ChemPubSoc Europe

DOI: 10.1002/chem.201901028

CHEMISTRY A European Journal Communication

Synthetic Methods | *Hot Paper*

Catalytic Asymmetric γ-Lactam Synthesis from Enolisable Anhydrides and Imines

Aarón Gutiérrez Collar, Cristina Trujillo, Bruce Lockett-Walters, Brendan Twamley, and Stephen J. Connon*[a]

Abstract: An anion-binding approach to the problem of preparing enantioenriched γ-lactams from enolisable anhydrides and imines is reported. A simple bisurea catalyst promotes the cycloaddition between α-aryl succinic anhydrides and either PMP- or benzhydryl-protected aldimines to provide γ-lactams with two contiguous stereocentres (one quaternary) with complete diastereocontrol and high to excellent enantioselectivity for the first time. A DFT study has provided insight into the catalyst mode of action and the origins of the observed stereocontrol.

γ-Lactams are a structural unit prevalent in a large number of natural products/medicinally relevant molecules, and as such, methods for their synthesis are highly prized.[1] Often these lactams are stereochemically dense and arylated. Examples (Figure 1 A) are the hepatoprotective, anti-viral hepatitis and anti-Alzheimer's disease natural product (−)-clausenamide (**1**)[2,3] and the transcription factor inhibitor (*rac*)-**2**; which was efficiently prepared as a racemate by Shaw and co-workers[4] by using a Castagnoli–Cushman-type cycloaddition[5] between an imine and an enolisable anhydride, as no catalytic enantioselective version of this reaction was available.[6]

The construction of these motifs is not trivial. Sheidt[7] has reported that hydrazide **3** could be reacted with enals such as cinnamaldehdye (**4**) in the presence of a binary catalyst system comprising the chiral N-heterocyclic carbene precursor **5** and a magnesium salt to furnish the *syn*-heterocycle **6** in 78% yield and excellent *ee* and d.r. (Figure 1 B; *ee* = enantiomeric excess; d.r. = diastereomeric ratio). N–N bond reduction could subsequently be carried out to yield the γ-lactam analogue. Very recently, Bolm and co-workers[8] have disclosed an efficient enantioselective methodology for the synthesis of analogous bis-C-arylated *trans*-γ-lactams such as **10** with excellent stereocontrol through the formal [3+2] cycloaddition of *o*-hydroxy aromatic imines such as **7** and enal **8** employing a chiral N-heterocyclic carbene precatalyst **9** and base (Figure 1 C).[9]

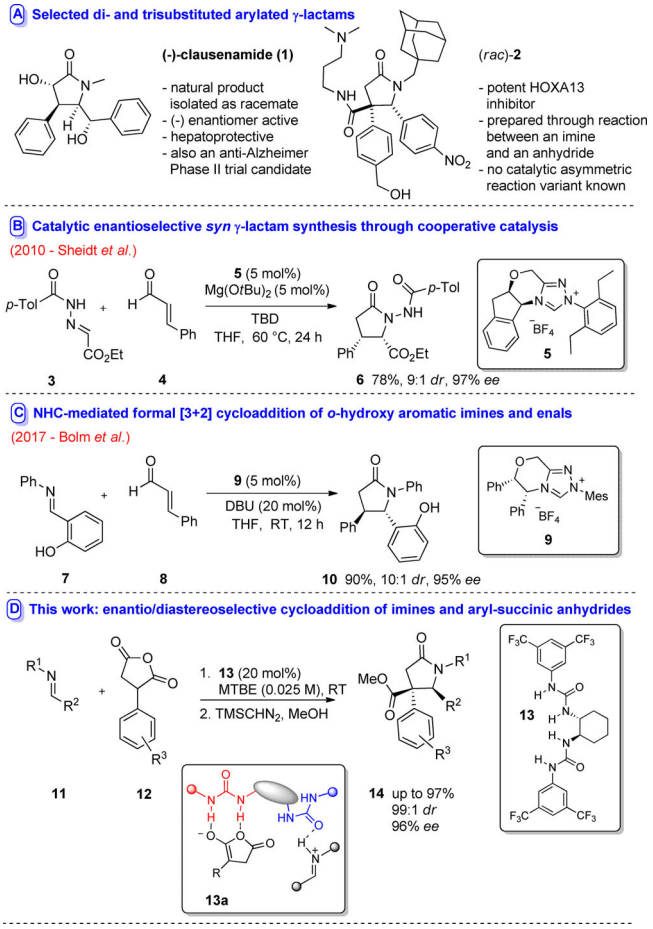


Figure 1. γ-Lactam molecules of medicinal interest and selected catalytic asymmetric γ-lactam syntheses. TDB = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; MTBE = methyl *tert*-butyl ether; $TMSCHN_2$ = trimethylsilyldiazomethane.

