Asymmetric Michael Addition

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**

*Nis Halland, Tore Hansen, and Karl Anker Jørgensen**

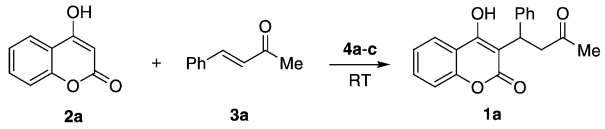
As optically active drugs become increasingly important for the treatment of diseases in patients, still more enantiopure drugs are introduced to the market either as new drugs or as the result of a racemic switch. An important goal for asymmetric catalysis is to develop new reactions that afford optically active compounds from simple and easily available starting materials and catalysts. However, the ultimate goal would be if the new reaction could be used directly for a one-step synthesis of optically active molecules that have important biological and pharmaceutical activities. Herein we present such an advance and its direct application in an atom-economic synthesis of optically active drugs based on the development of a new organocatalytic enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated ketones.[1]

The present development leads to a catalytic enantioselective one-step procedure for the formation of one of the most widely used anticoagulants, warfarin (coumadin), and related important compounds. Warfarin has been prescribed as a racemate for more than 40 years and it is well-known that the anticoagulant activity of the *S* enantiomer is about 5–8 times higher than of the *R* enantiomer.[2] Furthermore, the enantiomers are metabolized by different pathways, which is reflected by the different half-lives in the human body, 21–43 and 37–89 h, for (*S*)- and (*R*)-warfarin, respectively.[2] Due to these very different half-lives, one of the major problems with racemic warfarin is the delivery and maintenance of a stable dose as too high doses might lead to internal hemorrhages in the patient. The dosage problem is further complicated by the fact that the peak pharmacological effect of a single dose is not achieved until after approximately 48 h, and the pharmacological effect lasts 4–5 days. As patients respond differently, it is expected that treatment of patients with optically pure warfarin will reduce the dosage problem. Another advantage of optically pure warfarin would be that weakened patients unable to tolerate the stronger racemic or (*S*)-warfarin could be treated with the milder (*R*)-warfarin.[3] However, probably the most important advantage of administering optically pure warfarin is the possibility of eliminating drug–drug interactions, which represents another serious problem with racemic warfarin, as enzymes that are responsible for metabolizing warfarin also metabolize many other drugs.[2]

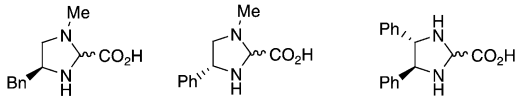
Three different approaches towards the synthesis of optically active warfarin have been reported: Demir et al. used a diastereoselective Michael addition in which chiral enamines of 4-hydroxycoumarin were treated with benzylideneacetone in the presence of LDA and superstoichiometric amounts of Lewis acid to obtain warfarin in moderate yield and enantiomeric excess.[4] Li and co-workers at DuPont Merck Pharmaceutical Company obtained enantioenriched warfarin from racemic warfarin through an oxidation procedure and subsequent asymmetric hydrogenation.[5] The diastereoselective synthesis by Cravotto et al. involved a tandem Knoevenagel/hetero-Diels–Alder approach; however, yields were low owing to the somewhat lengthy synthesis.[6]

Herein we present, besides the development of a new organocatalytic enantioselective reaction, a simple, effective and highly atom-economical synthesis of optically active warfarin (**1a**) from 4-hydroxycoumarin (**2a**) and benzylideneacetone (**3a**) in the presence of imidazolidine catalysts (Table 1).[7] Furthermore, the scope and potential of this new one-step, organocatalytic enantioselective Michael addition is demonstrated by the formation of a number of important

Table 1: Screening of catalysts for the organocatalytic asymmetric formation of **1a**.[a]



