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Abstract:

Direct hydrogen isotope exchange represents a distinctive strategy for deuterium labelling, where the protium is directly replaced by deuterium. In this graphic review, we summarized the progress in deuteration via transition metal catalyzed hydrogen isotope exchange. The review was organized according to the mechanism of C-H bond activation in the homogeneous catalysis, and the heterogeneous catalysis was also discussed according to the catalyst type. Representative mechanistic processes were depicted, and proven cases for tritiation were also highlighted.

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Transition Metal Catalyzed Deuteration via Hydrogen Isotope Exchange

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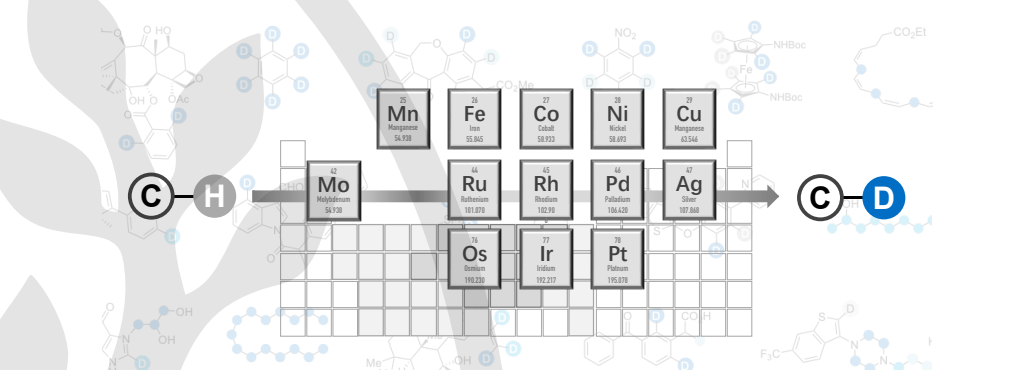
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Abstract Direct hydrogen isotope exchange represents a distinctive strategy for deuterium labelling, where the protium is directly replaced by deuterium. In this graphic review, we summarized the progress in deuteration via transition metal catalyzed hydrogen isotope exchange. The review was organized according to the mechanism of C-H bond activation in the homogeneous catalysis, and the heterogeneous catalysis was also discussed according to the catalyst type. Representative mechanistic processes were depicted, and proven cases for tritiation were also highlighted.

Key words H/D exchange, C-H activation, hydrogen-borrowing, deuterium labelling, heavy water, deuterium gas

Deuterium labelling has become an increasingly important tool in biomedical and materials science, with its successful applications in drug development,¹ biological compound imaging and tracking² and organic light-emitting diodes (OLEDs).³ Their application has been accompanied by the development of synthetic strategies for efficient deuterium incorporation, such as conventional chemical transformation by catalytic hydrogenation on unsaturated bonds, and the defunctionalization of aromatic halides.⁴ Meanwhile, in contrast to the transformation of functional groups, the direct hydrogen isotope exchange (HIE) of C-H bonds had also been extensively developed since the early days of deuterium incorporation, especially under a pH-dependent manner with harsh acid or base environments, which is still employed industrially in the current production of massive deuterium compounds. Therefore, the strategy development of milder and environmentally friendly deuteration remains a necessity, especially with which is compatible with economic deuterium sources, such as heavy water or deuterium gas.

Accompanied with the in-depth understanding of the characteristic of C-H activation with transition metals,⁵ scattered cases of transition metal facilitated HIE have been used as a chemical tool to check the



