

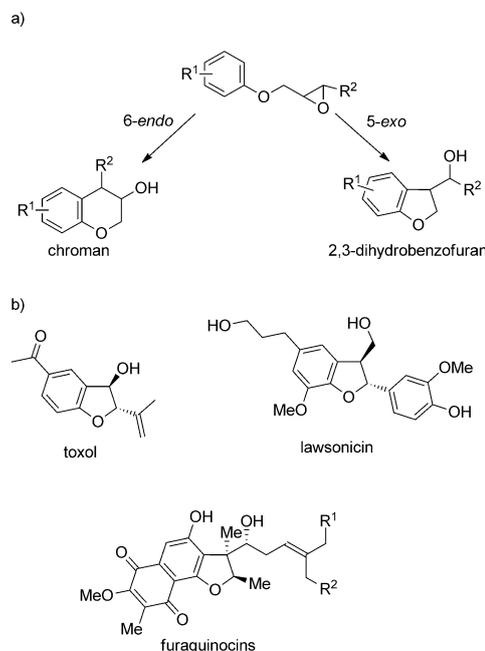
## Asymmetric Catalysis

## Taming the Friedel–Crafts Reaction: Organocatalytic Approach to Optically Active 2,3-Dihydrobenzofurans\*\*

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The Friedel–Crafts reaction constitutes one of the fundamental reactions in organic chemistry and allows facile functionalization of aromatics and heteroaromatics.<sup>[1]</sup> Asymmetric variants of this reaction that enable the introduction of benzylic stereocenters are well recognized.<sup>[2]</sup> Whereas imines constitute a particularly attractive group of electrophilic reagents commonly employed in the Friedel–Crafts reaction, the application of epoxides as electrophiles has been much less studied.<sup>[2a,3,4]</sup> Intramolecular epoxide openings have been successfully applied to the construction of heterocyclic systems.<sup>[3a-c,4]</sup> However, since epoxide opening can proceed through two different pathways (Scheme 1 a), regioselectivity of the reaction is an important issue. Whereas 6-*endo* cyclizations were shown to be a reliable tool for the construction of chroman derivatives,<sup>[4]</sup> the application of 5-*exo* cyclizations for the synthesis of 2,3-dihydrobenzofurans is, to the best of our knowledge, unprecedented.

The *trans*-2,3-disubstituted-2,3-dihydrobenzofuran is a moiety often encountered in nature.<sup>[5,6]</sup> Compounds incorporating this structural motif have been isolated from different species of higher plants for example, Asteraceae.<sup>[5a,b]</sup> Toxol,<sup>[5a]</sup> a natural product of *Encelia californica* and lawsonicin,<sup>[5d]</sup> as well as other structurally related neolignans<sup>[5e-h,7b]</sup> constitute representative examples of such naturally occurring 2,3-dihydrobenzofurans (Scheme 1 b). The biological activity of these systems is also well recognized.<sup>[5a]</sup> For example, the furaquinocins are a family of cytotoxic antibiotics.<sup>[6]</sup> Intriguing biological properties combined with wide occurrence in nature has become a driving force for the development of synthetic methods leading to these structural motifs.<sup>[7]</sup> However, methods for their preparation in an asymmetric fashion are limited and rely mainly on the application of kinetic resolution,<sup>[8]</sup> chiral auxiliaries,<sup>[9]</sup> or chiral starting materials.<sup>[10]</sup> Enantioselective, catalytic methods are also known,<sup>[11]</sup> although, drawbacks related to low efficiency or scope restrictions occur in most cases.



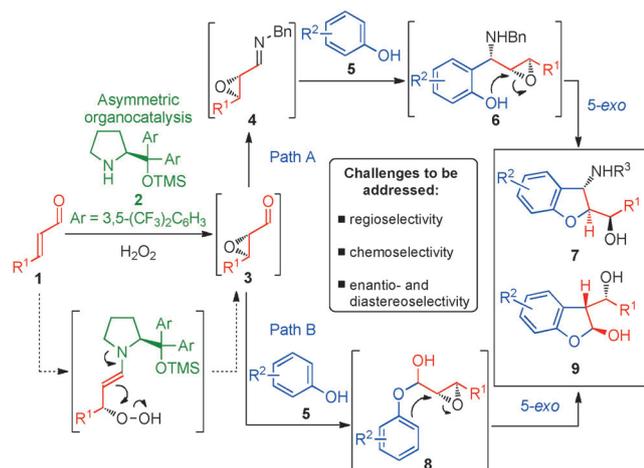
**Scheme 1.** a) Synthesis of heterocycles through the regioselective intramolecular Friedel–Crafts reaction with epoxides. b) Structures containing the 2,3-dihydrobenzofuran motif.

