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Asymmetric Formation of Bridged Benzoxazocines through an Organocatalytic Multicomponent Dienamine-Mediated One-Pot Cascade

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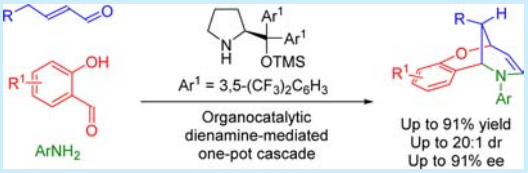
Supporting Information

ABSTRACT: An organocatalytic one-pot cascade leading to the stereoselective formation of novel bridged benzoxazocines is presented. The developed methodology is based on the first example of a γ-selective-Mannich-initiated cascade reaction and allows for direct annulation of the bridged benzoxazocines by incorporation of various α,β-unsaturated aldehydes, electron-rich anilines, and electron-deficient salicylaldehydes. The synthetic applicability of the products is demonstrated by relevant transformations.

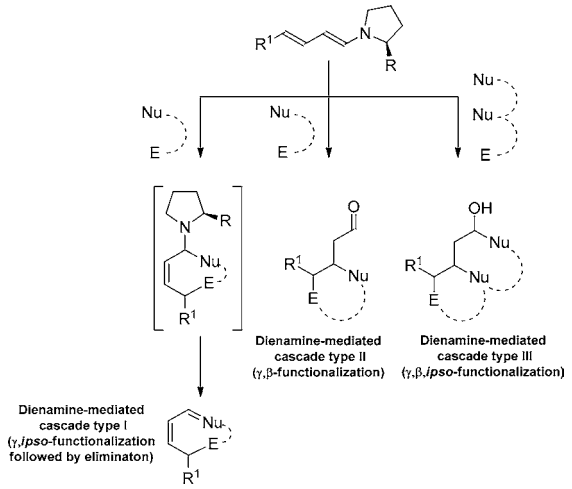


Designing new reaction profiles dedicated toward the synthesis of privileged structural scaffolds constitutes an important challenge in modern organic chemistry.[1] In particular, cascade reactivities, where more than one bond is being formed in a reaction sequence without isolation of the corresponding intermediates, have received increased attention in the chemical community.[2] Among such strategies, enantioselective approaches employing chiral catalysts occupy a prominent position.[2]

Recently, aminocatalysis, where simple primary or secondary amines are used as chiral inductors and reaction rate enhancers, emerged as a highly reliable tool in the field.[3] The different reaction profiles offered by aminocatalytic activation modes make them particularly well-suited for applications in cascade reactions. In particular, dienamine intermediates, offering the possibility to introduce stereogenic centers up to five bonds away from the chirality of the catalyst, have been employed in various cascade reactions affording access to carbo- and heterocyclic frameworks.[4] Various dienamine-mediated remote functionalization cascade reactivities are summarized in Scheme 1. Most of these reactions are induced by a γ-selective Michael addition followed by cyclization in either the *ipso*-position (cascade type **I**)[5] or the β-position (cascade type **II**).[6] Surprisingly, examples of double cyclizations occurring in both β- and *ipso*-positions are much less common (cascade type **III**).[7] Furthermore, dienamine-mediated reactions initiated by reactions other than Michael addition are rare and, to the best of our knowledge, no γ-selective-Mannich-initiated cascade reactivity has been reported.

The tetrahydrobenzo[1,5]oxazocine framework constitutes an important structural motif present in biologically active molecules (Figure 1). Their inhibitory activity against hepatitis C,[8] as well as CNS and analgesic activity,[9] is well recognized.