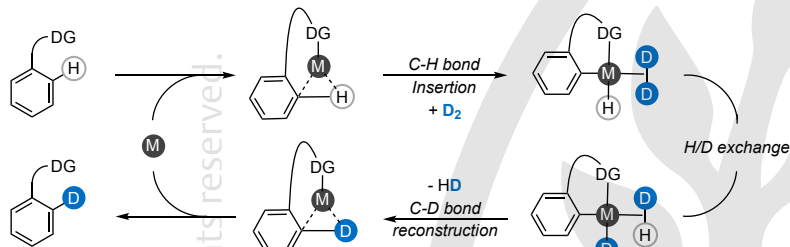
reversibility of the unit reaction. Thus, benefiting from the mechanistic investigation, catalytic HIE was enabled based on reversible manipulation of established catalytic systems.⁶ For instance, Crabtree's catalyst designed for hydrogenation was found to facilitate dehydrogenation under low H₂ pressure.^{7a} This finding was further developed as a major genre of HIE process based on reversible oxidative addition, catalyzed by a family of iridium catalysts such as Kerr's catalysts,⁸⁻⁹ with D₂ gas as main source of deuterium. Similar HIE processes had also been employed with HIEs with Ir, Rh, Ru, and Pt,^{10-12g,13,15} and earth-abundant metals such as Fe, Co and Ni had also shown promising reactivities.^{12f-h,14} On the other hand, the recently burgeoning strategy of concerted metalation-deprotonation (CMD) was also converted in a reversible manner,¹⁶⁻²² which employing D₂O or deuterated acids as deuterium source. Despite the CMD's challenge of subsequent route control between functionalization and C-D bond reconstruction, *ortho*- or *meta*-selective, as well as undirected deuteration had been developed mainly based Pd-catalysis,²⁰⁻²² where Mn,^{21a} Co,^{18d} Ni,^{18f} and Ag¹⁹ had also shown their HIE activity recently. Moreover, HIE could also be accomplished through scheme of hydrogen borrowing strategy by exploiting the remarkable kinetic isotope effect of deuterium.²³⁻²⁴ Its reversible process had also been utilized in HIE on olefins.²⁵ Additionally, some other specialized strategies had also been reported, including Lewis acid enhanced local acidity of proton,²⁶ η^6 complex facilitated arenes activation,²⁷ and σ -metathesis enabled H/D exchange between metal and D₂.²⁸ On the other hand, heterogeneous catalysts also comprise a large family for HIE based on a similar strategy of reversibility control under low D₂ pressure,³¹⁻³⁷ where recent findings suggest that the nanoparticle collides,³⁸⁻³⁹ and corresponding ligand-loaded nanoparticles⁴⁰ may also achieve astonishing regioselectivity as their homogeneous alternatives. Noticeably, in most cases, the tritiation could be easily achieved by replacing the deuterium sources with the corresponding tritium sources. We hope that this graphical review will stimulate further research on the development of innovative HIE strategies in this rapid evolving field.

Biosketches

	Dr. Zhi-Jiang Jiang was born in 1990 in Ningbo, China. He obtained his B. Sc. in pharmaceutical science at Zhejiang University of Technology. He completed his Ph.D. under the supervision of Prof. Wei-Ke Su and Prof. Alexandre. V. Dushkin at Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, where he explored the phenomenon of liquid-assisted grinding in mechanochemistry. He joined the school of biological and chemical engineering of NingboTech University as assistant professor in 2019. Currently, his research interests focused on the development of tools and strategies for selective deuterium-labelling.
	Dr. Jian-Fei Bai graduated from Lanzhou University in 2007 and received his Ph.D. from the University of Chinese Academy of Sciences in 2012 under the supervision of Professor Lixin Wang. In the same year, he joined the group of Professor P. Vogel as a postdoctoral researcher at the Swiss Federal Institute of Technology in Lausanne (EPFL). He continued his postdoctoral work at Kyoto University in 2015, working with Professor Keiji Maruoka. In 2019, Dr. Bai was appointed as an associate professor at the Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, before moving to NingboTech University in 2021. His research focuses on the development and application of site-specific synthesis of deuterium-labeled compounds.
	Dr. Zhanghua Gao obtained his Ph.D. (2005) under the supervision of Prof. Wei-Dong Z. Li from Lanzhou University. He joined the group of Prof. Philip J. Kocienski FRS at University of Leeds (2006) as a postdoctoral associate, continuing the research in natural product synthesis. After a one-year stay in chemical industry, he joined the University of Oxford (2010), working with Prof. Véronique Gouverneur FRS and Prof. Benjamin G. Davis FRS on fluorine-18 radiolabelling of amino acids and protein. He moved to Ningbo University (2015) as an associated professor and became a full professor in 2016 at NingboTech University. His research interests include isotope labelling methodology/technology and its application in drug discovery and functional materials.

