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Organocatalytic Michael–Knoevenagel–Hetero-Diels–Alder Reactions: An Efficient Asymmetric One-Pot Strategy to Isochromene Pyrimidinedione Derivatives

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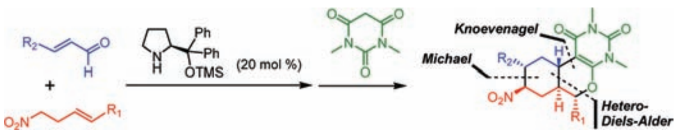
ABSTRACT



Synthesis of isochromene pyrimidinedione derivatives having five stereocenters has been achieved by a one-pot Michael–Knoevenagel condensation–inverse-electron-demand hetero-Diels–Alder reaction of α, *β*-unsaturated aldehydes, olefinic nitroalkanes, and 1,3-dimethylbarbituric acid via a one-pot strategy with excellent diastereo- and enantioselectivities (up to 99% *ee*). The structures and absolute configurations of the products were confirmed by X-ray analysis.

With the recent advent of cascade and sequential organocatalysis, stereoselective syntheses of polycycles have entered into a new era of flourishing development. The many examples of organocatalyzed annulations[1] have included the Michael,[2] Diels–Alder,[3] aldol,[4] Morita–Baylis–Hillman,[5] Knoevenagel,[6] and Henry reactions.[7] Among the strategies employed in these organocatalyzed annulations, multicomponent approaches[8] with multiple bonds and numerous stereocenters selectively generated in a cascade or one-pot manner stand out as particularly attractive. These approaches are characterized by their efficiency, versatility, and flexibility, and they remain of great interest to the synthetic community. Molecules with the pyrimidinedione moiety have displayed a wide range of pharmacological activities, including anti-HIV, antiproliferative, anti-inflammatory, antibacterial, anti-hepatitis B virus, and sustained reduction of plasma DPP-4 activity, and have attracted much attention in medicinal and

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[3] For a recent review: (i) Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Synthesis* **2010**, 1. For examples:(a) Enders, D.; Hüttl, M. R. M.; Runsink, J.; Gerhard, R.; Bianca, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 467. (b) Hayashi, Y.; Samanta, S.; Gotoh, H.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6634. (c) Gotoh, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 2859. (d) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9236. (e) He, H.; Pei, B.-J.; Chou, H.-H.; Tian, T.; Chan, W. H.; Lee, A. W. M. *Org. Lett.* **2008**, *10*, 2421. (f) Xu, D.-Q.; Xia, A.-B.; Luo, S.-P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 3821. (g) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *Chem. Commun.* **2009**, *45*, 1956. (h) Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, H.; Takano, N.; Kohari, Y. *Chem. Commun.* **2010**, *46*, 4827. (i) Zheng, C.; Lu, Y.; Zhang, J.; Chen, X.; Chai, Z.; Ma, W.; Zhao, G. *Chem.—Eur. J.* **2010**, *16*, 5853. (j) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053.

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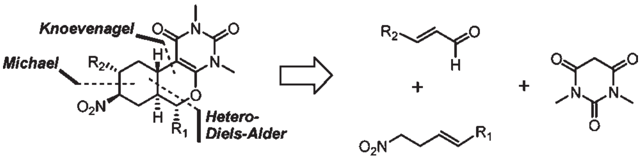
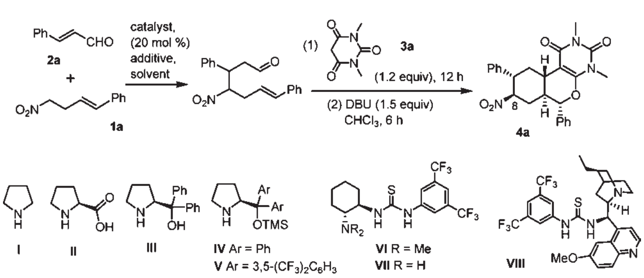
Scheme 1. Retrosynthetic Analysis



