Applications and Synthesis of Deuterium-Labeled Compounds

Christopher Prier

MacMillan Group Meeting

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Deuterium: A Stable Isotope of Hydrogen

$^{1}_{1}H$

1.008 amu

$^{2}_{1}D$

2.014 amu

0.015% natural abundance

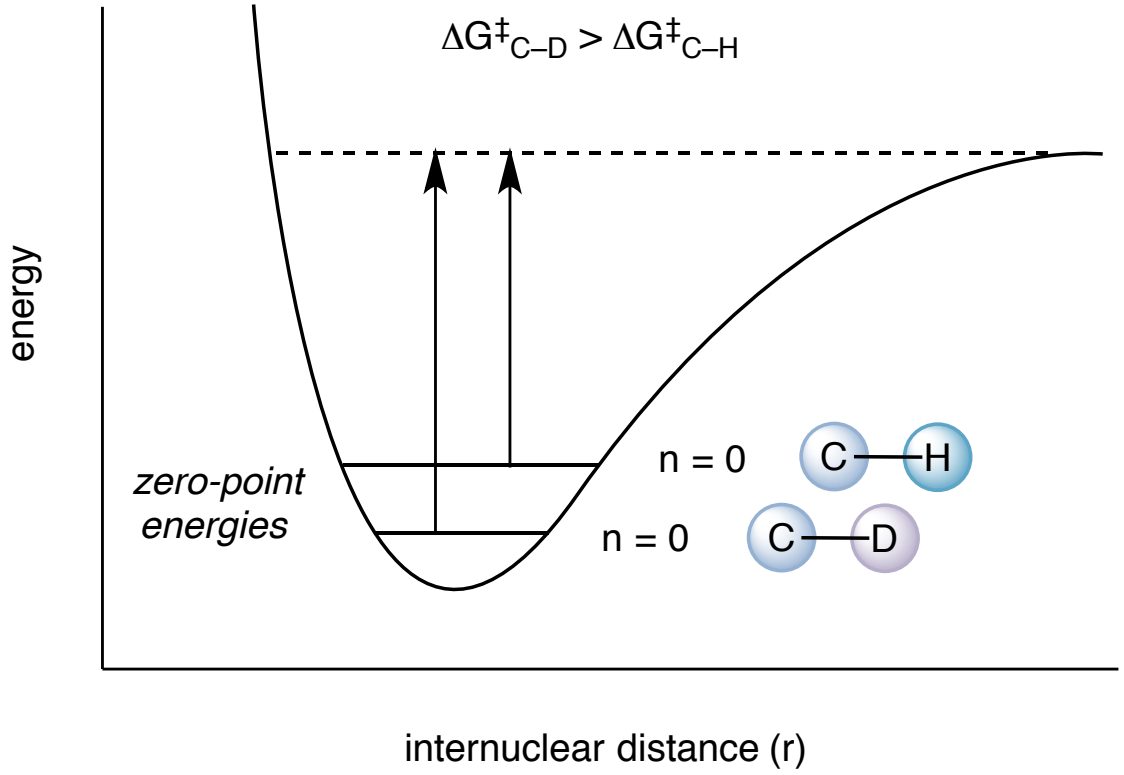
Harold C. Urey

- 1932: Urey, Brickwedde, and Murphy report spectroscopic evidence for heavy hydrogen
- 1933: Lewis and MacDonald isolate a pure sample of deuterium oxide (D_2O)
- Urey awarded the Nobel Prize for his discovery in 1934; coins the name "deuterium"
- Deuterium now broadly employed in organic chemistry, organometallic chemistry, enzymology, spectroscopy, pharmacology, and many other fields

Wiberg, K. B. *Chem. Rev.* **1955**, *55*, 713.

The Kinetic Isotope Effect

- KIE is the observation that isotopically substituted molecules react at different rates: $k_H \neq k_D$
- Vibrational energy of a bond is dependent on the reduced mass of the two atoms (μ)
- Larger activation energy for C–D bond homolysis than for C–H bond homolysis



$$E_n = (n + 1)\, h\nu$$

$$\nu = \frac{1}{2\pi c}\sqrt{\frac{k}{\mu}}$$

$$\mu = \frac{m_1 \cdot m_2}{m_1 + m_2}$$

$$\mu_{C-H} = 0.92$$

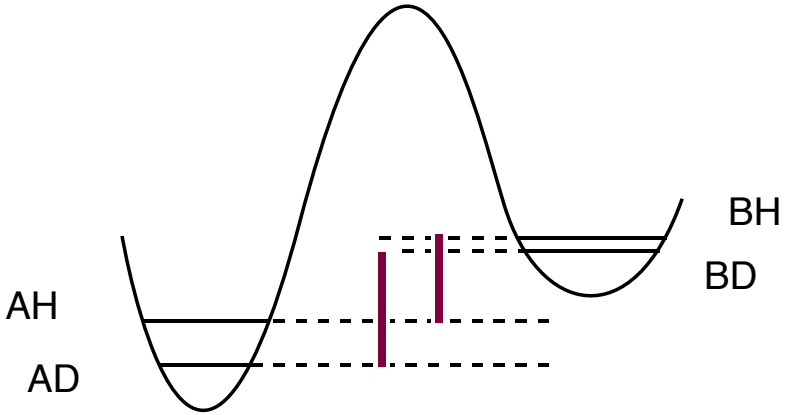
$$\mu_{C-D} = 1.71$$

Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, 2006.

The Equilibrium Isotope Effect

- The distribution of deuterium in an equilibrium is determined by a thermodynamic isotope effect

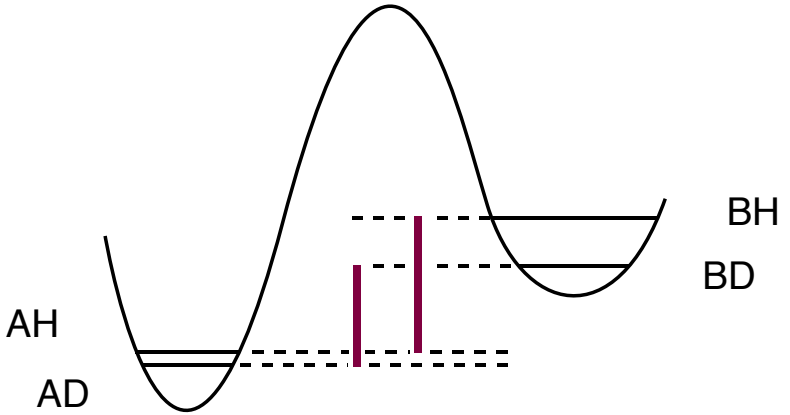
case 1



$\Delta ZPE_{C-D} > \Delta ZPE_{C-H}$

equilibrium favors AD + BH

case 2



$\Delta ZPE_{C-D} < \Delta ZPE_{C-H}$

equilibrium favors AH + BD

deuterium prefers the bond with the larger force constant

Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, 2006.

Applications of Deuterated Compounds

- Study of reaction mechanisms
- Elucidation of biosynthetic pathways
- Total synthesis: alter reaction selectivity
- Internal standards for mass spectrometry
- Enhance metabolic stability of a drug

And many more!

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- Study of reaction mechanisms
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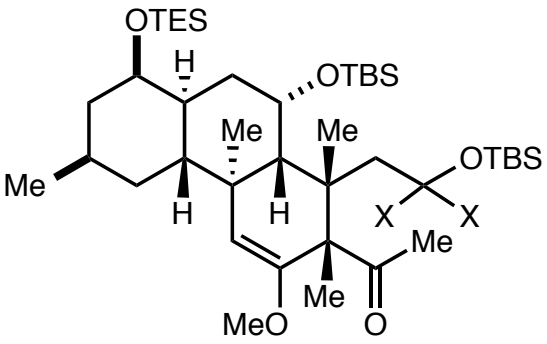
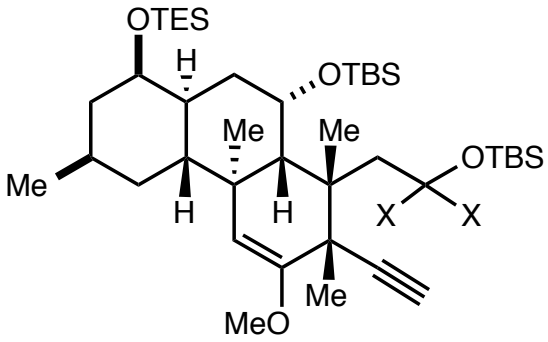
Deuterium in the Total Synthesis of Norzoanthamine

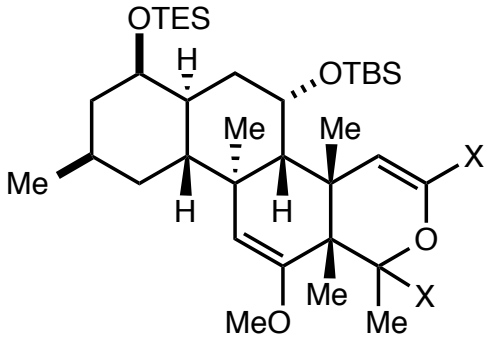
- Introduction of deuterium suppresses an undesired pathway via the kinetic isotope effect



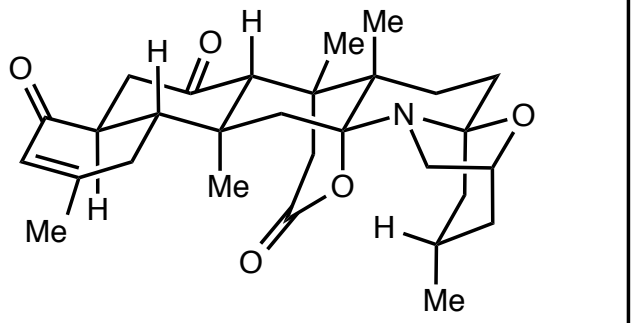
2,6-di-*t*-Bu-py
Tf_2O

then DBU





X = H	66%	30%
X = D	81%	9%



norzoanthamine

undesired
1,5-hydride
shift

Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495.

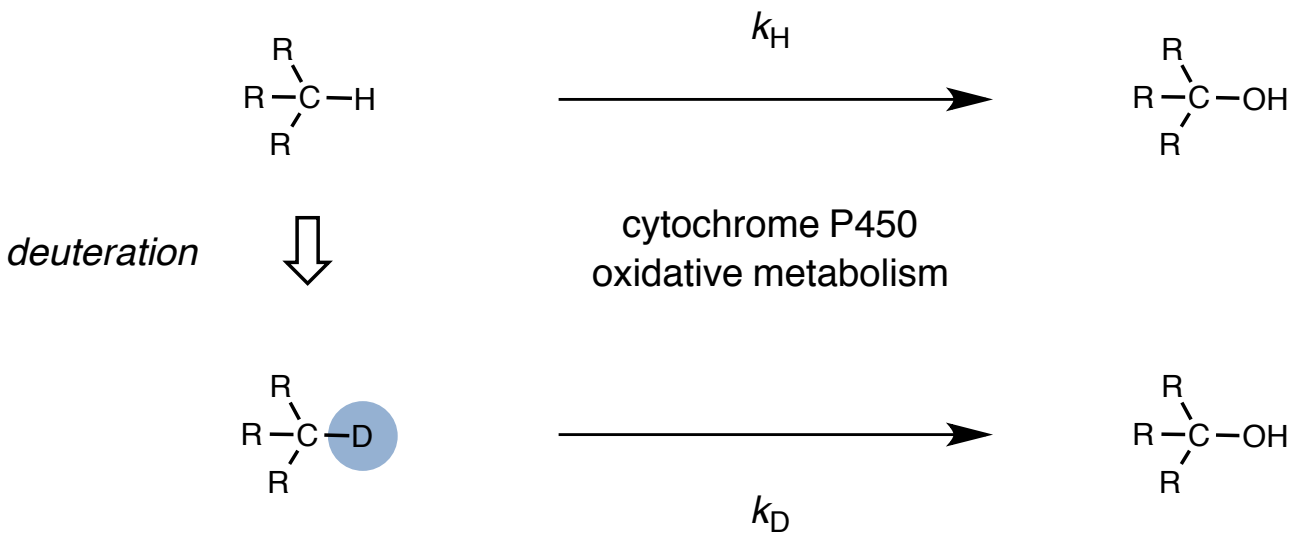
Applications of Deuterated Compounds

- Study of reaction mechanisms
- Elucidation of biosynthetic pathways
- Total synthesis: alter reaction selectivity
- Internal standards for mass spectrometry
- **Enhance metabolic stability of a drug**

And many more!

