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Asymmetric synthesis of warfarin and its analogs catalyzed by C_2-symmetric squaramide-based primary diamines

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Abstract: Novel C_2-symmetric N,N'-bis(2-amino-1,2-diphenylethyl) squaramides with 1,2-di(pyridin-2-yl)ethane and 1,2-diphenylethane spacer groups were designed and applied as organocatalysts in asymmetric additions of 4-hydroxycoumarin and 4-hydroxy-6-methyl-2H-pyran-2-one to α,β-unsaturated ketones. Both enantiomers of anticoagulant warfarin and its analogs were prepared in up to 96% yield and with 96% *ee*. Recyclability of the developed catalysts and synthetic utility of the prepared Michael adducts for asymmetric synthesis of potential chiral medications via acylation reactions were demonstrated.

Introduction

Asymmetric organocatalysis is a vigorously developing area of current organic chemistry[1] that shows great promise for medicinal chemistry.[2] Enantioselective Michael addition of β-dicarbonyl compounds to α,β-unsaturated ketones is especially important among pharmacology-oriented organocatalytic transformations.[3] Useful products of these reactions, in particular of those between 4-hydroxycoumarin and benzylideneacetone derivatives, are a clinically valuable indirect action anticoagulant of warfarin (the WHO assigns it to the most efficacious, safe and cost–effective medicines for priority conditions[4]) and some of its analogs used as rodenticides.[5] Of the two warfarin enantiomers, the (*S*)-enantiomer proved to be 2–5 times more active than the (*R*)-enantiomer.[6] Various chiral 1,2-diamines[7] or their derivatives bearing thiourea,[8] imidazolidine[9] or acyl groups,[10] Cinchona alkaloid derivatives[11] and some other chiral amines [12] are used as catalysts of these asymmetric transformations. Among them, primary diamines **I-III** provided the best yield and enantiomeric purity of the drug product (> 90% *ee*) (Fig. 1).

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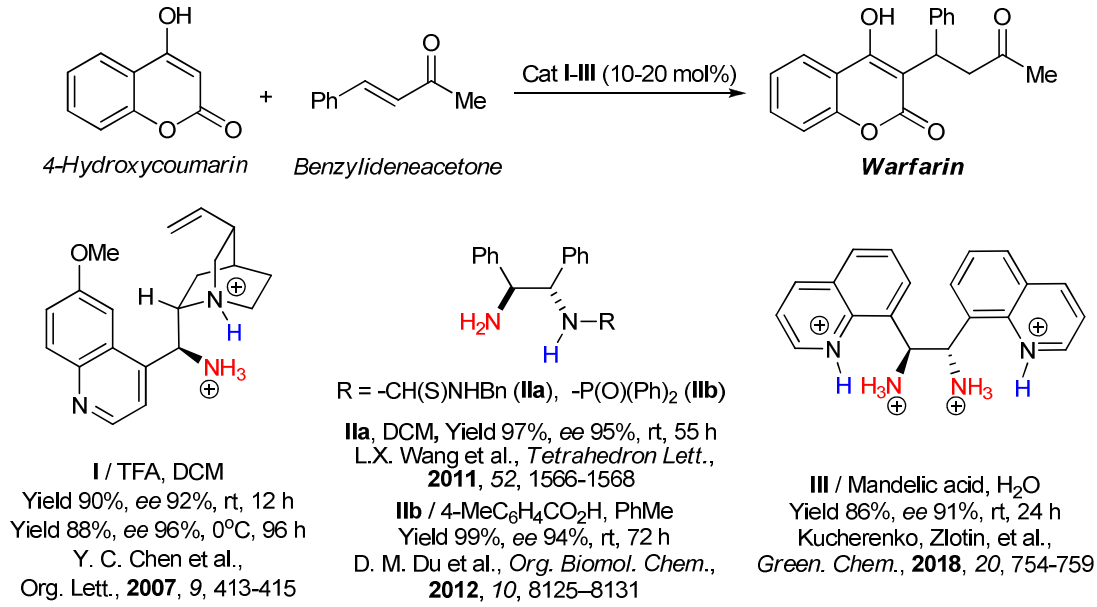

Fig. 1 Most efficient catalysts for asymmetric addition of 4-hydroxycoumarin to α,β-enones.

In the presence of 9-amino-9-deoxyepiquinine **I** / TFA salt, warfarin was generated with 96% *ee* in CH_2Cl_2 at 0°C, although the reaction was rather sluggish (it took 96 h to achieve full conversion).[11] A noticeable acceleration was observed at room temperature, yet at the expense of selectivity (92% *ee*). Excellent stereoinduction (95% *ee*) was reported for simple primary amine–thiourea catalyst **IIa**,[8] whereas its activity was moderate under the proposed conditions (CH_2Cl_2, r.t.). Primary amine phosphinamide bifunctional catalyst **IIb**[7e] (10 mol%) in combination with 4-methylbenzoic acid (20 mol%) also exhibited excellent results (99% yield and 94% *ee*) in toluene, though, a prolonged reaction time (72 h) was needed for complete conversion. C_2-Symmetric 1,2-diamine **III**, bearing 8-quinoline fragments (Figure 1), in combination with mandelic acid (MA) has been recently identified as catalyst of choice for asymmetric synthesis of warfarin in pure water.[13] Nearly complete conversion was attained in 24 h at room temperature and generated warfarin had a record optical purity 91% *ee* (99% *ee* after single re-crystallyzation) ever detected in the aqueous medium. However, water, a perspective solvent in terms of green chemistry, dissolves poorly a majority of organic reagents, which significantly restricts applicability of the aqueous environment to organic synthesis.[7c]

