CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Organocatalytic Stereoconvergent Synthesis of α-CF3 Amides; Triketopiperazines and Their Heterocyclic Metamorphosis

Authors: Nigel Simon Simpkins, Robert Foster, Eva Lenz, and Darren Stead

To be cited as: *Chem. Eur. J.* 10.1002/chem.201701548

Link to VoR: http://dx.doi.org/10.1002/chem.201701548

Supported by
ACES

WILEY-VCH

10.1002/chem.201701548

WILEY-VCH

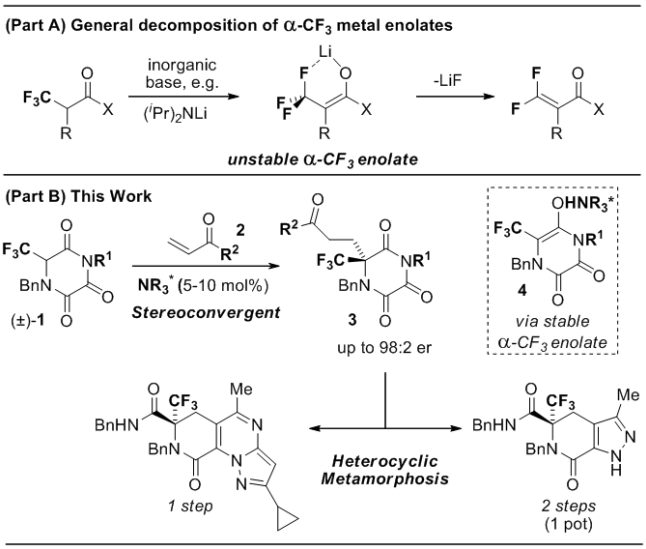
COMMUNICATION

Organocatalytic Stereoconvergent Synthesis of α-CF_3 Amides; Triketopiperazines and Their Heterocyclic Metamorphosis

Robert W. Foster,*[a] Eva N. Lenz,[a] Nigel S. Simpkins,*[b] and Darren Stead*[a]

Abstract: The highly enantioselective alkylation of α-CF_3 enolates, generated from triketopiperazines, has been accomplished through use of a bifunctional thiourea organocatalyst to facilitate 1,4-addition to varied enone acceptors. On treatment with appropriate nitrogen nucleophiles, the chiral triketopiperazine products undergo a metamorphosis, to provide novel fused heterocyclic lactams, such as extended pyrazolopyrimidines.

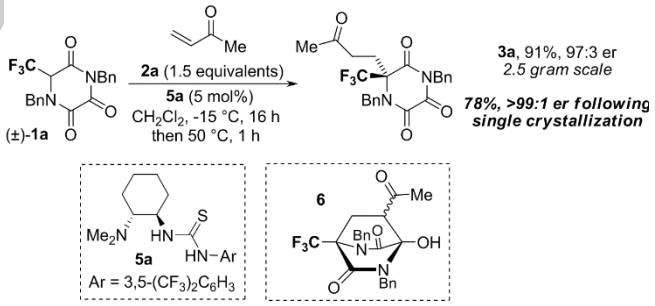
The selective incorporation of fluorine within heterocyclic compounds is a valuable strategy in drug discovery, most notably for tuning the pharmacokinetic properties of bio-active compounds in lead optimization.[1] However, the polar nature of the C-F bond that makes fluorine so valuable in pharmacology can make the synthesis and manipulation of fluorinated compounds particularly challenging.[2] An important example is the general instability of α-CF_3 carbanions, which presents a major obstacle in the synthesis of fluorinated building-blocks.[3]



Scheme 1. α-CF_3 Enolates and this work.

