CrossMark
click for updates

View Article Online
View Journal

ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: T. Nishimine, H. Taira, S. Mori, O. Matsubara, E. Tokunaga, H. Akiyama, V. Soloshonok and N. Shibata, *Chem. Commun.*, 2016, DOI: 10.1039/C6CC08830A.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the author guidelines.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the ethical guidelines, outlined in our author and reviewer resource centre, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Please do not adjust margins

ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/C6CC08830A

Journal Name

COMMUNICATION

Synthesis of chiral (tetrazolyl)methyl-containing acrylates via silicon-induced organocatalytic kinetic resolution of Morita–Baylis–Hillman fluorides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

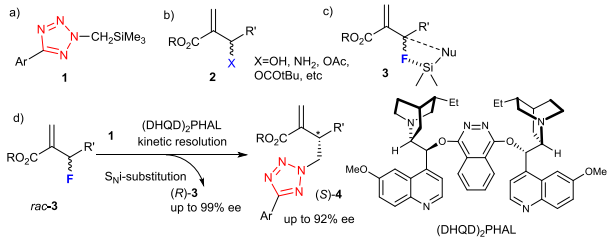
www.rsc.org/

Takayuki Nishimine,[a] Hiromi Taira,[a] Satoru Mori,[a] Okiya Matsubara,[a] Etsuko Tokunaga,[a] Hidehiko Akiyama,[b] Vadim A. Soloshonok,[c] and Norio Shibata*[a]

Reported herein is a new approach for the asymmetric installation of a (tetrazolyl)methyl group via Si/F activation using organocatalytic kinetic resolution of racemic MBH-fluorides.

Tetrazoles are entirely man-made, as this type of compound does not occur naturally.[1] Being originally introduced as an exotic chemical entity, tetrazoles made all the way from a mere curiosity to valuable compounds with numerous practical applications ranging from energetic materials[2] and nano-engineering[3] to the design ofnew generations of organocatalysts[4] and pharmaceuticals.[5] Consequently, the development of new methods for preparation of tetrazole-containing compounds is in extremely high demand in current catalysis and health-care research.[1-5] Bulk of the known methodology affords the structural type in which a tetrazole ring is directly bonded to an aromatic moiety. On the other hand, synthesis of *N*-alkyl-substituted tetrazoles, which show notable bioactivities,[6] is virtually unstudied due to the inherent problem of poor regio-control of the tetrazole ring *N*-alkylation.[7] Thus, only a handful of synthetically useful examples of the regio- and stereo-selective preparation of *N*-alkyl-substituted tetrazoles has been described.[8] One of the potential solutions is the application of 2-[(trimethylsilyl)methyl]-2H-tetrazoles **1** (Scheme 1a).[9] Reagents **1** were reported in 1986 by Ogata,[9a] but only a handful of data is available regarding their properties and reactivity.[9] This is presumably due to the destabilization of the corresponding CH_2 carbanion by the neighboring electron-rich tetrazole ring.

The Morita-Baylis-Hillman (MBH) adducts **2**[10] such as α-methylene-β-hydroxy-carbonyl derivatives (X=OH) or α-methylene-β-amino-carbonyl derivatives (X=NH_2) are highly valuable building blocks in organic synthesis. In particular, MBH-acetates **2** (X=OAc) have received a considerable attention as useful synthetic intermediates for preparation of medicinally relevant compounds as well as complex natural products (Scheme 1b).



