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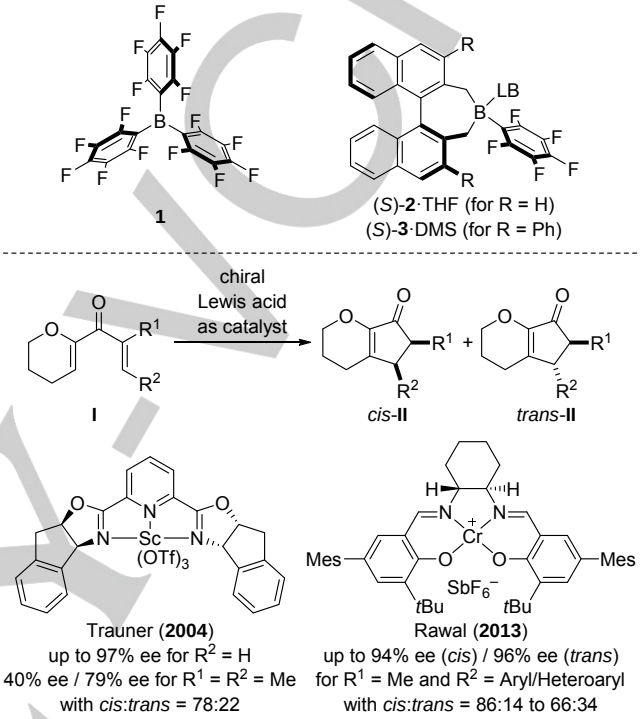
Enantioselective Nazarov Cyclizations Catalyzed by an Axial Chiral, C_6F_5-Substituted Boron Lewis Acid

Lars Süsse, Maria Vogler, Marius Mewald, Benedict Kemper, Elisabeth Irran, and Martin Oestreich*

Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 85th birthday

Abstract: A chiral variant of $B(C_6F_5)_3$ with a 3,3'-disubstituted binaphthyl backbone is shown to catalyze Nazarov cyclizations with high levels of enantio- and diastereocontrol. Parent $B(C_6F_5)_3$ also promotes these ring closures efficiently. This electrocyclization is another example of the still small family of carbon–carbon bond formations mediated by $B(C_6F_5)_3$ as catalyst.

The Nazarov cyclization is a highly useful method to access functionalized cyclopent-2-en-1-ones.[1] A variety of Lewis and Brønsted acids have been shown to act as efficient catalysts for this transformation, including the ubiquitous boron Lewis acid $BF_3{\cdot}OEt_2$.[2] Interestingly, the now popular tris(pentafluorophenyl)borane ($B(C_6F_5)_3$ (**1**); Scheme 1, top) and derivatives thereof have not employed yet despite their similar Lewis acidity.[3] We are aware of just one example where **1** was employed as a promoter of decarboxylative Nazarov cyclizations.[4] Moreover, enantioselective variants based on boron Lewis acids are not known to date. We anticipated that chiral $B(C_6F_5)_3$ congeners introduced by us such as (*S*)-**2**·THF[5] and the more sterically hindered (*S*)-**3**·DMS[6] with binaphthyl backbones could serve as catalysts (Scheme 1, top). High levels of enantiocontrol are still rare for these ring closures when catalyzed by Lewis acids.[7] For example, only two enantioselective protocols have been described so far for converting alkoxy-activated **I** into *cis*-**II** and *trans*-**II** (Scheme 1, bottom).[8–10] Trauner made use of a Sc(III)-pybox complex[8] and Rawal used a Cr(III)-salen complex;[9] the cyclopentenones **II** were obtained with high enantiomeric excess and moderate diastereoselectivity favoring the *cis* isomer. We report here metal-free methods for both the racemic (with **1**) and the enantioselective Nazarov cyclization (with (*S*)-**3**·DMS) of precursors **I** with good diastereoselectivities.



Scheme 1. Boron Lewis acids used in the present study (top) and reported enantioselective Nazarov cyclizations catalyzed by chiral Sc(III) and Cr(III) Lewis acids (bottom). DMS = dimethyl sulfide; LB = Lewis base; Tf = trifluoromethanesulfonyl; Mes = mesityl.

