

Diastereodivergent Synthesis of Hexahydro-6*H*-benzo[*c*]chromen-6-one Derivatives Catalyzed by Modularly Designed Organocatalysts

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Abstract: The diastereodivergent synthesis of hexahydro-6*H*-benzo[*c*]chromen-6-one with good to high diastereoselectivities (up to 98:2 dr) and enantioselectivities (up to >99% ee) has been achieved by using a domino Michael/Michael/hemiacetalization reaction between *trans*-2-hydroxy- β -nitrostyrenes and *trans*-7-oxo-5-heptenals followed by oxidation. Using appropriate modularly designed organocatalysts (MDOs) that are self-assembled in situ from amino acid derivatives and cinchona alkaloid derivatives, two different diastereomers of the desired hexahydro-6*H*-benzo[*c*]chromen-6-ones are obtained from the same substrates.

Introduction

With the exponential development of organocatalytic methods in recent years, organocatalysis has now been established as a very powerful tool in organic synthesis.^[1] Nonetheless, for compounds containing multiple stereogenic centers, most of the current organocatalytic methods are only dealing with enantio- and diastereoselective reactions that aim at the selective synthesis of one of all of the possible relative configurations. Unlike the synthesis of individual enantiomers, which can be readily obtained from the same substrate(s) by using enantiomeric catalysts, the synthesis of each and every one of all the possible diastereomers with high stereocontrol still remains a great challenge for organic chemists.^[2] In this regard, diastereodivergent catalysis is arguably the most efficient method for obtaining multiple diastereomeric products from the same substrates.^[2]

The chroman-2-one, or dihydrocoumarin, skeleton that can be found in many natural products and biologically active molecules is an important scaffold, because compounds containing this scaffold often exhibit a variety of biological and/or pharmacological activities.^[3] Among the chroman-2-one

derivatives, the stereoselective synthesis of the tricyclic hexahydro-6*H*-benzo[*c*]chromene skeleton, which can be found in many naturally occurring and synthetic biologically active compounds (Figure 1), has received considerable amount of interest latterly, and several organocatalytic methods have been developed for the efficient assembly of such tricyclic skeleton.^[4] However, to our knowledge, there is no method that can achieve the catalytic diastereodivergent synthesis of hexahydro-6*H*-benzo[*c*]chromene derivatives.

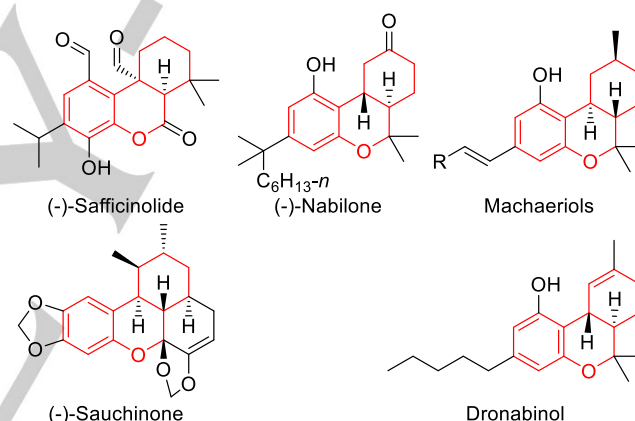


Figure 1. Some biologically active hexahydro-6*H*-benzo[*c*]chromene derivatives.

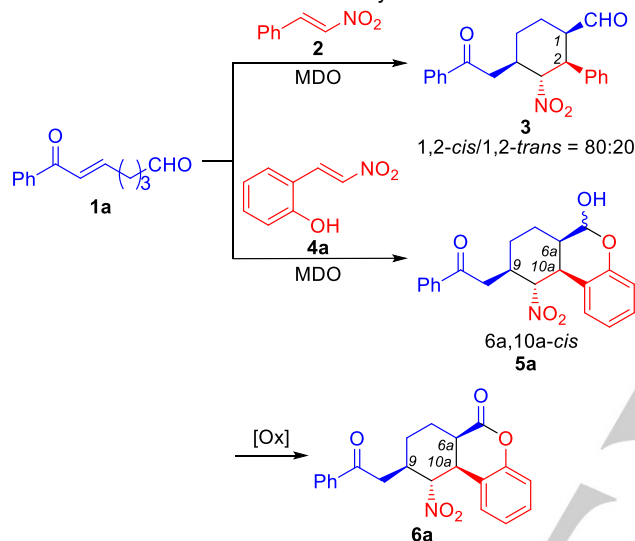
Previously we demonstrated that modularly designed organocatalysts (MDOs),^[5-7] which are self-assembled^[8] from amino acids and cinchona alkaloid derivatives in the reaction medium, were able to achieve high enantioselective and diastereodivergent synthesis of cyclohexane derivatives with four contiguous stereogenic centers via a domino Michael-Michael reaction between **1a** and *trans*- β -nitrostyrene (**2**) (Scheme 1, upper equation).^[7a] However, it was found that the formyl-substituted C₁ stereogenic center of the 2-aryl-substituted cyclohexane products, such as **3**, were very susceptible to epimerization under the reaction conditions, and as a result, lower 1,2-*cis*/1,2-*trans* diastereoselectivities were observed (Scheme 1, upper equation).^[7a] In order to obviate the epimerization problem, we proposed to use *o*-hydroxy-substituted *trans*- β -nitrostyrene substrates, such as **4a**, to trap

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the formyl group in situ through a hemiacetal formation reaction immediately after the cyclization reaction (Scheme 1, lower equation).^[6,9] Moreover, the tricyclic hemiacetal products, such as **5a**, can be readily converted to tricyclic hexahydro-6H-benzo[c]chromen-6-one derivatives, such as **6a**, via an oxidation. Herein, we wish to report that, using appropriate MDOs as the catalysts, the highly enantio- and diastereodivergent synthesis of two diastereomers of the tricyclic chroman-2-one derivatives can be readily achieved from the same substrates by employing a domino^[10] Michael-Michael-hemiacetalization reaction followed by a PCC oxidation.



