

Enantioselective Synthesis of 2,3-Disubstituted *trans*-2,3-Dihydrobenzofurans Using a Brønsted Base/Thiourea Bifunctional Catalyst

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

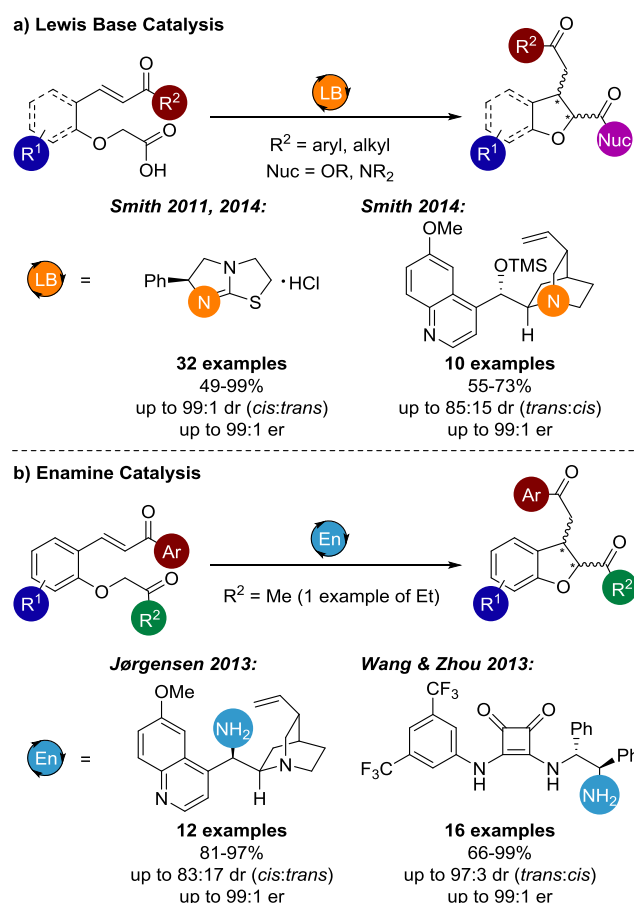
www.rsc.org/

Diego-Javier Barrios Antúnez, Mark D. Greenhalgh, Charlene Fallan, Alexandra M. Z. Slawin, and Andrew D. Smith*

The diastereo- and enantioselective synthesis of 2,3-disubstituted *trans*-2,3-dihydrobenzofuran derivatives (15 examples, up to 96:4 dr, 95:5 er) *via* intramolecular Michael addition has been developed using keto-enone substrates and a bifunctional tertiary amine-thiourea catalyst. This methodology was extended to include non-activated ketone pro-nucleophiles for the synthesis of 2,3-disubstituted indane and 3,4-disubstituted tetrahydrofuran derivatives.

Introduction

Substituted dihydrobenzofurans form the core structure in a variety of natural products, pharmaceuticals and bio-active compounds.¹ The biological activities ascribed to such molecules has inspired the development of a plethora of synthetic strategies for the preparation of this core motif.² Methods for the diastereo- and enantioselective synthesis of these compounds are still relatively limited however, and traditionally rely upon the use of transition metal catalysts.^{2,3} In recent years the use of enantioselective organocatalytic methods for the synthesis of 2,3-disubstituted 2,3-dihydrobenzofurans has been investigated by a number of groups.⁴ As part of our on-going development of Lewis base catalysis for the enantioselective synthesis of heterocycles,⁵ we have reported the use of isothiurea and cinchona alkaloid catalysts for the stereodivergent synthesis of 2,3-dihydrobenzofurans and tetrahydrofurans (Scheme 1a).⁶ Using enone acid substrates, *cis*-disubstituted products were obtained using (*S*)-(-)-tetramisole [up to 99:1 dr (*cis:trans*), 99:1 er], whilst the *trans*-products could be obtained using a quinidine-derived catalyst [up to 85:15 dr (*trans:cis*), 99:1 er]. Jørgensen and co-workers, as well as Wang and Zhou, independently reported the use of enamine catalysis for the synthesis of disubstituted dihydrobenzofurans using intramolecular Michael addition reactions (Scheme 1b).⁷ Using a primary amine analogue of quinidine, Jørgensen reported moderate to good diastereoselectivity and excellent enantioselectivity for the synthesis of *cis*-2,3-disubstituted



Scheme 1. Organocatalytic enantioselective synthesis of 2,3-dihydrobenzofurans using intramolecular Michael additions.

dihydrobenzofurans [up to 83:17 dr (*cis:trans*), 99:1 er].^{7a} Wang and Zhou found that a bifunctional primary amine-squaramide catalyst provided complementary access to *trans*-dihydrobenzofurans with excellent diastereo- and enantioselectivity [up to 97:3 dr (*trans:cis*), 99:1 er].^{7b} Although

EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, KY16 9ST, U.K.

