Universität Konstanz

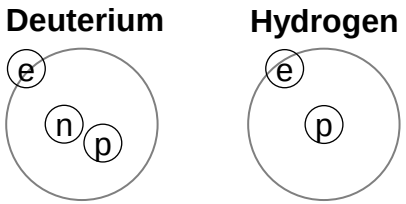
Deuterium in Drug Development (2010 – 2022)

Tatjana List

Konstanz, 02.11.2022

1. Introduction

1.1 Deuterium



- Naturally-occurring, stable, non-radioactive isotope of hydrogen
- Single electron, but nucleus contains one neutron and one proton
- Natural abundance: 0.0015%
- Chemical properties of deuterium:
  - Slightly less lipophilic than H
  - Smaller molar volume than H
- C-D vs. C-H bonds:

  C-D bonds have…
  - Lower vibrational frequency and lower zero-point energy
  - Higher activation energy and slower rate for C-D bond cleavage → **deuterium kinetic isotope effect (DIE)**
  - Shorter length than C-H bonds
  - Reduced electronic polarizability
  - Less hyperconjugative stabilization of adjacent bonds
  - Potentially weaker van-der-Waals stabilization

  → C-D diatomic pair is a non-radioactive bioisosteric, isotopic, isoelectronic replacement for C-H bonds
- Deuterium substitution of hydrogen yields a deuterated compound that is quite similar to the all-hydrogen compound

- Deuteration decreases acidity of carboxylic acids and phenols
- Deuteration increases basicity of amines

S. L. Harbeson and R. D. Tung, *Medchem News* **2014**, *2*, 8-22.
T. G. Gant, *J. Med. Chem.* **2014**, *57*, 3595-3611.
N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.

1. Introduction

1.2 Deuterium Kinetic Isotope Effect (DIE)

- Historically: deuterium incorporation into drug analogues to elucidate metabolic pathways of drug molecules, create mass spectrometry standards, use in protein crystallography, NMR, MS and medical imaging
- Deuterated drug is virtually indistinguishable from its medicinal protio predecessor in so many ways (e.g. *in vitro* pharmacodynamics (PD) and physiochemical properties)
- Exception: processes that involve bond breaking at oxidatively labile C-H site(s)
- Prerequisite to observe deuterium kinetic isotope effect (DIE): bond breaking has to be rate-determining step within a biological setting
  - → Then, C-D bonds may be substantially more stable to oxidative processes

- Cytochrome P450s (CYPs) are the most important enzymes that catalyze phase 1 metabolism of most drugs
- Complex metabolic cycle in which competing effects might mask the DIE
- Incorporation of deuterium instead of hydrogen at sites of metabolism where H atom abstraction is the rate determining step can impede metabolism and redirect metabolic pathways
- Oxidation of C-H bonds is central to life
- Cytochrome acts as electron acceptor and converts hydrophobics into hydrophilics → oxidation of C-H bond results in alcohol + potential additional oxidations
- Intermolecular interaction between drug molecules and proteins are also changed by D/H exchange, e.g. deuteration of cGMP phosphodiesterase V inhibitor sildenafil affects the enzyme selectivity by 2- to 5-fold

S. L. Harbeson and R. D. Tung, *Medchem News* **2014**, *2*, 8-22.
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1. Introduction

1.2 Deuterium Kinetic Isotope Effect (DIE)

- Deuterium incorporation might confer stability to specifically targeted C-H bonds
  - → Reduce propensity for reactive metabolites
  - → Increase safety
  - → Facile screening for such improvements using glutathione-capture assays and DNA adduct measurements
- Human body of a typical size contains 1 g deuterium all of the time, distributed in body water as DHO
- Typical medication doses: 100 mg per day
  - → Increase in deuterium load <<1 µg per day
  - → Less than 0.1% increase in deuterium load (mammals can tolerate doses of >25% total replacement of body water)

- False assumption that replacing a C-H pair that is subject to oxidation with a C-D pair will confer stability → no hard and fast rules to predict which examples will work
- Bioengineering with deuterium: techniques for producing small molecules in heavy water culture have been around for decades
- Deuterium analogues can be obtained by semisynthesis from perdeuterated starting materials or by deuterium incorporation into protio materials

S. L. Harbeson and R. D. Tung, *Medchem News* **2014**, *2*, 8-22.
T. G. Gant, *J. Med. Chem.* **2014**, *57*, 3595-3611.
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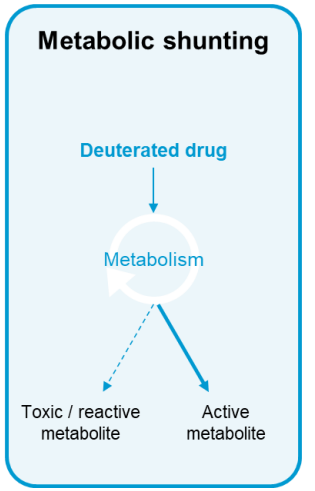
2. Pharmacological effects of drug deuteration

2.1 Metabolic shunting

- Deuterium substitution reduces the formation of an undesired or toxic metabolite and enhances the formation of a desired metabolite

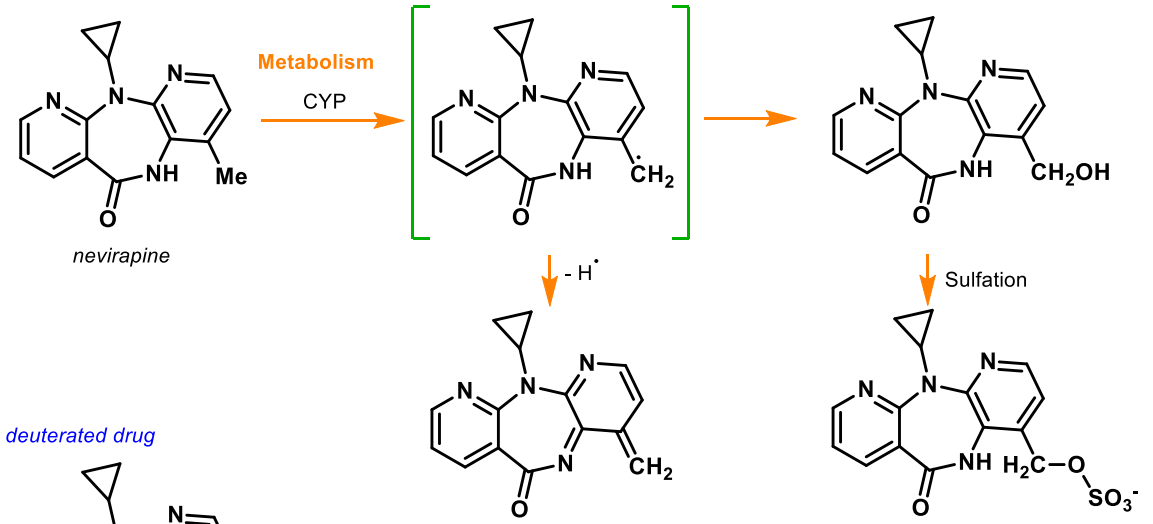
➢ Safety and efficacy



Examples:

a) Nevirapine

- Non-nucleoside reverse transcriptase inhibitor
- Treatment of HIV infection
- Associated with high incidence of skin rash and hepatotoxicity in humans
- CYP metabolism produces a radical intermediate
  → → reactive metabolite that modifies skin proteins



- Deuterated compound
  - Reduced covalent binding to hepatic proteins
  - Faster clearance of the drug

  → metabolic switching away from the postulated reactive metabolite that inactivates CYP450

  → less CYP inhibition and faster *in vivo* clearance

S. L. Harbeson and R. D. Tung, *Medchem News* **2014**, *2*, 8-22.

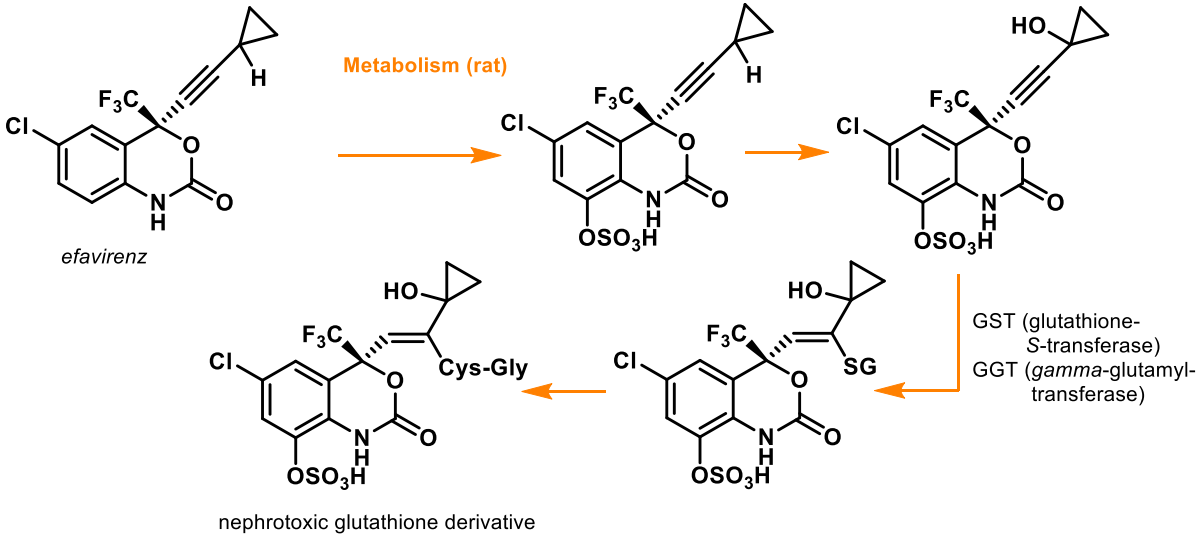
2. Pharmacological effects of drug deuteration

2.1 Metabolic shunting

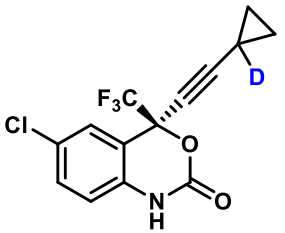
Examples:

b) Efavirenz

- Non-nucleoside reverse transcriptase inhibitor
- Treatment of HIV infection
- Nephrotoxicity in rats
- Specific metabolic pathway in rats
  → reactive metabolite



- Replacement of the cyclopropyl methine hydrogen for deuterium
  - Reduced oxidative metabolism
  - Reduced incidence and severity of nephrotoxicity