We anticipated that chiral primary amines with the squaramide fragment would be suitable promotors for asymmetric synthesis of warfarin. Seminal works by Rawal,[14] Du,[15] Jørgensen[16] and other chemists [17] revealed a high stereocontrolling potential of this fragment. Similar to the thiourea group, it favorably locates reagents at corresponding transition states via stereoselective formation of hydrogen bonds and is more robust than thiourea analogs in catalytic reactions.[18]

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C_2-Symmetric squaramide-type organocatalysts may be particularly useful. They are easier to prepare, and the doubled number of incorporated squaramide groups may enhance reaction selectivity especially in the presence of a properly designed linker group (for example, containing heteroaromatic fragments).

Recently, we have prepared C_2-symmetric N,N'-bis-[(pyrrolidin-2-yl)methyl-squaramide] TFA salts **IV** bearing (*R*,*R*)- or (*S*,*S*)-1,2-di(pyridin-2-yl)ethane spacer groups which acted as efficient recyclable organocatalysts of enamine-type asymmetric additions of cyclohexanone derivatives to *β*-nitrostyrenes (Fig. 2).[19] However, as far as we know, C_2-symmetric primary amine–squaramides capable of catalyzing iminium-type asymmetric Michael reactions have not been reported so far. Furthermore, squaramide-based organocatalysts frequently utilized in the stereoselective synthesis of various bioactive compounds[20] have never been used for the enantioselective preparation of warfarin and its analogs.

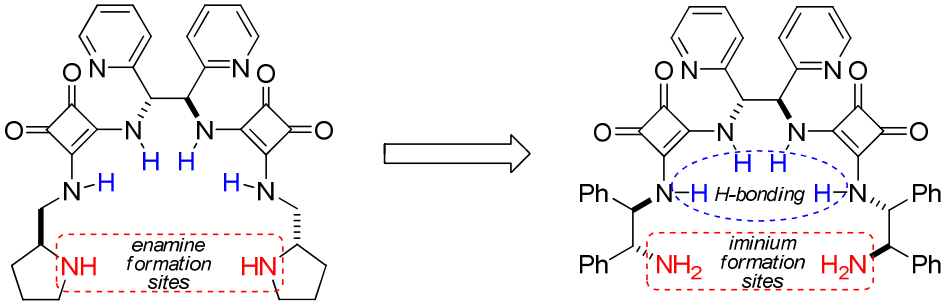

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Fig. 2 Research strategy.

Results and discussion

A synthesis of C_2-symmetric catalysts **V** demanded selective protection of one of the two amino groups present in chiral 1,2-diamine **1a**. However, reported yields for N-Cbz-**1a** and N-Cbz-**1b** were moderate (≤ 61%).[7d] Furthermore, we expected that subsequent deprotection (catalytic hydrogenation) of catalyst precursors bearing a pyridine fragment would be complicated by their ability to poison palladium catalysts[21]. Therefore, we decided to use the Boc group, easily removable by TFA, as an appropriate protective group in this case. There are surprisingly few reports on mono-Boc-protection of chiral 1,2-diamines in the literature. Commonly, a large excess of expensive diamine had to be consumed and product yields were not high.[22] The recently developed procedures are based on pre-deactivation of one of the amino groups by its protonation with the stoichiometric amount of strong Brønsted acid (HBr or HCl)

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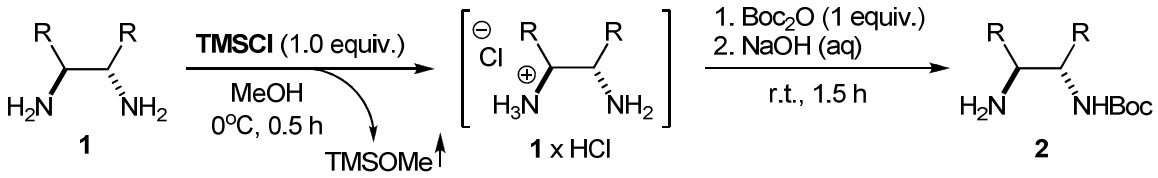
taken as an alcohol solution.[23] The solution has to be carefully titrated before each run because of the acid volatility, which creates major inconvenience.[23b] In this research, we simplified the procedure by replacing gaseous HCl for available and readily measurable TMSCl that reacted with MeOH directly in the reaction vessel to avoid the requirement of the strictly defined amount of HCl required for protonation of just one amino group in compound **1a**. By-produced TMSOMe (b.p. 57-58 °C, 1 bar) did not interfere with the bocylation reaction and could be readily removed. The procedure is applicable to mono-bocylation of chiral 1,2-diamines **1a-c** bearing aromatic, aliphatic and heteroaromatic groups (Table 1). Yields of known compounds **2a** and **2b** (85-86%) were higher than those reported in the literature. The reaction is readily scalable and practicable for synthesizing tens of grams of valuable chiral synthons **2** in a single operation.