2a **3a** **1a**



4a **4b** (*S*,*S*)-**4c**

Entry	Catalyst	[mol%]	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	(*S*)-proline	50	DMSO	15	85	0
2	**4a**	10	CH_2Cl_2	70	77	62 (*S*)
3	**4a**	5	THF	70	85	70 (*S*)
4	**4a**	10	EtOH	70	69	47 (*S*)
5	**4a**	10	H_2O	90	22	49 (*S*)
6	**4b**	10	THF	130	83	56 (*R*)
7	(*R*,*R*)-**4c**	10	CH_2Cl_2	150	96	82 (*R*)[d]
8	(*S*,*S*)-**4c**	10	THF	130	90	80 (*S*)[d]

[a] Experimental conditions: A mixture of **3a** (0.5 mmol), **2a** (0.525 mol, 1.05 equiv), and the catalyst was stirred at ambient temperature for the time indicated. The crude mixture was then purified by flash chromatography. [b] Yield of product isolated after flash chromatography. [c] Enantiomeric excess determined by CSP-HPLC. The absolute configuration of the major enantiomer is indicated in parentheses. [d] Enantiomeric purity increased to >99.9% by a single recrystallization in acetone/water.

[*] Prof. Dr. K. A. Jørgensen, Dr. N. Halland, Dr. T. Hansen
The Danish National Research Foundation:
Center for Catalysis, Department of Chemistry
Aarhus University
8000 Aarhus C (Denmark)
Fax: (+45) 8919-6199
E-mail: kaj@chem.au.dk

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Supporting information for this article (including films of hearts before and after treatment) is available on the WWW under http://www.angewandte.org or from the author.

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optically, biologically, and pharmaceutically active compounds.

We envisioned that the imidazolidine catalysts **4a–c**[8] would be efficient catalysts for the addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds. Table 1 shows some screening results for the reaction of **2a** with **3a**.

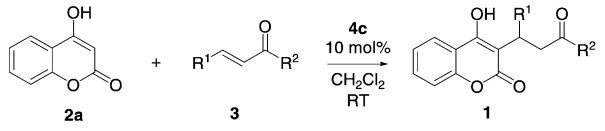
Initially, (*S*)-proline was investigated as the organocatalyst, but only racemic warfarin (**1a**) was obtained (Table 1, entry 1). We then turned our attention to the amino acid derived imidazolidine catalysts **4a,b**. To our delight we found that when the reaction was catalyzed by **4a**, optically active **1a** was formed in high yields with up to 70% *ee* (Table 1, entries 2–5). However, organocatalyst **4c**, formed by the condensation of 1,2-diphenylethanediamine with glyoxylic acid, proved to be superior to **4a,b**, and **1a** was obtained with up to 82% *ee* (Table 1, entries 7 and 8). In all cases the reaction proceeded smoothly at ambient temperature in the absence of an external base and without the formation of any by-products. To improve the enantiomeric purity of the Michael adduct, a single recrystallization from a water/acetone mixture provided the enantiopure (>99.9% *ee*) warfarin **1a** when starting from a sample with 79% *ee*.

This new organocatalytic asymmetric Michael reaction also proceeds on a kilogram scale when catalyzed by imidazolidine **4a** without any decrease in yield or enantioselectivity. Recycling of the catalyst was also possible, and thus the reaction provides very easy and inexpensive access to large quantities of enantiopure warfarin.

The scope of the present organocatalytic asymmetric Michael reaction using catalyst **4c** was extended to various α,β-unsaturated enones and the results are given in Table 2. The results in Table 2 demonstrate that the Michael addition of **2a** to a number of α,β-unsaturated enones **3b–i** that bear alkyl, branched alkyl, as well as various aromatic and heteroaromatic R^1 substituents proceeds smoothly to afford Michael adducts **1b–i** in high yields and enantioselectivities. The ketone substituent (R^2) could also be varied from methyl to ethyl and isopropyl; although a slightly lower yield of the Michael adduct **1k** was obtained, good enantioselectivities were maintained.

