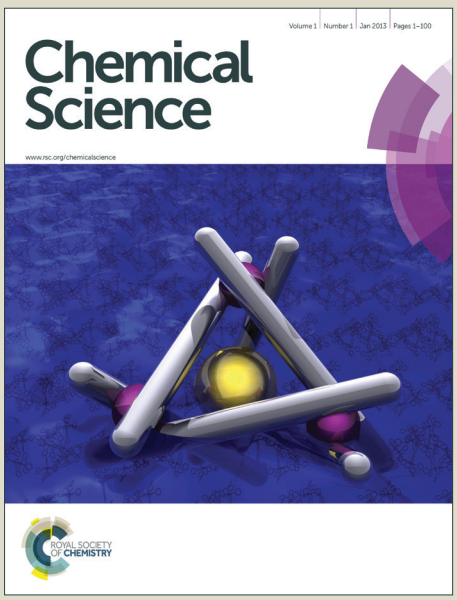
Chemical Science

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemicalscience

Journal Name

RSCPublishing

ARTICLE

Remarkable influence of secondary catalyst site on enantioselective desymmetrization of cyclopentenedione

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Madhu Sudan Manna and Santanu Mukherjee*

An efficient, robust and highly enantioselective catalytic desymmetrization of 2,2-disubstituted cyclopentene-1,3-diones is developed via direct vinylogous nucleophilic addition of deconjugated butenolides. A remarkable influence of the secondary catalyst site on the enantioselectivity points towards an intriguing mechanistic scenario, possibly by triggering a change in catalyst conformation.

Introduction

Functionalized cyclopentanes are ubiquitous structural motif in many biologically active natural and non-natural compounds including steroids, prostaglandins, polyquinanes, guaianes, hamigerans etc.[1] In this context, particularly important are functionalized cyclopentanes decorated with an all carbon quaternary stereogenic center. In general, enantioselective construction of all carbon quaternary stereogenic centers is considered challenging due to steric reasons.[2] Enantioselective desymmetrization of prochiral molecules is a powerful tool for accessing complex architectures with multiple stereogenic centers.[3] In recent years, this strategy has been elegantly exploited using a wide range of reactions under metal and organocatalysis.[4] However compared to the vast popularity of this strategy for accessing enantioenriched cyclohexanyl scaffold,[5] the application of the same to the corresponding cyclopentanes,[6] especially those containing an all carbon quaternary stereogenic center,[7] remains rare. In 2007, during the synthesis of estrone, Corey et al. employed enantioselective reduction of cyclopentan-1,3-dione using oxazaborolidine as the key step (Scheme 1).[8] Recently, Mikami and co-workers reported a Cu(I)-phosphoramidite catalyzed conjugate addition of dialkylzinc to cyclopentene-1,3-diones, for generating cyclopentane containing an all carbon quaternary stereocenter (Scheme 1).[9]

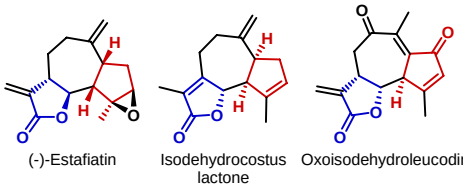
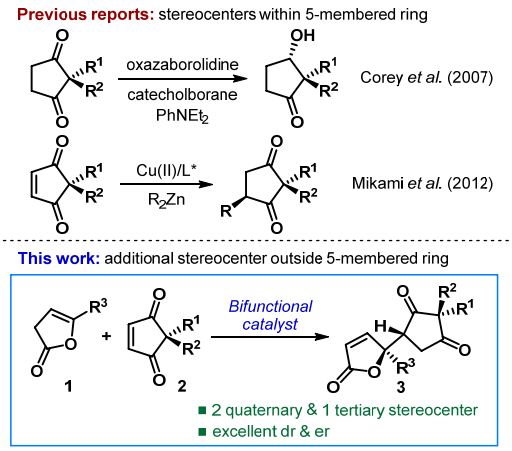


Figure 1 Representative examples of natural products containing both butenolide and cyclopentane scaffold.

Keeping the same objective in mind, we sought to apply vinylogous nucleophilic addition to cyclopentene-1,3-diones, a transformation that could potentially generate multiple quaternary stereocenters not only within, but also outside the cyclopentane scaffold (Scheme 1). We have recently employed deconjugated butenolides (**1**) as nucleophile in a number of direct vinylogous addition reactions for generating quaternary stereocenters with the help of tertiary amine-thiourea based bifunctional catalysts.[10-12] Continuing along the same line, we questioned whether the same catalysis strategy could be applicable for the desymmetrization of 2,2-disubstituted cyclopentene-1,3-diones **2**. Our selection of deconjugated butenolides as the vinylogous nucleophile once again was guided by the wide abundance of butenolide moiety in natural products (Figure 1) and its utility as versatile chiral building block.[13]



Scheme 1 Desymmetrization approach to chiral cyclopentanes.

