

Tuning Chemoselectivities through the H-Cube - Fast Screening and Batch Transfer

**ThalesNano UGM
October 21, 2010, Budapest**

Green Chemistry
& Catalysis Lab

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www.givaudan.com
<http://en.wikipedia.org/wiki/Givaudan>

OUR VISION

To be our customers' essential partner in developing sustainable fragrance and flavour creations...

...by engaging with our customers in collaborative dialogues during the development, creation and refinement of their products.



www.givaudan.com
<http://en.wikipedia.org/wiki/Givaudan>

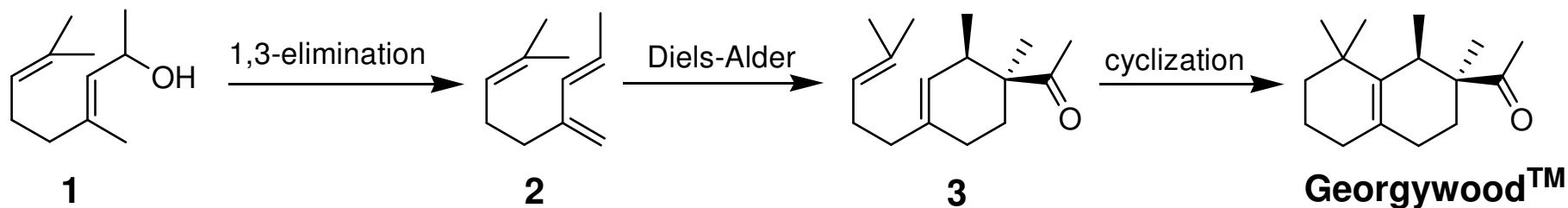
Methodologies developed at Givaudan 2005 - 2010

- a) **Dienes** through Pd-cat. 1,3-Elimination of allylic alcohols
- b) **Polyene** Cyclizations
- c) Diels-Alder reaction of acrylonitriles (with **dienes**)
- d) Regioselective cyclopropanation (of **alkenes**)

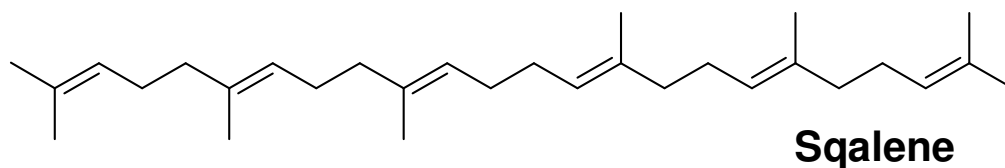
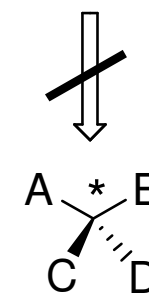
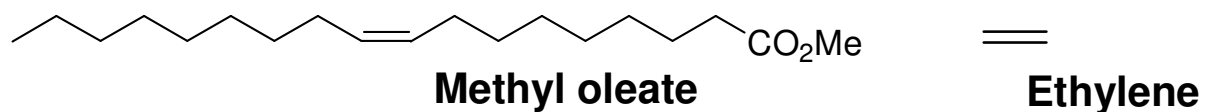
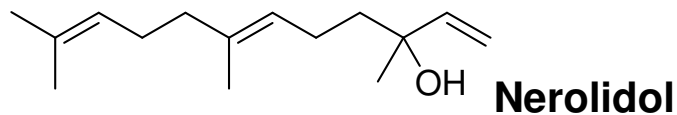
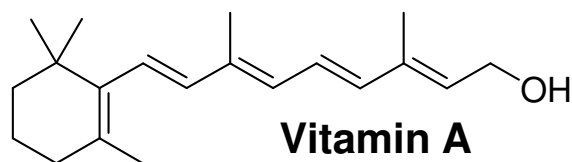
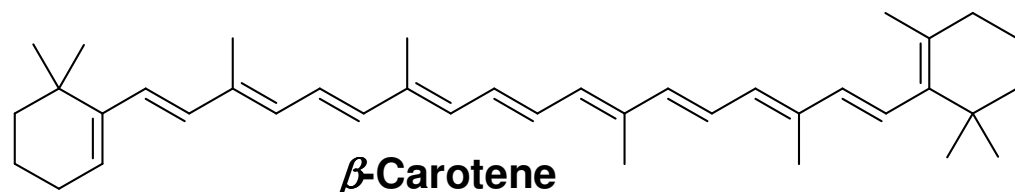
- a,b) *Chimia* 60, 574 (2006)
- b) *JOC* 72, 1112 (2007)
- d) *JOC* 73, 7543 (2008)
- b,c) *Tetrahedron* 65, 10495 (2009)

Stereoselective generation and transformation of alkenes

Example:



Seeing the Flavour & Fragrance world through the alkene eye-glass



Givaudan – Karrer Lectures (University of Zürich):
 Dirk Trauner, Lecture III: „Vitamins, Odorants and Drugs“ (2010)
 Victor Snieckus: „Sightseeing the Flatland“ (2008)

Conclusion after 10 years of fragrance research

- The stereoselective generation and transformation of alkenes is a fundamental challenge in fragrance chemistry and beyond

Nobel Prize
2001, 2005,
2010

- Among these transformations the **catalytic hydrogenation** bears inherent process advantages:
 - high volume yield (or even solvent-free)
 - high “atom-efficiency”
 - low process costs
 - unsaturated natural terpene precursors are abundant
 - alkenes are easily synthesized

Knowles, Noyori, Sharpless (2001)
Chauvin, Grubbs, Schrock (2005)
Heck, Negishi, Suzuki (2010)

