

Article

Enantioselective Michael Addition of Cyclic β -Diones to α,β -Unsaturated Enones Catalyzed by Quinine-Based Organocatalysts

Qingqing Wang ¹, Wei Wang ¹, Ling Ye ², Xuejun Yang ¹, Xinying Li ¹, Zhigang Zhao ¹ and Xuefeng Li ^{1,*}

¹ College of Chemistry and Environment Protection Engineering, Southwest Minzu University, Chengdu 610041, China; wqqing767@163.com (Q.W.); m18328594286@163.com (W.W.); yangxuejun@swun.cn (X.Y.); lixinying1984@163.com (X.L.); zzg63129@163.com (Z.Z.)

² Faculty of Geosciences and Environmental Engineering, Southwest Jiaotong University, Chengdu 610031, China; yeling_2004@126.com

* Correspondence: lixuefeng@swun.edu.cn; Tel.: +86-28-8552-2315

Received: 16 May 2017; Accepted: 26 June 2017; Published: 30 June 2017

Abstract: An enantioselective (52–98% ee) Michael addition between cyclic β -diones and α,β -unsaturated enones was established in the presence of quinine-based primary amine or squaramide. A variety of cinnamones were smoothly converted into the desired 3,4-dihydropyrans in moderate to high yields (63–99%). Chalcones were also suitable acceptors and gave rise to the expected adducts in satisfactory yields (31–99%). The resulting adducts readily underwent further modification to form fused 4H-pyran or 2,3-dihydrofuran.

Keywords: cyclic β -dione; cinnamone; chalcone; michael addition; enantioselective

1. Introduction

The Michael addition of α,β -unsaturated compounds is an atom-economic carbon-carbon bond-forming reaction in organic synthesis, and the development of the enantioselective catalytic approach for this transformation, has attracted intensive attention [1–4]. Among the often-used acceptors, unactivated α,β -unsaturated enones always exhibit relatively sluggish reactivity and emerge as a class of historically challenging substrates for metal- and organocatalytic approaches [5–11]. In this context, the elegantly-designed chiral primary amines, especially those based on cinchona alkaloids, provide a particularly efficient LUMO-lowering (LUMO: lowest unoccupied molecular orbital) activation mode through the formation of iminium ions with these unsaturated enones [12–14]. Therefore, a broad range of conjugate additions of α,β -unsaturated enones with various different nucleophiles have been successfully established with constantly high enantiocontrol [15–19]. However, the asymmetric Michael addition of cyclic 1,3-dicarbonyl compounds [20–27], except for 4-hydroxycoumarin and its analogues [7,28–36], to α,β -unsaturated enones, especially chalcones, generally draws less attention in comparison with other type of donors [37–39], albeit the adducts of such a conjugate addition reaction are versatile precursors to construct several classes of compounds possessing enormous bioactivities [40,41]. Liu and Feng have successfully developed an efficient Michael addition between dimedone and cinnamones employing the unmodified chiral diphenylethylenediamine (DPEN) [37]. In contrast, only moderate enantioselectivity was obtained for the Michael addition of dimedone to unfunctionalized chalcone according to Singh's protocol [38]. Consequently, the development of the enantioselective Michael addition of cyclic β -diones to α,β -unsaturated enone is still highly sought.

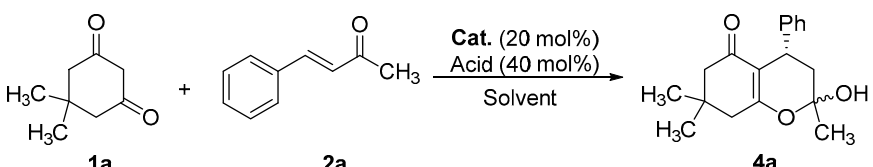
Based on our continuous interest in asymmetric Michael reactions involving α,β -unsaturated enones [42–45], herein we would like to further extend the scope of donor to cyclic β -diones [20–

23,46–49]. Dimedone and its analogues smoothly react with a variety of α,β -unsaturated enones, furnishing the corresponding adducts in good yields and high levels of optical purities. The synthetic potential of the desired Michael adduct is demonstrated by the easy formation of enantioenriched 4*H*-pyran and 2,3-dihydrofuran.

2. Results and Discussion

We were pleased to find that the Michael addition of dimedone **1a** to cinnamone **2a** proceeded smoothly in the presence of 9-amino(9-deoxy)-epi-quinine **3a** (Figure 1) in combination with a series of different acid co-catalysts. It was documented that the acid co-catalyst had a great influence on the yield and enantioinduction [16]. The aromatic carboxylic acids displayed superior catalytic effect compared with sulfonic acid and aliphatic acids (Table 1, entries 4–9 vs. entries 1–3). The desired 3,4-dihydropyran **4a** was generated with good to excellent enantioselectivities (87–90% ee) in the presence of various aromatic acids. In contrast, salicylic acid (SA) afforded an optimal yield (99%) and a superior enantioselectivity (90% ee) (entry 9 vs. entries 4–8) [50]. Having identified salicylic acid as the preferential acid co-catalyst, we turned our attention to evaluate the effect of other primary amines **3b** and **3c** (Figure 1) derived from naturally occurring cinchona alkaloids [51]. Both **3b** and **3c** delivered the expected 3,4-dihydropyran **4a** possessing opposite configurations to the adduct afforded by **3a** (entries 10 and 11). Moreover, these two pseudo-enantiomers displayed poorer catalytic activities and enantioselectivities compared with 9-amino(9-deoxy)-epi-quinine **3a** (entries 10 and 11 vs. entry 9). Subsequently, we examined the effect of the solvent with a combination of **3a** and salicylic acid. Tetrahydrofuran (THF) emerged as the favorable one in terms of reactivity and enantioselectivity (entry 15 vs. entries 9, 12–14). Notably, the model process proceeded equally smoothly when the amount of cinnamone was decreased to 1.2 equivalents (entry 16 vs. entry 15). Reducing the reaction temperature (0 °C) led to a slightly higher enantioselectivity (97% ee) (entry 17).

Table 1. Optimization of reaction conditions for the Michael addition of dimedone **1a** to cinnamone **2a**. ^a



Entry	Cat.	Acid	Solvent	Time (h)	Yield (%) ^b	ee (%) ^c
1	3a	TsOH	toluene	48	60	66
2	3a	TFA	toluene	48	65	75
3	3a	AcOH	toluene	48	82	85
4	3a	BA	toluene	24	89	90
5	3a	ONBA	toluene	36	91	90
6	3a	PNBA	toluene	36	96	89
7	3a	OFBA	toluene	24	96	88
8	3a	<i>p</i> -MeOC ₆ H ₄ CO ₂ H	toluene	36	91	87
9	3a	SA	toluene	24	99	90
10	3b	SA	toluene	96	89	−82
11	3c	SA	toluene	36	89	−82
12	3a	SA	PhCF ₃	24	96	85
13	3a	SA	DCM	24	55	83
14	3a	SA	EtOH	24	99	69
15	3a	SA	THF	24	99	94
16 ^d	3a	SA	THF	24	99	94
17 ^{d,e}	3a	SA	THF	96	99	97

^a Unless otherwise noted, the reaction was performed with 0.1 mmol of **1a**, 0.15 mmol of **2a**, 20 mol % of **3a**, and 40 mol % of acid in 1 mL of solvent at room temperature (r.t.). TsOH = *p*-toluenesulfonic acid, TFA = trifluoroacetic acid, BA = benzoic acid, ONBA = *o*-nitrobenzoic acid, PNBA = *p*-nitrobenzoic acid, OFBA = *o*-fluorobenzoic acid, DCM = dichloromethane. ^b Isolated yield after flash chromatography on silica gel. ^c Determined by HPLC analysis on a chiral stationary phase (Chiralcel AD-H). ^d 0.12 mmol of **2a** was employed. ^e Carried out at 0 °C.

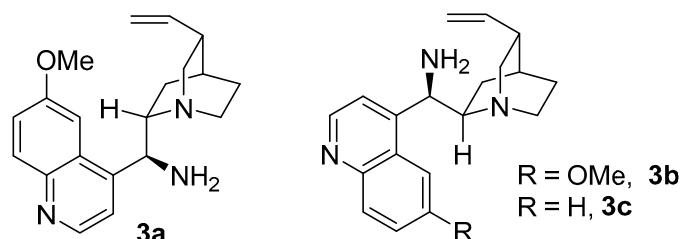


Figure 1. Structures of the chiral primary amine catalysts used.

With the optimal reaction conditions in hand, various cinnamones **2** were treated with dimedone **1a** to determine the scope and generality of this Michael addition. As presented in Table 2, the electronic property exerted marginal impact on this asymmetric process. The electron-deficient cinnamones **2c–2f** generally provided the corresponding 3,4-dihydropyrans in slightly higher chemical yields, in contrast with the electron-rich acceptors **2g** and **2h** (Table 2, entries 3–6 vs. entries 7 and 8). Meanwhile, all these enones gave rise to the desired adducts with excellent enantioselectivities (96–97% ee) irrespective of electronic nature (entries 3–8). On the other hand, the steric hindrance slightly impaired the reactivity of this conjugate addition reaction. In this context, the *ortho*-substituted enone **2b** afforded somewhat poorer conversion (87% yield) in comparison with other electron-poor cinnamones **2c–2f** (96–99% yield) (entry 2 vs. entries 3–6). Gratifyingly, **2i** and **2j**, both possessing a bulky naphthyl group at the β -site, were also compatible with this catalytic system (entries 9 and 10). The resulting adducts **4ai** and **4aj** were formed in excellent yields and with high levels of enantioselectivities. The heteroaromatic enones **2k** and **2l** were all suitable partners for this Michael reaction (entries 11 and 12). The alkyl-substituted enones **2m** and **2n** were found to react relatively slowly with dimedone, however, synthetically useful yields and satisfactory enantiocontrol were still obtained (entries 13 and 14). Remarkably, cyclic enone **2o** was also a competent acceptor, furnishing the bridged-ring compound **4ao** in 91% yield and 98% ee (entry 15) [37]. The ketone substituent (R_2) could also be varied from methyl group to ethyl group. Although relatively poorer conversion was detected, excellent enantioselectivity was maintained for this sterically more hindered acceptor (entry 16). It seemed to be an effect of increased steric bulk on the ketone, retarding the acceptor to approach the catalyst, thereby slowing down the reaction rate. On the other hand, the unsubstituted cyclic β -dione, 1,3-cyclohexanedione, was also tolerated by this catalytic system. Acceptable yields (67–78%) and high degrees of enantiomeric excesses (94–96% ee) were successfully achieved (entries 17–19), despite its relatively lower reactivity in contrast with dimedone [20,52]. Notably, a one mmole-scale Michael addition of cinnamone **2a** and dimedone **1a** was performed under optimal reaction conditions. Excellent chemical yield (95%) and enantiopurity (94% ee) were both obtained (entry 1).

