Tetrahedron: *Asymmetry* 27 (2016) 384–388

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A bis-Lewis basic 2-aminoDMAP/prolinamide organocatalyst for application to the enantioselective synthesis of Warfarin and derivatives

Murat Işık [a,b], H. Ufuk Akkoca [a], İ. Mecidoğlu Akhmedov [c], Cihangir Tanyeli [a,*]

[a] Department of Chemistry, Middle East Technical University, 06800 Ankara, Turkey
[b] Department of Metallurgical and Materials Engineering, Bingöl University, 12400 Bingöl, Turkey
[c] Department of Chemistry, Baku State University, Z. Khalilov, Baku, Azerbaijan

ARTICLE INFO

Article history:
Received 8 March 2016
Accepted 11 April 2016
Available online 20 April 2016

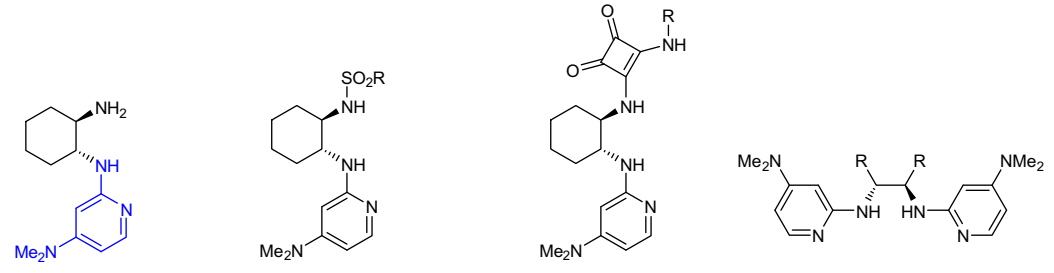
ABSTRACT

A new chiral *sec*-amine/amidine-base hybrid catalyst, 2-aminoDMAP/prolinamide, is reported, which is able to catalyze conjugate addition of 4-hydroxycoumarin and various benzylideneacetones, a reaction that directly gives anticoagulant Warfarin and its analogues, with good yields (70–87%) and enantioselectivities (58–72%).

1. Introduction

The field of asymmetric organocatalysis abounds with H-bonding catalysts, especially with those carrying both an H-bond donor and an H-bond acceptor appropriately placed around a chiral environment—acid/base type bifunctional organocatalysts.[1] These small, purely organic molecules activate substrate(s) with the H-bond donor part being responsible for lowering the LUMO energy level of the electrophile and the acceptor part for raising the HOMO energy level of the nucleophile, and thus creates stereochemical molecular complexity.[2] Besides this attractive design approach, another equally abundant, powerful, and well-established modality relies on covalent catalysis by chiral primary or secondary amines, which operates through either enamine[3] or iminium[4] activation mechanistic pathways. Taken together, and encouraged by the influential works of Fu,[5] Kotsuki,[6] Johnston,[7] and Wulff[8] in particular, we have recently developed several bifunctional organocatalyst libraries that were built on a new *superbasic* unit[5–11] (2-aminoDMAP, **1**) which might act as Lewis or Brønsted base depending on the context (Fig. 1).[10–12]

When coupled with H-bond donors through modification of the remaining primary amine of the *trans*-cyclohexane-1,2-diamine chiral backbone, **1** yielded 2-aminoDMAP/sulfonamides **2**[10] and 2-aminoDMAP/squaramides **3**,[11] both of which were found to be



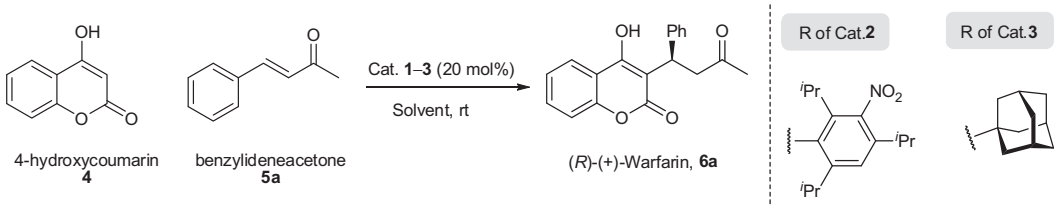
2-aminoDMAP, **1** | 2-aminoDMAP/sulfonamides, **2** | 2-aminoDMAP/squaramides, **3** | C_2-symmetrical nucleophiles

Figure 1. 2-AminoDMAP based organocatalysts.