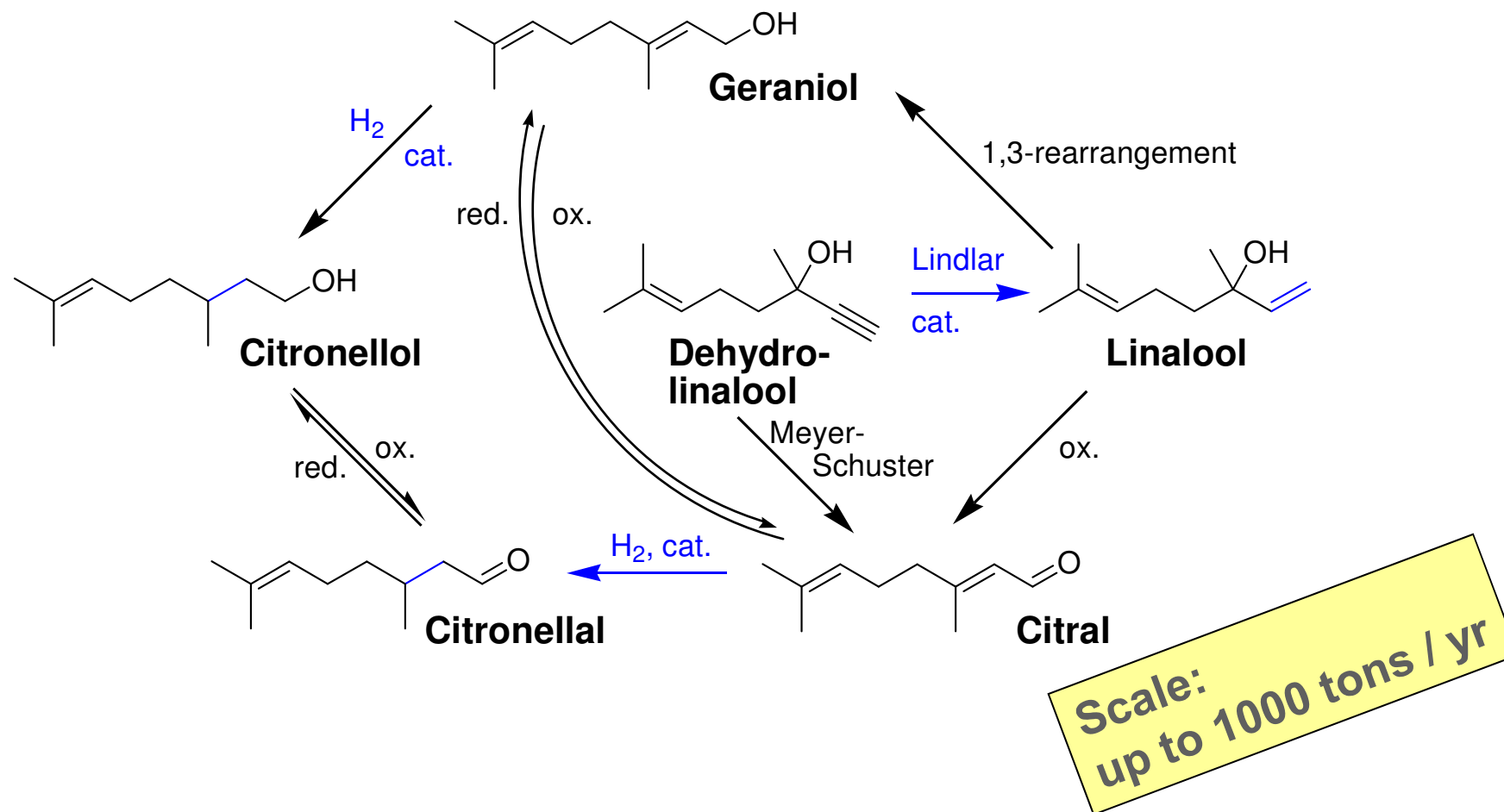
„Famous“ Hydrogenation Examples in the fine chemical industry...

are abundant!

"Handbook of Asymmetric Heterogeneous Catalysis",
Ding, K.; Uozumi, Y. (Eds), 2008 Wiley-VCH, Weinheim, Germany,
**last chapter: "Industrial Application of Heterogeneous Enantioselective
Catalysts,, (H.-U.Blaser)**

„Asymmetric Catalysis on Industrial Scale“,
H.-U.Blaser, E.Schmidt (Eds), Wiley-VCH 2004, Weinheim, Germany,
**contains well-known homogeneous hydrogenation examples (L-DOPA)
with emphasis on catalyst immobilization**

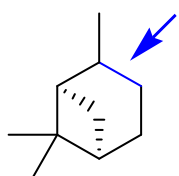
Fragrance Compounds through Hydrogenation: Six Key Terpenes



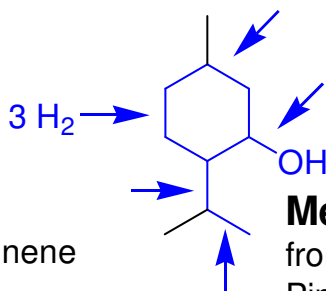
Fragrance Compounds through Hydrogenation (selected examples)

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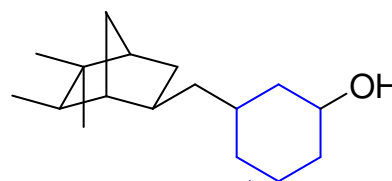
Scale:
up to 10 kt / yr



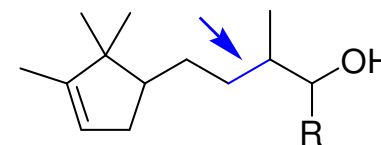
Pinane
from α -Pinene



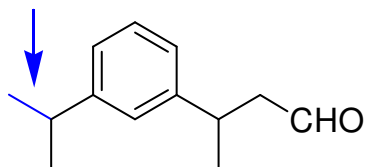
Menthol
from Thymol, Pulegone,
Piperitone



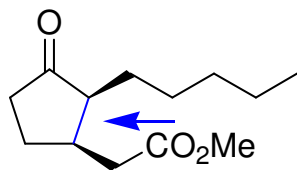
SandelaTM
from Neopol



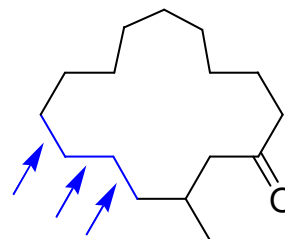
BrahmanolTM R = H
SandaloreTM R = Me



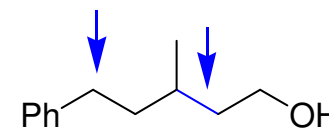
FlorhydalTM
Pd/C



Hedione HCTM
Pd/C:70% *cis*



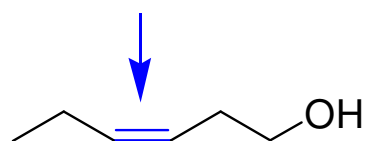
Muscone
Pd/C or
Raney nickel



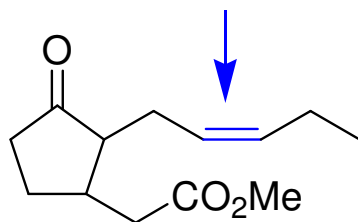
PhenoxanolTM

D.Pybus, C.Sell, *The Chemistry of Fragrances*, RSC (1999)
L.A.Saudan, *Acc.Chem.Res.*40, 1309 (2007)