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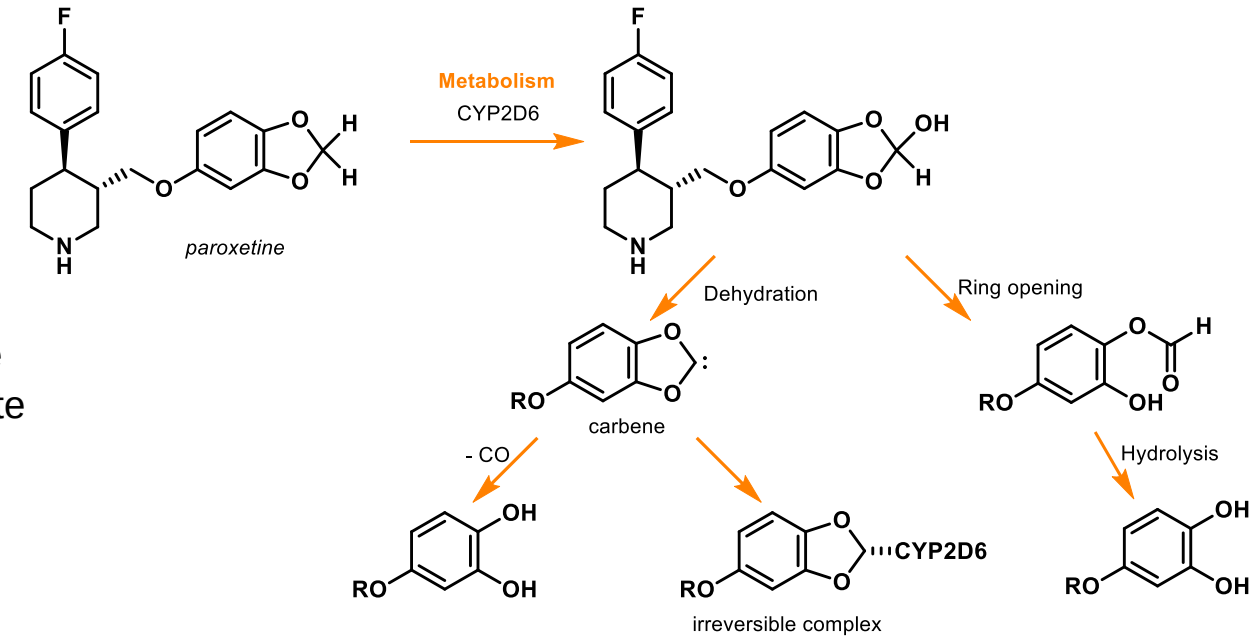
2. Pharmacological effects of drug deuteration

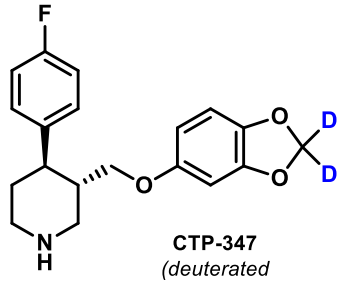
2.1 Metabolic shunting

Examples:

c) Paroxetine (clinical experience)

- Centrally acting serotonin reuptake inhibitor
- Metabolized by CYP2D6
- Inhibits its own metabolism by irreversibly inactivating CYP2D6 enzymes
  → formation of highly reactive carbene metabolite that can complex the catalytic iron at the active site of CYP2D6
- Deuterated paroxetine (CTP-347)
  - Little or no CYP2D6 inactivation
  - Metabolic shunting towards ring opening pathway → innocuous metabolites
  - Clinical studies (phase 1): Volunteers received deuterated drug + dextromethorphan (selective probe for CYP2D6 activity by measuring urinary levels of dextrorphan, the CYP2D6 metabolite)
  - With deuterated drug: greater CYP2D6 activity retained and greater ability to metabolize dextromethorphan





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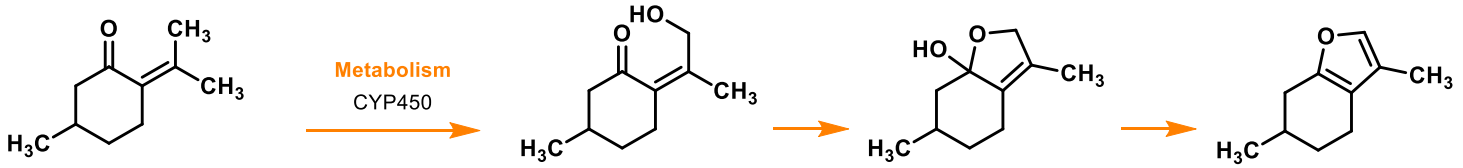
2. Pharmacological effects of drug deuteration

2.1 Metabolic shunting

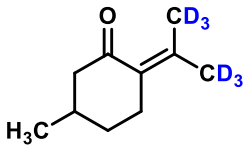
Examples:

d) Pulegone

- Major metabolic pathway:
- CYP450-mediated allylic oxidation to allylic alcohol
  → furan metabolite
  → activation to species that accounts for hepatotoxicity
- Perdeuteration of allylic methyl groups:
  - Attenuation of hepatotoxicity in mice
  - Reduced CYP450-mediated allylic oxidation



pulegone



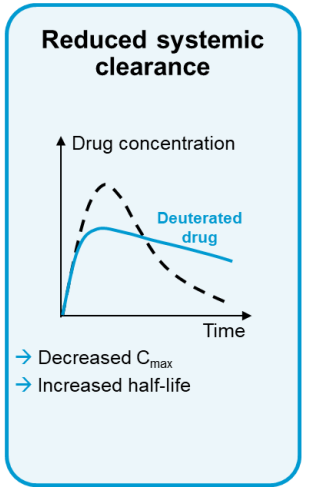
deuterated pulegone

N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.

2. Pharmacological effects of drug deuteration

2.2 Reduced rate of systemic clearance

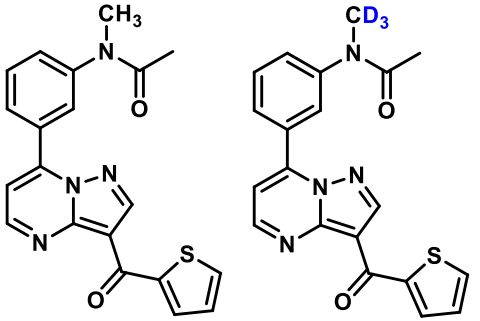
- Increased biological half-life of the compound → similar systemic exposure might be achieved with decreased peak levels
- ➢ Tolerability and Efficacy



Examples:

a) Indiplon

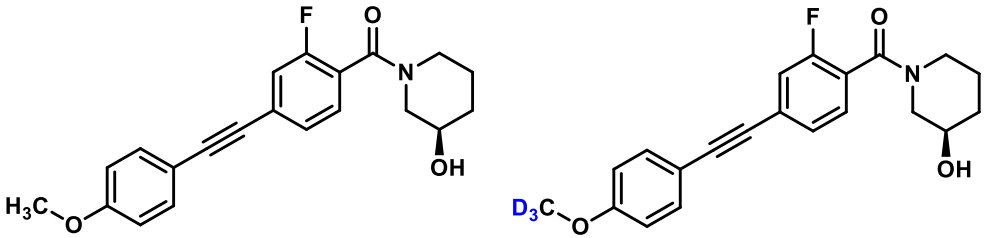
- $GABA_A$ agonist sleep agent
- Deuterated analogue:
  - Decreased systemic clearance and longer half-life
  - Similar receptor affinity



indiplon *deuterated drug*

b) ML-337

- Negative allosteric modulator at the sub-type 3 G-protein coupled metabotropic glutamate receptor
- *para*-Methoxy substituent required for desired pharmacology
- Major metabolic pathway: CYP-mediated demethylation
- Deuterated methoxy group showed improved metabolic stability



ML-337 *deuterated drug*

S. L. Harbeson and R. D. Tung, *Medchem News* **2014**, *2*, 8-22.

2. Pharmacological effects of drug deuteration

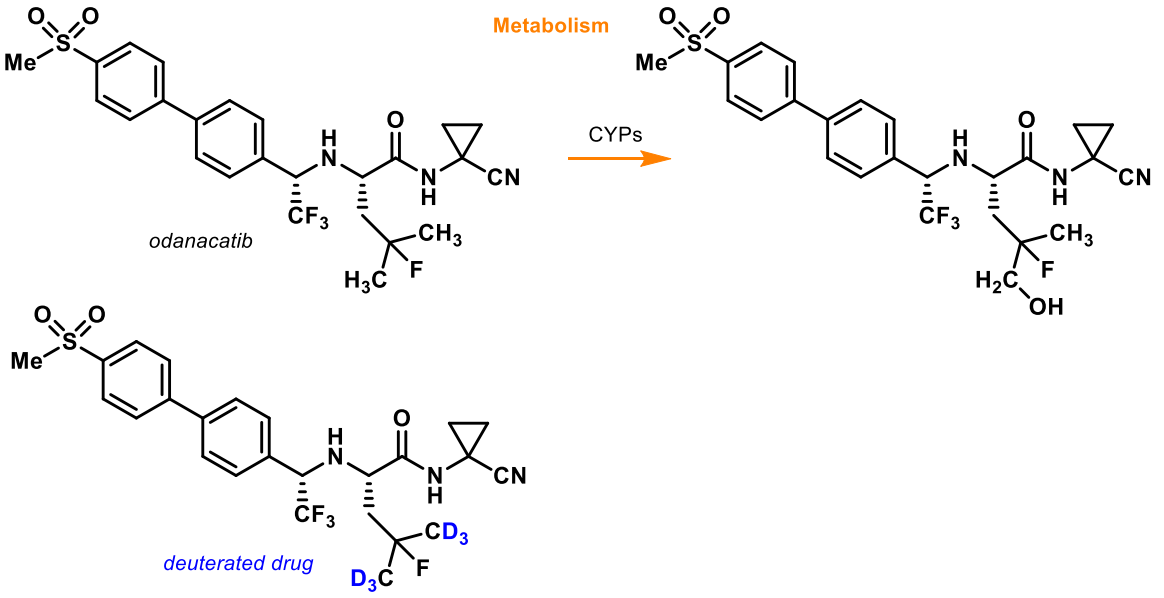
2.2 Reduced rate of systemic clearance

Examples:

c) Odanacatib

- Cathepsin K inhibitor
- Treatment of post-menopausal osteoporosis
- Major metabolic pathway: CYP
  → hydroxylation of fluoro-isobutyl side chain

- Deuterated analogue:
  - 3-fold greater exposure
  - 3-fold lower clearance



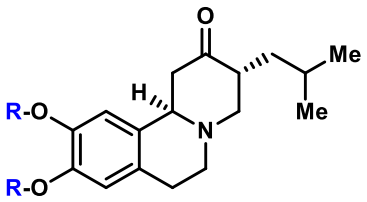
S. L. Harbeson and R. D. Tung, *Medchem News* **2014**, *2*, 8-22.

2. Pharmacological effects of drug deuteration

2.2 Reduced rate of systemic clearance

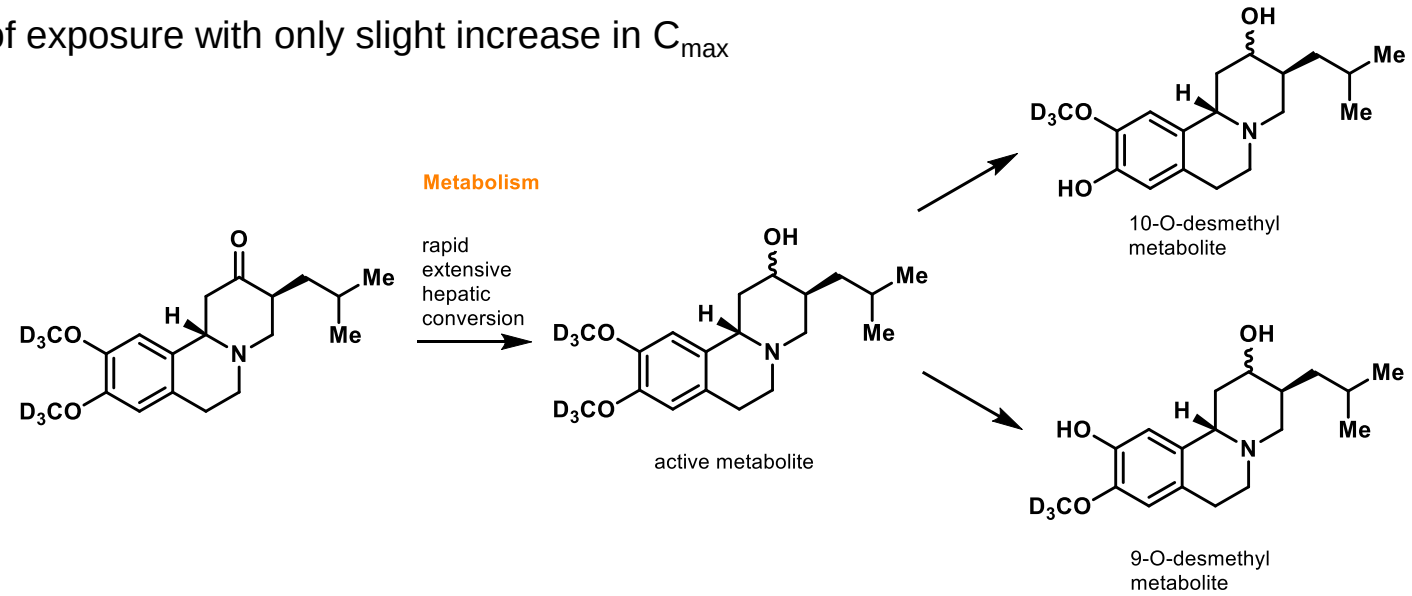
Examples:

d) Deutetrabenazine



R = CD_3: deutetrabenazine
R = CH_3: tetrabenazine

- Treatment of chorea (involuntary movement disorder) associated with Huntington's disease and tardive kinesia
- After oral dosing rapid and extensive metabolism to the major circulating active metabolites → further metabolism by CYP2D6
- Deuterated analogue:
  - Half-life of the reactive metabolites almost doubled
  - Doubling of exposure with only slight increase in C_{max}