Table 1 Selective mono-Boc protection of chiral diamines **1a-d** with TMSCl-MeOH system.[a]



Entry	Diamine **1**, R	Product **2**	Yield, %
1	(*R*,*R*)-**1a**, Ph	(*R*,*R*)-**2a**	85 (80[b])
2	(*S*,*S*)-**1a**, Ph	(*S*,*S*)-**2a**	86 [80[c], 65[d]]
3	(*R*,*R*)-**1b**, -$(CH_2)_4$-	(*R*,*R*)-**2b**	85 [78[c], 80[e],72[f]]
4	(*R*,*R*)-**1c**, 2-Pyridyl	(*R*,*R*)-**2c**	78 [n.d.]

[a] The reactions were carried out with TMSCl (0.01 mol, 1.26 mL), 1,2-diamine **1a-c** (0.01 mol) and $(Boc)_2O$ (0.012 mol, 2.6 g) in MeOH for 1.5 h. For more information see Experimental Section. [b] Di-amine **1a** loading was 10 g.[c] Ref [23b]. [d] Ref [23d] [e] Ref [23a]. [f] Ref [23c].

A further synthetic scheme included half-amidation of dimethyl squarate **3** with **1a** or **1c**, reactions of the prepared bis-amidoesters **4** or **5** with mono-protected (*S,S*)- or (*R,R*)-**2a**, and deprotection of corresponding bis-amides with TFA (Scheme 1). The reactions were carried out under simple experimental conditions (MeOH, r.t.) on air without moisture protection. Intermediates **4**, **5** and products **6**, **7** were obtained in the pure form without resort to chromatography. The absolute configuration of stereogenic centers in enantiomerically pure primary amines **6** and **7** was consistent with their configuration in chiral synthons **1** and **2** (Fig. 3).

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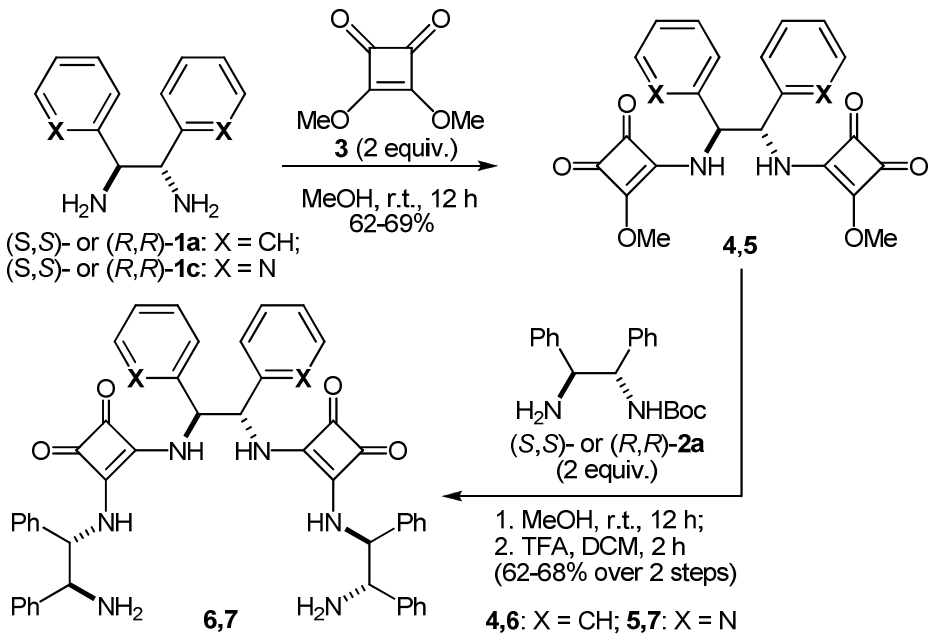

Scheme 1 Synthesis of catalysts **6** and **7**.

