Asymmetric Synthesis (1)

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Asymmetric Synthesis of Natural Product Inspired Tricyclic Benzopyrones by an Organocatalyzed Annulation Reaction**

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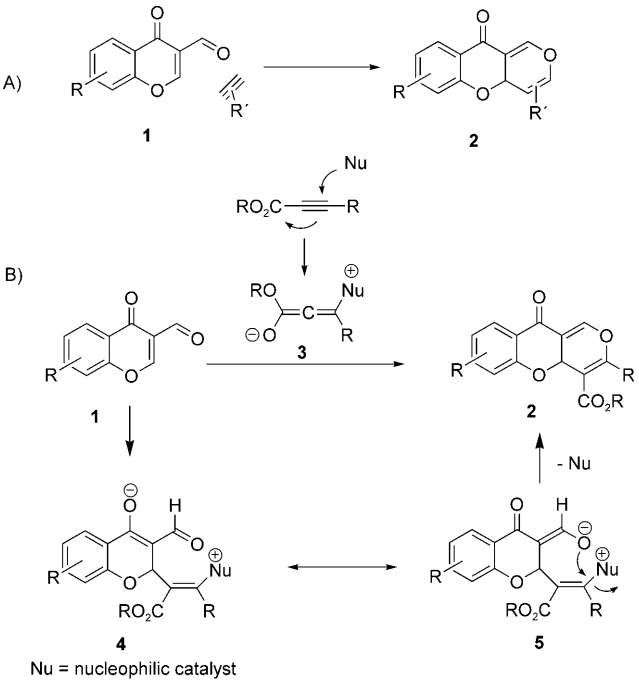
The structural frameworks of natural product classes provide evolutionary-selected and biologically prevalidated starting points in vast chemical structure space for compound development in chemical biology and medicinal chemistry research.[1] The synthetic challenges often posed by natural products and analogues thereof call for the development of new enantioselective synthesis methods amenable to the synthesis of compound collections.[1–4] Recently, a group of natural products with a tricyclic benzopyrone core structure was reported as a new class of inhibitors for bacterial metallo-β-lactamases. This promising class of inhibitors was proposed for a potential combination treatment of clinically relevant pathogens, in particular against multidrug-resistant strains.[5] The pyrano-benzopyrone core also occurs in other natural products, for example, in the fungal metabolite fulvic acid.[6] As a result of this biological relevance and prevalidation in structural space, and since new antibiotic candidate classes are in urgent demand, we aimed at the development of a synthesis method that would give rapid and flexible access to a collection of compounds with the tricyclic benzopyrone core structure (**2**, Scheme 1).

For the development of a catalytic enantioselective methodology, we envisioned employing a [4+2] ring annulation reaction of 3-formylchromones with electron-poor acetylenes as the key step (Scheme 1 A). While non-asymmetric [4+2] cycloadditions between 3-formylchromone and electron-rich olefins (for example, vinyl ethers) have been described by Coutts and Wallace,[7] the corresponding annulations between this oxa diene and electron-deficient alkynes are unprecedented.[8,9] We hypothesized that nucleophilic catalysis by means of phosphines or tertiary amines could provide an opportunity to catalyze this transformation. In this approach, one of two electronically similar substrates (for example, two electrophiles) reacts with the catalyst to form an intermediate with altered electronic properties which can then undergo the desired reaction with the now electronically complementary partner.[10,11] Here we report on the successful implementation of this strategy and the extension of this new annulation reaction to the synthesis of dehydropyrans.



Scheme 1. Ring-annulation strategy employing 3-formylchromones and Schiff bases derived from them (A), and the postulated mechanism for nucleophilic catalysis (B).

