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Synthesis of α-alkylated γ-butyrolactones with concomitant anhydride kinetic resolution using a sulfamide-based catalyst†

Romain Claveau, Brendan Twamley‡ and Stephen J. Connon *

The Kinetic Resolution (KR) of α-alkylated enolisable disubstituted anhydrides has been shown to be possible for the first time. In the presence of an *ad hoc* designed novel class of bifunctional sulfamide organocatalyst, a regio-, diastereo- and enantioselective cycloaddition reaction between the enolisable anhydride and benzaldehydes provides densely functionalised γ-butyrolactones in one pot (up to 19 : 1 dr, 94% ee) with control over three contiguous stereocentres. The concomitant resolution of the starting material anhydride, provides access to a range of chiral succinate derivatives with selectivity factors up to *S = 10.5.**

γ-Butyrolactones substituted at each saturated carbon constitute a highly important structural *motif* in organic chemistry which serve as scaffolds in a wide range of complex natural products such as **1–3** (Fig. 1A).[1] Derivatives bearing a β-substituted carboxylic acid moiety to the carbonyl group are known as paraconic acids (**4**)[2] – an important butyrolactone natural product subclass (*e.g.* **5–7**) possessing diverse biological activities[2,3] (Fig. 1B).

The development of one-pot catalytic asymmetric methods for the preparation of these important structural cores remains a challenge which attracts considerable attention.[4,5] In particular, such a methodology for the construction of the often-encountered α-methyl substituted analogues is not known. These methylated butyrolactones are precursors (*via* an α-selenation/oxidation/β-elimination sequence[6]) to the widely bioactive α-methylene-γ-butyrolactones (*e.g.* **8**, Fig. 1B) which have been estimated to be present in over 14 000 natural products.[7]

In 2012, we reported the catalytic dynamic kinetic resolution (DKR) reaction between racemic α-aryl succinic anhydrides (rather unusually behaving as nucleophiles in the first reaction step) with aldehydes as electrophiles.[8–10] When mediated by a cinchona alkaloid-based organocatalyst, under mild conditions, these enolisable anhydrides underwent reaction with a range of aromatic and aliphatic aldehydes to furnish γ-butyrolactone derivatives in excellent yields, diastereo- and enantioselectivities.

Recently we expanded the scope to include the DKR of bis-aryl succinic anhydrides of general type (*rac*)-**9** (Fig. 2A) involving reaction with aldehydes **10** mediated by catalyst **12** to afford lactones of general type **11** *via* enolate **13**[9h] with good to excellent levels of enantio- and diastereocontrol.[11] Rapid (relative to addition) enolate transfer between carbonyl units (thereby racemising the starting material *via* its achiral *meso* form) allows for efficient DKR. Processes involving α-*alkylated*-succinic anhydrides are much less studied.

Parallel kinetic resolution (where both enantiomers of the starting material react but form non-enantiomeric products) of chiral α-alkyl succinic anhydrides has been reported. Seebach and co-workers[12] showed that in the presence of a stoichiometric Ti-complex, that the net transfer of isopropanol to anhydride **14** could occur in a face-selective manner to

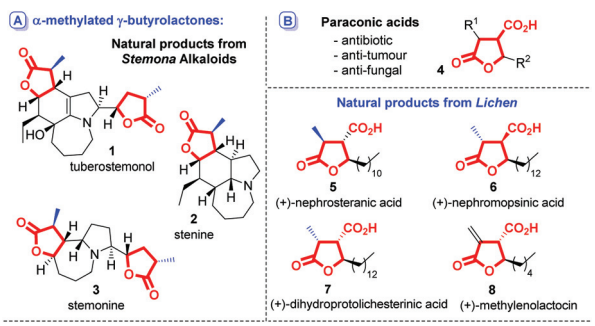


Fig. 1 Natural products incorporating the trisubstituted butyrolactone *motif*.