Deuterium Effects in Drug Metabolism

- Deuteration has the potential to impact a drug's stability when metabolism involves cleavage of a C–H bond



- Deuteration typically has no effect on biological potency or selectivity
- Potential for a drug to have a longer half-life or reduced/less frequent dosing
- Improve metabolite profile: prevent formation of toxic metabolites or those that inhibit CYP
- *To date there are no approved deuterium-enriched pharmaceuticals*

Foster, A. B. *Trends Pharmacol. Sci.* **1984**, *5*, 524.

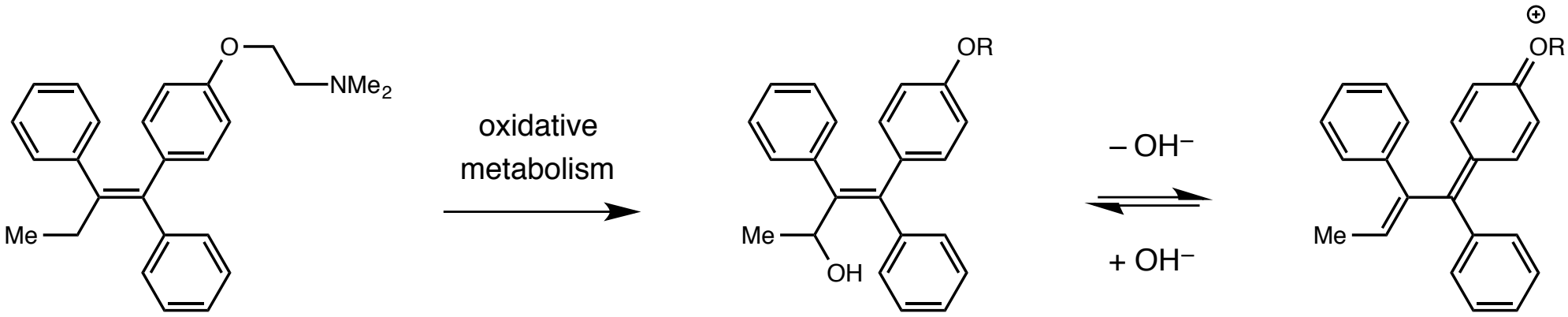
Kushner, D. J.; Baker, A.; Dunstall, T. G. *Can. J. Physiol. Pharmacol.* **1999**, *77*, 79.

Harbeson, S. L.; Tung, R. D. *Annu. Rep. Med. Chem.* **2011**, *46*, 403.

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

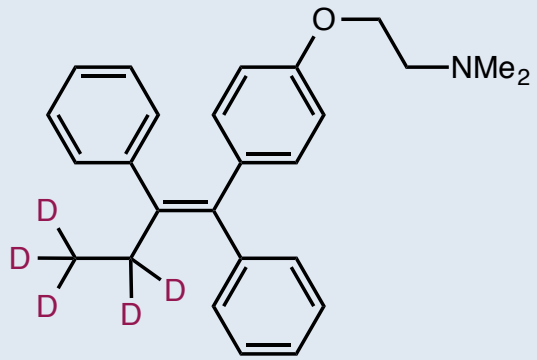
Metabolism and Deuteration of Tamoxifen

- Tamoxifen forms adducts with DNA in rats, leading to liver cancer; proposed to proceed via quinone methide



tamoxifen
breast cancer treament

proposed intermediates leading to DNA conjugates



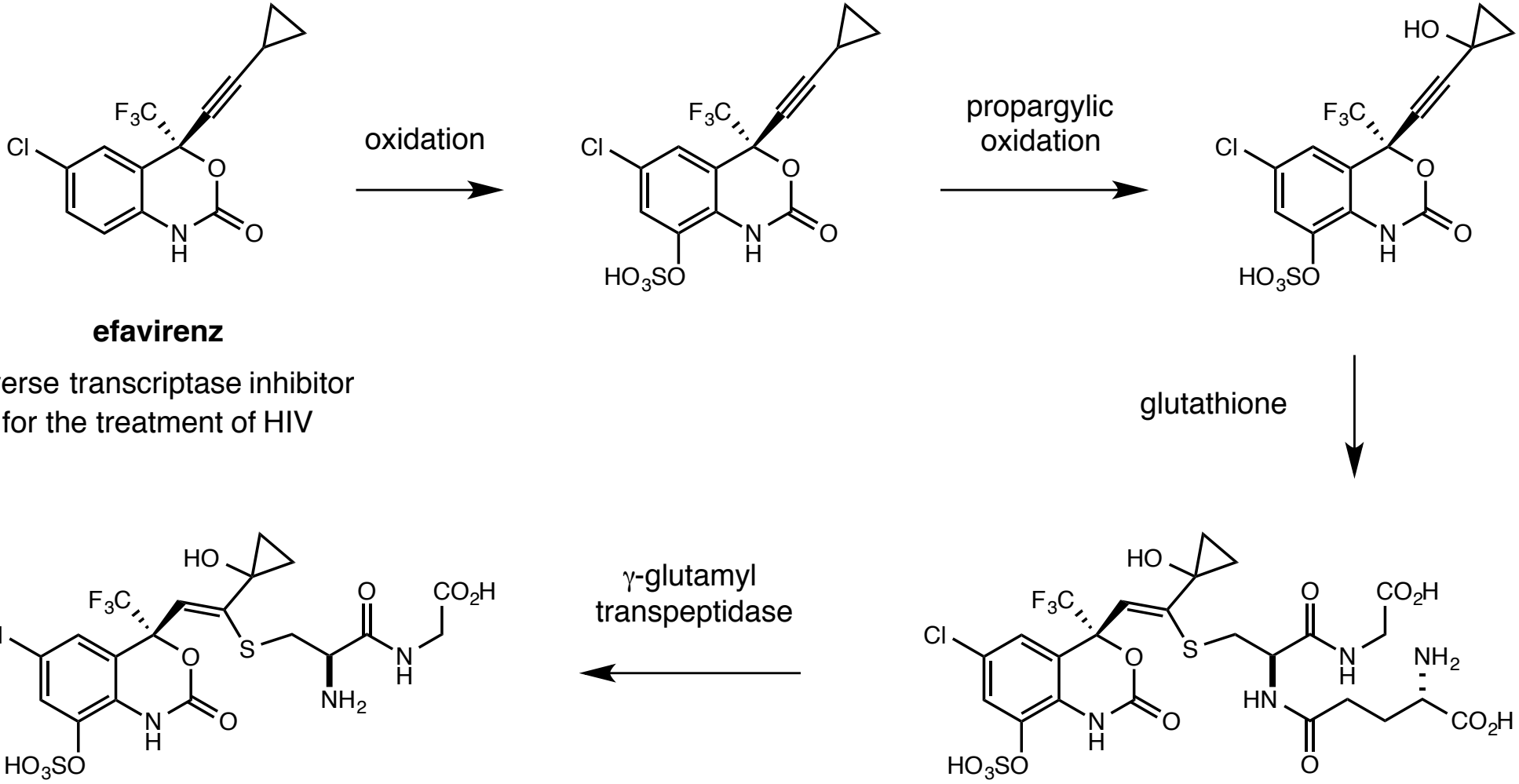
tamoxifen-d_5

- Isotope effect hypothesized to reduce extent of DNA alkylation
- Reduced genotoxicity observed: ~2-fold reduced adduct formation

Phillips, D. H.; Potter, G. A.; Horton, M. N.; Hewer, A.; Crofton-Sleigh, C.; Jarman, M.; Venitt, S. *Carcinogenesis* **1994**, *15*, 1487.
Jarman, M.; Poon, G. K.; Rowlands, M. G.; Grimshaw, R. M.; Horton, M. N.; Potter, G. A.; McCague, R. *Carcinogenesis* **1995**, *16*, 683.

Metabolism of Efavirenz

- Metabolism of efavirenz to a toxic metabolite in rats involves a propargylic oxidation of the cyclopropane



efavirenz

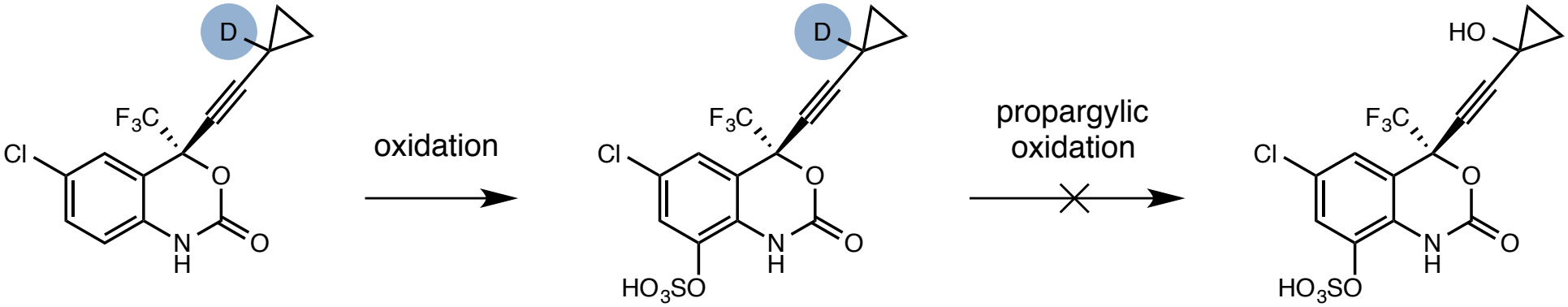
reverse transcriptase inhibitor for the treatment of HIV

metabolite responsible for nephrotoxicity

Mutlib, A. E.; Gerson, R. J.; Meunier, P. C.; Haley, P. J.; Chen, H.; Gan, L. S.; Davies, M. H.; Gemzik, B.; Christ, D. D. et al. *Toxicol. Appl. Pharmacol.* **2000**, *169*, 102.

Metabolism of Efavirenz

- Installation of a single deuterium atom at the site of propargylic oxidation reduces toxic metabolite formation



efavirenz-d_1

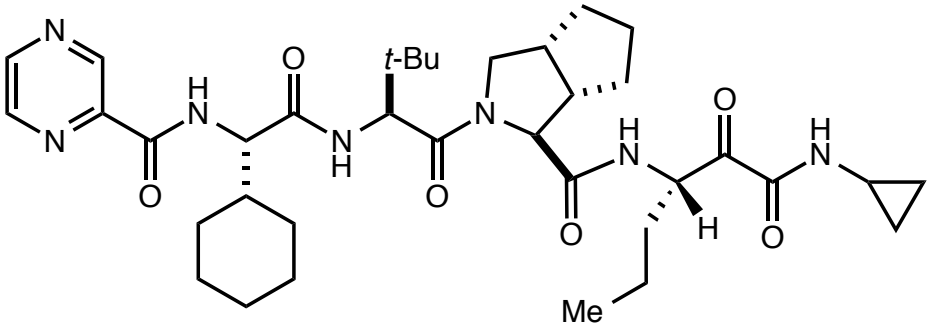
	concentration of toxic metabolite in urine
efavirenz	28.1 ± 13.0 μg/mL
efavirenz-d_1	4.0 ± 1.1 μg/mL

	no. of rats with renal cortical epithelial cell necrosis	
severity	efavirenz	efavirenz-d_1
0 (unaffected)	0	2
1 (minimal)	2	4
2 (mild)	4	3
3 (moderate)	2	1
4 (severe)	2	0

Mutlib, A. E.; Gerson, R. J.; Meunier, P. C.; Haley, P. J.; Chen, H.; Gan, L. S.; Davies, M. H.; Gemzik, B.; Christ, D. D. et al. *Toxicol. Appl. Pharmacol.* **2000**, *169*, 102.