synthetic studies.[9] In fact, some of these derivatives are marketed as medicinal drugs, e.g., idoxuridine, primidone, trifluridine, fluorouracil, urapidil, zenarestat (FK 366), gemcitabine, capecitabine, and alogliptin (SYR-322). Moreover, several rare examples have been reported for the asymmetric multicomponent synthesis of hydroisochromenes, a unique skeleton possessing pharmacological activities.[10] Considering the above background in the context of organocatalytic asymmetric annulations,[11] we envisioned an approach to the isochromene pyrimidinedione system that could be accomplished by a Michael–Knoevenagel condensation–inverse-electron-demand hetero-Diels–Alder reaction[12,13] of α, β-unsaturated aldehydes, olefinic nitroalkanes and 1,3-dimethylbarbituric acid via a one-pot strategy (Scheme 1).[14] Herein, we describe the details of such an approach and the methodology that permits efficient production of isochromene pyrimidinedione derivatives in excellent yields and stereoselectivities with up to > 20:1 dr and 99% *ee*.

Initially, we chose 1-((*E*)-4-nitrobut-1-enyl)benzene **1a** and cinnamaldehyde **2a** for testing the feasibility of the proposed Michael–Knoevenagel–hetero-Diels–Alder reaction (Table 1). Gratifyingly, reaction of **1a** and **2a** with 20 mol % of pyrrolidine and acetic acid in ethanol for 46 h, followed by the addition of 1.2 equiv of 1,3-dimethylbarbituric acid (**3a**) with stirring for 12 h, afforded a 47% yield of the expected product **4a** although in an ~1:1 ratio of diastereomers, as depicted in Table 1, with the C-8 epimer.[15] Subsequently, treatment of the unpurified diastereomeric mixtures with 1.5 equiv of DBU in $CHCl_3$ resulted in an isomerization to give the product **4a** as the only observable isomer (Table 1, entry 1).[16]

Table 1. Screening of the Catalysts, Solvents, and Reaction Conditions for the Reactions[a]



entry	catalyst	additive[b]	solvent	time (h)[c]	yield (%)[d]	*ee* (%)[e]
1	**I**	$PhCO_2H$	EtOH	46	47	0
2	**II**	-	EtOH	45	55	3
3	**III**	$PhCO_2H$	EtOH	48	63	69
4	**IV**	$PhCO_2H$	EtOH	48	68	71
5	**V**	$PhCO_2H$	EtOH	72	39	61
6	**VI**	-	EtOH	82	42[f]	40
7	**VII**	-	EtOH	60	54[f]	17
8	**VIII**	-	EtOH	120	10[f]	nd
9	**IV**	$PhCO_2H$	DMF	70	54	93
10	**IV**	$PhCO_2H$	CH_3CN	60	63	96
11	**IV**	$PhCO_2H$	DCM	84	50	88
12	**IV**	$PhCO_2H$	THF	168	41	nd
13	**IV**	$PhCO_2H$	$CHCl_3$	192	54	nd
14	**IV**	$PhCO_2H$	toluene	216	49	nd
15	**IV**	NaOAc[g]	EtOH	20	31	75
16	**IV**	NaOAc[g]	CH_3CN	28	40	98
17	**IV**	$PhCO_2H$ DBU[h]	CH_3CN	24	70	93

[a] Unless otherwise noted, the reactions were performed in 0.2 M **1a** with a 1/1.2 ratio of **1a**/**2a** at rt (~25 °C). [b] Unless otherwise noted, 20 mol % of additive was used. [c] Reaction time for the first-step reaction of **1a** and **2a**. [d] Isolated yields of **4a**. [e] Determined by HPLC with a chiral column (Chiralpak IA). [f] 24 h was required for the second-step reaction: Knoevenagel–hetero-Diels–Alder reaction. nd = not determined. [g] 150 mol %. [h] $PhCO_2H$ (30 mol %), DBU (20 mol %).