* Corresponding author.
E-mail address: tanyeli@metu.edu.tr (C. Tanyeli).

http://dx.doi.org/10.1016/j.tetasy.2016.04.001
0957-4166/

Table 1
Screening of the catalysts **1**–**3** in Warfarin synthesis[a]



Entry	Cat.	Solvent	Time[b] (h)	Yield[c] (%)	ee[d] (%)
1[e]	**3**	Dichloromethane	120	–	–
2[f]	**2**	Dichloromethane	120	–	–
3	**1**	Dichloromethane	120	70	22
4	**1**	Dimethyl sulfoxide	96	–	–
5	**1**	Tetrahydrofuran	96	–	–
6	**1**	Toluene	96	–	–
7[g,h]	**1**	Dichloromethane	96	–	–

[a] Reactions were carried out in 0.05 M concentration of 4-hydroxycoumarin **4** with 1.5 equiv of benzylideneacetone **5a**.
[b] Time for indicated conversion.
[c] Reaction mixture was directly loaded onto silica gel column for isolation.
[d] Enantiomers were separated by HPLC using the chiral stationary phase.
[e] Alkyl group of the sulfonamide is shown on the table scheme.
[f] Alkyl group of the squaramide is shown on the table scheme.
[g] 20 mol % Trifluoroacetic acid was added.
[h] 40 mol % Trifluoroacetic acid was added.

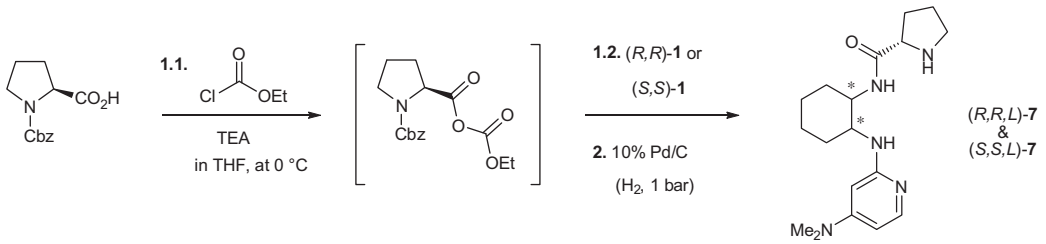
highly efficient bifunctional acid/base type catalysts for asymmetric Michael addition of *trans*-nitroolefins and some β-dicarbonyl compounds. Among these, squaramides **3** were found to be particularly active/useful catalysts requiring only 1–2 mol % loadings to complete conjugate additions (vide supra) in short reaction times (typically 3–6 h). Because of their swift action and high stereoselectivity, we also wanted to exploit them in the Michael addition of 4-hydroxycoumarin **4** to the benzylideneacetone **5a**, a reaction that directly gives Warfarin **6a**,[13] an anticoagulant drug active-compound, for which current organocatalytic protocols typically take days to week and are rarely truly selective (Table 1).[14–21]

2. Results and discussion

To this end, we have reacted **4** and **5a** in the presence of the catalysts we have developed so far (Fig. 1 and Table 1) in dichloromethane at room temperature. We saw no trace of Warfarin formation (TLC monitoring) when using catalyst **2** or **3**, respectively (entries 1 and 2 of Table 1). We reasoned that the underlying causes might be twofold: (1) Although, the catalysts **2** and **3** were shown to be very active in deprotonating acyclic β-diketones like acetyl acetone or dibenzoylmethane, here however, they are inactive because of the cyclic nature of the **4** making it impossible to form double H-bonding with 2-aminoDMAP unit, basic part of the cat. **2** and **3**. (2) Another plausible explanation can be the low or insufficient activation of **5a** by sulfonamide or squaramide units. The latter reasoning together with the common choice of primary-amine-catalysts of previous lit. for this very same reaction provoked us to consider our precatalyst 2-aminoDMAP **1** itself for this reaction. The primary amine catalysts can form transient iminium structures when coupled with enone **5a** and thereby lower the LUMO thereof. Despite low in enantioselectivity (entry 3, 22% ee), the reaction was made possible by **1**. The use of toluene, dimethyl sulfoxide, or tetrahydrofuran as the solvent gave no product. We added trifluoroacetic acid as the co-catalyst; but the reaction halted (entry 7). Addition of water, with the hope of accelerating the reaction, enhanced both yield and enantioselectivity (entry 8), albeit a little. Increasing the amount of water further to 10 or 20 equiv affected the yields a little more, but this time lowered selectivity.

