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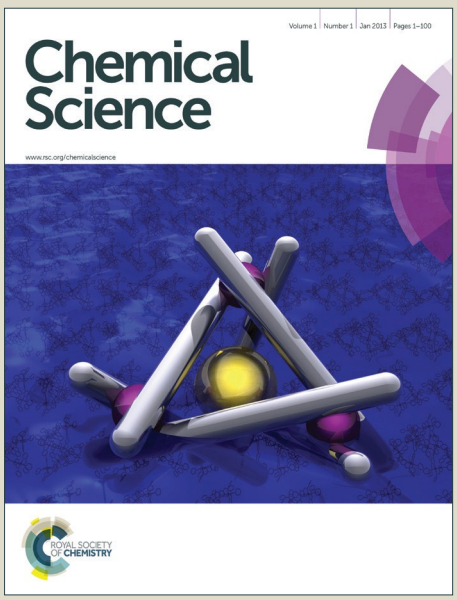

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EDGE ARTICLE

Diastereodivergent organocatalysis for the asymmetric synthesis of chiral annulated furans

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Disclosed herein is a stereoselective method for the synthesis of 2,3-furan fused carbocycles bearing adjacent quaternary and tertiary carbon stereocenters. The chemistry is based on an asymmetric addition of β-ketoesters to 2-(1-alkynyl)-2-alkene-1-ones catalysed by natural cinchona alkaloids followed by a silver-catalysed intramolecular cycloisomerisation. By exploiting distinct catalysis modes of quinine, which can act either as a general base or, upon opportune modifications, as a phase transfer catalyst, a complete switch of the enforced sense of diastereo-induction is achieved. The stereodivergent systems enable access to the full matrix of all possible stereoisomeric products.

Introduction

This research project was motivated by our interest in devising a direct and versatile strategy for stereoselectively assembling chiral annulated furans.[1] As shown in Figure 1, many biologically active compounds and natural products possess a furan system fused to rings of various sizes and adorned with multiple stereocenters.[2] Despite significant advances in preparing racemic 2,3-furan-fused carbocycles,[3] there are only a few catalytic strategies for their direct stereoselective synthesis.[4]

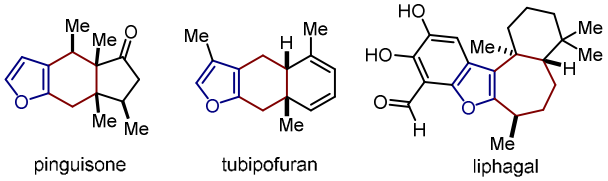
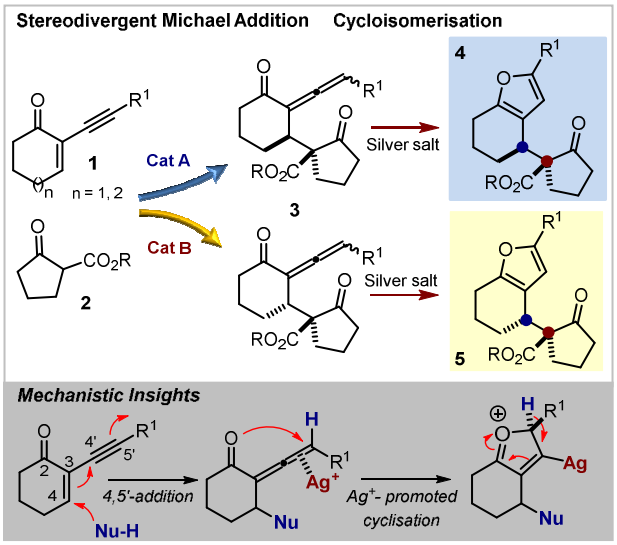


Figure 1. Naturally occurring chiral annulated furans.

