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Aminocatalysis

Direct Organocatalysed Double Michael Addition of α-Angelica Lactone to Enones

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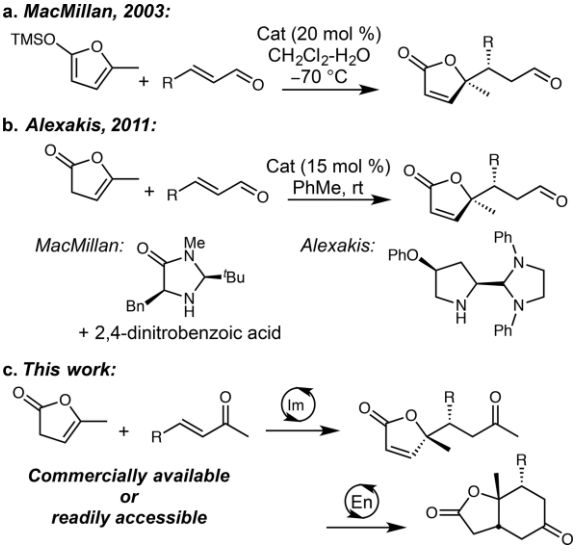
Abstract: The direct vinylogous Michael addition of unactivated α-Angelica lactone to enones under iminium activation using 9-amino-9-deoxy-*epi*-quinine as catalyst along with 2-hydroxy-1-naphthoic acid as co-catalyst has led to the formation of γ,γ-disubstituted butenolides in high yields, moderate-to-good diastereoselectivities and excellent enantioselectivities. The readily available catalytic system over-rides the steric hindrance, which would otherwise lead to the preferential formation of the *syn* isomer, to afford the *anti* isomer instead. Under enamine activation, the *anti* isomer selectively undergoes cyclisation to the hexahydrobenzofuran-2(3*H*)-one, which is readily separated from the left-over *syn* isomer. Mechanistic details, including the fate of the pro-nucleophile and the origin of the diastereoselectivity, are also discussed.

Introduction

Accessing structural complexity rapidly, efficiently and in a highly chemo-, regio-, enantio- and diastereoselective manner is at the forefront of organic synthesis. Developing such synthetic methodologies to be operationally easy, using renewable commercially or synthetically readily available starting materials and catalytic systems under safe and environmentally benign reaction conditions is of particular interest to the synthetic organic practitioner, in particular in the context of green chemistry. To this end, organocatalysis has emerged as a powerful tool, which has revealed its might with the development of spectacular tandem and cascade reactions under very mild conditions to allow access to highly functionalised synthetically and biologically relevant structures.[1]

Butenolides and lactones are present in around 10% of all natural products.[2] Thus, developing synthetic approaches to access these structures has drawn a lot of attention from the synthetic community.[3] In 2003, MacMillan and co-workers reported the first vinylogous Michael addition of α-Angelica lactone, activated as its silyl enol ether, to enals (Scheme 1, a).[4] In 2011, our group reported the first direct conjugate addition of unactivated α-Angelica lactone to enals (Scheme 1, b).[5] More recently, Pihko and co-workers proposed an approach to allow for an extension of the scope to α-substituted enals.[6]

The γ-butenolide resulting from these transformations presents an unsaturation, which we envisioned could be taken advantage of for further cyclisation in an iminium/enamine cascade reaction when using an alkyl enone partner (Scheme 1, c). The envisioned transformation would allow access to substituted hexahydrobenzofuran-2(3*H*)-ones and a broad range of



Scheme 1. Vinylogous Michael additions of α-Angelica lactone to enals (a,b) and proposed transformation (c).

structurally related lactols, acetals and dihydro- and tetrahydrofuran derivatives (Scheme 2).[7] We also anticipated that the cyclisation would be highly *syn* selective at the ring junction,[4,8] thereby giving access to the core structure of poorly studied natural products such as Dukunolides D–F, Granatoine, Xylogranatins F and H, Hainangranatumin G and Acromelactone A.[9] In addition, being able to control the cyclisation event would be advantageous to access natural products structurally related to the first conjugate addition product, such as the Cneorins and their structural congeners.[10]

The potentially difficult tautomerisation step in the envisaged iminium/enamine cascade was felt not insurmountable as comparable transformations involving Michael/Michael,[11] Michael/aldol[12] and Michael/Mannich[13] sequences have been reported, which encouraged us in our proposal. When this in-

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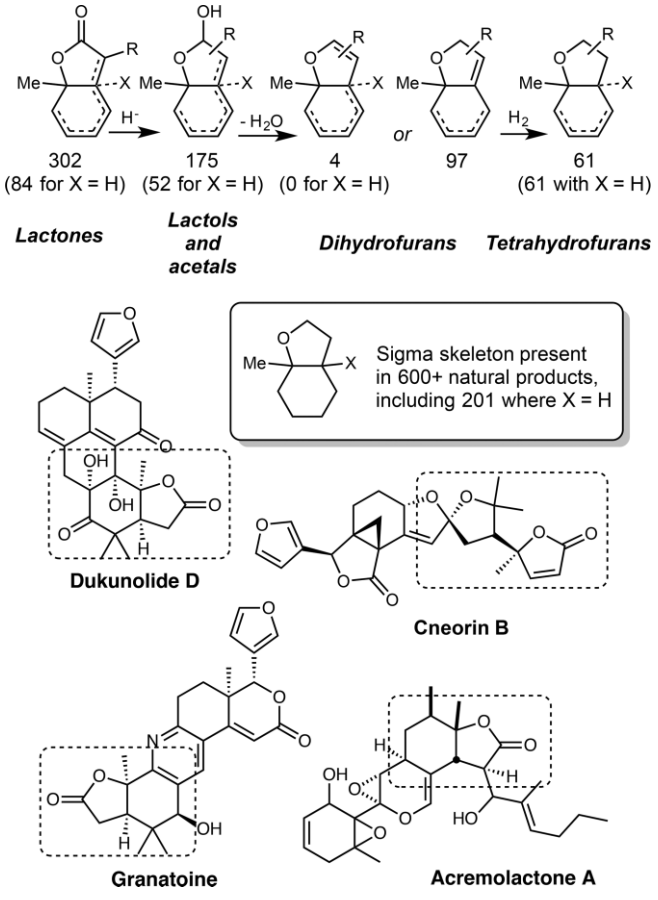


Scheme 2. Synthetic relationship between hexahydrobenzofuranones and hexahydrobenzofurans, and examples of structurally related natural products.

vestigation was initiated, only one conjugate addition of an α-butenolide to enones had been reported by Huang and co-workers.[14] Their bifunctional tertiary amine/thiourea catalyst led to the formation of the *anti* isomer, but the system was limited to aryl enones. Soon after, three other reports by Wang,[15] Feng[16] and Lin[17] and their co-workers followed. Under Lewis acid catalysis in the first two reports and Brønsted acid catalysis for the third, only the *syn* conjugate adducts were obtained, and in all cases the scope was limited to aryl enones. Most recently, Shibasaki and co-workers reported the direct conjugate addition of α-butenolides to α,β-unsaturated thioamides and one application demonstrated the possibility of accessing methyl ketones, but the *syn* adduct was again obtained.[18] We had, however, observed that only the *anti* diastereomer underwent cyclisation (see below), which prompted us to pursue our study. Unfortunately, as this study was reaching completion,[19] Ye and Dixon published a diastereodivergent version of the conjugate addition that gave high yields, diastereoselectivities and enantioselectivities for a broad scope of nucleophiles and electrophiles.[20] Their report, however, did not mention any cyclisation of their conjugate adducts, either in situ or in a subsequent step. We herein report our results, including some mechanistic studies, which completes their work and may shed some light on the origin of the enantio- and diastereoselectivities observed in their transformation.