Scheme 1. Improving the 1,2-*cis* diastereoselectivity via hemiacetal formation.

Results and Discussion

Using *trans*-7-oxo-7-phenyl-5-heptenal (**1a**) and *trans*-2-hydroxy-β-nitrostyrene (**4a**) as the model substrates, we first screened the MDOs self-assembled from the precatalyst modules (Figure 2) for their capability to catalyze the desired domino Michael-Michael-hemiacetalization reaction and to control enantio- and diastereoselectivities in the products. The initially obtained hemiacetal products were oxidized by PCC to give the tricyclic chroman-2-one products. The results of the catalyst screening are summarized in Table 1.

As the results in Table 1 show, when the MDO **8a/9a** was employed as the catalyst, the desired tricyclic 2-chromanone **6a** were obtained in 87% yield, 96:4 dr, and >99% ee (entry 1). Control reactions carried out with **8a** or **9a** alone as the catalyst under otherwise identical conditions did not yield any product (entries 2-3). These results confirm that the observed catalytic activity is indeed due to the MDO. Interestingly, a different diastereomer *ent*-**7a** was obtained as the major product when the pseudo-diastereomeric MDO **8a/9b** was applied,

although the product yield, dr, and ee value were only moderate (entry 4). Further screening of the MDOs self-assembled from different amino acids and **8a** revealed that octahydroindolecarboxylic acid **9d** (entry 6) was a slightly poorer precatalyst module than L-proline, while L-thioproline (**9c**, entry 5) and L-phenylglycine (**9e**, entry 7) were very poor modules since no product was obtained.

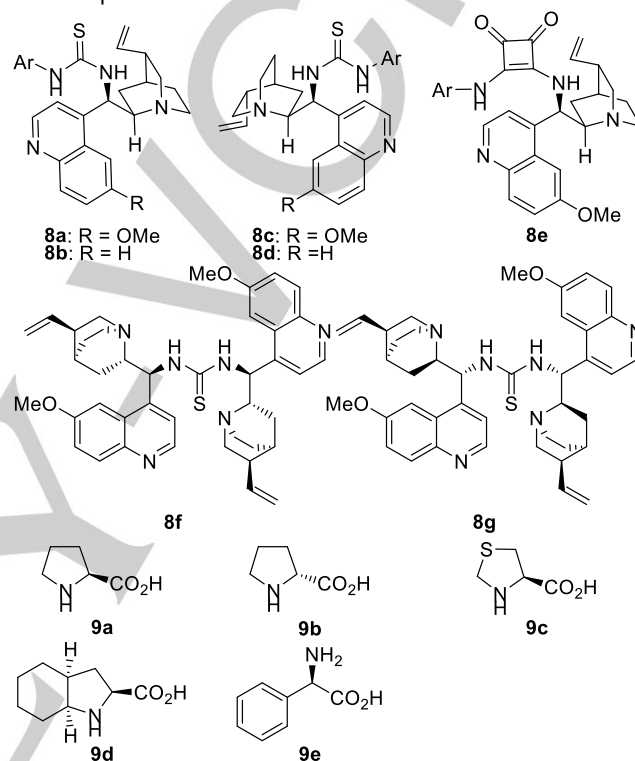
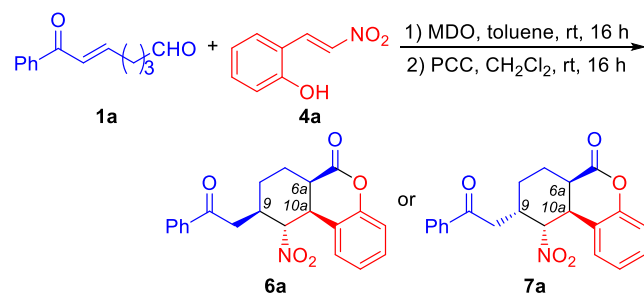


Figure 2. Structure of the precatalyst modules [Ar = 3,5-(CF₃)₂C₆H₃-].

Next, the cinchona alkaloid derivatives were screened, and it turned out that among the MDOs that yielded **6a** as the major product (entries 1, 6, 8, 11, 14, and 16), **8a/9a** (entry 1), **8b/9a** (entry 8), and **8e/9a** (entry 11) all produced very good results, with the best results being achieved by the MDO **8a/9a** (entry 1). In addition, the MDO **8d/9b** led to the formation of *ent*-**6a** in high selectivities (entry 16). For those MDOs that yielded the other diastereomer **7a** as the major product (entries 4, 9, 10, 12, 13, 15, 17, and 18), good results were obtained with the MDO **8d/9d** (entry 17), while the rest all produced poor stereoselectivities. With most of the MDOs screened, only diastereomers **6a** and **7a** were found in the product mixture (entries 4, 6, 9, 10, 12-18), with either **6a** or **7a** obtained as the major diastereomer. Nonetheless, with the MDOs **8a/9a** (entry 1), **8b/9a** (entry 8), and **8e/9a** (entry 11), a third diastereomer was obtained as the minor product. Its relative configuration was tentatively assigned as *6a*,10a-*trans* by a COSY experiment followed by coupling

