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Substrate-Directed Stereoselectivity in Vicinal Diamine-Catalyzed Synthesis of Warfarin

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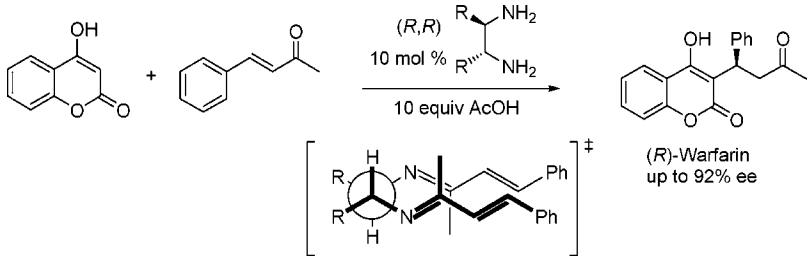
ABSTRACT



A new mechanism involving a diimine intermediate is proposed for vicinal diamine-catalyzed synthesis of warfarin. Decreasing the NCCN dihedral angle by varying the diamine results in an increase in the enantioselectivity of warfarin synthesis.

There has been much recent interest in developing stereoselective organocatalysts for making new carbon−carbon bonds.[1−3] In an elegant and innovative study,[4] a chiral imidazolidine (**1**) was used as a catalyst for stereoselective coupling of 4-hydroxycoumarin (**2**) and *trans*-4-phenyl-3-buten-2-one (**3**) to make warfarin (**4**), a widely prescribed anticoagulant used for treating thrombosis (Scheme 1).[5] However, the mechanism provided in the study[4] leads one to predict the sense of stereoselectivity for the reaction that is opposite to the one observed.[6] Our interest in finding the correct mechanism and the origin of stereoselectivity led us

(1) (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175. (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719−724. (c) List, B. *Acc. Chem. Res.* **2004**, *37*, 548−557. (d) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558−569. (e) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570−579. (f) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580−591.

(2) For selected organocatalytic conjugate additions to α,β-unsaturated ketones, see: (a) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975−2978. (b) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331−8338. (c) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661−665. (d) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151−4157. (e) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272−1277. (f) Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958−3960. (g) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598−11599. (h) Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036−15037. (i) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028−16029. (j) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897−3900.

(3) For selected organocatalytic conjugate additions to α,β-unsaturated aldehydes, see: (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172−1173. (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894−7895. (c) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192−1194. (d) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051−15053. (e) Wang, W.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 1637−1639. (f) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437−3440. (g) Xie, J.-W.; Yue, L.; Xue, D.; Ma, X.-L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Chem. Commun.* **2006**, 1563−1565.

(4) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955−4957.

(5) For stereoselective warfarin synthesis, see: (a) Demir, A. S.; Tanyeli, C.; Gülbeyaz, V.; Akgün, H. *Turk. J. Chem.* **1996**, *20*, 139−145. (b) Robinson, A.; Li, H.-Y.; Feaster, J. *Tetrahedron Lett.* **1996**, *37*, 8321−8324. (c) Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Tetradedron: Asymmetry* **2001**, *12*, 707−709.

(6) In Figure 1 (right) of the original report,[4] the (*R*,*R*) form of the imidazolidine catalyst forms an aminal intermediate with the ketone substrate. According to this figure, hydroxycoumarin is expected to attack from the *Si* face since the *Re* face is blocked. This leads one to predict that the (*R*,*R*) form of the catalyst would give the *S* form of warfarin in conflict with the experimental result (Table 1 of the original report).

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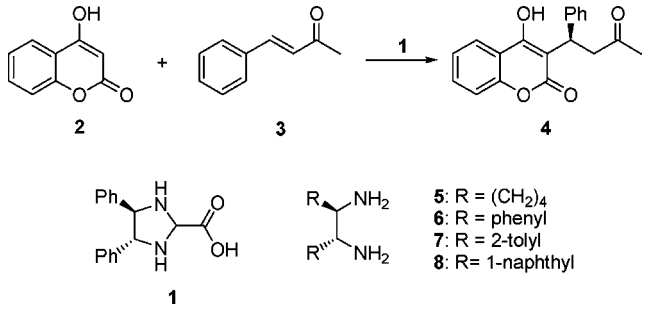
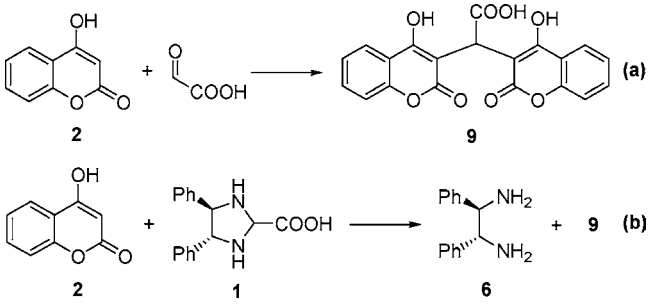
to investigate chiral vicinal diamine (**5**−**8**) catalyzed synthesis of warfarin. Compounds **7** and **8** were synthesized[7] in enantiomerically pure form using our general method for making chiral diamines (see the Supporting Information).