Scheme 1 (a) 2-[(trimethylsilyl)methyl]-2H-tetrazoles **1**; (b) Well-known MBH-adducts **2**; (c) Concept of substitution of MBH-fluorides **3**; (d) Synthesis of chiral *N*-alkyl tetrazole acrylates **4** accessible via enantioselective S_Ni substitutions of **3** with **1** (this work)

The reaction of MBH-acetates is based on the $S_{N}2'$ attack of various nucleophiles on the terminal alkene sites. Recently we discovered a new concept for allylic substitution based on the silicon-induced carbon-fluorine (C-F) activation of MBH-fluorides **3** by silylated nucleophiles under metal-free, organocatalytic conditions.[11] In this transformation, the silicon (Si) atom activates the C-F bond of **3** to furnish allylic substituted compounds **4** via the S_Ni substitution mode (Scheme 1c). The key for this transformation is the generation of F^- *in-situ* followed by the *in-situ* generation of unstable carbanions such as the trifluoromethyl anion ($^-CF_3$) and acetylides ($^-C{\equiv}CR$). In this context, we are interested in the application of this C-F bond-cleavage-induced allylic substitution reaction of silylated nucleophiles for the synthesis of previously unknown *N*-alkyl tetrazole acrylates **4** by the reaction of 2-(trimethylsilyl)methyltetrazoles **1** with MBH-fluorides **3**. *In-situ* activation of **1** by *in-situ* generated F^- from **3** *via* S_Ni substitution mode should be suitable for the nucleophilic installation of the unstable methyltetrazole anion.[11c] We disclose herein the first allylic installation of a (tetrazolyl)methyl group to MBH-adducts giving rise to *N*-alkyl tetrazole-acrylates **4** (Scheme 1d). Chiral *N*-alkyl tetrazole-acrylates **4** are obtained by this method in the presence of a cinchona alkaloid catalyst. The asymmetric C-F activation of MBH-fluorides **3** by the Si atom of **1** via kinetic resolution of racemic **3** by S_Ni

[a] Department of Nanopharmaceutical Sciences, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya466-8555, Japan
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Published on 21 December 2016. Downloaded by University of California - San Diego on 21/12/2016 16:37:05.

ChemComm Accepted Manuscript

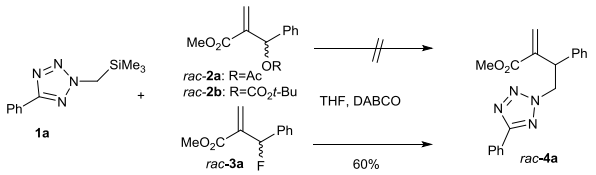
Please do not adjust margins

View Article Online DOI: 10.1039/C6CC09565C

Published on 21 December 2016. Downloaded by University of California - San Diego on 21/12/2016 16:37:05.

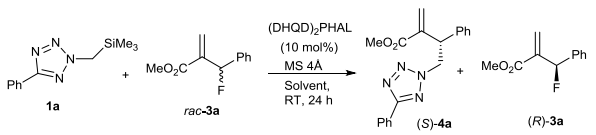
substitution is a key to its success. The products **4** with structural features such as the acrylate moiety and the appendant (tetrazolyl)methyl group were obtained in reasonable, kinetic resolution yields with excellent enantioselectivities of up to 92% ee. These are expected to show antitumor activity from a view point of structural similarity to the reported tetrazole acrylates[12] (See ESI).

Based on the literature data , we started to test the reactivity of 5-phenyl-(trimethylsilyl)methyl-tetrazole (**1a**) towards conventional MBH-acetate **2a** and MBH-carbonate **2b**. As generic reaction conditions, we used THF as a solvent and DABCO as a base (Scheme 2). The reactions were conducted at various temperatures (0—60 °C); however, not even a trace of the desired product was detected in the reaction mixture. Taking advantage of the Si/F activation concept recently discovered by our group,[11,13] MBH-fluoride **3a** was treated with **1a** under the same conditions. In sharp contrast to the MBH adducts **2a**,**b**, the reaction readily took place at 0 °C, giving rise to desired product **4a** with 60% isolated yield. This positive reaction outcome encouraged us to wonder whether the stereochemical outcome of this reaction could be controlled by using a chiral base instead of DABCO.



Scheme 2 Reactivity of MBH acetate **2a**, carbonate **2b** and MBH-fluoride **3a** towards 2-(trimethylsilyl)methyl-tetrazole **1a**.