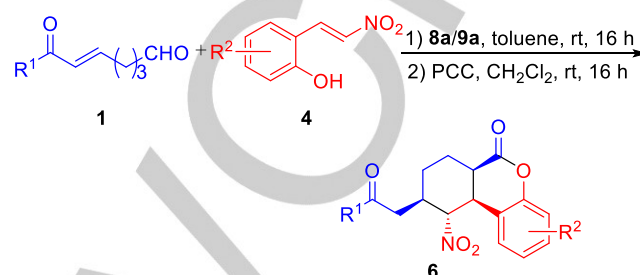
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Table 1: Catalyst screening and optimization of the reaction conditions^[a]

Entry	MDO	6a/7a	Yield [%] ^[b]	dr ^[c] (6a/7a)	ee [%] ^[d]
1	8a/9a	6a	87	96:4 ^[e]	>99
2	8a	-	NR ^[f]	-	-
3	9a	-	NR ^[f]	-	-
4	8a/9b	ent-7a	55	40:60	84
5	8a/9c	-	trace	-	-
6	8a/9d	6a	74	78:22	>99
7	8a/9e	-	NR ^[f]	-	-
8	8b/9a	6a	80	95:5 ^[e]	>99
9	8c/9a	7a	56	36:64	91
10	8d/9a	ent-7a	60	28:72	81
11	8e/9a	6a	65	93:7 ^[e]	99
12	8f/9a	ent-7a	64	32:68	26
13	8g/9a	ent-7a	63	30:70	55
14	8c/9b	ent-6a	73	82:18	86
15	8c/9d	7a	71	22:78	86
16	8d/9b	ent-6a	81	88:12	>99
17	8d/9d	7a	74	20:80	90
18	8g/9b	ent-7a	51	39:61	33
19 ^[g]	8d/9d	7a	74	20:80	93

^[a]Unless otherwise indicated, all reactions were performed with **1a** (0.14 mmol), **4a** (0.12 mmol), and the modules **8** and **9** (0.012 mmol, or 10 mol %, each) in toluene (1.0 mL) at rt for 16 h, followed by the oxidation using PCC. ^[b]Yield of the major diastereomer isolated after column chromatography. ^[c]Unless otherwise indicated, ratio of **6a/7a** as determined by ¹H NMR analysis of the crude reaction mixture. ^[d]Determined by HPLC analysis. ^[e]Ratio of **6a** to a third diastereomer, which was tentatively assigned a 6a,10a-*trans* configuration by a COSY

experiment followed by coupling constant analysis. ^[f]No reaction. ^[g]Performed in 0.5 mL toluene.

Table 2: Synthesis of hexahydro-6H-benzo[c]chromen-6-one diastereomers **6**^[a]

Entry	R ¹	R ²	6/Yield [%] ^[b]	dr ^[c]	ee [%] ^[d]
1	Ph	H	6a/87	96:4	>99
2	Ph	4-Cl	6b/81	89:11	>99
3	Ph	4-Br	6c/81	90:10	>99
4	Ph	4-Me	6d/84	97:3	>99
5	Ph	4-MeO	6e/86	98:2	>99
6	Ph	3-Me	6f/68	85:15	>99
7	4-FC6H4	H	6g/73	89:11	>99
8	4-ClC6H4	H	6h/81	93:7	>99
9	4-MeC6H4	H	6i/80	93:7	>99
10	4-MeOC6H4	H	6j/83	93:7	>99
11	Me	H	6k/61	93:7	>99
12	t-Bu	H	6l/78	95:5	>99
13 ^[e]	Ph	H	6a/82	91:9	>99

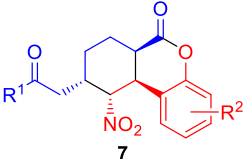
^[a]Unless otherwise indicated, all reactions were performed with **1** (0.14 mmol), **4** (0.12 mmol), and the modules **8a** (0.012 mmol, 10 mol %) and **9a** (0.012 mmol, 10 mol %) in toluene (1.0 mL) at rt for 16 h, followed by the oxidation with PCC. ^[b]Yield of the major diastereomer isolated after column chromatography. ^[c]Ratio of **6** to the 6a,10a-*trans* diastereomer, as determined by ¹H NMR analysis of the crude product. ^[d]Determined by HPLC analysis. ^[e]Reaction carried out at 1.0 mmol scale.

constant analysis. After further optimization of the solvents and concentrations (For details, please see the Supporting Information), both diastereomers **6a** (entry 1) and **7a** (entry 19) may be obtained in good yields and high stereoselectivities in toluene. On the other hand, lowering the reaction temperature

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from rt to 0 °C resulted in very low conversion of the substrates (data not shown).