Given the importance of optically active *trans*-2,3-disubstituted-2,3-dihydrobenzofurans, studies on a synthetic methodology offering general and enantioselective access to these compounds were initiated. Our plan was focused on the development of one-pot reaction cascades that enable efficient control of the regio- and chemoselectivity of the overall reaction sequence through structural modifications of the intermediates involved. Such strategies, if successful, would offer an easy entry to diversely substituted products starting from common precursors. The approach is depicted in Scheme 2. It was envisioned that diversity-oriented approaches to the differently substituted 2,3-dihydrobenzofurans **7** and **9** could rely on the application of 2,3-epoxy aldehydes **3** as common intermediates. These interesting 1,2-di-electrophilic species are easily available by asymmetric organocatalytic<sup>[12]</sup> epoxidation of the  $\alpha,\beta$ -unsaturated aldehydes **1**.<sup>[13]</sup> It was expected that initial imine formation from **3** should enable Friedel–Crafts reaction with the electron-rich hydroxyarenes **5** to occur at the imine group of **4**. Subsequent 5-*exo*-tet epoxide opening of **6** through the hydroxyarenic oxygen atom should result in formation of the 2,3-dihydrobenzofurans **7**. Alternatively, it was anticipated that direct

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**Scheme 2.** Asymmetric organocatalytic approach to optically active 2,3-dihydrobenzofurans. TMS = trimethylsilyl.

reaction of the 2,3-epoxy aldehydes **3** with hydroxyarenes **5** might proceed in the following sequence: 1,2-addition of hydroxyarenic hydroxy group to the carbonyl group of **3** to give intermediate **8** with subsequent 5-*exo*-tetraepoxide opening to afford **9**. In such a manner molecular complexity and diversity should be attainable from easily available starting materials by simple modification of the structure of the key intermediates, thus resulting in a different reactivity pattern. However, at the outset of our studies the concept seemed particularly challenging since issues regarding regioselectivity (alkylation of the electron-rich hydroxyarenes **5** at different positions or epoxide opening 5-*exo* versus 6-*endo*), chemoselectivity (arylation of 1,2-di-electrophilic species **3** or **4** at different positions; carbonyl or imine moiety versus epoxide carbon atoms), and diastereoselectivity (new stereogenic center formed) of the Friedel–Crafts step needed to be taken into consideration.

Herein we report on the efficient asymmetric diversity-oriented access to optically active *trans*-2,3-disubstituted-2,3-dihydrobenzofurans based on organocatalytic one-pot reaction cascades.<sup>[12f]</sup> The diversity of the methodology is additionally expanded by application of the resulting 2,3-dihydrobenzofurans for the construction of more elaborate derivatives.

We initiated our studies with the goal of finding optimal reaction conditions for the synthesis of *trans*-3-(benzylamino)-2-(hydroxyalkyl)-2,3-dihydrobenzofurans **7** (Scheme 2, Path A). Optimization studies using *trans*-2-nonenal (**1a**; R<sup>1</sup> = n-hexyl) and 3,5-dimethoxyphenol (**5a**) as model substrates (for detailed results see the Supporting Information) revealed that the reaction sequence involving epoxidation/imine formation/Friedel–Crafts reaction/epoxide opening is possible. To our delight, the Friedel–Crafts reaction proceeded with complete regio- and chemoselectivity, thus affording **6a** exclusively. Moreover, remarkably high diastereoselectivity (> 20:1 d.r.) was obtained both at –20 °C and at room temperature. Further screening revealed that a base must be employed to accomplish the epoxide opening, with DBU proving to be the most effective. Under these reaction

conditions epoxide opening proceeded by a 5-*exo* pathway to give the 2,3-dihydrobenzofuane **7a** through a TypeA-4-1C3X one-pot reaction sequence<sup>[12f]</sup> (Table 1, entry 1). Gratifyingly, applying these optimized reaction conditions to various linear

