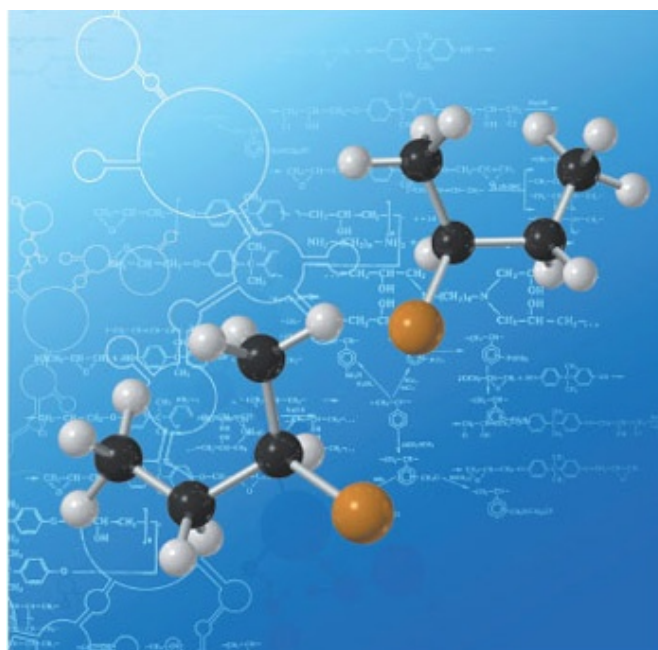This article is part of the

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COMMUNICATION

Catalytic, *enantio*- and diastereoselective synthesis of γ-butyrolactones incorporating quaternary stereocentres†‡

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A new, highly *enantio*- and diastereoselective catalytic asymmetric formal cycloaddition of aryl succinic anhydrides and aldehydes which generates paraconic acid (γ-butyrolactone) derivatives is reported.

It has been known for over 140 years that enolisable anhydrides can participate in aldol-like coupling chemistry with aldehyde electrophiles to furnish α,β-unsaturated acid products in the presence of carboxylate bases.[1] Later it was realised that–in a related process–cyclic (*e.g.* succinic/glutaric) anhydrides **1** can react with aldehydes (in the presence of stoichiometric base/Lewis acid) to form lactone products **2** (Scheme 1A).[2–5]

These reactions generate synthetically malleable products with (in most instances) the creation of two new stereocentres. Current thinking regarding the mechanism involves initial enolisation of the anhydride, followed by its addition to the aldehyde electrophile to generate the tetrahedral intermediate **3**, which then rapidly lactonises.[5] This hypothesis is supported by (*inter alia*) the observation that homophthalic anhydrides of general type **4**—the enol form of which (*i.e.* **5**) are stabilised by conjugation with the aromatic ring—are considerably more reactive substrates than simpler, non-benzo fused analogues (which usually[6] react at elevated temperatures in the presence of either a stoichiometric Lewis acid[4,7] or carboxylate base[2a–d,8]) and can be converted to dihydroisocoumarins under mild conditions, often in the absence of a catalyst.[5]

Recently, we disclosed the first examples of an enantio-selective variant of this process (Scheme 1B).[9] The methodology exploits the aforementioned relative acidity of homophthalic anhydrides such as **6** in conjunction with an *ad hoc*-designed bifunctional organocatalyst, which we suggested was capable of promoting both enol formation and face-selective addition to the aldehyde electrophile. The process generates bicyclic lactone products such as **8** which incorporate the

dihydroisocoumarin core (a unit–highlighted in blue–present in a wide range of natural products and other molecules of medicinal/pharmaceutical interest[10]) with excellent yield and *enantio*/diastereocontrol under convenient conditions.

While the scope of the process with respect to the aldehyde component was quite broad, an obvious limitation in terms of synthetic utility is the requirement for the enol-stabilising benzo-fused anhydride, which restricts the potential scope considerably.

Accordingly, we became interested in exploring the possibility of utilising other anhydrides. As a starting point, we targeted the use of simple succinic anhydrides, which would potentially allow one-pot access to γ-butyrolactones (a highly abundant feature of natural product structures,[11] and in particular, the carboxylic acid group-bearing paraconic acid class of anti-tumour, antifungal and antibiotic natural products).[12,13]

In preliminary experiments, we attempted the catalytic formal cycloaddition of succinic anhydride (**9**) with benzaldehyde (**7**) in the presence of catalyst **10** (Scheme 2). Under conditions previously found to be conducive to the formal cycloaddition of **7** and homophthalic anhydride **6**, succinic anhydride proved completely unreactive. Elevation of the reaction temperature also failed to furnish the paraconic acid natural product (**11**).

