Asymmetric Organocatalysis

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Benzofulvenes in Trienamine Catalysis: Stereoselective Spiroindene Synthesis

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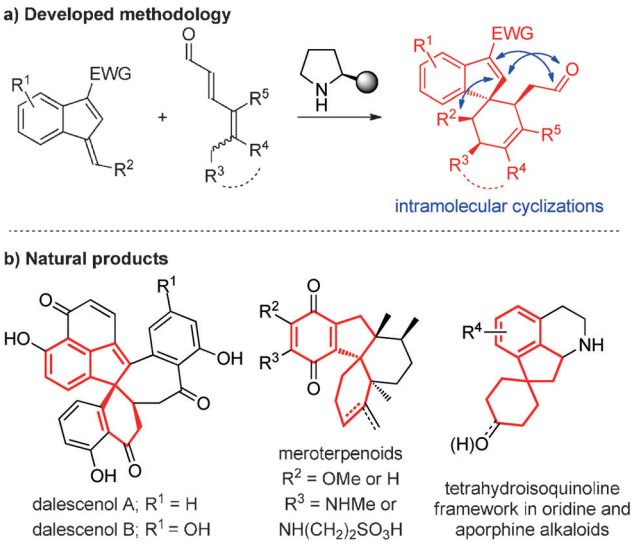
Abstract: *The asymmetric formation of spiroindenes containing up to four contiguous stereocenters from the reaction of benzofulvenes with 2,4-dienals through trienamine catalysis is described. The benzofulvene core was found to be an excellent starting point for the synthesis of interesting spiroindenes through a formal cycloaddition pathway. The reaction was mediated by a diphenylprolinol silyl ether catalyst, and a diverse array of spiroindenes were obtained in high yields with excellent stereoselectivity. An attractive feature of the developed system is the possibility to diversify the product scaffold significantly by further manipulation of the chiral spiroindenes. Thus, three intramolecular ring-closing reactions following the organocatalytic step resulted in highly complex polycyclic systems.*

Benzofulvenes have often been applied as monomers in polymer chemistry[1] and for the construction of porphyrin-like structures.[2] The all-carbon benzofulvene core constitutes an interesting semiaromatic system with a polarized exocyclic double bond. These benzofulvenes have rarely been utilized in small-molecule synthesis, and to the best of our knowledge, no catalytic asymmetric methodologies involving benzofulvenes exist.[3] An electron-withdrawing substituent introduced at the 3-position to increase the reactivity of the benzofulvene core would be expected to further polarize the exocyclic double bond. This feature leads to interesting opportunities for transformations of the final products and simplifies the synthesis of the benzofulvenes, which are prepared by condensation of the corresponding indenes with suitable aldehydes.

The interest in spirocyclic structures has increased in recent years owing to their frequent application in medicinal chemistry[4] and their presence in a multitude of natural products.[5] In methodology development, the emphasis within this field has mainly been on the formation of heteroatom-containing spiro compounds, such as spirooxindoles, for which an abundance of catalytic asymmetric procedures have been disclosed.[6] Catalytic asymmetric strategies aimed at the analogous spiroindenes are more scarce.[7]

We envisioned that organocatalysis[8] could be applied to the stereoselective formation of spiroindenes from benzofulvenes. A strategy based on trienamine catalysis was chosen, which would grant access to indenes spiro-fused to cyclohexenes by a formal [4+2] cycloaddition (Scheme 1 a).[9] The spiroindene products targeted by the envisioned strategy offer a number of molecular handles for further modifications. Most notably, a Michael acceptor present in the indene ring was demonstrated to facilitate intramolecular cyclizations to yield complex polycyclic products containing a spiroindane core.



Scheme 1. a) Envisioned enantioselective route to spiroindenes and possibilities for intramolecular cyclization reactions. b) Natural products containing the spiroindene or spiroindane core. EWG = electron-withdrawing group.