School of Chemistry Trinity Biomedical Sciences Institute, Trinity College Dublin 152-160, Pearse Street, Dublin 2, Ireland. E-mail: connons@tcd.ie; Tel: +35318961306

†Electronic supplementary information (ESI) available: Procedures for the syntheses of starting materials, catalysts and additional data: NMR spectra of the products, HPLC chromatograms, *etc*. CCDC 1866833 and 1866834. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob02248h

‡X-Ray crystallography facility: twamleyb@tcd.ie

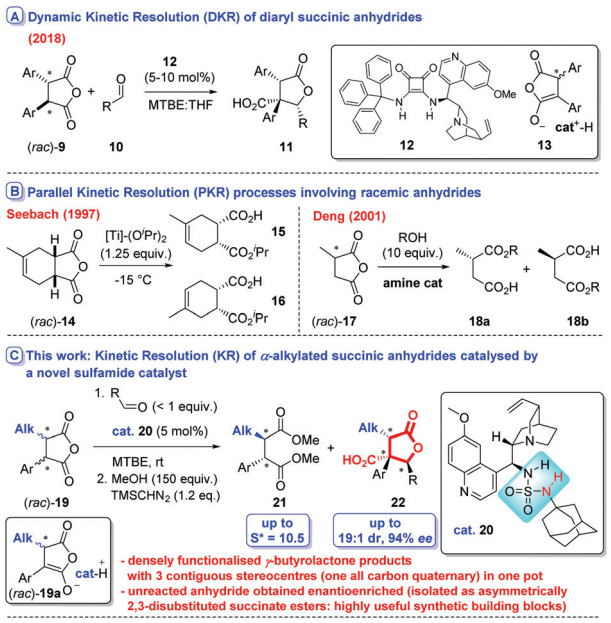


Fig. 2 Previous DKR/PKR of anhydrides and the current KR approach.

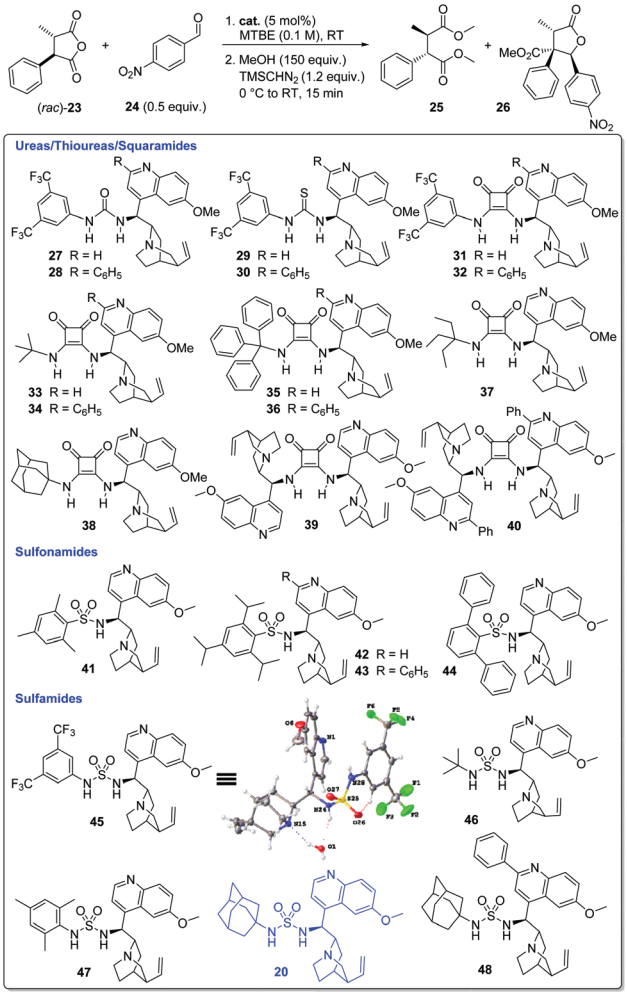


Fig. 3 Catalysts designed for use in anhydride KR.

