Organocatalytic Synthesis of Enantioenriched β-Arylsplitomicins

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Abstract: By employing a chiral bifunctional thiourea–tertiary amine as catalyst, domino Michael-type Friedel–Crafts alkylation/cyclization of β-naphthols with akylidene Meldrum's acids was realized. The reactions afforded various enantioenriched β-arylsplitomicins with good yields (up to 99%) in moderate enantioselectivities (up to 79%).

Key words: domino reaction, alkylation, cyclization, phenols, organocatalysis, asymmetric catalysis

Splitomicin analogues are important inhibitors of sirtuins.[1] Splitomicin was also proved to suppress human platelet aggregation via inhibition of cyclic AMP phosphodiesterase and intracellular Ca^{++} release.[1h] Splitomicin (**1**, Figure 1) itself is inhibitor of yeast sirtuins. However, it does not inhibit human sirtuin subtypes and is prone to hydrolysis in aqueous medium. Recently, several β-arylsplitomicins such as β-phenyl-8-methylsplitomicin (**2**) and β-*para*-tolyl-8-methylsplitomicin (**3**) were found to inhibit recombinant SIRT 2 and exhibit antiproliferative properties and tubulin hyperacetylation in MCF7 breast cancer cells.[1g] In addition, the instability of the lactone can be overcome by β-arylsplitomicins.[1i] Thus they are promising candidates for further optimization as potential anticancer drugs.[1g] Notably, the stereochemistry at the substituted β-carbon atom is of great importance. Compounds (*R*)-**2** and (*R*)-**3** were found to be much more active than (*S*)-enantiomers.[1g,i]

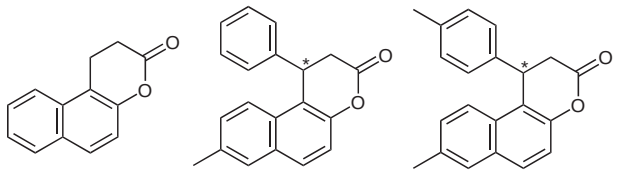

Figure 1 Representative examples of splitomicin analogues

Therefore, synthesis of enantioenriched β-arylsplitomicins is important for further structure–activity studies and development of new pharmaceuticals. Up to now, synthesis of racemic β-arylsplitomicin derivatives has been well developed.[1g,2] Manfred Jung and co-workers synthesized a series of racemic β-arylsplitomicins by the acid-catalyzed cyclization of β-naphthols with cinnamic acids.[1g] Kitamura et al. employed triflic acid to promote cyclization of β-naphthols with cinnamic acid esters to give β-arylsplitomicins in high yields.[2a] Yuan and co-workers synthesized β-phenylsplitomicin through solid acid catalyzed tandem esterification–Friedel–Crafts alkylation of β-naphthol and cinnamoyl chloride under microwave irradiation.[2b] Yao et al. reported TBAF catalyzed multicomponent reactions of aldehydes, β-naphthol and Meldrum's acid to give various β-arylsplitomicins in good yields.[2c] However, synthesis of enantioenriched β-arylsplitomicins has been rarely explored. Manfred Jung and co-workers employed a chiral rhodium catalyst to catalyze the conjugated addition of arylboronic acids to 8-methyl-3*H*-benzo[*f*]chromen-3-one to generate β-phenyl-8-methylsplitomicin (**2**) and β-*para*-tolyl-8-methylsplitomicin (**3**) in excellent enantioselectivities (up to 99% ee) but with very poor yields (18%).[1g] Jeffry W. Bode and co-workers demonstrated an enantioselective annulation of 3-phenylpropiolaldehyde and 2-naphthol promoted by a chiral N-heterocyclic carbene catalyst. The reaction gave β-phenylsplitomicin in moderate yield with moderate ee value and there was only one example.[3] To our knowledge, systematic research of asymmetric synthesis of β-arylsplitomicins has not been reported and is worth exploration in view of the great importance of this kind of compounds.

Recently, chiral bifunctional organocatalysts were applied successfully in promoting Friedel–Crafts alkylations of electron-rich phenols.[4] Among these phenols, naphthols were frequently subjected to organocatalyzed asymmetric reactions with various electrophiles.[4a–d,f] Hence, we envisioned that chiral bifunctional organocatalysts would catalyze enantioselective Michael-type Friedel–Crafts alkylation of β-naphthols with alkylidene Meldrum's acids[5] followed by intramolecular cyclization to generate enantioenriched β-substituted splitomicins as outlined in Scheme 1.