Herein we describe a catalytic desymmetrization of 2,2-disubstituted cyclopentene-1,3-diones via vinylogous nucleophilic addition of deconjugated butenolides, that proceeds with outstanding diastereoselectivity and excellent enantioselectivity (Scheme 1). Moreover, a remarkable

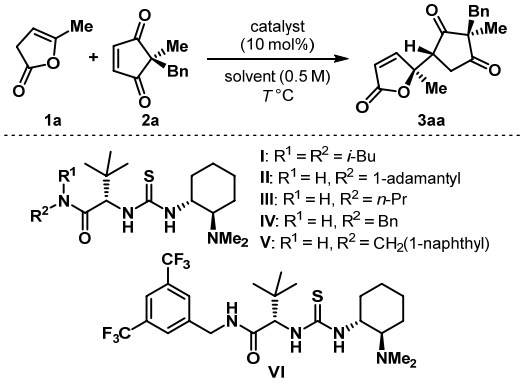
influence of secondary catalyst site on the enantioselectivity is also presented.

Results and discussion

We began our investigation with the prochiral 2-benzyl-2-methylcyclopent-4-ene-1,3-dione **2a** (Table 1), which was easily obtained via benzylation of 2-methylcyclopentane-1,3-dione followed by oxidation (see Supporting Information). α-Angelica lactone **1a** was used as the model nucleophile considering its easy accessibility. As expected, no reaction took place in the absence of any catalyst even after 72 h when the reaction was performed in chloroform at 25 °C (entry 1). Preliminary catalyst screening revealed tertiary amino thioureas derived from the '*matched*' combination of (*S*)-*tert*-leucine and (1*R*,2*R*)-diaminocyclohexane[14] as the best catalyst candidates.[15] In the presence of 10 mol% of such a catalyst **I** containing a tertiary amide unit at 25 °C, product **3aa** was obtained practically as racemate (entry 2). Under these conditions substantial product decomposition occurred, which results in incomplete conversion and low yield. Suppression of product decomposition and complete conversion could be achieved by conducting the reaction at 0 °C with minor increase in er (entry 3). Secondary amide containing catalysts **II-VI** appeared to be considerably more enantioselective with **VI**, having a 3,5-bis(trifluoromethyl)benzyl group on the amide nitrogen, emerging as the optimal in terms of activity and enantioselectivity (entry 8). Superior reaction rate observed in dichloromethane (entry 9) allowed for the decrease in reaction temperature up to –40 °C, when enantioselectivity increased up to 98.5:1.5 er (entry 14). Finally, a minor variation in substrate stoichiometry allowed the product to be isolated in 94% yield essentially as a single diastereomer with 99:1 er (entry 15).

The optimal catalyst and the reaction conditions (Table 1, entry 15) were then adopted to demonstrate the generality of this desymmetrization protocol, with α-angelica lactone **1a** as

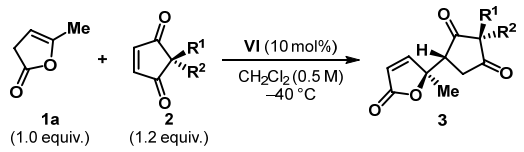
Table 1 Catalyst identification and reaction conditions optimization[a]



Entry	Cat.	Solvent	T/°C (*t*/h)	Yield (%)[b]	dr[c]	er[d]
1	-	$CHCl_3$	25 (72)	n.r.[e]	-	-
2	**I**	$CHCl_3$	25 (48)	40	17:1	51:49
3	**I**	$CHCl_3$	0 (68)	80	>20:1	58:42
4	**II**	$CHCl_3$	0 (48)	92	>20:1	69:31
5	**III**	$CHCl_3$	0 (50)	92	>20:1	86:14
6	**IV**	$CHCl_3$	0 (40)	94	>20:1	96:4
7	**V**	$CHCl_3$	0 (60)	55	>20:1	93:7
8	**VI**	$CHCl_3$	0 (17)	94	>20:1	97:3
9	**VI**	CH_2Cl_2	0 (10)	92	>20:1	98:2
10	**VI**	Toluene	0 (20)	86	>20:1	88:12
11	**VI**	$(CH_2Cl)_2$	0 (10)	94	>20:1	97.5:2.5
12	**VI**	TBME[f]	0 (35)	89	>20:1	79:21
13	**VI**	CH_2Cl_2	–20 (15)	94	>20:1	98:2
14	**VI**	CH_2Cl_2	–40 (20)	93	>20:1	98.5:1.5
15[g]	**VI**	CH_2Cl_2	–40 (22)	94	>20:1	99:1
16[h]	**VI**	CH_2Cl_2	–40 (27)	90	>20:1	98.5:1.5

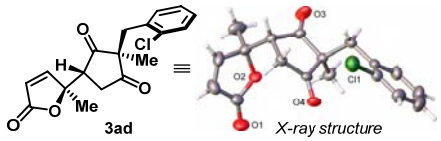
[a] Unless otherwise stated, reactions were carried out using 1.0 equiv. of **1a** and 1.5 equiv. of **2a**. [b] Yield of the isolated product after column chromatography. [c] Diastereomeric ratio (dr) was determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] Enantiomeric ratio (er) was determined by HPLC analysis using a stationary phase chiral column. [e] n.r. = no reaction. [f] TBME: *tert*-Butyl methyl ether. [g] Reaction using 1.2 equiv. of **2a**. [h] Reaction using 1.1 equiv. of **2a**.