Conducting the same Michael–Knoevenagel condensation–inverse-electron-demand hetero-Diels–Alder reaction with L-proline, followed by the addition of 1.5 equiv of DBU, resulted in the formation of expected product **4a** as the only observable diastereomer in 55% yield but with very low enantioselectivity (Table 1, entry 2). A series of organocatalysts were then screened in the reactions

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(9) Manickam, B.; Govindan, S.; Damodharan, K. *Org. Lett.* **2009**, *11*, 4466.

(10) For examples, ochratoxin A, citrinin, A-77636, galaxolide, hydrangenol, mellein, phyllodulcin, nabilone, L-759, L-656, and HU-210.

(11) For our recent efforts in exploring new organocatalytic annulations, see: (a) Hong, B.-C.; Dange, N. S.; Hsu, C.-S.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2011**, *13*, 1338. (b) Hong, B.-C.; Nimje, R. Y.; LinC.-W.; Liao, J.-H. *Org. Lett.* **2011**, *13*, 1278. (c) Hong, B.-C.; Kotame, P.; Liao, J.-H. *Org. Biomol. Chem.* **2011**, *9*, 382. (d) Hong, B.-C.; Dange, N. S.; Hsu, C.-S.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 4812. (e) Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 776. (f) Hong, B.-C.; Jan, R.-H.; Tsai, C.-W.; Nimje, R. Y.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2009**, *11*, 5246. (g) Hong, B.-C.; Nimje, R. Y.; Liao, J.-H. *Org. Biomol. Chem.* **2009**, *7*, 3095. (h) Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tetrahedron Lett.* **2009**, *50*, 704. (i) Hong, B.-C.; Nimje, R. Y.; Sadani, A. A.; Liao, J.-H. *Org. Lett.* **2008**, *10*, 2345. (j) Hong, B.-C.; Nimje, R. Y.; Wu, M.-F.; Sadani, A. A. *Eur. J. Org. Chem.* **2008**, 1449 and references cited therein.

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(13) For examples of the organocatalytic inverse-electron-demand Diels–Alder reaction, see: (a) Xie, H.; Zu, L.; Oueis, H. R.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1923. (b) Li, J.-L.; Kang, T.-R.; Zhou, S.-L.; Li, R.; Wu, L.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2010**, *36*, 6418. (c) Xu, Z.; Liu, L.; Wheeler, K.; Wang, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3484.

(14) For recent examples of the organocatalytic approaches to enantiomerically pure cyclohexanes, see: (a) Inokoishi, Y.; Sasakura, N.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Org. Lett.* **2010**, *12*, 1616–1619. (b) Li, J.-L.; Kang, T.-R.; Zhou, S.-L.; Li, R.; Wu, L.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6418–6420. (c) Alemán, J.; Marcos, V.; Marzo, L.; Ruano, J. L. G. *Eur. J. Org. Chem.* **2010**, 4482–4491.

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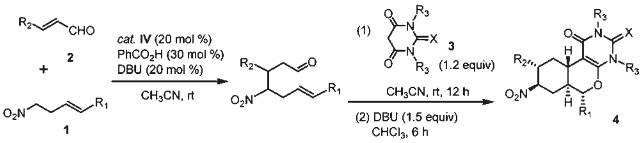
(16) Reaction of the *syn*/*anti* mixtures with DBU in EtOH or CH_3CN, *vide infra*, gave low yields. Changing the reaction media by evaporation of solvent followed by the addition of $CHCl_3$ and DBU provided better yields.