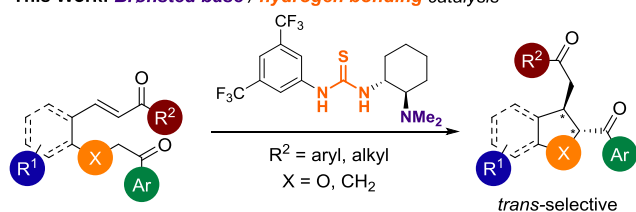
Email: ads10@st-andrews.ac.uk

† Electronic Supplementary Information (ESI) available: Experimental procedures; product characterisation data; copies of NMR (¹H, ¹³C, ¹⁹F, ³¹P) and HPLC traces;²¹ X-ray crystallographic data file for compound **20**. See DOI: 10.1039/x0xx00000x

a range of substitution patterns on the benzofuran core were demonstrated, these enamine-catalysed methodologies were limited to aryl-substituted enone Michael acceptors and unhindered alkyl-substituted α -aryloxy ketone donors ($R^2 = \text{Me}$, one example of Et, Scheme 1b).

To extend the range of methodologies available for the stereoselective synthesis of dihydrobenzofurans, we sought to develop alternative methods for the cyclisation of α -aryloxy-substituted ketone derivatives containing a pendant enone Michael acceptor (Scheme 2). Specifically, the use of α -aryloxy-substituted acetophenone derivatives with both aryl and alkyl-substituted Michael acceptors were targeted in order to provide *product architectures currently inaccessible by organocatalytic methods*. Herein we report the development of a Brønsted base catalytic approach for the diastereo- and enantioselective synthesis of *trans*-2,3-disubstituted 2,3-dihydrobenzofurans. This approach was found to be most effective when combined in concert with hydrogen bonding catalysis. The wider applicability of the methodology is also demonstrated through extension to the synthesis of tetrahydrofuran and indane core structures.

This Work: *Brønsted base / hydrogen bonding catalysis*



Scheme 2. Brønsted base/hydrogen bonding catalytic approach to the enantioselective synthesis of 2,3-dihydrobenzofurans.

Results and Discussion

Reaction Optimisation

Initial studies focused on the use of a selection of Brønsted bases for the cyclisation of keto-enone **1** (Table 1). This substrate could be easily prepared in two steps from salicylic aldehyde and represented a substrate class which was not amenable to cyclisation using the organocatalytic methods previously reported by ourselves,⁶ Jørgensen,^{7a} and Wang and Zhou.^{7b} Pleasingly, the use of C_2 -symmetric guanidine **3**⁸ provided *trans*-dihydrobenzofuran **2** in high yield and with excellent diastereoselectivity, albeit with only modest enantioselectivity (entry 1). The use of alternative Brønsted base catalysts **4**⁹ and **5**¹⁰ gave *trans*-dihydrobenzofuran **2** with improved enantioselectivity, but with relatively low diastereoselectivity (entries 2-3). Takemoto's bifunctional tertiary amine-thiourea catalyst **6**¹¹ provided *trans*-dihydrobenzofuran **2** with promising levels of diastereo- and enantiocontrol (entry 4). Variation of the bifunctional catalyst framework by using cinchona alkaloid-derived thiourea **7**¹² and Jacobsen's amide-substituted thiourea **8**¹³ gave inferior conversions and levels of stereocontrol (entries 5-6). Based on the promising diastereo- and enantioselectivities obtained, further optimisation was

undertaken using guanidine **3** and bifunctional tertiary amine-thiourea **6** (Tables 2 and 3).

Table 1. Reaction optimisation: Initial catalyst screen^a

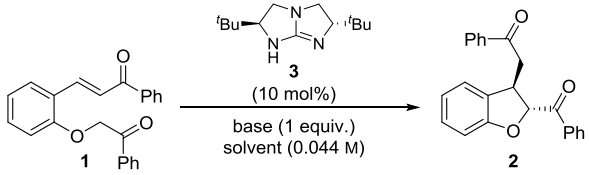
entry	catalyst	time (h)	conv. ^b (%)	dr ^b (<i>trans</i> : <i>cis</i>)	er ^c (<i>R,R</i> : <i>S,S</i>)
1 ^d	3	48	100	95:5	35:65
2 ^d	4	16	58	78:22	68:32
3 ^d	5	18	75	62:38	78:22
4	6	96	93	93:7	78.5:21.5
5	7	24	7	62:38	n.d. ^e
6	8	120	86	83:17	68:32

^a Conditions: **1** (0.044 mmol), catalyst (10 mol%), CH₂Cl₂ (0.044 M), r.t. ^b Measured by ¹H NMR spectroscopy. ^c Measured by chiral HPLC (major diastereoisomer). ^d *i*-Pr₂NEt (0.044 mmol) added. ^e Not determined.

