Catalytic formal cycloadditions between anhydrides and ketones: excellent enantio and diastereocontrol, controllable decarboxylation and the formation of adjacent quaternary stereocentres

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EDGE ARTICLE

Catalytic formal cycloadditions between anhydrides and ketones: excellent enantio and diastereocontrol, controllable decarboxylation and the formation of adjacent quaternary stereocentres

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It has been shown for the first time that enolisable anhydrides can participate in highly efficient and diastereo/enantioselective additions to activated ketones. In these reactions the anhydride component formally acts (initially) as the nucleophilic component. These processes are promoted by novel, readily prepared urea-substituted cinchona alkaloid-derived catalysts at low loadings under mild conditions. Three classes of enolisable anhydride and three different types of activated ketone were shown to be compatible with the process – generating a diverse range of structurally distinct and densely functionalised lactone products with the formation of two new stereocentres, one of which is quaternary. In one example, a product incorporating two contiguous quaternary stereocentres (one all carbon) was formed with outstanding enantiocontrol. It has been shown in the case of glutaconic anhydride derivatives that the cycloaddtion process is reversible, and can be accompanied by decarboxylation and olefin isomerisation. Reaction conditions can be modified to give access to three types of product with good-excellent *ee*.

The formal cycloaddition reaction between enolisable cyclic anhydrides **1** and aldehydes **2** to generate structures of general type **3** was first discovered by Fittig in 1883 (Figure 1A).[1,2,3] Despite a history punctuated by long periods of inactivity, the reaction is now a time-honoured methodology for the rapid construction of racemic carboxy-lactones.[4,5] It has been suggested that the reaction proceeds through the intermediate **4**; derived from the addition of the enol tautomer of the anhydride to the aldehyde followed by proton transfer. Subsequent lactonisation leads to **3**. This putative aldol-type process is noteworthy as it places the anhydride – normally considered only as electrophilic agents – in an initially nucleophilic role. This is supported by the finding that homophthalic anhydrides **5** react considerably faster than non-benzo-fused analogues, presumably due to the former possessing more accessible enol tautomers **6**.[4,6,7]

Recently we developed the first catalytic asymmetric variant of this reaction.[8,9,10] For instance, benzaldehyde (**7**) could be reacted with homophthalic anhydride (**8**) in the presence of the bifunctional squaramide-based organocatalyst **10** to afford the dihydroisocoumarin **9** (a structural unit which is a feature of many bioactive natural products with diverse modes of action[11]) with excellent yield, diastereo- and enantiocontrol. It seems likely (but is not certain) that **10** catalyses the keto-enol tautomeric equilibrium and promotes the attack of the enol on the aldehyde *via* general acid-base catalysis.

The use of less electrophilic ketone electrophiles in these reactions has historically proved a considerably more difficult challenge. Only three studies on this topic have emerged. In 1984 Lawlor *et al.*[12] reported the cycloaddition of succinic anhydride (**11**, *via* its zinc enolate **11a**) with symmetrical ketones such as **12a**,**b** to yield the butyrolactones **13a**,**b**. The scope was narrow, yields were variable, and 2.0 equivalents of both a base and a Lewis acid were required (Figure 1B). Gesquiere *et al.*[13] later used ketones with **8** promoted by a large excess of BF_3•Et_2O. Aromatic ketones such as benzophenone and acetophenone failed to react, whereas acetone (**14a**) and butan-2-one (**14b**) afforded δ-lactones **15a,b** in low to moderate yields. It is noteworthy that the use of **14b** represents the only known example of the employment of an asymmetric ketone in these reactions thus far. More recently, Palamareva[14] employed a similar stoichiometric Lewis acid-mediated methodology for the cycloaddition between **8** and cyclohexanone (**14c**) to form the spirolactone **15c** in excellent yields.