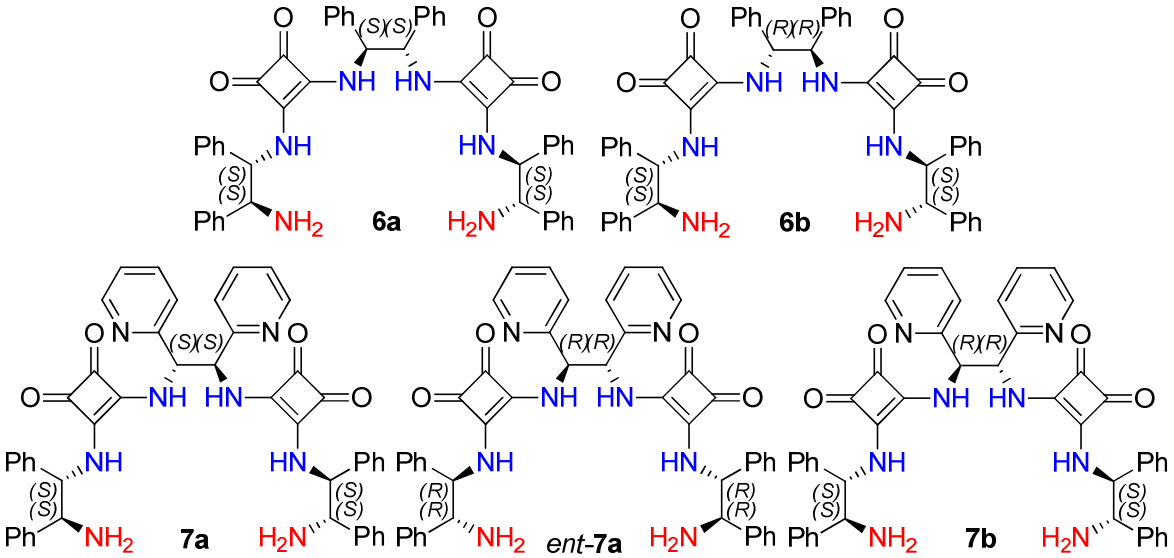

Fig. 3 Absolute configuration of stereogenic centers in C_2-symmetric squaramides **6** and **7.**

At first, we compared catalytic performance of compounds **6a**, **6b**, **7a** and **7b** having the (*S*)-configuration of stereogenic centers at primary amino groups in the asymmetric reaction of 4-hydroxycoumarin **8a** with benzylidene acetone **9a** under comparable conditions (catalyst loading 10 mol%, CH_2Cl_2, r.t., 24 h) (Table 2, entries 1-4). In all cases, (*S*)-warfarin **10a** was generated as the main product. However, the yield and enantiomeric enrichment of (*S*)-**10a** were superior with pyridine-containing catalysts **7** than in the presence of diamines **6** bearing the 1,2-diphenylethane-1,2-diamine linker group. Furthermore, of two diastereomeric catalysts **7a** and

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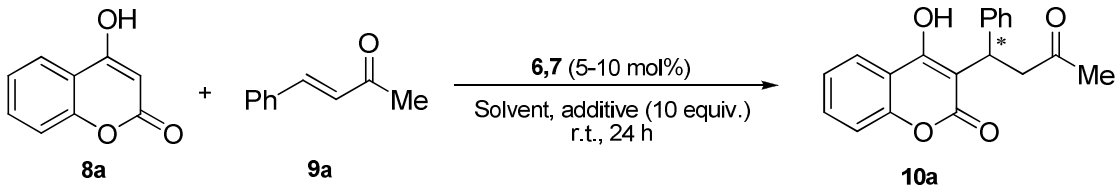
7b, compound **7a**, in which all chiral carbon atoms had similar configuration, appeared a more efficient activator (yield 94% *vs*. 91%) and stereoinductor (82% *ee vs*. 65% *ee*, entries 3 and 4). Having in hand **7a** as catalyst of choice, we decided to further optimize the reaction conditions. Testing of various aprotic (THF, PhMe, EtOAc) or protic solvents (*i*-PrOH or H_2O) did not bring positive results (entries 5-8). Nonetheless, we managed to improve the enantiomeric purity of (*S*)-**10a** up to 96% *ee* by carrying out the reaction in the presence of AcOH as an acidic additive (10 equiv. with respect to **8a**, entry 9). This condition proved to be optimal: higher temperature (50 ^{o}C, entry 10), reduced catalyst loading (5 mol%, entry 11) or an alternative proton source (TFA, BzOH or H_2O, entries 12-14) led to inferior stereochemical results. The procedure is stereodivergent: (*R*)-**10a** was obtained with similar yield and enantioselectivity in the presence of antipode *ent*-**7a** (Entry 9). It should be highlighted that diamine **7a** is one of the best known catalysts for asymmetric synthesis of warfarin in terms of activity and stereoinduction.

Table 2 Optimization of asymmetric synthesis of warfarin. [a]



Entry	Cat	Solvent	Additive	Yield, **10a** %[b]	*ee*, **10a** %[c] (*configuration*)
1	**6a**	CH_2Cl_2	–	76	49 (*S*)
2	**6b**	CH_2Cl_2	–	67	33 (*S*)
3	**7a**	CH_2Cl_2	–	94	82 (*S*)
4	**7b**	CH_2Cl_2	–	91	65 (*S*)
5	**7a**	THF	–	72	78 (*S*)
6	**7a**	PhMe	–	60	74 (*S*)
7	**7a**	EtOAc	–	69	77 (*S*)
8	**7a**	^{i}PrOH *or* H_2O	–	10-15	n.d.
9	**7a** (*ent*-**7a**)	CH_2Cl_2	AcOH	96 (94)	96 (*S*) [94 (*R*)]
10[d]	*ent*-**7a**	CH_2Cl_2	AcOH	97	84 (*R*)
11[e]	*ent*-**7a**	CH_2Cl_2	AcOH	81	93 (*R*)
12	*ent*-**7a**	CH_2Cl_2	TFA	10	n.d.
13	*ent*-**7a**	CH_2Cl_2	BzOH	92	78 (*R*)
14	*ent*-**7a**	CH_2Cl_2	H_2O	64	55 (*R*)

[a] Unless otherwise specified, the reactions were performed with **8a** (16.0 mg, 0.126 mmol), **9a** (22 mg, 0.151 mmol), catalyst **6** or **7** (10.0 mg, 12.6 μmol), additive (1.26 mmol, entries 9-14) in the corresponding solvent (300 μL). [b] Isolated yield of product **10** after flash-chromatography on silica gel. [c] HPLC data (*Chiralpak AD-H*, *n*-hexane / ^{i}PrOH 7/3, 0.8 mL min^{-1}, 254 n.m., t_R = 5.1 min ((*S*)-isomer), t_R = 9.5 min ((*R*)-isomer)). The absolute configuration of (*S*)-**10a** was determined by comparing its optical rotation $[\alpha]_D^{20}$ = -10.2 (c, 1, MeCN, 96% *ee*) with the reported data $[\alpha]_D^{20}$ = -10.7 (c, 1, MeCN, >99% *ee*) [7c]. [d] The reaction was carried out at 50°C, [e] The catalyst loading was 5 mol%.