Results and Discussion

Studies towards the Cascade Reaction Using a Single Catalyst

To assess the feasibility of the reaction, a set of readily available catalysts (Figure 1) were screened under standard conditions (Table 1). L-Proline (**I**; entry 1) was used for a Michael/aldol cascade reaction of enones,[12] but it was inefficient in promoting the desired transformation. Quinine-derived primary amine catalyst **II** (entry 2) was found to be slightly *anti*-selective with virtually perfect enantioselectivity for *anti*-**3**. A low conversion was, however, observed, and it was unable to promote the cyclisation reaction. In sharp contrast, primary amine-thiourea bifunctional catalysts **IV** and **V** (entries 3 and 4) were found to rather efficiently promote the vinylogous Michael addition and to a limited extent the cyclisation of *anti*-**3** to **4**.[21,22] However, moderate enantio- and diastereoselectivities were observed. This difference in reactivity suggested that the thiourea is essential for reactivity, and we set out to reverse the diastereoselectivity as well as to improve the enantioselectivity.

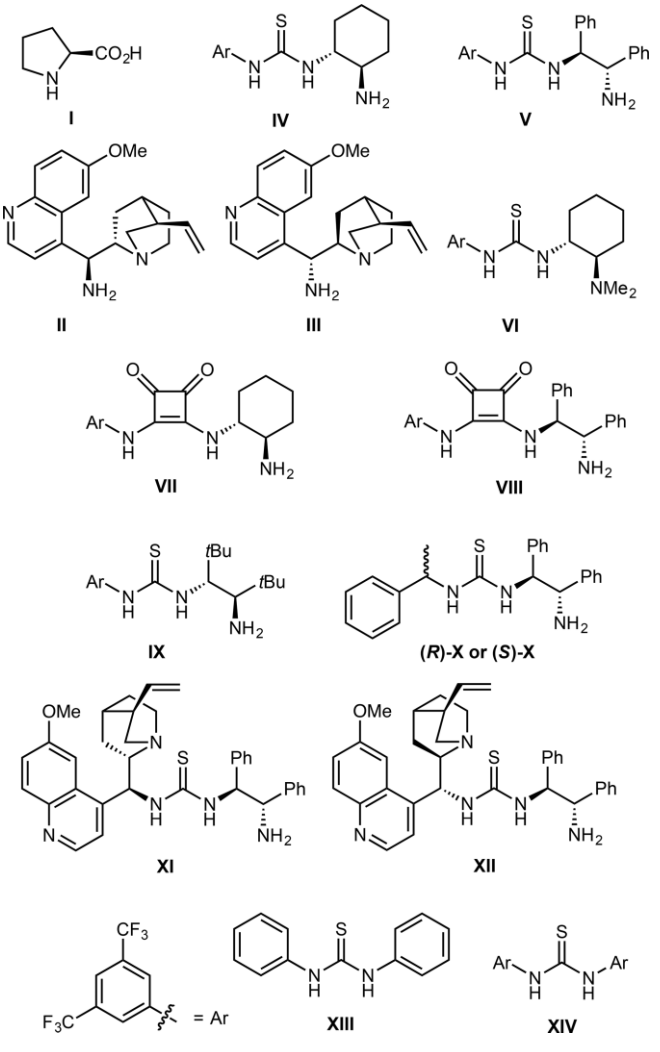
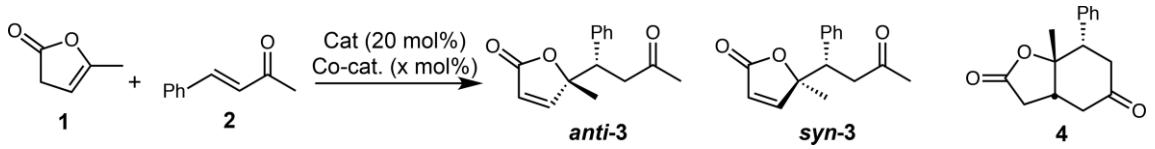


Figure 1. Catalysts used in this study.

Table 1. Screening of catalysts.[a]y



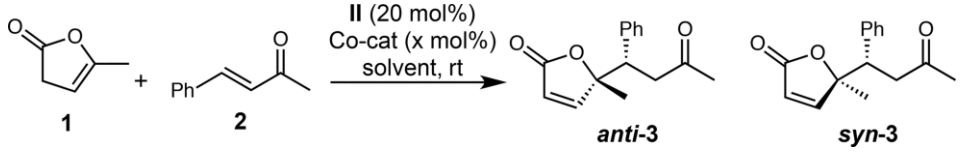
Entry	Cat.	Co-cat. (amount [mol%])	Conv. [%][b]	*anti*-**3**/*syn*-**3**[b]	*anti*-**3** *ee* [%][c]	*syn*-**3** *ee* [%][c]	Yield **4** [%][b]
1	**I**	–	<1	–	–	–	–
2	**II**	$C_6H_5CO_2H$ (40)	5	1.6:1	99	–56	–
3	**IV**	$C_6H_5CO_2H$ (40)	63	1:1.1	–66	6	8
4	**V**	$C_6H_5CO_2H$ (40)	83	1:2.9	77	51	3
5	**VI**	$C_6H_5CO_2H$ (40)	<1	–	–	–	–
6	**VII**	$C_6H_5CO_2H$ (40)	26	1.1:1	78	–6	–
7	**VIII**	$C_6H_5CO_2H$ (40)	19	1.5:1	–67	–6	–
8	**IX**	$C_6H_5CO_2H$ (40)	<1	–	–	–	–
9	(*S*)-**X**	$C_6H_5CO_2H$ (40)	86	1:1.2	80	50	8
10	(*R*)-**X**	$C_6H_5CO_2H$ (40)	92	1:1.2	78	48	8
11	**XI**	$C_6H_5CO_2H$ (60)	42	1.4:1	65	38	–
12	**XII**	$C_6H_5CO_2H$ (60)	55	1.4:1	60	39	–
13	**II**	*N*-Boc-D-Phg (40)	45	2.7:1	99	–12	–
14[d]	**II**	*N*-Boc-D-Phg (40)	45	2.1:1	79	26	–
15[e]	**II**	*N*-Boc-D-Phg (40)	54	1.5:1	44	45	–

[a] Reactions performed in toluene (0.1 M) at room temperature for 48 h. [b] Determined by ^{1}H NMR and GC–MS analyses of the crude product. [c] Determined by supercritical fluid chromatography (SFC) analysis of the product after column chromatography. [d] Catalyst **XIII** (40 mol%) was added. [e] Catalyst **XIV** (40 mol%) was added.