Herein we would like to describe the organocatalytic domino Michael-type Friedel–Crafts alkylation/cyclization of β-naphthols with alkylidene Meldrum's acids, through which a variety of enantioenriched β-arylsplitomicins were obtained with moderate to good yields in moderate enantioselectivities.

First, various chiral bifunctional organocatalysts **4a–k**[6] (Figure 2) were tested in the domino Michael-type Friedel–Crafts alkylation/cyclization of 2-naphthol **5a** with 4-nitrobenzylidene Meldrum's acid **6a** in dichloromethane at 20 °C for 24 hours. Because of the poor reac-

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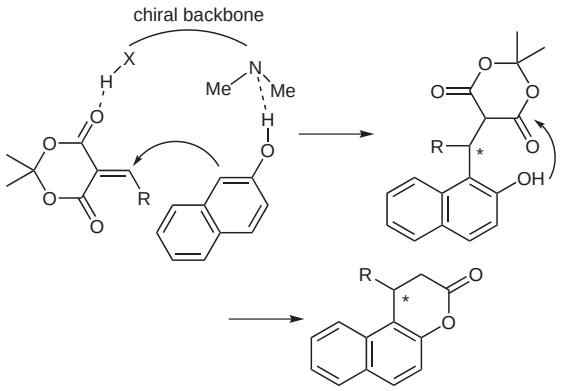


Scheme 1 Proposed domino Michael-type Friedel–Crafts alkylation/cyclization of β-naphthols with alkylidene Meldrum's acids

tivity, benzylidene Meldrum's acid was not selected as the standard substrate. As can be seen in Table 1, several cinchona alkaloids cinchonidine **4a**, qinine **4b** and cupreine **4c**[6a] resulted in very poor ee values (Table 1, entries 1–3). Cinchona alkaloids derived thiourea–tertiary amine catalysts **4d**[6b,c] and **4e**[6b,c] also gave low enantioselectivities (Table 1, entries 4 and 5). Better results were observed with **4f**[6b,c] and **4g**[6b,c] (Table 1, entries 6 and 7). (1*R*,2*R*)-1,2-Diphenyl-1,2-diamine-derived catalyst **4h**[6d] gave only moderate yield and enantioselectivity (Table 1, entry 8). Screen of the thiourea–tertiary amine catalysts, which were derived from (1*R*,2*R*)-cyclohexane-1,2-diamine, revealed that **4i**[6e,f] turned out to be the optimal catalyst in terms of yield and enantioselectivity (Table 1, entries 9–11).

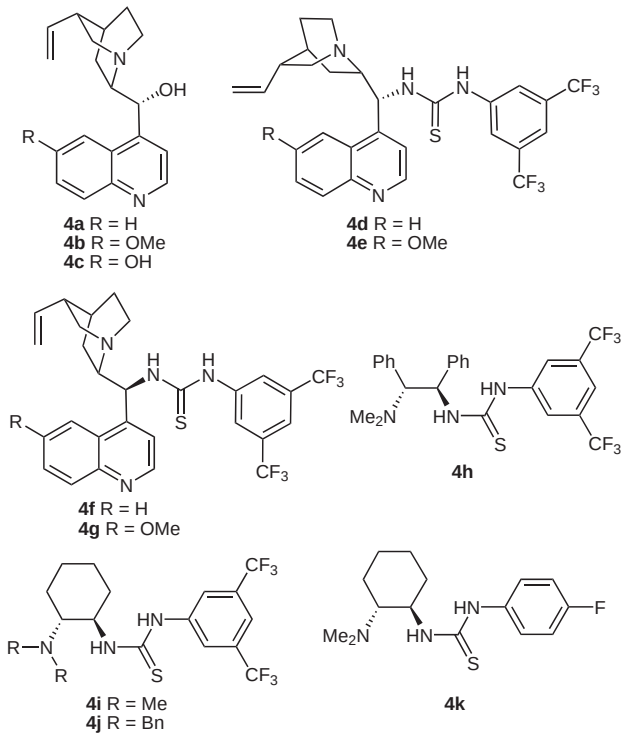


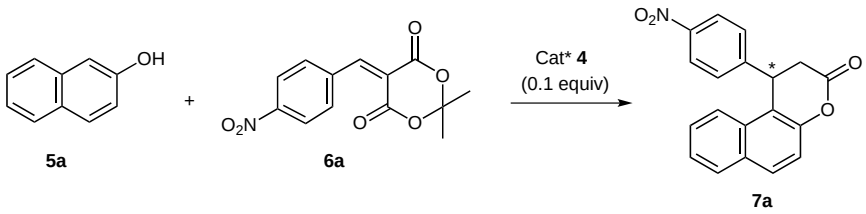
Figure 2 Bifunctional organocatalysts evaluated in this study