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The 3,3-disubstituted 3,4-dihydroisocoumarin unit is present in a number of chiral molecules with interesting biological properties (*e.g.* **16**,[15] **17**[16] and **18**[17] - the latter two molecules were synthesised as racemates and subsequently resolved - Figure 1C). However, perhaps unsurprisingly given the greater difficulty associated with face-selective additions to ketones relative to aldehydes (*e.g.* reduced electrophilicity, smaller steric discrepancy between the substituents flanking the carbonyl carbon), *no examples of either the catalytic or enantioselective cycloaddition of ketones to anhydrides have appeared to date*. Herein we report the first such processes involving the organocatalytic cycloaddition of a range of enolisable anhydrides **19** with activated, *unsymmetrical* ketones **20** to furnish cycloadducts **21** with excellent enantio- and diastereocontrol. We will also show that the methodology is capable of generating products such as **22**, which incorporates two contiguous quaternary stereocentres, (one completely carbogenic) with outstanding stereocontrol.

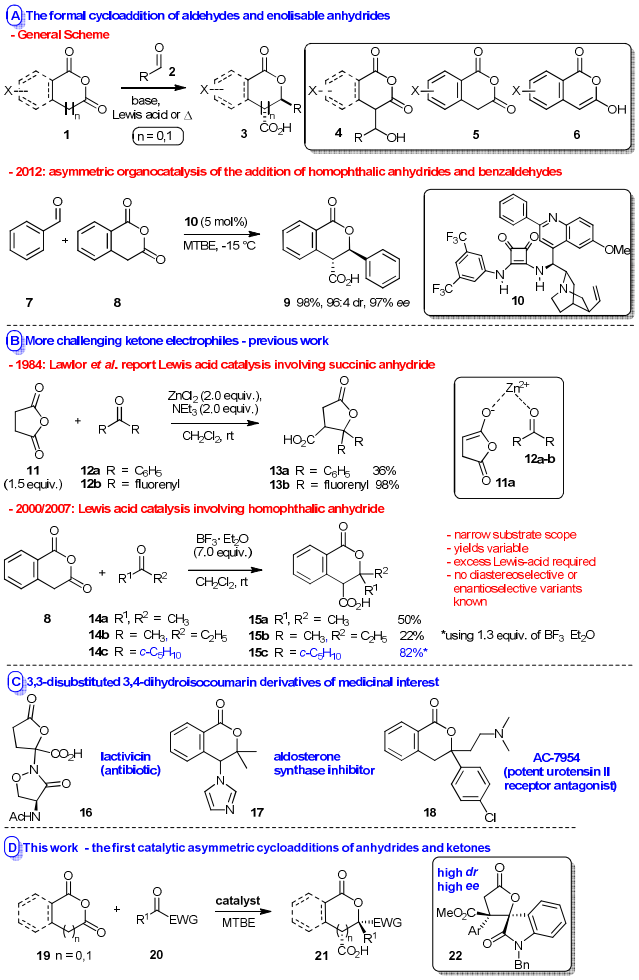
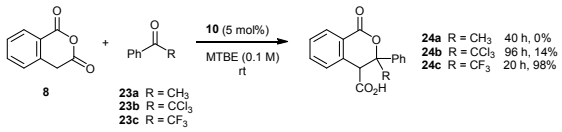


Fig. 1 Formal cycloadditions between ketones and enolisable anhydrides

Our investigation began with initial experiments to ascertain the magnitude of the ketone electrophilicity problem. With this in mind, we reacted acetophenone (**23a**), trichloroacetophenone (**23b**) and trifluoroacetophenone (**23c**) with **8** in the presence of catalyst **10** in MTBE at ambient temperature (Scheme 1). As expected, the relatively electron rich substrate **23a** proved resistant to cycloaddition, however, we were pleased to find that the more activated (non-enolisable) **23b** participated in a slow, low-yielding reaction to give **24b** – the first organocatalysed process involving ketones of its kind. The considerably more electrophilic **23c** provided the acid product **24c** as a mixture of diastereomers in near quantitative yield after 20 h.[18]