Screening other solvents and co-catalysts did not lead to noticeable improvement,[23] and we settled on the initial reaction conditions and screened other catalysts. The loss of reactivity with the Takemoto catalyst **VI** (entry 5) comforted us with the idea that a primary amine is necessary for catalysis to take place. The squaramide analogues **VII** and **VIII**, with their more extensive hydrogen bonding, were thought to better orient the pro-nucleophile. Although they did reverse the diastereoselectivity, lower conversions were obtained, and none of the desired **4** was observed. Bulky analogue **IX** did not catalyse the reaction (entry 8). In an attempt to stabilise one diastereomeric transition state, we tried the reaction with catalysts (*S*)-**X** and (*R*)-**X** (entries 9 and 10). Although no match/mismatch was observed, the catalytic activity was restored, but not satisfactorily, despite their ability to promote the cyclisation to a limited extent. Along the same lines, pseudo-diastereomeric catalysts **XI** and **XII** were tested (entries 11 and 12). But again, despite the absence of match/mismatch and a reversed diastereoselectivity in favour of *anti*-**3**, loss of reactivity and lower enantioselectivity were observed and none of the desired **4** was observed. This screening of ligands and conditions highlighted the need for both a primary amine and a thiourea. On the other hand, quinine-derived catalyst **II** readily provided *anti*-**3** as the major diastereomer and in excellent enantioselectivity. Yet, its combination with benzoic acid as co-catalyst is far from optimal and combination with *N*-Boc-D-phenylglycine (*N*-Boc-D-Phg) is often preferred.[24] We therefore probed the influence of this well-established catalytic system in combination with thiourea catalysts **XIII** and **XIV**. In the reaction with **II** and *N*-Boc-D-Phg, despite the absence of a thiourea co-catalyst, a great improvement in the conversion was observed and excellent enantioselectivity was retained (entry 13). However, the diastereoselectivity remained low, although in favour of *anti*-**3**, and **4** was not observed. In contrast, negligible improvement of the conversion was observed upon addition of thioureas **XIII** or **XIV**, both the diastereoselectivity and the enantioselectivity were eroded (entries 14 and 15). And again, the desired **4** was not formed.

We soon understood that a thiourea, contrary to what was initially thought, increases the rate of unwanted side-reactions, which may also explain the lower diastereo- and enantioselectivities observed previously. Furthermore, we also felt that carrying out the two transformations in a single step would remain illusory. To this end, we screened a broad range of co-catalysts and solvents (Table 2).[25] In the absence of an acid co-catalyst (entry 1), no reaction took place. The more acidic *p*-nitrobenzoic acid improved neither the conversion nor the diastereoselectivity, but returned a perfect enantioselectivity (entry 3). Other benzoic acid derivatives also failed. Gratifyingly, salicylic acid (entry 4) remarkably improved the conversion and the diastereoselectivity as well as maintaining a perfect enantioselectivity. It even performed better than the established **II**/*N*-Boc-D-phenylglycine catalytic system (entry 5).[24] We then set out to screen different solvents. DMSO (entry 6) led to complete conversion but poor diastereoselectivity, and interestingly, to complete reversal of the enantioselectivity, thereby underlining the importance of tight ion-pairing in the enantiocontrol. Surprisingly, the reaction was found to be rather sluggish in chlorinated solvents such as dichloromethane (entry 7). The solvent screening finally revealed that aromatic solvents are preferred,

Table 2. Optimisation of the reaction conditions.[a]



Entry	Co-cat. (amount [mol%])	Solvent	Conv. [%][b]	*dr*[b]	*anti*-**3** *ee* [%][c]	*syn*-**3** *ee* [%][c]
1	–	PhMe	<1	1.8:1	n.d.	n.d.
2	$C_6H_5CO_2H$ (40)	PhMe	5	1.6:1	99	–56
3	4-NO_2-$C_6H_4CO_2H$ (40)	PhMe	9	1.4:1	99	–13
4	2-HO-$C_6H_4CO_2H$ (40)	PhMe	62	4.9:1	99	–37
5	*N*-Boc-D-Phg (40)	PhMe	54	2.8:1	97	–17
6	2-HO-$C_6H_4CO_2H$ (40)	DMSO	99	1.3:1	–92	74
7	2-HO-$C_6H_4CO_2H$ (40)	CH_2Cl_2	22	3.6:1	97	42
8	2-HO-$C_6H_4CO_2H$ (40)	PhH	63	5.9:1	99	–28
9[d]	2-HO-$C_6H_4CO_2H$ (40)	PhMe	<1	nd	n.d.	n.d.
10	2-HO-$C_6H_4CO_2H$ (60)	PhMe	81	6.3:1	99	–34
11	2-HO-1-naphthoic acid (60)	PhMe	79	8.0:1	99	–51
12	1-HO-2-naphthoic acid (60)	PhMe	84	4.6:1	99	–44
13	3-HO-2-naphthoic acid (60)	PhMe	94	4.5:1	99	–34
14	2-MeO-$C_6H_4CO_2H$ (60)	PhMe	8	1.6:1	n.d.	n.d.
15	*N*-Boc-D-Phg (60)	PhMe	70	2.9:1	98	–43
16	2-F-$C_6H_4CO_2H$ (60)	PhMe	40	2.6:1	14	–53
17[e]	2-HO-1-naphthoic acid (60)	PhMe	81	6.3:1	98	–41
18[f]	2-HO-1-naphthoic acid (60)	PhMe	85	8.0:1	99	–51
19[g]	2-HO-1-naphthoic acid (60)	PhMe	91	8.0:1	99	–49

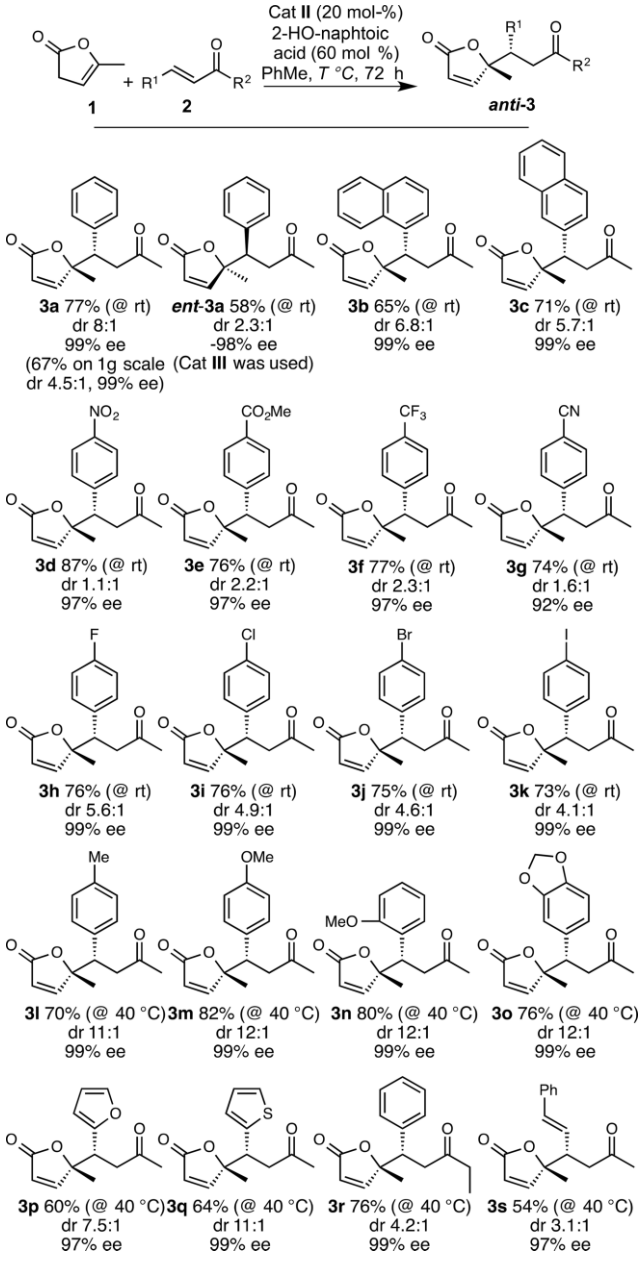
[a] Unless otherwise stated, a mixture of **2** (0.1 mmol), **II** (20 mol%) and co-catalyst (*x* mol%) in toluene (0.1 M) was stirred for 30 min, after which time α-Angelica lactone (2 equiv.) was added and the reaction mixture left to stir for 48 h. [b] Determined by ^{1}H NMR and GC–MS analyses of the crude product. [c] Determined by SFC analysis of the product after column chromatography. [d] Catalyst **II** was omitted. [e] α-Angelica lactone (5 equiv.) added in one shot. [f] α-Angelica lactone (3 equiv.) was added in portions over 48 h. [g] α-Angelica lactone (3 equiv.) was added in three portions over 48 h, 0.3 mmol scale for 72 h, with 77% isolated yield.

with benzene performing best (entry 8). However, for the sake of using benign conditions, we chose to pursue our study with the slightly inferior toluene.

