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Combining Silver Catalysis and Organocatalysis: A Sequential Michael Addition/Hydroalkoxylation One-Pot Approach to Annulated Coumarins

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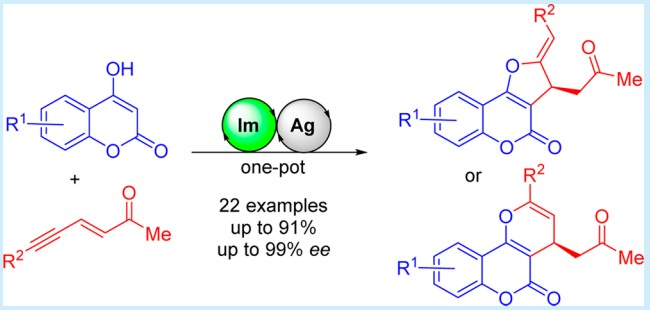
Supporting Information

ABSTRACT: A highly stereoselective one-pot procedure for the synthesis of five-membered annulated hydroxycoumarins has been developed. By merging primary amine catalysis with silver catalysis, a series of functionalized coumarin derivatives were obtained in good yields (up to 91%) and good to excellent enantioselectivities (up to 99% ee) via a Michael addition/hydroalkoxylation reaction. Depending on the substituents on the enynone, the synthesis of annulated six-membered rings is also feasible.



Secondary metabolites from phytobiochemical pathways fulfill various life-sustaining roles in plants. For example, coumarins, which originate from the shikimic acid pathway, are vital for the regulation of oxidative stress, hormonal regulation, and plant protection (Figure 1).[1] Interestingly, biological activity is not limited to plants only, as shown by warfarin and phenprocoumon, which belong to the class of vitamin K antagonists. Both inhibit the enzyme vitamin K epoxide reductase, thus preventing blood clotting in humans and animals.[2] As a result, these anticoagulants have found wide application as pharmaceuticals or rodenticides over the years.

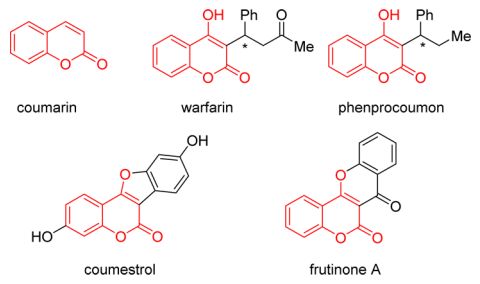


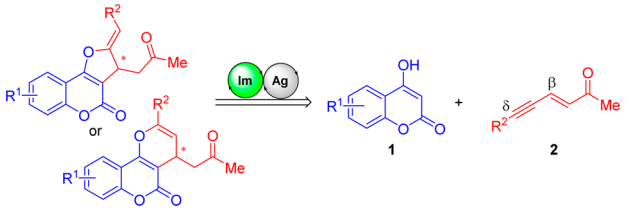
Figure 1. Bioactive coumarin derivatives.

Although the unprotected 4-hydroxyl group is necessary for anticoagulant activity, other biologically active natural products have been discovered in which the oxygen is embedded in an annulated ring structure, as found in coumestrol and frutinone A.[3,4] The former interacts with estrogen receptors ERα and -β in humans, while the latter is a potent inhibitor of CYP1A2.

Recently, the combination of transition metals with organocatalysts has emerged as a versatile one-pot strategy for the synthesis of valuable chiral entities, especially in the context of sequential catalysis.[5] However, most reported procedures mainly rely on expensive metal complexes, such as gold, palladium, and iridium. Silver is a comparably cheaper metal and can be employed as an alternative to facilitate these sequential transformations. Silver salts of chiral organic molecules have been used as binary catalytic systems in many asymmetric transformations, but the sequential catalysis employing silver and organocatalysts is less explored.[6,7] Owing to the wide applicability of coumarin derivatives and knowing the potential of sequential catalysis,[8] we envisaged the combination of silver salts with chiral primary amines for the one-pot sequential Michael addition/hydroalkoxylation of 4-hydroxycoumarins **1** with enynones **2** (Scheme 1).

