So Many Hof(f)man(n)s

Hof(f)man(n)s Discussed

K. A. Hofmann and J. Sand (Paper from 1900, no other info available)
- oxymercuration of alkenes

August Wilhelm von Hofmann (1818-1892)
- many named reaction and aniline dyes

Felix Hoffmann (1868-1946)
- first useful synthesis of aspirin and heroin

Albert Hofmann (1906-2008)
- father of LSD and first synthesis of psilocybin

Roald Hoffmann (Cornell University)
- organic and inorganic chemist, 1981 Nobel Prize (orbital symmetry)

Robert V. Hoffman (Professor Emeritus, New Mexico State University)
- chemistry of N-sulfonyloxy compounds

Reinhard W. Hoffmann (Professor at University of Marburg, Germany)
- natural product synthesis and reactive organometallic compounds

H. Martin R. Hoffmann (Professor at Hannover University, Germany)
- chiral allyl cations, chemistry of cinchona alkaloids, natural product synthesis

Hof(f)man(n) #1 (not much known on this one)

(K. A.) Hofmann-Sand Reaction (not the Hofmann with all the other reactions)
Oxymercuration of double bonds

Hof(f)man(n) #2 (Many contributions to chemistry)

- studied under Justus von Liebig (University of Giessen)
- taught in Bonn, London and Berlin
- first to use molecular models (colors still conserved)
- invented many named reactions
- his student (Perkin) responsible for aniline dyes

Hofmann Rearrangement (Ber. 1881, 14, 2725.)

\[
\begin{align*}
\text{R-N-C(O)}_2 & \xrightarrow{\text{Br}_2, \text{NaOH}} \text{R} - \text{N}^+\text{C}(-\text{O})_2^- \\
& \xrightarrow{\text{H}_2\text{O}, \text{MeOH}} \text{R-NH}_2
\end{align*}
\]

For base sensitive substrates can use hypervalent iodine or lead tetraacetate

Example from Recent Literature (J. Am. Chem. Soc. 1998, 120, 8259)

Hofmann Elimination (Annalen der Chemie und Pharmacie 1851, 78, 253)

alkene formed often does not follow Zaitsev's rule
Which Hof(f)man(n) is Which?

**Recent Example of Hofmann Elimination** *(Tetrahedron Lett. 1989, 30, 5989)*

**Hofmann-Martius Reaction** *(Ber. 1871, 4, 742)*

- Similar to Fries Rearrangement
- R-group must be able an efficient cation stabilizer

**Hofmann-Löffler-Freytag Reaction** *(Ber. 1883, 16, 558)*

**Creation of the Textile Dyeing Industry**

- Hofmann had his student (Perkin) attempt to oxidize aniline to quinine
- led to black tar that made a bright purple solution in ethanol
- purple solution was used to dye silk, Perkin became rich

**Hofmann Isocyanide Synthesis** *(aka carbylamine test)*

"smell of isocyanides described by Hofmann and Guatier as "highly specific, almost overpowering, horrible, and extremely distressing"

prior to mauveine, purple dye came from the fresh mucus secretion from the hypobranchial gland of a medium sized predatory sea snail (extremely expensive!!)
Hof(f)man(n) #3 - Bayer Pharmaceutical Chemist
- synthesized aspirin (1897) and heroin (1897) in forms that could be used medicinally

Felix Hoffmann

Hof(f)man(n) #4 - Father of LSD (and psilocybin)
- first to synthesize, ingest and study the psychedelic effects of LSD (synthesis 1938, test 1943)
- was a chemist at Sandos (now Novartis)
- accidently absorbed some through fingertip, then rode bike home (purposely ingested 0.25 mg the next day, see results below)
- recently passed away (april 29, 2008, age 102)

Albert Hofmann

Hof(f)man(n) #5 - of Woodward-Hoffmann Rule Fame
- professor at Cornell University
- interests lie in the application of theoretical and computational methods to inorganic and organic systems
- Awards include: 1981 Nobel Prize
  Priestly Medal
  ACS Organic and Inorganic Award
  Arthur C. Cope Award
  National Medal of Science
- also has an interest in and writes poetry