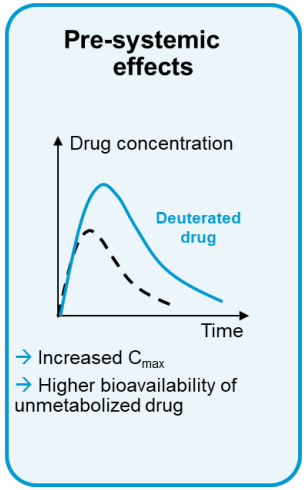
S. L. Harbeson and R. D. Tung, *Medchem News* **2014**, *2*, 8-22.

2. Pharmacological effects of drug deuteration

2.3 Pre-systemic effect of deuteration

- Decreased pre-systemic metabolism results in higher bioavailability of the unmetabolized drug
- Increased exposure of the drug without changing the rate of systemic clearance → reduced dosing requirements and lower metabolite loads

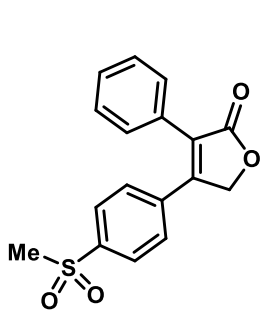
➢ Bioavailability and tolerability



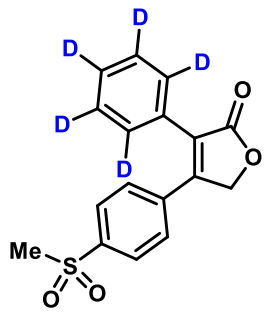
Examples:

a) Rofecoxib

- COX-2 selective non-steroidal anti-inflammatory drug (NSAID)
- Withdrawal from market in 2004 → safety concerns about increased risk of heart attack and stroke
- Deuterated compound:
  - Improved pharmacokinetic profile:
  - Mean C_{max} value increased 1.6-fold
  - Mean exposure increased 1.5-fold
  - Unchanged COX-2 enzyme activity



rofecoxib



deuterated analogue (BDD-11602)

S. L. Harbeson and R. D. Tung, *Medchem News* **2014**, *2*, 8-22.

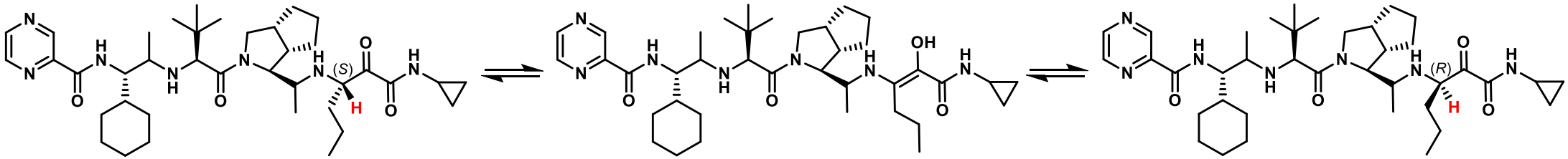
2. Pharmacological effects of drug deuteration

2.3 Pre-systemic effect of deuteration

Examples:

b) Telaprevir

- Inhibitor of hepatitis C viral NS3-4A protease
- *S*-diastereomer epimerizes *in vivo* (at higher pH) *via* enol intermediate to *R*-diastereomer (= major circulating metabolite in plasma, but 30-fold less active protease inhibitor)
- Deuteration slowed epimerization by 4-7-fold



telapevir
S-α-ketoamide

enol intermediate

R-diastereomer

S. L. Harbeson and R. D. Tung, *Medchem News* **2014**, *2*, 8-22.
N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.

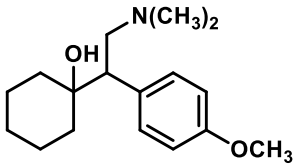
2. Pharmacological effects of drug deuteration

2.3 Pre-systemic effect of deuteration

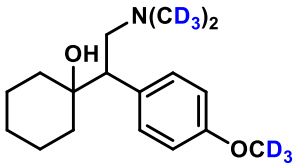
Examples:

c) Venlafaxine

- Serotonin / norepinephrine reuptake inhibitor
- Treatment of depression
- Major metabolic pathway: *O*-demethylation by CYP enzymes 2D6 and 2C19 (*N*-demethylation has secondary role)
- Deuteration at primary metabolic sites reduced rate of metabolism *in vivo* by 50%
  → increased exposure of parent drug and less *O*-demethylated metabolite



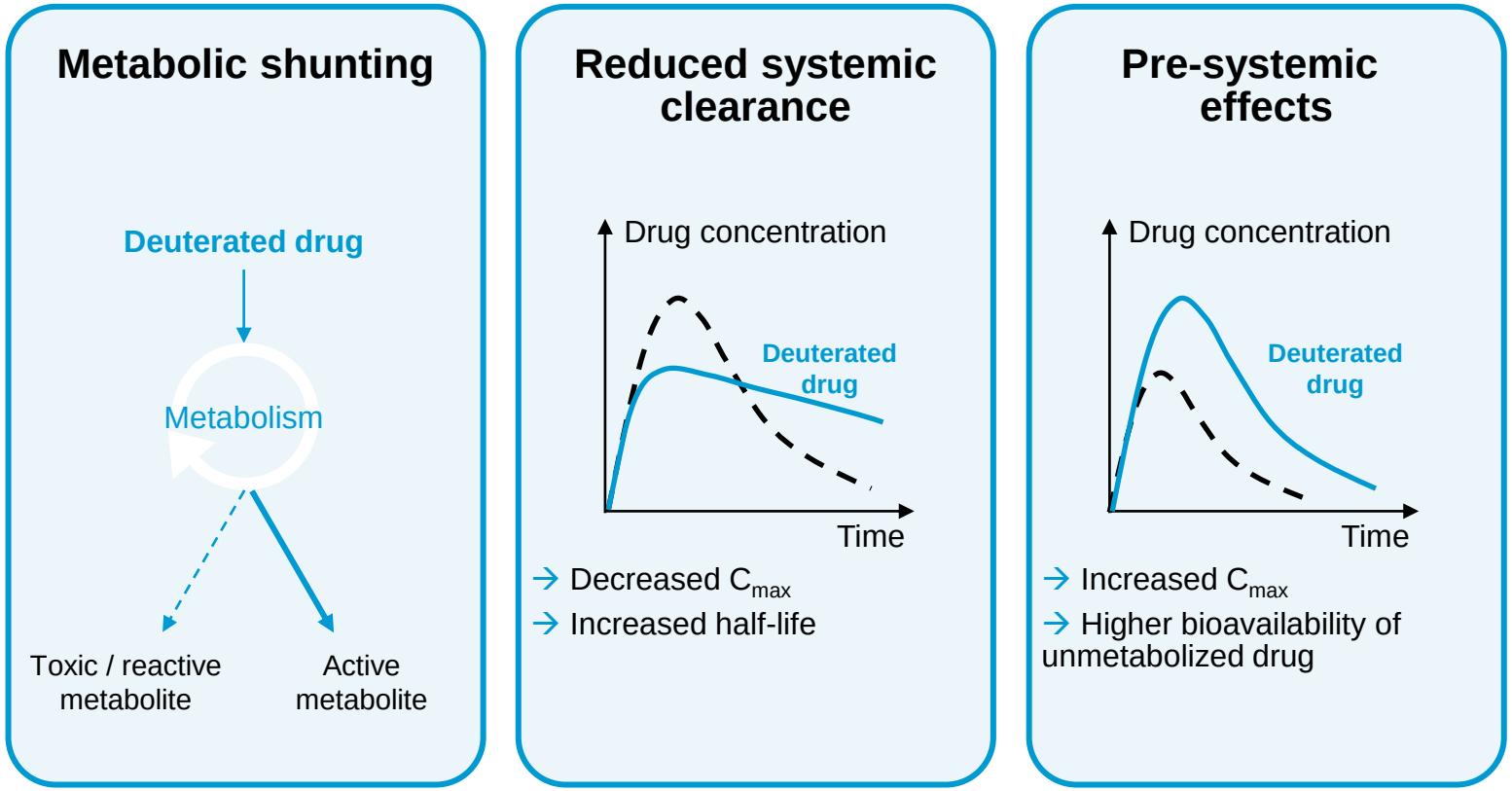
venlafaxine



SD-254
(deuterated venlafaxine)

N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.

2. Pharmacological effects of drug deuteration – Summary



- Deuterium effects on the metabolic profile of a therapeutic are not predictable and must be explored for each compound
- Application of deuterium in medicinal chemistry might provide a risk-reduced approach to creating new drugs that address important unmet medical needs

S. L. Harbeson and R. D. Tung, *Medchem News* **2014**, *2*, 8-22.

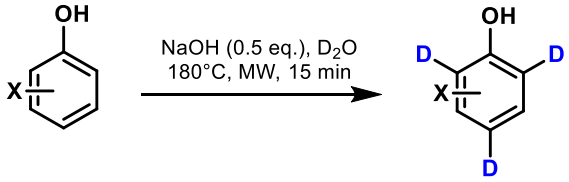
3. Deuterium Incorporation by Organocatalysis

3.1 Base-Mediated Labeling

Labeling phenols

- Known methods: low efficiencies of deuterium exchange, expensive / difficult-to-access catalysts and deuterium sources
- Unselective perdeuteration of phenols
- Chen *et al.*: Regioselective deuteration through electrophilic aromatic substitution under basic conditions

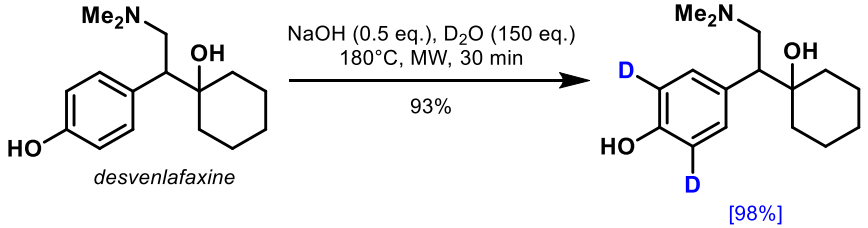
General method



→ Generation of phenoxide ion under basic conditions
→ Selectivity: *ortho/para*
→ High functional group tolerance

Example: desvenlafaxine

- Treatment of adult patients with major depressive disorder
- Deuterium incorporation of 98% with a yield of 93%



