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.

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.

Figure 1. Bioactive coumarin derivatives.

Scheme 1. Intended Strategy

Received: August 29, 2014
Published: September 24, 2014
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-hydroxycumarin 1a to enyne 2a using cinchona-derived primary amines.11 The reaction of 1a with 2a in CH₂Cl₂ 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 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). Ag₂CO₃ 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 Ag₂CO₃. 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 alanine.

### Table 1. Optimization Studies on the Michael Addition

| entry | cat. | additive | solvent | t (h) | yield (%) | ee (%) |
|-------|------|----------|---------|-------|----------|--------|
| 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      | CHCl₃   | 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-alanine | THF | 24 | 95 | 82 |
| 10    | A    | (S)-N-Boc-phenylalanine | THF | 24 | 65 | 81 |
| 11    | A    | (S)-N-Boc-leucine | THF | 24 | 94 | 80 |
| 12    | A    | (S)-N-Boc-valine | THF | 24 | 48 | 80 |
| 13    | A    | (S)-N-Boc-alanine | THF | 4   | 94 | 76 |
| 14    | A    | (S)-N-Boc-phenylalanine | THF | 26 | 95 | 86 |
| 15    | A    | (S)-N-Boc-leucine | THF | 96 | 88 | 57 |
| 16    | A    | (S)-N-Boc-alanine | THF | 72 | 88 | 75 |

### Table 2. Optimization of the Cycloisomerization of 4a

| entry | catalyst | solvent | t (min) | yield (%) |
|-------|----------|---------|---------|-----------|
| 1     | PPh₃AuCl/AgNTf₂ | toluene | 60     | 97       |
| 2     | AgNTf₂ | toluene | >1 d | traces   |
| 3     | AgNTf₂ | THF     | >240   |         |
| 4     | AgNO₃ | toluene | 40 | 91       |
| 5     | Ag₂CO₃ | toluene | 40 | 97       |
| 6     | Ag₂OAc | toluene | 40 | 94       |
| 7     | AgOTf | toluene | 50 | 91       |
| 8     | Ag₅B₇F₁₆ | toluene | 30 | 91       |
| 9     | Cal | toluene | >1 d | traces   |
| 10    | PtCl₂ | toluene | >1 d | traces   |
| 11    | Ag₂CO₃ | toluene/THF 4:1 | 4 h | 94       |
| 12*    | Ag₂CO₃ | toluene | 40 | 97       |

*Reaction conditions: 0.13 mmol of 3a, 10 mol % of catalyst, 1.3 mL solvent, rt. *Yield of isolated 4a after flash column chromatography. Complicated mixture of products which could not be separated. *In the presence of 20 mol % A and 40 mol % (S)-N-Boc alanine.
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 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 1H-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 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

| product  | R1 | R2          | yield (%)b,e | ee (%)d,e |
|----------|----|-------------|--------------|-----------|
| 4a       | H  | Ph          | 84 [52]      | 88 [94]   |
| 4b       | H  | 4-F-C6H5    | 76 [55]      | 89 [94]   |
| 4c       | H  | 4-Br-C6H5   | 76 [56]      | 85 [89]   |
| 4d       | H  | 4-F-C6H5    | 75            | 93        |
| 4e       | H  | 2,3-CH2OCH2-C6H5 | 67 [47] | 81 [98]   |
| 4f       | H  | 3-Me-C6H5   | 80 [53]      | 89 [97]   |
| 4g       | H  | 3-MeO-C6H5  | 82            | 93        |
| 4h       | H  | 2-naphthyl  | 79            | 92        |
| 4i       | H  | 2-C6H5      | 81            | 94        |
| 4j       | H  | 1-naphthyl  | 75            | 80        |
| 4k       | H  | 2-furanil   | 78            | 99        |
| 4l       | H  | 2-thienyl   | 76 [59]      | 77 [96]   |
| 4m       | 6-Me|            | 54            | 92        |
| 4n       | 6,7-CH2OCH2 |            | 56            | 94        |
| 4o       | 7-MeO|           | 74            | 94        |
| 4p       | 6-Cl|            | 60            | 98        |
| 4q       | 6-Cl|            | 91            | 73        |
| 4r       | 7-MeO|           | 58            | 93        |
| 4s       | 6,7-CH2OCH2|           | 72            | 83        |
| 4t       | H  | H           | 84            | 70        |
| 5b       | H  | butyl       | 52            | 90        |
| 5c       | H  | cyclopentyl | 32            | 89        |

* 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 % Ag2CO3, rt, 1−24 h. bYield of isolated or 5 after flash column chromatography. cIn brackets, yield after one recrystallization from n-pentane/ethyl acetate. dEnantiomeric excess was determined by HPLC analysis on a chiral stationary phase. eIn brackets, enantiomeric excess after one recrystallization from n-pentane/ethyl acetate.
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 $\pi$-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.

**ACKNOWLEDGMENTS**

D.H. thanks the DFG (International Research Training Group “Selectivity in Chemo- and Bio catalysis”-Seleca) and D.E. thanks the European Research Council (ERC Advanced Grant 320493 “DOMINOCAT”) for financial support. Dedicated to Professor Johann Mulzer on occasion of his 70th birthday.

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