Scheme 1 Preliminary experiments investigating substrate scope

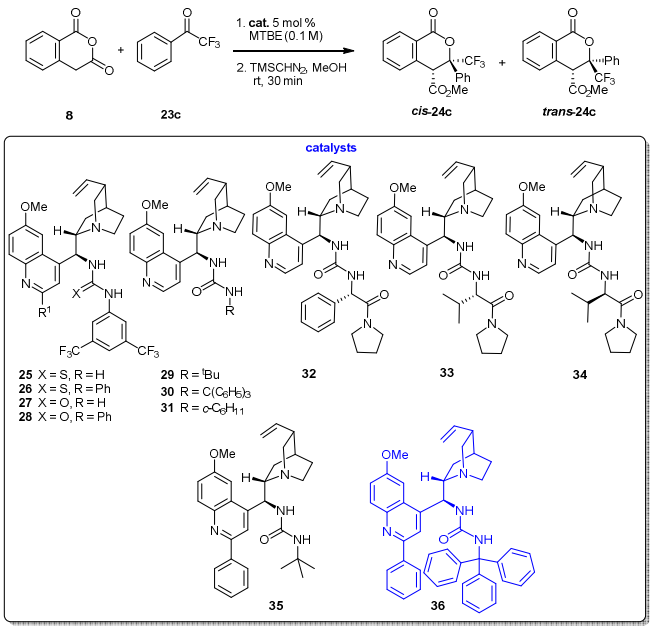
Next, we initiated a screening study to optimise both the catalyst structure and the reaction conditions (Table 1). Catalyst **10** (the superior system identified in our previous study using aldehydes[8]) promoted the process with mediocre diastereoselectivity (favouring ***cis*-24c**) and moderate enantioselectivity (entry 1). Exchange of the squaramide functionality for a thiourea unit (both without and with C-2 phenyl substituents – catalysts **25** and **26** respectively) led to improved diastereocontrol but lower product *ee* (entries 2-3). At the lower temperature of -15 °C, catalyst **10** is sparingly soluble in MTBE. It is more soluble in THF at this temperature, however enantioselectivity was lower in this solvent (entry 4). Interestingly, ureas **27** and **28** (analogous to **25** and **26**) are soluble in MTBE at -15 °C; both catalysts allowed the formation of the product with 90:10 *dr*, while the reaction catalysed by the C-2 phenyl-substituted variant was appreciably more enantioselective (72% *ee*, entries 4-5).

Thus it appeared that the use of an urea-based hydrogen bond donating moiety and steric bulk at the quinoline catalyst unit are important features contributing to overall stereocontrol. The contribution of the urea substituents was next investigated through the synthesis and evaluation of catalysts **29-34**. The use of bulky, aliphatic *N*-substituents (*i.e.* catalysts **29-31**) brought about a significant increase in both diastereo- and enantiocontrol, with the *t*-butyl group (*i.e.* **29**) proving optimal (entries 7-9) as it promoted faster chemistry with similar levels of stereocontrol (albeit with slightly lower diastereocontrol) than the trityl-substituted variant **30**. Since this region of space around the urea group seemed to be important – we were intrigued as to the possibility of fine-tuning through the introduction of an additional stereocentre adjacent to the urea unit (*i.e.* catalysts **32-34**). While it is clear that the additional stereocentre influenced the stereochemical outcome of the process dramatically (entries 10-12), no overall improvement in performance relative to the more simple structure **29** was detected.

With the best hydrogen bond donating unit and urea-substituents identified, our attention turned to the quinoline functionality. The modification of catalyst **29** through the installation of a C-2 phenyl moiety (*i.e.* catalyst **35**) allowed greater enantiocontrol (entry 13). Finally, augmentation of the steric requirement of the urea group gave rise to **36**, the most effective catalyst yet from a stereocontrol standpoint (entry 14).

Subsequent optimisation of the reaction conditions allowed the efficient synthesis of ***cis*-24c** catalysed by **36** with 97:3 *dr* and 92% *ee* (entries 14-16).