Table 2. Substrate scope of the Michael addition of cyclic β -diones to cinnamones and its analogues. ^a

$R_1 = \text{Me, } \mathbf{1a}$
 $R_1 = \text{H, } \mathbf{1b}$

Entry	1	R_2	R_3	2	4	Yield (%) ^b	ee (%) ^c
1	1a	Ph	Me	2a	4aa	99 (95) ^d	97 (94) ^d
2	1a	<i>o</i> -ClC ₆ H ₄	Me	2b	4ab	87	91
3	1a	<i>m</i> -ClC ₆ H ₄	Me	2c	4ac	99	96
4	1a	<i>p</i> -ClC ₆ H ₄	Me	2d	4ad	99	97 (S) ^e
5	1a	<i>p</i> -FC ₆ H ₄	Me	2e	4ae	96	96
6	1a	<i>p</i> -BrC ₆ H ₄	Me	2f	4af	99	97
7	1a	<i>p</i> -MeC ₆ H ₄	Me	2g	4ag	95	97
8	1a	<i>p</i> -MeOC ₆ H ₄	Me	2h	4ah	89	97
9	1a	1-naphthyl	Me	2i	4ai	89	96

10	1a	2-naphthyl	Me	2j	4aj	98	98
11	1a	2-furanyl	Me	2k	4ak	78	95
12	1a	2-thiophenyl	Me	2l	4al	97	91
13	1a	Me	Me	2m	4am	69	91
14	1a	<i>n</i> -Bu	Me	2n	4an	75	94
15	1a	-C ₃ H ₆ -		2o	4ao	91	98
16	1a	Ph	Et	2p	4ap	63	98
17	1b	Ph	Me	2a	4ba	71	94
18	1b	<i>p</i> -ClC ₆ H ₄	Me	2d	4bd	78	95
19	1b	<i>p</i> -BrC ₆ H ₄	Me	2f	4bf	67	96

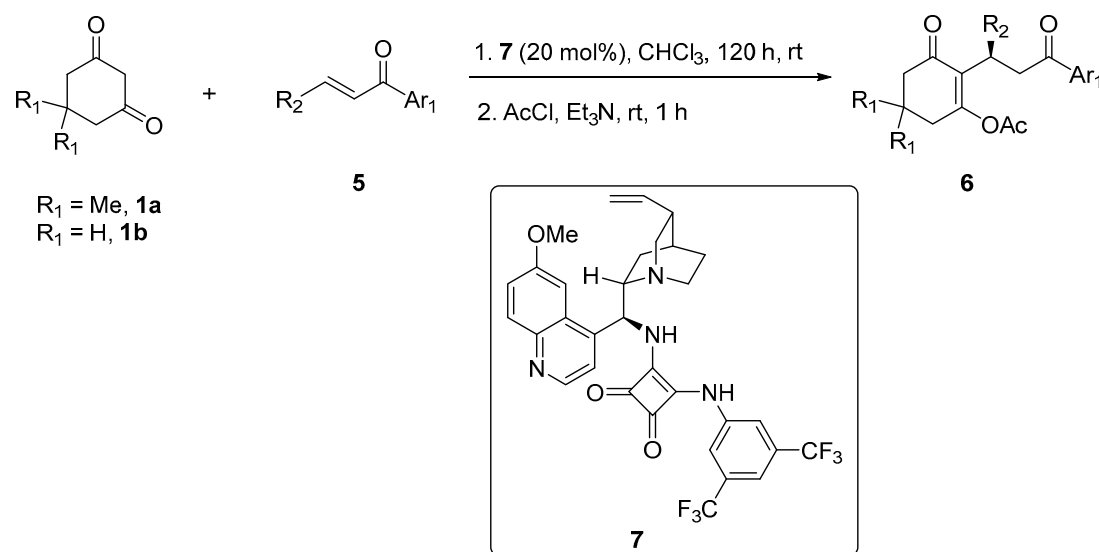
^a Unless otherwise noted, the reaction was performed with 0.1 mmol of **1a**, 0.12 mmol of **2a**, 20 mol% of **3a**, and 40 mol % of salicylic acid in 1 mL of THF at 0 °C for 96 h. ^b Isolated yield after flash chromatography on silica gel. ^c Determined by HPLC analysis on a chiral stationary phase. ^d Data within parentheses is that performed on an one-mmol scale. ^e Configuration of **4ad**.

Having identified cinnamones as the suitable acceptors, we successively turned our attention to chalcone (Scheme 1), a class of challenging substrates for iminium ion activation [16]. Different than cinnamones, the bulky benzene group might retard the later annulation process, therefore only the initial Michael adduct was accessed. Considering the unstability of the Michael adduct due to aerobic oxidation [53], a subsequent acetylation was conducted after the initial conjugate addition in a one-pot manner. To our disappointment, the titled process allowed access to the final acetyl derivative **6aa** in fairly low yield (<20%), even when the initial Michael addition was performed at room temperature.



Scheme 1. Michael addition of dimedone to chalcone.

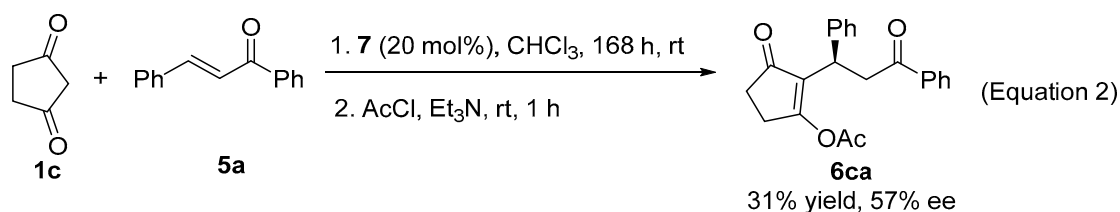
Fortunately, we finally found that the Michael addition of chalcone worked properly in the presence of squaramide **7** derived from quinine (see supporting material) [54,55]. As outlined in Table 3, this Michael addition was independent of the electronic nature of the substituents on the aromatic rings. Both the electron-rich acceptors **5b** and **5f** and the electron-deficient acceptors **5c** and **5g** generated the expected adducts in satisfactory yields and excellent optical purities (Table 3, entries 2 and 6 vs. entries 3 and 7). Moreover, the steric hindrance exerted influence on this Michael addition to a certain extent. The enone **5e** possessing a naphthyl group afforded relatively lower isolated yield (68%) even after a prolonged reaction time, albeit accompanied by outstanding enantioselectivity (entry 5). Heteroaromatic chalcones **5d** and **5h** were also favorable partners, giving rise to the final acetyl derivatives with high levels of enantiopurities (entries 4 and 8). Except for dimedone, 1,3-cyclohexanedione **1b** was a competent donor as well, albeit a longer reaction time was required in order to achieve complete conversion (entry 9). In contrast with Singh's precedent study (72% ee for **6aa**) [38], our protocol efficiently improved the enantioselectivity and displayed a wide substrate generality for this Michael addition of cyclic β-dione to chalcone [56]. Moreover, a one mmole-scale Michael addition of chalcone **5a** with dimedone **1a** proceeded smoothly as well. The expected acetyl derivate **6aa** was formed in an almost quantitative yield and with satisfactory enantioselectivity (entry 1). The alkyl-substituted enone **5i** was also a suitable acceptor, albeit unsatisfactory enantioselectivity was obtained for the resulting Michael adduct (entry 10).

Table 3. Substrate scope of the Michael addition of cyclic β -diones to chalcones. ^a

Entry	1	R ₂	Ar ₁	5	6	Yield (%) ^b	ee (%) ^c
1	1a	Ph	Ph	5a	6aa	95 (99) ^d	93 (91) ^d (<i>R</i>) ^e
2	1a	<i>p</i> -ClC ₆ H ₄	Ph	5b	6ab	99	94
3	1a	<i>p</i> -MeC ₆ H ₄	Ph	5c	6ac	96	93
4 ^f	1a	2-thiophenyl	Ph	5d	6ad	95	91
5 ^f	1a	2-naphthyl	Ph	5e	6ae	68	91
6	1a	Ph	<i>p</i> -ClC ₆ H ₄	5f	6af	98	87
7	1a	Ph	<i>p</i> -MeC ₆ H ₄	5g	6ag	99	95
8	1a	Ph	2-thiophenyl	5h	6ah	99	97
9 ^f	1b	Ph	Ph	5a	6ba	93	91
10 ^g	1a	<i>n</i> -Pr	Ph	5i	6ai	93	52

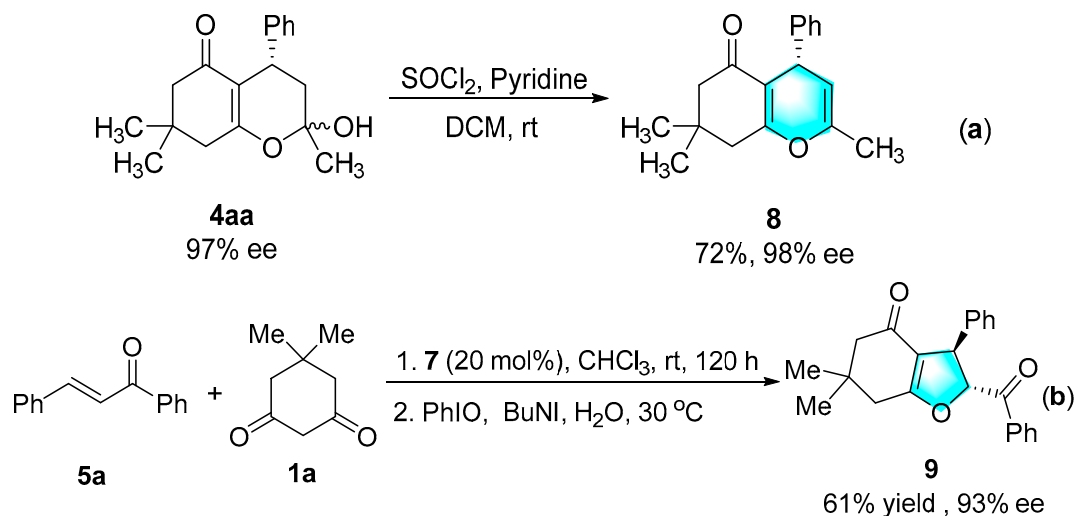
^a Unless otherwise noted, the Michael addition was performed with 0.1 mmol of **1**, 0.12 mmol of **5**, and 20 mol % of **7** in 1 mL of chloroform at rt for 120 h. ^b Isolated yield after flash chromatography on silica gel. ^c Determined by HPLC analysis on a chiral stationary phase. ^d Data within parentheses is that performed on a one-mmol scale. ^e Configuration of **6aa**. ^f Performed with 168 h. ^g Performed with 72 h.

The five-membered cyclic dione, 1,3-cyclopentadione **1c**, was also tolerated by our catalytic protocol (Scheme 2). However, it proved to be an inferior donor in terms of reactivity and enantioselectivity, in contrast with the six-membered cyclic dione. The related acetyl derivative **6ca** was obtained in an unsatisfactory yield and with moderate optical purity.