Scheme 1. Synthesis of Optically Active Warfarin



Coumarin dimers (**9**) can be prepared from the reaction of 4-hydroxycoumarin with a variety of alkyl and aryl aldehydes including glyoxylic acid (Scheme 2a).[8] We find

Scheme 2. Formation of Coumarin Dimer



that imidazolidines (including **1**) formed from diphenylethylenediamine (dpen or **6**) and aldehydes also react with 4-hydroxycoumarin (**2**) to give coumarin dimers and **6** (Scheme 2b). Thus, **1** may not be the actual catalyst for making warfarin from **2** and **3** as previously thought. It may be that dpen (**6**) formed from the reaction of **2** and **1** is the true catalyst for making warfarin. Indeed, **6** and **5** (1,2-diaminocyclohexane) have already been shown to be catalysts for making warfarin.[9]

When **2** is added to **1** (20 mol %) dissolved in THF, the coumarin dimer (**9**) and dpen (**6**) are formed cleanly and to completion within 24 h at ambient temperature as shown by ^{1}H NMR (Supporting Information).[10] When **2** (Figure 1;

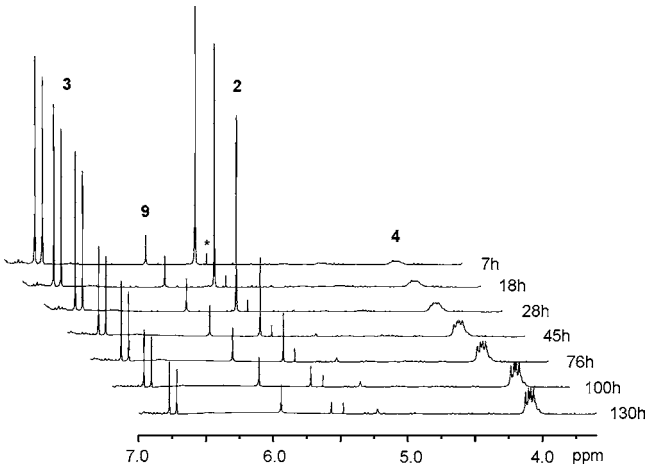


Figure 1. ^{1}H NMR spectra of the reaction mixture of **1**−**3** taken in THF-d_8. Time-dependent change in signals due to compounds **3**, **9**, **2**, and **4**. CH_2Cl_2 (*) as reference.

C−H next to carbonyl) and **3** (Figure 1; vinyl C−H next to the carbonyl group) are added together to **1** (10 mol %) in THF-d_8 (1 mL), warfarin (**4**; C−H at the chirality center) synthesis lags considerably behind the formation of the coumarin dimer (**9**; alkyl C−H). These data provide interesting insights into the mechanism and the origin of stereoselectivity in vicinal diamine-catalyzed synthesis of warfarin (**4**) as shown in Figure 2.

Although the imidazolidine (**1**) breaks down to **6** and **9** rapidly during the catalytic synthesis of warfarin (Figure 1, Scheme 2b), the stereoselectivity is significantly lower (50% vs 78% ee) when the diamine (**6**) is used instead of the imidazolidine (**1**) to make the drug. We reasoned that the carboxylic acid group in **9** may be acting as a cocatalyst and enhancing the stereoselectivity of the diamine (**6**) catalyzed synthesis of warfarin. Indeed, acetic acid not only increases the rate but also dramatically increases the stereoselectivity for **6**-catalyzed synthesis of warfarin (Table 1, entries 3 and 4). In contrast, acetic acid does not increase the rate or the stereoselectivity of **5**-catalyzed synthesis of warfarin (entries 1 and 2). The more basic alkyl diamine (**5**) is more reactive than the less basic aryl diamines (**6**−**8**) and does not require the cocatalyst.[11] The effect of acetic acid has not been reported in the previous study involving **5**- and

(7) (a) Kim, H.-J.; Kim, H.; Alhakimi, G.; Jeong, E. J.; Thavarajah, N.; Studnicki, L.; Koprianiuk, A.; Lough, A. J.; Suh, J.; Chin, J. *J. Am. Chem. Soc.* **2005**, *127*, 16370−16371. (b) Kim, H.-J.; Kim, W.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2005**, *127*, 16776−16777. (c) Chin, J.; Mancin, F.; Thavarajah, N.; Lee, D.; Lough, A. J.; Chung, D. S. *J. Am. Chem. Soc.* **2003**, *125*, 15276−15277.