The co-catalyst alone, that is, in the absence of catalyst **II**, did not achieve the transformation (entry 9). We thus probed the influence of the amount of co-catalyst used and found that the level of conversion and diastereoselectivity plateaued with 60 mol% (entry 10). Bulkier salicylic acid analogues were tested, and 2-hydroxy-1-naphthoic acid was found to be the best co-catalyst in terms of diastereoselectivity (entries 11–13). Other analogues, such as 2-methoxybenzoic acid (entry 14), gave poor results, providing evidence that hydrogen bonding involving an unhindered phenol plays a crucial role in activating and presenting the nucleophile to the enone (see below). In addition, the efficacy of our catalytic system was found to be superior to that of the well-established passe-partout systems using *N*-Boc-D-phenylglycine or 2-fluorobenzoic acid as co-catalyst (entries 15 and 16).[24] Finally, modifying the amounts and mode of addition of the pro-nucleophile as well as slightly increasing the reaction time led to the final optimised procedure.[25]

With these conditions in hand, we set out to explore the scope of the reaction catalysed by the combination **II**/2-hydroxy-1-naphthoic acid (Scheme 3).[26] The reaction could be carried out on the gram scale, and the pseudo-enantiomeric catalyst **III** allowed access to the opposite enantiomer *ent*-**3a**. Naphthyl-substituted enones (giving **3b** and **3c**) provide insight into the influence of the steric hindrance on the reaction rates. Electron-poor aryl-substituted enones readily reacted at room temperature to give **3d**–**k** in high yields and enantioselectivities but low diastereoselectivities, which could not be improved by running the reactions at lower temperatures. In contrast, electron-rich aryl-substituted enones (giving **3l**–**o**) displayed lower reactivity and the reactions were performed at 40 °C. Under these conditions, high yields and excellent enantioselectivities were observed along with higher diastereoselectivities. Lower diastereoselectivities were observed for heteroaromatic substrates (giving **3p** and **3q**) and ethyl enone **2r** also reacted successfully to provide **3r**, albeit with a lower yield and diastereoselectivity, showing steric hindrance in the formation of the iminium intermediate. Finally, a dienone could also be used as substrate in this reaction, with **3s** as the product.

An sp^2 substituent at the γ position of the enone seems to be necessary for the reaction to take place. Indeed, the reactions of various alkyl enones (Figure 2, **2t**–**z**) were found to be sluggish, even at 40 °C, and only trace amounts of the products were observed, along with recovery of the untouched starting enone and decomposition products of the pro-nucleophile (see below). This contrasts with the work of Ye and Dixon, who mostly used alkyl enones as substrates with only a few examples of aryl enones. Additionally, extending the bulk on the ketone moiety to isopropyl (**2aa**, compared with ethyl **2r** in Scheme 3) led to loss of reactivity. For ketones with a cycloalkane substituent, no reaction took place (**2ab** and **2ac**). Finally, chalcone **2ad** was also unreactive.



Scheme 3. Scope of the Michael addition reaction.

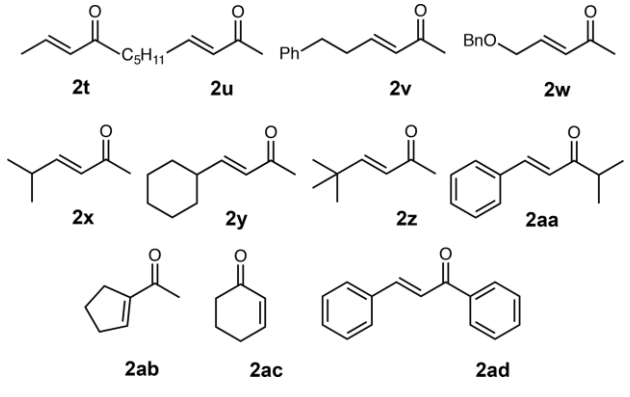


Figure 2. Enones that failed to undergo conjugation addition with the present catalytic system.

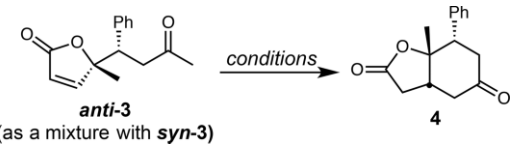
As a Two-Step Procedure — Preparation of Hexahydrobenzofuran-2(3*H*)-ones

With an efficient access to highly enantioenriched conjugate adducts *anti*-**3** as the major diastereomer in all cases, we turned our attention to studying the cyclisation step. This transformation appeared to be unexpectedly difficult to bring about, and various conditions were tested (Table 3). DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or triethylamine were found ineffective in promoting the cyclisation (entries 1 and 2), whereas *t*BuOK led to decomposition of the substrate (entry 3). Aqueous NaOH in methanol (entry 4) led to the complete conversion of *anti*-**3** into **4** along with non-negligible amounts of hydrolysis products, as did LiOH in THF (entry 5). L-Proline (entry 6) promoted the desired cyclisation, but rather slowly. Not unexpectedly, **IV** promoted the cyclisation reaction (entry 7). When the reaction was performed with *rac*-**3** and purposely stopped at 50% conversion to measure a potential enantioenrichment in both **3** and **4**, a low 16% *ee* was observed for both (entry 8). Thus, the cyclisation reaction was attempted on enantioenriched **3** with *rac*-**IV**; the complete conversion of *anti*-**3** into **4** with no erosion of enantioselectivity was achieved (entry 9). This suggests that catalyst **IV** is not competent for promoting a retro-Michael addition, which would otherwise have led to epimerisation in **3** and result in an *ee* value lower for **4** than for *anti*-**3**. Catalyst **II** proved inefficient in promoting cyclisation even in the presence of thiourea catalyst **XIV** (entries 10 and 11), benzylamine allowed cyclisation only very slowly even in the presence of **XIV** (entries 12 and 13) and Takemoto catalyst **VI** also failed to promote the cyclisation (entry 14), which suggests that the cyclisation event takes place by enamine activation. Finally, to probe the feasibility of adding *rac*-**IV** to the reaction mixture of the first conjugate addition in a one-pot procedure, we used α-Angelica lactone and salicylic acid as additives (entries 15 and 16), and found that both inhibited the cyclisation to some extent.

With the mild conditions for the cyclisation in hand, we then explored the scope of this reaction with a small yet representative set of substrates. As catalyst **II** does not promote the cyclisation, one may think it convenient to simply add *rac*-**IV** to the reaction mixture after completion of the first step. This was disproved by the observed inhibition of the cyclisation reaction by both α-Angelica lactone and salicylic acid. Furthermore, as complete conversion of the starting enone is not reached during the first step while some α-Angelica lactone is still present in the mixture, we found it easier to carry out an easy and rapid separation of the conjugate adducts from the rest of the components, allowing for measurement of the enantioselectivity, and then to submit them to the cyclisation conditions, which resulted in an *ee* for **4** equal to that of the starting *anti*-**3** (Scheme 4).