Table 3: Synthesis of hexahydro-6*H*-benzo[*c*]chromen-6-one diastereomers **7**^[a]

$1 + 4 \xrightarrow[2) \text{PCC, CH}_2\text{Cl}_2, \text{rt, 16 h}]{1) \text{8d/9d, toluene, rt, 16 h}}$ 					
Entry	R ¹	R ²	7/Yield (%) ^[b]	dr ^[c] (7/6)	ee (%) ^[d]
1	Ph	H	7a /74	80:20	95
2	Ph	4-Cl	7b /67	79:21	90
3	Ph	4-Br	7c /70	78:22	90
4	Ph	4-Me	7d /65	77:23	98
5	Ph	4-MeO	7e /75	88:12	98
6	Ph	3-Me	7f /63	76:24	97
7	4-FC ₆ H ₄	H	7g /62	79:21	96
8	4-ClC ₆ H ₄	H	7h /67	77:23	95
9	4-MeC ₆ H ₄	H	7i /71	83:17	96
10	4-MeOC ₆ H ₄	H	7j /72	84:16	98
11	Me	H	7k /49	82:18	84
12	<i>t</i> -Bu	H	7l /75	89:11	94
13 ^[e]	Ph	H	7a /75	84:16	98

^[a]Unless otherwise indicated, all reactions were performed with **1** (0.14 mmol), **4** (0.12 mmol), and the modules **8d** (0.012 mmol, 10 mol %) and **9d** (0.012 mmol, 10 mol %) mmol) in toluene (0.5 mL) at rt for 16 h, followed by oxidation with PCC. ^[b]Yield of the major diastereomer isolated after column chromatography. ^[c]Ratio of **7/6**, as determined by ¹H NMR analysis of the crude product. ^[d]Determined by HPLC analysis. ^[e]Reaction carried out at 1.0 mmol scale.

The scope of this diastereodivergent reaction was then established by screening more substrates under the optimized conditions. The results are summarized in Tables 2 and 3. As the results in these two tables show, substituted *trans*-2-hydroxy- β -nitrostyrenes and 7-substituted *trans*-7-oxo-5-heptenals are both good substrates for this diastereodivergent reaction. In general, products **6** (Table 2), obtained by using the MDO **8a/9a** as the catalyst, have much higher dr and ee values than those of the diastereomeric products **7** (Table 3), obtained by using the MDO **8d/9d** as the catalyst. The electronic nature of the substituent on

the phenyl ring of the *trans*-2-hydroxy- β -nitrostyrenes has minimal effects on the diastereo- and enantioselectivities of both reactions (Tables 2 and 3, entries 1-5). However, 3-methyl-substituted *trans*-2-hydroxy- β -nitrostyrene led to lower diastereoselectivities for both diastereomers (Tables 2 and 3, entry 6), probably due to steric reasons. Similarly, the electronic nature of the substituent on the phenyl ring of the 7-aryl-substituted enals has only minimal effects on the diastereo- and enantioselectivities (Tables 2 and 3, entries 7-10). 7-Alkyl-substituted enals, such as 7-methyl- and 7-*t*-butyl-substituted *trans*-7-oxohept-5-enals are also good substrates for this diastereodivergent domino reaction. Diastereomers **6** were obtained in decent yields and excellent stereoselectivities (Table 2, entries 11 and 12). On the other hand, for diastereomers **7**, while a slightly lower ee value was obtained for the product of *trans*-7-methyl-7-oxohept-5-enal (Table 3, entry 11), that of *trans*-7-*t*-butyl-7-oxohept-5-enal is comparable with the rest substrates (Table 3, entry 12). When the reactions were conducted in 1.0 mmol scale, products **6a** and **7a** were obtained in comparable yields, dr, and ee values as those of the small-scale reactions (Tables 2 and 3, entry 13 vs. entry 1).