**Scheme 2.** Michael addition of 1,3-cyclopentadione to chalcone.

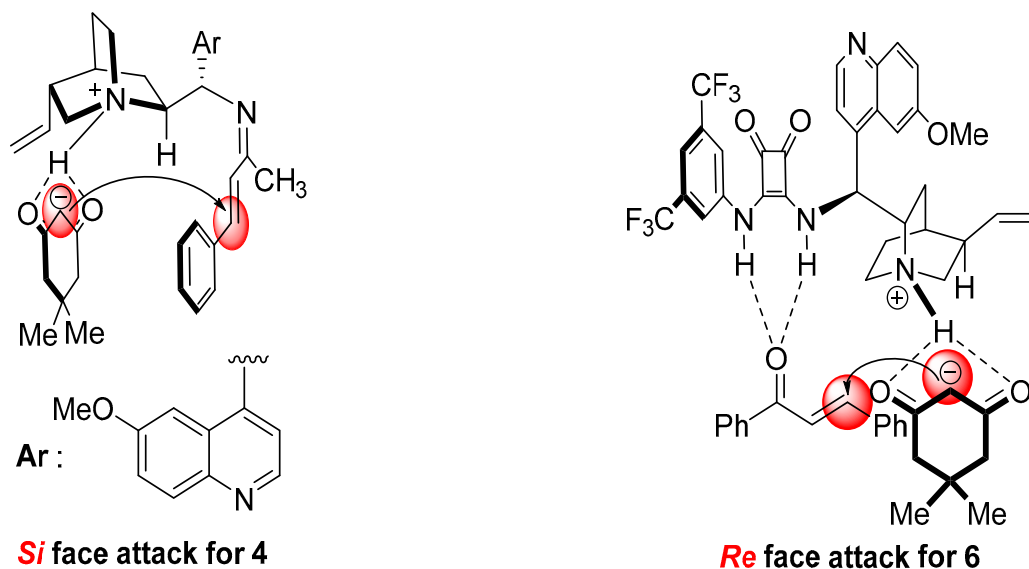
To demonstrate the synthetic potential of this Michael reaction, product modification was performed on the Michael adducts. 3,4-Dihydropyran **4aa** readily underwent a dehydrating procedure to afford 4*H*-pyran **8** without the loss of optical purity (Scheme 3a) [20]. The Michael adduct of chalcone could be utilized for the facile preparation of the biologically interesting 2,3-dihydrofuran **9** via a successive stereoselective oxidative cyclization process (Scheme 3b) [57]. The fused 2,3-

dihydrofuran **9** was obtained as a single *trans*-diastereomer in a synthetically useful yield and with excellent enantioselectivity.



Scheme 3. Synthetic elaborations of the Michael adducts.

The absolute configuration of the Michael adduct **4ad** (Table 2, entry 4) was determined to be *S* via comparison of the optical rotation value and HPLC traces with that of the previous literature reports [37]. On the other hand, the absolute configuration of **6aa** (Table 3, entry 1) was established as *R* by the analysis of the optical rotation value with Singh's protocol [38]. To account for the observed stereochemical outcome of these Michael reactions, the corresponding transition state models were proposed and described in Scheme 4. The primary amine motif of 9-amino(9-deoxy)-*epi*-quinine **3a** was engaged in iminium formation with the carbonyl group of benzalacetone **1a**. Meanwhile, dimedone was deprotonated by the tertiary amine moiety of aminocatalyst **3a** and orientated via hydrogen-bonding, thereby leading to a favorable attack toward the *si*-face of cinnamon **1a**. As a result, the desired *S*-configured product **4a** was obtained. On the other hand, chalcone **5a** was efficiently activated via hydrogen-bonding interactions between the NH moiety of the squaramide **7** and the carbonyl group of chalcone. Furthermore, the *re*-face approach of dimedone was induced by the tertiary amine of the squaramide **7** and led to the formation of the major stereoisomer with the *R* configuration [58].



Scheme 4. Proposed transition state models.

3. Materials and Methods

3.1. General Remarks

¹H- and ¹³C-NMR spectra were recorded on Varian 400 MHz spectrometers. Chemical shifts (δ) are reported in ppm downfield from CDCl₃ (δ = 7.26 ppm) for ¹H-NMR and relative to the central CDCl₃ resonance (δ = 77.0 ppm) for ¹³C-NMR spectroscopy. Coupling constants (J) are given in Hz. ESI-HRMS spectrometry was performed with a Bruker Daltonics LCQDECA ion trap mass spectrometer. Enantiomeric excess was determined by HPLC analysis on Chiralpak AD-H, OD-H, and IC columns in comparison with the authentic racemates. Optical rotation data were recorded on a Rudolph Autopol I automatic polarimeter. Commercial grade solvents were dried and purified by standard procedures as specified in reference [59]. THF (AR grade) was used as received. All other reagents were purchased from commercial sources and were used without further purification.

3.2. General Procedure for the Asymmetric Michael Reaction of Cinnamones

9-Amino-*epi*-quinine **3a** (6.5 mg, 0.02 mmol), α,β-unsaturated enones (0.12 mmol), dimedone (14.0 mg, 0.1 mmol), and salicylic acid (4.9 mg, 0.04 mmol) were dissolved in THF (1 mL) without stirring. Once the solution was cooled down to 0 °C, the reaction mixture was stirred for 96 h. After the solvent was removed in vacuo, the residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether) to afford the desired 3,4-dihydropyran.

2-Hydroxy-2,7,7-trimethyl-4-phenyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4aa) [37]. Colorless oil; 99% yield purified by flash column chromatography; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.30–7.23 (m, 2H), 7.19–7.12 (m, 3H), 4.03 (br s, 0.6H), 3.84 (t, J = 8.4 Hz, 0.6H), 3.31 (br s, 0.4H), 3.16–3.12 (m, 0.4H), 2.50–2.15 (m, 6H), 1.48 (s, 1.7H), 1.46 (s, 1.3H), 1.19 (s, 1.7H), 1.16 (s, 1.3H), 1.11 (s, 1.7H), 1.07 (s, 1.3H); ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 197.3, 196.9, 169.6, 168.6, 144.9, 142.9, 128.8, 128.2, 127.8, 127.7, 126.9, 126.8, 126.5, 125.7, 113.0, 110.5, 99.8, 99.2, 50.6, 50.5, 42.9, 42.8, 42.7, 40.5, 33.9, 32.8, 31.9, 31.4, 29.5, 28.6, 28.3, 27.8, 27.4, 27.1; 97% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, *t*_{minor} = 4.820 min, *t*_{major} = 7.627 min; [α]_D²⁰ = −4.2° (c = 0.028, EtOH).

4-(2-Chlorophenyl)-2-hydroxy-2,7,7-trimethyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4ab) [60]. Colorless oil; 87% yield purified by flash column chromatography; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.36–7.29 (m, 1H), 7.10–7.05 (m, 3H), 4.36–4.24 (m, 1H), 3.83 (br s, 0.5H), 3.43 (br s, 0.5H), 2.49–2.11 (m, 6H), 1.49 (s, 1.4H), 1.48 (s, 1.6H), 1.18 (s, 1.6H), 1.16 (s, 1.4H), 1.09 (s, 1.6H), 1.07 (s, 1.4H); ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 196.7, 196.5, 169.7, 140.5, 133.6, 129.9, 129.5, 127.8, 127.6, 126.9, 126.7, 126.6, 112.6, 110.4, 99.7, 98.1, 50.7, 50.6, 42.9, 42.8, 37.7, 31.9, 31.5, 29.4, 28.9, 28.2, 27.9, 27.6, 27.3; 91% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 254 nm, *t*_{minor} = 7.703 min, *t*_{major} = 9.353 min; [α]_D²⁰ = −32.8° (c = 0.021, EtOH).

4-(3-chlorophenyl)-2-hydroxy-2,7,7-trimethyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4ac) [37]. Colorless oil; 99% yield purified by flash column chromatography; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.19–7.09 (m, 3H), 7.02 (t, J = 7.8 Hz, 1H), 4.34 (br s, 0.5H), 3.89 (t, J = 4.8 Hz, 0.5H), 3.82–3.77 (m, 1H), 2.48–2.09 (m, 6H), 1.44 (s, 3H), 1.18 (s, 1.3H), 1.15 (s, 1.7H), 1.09 (s, 1.3H), 1.07 (s, 1.7H); ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 197.3, 197.0, 169.9, 169.1, 147.3, 145.9, 134.2, 133.9, 129.6, 129.5, 129.1, 127.9, 127.5, 127.1, 126.4, 125.9, 125.27, 125.25, 112.6, 110.3, 99.6, 98.1, 50.6, 50.5, 42.9, 42.8, 42.5, 40.5, 33.9, 33.3, 31.9, 31.5, 29.9, 29.5, 28.6, 28.3, 27.8, 27.4, 26.9; 96% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, *t*_{minor} = 5.267 min, *t*_{major} = 7.583 min; [α]_D²⁰ = +5.5° (c = 0.039, EtOH).

4-(4-Chlorophenyl)-2-hydroxy-2,7,7-trimethyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4ad) [37]. Colorless oil; 99% yield purified by flash column chromatography; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.23 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 3.95 (d, J = 4.4 Hz, 0.5H), 3.81 (d, J = 8.6 Hz, 0.5H), 3.16–3.09 (m, 0.5H), 2.95 (br s, 0.4H), 2.49–2.17 (m, 6H), 1.53 (s, 1.5H), 1.50 (s, 1.5H), 1.18 (s, 1.5H), 1.15 (s, 1.5H), 1.10 (s, 1.4H), 1.08 (s, 1.6H); ¹³C-NMR (100 MHz, CDCl₃) δ (ppm) 196.9, 196.6, 169.3, 168.3, 143.5, 141.9, 132.1, 131.3, 129.1, 128.8, 128.49, 128.47, 128.3, 127.9, 112.9, 110.5, 99.5, 97.9, 50.74, 50.72, 42.9, 42.8, 42.5, 40.3, 33.6, 32.6, 32.0, 31.5, 29.5, 28.7, 28.3, 28.1, 27.5, 27.4;

97% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 5.493$ min, $t_{\text{major}} = 8.417$ min; $[\alpha]_{\text{D}}^{20} = +13.8^\circ$ ($c = 0.039$, EtOH), $[\alpha]_{\text{D}}^{20} = +10.5^\circ$ ($c = 0.039$, DCM).

4-(4-Fluorophenyl)-2-hydroxy-2,7,7-trimethyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4ae) [37]. Colorless oil; 96% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.13 (t, $J = 6.4$ Hz, 1H), 7.08 (t, $J = 6.4$ Hz, 1H), 6.94 (t, $J = 9.4$ Hz, 1H), 6.92 (t, $J = 8.8$ Hz, 1H), 3.94 (br s, 0.5H), 3.82 (dd, $J = 9.8, 8.2$ Hz, 0.5H), 3.51–3.27 (m, 1H), 2.48–2.11 (m, 6H), 1.47 (s, 3H), 1.78 (s, 1.4H), 1.14 (s, 1.6H), 1.09 (s, 1.4H), 1.07 (s, 1.6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 197.2, 196.9, 169.5, 168.6, 161.2 (d, $J_{\text{C-F}} = 243.3$ Hz), 160.9 (d, $J_{\text{C-F}} = 241.8$ Hz), 140.6 (d, $J_{\text{C-F}} = 3.2$ Hz), 139.0 (d, $J_{\text{C-F}} = 3.3$ Hz), 129.2, 129.1, 128.5 (d, $J_{\text{C-F}} = 7.8$ Hz), 128.2 (d, $J_{\text{C-F}} = 7.8$ Hz), 115.4 (d, $J_{\text{C-F}} = 21.1$ Hz), 115.0 (d, $J_{\text{C-F}} = 21.2$ Hz), 114.6, 114.4, 113.0, 110.7, 99.6, 98.1, 60.4, 50.7, 50.6, 42.9, 42.8, 42.7, 40.6, 33.4, 32.6, 31.9, 31.4, 29.5, 28.6, 28.3, 27.9, 27.3, 27.0, 20.9, 14.1; 96% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 5.043$ min, $t_{\text{major}} = 9.330$ min; $[\alpha]_{\text{D}}^{20} = -5.4^\circ$ ($c = 0.041$, EtOH).