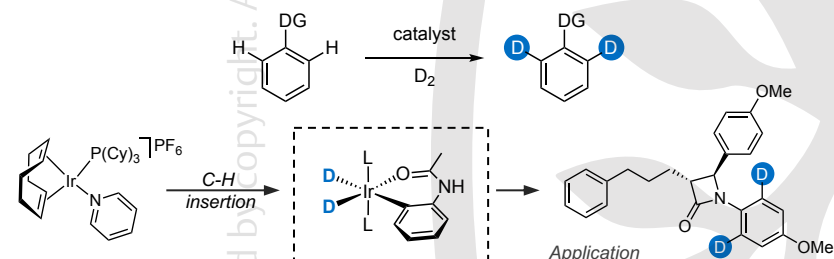
Basic process for OA based H/D exchange

- C-H bond cleavage via oxidative addition (OA)
- Deuterium gas (D_2) as deuterium source
- Labelling site selectivity under ortho-directing or non-directing system



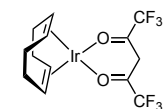
Seminal studies

Directing group led ortho-deuteration



Crabtree's catalyst

(7a) Hesk, *J. Label. Compd. Radiopharm.* **1995**, 36, 497

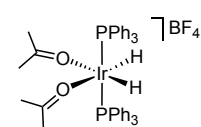


(7b) Lockley, *Tetrahedron Lett.* **2000**, 41, 2705;

(7c) Lockley, *Tetrahedron Lett.* **2003**, 44, 3959;

(7d) Lockley, *J. Label. Compd. Radiopharm.* **2003**, 46, 1191

(7e) Lockley, *J. Label. Compd. Radiopharm.* **2005**, 48, 75



(7f) Heys, *J. Chem. Soc., Chem. Commun.* **1992**, 680;

(7g) Heys, *J. Label. Compd. Radiopharm.* **1993**, 33, 431;

(7h) Heys, *J. Organomet. Chem.* **1996**, 524, 87;

(7i) Heys, *J. Label. Compd. Radiopharm.* **1997**, 39, 291;

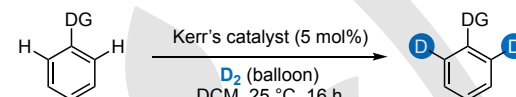
(7j) Heys, *J. Label. Compd. Radiopharm.* **1999**, 42, 797;

(7k) Heys, *Tetrahedron Lett.* **2000**, 41, 9015.

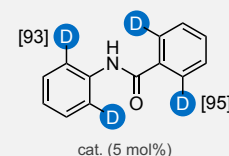
Further reading:

(7l) Herbert, *Tetrahedron* **2001**, 57, 9487; (7m) Herbert, *Tetrahedron* **2003**, 59, 3349; (7n) Herbert, *J. Label. Compd. Radiopharm.* **2004**, 47, 1; (7o) Salter, *J. Label. Compd. Radiopharm.* **2003**, 46, 489; (7p) Fels, *Eur. J. Org. Chem.* **2005**, 1402.

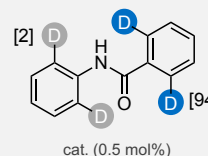
Kerr's catalysts



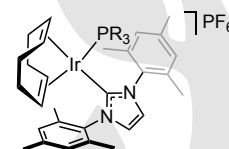
DG = Ac, Bz, CONH₂, CONEt₂, 2-Pyr, *N*-pyrazolyl, NO₂, NHAc, CONHPh, ...