Scheme 1. Different Cascade Types in Dienamine-Mediated Catalysis



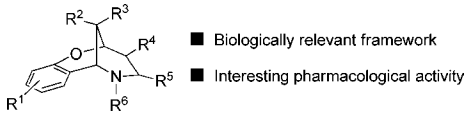


Figure 1. Bridged benzoxazocine-privileged core structure.[8,9]

Interestingly, synthetic methods toward benzo[1,5]oxazocines are rare and no enantioselective method for their preparation exists in the literature.[10]

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Herein, we report a novel multicomponent one-pot cascade approach for the synthesis of enantiomerically enriched methylene bridged benzo[1,5]oxazocines. It utilizes initial condensation of the corresponding aniline with salicylaldehyde followed by a dienamine-mediated γ-selective Mannich-initiated cycloaddition. Subsequent cyclization via oxy-Michael addition furnishes a benzo[1,5]oxazocine framework in an enantioselective manner (Figure 2).

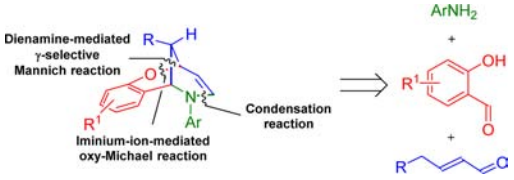


Figure 2. Strategy for the multicomponent-one-pot cascade formation of bridged benzoxazocines from simple starting materials.

Investigations were initiated using *E*-2-pentenal **4a** and 3-nitrosalicylaldehyde **1a** as model substrates. Preliminary results showed that imine formation, with an aniline **2a**, and the subsequent organocatalytic step could be performed in a one-pot fashion, providing the envisioned bridged benzoxazocine **5** in reasonable yield, but with modest diastereoselectivity (Table 1, entry 1).

To investigate the substrate dependence, a range of anilines was tested (Table 1, entries 2−4). Introduction of an electron-donating *para*-methoxy substituent increased the rate of the initial condensation, but slowed down the second step of the cascade, thereby negatively affecting the overall yield (entry 2). In contrast, an electron-poor system allowed for a rapid reaction, unfortunately in an uncatalyzed fashion (entry 3). Gratifyingly, the improved diastereoselectivity observed could be attributed to steric properties, as the application of a disubstituted electron-rich aniline afforded the product in a similar diastereomeric ratio and improved enantiomeric excess (entry 4).

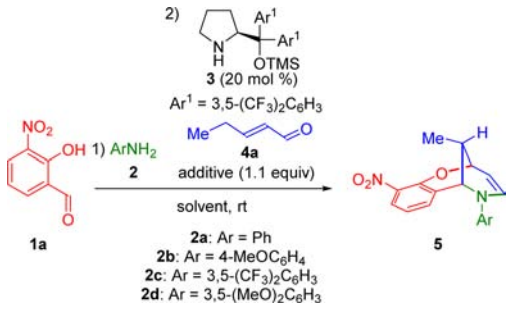
With the model substrate established, the optimization studies were directed toward the reaction solvent (Table 1, entries 5−8). The results obtained were not conclusive, although the yield of the reaction became unsatisfying for very polar solvents (entry 7). However, preliminary investigations had revealed that the use of toluene resulted in better diastereocontrol for less optimal substrates, and it was therefore chosen as the best suited solvent.

The application of additives in the reaction showed a remarkable effect (Table 1, entries 8−11). Addition of *ortho*-nitrobenzoic acid (*o*-NBA) resulted in complete product decomposition (entry 9), while use of sodium acetate allowed for a cleaner reaction, thereby improving the obtained yield (entry 10). Interestingly, while other acetates afforded similar results, the application of cesium acetate dramatically slowed down the reaction (entry 11).

The use of other secondary aminocatalysts under the optimized conditions did not improve the reaction outcome (Table 1, entries 12, 13). Finally, cooling of the reaction mixture resulted in a slower reaction with a lower yield and only marginally improved enantioselectivity, and the reaction at room temperature was therefore found to be preferable.

With the optimized reaction conditions in hand, the scope of the reaction with regard to the aldehyde substrate was investigated (Table 2).