**Table 1:** Enantioselective synthesis of *trans*-3-(benzylamino)-2-(hydroxyalkyl)-2,3-dihydrobenzofurans **7**: Aldehyde scope.<sup>[a]</sup>

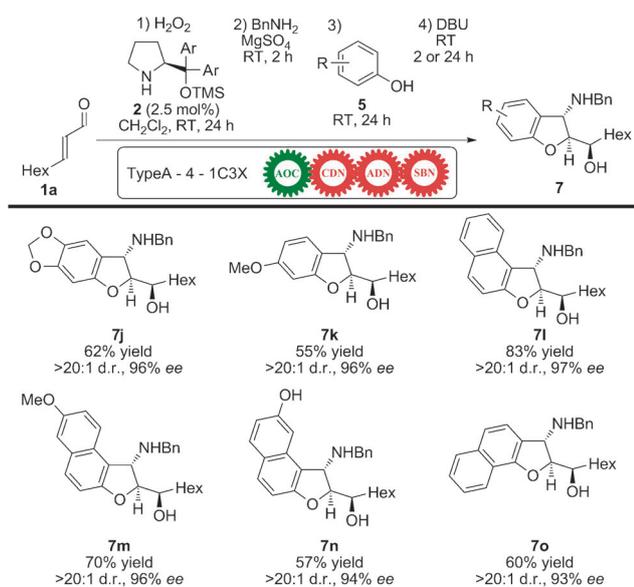
Entry	<b>1</b> (R <sup>1</sup> )	Yield [%] <sup>[b]</sup>	d.r. <sup>[c]</sup>	ee [%] <sup>[d]</sup>
1	<b>1a</b> (Hex)	<b>7a</b> : 70	> 20:1	96
2	<b>1b</b> (Pentyl)	<b>7b</b> : 52	> 20:1	92
3	<b>1c</b> ( <i>n</i> Pr)	<b>7c</b> : 62	> 20:1	95
4	<b>1d</b> ( <i>i</i> Pr)	<b>7d</b> : 60	> 20:1	97
5 <sup>[e]</sup>	<b>1e</b> (Me)	<b>7e</b> : 56	> 20:1	94
6	<b>1f</b> (CH <sub>2</sub> CH <sub>2</sub> ,Ph)	<b>7f</b> : 69	> 20:1	97
7	<b>1g</b> (CH <sub>2</sub> OTBS)	<b>7g</b> : 45	> 20:1	95
8	<b>1h</b> (CO <sub>2</sub> Et)	<b>7h</b> : 44	> 20:1	95
9	<b>1i</b> ( <i>E</i> -Hex-3-enyl)	<b>7i</b> : 60	> 20:1	97

[a] Reactions performed on 0.2 mmol scale in 0.4 mL CH<sub>2</sub>Cl<sub>2</sub> (see the Supporting Information for details). [b] Overall yield given. [c] Determined by <sup>1</sup>H NMR spectroscopy. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Epoxidation performed using 10 mol % of **2**. Nomenclature legend: Type A refers to the position of the enantiodifferentiating manual operation (at the start); 4 refers to the number of manual operations; 1C3X refers to the number of C–C bonds (*m*C) and C–X bonds (*n*X) formed in the one-pot reaction cascade. ADN = addition reaction, AOC = asymmetric organocatalysis, Bn = benzyl, CDN = condensation, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, SBN = substitution reaction.

and  $\gamma$ -branched aliphatic aldehydes (**1b–e**) proved successful and afforded the highly enantiomerically enriched 2,3-dihydrobenzofurans **7b–e** in good overall yields as single regio- and diastereoisomers (Table 1, entries 2–5). Furthermore, the functional-group tolerance of the developed TypeA-4-1C3X cascade was high as various functional groups could be present in the side chain of the starting  $\alpha,\beta$ -unsaturated aldehydes **1f–i** (Table 1, entries 6–9). However, the use of aromatic enals, for example, cinnamaldehyde, did not give satisfactory results, presumably because of the lack of regioselectivity in the epoxide opening reaction.

