Chemistry in Germany - The Young Generation

... a personal selection
"I find it amazing that ... I am getting paid for sitting in my office and playing with toys and that my imagination occasionally corresponds to the material world."

"In a nutshell, my research involves ... natural products and neurons."
(Total synthesis of bioactive natural products, synthetic methodology, and chemical neurobiology)

**Total Synthesis of Morphine and Hasubanan Alkaloids: The Hydrophenanthrenone Approach**

\[
\begin{align*}
\text{(-)-morphine} & \\
\text{(-)-hasubanonine} &
\end{align*}
\]

\[\text{Angew. Chem., Int. Ed. 1997, 35, 2830.} \]
\[\text{Synlett 1997, 5, 441.} \]
\[\text{Synthesis 1998, 653.} \]
\[\text{J. Org. Chem. 1998, 63, 5908.} \]
\[\text{Chirality 1999, 11, 475.} \]

**\(\alpha\)-haloketone effect**
\(\alpha\)-bromocyclohexanones prefer a conformation with axial bromine in order to minimize electrostatic interaction of the dipolar C–Br and C=O bonds or maximize overlap between the corresponding \(\sigma^*\) and \(p\)-orbitals
- only 13 isolated intermediates
- all of which are crystalline
- total yield: 11.5%
- inexpensive and readily available sm
- recycling of undesired isomers
Total Synthesis of Halichlorin

halichlorin

phenylglycinol

Meyer's lactam

pinnac acid

- halichlorin exhibit considerable structural homology (e.g. quinolizidine subunit), but act upon different biological targets (VCAM-1 vs. cPLA2)
- VCAM-1 has recently emerged as a potential target for drug discovery since it is supposed to be involved in regulating leukocyte trafficking
- derivatives for SAR studies

excellent review on β-alkyl Suzuki-Miyaura cross-coupling reactions:

Angew. Chem., Int. Ed. 2001, 40, 4544
11. $t$BuOAc, LiHMDS, THF, 63%
12. $H_2CO$, EtOH
13a. LiHMDS, THF, 0°C, 86%
13b. $Cp_2Zr(H)Cl$, rt
14. HF*pyridine, THF
15. TPAP, NMO, MeCN, 57%
16. Seyferth-Gilbert, KOtBu, THF

17a. $Cp_2Zr(H)Cl$, DCM
17b. Zn$_2$Me, heptane, -78 °C
17c. A, -65 to -30 °C
17d. B, -30 to rt, 67%
4:1 mix. of epimers

18. TBSOTf, 66%
19. TBAF
20. EDCI, DMAP, CHCl$_3$/THF, 51%
21. HF*pyridine

- 21 steps
- 1.3% overall yield

key steps:
- use of Meyer's lactam to install core structure
- β-alkyl-Suzuki coupling
- Claisen-Mannich sequence
- hydrozirconation-transmetalation-asymmetric addition

Biomimetic Syntheses applying Electrocyclization Cascades

9,10-deoxytridachione

Soai's aminoalcohol

Baran Group Meeting  Chemistry in Germany - The Young Generation  Daniel Goetz

9,10-deoxytridachione

6π

common synthetic precursor?!

1. Still-Gennari 2. DiBAlH, DCM 73%

single diastereomer
divergent access to both frameworks

6. Weinreb 7. EtMgBr

59% (95% brsm)

LiHMDS, CO₂Et

FSO₂OMe, DCM 77%

benzene, Δ 95%

73%

E. crispata, the "lettuce slug"...

see also:

(-)-crispatene


Biological activity...
**Total Synthesis of Guanacastepene E**

**key disconnection**


**also: Friedel-Crafts triflation**

Total Synthesis of Guanacastepene E

**intramolecular**


Org. Lett. 2006, 8, 5429.

**building block A**

**building block B**

**asymmetric carbonyl ene-reaction**


**building block B**

61%
Biomimetic Total Synthesis of Rubioncolin B

Chemistry in Germany - The Young Generation

Daniel Goetz

tris(dimethylamino)sulfonium difluorotrimethylsilicate (anhydrous fluoride source)

endo transition state

ortho-quinone methide

rubioncolin B

racemate in nature!
**Biomimetic Synthesis of Exiguamines**


- R = H: exiguamine A
- R = OH: exiguamine B

1. BnCl, K₂CO₃
2a. N₂CH₂CO₂Me, NaOMe, MeOH
2b. o-xylene, 160 °C

39%

3a. NaOH
3b. decarbox.
4. POCl₃, DMF
5. MeNO₂

29%

6. LiAlH₄
7. Boc₂O, DMAP

80%

8. Pd(PPh₃)₄, CuCl, LiCl, DMSO, 60 °C

71%

- two oxidations
- amine ring closure
- tautomerization
- oxo-6π-electrocyclization
**Baran Group Meeting**

