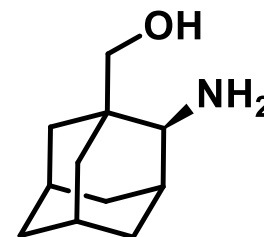
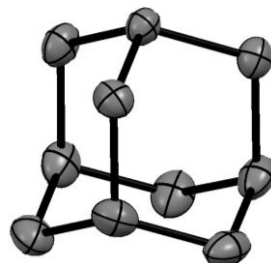


Treatment of diabetes



Giessen 2014

Synthetic Chemistry for Modulation of Biological Processes

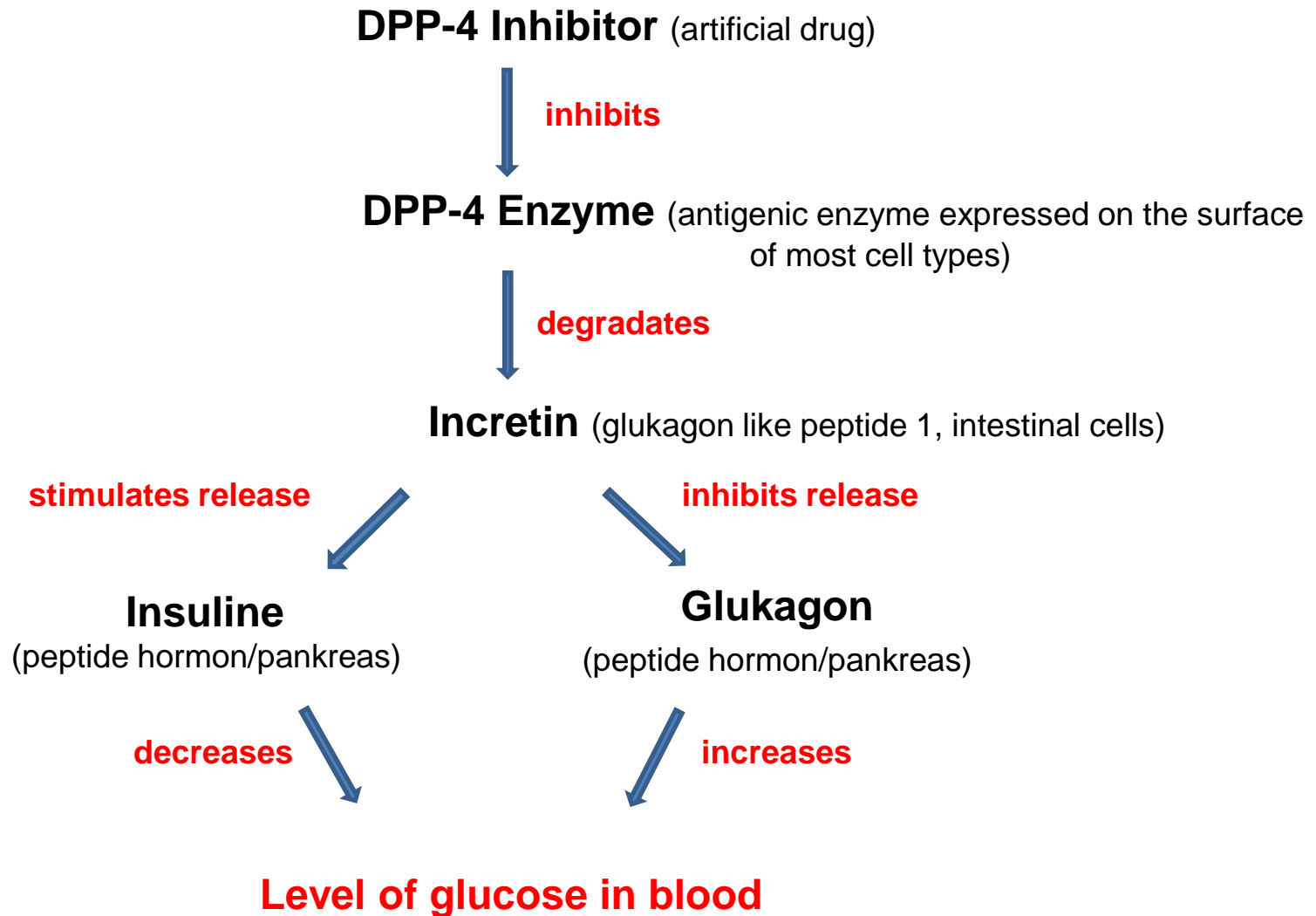


*Somewhere
in the future*

Hodonín 1933

2015-22-05

Towards new DPP-4 inhibitors



Wikipedia: DPP-4 plays a major role in the metabolism of glucose
Furthermore, it appears to work as a suppressor in the development of tumour growth.

Nausea, diarrhea, headaches, and dizziness are common with both of the available GLP-1 receptor agonists.
Upper respiratory tract infections, nasopharyngitis, and headaches are common with the DPP-4 inhibitors.

Glukagon like peptide 1 agonists

GLP-1 agonists (artificial drug)



acts like

Incretin (glukagon like peptide 1, intestinal cells)

Exenatide (2005, Byetta/Bydureon, Astrazeneca)

(peptide, synthetic version of a hormone found in the saliva of the Gila monster (lizard))

Liraglutide (2010, Victoza, Saxenda, Novo Nordisk)

(peptide, derivative of human GLP-1)

Lixisenatide (2013, Lyxumia, Sanofi)

(it is derived from the first 39 amino acids in the sequence of the peptide found in the Gila monster, omitting proline at position 38 and adding six lysine residues)

Albiglutide (2014, Tanzeum, GlaxoSmithKline)

(GLP-1 dimer fused to human albumin (globular peptide))

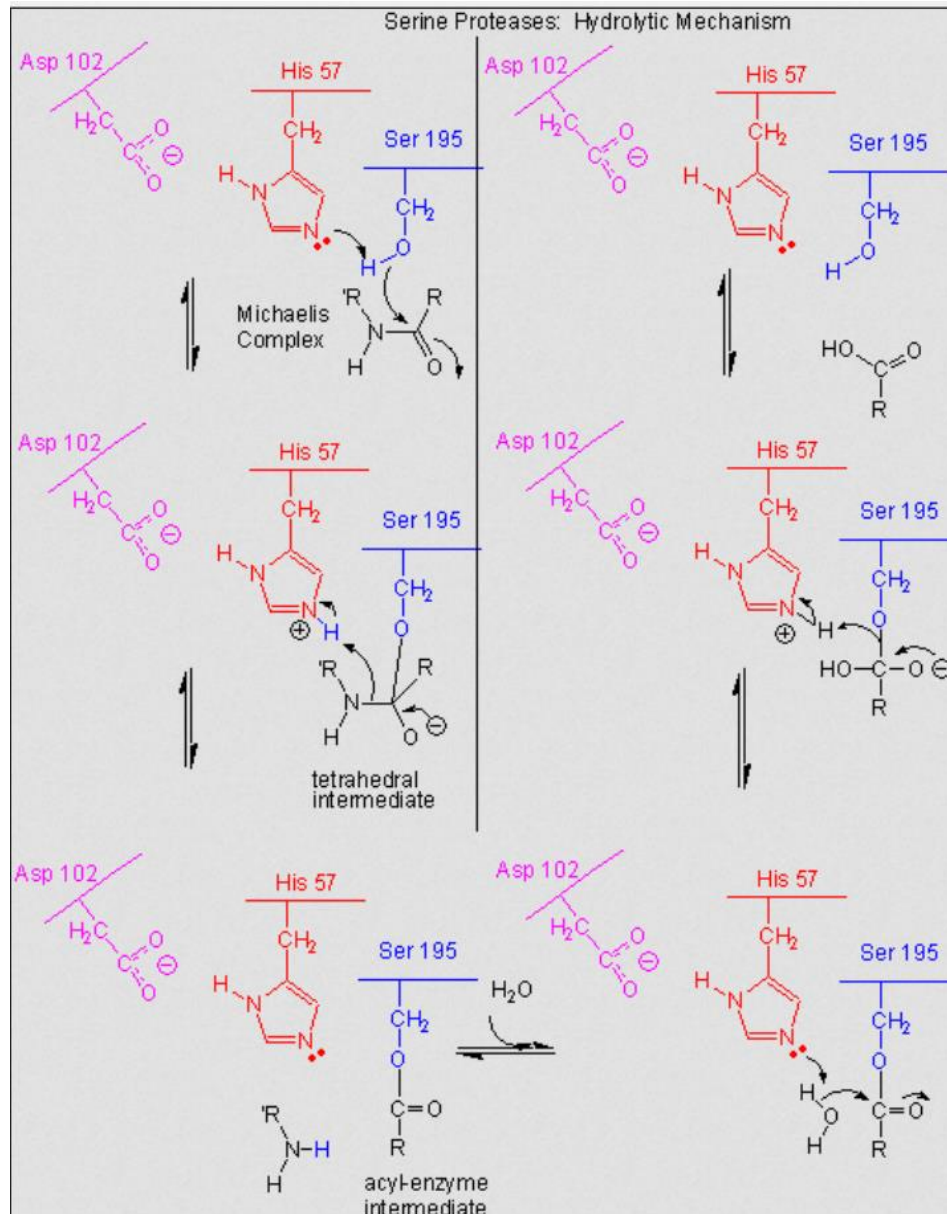
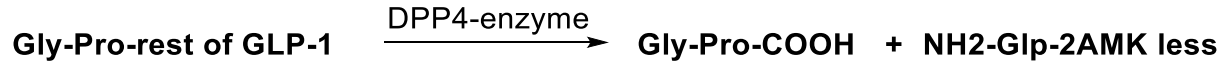
Dulaglutide (2014, Trulicity, Eli Lilly)