Several interesting natural products containing an indene or indane ring spiro-fused to a six-membered carbocycle are known. These compounds include the immunosuppressing dalescenols,[10] a series of antimicrobial meroterpenoids,[11] and several tetrahydroisoquinoline alkaloids (Scheme 1 b).[12]

Initial test reactions of the nitrile-substituted benzofulvene **1a** (1.2 equiv) and 2,4-dienal **2a** (1 equiv) in the presence of diphenylprolinol silyl ether catalyst **3a** (20 mol %) in toluene displayed the desired reactivity.[13] Full conversion into the spiroindene **4a** with excellent stereoselectivity (d.r. 18:1, 98 % *ee*) was observed in the presence of benzoic acid (40 mol %; Table 1, entry 1). A change in the additive from benzoic acid to *ortho*-fluorobenzoic acid facilitated full conversion within 24 h with a 10 mol % catalyst loading (Table 1, entries 2 and 3). In toluene, further lowering of the catalyst loading to 5 mol %

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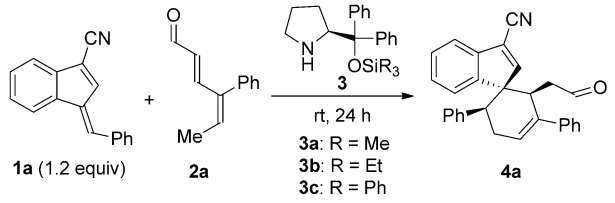
Table 1: Reaction optimization.



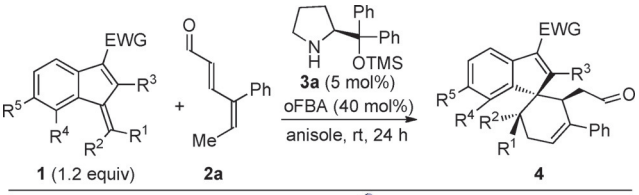
Entry[a]	Cat. **3** (mol%)	Additive (mol%)	Solvent	Conv.[b] [%]	d.r.[b]	*ee*[c] [%]
1	**3a** (20)	BA (40)	toluene	>95	18:1	98
2	**3a** (10)	BA (40)	toluene	94	16:1	98
3	**3a** (10)	oFBA (40)	toluene	>95	17:1	98
4	**3a** (5)	oFBA (40)	toluene	78	18:1	98
5	**3a** (5)	oFBA (40)	anisole	>95	16:1	98
6	**3b** (5)	oFBA (40)	anisole	>95	8.3:1	98
7	**3c** (5)	oFBA (40)	anisole	>95	3.0:1	>99

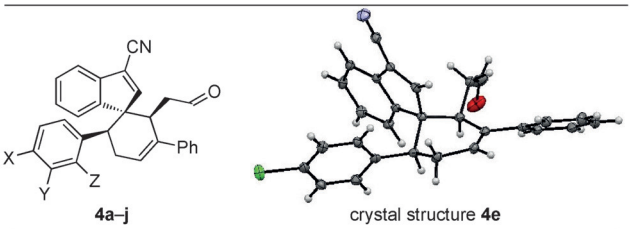
[a] Reactions were performed on a 0.05 mmol scale in 0.1 mL of the solvent. BA = benzoic acid, oFBA = *ortho*-fluorobenzoic acid. [b] The conversion and diastereomeric ratio were determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The *ee* value was determined by chiral-stationary-phase ultraperformance conversion chromatography (UPC^2).

decreased the reaction rate significantly (Table 1, entry 4), but in anisole the reaction reached full conversion in 24 h (Table 1, entry 5). The greater bulkiness of diphenylprolinol silyl ether catalysts **3b**,**c** was found to have a negative impact on the diastereoselectivity (Table 1, entries 6 and 7).