M. Zhan, R. Xu, Y. Tian, H. Jiang, L. Zhao, Y. Xie, Y. Chen, *Eur. J. Org. Chem.* **2015**, 3370–3373.

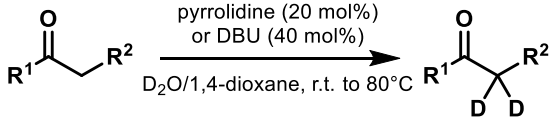
3. Deuterium Incorporation by Organocatalysis

3.1 Base-Mediated Labeling

H/D exchange of acidic protons in carbonyl containing compounds under mild conditions

Chen *et al.*: Labeling of aryl methyl ketones with deuterium and secondary amine as catalyst

General method

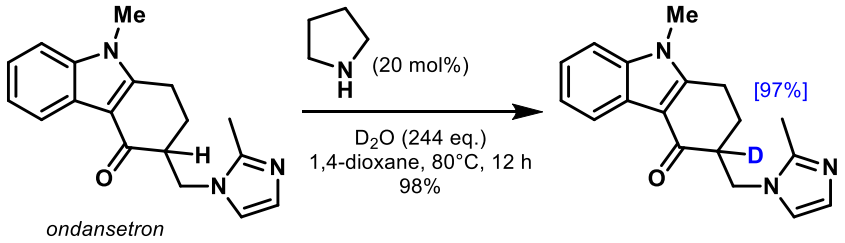


→ Selectivity: *α*-carbonyl

→ Proposed mechanism *via* enamine and/or iminium ion

Example: ondansetron

- Drug to prevent nausea and vomiting caused by chemotherapy, radiation therapy, and surgery



ondansetron

M. Zhan, T. Zhang, H. Huang, Y. Xie, Y. Chen. *J. Label Compd. Radiopharm* **2014**, *57,* 533–539.

Further reading:

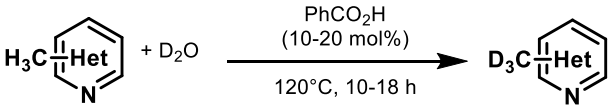
- Synthesis of deuterium labeled amines and nitrogen-containing heterocycles: Y. Hu, L. Liang, W. Wei, X. Sun, X. Zhang, M. Yan, *Tetrahedron* **2015**, *71*, 1425–1430.
- Enantioselective deuteration of amino acids: K. Moozeh, S. M. So, J. Chin, *Angew. Chem. Int. Ed.* **2015**, *54*, 9381–9385; *Angew. Chem.* **2015**, *127*, 9513–9517.

3. Deuterium Incorporation by Organocatalysis

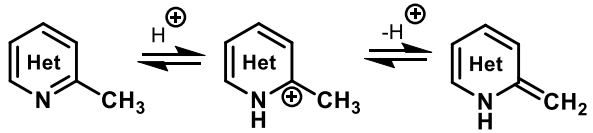
3.2 Acid-Mediated Labeling

Deuteration at methyl groups of *N*-heteroarylmethanes

General method



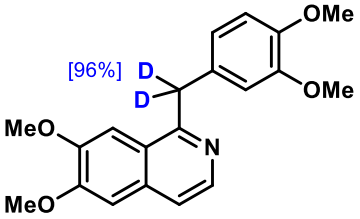
Mechanistic proposal:



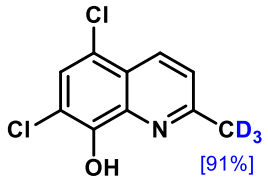
→ *Via* enamine intermediate

Examples:

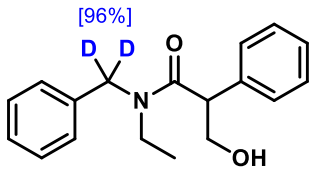
- Papaverine (relaxation of the tonus of all smooth muscles)
- Chloroxine
- Tropicamide (treatment of pseudomyopia)



papaverine



chloroxine



tropicamide

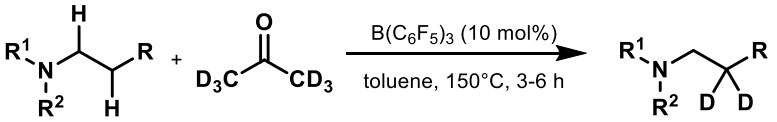
M. Liu, X. Chen, T. Chen, S.-F. Yin, *Org. Biomol. Chem.* **2017**, *15*, 2507-2511.

3. Deuterium Incorporation by Organocatalysis

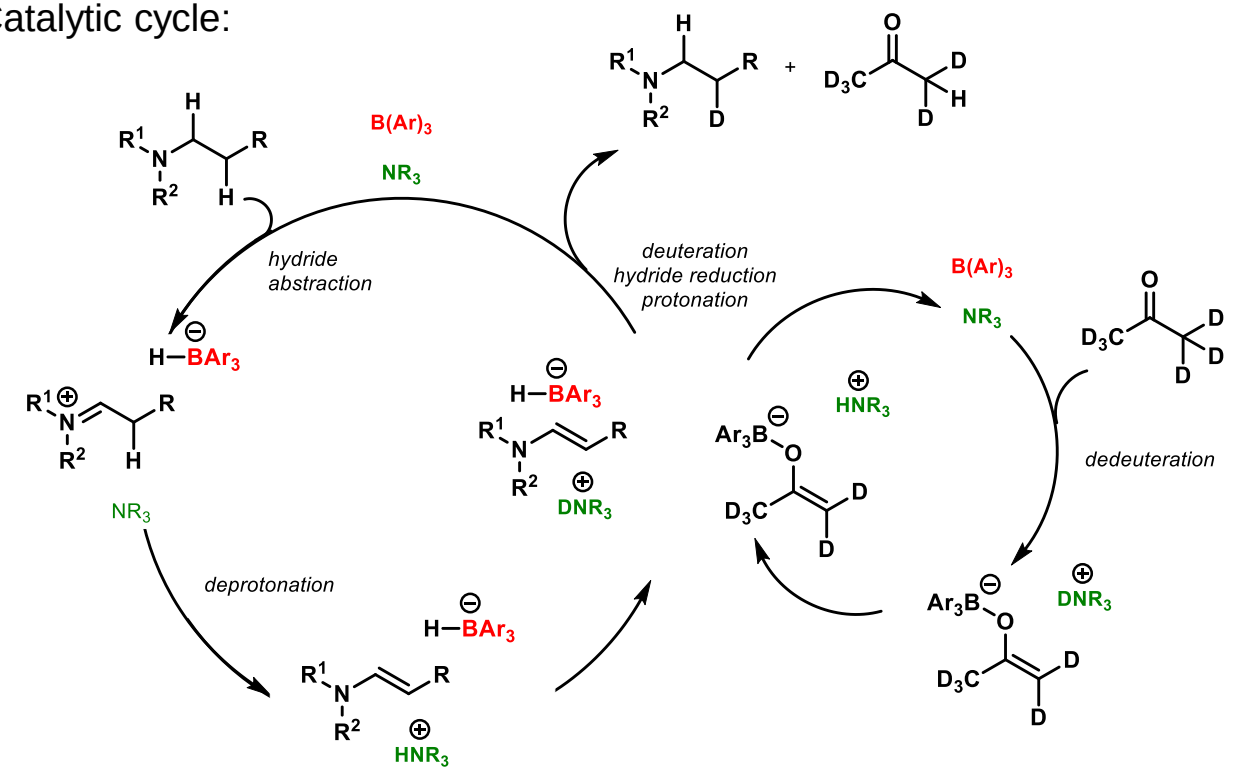
3.2 Acid-Mediated Labeling

***β*-Deuteration of *N*-alkylamines** by cooperative acid/base catalysis using $B(C_6F_5)_3$ and *N*-alkylamine (Wasa *et al.*)

General method

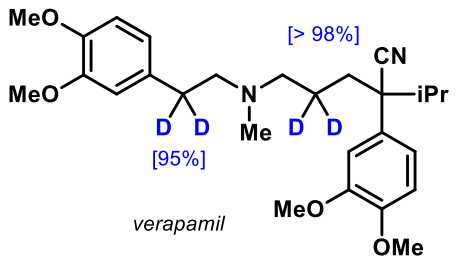


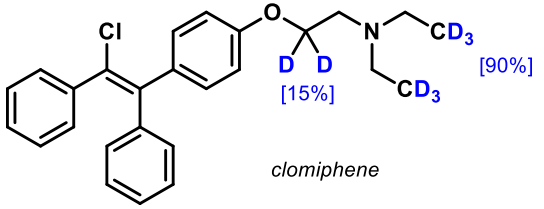
Catalytic cycle:



Examples:

- Verapamil (calcium channel blocker)
- Chlomiphene (ovulatory stimulant)





Y. Chang, A. Yesilcimen, M. Cao, Y. Zhang, B. Zhang, J. Z. Chan, M. Wasa, *J. Am. Chem. Soc.* **2019**, *141*, 14570-14575.

3. Deuterium Incorporation by Organocatalysis

3.2 Acid-Mediated Labeling

Further reading:

- Preparation of deuterium-labeled amino acids or peptides: L. Wang, Y. Murai, T. Yoshida, M. Okamoto, K. Masuda, Y. Sakihama, Y. Hashidoko, Y. Hatanaka, M. Hashimoto, *Biosci. Biotechnol. Biochem.* **2014**, *78*, 1129–1134.
- Deuteration of anilines under microwave conditions: A. Martins, M. Lautens, *Org. Lett.* **2008**, *10*, 4351–4353.
- Arenium acid catalyzed deuteration of polycyclic aromatic hydrocarbons: S. Duttwyler, A. M. Butterfield, J. S. Siegel, *J. Org. Chem.* **2013**, *78*, 2134–2138.
- Asymmetric reductive deuteration of imines: T. Sakamoto, K. Mori, T. Akiyama, *Org. Lett.* **2012**, *14*, 3312–3315.
- Lewis acid assisted labeling in acidic media: D. Munz, M. Webster-Gardiner, R. Fu, T. Strassner, W. A. Goddard, T. B. Gunnoe, *ACS Catal.* **2015**, *5*, 769–775.
- H/D exchange at aromatic and aliphatic C-H/C-D bonds: M. H. G. Prechtl, M. Teltewskoi, A. Dimitrov, E. Kemnitz, T. Braun, *Chem. Eur. J.* **2011**, *17*, 14385 –14388.

3.3 Photoredox Catalysis

- Deuteration of tertiary amines in α-position: Y. Y. Loh, K. Nagao, A. J. Hoover, D. Hesk, N. R. Rivera, S. L. Colletti, I. W. Davies, D. W. C. MacMillan, *Science* **2017**, *358*,1182-1187.
- Deuteration in peptides: F. Legros, P. Fernandez-Rodriguez, A. Mishra, R. Weck, A. Bauer, M. Sandvoss, S. Ruf, M. Méndez, H. Mora-Radó, N. Rackelmann, C. Pöverlein, V. Derdau, *Chem. Eur. J.* **2020**, *26*, 12738-12742.