**Chemistry in Germany - The Young Generation**

**Daniel Goetz**

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S-(+)-frondosin B


**O**

**HO**

**Me**

**S**

**(+-)**-frondosin B


**X** = NO₂: aureothin

**X** = NHAc: N-acetyl-aureothamine

**X** = CN: auronitrile

ae

amathaspiramide F

Angew. Chem., Int. Ed. 2002, 41, 4556

**REVIEW**: "Biosynthetic and Biomimetic Electrocyclizations."


Rhinilam

---

**Org. Lett. 2005, 7, 2837**

**O**

**Me**

**O**

**OMe**

**H**

**Org. Lett. 2005, 7, 4475.**

**Org. Lett. 2005, 7, 5865.**

**Org. Lett. 2005, 7, 2901.**

**Angew. Chem., Int. Ed. 2005, 44, 4602.**

**J. Org. Chem. 2009, 74, 1581.**

**Org. Lett. 2005, 7, 5207.**

**Org. Lett. 2005, 7, 2837.**

**Org. Lett. 2005, 7, 4109.**

**Org. Lett. 2005, 7, 2901.**

**Angew. Chem., Int. Ed. 2005, 44, 4602.**


**Microphyllaquinone**

**Elysiapyrone A**

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**REVIEW**: "Biosynthetic and Biomimetic Electrocyclizations."


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**SNF4435**

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**Pinnatal (1)**

---

**RuCl₃(PPh₃)₃**

---

**Elysiapyrone A**

---

**Org. Lett. 2005, 7, 2901.**

**Angew. Chem., Int. Ed. 2005, 44, 4602.**
Daniel Goetz

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newbouldine

shimalactone A
*Org. Lett.* 2008, 10, 149.

sменochromene B
*Tetrahedron* 2007, 63, 6529.

halenaquinone
*(Vinyl Quinones as Diels-Alder Dienes)*

bipinnatin J

inricarene
*Org. Lett.* 2006, 8, 5901.

pycnanthuquinone C

coraloidolide E

Sc(OTf)₃ • xH₂O

DBU

coraloidolide B

*coraloidolide C*

variecolortide A


crocipodin


not covered: "Chemical Neurobiology"

excellent review: Introduction: Chemical Approaches to Neurobiology,

... don't miss the zebra-fish experiment!
(Nature 2009, 461, 407-410.)
Thorsten Bach:
- born: 1965, Ludwigshafen, Germany
- studies in chemistry, University of Heidelberg / USC LA
- 1991 PhD with Manfred Reetz, University of Marburg
  ("Enantioselective C-C Coupling Using Chiral Catalysts")
  ("Histidine Analogs by Pd-mediated C,C Bond Formation")
- 1992-1996 Habilitation, University of Münster
- 1997-2000 Full Professor, University of Marburg
- since 2000 Chair of Organic Chemistry I, TU Munich
- 188 publications

main research interests:
- photochemistry
- catalysis
- chemistry of heterocycles
- total synthesis

Total Synthesis of Meloscine


enantioselective [2+2] photocycloaddition

Total Synthesis of Meloscine
**Total Synthesis of Podophyllotoxin**


(chiral carbocations, theoretical investigations)

*Synlett* 2011, 1235-1238.

(enantioselective FC with chiral Broensted acids)

- lignane class of natural products
- antiviral properties
- several total syntheses (e.g. 1st synthesis by Meyers, 24 steps)
Chiral Carbenium Ions


<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>FG</th>
<th>product</th>
<th>yield [%]</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 a</td>
<td>'Bu</td>
<td>17 a</td>
<td>84</td>
<td>3:97</td>
</tr>
<tr>
<td>2</td>
<td>4 a</td>
<td>Ph</td>
<td>18 a</td>
<td>97</td>
<td>77:23</td>
</tr>
<tr>
<td>3</td>
<td>5 a</td>
<td>CN</td>
<td>19 a</td>
<td>86</td>
<td>76:24</td>
</tr>
<tr>
<td>4</td>
<td>6 a</td>
<td>PO(OEt)₂</td>
<td>20 a</td>
<td>87</td>
<td>74:26</td>
</tr>
</tbody>
</table>

diastereoselective Ritter reactions:

Total Synthesis of Cystothiazole E


Regioselective cross-coupling on polyhalogenated heterocycles

1. Pd(PPh3)4, THF
2. H2, Pd/C, EtOH
ClZn
68%

3. 1BuLi, Et2O, -78 °C;
ZnCl2, 25 °C, THF;
PdCl2(PPh3)2,
THF, 60 °C
97%

4. Pd(PPh3)4, CsOH,
benzene/EtOH/H2O,
95 °C

- 10 steps
- 21% overall yield
- three sequential couplings as key sequence
- usually bithiazole core established by classical Hantzsch thiazole methodology
  (e.g. Boger's bleomycin synthesis; Angew. Chem. Int. Ed. 1999, 38, 448-476.)


Heterocycles 2007, 74, 569-594.

Regioselective C,C Coupling Reactions on Polyhalogenated Heterocycles

kelsoene

Stereoselective [2+2] Photocycloadditions (e.g. Paterno-Büchi Reactions)

wailupemycin

furanocembranes

GE2270 A

... a potent antibiotic thiazolylpeptide

structure variation in other GE2270 antibiotics

(+)-preussin

punctaporonin C


Light-Driven Organocatalysis

hv (366 nm), -25 °C, PhCF₃, 10 mol% catalyst

\[
\text{ratio 79:21}
\]

94% ee

94% ee

ratio 79:21

94% ee

Stefan Bräse:
- born: November 30th 1967, Kiel, Germany
- studies in chemistry, University of Göttingen
- 1995 PhD with Armin de Meijere
- 1995-1996 Postdoc with J. Bäckvall, University of Uppsala
- 1996-1997 Postdoc with K.C. Nicolaou, TSRI, La Jolla
- 1997-2001 Habilitation, RWTH Aachen (mentor: D. Enders)
- 2001-2003 Full Professor, University of Bonn, Germany
- since 2003 KIT, Karlsruhe, Germany
- around 110 publications

main research interests:
- combinatorial chemistry
- solid-phase chemistry
- nanostructures
- total synthesis

"If I were a car... I would be an Audi RS6."

My motto is... "I know!".

Hobbies: Chemistry...

Chiral Lewis Acids in Enantioselective Photochemistry

hv (366 nm), -35 °C, ClCH₂CH₂Cl, 20 mol% catalyst

87%

78% ee


Total Synthesis of Diversonol


- isolated from Penicillium diversum
- absolute configuration unknown

diversonol


Domino Oxa-Michael Aldol

1. imidazole, dioxane/H2O
2. MEMCl
3. nBu4NBr3, THF/H2O
4. DABCO
5. TPAP, NMO
6. MeLi, CuCN
7. tBuLi, NaHCO3
8. MMPP, EtOH
9. BBr3
10. NaBH4

 cis/trans 1.5:1

standard amide coupling reagents

- stable towards: reductions, fluoride sources, bases, weak acids, click reactions with copper, ...
- easily removed in >95% yield


Solid Phase Synthesis

HBF4*OEt2, C6F14

- suppression of side product formation
- mild reactions conditions (80 °C)
- applicable to solid phase and in solution

... also worth reading:

Frank Glorius:
- born: XX. XX. 1972, XX, Germany.
- studies in chemistry, University of Hannover
- 1995-1996 Research with Paul A. Wender, Stanford
- 2000 PhD with Andreas Pfaltz, MPI/University of Basel
- 2000-2001 Postdoc with D. A. Evans, Harvard University
- 2001-2004 Habilitation, MPI Mühlheim (mentor: A. Fürstner)
- 2004 Associate Professor, University of Marburg, Germany
- since 2007 Full Professor, University of Münster, Germany
- 91 publications

main research topics:
- sterically demanding NHCs
- functional MOFs
- challenging cross-couplings
- CH activation
- asymmetric organocatalysis
- heterocyclic chemistry

“When I wake up I… can’t believe it’s that time already.”

Indoles from Enamines by CH Activation

\[ \text{Indole synthesis from enamines.} \]

- very wide substrate scope
- steric demand determines outcome, not electronic influence; rarely regioisomers
- good yields, scalable
- one-pot reaction possible (see below)
Initial mechanistic investigations unambiguously support a σ-bond metathesis or deprotonation pathway and not an electrophilic aromatic palladation of the aniline ring.

**NHC-Catalyzed Hydroacylation of Unactivated Double Bonds**

_(cp. Stetter reaction)_


*Org. Lett.* **2008**, *10*, 4243-4246 (synthesis of NHC A).