The effect of temperature on stereocontrol was first investigated using guanidine **3** (Table 2, entries 1-3). It was found that improved enantioselectivity was obtained at lower reaction temperatures, with -20 °C giving the best combination of enantioselectivity and reactivity (entry 2). A solvent screen identified 1,2-dichloroethane as optimal, with much shorter reaction times providing full conversion and comparable levels of stereocontrol (entries 4-6). A base screen showed that the tertiary amine *i*-Pr₂NEt gave the highest enantioselectivity (entry 6). The use of a secondary amine (*i*-Pr₂NH) resulted in lower conversion and stereocontrol (entry 7), whilst the use of an amidine (DBU) or inorganic base (Cs₂CO₃) gave *trans*-dihydrobenzofuran **2** as a racemate (entries 8-9). These results may be explained by a competitive racemic background reaction, as in the absence of catalyst **3** both DBU and Cs₂CO₃ gave full conversion to *trans*-dihydrobenzofuran **2** in the same reaction time. An analogous control reaction using *i*-Pr₂NEt in the absence of catalyst **3** resulted in just 4% conversion in 91 h, indicating that the rate of racemic background reaction was insignificant using this base. Interestingly, in the absence of an auxiliary base no reaction took place, despite the overall reaction being a proton-neutral process (entry 10). Finally, it was found that using an immersion cooler to maintain a more constant reaction temperature resulted in an improved enantioselectivity of 82.5:17.5 er, albeit following a 115 h

reaction time. As satisfactory optimisation could not be achieved using guanidine **3**, attention was focussed on reaction optimisation using Takemoto's catalyst **6**.

Table 2. Reaction optimisation using C₂-symmetric guanidine **3**^a



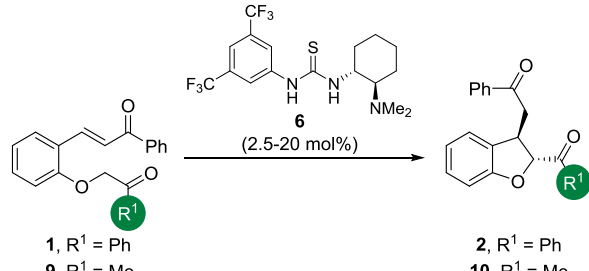
entry	temp (°C)	Solvent	Base	time (h)	conv. ^b (%)	dr ^b (<i>trans:cis</i>)	er ^c (<i>R,R:S,S</i>)
1	r.t.	CH ₂ Cl ₂	<i>i</i> -Pr ₂ NEt	48	100	95:5	35:65
2	-20→r.t.	CH ₂ Cl ₂	<i>i</i> -Pr ₂ NEt	60	100	94:6	21.5:78.5
3	-78→r.t.	CH ₂ Cl ₂	<i>i</i> -Pr ₂ NEt	96	100	93:7	21.5:78.5
4	-20→r.t.	PhMe	<i>i</i> -Pr ₂ NEt	60	100	95:5	33.5:66.5
5	-20→r.t.	EtOAc	<i>i</i> -Pr ₂ NEt	16	23	90:10	42:58
6	-20→r.t.	(ClCH ₂) ₂	<i>i</i> -Pr ₂ NEt	16	95	94:6	21.5:78.5
7	-20→r.t.	(ClCH ₂) ₂	<i>i</i> -Pr ₂ NH	16	65	93:7	38.5:61.5
8 ^d	-20→r.t.	(ClCH ₂) ₂	DBU	16	97	97:3	50:50
9 ^d	-20→r.t.	(ClCH ₂) ₂	Cs ₂ CO ₃	16	98	96:4	51:49
10	-20→r.t.	(ClCH ₂) ₂	-	16	0	-	-
11	-20	(ClCH ₂) ₂	<i>i</i> -Pr ₂ NEt	115	91	93:7	17.5:82.5

^a Conditions: **1** (0.044 mmol), catalyst (10 mol%), solvent (0.044 M). ^b Measured by ¹H NMR spectroscopy. ^c Measured by chiral HPLC (major diastereoisomer). ^d Same conversion and dr obtained under the same reaction conditions in the absence of catalyst **3**.

An initial solvent screen using Takemoto's catalyst **6** at room temperature revealed toluene to be optimal, giving *trans*-dihydrobenzofuran **2** in full conversion and with improved enantioselectivity (88:12 er, Table 3, entry 5). Using this catalyst an auxiliary base was not required in order to obtain good reactivity. Interestingly, whilst lowering the reaction temperature resulted in excellent diastereocontrol, the enantioselectivity of the reaction was significantly reduced (entries 6-7). In contrast, increasing the reaction temperature gave an improvement in both enantioselectivity and conversion (entries 8-9).¹⁴ Conducting the reaction at 50 °C allowed the catalyst loading to be dropped to 5 mol%, with *trans*-dihydrobenzofuran **2** isolated in 83% yield with excellent diastereo- and enantioselectivity (94:6 dr, 95:5 er, entry 10). The catalyst loading could be reduced to 2.5 mol% without significant loss in diastereo- or enantiocontrol, however extended reaction times were required for high conversion (entry 11). Increasing the reaction temperature to 80 °C in an attempt to improve conversion resulted in decreased enantioselectivity (entry 12). The use of 5 mol% of Takemoto's catalyst **6** in toluene at 50 °C was therefore chosen as the optimal reaction conditions (entry 10). Under these conditions, the cyclisation of α -aryloxy methyl ketone **9**, previously used by Jørgensen,^{7a} and Wang and Zhou,^{7b} was investigated. This substrate was found to react slowly and give 2,3-dihydrobenzofuran **10** as a racemate (entry 13). This result, in combination with the successful cyclisation of keto-enone **1**, demonstrates high complementarity between the developed method using Brønsted base/hydrogen bonding catalysis and

the enamine catalysis methods previously reported by Jørgensen,^{7a} and Wang and Zhou.^{7b}