Table 1 $(DHQD)_2PHAL$-catalyzed reactions of MBH-fluoride **3a** with (trimethylsilyl)methyl-tetrazole **1a**



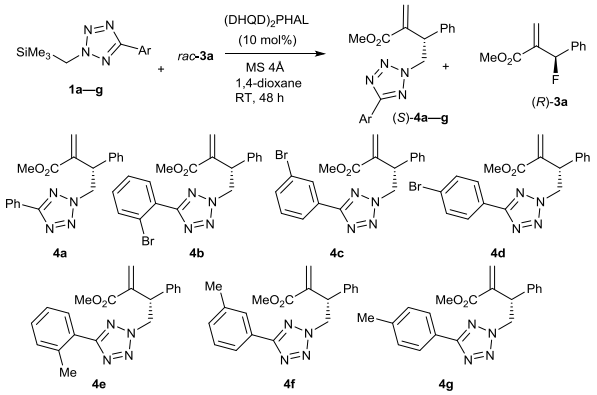
Entry	Solvent	**4a** Yield (%)[a]	Ee (%)[b]
1	THF	< 5[d]	ND
2	DME	12	80
3	1,4-dioxane	51	92
4	CH_2Cl_2	59	80
5[c]	$CHCl_3$	12	89
6	$ClCH_2CH_2Cl$	43	80
7	toluene	< 5[d]	ND

[a]Isolated yield. [b]Determined by chiral HPLC. [c]CCl_3 Adduct was observed. [d]Determined by ^{1}H-NMR.

After a number of experiments using various chiral organic bases (Table S1, in ESI), we found that the excellent level of enantioselectivity in the reaction of MBH-fluoride **3a** with **1a** could be obtained with application of $(DHQD)_2PHAL$ as an organocatalyst. Quite interestingly, the stereochemical outcome of the reactions was unusually sensitive to the reaction solvent. As can be seen from the data presented in Table 1, $(DHQD)_2PHAL$ did not show any catalytic activity in THF (entry 1). On the other hand, the base was efficient in other ether-type solvents, yet, noticeably different activity was observed in dimethoxyethane (DME, entry 2) vs. 1,4-dioxane (entry 3). Remarkably, in both solvents, the enantioselectivity was appreciable, recording 80 and 92% ee, respectively. The application of $(DHQD)_2PHAL$ in a series of chlorinated solvents (entries 4-6) was also successful, but again, with a variable outcome. For example, the highest yield of product (*S*)-**4a** was obtained in those reactions conducted in dichloromethane (CH_2Cl_2) (entry 4), while the best enantioselectivity was observed in chloroform (entry 5). Stranger yet, attempts to use toluene as a solvent (entry 7) were unsuccessful, clearly indicating that medium polarity of the reaction medium is essential for the substitution to take place. Considering these results, we decided to advance with a substrate generality study using 1,4-dioxane (entry 3) as a solvent even though highest yield had been obtained in CH_2Cl_2 (entry 4). The asymmetric induction is supposed to be induced via kinetic resolution[14] of racemic **3a** by S_Ni substitution, thus around 50% yield is considered to be a suitable outcome. An enantio-enriched (*R*)-**3a** was recovered in most cases (entries 2-6).

Thus, to briefly explore the substituent effect on the tetrazole ring in methyl-tetrazole reagents **1**, we selected two series of *o*-, *m*- and *p*-substituted derivatives bearing a bromine atom and a methyl, generically representing moderately bulky electron-withdrawing and –donating groups (Table 2).

Table 2 Substrate generality study of the substitution reactions of 2-(trimethylsilyl)methyl-tetrazoles **1a-g** with MBH-fluoride **3a**.