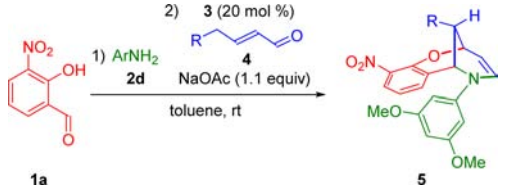
Table 1. Optimization of Reaction Conditions for One-Pot Formation of Asymmetric Bridged Benzoxazocines 5[a]



entry	Ar (**2**)	solvent	additive	yield [%]	dr	ee [%]
1	**2a**	toluene	–	86	6:1	81
2	**2b**	toluene	–	59	5:1	82
3	**2c**	toluene	–	73	10:1	0
4	**2d**	toluene	–	50	>20:1	85
5	**2d**	Et_2O	–	42	>20:1	84
6	**2d**	dioxane	–	86	>20:1	81
7	**2d**	CH_3CN	–	28	>20:1	82
8	**2d**	$CHCl_3$	NaOAc	59	>20:1	86
9	**2d**	toluene	*o*-NBA	nd	nd	nd
10	**2d**	toluene	NaOAc	77	>20:1	87
11	**2d**	toluene	CsOAc	16	>20:1	82
12[b]	**2d**	toluene	NaOAc	78	>20:1	80
13[c]	**2d**	toluene	NaOAc	73	>20:1	81
14[d]	**2d**	toluene	NaOAc	63	>20:1	89

[a]Reactions performed on 0.1 mmol scale (see Supporting Information for detailed reaction conditions). [b]Using a diphenyl catalyst (Ar^1 = Ph). [c]Using TBS-protected catalyst. [d]Reaction at 5 °C.

Table 2. Aldehyde Scope for the Organocatalytic One-Pot Formation of Optically Active Bridged Benzoxazocines 5[a]



entry	R	product	yield [%]	dr	ee [%]
1	Me	**5a**	77	>20:1	87
2	H	**5b**	44	>20:1	73
3	Et	**5c**	44	>20:1	85
4	Pen	**5d**	41	>20:1	76
5	*E*-Pent-2-enyl	**5e**	42	>20:1	80
6	CH_2Ph	**5f**	42	>20:1	76
7	OBn	**5g**	22	>20:1	88

[a]Reactions performed on 0.1 mmol scale (see Supporting Information for detailed reaction conditions).

Application of crotonaldehyde **4b** afforded the product **5b**, with no substituent on the methylene bridge, in an acceptable yield and enantiomeric excess (Table 2, entry 2). Notably, this product can only be formed as one diastereomer, as the bridge carbon atom is not a stereogenic center and a *cis*-relationship of the two bridgehead hydrogens is imposed in the cyclization step. The introduction of alkyl chains resulted in a decrease in both yield and enantioselectivity, although the diastereocontrol

