Med. Chem.*, 2007, **50**, 897; (b) T. Ishii, S. Fujioka, Y. Sekiguchi and H. Kotsuki, *J. Am. Chem. Soc.*, 2004, **126**, 9558.
- For racemic synthesis of *N*-heteroaryl substituted pyrrolidines see (a) M. R. Chaulagain and Z. D. Aron, *J. Org. Chem.*, 2010, **75**, 8271; (b) K. Gräbe, B. Zwafelink and S. Doye, *Eur. J. Org. Chem.*, 2009, 5565.
- For a review on the field, see: (a) S. Hoekman, J. M. M. Verkade and F. P. J. T. Rutjes, in *Enantioselective Organocatalyzed Reactions II*, ed. R. Mahrwald, Springer, Netherlands, 2011, p. 343. For recent contributions, see: (b) T. Kano, S. Song, Y. Kubota and K. Maruoka, *Angew. Chem., Int. Ed.*, 2012, **51**, 1191; (c) S. A. Moteki, J. Han, S. Arimitsu, M. Akakura, K. Nakayama and K. Maruoka, *Angew. Chem., Int. Ed.*, 2012, **51**, 1187; (d) T. Kano, R. Sakamoto, M. Akakura and K. Maruoka, *J. Am. Chem. Soc.*, 2012, **134**, 7516; (e) M. R. Monaco, P. Renzi, D. M. Scarpino Schietroma and M. Bella, *Org. Lett.*, 2011, **13**, 4546. See also ref. 7 and; (f) J. W. Yang, C. Chandler, M. Stadler, D. Kampen and B. List, *Nature*, 2008, **452**, 453–455; (g) A. Córdova, S.-I. Watanabe, F. Tanaka, W. Notz and C. F. Barbas III, *J. Am. Chem. Soc.*, 2002, **124**, 1866.
- (a) For a recent review on hydroamination, see: T. E. Müller, K. C. Hultsch, M. Yus, F. Foubelo and M. Tada, *Chem. Rev.*, 2008, **108**, 3795(b) An unwanted acid-mediated cycloetherification of 6-alkynylpurines was previously reported: T. C. Berg, L.-L. Gundersen, A. B. Eriksen and K. E. Malterud, *Eur. J. Org. Chem.*, 2005, 4988.
- (a) M. Pouliquen, J. Blanchet, M.-C. Lasne and J. Rouden, *Org. Lett.*, 2008, **10**, 1029; (b) T. Kano, Y. Hato, A. Yamamoto and K. Maruoka, *Tetrahedron*, 2008, **64**, 1197; (c) H. Zhang, S. Mitsumori, N. Utsumi, M. Imai, N. Garcia-Delgado, M. Mifsud, K. Albertshofer, P. H.-Y. Cheong, K. N. Houk, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2008, **130**, 875.
- The Sonogashira coupling of 2-bromopyridine and pent-4-ynol followed by oxidation of the resulting alcohol **8a** yielded **6a** (see ESI† for details).
- The absolute configuration was deduced from our previous study (ref. 6a).
- (a) P. A. Jacobi and S. Rajeswari, *Tetrahedron Lett.*, 1992, **33**, 6231; (b) K. Hiroya, R. Jouka, M. Kameda, A. Yasuhara and T. Sakamoto, *Tetrahedron*, 2001, **57**, 9697.
- (a) J. Cossy, D. Belotti, V. Bellosta and C. Boggio, *Tetrahedron Lett.*, 1997, **38**, 2677; (b) J. Cossy and D. Belotti, *Synlett*, 1997, 1249.
- C. Vaxelaire, P. Winter and M. Christmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 3605.
- See ESI† for representation. CCDC 891357 (**16**) contains the supplementary crystallographic data for this paper.