Sulfoxonium Ylides in Aminocatalysis: An Enantioselective Entry to Cyclopropane-Fused Chromanol Structures

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ABSTRACT: The 1,1a,2,7b-tetrahydrocyclopropa[c]chromene, arising from fusion of chromane and cyclopropane rings is the core of medicinally relevant compounds. Engaging sulfoxonium ylides in enantioselective aminocatalytic reactions for the first time, a convenient entry to this scaffold is presented. Several ring-fused derivatives were obtained in moderate-to-good yields and enantioselectivities and with perfect diastereoselectivity at the cyclopropane, using an α,α-diphenylprolinol aminocatalyst. The versatility of the hemiacetal moiety in the products was leveraged to effect various synthetic manipulations.

The cyclopropane ring is present in numerous pharmacologically active compounds. The fame of this ring in medicinal chemistry is not only due to the strain of the cycle, which reserves a reactivity somewhat similar to an olefin, but also to the presence of C–H bonds shorter and stronger than those of common alkanes. Furthermore, the coplanarity of the three carbon atoms makes the reactivity displayed by cyclopropane truly unique.1 In this context, the specific tricyclic 1,1a,2,7b-tetrahydrocyclopropa[c]chromene framework, arising from fusion of chromane and cyclopropane rings, is the core of several medicinally relevant compounds (Scheme 1a). Examples include 8-carboxy-7-sulfonamido derivatives I, whose activity against methionyl aminopeptidase 2 suggests their use in the treatment of liver disorders and obesity;2 urea II (MIV-160), a reverse transcriptase inhibitor studied for anti-HIV therapy,3 and carboxylic acid III, a member of a series of fused cyclopropane derivatives agonists of G-protein coupled receptor 40 (GP40) and potentially useful in the treatment of type 2 diabetes.4 Furthermore, “cyclopropoanochroman” natural products, such as radulains I–K (IV–VI), have been isolated from liverwort extracts in racemic or enantiopure form.5 Radulain K from Radula javanica has shown to inhibit the release of superoxide anion radical from guinea pig macrophage.6

In the frame of our interest in asymmetric aminocatalysis7 and sulfoxonium ylide chemistry,8 we herein report an enantioselective access to cyclopropane-fused chromanol derivatives 3 via aminocatalytic Corey–Chaykovsky-type cyclopropanation9 of 2’-hydroxycinnamaldehydes 1 with stabilized sulfoxonium ylides 2 (Scheme 1b). Aminocatalytic cyclopropanation reactions of other α,β-unsaturated aldehydes have been reported. In this context, examples of Corey–Chaykovsky-type reactions are relatively rare and restricted to α-keto sulfonium ylides9c–f while cyclopropanations with α-halo(di)carbonyl compounds, 1-bromonitroalkanes, and activated benzylic halides (e.g., 2,4-dinitrobenzyl chloride) are more abundant.10 The latter group of reactions is generally performed with Jørgensen–Hayashi type catalysts,9 whose simplest congener proved to be effective in our case too (Scheme 1b). This reaction represents the first example of utilization of sulfoxonium ylides in asymmetric aminocatalysis12 and affords the tricyclic ring-fused derivatives 3 with very good stereocontrol. Importantly, the connectivity and relative stereochemistry of these compounds match the core of GP40 agonist III (Scheme 1a). Lastly, besides providing an alternative, and enantioselective, approach to this scaffold,13,14 this methodology affords adducts (3) carrying a hemiacetal functionality, which can be leveraged as a synthetic handle enabling access to a variety of compounds.