Most of the organocatalytic asymmetric transformations involving 4-hydroxycoumarins focus on Michael additions to common electrophiles, such as simple enones, which undergo electrophilic activation in the presence of primary amines.[9,10] In contrast, enynones **2** have not been used in this context so far.

Scheme 1. Intended Strategy



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These enynones are challenging Michael acceptors because both the β- and δ-position are prone to nucleophilic addition after electrophilic activation.

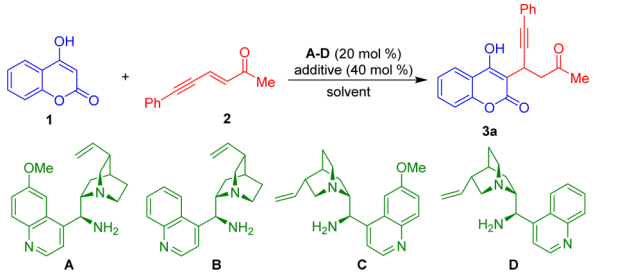
To achieve our goal, we started the investigation by optimizing the organocatalytic Michael addition of 4-hydroxycoumarin **1a** to enynone **2a** using cinchona-derived primary amines.[11] The reaction of **1a** with **2a** in CH_2Cl_2 at room temperature in the presence of 20 mol % 9-amino(9-deoxy)*epi*-quinine **A** and 40 mol % TFA afforded the desired product **3a** within 16 h in 63% yield and 68% *ee* (Table 1, entry 1). To circumvent this low asymmetric induction, we replaced the catalyst **A** with primary amines derived from cinchonidine **B**, quinidine **C**, and cinchonine **D**, but no beneficial effect was observed (entries 2–4). In contrast, the choice of solvent had a noticeable effect on the yield and enantiomeric excess, revealing THF as the most suitable solvent (entry 6).

We questioned whether the enantiomeric excess could be increased if chiral acidic additives, especially Boc-protected amino acids, were employed instead of TFA, as shown in a seminal publication by Melchiorre et al.[12] This would change the mechanism of activation and stereoinduction from pure iminium activation to a mixed activation mode in which the chiral protonated iminium ion is coordinated by a chiral anion, a concept known as asymmetric counteranion directed catalysis (ACDC).[13] As anticipated, we observed a slight increase in enantiomeric excess for the majority of chiral additives with comparable yields (entries 8–12). With (*S*)-*N*- Boc-alanine in hand as the best additive, we focused on the influence of the temperature on the reaction. Naturally, a higher temperature resulted in a faster but less selective reaction (entry 13), while at 4 °C a negligible increase in reaction time and yield was observed, albeit with better enantiomeric excess (entry 14). However, a lower temperature had a deleterious effect, leading to longer reaction times and lower enantioselectivities (entry 15). A similar impact was observed when the catalyst loading was decreased to 10 mol %; thus, 20 mol % had to be used (entry 16).

With the optimized conditions for the Michael addition in hand, we shifted our focus to the cycloisomerization reaction (Table 2). We envisioned that phosphine Au(I) catalysts, which are known to activate internal alkynes, would be an optimal choice for this reaction. However, the initial reaction conditions gave rise to a complex mixture of different products, most likely 6-*endo*-, 5-*exo*-, and other unidentified products (entry 1). In contrast, a number of Ag(I) salts gave the 5-*exo* product in excellent yields within 1 h in the absence of gold catalysts (entries 2–9). Ag_2CO_3 turned out to be the best catalyst, giving the desired product **4a** in 97% yield within 40 min. In addition, we also tested other metal sources which act as carbophilic Lewis acids, but the reaction seemed to be limited to silver salts only (entries 9–10).