Table 1 The cycloaddition of **8** with **23c**: catalyst identification and optimisation of the reaction conditions

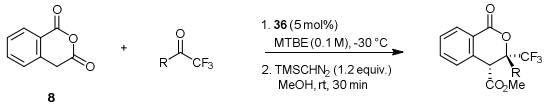


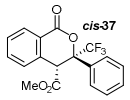
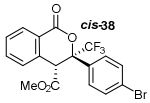
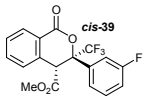
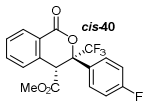
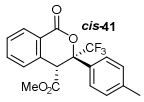
Entry	Cat.	Temp. (°C)	Time (h)	Yield (%)[a]	dr[b] (*cis*:*trans*)	ee_{cis} (%)[c]
1	**10**	rt	20	98	85:15	64
2	**25**	rt	47	>95	91:9	48
3	**26**	rt	47	>95	91:9	56
4[d]	**10**	-15	120	73	90:10	54
5	**27**	-15	63	81	90:10	56
6	**28**	-15	55	76	90:10	72
7	**29**	-15	64	85	93:7	84
8	**30**	-15	64	65	97:3	84
9	**31**	-15	64	84	94:6	74
10	**32**	-15	69	64	96:4	62
11	**33**	-15	69	71	97:3	84
12	**34**	-15	69	58	97:3	-38
13	**35**	-30	61	88	91:9	88
14	**36**	-15	64	78	95:5	90
15	**36**	-30	63	79	96:4	92
16[e]	**36**	-30	64	>95	97:3	92

[a]Yield of the combined diastereoisomers: determined by ^{1}H NMR spectroscopy using *p*-iodoanisole as an internal standard. [b]Diastereomeric ratio: determined by ^{1}H NMR spectroscopy. [c]Determined by CSP-HPLC. [d]Reaction in THF. [e]1.5 eq. of anhydride **8**.

The process can be used to easily transform other trifluoromethylacetophenones (Table 2). Under optimised conditions the lactone derived from the archetypal **23c** could be obtained in excellent *dr*, *ee*, and isolated yield (entry 1). *m*- And *p*-halo substituted analogues ***cis*-38-40** could also be prepared in high yield and with similar levels of stereocontrol (entries 2-4). Interestingly, the synthesis of the corresponding *p*-methyl derivative ***cis*-41** (derived from a relatively deactivated ketone substrate) was formed with significantly lower (albeit acceptable) yield and *dr*, but with excellent enantiocontrol (entry 5)

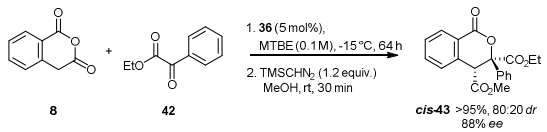
Table 2 The cycloaddition of **8** with α,α,α,-trifluroacetophenones: substrate scope



Entry	Product	Time (h)	Yield (%)[a]	dr[b] (*cis*:*trans*)	ee_{cis} (%)[c]
1[d]	 *cis*-37	64	93	97:3	92
2	 *cis*-38	61	85	98:2	95
3	 *cis*-39	95	89	97:3	92
4	 *cis*-40	94	79	97:3	92
5[d]	 *cis*-41	94	61	88:12	91

[a]Isolated yield. [b]Diastereomeric ratio: determined by ^{1}H NMR spectroscopy. [c]Determined by CSP-HPLC. [d]1.5 eq. of anhydride **8**.

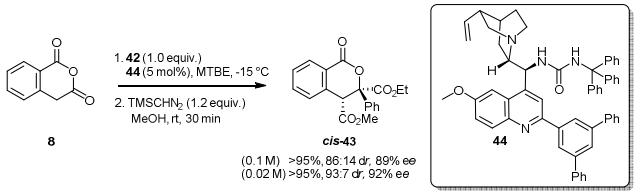
We were next interested in attempting to react **8** with activated ketone electrophiles incorporating electron-withdrawing functionality more synthetically malleable than the trifluoromethyl group. It was found that ethylbenzoyl formate could undergo the cycloaddition process with **8** catalysed by **36** (Scheme 2) at -15 °C with good diastereocontrol and 88% *ee*. While the participation of this type of electrophile in the reaction for the first time was encouraging, the level of stereocontrol was lower than that obtained using **23c**. Significant experimentation aimed at optimising the conditions did not lead to improvements.