(GLP-1-Analog, 90% similarity to human GLP-1, modified to resist DPP-4 enzyme)

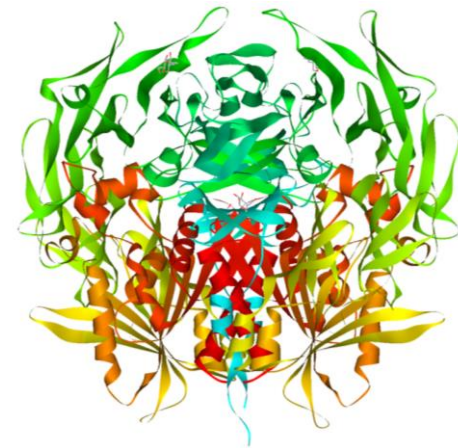


DPP-4 enzyme

Function:



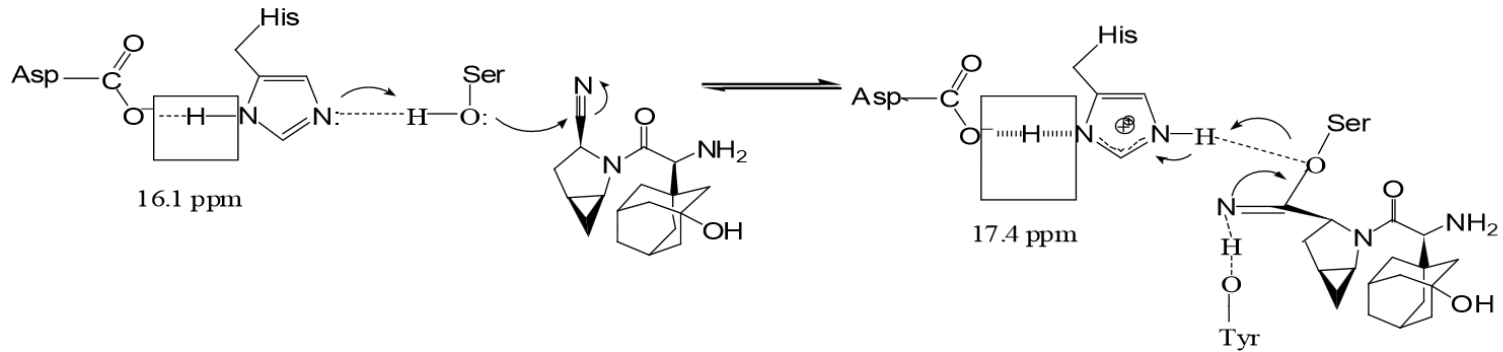
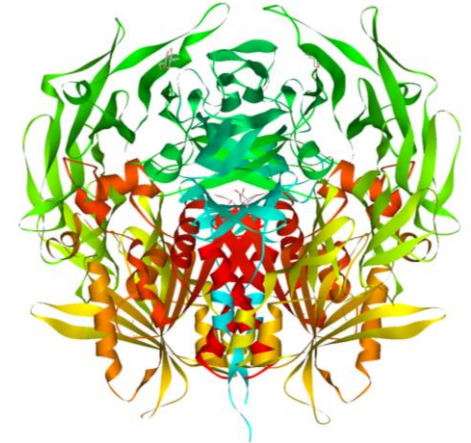
DPP-4 is a serine protease, selectively cleaves two amino acids from GLP-1, which has proline in the second position



Y. B. Kim, L. M. Kopcho, M. S. Kirby, L. G. Hamann, C. A. Weigelt, W. J. Metzler, J. Marcinkeviciene *Archives of Biochemistry and Biophysics* **2006**, 9 – 18.

DPP-4 inhibitor

Function:

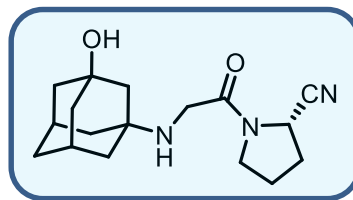


Y. B. Kim, L. M. Kopcho, M. S. Kirby, L. G. Hamann, C. A. Weigelt, W. J. Metzler, J. Marcinkeviciene *Archives of Biochemistry and Biophysics* **2006**, 9 – 18.

Towards new DPP-4 inhibitors

DPP-4 Inhibitors (commercial drugs)

Sitagliptin (2006, Merck, Januvia)



Vildagliptin (2007, Novartis, Galvus)

Saxagliptin (2009, Novartis, Onglyza)

Linagliptin (2011, Eli Lilly Co and Ingelheim Boehringer, Tradjenta)