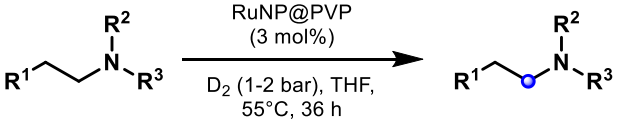
4. Transition-Metal-Catalyzed Hydrogen Isotope Exchange (HIE)

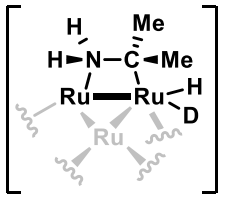
4.1 Ruthenium

4.1.1 Heterogeneous catalysis

Application of Ru@PVP (polyvinylpyrrolidone) nanoparticle to deuterate aza-compounds with retention of chirality

General method



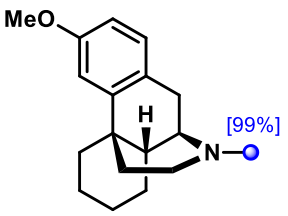


key intermediate

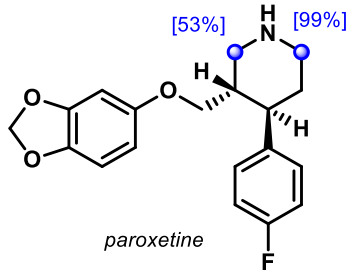
→ *four-membered dimetallacycle is responsible for the selectivity in α–position to the nitrogen*

Examples:

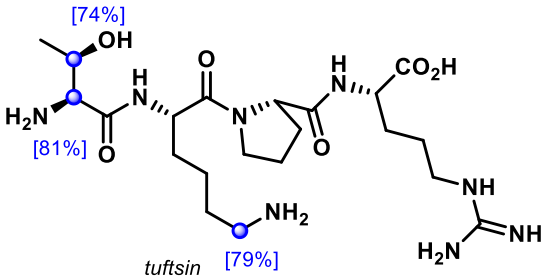
- Dextromethorphan
- Paroxetine (selective serotonin reuptake inhibitor, antidepressant)
- Tuftsin (Ig-associated tetrapeptide that triggers the immunogenic function of macrophages)



dextromethorphan



paroxetine



tuftsin

G. Pieters, C. Taglang, E. Bonnefille, T. Gutmann, C. Puente, J. Berthet, C. Dugave, B. Chaudret, B. Rousseau, *Angew. Chem. Int. Ed.* **2014**, *53*, 230-234.
C. Taglang, L. M. Martinez-Prieto, I. del Rosal, L. Maron, R. Poteau, K. Philippot, B. Chaudret, S. Perato, A. S. Lone, C. Puente, C. Dugave, B. Rousseau, G. Pieters, *Angew. Chem. Int. Ed.* **2015**, *54*, 10474-10477.

Further reading:

Deuteration of C-H bonds *α* to hydroxyl, thio and amino groups (e.g.: deuteration of sugars and thioethers): Y. Sawama, Y. Yabe, H. Iwata, Y. Fujiwara, Y. Monguchi, H. Sajiki, *Chem. Eur. J.* **2012**, *18*, 16436-16442.

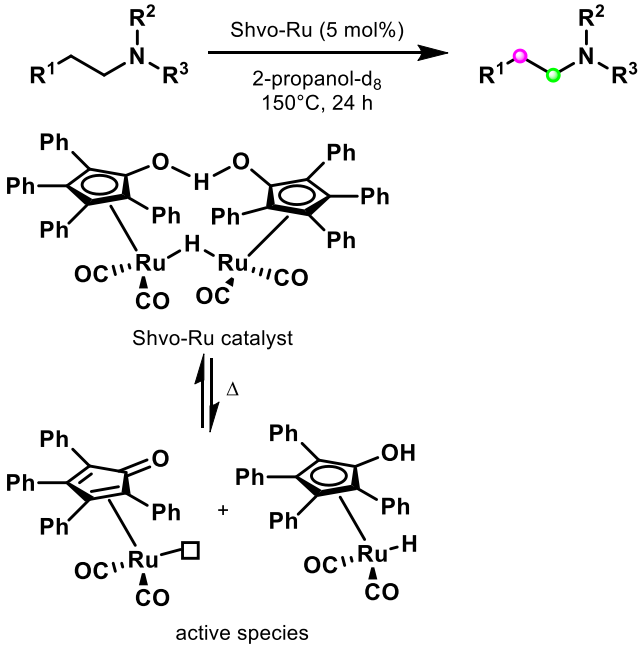
4. Transition-Metal-Catalyzed Hydrogen Isotope Exchange (HIE)

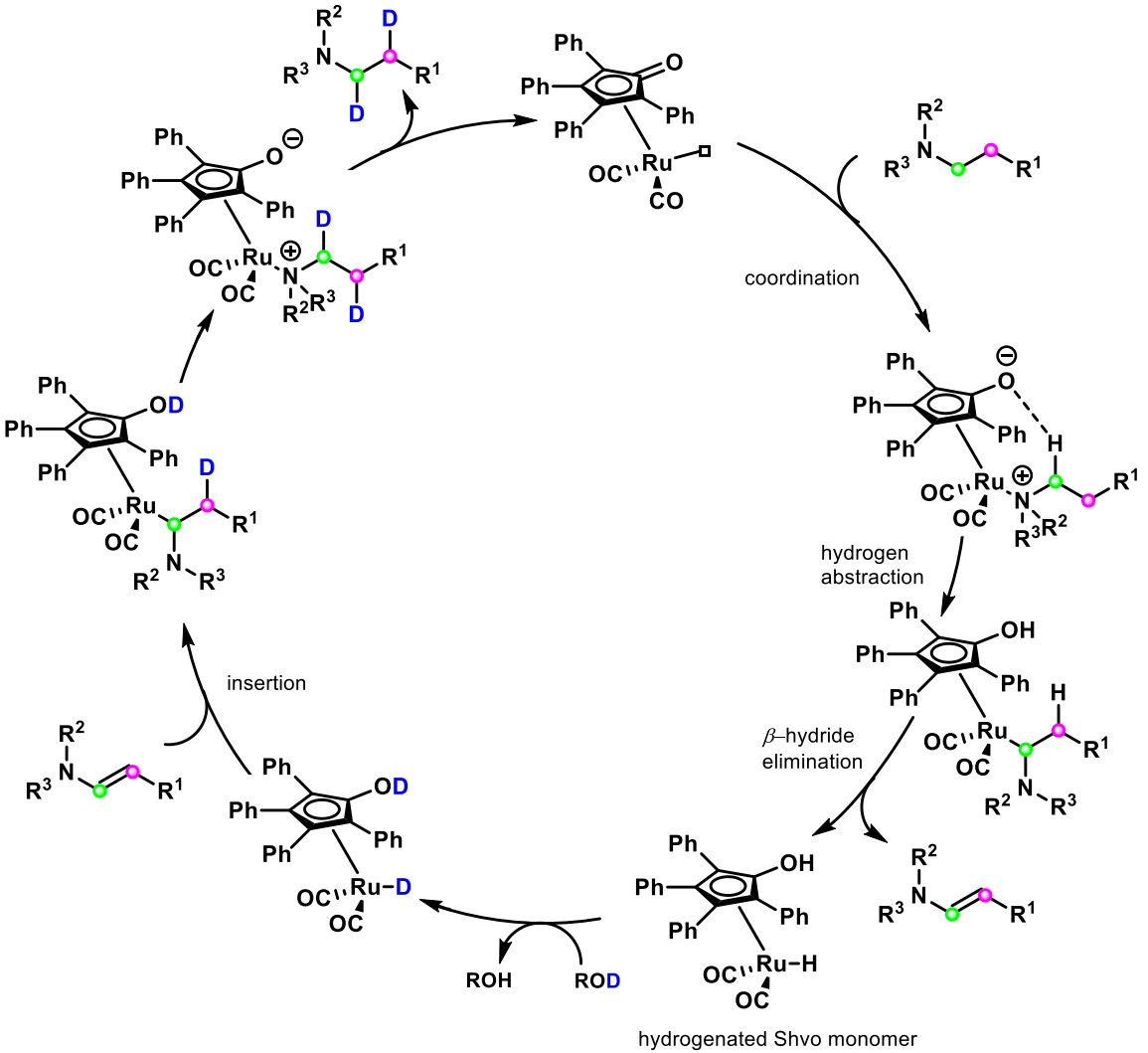
4.1 Ruthenium

4.1.2 Homogeneous catalysis

Shvo-Ru catalyst for labeling of tertiary amines in α– and β–position

General method





L. Neubert, D. Michalik, S. Bähn, S. Imm, H. Neumann, J. Atzrodt, V. Derdau, W. Holla, M. Beller, *J. Am. Chem. Soc.* **2012**, *134*, 12239–12244.

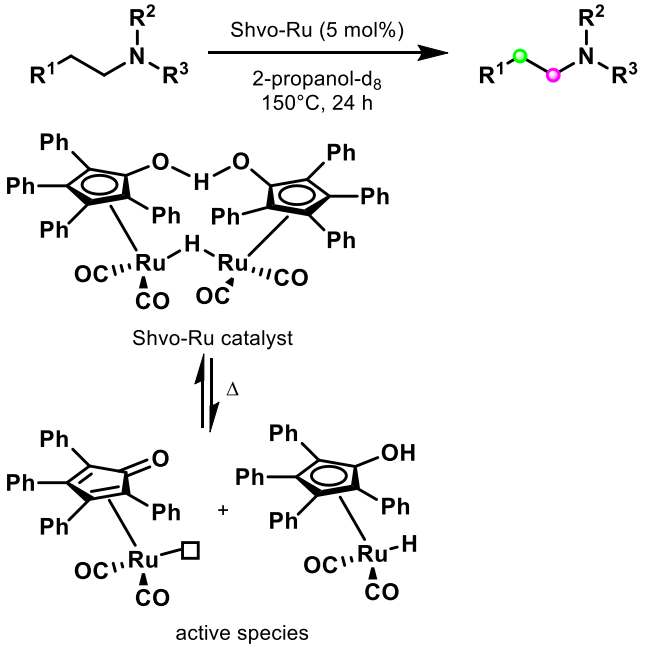
4. Transition-Metal-Catalyzed Hydrogen Isotope Exchange (HIE)

4.1 Ruthenium

4.1.2 Homogeneous catalysis

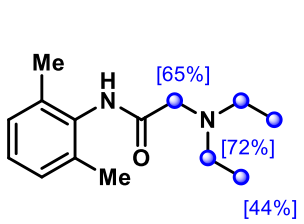
Shvo-Ru catalyst for labeling of tertiary amines in α– and β–position

General method

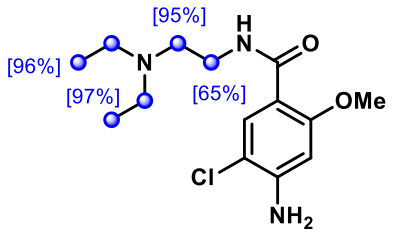


Examples

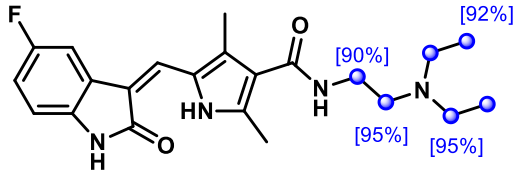
- Lidocaine (local anesthetic)
- Metoclopramide (antiemetic drug)
- Sunitinib (multi-targeted receptor tyrosine)



lidocaine



metoclopramide



sunitinib

L. Neubert, D. Michalik, S. Bähn, S. Imm, H. Neumann, J. Atzrodt, V. Derdau, W. Holla, M. Beller, *J. Am. Chem. Soc.* **2012**, *134*, 12239–12244.