Entry	**1**	R	**4**	Yield (%) (**4**+**3a**)[a]	Ratio (**4**/**3a**)[b]	Ee (**4**/**3a**) (%)[c]
1	**1a**	Ph	**4a**	74	58/42	92/75
2	**1b**	2-BrC_6H_4	**4b**	64	67/33	82/95
3	**1c**	3-BrC_6H_4	**4c**	47	53/47	90/94
4	**1d**	4-BrC_6H_4	**4d**	67	57/43	90/96
5	**1e**	2-MeC_6H_4	**4e**	72	58/42	90/97
6	**1f**	3-MeC_6H_4	**4f**	83	70/30	90/96
7	**1g**	4-MeC_6H_4	**4g**	89	71/29	90/99

[a]Isolated yield. [b]Calculated by isolated yields. [c]Determined by HPLC.

The treatment of **1** with **3a** was conducted in the presence of a catalytic amount of $(DHQD)_2PHAL$ in 1,4-dioxane at room temperature and the reaction was stopped after stirring for 48 h. A mixture of products **4** accompanied by the recovered **3a** was obtained in 47—89% yields, and the ratio of **4**/**3a** were calculated after the isolation of **4**/**3a**. To ensure the accuracy of the reported ee values, we conducted SDE[15] tests via achiral chromatography and sublimation. Using compound **4a** as a model, we found that the magnitude of SDE was insignificant and did not interfere with the accurate determination of the stereochemical outcome. The major conclusion revealed by these experiments is the consistently excellent level of enantioselectivity of both products **4** (82—92% ee) and recovered **3** (75—99% ee), practically not influenced by the electronic nature or by the position of the substituents on the aromatic ring in 5-phenyl derivatives **1**. On the other hand, the total yields and ratios of product and recovered starting material **4**/**3** were

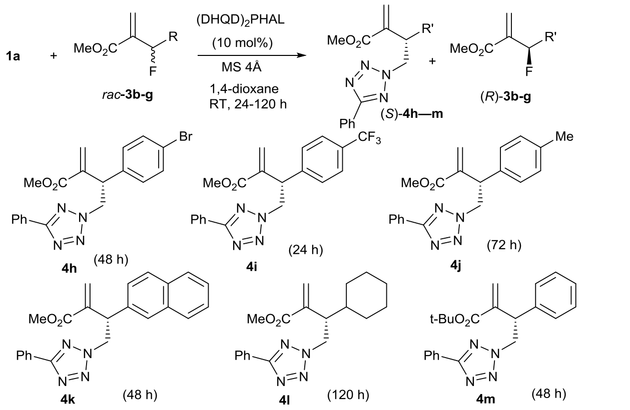
ChemComm Accepted Manuscript

 This journal is © The Royal Society of Chemistry 20xx

variable, but without any clear substituent-dependent trends or patterns. This observation led us to examine the reaction mixtures in detail and subsequent isolation of MBH-fluoride (*R*)-**3a** of exceptionally high enantiomeric purity. Thus, virtually in almost all cases studied, enantiomeric excess of (*R*)-**3a** was greater than that of desired products (*S*)-**4**.

This discovery clearly indicated that we were dealing with a case of kinetic resolution,[14] in which the (*S*)-enantiomer of starting *rac*-**3** was significantly more reactive in the presence of $(DHQD)_2$PHAL than the remaining (*R*)-**3a**. The absolute configuration of **3a** was assigned by chiral HPLC analysis and optical rotation after comparison with the reported data.[11a] Taking advantage of the high crystallinity of derivative **4d**, a single crystal X-ray analysis was performed showing its (*S*) configuration (CCDC1501566). Taking into account the close similarity of spectroscopic, chiroptical and chromatographic properties, all major products **3** and **4** were assigned an (*R*) and (*S*) absolute configuration, respectively.

Table 3 Substrate generality study of the substitution reactions of 2-(trimethylsilyl)methyl-tetrazole **1a** with MBH-fluorides **3**[a]



Entry	3	R	4	Yield (%) (4+3)[b]	Ratio (4/3)[c]	Ee (4/3) (%)[d]
1	**3b**	4-BrC_6H_4	**4h**	77	68/32	86/87
2	**3c**	4-$CF_3C_6H_4$	**4i**	72	64/36	85/90
3	**3d**	4-MeC_6H_4	**4j**	81	46/54	91/87
4	**3e**	2-naphthyl	**4k**	83	59/41	86/90
5	**3f**	cyclohexyl	**4l**	71	39/61	86/48
6[e]	**3g**	Ph	**4m**	88	51/49	87/85

[a]The reaction was carried out in 0.1 M except for entries 5 and 6. Reaction time is shown in parenthesis. [b]Isolated yield. [c]Calculated by isolated yields. [d]Determined by HPLC. [e]*t*-Bu ester **3g** was used instead of methyl ester.