Scheme 2 Asymmetric cycloaddition between **8** and ketoester **42**.

The catalyst structure was therefore re-examined. We had found (Table 1) that augmentation of the steric bulk of both the aliphatic *N*-aryl substituent and the quinoline moiety improved catalyst performance. However, since the trityl unit is already of

considerable size, we focussed on the quinoline group, and synthesied and evaluated catalyst **44**, which incorporates a terphenyl group not previously employed in cinchona-alkaloid-based bifunctional catalysis. Use of this catalyst resulted in improved diastereocontrol and marginally superior *ee*. However, on reduction of the reaction concentration to 0.02 M, synthetically useful levels of diastereo- and enantioselectivity were obtained (Scheme 3).

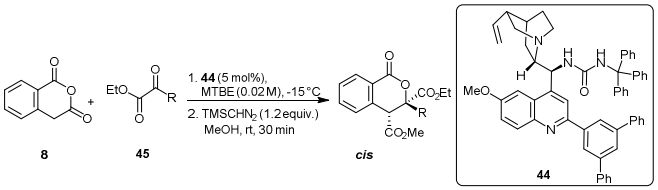


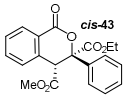
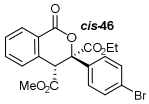
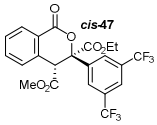
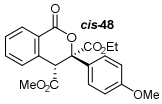
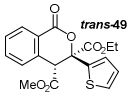
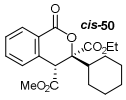
Scheme 3 Synthesis of ***cis*-43** using the improved catalyst **44**.

The new catalyst **44** could promote the cycloaddition of **8** with a variety of α-ketoesters of general type **45** (Table 3). The archetypal phenyl substituted derivative ***cis*-43** could be prepared using this method in excellent isolated yield, dr and *ee* (entry 1). The *p*-bromo substituted variant ***cis*-46** was formed with superior stereocontrol still (entry 2), however lactones derived from more activated-, less activated- and heterocyclic-ketoesters (*i.e.* products ***cis*-47**, ***cis*-48** and ***trans*-49**, entries 3-5 respectively) were synthesised with slightly lower levels of enantiomeric excess. The cyclohexyl analogue ***cis*-50** was the only lactone to be formed with moderate *ee* (albeit with good diastereocontrol), indicating that perhaps π-stacking may be involved in the facial recognition by the catalyst (entry 6).

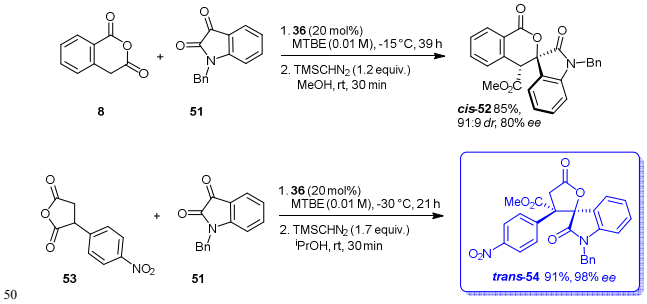
N-benzyl isatin (**51**) is an interesting substrate potentially capable of being transformed into spirocyclic oxindole scaffolds - a structural unit present in a wide range of biologically active compounds.[19] When utilised in conjunction with homophthalic anhydride (**8**) in the presence of catalyst **36** it provided the novel spiro tetracyclic product ***cis*-52** in good yield, *dr* and *ee*. The exchange of **8** for the aryl-succinic anhydride **53** (previously shown to be amenable to the corresponding reaction with aldehydes[9]) furnished ***trans*-54** in 91% isolated yield and 98% *ee* at -30 °C. This reaction represents a rare example of an organocatalytic process generating *two contiguous quaternary stereocentres* (one completely carbonaceous) with excellent efficiency and stereocontrol (Scheme 4).[20]