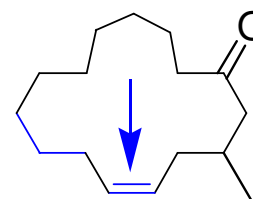
Fragrance Compounds through Hydrogenation from alkynes to cis-alkenes with Lindlar catalysts (selected examples)



Leaf alcohol



Methyl jasmonate



MuscenoneTM

D.Pybus, C.Sell, *The Chemistry of Fragrances*, RSC (1999)

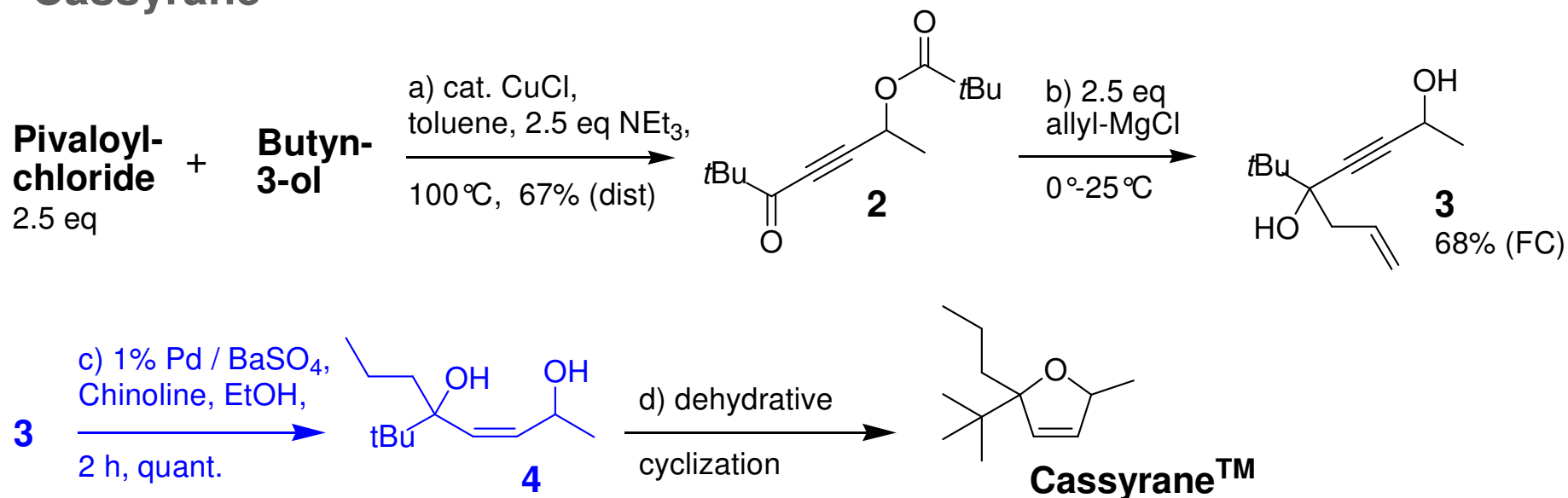
L.A.Saudan, *Acc.Chem.Res.*40, 1309 (2007)

**Scale:
up to 50 tons / yr**

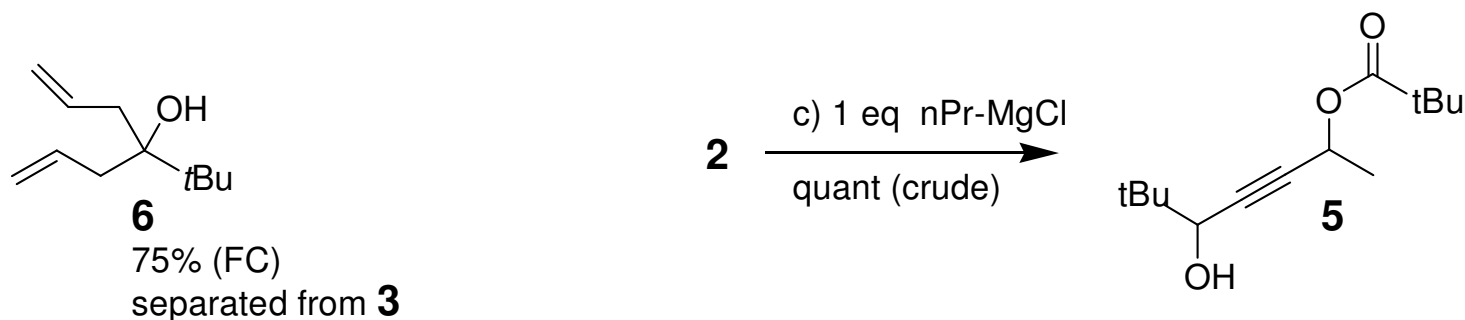
General Strategy

- Synthesis and olfactory screening: structural analogs
- Process development: screening of catalysts, turnover
- Upscaling: mass transfer, recycling of catalysts, solvents

Fragrance Compounds through Hydrogenation: Cassyrane[™]



- Step c: First experiment successful
- Step d: P.Kraft et al., *Synthesis* (2005)



H-Cube:

a) Synthesis and olfactory Screening

- Fast screening tool: Substrate 1% in ethanol. Comparison with product 1% in ethanol within 10 min (no distillation) → mg-quantities → GCMS, NMR
- minimal exposure to reagents and reaction conditions: no olfactory off-notes (flow conditions, no distillation)
- g-quantities for further evaluation if necessary
- target- or diversity-oriented screening
- up to 90 °C / 90 bar



H-Cube Mini
Hasteloy tubings

b) Process development: screening of catalysts, turnover

- Cartridges ordered from or to be filled at ThalesNano
- mg → g quantities
- 1:1 transfer flow → batch