In the course of further studies, the possibility to employ various electron-rich hydroxyarenes in the TypeA-4-1C3X one-pot reaction sequence was evaluated (Scheme 3). Delightfully, the developed cascade proved to be general as various electron-rich phenols and the naphthols **5b–g** reacted smoothly to afford the target products **7j–o** in moderate to good overall yields (55–83 %) and excellent enantioselectivities (93–97 % *ee*). Moreover, complete regio- and diastereoselectivity was observed in all cases.

With the goal of achieving high control of the regio- and chemoselectivity in the Friedel–Crafts reaction utilizing 2,3-epoxy imines as 1,2-di-electrophilic species being accom-



**Scheme 3.** Enantioselective synthesis of *trans*-3-(benzylamino)-2-(hydroxyalkyl)-2,3-dihydrobenzofurans **7**: Hydroxyarene scope (see the Supporting Information for details).

plished, we turned our attention to the 2,3-epoxy aldehyde counterparts. We were aware of an earlier report showing that under basic conditions similar 2,3-epoxy aldehydes react with electron-rich hydroxyarenes leading to the formation of 3-hydroxy-2,3-dihydrobenzofurans in a non-diastereoselective manner,<sup>[14]</sup> and we therefore focused on the development of a complementary route that would allow stereoselective preparation of the 2-hydroxy-2,3-dihydrobenzofurans **9** (Scheme 2, Path B). In such a manner formal  $\alpha$ -arylation- $\beta$ -hydroxylation of  $\alpha,\beta$ -unsaturated aldehydes would be accomplished since the aldehyde moiety in **9** is masked as the corresponding cyclic hemiacetal.<sup>[15]</sup> To our delight initial experiments showed that in the absence of base the desired reaction pathway was accessible (Table 2). It was found that elevated temperature (40 °C) as well as the presence of an acidic cocatalyst (Table 2, compare entries 1 and 2) are beneficial for the TypeA-2-1C2X reaction cascade. Under these reaction conditions various  $\alpha,\beta$ -unsaturated aldehydes **1** were effectively reacted with 3,5-dimethoxyphenol (**5a**), thus offering an enantio-, diastereo-, and regioselective entry to the 3-(hydroxyalkyl)-2,3-dihydrobenzofuran-2-ols **9** (Table 2, entries 1 and 3–7). Furthermore, other electron-rich hydroxyarenes were successfully employed in the developed reaction cascades as demonstrated for the  $\beta$ -naphthol (**5d**; Table 2, entry 8) and the 2,7-dihydroxynaphthalene (**5f**; Table 2, entry 9). However, longer reaction times were required to achieve full conversion in the annulation step for these substrates.

Interestingly, when 3-dimethylaminophenol (**5h**) was subjected to the optimized reaction conditions the unexpected formation of the dihydrobenzofuran **11** was observed (twofold excess of the starting **5h** was required to accomplish full conversion of **1a**; Scheme 4). We assume that as a result of the strong electron-donating ability of the dimethylamino substituent, the reaction sequence is not terminated at the

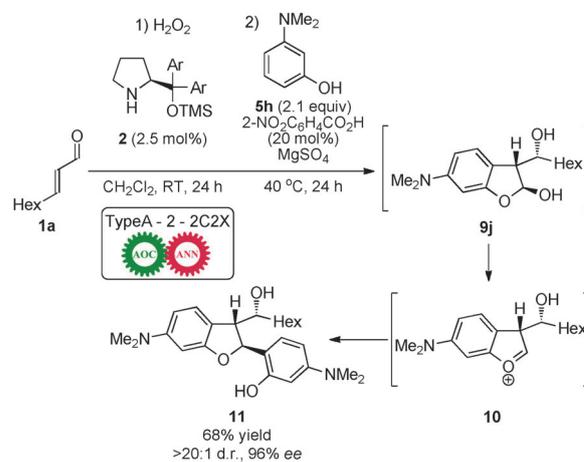
**Table 2:** Enantioselective synthesis of the *trans*-3-(hydroxyalkyl)-2,3-dihydrobenzofuran-2-ols **9**.<sup>[a]</sup>

1) H<sub>2</sub>O<sub>2</sub>  
2) R<sup>2</sup>  
OH  
5  
2-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H  
(20 mol%)  
MgSO<sub>4</sub>  
40 °C, 24 h