Table 3 The cycloaddition of **8** with α–ketoesters



Entry	Product	Time (h)	Yield (%)[a]	dr[b] (*cis*:*trans*)	ee_{cis} (%)[c]
1	 ***cis*-43**	36	89	93:7	92
2	 ***cis*-46**	41	94[d]	97:3	95 (91)[e]
3[f]	 ***cis*-47**	94	92	97:3	85
4[g]	 ***cis*-48**	72	61	81:19	87
5	 ***trans*-49**	86	75	6:94	88
6	 ***cis*-50**	72	85	90:10	66

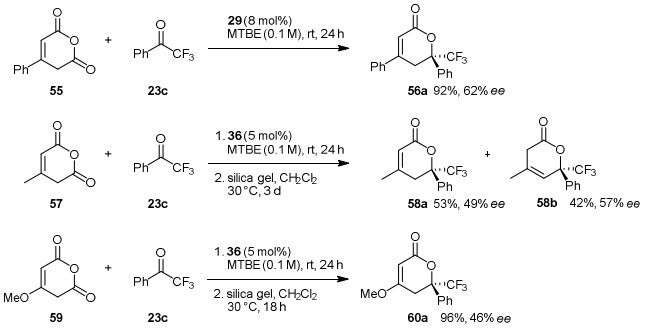
[a]Isolated yield. [b]Diastereomeric ratio: determined by ^{1}H NMR spectroscopy (400 MHz). [c]Determined by CSP-HPLC. [d]Diastereomers inseparable: combined isolated yield. [e]*ee* of *trans*-isomer in parenthesis. [f]Reaction performed at -50 °C. [g]10 mol% catalyst loading



Scheme 4 Use of *N*-benzyl isatin as an electrophile

Prompted by the suitability of succinic anhydride **53** as a substrate, we next evaluated the use of substituted glutaconic anhydride derivatives such as **55** and **57** (Scheme 5) - which we

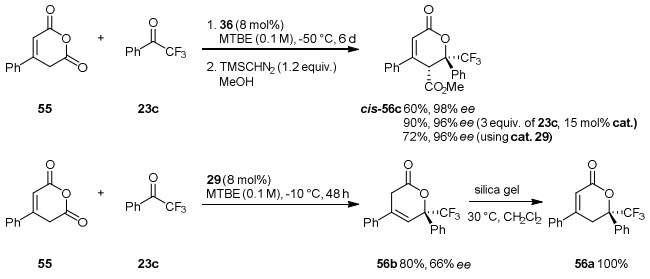
have recently shown to participate in asymmetric Tamura cycloaddition reactions with activated Michael acceptors.[10] We were pleased to observe that these reacted with ketone **23c** at ambient temperature, with both the phenyl- and methyl-substituted glutaconic anhydride derivatives (**55** and **57** respectively) undergoing conversion to **56** and **58**. In addition, the potentially more synthetically pliable methoxy-substituted analogue **59** (which had not been previously evaluated in Tamura cycloadditions[10]) also participated in the reaction. In all three cases decarboxylation and olefin isomerisation accompanied cycloaddition, however, while this process gave the highly conjugated α,β-unsaturated lactone **56a** exclusively from anhydride **55**, mixtures of olefin isomers were obtained using **57** and **59**, which appeared to interconvert during column chromatography. Therefore we repeated the reactions and attempted to quantitatively isomerise the olefin products by heating in dichloromethane at 30 °C in the presence of silica gel. Under these conditions the kinetic methyl-substituted product **58b** could be partially converted to **58a**, while the methoxy analogue **60b** (not shown) could be completely transformed into **60a**. Enantioselectivity was encouraging, yet moderate.