Deuteration of Telaprevir

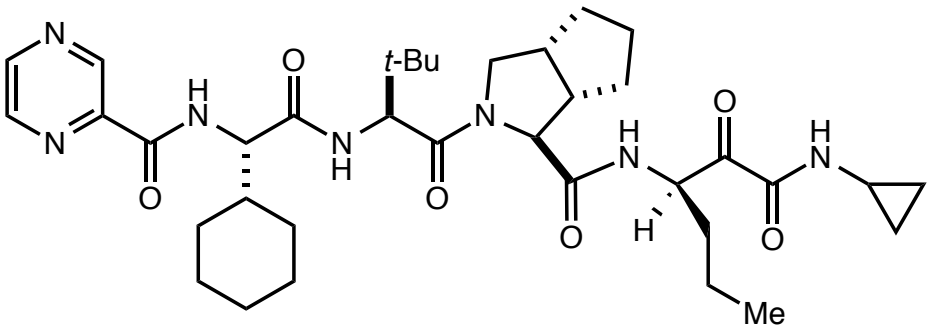
- Telaprevir undergoes epimerization *in vivo* to its less potent (*R*)-epimer



telaprevir

- Vertex, Johnson & Johnson
- Hepatitis C protease inhibitor

pH ≥ 7



telaprevir (*R*)-epimer

- Major metabolite of telaprevir
- 30-fold lower inhibitory activity

Maltais, F.; Jung, Y. C.; Chen, M.; Tanoury, J.; Perni, R. B.; Mani, N.; Laitinen, L.; Huang, H.; Liao, S.; Gao, H. et al. *J. Med. Chem.* **2009**, *52*, 7993.

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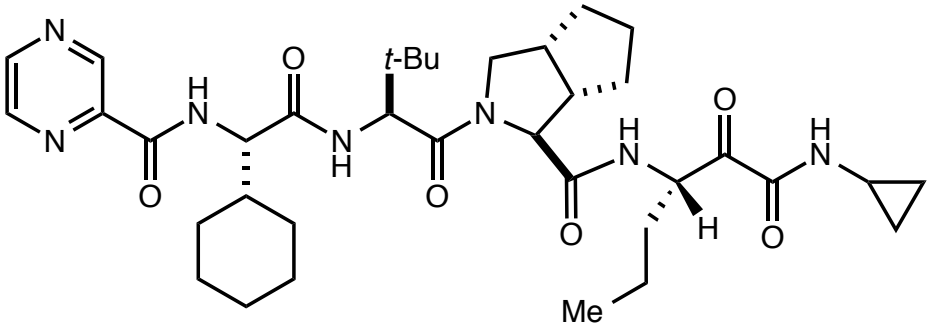
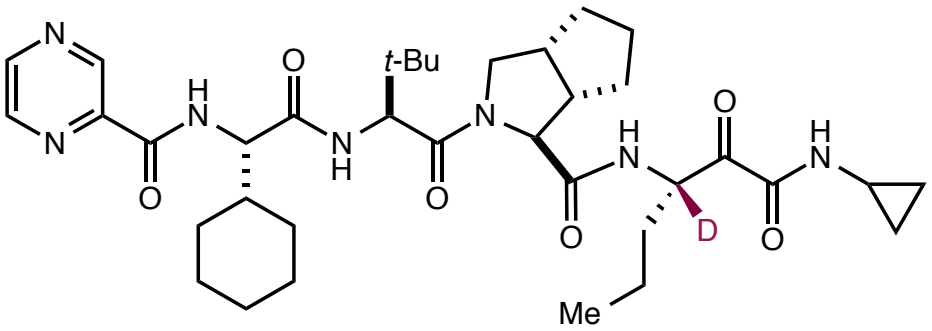


telaprevir

- Vertex, Johnson & Johnson
- Hepatitis C protease inhibitor



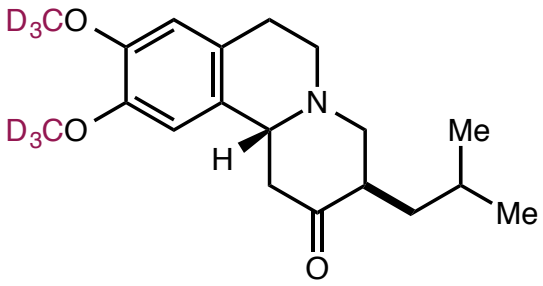
telaprevir-d_1

- As efficacious as protio-telaprevir in protease inhibition and viral replication assays
- Significantly more resistant to epimerization ($k_H/k_D \approx 5$)
- ~13% increase in AUC in rats

Maltais, F.; Jung, Y. C.; Chen, M.; Tanoury, J.; Perni, R. B.; Mani, N.; Laitinen, L.; Huang, H.; Liao, S.; Gao, H. et al. *J. Med. Chem.* **2009**, *52*, 7993.

Deuterated Drugs in Clinical Trials

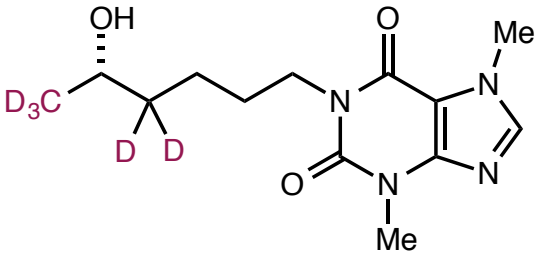
AUSPEX PHARMACEUTICALS



SD-809

- In Phase III for treatment of chorea associated with Huntingdon's disease
- Deuterated analog of tetrabenazine

CoNCERT Pharmaceuticals Inc.

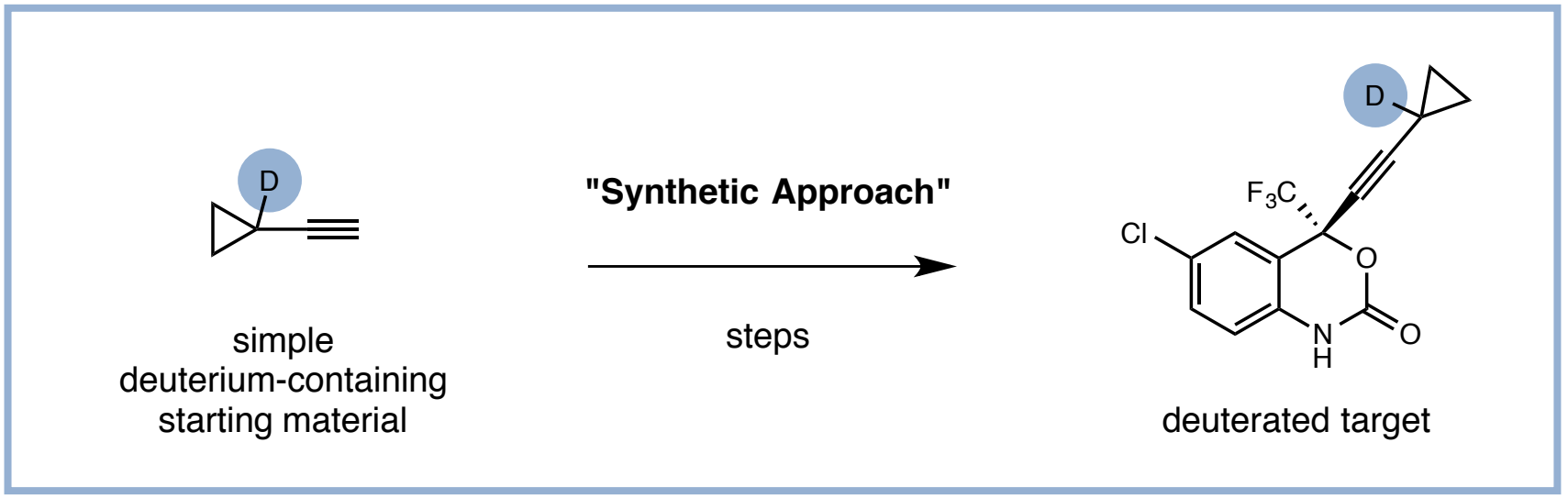


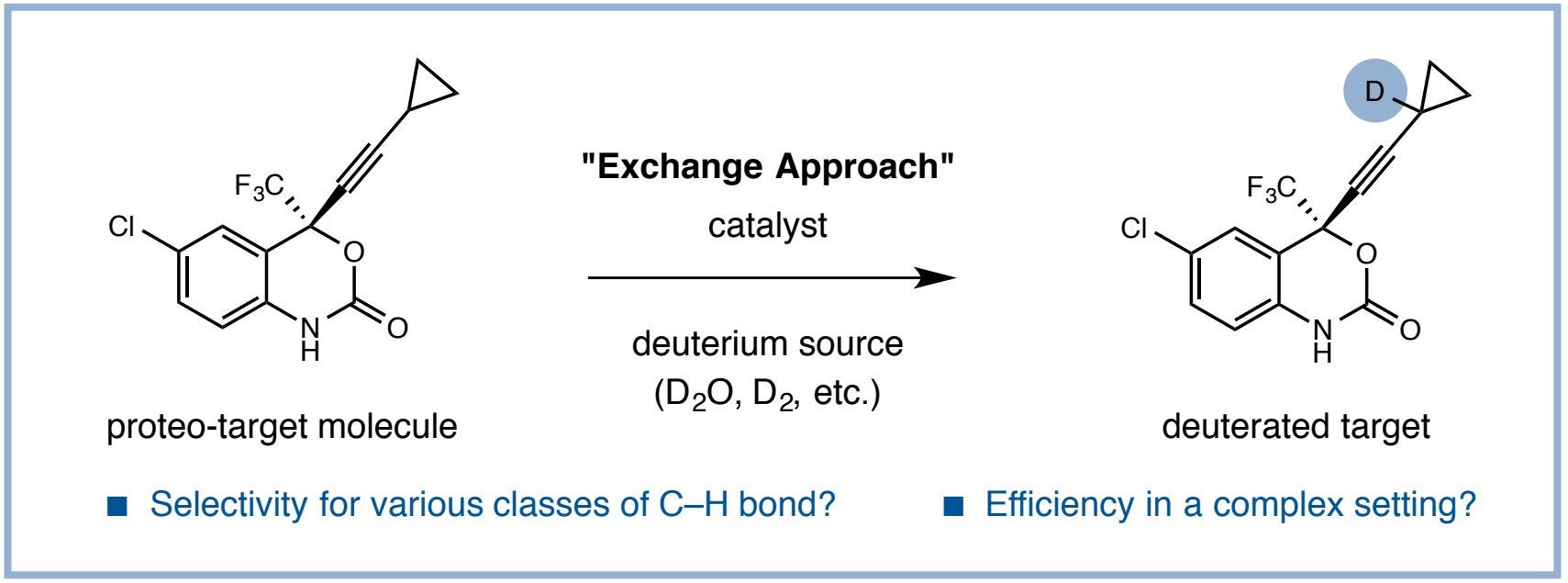
CTP-499

- In Phase II for diabetic nephropathy
- Deuterated analog of the active metabolite of pentoxifylline
- Phosphodiesterase inhibitor

Katsnelson, A. *Nature Med.* **2013**, *19*, 656.