4-(4-Bromophenyl)-2-hydroxy-2,7,7-trimethyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4af) [37]. Colorless oil; 99% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.37 (d, $J = 8.4$ Hz, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 3.90 (t, $J = 5.4$ Hz, 0.5H), 3.72 (pseudo triple, $J = 5.4$ Hz, 0.6H), 3.50 (br s, 0.5H), 3.19 (br s, 0.4H), 2.48–2.07 (m, 6H), 1.49 (s, 1.6H), 1.48 (s, 1.4H), 1.17 (s, 1.4H), 1.14 (s, 1.6H), 1.09 (s, 1.4H), 1.07 (s, 1.6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 197.0, 196.7, 169.4, 168.4, 144.1, 142.6, 131.6, 131.4, 130.9, 129.6, 128.9, 128.7, 120.0, 119.4, 112.8, 110.4, 99.5, 97.9, 50.7, 50.6, 42.9, 42.8, 42.4, 40.3, 33.7, 32.8, 31.9, 31.5, 29.5, 28.7, 28.3, 28.1, 27.4, 27.3; 97% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 5.720$ min, $t_{\text{major}} = 10.570$ min; $[\alpha]_{\text{D}}^{20} = +13.9^\circ$ ($c = 0.010$, EtOH).

2-Hydroxy-2,7,7-trimethyl-4-(*p*-tolyl)-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4ag) [60]. Colorless oil; 95% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.16–7.01 (m, 4H), 3.99 (br s, 0.6H), 3.80 (pseudo triple, $J = 8.8$ Hz, 0.6H), 3.33 (pseudo double, $J = 9.6$ Hz, 0.8H), 2.50–2.13 (m, 9H), 1.47 (s, 3H), 1.19 (s, 1.7H), 1.15 (s, 1.3H), 1.10 (s, 1.7H), 1.07 (s, 1.3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 197.1, 196.7, 169.2, 169.1, 141.8, 139.6, 136.2, 135.1, 129.8, 129.0, 128.7, 127.5, 126.8, 126.7, 113.3, 110.5, 99.7, 98.1, 50.7, 42.9, 42.8, 42.7, 40.3, 33.6, 31.9, 31.5, 29.5, 28.8, 28.3, 27.9, 27.4, 27.3, 21.0, 20.9; 97% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 5.313$ min, $t_{\text{major}} = 7.733$ min; $[\alpha]_{\text{D}}^{20} = +6.2^\circ$ ($c = 0.041$, EtOH).

2-Hydroxy-4-(4-methoxyphenyl)-2,7,7-trimethyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4ah) [37]. Colorless oil; 89% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.10 (d, $J = 8.8$ Hz, 1.1H), 7.05 (d, $J = 8.8$ Hz, 0.9H), 6.82 (d, $J = 7.6$ Hz, 1.1H), 6.79 (d, $J = 8.4$ Hz, 0.9H), 3.99 (br s, 0.6H), 3.80 (pseudo triple, $J = 8.8$ Hz, 0.6H), 3.75 (s, 3H), 3.59 (br s, 0.4H), 3.31 (br s, 0.6H), 2.49–2.11 (m, 6H), 1.47 (s, 1.7H), 1.46 (s, 1.3H), 1.19 (s, 1.7H), 1.15 (s, 1.3H), 1.10 (s, 1.7H), 1.07 (s, 1.3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 197.0, 196.7, 169.1, 167.9, 158.2, 157.6, 136.8, 134.4, 128.7, 127.9, 127.8, 114.5, 113.8, 113.4, 113.3, 110.6, 99.7, 88.1, 55.2, 55.1, 50.8, 42.9, 42.8, 42.7, 40.1, 33.2, 31.9, 31.49, 31.47, 29.5, 28.8, 28.3, 27.9, 27.5; 97% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 6.353$ min, $t_{\text{major}} = 12.270$ min; $[\alpha]_{\text{D}}^{20} = +6.5^\circ$ ($c = 0.030$, EtOH).

2-Hydroxy-2,7,7-trimethyl-4-(naphthalen-1-yl)-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4ai). Colorless oil; 89% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 8.18 (d, $J = 8.0$ Hz, 0.3H), 8.13 (d, $J = 8.4$ Hz, 0.7H), 7.90 (d, $J = 8.0$ Hz, 0.7H), 7.85 (d, $J = 7.6$ Hz, 0.3H), 7.74 (d, $J = 8.4$ Hz, 0.7H), 7.68 (d, $J = 8.0$ Hz, 0.3H), 7.65–7.54 (m, 2.5H), 7.34 (t, $J = 7.2$ Hz, 1H), 7.27 (d, $J = 5.6$ Hz, 0.5H), 4.82 (d, $J = 6.8$ Hz, 0.8H), 4.70 (br s, 0.5H), 3.39 (br s, 0.8H), 2.63–2.23 (m, 6H), 1.47 (s, 3H), 1.27 (s, 2H), 1.24 (s, 1H), 1.17 (s, 2H), 1.12 (s, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 196.9, 196.7, 169.7, 138.6, 134.7, 130.8, 129.3, 128.9, 127.9, 126.2, 125.8, 125.4, 125.3, 125.2, 123.3, 122.5, 118.8, 117.1, 110.2, 99.5, 98.3, 50.8, 50.7, 43.1, 42.9, 37.9, 32.1, 31.5, 29.4, 29.2, 28.0, 27.9, 27.83, 27.80; ESI-HRMS calcd. for $\text{C}_{22}\text{H}_{24}\text{O}_3 + \text{H}^+$ 337.1804, found 337.1798; 96% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 4.927$ min, $t_{\text{major}} = 6.790$ min; $[\alpha]_{\text{D}}^{20} = -88.9^\circ$ ($c = 0.045$, EtOH).

2-Hydroxy-2,7,7-trimethyl-4-(naphthalen-2-yl)-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4aj) [37]. Colorless oil; 98% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.81–7.69 (m,

3H), 7.59 (s, 0.5H), 7.55 (s, 0.5H), 7.44–7.35 (m, 2.5H), 7.27–7.26 (m, 0.5H), 4.19 (br s, 0.5H), 4.01 (pseudo triple, $J = 8.6$ Hz, 0.5H), 3.29–3.17 (m, 1H), 2.57–2.17 (m, 6H), 1.49 (s, 3H), 1.26 (s, 2H), 1.19 (s, 1H), 1.13 (s, 1.6H), 1.09 (s, 1.4H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 197.2, 196.9, 169.7, 168.6, 142.3, 140.5, 133.6, 133.5, 132.3, 132.1, 128.8, 127.9, 127.7, 127.53, 127.52, 127.4, 126.1, 125.7, 125.65, 125.57, 125.52, 125.4, 124.9, 124.8, 113.0, 110.4, 99.8, 98.2, 50.7, 50.6, 42.9, 42.8, 42.5, 40.0, 34.1, 32.9, 32.0, 31.5, 29.9, 29.5, 28.7, 28.4, 27.9, 27.5, 27.2; 98% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 7.073$ min, $t_{\text{major}} = 13.053$ min; $[\alpha]_{\text{D}}^{20} = +60.2^\circ$ ($c = 0.051$, EtOH).

4-(Furan-2-yl)-2-hydroxy-2,7,7-trimethyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4ak) [37]. Colorless oil; 78% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 7.36 (s, 0.6H), 7.29 (s, 0.4H), 6.28 (dd, $J = 3.0, 1.8$ Hz, 1H), 6.02 (d, $J = 3.2$ Hz, 0.7H), 5.95 (d, $J = 2.0$ Hz, 0.3H), 4.15 (d, $J = 6.8$ Hz, 1H), 4.04 (br s, 1H), 2.55–2.22 (m, 6H), 1.55 (s, 2.2 H), 1.41 (s, 0.8H), 1.17 (s, 3H), 1.11 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 196.7, 168.9, 155.5, 141.9, 140.3, 110.6, 110.3, 108.4, 106.0, 105.3, 98.3, 50.7, 42.8, 35.9, 32.0, 28.6, 28.2, 27.9, 26.1; 95% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 5.327$ min, $t_{\text{major}} = 6.257$ min; $[\alpha]_{\text{D}}^{20} = -12.9^\circ$ ($c = 0.015$, EtOH).

2-Hydroxy-2,7,7-trimethyl-4-(thiophen-2-yl)-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4al). Brown oil; 97% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 7.17 (d, $J = 4.8$ Hz, 0.6H), 7.06 (d, $J = 4.8$ Hz, 0.6H), 6.89–6.87 (m, 1H), 6.81 (s, 1H), 4.32 (d, $J = 5.6$ Hz, 0.6H), 4.23 (pseudo triple, $J = 8.0$ Hz, 0.4H), 3.53 (br s, 1H), 2.51–2.11 (m, 6H), 1.52 (s, 2H), 1.46 (s, 1H), 1.19 (s, 2H), 1.16 (s, 1H), 1.10 (s, 2H), 1.07 (s, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 196.8, 196.7, 169.1, 168.1, 148.7, 147.2, 127.0, 126.4, 124.6, 124.2, 123.8, 123.7, 123.2, 122.4, 112.9, 110.7, 99.4, 98.4, 50.6, 42.8, 42.7, 39.9, 31.9, 31.4, 29.4, 29.3, 28.5, 28.4, 27.7, 27.66, 27.61, 27.3; ESI-HRMS calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_3\text{S} + \text{H}^+$ 293.1211, found 293.1206; 91% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 5.850$ min, $t_{\text{major}} = 7.423$ min; $[\alpha]_{\text{D}}^{20} = -18.9^\circ$ ($c = 0.047$, EtOH).

2-Hydroxy-2,4,7,7-tetramethyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4am). Colorless oil; 69% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 3.66–3.35 (m, 1H), 2.77–2.66 (m, 1H), 2.29–2.06 (m, 6H), 1.55 (s, 1.4H), 1.50 (s, 1.6H), 1.23 (d, $J = 7.6$ Hz, 2H), 1.21 (d, $J = 7.6$ Hz, 1H), 1.05 (s, 3H), 1.02 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 213.5, 198.5, 197.9, 170.7, 166.7, 166.5, 117.1, 114.9, 114.3, 99.1, 97.8, 51.3, 51.2, 51.1, 49.2, 43.2, 42.8, 42.7, 41.5, 39.2, 31.9, 31.4, 29.8, 29.2, 28.4, 28.1, 28.0, 27.2, 26.9, 24.3, 22.9, 22.1, 19.7, 19.4, 18.5; ESI-HRMS calcd. for $\text{C}_{13}\text{H}_{20}\text{O}_3 + \text{H}^+$ 225.1491, found 225.1485; 91% ee was determined by HPLC on IC column, hexane/*i*-propanol (95/5), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 49.740$ min, $t_{\text{major}} = 77.910$ min; $[\alpha]_{\text{D}}^{20} = -5.5^\circ$ ($c = 0.017$, EtOH).

4-Butyl-2-hydroxy-2,7,7-trimethyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4an). Colorless oil; 75% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 3.19–3.10 (m, 1H), 2.93–2.87 (m, 0.5H), 2.64 (s, 0.3H), 2.59 (s, 0.3H), 2.30–2.09 (m, 6H), 2.01–1.89 (m, 1H), 1.79–1.73 (m, 1H), 1.65–1.45 (m, 3H), 1.35–1.19 (m, 4H), 1.06–1.02 (m, 6H), 0.89–0.81 (m, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 213.8, 198.6, 197.8, 171.5, 167.1, 166.7, 115.7, 114.2, 113.9, 99.3, 97.9, 51.4, 51.3, 51.2, 48.3, 43.2, 42.9, 42.8, 38.2, 35.1, 32.1, 31.8, 31.7, 31.3, 30.9, 30.5, 29.8, 29.7, 29.4, 29.3, 28.5, 28.3, 28.2, 28.1, 28.0, 27.9, 27.1, 26.8, 22.8, 22.7, 22.4, 14.1, 14.0; ESI-HRMS calcd. for $\text{C}_{16}\text{H}_{26}\text{O}_3 + \text{H}^+$ 267.1960, found 267.1964; 94% ee was determined by HPLC on IC column, hexane/*i*-propanol (70/30), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 4.440$ min, $t_{\text{major}} = 8.093$ min; $[\alpha]_{\text{D}}^{20} = -13.0^\circ$ ($c = 0.034$, EtOH).