Table 2. Scope of the Michael–Knoevenagel Condensation–Inverse-Electron-Demand Hetero-Diels–Alder Reactions[a]



entry	product **4**	time (h)[b]	yield (%)[c]	*ee* (%)[d]
1	**4a** $R_1 = R_2 = Ph$; $R_3 = Me$; $X = O$	24	70	93
2	**4b** $R_1 = Ph$; $R_2 = 4\text{-}BrC_6H_4$; $R_3 = Me$; $X = O$	17	61	91
3	**4c** $R_1 = Ph$; $R_2 = 4\text{-}MeOC_6H_4$; $R_3 = Me$; $X = O$	30	62	91
4	**4d** $R_1 = Ph$; $R_2 = 4\text{-}NO_2C_6H_4$; $R_3 = Me$; $X = O$	14	53	92
5	**4e** $R_1 = Ph$; $R_2 = 4\text{-}ClC_6H_4$; $R_3 = Me$; $X = O$	20	60	97
6	**4f** $R_1 = 4\text{-}BrC_6H_4$; $R_2 = Ph$; $R_3 = Me$; $X = O$	24	64	96
7	**4g** $R_1 = 4\text{-}ClC_6H_4$; $R_2 = Ph$; $R_3 = Me$; $X = O$	22	62	92
8	**4h** $R_1 = 4\text{-}CH_3C_6H_4$; $R_2 = Ph$; $R_3 = Me$; $X = O$	23	66	97
9	**4i** $R_1 = 4\text{-}MeOC_6H_4$; $R_2 = Ph$; $R_3 = Me$; $X = O$	32	67	99
10	**4j** $R_1 = 4\text{-}ClC_6H_4$; $R_2 = 4\text{-}BrC_6H_4$; $R_3 = Me$; $X = O$	22	61	94
11	**4k** $R_1 = R_2 = Ph$; $R_3 = Et$; $X = S$	25	60[e]	88 (96)[f]

[a] Unless otherwise noted, the reactions were performed in 0.2 M **1** with a ratio of 1/1.2 of **1**/**2** at rt (~25 °C). [b] Reaction time for the first-step reaction of **1** and **2**. [c] Isolated yields of product **4**. [d] Determined by HPLC with a chiral column (Chiralpak IA). [e] 48 h was required for the second-step reaction: Knoevenagel–hetero-Diels–Alder reaction. [f] First-step Michael reactions at 10 °C for 56 h.

(Table 1, entries 3–8). Among them, reactions with the prolinol derivatives **III**–**V**, especially the Jørgensen–Hayashi catalyst **IV**, gave promising results with good yields and better enantioselectivities (e.g., 68% yield and 71% *ee* in Table 1, entry 4). The reactions with thiourea catalysts **VI**–**VIII** afforded lower yields of the product **4a** (Table 1, entries 6–8). To optimize the yields and enantioselectivities, the reaction was conducted in various solvents (Table 1, entries 9–14), and the best result was obtained with CH_3CN to give a 63% yield with 96% *ee* (Table 1, entry 10). To accelerate the first-step Michael reaction, we increased the nucleophilicity of the nitroalkane by replacing benzoic acid with a base, e.g., NaOAc, and then screened the reactions. Although this modification facilitated the first-step Michael reaction, it also afforded lower yields of product **4a**, but with similar enantioselectivities (Table 1, entries 15–16). Notably, using a combination of acid and base additives with catalyst **IV** (Table 1, entry 17), the first-step Michael reactions were facilitated and the optimal yield (70% yield) was obtained with a slight excess of $PhCO_2H$ to DBU (30–20 mol %).

Having established the optimal reaction conditions (Table 1, entry 17), we next examined the scope and limitation of the above system with variants of reactants **1**, **2**, and **3**. Despite a subtle decrease in the enantioselectivity, the condition of **IV**–$PhCO_2H$–DBU was selected for these reactions since it gave the best yield as well as included a short reaction time in the first-step Michael reaction. As shown in Table 2, the reaction appears quite general with respect to the substrates tested, providing the desired adducts with excellent enantioselectivities and diastereomeric ratios (dr) (> 20:1) in good yields. In addition, for the reaction with thioxopyrimidinedione (**3b**), the second-step reaction, the Knoevenagel–hetero-Diels–Alder reaction, required a longer reaction time than the examples using **3a** (48 vs 12 h), Table 2, entry 11. The structure and the absolute configuration of the products were assigned based on the X-ray analysis of (+)-**5**[17] and (+)-**6**,[18] which were obtained from the respective reductions of **4a** and **4b** by DIBAL-H (Figure 1).