Diving into the Flow: Chemoselective H-Cube Hydrogenations

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a) Alkenyl-cyclopropanecarbinols: Alkene versus cyclopropylcarbinol

b) Conjugated Ketones

Pashminol™

c) Unsaturated aldehydes

cis-Javanol

d) Conjugated aldehydes

e) Alkenols

f) Substituted Phenols

Raspberry Ketone

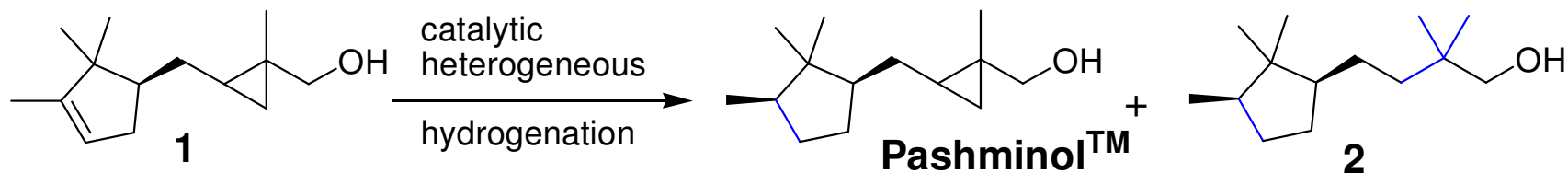
g) ...

Cassyrane™

- flow reactions through the H-Cube with
1 ml / min (+/-) in ethanol unless not otherwise indicated
- hydrogenation sites indicated (blue arrows)



a) Alkenyl-cyclopropanecarbinols: Pashminol[™] Alkene versus Cyclopropylcarbinol



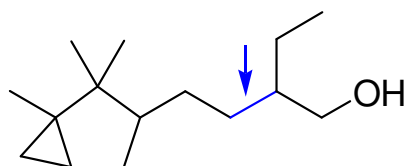
- Problem: Cyclopropylcarbinol cleavage with Pd/C
- H-Cube-screening suggested better catalysts: Pt/C, Raney nickel, Pd/CaCO₃....

run	cartridge	T / p	cyclopropane cleavage to 2	substrate 1	product Pashminol
a	10% Pd / C	25 °C / 1 bar	5	3	73
b	5% Pd / Al ₂ O ₃	25 °C / 1 bar	15	17	53
c	5% Pt / C	25 °C / 1 bar	0	1	84
d	Raney nickel	80 °C / 1 bar	1	2	87
e	5% Pd / CaCO ₃	25 °C / 1 bar	1	1	83

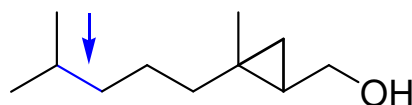
Table:
H-cube hydrogenation of **1**.
GC-conversion.
Selected examples.

- Selective hydrogenation of alkenes in the presence of cyclopropylcarbinols
- Transfer to batch conditions: Scalable Synthesis of Pashminol

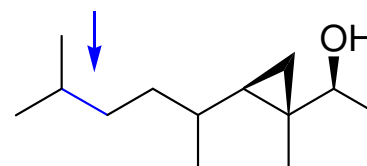
a) Alkenyl-cyclopropanecarbinols: Alkene versus Cyclopropylcarbinol



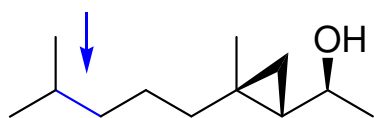
1
Raney nickel
ex **Ebanol**TM



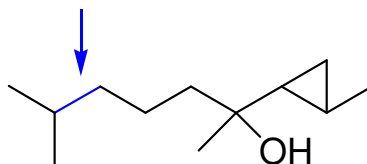
2
Pd/CaCO₃ (5g)
ex **Geraniol**



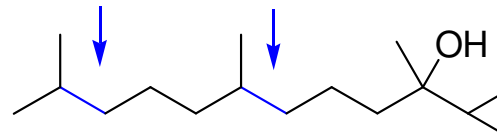
3
Pd/CaCO₃
ex **Melonol**TM



4
Pd/CaCO₃
ex **Citral**



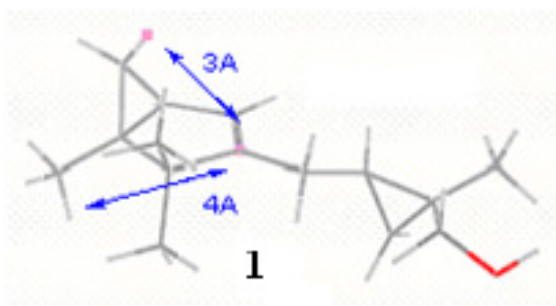
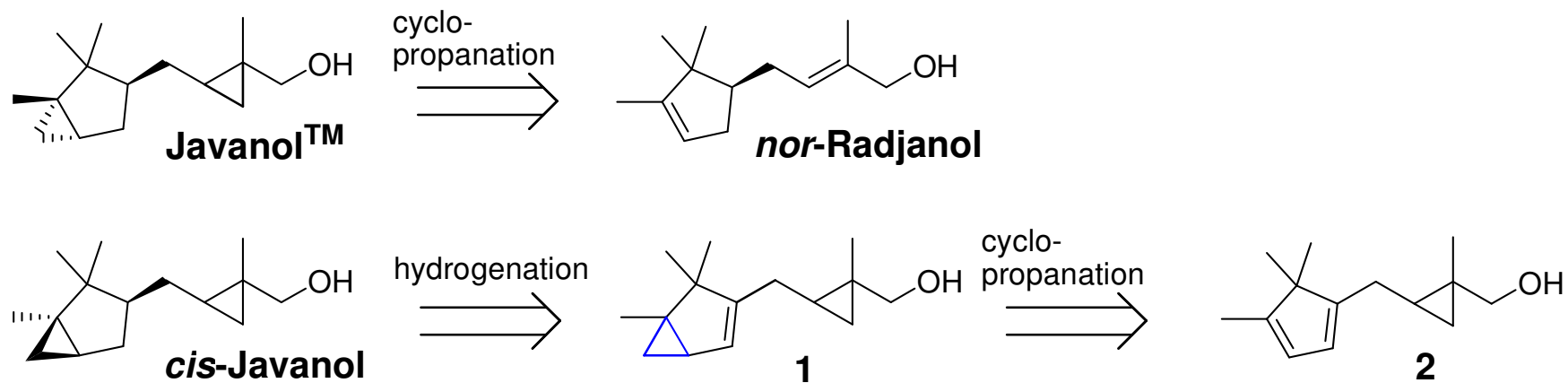
5
Pd/CaCO₃
ex **Methylheptenone**