Table 2 Scope of cyclopentene-1,3-dione for the catalytic enantioselective desymmetrization [a,b,c]

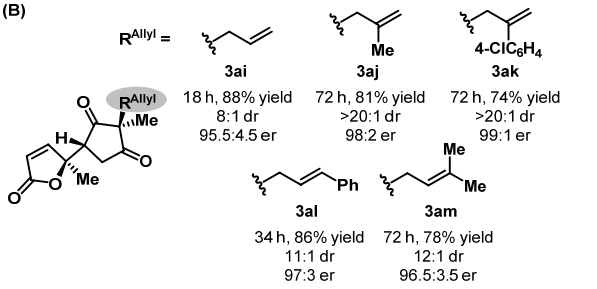


(A)

Ar	*t* [h]	Yield [%]	dr	er
Ph (**3aa**)	22	94	>20:1	99:1
4-ClC_6H_4 (**3ab**)	20	94	>20:1	98.5:1.5
3-ClC_6H_4 (**3ac**)	22	97	>20:1	99:1
2-ClC_6H_4 (**3ad**)	40	87	>20:1	97.5:2.5
4-$CF_3C_6H_4$ (**3ae**)	16	94	16:1	98:2
1-naphth (**3af**)	36	94	>20:1	99:1
2-naphth (**3ag**)	24	97	>20:1	99:1
(**3ah**)	24	93	13:1	98:2



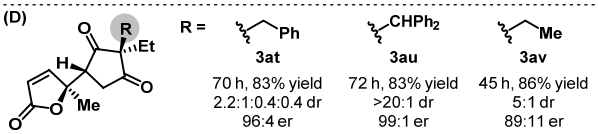
(B)



(C)

R	*t* [h]	Yield [%]	dr	er
n-Pr (**3an**)	36	72	11:1	98:2
i-Bu (**3ao**)	40	78	18:1	98:2
i-Amyl (**3ap**)	40	84	>20:1	97.5:2.5
Ph (**3aq**)	22	89	10:1:1	95:5
CH_2CO_2Me (**3ar**)	32	90	6:1.2:1	97:3
$CHPh_2$ (**3as**)	22	96	>20:1	99:1

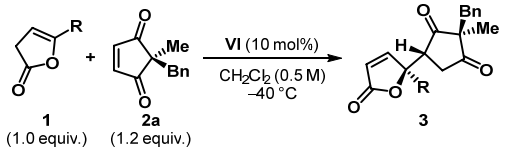
(D)



[a] Yields correspond to the isolated product after column chromatography. [b] Diastereomeric ratio (dr) was determined by ^{1}H-NMR analysis of the crude reaction mixture. [c] Enantiomeric ratio (er) was determined by HPLC analysis using a stationary phase chiral column (See the Supporting Information for details).

the nucleophile. We were pleased to find that a variety of 2,2-disubstituted cyclopentene-1,3-dione derivatives with respect to the substituents at the quaternary center underwent smooth desymmetrization under our standard reaction conditions (Table 2). The combination of methyl not only with benzylic (Table 2A) and allylic (Table 2B), but also with alkyl, aryl and even functionalized alkyl (Table 2C) could be employed. Outstanding diastereo- and enantioselectivities were observed in the case of benzylic substituents, irrespective of their steric and electronic environment (Table 2A). In the case of allylic, both simple allyl and differently substituted allyl groups at various positions were found to be equally suitable (Table 2B). Particularly noteworthy is the products **3an**, where the catalyst was able to withstand steric difference as little as those between methyl and *n*-propyl, and ensured sufficiently high diastereoselectivity (11:1 dr) and excellent enantioselectivity (98:2 er). Besides methyl, combinations of ethyl and other substituents were also tested: high dr and er were maintained for the benzhydryl-substituted product **3au**, but simple benzylated product (**3at**) returned with noticeably inferior diastereoselectivity (Table 2D). Nevertheless, the major diastereomer was obtained with good er. Symmetrical 2,2-diethylcyclopent-4-ene-1,3-dione (**2v**) was also tested as the electrophile (Table 2D): although this example doesn't represent a desymmetrization, product **3av** was obtained with significantly reduced dr and er. Single crystal X-ray analysis of the product **3ad** (Table 2A) confirmed its relative and absolute configuration. Assuming a similar catalytic mechanism is followed, the configuration of other adducts were tentatively assigned the same by analogy.

Table 3 Scope of nucleophile for the catalytic enantioselective desymmetrization of cyclopentene-1,3-dione **2a**.