Roald Hoffmann

Hof(f)man(n) #6 - Professor Emeritus, New Mexico State
\[ \text{α-oxidation and installation of a leaving group} \]
\[ \text{Synthesis 1985, 760} \]

\[ \begin{align*}
R^1 \quad OAc & \quad + \quad (Ar\text{-SO}_2\text{-O})_2 \\
R^2 & \quad R^3
\end{align*} \]

\[ \text{Ethyl Acetate Methanol} \quad 81-95\% \]

\[ \begin{align*}
R^1 \quad R^3 & \quad O \\
& \quad \text{SO}_2\text{Ar}
\end{align*} \]

Robert V. Hoffman

Also applied to enamines (J. Org. Chem. 1985, 50, 5148) and β-ketoesters (J. Org. Chem. 1990, 55, 1267)

C-to-N Rearrangement of N-(Arylsulfonylamino)amine
(J. Org. Chem. 1988, 53, 3317)

First Accidental Experience With LSD - "In a dreamlike state, with eyes closed, I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors. After some two hours, this condition faded away."

Second (0.25 mg experience), excerpts - commenting on his neighbour "She was no longer Mrs. R. but rather a malevolent, insidious witch with a colored mask."

"A demon had invaded me, had taken possession of my body, mind and soul. I jumped up and screamed, trying to free myself of him, but sank down again and lay helpless on the sofa."
Which Hofmann is Which?

Synthesis of α-azidoketones \( (J. \text{ Org. Chem. 1994, 59, 2902}) \)

- installation of halogen can be difficult
- doesn’t work well when β-hydrogens

Solution

- ONs can be installed regiospecifically
- reaction conditions milder than halide (rt)
- yields range from 68-96%

Generation and Trapping of α-Lactams by Weak Nucleophiles \( (J. \text{ Org. Chem. 2000, 65, 2591}) \)

General Reaction

If a primary amine and excess base is used.

Sonication no nucleophile added

Preparation of phosphonomethyl ureas

Synthesis of 2-Oxazolone-4-carboxylates \( (J. \text{ Org. Chem. 2002, 67, 1102}) \)

The Products can be hydrolyzed (ester), acylated (nitrogen), reduced (ester)

Hofmann #7 - Professor, University of Marburg, Germany

Main Research Focuses
1) Total Synthesis of Natural Products
2) Chiral Organometallic Reagents
3) Stereoselective allylboration reactions

Example of Research Focus 1 and 3 \( (J. \text{ Am. Chem. Soc. 1997, 119, 7499}) \)

Yields are low and the example to form the cis has never been exploited further
So Many Hof(f)man(n)s

Laurencin Continued - Use of Masking Strategy

Interesting transformations along the way to the tetrahydropyran

Research Area #2 - Chiral Grignard Chemistry

Example of Research Focus 1 and 3  *Org. Lett. 2006, 8, 3829*

Retro Synthesis
Which Hof(f)man(n) is Which?

Reactions of Chiral Grignards *(Angew. Chem. Int. Ed. 2000, 39, 3072)*

\[ \text{ClMg} + \text{Ph} \rightarrow \text{Ph} \]
\[ \text{ClMg} + \text{Ph} \rightarrow \text{Ph} \]
\[ \text{ClMg} + \text{Br} \rightarrow \text{Ph} \]

Kumada Couplings *(Chem. Commun. 2003, 732)*

Phenalamide A2 *(Org. Lett. 1999, 1, 1713)*

Hof(f)man(n) #8 - Professor, University of Hannover
- has impressive pedigree: PhD - Ingold
  - Postdoc - Cram and Woodward

Major Areas of Research:
1) Total Synthesis of Natural Products
2) Chemistry of the Cinchona Alkaloids
3) Allyl Cation Chemistry
4) Methodology Development

H. Martin R. Hoffmann

Preparation of Conjunctive Reagent

Reagent allows for allylboration and subsequent cycloversion of the dioxene ring to install an additional enal unit.
**Which Hof(f)man(n) is Which?**

**Cinchona Alkaloid Chemistry** (Research Area 2)

- approximately 700 t/year are isolated from the bark of the Cinchona tree
- quinine is a traditional antimalarial drug, quinidine treats irregular heart beat
- cinchonidine and cinchonine and their salts crystallize well (resolutions)
- are used as chiral ligands (Sharpless Asymmetric Dihydroxylation)
- used for the resolution of naproxen

\[ R = \text{OMe quinine} \quad R = \text{H cinchonidine} \quad R = \text{OMe quinidine} \quad R = \text{H cinchonine} \]

- it has been suggested that the Cinchona bases are unlikely to find application as chiral building blocks. J. Crosby, *Chirality in Industry, 1992*, pp 19-20.