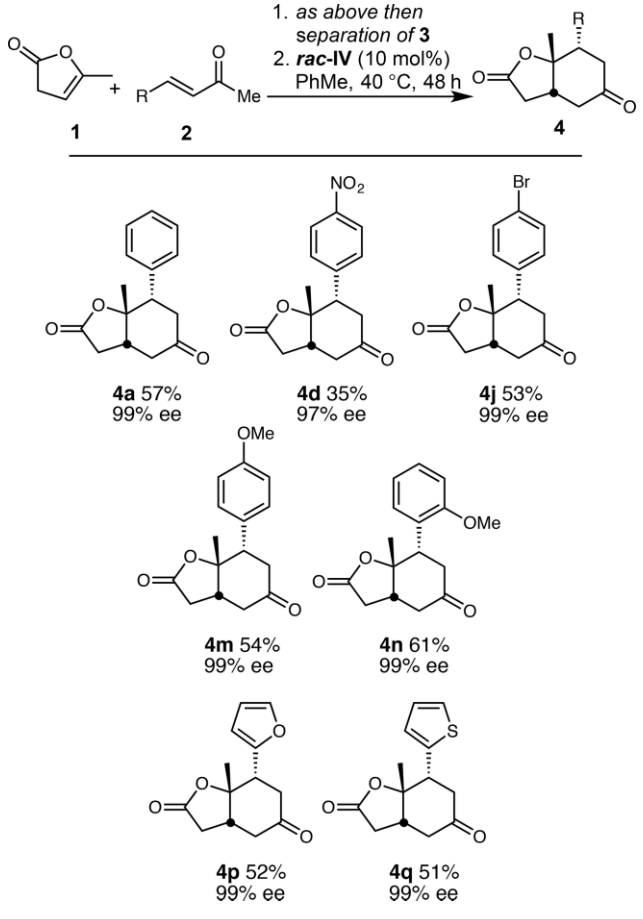
The cyclisation reaction readily took place with all substrates, and the cyclised products could be easily separated as single diastereomers with excellent enantioselectivities by column chromatography, which we found more convenient than a simple filtration of the reaction mixture despite the fact that these compounds readily precipitate out of the reaction mixture. The lower yield observed for **4d** reflects the lower diastereomeric

Table 3. Study of the conditions for the cyclisation reaction.[a]



Entry	Conditions	Conv. [%][b]	*anti*-**3** *ee* [%][c]	**4** *ee* [%][c]
1	DBU, CH_2Cl_2, r.t., 24 h	<1	–	–
2	Et_3N, CH_2Cl_2, r.t., 24 h	<1	–	–
3	*t*BuOK, THF, 0 °C, r.t.	decomp.	–	–
4	Aq. NaOH, MeOH, r.t., 24 h	hydrolysis	–	–
5	LiOH, THF, r.t., 24 h	hydrolysis	–	–
6	**I** (10 mol%), MeOH, 40 °C, 24 h	44	–	–
7	(*R*,*R*)-**IV** (10 mol%), PhMe, 40 °C, 24 h	91	–	–
8	(*R*,*R*)-**IV** (10 mol%), PhMe, 40 °C, 6 h	50[d]	16	16
9[e,f]	*rac*-**IV** (10 mol%), PhMe, 40 °C, 48 h	98 (74)	–	99
10	**II** (20 mol%), PhMe, 40 °C, 24 h	<1	–	–
11	**II** + **XIV** (20 mol%), PhMe, 40 °C, 24 h	<1	–	–
12	$BnNH_2$ (20 mol%), PhMe, 40 °C, 24 h	11	–	–
13	$BnNH_2$ + **XIV** (20 mol%), PhMe, 40 °C, 24 h	31	–	–
14	(*R*,*R*)-**VI** (20 mol%), PhMe, 40 °C, 24 h	<1	–	–
15[g]	*rac*-**IV** (10 mol%), PhMe, 40 °C, 48 h	37	–	–
16[h]	*rac*-**IV** (10 mol%), PhMe, 40 °C, 48 h	54	–	–

[a] Unless otherwise stated, a racemic 1:1.6 mixture of *anti*-**3** and *syn*-**3** was used. [b] Determined by ^{1}H NMR and GC–MS analyses of the crude product, and reported with respect to starting *anti*-**3**. [c] Determined by SFC analysis of the product after column chromatography. [d] A racemic 1:1.6 mixture of *anti*-**3** and *syn*-**3** was used and the reaction was run until 50% conversion was achieved, after which time the products were separated and analysed by SFC. [e] Enantioenriched *anti*-**3** (99% *ee*, *dr* 8:1) was used. [f] Isolated yield based on total **3** added as substrate is given in parentheses. [g] α-Angelica lactone (1 equiv.) was added. [h] 2-HO-$C_6H_4CO_2H$ (10 mol%) was added.



Scheme 4. Representative scope of the vinylogous Michael addition/cyclisation sequence (0.5 mmol scale, yields over two steps).

ratio in the conjugate adduct **3d** prior to cyclisation. Single-crystal X-ray crystallography of **4j** provided the ultimate proof of the absolute and relative configuration (Figure 3).[27] It is interesting to note that the six-membered ring is forced into an unusual boat conformation.

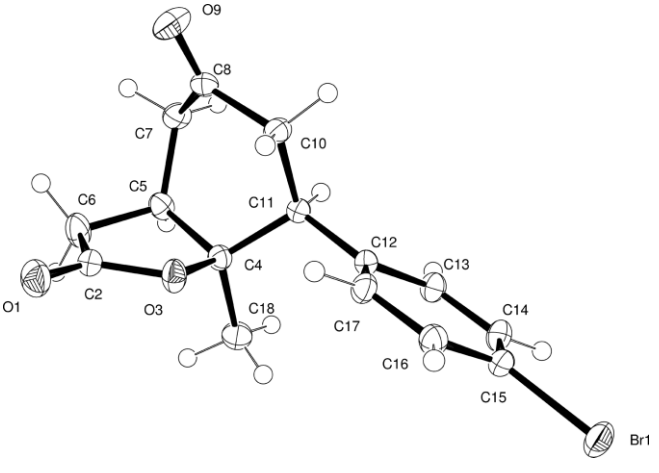
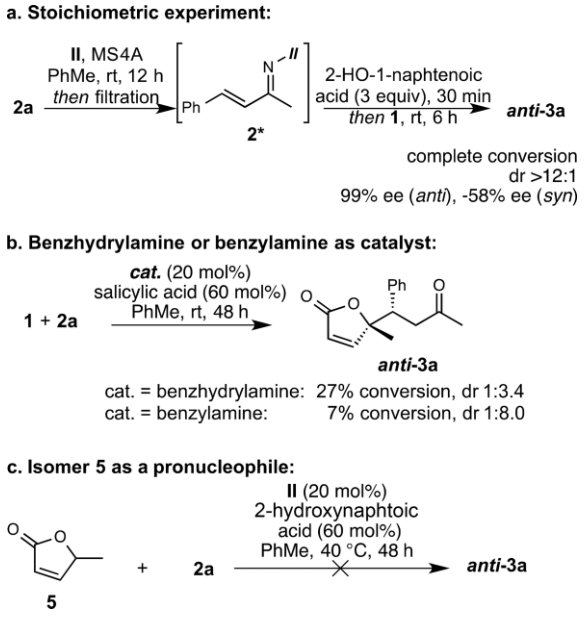


Figure 3. X-ray crystal structure of **4j**. Thermal ellipsoids are drawn at the 50% probability level.

Mechanistic Aspects

From a more mechanistic point of view, three aspects relating to the vinylogous Michael addition step remained to be addressed: the origin of the excellent enantioselectivity observed for *anti*-**3**, the origin of *syn*-**3** and its consistently poor enantioselectivity, and the fate of α-Angelica lactone during the course

of the reaction. To gain more insight, we carried out two control experiments (Scheme 5).