Table 1 Catalyst screening

Entry	Cat.	t (h)	Conv.[a] (%)	ee[b] (%) **25**	S^*	dr[a] **26** (**a** : **b** : **c** : **d**)	ee[b] (%) **26a**
1	**27**	72	70[d]	n.d.[c]	n.d.[c]	72 : <1 : <1 : 28	3
2	**28**	96	37	n.d.[c]	n.d.[c]	58 : <1 : <1 : 42	15
3	**29**	120	33	10	1.7	59 : <1 : <1 : 41	14
4	**30**	96	32	n.d.[c]	n.d.[c]	63 : <1 : <1 : 37	17
5	**31**	96	37	6	1.3	80 : <1 : <1 : 20	12
6	**32**	96	30	n.d.[c]	n.d.[c]	94 : <1 : <1 : 6	41
7	**33**	168	44	35	3.6	79 : <1 : <1 : 21	30
8	**34**	216	52[d]	26	2.0	90 : <1 : <1 : 10	36
9	**35**	168	44	40	4.5	64 : <1 : <1 : 36	6
10	**36**	168	42	43	5.9	65 : <1 : <1 : 35	10
11	**37**	168	40	33	4.0	76 : <1 : <1 : 24	30
12	**38**	168	43	27	2.7	82 : <1 : <1 : 18	21
13	**39**	96	46	37	3.6	69 : <1 : <1 : 31	29
14	**40**	168	35	n.d.[c]	n.d.[c]	67 : <1 : <1 : 33	33
15	**41**	144	43	n.d.[c]	n.d.[c]	81 : <1 : <1 : 19	57
16	**42**	168	45	50	6.7	95 : <1 : <1 : 5	59
17	**43**	168	46	39	3.9	94 : <1 : <1 : 6	56
18	**44**	168	46	3	1.1	82 : <1 : <1 : 18	5
19	**45**	144	43	26	2.6	97 : <1 : <1 : 3	48
20	**46**	120	45	47	5.8	96 : <1 : <1 : 4	47
21	**47**	96	46	47	5.4	94 : <1 : <1 : 6	47
22	**20**	168	48	64	10.5	95 : <1 : <1 : 5	63
23	**48**	144	48	52	5.9	94 : <1 : <1 : 6	55

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by CSP-HPLC, refers to the major diastereomer. [c] Not determined. [d] **24** (0.7 eq.).

produce hemiesters **15–16**.[13] In 2001, Deng and Chen[14] developed an efficient, modified cinchona alkaloid-catalysed simultaneous enantioselective and regioselective alcoholysis of the two enantiomers of the racemic anhydride **17** – leading to the formation of enantioenriched hemiesters **18a–b**.

To the best of our knowledge, the simple kinetic resolution of an α-substituted anhydride which provides access to enantioenriched unreacted anhydride starting material is unknown.

Herein we report the development of the first KR of asymmetrically substituted racemic anhydrides, which also represents an exceedingly rare example of the challenging catalytic kinetic resolution of a racemic enolate.[15] In the presence of a novel sulfamide catalyst **20**, anhydrides such as **19** could be resolved *via* reaction with substoichiometric aldehydes to yield densely functionalised γ-butyrolactone products **22** with up to 19 : 1 dr and 94% ee. The slower reacting anhydride enantiomer can be derivatised *in situ* for HPLC analysis to yield enantioenriched 2,3-asymmetrically disubstituted succinate derivatives **21** – a highly important class of 1,4-dioxygenated synthetic building block in natural product – and medicinal chemistry.[16]

Our study began with a catalyst screen (Table 1). The 2-methyl-3-phenyl succinic anhydride (***rac***)-**23** was reacted with 4-nitro benzaldehyde (0.5 eq., **24**) in the presence of catalyst (5 mol%) in MTBE at ambient temperature (Fig. 3). The reactions were quenched with MeOH (150 eq.) and both the ring opened hemiesters (derived from unreacted **23**) and the lactone carboxylic acid stemming from the reaction were esteri-

fied (to give **25** and **26** respectively) *in situ* through the addition of trimethylsilyldiazomethane. The results of these experiments are outlined in Table 1. While **25** was always formed with near perfect diastereocontrol, this product does possesses more than one stereogenic centre, so the determination of the conversion-independent selectivity factor ($S = k_{fast}/k_{slow}$) is not straightforward. Therefore, in these studies we utilised an approximate, simplified parameter S^*,[15] based on conversion determined by ^{1}H NMR spectroscopy and the ee data associated with the major product diastereomer only, which served solely as a guide for catalyst design. Use of the prototype urea and thiourea-substituted cinchona alkaloid catalysts[17] (both with and without the *C*-2 aryl modification) **27**–**30** provided poor levels of diastereocontrol and enantiodiscrimination (entries 1–4).