6
Pd/CaCO₃
ex **Δ-Nerolidol**

- Selective hydrogenation of alkenes in the presence of cyclopropylcarbinols with Pd/CaCO₃ and Raney nickel
- Raney nickel avoids deoxygenation of **1** (as encountered with Pd/CaCO₃ and Pt/C)
 - Compound **2**: flow → batch

a) Alkenyl-cyclopropylcarbinols: Retrosynthesis of *cis*-Javanol

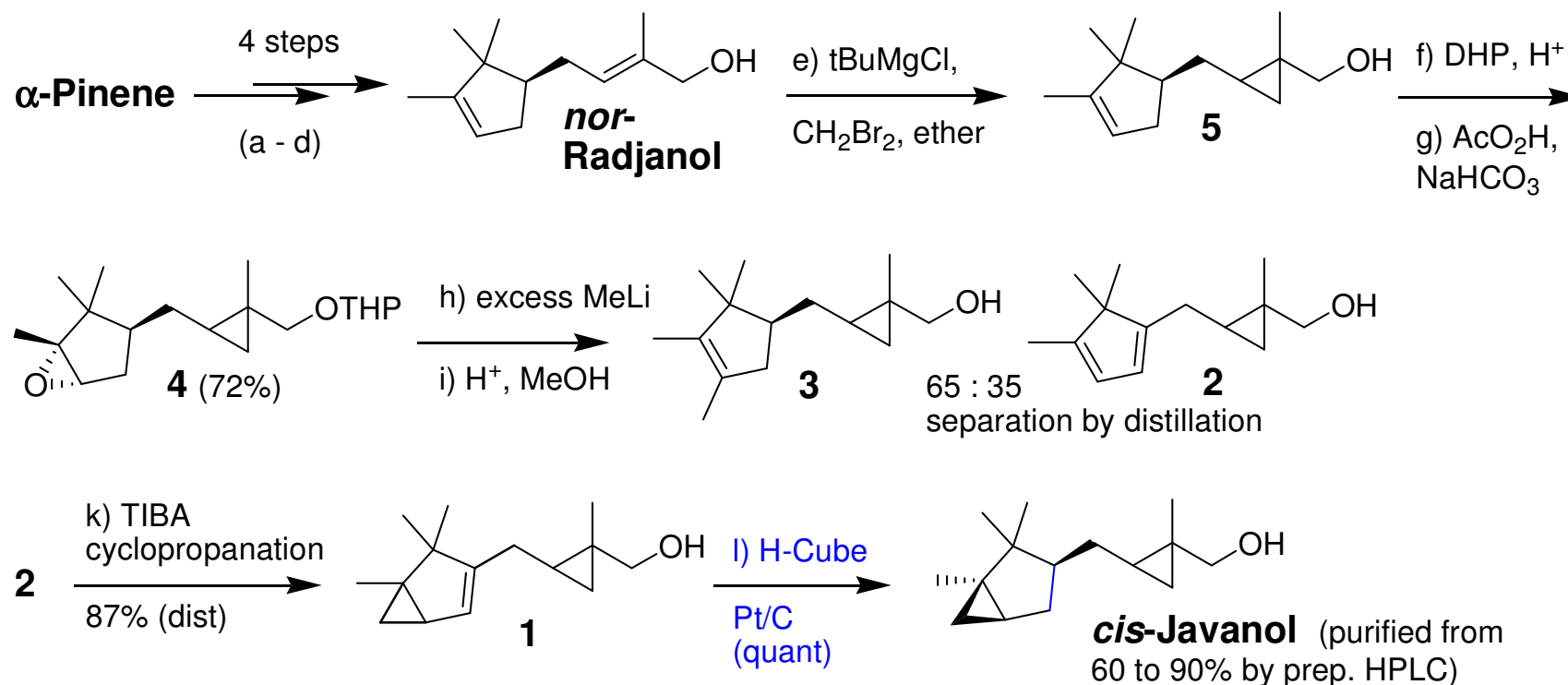


quick'n dirty synthesis
envisaged...

JOC in press

...which worked better than expected:
Synthesis of cis-Javanol (dedicated to Georg Frater)

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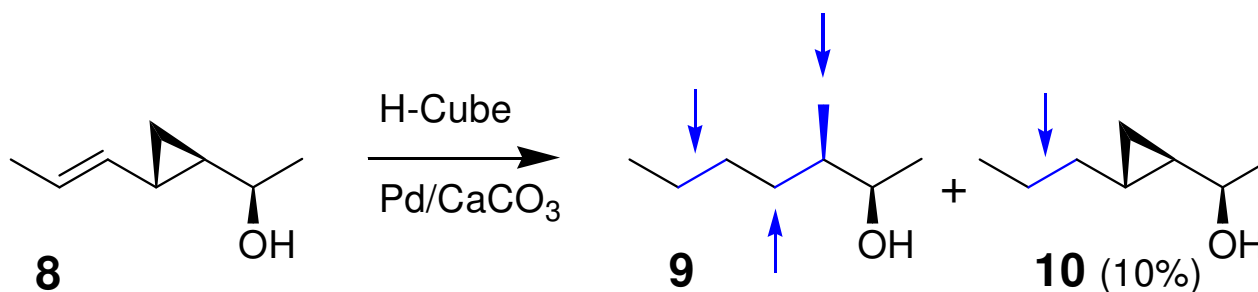
step e) proximal-selective Grignard cyclopropanation (*JOC* 73, 7543, 2008)

step h) epoxide double elimination

step k) distal-selective TIBA cyclopropanation

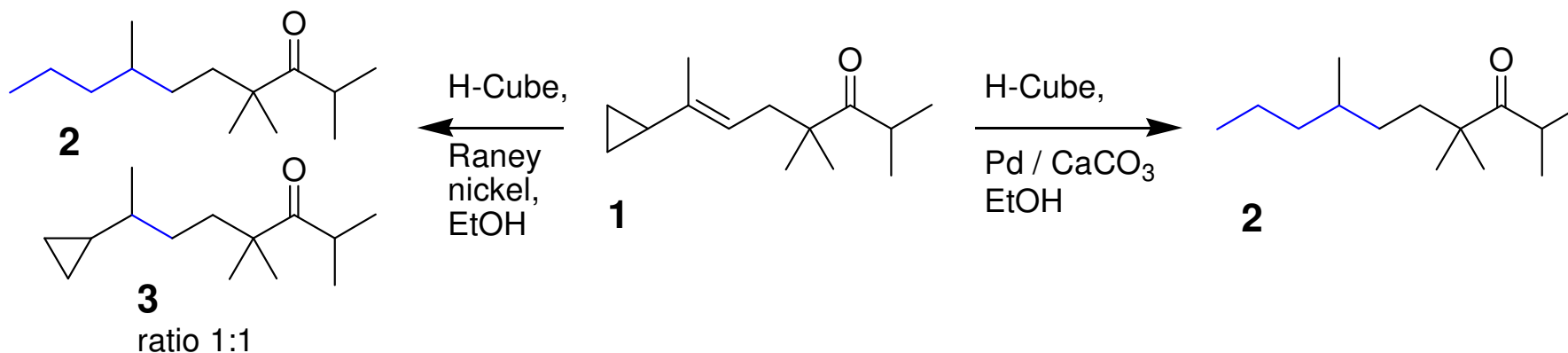
step l) chemoselective double bond hydrogenation (flow \rightarrow batch, excess Pt/C)