We were interested in the enantioselective substitution of prochiral enolates derived from α-CF_3 carbonyl compounds.[4] However, the synthetic application of α-CF_3 enolates has been limited by facile beta-fluoride elimination (Scheme 1, Part A).[5] While a number of approaches have been developed to exploit α-CF_3 enolates,[6] these typically depend on the pre-formation of titanium, silicon or boron enolates using stoichiometric reagents and bases. A more attractive approach is catalytic enolate generation,[7] but achieving this with stereocontrol is a major challenge. To date the only enantioselective method reported for the transformation of α-CF_3 enolates is the copper(II)-catalyzed Mannich-type reaction of α-CF_3 7-azaindoline acetamides and *N*-Boc imines developed by Kumagai and Shibasaki.[8]

Herein we report the first use of an amine base[9] for the catalytic generation and reaction of α-CF_3 enolates through the stereoconvergent reaction of triketopiperazines (±)-**1** (Scheme 1, Part B). We hypothesized that by switching from an inorganic base to an amine base, and by exploiting the resonance-stabilized nature of triketopiperazine enolates, that enolate **4** would be stable to fluoride elimination. A stabilized enolate would allow for an organocatalytic, enantioselective 1,4-addition reaction with enones to give piperazines **3**.[10] Further to this, we recognized the potential for the rapid transformation of these products into polar heterocyclic scaffolds by a rearrangement process that we have termed heterocyclic metamorphosis.



Scheme 2. Optimized organocatalytic 1,4-addition. Enantiomeric ratio (er) determined by chiral supercritical fluid chromatography (SFC).

The 1,4-addition of triketopiperazine (±)-**1a** and methyl vinyl ketone **2a** was investigated and, following a screen of organocatalytic bases and reaction conditions [see Supporting Information], it was found that using commercially sourced thiourea catalyst[11] **5a** in CH_2Cl_2 at –15 °C gave 1,4-addition product **3a** with optimal yield and enantiocontrol. Crucially no evidence of fluoride elimination was observed. It was found that quenching the reaction at –15 °C gave a mixture of 1,4-addition product **3a** and bridged isomer **6** (as a mixture of diastereoisomers). We suspected that **6** was an intermediate in

[a] Dr R. W. Foster, Dr E. M. Lenz, Dr D. Stead,
Oncology, Innovative Medicines and Early Development,
AstraZeneca
Darwin Building, 310 Cambridge Science Park, UK, CB4 0WG
E-mail: robert.foster1@astrazeneca.com
[b] Professor Dr N. S. Simpkins
School of Chemistry
University of Birmingham
Birmingham, UK, B15 2TT
E-mail: n.simpkins@bham.ac.uk

Supporting information for this article is given via a link at the end of the document.

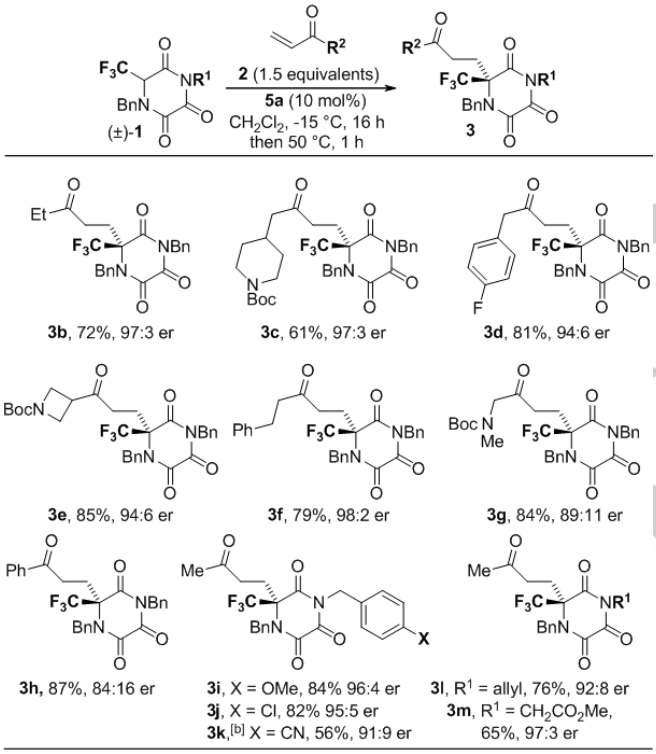
10.1002/chem.201701548
WILEY-VCH

COMMUNICATION

the formation of **3a** and found that the reaction could be driven to provide **3a** exclusively by warming the reaction mixture to 50 °C once triketopiperazine (±)-**1a** was consumed. Using this approach, 1,4-addition product **3a** was isolated in 91% yield and 97:3 enantiomeric ratio (er) on a 2.5 gram scale. A single crystallization improved the enantiopurity of **3a** to >99:1 er (78% overall yield) and the absolute stereochemistry was determined by X-ray diffraction crystallography.[12]