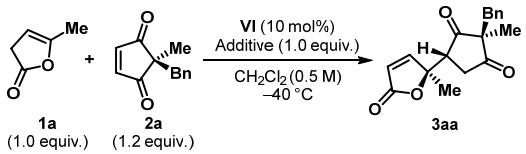


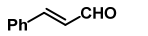
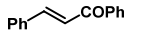
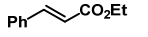
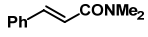
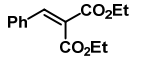
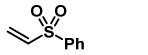
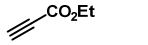
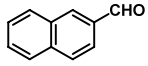
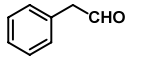
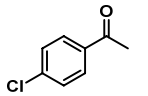
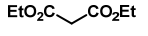
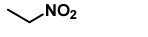
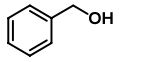
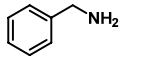
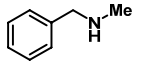
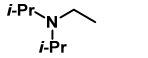
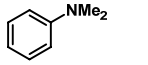
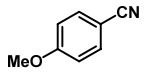
Entry	R	t/h	3	Yield[a] (%)	dr[b]	er[c]
1	Et	16	**3ba**	**96**	>20:1	99:1
2	*n*-Pr	16	**3ca**	**93**	>20:1	99:1
3	*n*-Pent	16	**3da**	**98**	>20:1	99:1
4	*n*-C_8H_{17}	20	**3ea**	**82**	>20:1	99:1
5	*n*-$C_{12}H_{25}$	24	**3fa**	**87**	>20:1	95.5:4.5
6	*i*-Bu	12	**3ga**	**99**	>20:1	99:1
7	Bn	12	**3ha**	**98**	>20:1	98:2
8	Ph	44	**3ia**	**87**	16:1	90:10
9	4-MeC_6H_4	15	**3ja**	**84**	16:1	95:5

[a] Yield of isolated product after column chromatography. [b] Diastereomeric ratio (dr) was determined by ^{1}H-NMR analysis of the crude reaction mixture. [c] Enantiomeric ratio (er) was determined by HPLC analysis using a stationary phase chiral column (See the Supporting Information for details).

The scope of the nucleophile is not limited to α-angelica lactone **1a** and various other butenolides could also be used. Table 3 shows the desymmetrization of cyclopentene-1,3-dione **2a** with an array of deconjugated butenolides, containing substituents at the γ-position. Impeccable diastereoselectivities and outstanding enantioselectivities were observed for butenolides containing simple and long chain alkyl (entries 1-5), branched alkyl (entry 6) and benzyl (entry 7) substituents and the products were obtained with uniformly high yield. For

Table 4 Robustness screening of the catalytic enantioselective desymmetrization of cyclopentene-1,3-dione.[a]

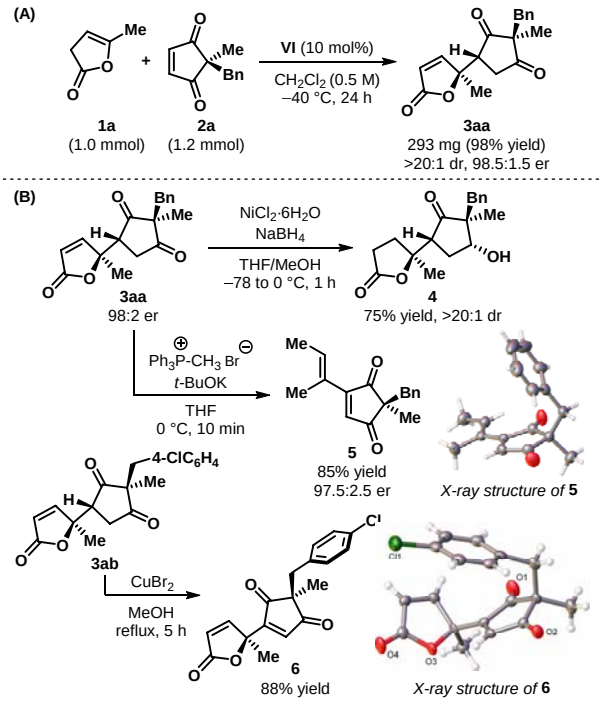


Entry	Additive	*t* (h)	Additive remaining (%)[b]	**3aa**[c,d,e] Yield (%)	er
1	None	22	-	94	99:1
2		30	>99	92	98.5:1.5
3		24	>99	90	98:2
4		24	>99	92	98:2
5		36	>99	88	96:4
6		24	>99	92	98:2
7		30	>99	93	98:2
8		26	>99	90	98.5:1.5
9		32	>99	88	96.5:3.5
10		24	>99	90	97.5:2.5
11		24	>99	93	98:2
12		26	>99	92	98:2
13		30	>99	90	98:2
14		30	>99	90	94:6
15		8	<5%	<5%	n.d.[f]
16		30	<5%	<5%	n.d.[f]
17		8	>99%	<5%	n.d.[f]
18		28	>99%	84%	98:2
19		30	>99	92	98:2
20		22	>99	93	99:1

[a] The reactions were carried out using 1.0 equiv. of **1a**, 1.2 equiv. of **2a** and 1.0 equiv. of the additive. [b] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [c] Yields correspond to the isolated product after column chromatography. [d] In all the cases, products were obtained with >20:1 dr. [e] Enantiomeric ratio (er) was determined by HPLC analysis using a stationary phase chiral column. [f] n.d. = not determined.

the γ-arylated butenolides, products were formed with somewhat reduced dr and er (entries 8-9).