Regrettably, further studies revealed that THF, which is used during the Michael addition, is inappropriate for the subsequent cyclization because, similar to the initial reaction conditions, a mixture of products was obtained (entry 3). Thus, the reaction must be performed either in a mixture of toluene and THF (entry 11) or with the solvents changed prior to the addition of Ag_2CO_3. To compensate for this inconvenience, there seemed to be no notable deactivation of the silver catalyst in the presence of the amine catalyst (entry 12), as there was no notable decrease in yield or increase in reaction time when the reaction was performed in the presence of amine catalyst **A** and (*S*)-*N*-Boc

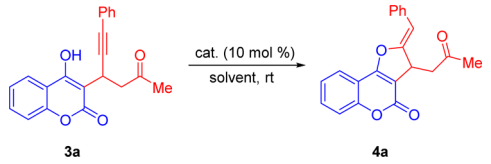
Table 1. Optimization Studies on the Michael Addition[a]



entry	cat.	additive	solvent	t (h)	yield (%)[b]	ee (%)[c]
1	**A**	TFA	DCM	16	63	68
2	**B**	TFA	DCM	20	74	59
3	**C**	TFA	DCM	19	61	−68
4	**D**	TFA	DCM	21	81	−60
5	**A**	TFA	$CHCl_3$	24	84	72
6	**A**	TFA	THF	16	85	78
7	**A**	TFA	MTBE	16	82	66
8	**A**	(*S*)-mandelic acid	THF	16	85	78
9	**A**	(*S*)-*N*-Boc-ala	THF	24	95	82
10	**A**	(*S*)-*N*-Boc-phe	THF	24	65	81
11	**A**	(*S*)-*N*-Boc-leu	THF	24	94	80
12	**A**	(*S*)-*N*-Boc-val	THF	24	48	80
13[d]	**A**	(*S*)-*N*-Boc-ala	THF	4	94	76
14[e]	**A**	(*S*)-*N*-Boc-ala	THF	26	95	86
15[f]	**A**	(*S*)-*N*-Boc-ala	THF	96	88	57
16[e,g]	**A**	(*S*)-*N*-Boc-ala	THF	72	88	75

[a]Reaction conditions: 0.5 mmol of **1a**, 0.6 mmol of **2a**, 20 mol % of catalyst, 40 mol % additive, 1.0 mL solvent, rt. [b]Yield of isolated **3a** after flash column chromatography. [c]Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase of the *O*-acetylated derivative **3a**′. [d]Reaction was carried out at 50 °C. [e]Reaction was carried out at 4 °C. [f]Reaction was carried out at −16 °C. [g]Reaction was carried out with 0.1 mol % of **A** and 20 mol % (*S*)-*N*-Boc alanine.

Table 2. Optimization of the Cycloisomerization of 4a[a]



entry	catalyst	solvent	t (min)	yield (%)[b]
1	$PPh_3AuCl/AgNTf_2$	toluene	60	–[c]
2	$AgNTf_2$	toluene	30	79
3	$AgNTf_2$	THF	>240	–[c]
4	$AgNO_3$	toluene	40	91
5	Ag_2CO_3	toluene	40	97
6	AgOAc	toluene	40	94
7	AgOTf	toluene	50	91
8	$AgSbF_6$	toluene	30	91
9	CuI	toluene	>1 d	traces
10	$PtCl_2$	toluene	>1 d	traces
11	Ag_2CO_3	toluene/THF 4:1	4 h	94
12[d]	Ag_2CO_3	toluene	40	97

[a]Reaction conditions: 0.13 mmol of **3a**, 10 mol % of catalyst, 1.3 mL solvent, rt. [b]Yield of isolated **4a** after flash column chromatography. [c]Complicated mixture of products which could not be separated. [d]In the presence of 20 mol % **A** and 40 mol % (*S*)-*N*-Boc alanine.