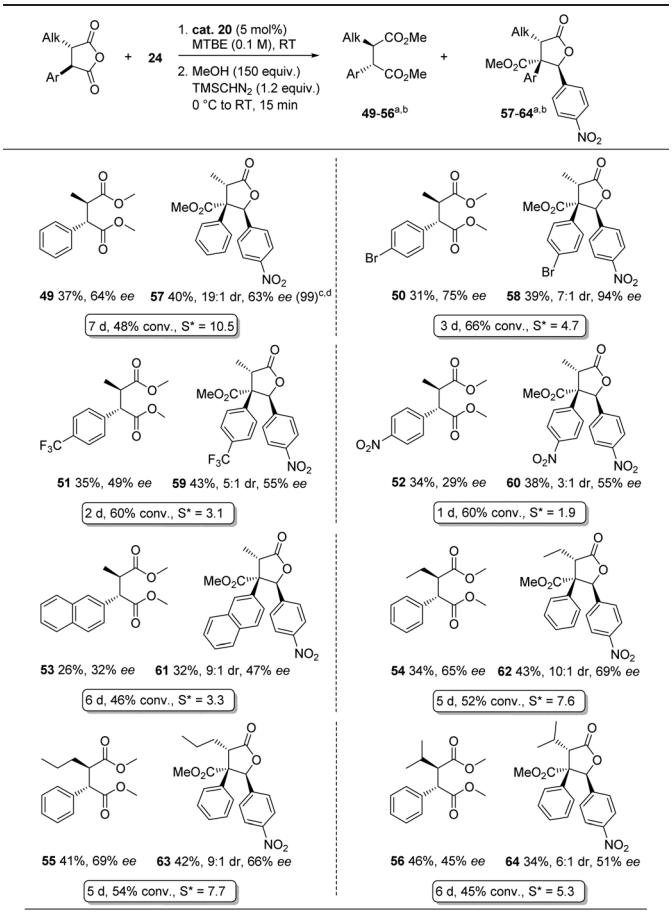
Squaramide-based bifunctional systems[18] were next investigated: the simple *N*-aryl catalyst **31** exhibited a similar level of performance to (thio)ureas **27**–**30** (entry 5), however an analogue where a phenyl unit had been installed at the catalyst's quinoline ring (*i.e.* **32**) promoted the highly diastereoselective formation of the major lactone **26a** with 41% ee at 30% conversion (entry 6). Squaramides characterised by the exchange of the *N*-aryl moiety for an *N*-alkyl group (despite considerable structure diversity) promoted less selective catalysis (entries 7–14).

We next evaluated the monoprotic yet more acidic sulfonamide-based alkaloid catalyst family – which have previously been shown[19] to effectively catalyse the enantioselective addition of nucleophiles to *meso*-anhydrides. This catalyst class proved superior: the hindered, mesityl-substituted material **41** allowed the preparation of **26a** (with good diastereocontrol) with considerably higher ee (and at higher conversion – which does not favour the formation of the product with high ee) than the hitherto best catalyst evaluated (compare entries 6 and 15). Augmentation of the steric demand of the sulfonamide aryl substituent (*i.e.* catalyst **42**) provided excellent diastereocontrol and a marginal improvement in product ee at similar conversion (*i.e.* **43**, entry 16), however the addition of the catalyst *C*-2 phenyl unit is not beneficial (entry 17). Increasing the steric bulk around the sulfonamide hydrogen-bond donor through the synthesis and evaluation of the diphenyl catalyst **44** proved a retrograde step (entry 18).

Given that we obtained encouraging results with both hindered squaramides and sulfonamides, we hypothesised that a sulfamide catalyst capable of both participating in bifurcated hydrogen bonding (similar to squaramides) but with acidity more akin to the successful sulfonamide class could serve as a superior promoter of the process. Several groups[20] have utilised sulfamides as organocatalysts, however their incorporation into a cinchona alkaloid backbone is, to the best of our knowledge, unknown. While **45** promoted resolutions twice as enantioselectively as its squaramide variant **31** (S^* = 1.3 *vs.* 2.6, entries 5 and 19), when the steric bulk of the sulfamide substituent is systematically increased (entries 20–22), enantioselectivity improves dramatically, leading to the adamantly-substituted catalyst **20**, which can mediate the resolution with selectivity generally regarded as synthetically useful (*i.e.* $S^* > 10$, entry 22). This allows the isolation of both the stereochemically dense lactone **26a** (with excellent diastereocontrol) and the unreacted enantioenriched anhydride derivative (*i.e.* the asymmetrically disubstituted succinate ester **25**) with >60% ee at *ca.* 50% conversion. The incorporation of a *C*-2 phenyl unit into catalyst **20** was not advantageous (entry 23). We also utilised benzaldehyde and hydrocinnamaldehyde as reacting partners, with inferior results (see ESI†).