Very recently Glorius and co-workers devised an ingenious protocol for the robustness screening of a particular method by conducting the reaction in the presence of various additives.[16] After successfully demonstrating the broad substrate generality, we decided to verify the robustness of our enantioselective desymmetrization reaction with respect to a variety of functional groups. Consequently, the desymmetrization of enedione **2a** with α-angelica lactone **1a** was carried out in the presence of equimolar amount of additive under otherwise standard reaction conditions. The results are summarized in

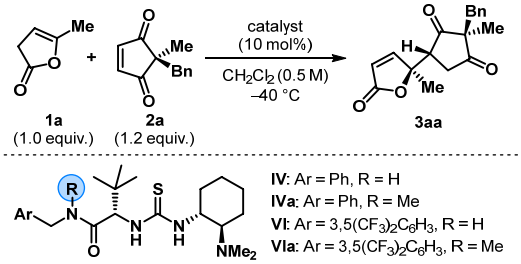


Scheme 2 (A) Large scale experiment and (B) synthetic elaboration of the product.

Table 4. A large number of potentially competing electrophiles as additive were tested including various Michael acceptors (entries 2-8), aldehydes (entries 9-10) and ketone (entry 11). No competing side reaction was observed in any of these cases and the desired product **3aa** was isolated in high yield. More importantly the impeccable diastereoselectivity of the reaction was maintained in most cases. The slight erosion of er and the relatively longer reaction times are possibly the result of the decrease in effective catalyst concentration in the presence of the additives. Needless to mention that in all these cases, additives remained completely unreacted at the end of the reaction, as confirmed by ^{1}H-NMR analysis of the crude reaction mixture. Similar observations were encountered when carbon-centered nucleophiles were used as additive (entries 12-13). The presence of alcohol led to slight erosion of enantioselectivity, possibly due to its interference with catalyst-substrate complex (entry 14). However, sufficiently Lewis/Brønsted basic amines completely suppressed the desired reaction (entries 15-17). Even though primary and secondary amines were completely consumed, tertiary amine remained unreacted after the reaction. To our delight, the reaction took its usual course when less basic amine was used as additive, although the yield of the reaction reduced to some extent (entry 18). Hydrogen bond acceptor (entry 19) as well as simple alkyne (entry 20) was found to be tolerated. These experiments clearly illustrate the robustness of our desymmetrization reaction towards a wide range of functionalities and therefore, successful application to more complex cyclopentene-1,3-diones could be anticipated.

To demonstrate the practicality of our protocol, we have conducted a desymmetrization experiment on 1.0 mmol scale (Scheme 2A). Not only high yield, excellent dr and high er of the product were maintained, but this larger scale experiment also allowed us to recover the catalyst (**VI**) in 88% yield. The utility of this enantioselective desymmetrization reaction was illustrated by elaboration of the products (**3aa-ab**) to synthetically attractive compounds (Scheme 2B). Selective reduction of the less hindered ketone is possible using $NiCl_2/NaBH_4$ and the resulting alcohol **4**, containing the saturated butanolide moiety, was obtained as a single diastereomer. An attempt to a similar selective Wittig olefination, quite unexpectedly, resulted in the chiral diene **5** via base-mediated decarboxylation. The structure of the diene **5** was confirmed by single crystal X-ray diffraction analysis. The reaction proceeded with nearly complete stereochemical fidelity. Additionally, a Cu(II)-mediated oxidation leads to enedione **6** in 88% yield. Although the olefins in **6** seem to be well placed for a double Michael addition for generating tricyclic compounds, our preliminary experiments towards this venture remained unsuccessful, probably due to steric crowding, as evident from the X-ray structure of **6**.

Table 5 Effect of amide functionality on the reaction outcome.



Entry	Catalyst	t/h	Yield[a] (%)	dr[b]	er[c]
1	**IV** (R = H)	60	79	>20:1	98:2
2	**IVa** (R = Me)	72	68	14:1	55:45
3	**VI** (R = H)	22	94	>20:1	99:1
4	**VIa** (R = Me)	72	72	17:1	75:25

[a] Yield of isolated product after column chromatography. [b] Diastereomeric ratio (dr) was determined by ^{1}H-NMR analysis of the crude reaction mixture. [c] Enantiomeric ratio (er) was determined by HPLC analysis using a stationary phase chiral column.