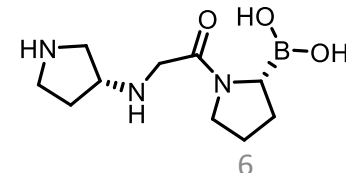
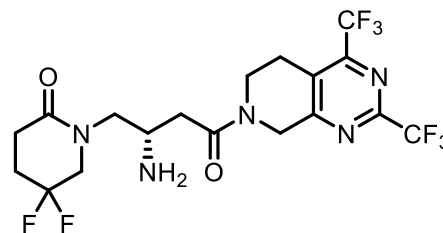
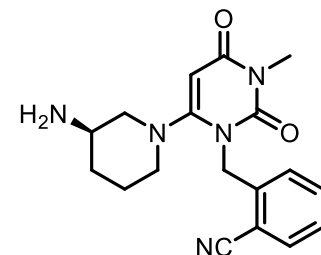
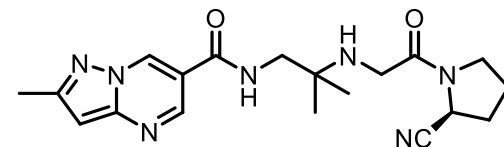
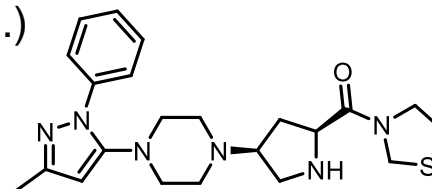
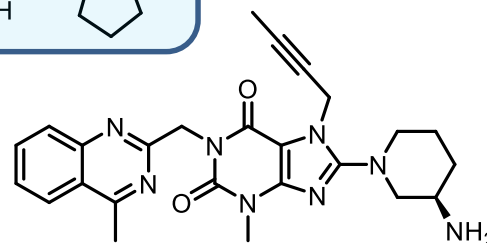
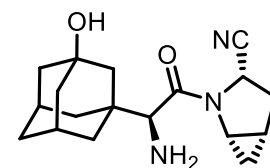
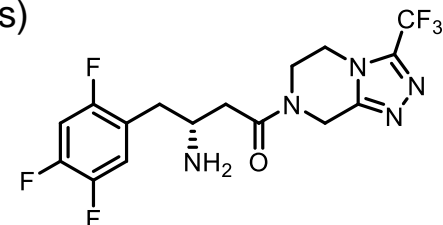
Anagliptin (2012, Sanwa Kagaku Kenkyusho Co., Ltd. and Kowa Company, Ltd.)

Tenegliptin (2012, Japan)

Alogliptin (2013, Takeda Pharmaceutical Company)

Gemigliptin (LG Life Sciences, development)

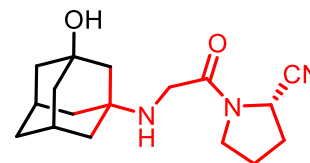
Dutogliptin (Phenomix corporation, phase 3)



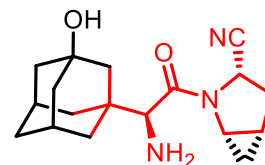
Similarities

DPP-4 Inhibitors (commercial drugs)

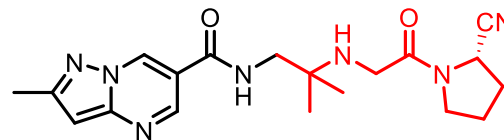
Vildagliptin (2007, Novartis, Galvus)



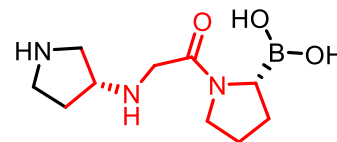
Saxagliptin (2009, Novartis, Onglyza)



Anagliptin (2012, Sanwa Kagaku Kenkyusho Co., Ltd. and Kowa Company, Ltd.)



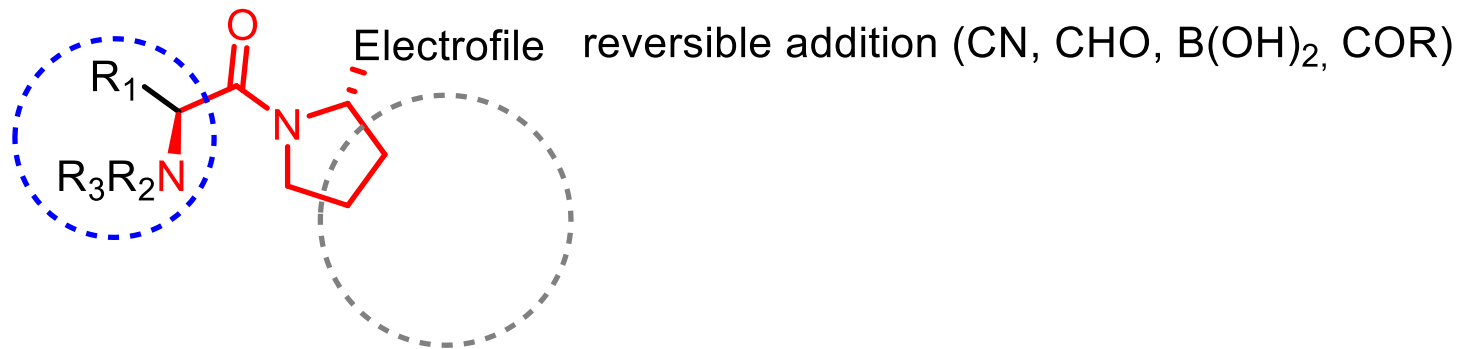
Dutogliptin (Phenomix corporation, phase 3)



Design your own DPP-4 inhibitor

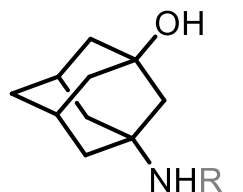
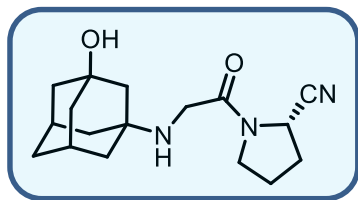
red part important for recognition

inside the enzyme
additional interactions

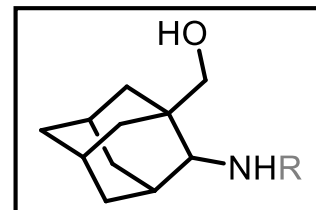


outside part for
physical properties

Vildagliptin analogs



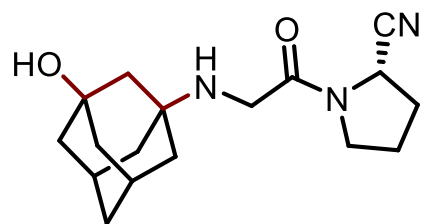
bioisosters



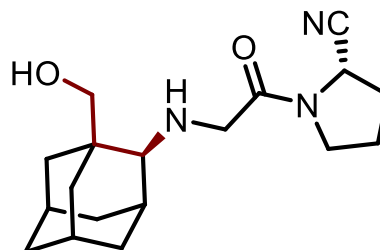
known bioactivity

unknown properties

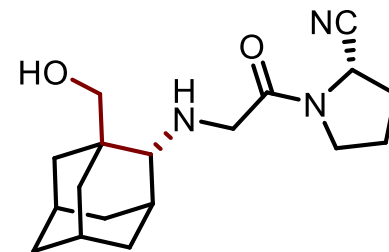
Analogs:



original structure

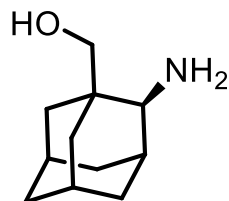


bioisoster 1

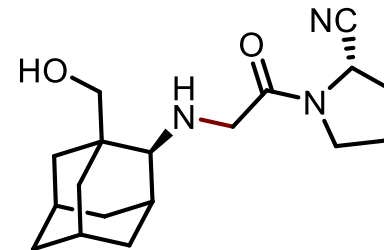
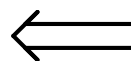
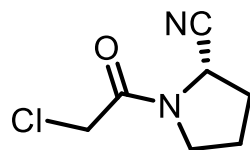


bioisoster 2

Preparation:



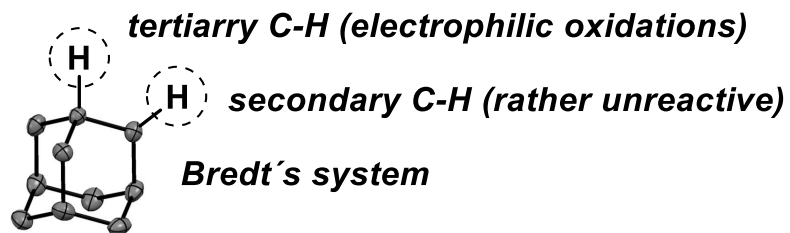
+



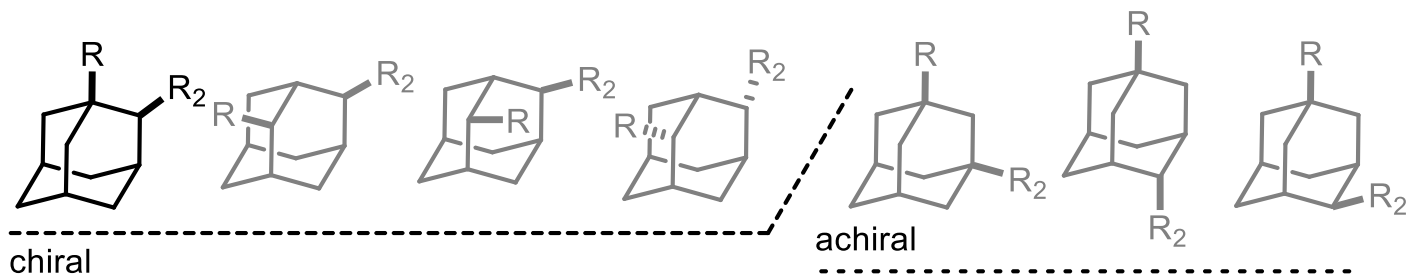
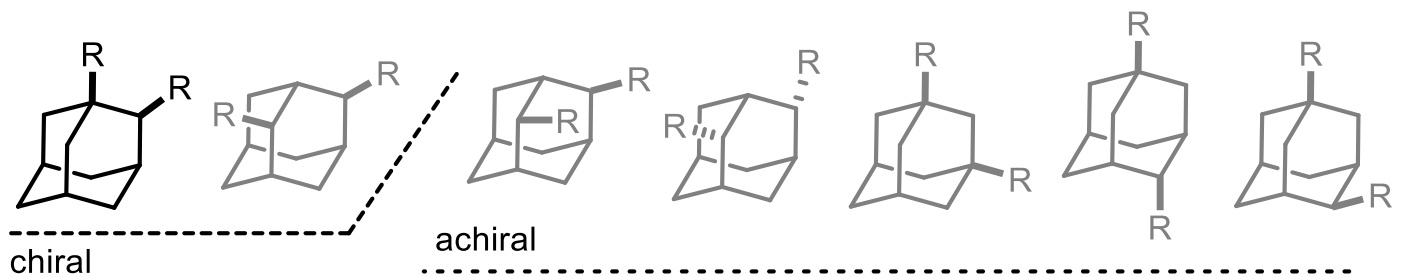
commercially available

Disubstitution pattern on adamantane

Properties of adamantane unit:

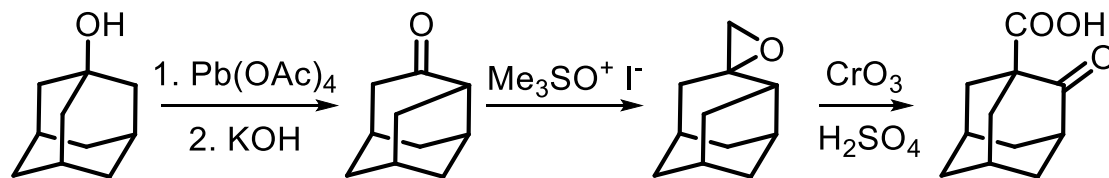


Stereoisomers:



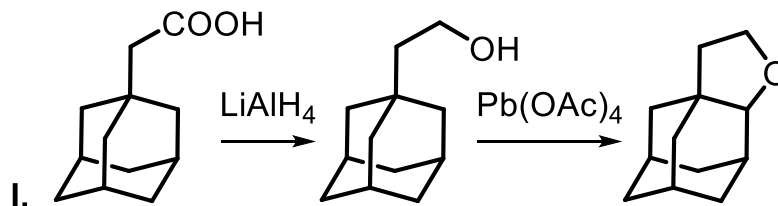
Synthesis of 1,2-disubstituted adamantane derivatives

Synthesis with cage opening step:

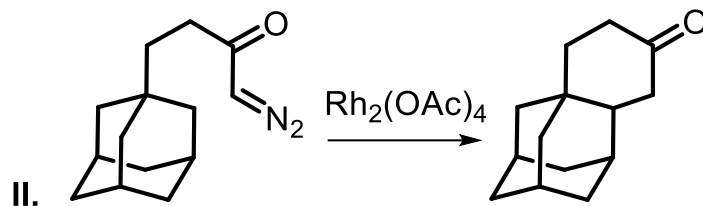


Cuddy, B. D.; Grant, D.; McKervey, M. A. *Journal of the Chemical Society C-Organic* **1971**, 3173.

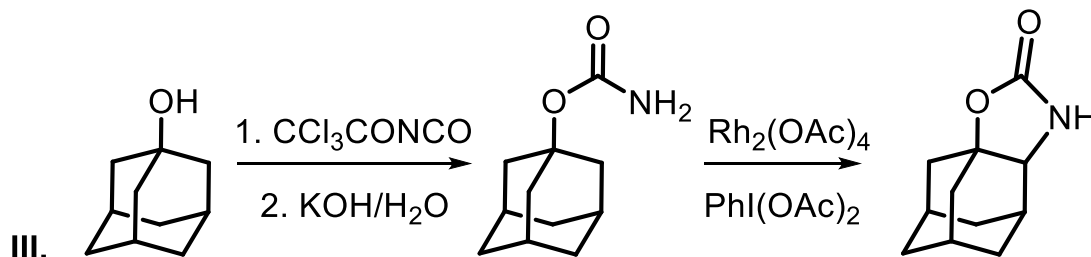
Previous examples:



Lunn, W. H. W.; Podmore, W. D.; Szinai, S. S. *Journal of the Chemical Society C-Organic* **1968**, 1657.



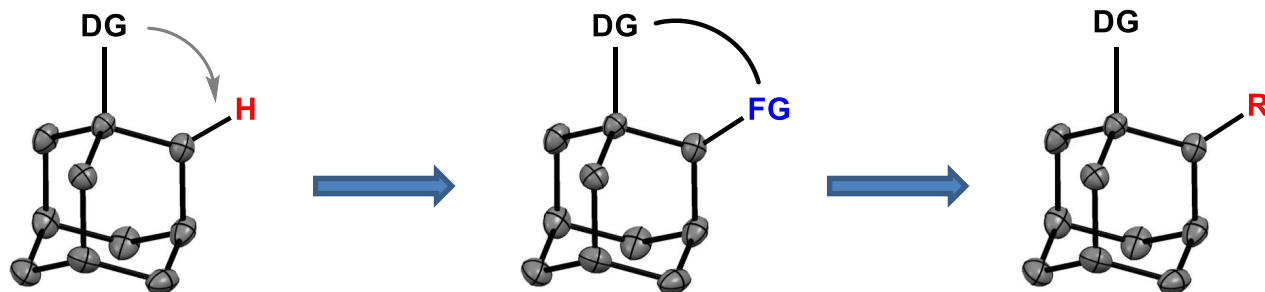
Nicolaou, K. C.; Stepan, A. F.; Lister, T.; Li, A.; Montero, A.; Tria, G. S.; Turner, C. I.; Tang, Y.; Wang, J.; Denton, R. M.; Edmonds, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 13110.