R<sup>1</sup>  
1  
TypeA - 2 - 1C2X  
AOC ANN  
9  
R<sup>2</sup>  
OH  
OH

Entry	5	1 (R <sup>1</sup> )	Yield [%] <sup>[b]</sup>	d.r. <sup>[c]</sup>	ee [%] <sup>[d]</sup>
1	5a	1a (Hex)	9a: 57	>20:1	96
2 <sup>[e]</sup>	5a	1a (Hex)	9a: 52	>20:1	96
3	5a	1c (Pr)	9c: 52	>20:1	96
4	5a	1d (iPr)	9d: 51	>20:1	95
5 <sup>[e]</sup>	5a	1e (Me)	9e: 47	>20:1	95
6	5a	1f (CH <sub>2</sub> CH <sub>2</sub> Ph)	9f: 46	>20:1	96
7	5a	1g (CH <sub>2</sub> OTBS)	9g: 62	>20:1	95
8 <sup>[f]</sup>	5d	1a (Hex)	9h: 39	>20:1	96
9 <sup>[g]</sup>	5f	1a (Hex)	9i: 47	>20:1	97

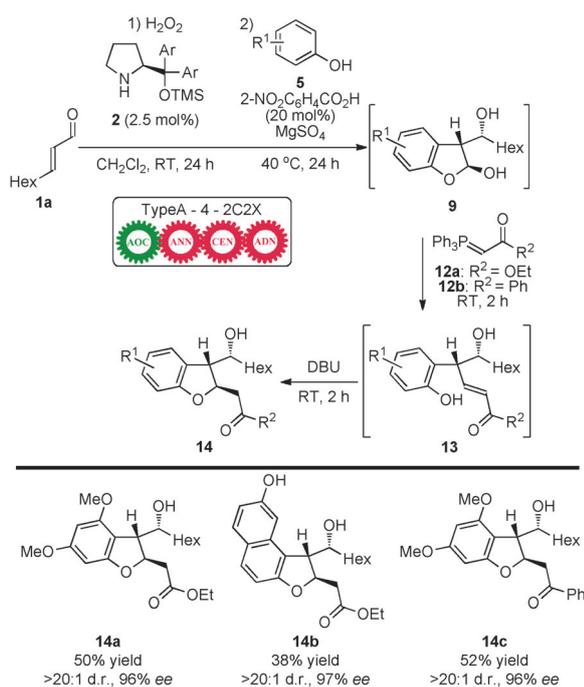
[a] Reactions performed on 0.2 mmol scale in 0.4 mL CH<sub>2</sub>Cl<sub>2</sub> (see the Supporting Information for details). [b] Overall yield given. [c] Determined by <sup>1</sup>H NMR spectroscopy. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Reaction performed in the absence of 2-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H. [f] 2nd step run for 8 days. [g] 2nd step run for 3 days. ANN = annulation, TBS = *tert*-butyldimethylsilyl.



**Scheme 4.** Enantioselective synthesis of *trans*-2-aryl-3-(hydroxyalkyl)-2,3-dihydrobenzofuran **11**.

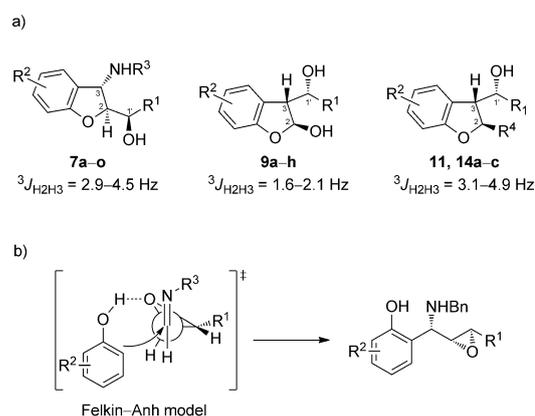
stage of the corresponding 2-hydroxy-2,3-dihydrobenzofuran **9j**. Instead the corresponding oxocarbenium ion **10** is formed, which undergoes a second, fully diastereoselective Friedel-Crafts reaction, thus resulting in the introduction of an aryl moiety at the 2-position of the target 2,3-dihydrobenzofuran **11**.