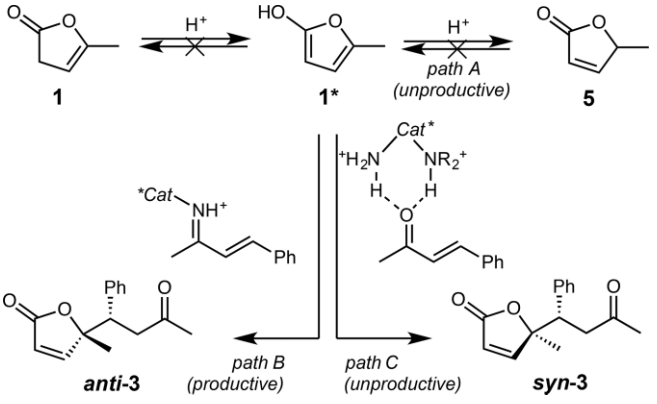
Scheme 5. a) Stoichiometric experiment, b) reaction with benzhydrylamine or benzylamine as catalyst and c) reaction with regioisomer **5** as pro-nucleophile.

In a stoichiometric experiment (Scheme 5, a), pre-formation of the iminium species led to a greatly accelerated reaction, which was complete within a few hours, and a sensibly higher diastereoselectivity. This confirms that conjugate adduct *anti*-**3** is obtained by conjugate addition to the enone activated as its iminium counterpart, and that *syn*-**3** is formed by a different activation mode, perhaps by Brønsted acid activation by an ammonium species derived from **II**, very much in analogy to the work of Lin and co-workers.[17]

Benzhydrylamine clearly lacks the quinuclidine moiety, which, with the participation of the acid co-catalyst in a tight ion pair, is known to block one face of the iminium species, but we felt it was inconsequential for a racemic experiment. It may, however, be regarded as sterically equivalent to catalyst **II**, but lacking the quinoline nitrogen. When benzhydrylamine was used as catalyst (Scheme 5, b), low reactivity with selectivity towards the formation of *syn*-**3** was observed.[28] This suggests the interaction of the nitrogen in the quinoline moiety with a molecule of co-catalyst, thereby explaining the improvements observed with up to 3 equivalents of co-catalyst per catalyst molecule, and the fact that this improvement plateaued beyond this value. This does not remove the steric factor from the equation, as benzylamine, which is electronically equivalent to benzhydrylamine, performed poorly as a catalyst for the transformation.

Finally, in the experiment with **5** as pro-nucleophile (Scheme 5, c), only trace amounts of *anti*-**3** were obtained, which suggests that the non-productive isomerisation of **1** to **5** by protonation of the dienol species, the actual nucleophile for the vinylogous Michael addition, leads to loss of the nucleophile, thereby explaining the need for the portionwise addition of **1** over an extended period of time.

This has allowed us to propose a divergent fate for **1** in the course of the reaction (Scheme 6). Under the reaction conditions, which are mildly acidic, **1** may tautomerise to the dienol species, which can follow three pathways. In path A, under acidic conditions, rapid γ protonation leads to the unproductive and irreversible formation of **5**,[29] which is not able to participate in the vinylogous Michael addition reaction. Alternatively, it can react with the enone to form either *anti*-**3** (path B) or *syn*-**3** (path C). The outcome of this reaction is due to a very fine balance between these three processes.



Scheme 6. Proposed fate of α-Angelica lactone **1** and origin of the formation of *anti*-**3** and *syn*-**3**.

According to numerous other reports cited herein, the formation of *syn*-**3** is kinetically favoured owing to a steric preference for *Si*-face approach of the butenolide on the enone/enal. The absence of reactivity with salicylic acid alone and the virtually perfect enantioselectivity for *anti*-**3** and moderate enantioselectivity for *syn*-**3** suggest that the catalyst is involved in both processes.

However, as iminium activation solely leads to the formation of the *anti* product (see above and below), a different mode of activation must operate for the formation of *syn*-**3**; we believe that Brønsted acid activation takes place, very much in agreement with the work of Lin and co-workers.[17,30] Under our reaction conditions, the excess of acid co-catalyst and the difference in pK_a suggest that the quinuclidine and the primary amine, when not engaged in iminium formation, are both fully protonated. The corresponding bis-ammonium species may in turn behave like a Brønsted acid, in analogy with thiourea catalysts, activating the enone or the pro-nucleophile or both. This non-covalent mode of activation is normally faster than the covalent iminium activation. With no change observed in diastereomeric ratios on longer exposure under the reaction conditions, both processes are irreversible under acidic conditions.

This suggests that the catalytic system not only accelerates iminium formation but also over-rides the steric preferences in the approach of the nucleophile towards the electrophile. This effect may be due to the unique architecture of the catalytic system involving the quinoline moiety in catalyst **II** on the one hand, but also, and especially, the appending phenolic groups in the co-catalyst, thereby allowing it to out-compete the Brønsted acid activation.

Our various observations have allowed us to propose a transition state (Figure 4). The orientation of the iminium ion is well established and documented.[31] So is the high selectivity for the attack on the *Re* face of the enone, due to efficient shielding of the *Si* face by a molecule of acid co-catalyst forming a tight ion-pair with the quinuclidine moiety in apolar solvents. This was confirmed by the reversed high enantioselectivity observed in DMSO, which breaks ion pairs and exposes the quinuclidinium moiety promoting the approach of the nucleophile from the *Si* face. A second molecule of the acid co-catalyst then protonates the imine to the activated iminium species, and its appending phenol may play the role of an activating and directing group for the incoming pro-nucleophile through hydrogen bonding. The proton transfer involved in the activation of the nucleophile may, however, be slow and a third molecule of co-catalyst could bridge the quinoline moiety to promote the deprotonation of the pro-nucleophile. This last event, along with the steric clash between the methyl group in **1** and the quinoline moiety in the catalyst, may be responsible for the high face selectivity in the approach of the nucleophile.[32] A priori entropically costly, this self-assembled dynamic hydrogen-bonding network may explain the robustness of this catalyst system towards higher temperatures.[33]

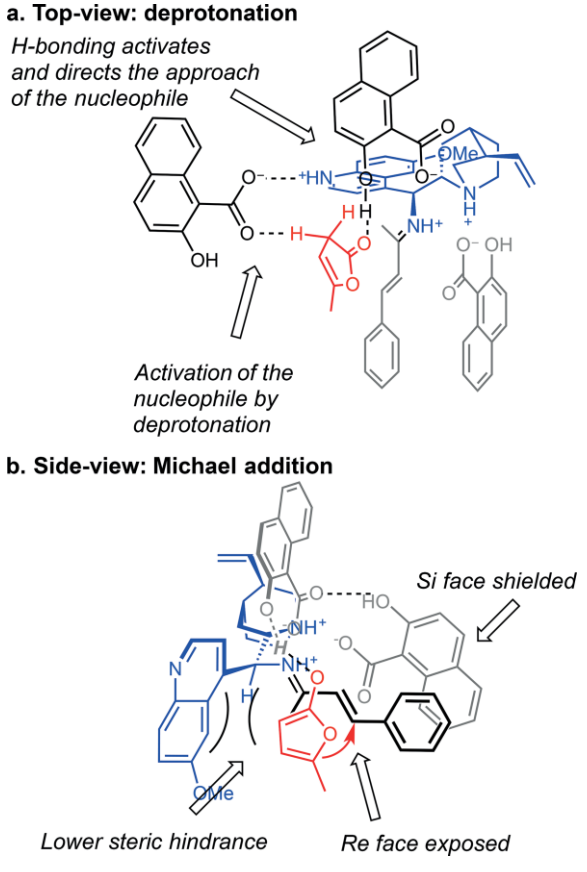


Figure 4. Proposed transition state for the formation of *anti*-**3**.