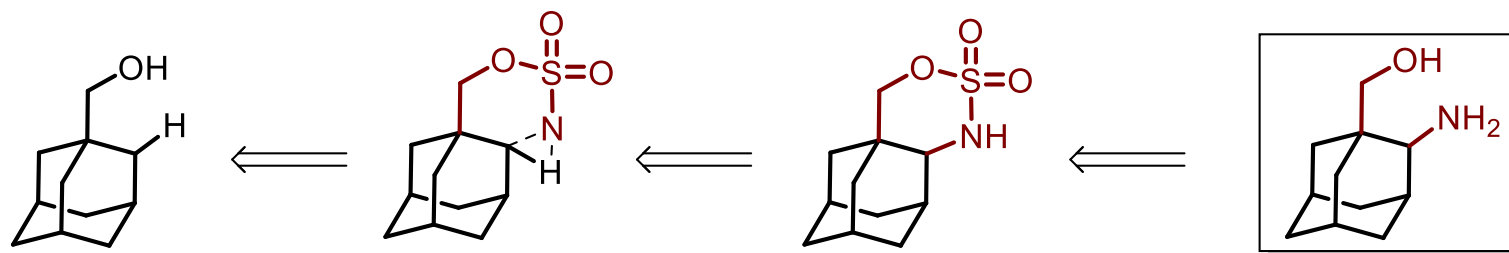
Rohde, J. J.; Pliushchev, M. A.; Sorensen, B. K.; Wodka, D.; Shuai, Q.; Wang, J. H.; Fung, S.; Monzon, K. M.; Chiou, W. J.; Pan, L. P.; Deng, X. Q.; Chovan, L. E.; Ramaiya, A.; Mullally, M.; Henry, R. F.; Stolarik, D. F.; Imade, H. M.; Marsh, K. C.; Beno, W. A.; Fey, T. A.; Droz, B. A.; Brune, M. E.; Camp, H. S.; Sham, H. L.; Frevert, E. U.; Jacobson, P. B.; Link, J. T. *J. Med. Chem.* **2007**, *50*, 149-164.

1,2-disubstitution pattern on adamantane

C-H functionalizations:

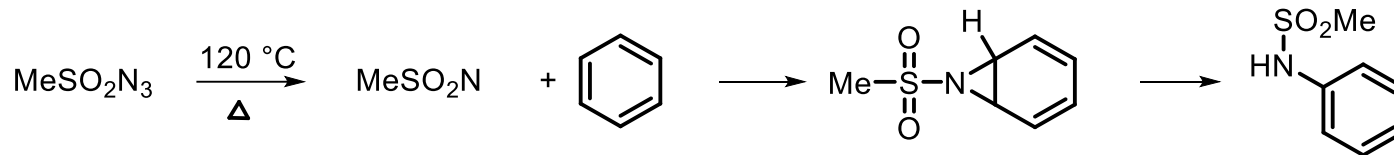


Retrosynthesis of the desired motif:

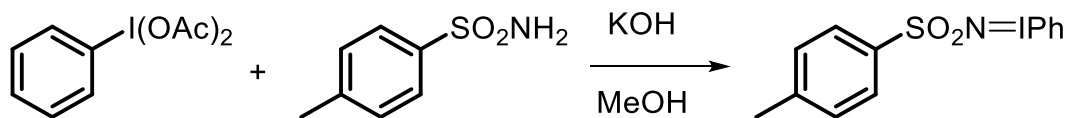


Development of sulfonamide insertions

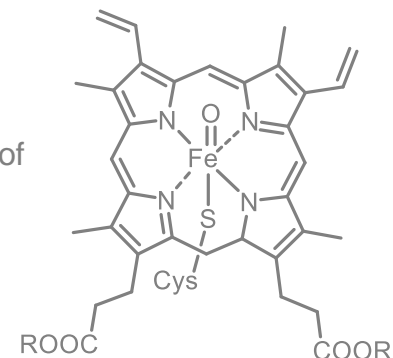
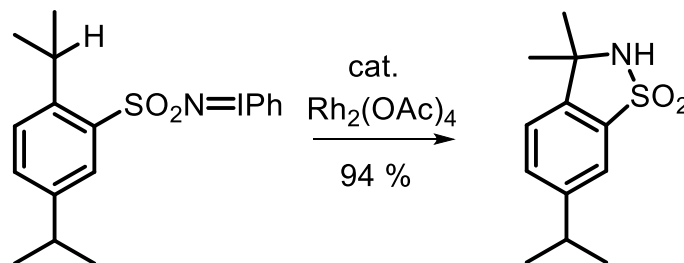
1974: „The Reaction of Methanesulfonyl Nitrene with Benzene. Attempts to Generate Sulfonyl Nitrenes from Sources Other than the Azides” R. A. Abramovitch, T. D. Bailey, T. Takaya, and V. Uma *JOC* **1974**, 39, 340.



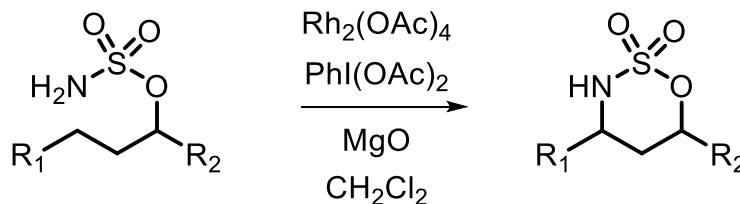
1975: „Synthesis and reaction of new type I-N ylide, N-tosyliminoiodinane” Yamada, Y.; Yamamoto, T.; Okawara M. *Chem. Lett.* **1975**, 361.



1983: „Intramolecular nitrene C-H insertions mediated by transition metal complexes as nitrogen analogs of cytochrome P-450 reactions” Breslow, R.; Gellmann, S. H. *J. Am. Chem. Soc.* **1983**, 105, 6728.

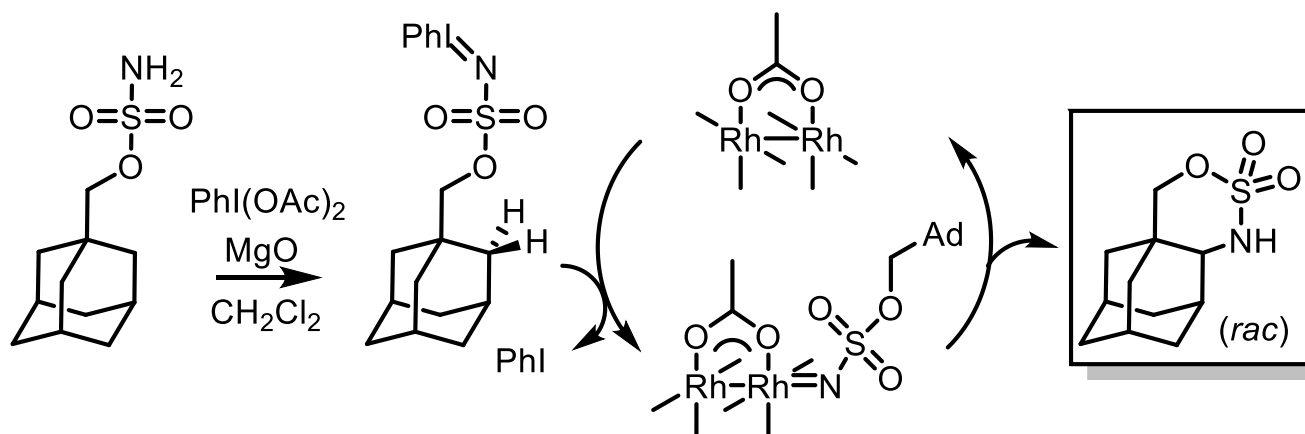


2001: „Synthesis of 1,3-Difunctionalized amine derivatives through selective C-H bond oxidation” Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois J. *J. Am. Chem. Soc.* **2001**, 123, 6935.