Following investigation of solvents demonstrated that several chlorinated solvents such as dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, chloroform and chlorobenzene resulted in good yields in which dichloromethane and 1,2-dichloroethane gave the best ee values (Table 1, entries 12–14, 17). Meanwhile tetrachloromethane, toluene and α,α,α-trifluorotoluene only afforded low to moderate yields, perhaps due to the poor solubility of 4-nitrobenzylidene Meldrum's acid **6a** in these solvents (Table 1, entries 15, 16 and 18). Afterward, when the reaction temperature was lowered to 0 °C, the reaction proceeded sluggishly to provide dramatically decreased ee value as well as poor yield even for prolonged reaction time (Table 1, entry 19). Therefore we tried to conduct the reaction at higher temperatures in 1,2-dichloroethane and evident increases in ee values were observed at 30 and 40 °C (Table 1, entries 20 and 21). Further enhancing the temperature did not improve the enantioselectivity any more (Table 1, entry 22). Addition of 4 Å MS in the reaction mixture gave rise to a slight increase in ee value (Table 1, entry 23).

In order to further improve the enantioselectivity, several bulkier 4-nitrobenzylidene Meldrum's acids **6b–f** were subjected to the reaction with 2-naphthol **5a** promoted by catalyst **4i** with 4 Å MS as additive in 1,2-dichloroethane at 40 °C for 20 hours. The results are summarized in Table 2. To our delight, cyclohexyl 4-nitrobenzylidene Meldrum's acid **6d** and adamantyl 4-nitrobenzylidene Meldrum's acid **6f** provided **7a** in good yields and obviously higher ee values (Table 2, entries 4 and 6). Therefore, cyclohexyl alkylidene Meldrum's acids were determined to be employed in the following investigations.

Hence, various cyclohexyl alkylidene Meldrum's acids were investigated in the titled reaction. The results are summarized in Table 3. As can be seen in Table 3,all of the alkylidene Meldrum's acids derived from *para*- or *meta*-substituted benzyl aldehydes afforded high yields of the corresponding products with moderate ee values (Table 3, entries 1, 3, 4, 6, 7, 9–13, 17). Meanwhile benzylidene Meldrum's acid **6g** exhibited much lower reactivity which gave the product **7b** with only moderate yield, however, in superior enantioselectivity (Table 3, entry 2). The absolute configuration of **7b** was determined as *S* by comparison of its optical rotation value with the literature data.[5] It is very interesting that either electron-donating substituents or electron-withdrawing substituents at *para* or *meta* position of the phenyl group improve the reactivity significantly. Additionally, *ortho* substitution at the phenyl group caused dramatic drops in ee values (Table 3, entries 5 and 8). Moreover, reaction of *ortho*-bromo substrate **6m** afforded the corresponding product in obviously lower yield (Table 3, entry 8). Apparently, the *ortho* substitution at the phenyl group made the substrates more sterically hindered so that they exhibited lower reactivity as well as enantioselectivity. Owing to the same reason, reaction of 1-naphthyl derivative **6t** provided the product with inferior yield and very poor ee value (Table 3, entry 15). 2-Thienyl derivative **6s** resulted in lower yield but ac-

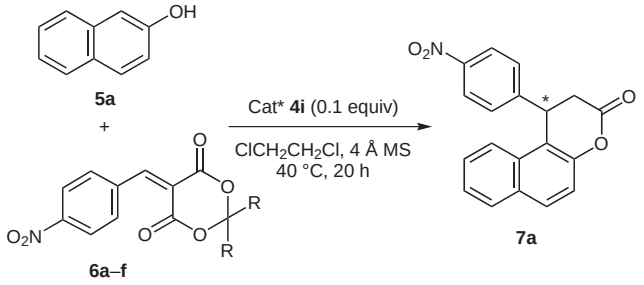
Table 1 Enantioselective Domino Michael-Type Friedel–Crafts Alkylation/Cyclization of 2-Naphthol **5a** with 4-Nitrobenzylidene Meldrum's Acid **6a**

