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Highly effective and enantioselective Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketones promoted by simple chiral primary amine thiourea bifunctional catalysts

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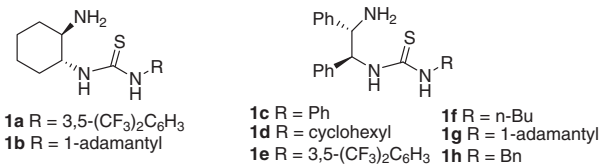
ABSTRACT

Highly asymmetric Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketones promoted by chiral primary amine thiourea bifunctional catalysts was developed and a series of Michael adducts were obtained in excellent yields (up to 97%) and enantioselectivities (up to 95% ee). Optically pure *S*-warfarin was easily obtained in 99% ee after single recrystallization.

The asymmetric Michael addition was considered as one of the most powerful and efficient methods for C–C bond formation in organic synthesis.[1] Particularly, the addition of 4-hydroxycoumarin to α,β-unsaturated ketones is a straightforward method to access *S*-warfarin **4a** which is an effective and relatively safe agent for preventing thrombosis and embolism and its anticoagulant activity is 5–8 times higher than that of *R*-enantiomer.[2] In 2003, Jørgensen reported the first example of enantioselective Michael reaction of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated ketones catalyzed by imidazolidine in good enantioselectivities (up to 85% ee).[3a] Chin demonstrated that chiral diamine using acetic acid as co-catalyst could afford similar or better results (up to 92% ee) compared with imidazolidine[3b] catalyst. Chen reported the highest enantioselectivity (99% ee) of *S*-warfarin and related analogues for the same addition catalyzed by 9-amino-9-deoxyepiquinine at 0 °C for four days.[3c] Recently, Feng developed a new type of C_2-symmetric secondary amine amide catalysts and good (up to 89% ee) enantioselectivies were obtained.[3d] Although several efficient methods have been achieved by these systems,[3] the highly efficient protocols of asymmetric Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketones for the preparation of *S*-warfarin and its analogues are still commercially needed. It is still desirable and challenging to develop simple, cheap, and commercially available and effective catalytic systems for this conversion.

In the past few years, bifunctional chiral thiourea catalysts have been proven to be effective in asymmetric Michael addition.[4] Among them, chiral primary amine thiourea catalysts were considered as powerful tools in many asymmetric procedures for the simultaneous activation of donors and acceptors and have been extensively investigated in asymmetric Michael additions.[5] Based on this background, we envisioned that the primary amine thiourea catalysts (**1a**–**h**; Fig. 1), which can be easily prepared from cheaply and commercially available chiral diamines, could activate the α,β-unsaturated ketones via an imine or enamine intermediate and 4-Hydroxycoumarin via H-bonding pathway as a double and synergetic catalysis. As part of our continuing interests in asymmetric synthesis[6] and pharmaceutical preparations,[7] herein we wish to report the enantioselective conjugate addition of 4-hydroxycoumarin to α,β-unsaturated ketones catalyzed by this kind of bifunctional catalysts to give *S*-warfarin and its analogues in high yields (up to 97%) and enantioselectivities (up to 95% ee) under mild conditions.

Initially, the reaction of 4-hydroxycoumarin (**2**) with benzylideneacetone (**3a**) was used as a model reaction and a series of chiral primary amine thiourea catalysts (**1a**–**h**; Fig. 1) were investigated at room temperature in CH_2Cl_2, and the results are summarized in Table 1. All catalysts gave moderate to good yields (49–92%) and enantioselectivitites (48–92% ee). Relatively, catalysts with 1,2-diphenylethane-1,2-diamine moiety (**1c**–**h**) gave higher ee values (75–92% ee, Table 1, entries 3–8) than those with diaminocyclohexane moiety (48% ee and 61% ee, Table 1, entries 1 and 2). Catalyst **1h**, giving the highest enantioselectivity and good yield (Table 1, entry 8, 92% ee, 87% yield), was selected for further optimizations.