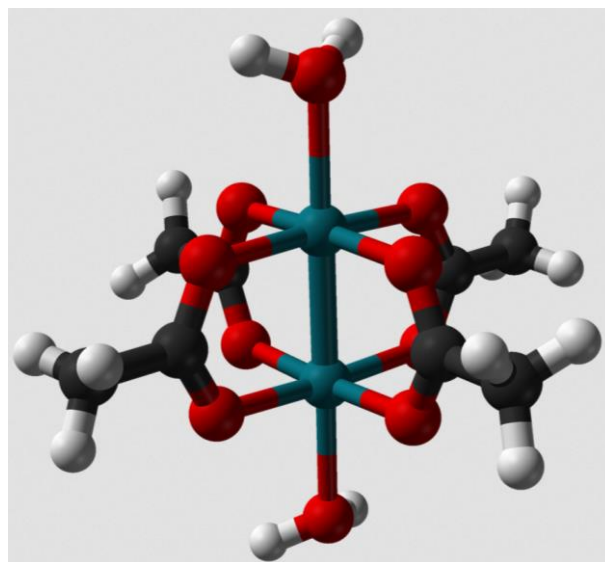


Metal catalyzed nitrenoid insertion

Catalytic cycle:



$\text{Rh}_2(\text{OAc})_4$:



If the insertion is slow then nitrenoid oxidises the amide

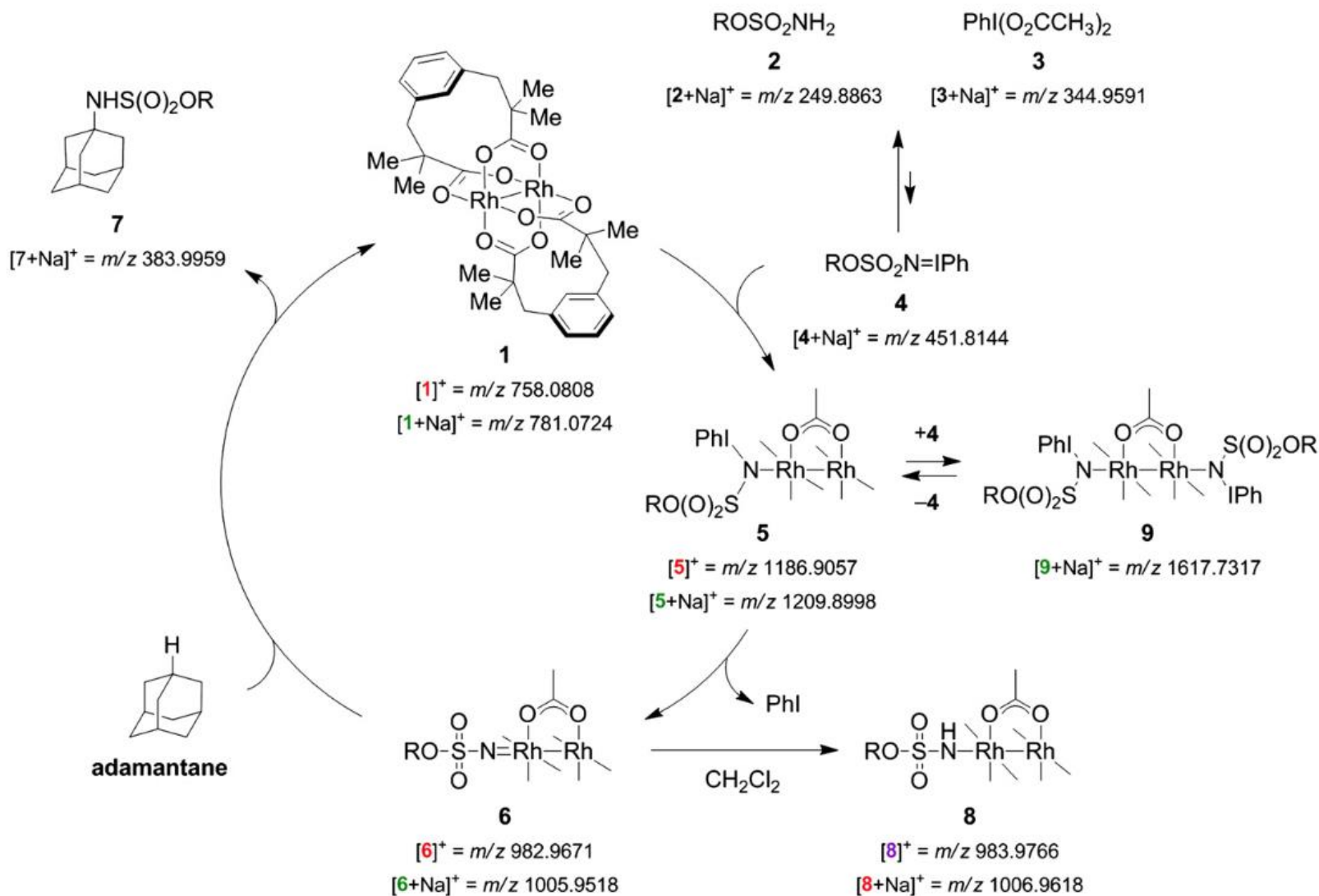
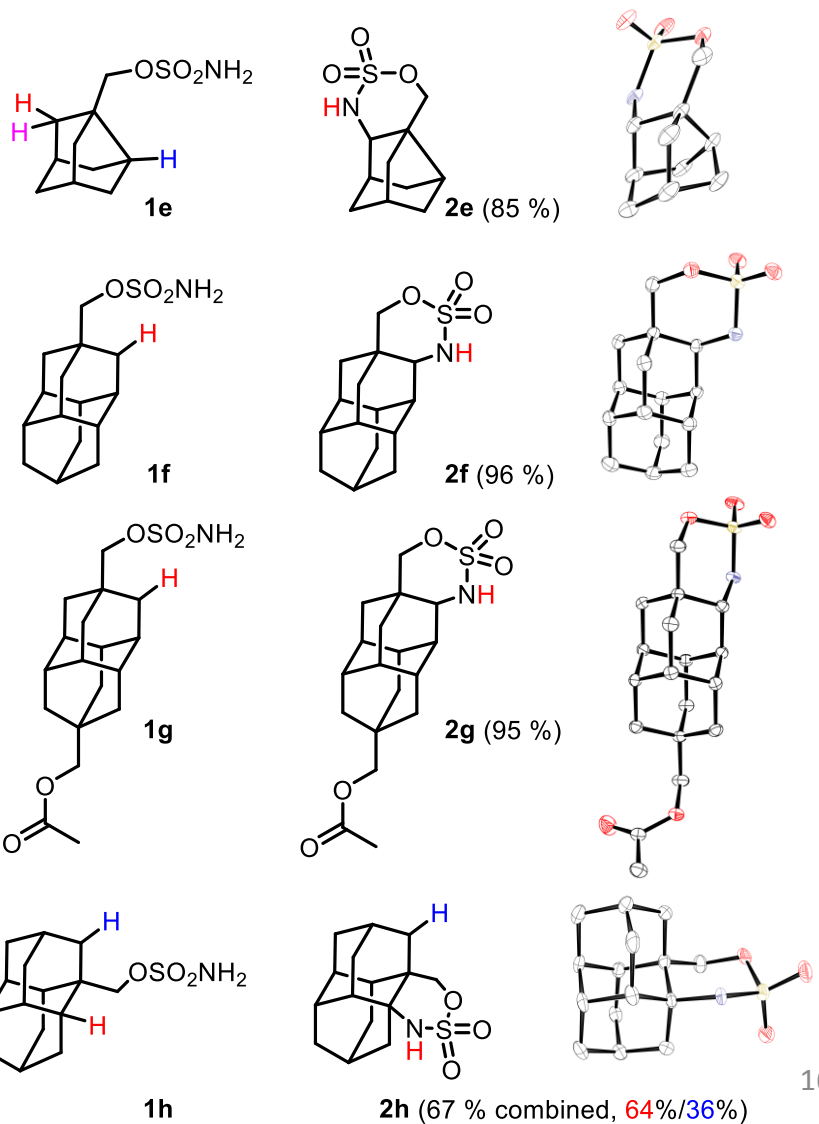
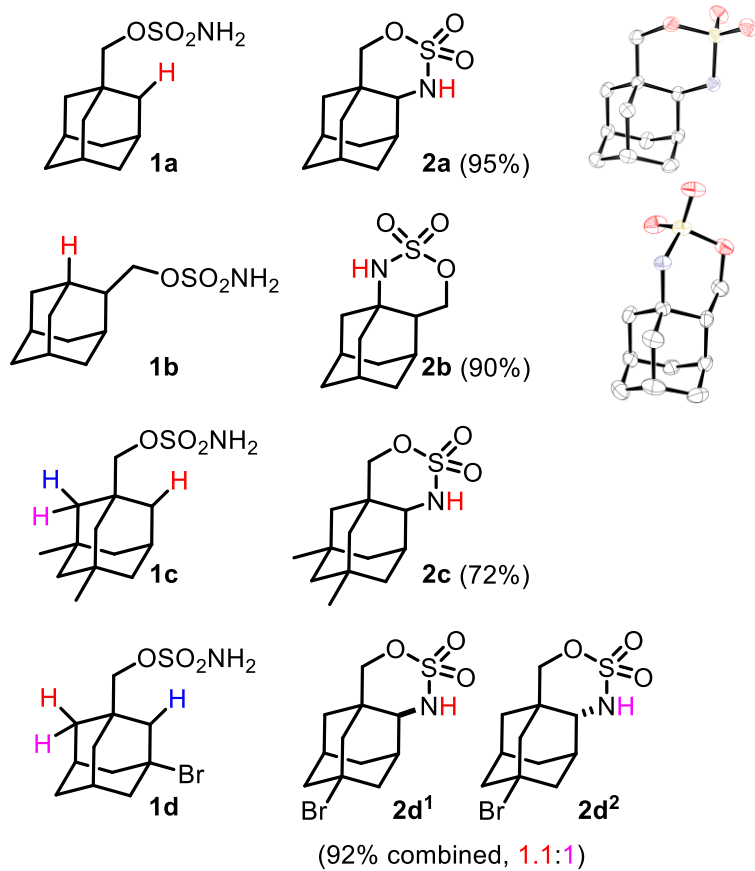
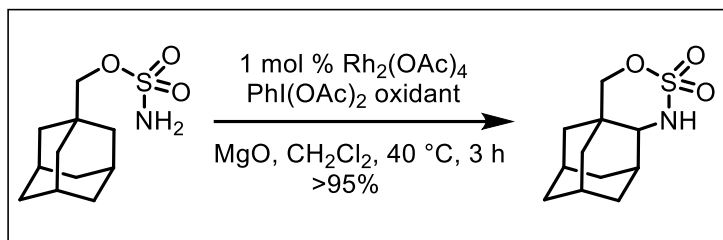