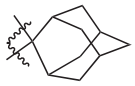


Entry[a]	Cat*	Solvent	T (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**4a**	CH_2Cl_2	20	24	55	8
2	**4b**	CH_2Cl_2	20	24	94	28
3	**4c**	CH_2Cl_2	20	24	82	0
4	**4d**	CH_2Cl_2	20	24	47	25
5	**4e**	CH_2Cl_2	20	24	86	17
6	**4f**	CH_2Cl_2	20	24	42	-35
7	**4g**	CH_2Cl_2	20	24	88	-45
8	**4h**	CH_2Cl_2	20	24	66	42
9	**4i**	CH_2Cl_2	20	24	99	45
10	**4j**	CH_2Cl_2	20	24	34	7
11	**4k**	CH_2Cl_2	20	24	38	32
12	**4i**	$ClCH_2CH_2Cl$	20	24	99	46
13	**4i**	$Cl_2CHCHCl_2$	20	24	97	42
14	**4i**	$CHCl_3$	20	24	88	41
15	**4i**	CCl_4	20	24	25	21
16	**4i**	toluene	20	24	66	33
17	**4i**	C_6H_5Cl	20	24	94	37
18	**4i**	$C_6H_5CF_3$	20	24	60	40
19	**4i**	CH_2Cl_2	0	48	53	22
20	**4i**	$ClCH_2CH_2Cl$	30	20	99	52
21	**4i**	$ClCH_2CH_2Cl$	40	20	99	55
22	**4i**	$ClCH_2CH_2Cl$	50	18	88	56
23[d]	**4i**	$ClCH_2CH_2Cl$	40	20	99	57

[a] Unless specified otherwise, reactions were carried out with 0.3 mmol of **5a**, 0.2 mmol of **6a** and 0.02 mmol of catalyst in 4 mL of solvent.
[b] Yield based on **6a**.
[c] The ee values were determined using chiral HPLC.
[d] With 30 mg of 4 Å MS as additive.

Table 2 Enantioselective Domino Michael-Type Friedel–Crafts Alkylation/Cyclization of 2-Naphthol **5a** with 4-Nitrobenzylidene Meldrum's Acids **6a–f**



Entry[a]	6	R, R	Yield (%)[b]	ee (%)[c]
1	**6a**	Me, Me	99	57
2	**6b**	Bn, Bn	94	44
3	**6c**	-$(CH_2)_4$-	91	58
4	**6d**	-$(CH_2)_5$-	94	64
5	**6e**	-$(CH_2)_6$-	63	59
6	**6f**		97	64

[a] Unless specified otherwise, reactions were carried out with 0.3 mmol of **5a**, 0.2 mmol of **6**, 0.02 mmol of **4i** and 30 mg of 4 Å MS in 4 mL of 1,2-dichloroethane at 40 °C for 20 hours.
[b] Yield based on **6**.
[c] The ee values were determined using chiral HPLC.

ceptable enantioselectivity (Table 3, entry 14). Cyclohexylidene Meldrum's acid **6u** was found to be almost inactive in this reaction system (Table 3, entry 16). Furthermore, 6-bromo-2-naphthol **5b** was also subjected to the reaction with 4-nitrobenzylidene Meldrum's acid **6d** to afford product **7p** in good yields with moderate ee value (Table 3, entry 17).

In summary, an organocatalytic domino Michael-type Friedel–Crafts alkylation/cyclization of 2-naphthols with alkylidene Meldrum's acids was developed. Through this transformation, a variety of chiral β-arylsplitomicins were prepared with good yields (up to 99%) in moderate enantioselectivities (up to 79%). The absolute configuration of product **7b** was determined as *S* by comparison of the optical rotation value with the literature data.