To acquire more experimental data and gain further insight into the reactivity and possible mechanism of this new chemical transformation, we proceeded to perform a second substrate generality study focusing, this time, on the structurally different MBH-fluorides (*rac*)-**3**. The reactions presented in Table 3 were performed under the same conditions as those described in Table 2, using 1,4-dioxane as a solvent and 10% of $(DHQD)_2$PHAL as an organocatalyst. The indicated yields and enantiomeric purity of products **3** and **4** are those of isolated analytically pure compounds. The choice of substrates included examples of phenyl ring-bearing electron-donating and –withdrawing groups, as well as a bulkier naphthyl group. Considering the special role of the aromatic trifluoromethyl group in the design of new pharmaceuticals,[16] preparation of *p*-CF_3-aryl-contaning tetrazole **4i** with 85% ee was particularly encouraging. Among other examples, it is worth noting product **4l**, which contains a *cyclo*-hexane ring in the place of phenyl. One may agree that this case is rather significant indicating that this method is not limited to aromatic compounds and has rather great methodological potential. Furthermore, we were interested to know if the nature of the ester alkyl group plays any role in the stereochemical outcome of these reactions. Thus, the corresponding substitution reaction of CO_2-*t*-Bu containing (*rac*)-**3g** proceeded at a slower rate, when compared with that of the CO_2Me analog, but afforded product **4m** of virtually the same excellent enantiomeric purity.

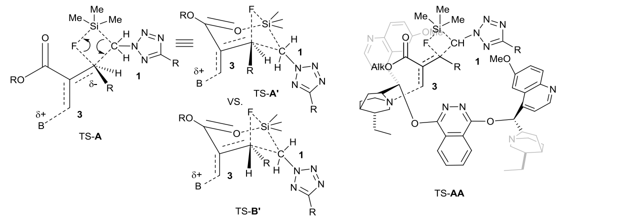


Figure 1 Plausible transition states (TS) **A**, **B** and **AA** accounting for the observed mode of substitution and the stereochemical outcome.

Finally, to account for the observed stereochemical outcome, we propose TS-**A** presented in Figure 1. While a conclusive description of all mechanistic details will require a specially focused investigation, we believe that the data collected in this work and our previous reports on the Si/F activation concept,[11,13] put us in a position to confidently suggest that the present reactions proceed via S_Ni substitution presented by general TS-**A**.[11c] Fully consistent with the literature's data[17] and the observed stereochemical outcome, highly sterically congested four-membered TS-**A** accounts for the determined kinetic resolution process and excellent enantiomeric purity of the corresponding products. To present a better view of the molecular interactions, we depicted TS-**A** in a chair-like form **A'**, which shows two important features: the Si-O coordination, and the pseudo-equatorial position of the stereocontrolling, larger substituent R, corresponding to the (*S*)-enantiomer of starting compounds **3**. Considering an alternative TS-**B'** allowing for the substitution of the opposite enantiomer (*R*)-**3**, one might agree that even though the substituent R is still pseudo-equatorial, it is located underneath the chair-like structure and is engaged in repulsive steric interactions. By contrast, in TS-**A'**, the substituent R is pointing away from any other groups, minimizing any destabilizing interactions. Another important feature of TS-**A** is that the positions of the reacting species are nearly perfectly aligned for activation of the C-F bond to be achieved via simultaneous Si/F and organocatalyst/allylic system interactions. These, in turn, make it possible for the substitution to proceed under mild conditions, without the formation of fully charged intermediates. To further corroborate the suggested mechanistic rationale, we attempted the corresponding reaction using (*R*)-**3a** instead of racemic **3a**. Quite remarkably and at the same time expectedly, no reaction was observed except for slow, gradual decomposition of (*R*)-**3a**. It should be noted that only bis-cinchona alkaloids showed high level of asymmetric induction (Table S1, ESI). We attempted to build TS-**AA** depicting the mode of substrate activation. As it clearly seen from TS-**AA** structure, one of the reactive sites is entirely blocked for the incoming nucleophile **1**, although computation could be required for further discussion. The steric effect of the tetrazolyl groups on the stereochemical outcome could be disregarded since the other non-heteroatom derived nucleophiles also gave similarly high enantioselectivity.[11]