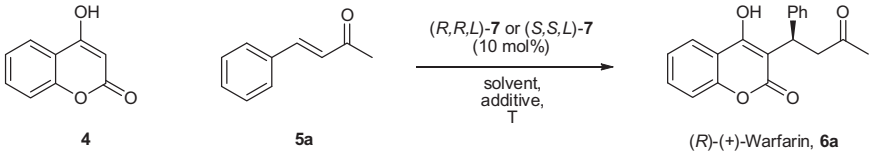
With these preliminary results in hand, we wondered to couple (L)-Proline with the **1** through an amide bond to create an amidine superbase/*sec*-amine hybrid catalyst in hope of affording higher selectivities. Ready availability of **1** in only one-step encouraged us to synthesize catalysts (*R*,*R*,*L*)-**7** and (*S*,*S*,*L*)-**7** to investigate the match-mismatch of the two chiral pools. The first step of the syntheses involves the activation of *N*-carboxybenzoyl-protected (L)-proline by converting it to its mixed anhydride of ethyl chloroformate in basic medium; to which then, a tetrahydrofuran solution of enantiomers of **1** was added, (*R*,*R*)-**1** and (*S*,*S*)-**1**. At the second and last step, the Cbz-group was cleaved by 10% Pd/C under approx. 1 bar of hydrogen atmosphere (balloon). As a result, the two catalyst candidates, (*R*,*R*,*L*)-**7** and (*S*,*S*,*L*)-**7**, were synthesized in 65–68% overall yields. We should here note that also at first we used *N*-^{t}Boc-protected L-proline and found it equally helpful to form the amide bond, but when it came to deprotect the ^{t}Boc-group with trifluoroacetic acid we could hardly get free base. The diastereomeric pair of 2-aminoDMAP/prolinamides made so were characterized by ^{1}H and ^{13}C NMR and HRMS analysis. The structure of (*R*,*R*,*L*)-**7** was further supported by COSY, HMBC, HMQC, ^{13}C-DEPT-90, and ^{13}C-DEPT-135 NMR experiments (Scheme 1).

Having two new 2-aminoDMAP/prolinamides at hand, namely (*R*,*R*,*L*)-**7** and (*S*,*S*,*L*)-**7**, we refocused on the conjugate addition of **4** and **5a** (Table 2). The first experiments revealed the supremacy of the (*R*,*R*,*L*)-**7** over the (*S*,*S*,*L*)-**7**, 64% ee versus 23% ee, respectively (entry 1 vs entry 3 of Table 2). The reaction with (*R*,*R*,*L*)-**7** took only 26 hours to give a 90% yield of Warfarin, **6a**. Seeing the strong mismatch of (*S*,*S*,)-diamine and (L)-Proline in (*S*,*S*,*L*)-**7**, we focused on the (*R*,*R*,*L*)-**7** for further reaction parameter optimization. In this regard, a number of solvent were tested; and chlorinated solvents (entries 4 and 13–15) consistently gave the best results, among all eleven. Because of its availability and low-cost we chose dichloromethane as the reaction solvent. Next, we wanted to add some external H-bond donors for co-catalytic purposes to improve the enantioselectivity. To this end, we made use of three carboxylic acids and four phenolic compounds as co-catalyst, and all were



Scheme 1. The synthesis of diastereomeric pair of 2-aminoDMAP/prolinamide, (*R*,*R*,*L*)-**7** and (*S*,*S*,*L*)-**7**.