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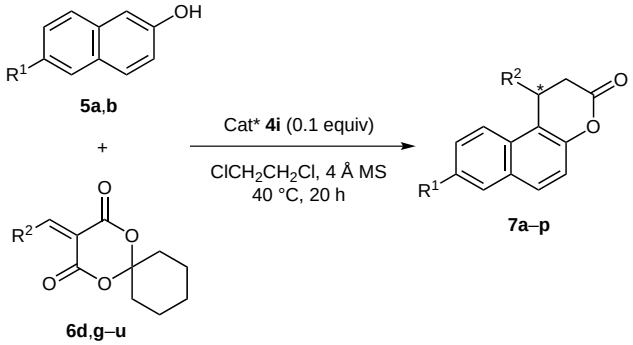
Table 3 Enantioselective Domino Michael-Type Friedel–Crafts Alkylation/Cyclization of 2-Naphthols **5a** and **5b** with Alkylidene Meldrum's Acids **6d**,**g–u**[7,8]



Entry[a]	R^1 (**5**)	R^2 (**6**)	7	Yield (%)[b]	ee (%)[c]
1	H (**5a**)	4-$O_2NC_6H_4$ (**6d**)	**7a**	94	64
2	H (**5a**)	Ph (**6g**)	**7b**	62	79 (*S*)[d]
3	H (**5a**)	4-FC_6H_4 (**6h**)	**7c**	91	69
4	H (**5a**)	4-ClC_6H_4 (**6i**)	**7d**	99	64
5	H (**5a**)	2-ClC_6H_4 (**6j**)	**7e**	99	39
6	H (**5a**)	4-BrC_6H_4 (**6k**)	**7f**	99	60
7	H (**5a**)	3-BrC_6H_4 (**6l**)	**7g**	99	63
8	H (**5a**)	2-BrC_6H_4 (**6m**)	**7h**	80	32
9	H (**5a**)	4-$F_3CC_6H_4$ (**6n**)	**7i**	95	60
10	H (**5a**)	4-NCC_6H_4 (**6o**)	**7j**	99	58
11	H (**5a**)	4-MeC_6H_4 (**6p**)	**7k**	99	68
12	H (**5a**)	4-$MeOC_6H_4$ (**6q**)	**7l**	99	66
13	H (**5a**)	3,4-$(MeO)_2C_6H_3$ (**6r**)	**7m**	89	61
14	H (**5a**)	2-thienyl (**6s**)	**7n**	71	70
15	H (**5a**)	1-naphthyl (**6t**)	**7o**	70	4
16	H (**5a**)	C_6H_{11} (**6u**)	–	trace	n.d.
17	Br (**5b**)	4-$O_2NC_6H_4$ (**6d**)	**7p**	95	59

[a] Unless specified otherwise, reactions were carried out with 0.3 mmol of **5**, 0.2 mmol of **6**, 0.02 mmol of **4h** and 30 mg of 4 Å MS in 4 mL of 1,2-dichloroethane at 40 °C for 20 hours.
[b] Yield based on **6**.
[c] The ee values were determined using chiral HPLC.
[d] The absolute configuration was determined by comparison of the optical rotation value of **7b** with the literature data.[5]

References

(1) (a) Bedalov, A.; Gottschling, D. E.; Gatbonton, T.; Irvine, W. P.; Simon, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 15113. (b) Hirao, M.; Posakony, J.; Nelson, M.; Hruby, H.; Jung, M.; Simon, J. A.; Bedalov, A. *J. Biol. Chem.* **2003**, *278*, 52773. (c) Posakony, J.; Hirao, M.; Stevens, S.; Bedalov, A.; Simon, J. A. *J. Med. Chem.* **2004**, *47*, 2635. (d) Posakony, J.; Hirao, M.; Bedalov, A. *Comb. Chem. High*

Throughput Screening **2004**, *7*, 661. (e) Denu, J. M. *Curr. Opin. Chem. Biol.* **2005**, *9*, 431. (f) Grubisha, O.; Smith, B. C.; Denu, J. M. *FEBS J.* **2005**, *272*, 4607. (g) Neugebauer, R. C.; Uchiechowska, U.; Meier, R.; Hruby, H.; Valkov, V.; Verdin, E.; Sippl, W.; Jung, M. *J. Med. Chem.* **2008**, *51*, 1203. (h) Liu, F. C.; Liao, C. H.; Chang, Y. W.; Liou, J. T.; Day, Y. *J. Thromb. Res.* **2009**, *124*, 199. (i) Freitag, M.; Schemies, J.; Larsen, T.; Gaghlab, K. E.; Schulz, F.; Rumpf, T.; Jung, M.; Link, A. *Bioorg. Med. Chem.* **2011**, *19*, 3669.