Mechanistically, it was envisioned that a nucleophilic catalyst would add to the alkyne to give rise to intermediate zwitterions **3** which would then add to the formylchromone **1** by a conjugate addition to yield intermediate **4** (Scheme 1 B). Ring closure, accompanied by liberation of the phosphine, would lead to the desired annulation product **2**. In an initial attempt, a 1:1 mixture of 3-formylchromone and dimethylacetylene dicarboxylate (DMAD) was heated to 80 °C in toluene in the presence of 50 mol % triphenylphosphine, and,

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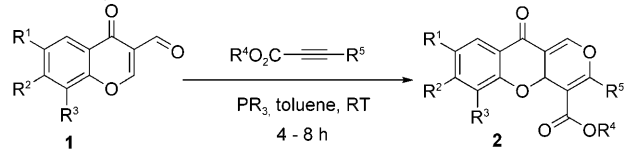
gratifyingly, the expected annulated product **2a** was obtained in 92% yield (Table 1, entry 1). Subsequent experimentation revealed that 30 mol% triphenylphosphine suffices for completion of the reaction at room temperature within 4–8 h. No reaction was observed in the absence of phosphine, even at higher temperatures. The reaction proceeds well in toluene and benzene but not in more polar solvents such as CH_2Cl_2 or THF. Furthermore, it was observed that the reactions proceed faster if tributylphosphine is used instead of triphenylphosphine. Diazabicyclo[2.2.0]octane (DABCO) also serves as a catalyst for this reaction. The annulation process is slower in the presence of this tertiary amine, and unlike with phosphines, polar solvents such as THF or acetone are preferable if DABCO is used.

Table 1: Phosphine-catalyzed [4+2] annulation of acetylene carboxylates with 3-formylchromones.



Entry	Prod.	R^1	R^2	R^3	R^4	R^5	PR_3	Yield **2** [%]
1	**2a**	H	H	H	Me	CO_2Me	PPh_3	92
2	**2a**	H	H	H	Me	CO_2Me	PBu_3	96
3	**2b**	*i*Pr	H	H	Me	CO_2Me	PBu_3	86
4	**2c**	*i*Pr	H	H	Et	CO_2Et	PBu_3	99
5	**2d**	H	H	H	Me	H	PPh_3	62
6	**2e**	*i*Pr	H	H	Me	H	PPh_3	75
7	**2f**	H	H	H	*t*Bu	H	PPh_3	60
8	**2g**	H	OBn[a]	Me	Me	CO_2Me	PBu_3	75
9	**2h**	H	OBn	Me	Et	CO_2Et	PBu_3	75
10	**2i**	H	OBn	Me	Me	H	PPh_3	60
11	**2j**	H	H	H	Et	Ph	PBu_3	65

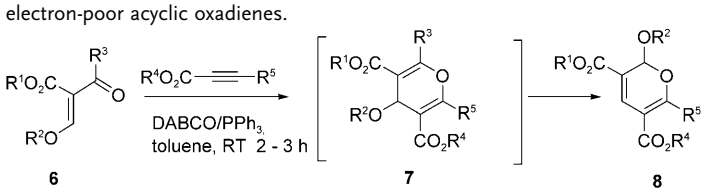
[a] Bn = benzyl.

The transformation tolerates variations in the substituents on the chromone ring and on the acetylene moieties (Table 1). Thus, unsubstituted as well as alkyl- and alkoxy-substituted chromones and esters of acetylene dicarboxylic acid, propiolic acid, and phenylpropiolic acid can be employed successfully. In general, the pyran-fused chromones are formed in high yields. They can be obtained from the reaction mixture in pure form by means of one simple flash chromatographic separation (see the Supporting information).

Notably, the reactions of alkynes with chromone-derived aldehydes did not yield α,β-unsaturated lactones, as has been observed before for related transformations with simple or activated aldehydes.[10b] The transformations are simple to carry out and a variety of formylchromones and substituted alkynes are commercially available. Thus, this reaction sequence should be readily amenable to the synthesis of collections of compounds for chemical biology and medicinal chemistry research.