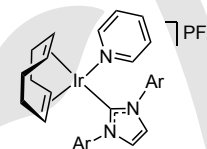
cat. (5 mol%)



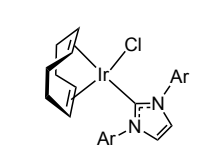
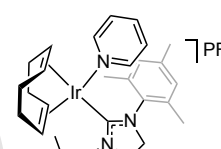
cat. (0.5 mol%)



PR₃ = PPh₃, PBN₃, PMe₂Ph



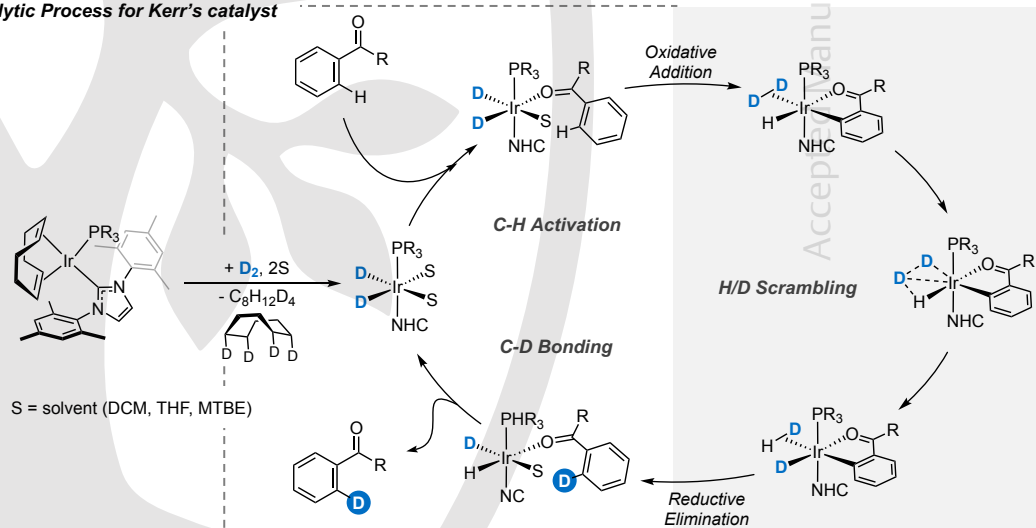
Ar = mesityl, 2,6-*i*-Pr₂Ph



Ar = mesityl, 2,6-*i*-Pr₂Ph

(8a) Kerr, *Chem. Commun.* **2008**, 1115; (8b) Nilsson and Kerr, *J. Label. Compd. Radiopharm.* **2010**, 53, 662; (8c) Kerr, *J. Label. Compd. Radiopharm.* **2013**, 56, 451; (8d) Kerr, *Synlett* **2015**, 27, 111; (8e) Kerr, *Chem. Sci.* **2021**, 12, 6747.

Catalytic Process for Kerr's catalyst



Further reading:

for parameter effect: (8f) Kerr, *Org. Biomol. Chem.* **2014**, 12, 3598; for counterion effect: (8g) Kerr, *Org. Biomol. Chem.* **2014**, 12, 7927; (8h) Kerr, *J. Label. Compd. Radiopharm.* **2016**, 59, 601; For mechanistic consideration: (8i) Kerr, *Adv. Synth. Catal.* **2014**, 356, 3551; (8j) Kerr and Nelson, *Catal. Sci. Technol.* **2020**, 10, 7249; (8k) Kerr, Lindsay and Nelson, *Catal. Sci. Technol.*, **2021**, 11, 5498; for improve radioactivity: (8l) Derau, *Green Chem.* **2022**, 24, 4824.

Figure 1 HIE based on oxidative addition with directing group (1): Early attempts of iridium catalysts,^{7a-p} and Kerr's iridium catalysts.^{8a-k}

[illegible]

Figure 1 displays the chemical structures of various deuterated compounds and catalysts used in the study. The structures are organized into a grid, showing the starting materials, catalysts, and reaction conditions for the deuteration reactions.