We began with $B(C_6F_5)_3$ (**1**) as catalyst and were pleased to see that 5.0 mol% of **1** promoted our model cyclization **4a** to **5a** in high yield and with good *cis*:*trans* ratio (Table 1, entry 1). This result is one of the few examples of a carbon–carbon bond formation catalyzed by $B(C_6F_5)_3$ (**1**).[11] For comparison, triphenylborane did not mediate this reaction (entry 2). We directly continued with chiral $B(C_6F_5)_3$ congeners (*S*)-**2**·THF and (*S*)-**3**·DMS; their Lewis acidities had been estimated approximately 80% of **1** by the Gutmann–Beckett method (see the Supporting Information for details and the molecular structure of (*S*)-**3**·Et_3PO).[5,12] Chiral (*S*)-**2**·THF indeed catalyzed the desired ring closure but far less cleanly than **1** (entry 3); 25% isolated yield of **5a** were obtained at full conversion of **4a** after two hours but the enantioselectivity of 31% ee was promising. In contrast, a smooth reaction was found with (*S*)-**3**·DMS under an otherwise identical setup (entry 4). After six hours, the isolated yield of **5a** was 92%, and the enantioselectivity was 90% ee and the *cis*:*trans* ratio 88:12. Also, the absolute configuration was opposite to that found with (*S*)-**2**·THF (entry 4 versus entry 3). These results were obtained in 1,2-$F_2C_6H_4$; a screening of related solvents led to lower enantiomeric excesses (entries 5–8), and Lewis-basic THF was detrimental to conversion (entry 9). Returning to 1,2-$F_2C_6H_4$ as the optimal solvent, less (1.0 mol%) and more (5.0 mol%) catalyst loading was tested (entries

[*] L. Süsse, M. Vogler, Dr. M. Mewald, Dr. E. Irran,[++] Prof. Dr. M. Oestreich
Institut für Chemie, Technische Universität Berlin
Strasse des 17. Juni 115, 10623 Berlin (Germany)
E-mail: martin.oestreich@tu-berlin.de
Homepage: http://www.organometallics.tu-berlin.de

Dr. M. Mewald, Dr. B. Kemper, Prof. Dr. M. Oestreich
Organisch-Chemisches Institut,
Westfälische Wilhelms-Universität Münster
Corrensstrasse 40, 48149 Münster (Germany)

[++] X-ray crystal-structure analyses.

Supporting information for this article is given via a link at the end of the document.

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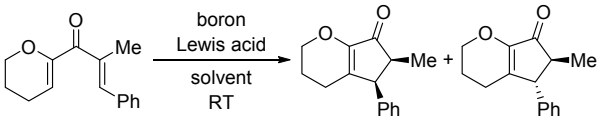
10 and 11). Compared to the routinely used 2.4 mol% of (*S*)-**3**·DMS (entry 4), the yields remained high in both cases but the enantioselectivity dwindled at the reduced catalyst loading.

Table 1. Development of Nazarov cyclizations catalyzed by C_6F_5-substituted boron Lewis acids.



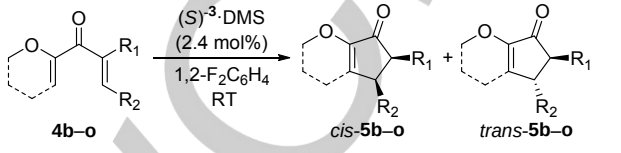
4a *cis*-**5a** *trans*-**5a**

Entry	Borane (mol%)	Solvent	Time	d.r.[a]	Yield [%][b]	ee[c] [%][d]
1	**1** (5.0)	CH_2Cl_2	6 h	87:13	93	—
2	Ph_3B (5.0)	CH_2Cl_2	14 h	—	n.r.	—
3	(*S*)-**2**·THF (2.4)	1,2-$F_2C_6H_4$	2 h	n.d.[e]	25	–31[f]
4	(*S*)-**3**·DMS (2.4)	1,2-$F_2C_6H_4$	6 h	88:12	92	90
5	(*S*)-**3**·DMS (2.4)	ClC_6H_5	4 h	90:10	85	82
6	(*S*)-**3**·DMS (2.4)	C_6H_6	4 h	88:12	95	82
7	(*S*)-**3**·DMS (2.4)	toluene	4 h	96:4	89	62
8	(*S*)-**3**·DMS (2.4)	CH_2Cl_2	4 h	85:15	95	87
9	(*S*)-**3**·DMS (2.4)	THF	4 d	78:22	25[g]	81
10	(*S*)-**3**·DMS (1.0)	1,2-$F_2C_6H_4$	6 h	91:9	93	83
11	(*S*)-**3**·DMS (5.0)	1,2-$F_2C_6H_4$	2 h	91:9	92	89

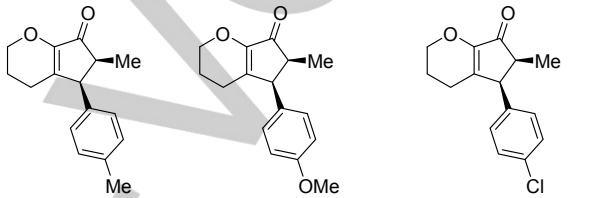
[a] *cis*:*trans* ratio determined by ^{1}H NMR spectroscopy prior to purification. [b] Combined isolated yield of both diastereomers after purification by flash chromatography on silica gel. [c] Enantiomeric excess of *cis* isomer. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Determination of the the diastereomeric ratio failed because of low purity. [f] Opposite absolute configuration. [g] 36% conversion. n.r. = no reaction. n.d. = not determined.