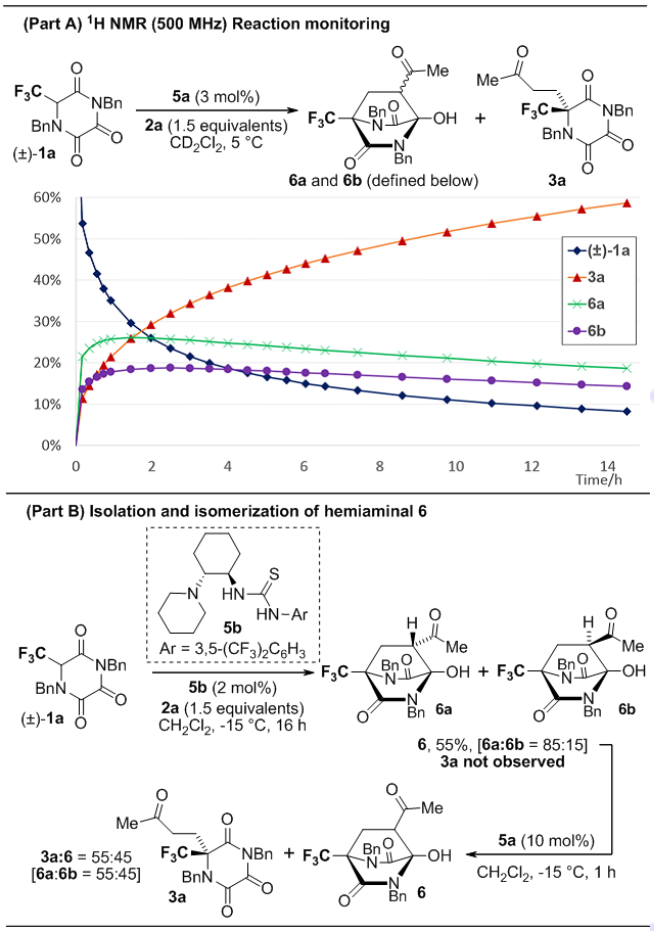
These conditions were used with a variety of enones **2** to give the corresponding 1,4-addition products **3b-h** in 61-87% yield (Table 1). The reaction tolerated a diverse selection of substituents including an *N*-Boc azetidine (**3e**, 85%, 94:6 er). The reaction conditions were also effective with a number of different triketopiperazines **3i-m**, with products isolated in 56-84% yields. It was possible to incorporate non-benzylic substituents on the imide nitrogen position, with methyl ester **3m** isolated in 65% yield and 97:3 er. The use of *trans*-chalcone as an electrophile was also explored but this resulted in no reaction.

Table 1. Organocatalytic 1,4-addition substrate scope.[a]



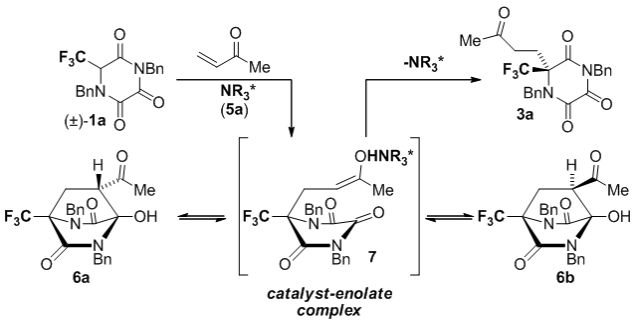
[a] Enantiomeric ratio (er) determined by chiral supercritical fluid chromatography (SFC). [b] Reaction heated at 50 °C for an additional 23 h.