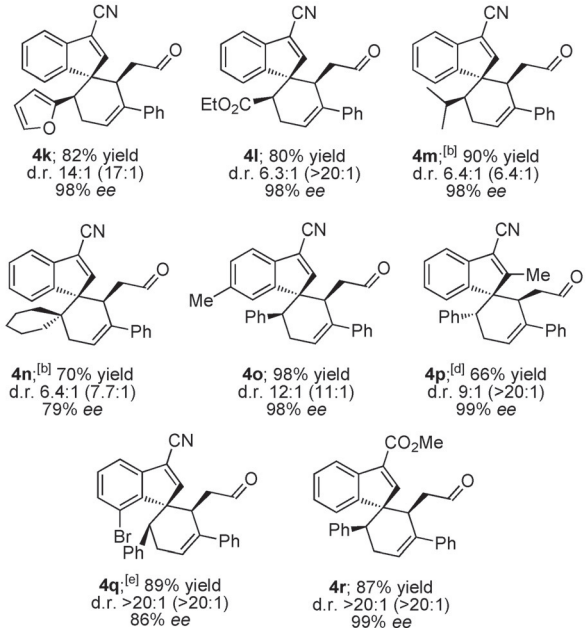
We investigated the scope of the reaction with respect to the benzofulvene substrate **1** under the optimized reaction conditions (Scheme 2). The standard benzofulvene **1a** provided product **4a** in excellent yield and stereoselectivity. Both electron-donating and electron-withdrawing substituents on the phenyl group were tolerated, and spiroindenes **4b–d** were obtained in high to excellent yields with high diastereoselectivity and excellent enantioselectivity. Similar results were obtained with halogenated benzofulvenes **1e**,**f**. The effects of the substitution pattern of the phenyl group attached to the exocyclic double bond of **1** were probed with a methyl substituent (products **4g–i**), and *ortho* substitution was found to decrease the diastereoselectivity of the reaction, although the excellent enantioselectivity and yield were maintained. A hydroxy substituent was also tolerated in the *ortho* position under slightly modified conditions owing to the low solubility of the substrate **1j**. Benzofulvenes bearing a 2-furanyl or an ester group at the exocyclic double bond gave the corresponding products **4k**,**l** in high yields with good to high diastereoselectivity and excellent enantioselectivity. An aliphatic R^1 substituent was also tolerated, and **4m** was obtained in excellent yield and enantioselectivity, whereas the diastereoselectivity decreased slightly. A remarkable example of the reaction is the formation of **4n** with two adjacent spirocyclic centers. Spiroindene **4n** was formed in 70% yield with moderate selectivity.

Substitution on the indene core was also tested, and a 6-methyl group gave excellent yield and stereoselectivity (product **4o**). The sterically demanding substrate **1p** was obtained with the *Z* configuration (R^1 = H, R^2 = Ph) at the





4; X, Y, Z	Yield [%]	d.r.	*ee* [%]
4a; H, H, H	95	16:1 (16:1)	98
4a;[a] H, H, H	88	16:1 (15:1)	98
4b; OMe, H, H	88	17:1 (>20:1)	97
4c; CO_2Me H, H	94	13:1 (13:1)	98
4d; CF_3, H, H	91	11:1 (12:1)	97
4e; Cl, H, H	81	12:1 (>20:1)	97
4f; Br, H, H	75	13:1 (>20:1)	97
4g; Me, H, H	93	14:1 (15:1)	98
4h; H, Me, H	82	19:1 (>20:1)	98
4i;[b] H, H, Me	87	6.0:1 (6.0:1)	98
4j;[c] H, H, OH	76	10:1 (>20:1)	99



Scheme 2. Exploration of the scope of the reaction with respect to the benzofulvene **1**. Reactions were performed on a 0.1 mmol scale in anisole (0.2 mL). Yields were determined following flash chromatography on silica gel. The diastereomeric ratios in the crude reaction mixture and in the isolated product (in parenthesis) were determined by ^{1}H NMR analysis. The *ee* values were determined by chiral-stationary-phase UPC^2. See the Supporting Information for details. [a] The reaction was carried out on a 1.0 mmol scale. [b] The product was reduced with $NaBH_4$ and isolated as the corresponding alcohol for purification and characterization purposes. [c] Compound **1j** used as the limiting reactant with **2a** (2.0 equiv) in anisole (0.4 mL). [d] The reaction was carried out with 20 mol% of **3a**. [e] The reaction was carried out in 0.3 mL of anisole.