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- very wide substrate scope
- good yields (70-96%)
- scalable
- formation of quartenary centers possible
- useful disconnection

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<table>
<thead>
<tr>
<th>entry</th>
<th>variation of the standard conditions</th>
<th>yield of 2a (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>69</td>
</tr>
<tr>
<td>2, 3</td>
<td>4 instead of 3</td>
<td>2</td>
</tr>
<tr>
<td>4, 5</td>
<td>6 instead of 3</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>DBU: 20 mol % instead of 40 mol %</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>TEA instead of DBU</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>K₂CO₃ instead of DBU</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>KOH•Bu instead of DBU</td>
<td>69</td>
</tr>
<tr>
<td>10</td>
<td>10 mol % of 3, 20 mol % DBU</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>reaction time: 2 h instead of 1 h</td>
<td>81 (85)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
**Intramolecular Direct Arylation of Benzoic Acids by Tandem Decarboxylation/C-H Activation**


$$\begin{align*}
\text{Pd}(\text{TFA})_2, \text{Ag}_2\text{CO}_3, \\
5\% \text{DMSO}/1,4\text{-dioxane}, \\
150 ^\circ\text{C}, 14 \text{ h} \\
\rightarrow \\
\text{dibenzofurans}
\end{align*}$$

51-85%

**A Sterically Demanding Chiral NHC Ligand**


**Mathias Christmann:**
- born: XX. XX. 1972, Peine, Germany.
- studies in chemistry, University of Braunschweig
- 2000 PhD with M. Kalesse, University of Hannover
- Total Synthesis of (+)-Ratjadone
- 2001-2002 Postdoc with C. J. Forsyth, Univ. of Minnesota
- since 2008 Associate Professor, TU Dortmund, Germany
- 36 independent publications

**main research topics:**
- total synthesis
- method development
- organocatalysis
- catalytic transformations of renewable resources

We have recently initiated a program that is aimed at making larger substructures within natural products available from terpene feedstock. Using simple bulk terpenes such as geranyl and neryl acetate or nepetalactone we are aiming to find efficient ways to modify the carbon skeleton using oxidations, organocatalytic and metal-catalyzed reactions such as hydroformylations.

**The Concept - e.g. (-)-Englerin A from (-)-Nepetalactone:**

*Angew. Chem. Int. Ed. 2009, 48, 9105 (1st generation synthesis).*

*Angew. Chem. Int. Ed. 2011, 50, 3998 (2nd generation synthesis).*

- multigram quantities of key intermediate available
- route allows for various late stage modifications for SAR studies
- derivatives with improved activity against renal cancer cell lines
The Concept - continued...

selected examples of prepared building blocks:

- epoxygeranyl acetate

\[
\begin{align*}
\text{AcO} & \quad \text{Ph} \\
\text{O} & \quad \text{OH} \\
\text{C} & \quad \text{H} \\
\text{O} & \quad \text{Ph}
\end{align*}
\]

- ripostatin B

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{C} & \quad \text{H} \\
\text{O} & \quad \text{Ph} \\
\text{C} & \quad \text{H}
\end{align*}
\]

- *TFA, K_2S_2O_8, LiCl, Cu(TFA)_2, MeCN/H_2O; then NaBH_4; then NaOH

\[
\begin{align*}
\text{NH} & \quad \text{NMe} \\
\text{Me} & \quad \text{tBu}
\end{align*}
\]

- NaIO_4, THF/H_2O

\[
\begin{align*}
\text{AcO} & \quad \text{O} \\
\text{C} & \quad \text{H} \\
\text{O} & \quad \text{Ph}
\end{align*}
\]

- 3 steps

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CO}_2 \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{C} & \quad \text{H} \\
\text{O} & \quad \text{Ph}
\end{align*}
\]

- full retention of DB configuration

- valuable building blocks on multigram scale

- 1. 2-methyl-1,3-dithiane, "BuLi, THF
- 2. PhI(TFA)_2, CaCO_3, MeOH/MeCN

not covered:
- Magnus Rüping, RWTH Aachen
- Dirk Menche, University of Heidelberg
- Armino Studer, University of Münster
- Benjamin List, MPI Mühlheim
- Christian Hertweck, HKI Jena
- Lutz Ackermann, University of Heidelberg
- ...

... part II to come ...

\[
\begin{align*}
\text{AcO} & \quad \text{O} \\
\text{C} & \quad \text{H} \\
\text{O} & \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{C} & \quad \text{H} \\
\text{O} & \quad \text{Ph}
\end{align*}
\]

... the end!