^{1}H NMR reaction monitoring provided more detail on the role of bridged hemiaminal **6** in the formation of triketopiperazine **3a** (Scheme 3, Part A). This experiment showed the rapid formation and subsequent gradual consumption of diastereoisomeric **6a** and **6b** and the slower formation of triketopiperazine **3a**, consistent with **6** being an intermediate in the formation of **3a**. Reaction conditions were developed in order to isolate **6** (Scheme 3, Part B). It was found that substituting dimethylamine catalyst **5a** by piperidine analogue **5b**, gave hemiaminal **6** (55% yield, **6a**:**6b** = 85:15), with no formation of **3a**. Subjecting a purified sample of **6** to catalyst **5a** under typical reaction conditions for 1 hour resulted in the formation of triketopiperazine **3a,** confirming that **6** was an intermediate of **3a**.



Scheme 3. Mechanistic investigations.

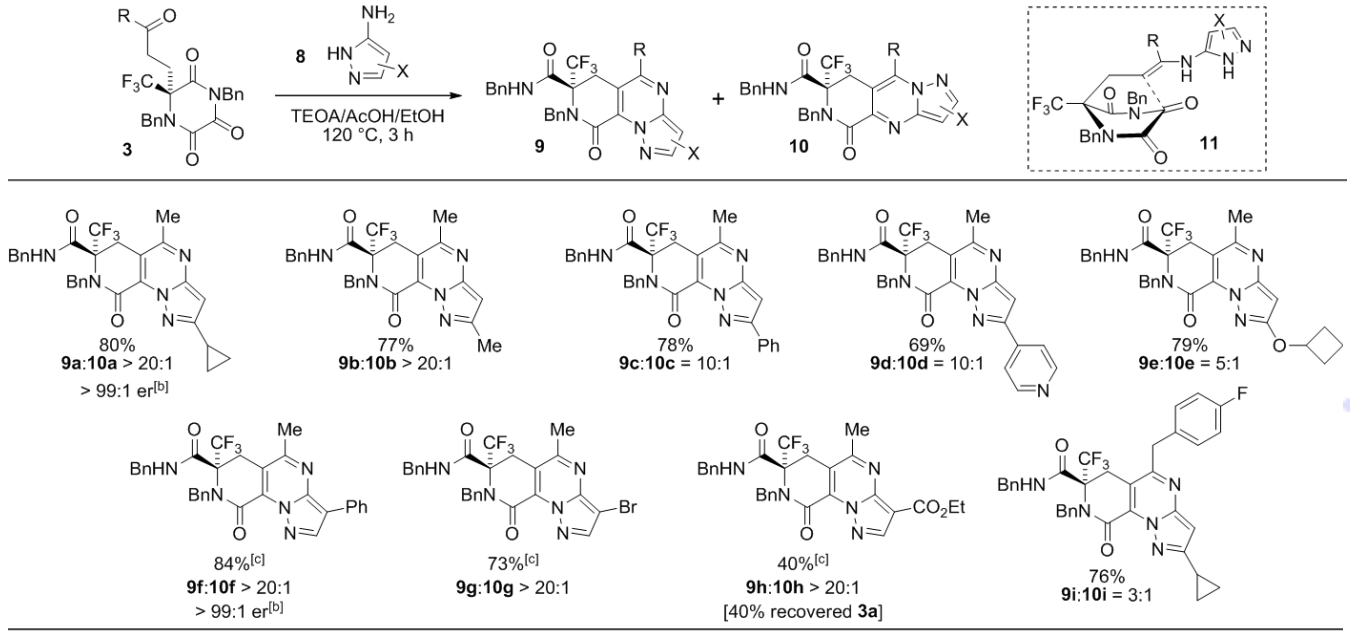
Taken together, these observations are consistent with a reaction pathway that starts with the catalyst-controlled 1,4-addition of the enone to give a catalyst-enolate complex **7**, which rapidly undergoes ring closure to give bridged hemiaminal **6** (Scheme 4). The evidence from the mechanistic studies indicated that this ring closure is reversible, and that enolate-catalyst complex **7** is regenerated under the reaction conditions. Complex **7** is ultimately able to undergo a keto-enol tautomerism and catalyst dissociation to give formal 1,4-addition product **3a**.



Scheme 4. Proposed mechanism.