To further expand the scope of this unprecedented annulation we investigated the use of acyclic oxadienes **6**, which contain an ester moiety in the α position to the aldehyde/ketoester.[12] The low stability of the oxadienes **6** necessitated their treatment with the zwitterions, generated by the reaction of the nucleophilic catalyst and the acetylene carboxylates, immediately after their formation (see the Supporting information). Thus, a solution of the diene **6** in toluene was treated with acetylene carboxylates in the presence of DABCO or PPh_3. The reaction of the conjugated aldehydes proceeded rapidly (1–3 h) in the presence of DABCO (Table 2, entries 1–6, R^3 = H). However, the intermediate [4+2] annulation products **7a–f** (detected by means of ^{1}H NMR spectroscopic investigation of the crude product mixtures) underwent a subsequent Claisen rearrangement to yield dehydropyrans **8a–f** in 54–65% yield over two steps (Table 2).[12] The conjugated ketoesters[13] reacted smoothly with the zwitterions generated from acetylene dicarboxylates and DABCO by a [4+2] annulation to yield the adducts **7g** and **7h** in high overall yields (Table 2, entries 7 and 8). Furthermore, alkyl propiolates could also successfully undergo PPh_3-catalyzed annulation reactions to yield the corresponding [4+2] adducts **7i** and **7j** (Table 2, entries 9 and 10). Thus, this nucleophile-catalyzed annulation reaction provides a novel route to highly electron-deficient dehydropyrans which could be further explored for the synthesis of interesting carbohydrates.[14]

Table 2: Organocatalyzed annulation of acetylene carboxylates with electron-poor acyclic oxadienes.



Entry	Prod.	R^1	R^2	R^3	R^4	R^5	Yield **7** or **8** [%][a]
1	**8a**	Me	Bz	H	Me	CO_2Me	65[b]
2	**8b**	Me	Ac	H	Me	CO_2Me	54[b]
3	**8c**	Et	Bz	H	Me	CO_2Me	61[b]
4	**8d**	Et	Ac	H	Me	CO_2Me	53[b]
5	**8e**	Et	Bz	H	Et	CO_2Et	55[b]
6	**8f**	Me	Bz	H	Et	CO_2Et	54[b]
7	**7g**	Me	Et	CO_2Me	Me	CO_2Me	68[b]
8	**7h**	Me	Et	CO_2Me	Et	CO_2Me	66[b]
9	**7i**	Me	Et	CO_2Me	Me	H	56[c]
10	**7j**	Me	Et	CO_2Me	Et	H	54[c]

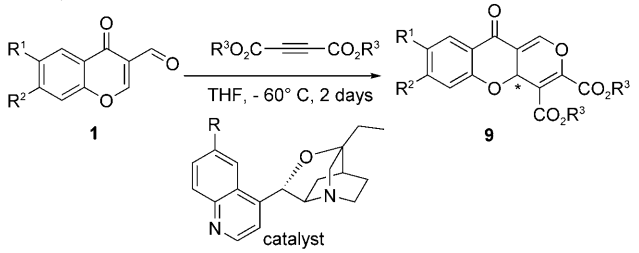
[a] Overall yields of isolated product over two steps. [b] DABCO (50 mol%) was used as catalyst. [c] PPh_3 (40 mol%) was used as catalyst. Bz = benzoyl.

A new stereocenter is formed in the ring annulation reaction of acetylene carboxylates with formylchromones, and thus an enantioselective [4+2] annulation could be envisaged. To this end, we initially investigated chiral phosphines as nucleophilic catalysts. However, disappointingly, the majority of the chiral phosphines employed did not catalyze the transformation at all, and only in a single case was induction of asymmetry observed, albeit with low stereoselectivity.