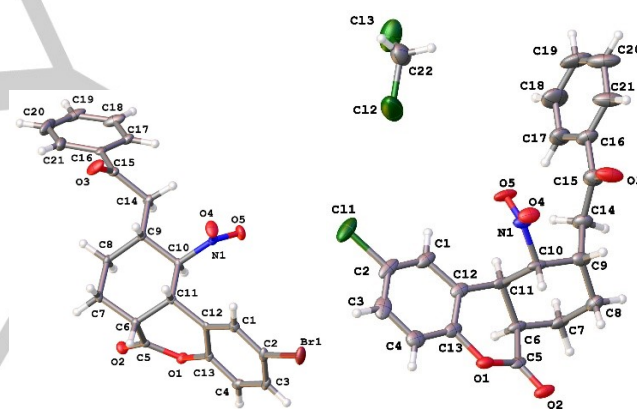
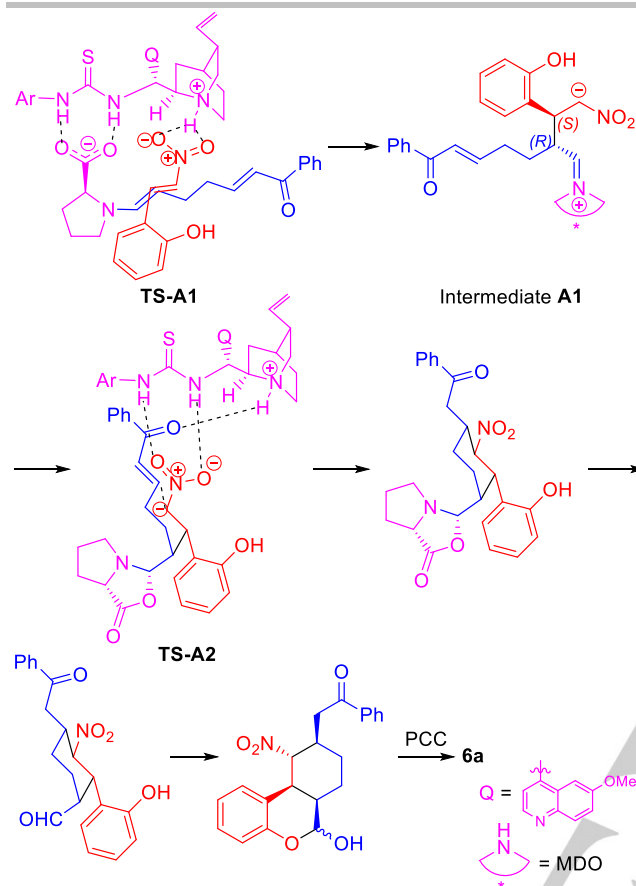
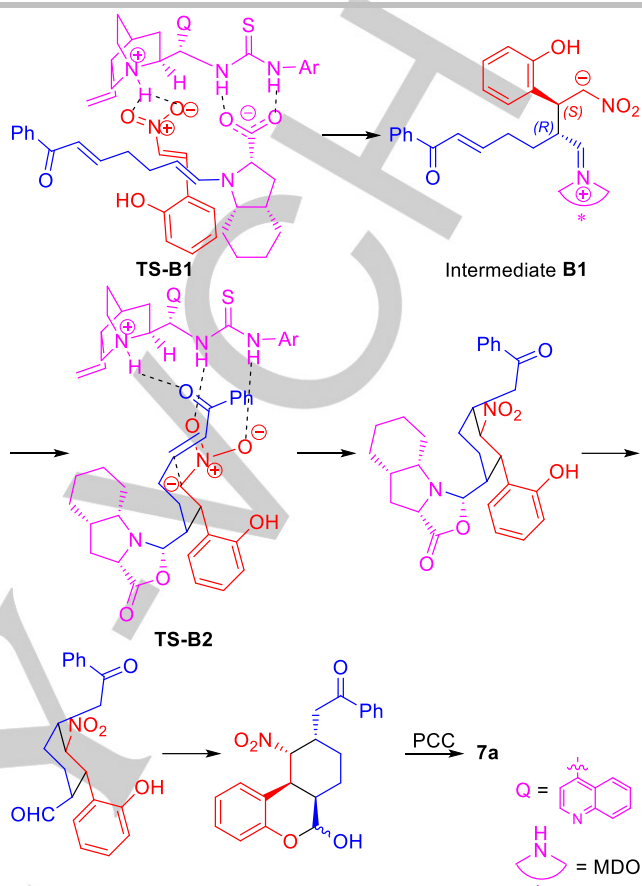


Figure 3. ORTEP drawing of **6c** and **7b** (CH₂Cl₂ solvate).

The absolute stereochemistry of the major diastereomers formed in this diastereodivergent reaction were determined by the X-ray crystallographic analysis of product **6c** and **7b** (Figure 3).^[11] It is clear from Figure 3 that diastereomers **6** and **7** only differ in the stereochemistry of the C9 stereogenic center. As aforementioned, most the MDO catalysts only lead to the formation of these two diastereomers with a 6*a*,10*a*-*cis* configuration (Table 1) and, therefore, the epimerization process is indeed completely inhibited by the acetalization reaction in those cases. For the few MDOs that lead to the formation of the minor 6*a*,10*a*-*trans* diastereomer, such as **8a/9a** (Table 1, entry 1), the formation of such minor diastereomer is either because the epimerization process is not completely inhibited or these MDOs



Scheme 2. Proposed mechanism for the formation of **6a** catalyzed by the MDO **8a/9a** [Ar = 3,5-(CF₃)₂C₆H₃-]



Scheme 3. Proposed mechanism for the formation of **7a** catalyzed by the MDO **8d/9d** [Ar = 3,5-(CF₃)₂C₆H₃-]

produce slightly lower *cis/trans* selectivity in the first Michael reaction step as compared to the other MDOs.

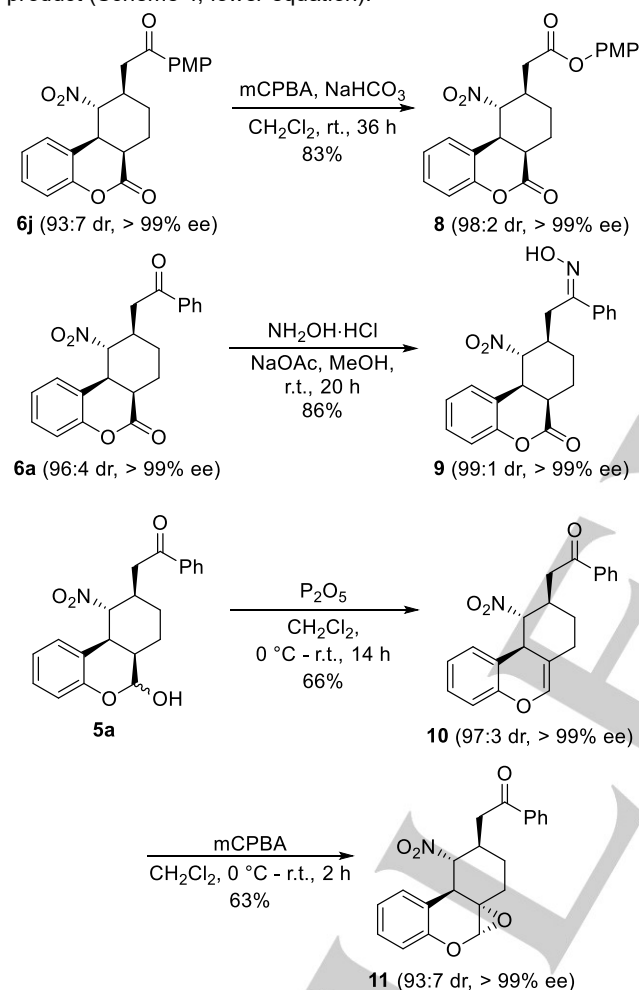
The observed product absolute stereochemistry and diastereodivergence may be rationalized by using the favored transition state models (Schemes 2 and 3), which were proposed based on the results of the computational study of a similar domino MDO-catalyzed Michael/Michael reaction.^[12] As shown in the transition states for the first Michael addition of the domino reaction, **TS-A1** and **TS-B1**, in Scheme 2 and 3, respectively, the amino acid moieties of the MDOs **8a/9a** and **8d/9d** react with the enal **1a** to form the favored *syn*-(*E*)-enamine intermediates^[12] that are hydrogen-bonded to the thiourea moiety of the MDOs. In the meantime, *trans*-2-hydroxy-β-nitrostyrene (**4a**) is hydrogen-bonded to the ammonium moiety of the MDOs. The *Si-Si* attack of the enamines to **4a** in both cases leads to the formation of the intermediates **A1** and **B1**, respectively. Despite the fact that the MDOs **8a/9a** and **8d/9d** are quite different, these two intermediates have the *same* absolute configuration, since the preferred approach of the substrates in the transition states