2-Hydroxy-9,9-dimethyl-2,3,4,5,6,8,9,10-octahydro-7H-2,6-methanobenzo[b]oxocin-7-one (4ao) [37]. White solid; 91% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 4.46 (s, 1H), 3.15 (s, 1H), 2.29 (s, 2H), 2.19 (s, 2H), 2.02 (d, $J = 12.8$ Hz, 1H), 1.93 (d, $J = 12.4$ Hz, 1H), 1.74 (d, $J = 15.2$ Hz, 1H), 1.16 (dd, $J = 13.0, 3.8$ Hz, 1H), 1.59 (d, $J = 11.2$ Hz, 2H), 1.45–1.33 (m, 2H), 1.04 (s, 6H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 196.7, 171.2, 112.3, 101.3, 50.3, 42.0, 38.7, 36.2, 32.3, 28.5, 28.4, 28.2, 26.9, 19.2; 98% ee was determined by HPLC on IC column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 254 nm, $t_{\text{major}} = 12.987$ min, $t_{\text{minor}} = 14.423$ min; $[\alpha]_{\text{D}}^{20} = +4.7^\circ$ ($c = 0.023$, EtOH).

2-Ethyl-2-hydroxy-7,7-dimethyl-4-phenyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4ap) [37]. Colorless oil; 63% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm)

7.24–7.16 (m, 2.5H), 7.12 (d, $J = 7.6$ Hz, 1H), 7.09–7.06 (m, 1.5H), 3.99 (br s, 0.5H), 3.76 (pseudo triple, $J = 9.0$ Hz, 0.5H), 3.15–3.00 (m, 1H), 2.44–2.09 (m, 6H), 1.69–1.63 (m, 2H), 1.13 (s, 1.6H), 1.09 (s, 1.4H), 1.04 (s, 1.6H), 1.00 (s, 1.4H), 0.89 (0.86) (t, $J = 7.6$ Hz, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 196.9, 196.5, 169.3, 168.0, 145.1, 142.9, 129.0, 128.3, 126.9, 126.7, 125.8, 113.3, 110.4, 101.3, 99.7, 50.8, 42.9, 42.8, 40.3, 38.0, 33.9, 33.6, 33.2, 32.0, 31.9, 31.5, 29.5, 28.9, 28.3, 27.5, 7.3, 7.2; 98% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 5.247$ min, $t_{\text{major}} = 11.667$ min; $[\alpha]_{\text{D}}^{20} = -5.4^\circ$ ($c = 0.018$, EtOH).

2-Hydroxy-2-methyl-4-phenyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4ba) [60]. White solid; 71% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 7.28 (t, $J = 7.2$ Hz, 1H), 7.24 (d, $J = 7.2$ Hz, 1H), 7.19–7.12 (m, 3H), 4.02 (br s, 0.5H), 3.84 (pseudo triple, $J = 8.8$ Hz, 0.5H), 3.36–3.31 (m, 0.5H), 2.63–2.45 (m, 2H), 2.42–2.30 (m, 2H), 2.27–2.15 (m, 2H), 2.11–1.95 (m, 2H), 1.47 (s, 1.5H), 1.45 (s, 1.5H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 197.2, 196.9, 171.1, 170.1, 144.8, 142.7, 128.9, 128.3, 127.9, 127.7, 126.79, 126.77, 126.6, 125.8, 114.4, 111.6, 99.6, 97.9, 42.8, 40.4, 36.9, 33.9, 32.5, 29.3, 29.2, 27.9, 27.2, 20.8, 20.2; 94% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 5.343$ min, $t_{\text{major}} = 6.693$ min; $[\alpha]_{\text{D}}^{20} = -8.2^\circ$ ($c = 0.019$, EtOH).

4-(4-chlorophenyl)-2-hydroxy-2-methyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4bd): White solid; 78% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 7.25 (d, $J = 7.2$ Hz, 0.6H), 7.21 (d, $J = 8.8$ Hz, 1.5H), 7.11 (d, $J = 8.8$ Hz, 0.6H), 7.07 (d, $J = 7.6$ Hz, 1.4H), 3.95 (pseudo triple, $J = 4.8$ Hz, 0.5H), 3.82 (pseudo triple, $J = 9.0$ Hz, 0.5H), 3.33 (br s, 0.5H), 3.05 (br s, 0.5H), 2.61–2.33 (m, 4H), 2.26–2.17 (m, 2H), 2.07–1.97 (m, 2H), 1.51 (s, 1.6H), 1.49 (s, 1.4H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 197.2, 196.8, 171.2, 170.2, 143.4, 141.8, 132.0, 131.2, 128.8, 128.4, 128.3, 128.2, 114.2, 111.6, 99.4, 97.8, 42.5, 40.3, 36.9, 33.5, 32.6, 29.3, 29.2, 28.1, 27.2, 20.7, 20.2; ESI-HRMS calcd. for $\text{C}_{16}\text{H}_{17}\text{ClO}_3 + \text{H}^+$ 293.0944, found 293.0937; 95% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 6.397$ min, $t_{\text{major}} = 8.430$ min; $[\alpha]_{\text{D}}^{20} = -11.9^\circ$ ($c = 0.007$, EtOH).

4-(4-Bromophenyl)-2-hydroxy-2-methyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one (4bf). White solid; 67% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 7.38 (d, $J = 8.8$ Hz, 0.8H), 7.36 (d, $J = 8.8$ Hz, 1.2H), 7.05 (d, $J = 10.0$ Hz, 0.8H), 7.03 (d, $J = 8.8$ Hz, 1.2H), 3.93 (pseudo triple, $J = 5.0$ Hz, 0.5H), 3.81 (pseudo triple, $J = 9.2$ Hz, 0.5H), 3.23 (br s, 0.5H), 2.99 (br s, 0.5H), 2.61–2.33 (m, 4H), 2.28–2.17 (m, 2H), 2.07–1.97 (m, 2H), 1.52 (s, 1.6H), 1.49 (s, 1.4H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 197.2, 196.8, 171.2, 170.2, 143.9, 142.4, 131.7, 131.4, 130.9, 129.6, 128.8, 128.6, 120.1, 119.4, 114.2, 111.6, 99.4, 97.8, 42.5, 40.3, 36.9, 36.8, 33.6, 32.7, 29.3, 29.2, 28.1, 27.2, 20.7, 20.2; ESI-HRMS calcd. for $\text{C}_{16}\text{H}_{17}\text{BrO}_3 + \text{H}^+$ 337.0439, found 337.0438; 96% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 6.780$ min, $t_{\text{major}} = 8.967$ min; $[\alpha]_{\text{D}}^{20} = -8.5^\circ$ ($c = 0.008$, EtOH).

3.3. Procedure for the Asymmetric Michael Reaction of Chalcones

Dimedone **1a** (14.0 mg, 0.1 mmol), chalcone **5a** (25.0 mg, 0.12 mmol), and quinine-based squaramide **7** (12.5 mg, 0.02 mmol) were dissolved in chloroform (1.0 mL). After stirring at room temperature for 120 h, triethylamine (41.7 μL , 0.3 mmol) was added in one portion. Subsequently, acetyl chloride (14.2 μL , 0.2 mmol) was added dropwise. Once the reaction completed (1 h), the crude product was purified over silica gel by column chromatography (EtOAc/petroleum ether) to afford **6aa** (37.1 mg, 95 % yield) as a colorless oil.

5,5-Dimethyl-3-oxo-2-(3-oxo-1,3-diphenylpropyl)cyclohex-1-en-1-yl acetate (6aa) [38,53]. ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 7.96 (d, $J = 8.0$ Hz, 2H), 7.54 (t, $J = 7.2$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.28–7.22 (m, 4H), 7.15 (t, $J = 6.6$ Hz, 1H), 4.79 (t, $J = 7.4$ Hz, 1H), 3.82 (ABX, $J_{\text{AB}} = 17.2$ Hz, $J_{\text{AX}} = 8.0$ Hz, 1H), 3.75 (ABX, $J_{\text{AB}} = 17.2$, $J_{\text{BX}} = 6.8$ Hz, 1H), 2.53 (AB, $J_{\text{AB}} = 18.0$ Hz, 1H), 2.42 (AB, $J_{\text{AB}} = 17.2$ Hz, 1H), 2.24 (s, 2H), 2.15 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 198.7, 198.6, 167.3, 163.9, 142.0, 136.8, 132.9, 128.9, 128.5, 128.2, 128.1, 127.4, 126.1, 116.4, 51.7, 42.7, 40.8, 35.7, 32.5, 28.1, 27.9, 20.9; 93% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 7.467$ min, $t_{\text{major}} = 10.760$ min; $[\alpha]_{\text{D}}^{20} = +41.5^\circ$ ($c = 0.032$, CHCl_3).

2-(1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)-5,5-dimethyl-3-oxocyclohex-1-en-1-yl acetate (6ab). Colorless oil; 99% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.95 (d, $J = 7.6$ Hz, 2H), 7.55 (t, $J = 7.2$ Hz, 1H), 7.45 (t, $J = 7.4$ Hz, 2H), 7.24–7.17 (m, 4H), 4.74 (t, $J = 7.2$ Hz, 1H), 3.79 (ABX, $J_{\text{AB}} = 17.6$ Hz, $J_{\text{AX}} = 7.2$ Hz, 1H), 3.72 (ABX, $J_{\text{AB}} = 17.8$ Hz, $J_{\text{BX}} = 7.8$ Hz, 1H), 2.53 (AB, $J_{\text{AB}} = 18.0$ Hz, 1H), 2.42 (AB, $J_{\text{AB}} = 17.6$ Hz, 1H), 2.24 (s, 2H), 2.20 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 198.8, 198.3, 167.4, 164.0, 140.5, 136.7, 133.1, 131.9, 128.9, 128.7, 128.6, 128.3, 128.1, 51.7, 42.7, 40.6, 35.3, 32.6, 27.9, 27.8, 20.9; ESI-HRMS calcd. for $\text{C}_{25}\text{H}_{26}\text{ClO}_4 + \text{H}^+$ 425.1514, found 425.1514; 94% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (70/30), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 6.560$ min, $t_{\text{major}} = 11.080$ min; $[\alpha]_{\text{D}}^{20} = +79.6^\circ$ ($c = 0.019$, EtOH).

5,5-Dimethyl-3-oxo-2-(3-oxo-3-phenyl-1-(*p*-tolyl)propyl)cyclohex-1-en-1-yl acetate (6ac). Colorless oil; 96% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.96 (d, $J = 7.2$ Hz, 2H), 7.54 (t, $J = 7.4$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 7.05 (d, $J = 8.0$ Hz, 2H), 4.74 (t, $J = 7.4$ Hz, 1H), 3.82 (ABX, $J_{\text{AB}} = 17.2$ Hz, $J_{\text{AX}} = 8.0$ Hz, 1H), 3.73 (ABX, $J_{\text{AB}} = 17.2$ Hz, $J_{\text{BX}} = 6.8$ Hz, 1H), 2.53 (AB, $J_{\text{AB}} = 17.6$ Hz, 1H), 2.43 (AB, $J_{\text{AB}} = 17.6$ Hz, 1H), 2.28 (s, 3H), 2.24 (s, 2H), 2.17 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 198.9, 198.8, 167.5, 163.8, 138.9, 136.9, 135.7, 132.9, 129.1, 128.9, 128.5, 128.1, 127.4, 51.8, 42.8, 40.9, 35.5, 32.6, 28.0, 27.9, 20.9; ESI-HRMS calcd. for $\text{C}_{26}\text{H}_{29}\text{O}_4 + \text{H}^+$ 405.2060, found 405.2061; 93% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (70/30), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 6.467$ min, $t_{\text{major}} = 13.007$ min; $[\alpha]_{\text{D}}^{20} = +70.1^\circ$ ($c = 0.018$, EtOH).