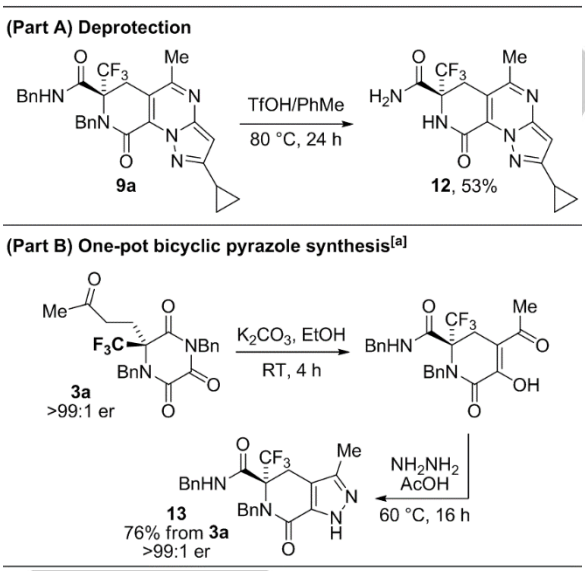
10.1002/chem.201701548

Table 2. Regioselective tricyclic pyrazolopyrimidine synthesis.[a]



[a] Reagents and conditions: 2.0 equivalents **8**, 8:2:1 EtOH:TEOA:AcOH (0.2 M), microwave reactor. Ratio **9:10** determined by ^{1}H NMR analysis of crude product (500 MHz). [b] Enantiomeric ratio (er) determined by chiral SFC. Reaction used crystallized **3a** (er >99:1). [c] 12 h Reaction time.

With an efficient route to α-CF_3 triketopiperazines in hand, we investigated their metamorphosis into polar semi-saturated heterocycles with properties suitable for use in drug discovery. Pyrazolopyrimidines are a class of *N*-heterocyclic compounds that have been widely exemplified in the development of pharmaceutical agents,[13] including a marketed insomnia therapy.[14] It was postulated that condensing the pendant ketone of **3** with 3-aminopyrazole **8** could afford an enamine-mediated rearrangement (*via* intermediate **11**, Table 2) to give a hemiaminal which could then collapse to an α-keto amide, with aromatization yielding tricyclic pyrazolopyrimidines **9**.[15] Conditions were developed for the synthesis of pyrimidine **9a** and it was found that both acetic acid and triethyl orthoacetate (TEOA) were beneficial in minimizing formation of regioisomer **10a** [see Supporting Information]. Using this approach, pyrimidine **9a** was isolated in 80% yield (**9a**:**10a** >20:1) on a 500 mg scale without racemization (er >99:1). This reaction of triketopiperazine **3a** was effective with a range of 3-aminopyrazoles **8**, with pyrimidines **9a**-**9h** isolated in 40-84% yield, typically with good regiocontrol. The reaction was extended beyond methyl ketone **3a**, with triketopiperazine **3d** yielding pyrimidine in 76% yield (**9i**:**10i** = 3:1).



Scheme 5. Deprotection and pyrazole synthesis. [a] Determined by chiral SFC.

The deprotection of the pyrazolopyrimidine **9a** was investigated and it was found that trifluoromethanesulfonic acid (TfOH) efficiently cleaved both benzyl groups to give pyrimidine **12** in 53% yield (Scheme 5). The methodology was also extended to bicyclic pyrazole **13**, by employing a base-mediated rearrangement of triketopiperazine **3a**.[16,17] This one-pot operation gave pyrazole **13** in 76% yield, with no loss of enantiopurity (>99:1 er).

In summary, we have reported the organocatalytic enantioselective 1,4-addition of enones and α-CF_3 enolates through use of the triketopiperazine scaffold. Furthermore, it has been demonstrated how this methodology can be used to access a wide variety of medicinally relevant tricyclic pyrazolopyrimidines with both stereo- and regiocontrol.

Acknowledgements

The authors would like to acknowledge Dr Matthew Sanders, Dr Jennifer Kingston, Dr Nichola Davies, Dr Paul Davey and the Centre for Chemical and Materials Analysis in the School of Chemistry at the University of Birmingham for analytical support,

Dr Kevin Blades for initial discussions and AstraZeneca IMED for funding. NSS acknowledges the Royal Society for the award of an Industry Fellowship.