Taking advantage of the aldehyde moiety, protected as the corresponding cyclic hemiacetal, in **9** we devised an alternative approach for the formation of *trans*-2,3-disubstituted-2,3-dihydrobenzofurans, thus further expanding the diversity obtained by the synthetic strategy. Merging the developed TypeA-2-1C2X reaction cascade (see Table 2) with a subsequent Wittig reaction, using the stabilized phosphorus ylides **12**, and subsequent base-induced oxa-Michael addition proved successful, thus affording access to the dihydrobenzofurans **14** (Scheme 5). In the case of the Wittig reagent **12b** the olefination reaction had to be performed at 40 °C. Notably, cyclization then proceeded spontaneously in the absence of base affording **14c** through a TypeA-3-2C2X one-pot reaction cascade.



**Scheme 5.** Enantioselective synthesis of the *trans*-2,3-dihydrobenzofurans **14** by a TypeA-4-2C2X one-pot reaction cascade. CEN = chain-elongation.

The absolute stereochemistry of the C2 and C1' stereogenic centers in the dihydrobenzofurans **7** as well as that of the C3 and C1' stereocenters in the products **9**, **11**, and **14** were assigned on the basis of our earlier results regarding 2,3-epoxy aldehydes and their applications in target-oriented syntheses.<sup>[16a-d]</sup> These assignments were additionally confirmed by single-crystal X-ray analysis (see the Supporting Information for details). This result also allowed assignment of the *trans* relationship between the H2 and H3 protons in **7**. Relative stereochemistry at the C2 and C3 stereogenic centers of the 2,3-dihydrobenzofuran ring in the products **7**, **9**, **11**, and **14** was further elucidated on the basis of the <sup>1</sup>H NMR data. In all cases, relatively small values of the <sup>3</sup>J<sub>H2H3</sub> coupling constants were observed, thus indicating a *trans* alignment of the H2 and H3 protons in the diastereoisomers obtained according to the Karplus equation<sup>[16c]</sup> as well as the literature



**Scheme 6.** a) Configurational assignments of the *trans*-2,3-dihydrobenzofurans **7**, **9**, **11**, and **14**. b) Rationalization for the diastereoselectivity of the Friedel–Crafts reaction leading to **7**.

data<sup>[16]</sup> (Scheme 6a). Based on the presented configurational assignments, a transition-state model explaining the high diastereoselectivity observed in the Friedel–Crafts reaction of the 2,3-epoxy imines **4** with hydroxyarenes **5** was proposed (Scheme 6b). This experimental result can be rationalized by the Felkin–Anh model in which the imine moiety of **4** (Scheme 2) is approached by the electron-rich aromatic system from the side opposite to the largest substituent. We postulate that hydrogen bonding between the phenolic or naphtholic hydroxy group and the epoxide oxygen atom is crucial for the high control of the diastereoselectivity in the formation of the C3 stereogenic center in **7**.<sup>[16a,b]</sup> In this context it is worth mentioning that the C2 stereogenic center in dihydrobenzofurans **9** is probably thermodynamically controlled. Furthermore, the formation of the C2 stereocenters in the products **11** and **14** can easily be rationalized by nucleophilic attack occurring from the least hindered faces of the electrophilic sites in **10** (Scheme 4) and **13** (Scheme 5), respectively; that is opposite to the large hydroxyalkyl moiety.

In summary, diversity-oriented one-pot reaction cascades for the preparation of optically active *trans*-2,3-disubstituted-2,3-dihydrobenzofurans having three contiguous stereogenic centers have been developed. Highly diverse substitution patterns of the final products could be achieved by simple modification of the structure of the key intermediates which resulted in different chemoselectivity of the particular reaction cascades.

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[1] a) C. Friedel, J. M. Crafts, *J. Chem. Soc.* **1877**, 32, 725; for a recent review, see: b) M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2010**, DOI: 10.3762/bjoc.6.6.