During our initial studies on the reaction between 2’-hydroxycinnamaldehyde 1a and sulfoxonium ylide 2a under the promotion of a common Jørgensen–Hayashi catalyst15 (Table 1), we noticed an immediate color change by mixing aldehyde 1a with the secondary amine catalyst in CDCl3. Such a color change can be attributed to the formation of a stable and nucleophilic hemiaminal adduct.16 In order to revert this hemiaminal to an electrophilic iminium ion species, presumably E-configured,16 20 mol% of benzoic acid co-catalyst was added followed by the nucleophilic sulfoxonium ylide 2a. To our delight, we observed the formation of the desired...
Chromanol derivative 3aa, which was derivatized by Wittig olefination into the corresponding 4aa, obtained as a highly prevalent E-isomer for isolation and determination of the enantiomeric excess. Immediately, we understood that the reaction was characterized by promising results in terms of yield and enantioselectivity. Indeed, when the reaction was performed under these standard conditions, 50% yield and 88% enantioselectivity were achieved (entry 1). Furthermore, regarding the chirality centers of the cyclopropane ring, the diastereoselectivity of the reaction appeared to be complete.

Because of the short reaction time, we decided to decrease the concentration of the reaction medium, which resulted in a cleaner reaction profile and increased values of yield and enantiomeric excess of product 4aa (entry 2). Next, we continued the optimization reaction using different co-catalysts and, among all the results (see also the SI), the reaction with acetic acid gave product 4aa with slightly better enantioselectivity, albeit longer reaction time (entry 3). At this stage, we decided to explore the buffer system AcONa/ACOH. When the reaction was performed with equal amounts of acetic acid and sodium acetate, an increment of the yield was achieved, while the enantioselectivity decreased (entry 4). Then, when the reaction was performed with different relative amounts of the acid and its conjugate base, two different behaviors were observed. With an excess of sodium acetate, the yield of product 4aa decreased again while its enantiomeric excess increased slightly (entry 5). Running the reaction with more acetic acid than sodium acetate improved the yield, but the enantioselectivity dropped (entry 6). Surprisingly, we found that when the reaction was performed with sodium acetate as the only co-catalyst both the yield and enantioselectivity of product 4aa increased (entry 7). Our current understanding is that the acidity of 2′-hydroxycinnamaldehyde 1a is enough to

Table 1. Representative Optimization Results 

| entry | solvent (M) | time (h) | co-catalysts (mol%) | yield of 4aa (%) | ee of 4aa (%) |
|-------|-------------|----------|---------------------|-----------------|--------------|
| 1     | CDCl₃ (0.5) | 1        | PhCOOH (20)         | 50              | 88           |
| 2     | CDCl₃ (0.1) | 2        | PhCOOH (20)         | 57              | 95           |
| 3     | CDCl₃ (0.1) | 12       | AcOH (20)           | 52              | 96           |
| 4     | CDCl₃ (0.1) | 12       | AcONa (20) + AcOH (20) | 74              | 79           |
| 5     | CDCl₃ (0.1) | 12       | AcONa (20) + AcOH (10) | 65              | 82           |
| 6     | CDCl₃ (0.1) | 12       | AcONa (20) + AcOH (20) | 75              | 74           |
| 7     | CDCl₃ (0.1) | 12       | AcONa (20)          | 67              | 97           |
| 8     | CHCl₃ (0.1) | 12       | AcONa (20)          | 41              | 96           |
| 9     | CHCl₃ (0.1) | 12       | AcONa (20)          | 65              | 97           |

*Reaction conditions: 1a (0.1 mmol), 2a (0.15 mmol), catalyst (0.02 mmol), additive, solvent, rt. Then phosphorus ylide, rt, 1 h. *Isolated yield after column chromatography. *Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography.
form sufficient amounts of the reactive iminium ion for the reaction to proceed. Meanwhile, sodium acetate might be helpful for scavenging more acidic species which could be harmful to the acid-sensitive sulfoxonium ylide. Indeed, a reaction performed without additives afforded product 4aa in comparably high enantiomeric excess but lower yield (entry 8). Having chosen sodium acetate as the best additive, we ascertained that the results in chloroform (entry 9) are in line with results obtained so far in the corresponding deuterated solvent. Interestingly, a reaction performed using a sulfoxonium, instead of sulfoxonium, ylide did not afford product 3aa under these reaction conditions. Furthermore, cinnamaldehyde was found to be unreactive toward sulfoxonium ylide 2a, even when the Jørgensen–Hayashi catalyst was combined with acid co-catalysts. Thus, 2′-hydroxycinnamaldehydes showcase a distinct reactivity compared to their simpler nonhydroxylated counterparts, at least for this reaction.