We then examined the scope of this enantioselective Nazarov cyclization with the optimized procedure (Scheme 2). For the preparation of the racemic mixtures, the same set of precursors was cyclized with $B(C_6F_5)_3$ (**1**) as catalyst (see the Supporting Information for yields and *cis*:*trans* ratios). Electronic and steric variation of the aryl group (R^2) in **4** had little effect on enantioinduction and diastereoselectivity except for strongly electron-donating OMe (**4c**→**5c**) and electron-withdrawing CF_3 groups (**4h**→**5h**) where the enantioselection eroded to 64 and 79% ee, respectively. The series regioisomeric aryl bromides **4e**–**g** afforded consistently high enantiomeric excesses and diastereomeric ratios with the highest ee for the *ortho* isomer. The diastereoselectivity collapsed with a 1,1'-biphenyl-4-yl group (**4i**→**5i**) but was restored with a β-naphthyl group (**4j**→**5j**). Heteroaryl groups such as fur-2-yl (**4k**→**5k**) and thien-2-yl (**4l**→**5l**) were also compatible but the enantiomeric excess was significantly lower in the latter case. In general, these results, particularly the *cis*:*trans* ratios, compare favorably with those obtained by Rawal and co-workers.[9] The absolute configuration of **5** was secured by X-ray diffraction; the molecular structures of **5d** and **5l** are reported in the Supporting Information.

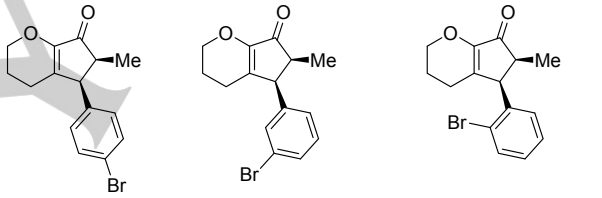
An Et instead of a Me group as R^1 had a dramatic effect on stereocontrol (**4m**→**5m**); both enantiomeric excess (90% versus 79%) and diastereomeric ratio (88:12 versus 63:37) were markedly diminished. The precursor with R^1 = R^2 = Me cyclized with no diastereocontrol (**4n**→**5n**); similar observations had been made before.[9] Acyclic substrate **4o** required three days for full conversion and the isolated yield was just 53% but the enantiomeric excess of **5o** was very good (86% ee; cf. 80% ee in Ref. [9]).



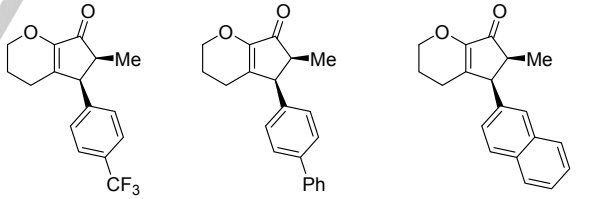
4b–o *cis*-**5b–o** *trans*-**5b–o**



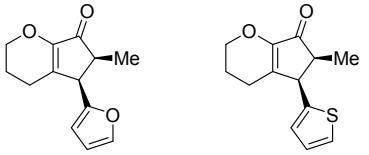
5b: 90% after 6 h, 93% ee (*cis*), *cis*:*trans* = 91:9 — **5c**: 85% after 6 h, 64% ee (*cis*), *cis*:*trans* = 92:8 — **5d** (X-ray): 86% after 6 h, 89% ee (*cis*), *cis*:*trans* = 89:11



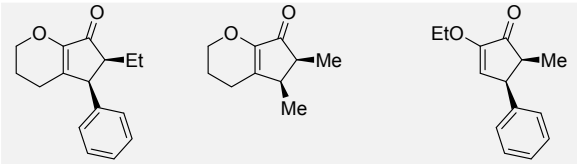
5e: 97% after 6 h, 93% ee (*cis*), *cis*:*trans* = 90:10 — **5f**: 84% after 6 h, 90% ee (*cis*), *cis*:*trans* = 90:10 — **5g**: 85% after 6 h, 96% ee (*cis*), *cis*:*trans* = 85:15



5h: 96% after 6 h, 79% ee (*cis*), *cis*:*trans* = 86:14 — **5i**: 83% after 1 d, 86% ee (*cis*), *cis*:*trans* = 77:23 — **5j**: 96% after 1 d, 85% ee (*cis*), *cis*:*trans* = 91:9



5k: 92% after 9 h, 92% ee (*cis*), *cis*:*trans* = 90:10 — **5l** (X-ray): 90% after 6 h, 79% ee (*cis*), *cis*:*trans* = 94:6



5m: 75% after 6 h, 79% ee (*cis*), *cis*:*trans* = 63:37 — **5n**: 86% after 9 h, 83% ee (*cis*), *cis*:*trans* = 57:43 — **5o**: 53% after 3 d, 86% ee (*cis*), *cis*:*trans* = n.d.