[2] For selected reviews on the enantioselective Friedel–Crafts reaction, see: a) M. Bandini, A. Melloni, A. Umami-Ronchi, *Angew. Chem.* **2004**, *116*, 560; *Angew. Chem. Int. Ed.* **2004**, *43*,

- 550; b) T. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903; c) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190; d) V. Terrasson, R. M. de Figueiredo, J. M. Campagne, *Eur. J. Org. Chem.* **2010**, 2635.
- [3] For selected examples of the intramolecular Friedel–Crafts reaction with epoxides, see: a) S. K. Taylor, G. H. Hockerman, G. L. Karrick, S. B. Lyle, S. B. Schramm, *J. Org. Chem.* **1983**, *48*, 2449; b) S. K. Taylor, C. L. Blankespoor, S. M. Havey, L. J. Richardson, *J. Org. Chem.* **1988**, *53*, 3309; c) S. Nagumo, I. Miyoshi, H. Akita, N. Kawahara, *Tetrahedron Lett.* **2002**, *43*, 2223; for intermolecular variants, see: d) F. Bertolini, P. Crotti, F. Macchia, M. Pineschi, *Tetrahedron Lett.* **2006**, *47*, 61; e) P. J. Linares-Palomino, G. K. S. Prakash, G. A. Olah, *Helv. Chim. Acta* **2005**, *88*, 1221.
- [4] For examples, see: a) Z. Shi, C. He, *J. Am. Chem. Soc.* **2004**, *126*, 5964; b) R. Marcos, C. Rodriguez-Esrich, C. I. Herrerias, M. A. Pericás, *J. Am. Chem. Soc.* **2008**, *130*, 16838; c) G.-X. Li, J. Qu, *Chem. Commun.* **2010**, 46, 2653.
- [5] For selected examples, see: a) P. Proksch, E. Rodriguez, *Phytochemistry* **1983**, *22*, 2335; b) L. Margl, C. Ettenhuber, I. Gyurján, M. H. Zenk, A. Bacher, W. Eisenreich, *Phytochemistry* **2005**, *66*, 887; c) F. N. Palmer, F. Lach, C. Poriel, A. G. Pepper, M. C. Bagley, A. M. Z. Slawin, C. J. Moody, *Org. Biomol. Chem.* **2005**, *3*, 3805; d) J. Meng, T. Jiang, H. A. Bhatti, B. S. Siddiqui, S. Dixon, J. D. Kilburn, *Org. Biomol. Chem.* **2010**, *8*, 107; e) S. Garcia-Muñoz, L. Jiménez-González, M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Synlett* **2005**, 3011; f) M. Okazaki, Y. Shuto, *Biosci. Biotechnol. Biochem.* **2001**, *65*, 1134; g) R. S. Ward, *Nat. Prod. Rep.* **1999**, *16*, 75; h) M. S. M. Yuen, F. Xue, T. C. W. Mak, H. N. C. Wong, *Tetrahedron* **1998**, *54*, 12429.
- [6] a) K. Komiyama, S. Funayama, Y. Anraku, M. Ishibashi, Y. Takahashi, S. Omura, *J. Antibiot.* **1990**, *43*, 247; b) M. Ishibashi, S. Funayama, Y. Anraku, K. Komiyama, S. Omura, *J. Antibiot.* **1991**, *44*, 390; c) T. Saito, T. Suzuki, M. Morimoto, C. Akiyama, T. Ochiai, K. Takeuchi, T. Matsumoto, K. Suzuki, *J. Am. Chem. Soc.* **1998**, *120*, 11633.
- [7] For general reviews, see: a) F. Bertolini, M. Pineschi, *Org. Prep. Proced. Int.* **2009**, *41*, 385; b) M. Sefkow, *Synthesis* **2003**, 2595; for selected recent examples, see c) J. Fischer, G. P. Savage, M. J. Coster, *Org. Lett.* **2011**, *13*, 3376; d) E. D. Coy, L. Jovanovic, M. Sefkow, *Org. Lett.* **2010**, *12*, 1976; e) P. Xie, Y. Huang, R. Chen, *Org. Lett.* **2010**, *12*, 3768; f) J. Barluenga, F. J. Fañanás, R. Sanz, C. Marcos, *Chem. Eur. J.* **2005**, *11*, 5397.
- [8] For examples, see: a) S. M. O. Van Dyck, G. L. F. Lemièrre, T. H. M. Jonckers, R. Dommissie, L. Pieters, V. Buss, *Tetrahedron: Asymmetry* **2001**, *12*, 785; b) L. Juhász, J. Visy, M. Simonyi, K. Krohn, S. Antus, *Tetrahedron: Asymmetry* **2002**, *13*, 1219; c) T. Itoh, K. Kawai, S. Hayase, H. Ohara, *Tetrahedron Lett.* **2003**, *44*, 4081.