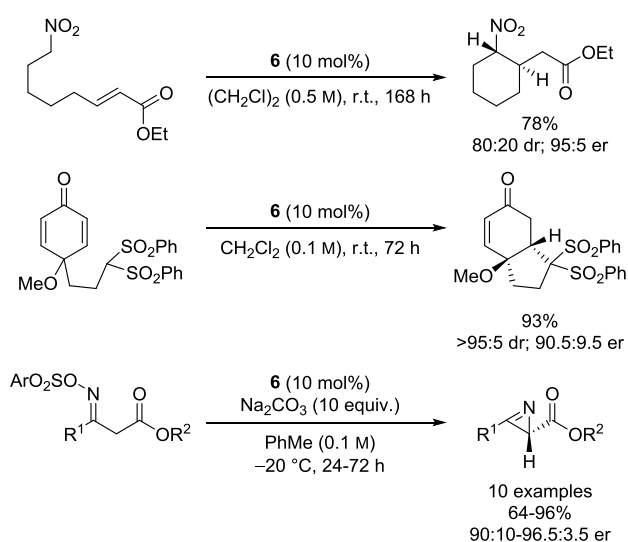
Table 3. Reaction optimisation using Takemoto's tertiary amine/thiourea bifunctional catalyst **6**^a



entry	Catalyst loading (mol%)	temp (°C)	Solvent	time (h)	conv. ^b (%)	dr ^b (<i>trans:cis</i>)	er ^c (<i>R,R:S,S</i>)
1	20	r.t.	CH ₂ Cl ₂	96	93	93:7	78:22
2	20	r.t.	EtOAc	96	35	94:6	86:14
3	20	r.t.	Dioxane	72	9	71:29	87.5:12.5
4	20	r.t.	THF	72	28	71:29	78.5:21.5
5	20	r.t.	PhMe	96	100	94:6	88:12
6	20	0	PhMe	48	13	99:1	65.5:34.5
7	20	10	PhMe	96	53	91:9	84:16
8	20	35	PhMe	18	89	93:7	92:8
9	20	50	PhMe	18	97	94:6	92:8
10 ^d	5	50	PhMe	42	92 (83) ^e	94:6	95:5
11	2.5	50	PhMe	72	97	96:4	92.5:7.5
12	2.5	80	PhMe	20	88	96:4	87:13
13 ^f	20	50	PhMe	144	53	65:35	50:50

^a Conditions: **1** (0.044 mmol), catalyst (2.5-20 mol%), solvent (0.044 M). ^b Measured by ¹H NMR spectroscopy. ^c Measured by chiral HPLC (major diastereoisomer). ^d Performed on 0.26 mmol scale, reaction concentration = 0.086 M. ^e Isolated yield. ^f **9** used in place of **1**.

Takemoto's catalyst **6**, and subsequent related derivatives, have been used to catalyse a wide range of highly diastereo- and enantioselective addition reactions.¹⁵ For reactions proceeding through Brønsted base/hydrogen bonding catalysis however, in general only highly activated pro-nucleophiles such as 1,3-dicarbonyls (pK_a ≈ 7-16 in DMSO),^{16a,b} nitroalkanes (pK_a ≈ 12-17 in DMSO)^{16c,d} and heterocycles which upon deprotonation gain aromaticity, have been used. In contrast, keto-enone **1** represents a much less-activated class of pro-nucleophile (pK_a ≈ 21 in DMSO).^{16e} Takemoto's catalyst **6**, and related derivatives, have been applied previously in intramolecular cyclisations,¹⁵ however the majority of these examples initially involve the *intermolecular* reaction between two achiral reactants to give a stereodefined intermediate, which then undergoes cyclisation. In these processes the role of the catalyst in the intramolecular cyclisation event is not well defined, with the formation of further stereocenters in the intramolecular reaction potentially proceeding under substrate control. Examples in which Takemoto's catalyst **6** has been used for C-C bond forming intramolecular reactions starting from achiral reactants are scarce (Scheme 3).¹⁷ It was therefore considered of interest to fully explore the scope of this novel intramolecular cyclisation process, with a focus on examining the use of less highly activated aryl-ketone pro-nucleophiles (pK_a ≥ 20 in DMSO).