View Article Online
Published on 21 December 2016. Downloaded by University of California - San Diego on 21/12/2016 16:37:05.
ChemComm Accepted Manuscript

View Article Online
DOI: 10.1039/C6CC08830A

Published on 21 December 2016. Downloaded by University of California - San Diego on 21/12/2016 16:37:05.

In summary, the results reported in this communication convincingly demonstrate that the asymmetric allylic installation of a (tetrazolyl)methyl group via Si/F activation under organocatalytic kinetic resolution of racemic MBH-fluorides **3** is a new and viable methodology of high synthetic value. Operationally convenient conditions and excellent enantioselectivity of the key S_Ni-substitution step offer a reliable, straightforward access to the target compounds containing a pharmacophoric (tetrazolyl)methyl group. A preliminary biological study of these structurally novel compounds against U937 cells supports the assumption of their medicinal potential (see Figures S1 and S2, in ESI), and we are currently actively exploring this line of research.

This research is partially supported by the Platform Project for Supporting in Drug Discovery and Life Science Research (Platform for Drug Discovery, Informatics, and Structural Life Science) from the Japan Agency for Medical Research and Development (AMED), the Advanced Catalytic Transformation (ACT-C) from the JST Agency, and the Kobayashi International Foundation. A series of tetrazole reagents **1** are commercially available and they were a gift from FUJIMOTO CHEMICALS CO., LTD.

Notes and references

1 (a) A. Maleki and A. Sarvary, *RSC Adv.* 2015, **5**, 60938–60955. (b) J. Roh, K. Vavrova and A. Hrabalek, *Eur. J. Org. Chem.*, 2012, **27**, 6101. 5 (c) G. I. Koldobskii, Russ. *J. Org. Chem.*, 2006, **42**, 469; (d) W.-K. Su, Z. Hong, W.-G. Shan and X.-X. Zhang, *Eur. J. Org. Chem.* 2006, 2723–2726. e) R. J. Herr, *Bioorg. Med. Chem.*, 2002, **10**, 3379. f) S. J. Wittenberger, *Org. Prep. Proced. Int.*, 1994, **26**, 499. g) H. R. Meier and H. Heimgartner, in *Methoden der Organische Chemie (Houben-Weyl)*, ed. E. Schumann, Georg Thieme. Stuttgart, 1994, vol. E8d, p. 664. h) R. N. Bulter in *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 5, p. 791.

2 (a) P. He, J.-G. Zhang, X. Yin, J.-T. Wu, L. Wu, Z.-N. Zhou and T.-L. Zhang, *Chem. – Eur. J.*, 2016, **22**, 7670–7685. (b) H. Gao and J. M. Shreeve, *Chem. Rev.*, 2011, **111**, 7377–7436.

3 (a) S. V. Voitekhovich, V. Lesnyak, N. Gaponik and A. Eychmueller, *Small*, 2015, **11**, 5728–5739. (b) L. Zhang and J. M. Cole, *ACS Appl. Mater. Interfaces*, 2015, **7**, 3427–3455. (c) Y. Jiang, J. Chen, C. Deng, E. J. Suuronen and Z. Zhong, *Biomaterials*, 2014, **35**, 4969–4985.