(i.e., *Si-Si*) is mainly governed by the amino acid configuration. The diastereodivergence in the reaction products is generated in the second Michael reaction. As shown in the transition states for this Michael reaction, **TS-A2** and **TS-B2**, the nitro group of the intermediates is hydrogen-bonded to the thiourea moiety of the MDOs and the ketone group of the enone moiety is hydrogen-bonded to the ammonium moiety of the MDOs.^[12] Since the cinchona thiourea moieties of these two MDOs are pseudo-enantiomeric, the enone moieties of the intermediates **A1** and **B1** have to adopt different positions (i.e., equatorial vs. axial) in the favored chair conformation in **TS-A2** and **TS-B2**, which eventually lead to the formation two different diastereomeric products **6a** and **7a** after oxidation, respectively.

To demonstrate the utility of the reaction products, compound **6j** was successfully oxidized to afford the corresponding ester **8** in a good yield with complete retention of the stereochemistry (Scheme 4, upper equation). Similarly, compound **6a** was selectively converted to the (*E*)-diastereomer^[13] of the oxime derivative **9** in a good yield with

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complete retention of the stereochemistry (Scheme 4, middle equation). Moreover, besides its conversion to the aforementioned tricyclic hexahydro-6*H*-benzo[*c*]chromen-6-one derivatives, the hemiacetal **5a** may also be dehydrated in the presence of P_2O_5 to furnish the 7*H*-benzo[*c*]chromene derivative **10** in a good yield and high stereoselectivities (Scheme 4, bottom equation). Treatment of **10** with mCPBA resulted in the selective formation of the epoxide diastereomer **11**,^[14] with the simultaneous creation of two new stereogenic centers in the product (Scheme 4, lower equation).



Scheme 4. Synthetic conversions of the reaction products (PMP = *p*-methoxyphenyl).

Conclusions

In summary, we have developed a highly diastereodivergent synthesis of both diastereomers of hexahydro-6*H*-benzo[*c*]chromen-6-one derivatives via domino Michael/Michael/hemiacetalization reactions catalyzed by MDOs

followed by oxidation. Using appropriate MDOs, both diastereomers may be obtained in good to high diastereoselectivities (up to 98:2 dr) and high to excellent enantioselectivities (up to >99% ee) from the same substrates.

Experimental Section

General experimental procedure for the synthesis of hexahydro-6*H*-benzo[*c*]chromen-6-ones via the domino Michael-Michael-hemiacetalization reaction followed by an oxidation reaction: To a vial were added sequentially the precatalyst modules **8a** (7.1 mg, 0.012 mmol, 10.0 mol %) and **9a** (1.38 mg, 0.012 mmol, 10.0 mol %) and freshly distilled dry toluene (1.0 mL). The resulting mixture was stirred at room temperature for 15 min. Compound **1a** (28.28 mg, 0.14 mmol, 1.2 equiv.) was then added and the mixture was further stirred for 5 min. before the addition of compound **4a** (19.8 mg, 0.12 mmol). The resulting solution was stirred at room temperature for 16 h until the reaction was complete (monitored by TLC). Then the reaction mixture was concentrated in vacuum and the residue was filtered through the silica gel bed to give the crude hemiacetal as a pale yellow solid. A solution of the hemiacetal in CH_2Cl_2 (3.0 mL) and PCC (77.58 mg, 0.36 mmol, 3.0 equiv.) was stirred at room temperature for 16 h until the completion of reaction (monitored by TLC). The suspension was filtered through silica gel and washed with ethyl acetate. Removing the solvents under vacuum afforded the crude product **6a**, which was then purified by flash chromatography with 20:80 EtOAc/hexane to afford product **6a** (38.5 mg, 87%) as a white solid.

To obtain the other diastereomer **7a**, the same procedure for the synthesis of **6a** was used except that the precatalyst modules **8d** and **9d** were used to form the MDO and 0.5 mL of toluene was used as the solvent for the reaction.