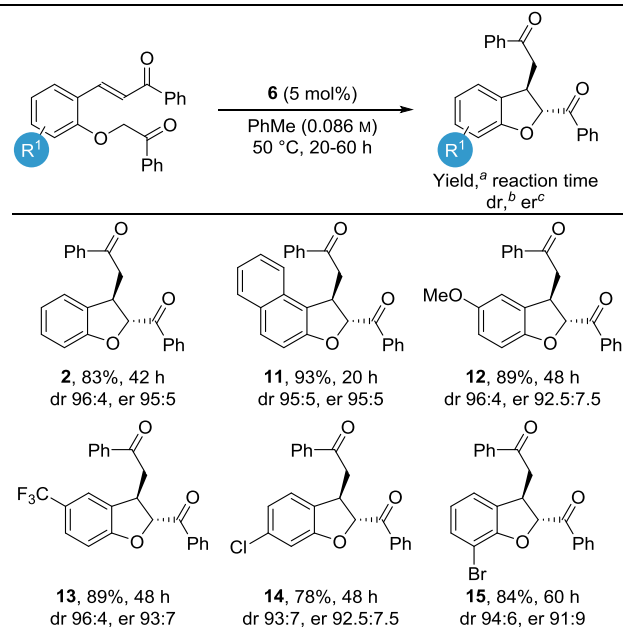


Scheme 3. Previous reports using Takemoto's catalyst **6** for intramolecular cyclisations using carbon-based pro-nucleophiles.

Reaction Scope and Limitations

An extensive investigation of the substrate scope and limitations of this methodology was next investigated (Tables 4–5, Scheme 4). Variation of the aromatic core was well tolerated, with cyclised products **11–15** bearing substitution in the 4-, 5-, 6- or 7-position, obtained in high yield and with excellent diastereo- and enantioselectivity (Table 4). Notably, the aromatic system could be extended to give dihydronaphthofuran derivative **11**, and the incorporation of both electron-donating and electron-withdrawing substituents was well tolerated.

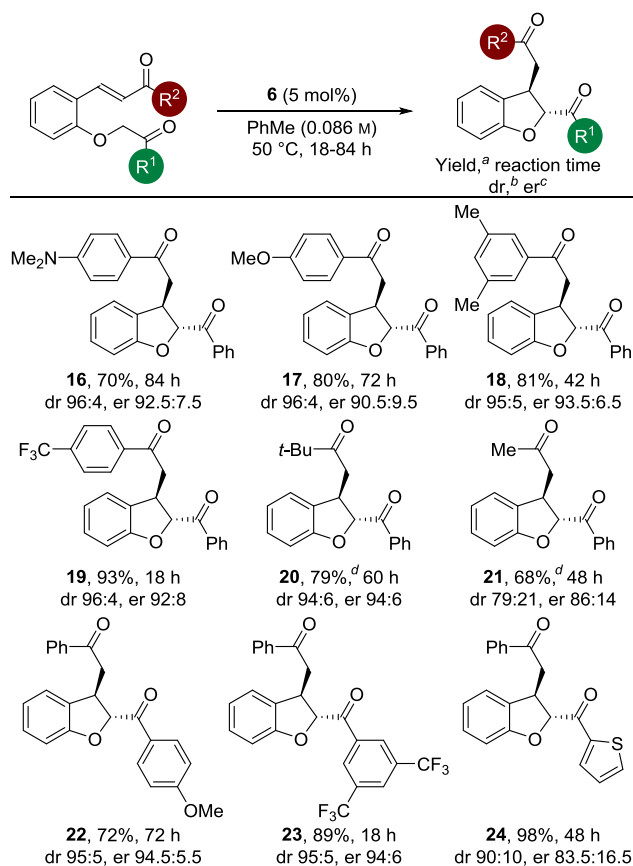
Table 4. Substrate Scope: Variation of aromatic core



^a Isolated yield. ^b Measured by ^1H NMR spectroscopy. ^c Measured by chiral HPLC (major diastereoisomer).

Variation of the Michael acceptor and the pro-nucleophilic groups of the substrates was then investigated (Table 5). The addition of electron-donating substituents (NMe_2 , OMe , Me) to the Michael acceptor gave *trans*-dihydrobenzofurans **16**, **17**, and **18** in high yield and with excellent diastereo- and enantiocontrol. Slightly extended reaction times were required in these cases, which may be rationalised by the lower electrophilicity of the Michael acceptor. In line with this proposal, substitution of the Michael acceptor with an electron-withdrawing substituent (CF_3) gave cyclised product **19** in a shorter reaction time, but with similarly high levels of diastereo- and enantiocontrol. Alkyl-substituted Michael acceptors were also tolerated. *tert*-Butyl-substituted *trans*-dihydrobenzofuran **20** was obtained in high yield and with excellent levels of stereocontrol, whilst methyl-substitution gave *trans*-dihydrobenzofuran **21** with only moderate diastereo- and enantioselectivity. Structural variation of the pro-nucleophilic ketone was also investigated, with both electron-donating and -withdrawing groups well tolerated. *trans*-Dihydrobenzofurans **22** and **23** were obtained in high yield and with excellent diastereo- and enantioselectivity, however the incorporation of a thiophenyl moiety resulted in lower levels of stereocontrol.