Approaches to the Synthesis of Labeled Compounds



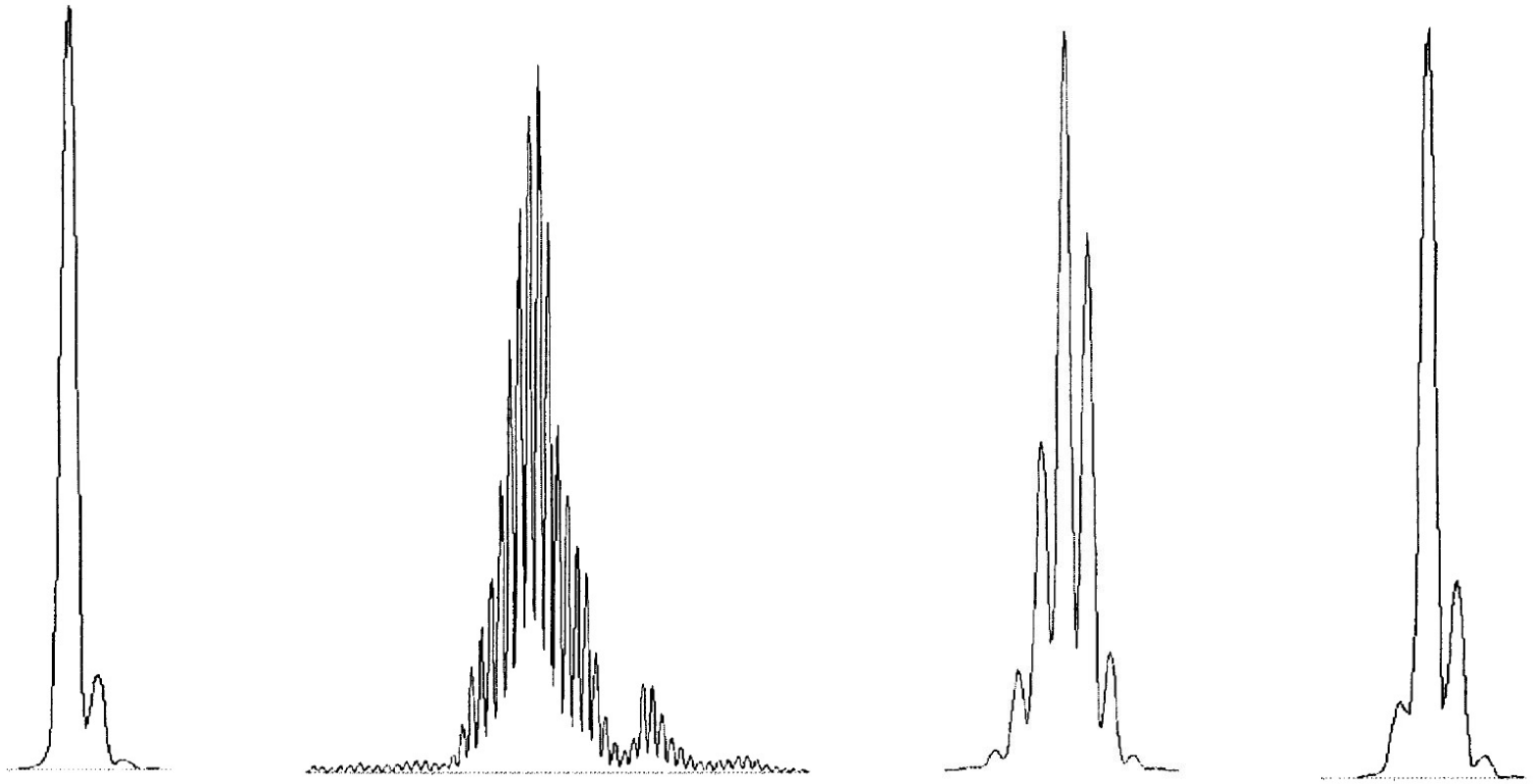


- Selectivity for various classes of C–H bond?
- Efficiency in a complex setting?

Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 7744.

Synthesis of Deuterated Compounds

- Deuterated compounds (especially internal standards) ideally possess a narrow isotopic distribution



Natural isotope distribution

unselective H/D exchange

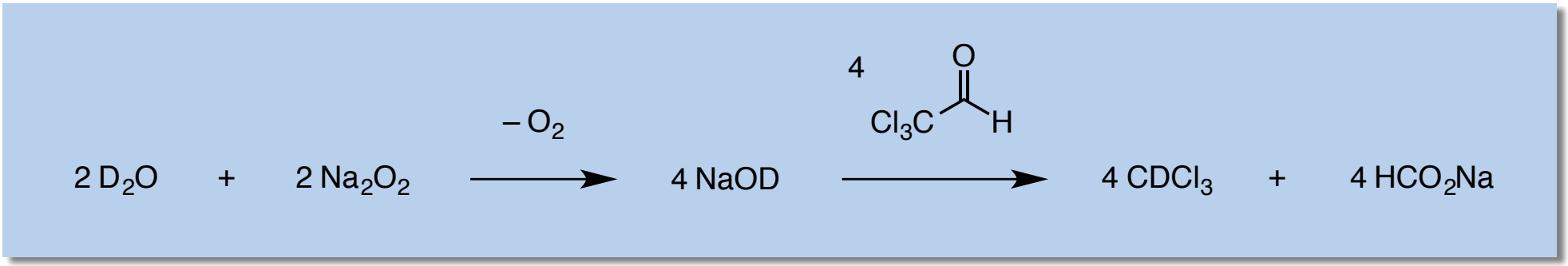
moderately selective H/D exchange

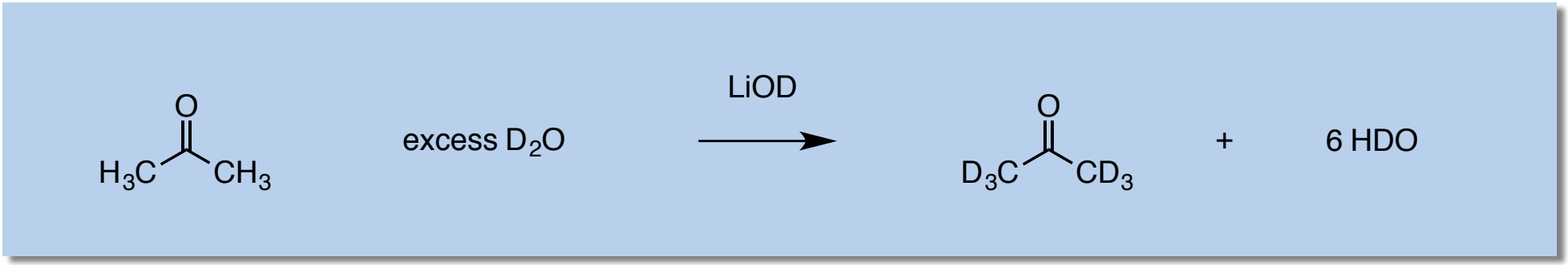
highly selective H/D exchange

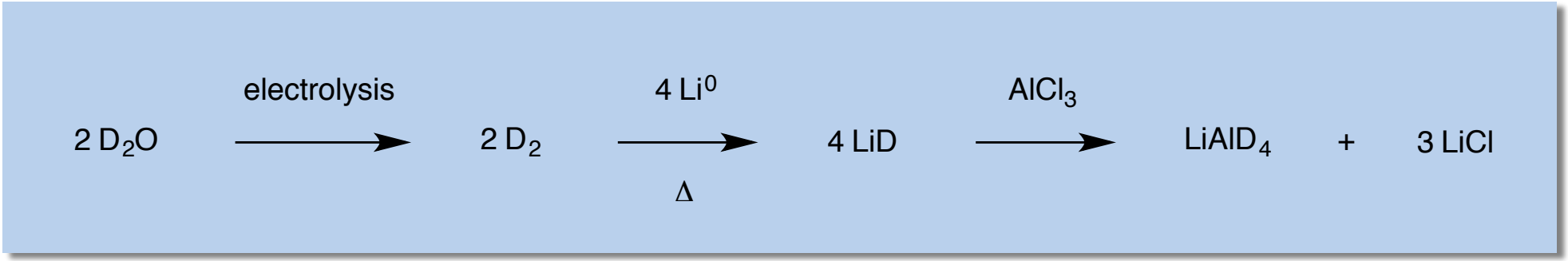
Atzrodt, J.; Derdau, V. *J. Label. Compd. Radiopharm.* **2010**, *53*, 674.

Synthesis of Deuterated Reagents

- The source of all deuterium-enriched material is deuterium oxide (D_2O)





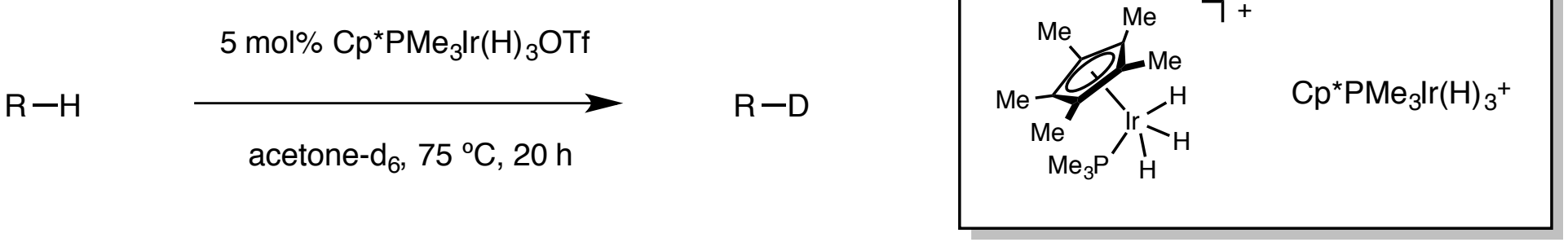


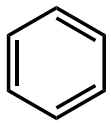
Kluger, R. *J. Org. Chem.* **1964**, *29*, 2045.

Paulsen, P. J.; Cooke, W. D. *Anal. Chem.* **1963**, *35*, 1560.

Iridium-Catalyzed H/D Exchange

- A cationic iridium trihydride complex catalyzes the H/D exchange of arenes, cyclic alkenes

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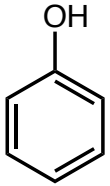

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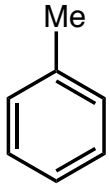

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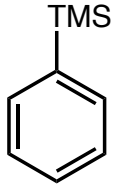

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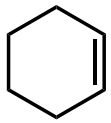
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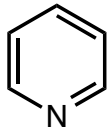

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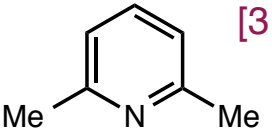
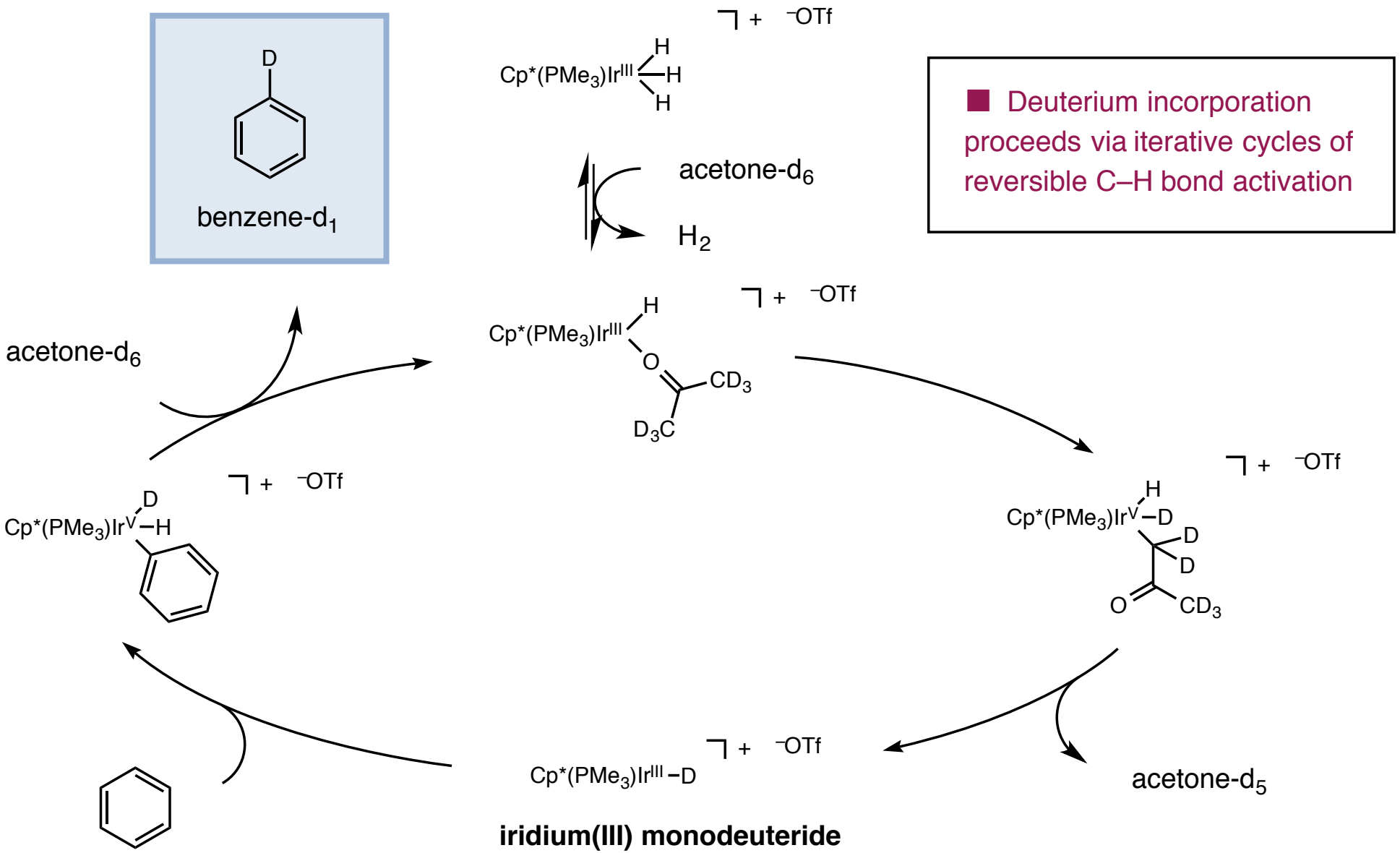


[31]
[27]

Yung, C. M.; Skaddan, M. B.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 13033.
Skaddan, M. B.; Yung, C. M.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 11.