Top Left: Deuteration of a triazole-substituted benzene derivative (98) using Ir catalyst, D₂, MeOH, 50 °C, 3 h, yielding 9e.

Top Right: Deuteration of a sulfonamide-substituted benzene derivative (95) using Ir catalyst, D₂ (balloon), DCM, 25 °C, 2 h, yielding 9f.

Middle Left: Deuteration of a benzimidazole derivative (84) using Ir catalyst, D₂, DCM, 25 °C, 1 h, yielding 9d.

Middle Right: Deuteration of a naphthalene sulfonamide derivative (60) using Ir catalyst, D₂, MTBE, 50 °C, 16 h, yielding 9g.

Bottom Left: Deuteration of a morpholine derivative (80) using Ir catalyst, D₂, MTBE, 50 °C, 16 h, yielding 9h.

Bottom Right: Deuteration of a complex heterocycle (94) using Ir catalyst, D₂, MTBE, 50 °C, 16 h, yielding 9i.

Catalyst Structures:

- Top Left:** Ir catalyst with PPh₃ and a chiral ligand (5 mol%).
- Top Right:** Ir catalyst with PPh₃ and a chiral ligand (5 mol%).
- Middle Left:** Ir catalyst with PPh₃ and a chiral ligand (1 mol%).
- Middle Right:** Ir catalyst with PPh₃ and a chiral ligand (5 mol%).
- Bottom Left:** Ir catalyst with PPh₃ and a chiral ligand (5 mol%).
- Bottom Right:** Ir catalyst with PPh₃ and a chiral ligand (5 mol%).

Chemical reaction scheme showing the Ir-catalyzed deuterium incorporation into benzaldehyde and various aromatic aldehydes. The main reaction shows benzaldehyde reacting with an Ir catalyst (1 mol%), D₂, and DCM at 25 °C for 3 h to form deuterated benzaldehyde [93]. An inset shows the proposed Ir hydride intermediate. Below, five other aromatic aldehydes are shown with their corresponding deuterated products and yields: 4-phenoxybenzaldehyde [97], 4-methylbenzaldehyde [78], 4-(trifluoromethyl)benzaldehyde [95], naphthalene-1-carbaldehyde [24], and 2-naphthalene-carbaldehyde [93].

Chemical reaction scheme showing the synthesis of deuterated indole derivatives. The reaction involves an indole-3-carboxamide derivative reacting with D_2 (1 atm, DCM, 1 h, r.t.) in the presence of a catalyst (Ir complex with PPh_3 and PF_6) to yield a deuterated indole derivative. The catalyst is shown as a key intermediate. The reaction is labeled with [92] and [6].

Chemical structures of various Ir(III) complexes and their corresponding photophysical data:

- Top Left:** Ir(III) complex with a ferrocenyl ligand, a phosphine (PPh₃), and a boronate ester (B(C₆F₅)₃). (ref. 9k)
- Top Middle:** Ir(III) complex with a ferrocenyl ligand, a chloride ligand, and a 1,2,4,5-tetraphenyl-1H-1,2,4-triazole ligand. (ref. 9l)
- Top Right:** Ir(III) complex with a ferrocenyl ligand, a chloride ligand, and a 1,2,4,5-tetraphenyl-1H-1,2,4-triazole ligand. (ref. 9m)
- Bottom Left:** Ir(III) complex with a ferrocenyl ligand, a phosphine (PPh₃), and a boronate ester (B(C₆F₅)₃). (ref. 9k)
- Bottom Middle:** Ir(III) complex with a ferrocenyl ligand, a chloride ligand, and a 1,2,4,5-tetraphenyl-1H-1,2,4-triazole ligand. (ref. 9l)
- Bottom Right:** Ir(III) complex with a ferrocenyl ligand, a chloride ligand, and a 1,2,4,5-tetraphenyl-1H-1,2,4-triazole ligand. (ref. 9m)