(8) (a) Sullivan, W. R.; Huebner, C. F.; Stahmann, M. A.; Link, K. P. *J. Am. Chem. Soc.* **1943**, *65*, 2288−2291. (b) Khan, K. M.; Iqbal, S.; Lodhi, M. A.; Maharvi, G. M.; Ullah, Z.-; Choudhary, M. I.; Rahman, A.-u.-; Perveen, S. *Bioorg. Med. Chem.* **2004**, *12*, 1963−1968.

(9) Halland, N.; Jørgensen, K. A.; Hansen, T. PCT Int. Appl. 2003 WO 03/050105.

(10) Solubility of **1** in THF is low. The NMR solution becomes clear once **1** is used up to form **9**. Compound **6** does not accumulate to an observable extent during the catalytic reaction. Reaction of **1** and **2** to give **6** and **9** in DMSO-d_6 can be monitored by ^{1}H NMR (Supporting Information).

(11) It may be that the rate-determining step for **6**-catalyzed synthesis of warfarin is the imine formation step and is acid catalyzed. In contrast, it appears that for **5**-catalyzed synthesis of warfarin, the imine formation step is fast and not rate determining. Background reaction involving direct addition of **2** to **3** should lower the stereoselectivity. Acetic acid is expected to increase the stereoselectivity by facilitating and activating the diimine pathway.

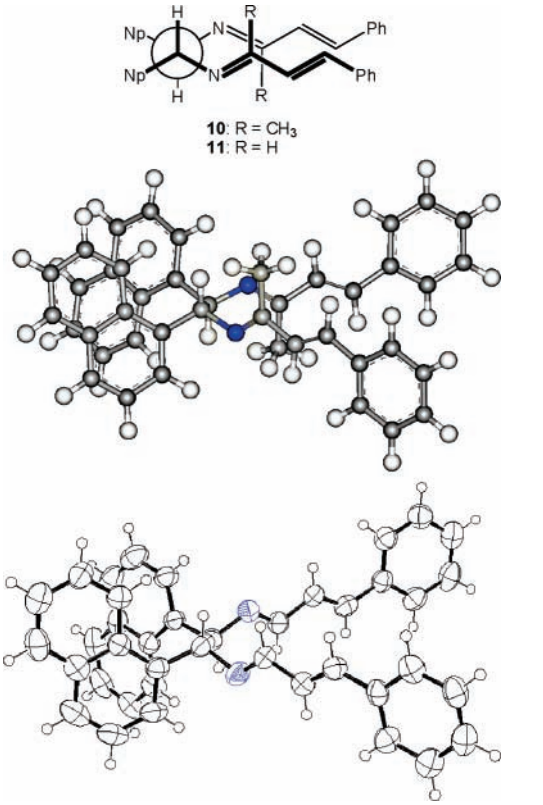


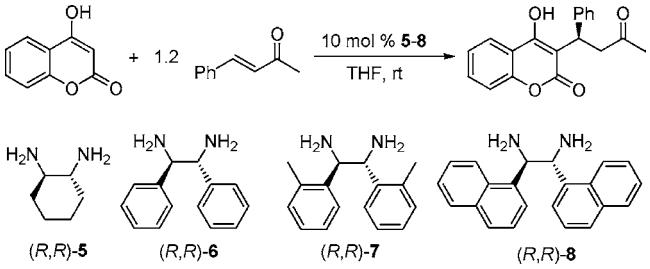
Figure 2. (a) Global energy minimum structure of **10**. (b) Crystal structure of **11** (50% thermal ellipsoid).

6-catalyzed synthesis of warfarin.[9] We compared **5**−**8**-catalyzed synthesis of warfarin with added acetic acid. In a typical experiment, 10 mol % of the diamine was mixed with **2**, **3**, and acetic acid (10 fold excess) in 1 mL of THF and stirred at ambient temperature for 1 day. Chiral HPLC was used to determine the enantiomeric excess of the product (Supporting Information). All of the diamines gave the same sense of stereoselectivity for the synthesis of warfarin albeit with a range of selectivity (47% to 92% ee). Thus, a single unified mechanism appears to be operating for the synthesis of warfarin by all of the diamines.

We propose that the mechanism of vicinal diamine-catalyzed synthesis of warfarin involves the formation of the diimine intermediate (**10**) from the diamine and the ketone substrate (**3**). ^{1}H NMR and ESI show that addition of acetic acid to **3** and dpen (**6**) dissolved in $CDCl_3$ results in complete conversion of the diamine to the corresponding diimine (Supporting Information). In order to gain some insight into the origin of stereoselectivity in the diamine-catalyzed synthesis of warfarin, we determined the global energy minimum structure (Figure 2a, DFT computation at the B3LYP/6-31G* level)[12] of the diimine intermediate (**10**). Michael addition of 4-hydroxycoumarin (**2**) to **10** followed by hydrolysis of the imine moiety is expected to give

(12) Density functional theory (DFT) calculation was performed using Spartan '04 Windows from Wavefunction, Inc. NCCN dihedral angles were obtained by molecular mechanics computation using the same software.