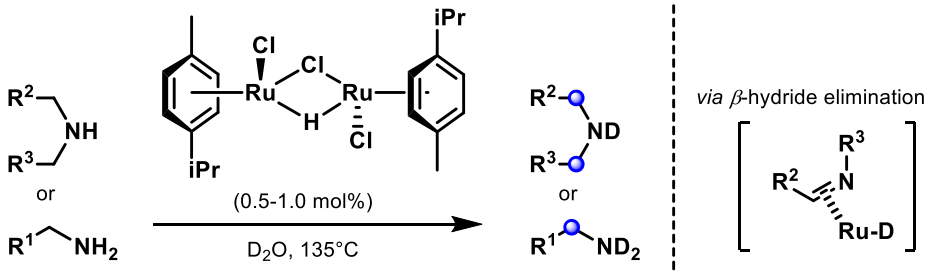
4. Transition-Metal-Catalyzed Hydrogen Isotope Exchange (HIE)

4.1 Ruthenium

4.1.2 Homogeneous catalysis

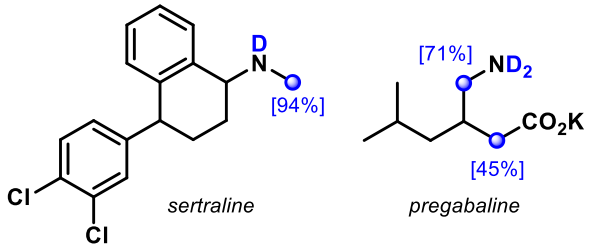
Monohydrido-bridged Ru complex for *α*–deuteration of primary and secondary amines

General method



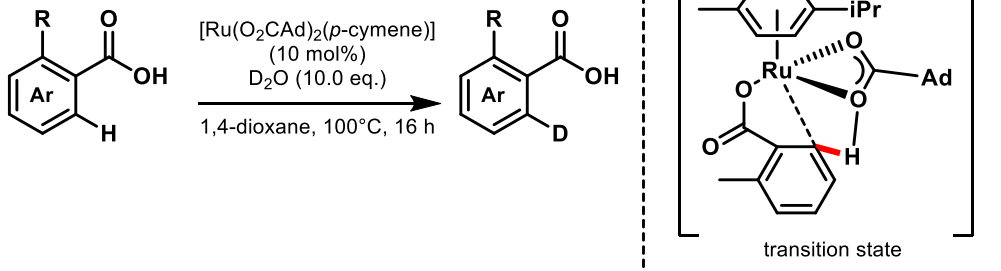
Examples:

- Sertraline (antidepressant)
- Pregabalin (treating pain by nerve damage)



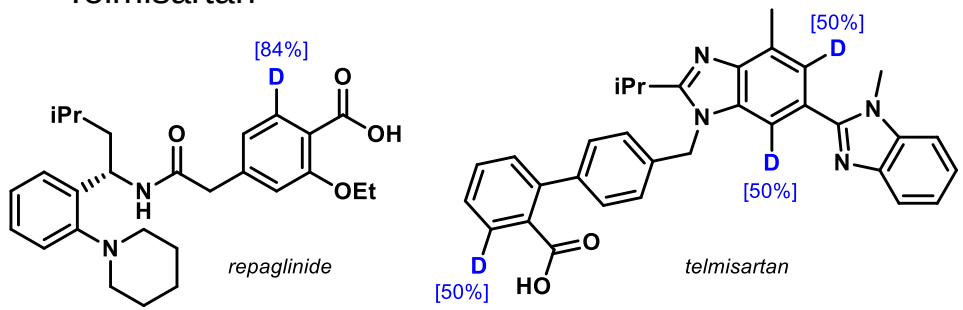
ortho-deuteration using Ru(II)-catalyst and carboxylic acid as directing group

General method



Examples:

- Repaglinide (anti-diabetic)
- Telmisartan



B. Chatterjee, V. Krishnakumar, C. Gunanathan, *Org. Lett.* **2016**, *18*, 5892–5895.

V. Müller, R. Weck, V. Derdau, L. Ackermann, *ChemCatChem* **2020**, *12*, 100-104.

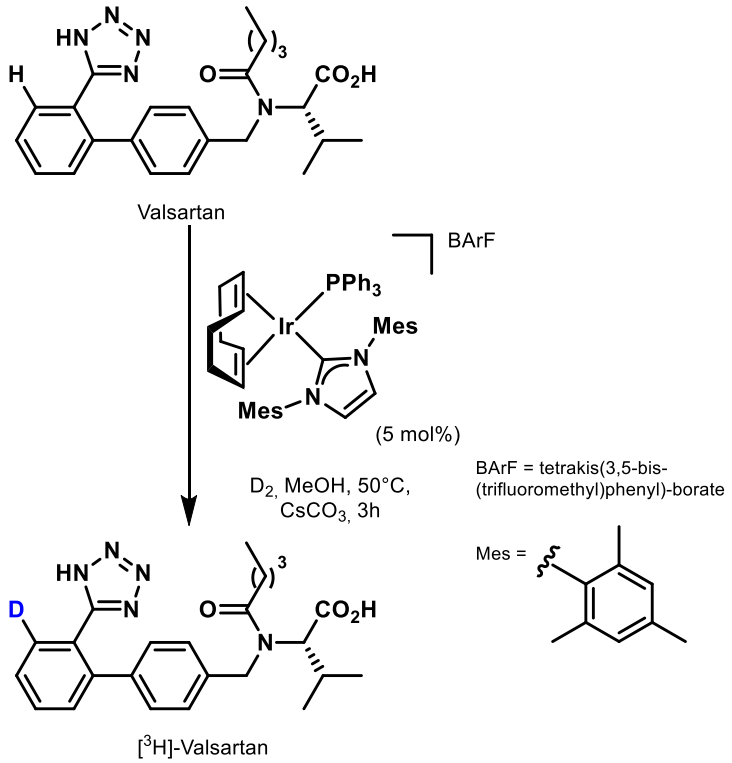
4. Transition-Metal-Catalyzed Hydrogen Isotope Exchange (HIE)

4.2 Iridium (Homogeneous catalysis)

Selective *ortho*-directed C–H activation with unprotected 2-aryltetrazoles

Example: Deuteration of valsartan

- Angiotensin receptor blocker

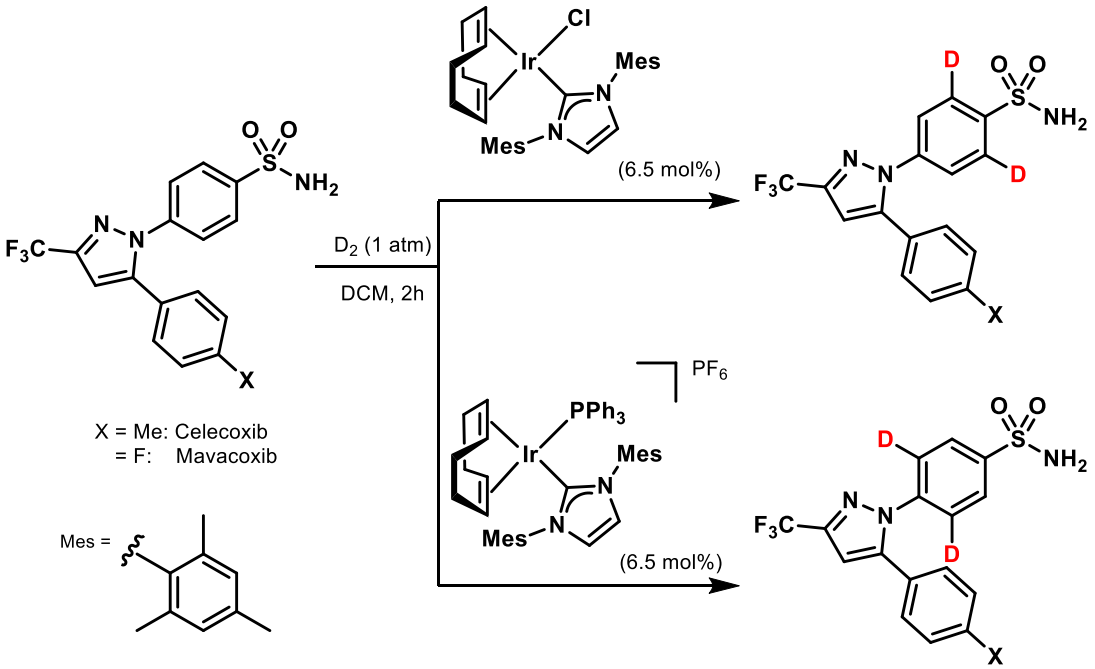


W. J. Kerr, D. M. Lindsay, M. Reid, J. Atzrodt, V. Derdau, P. Rojahn, R. Weck, *Chem. Commun.* **2016**, *52*, 6669–6672.

Iridium-catalyzed C-H activation and deuteration of primary sulfonamides

Example: Catalyst-controlled site selectivity in the labeling of Celecoxib and Mavacoxib

- COX2 inhibitors

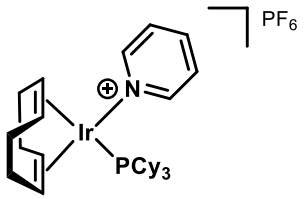


W. J. Kerr, M. Reid, T. Tuttle, *ACS Catal.* **2015**, *5*, 402–410.

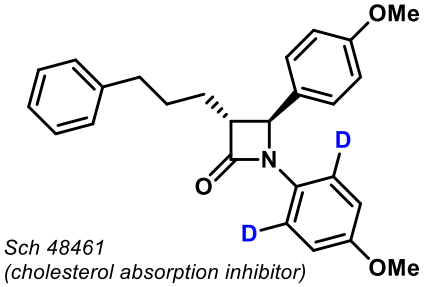
4. Transition-Metal-Catalyzed Hydrogen Isotope Exchange (HIE)

4.2 Iridium catalysts – a collection

Crabtree's catalyst (late-stage HIE of aromatics)



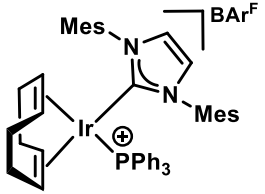
Crabtree's catalyst

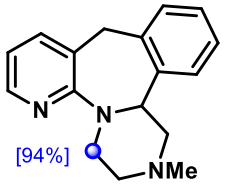


Sch 48461
(cholesterol absorption inhibitor)

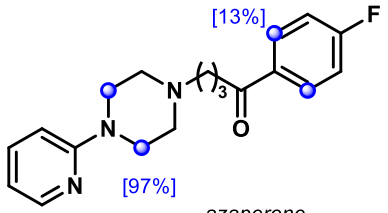
D. Hesk, P. R. Das, B. Evans, *J. Labelled Compd. Radiopharm.* **1995**, *36*, 497-502.