Based on the observation that DABCO also catalyzes the annulation reaction with 3-formylchromones (see above), we investigated several cinchona alkaloids and derivatives

thereof as chiral catalysts. Cinchonine and cinchonidine did not lead to preperatively viable results. However, gratifyingly, 20 mol% β-isoquinidine **10**,[15] which contains a cyclic ether between the isoquinuclidine system and the quinoline-substituted side chain, catalyzed the transformation at −50 °C in THF to yield the tricyclic benzopyrone **9a** with 54% *ee* (Table 3, entry 1). The major enantiomer of compound **9a** was subjected to crystal-structure analysis (see the Supporting Information) to determine its absolute configuration and the sense of the stereoinduction; this analysis revealed that in this case the *S* isomer was formed preferentially.

Table 3: Asymmetric [4+2] annulation of acetylene dicarboxylates with 3-formylchromones.



10; R = OMe; **11**; R = OH
12; R = H; **13**; R = Ph
14; R = Naph

Entry	Prod.	R^1	R^2	R^3	Cat.	*ee* [%][a]	Yield **9** [%][b]
1	**9a**	H	H	Me	**10**	54	84[c]
2	**9a**	H	H	Me	**12**	56	66[c]
3	**9a**	H	H	Me	**13**	83	91[d]
4	**9b**	Cl	H	Me	**13**	82	78[d]
5	**9c**	Br	H	Me	**13**	83	70[d]
6	**9d**	*i*Pr	H	Me	**13**	81	52[d]
7	**9e**	Cl	Me	Me	**13**	81	55[e]
8	**9f**	H	H	Et	**13**	87	52[d]
9	**9g**	Cl	H	Et	**13**	84	46[e]
10	**9h**	Br	H	Et	**13**	85	46[e]
11	**9i**	*i*Pr	H	Et	**13**	85	67[d]

[a] The enantiomeric ratio was determined by means of HPLC using chiralpak columns. [b] Yield of isolated product. [c] The reaction was performed at −50 °C in acetone. [d] The reaction was performed at −60 °C. [e] The reaction was performed at −70 °C.

Several derivatives of the cinchona catalyst were synthesized by palladium-catalyzed Suzuki reactions of different aryl boronic acids and β-isocupreidine triflate in an attempt to improve the stereoselectivity (see the Supporting Information). The O-demethylated catalyst **11** did not catalyze the reaction at all, and, surprisingly, when the demethoxy analogue **12** was employed, product formation occurred, but the opposite enantiomer was preferred (Table 3, entry 2). Since cinchona alkaloids are not generally available in both enantiomeric forms, this finding is highly advantageous. Further experimentation revealed that catalyst **13**, which carries a phenyl ring at the C6-position of the quinoline moiety, provided a marked improvement in both the yield and enantioselectivity of the products. Adding further substituents to the phenyl ring, for example, in the *ortho* or *para* positions, did not improve the yield or enantioselectivity. Catalyst **14**, with a naphthyl substituent on the quinoline ring, yielded the desired products with similar stereoselectivity, but in slightly lower yields than **13**. Therefore, **13** was used in all subsequent transformations (Table 3).

These findings indicate that the presence of the quinidine ring in the catalyst and its decoration with substituents are essential for the steric steering of the annulation reactions. In addition, the tricyclic catalysts are sufficiently nucleophilic for catalysis even at low temperatures (analogues lacking an oxa ring were only sluggish catalysts; data not shown). Substituted formylchromones react with acetylene carboxylates at −60 to −70 °C in the presence of catalyst **13** to provide the desired tricyclic benzopyrones **9** with moderate to good yields and with *ee* values between 80 and 87% (Table 3).

In conclusion, a new enantioselective organocatalyzed asymmetric [4+2] annulation between electron-deficient heterodienes and acetylene derivatives has been developed that gives rise to natural product inspired tricyclic benzopyrones and dehydropyrans. To the best of our knowledge, this is the first report of an asymmetric annulation involving zwitterions generated from acetylene carboxylates. The synthesis route developed and described above is efficient and operationally simple, and thus amenable to the synthesis of collections of compounds for chemical biology and medicinal chemistry research.

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