Finally, the high selectivity observed for the cyclisation of only diastereomer *anti*-**3** under the reaction conditions may be solely due to conformational restrictions (Figure 5). The thiourea moiety may play an important role in enhancing the electrophilicity of the butenolide by hydrogen bonding to the carbonyl. The absence of reactivity with tertiary amine-thiourea catalyst **VI** suggests that the substrate cyclises under enamine activation by a primary amine. Catalyst **IV** is less bulky than **II**, which perhaps prevents access to a conformation allowing for cyclisation. Thus, even if the enamine may be formed, this may explain the absence of cyclisation when **II** was used as catalyst, even in the presence of a thiourea.

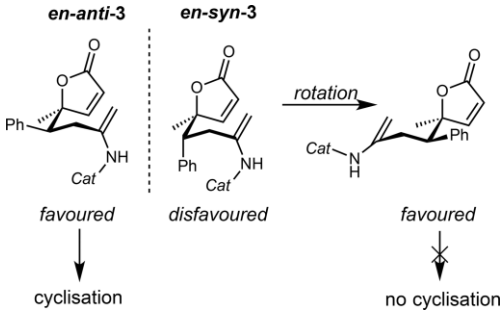


Figure 5. Proposed rationale for the selective cyclisation of *anti*-**3** (only the enamine activation is represented for clarity).

Although cyclisation product **4** presents an a priori rather unfavourable boat conformation, the cyclisation of *anti*-**3** may proceed through a lower-energy chair conformation in which the phenyl substituent is equatorial. In contrast, in order to cyclise, *syn*-**3** would require this phenyl substituent to be axial, leading to steric hindrance with the nearby γ-methyl and β-hydrogen of the butenolide. This forces rotation, which may minimise the energy of the system, but also places the reactive moieties far apart thereby preventing cyclisation.

Conclusion

We have developed an efficient protocol for the divergent access to γ,γ-disubstituted butenolides and hexahydrobenzofuran-2(3*H*)-ones, and we believe that these transformations will find applications in the total synthesis of natural products and other medicinally relevant compounds. Indeed, the inability of the catalyst to promote the cyclisation was turned to our advantage to access both the conjugate adducts in generally high yields, excellent enantioselectivities and modest-to-excellent diastereoselectivities and the bicyclic structures in a subsequent step in a highly diastereoselective manner. The protocol is operationally easy and the conjugate addition is achieved from readily available starting materials, catalyst and co-catalyst under mild reaction conditions. This new self-assembled catalytic system has also demonstrated its robustness and out-performed already established systems and will certainly find applications in other difficult reactions involving Michael additions to enones under iminium activation. In addition, a broad range of aryl- and heteroaryl-substituted enones could be used as substrate for the vinylogous Michael addition. Extension of the scope of this reaction to aliphatic enones proved, however, to be difficult due to their lower reactivity. The contribution by Ye and Dixon, however, may well plug into this work to access further diversity in the preparation of synthetically relevant

hexahydrobenzofuran-2(3*H*)-ones and for their application as synthons in natural product synthesis.

Experimental Section

Representative Procedure for the Vinylogous Michael Addition Reaction: A solution of 9-amino-9-deoxy-*epi*-quinine (**II**; 0.02 mmol) in toluene (1 mL, 0.1 M) was added to a 5-mL vial equipped with a magnetic stirring bar and charged with 2-hydroxy-1-naphthoic acid (0.06 mmol, 60 mol%). After stirring at room temperature for 10 min, all the acid had dissolved and enone **2** (0.1 mmol, 1 equiv.) was added to the yellow solution. After stirring at the same temperature for 10 min, α-Angelica lactone (0.1 mmol, 1 equiv.) was added dropwise, neat or as a solution in toluene (typically 100 μL), and the reaction was stirred at the same temperature. Further portions of α-Angelica lactone (0.1 mmol, 1 equiv.) were added at 24 h and 48 h. After 72 h, the reaction mixture was diluted with EtOAc, washed successively with water, saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The diastereomeric ratio was measured by ^1H NMR and GC–MS analyses. The residue was dry-loaded and purified by flash column chromatography on silica gel using cyclohexane/EtOAc (10:1 to 2:1) as eluent to afford, upon evaporation, the desired conjugate adduct **3**. SFC analysis using the stated column and elution conditions provided the enantiomeric excess.

Representative Procedure for the Cyclisation: The catalyst *rac*-**IV** (0.01 mmol, 10 mol%) was added to a 5-mL vial equipped with a magnetic stirring bar and charged with a solution of conjugate adduct **3** (0.1 mmol) in toluene (1 mL). The resulting reaction mixture was stirred at 40 °C for 48 h. The mixture was diluted with EtOAc, successively washed with water and brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dry-loaded and purified by flash column chromatography on silica gel using cyclohexane/EtOAc (10:1 to 1:1) as eluent to afford, upon evaporation, the desired bicyclic compound **4**.

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Keywords: Organocatalysis · Asymmetric synthesis · Enantioselectivity · Michael addition · Lactones

[1] For selected reviews on organocatalysed cascade reactions, see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; *Angew. Chem.* **2007**, *119*, 1590–1581; b) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; c) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037–2046; d) A.-N. Alba, X. Companyo, M. Viciano, R. Rios, *Curr. Org. Chem.* **2009**, *13*, 1432–1474; e) C. Grondal, M. Jeanty, D. Enders, *Nature Chem.* **2010**, *2*, 167–178; f) B. Westermann, M. Ayaz, S. S. van Berkel, *Angew. Chem. Int. Ed.* **2010**, *49*, 846; *Angew. Chem.* **2010**, *122*, 858–849; g) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390–2431; for books on the the subject, see: h) P.-F. Xu, J.-B. Ling, *Catalytic Cascade Reactions* (Eds.: P.-F. Xu, W. Wang), Wiley-VCH, Weinheim, Germany, **2014**, p. 123–144.

[2] M. Seitz, O. Reiser, *Curr. Opin. Chem. Biol.* **2002**, *6*, 453–458.

[3] For reviews, see: a) Q. Zhang, X. Liu, X. Feng, *Curr. Org. Synth.* **2013**, *10*, 764–785; b) C. Schneider, F. Abels, *Org. Biomol. Chem.* **2014**, *12*, 3531–3543.

[4] S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194.

[5] A. Quintard, A. Lefranc, A. Alexakis, *Org. Lett.* **2011**, *13*, 1540–1543.

[6] E. K. Kemppainen, G. Sahoo, A. Piisola, A. Hamza, B. Kótai, I. Pápai, P. M. Pihko, *Chem. Eur. J.* **2014**, *20*, 5983–5993.

[7] Reaxys search for natural products consisting of variably substituted and unsaturated 7a-methylhexahydrobenzofuran-2(3*H*)-ones and structurally related lactols, acetals, dihydro- and tetrahydrofuran derivatives, March **2015**.

[8] a) H.-L. Cui, J.-R. Huang, J. Lei, Z.-F. Wang, S. Chen, L. Wu, Y.-C. Chen, *Org. Lett.* **2010**, *12*, 720; b) X. Huang, J. Peng, L. Dong, Y.-C. Chen, *Chem. Commun.* **2012**, *48*, 2439–2441.

[9] For Dukunolides D–F, see: a) M. Nishizawa, Y. Nademoto, S. Sastrapradja, M. Shiro, Y. Hayashi, *J. Chem. Soc., Chem. Commun.* **1985**, 395–396; b) M. Nishizawa, Y. Nademoto, S. Sastrapradja, M. Shiro, Y. Hayashi, *Phytochemistry* **1988**, *27*, 237–239; c) N. Saewan, J. D. Sutherland, K. Chantrapromma, *Phytochemistry* **2006**, *67*, 2288–2293; for Granatoine, see: d) J. Cui, J. Ouyang, Z. Deng, W. Lin, *Magn. Reson. Chem.* **2008**, *46*, 894–897; for Xylogranatins F and H, see: e) J. Wu, S. Zhang, T. Bruhn, Q. Xiao, H. Ding, G. Bringmann, *Chem. Eur. J.* **2008**, *14*, 1129–1144; for Hainangranatumin G, see: f) J.-Y. Pan, S.-L. Chen, M.-Y. Li, J. Li, M.-H. Yang, J. Wu, *J. Nat. Prod.* **2010**, *73*, 1672–1679; for Acremolactone A, see: g) T. Sassa, H. Kinoshita, M. Nukina, T. Sugiyama, *J. Antibiot.* **1998**, *51*, 967–969.