5,5-Dimethyl-3-oxo-2-(3-oxo-3-phenyl-1-(thiophen-2-yl)propyl)cyclohex-1-en-1-yl acetate (6ad). Colorless oil; 95% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.72–7.67 (m, 1H), 7.54 (d, $J = 4.0$ Hz, 1H), 7.20–7.16 (m, 4H), 7.10–7.09 (m, 1H), 7.05–7.00 (m, 1H), 4.71 (t, $J = 7.4$ Hz, 1H), 3.72 (ABX, $J_{\text{AB}} = 16.2$ Hz, $J_{\text{AX}} = 8.4$ Hz, 1H), 3.57 (ABX, $J_{\text{AB}} = 16.4$ Hz, $J_{\text{BX}} = 6.4$ Hz, 1H), 2.45 (AB, $J_{\text{AB}} = 18.0$ Hz, 1H), 2.36 (AB, $J_{\text{AB}} = 17.6$ Hz, 1H), 2.16 (s, 2H), 2.12 (s, 3H), 0.93 (s, 6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 198.8, 191.7, 167.4, 164.1, 144.3, 141.8, 133.7, 132.1, 128.7, 128.2, 128.0, 127.4, 126.2, 51.7, 42.7, 41.3, 36.0, 32.6, 27.9, 27.8, 20.9; ESI-HRMS calcd. for $\text{C}_{23}\text{H}_{25}\text{O}_4\text{S} + \text{H}^+$ 397.1468, found 397.1468; 91% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (70/30), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 6.903$ min, $t_{\text{major}} = 10.567$ min; $[\alpha]_{\text{D}}^{20} = +29.6^\circ$ ($c = 0.016$, EtOH).

5,5-Dimethyl-2-(1-(naphthalen-2-yl)-3-oxo-3-phenylpropyl)-3-oxocyclohex-1-en-1-yl acetate (6ae). Colorless oil; 68% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 8.00 (d, $J = 8.0$ Hz, 2H), 7.78–7.73 (m, 4H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.46 (t, $J = 7.4$ Hz, 2H), 7.43–7.39 (m, 3H), 4.97 (t, $J = 7.2$ Hz, 1H), 3.94 (ABX, $J_{\text{AB}} = 17.6$ Hz, $J_{\text{AX}} = 8.4$ Hz, 1H), 3.88 (ABX, $J_{\text{AB}} = 17.0$ Hz, $J_{\text{BX}} = 7.0$ Hz, 1H), 2.56 (AB, $J_{\text{AB}} = 18.0$ Hz, 1H), 2.43 (AB, $J_{\text{AB}} = 18.0$ Hz, 1H), 2.28 (AB, $J_{\text{AB}} = 16.8$ Hz, 1H), 2.24 (AB, $J_{\text{AB}} = 17.6$ Hz, 1H), 2.15 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 198.8, 198.6, 167.4, 164.1, 139.5, 136.9, 133.3, 133.0, 132.0, 128.8, 128.5, 128.1, 127.9, 127.7, 127.5, 126.5, 125.8, 125.6, 125.3, 51.7, 42.8, 40.8, 35.9, 32.6, 27.9, 27.8, 20.9; ESI-HRMS calcd. for $\text{C}_{29}\text{H}_{29}\text{O}_4 + \text{H}^+$ 441.2060, found 441.2061; 91% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (70/30), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 7.943$ min, $t_{\text{major}} = 11.667$ min; $[\alpha]_{\text{D}}^{20} = +79.7^\circ$ ($c = 0.011$, EtOH).

2-(3-(4-Chlorophenyl)-3-oxo-1-phenylpropyl)-5,5-dimethyl-3-oxocyclohex-1-en-1-yl acetate (6af). White solid; 98% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.90 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.26–7.23 (m, 4H), 7.20–7.23 (m, 1H), 4.77 (t, $J = 7.4$ Hz, 1H), 3.82 (ABX, $J_{\text{AB}} = 17.2$ Hz, $J_{\text{AX}} = 8.0$ Hz, 1H), 3.70 (ABX, $J_{\text{AB}} = 17.2$ Hz, $J_{\text{BX}} = 6.8$ Hz, 1H), 2.54 (AB, $J_{\text{AB}} = 17.6$ Hz, 1H), 2.42 (AB, $J_{\text{AB}} = 18.0$ Hz, 1H), 2.24 (s, 2H), 2.17 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 198.9, 197.5, 167.3, 164.0, 141.8, 139.3, 135.1, 129.5, 128.75, 128.72, 128.2, 127.4, 126.2, 51.7, 42.7, 40.7, 35.8, 32.5, 27.8, 20.9; ESI-HRMS calcd. for $\text{C}_{25}\text{H}_{26}\text{ClO}_4 + \text{H}^+$ 425.1514, found 425.1514; 87% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (70/30), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 9.913$ min, $t_{\text{major}} = 15.547$ min; $[\alpha]_{\text{D}}^{20} = +57.9^\circ$ ($c = 0.016$, EtOH).

5,5-Dimethyl-3-oxo-2-(3-oxo-1-phenyl-3-(*p*-tolyl)propyl)cyclohex-1-en-1-yl acetate (6ag). Colorless oil; 99% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.87 (d, $J = 8.0$ Hz, 2H), 7.29–7.23 (m, 6H), 7.19–7.11 (m, 1H), 4.79 (t, $J = 7.4$ Hz, 1H), 3.79 (ABX, $J_{\text{AB}} = 16.4$ Hz, $J_{\text{AX}} = 7.6$ Hz,

1H), 3.73 (ABX, J_{AB} = 16.8 Hz, J_{BX} = 6.8 Hz, 1H), 2.53 (AB, J_{AB} = 18.0 Hz, 1H), 2.42 (AB, J_{AB} = 17.6 Hz, 1H), 2.40 (s, 3H), 2.25 (s, 2H), 2.17 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 198.8, 198.3, 167.4, 163.8, 143.7, 142.1, 134.4, 129.1, 129.0, 128.2, 128.1, 127.5, 126.1, 51.7, 42.7, 40.6, 35.7, 32.6, 27.9, 21.6, 20.9; ESI-HRMS calcd. for $\text{C}_{26}\text{H}_{29}\text{O}_4 + \text{H}^+$ 405.2060, found 405.2061; 95% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, t_{minor} = 9.573 min, t_{major} = 13.540 min; $[\alpha]_{\text{D}}^{20}$ = +77.1° (c = 0.018, EtOH)

5,5-Dimethyl-3-oxo-2-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)cyclohex-1-en-1-yl acetate (6ah). Colorless oil; 99% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 7.88 (d, J = 7.6 Hz, 2H), 7.47 (t, J = 7.2 Hz, 1H), 7.36 (t, J = 7.4 Hz, 2H), 7.03–6.97 (m, 1H), 6.83–6.74 (m, 2H), 4.97 (t, J = 7.0 Hz, 1H), 3.82 (ABX, J_{AB} = 17.4 Hz, J_{AX} = 7.8 Hz, 1H), 3.70 (ABX, J_{AB} = 17.6 Hz, J_{BX} = 6.4 Hz, 1H), 2.49 (AB, J_{AB} = 18.0 Hz, 1H), 2.38 (AB, J_{AB} = 17.6 Hz, 1H), 2.19 (s, 2H), 2.15 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 198.4, 198.0, 167.3, 164.1, 145.7, 136.6, 133.0, 128.5, 128.2, 128.1, 126.4, 124.1, 123.3, 51.6, 42.6, 42.3, 32.6, 31.5, 27.9, 27.8, 20.9; ESI-HRMS calcd. for $\text{C}_{23}\text{H}_{25}\text{O}_4\text{S} + \text{H}^+$ 397.1468, found 397.1469; 97% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, t_{minor} = 7.623 min, t_{major} = 9.193 min; $[\alpha]_{\text{D}}^{20}$ = +102.9° (c = 0.019, EtOH)

3-Oxo-2-(3-oxo-1,3-diphenylpropyl)cyclohex-1-en-1-yl acetate (6ba). Colorless oil; 93% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 7.97 (d, J = 7.6 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.29–7.23 (m, 4H), 7.16 (t, J = 6.6 Hz, 1H), 4.80 (t, J = 7.2 Hz, 1H), 3.81 (ABX, J_{AB} = 17.8 Hz, J_{AX} = 6.6 Hz, 1H), 3.75 (ABX, J_{AB} = 17.6 Hz, J_{BX} = 7.6 Hz, 1H), 2.65 (dt, J = 18.0, 6.4 Hz, 1H), 2.53 (dt, J = 18.0, 5.9 Hz, 1H), 2.37 (t, J = 6.4 Hz, 2H), 2.17 (s, 3H), 1.98–1.89 (m, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 198.8, 198.7, 167.3, 165.6, 142.0, 136.8, 132.9, 130.1, 128.5, 128.1, 128.0, 127.5, 126.1, 40.8, 37.9, 35.7, 29.0, 20.9, 20.7; ESI-HRMS calcd. for $\text{C}_{23}\text{H}_{23}\text{O}_4 + \text{H}^+$ 363.1591, found 363.1591; 91% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (70/30), 1.0 mL/min, UV 254 nm, t_{minor} = 7.667 min, t_{major} = 10.660 min; $[\alpha]_{\text{D}}^{20}$ = +92.4° (c = 0.016, EtOH).

3-Oxo-2-(3-oxo-1,3-diphenylpropyl)cyclopent-1-en-1-yl acetate (6ca). Colorless oil; 31% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 7.94 (d, J = 7.6 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 7.0 Hz, 2H), 7.36–7.34 (m, 2H), 7.26 (t, J = 6.8 Hz, 2H), 7.18 (t, J = 7.0 Hz, 1H), 4.49 (t, J = 7.2 Hz, 1H), 4.06 (ABX, J_{AB} = 17.6 Hz, J_{BX} = 8.8 Hz, 1H), 3.56 (ABX, J_{AB} = 17.6 Hz, J_{BX} = 6.0 Hz, 1H), 2.93–2.79 (m, 2H), 2.47–2.38 (m, 2H), 2.21 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 205.3, 198.3, 176.7, 166.5, 141.9, 136.8, 133.1, 129.9, 128.6, 128.5, 128.0, 127.8, 126.7, 40.8, 35.8, 34.7, 26.9, 21.1; ESI-HRMS calcd. for $\text{C}_{22}\text{H}_{22}\text{O}_4 + \text{H}^+$ 349.1440, found 349.1437; 57% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, t_{minor} = 8.787 min, t_{major} = 12.983 min; $[\alpha]_{\text{D}}^{20}$ = +29.0° (c = 0.014, EtOH).