a) Alkenyl-cyclopropylcarbinols :
Alkene Hydrogenation versus Cyclopropane Cleavage



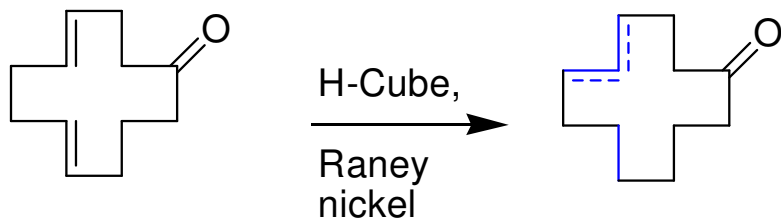
- Cyclopropyl-cleavage of Δ -alkenyl-cyclopropylcarbinols
- a) cyclopropyl-cleavage (neighbor-group effect) then b) alkene hydrogenation \rightarrow **9**
- in case of **10** first alkene hydrogenation, with **10** being relatively inert against cyclopropyl cleavage

b) Alkenyl-cyclopropylketones : Alkene versus Cyclopropane Cleavage



- Preferred cyclopropyl-cleavage with Pd / CaCO₃: a) cyclopropyl-cleavage (neighbor-group effect), then b) alkene hydrogenation → **2**
- in case of Raney nickel first alkene hydrogenation, with **3** being inert against cyclopropyl cleavage
- Cyclopropyl-cleavage of cyclopropyl-vinyl units under hydrogen unknown

b) Unsaturated Ketones



**Cyclododeca-
4,8-dienone**

E/Z = 1:1 [178]

2

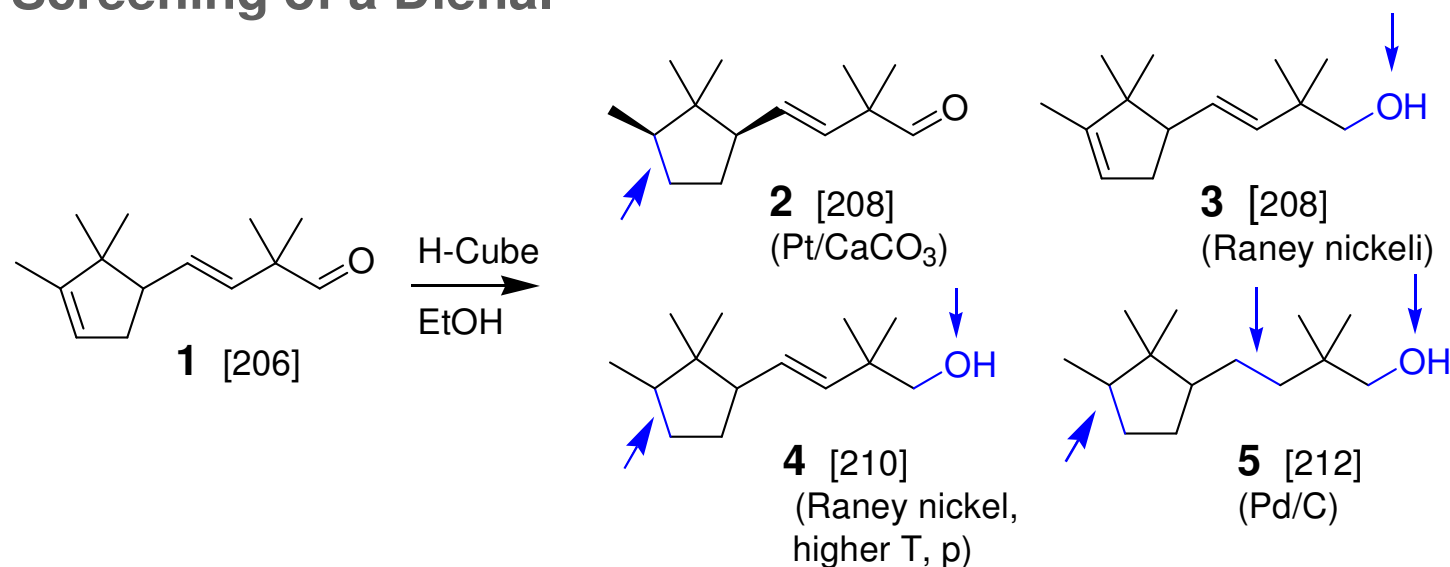
25% substrate [178]

46% mono-alkene [180]

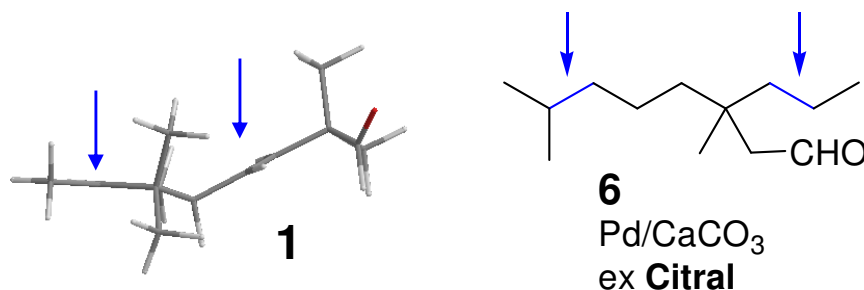
26% cyclododecanone [182]