Procedure for the 1.0 mmol-scale reaction: To a round bottom flask were added sequentially the precatalyst modules **8a** (59.4 mg, 0.10 mmol, 10.0 mol %) and **9a** (11.5 mg, 0.10 mmol, 10.0 mol %) and freshly distilled dry toluene (8.3 mL). The resulting mixture was stirred at room temperature for 15 min. Compound **1a** (242 mg, 1.2 mmol, 1.2 equiv.) was then added and the mixture was further stirred for 5 min. before the addition of compound **4a** (165 mg, 1.0 mmol). The resulting solution was stirred at room temperature for 16 h until the reaction was complete (monitored by TLC). Then the reaction mixture was concentrated in vacuum and the residue was filtered through the silica gel bed to give the crude hemiacetal as a pale yellow solid. A solution of the hemiacetal in CH_2Cl_2 (25.0 mL) and PCC (646.5 mg, 3.0 mmol, 3.0 equiv.) was stirred at room temperature for 16 h until the completion of reaction (monitored by TLC). The suspension was filtered through silica gel and washed with ethyl acetate. Removing the solvents under vacuum afforded the crude product **6a**, which was then purified by flash chromatography with 20:80 EtOAc/hexane to afford product **6a** (299 mg, 82%) as a white solid.

To obtain the other diastereomer **7a**, the same procedure for the synthesis of **6a** was used except that the precatalyst modules **8d** and **9d** were used to form the MDO and 4.2 mL of toluene was used as the solvent for the reaction. After purification, diastereomer **7a** (275 mg, 75%) was obtained as a white solid.

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Conflict of interest

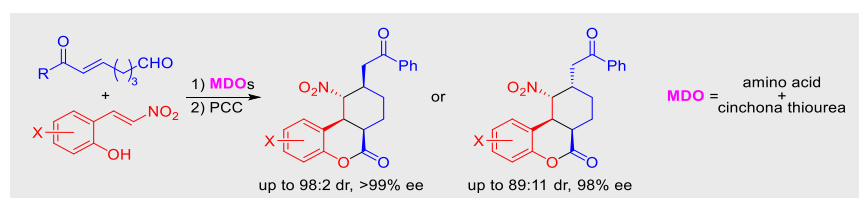
The authors declare no competing financial interest.

Keywords: enantioselectivity • organocatalyst • self-assembly • diastereodivergent catalysis • chromanone • domino reaction