C(sp³)-H functionalization





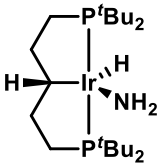
mirtazapine



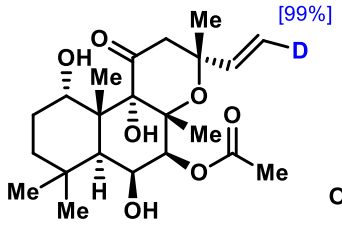
azaperone

W. J. Kerr, R. J. Mudd, M. Reid, J. Atzrodt, V. Derdau, *ACS Catal.* **2018**, *8*, 10895-10900.

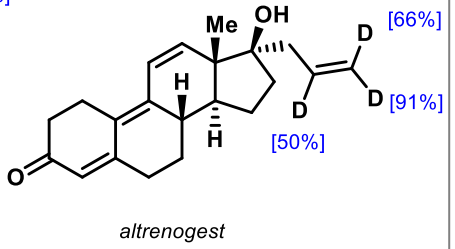
Pincer-type Ir catalyst (selective labeling of olefins)



(5 mol%), C_6D_6, r.t.



forskolin

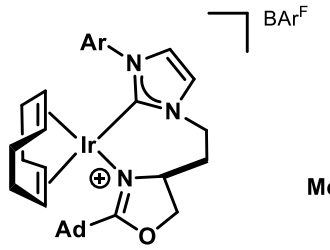


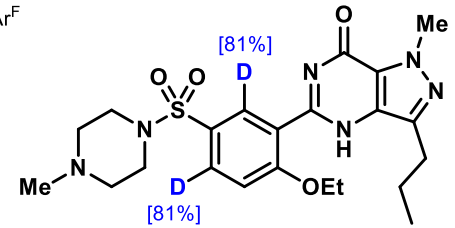
altrenogest

J. Zhou, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2008**, *47*, 5783-5787.

Ir(I)-complexes (labeling of bioactive molecules)

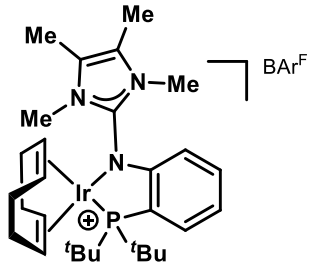
Burgess' catalyst:

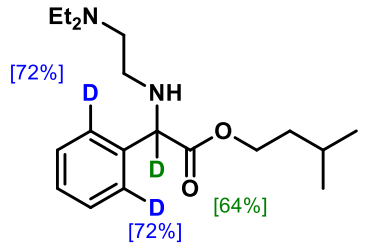




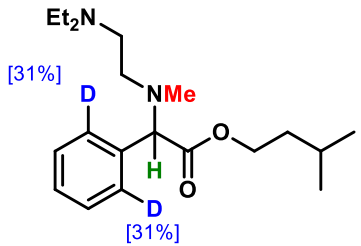
sildenafil

Tamm's catalyst:





camylofine
(phosphodiesterase IV inhibitor
to treat stomachache)



deuteration of aromatic positions (*ortho*)
and at the benzylic position

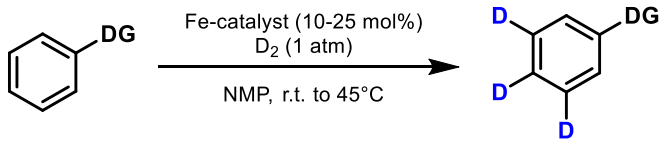
A. Burhop, R. Weck, J. Atzrodt, V. Derdau, *Eur. J. Org. Chem.* **2017**, 1418-1424.
M. Valero, D. Becker, K. Jess, R. Weck, J. Atzrodt, T. Bannenberg, V. Derdau, M. Tamm, *Chem. Eur. J.* **2019**, *25*, 6517-6522.

4. Transition-Metal-Catalyzed Hydrogen Isotope Exchange (HIE)

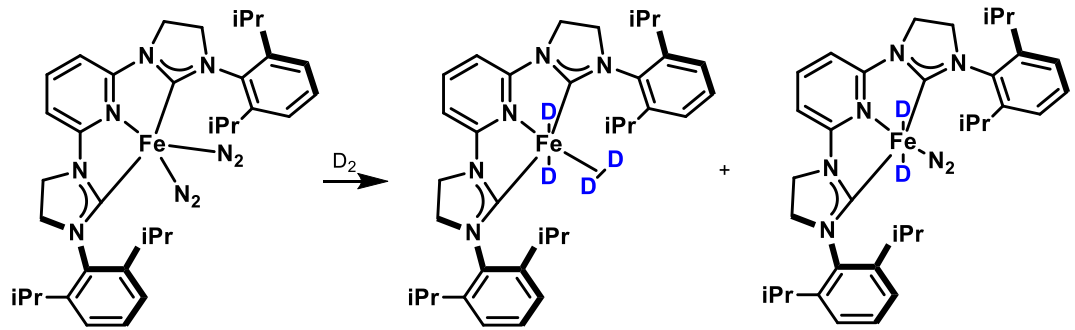
4.3 Iron

Fe-catalyzed C(sp^2)-H labeling

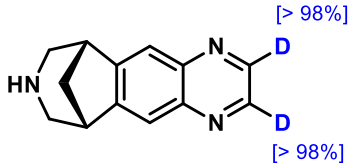
General method



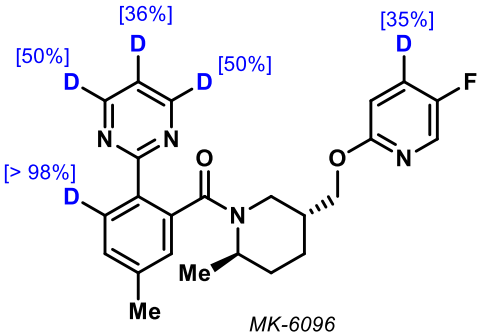
Formation of the active catalyst species: oxidative addition of the initial catalyst to the D-D bond



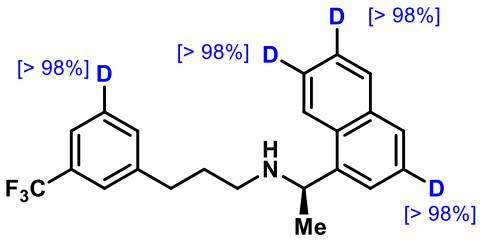
Examples:



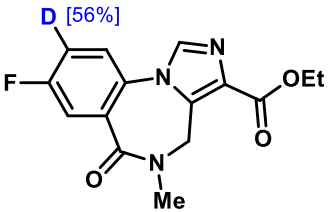
varenicline
(nicotine addiction)



MK-6096
(insomnia)



cinacalcet
(calcimimetic)



flumazenil
(sedative-induced drowsiness)

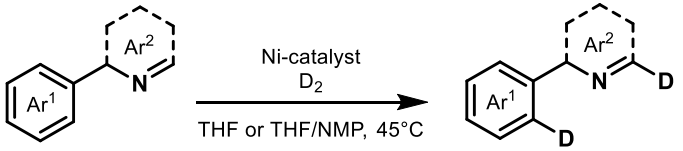
R. P. Yu, D. Hesk, N. Rivera, I. Pelczer, P.J. Chirik, *Nature* **2016**, *529*, 195-199.
R. P. Yu, J. M. Darmon, S. P. Semproni, Z. R. Turner, P. J. Chirik, *Organometallics* **2017**, *36*, 4341-4343.

4. Transition-Metal-Catalyzed Hydrogen Isotope Exchange (HIE)

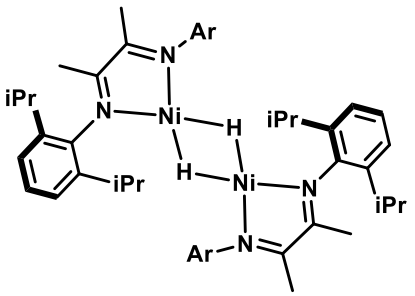
4.4 Nickel

Ni-catalyzed site-selective labeling of C(sp^2)-H bonds in nitrogen heteroarenes

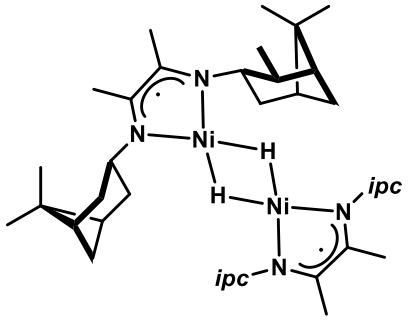
General method



First generation catalyst

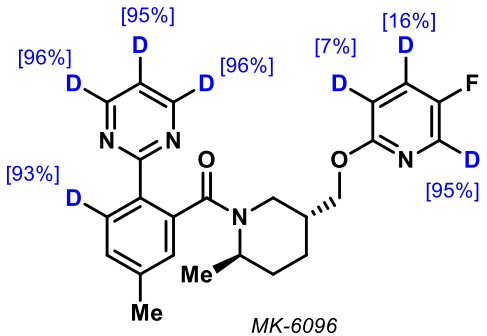


Second generation Ni precatalyst with superior HIE performance

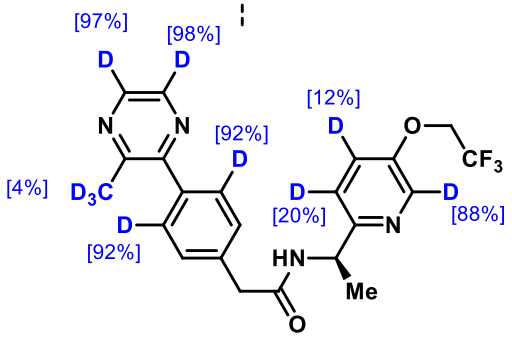


a-diimine nickel hydride complex
bulky and electron-releasing diimine is labile and dissociates easily to monomeric nickel hydride which is the catalytic-active species for C-H activation

Examples:



MK-6096
(insomnia)



MK-5395

H. Yang, C. Zarate, W. N. Palmer, N. Rivera, D. Hesk, P.J. Chirik, *ACS Catal.* **2018**, *8*, 10210-10218.
C. Zarate, H. Yang, M. J. Bezdek, D. Hesk, P. J. Chirik, *J. Am. Chem. Soc.* **2019**, *141*, 5034-5044.

4. Transition-Metal-Catalyzed Hydrogen Isotope Exchange (HIE)

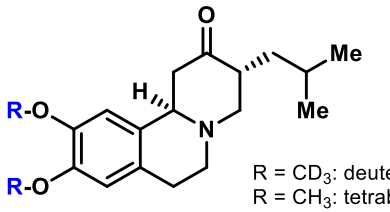
4.5 Palladium – further reading

Heterogeneous catalysis

- Deuteration of purine nucleosides at sp^2 carbon: H. Sajiki, H. Esaki, F. Aoki, T. Maegawa, K. Hirota, *Synlett* **2005**, 1385-1388.
- Selective, racemization-free deuteration of of amino acids, peptides and other bioactive molecules (e.g. insulin):
  (a) Y. A. Zolotarev, A. K. Dadayan, Y. A. Borisov, V. S. Kozik, *Chem. Rev.* **2010**, *110*, 5425-5426.
  (b) G. V. Sidorov, N. F. Myasoedov, S. N. Lomin, G. A. Romanov, *Radiochemistry* **2015**, *57*, 108-110.
  (c) V. P. Shevchenko, I. Y. Nagaev, N. F. Myasoedov, *Radiochemistry* **2014**, *56*, 292-295.