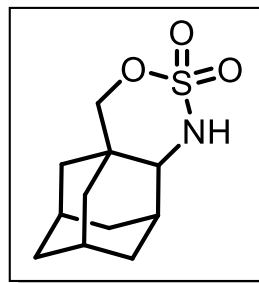
Fig. 1. Proposed mechanism for Rh₂(esp)₂-catalyzed C–H amination (R = CH₂CCl₃). The specific ionic species and experimental *m/z* values are shown below each structure. Each experimental *m/z* value is within 5 ppm of the calculated value, which is well within the uncertainty of the LTQ Velos Orbitrap mass spectrometer. The Rh²⁺/Rh²⁺, Rh²⁺/Rh³⁺, and Rh³⁺/Rh³⁺ species are shown in green, red, and purple, respectively.

Scope



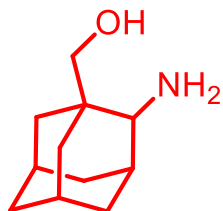
Cleavage of the sulphonamide moiety

made on gram scale

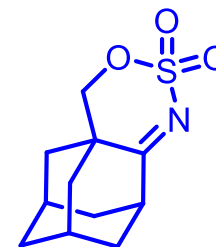


$\text{MeEt}_2\text{N} + \text{LiAlH}_4 \rightarrow \text{Li}_3\text{AlH}_6 + \text{MeEt}_2\text{N-AlH}_3$ in toluene

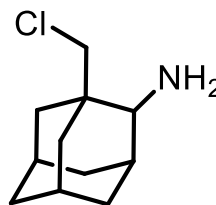
reduction
75%



$\text{KMnO}_4, \text{KOH}, \text{H}_2\text{O}$
oxidation
90%

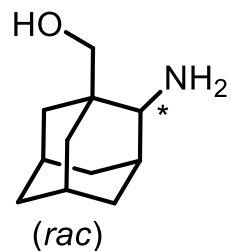


HCl
microwave

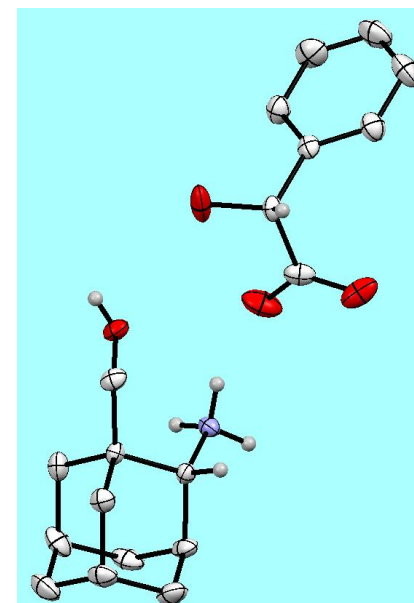
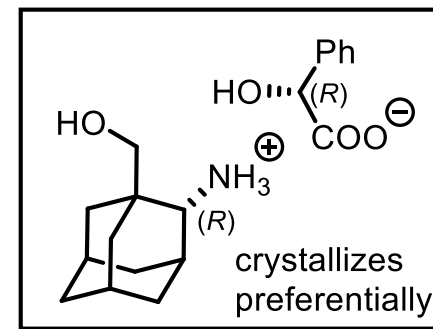
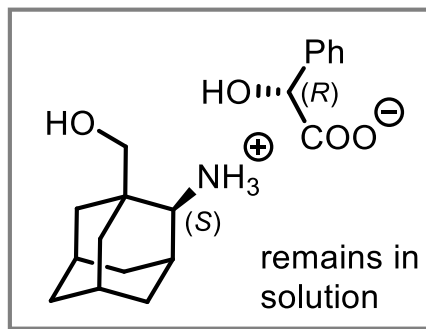
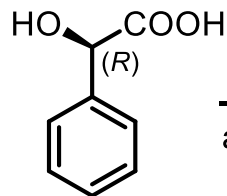


unoptimised

Resolution of enantiomers

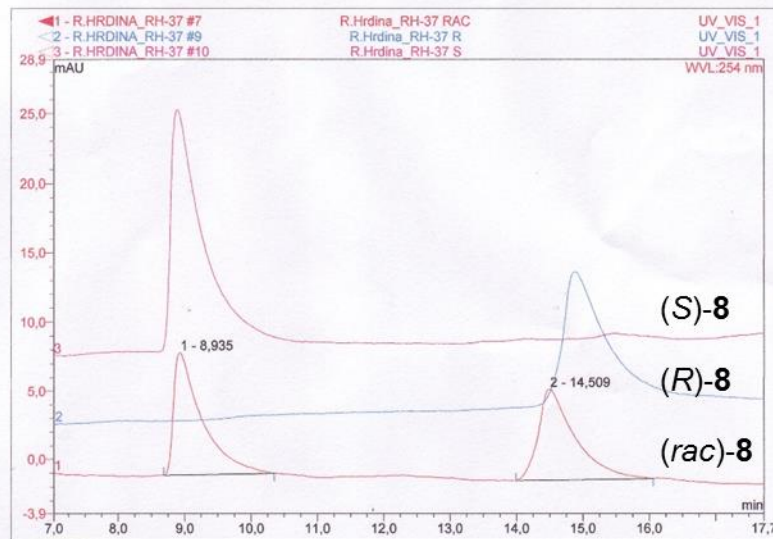
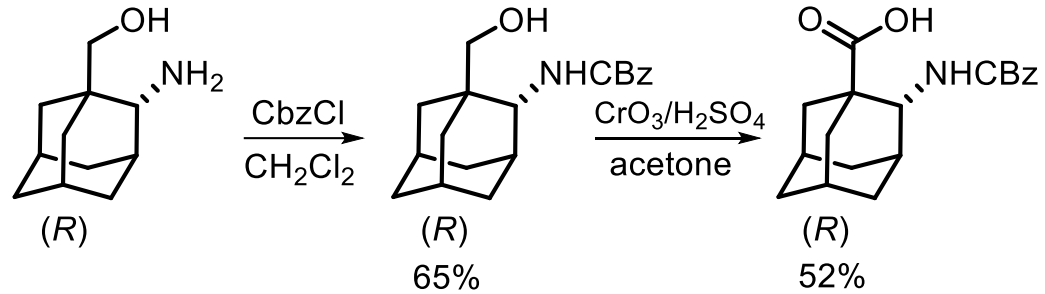


+



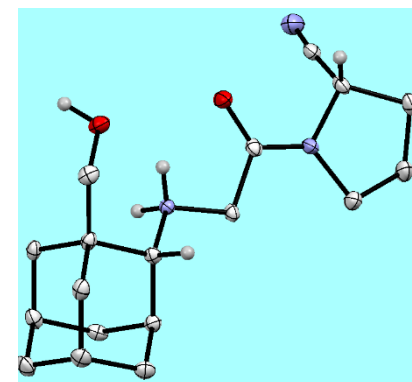
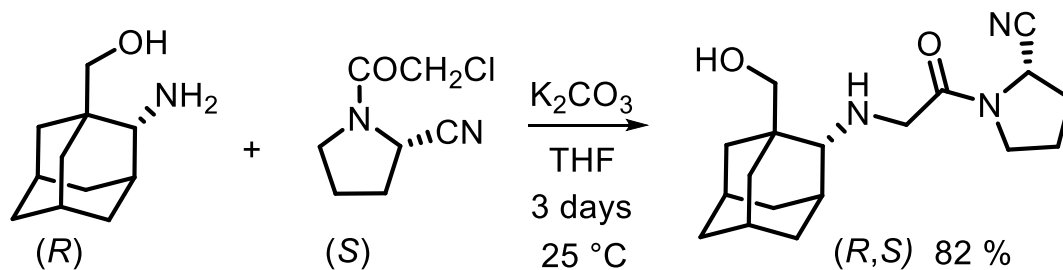
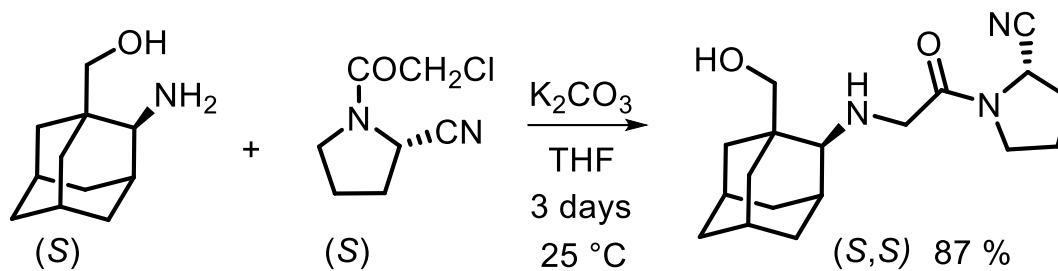
X-ray of the salt

Purity control



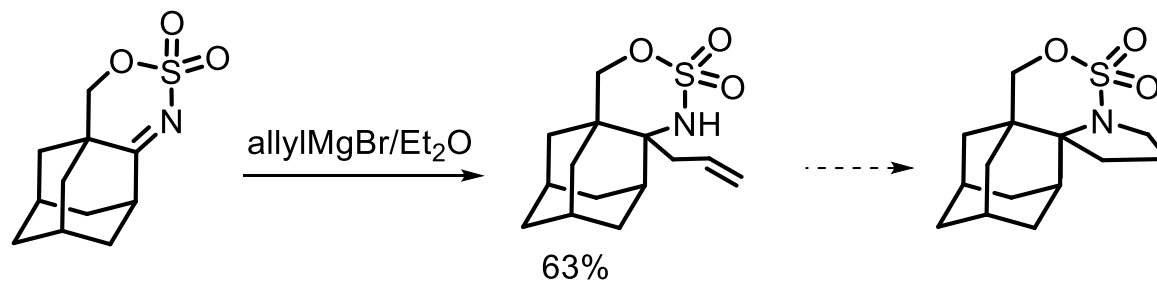
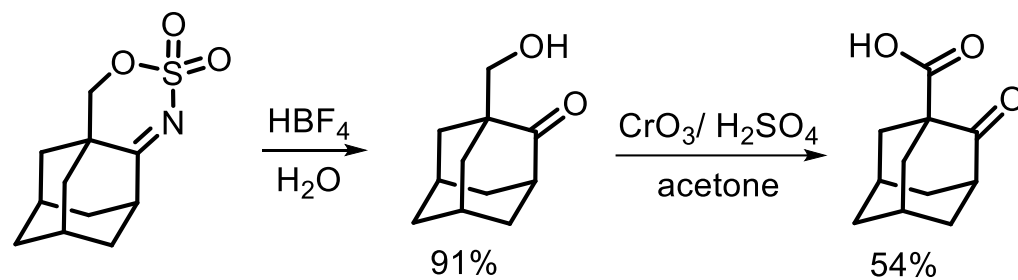
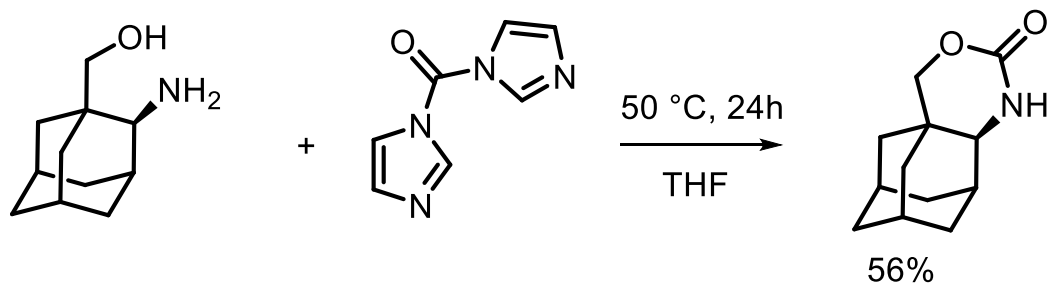
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8,94	n.a.	8,925	4,387	51,02	n.a.	BMB
2	14,51	n.a.	6,611	4,211	48,98	n.a.	BMB
Total:			15,536	8,598	100,00	0,000	

Synthesis of Vildagliptin analoga



**X-ray of the salt
with mandelic acid**

Derivatisation reactions



Acknowledgement

Peter R. Schreiner

Marta Larrosa-Ferreiro

Jan-Philipp Berndt

Fabian M. Metz

Yevgeniya Y. Zhygadlo

Christian Eschmann

Sabine Becker

Jonathan Becker

Paul Kahl

Boryslav A. Tkachenko

Natalia A. Fokina

Andrei A. Fokin

Dhaka Bhandari

Erwin Röcker

and the dream teams

from 5th, 6th, 7th, 8th floors