Attention next turned to the question of substrate scope. A range of 2,3-disubstituted succinic anhydrides in which either the alkyl- or the aryl unit was varied could be resolved *via* reaction with **27** in the presence of catalyst **20** to form (after derivatisation) succinate esters **49**–**56** and γ-butyrolactones **57**–**64** with moderate-good selectivity factors (S^*, Table 2). In general, substitution of the anhydride's aromatic ring with an electron-withdrawing group led to faster but less selective resolution (*i.e.* products **49**–**52** and **57**–**60**). Extension of the aromatic substituent also attenuated enantioselectivity (*i.e.* **53** and **61**). It seems likely that interactions with the catalyst in the preferred

Table 2 Evaluation of substrate scope



[a] Isolated yield. [b] dr determined by ^{1}H NMR spectroscopic analysis. ee determined using CSP-HPLC. $S^* = \ln[(1 - C)(1 - ee_{SM})]/\ln[(1 - C)(1 + ee_{SM})]$. [c] Data reproduced from Table 1. [d] Enantiomeric excess after recrystallisation from $CHCl_3$ indicated in parentheses.

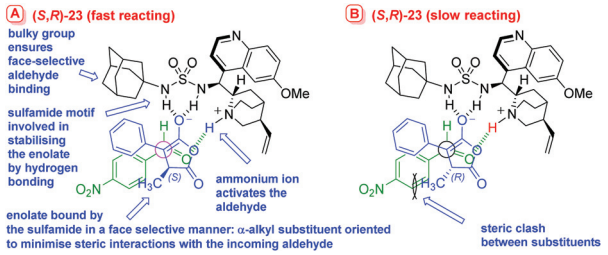


Fig. 4 Stereochemical rationale.

transition state are hampered (relative to the other aromatic substrates) in this instance. With regards to the alkyl substituents: ethyl- and propyl-substituted analogues (*i.e.* leading to products **54–55** and **62–63**) could be resolved with S^* of 7.6 and 7.7 respectively, while the bulkier isopropyl-variants **56** and **64** were formed in a less selective process which still had an associated S^* of 5.3.

A single recrystallisation of the major lactone diastereomer produced by the reaction afforded an enantiomerically pure sample of **57** (>99% ee) which was suitable for single crystal X-ray diffraction pattern analysis (see ESI†). The absolute configuration of **57** (Fig. 3) was subsequently assigned as (*S*,*S*,*S*).[21] A stereochemical rationale consistent with the calculated mechanism[9h] for these types of reactions is presented in Fig. 4.

In summary, we have developed the first kinetic resolution (in the traditional sense) of racemic chiral anhydrides. The reaction provides access to resolved enantioenriched anhydrides for the first time, which can be ring-opened and esterified *in situ* to form synthetically valuable 2,3-disubstituted succinate esters. The resolution processes were accompanied with the simultaneous formation of stereochemically dense α-alkylated γ-butyrolactones *via* control over 3 contiguous stereocentres (one quaternary) with modest to excellent enantioselectivity (up to 94% ee, S^* = 10.5) and excellent diastereocontrol. These reactions were mediated by a new class of chiral sulfamide bifunctional catalysts based on a cinchona alkaloid scaffold, the bulkiest of which bears an adamantyl unit and easily outperforms more traditional bifunctional catalyst structures in this process. Studies to further improve the performance and scope of this new KR process as well as the evaluation of the potential of the novel alkaloid-based sulfamide organocatalysts are underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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21 The stereochemical assignment of diester **25** was made following a combination of ^{1}H NMR spectroscopic analysis and by analogy with the absolute stereochemistry of the cognate lactone product (known from XRD analysis) – see the ESI.†