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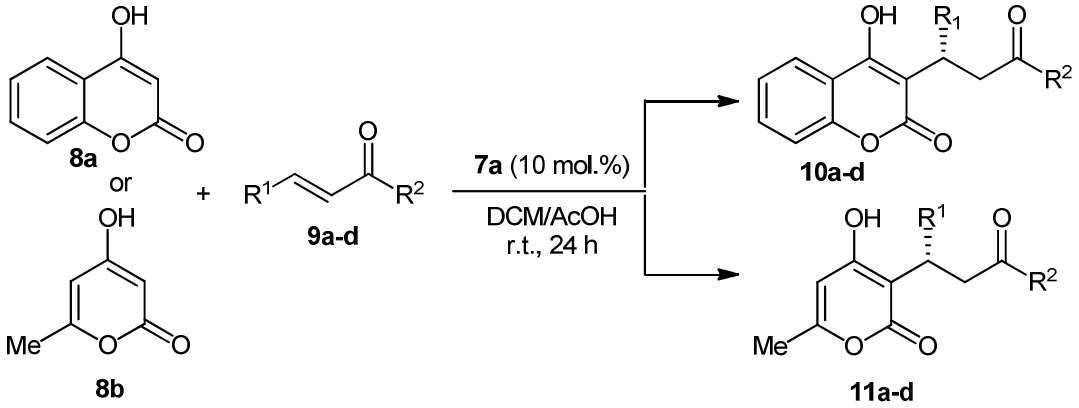
The developed **7a**/AcOH catalytic system appeared suitable for asymmetric synthesis of warfarin analogs. In the optimal conditions, α,β-enones **9a-c** reacted with 4-hydroxycoumarin (**8a**) or non-annelated 4-hydroxy-6-methyl-2H-pyran-2-one (**8b**) to afford corresponding Michael adducts **10a-c** and **11a-c** in high yield (91-97%) with enantioselectivity 84-96% *ee* (Table 3). Such data for **11a**, the only known **8b**-derived product, were superior to those reported in the literature.[9] Cyclohexenone (**9d**) also reacted with **8a** and **8b** in the presence of catalyst **7a**, although stereoinduction in these reactions was significantly lower (50-67% *ee*, entries 4 and 8) than in corresponding reactions with linear α,β-enones **9a-c**. It should be mentioned that 4-hydroxy-2H-pyran-2-one derivative **11c** was studied along with warfarin **10a** for efficient treatment of thromboses.[24]

Table 3 Asymmetric synthesis of Warfarin analogs. [a]



Entry	Carbon acid	R^1,R^2	Product	Yield[b], **10** % [lit]	*ee*[c], **10** % [lit]
1	**8a**	(**9a**) C_6H_5, CH_3	**10a**	96	96 (*S*)
2[d]	**8a**	(**9b**) 4-$CH_3OC_6H_4$, CH_3	**10b**	93	84 (*R*)
3[d]	**8a**	(**9c**) 4-ClC_6H_4, CH_3	**10c**	91	88 (*R*)
4	**8a**	(**9d**) -$(CH_2)_3$-	**10d**	89	50 (*S*)
5	**8b**	(**9a**) C_6H_5, CH_3	**11a**	97 [76[e]]	94 (*S*) [85[e]]
6	**8b**	(**9b**) 4-$CH_3OC_6H_4$, CH_3	**11b**	95	86 (*S*)
7	**8b**	(**9c**) 4-ClC_6H_4, CH_3	**11c**	95	89 (*S*)
8	**8b**	(**9d**) -$(CH_2)_3$-	**11d**	91	67 (*S*)

[a] Unless otherwise specified, the reactions were performed with **8a** or **8b** (0.126 mmol), **9a-d** (0.151 mmol), catalyst **7a** (10.0 mg, 12.6 μmol), AcOH (70 μL) in DCM (0.3 mL). [b] Isolated yield of products after flash-chromatography on silica gel. [c] HPLC data (*Chiralpak AD-H*, *Chiralpak AS-H*, *Chiralcel OD-H* or *Chiralcel OJ-H*); Absolute configurations were assigned to adducts **10b-d** and **11a-d** by analogy with **10a**. [d] Catalyst *ent*-**7a** was used. [e] Ref. [9].

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Most likely, α,β-enones **9** are activated in the catalytic reactions via the formation of highly electrophilic iminium cation with a primary amino group of catalyst **7a**. Simultaneously, adjacent squaramide and pyridinium fragments of the bifunctional catalyst activate β-dicarbonyl compound **8** through establishing a rigid network of hydrogen bonds with oxygen atoms which ensure highly enantioselective re-face attack of **8** in the transition state **TS** (Fig. 4). An important role of the protonated with AcOH pyridine fragment of catalyst **7a** is in agreement with significantly lower activity and stereoinduction of corresponding pyridine-free catalyst **6a** unable to form the extra H-bond with the nucleophilic reagent (see Table 2, entry 1 *vs* entry 3).