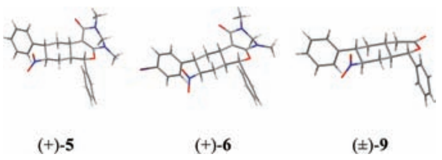


Figure 1. Stereo plots of the X-ray crystal structures of (+)-**5**, (+)-**6**, and (±)-**9**: C, gray; N, blue; O, red; Br, purple.

To explain the stereochemistry of this transformation, a plausible mechanism was proposed, as shown in Scheme 2. Initial nucleophilic attack of nitroalkane **1** on the iminium-activated cinnamaldehyde **2** from the *Re* face under the control of the catalyst (**TS A**) gives intermediate enamine **B**, which was transformed to iminium **C** and then reacted with 1,3-dimethylbarbituric acid **3** via Knoevenagel condensation to afford pyrimidinetrione **D**. Subsequently, the intermediate **D** underwent the intramolecular hetero-Diels–Alder reaction (IMDA) via the transition state (**TS E**) to give a 1:1 ratio of the diastereomeric product **4** (8,9-*syn* and 8,9-*anti*), which was subsequently isomerized by DBU to afford **4** (8,9-*anti*) predominately. The intriguing and excellent diastereoselective IMDA reaction[19] may arise from the severe steric hindrance conferred by the phenyl substituents at C-9 (denoted by an asterisk in Scheme 2), which hampers the reaction through the transition state (**TS F**).[20] Notably, the reaction demonstrates a proof-of-principle of the control of facial selectivity in IMDA by the remote stereogenic center generated *in situ* by the domino organocatalysis reaction.[21]

Finally, we explored the possibility of extending the protocol to hexahydro-1*H*-isochromen-3(4*H*)-one (Scheme 3).

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(17) X-ray data was deposited in data bank (CCDC-842679). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

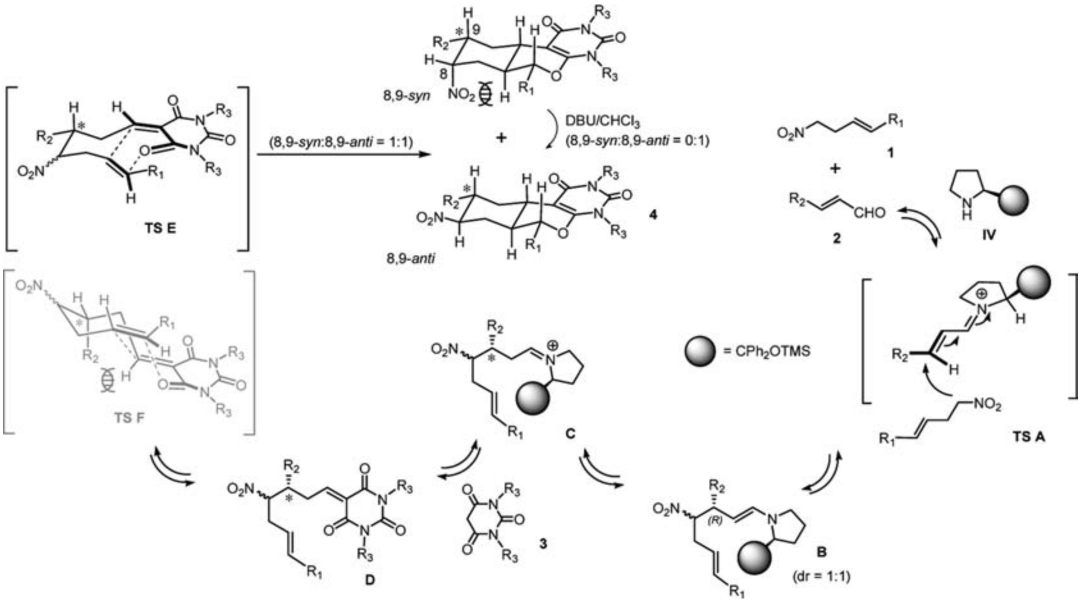
(18) X-ray data was deposited in data bank (CCDC-842680).