Table 2
Screening of the catalysts (*R*,*R*,*L*)-**7** and (*S*,*S*,*L*)-**7** in Warfarin synthesis[a]



4 **5a** (*R*)-(+)-Warfarin, **6a**

Entry	Cat.	Solvent	Additive	Time[b] (h)	Yield[c] (%)	ee[d] (%)
1[e]	(*S*,*S*,*L*)-**7**	Dichloromethane	—	96	81	23
2[e]	(*S*,*S*,*L*)-**7**	Dimethyl sulfoxide	—	96	91	7
3[e]	(*R*,*R*,*L*)-**7**	Dichloromethane	—	96	75	64
4	(*R*,*R*,*L*)-**7**	Dichloromethane	—	26	90	64
5	(*R*,*R*,*L*)-**7**	Dimethyl sulfoxide	—	35	65	25
6	(*R*,*R*,*L*)-**7**	Tetrahydrofuran	—	27	65	47
7	(*R*,*R*,*L*)-**7**	Toluene	—	27	64	52
8	(*R*,*R*,*L*)-**7**	Benzene	—	27	75	40
9	(*R*,*R*,*L*)-**7**	Ethyl acetate	—	23	92	57
10	(*R*,*R*,*L*)-**7**	Acetone	—	260	70	33
11	(*R*,*R*,*L*)-**7**	Methanol	—	140	91	22
12	(*R*,*R*,*L*)-**7**	Water	—	40	65	38
13	(*R*,*R*,*L*)-**7**	Chloroform	—	27	80	62
14	(*R*,*R*,*L*)-**7**	1,2-Dichloroethane	—	26	90	63
15	(*R*,*R*,*L*)-**7**	Chlorobenzene	—	27	90	61
16	(*R*,*R*,*L*)-**7**	Dichloromethane	Trifluoroacetic acid	53	75	61
17	(*R*,*R*,*L*)-**7**	Dichloromethane	Benzoic acid	48	88	62
18	(*R*,*R*,*L*)-**7**	Dichloromethane	3,5-Dinitrobenzoic acid	60	84	60
19	(*R*,*R*,*L*)-**7**	Dichloromethane	Phenol	40	91	63
20	(*R*,*R*,*L*)-**7**	Dichloromethane	Picric acid	40	96	58
21	(*R*,*R*,*L*)-**7**	Dichloromethane	α-Naphthol	40	93	60
22	(*R*,*R*,*L*)-**7**	Dichloromethane	β-Naphthol	40	94	64
23[f]	(*R*,*R*,*L*)-**7**	Dichloromethane	—	48	85	70
24[g]	(*R*,*R*,*L*)-**7**	Dichloromethane	—	120	78	68
25[f]	(*R*,*R*,*L*)-**7**	Dichloromethane	β-Naphthol	55	80	72

[a] Reactions were carried out in 0.1 M concentration of 4-hydroxycoumarin **4** with 3 equiv of benzylideneacetone **5a**.
[b] Time for indicated conversion.
[c] Reaction mixture was directly loaded onto silica gel column for isolation.
[d] Enantiomers were separated by HPLC using the chiral stationary phase.
[e] 20 mol % of the catalysts was used.
[f] Reaction was carried out at 10 °C.
[g] Reaction was carried out at 0 °C.

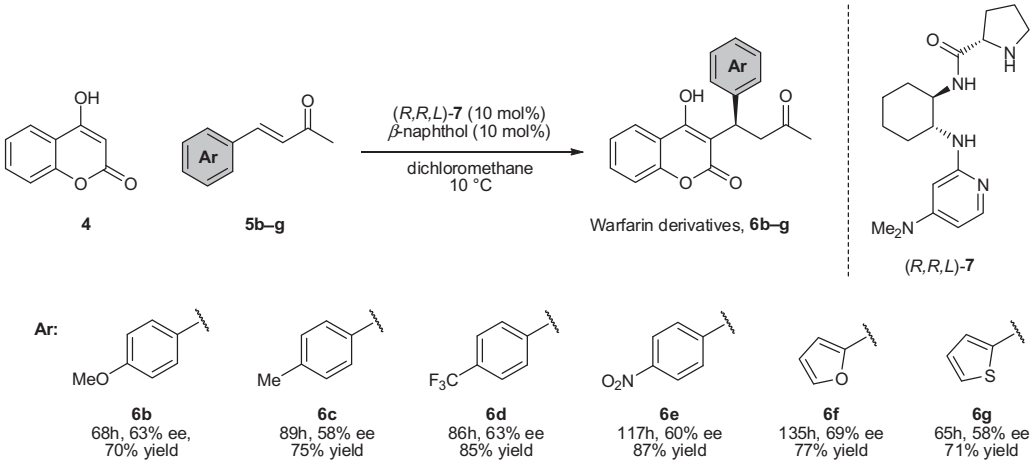
found to be almost equally selective (entries 16–22). When the reactions were carried out at colder temperatures, selectivities increased a little, but not much. At best, we could get **6a** at 80% yield with 72% ee, when we ran reactions with 10 mol % of both (*R*,*R*,*L*)-**7** and β-naphthol in dichloromethane for 55 h of stirring at 10 °C.