Keywords: organocatalysis • trifluoromethyl • triketopiperazine • pyrimidine

[1] a) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315-8359; b) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422-518.

[2] a) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308-319; b) C. Ni, J. Hu, *Chem. Soc. Rev.* **2016**, *45*, 5441-5454.

[3] K. Uneyama, T. Katagiri, H. Amii, *Acc. Chem. Res*. **2008**, *41*, 817-829.

[4] a) R. Smits, C. D. Cadicamo, K. Burger, B. Koksch, *Chem. Soc. Rev*. **2008**, *37*, 1727–1739; b) C. Caupène, G. Chaume, L. Ricard, T. Brigaud, *Org. Lett.* **2009**, *11*, 209-212; c) K. Morisaki, M. Sawa, J. Nomaguchi, H. Morimoto, Y. Takeuchi, K. Mashima, T. Ohshima, *Chem. Eur. J.* **2013**, *19*, 8417-8420; d) Y. Wu, L. Hu, Z. Li, L. Deng, *Nature* **2015***, 523*, 445-450.

[5] Y. Itoh, M. Yamanaka, K. Mikami, *J. Am. Chem. Soc.* **2004**, *126*, 13174-13175.

[6] a) X. Franck, B. Seon-Meniel, B. Figadère, *Angew. Chem. Int. Ed.* **2006**, *45*, 5174-5176; *Angew. Chem*. **2006**, *118*, 5298-5300; b) T. Shimada, M. Yoshioka, T. Konno, T. Ishihara, T, *Org. Lett.* **2006**, *8*, 1129-1131; c) T. Shimada, M. Yoshioka, T. Konno, T. Ishihara, *Chem. Commun.* **2006**, 3628-3630; d) P. V. Ramachandran, G. Parthasarathy, P. D. Gagare, *Org. Lett.* **2010**, *12*, 4474-4477.

[7] a) N. Shibata, S. Suzuki, T. Furukawa, H. Kawai, E. Tokunaga, Z. Yuan, D. Cahard*, Adv. Synth. Catal.* **2011**, *353*, 2037-2041; b) L. Li, Q. –Y. Chen, Y. Guo, *Chem. Commun*. **2013**, *49*, 8764-8766; c) Y. Guo, X. Zhao, D. Zhang, S. -I. Murahashi, *Angew. Chem. Int. Ed.* **2009**, *48*, 2047-2049; *Angew. Chem*. **2009**, *121*, 2081-2083; d) Q. Wang, F. Huan, H. Shen, J. –C. Xiao, M. Gao, X. Yang, X; S. -I. Murahashi, Q. -U. Chen, Y. Guo, *J. Org. Chem.* **2013**, *78*, 12525-12531.

[8] a) L. Yin, L. Brewitz, N. Kumagai, M. Shibasaki. *J. Am. Chem. Soc.* **2014**, *136*, 17958-17961; b) L. Brewitz, F. A. Arteaga, L. Yin, K. Alagiri, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2015**, *137*, 15929-15939.

[9] a) T. Tatsumi, T. Misaki, T. Sugimura, *Chem. Eur. J.* **2015**, *21*, 18971-18974; b) B. Zhu, R. Lee, J. Li, X. Ye, X. S. –N. Hong, S. Qiu, M. L. Coote, Z. Jiang, *Angew. Chem. Int. Ed.* **2016***, 55*, 1299-1303; *Angew. Chem.* **2016***, 128,* 1321-1325; c) E. Badiola, B. Fiser, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2014**, *136*, 17869-17881.

[10] a) A. Cabanillas, C. D. Davies, L. Male, N. S. Simpkins, *Chem. Sci*. **2015**, *6*, 1350-1354; b) M. Rees, N. S. Simpkins, L. Male, *Org. Lett.* 10.1021/acs.orglett.7b00193; c) T. Y. Liu, R. Li, Q. Chai, J. Long, B. J. Li, Y. Wu, L. S. Ding, Y. C. Chen, *Chem. Eur. J.* **2007**, *13*, 319–327.