Scheme 5 Glutaconic anhydride derivatives as pronucleophiles

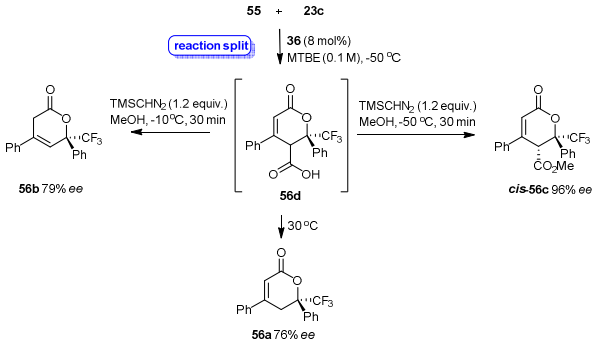
Speculating that the entropically favourable process would be disfavoured at lower temperatures, we next repeated the reaction between **23c** and **55** at -50 °C. Under these conditions, the intermediate carboxylic acid could be trapped by *in situ* esterification to yield the methyl ester ***cis*-56c** in 60% yield and 98% *ee* (Scheme 6). Product yields could be improved using increased catalyst and ketone loading. Interestingly, it was found that the *t*-butyl substituted catalyst **29** (devoid of a C-2 phenyl substituent) also performed well in this reaction – promoting the formation of ***cis*-56c** in good yield and with excellent enantiomeric excess.

Since decarboxylation and isomerisation are favoured at the higher temperature, we wondered as to which product would dominate at a temperature intermediate between ambient and -50 °C. Catalysis of the cycloaddition between **23c** and **55** by **29** at -10 °C furnished the β,γ-unsaturated lactone **56b** in 80% yield and with moderate enantiomeric excess. This product could be quantitatively isaomerised to 60a by heating in the presence of silica gel.



Scheme 6 Product ratios at -50 and -10 °C.

In order to shed some light on the mechanism of these reactions involving glutaconic anhydride derivatives, **23c** and **55** were reacted in the presence of catalyst **36** at -50 °C. A sample of the reaction was then esterified at that temperature, to afford the expected product **56c** in 96% *ee*. A further sample was then allowed to warm to -10 °C and then treated with trimethylsilyldiazomethane. In this instance, **56b** was isolated (in the absence of any esterified products) in 79% *ee*. Finally, a sample was allowed to warm to 30 °C, which generated **56a** in a similar *ee* of 76% (Scheme 7). Assuming that no kinetic resolution occurs during the *in situ* esterification process (highly implausible), and in the absence of any other plausible racemisation mechanism, these results strongly indicate that these cycloaddition processes are reversible. At -50 °C, highly enantioselective cycloaddition to the kinetic product **56d** occurs, however, if esterification at this temperature is not carried out, then increasing the reaction temperature leads to an erosion of the product enantiomeric excess *via* a cycloreversion, (less enantioselective) cycloaddition and decarboxylation sequence.

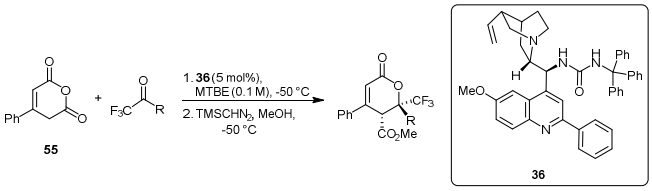


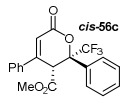
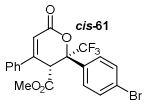
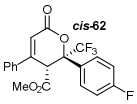
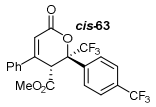
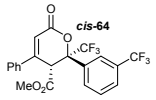
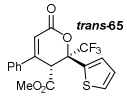
Scheme 7 Dependency of product *ee* on reaction temperature