It appeared likely that the failure of **9** to serve as an effective substrate was due to ineffective catalysis of the tautomeric equilibrium under these mild conditions, leading to impracti-cally low concentrations of the enol **12** in solution. If this hypothesis was correct, then the installation of an enol-stabilising group (*i.e.* **13**, Scheme 2) would (if appropriately chosen) circumvent the problem. We were encouraged by an earlier observation by Cushman *et al.*[14] in the corresponding uncatalysed imine-based reaction (which is not thought to proceed *via* the same mechanism, but which involves a likely

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‡ Electronic supplementary information (ESI) available: Experimental procedures and characterisation data. CCDC 872935. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc32147e
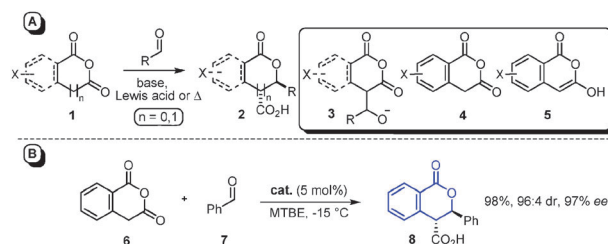
Scheme 1 The formal cycloaddition of anhydrides and aldehydes.
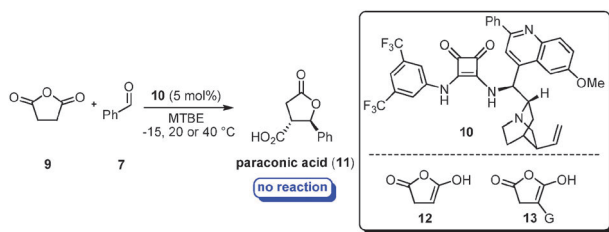
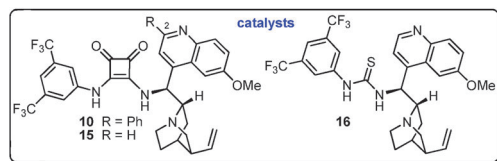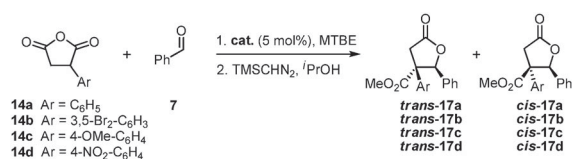**Scheme 2** Attempted one-step synthesis of paraconic acid.

rate-determining distinct enolisation step[5]) that phenylsuccinic anhydride reacted under milder conditions than succinic anhydride itself.[15]

The idea of employing aryl succinic anhydrides was therefore appealing: it affords the opportunity to tune the keto-enol equilibrium through the variation of the electronic characteristics of the aromatic substituent, while rendering one of the two new stereocentres formed in the C–C bond forming event quaternary.[16]

The reaction described in Scheme 2 was now repeated at room temperature using phenylsuccinic anhydride (**14a**). In our previous study concerning homophthalic anhydrides, we found that thiourea-based cinchona alkaloids possessed similar activity and selectivity profiles to the marginally superior squaramide analogues. Therefore, in the current study, in addition to the previous benchmark catalyst **10**, we evaluated the squaramide variant devoid of the C–2 phenyl substituent (*i.e.* **15**) and the corresponding thiourea-based catalyst **16** (Table 1).

In the absence of catalyst, no reaction occurs (entry 1). In the presence of **10** however, phenylsuccinic anhydride (**14a**) underwent conversion to the corresponding phenyl paraconic acid product **17a** (which was esterified to facilitate CSP-HPLC analysis) at ambient temperature in 44% yield with good diastereocontrol and moderate enantioselectivity (entry 2). The importance of the presence of a C–2 phenyl substituent

to the performance of **10** in this reaction is highlighted by the clear inferiority of the unsubstituted variant **15** (entry 3). The thiourea-based catalyst **16** proved comparable to **10** in terms of activity and product diastereoselectivity but not enantioselectivity (entry 4). At reduced temperature, **10** can mediate the formal cycloaddition with excellent diastereocontrol and good *enantio*- and diastereoselectivity (favouring the *trans*-diastereomer), at the expense of a synthetically useful product yield (entries 5 and 6).

It was therefore decided to attempt to further influence the susceptibility of the keto-enol tautomeric equilibrium to catalysis by **10** through the variation of the electronic characteristics of the aromatic substituent. Replacement of a the phenyl unit with a 3,5-bromophenyl analogue ($-Br \ \sigma_m = 0.37$) resulted in faster, more efficient formation of **17b**. Diastereoselectivity and enantioselectivity diminished marginally (entry 7). As expected, use of an enol-destabilising electron rich aryl unit ($-OMe \ \sigma_p = -0.28$) almost shut down the catalytic cycle (entry 8). With the principle of electronic control over activity established, we were cognisant of the importance of choosing a powerful enol-stabilising unit which could serve as a useful functional group for further product elaboration, but which could be removed if required. We therefore evaluated the *p*-nitro substituted variant **14d** ($-NO_2 \ \sigma_p = 0.81$). Gratifyingly, excellent product yield and diastereocontrol were now possible with an attendant increase in product *ee* to 86% (entry 9).