Seidel, Vetticatt, and co-workers[10] have very recently disclosed an elegant anion-binding approach to asymmetric cycloadditions between imines and homophthalic anhydride to produce 3,4-dihydroisoquinolones (see the preceding Communication in this issue, DOI: 10.1002/chem.201900119). The reaction is highly efficient; however only homophthalic anhydride was used as the enolate precursor, meaning that all products contained the specific fused bicyclic dihydroisoquinolone core. Previously, we had developed a mechanistically distinct (less enantioselective) organocatalytic cycloaddition between homo-

[a] A. G. Collar, Dr. C. Trujillo, B. Lockett-Walters, Dr. B. Twamley, Prof. S. J. Connon
School of Chemistry Trinity Biomedical Sciences Institute
Trinity College Dublin
152-160 Pearse Street, Dublin 2 (Ireland)
E-mail: connons@tcd.ie

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.201901028.

phthalic anhydride and N-mesyl imines.[11] Again, only the use of homophthalic anhydride was possible. Homophthalic anhydride ($pK_a = 8.2$)[12] is a substrate particularly well-disposed towards enolate formation, however most anhydrides do not possess the requisite acidity for deprotonation by an amine or imine to occur significantly at room temperature. Consequently, the substrate scope with respect to the anhydride component is now the key challenge associated with these potentially very powerful cycloadditions.

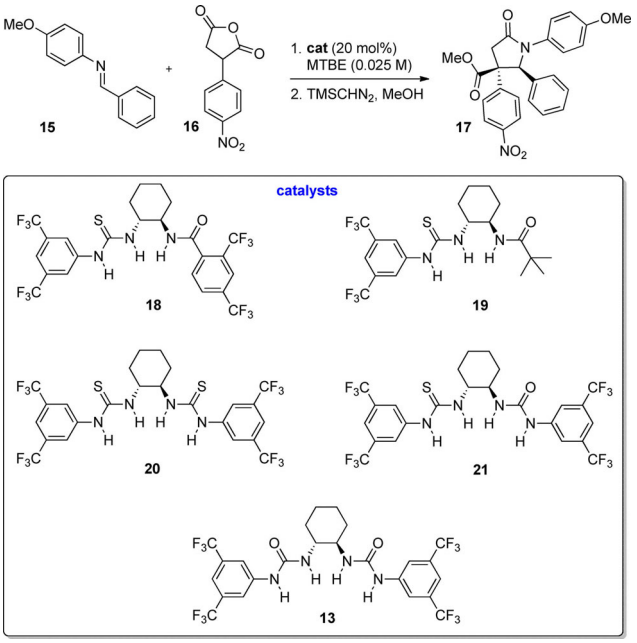
Following our application of Seidel's anion-binding[13] approach to the Tamura cycloaddition (see the preceding Communication in this issue) we herein report the expansion of the scope of the process involving the cycloaddition of simple imines **11** by utilising α-substituted succinic anhydrides **12**[14,15] in the presence of the simple catalyst **13** to yield enantioenriched trisubstituted γ-lactams **14** with excellent enantio- and diastereocontrol (Figure 1 D) through anion binding catalysis (**13 a**).

We began by investigating the influence of various hydrogen bond-donating catalysts on the cycloaddition between the *p*-methoxyphenyl (PMP)-protected benzaldehyde-derived imine **15** and the *p*-nitrophenyl-substituted succinic anhydride **16** in MTBE at ambient temperature. To facilitate CSP-HPLC analysis the carboxylic acid unit was esterified after reaction with methanol/trimethylsilyldiazomethane to yield the γ-lactam **17** (Table 1).

Catalyst **18** (entry 1), which promoted highly enantioselective cycloadditions in Seidel's study involving homophthalic anhydride, promoted the formation of **17** as a single diastereomer with 80% *ee*. Its *tert*-butyl substituted analogue **19** (designed as part of the Tamura cycloaddition optimisation process, see the preceding Communication in this issue) proved less effective here (entry 2). Interestingly, use of Nagasawa's catalyst **20**[16] (entry 3) led to only moderate product *ee*, whereas a mixed urea/thiourea variant **21** allowed catalysis to proceed with substantially improved enantiocontrol (entry 4). This prompted the evaluation of the bisurea analogue **13** (entry 5), which allowed for the formation of **17** with near perfect diastereocontrol and in 91% *ee*. Further investigation of the use of both **18** and **13** at lower temperatures failed to deliver superior stereocontrol (entries 6–8). It is interesting that **13**—which Seidel had shown to be an effective anion-binding-catalyst for acyl transfer[17] but was a less effective chiral catalyst in the Tamura chemistry in the preceding Communication in this issue—is superior here. This is advantageous from a practical perspective considering that **13** is readily prepared in a single step from commercially available starting materials.

A variety of substituted aryl succinic anhydrides are compatible with the catalytic process. Substitution which facilitates enolate formation allows for smooth catalyst-mediated formation of γ-lactams **24** from the anisaldehyde-derived PMP-protected imine **22**[18] and various anhydrides **23** (Scheme 1). Installation of nitrile- (i.e., **25**), bistrifluoromethyl- (i.e., **26** and **27**), dibromo- (i.e., **28**), nitro- (i.e., **29**) and trifluoro-substituted (i.e., **30**) phenyl units on the succinic anhydride allowed the isolation of the desired γ-lactams in ≥90% yield, >99:1 d.r. and ≥95% *ee* in all cases.

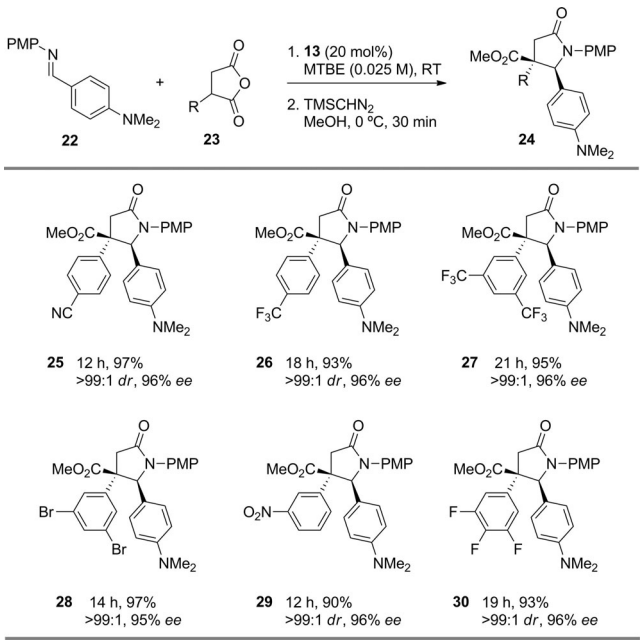
Table 1. Catalyst screening.



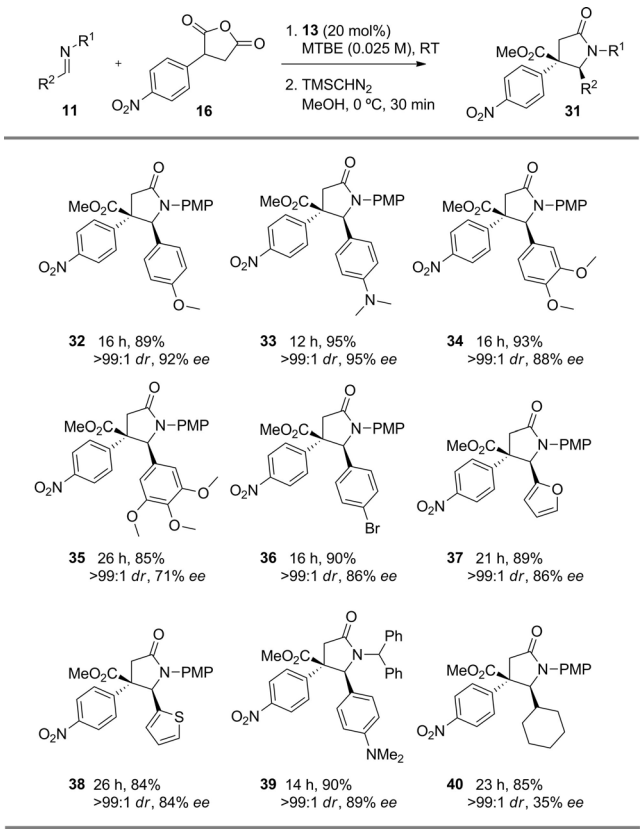
Entry	Catalyst	*T* [°C]	*t* [h]	Conversion [%][a]	d.r.[b] (*syn*/*anti*)	*ee* [%][c]
1	**18**	RT	20	>99	>99:1	80
2	**19**	RT	20	>99	>99:1	78
3	**20**	RT	20	>99	>99:1	69
4	**21**	RT	20	>99	>99:1	88
5	**13**	RT	20	>99	>99:1	91
6	**18**	0	24	>99	>99:1	83
7	**13**	0	24	>99	>99:1	90
8[d]	**13**	−15	47	>99	>99:1	82

[a] Determined by ^{1}H NMR spectroscopy using *p*-iodoanisole as the internal standard. [b] Diastereomeric ratio (determined by ^{1}H NMR spectroscopy). [c] Determined by CSP-HPLC (CSP = chiral stationary phase), see Supporting Information. [d] Concentration 0.1 M.

Attention next turned to the imine component (Scheme 2) through the reaction of various imines **31** with the nitrophenyl succinic anhydride **16** in the presence of catalyst **13** to afford lactams of general type **31**. Given that the mechanism most likely proceeds via deprotonation of the anhydride by the imine and organisation of the resulting ion pair by the catalyst (vide infra),[10] it is perhaps unsurprising that lactams derived from more electron-rich imines (i.e., **32** and **33**) were formed with excellent enantiocontrol. Again, these materials were formed as a single diastereomer. The introduction of methoxy substituents in the 3- and 5-positions (OMe, $\sigma_M = 0.10$) attenuated enantiomeric excess (i.e., **34** and **35**): a single methoxy group was tolerated but addition of a second led to a large reduction in product *ee* and slower product formation. The PMP-protected imine derived from *p*-bromobenzaldehyde could undergo cycloaddition with **16** to form lactam **36** in high *ee*. Similar levels of enantiocontrol were observed when the imine bore 5-membered aromatic heterocycles (i.e., **37** and **38**). The benzhydryl protecting group is also compatible: lactam **39** was generated with similar (but marginally lower) levels of enantio-



Scheme 1. Substrate scope: the anhydride component.



Scheme 2. Substrate scope: the imine component.

control to **32**. At this juncture imines-derived from aliphatic aldehydes appear to provide products with dramatically reduced enantioselectivity, albeit with high yield and excellent diastereocontrol (i.e., **40**)

A DFT study (M062X/6-311+G**//M062X/6-31G*, SMD-diisopropylether, 298 K) was useful in rationalising the formation of the observed lactam antipodes. The free energy profile for the formation of both enantiomers of **30** (Figure 2) indicates that cyclisation is both essentially irreversible and rate determining. The catalyst organises the iminium-enolate ion pair to facilitate the Mannich-type step with a barrier associated with eventual formation of the major product enantiomer 3.7 kcal mol^{-1} lower than that associated with the minor antipode. A similar situation is calculated to arise at the cyclisation stage: ring-closure to the major enantiomer is characterised by a barrier 4.9 kcal mol^{-1} lower that its counterpart leading to the minor product (Figure 2). Overall barriers are higher than calculated for the asymmetric Tamura chemistry (see the preceding Communication in this issue)—consistent with the need for ambient temperature required for lactam generation as opposed to the smooth cycloadditions observed at −40 °C in the Tamura process.

To probe the origins of the observed sense of asymmetric induction, we examined the transition states associated with the key first stereocentre forming Mannich-like step reaction step for both major and minor enantiomers (Figure 3). The binding mode was analogous to that calculated by Seidel and Vetticat for anion binding catalysis involving imines and homophthalic anhydride.[10]

Inspection of the calculated transition state leading to the major antipode (*R*,*S*)-**30** (Figure 3, top) allows for appreciation of why the simple bisurea catalyst **13**,which did not emerge as the optimum promoter either our study on Tamura cycloadditions, was superior in this process and also sheds light on the catalyst-substrate interactions which render aromatic aldehyde-derived imines considerably more amenable to highly enantioselective cycloaddition than aliphatic analogues. Catalyst **13** forms a discernible hydrophobic "pocket" between its bis(trifluoromethyl)phenyl rings in which the imine aromatic unit resides [and interacts with through multiple π–π interactions identified by quantum theory of atoms in molecules (QTAIM) calculations, see Sup-

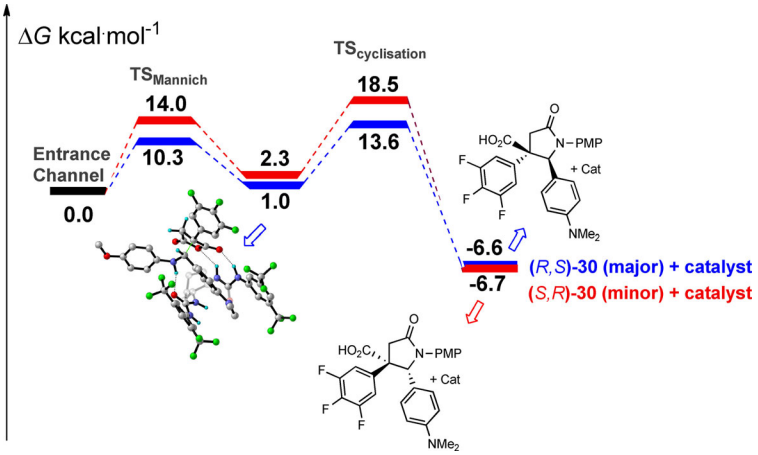


Figure 2. Calculated (DFT) free energy profile associated with the formation of both enantiomers of **30**.

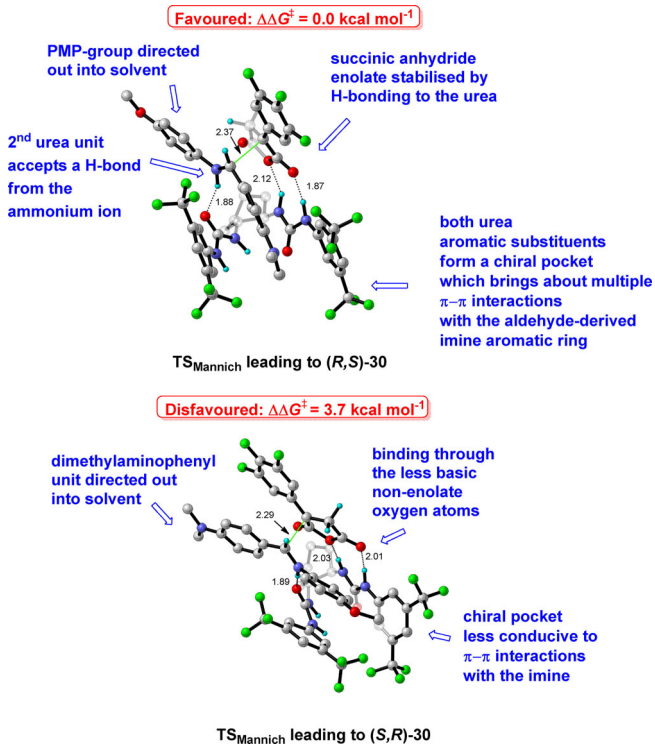


Figure 3. Calculated (DFT) lowest energy transition state structures associated with both enantiomers of **30**.

porting Information] in the transition state. This, together with the binding of the iminium ion N–H proton to one of the urea carbonyl groups, aligns the electrophile. This may explain why imines incorporating more electron-rich aromatic rings provide products with higher *ee*, considering that could better interact with the catalyst relatively electron-deficient bis(trifluoromethyl)phenyl substituents which comprise the boundary of the pocket. The other catalyst urea moiety is involved in stabilising the nucleophilic reaction component via double hydrogen bond donation to the enolate oxygen atom and its neighbour. The transition state leading to the minor (***S,R***)-**30** enantiomer (Figure 3, bottom) occurs considerably later (i.e. the C–C distance for the forming bond is 0.08 Å shorter in the transition state leading to (***S,R***)-**30** than the corresponding distance in the transition state leading to (***R,S***)-**30**). The anhydride enolate must be bound through its less basic oxygen atoms to achieve a Bürgi–Dunitz trajectory. In addition, the PMP group occupies the now less pronounced "pocket" and interacts only weakly with the catalyst aromatic rings (see Supporting Information), which likely contributes to the 3.7 kcal mol^{-1} difference in barrier heights calculated.

In summary, the development of the first highly enantioselective cycloaddition reactions between imines and succinic anhydrides is reported. This broadens the scope beyond dihydroisoquinolone products for the first time. The reaction does not require specialised imines incorporating electron-withdrawing (basicity dampening) groups at nitrogen. Aromatic *N*-PMP imines react with α-aryl succinic anhydrides in the presence of an exceedingly simple catalyst—which can be prepared in one step from commercially available starting materials—to afford stereochemically dense γ-lactam products, which are the core of natural products and molecules of pharmacological value with outstanding diastereocontrol and high-excellent enantiocontrol. DFT calculations indicate a catalyst mode of action involving selective binding of the enolate and iminium ion components and the creation of a pocket between the catalyst aromatic rings, in which the imine sits. This allows for the rationalisation of the stereocontrol observed in the process.

Acknowledgements

This publication has emanated from research supported by the Science Foundation Ireland (SFI-12-IA-1645). We are grateful to the Irish Centre for High-End Computing (ICHEC) for the provision of computational facilities. We are indebted to Dr. Goar Sánchez from ICHEC for the AIM graphical outputs.

Conflict of interest

The authors declare no conflict of interest.

Keywords: cyclic anhydrides · cycloadditions · DFT · imines · lactams

[1] For a recent review concerning biologically active lactams see: J. Caruano, G. G. Muccioli, R. Robiette, *Org. Biomol. Chem.* **2016**, *14*, 10134.
[2] W. Hartwig, L. Born, *J. Org. Chem.* **1987**, *52*, 4352.
[3] For a review see: S.-F. Chu, J.-T. Zhang, *Acta Pharm. Sin. B* **2014**, *4*, 417.
[4] P. Y. Ng, Y. Tang, W. M. Knosp, H. S. Stadler, J. T. Shaw, *Angew. Chem. Int. Ed.* **2007**, *46*, 5352; *Angew. Chem.* **2007**, *119*, 5448.
[5] a) N. Castagnoli, *J. Org. Chem.* **1969**, *34*, 3187; b) N. Castagnoli, M. Cushman, *J. Org. Chem.* **1971**, *36*, 3404; c) M. Cushman, N. Castagnoli, *J. Org. Chem.* **1972**, *37*, 1268; d) M. Cushman, N. Castagnoli, *J. Org. Chem.* **1974**, *39*, 1546; e) M. Cushman, N. Castagnoli, *J. Org. Chem.* **1973**, *38*, 440.
[6] For an excellent review of the racemic process see: M. González-López, J. T. Shaw, *Chem. Rev.* **2009**, *109*, 164.
[7] D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766.
[8] S. Dong, M. Frings, D. Zhang, Q. Guo, C. G. Daniliuc, H. Cheng, C. Bolm, *Chem. Eur. J.* **2017**, *23*, 13888.
[9] For representative other NHC-catalysed methodologies for γ-lactam synthesis see: a) M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131; b) M. Rommel, T. Fukuzumi, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 17266; c) X. Zhao, D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 12466; d) B. Zhang, P. Feng, L.-H. Sun, Y. X. Cui, S. Ye, N. Jiao, *Chem. Eur. J.* **2012**, *18*, 9198; e) H. Lv, B. Twari, J. Mo, C. Xing, Y. G. Chi, *Org. Lett.* **2012**, *14*, 5412.
[10] C. L. Jarvis, J. S. Hirschi, M. J. Vetticatt, D. Seidel, *Angew. Chem. Int. Ed.* **2017**, *56*, 2670; *Angew. Chem.* **2017**, *129*, 2714.
[11] S. A. Cronin, A. G. Collar, S. Gundala, C. Cornaggia, E. Torrente, F. Manoni, A. Botte, B. Twamley, S. J. Connon, *Org. Biomol. Chem.* **2016**, *14*, 6955.
[12] N. Mofaddel, N. Bar, D. Villemin, P. L. Desbène, *Anal. Bioanal. Chem.* **2004**, *380*, 664.
[13] Representative recent reviews on anion-binding catalysis: a) J. Lacour, D. Moraleda, *Chem. Commun.* **2009**, 7073; b) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187; c) S. Beckendorf, S. Asmus, O. G. Mancheño, *ChemCatChem* **2012**, *4*, 926; d) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603; e) J.-F. Brière, S. Oudeyer, V. Dalla, V. Levacher, *Chem. Soc. Rev.* **2012**, *41*, 1696; f) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518; *Angew. Chem.* **2013**, *125*, 540; g) K. Brak,