Herein, we describe a straightforward synthetic strategy for accessing six- and seven-membered-ring furan derivatives bearing adjacent quaternary and tertiary carbon stereocentres in very high yields and stereoselectivities. The chemistry, which uses readily available substrates and catalysts, is based on a two-step sequential process whereby an organocatalytic asymmetric addition of β-ketoesters **2** to cyclic 2-(1-alkynyl)-2-alkene-1-ones **1**[5,6] is followed by a silver-catalysed intramolecular cycloisomerisation of the transient allenyl ketone[7] intermediate **3** (Scheme 1). Significantly, we have identified two distinct catalytic systems which infer complementary diastereoselectivities, thereby enabling access to the full complement of stereoisomers of the annulated products **4** and **5** at will.[8]



Scheme 1. Diastereodivergent and enantioselective synthesis of chiral 2,3-furan fused carbocycles via an organocatalytic 4,5'-addition/cycloisomerisation sequence promoted by distinct organocatalysts (Cat A & Cat B) and a silver catalyst, respectively.

Results and Discussion

Our initial explorations focused on the reaction between 2-phenylethynyl-2-cyclohexen-1-one **1a**[9] and the cyclic ketoester **2a** in DCM and in the presence of 5 mol% of a chiral tertiary amine, which could act as a general base catalyst (deprotonative activation of **2a**). The process was conducted in two sequential steps, with the initial organocatalytic path exclusively providing the corresponding allenyl ketone of type **3**[10] (Scheme 1) by means of a selective 4,5'-addition manifold.[6] Upon filtering out the

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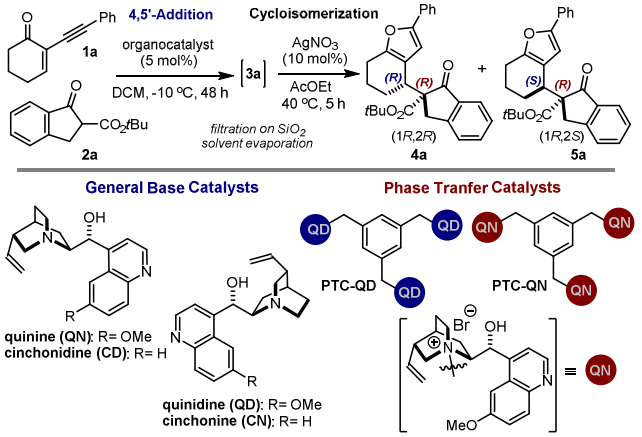
†Electronic Supplementary Information (ESI) available: complete experimental procedures and full compound characterisation, including HPLC traces and NMR spectra (PDF).

chiral amine on SiO_2 and evaporation of the solvent, the cycloisomerisation of crude **3a** was achieved by applying a slightly modified Marshall procedure[7,11] (10 mol% of $AgNO_3$, AcOEt, 40 °C) to afford the diastereomeric adducts **4** and **5**.

We focused on identifying chiral organocatalysts that could infer high stereocontrol in the initial 4,5'-addition reaction. Representative results of our extensive studies are listed in Table 1, with more details reported in the Supporting Information (SI). Intriguingly, natural cinchona alkaloid derivatives,[12] acting as general base catalysts,[13] afforded impressive levels of stereoselectivity (**4a** formed with dr up to 19:1, ee up to 99%, entries 1-4), largely outperforming any other synthetic catalyst tested (see SI).

Table 1 Selected optimisation studies on the model reaction.[a]



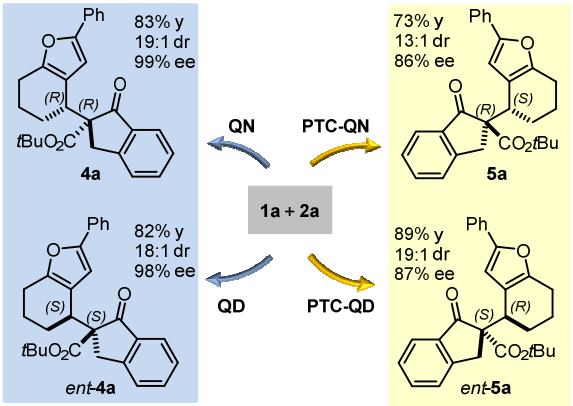
Entry	Catalyst	Yield (%)[b]	**4a**:**5a** ratio[c]	ee (%) major isomer[d]
1	**QN**	66	19:1	99 (1***R***,2***R***)
2	**CD**	62	12:1	99 (1***R***,2***R***)
3	**QD**	82	18:1	98 (1***S***,2***S***)
4	**CN**	84	17:1	98 (1***S***,2***S***)
5[e]	**QN**	83	19:1	99 (1***R***,2***R***)
6	OMe-**QN**	15	1:1.5	<5
7	**QN-OH**	<5	-	-
8[f,g]	**PTC-QN**	73	1:13	86 (1***R***,2***S***)
9[f]	**PTC-QD**	89	1:19	87 (1***S***,2***R***)