Concerning the mechanism of the reaction, we were intrigued by the selectivity difference between the tertiary and secondary amide functionality of the catalyst encountered during catalyst optimization (see Table 1) and looked to probe this effect even further. Consequently we compared the efficiencies of catalyst **IV** and **VI**, with their methylated counterparts **IVa** and **VIa**, respectively, under our standard reaction conditions (Table 5). A remarkable influence of the amide functionality on the enantioselectivity of this reaction became apparent: the methylated catalysts resulted in product with drastically reduced er (cf. entry 1 vs. 2 and 3 vs. 4). Although less pronounced, methylation also had a negative influence on the diastereoselectivity of the reaction. Besides its

effect on the stereoselectivity of the desymmetrization reaction, catalytic activity of the thiourea derivatives were diminished upon methylation of the amide nitrogen.

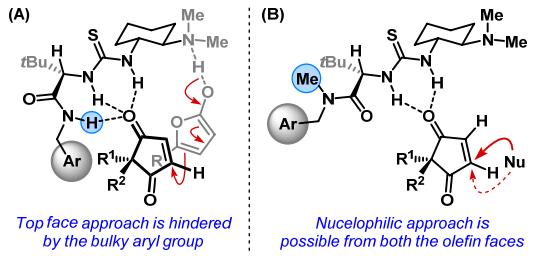


Figure 2 Preferred catalyst conformation and mechanistic rationale.

Even though further investigation is necessary, the amide side chain of the catalyst seems to play a dual role. First, an additional H-bonding from the secondary amide N–H to the electrophilic substrate (Figure 2A) could account for the enhanced catalytic activity of **IV** (compared to **IVa**) and **VI** (compared to **VIa**). The superior catalytic activity of **VI** compared to **IV** could stem from the higher acidity of the former's amide NH proton as a result of the more electron deficient bis(trifluoromethyl)phenyl group. Second and more importantly, we believe that a conformational change takes place (with respect to the rotation around C–CO bond) upon substitution at the amide nitrogen. In the case of secondary amide, all three NHs point to the same direction and result in the shielding of one thiourea face by the aryl ring, which leads to diastereofacial discrimination of the cyclopentene-1,3-dione substrates (Figure 2A). In contrast, methylation aligns C=O towards thiourea NHs and orients the benzyl group away from thiourea, thereby opening both the faces of the cyclopentene-1,3-dione for nucleophilic attack.

Such variation of conformations between secondary and tertiary amide side chain of thiourea derivatives is evident from the X-ray crystal structures reported in the literature by others[14b,17] as well as from our own studies.[10c] Whereas the previously reported X-ray structures reveal the same conformation for tertiary amide side chain (as shown in Figure 2B) regardless of the size of the N-substituents,[14b,17] we have recently reported the existence of the other conformation (Figure 2A) for secondary amide side chain with *N*-(1-adamantyl) amide.[10c] Theoretical support for this conformational switch can be obtained from the computational investigation on the mechanism of cyanosilylation of ketones[18b] and hydrocyanation of imines[18a] by Zuend and Jacobsen: for N-substituent as small as methyl, the same conformational switch was observed. Based on these reports, it is reasonable to assume that a similar conformational effect of the catalyst side chain is responsible for the observed difference in enantioselectivities as disclosed in Table 5 and Figure 2. Nevertheless, the mechanistic model presented here may be considered as preliminary hypothesis and overall, the results presented here offer a model scenario for further mechanistic investigations.

Conclusions

In conclusion, we have developed a highly efficient desymmetrization protocol for 2,2-disubstituted cyclopentene-1,3-diones via direct vinylogous nucleophilic addition of deconjugated butenolides with the help of a tertiary amine-thiourea bifunctional catalyst. The products containing two quaternary and a tertiary stereocenter are obtained in outstanding diastereoselectivity and excellent enantioselectivity. The remarkable influence of the secondary catalyst site on the enantioselectivity points towards an intriguing mechanistic scenario. To the best of our knowledge, this is the first time such an effect is observed in the context of asymmetric catalysis. Considering the operational simplicity, mild reaction conditions and robustness towards various functionalities, this protocol should find applications in synthesis and beyond.

Acknowledgements

This research program is funded by the Department of Science and Technology (DST), New Delhi [Grant No. SR/FT/CS-90/2010] and the Council of Scientific and Industrial Research (CSIR), New Delhi [Grant No. 01 (2505)/11/EMR-II]. M.S.M. thanks CSIR for a doctoral fellowship. We wish to thank Mr. Dipak Samanta (Department of Inorganic and Physical Chemistry, IISc, Bangalore), Mr. Pavan M.S. and Mr. Vijith Shetty (Solid State and Structural Chemistry Unit, IISc, Bangalore) for their help with the X-ray diffraction analysis.

Notes and references

[a]Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India. E-mail: sm@orgchem.iisc.ernet.in; Fax: +91-80-2360-0529.

† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data for all relevant compounds together with HPLC traces for all the products. CCDC 965956 (**3ad**), CCDC 965957 (**5**), CCDC 965958 (**6**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

1 For selected reviews, see: (a) S. Das, S. Chandrasekhar, J. S. Yadav, R. Grée, *Chem. Rev.*, 2007, **107**, 3286; (b) J.-F. Biellmann, *Chem. Rev.*, 2003, **103**, 2019; (c) L. F. Silva, Jr., *Tetrahedron*, 2002, **58**, 9137; (d) D. J. Faulkner, *Nat. Prod. Rep.*, 2002, **19**, 1; (e) G. Mehta, A. Srikrishna, *Chem. Rev.*, 1997, **97**, 671.

2 For reviews, see: (a) C. Hawner, A. Alexakis, *Chem. Commun.*, 2010, **46**, 7295; (b) M. Bella, T. Gasperi, *Synthesis*, 2009, 1583; (c) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.*, 2007, 5969; (d) B. M. Trost, C. Jiang, *Synthesis*, 2006, 369; (e) J. Christoffers, A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473; (f) J. Christoffers, A. Baro, *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, 2005; (g) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci.*, USA 2004, **101**, 5363; (h) J. Christoffers, A. Mann, *Angew. Chem., Int. Ed.*, 2001, **40**, 4591; (i) E. J. Corey, A. Guzman-Perez, *Angew. Chem., Int. Ed.*, 1998, **37**, 388.

3 For reviews, see: (a) A. K. Mourad, C. Czekelius, *Synlett*, 2013, **24**, 1459; (b) Á. E.-García, E. P. Kündig, *Chem. Soc. Rev.*, 2012, **41**, 7803; (c) M. D. D. de Villegas, J. A. Gálvez, P. Etayo, R. Badorrey, P. López-Ram-de-Víu, *Chem. Soc. Rev.*, 2011, **40**, 5564; (d) T. Rovis in *New Frontiers in Asymmetric Catalysis*, Eds.: K. Mikami and M. Lautens, Wiley, Hoboken, NJ, 2007, pp. 275; (e) E. García-Urdiales, I. Alfonso, V. Gotor, *Chem. Rev.*, 2005, **105**, 313; (f) M. C. Willis, J. *Chem. Soc., Perkin. Trans. 1*, 1999, 1765; (g) R. S. Ward, *Chem. Soc. Rev.*, 1990, **19**, 1.

4 For selected recent examples, see: (a) F. Zhou, C. Tan, J. Tang, Y.-Y. Zhang, W.-M. Gao, H.-H. Wu, Y.-H. Yu, J. Zhou, *J. Am. Chem. Soc.*, 2013, **135**, 10994; (b) W. Wu, X. Li, H. Huang, X. Yuan, J. Lu, K. Zhu, J. Ye, *Angew. Chem., Int. Ed.*, 2013, **52**, 1743; (c) M. Wilking, C. Mück-Lichtenfeld, C. G. Daniliuc, U. Hennecke, *J. Am. Chem. Soc.*, 2013, **135**, 8133; (d) Z. Wang, Z. Chen, J. Sun, *Angew. Chem., Int. Ed.*, 2013, **52**, 6685; (e) N. Manville, H. Alite, F. Haeffner, A. H. Hoveyda, M. L. Snapper, *Nat. Chem.*, 2013, **5**, 768; (f) M. T. Corbett, J. S. Johnson, *Chem. Sci.*, 2013, **4**, 2828; (g) N. R. Babij, J. P. Wolfe, *Angew. Chem., Int. Ed.*, 2013, **52**, 9247; (h) A. K. Mourad, J. Leutzow, C. Czekelius, *Angew. Chem., Int. Ed.*, 2012, **51**, 11149; (i) M. Hayashi, N. Shiomi, Y. Funahashi, S. Nakamura, *J. Am. Chem. Soc.*, 2012, **134**, 19366; (j) F. Zhou, J. Guo, J. Liu, K. Ding, S. Yu, Q. Cai, *J. Am. Chem. Soc.*, 2012, **134**, 14326; (k) X. Sun, A. D. Worthy, K. L. Tan, *Angew. Chem., Int. Ed.*, 2011, **50**, 8167; (l) C. K. De, D. Seidel, *J. Am. Chem. Soc.*, 2011, **133**, 14538.

5 For selected examples, see: (a) L. Yao, K. Liu, H.-Y. Tao, G.-F. Qiu, X. Zhou, C.-J. Wang, *Chem. Commun.*, 2013, **49**, 6078; (b) D. M. Rubush, M. A. Morges, B. J. Rose, D. H. Thamm, T. Rovis, *J. Am. Chem. Soc.*, 2012, **134**, 13554; (c) K. Ikeuchi, S. Ido, S. Yoshimura, T. Asakawa, M. Inai, Y. Hamashima, T. Kan, *Org. Lett.*, 2012, **14**, 6016; (d) S. Takizawa, T. M.-N. Nguyen, A. Grossmann, D. Enders, H. Sasai, *Angew. Chem., Int. Ed.*, 2012, **51**, 5423; (e) Q. Gu, S.-L. You, *Org. Lett.*, 2011, **13**, 5192; (f) Q. Gu, S.-L. You, *Chem. Sci.*, 2011, **2**, 1519; (g) R. Leon, A. Jawalekar, T. Redert, M. J. Gaunt, *Chem. Sci.*, 2011, **2**, 487; (h) Q. Gu, Z.-Q. Rong, C. Zheng, S.-L. You, *J. Am. Chem. Soc.*, 2010, **132**, 4056; (i) J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem., Int. Ed.*, 2008, **47**, 7656; (j) N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 404; (k) E. Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell, K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 9202; (l) Q. Liu, T. Rovis, *J. Am. Chem. Soc.*, 2006, **128**, 2552.