1a R = 3,5-$(CF_3)_2C_6H_3$
1b R = 1-adamantyl
1c R = Ph
1d R = cyclohexyl
1e R = 3,5-$(CF_3)_2C_6H_3$
1f R = n-Bu
1g R = 1-adamantyl
1h R = Bn

Figure 1. Primary amine thiourea catalysts.

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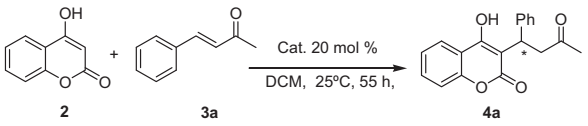
Table 1
The screening of chiral bifunctional catalysts **1a**–**h**[a]

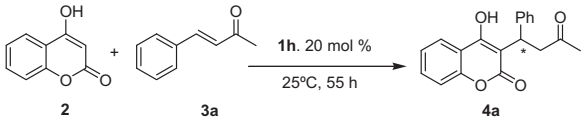


Entry	Catalyst	Yield[b] (%)	ee[c] (%)
1	**1a**	49	48 (*R*)[d]
2	**1b**	84	61 (*R*)
3	**1c**	89	86 (*S*)
4	**1d**	91	88 (*S*)
5	**1e**	84	89 (*S*)
6	**1f**	89	75 (*S*)
7	**1g**	92	89 (*S*)
8	**1h**	87	92 (*S*)

[a] Unless noted otherwise, the reactions were carried out with **2** (0.20 mmol) and **3a** (0.24 mmol) in the presence of the catalyst (20 mol %) in CH_2Cl_2 (1.5 mL) at 25 °C for 55 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] The absolute configuration was determined by comparing with the literature (Ref. 8).

To further improve the enantioselectivity, a series of solvents and additives were investigated and the results were listed in Table 2. The results indicated that solvents have remarkable effects on the yields and enantioselectivities (Table 2, entries 1–12). Aprotic solvents, such as CH_2Cl_2, $CHCl_3$, toluene and 1,4-dioxane gave good to excellent enantioselectivities and moderate to excellent yields (79–95% ee, 31–97% yield, Table 2, entries 1–9), whereas protic solvents, such as CH_3OH and *t*-BuOH gave moderate enantioselectivities (50% ee and 18% ee, Table 2, entries 10 and 12). Remarkably, when 1,4-dioxane was used, the highest yield (97%) and enantioselectivity (95% ee, Table 2, entry 8) were observed. The effects of additives were also investigated and are summarized in Table 2 (Table 2, entries 13–17). TFA has a significantly negative effect on the yield (29%, Table 2, entry 13), contrary to the reported

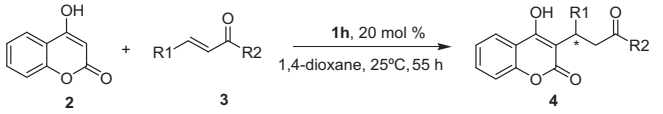
Table 2
The screenings of solvents and additives[a]



Entry	Solvent	Additive (mol %)	Yield[b] (%)	ee[c] (%)
1	Toluene	—	68	92
2	$ClCH_2CH_2Cl$	—	81	86
3	CH_2Cl_2	—	87	92
4	$CHCl_3$	—	69	87
5	Et_2O	—	76	87
6	EtOAc	—	84	90
7	THF	—	63	90
8	1,4-Dioxane	—	97	95
9	Acetonitrile	—	31	79
10	*t*-Butyl alcohol	—	25	18
11	DMF	—	31	18
12	MeOH	—	76	50
13	1,4-Dioxane	TFA (40)	29	90
14	1,4-Dioxane	DMAP (20)	94	91
15	1,4-Dioxane	Et_3N (40)	92	80
16	1,4-Dioxane	Et_3N (20)	90	89
17	1,4-Dioxane	Et_3N (10)	95	92

[a] Unless noted otherwise, the reactions were carried out with **2** (0.20 mmol) and **3a** (0.24 mmol) in the presence of catalyst **1h** (20 mol %) in solvent (1.5 mL) for 55 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.