We also wanted to show the generality of this protocol by employing different enones **5b**–**g** (Scheme 2). All these enones gave moderate and virtually similar levels of enantioselectivity, around 60% or so. Both enantioselectivity and chemical yields of the reactions were apparently insensitive to the electronic structure of the aryl unit of enone.

To rationalize the enantioselective reactions catalyzed by (*R*,*R*,*L*)-**7**, we suggest following stereochemistry predicting model given in Figure 2. According to this model, we propose that the reaction is mainly driven by iminium reactive formation at proline site. Here, we should note also that β-naphthol may help facilitate iminium ion formation. Additionally, we think that 4-hydroxycoumarin is activated by a network of H-bonding, and therefore is kept close to the *si* face of the iminium ion, which gives the enantiomerically enriched product when hydrolysed by a molecule of water.

3. Conclusion

Overall, we synthesized two bis-Lewis basic 2-aminoDMAP/prolinamides catalysts, (*R*,*R*,*L*)-**7** and (*S*,*S*,*L*)-**7**, and successfully employed them in enantioselective synthesis of Warfarin and its



Scheme 2. The scope of enones.

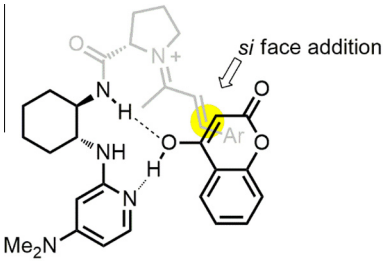


Figure 2. Plausible TS for conjugate additions of **5a–g** and **4** catalyzed by (*R,R,L*)-**7**.

analogues. Among the catalysts, (*R,R,L*)-**7** proved to be the match-pair. Our previously developed catalysts, sulfonamide **2** and squaramide **3** (those lacking a primary or secondary amine functionality), failed; even no products were observed. Comparing the activities of catalysts **1**–**3** and (*R,R,L*)-**7**, we conclude that the reaction demands either a primary or a secondary amine catalyst for activating these mutually quite unreactive partners, although alone not enough for a satisfactory enantioselectivity and yield. The faster reactions obtained with (*R,R,L*)-**7**, when compared with the precedent primary/secondary amine catalysts, reveals the rate enhancing ability of 2-aminoDMAP superbase as well. Research along these directions is in progress.

4. Experimental

4.1. General

Following instruments and materials were used for purification and characterization studies. Bruker DPX 400 spectrometer was used to record ^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ (triplet centered at 77.0 ppm at 100 MHz). Chemical shifts were represented as ppm taking tetramethylsilane as an internal standard. Spin multiplicities are expressed as; s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Rudolph Research Analytical Autopol III, automatic polarimeter was used for measuring Optical rotations; and Mel-Temp 1002D for determining melting points. ThermoFinnigan Spectra System instrument was used for HPLC measurements by making use of Chiralcel AD analytical column (250 × 4.60 mm) with hexane/2-propanol/TFA (70:30:0.1) as eluent. Flash column chromatography was done by employing thick-walled glass columns with a flash grade silica gel (Merck Silica Gel 60, particle size: 0.040–0.063 mm, 230–400 mesh ASTM). Reactions were monitored by thin layer chromatography by using pre-coated silica gel plates (Merck Silica Gel PF-254). In addition, generally EtOAc/hexane and DCM/MeOH solvent systems are used as the eluants in TLC and in flash column chromatography. Magnesium sulfate and sodium sulfate were used to dry organic extracts before they were concentrated on a rotary evaporator. Characterization data of novel compounds are given only. Chiral 2-aminoDMAP (**1**) was prepared according to published procedure.[10] The synthesis of mismatched 2-aminoDMAP/prolinamide (*S,S,L*)-**7** followed the same procedure as that of (*R,R,L*)-**7**.