- it was HMR Hoffmann's goal to prove this statement incorrect


**Synlett 1996, 690.** For mechanism see paper, it is crazy

\[ \text{LiAlH}_4, \text{PrOH, THF; then O}_2, \text{r.t.} \rightarrow 45 ^\circ C \]

mechanism involves radical, radical ion-SET and ionic chemistry with sequential oxidation and also hydrogenation steps, all in a single flask. Has been carried out on 100 kg scale.

Preparation of bidentate ligands (*Tetrahedron* 2000, 56, 4453)

**Applications of Ligands** (For references see within *Eur. J. Org. Chem.* 2004, 4293, not HMRH)

Hydroboration

Kumada-Corriu

- Mechanism of the last step???
Which Hof(f)man(n) is Which?

Further Applications (note: diamine Ligands this time)
(*Org. Biomol. Chem. 2003, 1, 2522, not HMRH*)


Preparation of Baylis-Hillman Catalyst (*Tetrahedron 1998, 54, 3495*)

Application to Asymmetric Baylis-Hillman Reaction
(*J. Am. Chem. Soc. 1999, 121, 10219; Not HMRH*)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>[IrCl(COD)]_2</td>
<td>Ligand 3</td>
<td>92% ee</td>
</tr>
<tr>
<td>Ligand 4</td>
<td>94% ee</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AgOBz</td>
<td>Q = quinoline</td>
<td></td>
</tr>
<tr>
<td>MeOH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- First practical example of asymmetric Baylis-Hillman reaction
- it was previously noted that a suitably disposed hydroxyl group on the amine catalyst increases yield and ee, the catalyst with -OMe instead of -OH on the quinoline led to greatly decreased ee (10%)
**Which Hof(f)man(n) is Which?**

**Chiral Allyl Cation Chemistry** *(Angew. Chem. Int. Ed. 1998, 37, 1266)*

**General Reaction**

\[
\begin{align*}
\text{O} & \quad \text{O}Me \\
\text{O} & \quad \text{O}Me \\
\text{LDA, TESCI} & \quad \text{THF, -78 °C} & \quad \text{LDA, TESCI} & \quad \text{THF, -78 °C}
\end{align*}
\]

\[
\text{quantitative} \quad \text{quantitative}
\]

Preparation of Mixed Chiral Acetal and Reaction

\[
\begin{align*}
\text{O} & \quad \text{O}Me \\
\text{O} & \quad \text{O}Me \\
\text{AcBr} & \quad \text{1-phenylethanol} & \quad \text{n-BuLi, ether}
\end{align*}
\]

\[
\begin{align*}
\text{89%} & \quad \text{92% BRSM} \\
\text{both enantiomers} & \quad \text{both enantiomers} \\
\text{of 1-phenylethanol} & \quad \text{of 1-phenylethanol} \text{ available}
\end{align*}
\]

**Improved Reaction Conditions** *(Chem. Eur. J. 2000, 6, 684)*

\[
\begin{align*}
\text{O} & \quad \text{O}Me \\
\text{O} & \quad \text{O}Me \\
\text{Ph} & \quad \text{LDA, TESCI} & \quad \text{THF, -78 °C}
\end{align*}
\]

\[
\begin{align*}
\text{OTMS} & \quad \text{OTMS} \\
\text{O} & \quad \text{O}Me \\
\text{TMSOTf} & \quad \text{TMSOTf} \\
\text{DCM, -95 °C} & \quad \text{DCM, -95 °C}
\end{align*}
\]

\[
\begin{align*}
\text{67% yield} & \quad \text{76% de} \\
\text{- the smaller Methoxy group is the leaving group under Lewis acid conditions} \\
\text{- Switching the phenyl of the auxiliary to a naphthyl increased de to 100% (no yield given)}
\end{align*}
\]


Hoffmann's concern was with construction of the dioxatricyclic framework

**Studies Towards Phorboxazole and Bryostatin 1 using Allyl Cations**

Methodology Applicable to Natural Products with 2,6-cis Tetrahydropyrans

**Phorboxazole A and B** *(Tetrahedron 1999, 55, 4315)*

**A:** \( R^1 = \text{OH}, R^2 = \text{H} \)

**B:** \( R^1 = \text{H}, R^2 = \text{OH} \)

Northern Half of Bryostatin 1

**Org. Lett. 2001, 3, 929**
Reasearch Area 4 - Development of New Methodologies
Deprotection of SEM Group Using MgBr₂ (Org. Lett. 2000, 2, 1447)