6 G. Dickmeiss, V. D. Sio, J. Udmark, T. B. Poulsen, V. Marcos, K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2009, **48**, 6650.

7 (a) K. Mori, T. Katoh, T. Suzuki, T. Noji, M. Yamanaka, T. Akiyama, *Angew. Chem., Int. Ed.*, 2009, **48**, 9652; (b) M. Wadamoto, E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 10098; (c) Y. Hayashi, H. Gotoh, T. Tamura, H. Yamaguchi, R. Masui, M. Shoji, *J. Am. Chem. Soc.*, 2005, **127**, 16028.

8 Y.-Y. Yeung, R.-J. Chein, E. J. Corey, *J. Am. Chem. Soc.*, 2007, **129**, 10346.

9 K. Aikawa, T. Okamoto, K. Mikami, *J. Am. Chem. Soc.*, 2012, **134**, 10329.

10 (a) V. Kumar, S. Mukherjee, *Chem. Commun.*, 2013, **49**, 11203; (b) V. Kumar, B. Ray, P. Rathi, S. Mukherjee, *Synthesis*, 2013, **45**, 1641; (c) M. S. Manna, S. Mukherjee, *Chem.–Eur. J.*, 2012, **18**, 15277; (d) M. S. Manna, V. Kumar, S. Mukherjee, *Chem. Commun.*, 2012, **48**, 5193.

11 For other examples of the use of deconjugated butenolides as nucleophile in asymmetric catalysis, see; (a) U. Das, Y.-R. Chen, Y.-L. Tsai, W. Lin, *Chem.–Eur. J.*, 2013, **19**, 7713; (b) D. Yang, L. Wang, D. Zhao, F. Han, B. Zhang, R. Wang, *Chem.–Eur. J.*, 2013, **19**, 4691; (c) 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; (d) X. Huang, J. Peng, L. Dong, Y.-C. Chen, *Chem. Commun.*, 2012, **48**, 2439; (e) L. Zhou, L. Lin, J. Ji, M. Xie, X. Liu, X. Feng, *Org. Lett.*, 2011, **13**, 3056; (f) A. Quintard, A. Lefranc, A. Alexakis, *Org. Lett.*, 2011, **13**, 1540; (g) H.-L. Cui, J.-R. Huang, J. Lei, Z.-F. Wang, S. Chen, L. Wu, Y.-C. Chen, *Org. Lett.*, 2010, **12**, 720.

12 For selected reviews on bifunctional organocatalysis, see: (a) L.-Q. Lu, X.-L. An, J.-R. Chen, W.-J. Xiao, *Synlett*, 2012, **23**, 490; (b) W.-Y. Siau, J. Wang, *Catal. Sci. Technol.*, 2011, **1**, 1298; (c) Y. Takemoto, *Chem. Pharm. Bull.*, 2010, **58**, 593; (d) S. J. Connon, *Chem. Commun.*, 2008, 2499; (e) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (f) M. S. Taylor, E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520.

13 (a) Y. Igarashi, H. Ogura, K. Furihata, N. Oku, C. Indananda, A. Thamchaipenet, *J. Nat. Prod.*, 2011, **74**, 670; (b) T. Montagnon, M. Tofi, G. Vassilikogiannakis, *Acc. Chem. Res.*, 2008, **41**, 1001; (c) K. Shiomi, H. Ui, H. Suzuki, H. Hatano, T. Nagamitsu, D. Takano, H. Miyadera, T. Yamashita, K. Kita, H. Miyoshi, A. Harder, H. Tomoda, S. Ōmura, *J. Antibiot.*, 2005, **58**, 50.

14 For selected early examples on *tert*-leucine-derived bifunctional thiourea-tertiary amine catalysts, see: (a) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.*, 2005, **127**, 8964; (b) A. Berkessel, S. Mukherjee, F. Cleemann, T. N. Müller, J. Lex, *Chem. Commun.*, 2005, 1898.

15 See the Supporting Information for a more comprehensive catalyst optimization study.

16 (a) N. Kuhl, N. Schröder, F. Glorius, *Org. Lett.*, 2013, **15**, 3860; (b) K. D. Collins, F. Glorius, *Tetrahedron*, 2013, **69**, 7817; (c) K. D. Collins, F. Glorius, *Nat. Chem.*, 2013, **5**, 597.

17 M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2005, **44**, 6700.

18 (a) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.*, 2009, **131**, 15358; (b) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.*, 2007, **129**, 15872.