[a] Reactions performed in DCM at -10 °C on a 0.2 mmol scale using 1.2 equiv of **2a**, $[\mathbf{1a}]_0$ = 0.1 M. After 48 hours, the 4,5'-addition was quenched by filtration through a pad of silica. Upon evaporation of the solvent, the cycloisomerisation of the intermediate **3a** was conducted by dissolving the crude residue in 2 mL of AcOEt and adding 10 mol% of $AgNO_3$. [b]Yield of the isolated products **4a** and **5a** (diastereomeric mixture). [c]Diastereomeric ratio determined by ^{1}H NMR analysis of the crude mixture upon cycloisomerisation. [d]Enantiomeric excess, as determined by HPLC analysis on chiral stationary phases, refers to the major diastereoisomer; the absolute configuration is specified between brackets. [e]$[\mathbf{1a}]_0$ = 0.5 M. [f]Performed at -20 °C in a 5:1 mixture of DCM/33% K_2CO_3 *aq*, $[\mathbf{1a}]_0$ = 0.2 M. [g]Using 10 mol% of catalyst.

Importantly, the use of the "pseudoenantiomeric" catalysts quinine (**QN**) and quinidine (**QD**) secured access to both antipodes of the adduct **4** with excellent selectivity (entries 5 & 3, respectively). Protection of the quinine hydroxy moiety resulted in a greatly reduced reactivity along with a complete loss of stereocontrol (entry 6). Mechanistically, this suggests that the cinchona catalysts might operate through a bifunctional activation mode, simultaneously binding and activating the two reacting partners.[13a,14] Interestingly, the cupreidine derivative **QN-OH**, a catalyst with a proven ability of promoting the highly stereoselective addition of β-ketoesters to cyclic enones, remained completely inactive in our system (entry 7).[15]

We then modified the cinchona alkaloid scaffold by alkylating the basic bridgehead nitrogen of the quinuclidine core, the classical approach for achieving catalysts suitable for phase transfer catalytic (PTC) conditions.[16] Among the many PTC catalysts tested in the model reaction (see SI for details), the cinchona-derived trimeric species **PTC-QN** and **PTC-QD**,[17] easily obtained by poly-alkylation of quinine and quinidine with 1,3,5-tris(bromomethyl)benzene, provided the most interesting results. When performing the reaction in DCM and in the presence of 33% K_2CO_3 *aq*, a complete switch of the enforced sense of diastereoinduction was achieved, so that the adduct **5** was almost exclusively formed in high optical purity (entries 8 & 9).

These findings allowed us to fully control the stereochemical outcome of the process, enabling at will the generation of any stereoisomer of the annulated furans **4** and **5**. This is considered a challenging goal because, when asymmetric catalysis is applied to processes that generate two stereogenic centres in one product, there is generally no obvious means of modifying a catalyst to modulate the relative sense of those two centres.[8] In this case, the two diastereodivergent systems are based on different organocatalysts, but derived from the common chiral core of natural cinchona alkaloids. The divergent stereocontrol arises from the ability of the cinchona catalysts to execute distinct modes of catalysis for activating the reagents (base catalysis *vs* phase transfer catalysis, Scheme 2).

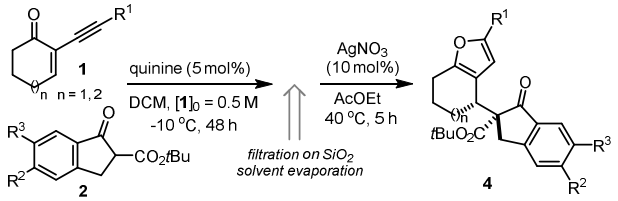


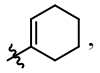
Scheme 2. Accessing the full matrix of the stereoisomers of the annulated furans **4a** and **5a**. When **QN** and **QD** function as general base catalysts, both enantiomers of the diastereoisomer **4a** could be accessed. Modifying the catalyst structure to induce a different activation pattern, namely PTC, enables direct access to both antipodes of **5a** using **PTC-QN** and **PTC-QD**.