5,5-Dimethyl-3-oxo-2-(1-oxo-1-phenylhexan-3-yl)cyclohex-1-en-1-yl acetate (6ai). Colorless oil; 93% yield purified by flash column chromatography; ^1H -NMR (400 MHz, CDCl_3) δ (ppm) 7.91 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 7.4 Hz, 2H), 3.32 (ABX, J_{AB} = 16.4 Hz, J_{BX} = 6.8 Hz, 1H), 3.23 (ABX, J_{AB} = 16.0 Hz, J_{BX} = 6.4 Hz, 1H), 2.46 (AB, J_{AB} = 18.0 Hz, 1H), 2.41 (AB, J_{AB} = 18.0 Hz, 1H), 2.27 (AB, J_{AB} = 15.6 Hz, 1H), 2.21 (AB, J_{AB} = 15.2 Hz, 1H), 2.20 (s, 3H), 1.77–1.68 (m, 2H), 1.54–1.47 (m, 1H), 1.21–1.16 (m, 2H), 1.06 (s, 3H), 0.99 (s, 3H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm) 199.7, 199.4, 167.7, 163.8, 137.2, 132.8, 128.6, 128.4, 128.1, 52.1, 42.7, 42.0, 35.0, 32.4, 31.6, 28.0, 27.9, 21.1, 20.9, 13.9; ESI-HRMS calcd. for $\text{C}_{22}\text{H}_{29}\text{O}_4 + \text{H}^+$ 357.2066, found 357.2064; 52% ee was determined by HPLC on IC column, hexane/*i*-propanol (99/1), 1.0 mL/min, UV 254 nm, t_{major} = 39.457 min, t_{minor} = 42.963 min; $[\alpha]_{\text{D}}^{20}$ = +4.75° (c = 0.022, EtOH).

3.4. Preparation of 4H-Pyran via Dehydrating

Thionyl chloride (7.3 μL , 11.9 mg, 0.1 mmol) was added dropwise to a solution of **4a** (28.6 mg, 0.1 mmol, 97% ee) and pyridine (14.1 μL , 15.8 mg, 0.2 mmol) in DCM (1.0 mL) at rt. After the reaction completed, the solvent was removed under reduced pressure. The residue was subjected to silica gel flash chromatography (EtOAc/petroleum ether) to provide **8** (19.3 mg, 72% yield) as a white solid.

2,7,7-Trimethyl-4-phenyl-4,6,7,8-tetrahydro-5H-chromen-5-one (8): $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.29–7.24 (m, 4H), 7.17–7.13 (m, 1H), 4.90 (d, $J = 4.8$ Hz, 2H), 4.28 (d, $J = 4.0$ Hz, 1H), 2.39 (s, 2H), 2.22 (AB, $J_{AB} = 16.0$ Hz, 1H), 2.16 (AB, $J_{AB} = 16.4$ Hz, 1H), 1.88 (s, 3H), 1.09 (s, 3H), 1.03 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 197.3, 164.7, 145.8, 145.6, 128.2, 127.8, 126.2, 112.2, 104.5, 50.8, 41.4, 35.2, 31.9, 29.1, 27.6, 18.6; ESI-HRMS calcd. for $\text{C}_{18}\text{H}_{20}\text{O}_2 + \text{H}^+$ 269.1542, found 269.1541; 98% ee was determined by HPLC on OD-H column, hexane/*i*-propanol (90/10), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 5.880$ min, $t_{\text{major}} = 8.550$ min; $[\alpha]_{\text{D}}^{20} = -182.7^\circ$ ($c = 0.024$, EtOH).

3.5. Preparation of Fused Dihydrofuran via Stereoselective Oxidative Cyclization

After the initial Michael addition between **5a** (49.9 mg, 0.24 mmol) and **1a** (28.0 mg, 0.2 mmol) was completed, the corresponding adduct was purified via flash column chromatography. Subsequently, the mixture of PhIO (66 mg, 0.3 mmol) and Michael adduct (69.6 mg, 0.2 mmol) in H_2O (1 mL) was treated with Bu_4NI (111 mg, 0.3 mmol). The reaction mixture was warmed up to 30°C and allowed to stir for 16 h. The reaction was followed by TLC until completion. The reaction mixture was successively quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (25 mL) and extracted by dichloromethane ($25\text{ mL} \times 3$). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether) to furnish 2,3-dihydrobenzofuran **9** in 61% yield as a colorless oil.

2-Benzoyl-6,6-dimethyl-3-phenyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (**9**) [61]. White solid; 61% yield purified by flash column chromatography; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.82 (d, $J = 7.2$ Hz, 2H), 7.61 (t, $J = 7.4$ Hz, 1H), 7.46 (t, $J = 7.6$ Hz, 2H), 7.36 (t, $J = 7.2$ Hz, 2H), 7.30–7.28 (m, 1H), 7.25–7.23 (m, 2H), 5.89 (d, $J = 4.8$ Hz, 1H), 4.40 (d, $J = 4.0$ Hz, 1H), 2.63 (ABX, $J_{AB} = 18.0$ Hz, $J_{AX} = 1.6$ Hz, 1H), 2.53 (AB, $J_{AB} = 17.6$ Hz, 1H), 2.25 (AB, $J_{AB} = 16.4$ Hz, 1H), 2.18 (AB, $J_{AB} = 16.4$ Hz, 1H), 1.17 (s, 6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm) 193.5, 192.8, 176.3, 141.2, 134.1, 133.1, 129.0, 128.89, 128.86, 127.6, 127.3, 115.1, 91.8, 51.1, 48.9, 37.6, 34.3, 29.0, 28.3; 93% ee was determined by HPLC on AD-H column, hexane/*i*-propanol (80/20), 1.0 mL/min, UV 254 nm, $t_{\text{minor}} = 10.843$ min, $t_{\text{major}} = 15.107$ min; $[\alpha]_{\text{D}}^{20} = -44.6^\circ$ ($c = 0.021$, EtOH).

4. Conclusions

In summary, we have successfully developed an enantioselective Michael addition of cyclic β -diones to α,β -unsaturated enones in the presence of quinine-based primary amine or squaramide. These asymmetric processes displayed especially broad substrate generalities, and various cinnamones and chalcones furnished the desired adducts in good to high yields. Although chalcones proved to be a class of challenging acceptors in the precedent study [38], good reactivities and excellent enantiopurities were achieved in the case of their Michael addition with cyclic β -diones via our protocol.

Supplementary Materials: The supplementary materials are available

Acknowledgments: This work is financially supported by the National Natural Science Foundation of China (No. 21402163) and the Fundamental Research Funds for the Central Universities of Southwest Minzu University (No. 2016NGJPY02). Wang Qingqing gratefully acknowledges the Graduate Innovation Project of Southwest Minzu University (No. CX2016SZ058).

Author Contributions: Q.W. and X.L. (Xuefeng Li) designed and planned the research. Q.W. and W.W. performed the experiments and analyzed the data. L.Y., X.Y., X.L. (Xinying Li), and Z.Z. characterized the compounds. X.L. (Xuefeng Li) prepared the manuscript for publication. All authors discussed the results and commented on the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sibi, M.P.; Manyem, S. Enantioselective conjugate additions. *Tetrahedron* **2000**, *56*, 8033–8061.
2. Christoffers, J.; Koripelly, G.; Rosiak, A.; Rösle, M. Recent advances in metal-catalyzed asymmetric conjugate additions. *Synthesis* **2007**, *9*, 1279–1300.

3. Krause, N.; Hoffmann-Röder, A. Recent advances in catalytic enantioselective Michael additions. *Synthesis* **2001**, 2, 171–196.
4. Almaşi, D.; Alonso, D.A.; Najera, C. Organocatalytic asymmetric conjugate additions. *Tetrahedron Asymmetry* **2007**, 18, 299–365.
5. Halland, N.; Hazell, R.G.; Jørgensen, K.A. Organocatalytic asymmetric conjugate addition of nitroalkanes to α,β -unsaturated enones using novel imidazoline catalysts. *J. Org. Chem.* **2002**, 67, 8331–8338.
6. Halland, N.; Aburel, P.S.; Jørgensen, K.A. Highly Enantioselective Organocatalytic Conjugate Addition of Malonates to Acyclic α,β -Unsaturated Enones. *Angew. Chem. Int. Ed.* **2003**, 42, 661–665.
7. Halland, N.; Hansen, T.; Jørgensen, K.A. Organocatalytic Asymmetric Michael Reaction of Cyclic 1,3-Dicarbonyl Compounds and α,β -Unsaturated Ketones—A Highly Atom-Economic Catalytic One-Step Formation of Optically Active Warfarin Anticoagulant. *Angew. Chem. Int. Ed.* **2003**, 42, 4955–4957.
8. Halland, N.; Aburel, P.S.; Jørgensen, K.A. Highly Enantio- and Diastereoselective Organocatalytic Asymmetric Domino Michael-Aldol Reaction of β -Ketoesters and α,β -Unsaturated Ketones. *Angew. Chem. Int. Ed.* **2004**, 43, 1272–1277.
9. Pulkkinen, J.; Aburel, P.S.; Halland, N.; Jørgensen, K.A. Highly Enantio- and Diastereoselective Organocatalytic Domino Michael-Aldol Reactions of β -Diketone and β -Ketosulfone Nucleophiles with α,β -Unsaturated Ketones. *Adv. Synth. Catal.* **2004**, 346, 1077–1080.
10. Prieto, A.; Halland, N.; Jørgensen, K.A. Novel imidazolidine-tetrazole organocatalyst for asymmetric conjugate addition of nitroalkanes. *Org. Lett.* **2005**, 7, 3897–3900.
11. Kwiatkowski, P.; Dudzinski, K.; Łyzwa, D. Effect of High Pressure on the Organocatalytic Asymmetric Michael Reaction: Highly Enantioselective Synthesis of γ -Nitroketones with Quaternary Stereogenic Centers. *Org. Lett.* **2011**, 13, 3624–3627.
12. Melchiorre, P. Cinchona-based Primary Amine Catalysis in the Asymmetric Functionalization of Carbonyl Compounds. *Angew. Chem. Int. Ed.* **2012**, 51, 9748–9770.
13. Xu, L.-W.; Luo, J.; Lu, Y. Asymmetric catalysis with chiral primary amine-based organocatalysts. *Chem. Commun.* **2009**, 1807–1821.
14. Chen, Y.-C. The Development of Asymmetric Primary Amine Catalysts Based on Cinchona Alkaloids. *Synlett* **2008**, 2008, 1919–1930.
15. Xie, J.W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.C.; Wu, Y.; Zhu, J.; Deng, J.G. Highly Asymmetric Michael Addition to α,β -Unsaturated Ketones Catalyzed by 9-Amino-9-deoxyepiquinine. *Angew. Chem. Int. Ed.* **2007**, 46, 389–392.
16. Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. Organocatalytic asymmetric Friedel-Crafts alkylation of indoles with simple α,β -unsaturated ketones. *Org. Lett.* **2007**, 9, 1403–1405.
17. Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. Organocatalytic Asymmetric Aziridination of Enones. *Angew. Chem. Int. Ed.* **2008**, 47, 8703–8706.
18. Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. Catalytic Enantioselective Peroxidation of α,β -Unsaturated Ketones. *J. Am. Chem. Soc.* **2008**, 130, 8134–8135.
19. McCooley, S.H.; Connon, S.J. Readily accessible 9-epi-amino cinchona alkaloid derivatives promote efficient, highly enantioselective additions of aldehydes and ketones to nitroolefins. *Org. Lett.* **2007**, 9, 599–602.
20. Calter, M.A.; Wang, J. Catalytic, asymmetric Michael reactions of cyclic diketones with β,γ -unsaturated α -ketoesters. *Org. Lett.* **2009**, 11, 2205–2208.
21. Yu, C.; Zheng, F.; Ye, H.; Zhong, W. Enantioselective synthesis of functionalized 3,4-dihydropyran derivatives organocatalyzed by a novel fluorinated-diphenylprolinolether. *Tetrahedron* **2009**, 65, 10016–10021.
22. Dong, Z.; Feng, J.; Fu, X.; Liu, X.; Lin, L.; Feng, X. Highly Enantioselective Conjugate Addition of Cyclic Diketones to β,γ -Unsaturated α -Ketoesters Catalyzed by an N,N'-Dioxide-Cu(OTf)₂ Complex. *Chem. Eur. J.* **2011**, 17, 1118–1121.
23. Zhang, G.; Wang, Y.; Zhang, W.; Xu, X.; Zhong, A.; Xu, D. Organocatalytic Michael Addition of Naphthoquinone with α,β -Unsaturated Ketones: Primary Amine Catalyzed Asymmetric Synthesis of Lapachol Analogues. *Eur. J. Org. Chem.* **2011**, 2011, 2142–2147.
24. Tan, B.; Lu, Y.; Zeng, X.; Chua, P.J.; Zhong, G. Facile Domino Access to Chiral Bicyclo[3.2.1]octanes and Discovery of a New Catalytic Activation Mode. *Org. Lett.* **2010**, 12, 2682–2685.
25. Tsakos, M.; Elsegood, M.R.J.; Kokotos, C.G. Organocatalytic asymmetric domino Michael-Henry reaction for the synthesis of substituted bicyclo[3.2.1]octan-2-ones. *Chem. Commun.* **2013**, 49, 2219–2221.