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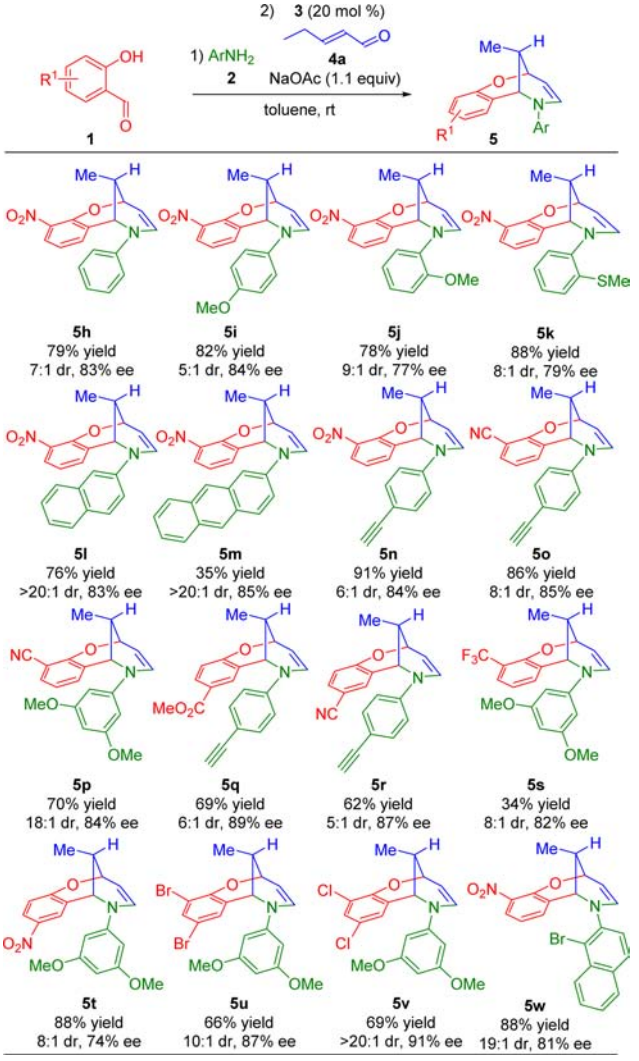
was still excellent (entries 3, 4). A similar result was observed with the introduction of alkyl substituents containing functional groups. Nonetheless, a double bond as well as a phenyl group was successfully introduced, with no further negative effect on the reaction outcome (entries 5, 6). Finally, a benzyl protected alcohol was shown to be compatible with the reaction conditions, allowing for the formation of product **5g**, carrying the alcohol directly on the methylene bridge, with excellent stereoselectivity, albeit with an unsatisfying yield (entry 7).

Having established the scope of α,β-unsaturated aldehydes, investigations on the use of other electron-deficient salicylaldehydes **1** and anilines **2** were initiated (Scheme 2).

Scheme 2. Salicylaldehyde and Aniline Scope[a]



[a]Reactions performed on 0.1 mmol scale (see Supporting Information for detailed reaction conditions). Enantiomeric excess reported for major diastereomer.

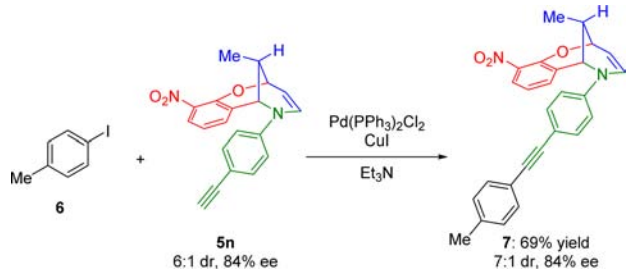
The use of unsubstituted aniline **2a** afforded product **5h** in good yield and stereoselectivity. Similar results were obtained through the application of less bulky *para*- and *ortho*-methoxy anilines, yielding products **5i** and **5j**, where the former carries a PMP-protecting group on the enamine nitrogen atom. Application of *ortho*-thiomethyl aniline for the formation of product **5k** afforded comparable results to the oxygen counterpart, albeit with increased yield. The introduction of polycyclic substituents allows for products **5l** and **5m** to be formed with high diastereo- and enantioselectivity. Nonetheless, inclusion of an anthracyl system in **5m** comes at the cost of a low yield, which can possibly be attributed to the reduced solubility of the *in situ* formed imine intermediate.

Interestingly, the incorporation of an ethynyl group results in clean and near-quantitative formation of product **5n**, with similar stereoselectivity to other *para*-substituted systems. The same trend was observed when a nitrile group was introduced at the 3-position of the salicylaldehyde (compare products **5o** and **5p**). The clean reactivity observed for application of *para*-ethynyl aniline was the key to successfully obtaining ester-substituted product **5q** and 5-cyano substituted product **5r**, which were both isolated with a good yield and stereocontrol.