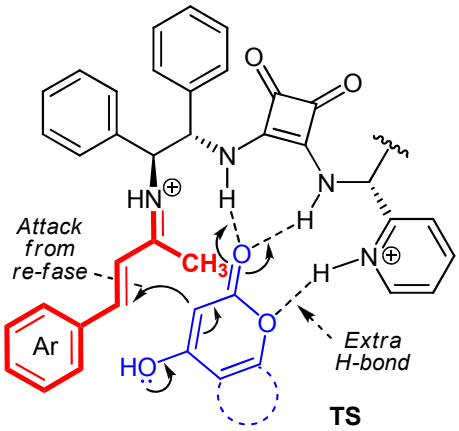

Fig. 4 Plausible transition state for **7a**/AcOH-catalyzed Michael reaction between **8** and **9**.

Catalyst **7a** poorly soluble in a majority of organic solvents could be recovered from the reaction mixtures and reused in the same reaction. After attaining high conversion, product **10a** was extracted with Et_2O, then new portions of reagents, AcOH and the solvent were added to the remaining catalyst and the reaction was re-performed. The scalable (1.62 g of **8a** was used) procedure was repeated thrice with a somewhat reduced conversion and, to a less extent, enantioselectivity (Table 4). The recorded gradual deactivation of catalyst **7a** may be attributed to by-side reactions of key iminium ions characteristic of primary amine-derived catalysts which gradually transferred them out of the catalytic cycle [see ref. [7d]].

Table 4 Recycling of catalyst **7a** in the asymmetric reaction between **8a** and **9a**.[a]

Cycle	T, h	Yield,%	*ee*,%
1	24	96	96
2	24	88	94
3	30	82	92
4	30	53	89

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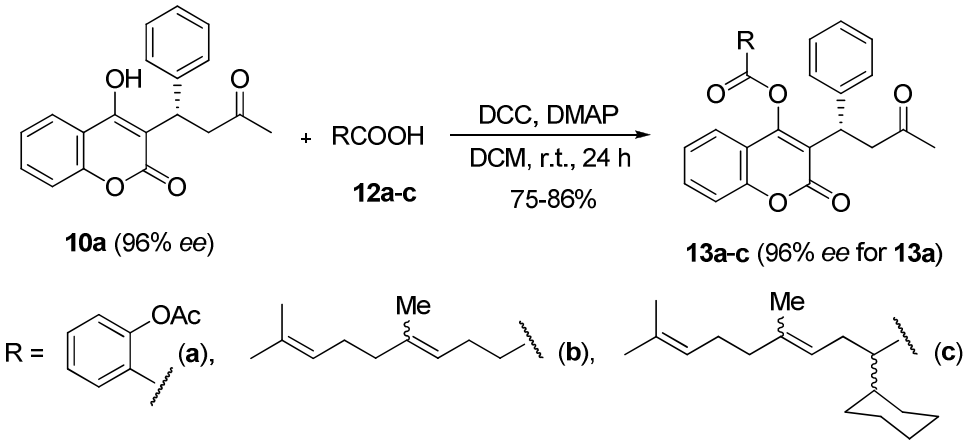
[a] The reactions were performed with catalyst **7a** (0.79 g, 1 mmol), **8a** (1.62 g, 10.0 mmol), **9a** (1.75 g, 12.0 mmol), AcOH (0.57 mL) and CH_2Cl_2 (5 mL).

The synthetic utility of the prepared compounds was demonstrated by selective acylation of warfarin **10a** with bioactive acids, namely acetylsalicylic (**12a**), 5,9-dimethyldeca-4,8-dienoic (**12b**), and 2-cyclohexyl-5,9-dimethyldeca-4,8-dienoic (**12c** – the active ingredient of the wound healing medication Cygerol),[25] in the presence of DCC/DMAP (Scheme 2). Corresponding chiral esters **13a-c** were obtained in high yield 75-86% and had the same enantiomeric purity as starting compound **10a** (HPLC data). Esters **13a-c** containing two privileged pharmacophoric groups are likely to selectively bind with different cellular receptors and have exotic pharmacological profiles (the 'twin drugs' concept[26]).



Scheme 2 Derivatization of Warfarin (**10a**) with bioactive carboxylic acids **12a-c**.

Conclusion

In summary, novel C_2-symmetric N,N'-bis(2-amino-1,2-diphenylethyl) squaramides with 1,2-di(pyridin-2-yl)ethane and 1,2-diphenylethane spacer groups have been synthesized from readily available chiral 1,2-diamines. In the presence of catalysts **7a** and *ent*-**7a** in combination with AcOH, 4-hydroxycoumarin and 4-hydroxy-6-methyl-2H-pyran-2-one reacted with linear or cyclic α,β-unsaturated ketones to afford corresponding Michael adducts in 89–97% yield with moderate to high enantioselectivity (50–96% *ee*). The developed procedure appeared particularly promising for asymmetric synthesis of the most active (*S*)-enantiomer of warfarin, a clinically useful anticoagulant. It was produced under the proposed conditions in 96% yield with 96% *ee* which are among the best ever reported results. Potential recyclability of catalyst **7a** poorly soluble in organic solvents was demonstrated. (*S*)-Warfarin esters which contain two privileged pharmacophoric groups were prepared by selective esterification of the drug molecule with bioactive acetyl salicylic and isoprenoid acids.