- [1] For reviews, see, see: a) M. Waser, in: *Progress in the Chemistry of Organic Natural Products*; A. D. Kinghorn, H. Falk, S. Gibbons, J. Kobayashi, Y. Asakawa, J.-K. Liu Eds., Springer, Berlin, **2012**, pp 1-150. b) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions and Applications*, P. I. Dalko Ed., Wiley-VCH, Weinheim, **2013**.
- [2] For selected recent examples of organocatalyzed diastereodivergent reactions, see: a) L. Zhang, H. Yuan, W. Lin, Y. Cheng, P. Li, W. Li, *Org. Lett.* **2018**, *20*, 4970-4974; b) W. Xiao, Q.-Q. Yang, Z. Chen, Q. Ouyang, W. Du, Y.-C. Chen, *Org. Lett.* **2018**, *20*, 236-239; c) S. B. J. Kan, H. Maruyama, M. Akakura, T. Kano, K. Maruoka, *Angew. Chem.* **2017**, *129*, 9615-9619; *Angew. Chem. Int. Ed.* **2017**, *56*, 9487-9491; d) S. Meninno, A. Roselli, A. Capobianco, J. Overgaard, A. Lattanzi, *Org. Lett.* **2017**, *19*, 5030-5033; for reviews, see: e) M. Bihani, J. C.-G. Zhao, *Adv. Synth. Catal.* **2017**, *359*, 534-575; f) L. Lin, X. Feng, *Chem. Eur. J.* **2017**, *23*, 6464-6482; g) S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2017**, *139*, 5627-5639; h) I. P. Beletskaya, C. Nájera, M. Yus, *Chem. Rev.* **2018**, *118*, 5080-5200.
- [3] For reviews, see: a) *Advances in Structure and Activity Relationship of Coumarin Derivatives* S. Penta Ed., Academic Press: Amsterdam, **2015**; b) D. P. Kamat, S. G. Tilve, V. P. Kamat, J. K. Kirtany *Org. Prep. Proced. Int.* **2015**, *47*, 1-79; c) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939-9953.
- [4] a) P. Kotame, B.-C. Hong, J.-H. Liao, *Tetrahedron Lett.* **2009**, *50*, 704-707; b) B.-C. Hong, P. Kotame, C.-W. Tsai, J.-H. Liao, *Org. Lett.* **2010**, *12*, 776-779; c) L. Liu, Y. Zhu, K. Huang, B. Wang, W. Chang, J. Li, *Eur. J. Org. Chem.* **2014**, 4342-4350; d) Z.-C. Geng, S.-Y. Zhang, N.-K. Li, N. Li, J. Chen, H.-Y. Li, X.-W. Wang, *J. Org. Chem.* **2014**, *79*, 10772-10785; e) B.-C. Hong, P. Kotame, J.-H. Liao, *Org. Biomol. Chem.* **2011**, *9*, 382-386; f) J.-H. Li, D.-M. Du, *Org. Biomol. Chem.* **2015**, *13*, 9600-9609; g) Y.-Y. Hsieh, A. Raja, B.-C. Hong, P. Kotame, W.-C. Chang, G.-H. Lee, *J. Org. Chem.* **2017**, *82*, 12840-12848; h) M. Kumar, P. Chauhan, S. J. Bailey, E. Jafari, C. von Essen, K. Rissanen, D. Enders, *Org. Lett.* **2018**, *20*, 1232-1235; i) M. Kumar, P. Chauhan, A. Valkonen, K. Rissanen, D. Enders, *Org. Lett.* **2017**, *19*, 3025-3028.
- [5] T. Mandal, C.-G. Zhao, *Angew. Chem.* **2008**, *120*, 7828-7831; *Angew. Chem. Int. Ed.* **2008**, *47*, 7714-7717.
- [6] For examples of MDO-catalyzed asymmetric reactions, see: a) S. Muramulla, C.-G. Zhao, *Tetrahedron Lett.* **2011**, *52*, 3905-3908; b) D. B. Ramachary, R. Sakthidevi, K. S. Shruthi, *Chem. Eur. J.* **2012**, *18*, 8008-8012; c) D. Sinha, T. Mandal, S. Gogoi, J. J. Goldman, J. C.-G. Zhao, *Chin. J. Chem.* **2012**, *30*, 2624-2630; d) S. Perera, D. Sinha, N. K. Rana, V. Trieu-Do, J. C.-G. Zhao, *J. Org. Chem.* **2013**, *78*, 10947-10953; e) S. Muramulla, J.-A. Ma, J. C.-G. Zhao, *Adv. Synth. Catal.* **2013**, *355*, 1260-1264; f) D. Sinha, S. Perera, J. C.-G. Zhao, *Chem. Eur. J.* **2013**, *19*, 6976-6979; g) D. B. Ramachary, K. S. Shruthi, *Org. Biomol. Chem.* **2014**, *12*, 4300-4304; h) D. B. Ramachary, K. S. Shruthi, R. Madhavachary, *Eur. J. Org. Chem.* **2015**, *2015*, 6413-6418; i) Z. Hang, J. Zhu, X. Lian, P. Xu, H. Yu, S. Han, *Chem. Commun.* **2016**, *52*, 80-83; j) S. Konda, J. C. G. Zhao, *Tetrahedron* **2018**, *74*, 6166-6172; k) R. Parella, S. Jakkampudi, H. Arman, J. C.-G. Zhao, *Adv. Synth. Catal.* **2019**, *361*, 208-213; l) S. Jakkampudi, R. Parella, J. C. G. Zhao, *Org. Biomol. Chem.* **2019**, *17*, 151-155.
- [7] a) N. K. Rana, H. Huang, J. C.-G. Zhao, *Angew. Chem.* **2014**, *126*, 7749-7753; *Angew. Chem. Int. Ed.* **2014**, *53*, 7619-7623; b) H. Huang, S. Konda, J. C.-G. Zhao, *Angew. Chem.* **2016**, *128*, 2253-2256; *Angew. Chem. Int. Ed.* **2016**, *55*, 2213-2216.
- [8] For recent examples of self-assembled organocatalysts, see: a) K. M. Ruiz-Pérez, B. Quiroz-García, M. Hernández-Rodríguez, *Eur. J. Org. Chem.* **2018**, 5763-5772; b) P. P. Poudel, K. Arimitsu, K. Yamamoto, *Chem. Commun.* **2016**, *52*, 4163-4166; for reviews, see: c) K. Anebuselvy, K. S. Shruthi, D. B. Ramachary, *Eur. J. Org. Chem.* **2017**, 5460-5483; d) J. Meeuwissen, J. N. H. Reek, *Nat. Chem.*, **2010**, *2*, 615-621.
- [9] For examples, see: a) D. B. Ramachary, R. Sakthidevi, *Org. Biomol. Chem.* **2010**, *8*, 4259-4265; b) D. B. Ramachary, R. Sakthidevi, *Chem. Eur. J.* **2009**, *15*, 4516-4522; c) D. Enders, X. Yang, C. Wang, G. Raabe, J. Runzik, *Chemistry – An Asian Journal* **2011**, *6*, 2255-2259; d) D. Enders, C. Wang, X. Yang, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 2869-2874; e) D. Lu, Y. Li, Y. Gong, *J. Org. Chem.* **2010**, *75*, 6900-6907.
- [10] For reviews: see: a) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253-281; b) T. Chanda, J. C.-G. Zhao, *Adv. Synth. Catal.* **2018**, *360*, 2-79.
- [11] CCDC-1883522 (**6c**) and CCDC-1883524 (**7b**) contain the supplementary crystallographic data for this paper.
- [12] B. Bhaskararao, R. B. Sunoj, *Chem. Sci.* **2018**, *9*, 8738-8747.
- [13] The (*E*)-configuration of the oxime was determined by NOE experiments.
- [14] The stereochemistry of the epoxide was determined by a NOESY experiment.

Entry for the Table of Contents

FULL PAPER



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**Diastereodivergent Synthesis of
Hexahydro-6H-benzo[c]chromen-6-
one Derivatives Catalyzed by
Modularly Designed Organocatalysts**

Diastereodivergence made easy by MDOs: An enantioselective and diastereodivergent synthesis of two diastereomers of the hexahydro-6H-benzo[c]chromen-6-one derivatives was achieved by using a domino Michael/Michael/hemiacetalization reaction catalyzed by the modularly designed organocatalysts (MDOs) followed by oxidation.