4.2. Synthesis of 2-aminoDMAP/prolinamide (*R,R,L*)-7: Preparation of Cbz-protected intermediate

To a 100 mL flask, a 10 mL THF solution of *N*-carboxybenzoyl-protected (L)-Proline (311.4 mg, 1.25 mmol) was added at 0 °C. To this solution, triethylamine (118 μL, 1.25 mmol) and ethyl chloroformate (174.4 μL, 1.25 mmol) was added successively. After 2 h of stirring, 5 mL THF solution of (1*R*,2*R*)-2-aminoDMAP **1** (234 mg, 1 mmol) was added. After 45 min of vigorous stirring, the mixture was washed with saturated $NaHCO_3$ (15 mL). Mixture was extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using successively EtOAc, EtOAc/TEA (99:1), EtOAc/TEA (98:2) solvent systems. The product was obtained as a white solid (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (br s, 1H), 1.17–1.30 (m, 4H), 1.58 (d, J = 48.9 Hz, 3H), 1.81 (s, 1H), 1.92–2.01 (m, 4H), 2.81 (s, 6H), 3.07 (s, 1H), 3.29 (dd, J = 22.6, 44.4 Hz, 2H), 3.76 (s, 1H), 3.99–4.29 (m, 2H), 4.89–5.22 (m, 2H), 5.40 (d, J = 29.8 Hz, 1H), 5.79–5.96 (m, 1H), 7.23–7.33 (m, 5H), 7.57 (s, 1H), 7.69 (dd, J = 5.7, 10.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.1, 23.3, 23.5, 24.3, 32.5, 38.1, 52.0, 57.3, 60.1, 62.3, 65.8, 98.4, 98.9, 102.8, 126.8, 127.4, 135.6, 146.2, 146.7, 154.7, 158.7, 171.4. HRMS (ESI) calculated for $C_{26}H_{35}N_5O_3$ $[M+H]^+$ 466.2818, found 466.2831.

4.3. Synthesis of 2-aminoDMAP/prolinamide (*R,R,L*)-7: Deprotection of Cbz-group

To a 25 mL flask, evacuated and backfilled with argon twice, 10 mL MeOH solution of above-prepared Cbz-protected intermediate (318 mg, 0.677 mmol) was introduced. Then, 10% Pd/C (72 mg, 0.0677 mmol) was added to the flask, flushed with H_2 gas to replace argon. The mixture was then stirred at overnight under a balloon of H_2 gas. The black suspension was filtered through celite remove Pd/C, and washed with some MeOH before it was

concentrated in vacuo. The residue was purified by column chromatography on silica gel by using successively DCM, DCM/DCM–MeOH–NH_3 (90:9:1) (50:50), DCM–MeOH–NH_3 (90:9:1) solvent systems. The product was obtained as white solid (80% yield). Mp: 112–114 °C. $[\alpha]_D^{31} = -10.5$ (c 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–1.17 (m, 7H), 169–1.53 (m, 3H), 1.95–1.86 (m, 2H), 2.02 (d, J = 12.9 Hz, 1H), 2.47 (dt, J_{AB} = 6.4, 10.1 Hz, 1H), 2.72 (dt, J_{AB} = 10.1, 6.7 Hz, 1H), 2.84 (s, 6H), 3.53 (dd, J = 5.3, 9.2 Hz, 1H), 3.60 (ddd, J = 4.9, 9.9, 14.8 Hz, 1H), 3.79 (ddd, J = 4.0, 10.5, 18.7 Hz, 1H), 4.61 (br s, 1H), 5.45 (s, 1H), 5.90 (dd, J = 2.3, 6.2 Hz, 1H), 7.65 (d, J = 6.2 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.7, 24.8, 28.6, 29.7, 31.0, 32.1, 38.2, 45.9, 52.9, 53.3, 59.5, 87.5, 98.1, 145.6, 154.9, 158.2, 174.6. IR (neat) 3284, 2925, 2853, 1603, 1523, 1290, 1164. HRMS (ESI) calculated for $C_{18}H_{30}N_5O$ $[M+H]^+$ 332.2455, found 332.2450.