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Experimental section

General information

The NMR ^{1}H and ^{13}C spectra were recorded by Bruker AM 300 in $CDCI_3$ and DMSO–d_6. The chemical shifts of ^{1}H and ^{13}C were measured relative to Me_4Si or $CDCl_3$, respectively. The high resolution mass spectra (HRMS) were measured by Bruker microTOF II with electrospray ionization (ESI). The optical rotations were measured on a polarimeter and calibrated with a pure solvent as a blank. The HPLC analyses were performed on an HPLC system equipped with chiral stationary phase columns, detection at 220 or 254 nm. Silica gel 0.060 – 0.200 was used for column chromatography. Linalool-derived isoprenoid acids **12b** and **12c** were used as mixtures of isomers with regard to the double bond at C^5 (*E*/*Z* ~4:1).[25]

General procedure for selective mono-Boc protection of diamines 1a-c

TMSCl (0.01 mol, 1.26 mL) was added to MeOH and the resulting solution was stirred for 10 min at 0˚C. Next, diamines **1a-c** (0.01 mol) were added at 0˚C. The mixture was stirred for 15 min at room temperature and the solution of $(Boc)_2O$ (0.01 mol, 2.16 g) in MeOH (15 mL) was added dropwise for 10 min. The resulting solution was stirred for 1.5 h. The mixture was concentrated in *vacuo*. The residue was transferred to a filter and washed by diethyl ether (3 × 30 mL). The resulting pale-yellow solid was successively treated with the 3 N NaOH solution (25 mL) and water (3 × 10 mL). The product was dried in *vacuo* to afford mono-Boc amines **2a-c** as colorless solids. Characterization data on known products **2a** and **2b** is given in Supporting Information.

***Tert*-butyl ((1*S*,2*S*)-2-amino-1,2-di(pyridin-2-yl)ethyl)carbamate (*R*,*R*-2c)**.

Colorless solid, 2.45 g (78%). Mp: 123-125 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, *J* = 4.4 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.26 – 6.99 (m, 4H), 6.15 (d, *J* = 6.2 Hz, 1H), 5.22 – 5.03 (m, 1H), 4.58 (d, *J* = 4.4 Hz, 1H), 2.62 (s, 2H), 1.36 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.4, 159.3, 155.7, 148.9, 148.8, 136.2, 136.1, 122.1, 122.1, 121.9, 79.2, 60.2, 28.2 ppm. HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{17}H_{22}N_4O_2$: 315.1816; found 315.1809; $[M + Na]^+$ calcd 337.1635; found 337.1631; $[M + K]^+$ calcd 353.1374 found 353.1369.

General procedure for Michael addition

The mixture of 4-hydroxycoumarin **8a** or 4-hydroxy-6-methyl-2H-pyran-2-one **8b** (0.126 mmol), *α*,*β*-unsaturated ketone **9** (0.151 mmol), catalyst **7a** or *ent*-**7a** (10 mg, 12.6 μmol), AcOH (70 μL), and CH_2Cl_2 (300 μL) was stirred at ambient temperature for 24 h. The solvent and AcOH

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were removed under reduced pressure (15 Torr) and the residue was extracted with Et_2O (5 x 3 mL). The combined organic extracts were evaporated under reduced pressure (15 Torr). Corresponding products **10** or **11** were purified via flash-chromatography on silica gel (*n*-hexane/EtOAc 2:1). Characterization data on all products is given in Supporting Information.

Scaling catalytic reaction and catalyst recovery

The mixture of 4-hydroxycoumarin **8a** (1.62 g, 10.0 mmol), *α,β*-unsaturated ketone **9a** (1.75 g, 12.0 mmol), catalyst **7a** (0.79 g, 1.0 mmol), AcOH (0.57 mL), and CH_2Cl_2 (5 mL) was stirred at ambient temperature for 24 h. The solvent and AcOH were removed under reduced pressure (15 Torr) and the residue was extracted with Et_2O (5 x 30 mL). The combined organic extracts were evaporated under reduced pressure (15 Torr) to afford the product **10a**. After extraction of product **10a** with Et_2O, remained catalyst **7a** was dried under reduced pressure (1.0 Torr, 30 min). Fresh portions of **8a**, **9a**, AcOH and CH_2Cl_2 were added to the recovered catalyst and the reaction was re-performed.

General procedure for Warfarin esterification

Warfarin **10a** (0.154 g, 0.5 mmol), acid **12** (0.5 mmol), DCC (0.11 g, 0.5 mmol), DMAP (*cat*.) and DCM (0.5 mL) were stirred for 24 h. The precipitate was filtered off and washed with DCM (3×5 mL). The combined organic washings were evaporated and the residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc, 4:1-2:1) to afford ester **13**.

2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 2-acetoxybenzoate (13a).