Mechanism of Iridium-Catalyzed H/D Exchange



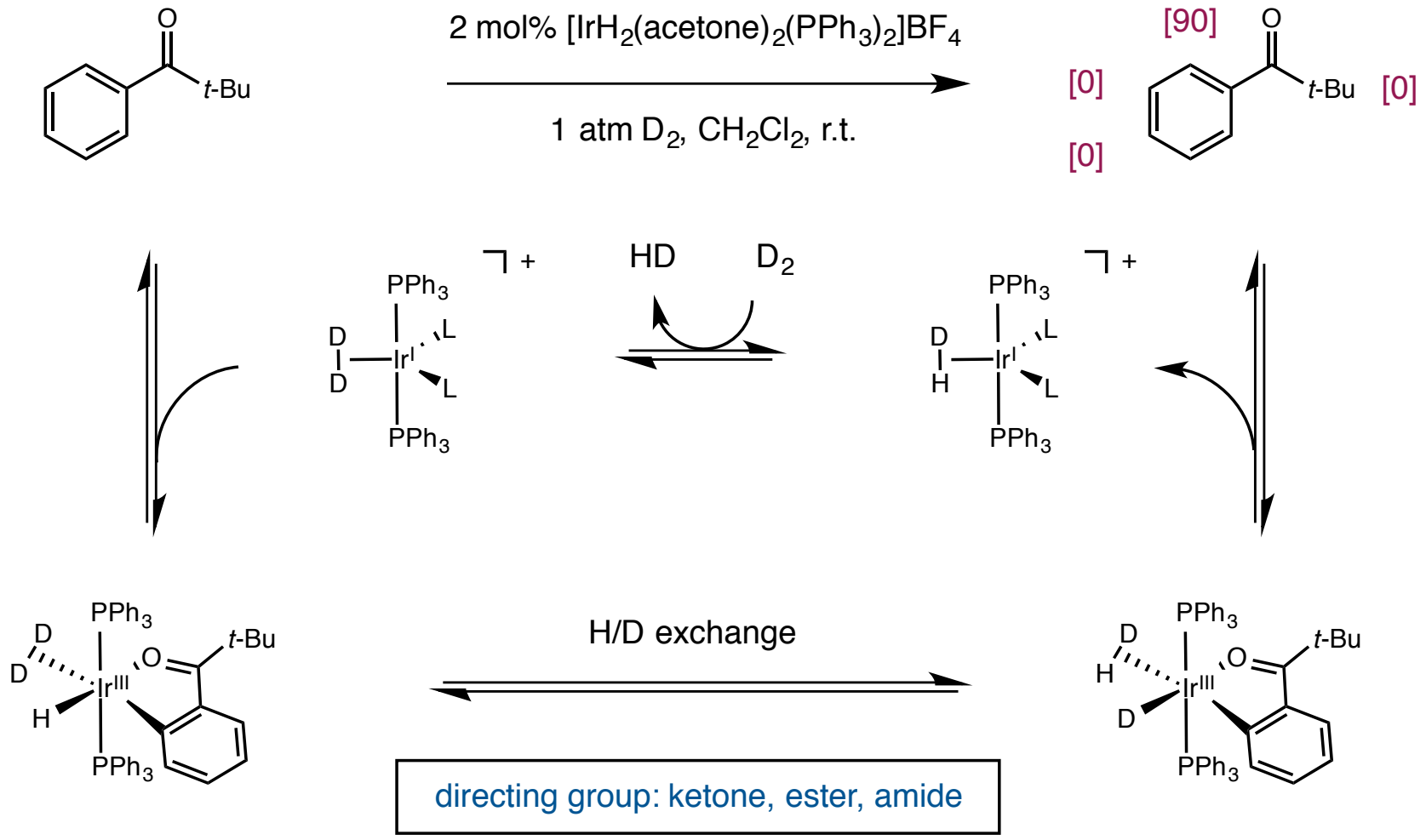
■ Deuterium incorporation proceeds via iterative cycles of reversible C–H bond activation

Yung, C. M.; Skaddan, M. B.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 13033.

Skaddan, M. B.; Yung, C. M.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 11.

Iridium-Catalyzed Ortho H/D Exchange

- Iridium catalysts promote selective *ortho*-deuteration via the formation of five-membered metallacycles

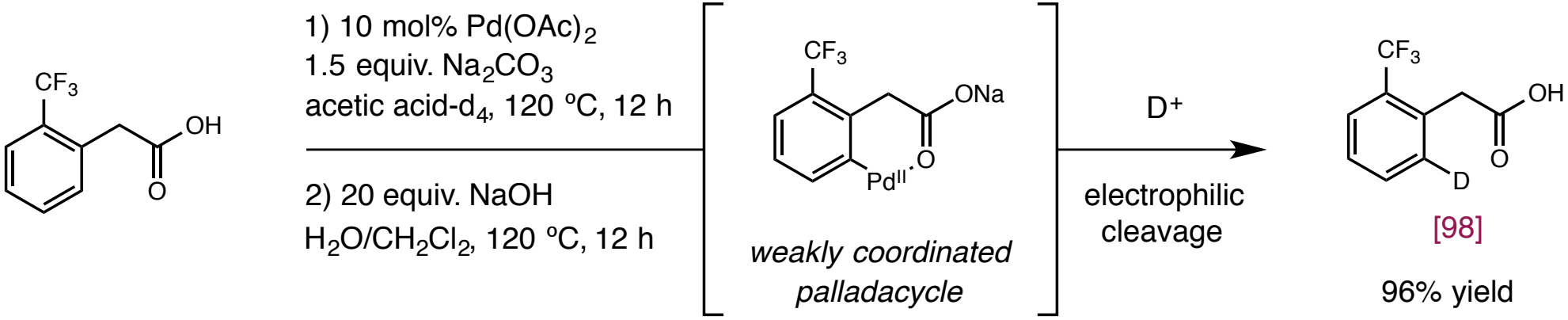


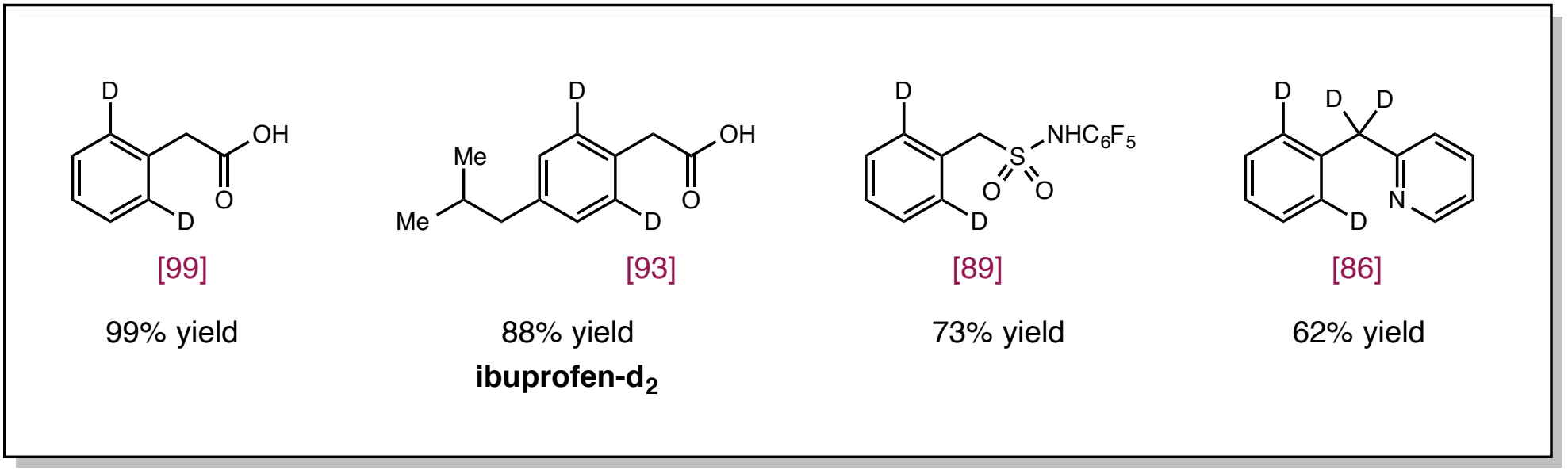
Heys, R. *J. Chem. Soc., Chem. Commun.* **1992**, 680.

Shu, A. Y. L.; Chen, W.; Heys, J. R. *J. Organomet. Chem.* **1996**, *524*, 87.

Ortho-Selective Deuteration of Arenes

- Palladium-catalyzed *ortho*-deuteration of arenes bearing weakly coordinating directing groups





Ma, S.; Villa, G.; Thuy-Boun, P. S.; Homs, A.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 734.

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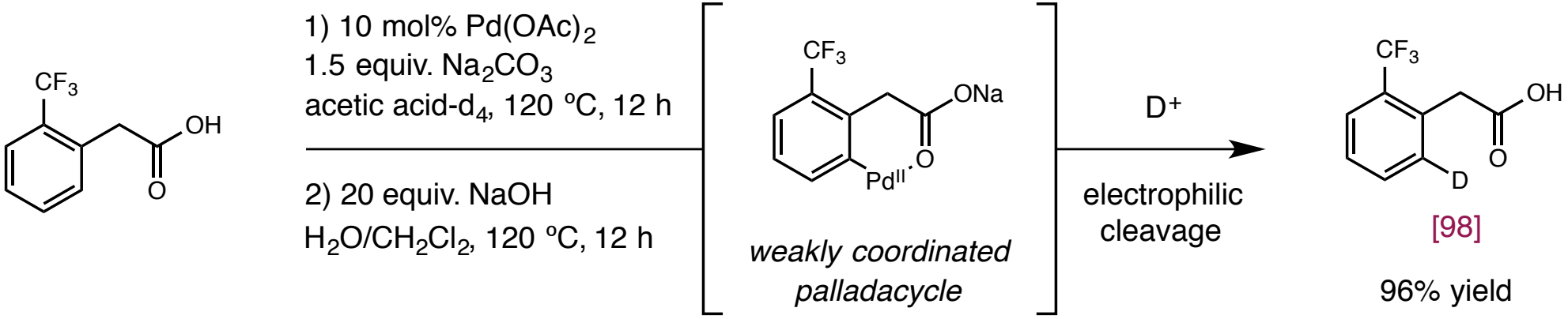
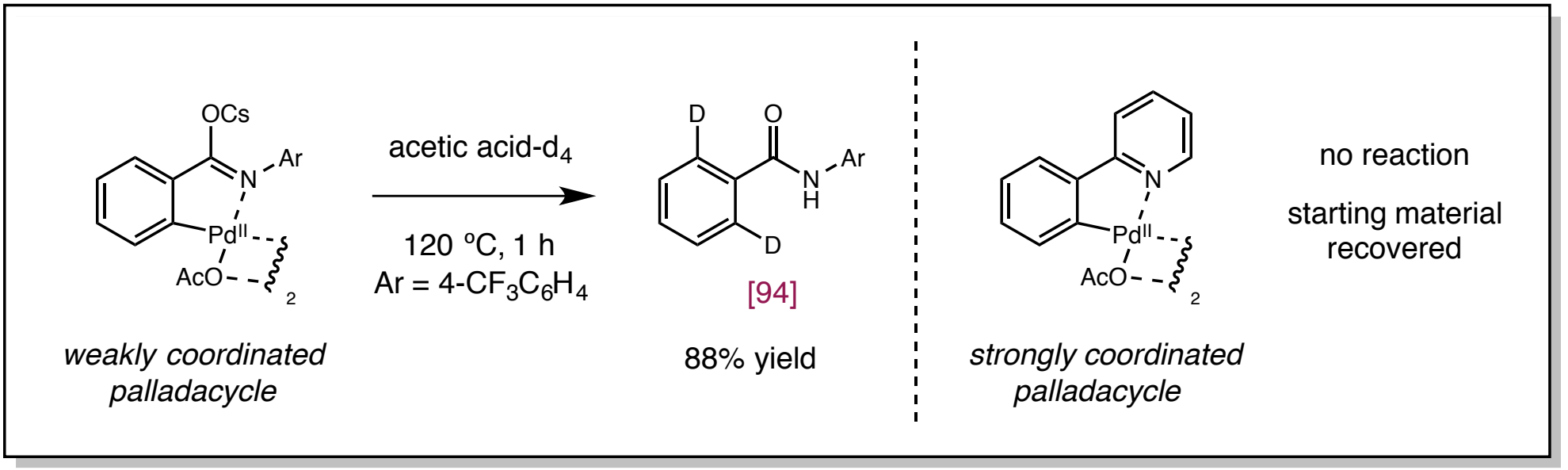
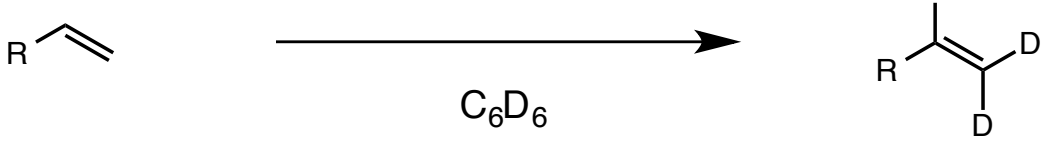