- Pd/C, Lindlar nonselective (M = 182)
- Best selectivities with Raney nickel

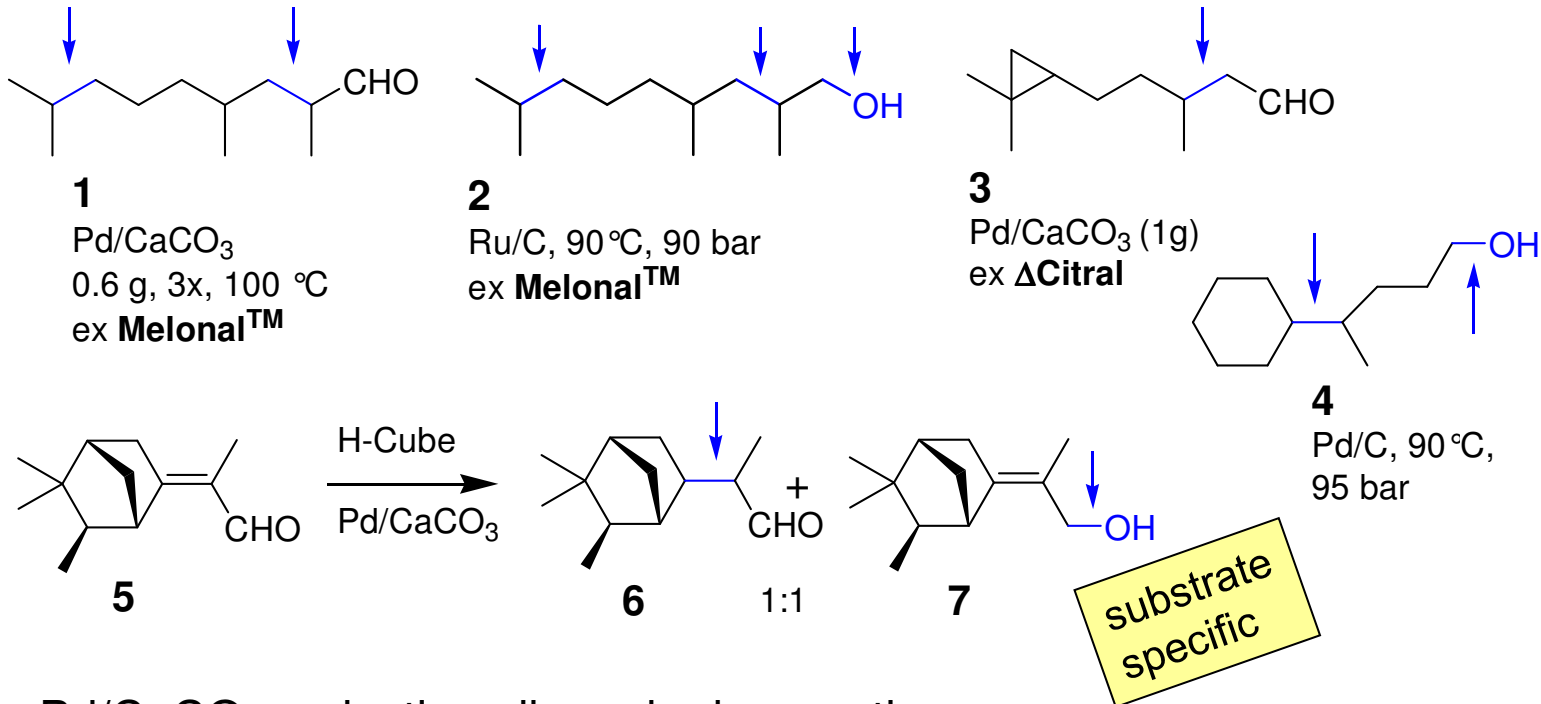
c) Selective Hydrogenation of unsaturated Aldehydes: Screening of a Dienal



- Pt/CaCO₃ and Pd/CaCO₃ : aldehyde function untouched
- Raney nickel: selective hydrogenation of the aldehyde function
- Pd/C: relatively unselective and drastic



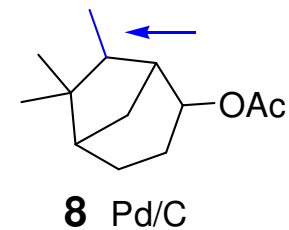
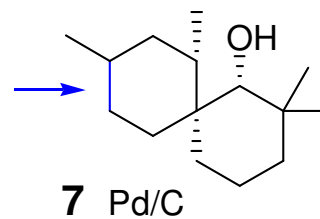
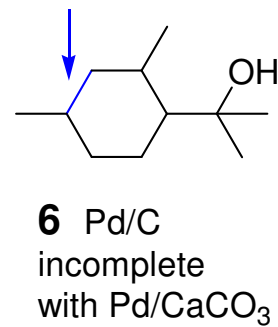
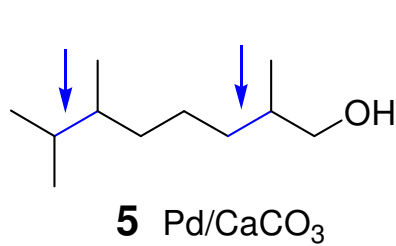
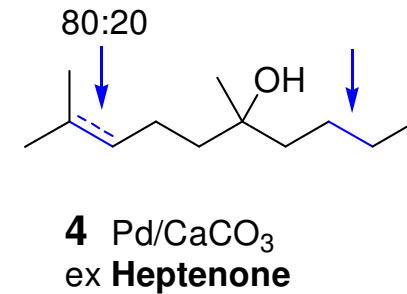
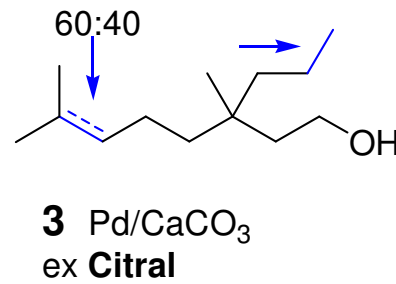
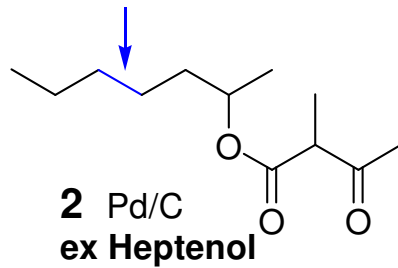
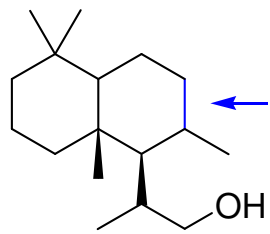
d) Selective Hydrogenation of conjugated Aldehydes