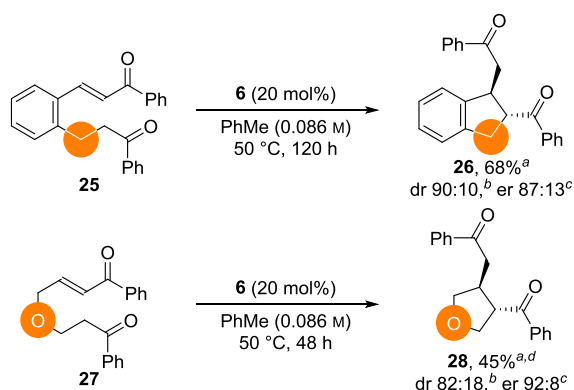
Table 5. Substrate Scope: Michael acceptor and pro-nucleophile scope



^a Isolated yield. ^b Measured by ^1H NMR spectroscopy. ^c Measured by chiral HPLC (major diastereoisomer). ^d 20 mol% **6** used.

Having demonstrated the synthesis of a range of dihydrobenzofurans, the generality of the methodology was

investigated through the use of substrates in which the pro-nucleophile was a simple unsubstituted ketone ($pK_a \approx 24-25$ in DMSO,^{16e,f} Scheme 4). Using **25**, an analogue of keto-enone **1** in which the oxygen linker was replaced with an all carbon tether, led to the formation of indane **26** in good yield, albeit with slightly lower levels of stereocontrol. This cyclisation required a higher catalyst loading and longer reaction time than that of **1**, consistent with the lower pK_a expected for the α -protons. The use of an acyclic substrate without an aromatic tether **27** was also investigated, with 3,4-disubstituted tetrahydrofuran **28** obtained in good yield and stereocontrol. To the best of our knowledge, the use of such pro-nucleophiles has not been reported previously using bifunctional tertiary amine-thiourea catalysts.



Scheme 4. Substrate Scope: Non-activated ketone pro-nucleophiles.

^a Isolated yield. ^b Measured by ¹H NMR spectroscopy. ^c Measured by chiral HPLC (major diastereoisomer). ^d Yield of major diastereoisomer.

The relative and absolute configuration within the major diastereoisomer of *tert*-butyl-substituted 2,3-dihydrobenzofuran **20** was confirmed by single crystal X-ray analysis.¹⁸ The absolute configuration of the remaining products were assigned by analogy. Based upon the absolute configuration of the product it is possible to propose a tentative rationale for the stereochemical outcome of the reaction (Figure 1). The mechanism of reactions promoted by bifunctional tertiary amine-thiourea catalysts have been studied experimentally and theoretically by a number of groups.¹⁹ Based on these works, it is assumed that the carbonyl of the pro-nucleophile binds to the thiourea, enhancing the acidity of the α -proton, and enabling deprotonation by the proximal tertiary amine to give a (*Z*)-enolate with subsequent stereodetermining C-C bond formation. The pre-transition state assembly for this step may be characterised by the thiourea binding the oxyanion of the enolate, with the ammonium ion hydrogen bonding to the enone (Figure 1, TS1).^{19c,e-g,i,j} An alternative plausible pre-transition state assembly would involve the thiourea moiety hydrogen bonding to the enone, with the enolate forming an ion pair with the ammonium (Figure 1, TS2).^{11,19d,h} Both pre-transition state assemblies would predict addition of the *re*-face of the (*Z*)-enolate to the *re*-face of the enone to give the observed (*2R,3R*)-configuration.²⁰

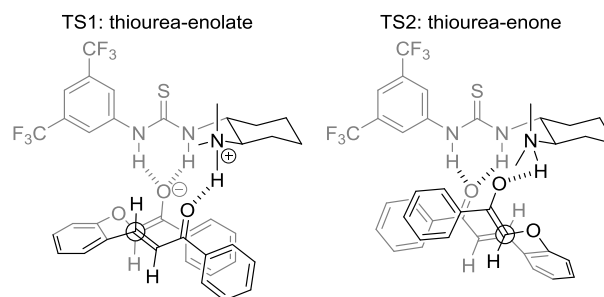


Figure 1. Proposed models for the pre-transition state assembly

Conclusion

In conclusion, the catalytic enantioselective synthesis of *trans*-2,3-disubstituted dihydrobenzofurans from readily-available salicylic aldehyde derivatives has been achieved using a bifunctional tertiary amine-thiourea catalyst **6**. This method provided a range of dihydrobenzofuran derivatives in high yield with generally good to high diastereo- and enantiocontrol (up to 96:4 dr and 95:5 er). The generality of the method was highlighted by extension to the synthesis of disubstituted 2,3-indane, and 3,4-tetrahydrofuran substructures. Ongoing work in this laboratory is focused on further applications of organocatalysis for the asymmetric synthesis of biologically-active compounds.

Acknowledgements

The research leading to these results (D.-J.B.A.; C. F.) has received funding from the ERC under the European Union's Seventh Framework Programme (FP7/2007-2013) / ERC grant agreement n° 279850. ADS thanks the Royal Society for a Wolfson Research Merit Award. We also thank the EPSRC UK National Mass Spectrometry Facility at Swansea University.