4 (a) M. Limbach. *Chem. Biodiversity*, 2006, **3**, 119–133. (b) D. A. Longbottom, F. Vilius and S. V. Ley, *Chimia*, 2007, **61**, 247–256. (c) B. Maji and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2014, **53**, 8714-8717. (d) P. Jiao, M. Kawasaki and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2009, **48**, 3333–3336. (e) Y. Yamamoto, N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 5962–5963. (f) H. Torii, M. Nakadai, K. Ishihara, S. Saito and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2004, **43**, 1983-1986.

5 (a) X.-M. Peng, G.-X. Cai and C.-H. Zhou, *Curr. Top. Med. Chem.*, 2013, **13**, 1963–2010. (b) P. B. Miniyar, P. R. Murumkar, P. S. Patil, M. A. Barmade and K. G. Bothara, *Mini-Rev. Med. Chem.*, 2013, **13**, 1607–1625. (c) P. B. Mohite and V. H. Bhaskar, *Int. J. PharmTech Res.*, 2011, **3**, 1557–1566. (d) B. F. King, *Br. J. Pharmacol.*, 2007, **151**, 565–567. (e) M. A. Malik, M. Y. Wani, S. A. Al-Thabaiti and A. S. Rayees, *J. Inclusion Phenom. Macrocyclic Chem.*, 2014, **78**, 15–37. (f) J. L. Kraus, P. Faury, A. S. Charvet and M. Camplo, *Res. Commun. Chem. Pathol. Pharmacol.*, 1994, **83**, 209–222. (g) A. M. Young, K. L. Audus, J. Proudfoot and M. Yazdanian, *J Pharm Sci.*, 2006, **95**, 717–725. (h) C. D. King, G. R. Rios, M. D. Green and T. R. Tephly, *Curr. Drug Metab.*, 2000, **1**, 143–161. (i) V. A. Ostrovskii, R. E. Trifonov and E. A. Popova, *Russ. Chem. Bull.*, 2012, **61**, 768–780. (j) G. M. Keating, *Drugs*, 2009, **69**, 1239–1265. (k) A. Maleki and A. Sarvary, *RSC Adv.*, 2015, **5**, 60938–60955. (l) C. Fenton and L. J. Scott, *Drugs*, 2005, **65**, 537–558.

6 (a) R. S. Upadhayaya, S. Jain, N. Sinha, N. Kishore, R. Chandra, and S. K. Arora, *Eur. J. Med. Chem*., 2004, **39**, 579–592. (b) G. Xia, X. You, L. Liu, H. Liu, J. Wang, Y. Shi, P. Li, B. Xiong, X. Liu and J. Shen, *Eur. J. Med. Chem.*, 2013, **62**, 1–10. (c) S. Gagliardi, G. Palombi and J. Rocher, WO2006048771 (A1), *Addex Pharmaceuticals, S.A.*, 2006. (d) F. Lenda, N. Crouzin, M. Cavalier, J. Guiramand, F. Lanté, G. Barbanel, C. Cohen-Solal, J. Martinez, F. Guenoun, F. Lamaty and M. Vignes, *Amino Acids*, 2011, **40**, 913–922. (e) N. A. McGrath, M. Brichacek and J. T. Njardarson, *J. Chem. Educ*., 2010, **87**, 1348–1349.

7 (a) Z. P. Demko and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, 2110-2113. (b) J. Roh, K. Vávrová and A. Hrabálek, *Eur. J. Org. Chem.*, 2012, 6101–6118. (c) S. V. Voitekhovich, O. A. Ivashkevich and P. N. Gaponik, *Russ. J. Org. Chem.*, 2013, **49**, 635–654.