(2) (a) Aoki, S.; Amamoto, C.; Oyamada, J.; Kitamura, T. *Tetrahedron* **2005**, *61*, 9291. (b) Zhang, Z.; Ma, Y.; Zhao, Y. *Synlett* **2008**, 1091. (c) Gao, S.; Tsai, C.-H.; Yao, C.-F. *Synlett* **2009**, 949.

(3) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P. G.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810.

(4) (a) Brandes, S.; Bella, M.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1147. (b) Liu, T.-Y.; Cui, H.-L.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Commun.* **2007**, 2228. (c) Wang, X.-S.; Yang, G.-S.; Zhao, G. *Tetrahedron: Asymmetry* **2008**, *19*, 709. (d) Wang, X.-S.; Zheng, C.-W.; Zhao, S.-L.; Chai, Z.; Zhao, G.; Yang, G.-S. *Tetrahedron: Asymmetry* **2008**, *19*, 2699. (e) Zhao, J.-L.; Liu, L.; Gu, C.-L.; Wang, D.; Chen, Y.-J. *Tetrahedron Lett.* **2008**, *49*, 1476. (f) Hong, L.; Wang, L.; Sun, W.; Wong, K.; Wang, R. *J. Org. Chem.* **2009**, *74*, 6881. (g) Sohtome, Y.; Shin, B.; Horitsugi, N.; Takagi, R.; Noguchi, K.; Nagasawa, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 7299. (h) Zhang, H.; Liao, Y. H.; Yuan, W. C.; Zhang, X. M. *Eur. J. Org. Chem.* **2010**, 3215.

(5) For review on chemistry of Meldrum's acids and alkylidene Meldrum's acids see: Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* **2010**, *43*, 440.

(6) (a) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (b) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (c) Vakulya, B.; Varga, S.; Csámpai, A. *Soós T.* **2005**, *7*, 1967. (d) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.-N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (e) Okino, T.; Hoashi, Y.; Takemoto, Y. J. *Am. Chem. Soc.* **2003**, *125*, 12672. (f) Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006**, *4*, 2097.

(7) **General Procedure for Organocatalytic Domino Michael-Type Friedel–Crafts Alkylation/Cyclization of 2-Naphthol 5a with Alkylidene Meldrum's Acids 6a–u**
Catalyst **4i** (8.2 mg, 0.02 mmol, 10 mol%), 2-naphthol **5a** or **5b** (0.3 mmol), corresponding alkylidene Meldrum's acid (0.2 mmol) and 30 mg of 4 Å MS were added to a 10 mL tube and warmed to 40 °C under argon. Then dry 1,2-dichloroethane (4.0 mL) were added. After the reaction was conducted at 40 °C for 20 hours, the mixture was subjected to flash chromatography on silica gel with petroleum ether–ethyl acetate as the eluent to give the pure product **7**. The ee value was determined using established HPLC techniques with chiral stationary phases.

(8) **1-(4-Nitrophenyl)-1*H*-benzo[*f*]chromen-3(2*H*)-one (7a)**
White solid, mp 55–56 °C. This product was obtained in 94% yield after flash chromatography and in 64% ee as determined by HPLC [Daicel Chirapak AD-H, *n*-hexane–*i*-PrOH = 70:30, 1.0 mL/min, λ = 254 nm]: t_R = 9.65 (major), 14.21 (minor) min. $[\alpha]_D^{25}$ +4.7 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.7 Hz, 2 H), 7.94–7.88 (m, 2 H), 7.68 (d, *J* = 7.1 Hz, 1 H), 7.51–7.46 (m, 2 H), 7.38 (d, *J* = 8.9 Hz, 1 H), 7.31 (d, *J* = 8.7 Hz, 2 H), 5.07 (d, *J* = 6.8 Hz, 1 H), 3.31 (dd, J_1 = 7.3 Hz, J_2 = 16.0 Hz, 1 H), 3.17 (dd, J_1 = 1.8 Hz, J_2 = 15.9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.18, 149.81, 147.75, 147.22, 131.05, 130.62, 130.53, 128.92, 128, 127.79, 125.53, 124.4, 122.39, 117.47, 115.95, 37.25, 36.83. ESI-HRMS Calcd for $C_{19}H_{13}NNaO_4$ $[M + Na]^+$: 342.0737. Found: 342.0741.