Having identified two distinct catalytic systems that can selectively channel the reaction manifolds toward complementary diastereochemical outcomes, we examined the scope of the two-step process using **QN** (5 mol%) as a general base catalyst. As revealed in Table 2, the method shows a wide substrate generality and an excellent level of stereoselectivity, providing access to a variety of complex annulated furans **4** adorned with two vicinal quaternary and tertiary stereocentres. We first tested the

possibility of modifying the cyclic scaffold of the 2-(1-alkynyl)-2-alken-1-one component **1**. The cycloheptenone derivative reacted smoothly to provide the seven-membered-ring furan **4b** in high optical purity (entry 2). In contrast, the cyclopentenone derivative was not a suitable substrate, since a complete lack of reactivity in the silver-catalysed intramolecular cycloisomerisation step was observed. Different substitution patterns at the aromatic moiety of **1** were well-tolerated, regardless of their electronic properties (entries 3–5). In addition, an alkyne bearing a vinylic substituent (entry 6) provided the corresponding furan **4f** with high stereocontrol, albeit with a moderate chemical yield. As a limitation of the system, we have thus far failed to react alkynes bearing alkyl or TMS groups, and linear substrates.

Table 2 Synthesis of chiral annulated furans by general base catalysis: nucleophile and electrophile scope.[a]



Entry	R^1, n	R^2	R^3	**4**	Yield (%)[b]	dr[c]	ee (%)[d]
1	Ph, 1	H	H	**a**	83	19:1	99
2	Ph, 2	H	H	**b**	75	12:1	97
3	4-MeOC_6H_4, 1	H	H	**c**	83	19:1	99
4	4-$CF_3C_6H_4$, 1	H	H	**d**	90	19:1	99
5	4-MeC_6H_4, 1	H	H	**e**	83	19:1	99
6	 , 1	H	H	**f**	25	19:1	95
7	Ph, 1	MeO	H	**g**	62	19:1	99
8	Ph, 1	H	Br	**h**[e]	82	19:1	98
9	Ph, 1	MeO	MeO	**i**	67	19:1	99
10	Ph, 1	H	Me	**j**	87	19:1	97
11	Ph, 1	F	H	**k**	88	19:1	98

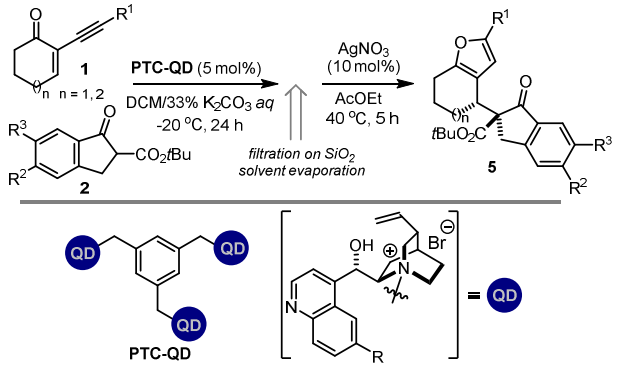
[a] Reactions performed at -10 °C on a 0.2 mmol scale and using 1.2 equiv of **2**. After 48 hours, the organocatalytic 4,5'-addition was quenched by filtration through a pad of silica. Upon evaporation of the solvent, the crude residue was dissolved in 2 mL of AcOEt and 10 mol% of $AgNO_3$ was added. [b]Yield of the isolated products **4** (diastereomeric mixture). [c]Diastereomeric ratio determined by ^{1}H NMR analysis of the crude mixture upon cycloisomerization. [d]Enantiomeric excess determined by HPLC analysis on chiral stationary phases. [e]The absolute configuration of **4h** was unambiguously inferred by X-ray analysis, see Ref. 18.