Colorless oil, 0.2 g (85%). $[\alpha]_D^{22}$ = +4.8 (c, 0.2, $CHCl_3$, 96 % *ee*), [HPLC Daicel Chiralcel AS-H; *n*-hexane/2-propanol, 99:1; flow rate = 0.8 mL/min; λ = 254 nm: t_1 = 22.22 min., t_2 = 24.19 min.]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85 (d, J = 7.9 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.54 – 7.05 (m, 11H), 4.06 – 3.82 (m, 1H), 3.00 – 2.69 (m, 1H), 2.16-2.06 (m, 1H), 2.05 (s, 3H), 1.94 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.9, 160.1, 157.7, 152.8, 143.3, 132.8, 128.8, 127.6, 126.7, 124.7, 123.1, 116.7, 115.1, 104.8, 103.0, 41.0, 34.9, 24.3, 22.1 ppm. HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{28}H_{22}O_7$: 471.1438; found 471.1435; $[M + NH_4]^+$ calcd 488.1704, found 488.1703.

2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 5,9-dimethyldeca-4,8-dienoate (13b).

Colorless oil, 0.21 g (86%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (d, J = 7.5 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.49 – 7.07 (m, 7H), 5.05 – 4.84 (m, 2H), 3.98 – 3.80 (m, 1H), 2.83 (m, 1H), 2.33

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(m, 2H), 2.13 (m, 2H), 2.05 – 1.83 (m, 6H), 1.78 (m, 2H), 1.66 – 1.39 (m, 9H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.9, 160.0, 157.7, 152.7, 143.2, 136.5, 136.4, 132.8, 131.3, 131.1, 128.8, 127.5, 126.7, 124.6, 124.4, 123.2, 123.0, 122.4, 116.7, 115.1, 104.8, 102.9, 102.9, 41.2, 35.2, 35.1, 31.8, 26.5, 26.3, 25.9, 25.8, 24.2, 23.5, 23.4, 17.9, 17.8, 16.2 ppm. HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{31}H_{34}O_5$: 487.2479; found 487.2469; $[M + NH_4]^+$ calcd 504.2744, found 504.2734; $[M + Na]^+$ calcd 509.2298, found 509.2288.

2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 2-cyclohexyl-5,9-dimethyldeca-4,8-dienoate (13c).

Colorless oil, 0.21 g (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.07 (m, 9H), 5.43 – 5.24 (m, 1H), 5.21 – 5.02 (m, 1H), 4.90 – 4.76 (m, 1H), 3.93 – 3.51 (m, 1H), 3.50 – 3.11 (m, 1H), 2.90 – 2.70 (m, 1H), 2.69 – 2.54 (m, 1H), 2.53 – 2.30 (m, 1H), 2.28 – 1.43 (m, 21H), 1.26 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 171.8, 171.8, 160.9, 152.5, 140.0, 138.2, 131.7, 131.6, 128.3, 127.8, 127.7, 126.7, 124.1, 124.0, 123.7, 121.2, 121.1, 116.6, 116.1, 109.9, 77.5, 77.1, 76.7, 52.0, 45.2, 40.0, 39.9, 39.8, 37.5, 36.5, 36.5, 31.4, 31.2, 30.3, 29.9, 27.0, 26.6, 26.4, 26.3, 26.2, 25.7, 23.5, 22.4, 17.8, 17.7, 16.3 ppm. HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{37}H_{44}O_5$: 569.3262, found 569.3257; $[M + NH_4]^+$ calcd 586.3527, found 586.3524; $[M + Na]^+$ calcd 591.3081, found 591.3076; $[M + K]^+$ calcd 607.2820, found 607.2821.

Conflicts of interest

There are no conflicts to declare.

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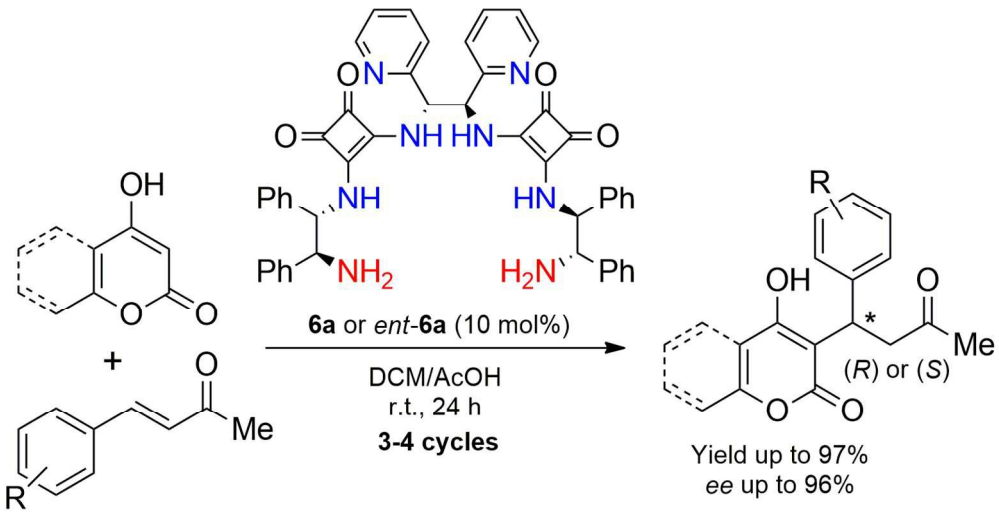

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