We then moved to evaluate the generality of the reaction after having verified that the reaction can be carried out with similar results on a 1 mmol scale (Scheme 2). The variation of the sulfoxonium ylide 2 reported in Scheme 2 showed that both short-chain and long-chain ester substituents are very well tolerated, giving products 4ab and 4ac with comparable results in terms of yield and very good enantioselectivity. In addition, bulky substituents such as the isobutyl or the tert-butyl group on the ester moiety give products 4ad and 4ae, respectively, in good yields and with high enantiomeric excesses. Similarly, the use of an allylic or a benzylic ester did not significantly affect either the yield or the enantioenrichment of products 4af and 4ag. Next, the sulfoxonium ylide 2h with a ketone instead of an ester substituent was tested. Product 4ah was obtained in a lower yield, possibly due to the less nucleophilic nature of this ylide, but with high enantiomeric excess. Finally, using a different phosphorus ylide, compound 4ab with two methyl esters was prepared, and its relative and absolute configurations were determined as 1R,2R,3S by means of NOESY-1D NMR and the electronic circular dichroism (ECD) method (see the SI). This assignment, fully in line with the proposed pathway, was extended by analogy to all products 4.

We then explored the reactivity of sulfoxonium ylide 2a with different 2′-hydroxycinnamaldehydes 1b–g, and the results are reported in Scheme 3. A 4′-methyl substituent gave product 4b in good yield and high enantiomeric excess, while the same group at the 5′ position led to product 4c in a lower yield but still high enantioselectivity. A more electron-donating substituent like a methoxy group at different positions was also tolerated, delivering products 4da, 4fa, and 4ga in moderate to good yields and good enantiomeric excesses. Interestingly, product 4fa bears an oxygenated substituent at the same position of the aryloxy group of GP40 agonist III (Scheme 1). Finally, using an electron-withdrawing substituent like a chlorine atom led to the corresponding product 4ea with good results.

As mentioned in the introduction, the backbone of the catalytic products is present in numerous natural and medicinal compounds. For this reason, we moved to explore their synthetic versatility (Scheme 4). When 3aa was treated with PCC, the hemiacetal group could be oxidized to deliver coumarin 5aa in moderate yield. The readily obtained methyl acetal of 3aa could be smoothly reduced to the corresponding chromane 6aa using triethylsilane in the presence of BF₃·OEt. Using sodium borohydride, the fleeting aldehydic function could instead be converted into a primary alcohol, obtaining product 7aa in very good yield. Protocols combining the catalytic reaction and these reductions or oxidations in one-pot fashion were also implemented (see the Supporting Information). Using these streamlined and convenient
methods, product 5aa was obtained with comparable yield, while 6aa and 7aa were afforded with lower yield values. Product 4aa resulting from Wittig olefination of 3aa was subjected to an intramolecular diastereodivergent oxa-Michael reaction. When the reaction was performed with bifunctional catalysts derived from pseudoenantiomeric Cinchona alkaloids, it was possible to direct the diastereoselectivity of the reaction either toward the cis-8aa or the trans-8aa derivative. The intrinsic diastereomeric relationship between the transitions states leading to the cis-8aa and to the trans-8aa isomer justifies the requirement of different (i.e., not enantiomeric) catalytic structures for the two reactions (see the Supporting Information).

In conclusion, we have developed a catalytic enantioselective reaction between 2’-hydroxycinnamaldehydes 1 and stabilized sulfoxonium ylides 2, affording cyclopropane-fused chromane derivatives 3 in moderate yields and excellent enantioselectivities. Besides the evident relevance of the scaffold of these products in medicinal compounds, the presence of a versatile hemiacetal moiety allowed us to perform various synthetic elaborations. Disclosing the first utilization of sulfoxonium ylides under aminocatalytic conditions, these results add an important piece to the still poorly disclosed puzzle of asymmetric organocatalysis with sulfoxonium ylide substrates.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02204.

Additional optimization studies, catalytic cycle, determination of the relative and absolute configuration of products 4′ab and 8aa, experimental section, copies of NMR and IR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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