References

- (a) A. Goel, A. Kumar and A. Raghuvanshi, *Chem. Rev.* 2013, **113**, 1614; (b) M. Saleem, H. J. Kim, M. S. Ali and Y. S. Lee, *Nat. Prod. Rep.* 2005, **22**, 696; (c) R. S. Ward, *Nat. Prod. Rep.* 1999, **16**, 75; (d) P. Proksch and E. Rodriguez, *Phytochemistry* 1983, **22**, 2335.
- For reviews see: (a) T. D. Sheppard, *J. Chem. Res.* 2011, **35**, 377; (b) F. Bertolini and M. Pineschi, *Org. Prep. Proced. Int.* 2009, **41**, 385.
- For selected recent examples see: (a) L. Pauli, R. Tannert, R. Schiel and A. Pfaltz, *Chem. Eur. J.* 2015, **21**, 1482; (b) H. Cong and G. C. Fu, *J. Am. Chem. Soc.* 2014, **136**, 3788; (c) T. Shibuta, S. Sato, M. Shibuya, N. Kanoh, T. Taniguchi, K. Monde and Y. Iwabuchi, *Heterocycles* 2014, **89**, 631; (d) H. Wang, G. Li, K. M. Engle, J.-Q. Yu and H. M. L. Davies, *J. Am. Chem. Soc.* 2013, **135**, 6774; (e) N. Ortega, S. Urban, B. Beiring and F. Glorius, *Angew. Chem. Int. Ed.* 2012, **51**, 1710.
- For selected examples see: (a) D. Enders, O. Niemeier and L. Straver, *Synlett* 2006, 3399; (b) J. Alemán, S. Cabrera, E. Maerten, J. Overgaard and K. A. Jørgensen, *Angew. Chem. Int. Ed.* 2007, **46**, 5520; (c) K. L. Jensen, P. T. Franke, L. T. Nielsen, K. Daasbjerg and K. A. Jørgensen, *Angew. Chem. Int. Ed.* 2010, **49**, 129; (d) Ł. Albrecht, L. K. Ransborg, V.