- Pd/CaCO₃: selective alkene hydrogenation
- but not in case of sterically hindered alkene **4**
- Compound **2**: flow → batch
- attempted selective reduction of the aldehyde function so far not possible

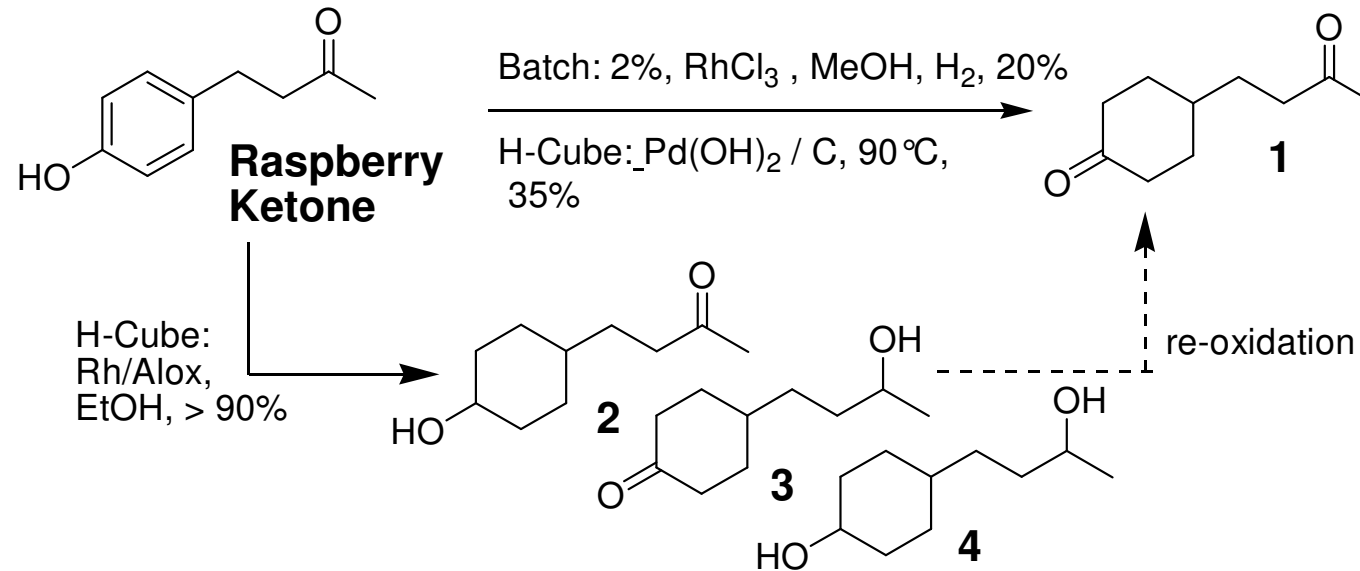
e) Alkenols

Givaudan[®]

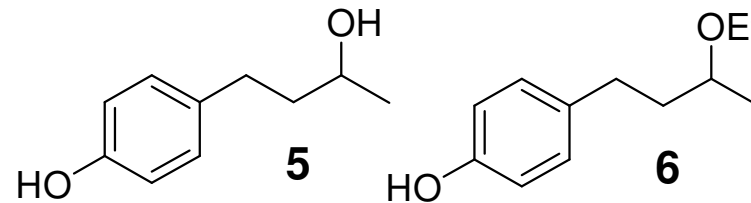


- no deoxygenation (sensitive tertiary alcohol **6**)
- Pd/C cartridge ideal for complete conversion

f) Phenols: Raspberry Ketone



- Screening: Pd/C, Rh/C, Ru/Alox, $\text{Pd}(\text{OH})_2$, Raney nickel, Rh/Pd/C...
- Rh/Alox reduced to **2** and **3** (88%). This mixture could be re-oxidized to diketone **1**. Byproducts



H-Cube Hydrogenations: Summary

- Selective hydrogenation of alkenylcyclopropanecarbinols and ketones, alkenols, unsat. aldehydes and other substrates
- Fragrance Compounds such as Pashminol™, *cis*-Javanol, and Cassyrane™ accessed through the H-Cube
- Upscaling (flow) and / or transfer to batch conditions
- Fast screening Tool for Fragrance Chemists
- Paradigm change: young technicians prefer the H-Cube against batchwise hydrogenation (balloon, autoclave)



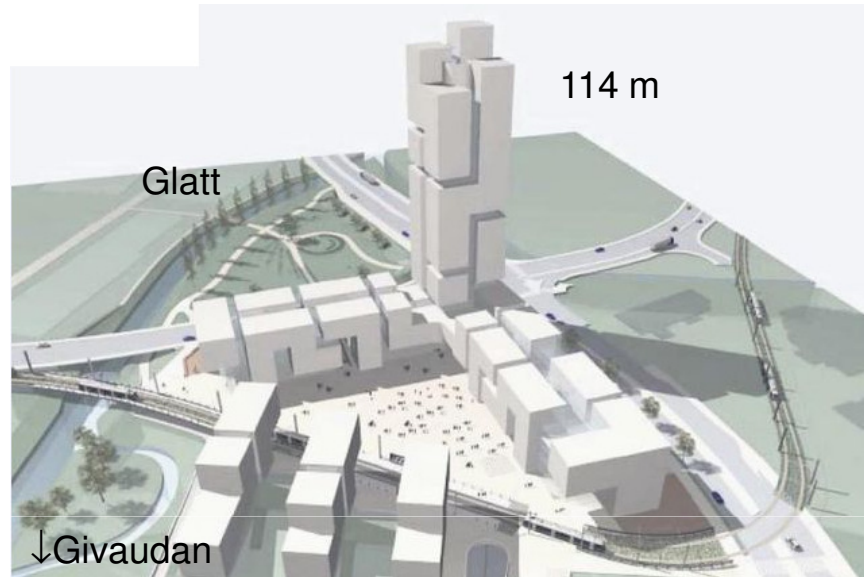
Glatt river, Dübendorf

*“The water of a river we touch,
is the last of what has past,
and the first of what is coming,
such with time present”*

Leonardo da Vinci

*“Optimizing flow reactions is
a multidimensional
mind-expanding enterprise”*





Dr. Simon Ellwood
Prof. G. Frater
Dr. Markus Gautschi
Dr. Andreas Goeke
Dr. Richard Jones

Construction building, Dübendorf

Acknowledgements

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