To extend the scope of the reaction further, several other cyclic 1,3-dicarbonyl compounds were utilized as Michael donors in the reaction with benzylideneacetone (**3a**) in the presence of catalyst **4c** (Table 3). The Michael reaction proceeded in good yields and with high enantioselectivities when using 4-hydroxycoumarin bearing either electron-withdrawing or electron-donating substituents (Table 3, entries 1–4), as well as when using 1-thio-4-hydroxycoumarin **2f**

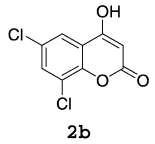
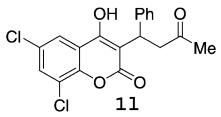
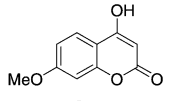
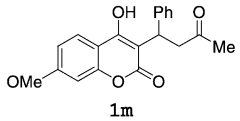
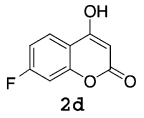
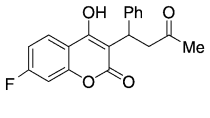
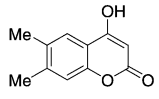
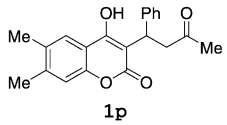
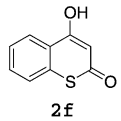
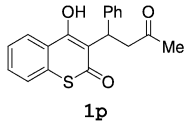
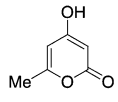
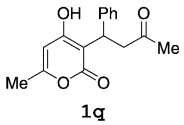
Table 2: Organocatalytic asymmetric Michael addition of **2a** to α,β-unsaturated enones **3b–k**.[a]



Entry	R^1	R^2	**3**	Catalyst	*t* [h]	**1**	Yield [%]	*ee* [%][b]
1	4-ClPh	Me	**b**	(*S*,*S*)-**4c**	130	**b**	86	82 (*S*)[c]
2[d]	4-ClPh	Me	**b**	(*S*,*S*)-**4c**	200	**b**	68	87 (*S*)
3	4-NO_2Ph	Me	**c**	(*S*,*S*)-**4c**	130	**c**	81	83 (*S*)
4	4-MeOPh	Me	**d**	(*S*,*S*)-**4c**	160	**d**	91	82 (*S*)[e]
5	2-Np	Me	**e**	(*S*,*S*)-**4c**	130	**e**	81	83 (*S*)[e]
6	*n*Bu	Me	**f**	(*R*,*R*)-**4c**	60	**f**	99	84 (*S*)[e]
7	*i*Pr	Me	**g**	(*S*,*S*)-**4c**	90	**g**	77	83 (*S*)[e]
8	2-thienyl	Me	**h**	(*R*,*R*)-**4c**	150	**h**	78	79 (*R*)[e]
9	2-furyl	Me	**i**	(*R*,*R*)-**4c**	150	**i**	75	75 (*R*)[e]
10	Ph	Et	**j**	(*S*,*S*)-**4c**	130	**j**	84	88 (*S*)[e]
11	Ph	*i*Pr	**k**	(*S*,*S*)-**4c**	180	**k**	71	85 (*S*)[e]

[a] Experimental conditions: The reaction mixture was treated with catalyst **4c** (10 mol%) in CH_2Cl_2 at ambient temperature for the time indicated. [b] Enantiomeric excess determined by CSP-HPLC. The absolute configuration of the major enantiomer is indicated in parentheses. [c] Enantiomeric purity increased to >99.9% *ee* after a single recrystallization in acetone/water. [d] Performed at 10°C. [e] Absolute stereochemistry assigned by analogy to **1a–c**.

Table 3: Organocatalytic asymmetric Michael addition of Michael donors **2b–g** to dibenzylideneacetone (**3a**).[a]

Entry	Michael donor	Michael adduct	Yield [%][b]	*ee* [%][c]
1[d]	 **2b**	 **1l**	65	79
2	 **2c**	 **1m**	81	85
3	 **2d**	 **1n**	68	83
4	 **2e**	 **1p**	84	85
5	 **2f**	 **1p**	84	78
6	 **2g**	 **1q**	76	85

[a] Reaction conditions: The reaction mixture was treated with catalyst (*S*,*S*)-**4c** (10 mol%) in CH_2Cl_2 at ambient temperature for 150 h. [b] Yield of product isolated after flash chromatography. [c] Enantiomeric excess determined by CSP-HPLC. [d] Performed in THF.