8 (a) M. Gandelman and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2005, **44**, 2393–2397. (b) P. Dinér, M. Nielsen, M. Marigo and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 1983–1987. (c) U. Uria, J. L. Vicario, D. Badıa and L. Carrillo, *Chem. Commun.*, 2007, 2509–2511. (d) K. Xu, W. Raimondi, T. Bury and B. Breit, *Chem. Commun.*, 2015, **51**, 10861–10863. (e) D. W. Piotrowski, A. S. Kamlet, A.-M. R. Dechert-Schmitt, J. Yan, T. A. Brandt, J. Xiao, L. Wei and M. T. Barrila, *J. Am. Chem. Soc.*, 2016, **138**, 4818−4823.

9 (a) S. Shimizu and M. Ogata, *J. Org. Chem.* 1986, **51**, 3897–3900. (b) C. J. Moody, C. W. Rees and R. G. Young, *Synlett*, 1990, 413–414. (c) C. J. Moody, C. W. Rees and R. G. Young, *J. Chem. Soc., Perkin Trans. 1* 1991, **2,** 323–327. (d) H. Umemoto, T. Onaka, Y. Miki, A. Nakamura and T. Maegawa, *Heterocycles*, 2014, **89**, 2545–2553. (e) H. Umemoto, T. Onaka, Y. Miki, A. Nakamura and T. Maegawa, *Synlett*, 2015, **26**, 205–208.

10 (a) G. Masson, J. Zhu and C. Housseman, *Angew. Chem. Int. Ed.*, 2007, **46**, 4614 – 4628. (b) Y. Wei and M. Shi, *Chem. Rev.*, 2013, **113**, 6659–6690. (c) X. Wang, P. Guo, Z. Han, X. Wang, Z. Wang and K. Ding, *J. Am. Chem. Soc.*, 2014, **136**, 405–411. (d) J. Liu, Z. Han, X. Wang, Z. Wang and K. Ding, *J. Am. Chem. Soc.*, 2015 **137**, 15346-15349. (e) Y.-Q. Jiang, Y.-L. Shi and M. Shi, *J. Am. Chem. Soc*., 2008, **130**, 7202–7203.

11 (a) T. Nishimine, K. Fukushi, N. Shibata, H. Taira, E. Tokunaga, A. Yamano, M. Shiro and N. Shibata, *Angew. Chem. Int. Ed.*, 2014, **53**, 517–520. (b) T. Nishimine, H. Taira, E. Tokunaga, M. Shiro and N. Shibata, *Angew. Chem. Int. Ed.*, 2016, **55**, 359–363. (c) S. Okusu, H. Okazaki, E. Tokunaga, V. A. Soloshonok and N. Shibata, *Angew. Chem. Int. Ed.*, 2016, **55**, 6744–6748.

12 C. N. S. S. P. Kumar, D. K. Parida, A. Santhoshi, A. K. Kota, B. Sridhar and V. J. Rao, *MedChemComm.*, 2011, **2**, 486–492.

13 (a) J. Tanaka, S. Suzuki, E. Tokunaga, G. Haufe and N. Shibata, *Angew. Chem., Int. Ed.*, 2016, **55**, 9432-9436. (b) G. Haufe, S. Suzuki, H. Yasui, C. Terada, T. Kitayama, M. Shiro and N. Shibata, *Angew. Chem. Int. Ed.*, 2012, **52**, 12275-12279.

14 D. E. J. E. Robinson and S. D. Bull, *Tetrahedron: Asymmetry*, 2003, **14**, 1407–1446.

15 V. A. Soloshonok, C. Roussel, O. Kitagawa and A. E. Sorochinsky, *Chem. Soc. Rev*., 2012, **41**, 4180–4188.

16 J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev*., 2014, **114**, 2432–2506.

17 (a) R. K. V. Devambatla, R. Velagaleti, N. Yarravarapu and F. F. Fleming, *Tetrahedron*, 2012, **68**, 2925–2942. (b) R. A. Moss, X. Fu and R. R. Sauers, *J. Phys. Org. Chem.*, 2007, **20**, 1–10. (c) A. Ardèvol, J. Iglesias-Fernández, V. Rojas-Cervellera and C. Rovira, *Biochem. Soc. Trans.*, 2016, **44**, 51–60.

ChemComm Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx