The first catalytic asymmetric cycloadditions of imines with an enolisable anhydride

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The first catalytic asymmetric cycloadditions of imines with an enolisable anhydride

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The first catalytic, asymmetric reactions of imines with homophthalic anhydride to form disubstituted 3,4-dihydroisoquinolones are reported. The use of *N*-mesyl aldimines is key, as more basic imines undergo rapid uncatalysed reactions, while imines possessing larger *N*-sulphonyl substituents form lactams with lower *ee*.

The formal cyclisation of imines with enolisable anhydrides[1] is a decades old process known to be useful for the formation of substituted lactam derivatives. In 1969,[2] Castagnoli reported the reaction of succinic anhydride (**1**, Figure 1A) with simple imines such as **2** in benzene under reflux to form the γ-lactam **3** in good yield as a mixture of diastereomers.[3] Later, Cushman *et al*. and Haimova *et al*. demonstrated highly efficient and diastereoselective cycloadditions (with the *cis* isomer kinetically favoured) using the more enolisable homophthalic anhydride (**4**, Figure 1A).[4] In terms of substrate scope – the reaction generally requires high temperatures if the anhydride does not incorporate enol-stabilising functionality, and aromatic aldimines are preferable to enolisable aliphatic analogues.[1,5] Multicomponent variants involving *in situ* imine formation (and even simultaneous *in situ* enolisable anhydride generation) and subsequent cycloaddition has also emerged as a highly efficient method for γ-lactam synthesis.[6]

Three mechanistic pathways have been proposed (Figure 1B). Cushman *et al*.[7] - based on the results of extensive studies on the influence of substituents on both rate and the stereochemical outcome of the reaction - posited a process involving iminolysis of the anhydride followed by tautomerisation to give the enolate **6**, which then undergoes 6-*endo*-trig cyclisation. Kaneti[8] has suggested – based on gas phase calculations - that this process could be concerted. Shaw and Cheong[9] more recently carried out a detailed computational study of the reaction between the relatively enolisable cyanosuccinic anhydride and imine **2**. This process was calculated to occur *via* a stepwise mechanism involving preliminary generation of the iminium enolate complex **7**. Subsequent rate-limiting C-C bond formation gives **8**, which lactamises to form **9**.

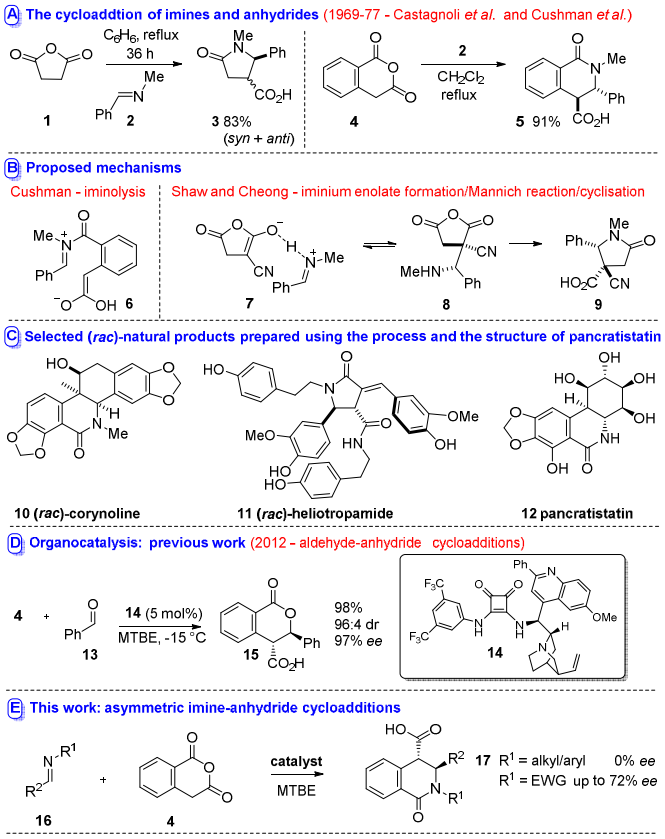


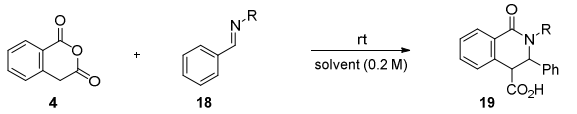
Fig. 1 Imine-anhydride cycloaddition reactions

The value in the methodology lies in its ability to prepare chiral lactam products directly from simple (usually achiral) imine and anhydride precursors in an atom-economic, coupling agent-free fashion. For instance, the process has been used to prepare a wide variety of polycyclic natural product lactam derivatives (Figure 1C) as racemates – for example the ACE inhibitor corynoline (**10**),[10,11] in addition to densely substituted monocyclic lactams such as

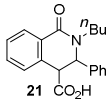
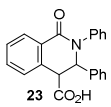
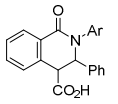
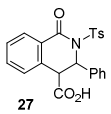
heliotropamide (**11**). However, there are no reports of a catalytic, enantioselective variant of this reaction in the literature. This considerably curtails the utility of the process; rendering it unlikely to be at the forefront of practitioners minds as a tool for the synthesis of enantiopure, stereochemically complex lactam-based targets such as the anti-tumour alkaloid pancratistatin (**12**).[12]

We have previously reported[13] that the squaramide-based organocatalyst **14** can promote the reaction of anhydride **4** with aldehyde **13** to generate the *trans*-lactone **15** with excellent yield, enantio- and diastereocontrol (Figure 1D).[14,15] Our working mechanistic hypothesis is that **14** acts as a catalyst of both the equilibrium between the anhydride and its enol tautomer and facilitates the encounter between the enol and the aldehyde *via* general acid-base catalysis. Here we show, for the first time, how the steric and electronic characteristics of imines of general type **16** can be modified (Figure 1D) to allow them to participate in catalytic asymmetric cycloaddition processes to form 3,4-dihydroisoquinolone structures (*i.e.* **17**), present in natural products such as pancratistatin and narciclasine,[16] which could also serve as useful (previously unutilised) precursors in the synthesis of the broad class of 3,4-dihydroisoquinoline alkaloids.[17]

Table 1 An examination of the effect of the *N*-substituent on substrate activity in the uncatalysed reaction



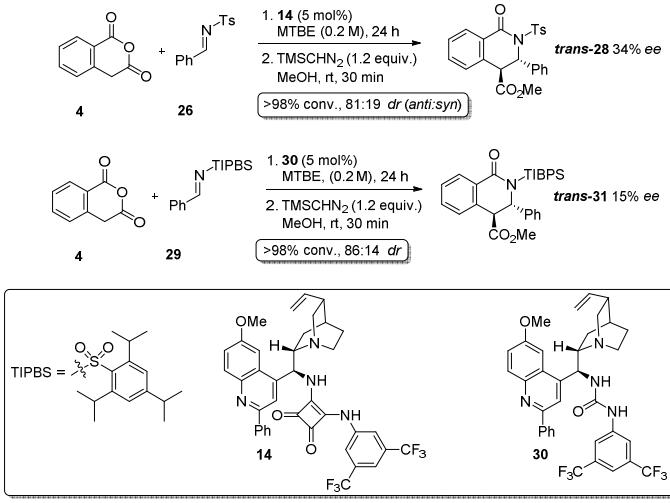
4 **18** **19**

Entry	Imine	Product	Sol.	T (°C)	t (h)	*Conv.* (%)[a]
1			THF	-30	15	>98
2			THF	-78	15	>98
3	**20**	**21**	MTBE	rt	2	62
4	 **22**	 **23**	MTBE	rt	4	39
5	 **24** Ar = 4-NO_2-C_6H_4	 **25** Ar = 4-NO_2-C_6H_4	MTBE	rt	24	0
6	 **26**	 **27**	MTBE	rt	24	0

[a]Conversion determined by ^{1}H NMR spectroscopy.

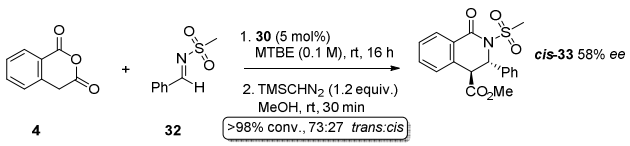
Our study began with an investigation into the reactivity of simple imines **18** towards homophthalic anhydride (**4**). The results of these studies are summarised in Table 1. Use of the simple *N*-butyl imine **20** in THF led to complete conversion to the lactam **21** at low temperatures (entries 1-2). While the rate diminished considerably in MTBE[18] (entry 3), the uncatalysed reaction continued to proceed at an impractically fast rate for convenient application in catalysis. Considering the proposed mechanisms outlined in Figure 1B, the activity of the relatively unhindered and basic imine **20** is perhaps unsurprising. We therefore next examined the *N*-phenyl analogue **22** (entry 4). While lactam **23** formed more slowly, 39% of the starting material had been converted after only 4 h reaction time at room temperature.

It was clear that a more powerful means of modulating *N*-atom basicity/nucleophilicity was required. This was achieved *via* the use of substrates incorporating either a highly electron accepting *N*-aryl unit (*i.e.* **24**) or an *N*-tosyl substituent (*i.e.* **26**); neither of which underwent cycloaddition with **4** to form either **25** or **27** respectively at room temperature over 24 h (entries 5 and 6). Since the *p*-nitrophenyl substituent does not undergo facile cleavage, the sulfonylimine **26** was selected as the candidate for studies involving asymmetric catalysis.



Scheme 1 Catalytic enantioselective imine-anhydride cycloadditions: preliminary experiments

Gratifyingly, the cycloaddition of **4** to **26** in the presence of the squaramide-based catalyst **14**Error! Bookmark not defined. afforded predominantly ***trans*-28** in moderate enantiomeric excess after *in situ* esterification with trimethylsilyl diazomethane (Scheme 1). To ascertain if the relatively low levels of product *ee* (compared to those associated with aldehyde substrates[13]) was related to the small steric discrepancy between the substrate phenyl ring and the tosyl substituent, we next evaluated the considerably larger imine **29** – which is also derived from benzaldehyde, yet possesses the bulky triisopropylbenzenesulfonyl *N*-substituent. The urea-based catalyst **30** promoted the reaction with marginally improved diastereocontrol and considerably reduced enantiocontrol.



4 **32**

Scheme 2 Evaluation of an *N*-mesyl imine as the substrate

With the augmentation of the steric requirement of the imine *N*-substituent having a deleterious effect on enantiocontrol, the smallest non-acidic *N*-sulfonyl imine analogue possible (*i.e.* **32**) was next

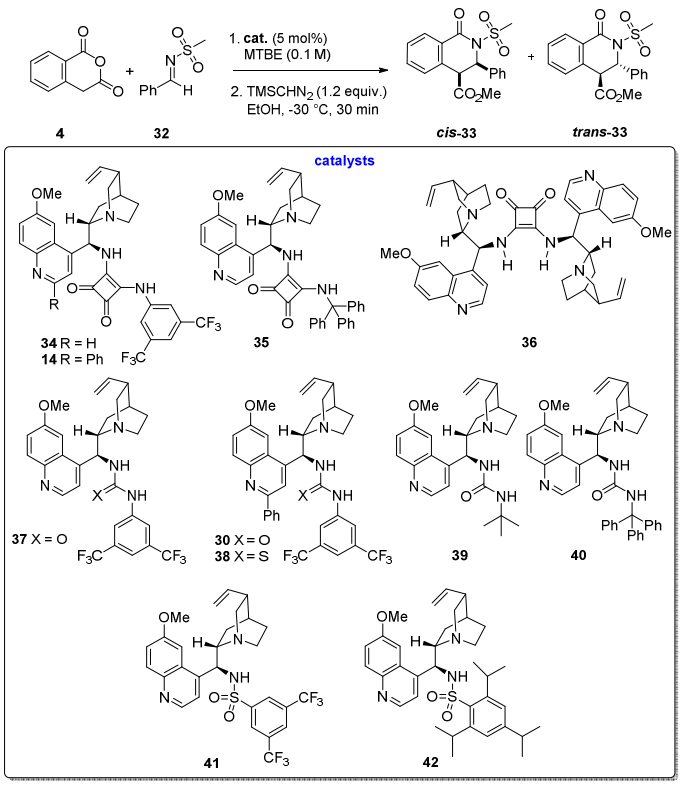
investigated (Scheme 2), resulting in the formation of ***trans*-33** in 58% *ee* and *ca*. 3:1 *dr*.

Encouraged by this finding, we set about the optimisation of the catalyst structure using this substrate (Table 2). At ambient temperature, both **14** and an analogue devoid of a C-2 phenyl substituent (*i.e.* catalyst **34**) promoted the reaction with reduced levels of enantiocontrol (entries 1-2). Replacement of the squaramide *N*-aryl unit from catalyst **34** for a bulky trityl substituent (i.*e.* **35**) resulted in improved enantiomeric excess of the minor *cis* diastereomer, however the *trans* stereoisomer was formed in almost racemic fashion (entry 3). The C_2-symmetric squaramide **36** proved a poor catalyst from an enantioselectivity standpoint (entry 4). Returning to urea-based bifunctional catalysts, we found that the installation of a phenyl moiety at the C-2 position of the quinoline ring allows the marginally more enantioselective formation of the *trans* diastereomer without impacting diastereocontrol (entries 5-6), while substitution of the urea hydrogen bond donor for a thiourea unit (*i.e.* **38**) led to slightly improved enantiocontrol and poorer diastereoselectivity (entry 7). Increasing the steric bulk of the urea-based catalysts did not lead to further improvements (entries 8-9), while sulfonamide-substituted catalysts provided products with disappointing levels of control (*i.e.* **41** and **42**, entries 10-11). The effect of temperature was also studied: using catalyst **30** at 40 °C stereocontrol was very similar to levels observed at ambient temperature, while at -30 °C enantiocontrol could be increased to 70% *ee* (entries 12-14). The corresponding thiourea also promoted more enantioselective reactions at this temperature (entry 15), however product *ee* was lower than that obtained using urea **30**, and thus the urea-based catalyst was selected for use in further studies.

Next attention turned to the question of substrate scope. We found that a range of *N*-mesyl imines incorporating aromatic substituents with electron neutral, election deficient, electron withdrawing, hindered- and heterocyclic π-excessive aromatic substituents were within the orbit of the process (Scheme 3), allowing the formation of substituted lactams **43**-**52** as a mixture of diastereomers. Lactams derived from α,β-unsaturated and aliphatic imines were also found to be compatible (*i.e.* **53** and **54** respectively). In all but two cases the *ee* of the major, *trans*-diastereomer (up to 79%) was higher than that of the *cis*-counterpart. This catalytic asymmetric process appears to be relatively insensitive to the electronic characteristics of the substrate, while an *o*-methyl group is not well tolerated in terms of enantiocontrol. Interestingly, the heterocyclic imine-derived lactams **51** and **52** did not follow this general pattern, and were formed as an almost 1:1 mixture of diastereomers, of comparable *ee*. Single crystal X-ray diffraction pattern analysis confirmed the absolute configuration of ***trans*-47** as 3*S*, 4*S* (Fig. 2).

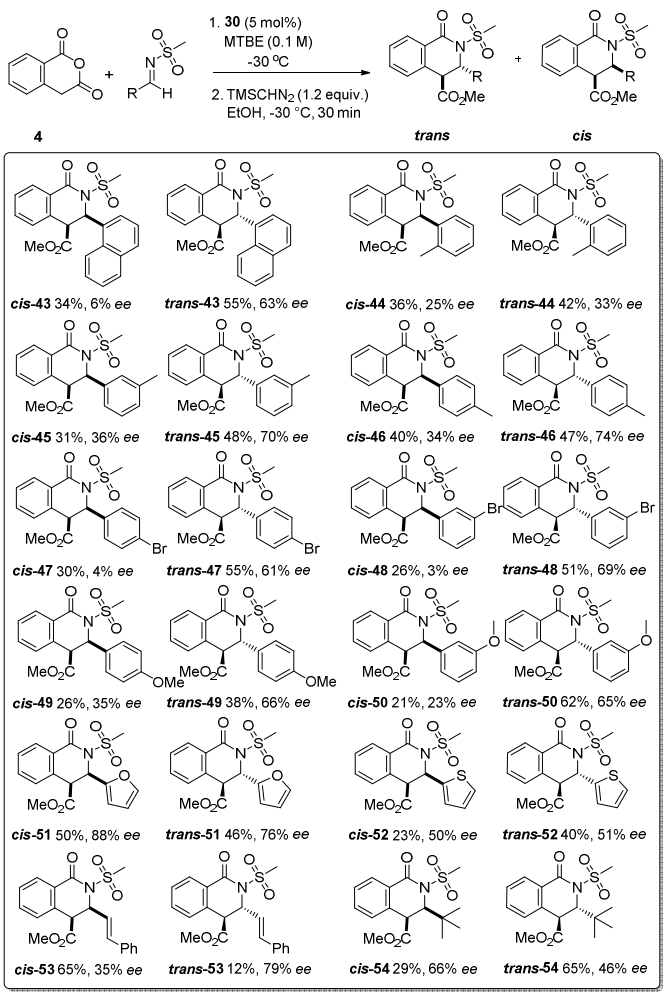
In conclusion, we have shown that the natural proclivity of *N*-alkyl and *N*-aryl imine substrates to undergo rapid cycloaddition with homophthalic anhydride can be suppressed through the use of *N*-sulphonamido substituents – which presumably reduce both the basicity and potential nucleophilicity of the imine component, thereby rendering it more amenable to asymmetric catalysis. A screen of bifunctional organocatalysts which had proven useful in related processes identified the simple urea derivative **30** as an efficient promoter of the reaction. Somewhat unusually, the use of larger imines with large *N*-sulfonamido groups led to the formation of almost racemic products, while installation of the smallest convenient group (*i.e.* mesyl) at the imine nitrogen atom proved optimal with respect to product *ee*. It was found that **30** could catalyse the enantioselective cycloaddition between a range of such *N*-mesyl imines and **4** to yield disubstituted dihydroisoquinolone products with excellent overall yield, poor-moderate diastereocontrol and with levels of enantiomeric excess of the *trans*-diastereomer in up to 79% *ee*. These are, to the best of our knowledge, the first catalytic asymmetric variants of this highly synthetically useful reaction involving imines and anhydrides in the literature. Investigations to ascertain the factors which influence enantio- and diastereocontrol are underway. We are grateful to the European Research Council, the Irish Research Council and Science Foundation Ireland for financial support.

Table 2 Refinement of the reaction conditions



Entry	Cat.	T (°C)	t (h)	Conv. (%)[a]	dr[a] *cis*:*trans*	ee_{cis} (%)[b]	ee_{trans} (%)[b]
1	**34**	rt	16	>98	45:55	29	33
2	**14**	rt	5	>98	26:74	0	31
3	**35**	rt	24	>98	31:69	59	15
4	**36**	rt	24	>98	39:61	12	10
5	**37**	rt	16	>98	23:77	16	53
6	**30**	rt	16	>98	23:77	12	58
7	**38**	rt	16	>98	26:74	43	61
8	**39**	rt	16	>98	31:69	6	56
9	**40**	rt	16	>98	31:69	15	46
10	**41**	rt	24	>98	34:66	21	31
11	**42**	rt	24	>98	38:62	13	47
12	**30**	40	5	>98	23:77	6	53
13	**30**	-30	48	95	36:64	27	70
14	**30**	-50	72	90	36:64	18	51
15	**38**	-30	66	>98	37:63	42	65

[a]Determined by ^{1}H NMR spectroscopy. [b]Determined by CSP-HPLC, see Experimental Section.



Scheme 3 Substrate scope

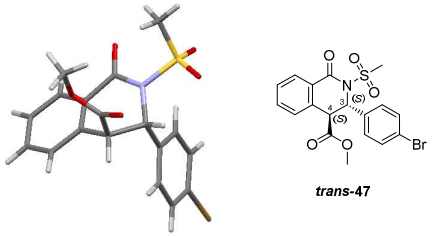


Fig. 2 Absolute configuration assignment of ***trans*-47**

Notes and references

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Electronic Supplementary Information (ESI) available: [Experimental procedures, spectral, X-ray and characterisation data]. See DOI: 10.1039/c000000x/

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