Table 1. Effect of Catalyst and Acetic Acid on Warfarin Synthesis



entry	catalyst	AcOH (equiv)	time (h)	yield[a] (%)	ee[b] (%)	angle[c] (deg)
1	(*R*,*R*)-**5**		12	98	54 (*R*)	
2	(*R*,*R*)-**5**	10	24	98	47 (*R*)	69
3	(*R*,*R*)-**6**		48	88	50 (*R*)	
4	(*R*,*R*)-**6**	10	48	94	86 (*R*)	52
5	(*R*,*R*)-**7**	10	24	99	92 (*R*)	46
6	(*R*,*R*)-**8**	10	24	97	88 (*R*)	52

[a] Yield of product isolated after flash chromatography. [b] Determined by HPLC using a Chiralpak AD-H column. [c] NCCN dihedral angle obtained by computation.[12]

warfarin. Although we were not able to obtain the crystal structure of the putative intermediate, the crystal structure of the diimine (**11**) formed between the diamine (**8**) and cinnamaldehyde was obtained as a model for the intermediate (Figure 2b).[13] There is excellent agreement between the computed structure of the proposed intermediate and the crystal structure of its model. Both compounds (**10** and **11**, Figure 2a and b) show extended structures with the two imine groups facing each other in a parallel fashion. In case of the diimine formed from the (*R*,*R*)-diamine, the two *Si* faces of the diimine (at the Michael attack position) are facing each other with the two *Re* faces exposed for nucleophilic attack by 4-hydroxycoumarin. Thus, *R*-warfarin is expected to be the major product in the (*R*,*R*)-diamine-catalyzed reaction. Indeed, we find that in the (*R*,*R*)-**8**-catalyzed reaction, *R*-wafarin is the major product (88% ee, 97% yield). The explanation given in the original study for **1**-catalyzed synthesis of warfarin leads one to predict the (*R*,*R*)-catalyst to give the *S*-warfarin in contrast to the *R*-warfarin observed.[4,6] If (*R*,*R*)-**1** was to be first converted to the corresponding (*R*,*R*)-diamine (**6**) according to Scheme 2b, the diamine is expected to catalyze the formation of *R*-warfarin as observed.

In the proposed intermediate (**10**) for the diamine-catalyzed synthesis of warfarin, the stereoselectivity is expected to be at its greatest when there is maximum overlap between the two extended imines. In the diimine formed from **5**, the overlap between the two imines is expected to be poor as the value of the computed[12] NCCN dihedral angle (69°) is too large (Table 1, last column). Furthermore, the dihedral

(13) Crystal structure of **11**: $C_{40}H_{32}N_2$, T = 150(2) K, monoclinic, *C2/c*, Z = 8, a = 36.957(3) Å, b = 9.8273(9) Å, c = 16.7524(17) Å, α = 90°, β = 104.949(4)°, γ = 90°, V = 5878.3(9) Å^3, R_1 = 0.0836, wR_2 = 0.1979 for $I > 2\sigma(I)$, GOF on F^2 = 1.019.

angle is rigidly held apart by the cyclohexane ring. In contrast, the values of the computed NCCN dihedral angles in the aryl diimines formed from **6**−**8** are smaller (46−52°) and more flexible. The smallest dihedral angle (46°) is found for the diimine formed with **7**, which also gives the best stereoselectivity for warfarin synthesis (92% ee Table 1).

In conclusion, we have shown that **1** is converted to dpen during the stereoselective synthesis of warfarin from **2** and **3**. We suggest that dpen (**6**) rather than **1** is the stereoselective catalyst since it is difficult to explain the observed sense of stereoselectivity in terms of **1** catalyzed synthesis of warfarin. Several vicinal diamines (**6**−**8**) have been shown to catalyze the stereoselective synthesis of warfarin. Acetic acid significantly enhances the reactivity and stereoselectivity of 1,2-diaryl-1,2-diaminoethanes (from about 50% ee to 90% ee). Furthermore, the stereoselectivity increases with decrease in the value of the NCCN dihedral angle of the proposed diimine intermediate (**10**). The observed sense of stereoselectivity for the diamine catalyzed synthesis of warfarin can be explained in terms of the computed structure of the diimine intermediate (**10**) and the crystal structure of an analog of this intermediate (**11**). These studies show that two substrates bound to the diamine catalyst control the stereoselectivity of warfarin synthesis.

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Supporting Information Available: Experimental data including crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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