- [9] For examples, see: a) E. Bolzacchini, G. Brunow, S. Meinardi, M. Orlandi, B. Rindone, P. Rummakko, H. Setala, *Tetrahedron Lett.* **1998**, *39*, 3291; b) M. G. N. Russell, R. Baker, J. L. Castro, *Tetrahedron Lett.* **1999**, *40*, 8667; c) M. Orlandi, B. Rindone, G. Molteni, P. Rummakko, G. Brunow, *Tetrahedron* **2001**, *57*, 371; d) W. Kurosawa, H. Kobayashi, T. Kan, T. Fukuyama, *Tetrahedron* **2004**, *60*, 9615.
- [10] For examples, see: a) M. A. Calter, N. Li, *Org. Lett.* **2011**, *13*, 3686; b) S. Antus, T. Kurtán, L. Juhász, L. Kiss, M. Hollósi, Z. S. Májer, *Chirality* **2001**, *13*, 493.
- [11] For examples, see: a) T. A. Engler, M. A. Letavic, R. Iyengar, K. O. LaTessa, J. P. Reddy, *J. Org. Chem.* **1999**, *64*, 2391; b) H. M. L. Davies, M. V. A. Grazini, E. Aouad, *Org. Lett.* **2001**, *3*, 1475; c) H. Saito, H. Oishi, S. Kitagaki, S. Nakamura, M. Anada, S. Hashimoto, *Org. Lett.* **2002**, *4*, 3887; d) L. Jiménez-González, S. Garcia-Muñoz, M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Eur. J.* **2006**, *12*, 8762.
- [12] For recent reviews, see: a) *Chem. Rev.* **2007**, *107*, 5413 (special issue on organocatalysis); b) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; d) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167; e) L.-W. Xu, L. Li, Z.-H. Shi, *Adv. Synth. Catal.* **2010**, *352*, 243; f) Ł. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem.* **2011**, *123*, 8642; *Angew. Chem. Int. Ed.* **2011**, *50*, 8492.
- [13] For a review, see: a) K. M. Weiß, S. B. Tsogoeva, *Chem. Rec.* **2011**, *11*, 18; for the first contribution, see: b) M. Marigo, J. Franzén, T. B. Poulsen, Z. Wei, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964.
- [14] Y. Zou, M. Lobera, B. B. Snider, *J. Org. Chem.* **2005**, *70*, 1761.
- [15] For examples of aminocatalytic  $\alpha$ -arylations of aldehydes, see: a) J. Alemán, S. Cabrera, E. Maerten, J. Overgaard, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 5616; *Angew. Chem. Int. Ed.* **2007**, *46*, 5520; b) K. C. Nicolaou, R. Reingruber, D. Sarlah, S. Bräse, *J. Am. Chem. Soc.* **2009**, *131*, 2086; c) J. C. Conrad, J. Kong, B. N. Laforteza, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11640; d) K. L. Jensen, P. T. Franke, L. T. Nielsen, K. Daasbjerg, K. A. Jørgensen, *Angew. Chem.* **2010**, *122*, 133; *Angew. Chem. Int. Ed.* **2010**, *49*, 129; e) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260.
- [16] a) H. Jiang, P. Elsner, K. L. Jensen, A. Falcicchio, V. Marcos, K. A. Jørgensen, *Angew. Chem.* **2009**, *121*, 6976; *Angew. Chem. Int. Ed.* **2009**, *48*, 6844; b) Ł. Albrecht, L. K. Ransborg, B. Gschwend, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 17886; c) Ł. Albrecht, A. Albrecht, L. K. Ransborg, K. A. Jørgensen, *Chem. Sci.* **2011**, *2*, 1273; d) Ł. Albrecht, L. K. Ransborg, A. Albrecht, L. Lykke, K. A. Jørgensen, *Chem. Eur. J.* **2011**, DOI: 10.1002/chem.201101817; e) H. Friebohn, *Basic One- and Two-Dimensional NMR Spectroscopy*, Wiley-VCH, Weinheim, **2005**, p. 90; f) F. Bertolini, P. Crotti, V. Di Bussolo, F. Macchia, M. Pineschi, *J. Org. Chem.* **2007**, *72*, 7761.