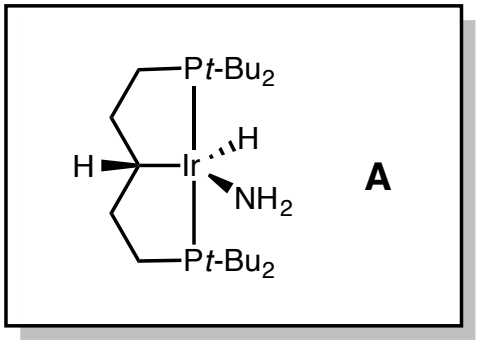


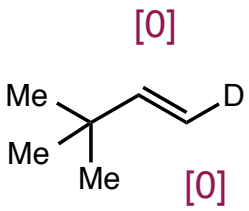
Ma, S.; Villa, G.; Thuy-Boun, P. S.; Homs, A.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 734.

Vinyl H/D Exchange by an Iridium-Pincer Complex

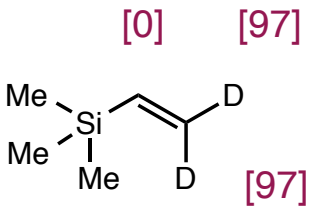
- Selective deuteration of vinyl groups is achieved with an iridium catalyst bearing an aliphatic pincer ligand



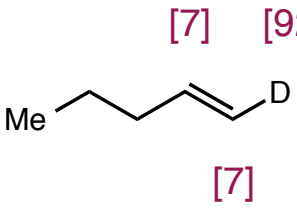




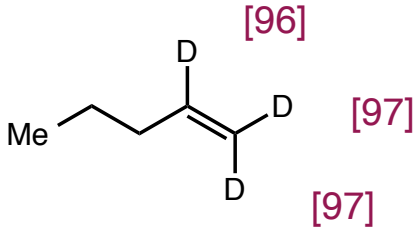
r.t., 1 min



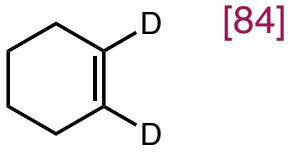
r.t., 1 min



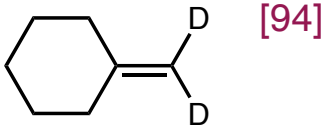
r.t., 5 min



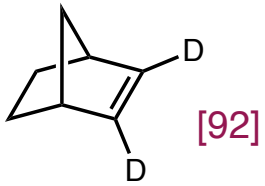
r.t., 20 h



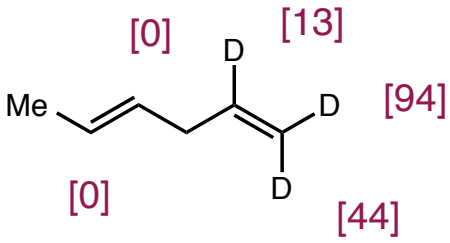
50 °C, 50 h



r.t., 40 h



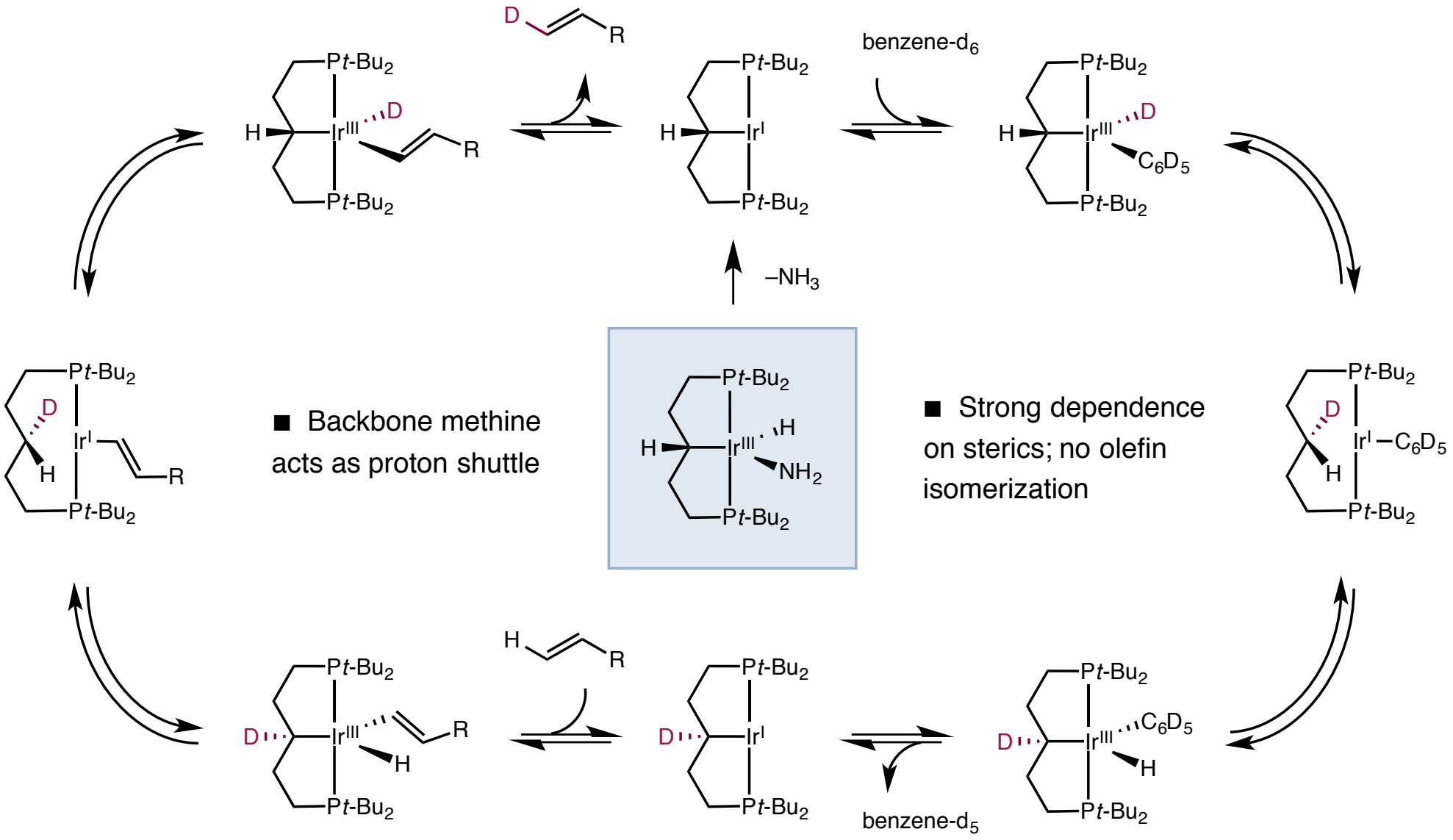
r.t., 3 h



r.t., 1.5 h

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

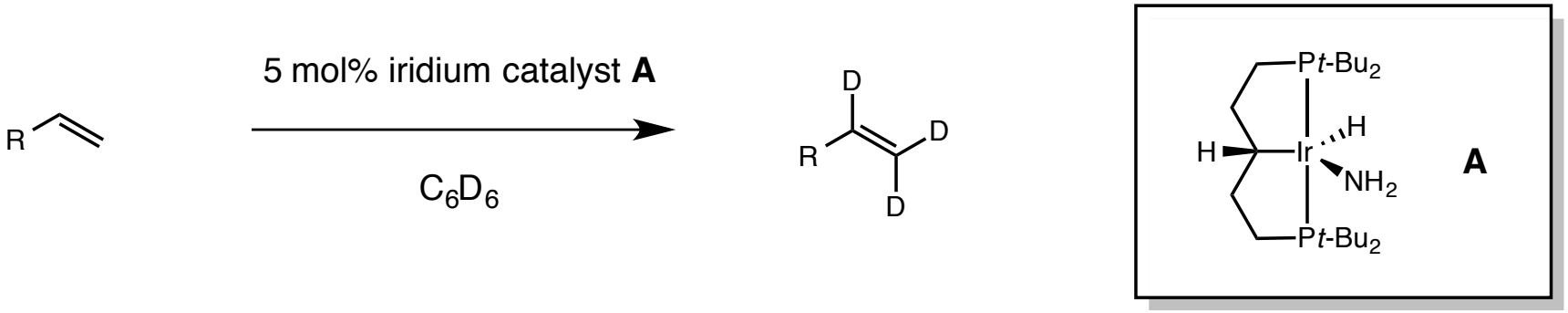
Vinyl H/D Exchange by an Iridium-Pincer Complex



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

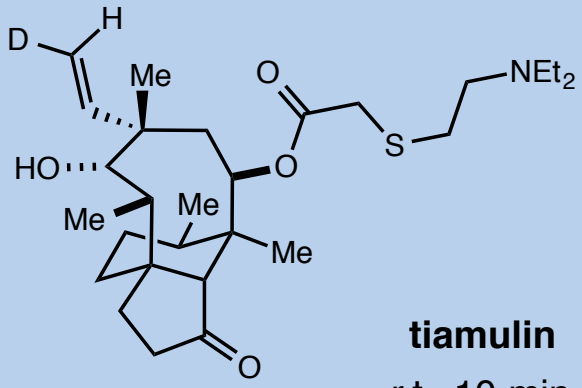
Vinyl H/D Exchange by an Iridium-Pincer Complex

- Selective deuteration of vinyl groups by an iridium catalyst bearing an aliphatic pincer ligand



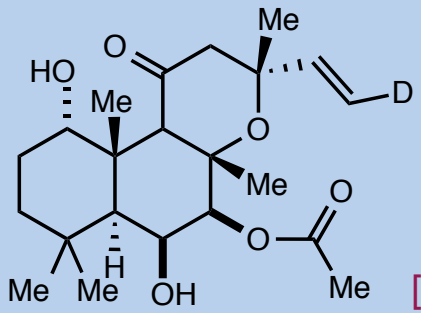
[7]

[90]



tiamulin

r.t., 10 min



[99]

[2]

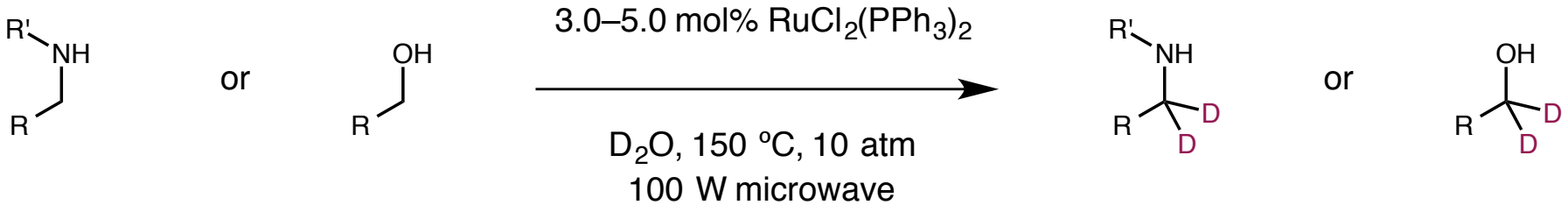
forskolin

r.t., 5 min

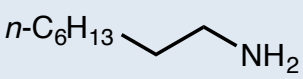
Zhou, J.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 5783.