[10] For a full report on Cneorins and structurally related natural products, see: a) A. Mondon, B. Epe, H. Callsen, *Liebigs Ann. Chem.* **1983**, 1760–1797; b) A. Mondon, D. Trautmann, U. Oelbermann, B. Epe, *Liebigs Ann. Chem.* **1983**, 1798–1806, and references cited therein.

[11] For an example of a Michael/Michael(/retro-Michael) sequence, see: J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Angew. Chem. Int. Ed.* **2007**, *46*, 389; *Angew. Chem.* **2007**, *119*, 393–392. The full sequence could not be achieved cleanly with 9-amino-9-deoxy-*epi*-quinine only, but subsequent cyclisation with benzylammonium trifluoroacetate allowed for clean cyclisation in a subsequent step.

[12] For examples of Michael/aldol sequences with a pyrazolidine derivative as catalyst, see: a) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 1272; *Angew. Chem.* **2004**, *116*, 1292–1277; b) J. Pulkkinen, P. S. Aburel, N. Halland, K. A. Jørgensen, *Adv. Synth. Catal.* **2004**, *346*, 1077–1080; for an example with L-Proline as catalyst, see: c) D. Gryko, *Tetrahedron: Asymmetry* **2005**, *16*, 1377–1383.

[13] For examples of Michael/Mannich sequences with 9-amino-9-deoxy-*epi*-quinine as catalyst, see: a) Q. Cai, C. Zheng, J.-W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2011**, *50*, 8665; *Angew. Chem.* **2011**, *123*, 8824–8669; b) Q. Cai, S.-L. You, *Org. Lett.* **2012**, *14*, 3040–3043.

[14] W. Zhang, D. Tan, R. Lee, G. Tong, W. Chen, B. Qi, K.-W. Huang, C.-H. Tan, Z. Jiang, *Angew. Chem. Int. Ed.* **2012**, *51*, 10069; *Angew. Chem.* **2012**, *124*, 10216–10073.

[15] D. Yang, L. Wang, D. Zhao, F. Han, B. Zhang, R. Wang, *Chem. Eur. J.* **2013**, *19*, 4691–4694.

[16] J. Ji, L. Lin, L. Zhou, Y. Zhang, Y. Liu, X. Liu, X. Feng, *Adv. Synth. Catal.* **2013**, *355*, 2764–2768.

[17] U. Das, Y.-R. Chen, Y.-L. Tsai, W. Lin, *Chem. Eur. J.* **2013**, *19*, 7713–7717.

[18] L. Yin, H. Takada, S. Lin, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2014**, *53*, 5327; *Angew. Chem.* **2014**, *126*, 5431–5331.

[19] Most of the results from this work were presented at the 6th ORCA meeting (COST action CM0905), Palermo, 8 May 2014: R. Lagoutte, A. Alexakis, *Organocatalysed Direct Double Michael Addition of Unactivated α-Angelica Lactone to Enones*.

[20] X. Li, M. Lu, Y. Dong, W. Wu, Q. Qian, J. Ye, D. J. Dixon, *Nature Commun.* **2014**, *5*, 4479. The protocol uses a mono-tosylated diphenylethylene diamine-derived L-*tert*-leucine-based primary amine catalyst in conjunction with *o*-nitrobenzoic acid as co-catalyst in CH_2Cl_2.

[21] The relative absolute configurations were determined by the preparation of **3** by an alternative route consisting of a conjugate addition according to ref.[5], treatment of the resulting aldehydes with MeMgBr and DMP oxidation of the resulting diastereomeric mixture of secondary alcohols, followed by assignment by ^1H NMR, GC–MS and SFC analyses (see Schemes S-2.1 and S-2.2, in: the Supporting Information for details).

[22] When a racemic 1:1.6 mixture of *anti*-**3** and *syn*-**3** was treated with *rac*-**IV**, an enriched 1:4.2 mixture was obtained along with **4** (26% conver-

sion, 65% based on *anti*-**3**; see Scheme S-2.3 in the Supporting Information for details).
[23] Attempts to optimise the reaction conditions with catalysts **IV** or **V** with the aim of steering the diastereoselectivity towards *anti*-**3** and improving the enantioselectivity failed in our hands. Indeed, a range of solvents and co-catalysts were screened, and the initial conditions were found to give the "best" results (see Tables S-3.2–S-3.5 in the Supporting Information for details).
[24] For a review, see: P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 9748; *Angew. Chem.* **2012**, *124*, 9886–9770.
[25] Concentrations, catalyst loading, temperature and additives were also screened. See Tables S-3.6 and S-4.1–S-4.7 in the Supporting Information for the full set of conditions screened.
[26] All the starting enones were obtained in good yields from the corresponding commercially available aldehydes by aldol condensation/elimination, Wittig olefination or by a two-step Grignard addition/MnO_2 oxidation sequence.
[27] CCDC 1433562 (for **4j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[28] Benzhydrylamine was used for the preparation of racemates and consistently provided diastereomeric ratios in favour of *syn*-**3**. Other systems were probed, but with benzylamine the reaction proceeded too poorly, and a pseudo-racemic mixture of **II** and **III** was found unsatisfactory owing to the difference in reactivity of the two catalysts.
[29] Y. Wu, R. P. Singh, L. Deng, *J. Am. Chem. Soc.* **2011**, *133*, 12458–12461.
[30] This does not mean that *syn*-**3** is always preferentially formed by Brønsted acid activation. In fact, when a mixture of **1** and **2** was treated with catalyst **VI** instead of **IV** under otherwise identical conditions, no reaction took place, thereby confirming that **IV** may activate the enone as the iminium species.
[31] A. Moran, A. Hamilton, C. Bo, P. Melchiorre, *J. Am. Chem. Soc.* **2013**, *135*, 9091–9098.
[32] The proposed transition state shows a really good match for a Diels–Alder reaction with an *endo* transition state stabilised by secondary orbital overlap. Thus, an alternative pathway involving a Diels–Alder cycloaddition/ring opening sequence cannot be ruled out. We have, however, never observed any intermediate pointing towards that possibility.
[33] When **2a** was treated with **1** and in the presence of the optimised catalytic system at 70 °C, *anti*-**3a** was obtained with over 99% *ee*, albeit with moderate conversion and lower diastereoselectivity due to other competing pathways.

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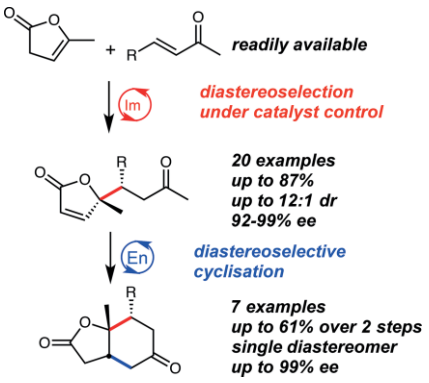

An efficient protocol for the divergent access to γ,γ-disubstituted butenolides and hexahydrobenzofuran-2(3*H*)-ones is described. The two steps are run under very mild conditions and use readily available catalysts and co-catalysts. A new co-catalyst class is described for the first step.

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