E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534; *Angew. Chem.* **2013**, *125*, 558; h) D. Seidel, *Synlett* **2014**, *25*, 783; i) N. H. Evans, P. D. Beer, *Angew. Chem. Int. Ed.* **2014**, *53*, 11716; *Angew. Chem.* **2014**, *126*, 11908; j) N. Busschaert, C. Caltagirone, W. Van Rossom, P. A. Gale, *Chem. Rev.* **2015**, *115*, 8038.

[14] For the use of these anhydrides in mechanistically distinct catalytic asymmetric cycloadditions with aldehydes see: F. Manoni, C. Cornaggia, J. Murray, S. Tallon, S. J. Connon, *Chem. Commun.* **2012**, *48*, 6502.

[15] For related catalytic asymmetric reactions involving enolisable anhydrides see: a) C. Cornaggia, F. Manoni, E. Torrente, S. Tallon, S. J. Connon, *Org. Lett.* **2012**, *14*, 1850; b) F. Manoni, S. J. Connon, *Angew. Chem. Int. Ed.* **2014**, *53*, 2628; *Angew. Chem.* **2014**, *126*, 2666; c) C. Cornaggia, S. Gundala, F. Manoni, N. Gopalasetty, S. J. Connon, *Org. Biomol. Chem.* **2016**, *14*, 3040; d) F. Manoni, U. Farid, C. Trujillo, S. J. Connon, *Org. Biomol. Chem.* **2017**, *15*, 1463; e) U. Nath, S. C. Pan, *J. Org. Chem.* **2017**, *82*, 3262; f) C. Trujillo, I. Rozas, A. Botte, S. J. Connon, *Chem. Commun.* **2017**, *53*, 8874; g) R. Claveau, B. Twamley, S. J. Connon, *Chem. Commun.* **2018**, *54*, 3231; h) M. L. Aiello, U. Farid, C. Trujillo, B. Twamley, S. J. Connon, *J. Org. Chem.* **2018**, *83*, 15499; i) H. Xu, F. Sha, Q. Li, X. Y. Wu, *Org. Biomol. Chem.* **2018**, *16*, 7214.

[16] Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589.

[17] a) C. K. De, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 17060; b) N. Mittal, K. M. Lippert, C. K. De, E. G. Klauber, T. J. Emge, P. R. Schreiner, D. Seidel, *J. Am. Chem. Soc.* **2015**, *137*, 5748.

[18] *N*-Allyl- and *N*-benzhydryl imines provided products with considerably lower enantiomeric excess ($>40\,\%ee$).

Manuscript received: March 5, 2019
Version of record online: ■■ ▮▮, 0000

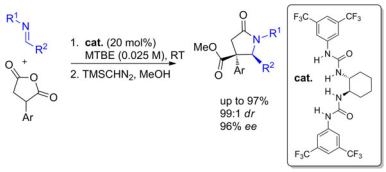
COMMUNICATION

Synthetic Methods

*A. G. Collar, C. Trujillo, B. Lockett-Walters, B. Twamley, S. J. Connon**

■■ – ■■

Catalytic Asymmetric γ-Lactam Synthesis from Enolisable Anhydrides and Imines



The scope of the asymmetric cycloaddition between simple imines and anhydrides has been expanded to include highly enantioselective synthesis of γ-lactams for the first time.