Table 3
Asymmetric Michael Addition of 4-hydroxycoumarin 2 to α,β-unsaturated ketones **3a**[a]



Entry	R_1	R_2 (3)	4	Yield[b] (%)	ee[c] (%)
1	Ph	Me (**3a**)	**4a**	97	95 (>99%)[d]
2	3-FC_6H_4	Me (**3b**)	**4b**	92	91
3	4-FC_6H_4	Me (**3c**)	**4c**	89	91
4	2-ClC_6H_4	Me (**3d**)	**4d**	95	88
5	4-ClC_6H_4	Me (**3e**)	**4e**	92	92
6	4-BrC_6H_4	Me (**3f**)	**4f**	93	93
7	3-$NO_2C_6H_4$	Me (**3g**)	**4g**	89	89
8	4-$NO_2C_6H_4$	Me (**3h**)	**4h**	96	91
9	2-$MeOC_6H_4$	Me (**3i**)	**4i**	87	93
10	4-$MeOC_6H_4$	Me (**3j**)	**4j**	80	90
11	4-MeC_6H_4	Me (**3k**)	**4k**	90	92
12	2-Furanyl	Me (**3l**)	**4l**	87	88
13	2-Thienyl	Me (**3m**)	**4m**	88	86
14	1-Naphthyl	Me (**3n**)	**4n**	83	89
15	Ph	Et (**3o**)	**4o**	96	88

[a] The reaction mixture of **2** (0.20 mmol) with **3** (0.24 mmol), **1h** (0.04 mmol) in 1.5 mL 1,4-dioxane at 25 °C for 55 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] After single recrystallization from EtOH.

results.[3c] Organic bases, such as DMAP and Et_3N, were also used and the same negative effects on the enantioselectivities of warfarin were observed.

Those screenings showed that 20 mol % of catalyst **1h**, 0.20 mmol of 4-hydroxycoumarin (**2**), 0.24 mmol of benzylideneacetone (**3a**) in 1.5 mL of 1,4-dioxane at 25 °C for 55 h may give the best results in both yield and enantioselectivity and were selected as the optimal parameters for further study.

Under the optimized reaction conditions, a wide range of α,β-unsaturated ketones were investigated and the results are shown in Table 3. All the additions were performed smoothly to afford Michael adducts in excellent yields (up to 97%) and good to excellent enantioselectivities (88–93% ee). Naphthyl α,β-unsaturated ketones, as well as aromatic α,β-unsaturated ketones with electron-withdrawing or electron-donating substituents afforded high enantioselectivities (88–95% ee) and yields (80–97%), and substituents on *para*- (Table 3, entries 3, 5, 6, 8, 10, 11), *meta*- (Table 3, entries 2 and 7) or *ortho*- position (Table 3, entries 4 and 9) in the aromatic ring slightly affected the yields and enantioselectivities. Heteroaromatic α,β-unsaturated ketones and bulkier alkyl enone also gave satisfactory yields and enantioselectivities (Table 3, entries 12, 13 and 15).

Notably, the enantiomeric excess value of (*S*)-warfarin can be enhanced from 95% to 99% by simple and single recrystallization in ethanol, thus rendering this method potentially useful for industrial applications.

In conclusion, a series of simple chiral primary amine thiourea catalysts, easily prepared from cheaply and commercially available chiral diamines, were successfully applied to catalyze the Michael reaction of 4-hydroxycoumarins with α,β-unsaturated ketones in excellent enantioselectivities (up to 95% ee) and yields (up to 97%). Optically pure *S*-warfarin was obtained in 99% ee after a simple and single recrystallization in alcohol, which provides a possible approach for the commercial production of *S*-warfarin.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.054.

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