The incorporation of a trifluoromethyl group proved challenging, and product **5s** was obtained in a low yield with a diastereomeric ratio lower than previously observed with 3,5-dimethoxy aniline **2d**, nonetheless with essentially preserved enantioselectivity. A comparable diastereomeric ratio was observed for 5-nitro substituted product **5t**, which was isolated in high yield and moderate enantiomeric excess. Double substitution of the salicylaldehyde was successfully demonstrated, allowing for the formation of products **5u** and **5v** with good results. Finally, a bromine substituted naphthyl system **5w** was synthesized with a high yield and stereoselectivity.

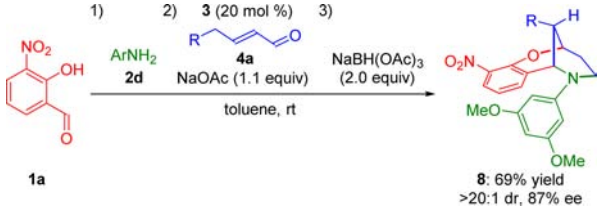
To demonstrate the synthetic applicability of the formed products **5**, investigations on selective transformations were initiated. The compatibility with palladium coupling reactions was verified through a Sonogashira coupling of **5n** to afford the extensively conjugated product **7** in high yield, and with a preserved diastereomeric ratio and enantioenrichment (Scheme 3).

Scheme 3. Application of Bridged Benzoxazocine Product 5n in a Sonogashira Coupling



Reduction of the enamine moiety was attempted under one-pot conditions, applying sodium triacetoxyborohydride as the reductant. The three-step one-pot cascade proceeded smoothly, affording the desired product **8** in good yield and with excellent stereoselectivity (Scheme 4).

Scheme 4. One-Pot Formation of Saturated Benzoxazocine 8



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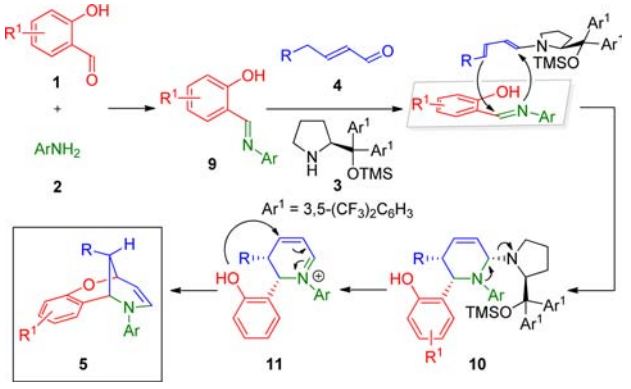
Based on the absolute configuration assignments established through the single crystal X-ray analysis of the product **5w**[11] a plausible reaction mechanism has been proposed (Scheme 5).

Scheme 5. Mechanistic Proposal for the Formation of Bridged Benzoxazocines 5 via a One-Pot Reaction Cascade



It is initiated by condensation of **1** with **2** to give *N*-aryl imine **9**. Subsequently, a Mannich-initiated cyclization reaction between imine **9** and the s-*cis* dienamine derived from **3** and **4** furnishes the cyclohexene framework **10**. Elimination of catalyst **3** to give highly reactive iminium ion **11** and a subsequent intramolecular oxy-Michael addition yield the target bridged benzoxazocines **5**. Importantly, employment of *N*-aryl imines possessing an extended electron-rich π-system might favor the [4 + 2]-cycloaddition pathway over a sequential reaction mechanism initiated by a γ-Mannich reaction involving an s-*trans*-configured dienamine intermediate.

In conclusion, the development of a novel asymmetric organocatalytic one-pot synthesis of bridged benzoxazocines has been presented. The cascade allows for direct $\gamma,\beta,ipso$-functionalization of the employed α,β-unsaturated aldehyde substrates and affords the target products in generally good yields and with high stereoselectivities.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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(11) See Supporting Information for details. CCDC 1009470 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.