SEM protecting group can be difficult to remove, especially in a selective manner
- Is quite resistant to TBAF, but TFA will remove (Harsh!!)
- MgBr₂ in ether/MeNO₂ is a good mild selective alternative to TFA and other harsh conditions

Examples of Utility

1.5 eq TBAF
THF, 0 °C, 1.5 h
99%

\[
\begin{align*}
OSEM & \quad OSEM \\
\text{OTBDPS} & \quad \text{OTBDPS}
\end{align*}
\]

MgBr₂ (14 eq)
Et₂O/MeNO₂
81%

\[
\begin{align*}
OSEM & \quad OSEM \\
\text{OTBDPS} & \quad \text{OTBDPS}
\end{align*}
\]

12 eq. TBAF, 4 Å MS
DMF, 45 °C, 0.5 h
decomposition

\[
\begin{align*}
CN & \quad OSEM \quad OBn \\
\text{OTBDPS} & \quad \text{OTBDPS}
\end{align*}
\]

20 eq MgBr₂
Et₂O/MeNO₂, 8 h
94%

\[
\begin{align*}
CN & \quad OBn \quad OH \\
\text{OTBDPS} & \quad \text{OTBDPS}
\end{align*}
\]

alcohols, esters, benzyl groups, dithians, methoxy acetals, TBS, TIPS, TBDPS and cyanohydrins are all tolerated under SEM deprotection conditions

\[
\begin{align*}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{Sml₂} & \quad \text{Sml₂}
\end{align*}
\]

\[
\begin{align*}
\Delta E & = 33.9 \text{ kcal mol}^{-1} \\
\text{76\% yield}
\end{align*}
\]

The large increase in strain energy, and the facility of the reaction suggests that this process could be applied to the synthesis of cyclobutanes, which are usually prepared by ionic or photochemical processes.

\[
\begin{align*}
\text{O} & \quad \text{CH₃} \\
\text{Sml₂} & \quad \text{Sml₂}
\end{align*}
\]

\[
\begin{align*}
\Delta E & = 41.4 \text{ kcal mol}^{-1} \\
\text{32\% yield}
\end{align*}
\]

yield not great, but the ring system is quite complex for one-step generation

\[
\begin{align*}
\text{CH₃} & \quad \text{CH₃} \\
\text{Sml₂} & \quad \text{Sml₂}
\end{align*}
\]

\[
\begin{align*}
\text{94\% yield}
\end{align*}
\]

yield very high in many examples and a variety of tricyclic ring systems were generated

More Almost Total Syntheses from the HMR Hoffmann Group

\[
\begin{align*}
\text{HO} & \quad \text{CHO} \\
\text{HO} & \quad \text{OHC}
\end{align*}
\]

- naturally occuring antimalarial compounds
- originally assigned structure was incorrect
- key steps are Knoevenagel condensation, hetero-Diels-Alder and aromatization

Robustadial A, isopropyl = β
Robustadial B, isopropyl = α
Which Hof(f)man(n) is Which?

Precursor to Robustadial Continued

\[\text{MeO}_2C + \text{OHC} \rightarrow \text{MeO}_2C\text{Me} \]

*mechanism?*

\[\text{MeO}_2C + \text{OHC} \rightarrow \text{MeO}_2C\text{Me} \]

\[
\begin{align*}
\text{HOAc (1.8 M)} & \\
\text{KOAc (0.1 eq)} & \\
\text{MS 3 Å, hydroquinone} & \\
\text{100 °C, 20 h, 80%} & \\
\text{BSA, DDQ} & \\
\text{dioxane} & \\
\text{110 °C} & \\
\end{align*}
\]

1) KF, HBr, DMF

2) Acetone, K₂CO₃

(MeO)₂SO₂

85% (2 steps)

selenation/oxidation, α-halogenation,

α-oxidation, and DDQ alone failed or
gave low yields. BSA necessary

\[\text{MeMgI} \rightarrow \text{MeMe} \]

ether reflux 98%

\[\text{HO} + \text{OMe} \rightarrow \text{OMe} \]

1) 85% H₂O₂, p-TsOH

2) pyr. (CF₃CO)₂O

3) CF₃CO₂H, H₂O/CH₂Cl₂

4) Acetone, K₂CO₃(MeO)₂SO₂

74%, 4 steps

*mechanism???