[11] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673; b) A. Quintard, D. Cheshmedzhieva, M. M. S. Duque, A. Gaudel-Siri, J. -V. Naubron, Y. Génisson, J. –C. Plaquevent, X. Bugaut, J. Rodriguez, T. Constantieux, *Chem. Eur. J.* **2015**, *21*, 778-790; c) H. Nakamura, C. Tsukano, M. Yasui, S. Yokouchi, M. Igarashi, Y. Takemoto, *Angew. Chem. Int. Ed.* **2015**, *54*, 3136-3139; *Angew. Chem*. **2015**, *127*, 3179–3182.

[12] CCDC 1525778 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[13] a) A. Lippa, P. Czobor, J. Stark, B. Beer, E. Kostakis, M. Gravielle, S. Bandyopadhyay, S. J. Russek, T. T. Gibbs, D. H. Farb, P. Skolnick, *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 7380–7385; b) R. E. Petroski, J. E. Pomeroy, R. Das, H. Bowman, W. Yang, A. P. Chen, A. C. Foster, *J. Pharmacol. Exp. Ther*. **2006**, *317*, 369–377; c) A. Kamal, J. R. Tamboli, V. L. Nayak, S. F. Adil, M. V. P. S. Vishnuvardhan, S. Ramakrishna, *Bioorg. Med. Chem. Lett*. **2013**, *23*, 3208–3215.

[14] R. Elie, E. Ruther, I. Farr, G. Emilien, E. Salinas, *J. Clin. Psychiatry* **1999**, *60*, 536–544.

[15] A more detailed mechanistic proposal can be found in Supporting Information.

[16] N. J. Howe, K. Blades, G. M. Lamont, *Synlett* **2015**, *26*, 228-232.

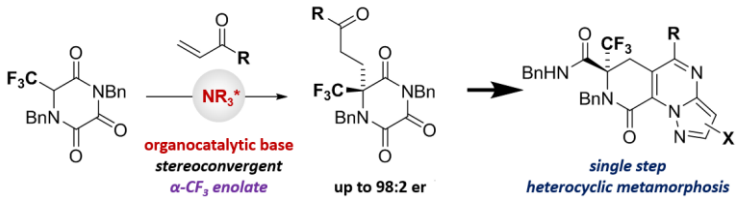
[17] For examples of fused pyrazololactams in medicinal chemistry see; a) D. J. P. Pinto, M. J. Orwat, S. Koch, K. A. Rossi, R. S. Alexander, A. Smallwood, P. C. Wong, A. R. Rendina, J. M. Luettgen, R. M. Knabb, K. He, B. Xin, R. R. Wexler, P. Y. S. Lam, *J. Med. Chem*. **2007**, *50*, 5339-5356; b) A. J. Duplantier, C. J. Andresen, J. B. Cheng, V. L. Cohan, C. Decker, F. M. DiCapua, K. G. Kraus, K. L. Johnson, C. R. Turner, J. P. UmLand, J. W. Watson, R. T. Wester, A. S. Williams, J. A. Williams, *J. Med. Chem.* **1998**, *41*, 2268-2277; c) M. J. Orwat, J. X. Qiao, K. He, A. R. Rendina, J. M. Luettgen, K. A. Rossi, B. Xin, R. M. Knabb, R. R. Wexler, P. Y. S. Lam, D. J. P. Pinto, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3341-3345.

10.1002/chem.201701548

WILEY-VCH

Entry for the Table of Contents

COMMUNICATION



R. W. Foster, E. N. Lenz, N. S. Simpkins* and D. Stead**

Page No. – Page No.
Organocatalytic Stereoconvergent Synthesis of α-CF_3 Amides; Triketopiperazines and Their Heterocyclic Metamorphosis

All about that base:The organocatalytic stereoconvergent synthesis of α-CF_3 amides has been developed. This approach has been used to access a diverse range of enantioenriched triketopiperazine products and a novel reaction mechanism has been elucidated. In addition, an enamine-mediated rearrangement was developed for the regioselective synthesis of enantiopure semi-saturated pyrazolopyrimidines.