4.4. General procedure for asymmetric synthesis of Warfarin and derivatives, 6a–g

To a dry Schlenk tube, a DCM solution (1 mL) of 4-hydroxycoumarin **4** (16.2 mg, 0.1 mmol), α,β-unsaturated ketone **5a–g** (0.3 mmol), 2-aminoDMAP/prolinamide (*R,R,L*)-**7** (10–20 mol %), and β-naphthol (10 mol %) was added. The reaction mixture stirred at 10 °C for about 55–135 h. The progress of the reactions was monitored by TLC analysis. After the time given in the Scheme 2, the solution was loaded onto silica gel filled column to purify the desired product by using EtOAc/hexane (1:5) eluant systems. The product (88% yield) was obtained as white solid. The enantiomeric excess value of the products were measured by HPLC analysis on a Chiralcel AD or AS columns.

4.4.1. Data for 6a

The use of enone **5a** gave chiral Warfarin adduct **6a** in 80% yield in 55 h. HPLC analysis using with Chiralcel AD column, *n*-hexane/*i*-PrOH/TFA 70:30:0.1, flow rate 1 mL min^{-1}, λ = 254 nm, t_{major} = 4.5 min and t_{minor} = 8.5 min, 72% ee. The spectroscopic data are in accordance with the literature values.[14]

4.4.2. Data for 6b

The use of enone **5b** gave chiral Warfarin derivative **6b** in 70% yield in 68 hours. HPLC analysis using with Chiralcel AD column, *n*-hexane/*i*-PrOH/TFA 70:30:0.1, flow rate 1 mL min^{-1}, λ = 254 nm, t_{major} = 4.7 min and t_{minor} = 9.9 min, 63% ee. The spectroscopic data are in accordance with the literature values.[14]

4.4.3. Data for 6c

The use of enone **5c** gave chiral Warfarin adduct **6c** in 75% yield in 89 h. HPLC analysis using with Chiralcel AD column, *n*-hexane/*i*-PrOH/TFA 70:30:0.1, flow rate 1 mL min^{-1}, λ = 254 nm, t_{major} = 5.7 min and t_{minor} = 13.8 min, 58% ee. The spectroscopic data are in accordance with the literature values.[14]

4.4.4. Data for 6d

The use of enone **5d** gave chiral Warfarin adduct **6d** in 85% yield in 86 h. HPLC analysis using with Chiralcel AD column, *n*-hexane/*i*-PrOH/TFA 70:30:0.1, flow rate 1 mL min^{-1}, λ = 254 nm, t_{major} = 4.0 min and t_{minor} = 8.9 min, 63% ee. The spectroscopic data are in accordance with the literature values.[14]

4.4.5. Data for 6e

The use of enone **5e** gave chiral Warfarin adduct **6e** in 87% yield in 117 h. HPLC analysis using with Chiralcel AD column, *n*-hexane/*i*-PrOH/TFA 70:30:0.1, flow rate 1 mL min^{-1}, λ = 254 nm, t_{major} = 7.3 min and t_{minor} = 21.2 min, 60% ee. The spectroscopic data are in accordance with the literature values.[14]

4.4.6. Data for 6f

The use of enone **5f** gave chiral Warfarin adduct **6f** in 77% yield in 135 h. HPLC analysis using with Chiralcel AS column, *n*-hexane/EtOH/TFA 70:30:0.1, flow rate 1 mL min^{-1}, λ = 254 nm, t_{major} = 5.0 min and t_{minor} = 7.3 min, 69% ee. The spectroscopic data are in accordance with the literature values.[14]

4.4.7. Data for 6g

The use of enone **5g** gave chiral Warfarin adduct **6g** in 71% yield in 65 h. HPLC analysis using with Chiralcel AS column, *n*-hexane/EtOH/TFA 70:30:0.1, flow rate 1 mL min^{-1}, λ = 254 nm, t_{major} = 5.2 min and t_{minor} = 9.3 min, 58% ee. The spectroscopic data are in accordance with the literature values.[14]

Acknowledgements

This work was supported by the Science Development Foundation under the President of the Republic of Azerbaijan-GrantN-EIF-2013-9(15)-46 \ 23 \ 4.