α-Deuteration of Amines and Alcohols

- Ru-catalyzed α-deuteration of amines and alcohols proceeds via a "borrowing hydrogen" mechansim

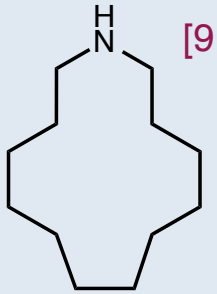


[94]



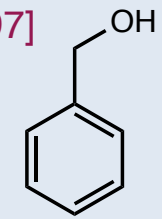
79% yield

[91]



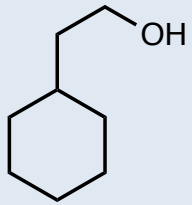
68% yield

[97]

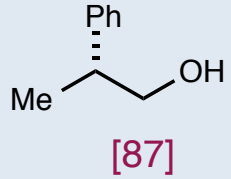


90% yield

[98]



96% yield



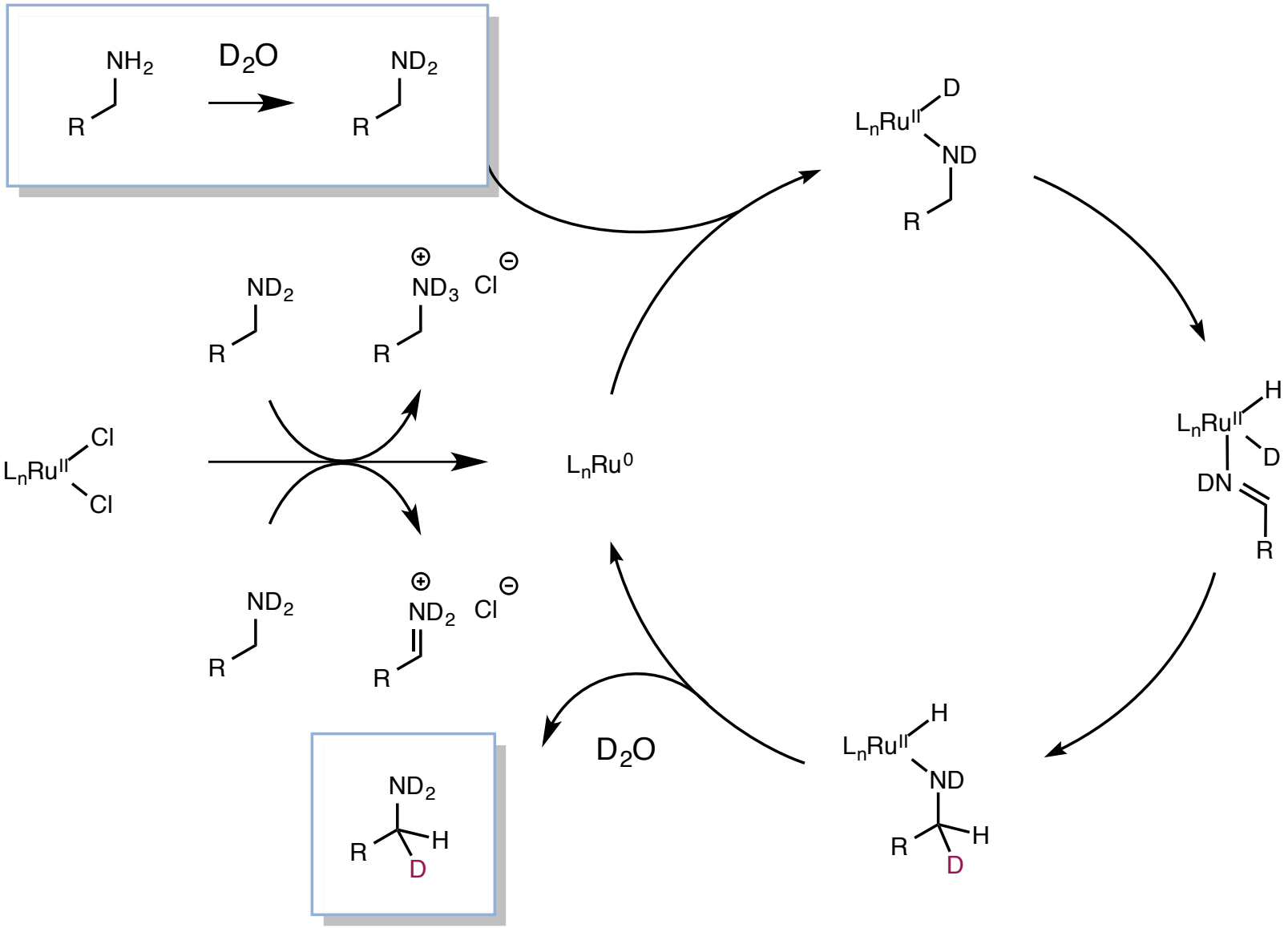
[87]

90% yield, >99% ee

Takahashi, M.; Oshima, K.; Matsubara, S. *Chem. Lett.* **2005**, *34*, 192.

α-Deuteration of Amines and Alcohols

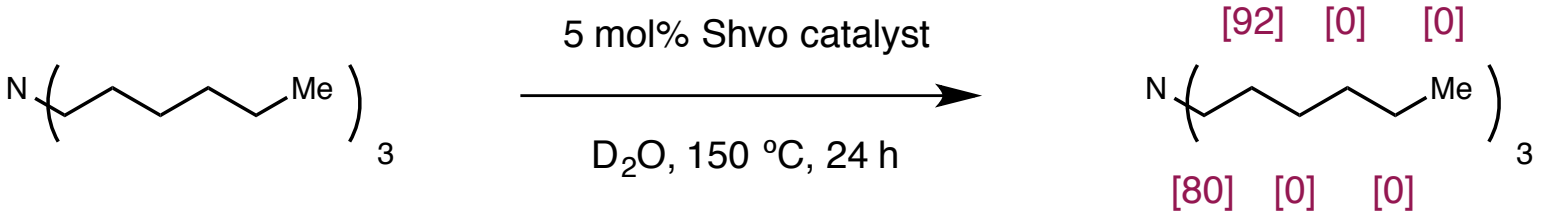
- Ru-catalyzed α-deuteration of amines and alcohols proceeds via a "borrowing hydrogen" mechansim

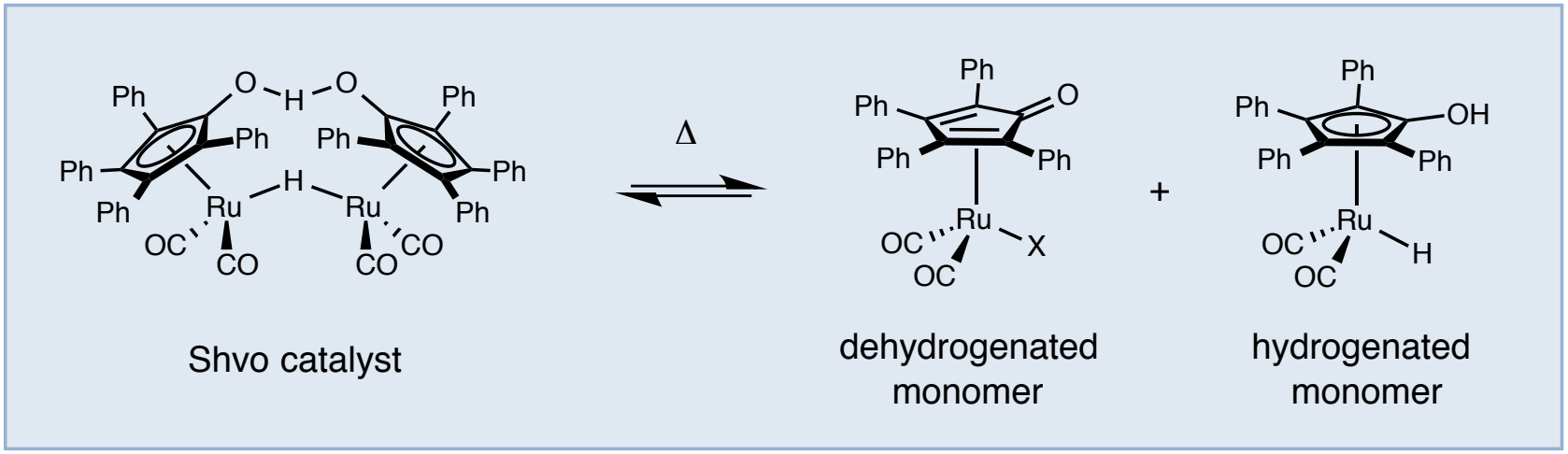


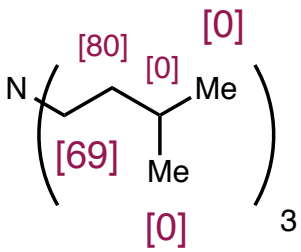
Takahashi, M.; Oshima, K.; Matsubara, S. *Chem. Lett.* **2005**, *34*, 192.

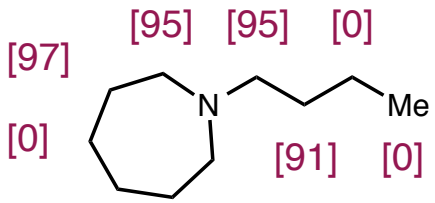
Selective α,β-Deuteration of Amines

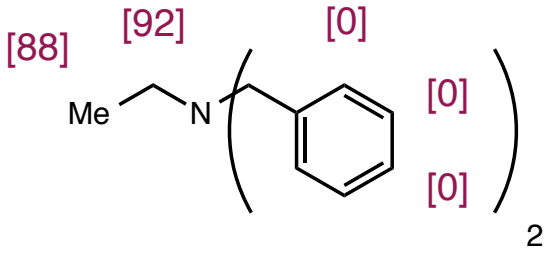
- The Shvo catalyst enables the selective α,β-deuteration of amines using deuterium oxide





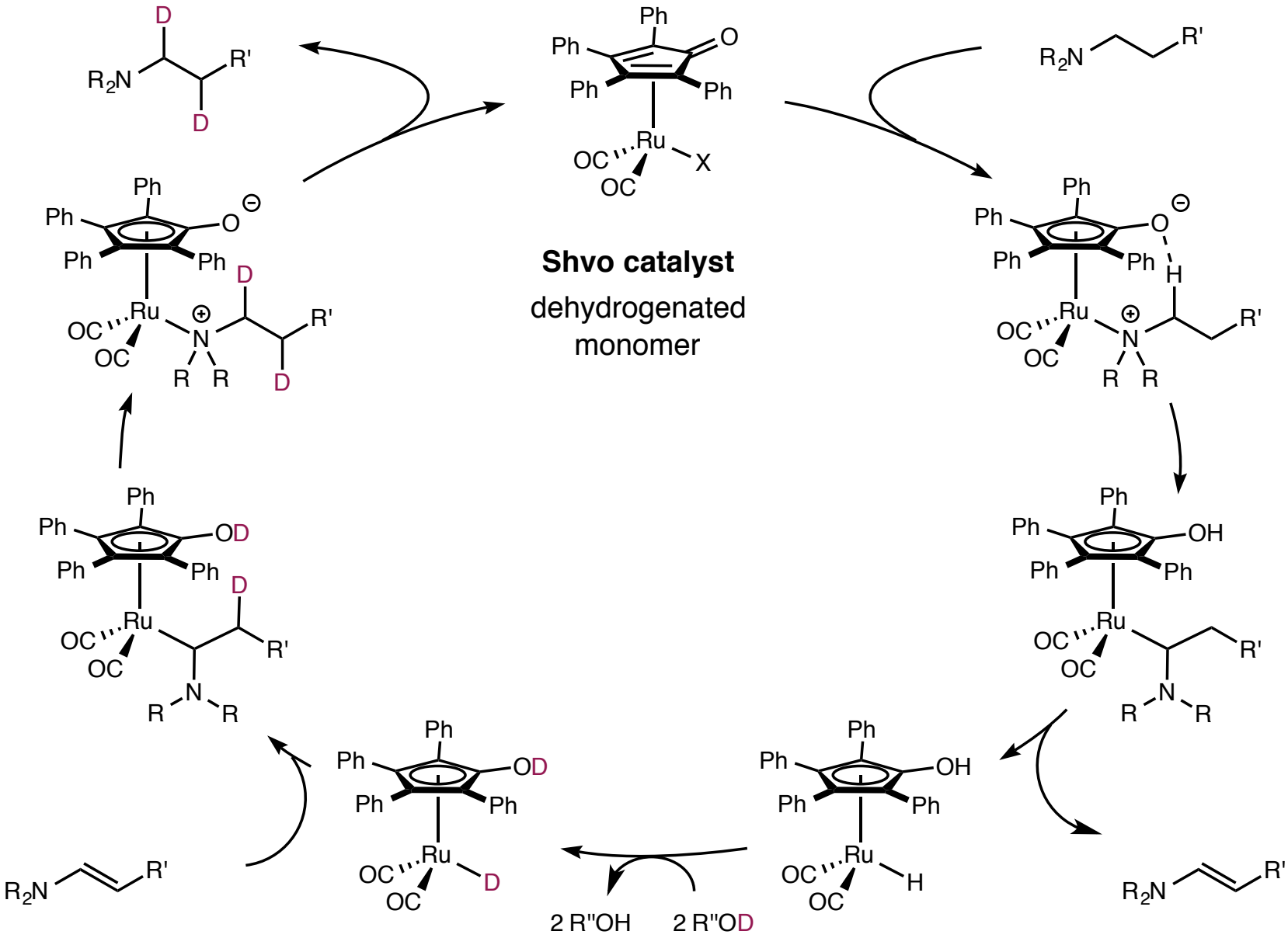






Neubert, L.; Michalik, D.; Bähn, S.; Imm, S.; Neumann, H.; Atzrodt, J.; Derdau, V.; Holla, W.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 12239.