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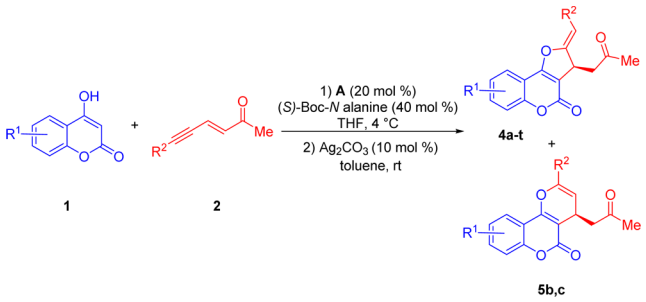
alanine. This is a decisive advantage compared to gold-catalyzed reactions, in which the presence of free amines or basic moieties deactivate the gold catalyst, and strong acidic additives such as TFA or harsher reaction conditions have to be employed to retrieve the active gold species.[14]

With these optimized conditions in hand, we tested the substrate scope of the one-pot Michael addition/cycloisomerization (Table 3). In the case of aryl-substituted enynones good

Table 3. Substrate Scope for the Sequential Catalysis[a]



product	R^1	R^2	yield (%)[b,c]	ee (%)[d,e]
4a	H	Ph	84 [52]	88 [94]
4b	H	4-F-C_6H_4	76 [55]	89 [94]
4c	H	4-Br-C_6H_4	76 [56]	85 [89]
4d	H	4-F_3C-C_6H_4	75	93
4e	H	2,3-CH_2OCH_2-C_6H_3	67 [47]	81 [98]
4f	H	3-Me-C_6H_4	80 [53]	89 [97]
4g	H	3-MeO-C_6H_4	82	93
4h	H	2-naphthyl	79	92
4i	H	2-Cl-C_6H_4	81	94
4j	H	1-naphthyl	75	80
4k	H	2-furanyl	78	99
4l	H	2-thienyl	76 [59]	77 [96]
4m	6-Me	4-Br-C_6H_4	54	92
4n	6,7-CH_2OCH_2-	4-F-C_6H_4	56	94
4o	7-MeO	1-naphthyl	74	94
4p	6-Cl	3-MeO-C_6H_4	60	98
4q	6-Cl	Ph	91	73
4r	7-MeO	Ph	58	93
4s	6,7-CH_2OCH_2-	Ph	72	83
4t	H	H	84	70
5b	H	butyl	52	90
5c	H	cyclopentyl	32	89

[a]Reaction conditions: 0.8 mmol of enynone, 0.5 mmol of hydroxycoumarin, 20 mol % of catalyst, 40 mol % (*S*)-*N*-Boc alanine, 1.0 mL of THF, 4 °C, 24−48 h; after completion, removal of THF, addition of 5.0 mL of toluene, 10 mol % Ag_2CO_3, rt, 1−24 h. [b]Yield of isolated **4** or **5** after flash column chromatography. [c]In brackets, yield after one recrystallization from *n*-pentane/ethyl acetate. [d]Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [e]In brackets, enantiomeric excess after one recrystallization from *n*-pentane/ethyl acetate.

yields (54−91%) and excellent enantioselectivities were obtained (73−99% ee) irrespective of electronic and steric effects (**4a−s**), though bulky substituents normally resulted with an increased reaction time in the cyclization step. Hydroxycoumarins bearing different substituents were also tolerated (**4m−s**). In all cases with aryl substituents on the enynone the 5-*exo*-products were obtained, which can be verified by ^4J-coupling of the olefinic proton (around −2 Hz) compared to the ^3J-coupling of the *endo*-product (around 4 Hz). In contrast, enynones with aliphatic substituents led to the formation of 6-*endo*-products with comparable ee values but lower yields due to a less selective ring formation (**5b−c**). In the case of a terminal alkyne the 5-*exo*-product was obtained exclusively, albeit with slightly lower enantioselectivity values (**4t**). Interestingly, we did not observe isomerization of the 5-*exo*-products to furans under the applied reaction conditions.

The proposed structure of the products, including the absolute configuration, could be assigned by X-ray crystal structure analysis of (*S*)-**4g** (Figure 2).[15] To further demonstrate the