(Table 3, entry 5) and 4-hydroxy-6-methylpyrone **2g** (Table 3, entry 6) as Michael donors.

The absolute configuration of coumachlor (**1b**) was determined by X-ray crystallographic analysis (see Supporting Information)[9] and by comparison of optical rotation for warfarin (**1a**)[10a] and acenocoumarin (**1c**).[10b] The observed stereochemical outcomes of the reactions catalyzed by **4a** is in accordance with previously proposed iminium-ion intermediates for the imidazolidine-catalyzed Michael reaction.[7g,h] For the imidazolidine catalyst (*S,S*)-**4c**, both an iminium-ion and an aminal intermediate species can be envisaged. Optimization using PM3 calculations show very little shielding of the alkene for the iminium-ion intermediate (Figure 1a).[11] On

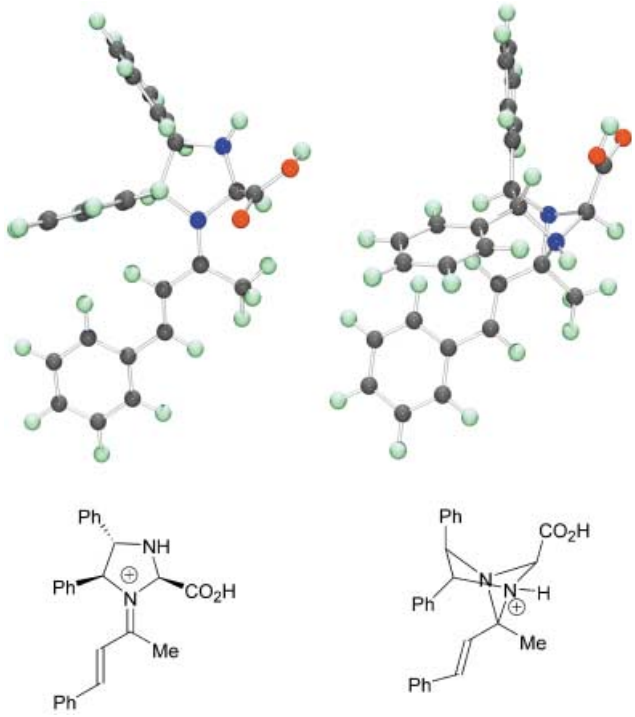


Figure 1. Possible intermediates for imidazoline-catalyzed Michael reaction. Left: iminium ion intermediate. Right: aminal intermediate.

the other hand, the bicyclic protonated aminal intermediate, formed by a nucleophilic displacement of the hemiaminal species, shows very good shielding of the *Re* face of the alkene (Figure 1b). The alkene fragment in the latter intermediate is activated[11] for addition of the 1,3-dicarbonyl compound and thus provides a possible explanation for the observed stereochemistry in the reaction.

In summary we have developed the first organocatalytic asymmetric Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated enones. This versatile and environmentally friendly Michael reaction affords warfarin and other Michael adducts in high yields and enantioselectivities in the presence of an easily available organic catalyst. Furthermore, it was demonstrated that enantiopure products could be obtained by a single recrystallization.

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[8] Catalysts were formed by condensation of commercially available glyoxylic acid with the corresponding diamine (see Supporting Information).

[9] CCDC-212540 and 212541 contain the supplementary crystallographic data for this paper (**1a** and **1b**, respectively). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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[11] PM3 calculations were performed by using the PC Spartan software. The alkene part in the hemiaminal species is significantly more activated (lower LUMO energy) towards nucleophilic addition than the alkene part in benzylideneacetone.