26. Franke, P.T.; Richter, B.; Jørgensen, K.A. Organocatalytic Asymmetric Synthesis of Functionalized 3,4-Dihydropyran Derivatives. *Chem. Eur. J.* **2008**, *14*, 6317–6321.
27. Rueping, M.; Sugiono, E.; Merino, E. Asymmetric Organocatalysis: An Efficient Enantioselective Access to Benzopyranes and Chromenes. *Chem. Eur. J.* **2008**, *14*, 6329–6332.
28. Kim, H.; Yen, C.; Preston, P.; Chin, J. Substrate-directed stereoselectivity in vicinal diamine-catalyzed synthesis of warfarin. *Org. Lett.* **2006**, *8*, 5239–5242.
29. Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. Highly enantioselective Michael addition of cyclic 1, 3-dicarbonyl compounds to α , β -unsaturated ketones. *Org. Lett.* **2007**, *9*, 413–415.
30. Dong, Z.; Wang, L.; Chen, X.; Liu, X.; Lin, L.; Feng, X. Organocatalytic Enantioselective Michael Addition of 4-Hydroxycoumarin to α , β -Unsaturated Ketones: A Simple Synthesis of Warfarin. *Eur. J. Org. Chem.* **2009**, *2009*, 5192–5197.
31. Kristensen, T.E.; Vestli, K.; Hansen, F.K.; Hansen, T. New Phenylglycine-Derived Primary Amine Organocatalysts for the Preparation of Optically Active Warfarin. *Eur. J. Org. Chem.* **2009**, *2009*, 5185–5191.
32. Zhu, X.; Lin, A.; Shi, Y.; Guo, J.; Zhu, C.; Cheng, Y. Enantioselective Synthesis of Polycyclic Coumarin Derivatives Catalyzed by an in Situ Formed Primary Amine-Imine Catalyst. *Org. Lett.* **2011**, *13*, 4382–4385.
33. Mei, R.-Q.; Xu, X.-Y.; Li, Y.-C.; Fu, J.-Y.; Huang, Q.-C.; Wang, L.-X. Highly effective and enantioselective Michael addition of 4-hydroxycoumarin to α , β -unsaturated ketones promoted by simple chiral primary amine thiourea bifunctional catalysts. *Tetrahedron Lett.* **2011**, *52*, 1566–1568.
34. Ray, S.K.; Singh, P.K.; Molleti, N.; Singh, V.K. Enantioselective Synthesis of Coumarin Derivatives by PYBOX-DIPH-Zn(II) Complex Catalyzed Michael Reaction. *J. Org. Chem.* **2012**, *77*, 8802–8808.
35. Dong, J.; Du, D.-M. Highly enantioselective synthesis of Warfarin and its analogs catalysed by primary amine-phosphinamide bifunctional catalysts. *Org. Biomol. Chem.* **2012**, *10*, 8125–8131.
36. Işık, M.; Akkoca, H.U.; Akhmedov, İ.M.; Tanyeli, C. A bis-Lewis basic 2-aminoDMAP/prolinamide organocatalyst for application to the enantioselective synthesis of Warfarin and derivatives. *Tetrahedron Asymmetry* **2016**, *27*, 384–388.
37. Liu, Y.; Liu, X.; Wang, M.; He, P.; Lin, L.; Feng, X. Enantioselective Synthesis of 3,4-Dihydropyran Derivatives via Organocatalytic Michael Reaction of α , β -Unsaturated Enones. *J. Org. Chem.* **2012**, *77*, 4136–4142.
38. Molleti, N.; Allu, S.; Ray, S.K.; Singh, V.K. Bifunctional chiral urea catalyzed highly enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to 2-enolpyridines. *Tetrahedron Lett.* **2013**, *54*, 3241–3244.
39. Ray, S.K.; Rout, S.; Singh, V.K. Enantioselective synthesis of 3, 4-dihydropyran derivatives via a Michael addition reaction catalysed by chiral pybox–diph–Zn (II) complex. *Org. Biomol. Chem.* **2013**, *11*, 2412–2416.
40. Kumar, A.; Sharma, S.; Tripathi, V.D.; Maurya, R.A.; Srivastava, S.P.; Bhatia, G.; Tamrakar, A.K.; Srivastava, A.K. Design and synthesis of 2,4-disubstituted polyhydroquinolines as prospective antihyperglycemic and lipid modulating agents. *Biorg. Med. Chem.* **2010**, *18*, 4138–4148.
41. Rodrigo, G.; Standen, N. ATP-sensitive potassium channels. *Curr. Pharm. Des.* **2005**, *11*, 1915–1940.
42. Li, X.; Cun, L.; Lian, C.; Zhong, L.; Chen, Y.; Liao, J.; Zhu, J.; Deng, J. Highly enantioselective Michael addition of malononitrile to α , β -unsaturated ketones. *Org. Biomol. Chem.* **2008**, *6*, 349–353.
43. Li, X.; Ma, Y.; Xing, Z.; Tang, N.; Zhu, J.; Deng, J. The asymmetric addition of malononitrile to α , β -unsaturated ketones catalyzed by $\text{RuCl}_2[(R,R)\text{-DPEN}](\text{PPh}_3)_2$ as the precatalyst. *Tetrahedron Lett.* **2014**, *55*, 3868–3872.
44. Zheng, Y.; Yao, Y.; Ye, L.; Shi, Z.; Li, X.; Zhao, Z.; Li, X. Highly enantioselective Michael addition of malononitrile to α , β -unsaturated pyrazolamides catalyzed by a bifunctional thiourea. *Tetrahedron* **2016**, *72*, 973–978.
45. Liu, S.; Wang, Q.; Ye, L.; Shi, Z.; Zhao, Z.; Yang, X.; Ding, K.; Li, X. A general, highly enantioselective Michael addition of nitroalkanes to α , β -unsaturated enones catalyzed by 9-amino (9-deoxy)-epi-quinine: A remarkable additive effect. *Tetrahedron* **2016**, *72*, 5115–5120.
46. Chen, X.K.; Zheng, C.W.; Zhao, S.L.; Chai, Z.; Yang, Y.Q.; Zhao, G.; Cao, W.G. Highly Enantioselective Michael Addition of Cyclic 1, 3-Dicarbonyl Compounds to β , γ -Unsaturated α -Keto Esters. *Adv. Synth. Catal.* **2010**, *352*, 1648–1652.
47. Wang, Y.F.; Wang, K.; Zhang, W.; Zhang, B.B.; Zhang, C.X.; Xu, D.Q. Enantioselective Asymmetric Michael Addition of Cyclic Diketones to β , γ -Unsaturated α -Keto Esters. *Eur. J. Org. Chem.* **2012**, *2012*, 3691–3696.
48. Zhang, G.; Zhang, Y.; Yan, J.; Chen, R.; Wang, S.; Ma, Y.; Wang, R. One-Pot Enantioselective Synthesis of Functionalized Pyranocoumarins and 2-Amino-4H-chromenes: Discovery of a Type of Potent Antibacterial Agent. *J. Org. Chem.* **2012**, *77*, 878–888.

49. Gao, Y.; Du, D.-M. Enantioselective synthesis of 2-amino-5,6,7,8-tetrahydro-5-oxo-4H-chromene-3-carbonitriles using squaramide as the catalyst. *Tetrahedron Asymmetry* **2012**, *23*, 1343–1349.
50. Feng, X.; Zhou, Z.; Zhou, R.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. Stereodivergence in Amine-Catalyzed Regioselective [4 + 2] Cycloadditions of β -Substituted Cyclic Enones and Polyconjugated Malononitriles. *J. Am. Chem. Soc.* **2012**, *134*, 19942–19947.
51. Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. Highly enantioselective conjugate addition of nitromethane to chalcones using bifunctional cinchona organocatalysts. *Org. Lett.* **2005**, *7*, 1967–1969.
52. Rueping, M.; Parra, A.; Uria, U.; Besselievre, F.; Merino, E. Catalytic asymmetric domino Michael addition–alkylation reaction: Enantioselective synthesis of dihydrofurans. *Org. Lett.* **2010**, *12*, 5680–5683.
53. Wang, G.-W.; Lu, Q.-Q.; Xia, J.-J. Three Types of Products Obtained Unexpectedly from the Reaction of Dimedone with Chalcones. *Eur. J. Org. Chem.* **2011**, *2011*, 4429–4438.
54. Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K.A. Squaramides: Bridging from Molecular Recognition to Bifunctional Organocatalysis. *Chem. Eur. J.* **2011**, *17*, 6890–6899.
55. Tsakos, M.; Kokotos, C.G. Primary and secondary amine-(thio)ureas and squaramides and their applications in asymmetric organocatalysis. *Tetrahedron* **2013**, *69*, 10199–10222.
56. Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. Organocatalytic enantioselective conjugate additions to enones. *J. Am. Chem. Soc.* **2006**, *128*, 12652–12653.
57. Ye, Y.; Wang, L.; Fan, R. Aqueous iodine (III)-mediated stereoselective oxidative cyclization for the synthesis of functionalized fused dihydrofuran derivatives. *J. Org. Chem.* **2010**, *75*, 1760–1763.
58. Yang, W.; Jia, Y.; Du, D.-M. Squaramide-catalyzed enantioselective Michael addition of malononitrile to chalcones. *Org. Biomol. Chem.* **2012**, *10*, 332–338.
59. Armarego, W.L.F.; Chai, C. *Purification of Laboratory Chemicals*, 7th ed.; Butterworth-Heinemann: Oxford, UK, 2012.
60. Jiang, L.; Wang, B.; Li, R.-R.; Shen, S.; Yu, H.-W.; Ye, L.-D. Catalytic promiscuity of Escherichia coli BioH esterase: Application in the synthesis of 3,4-dihydropyran derivatives. *Process Biochem.* **2014**, *49*, 1135–1138.
61. Ye, Y.; Wang, L.; Fan, R. Aqueous Iodine(III)-Mediated Stereoselective Oxidative Cyclization for the Synthesis of Functionalized Fused Dihydrofuran Derivatives. *J. Org. Chem.* **2010**, *75*, 1760–1763.

Sample Availability: Samples of the compounds **4**, **6**, **8** and **9** are available from the authors.



© 2017 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).