Scheme 2. Scope of the enantioselective Nazarov cyclization catalyzed by (*S*)-**3**·DMS (*cis*:*trans* ratios determined by ^{1}H NMR spectroscopy prior to

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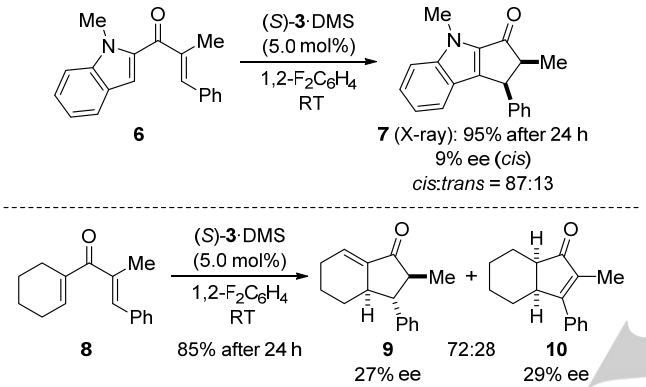
purification; combined yields determined after purification by flash chromatography on silica gel; enantiomeric excesses determined by HPLC analysis on chiral stationary phases). n.d. = not determined.

Indole-derived **6** had recently been a challenging precursor in an investigation by Zhu, Zhou, and co-workers using cooperative catalysis (**6**→**7** with 59% ee (*cis*) and 97% ee (*trans*) and *cis*:*trans* = 60:40).[13] Our protocol converted **6** predominantly into the *cis* isomer of **7** in high yield but the enantiomeric excess was low (Scheme 3, top); the relative configuration of **7** was established as *cis* by X-ray diffraction (the molecular structure is reported in the Supporting Information). Also, the unactivated substrate **8** did undergo the ring closure but led to regioisomeric **9** and **10** with poor enantiomeric excesses (Scheme 3, bottom). These systems had furnished the best results with Rawal's method [e.g., **9** (*trans*): 78%, 86% ee, *trans*:*cis* > 95:5).[9]



Scheme 3. Limitations the enantioselective Nazarov cyclization catalyzed by (*S*)-**3**·DMS (*cis*:*trans* and regioisomeric ratios determined by ^{1}H NMR spectroscopy prior to purification; combined yields determined after purification by flash chromatography on silica gel; enantiomeric excesses determined by HPLC analysis on chiral stationary phases.

To summarize, we have disclosed here an efficient enantioselective Nazarov cyclization catalyzed by an axial chiral variant of $B(C_6F_5)_3$. As in previous but unrelated work,[6a] the steric hindrance exerted by the 3,3'-disubstituted binaphthyl backbone of the boron Lewis acid (*S*)-**3**·DMS is crucial for achieving high enantioinduction. Enantiomeric excesses are high (up to 96% ee) and *cis*:*trans* ratios often synthetically useful. Our work complements the existing metal-catalyzed procedures[8,9] and important contributions by Rueping and co-workers using chiral Brønsted acids.[10] This electrocyclization also expands the application of $B(C_6F_5)_3$ and its chiral congeners to carbon–carbon bond-forming reactions.[11]

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Keywords: asymmetric catalysis • boron • C–C bond formation • electrocyclic reactions • Lewis acids

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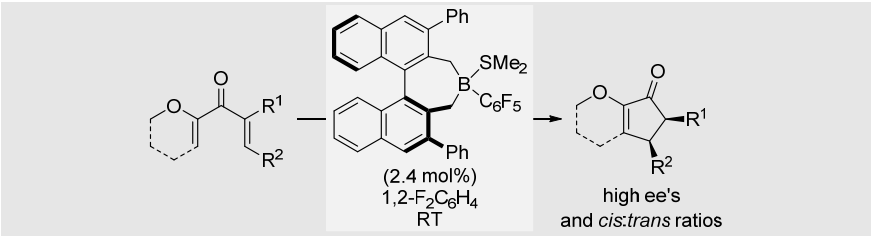

Boron with torque! An axial chiral variant of tris(pentafluorophenyl)borane, $B(C_6F_5)_3$, promotes Lewis acid-catalyzed Nazarov cyclizations of activated precursors with high enantiomeric excesses (see scheme). The diastereoselectivity is also good, usually favoring the *cis* isomer in synthetically useful ratios. $B(C_6F_5)_3$ catalyzes the ring closure of the same set of substrates in racemic fashion.

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