References

1. (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley VCH: Weinheim, 2005; (b) Wang, Y.; Deng, L. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 3rd ed.; Wiley VCH: New York, 2010; pp 59–94; (c) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638; (d) Macmillan, D. W. C. *Nature* **2008**, *455*, 304; (e) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584.
2. Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.
3. Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
4. Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.
5. Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006.
6. Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558.
7. (a) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418; (b) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466; (c) Dobish, M. C.; Johnston, J. N. *Org. Lett.* **2010**, *12*, 5744; (d) Vara, B. A.; Struble, T. J.; Wang, W.; Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2015**, *137*, 7302; (e) Schwieter, K. E.; Johnston, J. N. *ACS Catal.* **2015**, *5*, 6559.
8. Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524.
9. For reviews see: (a) Ishikawa, T. *Superbases for Organic Synthesis*; Wiley: New York, 2009; (b) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737; For selected chiral superbase catalysis examples see: (c) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910; (d) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245; (e) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454; (f) Yu, Z.; Liu, X.; Zhou, L.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 5195; (g) Sohtome, Y.; Shin, B.; Horitsugi, N.; Takagi, R.; Noguchi, K.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 7299; (h) Sohtome, Y.; Tanaka, S.; Takada, K.; Yamaguchi, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 9254; (i) Chen, X.; Dong, S.; Qiao, Z.; Zhu, Y.; Xie, M.; Lin, L.; Liu, X.; Feng, X. *Chem. Eur. J.* **2011**, *17*, 2583; (j) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392; (k) Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012**, *134*, 19370; (l) Corbett, M. T.; Uraguchi, D.; Ooi, T.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 4685; (m) Takeda, T.; Terada, M. *J. Am. Chem. Soc.* **2013**, *135*, 15306; (n) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552; (o) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799; (p) Bandar, J. S.; Sauer, G. S.; Wulff, W. D.; Lambert, T. H.; Vetticatt, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 10700; (r) Bandar, J. S.; Barthelme, A. P.; Mazori, A. Y.; Lambert, T. H. *Chem. Sci.* **2015**, *6*, 1537; (s) Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348; (t) Farley, A. J. M.; Sandford, C.; Dixon, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 15992; (u) Goldys, A. M.; Núñez, M. G.; Dixon, D. J. *Org. Lett.* **2014**, *16*, 6294; (v) Fang, B.; Liu, X.; Zhao, J.; Tang, Y.; Lin, L.; Feng, X. *J. Org. Chem.* **2015**, *80*, 3332.
10. Isik, M.; Tanyeli, C. *J. Org. Chem.* **2013**, *78*, 1604.
11. Işık, M.; Unver, M. Y.; Tanyeli, C. *J. Org. Chem.* **2015**, *80*, 828.
12. Yazıcıoğlu, E. Y.; Tanyeli, C. *Tetrahedron: Asymmetry* **2012**, *23*, 1694.
13. For an indirect, early enantioselective synthesis that use chiral auxiliary approach, see: Demir, A. S.; Tanyeli, C.; Gülbeyaz, V.; Akgün, H. *Turk. J. Chem.* **1996**, *20*, 139.
14. Halland, N.; Hansen, T.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955.
15. Kim, H.; Yen, C.; Preston, P.; Chin, J. *Org. Lett.* **2006**, *8*, 5239.
16. Xie, J. W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J. G.; Chen, Y. C. *Org. Lett.* **2007**, *9*, 413.
17. Dong, Z. H.; Wang, L. J.; Chen, X. H.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Eur. J. Org. Chem.* **2009**, 5192.
18. Kristensen, T.; Vestli, K.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem.* **2009**, 5185.
19. Yang, H. M.; Li, L.; Jiang, K. Z.; Jiang, J. X.; Lai, G. Q.; Xu, L. W. *Tetrahedron* **2010**, *66*, 9708.
20. Wong, T. C.; Sultana, C. M.; Vosburg, D. A. *J. Chem. Ed.* **2010**, *87*, 194.
21. Rogozińska, M.; Adamkiewicz, A.; Mlynarski, J. *Green Chem.* **2011**, *13*, 1155.