(19) For review in IMDA, see: (a) Martin, J.; David, T. *Chem. Soc. Rev.* **2009**, *38*, 2983. (b) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779. (c) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 821. For our previous effort in the IMDA reaction, see:Hong, B.-C.; Chen, F.-L.; Chen, S.-H.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2005**, *7*, 557.

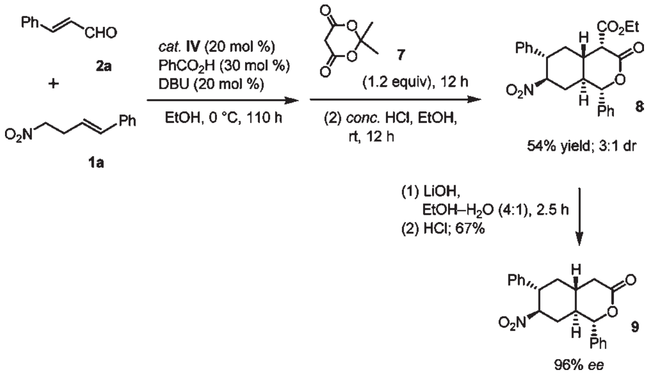
(20) In addition, the secondary orbital interaction between the electron-rich phenyl group and the electron-poor enone may play a role in the diastereoselective IMDA reaction.

(21) For other examples of hetero-Diels–Alder reactions, see: (a) Dickmeiss, G.; Jensen, K. L.; Worgull, D.; Franke, P. T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1580–1583. (b) Jensen, K. L.; Dickmeiss, G.; Donslund, B. S.; Poulsen, P. H.; Jørgensen, K. A. *Org. Lett.* **2011**, *13*, 3678.

Scheme 2. Plausible Reaction Mechanism



Scheme 3. Synthetic Extension to **8** and **9**



Replacing the 1,3-dimethylbarbituric acid **3** with Meldrum's acid (**7**), the domino reaction, after acid hydrolysis, afforded hexahydro-1*H*-isochromen-3(4*H*)-one (**8**) in 54% yield.[22] Treatment of the *syn*- and *anti*-**8** mixture with LiOH in EtOH followed by acidification gave the decarboxylation product **9** in 67% yield, 96% *ee*. The structure was confirmed by X-ray analysis of (±)-**9**[23] (Figure 1).

In summary, we have achieved the first organocatalytic one-pot Michael–Knoevenagel condensation–inverse-electron-demand hetero-Diels–Alder reaction to provide isochromene pyrimidinediones having five stereocenters with excellent diastereo- (>20:1) and enantioselectivities (up to 99% ee). The reaction not only adds to the limited repertory of examples of organocatalytic one-pot four consecutive reaction sequences but also demonstrates a one-pot synthesis of isochromene pyrimidinediones with an ecological and economical protocol. The methodology also reveals a strategy and provides an example of the control of facial selectivity of IMDA by a remote stereogenic center generated *in situ* via the organocatalysis reaction. The one-pot tactics and the benign reaction media at ambient temperature further manifest the merit of this strategy. The structure as well as the absolute configurations of the products were confirmed by X-ray analysis of the appropriate adducts. Further work is underway to explore and to elaborate the synthetic applications.

Acknowledgment. We acknowledge the financial support for this study from the National Science Council, Taiwan, ROC. Thanks to the National Center for High-Performance Computing (NCHC) for their assistance in literature searching and the instrument center of National Science Council for compounds analysis.

Supporting Information Available. Experimental procedures and characterization data for the new compounds and X-ray crystallographic data for (+)-**5**, (+)-**6**, and (±)-**9** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org

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[22] For the same solvent system with the subsequent ethanolysis, the Michael reaction proceeded in EtOH at 0 °C for 110 h.

[23] X-ray data was deposited in data bank (CCDC-842838).