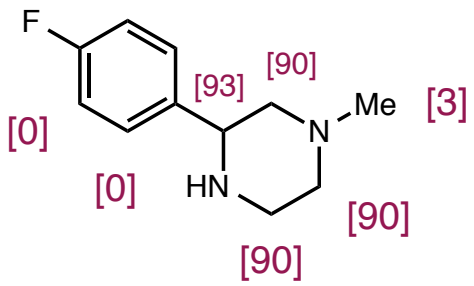
Mechanism of Amine α,β-Deuteration by the Shvo Catalyst



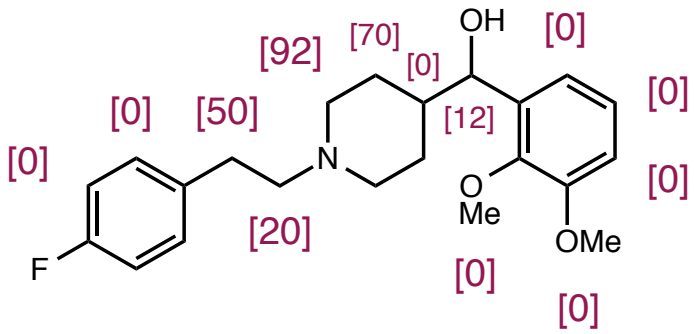
Neubert, L.; Michalik, D.; Bähn, S.; Imm, S.; Neumann, H.; Atzrodt, J.; Derdau, V.; Holla, W.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 12239.

α,β-Deuteration of Complex Amine-Containing Molecules

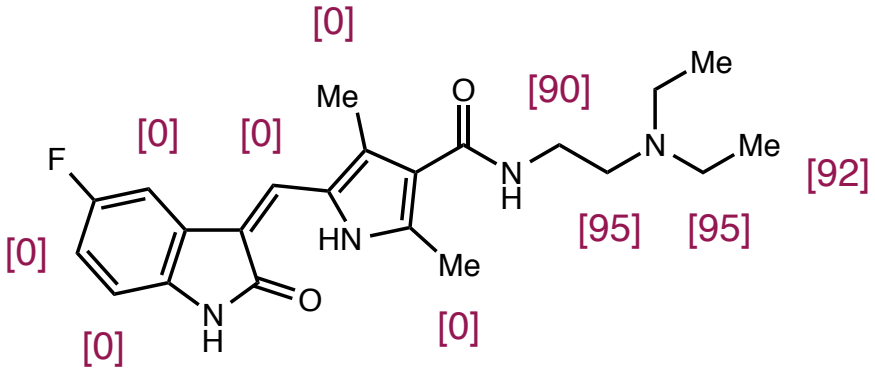
Conditions: 10 mol% Shvo catalyst, *i*-PrOD-d_8 or *t*-BuOD, toluene, microwave heating, 150 °C



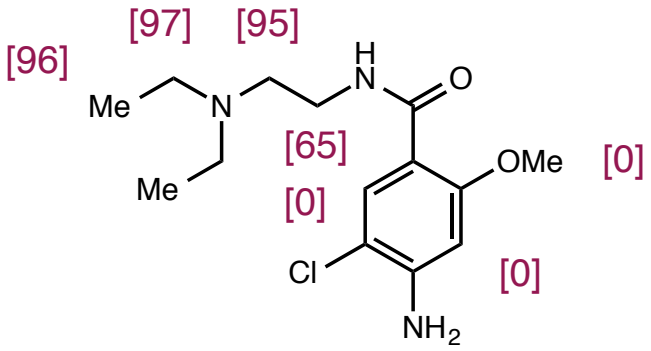
74% yield



71% yield



sunitinib, 67% yield
Pfizer, tyrosine kinase inhibitor

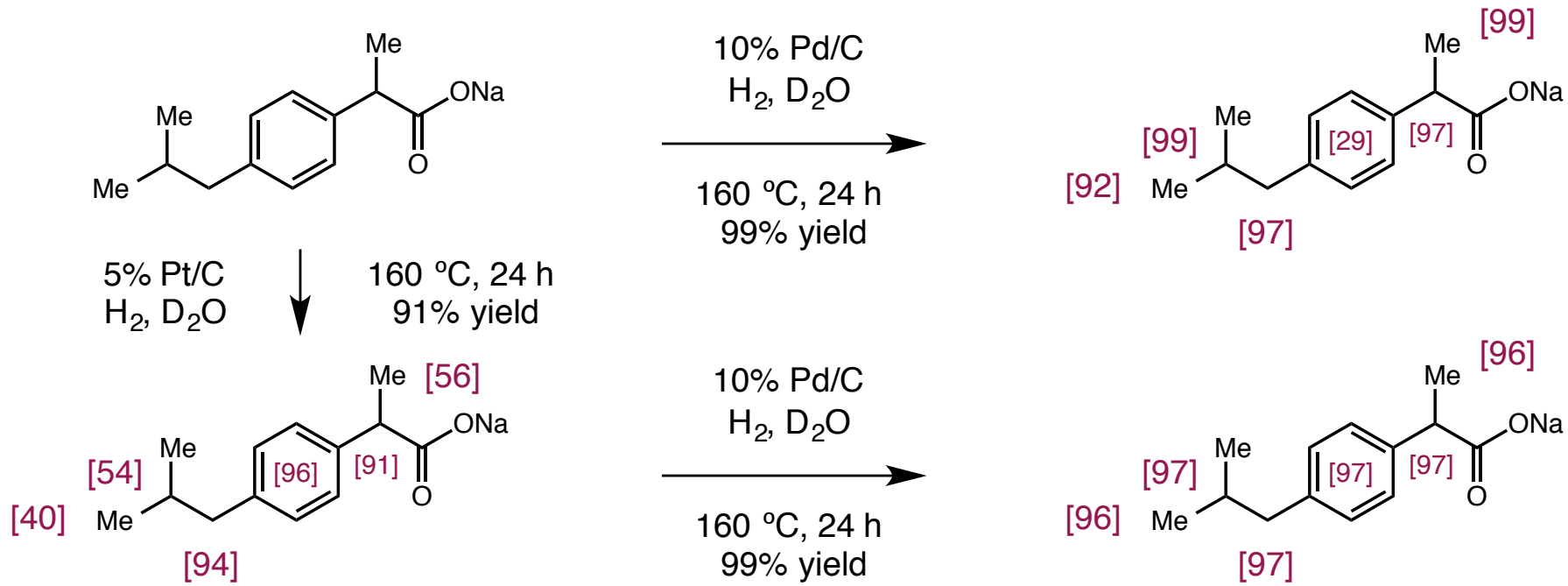


metoclopramide, 83% yield
antiemetic

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

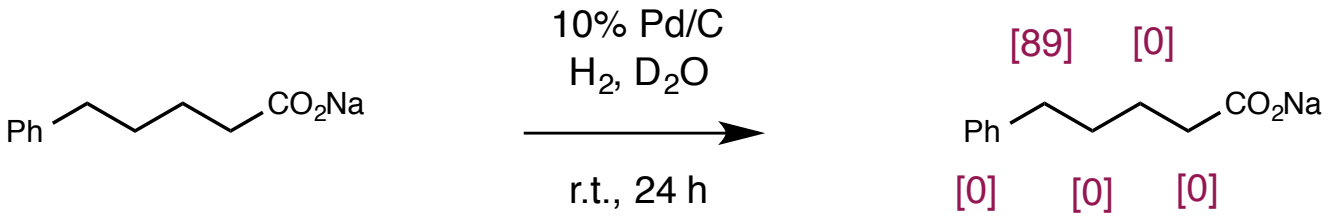
Heterogeneous Metal Catalysis for H/D Exchange

- Palladium-based catalyst systems preferentially deuterate aliphatic C–H bonds; platinum catalyst systems show selectivity for deuteration of aryl C–H bonds



Sajiki, H.; Ito, N.; Esaki, H.; Maesawa, T.; Maegawa, T.; Hirota, K. *Tetrahedron Lett.* **2005**, *46*, 6995.

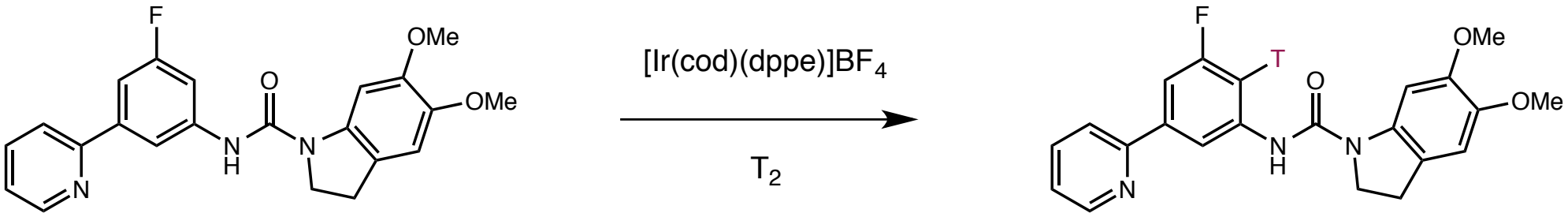
- Selectivity for benzylic H/D exchange can be obtained under less forcing conditions



Sajiki, H.; Aoki, F.; Esaki, H.; Maegawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 1485.

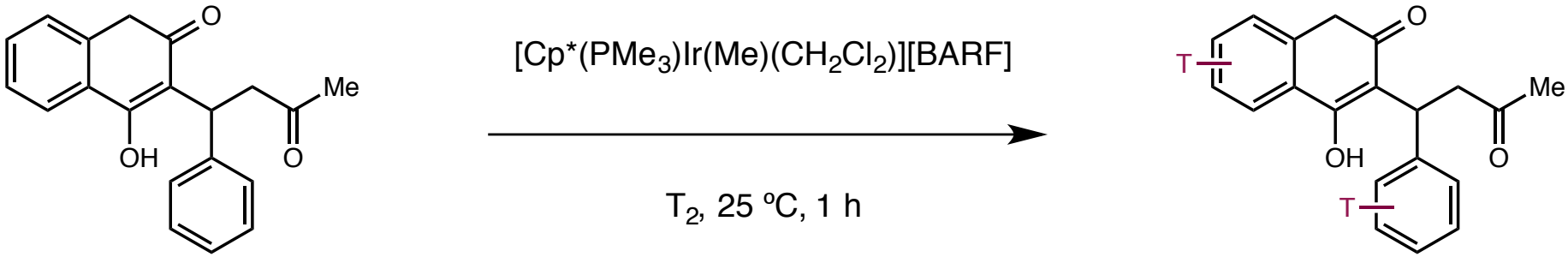
Tritium-Labeling of Organic Molecules

- Methods developed for deuteration are often also applicable to the installation of tritium ($^3_1$H, T)



single regioisomer

Shu, A. Y. L.; Saunders, D.; Levinson, S. H.; Landvatter, S. W.; Mahoney, A.; Senderoff, S. G.; Mack, J. F.; Heys, J. R. *J. Labelled Cpd. Radiopharm.* **1999**, *42*, 797.



warfarin

8.37 mCi [T]warfarin

Skaddan, M. B.; Yung, C. M.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 11.