As for the nucleophilic partners **2**, electronic variations in the indanone ring were possible, as both electron donating and withdrawing substituents gave the desired product in high yields and excellent diastereo- and enantioselectivities (entries 7-11). Efforts to react six-membered cyclic and linear β-ketoesters need further optimization, since only traces of the corresponding products can be obtained so far.

We then evaluated the synthetic potential of the PTC-mediated system. As depicted in Table 3, the reactions catalysed by 5 mol% of **PTC-QD** showed a comparable versatility to the system under general base catalysis, but secured a complementary diastereoselectivity, since the opposite diastereoisomer **5** of the annulated furans were almost exclusively formed with a high enantiocontrol.

The relative and absolute configuration of products **4h** and **5a** was unambiguously inferred by anomalous dispersion X-ray crystallographic analysis.[18]

Table 3 Synthesis of chiral annulated furans under PTC conditions: nucleophile and electrophile scope.[a]



Entry	R^1, n	R^2	R^3	**5**	Yield (%)[b]	dr[c]	ee (%)[d]
1[e]	Ph, 1	H	H	**a**	89	19:1	87
2	Ph, 2	H	H	**b**	81	9.5:1	93
3	4-MeOC_6H_4, 1	H	H	**c**	87	19:1	89
4	4-$CF_3C_6H_4$, 1	H	H	**d**	84	8:1	81
5	4-MeC_6H_4, 1	H	H	**e**	82	19:1	91
6[f]	 , 1	H	H	**f**	53	19:1	92
7[f]	Ph, 1	MeO	MeO	**i**	62	16:1	72
8[f]	Ph, 1	H	Br	**h**	78	11:1	77
9	Ph, 1	H	Me	**j**	87	19:1	87
10	Ph, 1	F	H	**k**	87	15:1	85
11	Ph, 1	Br	H	**l**	70	19:1	83

[a] Reactions performed at -20 °C in a 5:1 mixture of DCM/33% K_2CO_3 *aq*, on a 0.2 mmol scale and using 1.2 equiv of **2**; [**1a**]$_0$ = 0.2 M. After 24 hours, the 4,5'-addition was quenched by filtration through a pad of silica. Upon evaporation of the solvent, the crude residue was dissolved in 2 mL of AcOEt and 10 mol% of $AgNO_3$ was added. [b]Yield of the isolated products **5** (diastereomeric mixture). [c]Diastereomeric ratio determined by ^{1}H NMR analysis of the crude mixture upon cycloisomerisation. [d]Enantiomeric excess determined by HPLC analysis on chiral stationary phases. [e]The absolute configuration of **5a** was unambiguously inferred by X-ray analysis, see Ref. 18. [f]Reactions performed at -10 °C using 1.5 mol% of catalyst.

Conclusions

In conclusion, we have developed an operationally simple, two-step process to access a variety of stereochemically dense 2,3-furan fused carbocycles bearing adjacent quaternary[19] and tertiary stereocentres. The salient feature of our study is that complementary organocatalytic systems, both using natural cinchona-derived catalysts, have been identified, which ensure a highly selective access to the full matrix of all possible stereoisomeric products at will.

Acknowledgments

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10 Under the reaction conditions detailed in Table 1, the allenyl ketone intermediate **3a** is produced with very poor diastereomeric purity (*dr* ranging from 1:1 to 1.5:1) as a consequence of the lack of stereocontrol over the axial chirality. This stereochemical information, however, is eventually lost during the cycloisomerisation to give the annulated furans.

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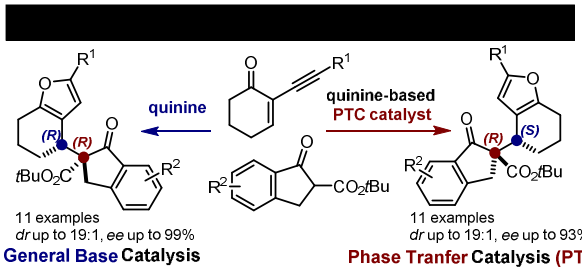

Stereoselective methods to prepare chiral annulated furans are reported. Complementary organocatalytic systems ensure access to all possible stereoisomeric products

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