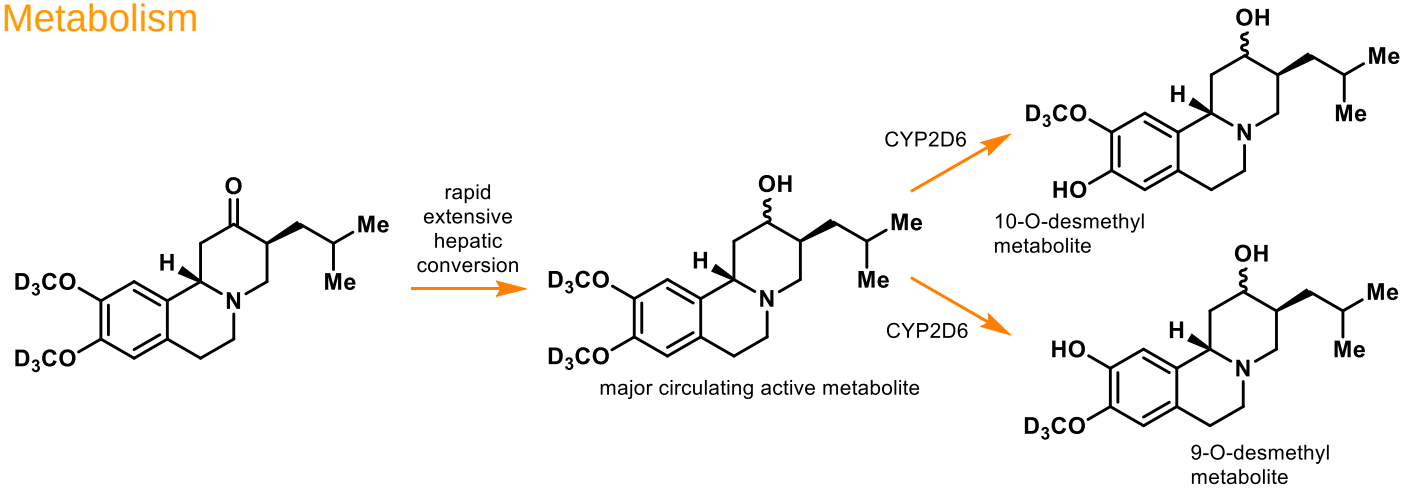
5. Deutetrabenazine – the First FDA-Approved Deuterated Drug

5.1 Facts



R = CD_3: deutetrabenazine
R = CH_3: tetrabenazine

- Analogue of the old drug tetrabenazine
- Treating chorea (involuntary movement disorder) associated with Huntington's disease and tardive dyskinesia
- Precise mechanism of action is unknown, but tetrabenazine inhibits vesicular monoamine neurotransmitters (e.g. norepinephrine, dopamine and serotonin) in synaptic regions
- Deutetrabenazine: two methoxy groups replaced by a pair of trideuteromethoxy groups
- Metabolism



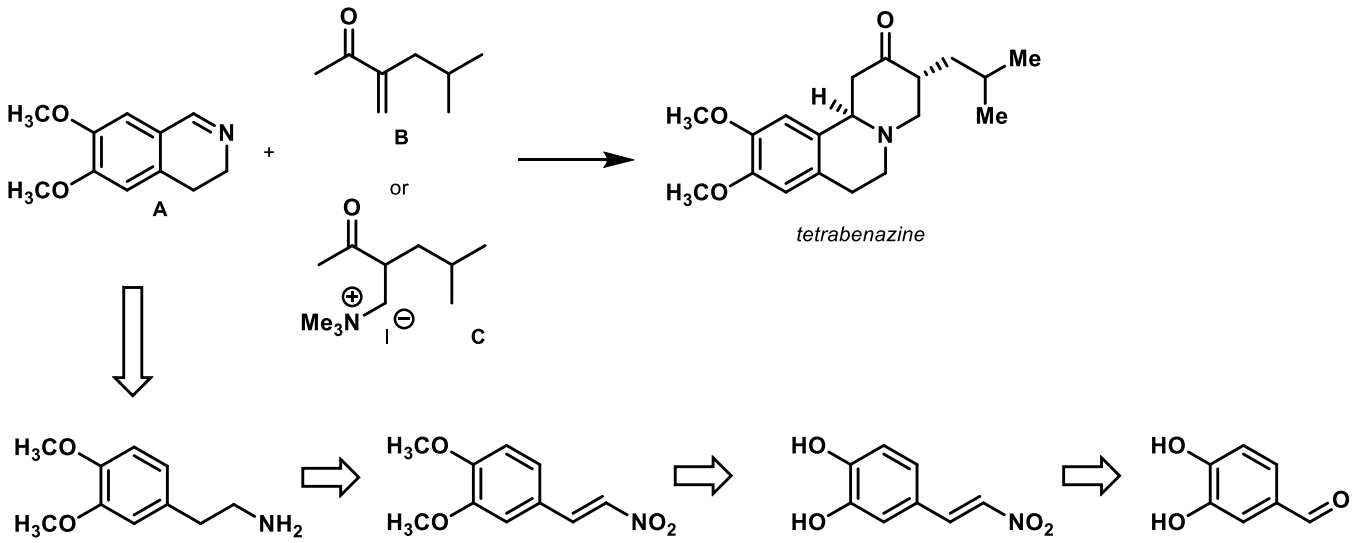
- Deuterium substitution impedes oxidative metabolism of the methoxy groups → deuterium kinetic isotope effect (DIE)
- Deutetrabenazine has prolonged *in vivo* half-life due to stabilization of metabolic conversion → slower depletion
- Less dosing per day (2x instead of 3x), dosing of smaller quantity → mitigation of undesirable side effects

S. H. DeWitt, B. E. Maryanoff, *Biochemistry* **2018**, *57*, 472−473.

5. Deutetrabenazine – the First FDA-Approved Deuterated Drug

5.2 Synthetic access to (deu-)tetrabenazine

- Tetrabenazine was invented by Hoffmann-La-Roche (first synthesis: 1960)
- Benzoquinolizine derivative
- Hoffmann-La-Roche: condensation of 6,7-dimethoxy-3,4-dihydroisoquinoline (A) with 3-methylene-5-methyl-2-hexanone (B) in an alkaline medium
  or (2-acetyl-4-methylpentyl)trimethylammonium iodide (C) in alcohol (Wellcome Foundation)

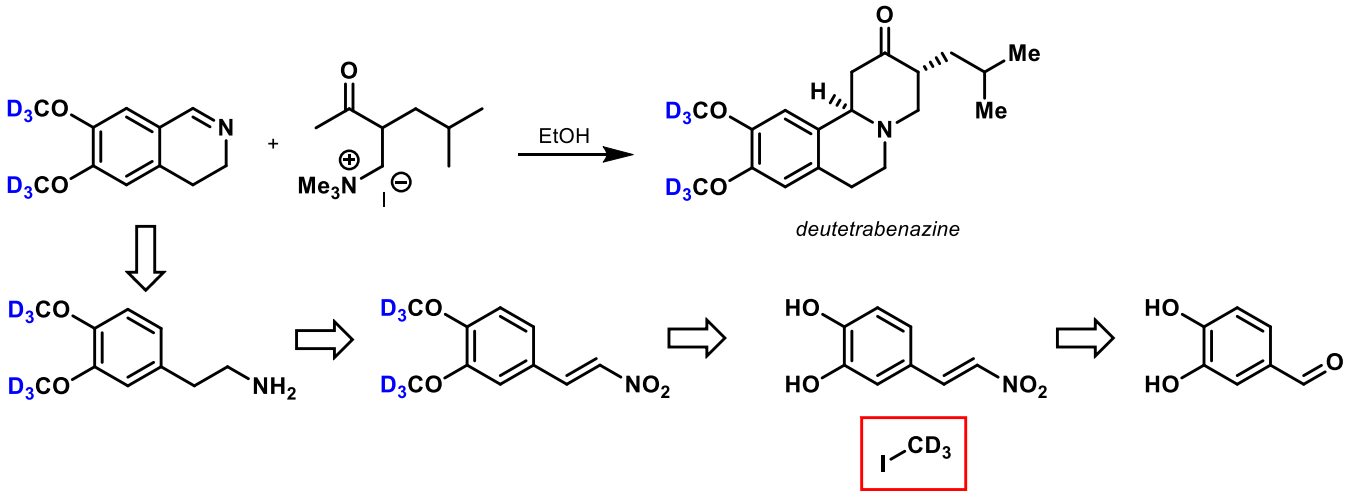


P. C. Ray, Y. D. Pawar, D. T. Singare, T. N. Deshpande, G. P. Singh *Org. Process Res. Dev.* **2018**, *22*, 520–526.

5. Deutetrabenazine – the First FDA-Approved Deuterated Drug

5.2 Synthetic access to (deu-)tetrabenazine

- Deutetrabenazine = stable non-radioactive deuterium analogue of tetrabenazine in which the six hydrogen atoms of the 9- and 10-methoxy substituents have been replaced by deuterium atoms
- First synthesis of deutetrabenazine by Auspex Pharmaceuticals in 2009
- Auspex: 6,7-dimethoxy-3,4-dihydroisoquinoline-*d6* and (2-acetyl-4-methylpentyl)trimethylammonium iodide in ethanol



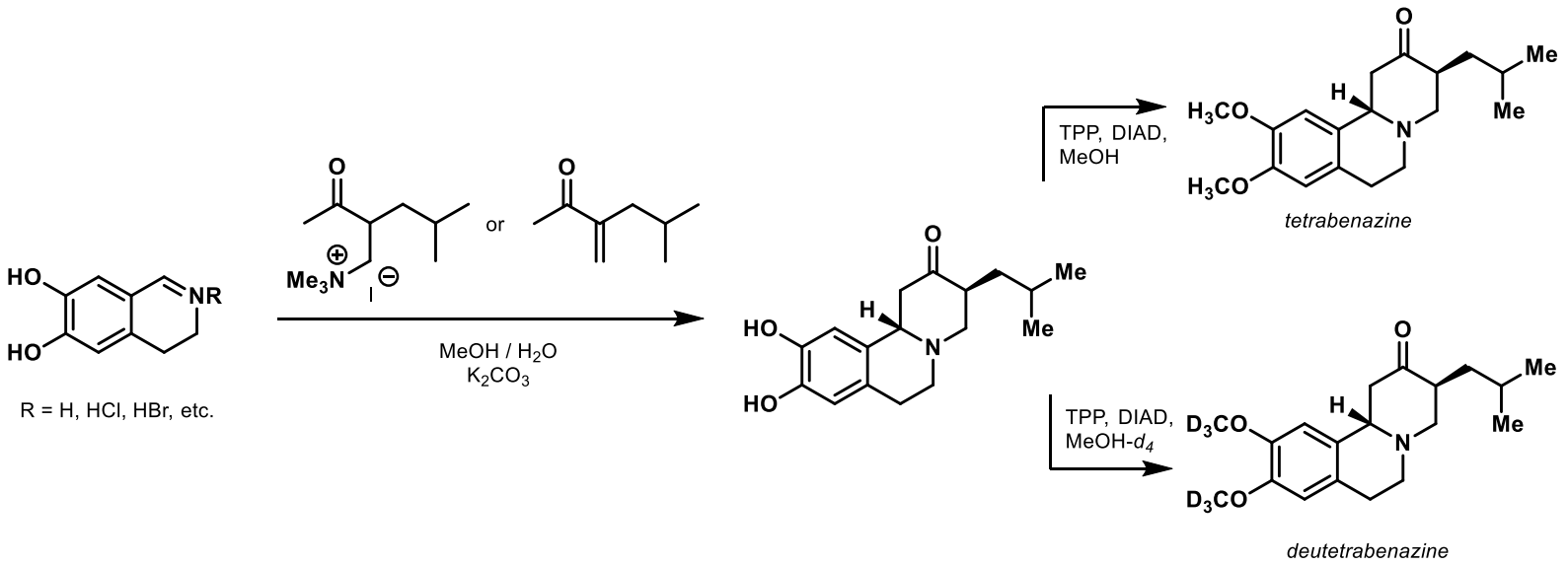
- Use of genotoxic iodomethane-*d3* and column chromatography → low yields

P. C. Ray, Y. D. Pawar, D. T. Singare, T. N. Deshpande, G. P. Singh *Org. Process Res. Dev.* **2018**, *22*, 520–526.

5. Deutetrabenazine – the First FDA-Approved Deuterated Drug

5.2 Synthetic access to (deu-)tetrabenazine

- Improved synthetic route: methanol and deuterated methanol (MeOH-*d4*) for methylation
- Starting material: 6,7-dihydroxy-3,4-dihydroquinoline + (2-acetyl-4-methylpentyl)trimethylammonium iodide or 3-methylene-5-methyl-2-hexanone in MeOH/water and K_2CO_3 as base at 65-70°C → key intermediate
- Key intermediate was treated with MeOH-*d4* to obtain deutetrabenazine using Mitsunobu-reaction
- Mitsunobu: triphenylphosphine (TPP), diisopropyl azodicarboxylate (DIAD), 25-30°C



P. C. Ray, Y. D. Pawar, D. T. Singare, T. N. Deshpande, G. P. Singh *Org. Process Res. Dev.* **2018**, *22*, 520–526.