With an optimal catalyst and substrate in hand, the substrate scope with respect to the aldehyde component was investigated (Table 2). Under identical conditions to those outlined in Table 1 entry 9, we found that electron-neutral (entry 1), activated (entries 2–3) and deactivated aldehydes (entry 4) could be reacted with **14d** to give the isolated *trans*-butyrolactones **17d** and **18–20** with product yields and levels of *enantio*/diastereocontrol in line with that expected from the results of our preliminary studies outlined in Table 1. Use of hindered (entry 5) and π-excessive heterocyclic (entries 6–7) aldehydes resulted in a sharp increase in enantioselectivity, which allowed the isolation of *trans*-**21–23** with excellent product *ee* (>90%) without diastereoselectivity being compromised. Aliphatic aldehydes are also tolerated by the catalyst.

Table 1 The evaluation of arylsuccinic anhydrides

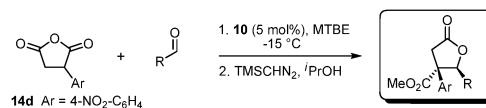| Entry	Cat.	Prod.	T/°C	t (h)	yield (%)[a]	dr[a] trans:cis	ee (%)[b]
1	—	17a	rt	24	0	—	—
2	10	17a	rt	24	44	90:10	68
3	15	17a	rt	24	21	80:20	35
4	16	17a	rt	24	41	88:12	34
5	10	17a	−15	110	34	97:3	83
6	10	17a	−30	110	17	>99:1	83
7	10	17b	−15	97	76	94:6	76
8	10	17c	−15	93	7	n.d.	n.d.
9	10	17d	−15	99	96	97:3	86

[a] Determined by ^{1}H NMR spectroscopy using either styrene/*p*-iodoanisole as an internal standard. [b] Of the *trans*-isomer. Determined by CSP-HPLC.

Table 2 Investigation of substrate scope (aldehyde component)

Entry	Prod.	t (h)	Yield (%)[a]	dr[b] trans:cis	ee (%)[c]
1	**17d** R = C_6H_5	99	92	97:3	86
2	**18** R = 4-Cl-C_6H_4	100	93	95:5	82
3	**19** R = 4-Br-C_6H_4	97	92	94:6	77
4	**20** R = 4-OMe-C_6H_4	164	71	92:8	73
5	**21** R = 2-CH$_3$-C_6H_4	161	63	95:5	91
6[d]	**22** R = 2-furanyl	98	95	99:1	99
7	**23** R = 2-thiophenyl	161	90	98:2	91
8[d]	**24** R = (CH$_2$)$_2$-C_6H_5	100	98	72:28	95
9[e]	**25** R = c-C_5H_{11}	98	56	88:12	95

[a] Isolated (*trans*-isomer). [b] Determined by ^{1}H NMR spectroscopy using either styrene/*p*-iodoanisole as a standard. [c] *Trans*-isomer. Determined by CSP-HPLC. [d] Diastereomers inseparable. [e] 20 mol% catalyst.
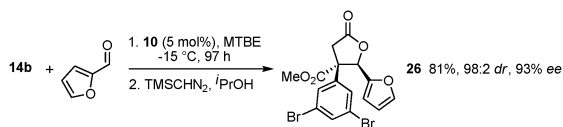
Scheme 3 The use of the dibromoanhydride **14b**.

Either α-unbranched (entry 8) or more hindered branched-aldehydes (entry 9) could be converted to *trans*-**24**–**25** using this protocol. Diastereocontrol is less efficient in these processes however facial control is excellent (95% *ee*).

The dibromoarylsuccinic anhydride **14b** is also a viable substrate under optimised conditions: the *trans*-lactone **26** (which offers the practitioner the option of either dehalogenation to the corresponding phenylsuccinic anhydride-derived lactone or elaboration *via* Pd(0)-mediated coupling chemistry) can be readily prepared with high enantioselectivity (Scheme 3).

In summary, it has been shown that succinic anhydride is unreactive in the organocatalytic asymmetric formal cyclo-addition of cyclic anhydrides and aldehydes—a reaction which has previously only been possible using homophthalic anhydride substrates. It was speculated that this inactivity is related to poor enolisability in the presence of the catalyst; a hypothesis which was supported by the finding that the more hindered (yet presumably more enolisable) phenylsuccinic anhydride participated in the reaction–albeit with unsatisfactory yield and product *ee*. After modification of the α-aryl substituent to incorporate electron withdrawing functionality, a significant increase in reactivity was observed, which allowed the optimisation of the protocol and the identification of the *p*-nitro analogue **14d** as a superior substrate which could react with benzaldehyde to furnish the aryl paraconic acid derivative **17d** in excellent yield and stereocontrol. This is the first example of such a catalytic, asymmetric reaction using a succinic anhydride derivative. Further investigation revealed that while simple aromatic aldehydes behave in a similar manner to benzaldehyde in the process; hindered, heterocyclic and aliphatic analogues undergo reaction with excellent levels of enantiocontrol.

This process provides one-pot access to highly synthetically malleable γ-butyrolactone materials (which are simple derivatives of a class of natural products of considerable pharmacological activity) with the formation of two new stereocentres–one of which is quaternary–under mild conditions with good-excellent stereocontrol. Investigations aimed at further broadening the scope of this promising methodology are underway.

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