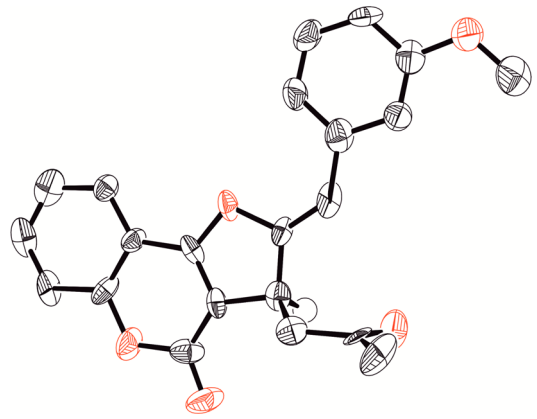
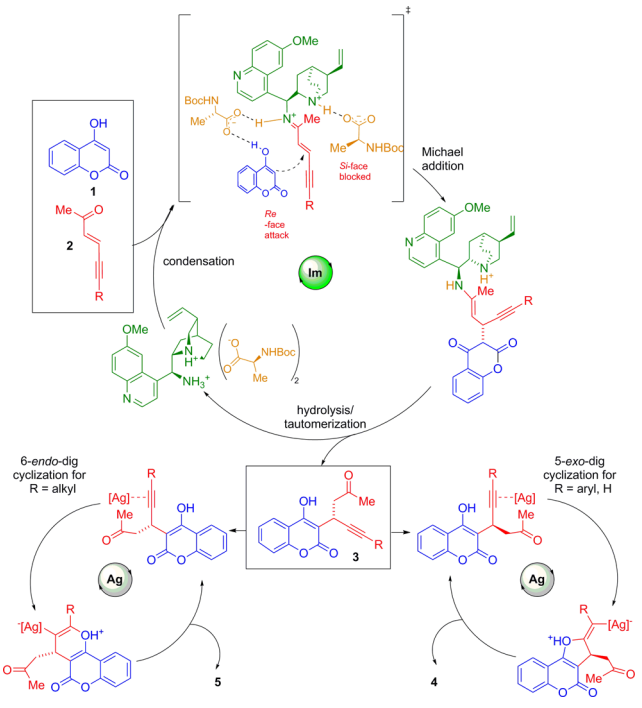


Figure 2. X-ray crystal structure of (*S*)-**4g**.

practicability of our new protocol, we carried out a larger scale synthesis of **4g** on a 4 mmol scale. We obtained the same yield (82%, 1.24 g) and a better stereoselectivity of 96% ee.

A plausible mechanism for the reported sequential catalysis is depicted in Scheme 2. Upon condensation with the primary amine **A** and interactions of two molecules of (*S*)-*N*-Boc alanine, the enynone **2** forms a LUMO-activated chiral iminium ion. Similar to recent DFT calculations by Melchiorre et al., the two

Scheme 2. Proposed Catalytic Mechanism



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molecules of (*S*)-*N*-Boc alanine should play a pivotal role in the reactivity and selectivity of this supramolecular catalytic assembly.[16] One of the counteranions will interact with the protonated quinuclidine moiety of the primary amine catalyst by hydrogen bonding, thus shielding the *Si*-face of the iminium ion. This represents the stereochemical defining element responsible for π-facial discrimination. The second counteranion acts as a mediator in a network of hydrogen bonds between the iminium proton and 4-hydroxy-coumarin. Thereby the nucleophile becomes activated while being set up to the *Re*-face for the subsequent attack on the iminium ion. The nucleophilic attack will yield intermediate **3** after hydrolysis, which will then enter the second catalytic cycle. This cycle is initiated by coordination of Ag(I) to the alkyne moiety and electrophilic activation that allows for the hydroalkoxylation of the triple bond by attack of the nucleophilic hydroxy group. Similar to Au(I)-catalyzed cycloisomerizations, the *trans*-specific addition should follow Markovnikov's rule and electronic factors. Thus, depending on the substituent on the alkyne, 5-*exo*-dig and 6-*endo*-dig ring formations are observed (see Supporting Information for a more detailed explanation). The products are obtained after regeneration of the silver catalyst and proton transfer.

In conclusion, we have developed a convenient one-pot sequential Michael addition/hydroalkoxylation by merging silver catalysis with primary amine catalysts. The combination gives rise to pharmaceutically interesting annulated coumarins in good yields and excellent enantioselectivities. Further investigations on the application of sequential catalysis by silver catalysis and organocatalysis are in progress in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Chemical synthesis, analytical data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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