- Lauridsen, M. Overgaard and K. A. Jørgensen, *Angew. Chem. Int. Ed.* 2011, **50**, 12496; (e) A. Lu, K. Hu, Y. Wang, H. Song, Z. Zhou, J. Fang and C. Tang, *J. Org. Chem.* 2012, **77**, 6208; (f) M. M. Calter and N. Li, *Org. Lett.* 2011, **13**, 3686; (g) C. Jarava-Barrera, F. Esteban, C. Navarro-Ranninger, A. Parra and J. Alemán, *Chem. Commun.* 2013, **49**, 2001; (h) X.-X. Sun, H.-H. Zhang, G.-H. Li, L. Meng and F. Shi, *Chem. Commun.* 2016, **52**, 2968.
- 5 For selected recent examples see: (a) C. Simal, T. Lebl, A. M. Z. Slawin and A. D. Smith, *Angew. Chem. Int. Ed.* 2012, **51**, 3653; (b) E. R. T. Robinson, C. Fallan, C. Simal, A. M. Z. Slawin and A. D. Smith, *Chem. Sci.* 2013, **4**, 2193; (c) D. Belmessieri, D. B. Cordes, A. M. Z. Slawin and A. D. Smith, *Org. Lett.* 2013, **15**, 3472; (d) L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox and A. D. Smith, *Chem. Sci.* 2013, **4**, 4146; (e) S. R. Smith, C. Fallan, J. E. Taylor, R. McLennan, D. S. B. Daniels, L. C. Morrill, A. M. Z. Slawin and A. D. Smith, *Chem. Eur. J.* 2015, **21**, 10530; (f) A. T. Davies, A. M. Z. Slawin and A. D. Smith, *Chem. Eur. J.* 2015, **21**, 18944.
- 6 (a) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc.* 2011, **133**, 2714; (b) D. Belmessieri, A. de la Houpliere, E. D. D. Calder, J. E. Taylor and A. D. Smith, *Chem. Eur. J.* 2014, **20**, 9762.
- 7 (a) J. Christensen, Ł. Albrecht and K. A. Jørgensen, *Chem. Asian J.* 2013, **8**, 648; (b) Y. Liu, A. Lu, K. Hu, Y. Wang.; H. Song, Z. Zhou and C. Tang, *Eur. J. Org. Chem.* 2013, **2013**, 4836.
- 8 (a) E. J. Corey and M. J. Grogan, *Org. Lett.* 1999, **1**, 157; (b) W. Ye, D. Leow, S. L. M. Goh, C.-T. Tan, C.-H. Chian and C.-H. Tan, *Tetrahedron Lett.* 2006, **47**, 1007.
- 9 Z. Yu, X. Liu, L. Zhou, L. Lin and X. Feng, *Angew. Chem. Int. Ed.* 2009, **48**, 5195.
- 10 J. S. Bandar and T. H. Lambert, *J. Am. Chem. Soc.* 2012, **134**, 5552.
- 11 (a) T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.* 2003, **125**, 12672; (b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.* 2005, **127**, 119.
- 12 (a) B. Vakulya, S. Varga, A. Csámpai and T. Soós, *Org. Lett.* 2005, **7**, 1967; (b) S. H. McCooney and S. J. Connon, *Angew. Chem. Int. Ed.* 2005, **44**, 6367.
- 13 D. E. Fuerst and E. N. Jacobsen, *J. Am. Chem. Soc.* 2005, **127**, 8964.
- 14 This temperature dependence may indicate that the enantioselectivity of the reaction is entropy-controlled, see: (a) H. Buschmann, H.-D. Scharf, N. Hoffmann and P. Esser, *Angew. Chem. Int. Ed. Engl.* 1991, **30**, 477; (b) Y. Inoue, T. Yokoyama, N. Yamasaki and A. Tai, *Nature* 1997, **341**, 225; (c) J. Otera, K. Sakamoto, T. Tsukamoto and A. Orita, *Tetrahedron Lett.* 1998, **39**, 3201; (d) Y. Sohtome, B. Shin, N. Horitsugi, R. Takagi, K. Noguchi and K. Nagasawa, *Angew. Chem. Int. Ed.* 2010, **49**, 7299.
- 15 For reviews see: (a) G. Jakab and P. R. Schreiner, in *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2013, vol. 2, ch. 12, pp. 315-341; (b) Y. Takemoto, *Chem. Pharm. Bull.* 2010, **58**, 593; (c) S. J. Connon, *Chem. Commun.* 2008, 2499; (d) W.-Y. Siau and J. Wang, *Catal. Sci. Technol.* 2011, **1**, 1298; (e) H. Xuehui, M. Zhiwei, W. Jianling and L. Hongmin, *Chin. J. Org. Chem.* 2014, **34**, 1509.
- 16 (a) W. N. Olmstead and F. G. Bordwell, *J. Org. Chem.* 1980, **45**, 3299; (b) E. M. Arnett, S. G. Maroldo, S. L. Schilling and J. A. Harrelson, *J. Am. Chem. Soc.* 1984, **106**, 6759; (c) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum and N. R. Vanier, *J. Am. Chem. Soc.* 1975, **97**, 7006; (d) F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. J. McCollum, M. Van Der Puy, N. R. Vanier and W. S. Matthews, *J. Org. Chem.* 1977, **42**, 321; (e) F. G. Bordwell, M. Van Der Puy and N. R. Vanier, *J. Org. Chem.* 1976, **41**, 1885; (f) F. G. Bordwell and J. A. Harrelson Jr., *Can. J. Chem.* 1990, **68**, 1714.
- 17 For catalyst-controlled C-C bond-forming cyclisations using bifunctional tertiary amine/thiourea catalysts see: (a) W. J. Nodes, D. R. Nutt, A. M. Chippindale and A. J. A. Cobb, *J. Am. Chem. Soc.* 2009, **131**, 16016; (b) Q. Gu and S.-L. You, *Org. Lett.* 2011, **13**, 5192; (c) S. Sakamoto, T. Inokuma and Y. Takemoto, *Org. Lett.* 2011, **13**, 6374.
- 18 CCDC 1469161 contains the supplementary crystallographic data for compound **20**.
- 19 For reviews see: (a) P. H.-Y. Cheong, C. Y. Legault, J. M. Um, N. Çelebi-Ölçüm and K. N. Houk, *Chem. Rev.* 2011, **111**, 5042; (b) Z. Zhang and P. R. Schreiner, *Chem. Soc. Rev.* 2009, **38**, 1187; For selected examples see: (c) A. Hamza, G. Schubert, T. Soós and I. Pápai, *J. Am. Chem. Soc.* 2006, **128**, 13151; (d) S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.* 2007, **129**, 15872; (e) B. T. Tan, Y. Lu, X. Zeng, P. J. Chua and G. Zhong, *Org. Lett.* 2010, **12**, 2682; (f) R. Manzano, J. M. Andrés, R. Álvarez, M. D. Muruzábal, Á. R. de Lera and R. Pedrosa, *Chem. Eur. J.* 2011, **17**, 5931; (g) X.-F. Wang, L. Peng, J. An, C. Li, Q.-Q. Yang, L.-Q. Lu, F.-L. Gu and W.-J. Xiao, *Chem. Eur. J.* 2011, **17**, 6484; (h) C. Reiter, S. López-Molina, B. Schmid, C. Neiss, A. Görling and S. B. Tsogoeva, *ChemCatChem* 2014, **6**, 1324; (i) T. Azuma, Y. Kobayashi, K. Sakata, T. Sasamori, N. Tokitoh and Y. Takemoto, *J. Org. Chem.* 2014, **79**, 1805; (j) A. Quintard, D. Cheshmedzhieva, M. M. Sanchez Duque, A. Gaudel-Siri, J.-V. Naubron, Y. Génisson, J.-C. Plaquevent, X. Bagaut, J. Rodriguez and T. Constantieux, *Chem. Eur. J.* 2015, **21**, 778.
- 20 Based upon previous computational work it would be expected that these two assemblies may be similar in energy, and therefore further discrimination at this time is not possible.
- 21 The data underpinning this research can be found at DOI: <http://dx.doi.org/10.17630/e2138b18-be8d-4632-8f92-6c1391a4d058>.