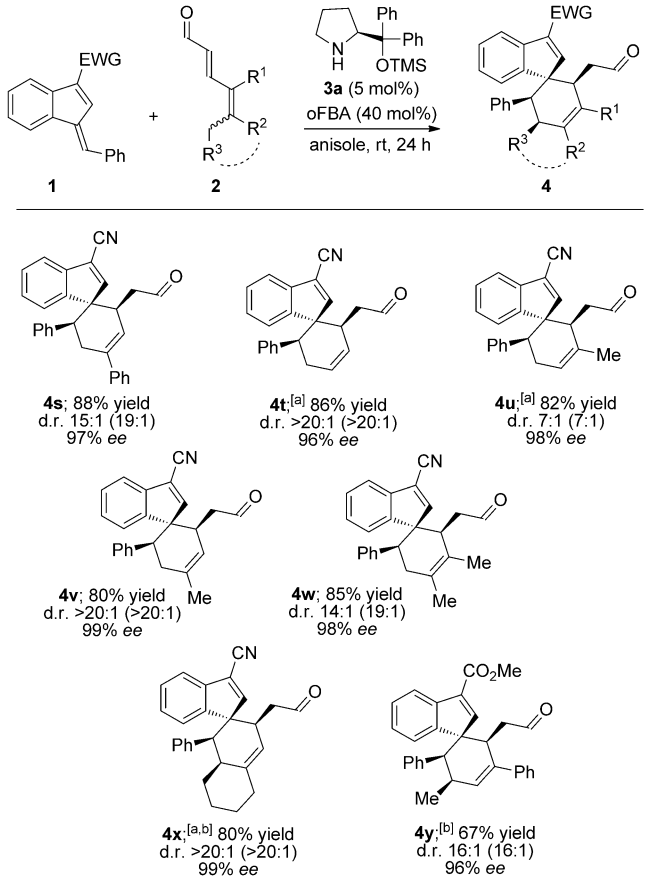
exocyclic double bond and required higher catalyst loading in the trienamine-mediated reaction. Nonetheless, the desired product **4p** was obtained in good yield and with good stereoselectivity. The *Z* configuration at the double bond resulted in the inversion of one stereocenter in the obtained product, as would be expected from the mechanism outlined in Figure 1 (see below). The configuration of **4p** was assigned on the basis of a NOE coupling between the hydrogen atom attached to the inverted stereocenter and the methyl group. With a 7-bromo substitution pattern only one diastereoisomer was observed, and the product **4q** was obtained in high yield, but a decrease in enantioselectivity (86% *ee*) was observed. No reactivity was observed if the electron-withdrawing group was not present in the benzofulvene. However, the nitrile group is not crucial, as an ester group facilitated the reaction as well with similar results (product **4r**). A reaction on a larger scale without modifications (1.0 mmol) was found to be feasible, and **4a** was obtained in high yield with no change in stereoselectivity. The absolute configuration of the major diastereoisomer of **4e** was determined by X-ray crystallography (Scheme 2), and the configuration of the remaining spiroindenes **4** was assigned by analogy.

A variety of 2,4-dienals **2** also delivered the desired spiroindenes **4** with good results (Scheme 3). By changing the position of the phenyl group, **4s** was obtained. The application of 2,4-hexadienal gave the desired product **4t** in high yield with excellent stereoselectivity. The methyl-substituted spiroindenes **4u–w** were obtained in high yields with excellent enantioselectivity. A fourth contiguous stereocenter and another ring were successfully introduced in product **4x** in high yield with close to perfect stereoselectivity. In an attempt to construct a fourth stereocenter with a methyl substituent, incomplete conversion and poor diastereoselectivity was observed with the benzofulvene substrate **1a**. However, the ester-substituted benzofulvene **1r** facilitated the formation of spiroindene **4y** in good yield with excellent stereoselectivity.

In Figure 1, a rationalization for the observed stereochemical outcome of the reaction is proposed: The reaction of an all-*E*-configured trienamine intermediate in an *s-trans,s-trans,s-cis* conformation with the benzofulvene via an *endo* transition state would give the product with the observed configuration. Charge stabilization in such a transition state, and possibly in a zwitterionic intermediate,[9g,14] between the nitrile group and the enamine moiety could be a significant factor. In support of this hypothesis, no reactivity was observed with enamine or dienamine catalytic systems. The structure and relative configuration of the obtained products **4** prompted the exploration of possible intramolecular cyclization reactions of these compounds.

Reduction of the aldehyde moiety in spiroindene **4a** by $NaBH_4$ gave the corresponding alcohol, and upon the addition of DBU to the reaction mixture, an intramolecular oxa-Michael ring closure onto the α,β-unsaturated nitrile group occurred (Scheme 4a, left). The tetracyclic spiro compound **5**, containing five contiguous stereocenters, was formed diastereoselectively in 58% yield, and the relative configuration was determined by X-ray crystallography (Scheme 4c, left). An intramolecular aza-Michael reaction was performed in a similar fashion starting from **4a** (Scheme 4a, right). Following reductive amination, spontaneous ring closure gave the expected bridged heterocyclic product **6**, which was isolated as one diastereoisomer in 54% yield. The configuration was assigned by analogy to compound **5**.