The scope of the process with respect to the 'electrophilic' reaction component was also briefly examined (Table 4). The phenyl-substituted anhydride **55** underwent cycloaddition with a range of trifluromethylacetophenones catalysed by **36** at -50 °C, followed by *in situ* esterification. The archetypal lactone ***cis*-56c** (derived from **23c**) could be isolated as a single diastereomer in excellent yield and with outstanding enantiomeric excess (entry 1). The *p*-halo substituted analogues ***cis*-61** and ***cis*-62** could be prepared with excellent efficacy, diastereo- and enantiocontrol (entries 2-3). The *p*-trifluoromethyl substituted ketone underwent

cycloaddition with excellent stereocontrol (***cis*-63**, entry 4), however, while *m*-substitution is tolerated and diastereocontrol remains total, ***cis*-64** was formed with lower (yet still high) enantiomeric excess (entry 5). The heterocyclic thiophene-based ketone proved a more disappointing substrate – it was the only ketone to fail to convert to a single product diastereomer, and the *ee* of the major diastereomer ***trans*-65** was significantly lower that that associated with the other trifluoromethylketone electrophiles (*i.e.* 82%, entry 6).

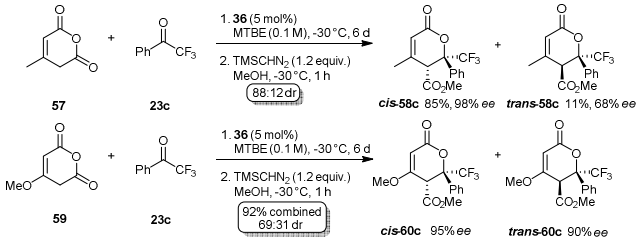
Table 4 The cycloaddition of **55** with trifluoroacetophenones



Entry	Product	Time (d)	Yield (%)[a]	dr[b] (*cis:trans*)	ee_{cis} (%)[c]
1	 ***cis*-56c**	6	92	>98:2	98
2	 ***cis*-61**	6	90	>98:2	99
3	 ***cis*-62**	6	92	>98:2	96
4	 ***cis*-63**	6	89	>98:2	96
5	 ***cis*-64**	6	96	>98:2	96
6	 ***trans*-65**	7	85[d]	17:83	82 (32)[e]

[a]Isolated yield. [b]Diastereomeric ratio: determined by ^{1}H NMR spectroscopy (400 MHz). [c]Determined by CSP-HPLC. [d]Diastereomers inseparable: combined isolated yield. [e]*ee* of *cis*-isomer in parenthesis.

Finally, we exposed the methyl- and methoxy-substituted anhydrides **57** and **59** to **23c** at low temperature in the presence of catalyst **36**, which allowed the generation of lactones ***cis*-58c** and ***cis*-60c** respectively after esterification, with good diastereo- and excellent enantioncontrol (Scheme 8).



Scheme 8 Reaction of **57** and **59** with **23c** under optimised conditions

Conclusions

In summary, the scope of asymmetric formal cycloadditions involving enolisable anhydrides has been extended to include activated ketones for the first time. Previously, examples of the reaction between anhydrides and ketones were extremely rare and were limited to racemic processes – with superstoichiometric 'catalyst' loadings required. This study has shown that in the presence of novel urea-based cinchona alkaloid-based catalysts, enolisable anhydrides readily undergo highly diastereo- and enantioselective cycloadditions with activated ketones such as trifluoromethyl acetophenone derivatives, α-ketoesters and *N*-benzyl isatin to generate densely functionalised, synthetically malleable products containing two new stereocentres, one of which is quaternary. In one example, the formation of a compound with two contiguous quaternary stereocentres (one all carbon) in 91% yield and 98% *ee* was demonstrated. Three different types of enolisable anhydride were shown to be compatible with the process – the benzo-fused homophthalic anhydride, an α-aryl succinic anhydride and glutaconic anhydrides (three different analogues) – which generate structurally distinct lactone products. It has been shown that cycloadditions involving the latter class of anhydrides (*e.g.* **55**) are reversible - the kinetic carboxylic acid product can be trapped *via in situ* esterification in excellent yield, dr and *ee* at low temperatures. At higher temperatures decarboxylation and olefin isomerisation occur. Studies to further explore the scope and mechanism of these intriguing reactions are in progress.

Acknowledgements

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GRAPHICAL ABSTRACT