Finally, an attempt was made to take advantage of the *ortho*-hydroxy functionality of **1j** in a one-pot procedure (Scheme 4b). After completion of the organocatalytic reaction, the addition of Et_3N facilitated nucleophilic attack of the phenol onto the α,β-unsaturated nitrile group. A subsequent



Scheme 3. Scope of the reaction for the formation of spiroindenes **4** with respect to the 2,4-dienal **2**. Reactions were performed on a 0.1 mmol scale in anisole (0.2 mL). Yields were determined following flash chromatography on silica gel. The diastereomeric ratios in the crude reaction mixture and in the isolated product (in parenthesis) were determined by ^{1}H NMR analysis. The *ee* values were determined by chiral-stationary-phase UPC^2. See the Supporting Information for details. [a] Reaction time: 48 h. [b] The configuration of the fourth stereocenter was assigned on the basis of NOE couplings in **4y**.

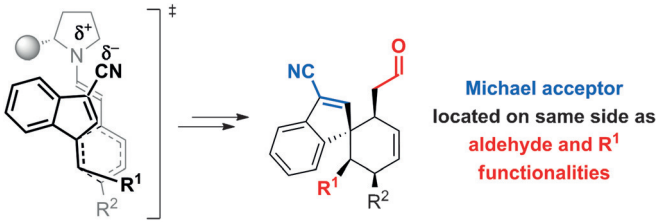
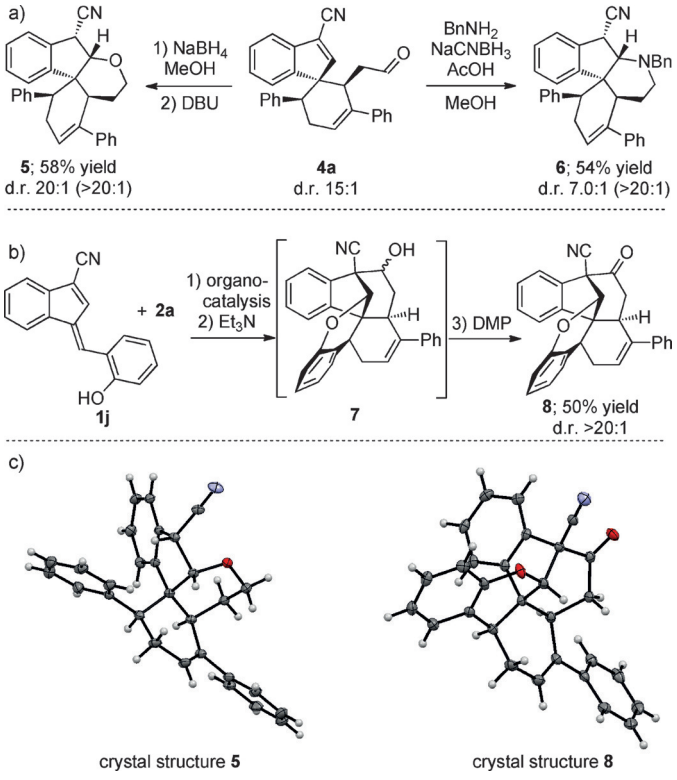


Figure 1. Rationale for the observed stereochemical outcome.



Scheme 4. Intramolecular cyclization reactions and crystal structures. Bn = benzyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMP = Dess–Martin periodinane. See the Supporting Information for further details.

ring closure from the α-carbon atom of the nitrile group to the aldehyde formed another bridging ring on the spirocyclic core. Prior to workup, oxidation of the secondary alcohol in **7** eliminated one stereocenter, which eased purification and characterization. The complex polycyclic product **8** was isolated as one diastereoisomer in 50% yield through a one-pot procedure from simple substrates. The structure of compound **8** was established by X-ray crystallography (Scheme 4c, right). These transformations demonstrate some of the opportunities for intramolecular transformations available for the synthesized chiral spiroindenes **4**, and significantly expand the chemical space explored in this study.

In conclusion, the reactivity of a variety of benzofulvenes in a trienamine-mediated asymmetric [4+2] cycloaddition has been explored. A range of interesting spiroindene compounds were formed efficiently in high yields with excellent stereoselectivity. Furthermore, it has been shown that complex polycyclic systems can be readily obtained through further synthetic manipulation of the spiroindene products of the organocatalytic step by exploiting the Michael acceptor present in these compounds.

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Keywords: asymmetric catalysis · benzofulvenes · spiro compounds · spiroindenes · trienamine catalysis

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