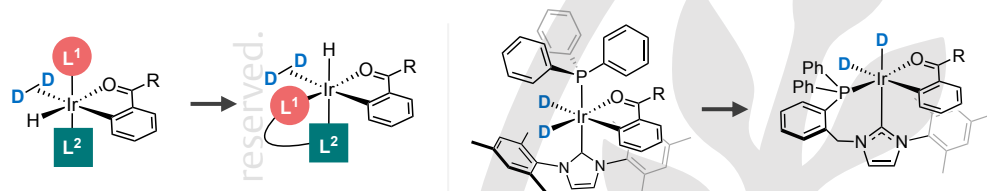
Photophysical data for the Ir(III) complexes:

Complex	λ _{exc} (nm)	λ _{em} (nm)	τ _{em} (ns)	Φ _{em}	Φ _{ISC}	Φ _{FL}	Φ _{ISC}	Φ _{FL}
[87]	350	450	1.5	0.1	0.9	0.1	0.9	0.1
[83]	350	450	1.5	0.1	0.9	0.1	0.9	0.1
[8]	350	450	1.5	0.1	0.9	0.1	0.9	0.1
[93]	350	450	1.5	0.1	0.9	0.1	0.9	0.1
[89]	350	450	1.5	0.1	0.9	0.1	0.9	0.1
[95]	350	450	1.5	0.1	0.9	0.1	0.9	0.1
[70]	350	450	1.5	0.1	0.9	0.1	0.9	0.1

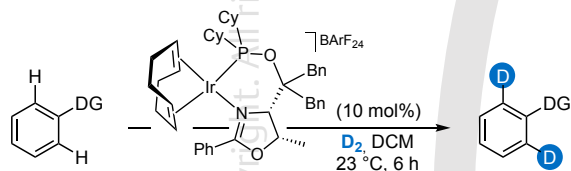
Thieme

Design concept of bidentate ligands for OA based H/D exchange

- Two ligands tethered with linker
- Ligand alignment changes from *trans* to *cis*-conformation
- Releasing steric hindrance on equatorial plane

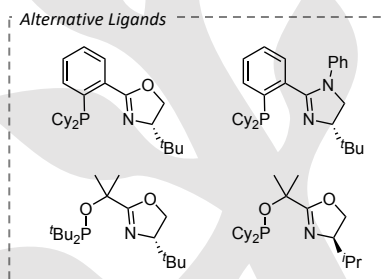


Phosphinite-Oxazoline system

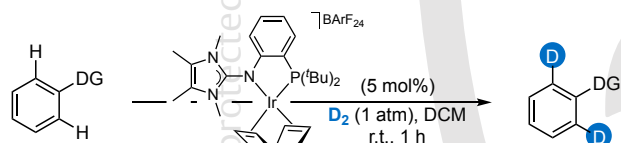


DG = Ac, NHAc, NO₂, CONHPh, SO₂Me, SO₂NHMe, ...

(10a) Muri, *Chem. Eur. J.* **2014**, *20*, 11496.

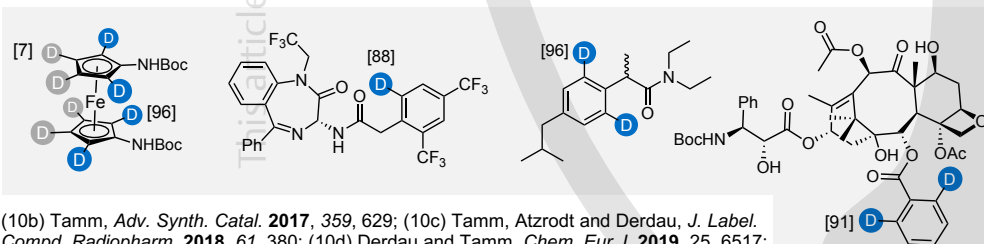
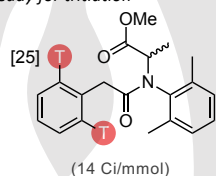


Phosphine-Imidazolin-2-imine system



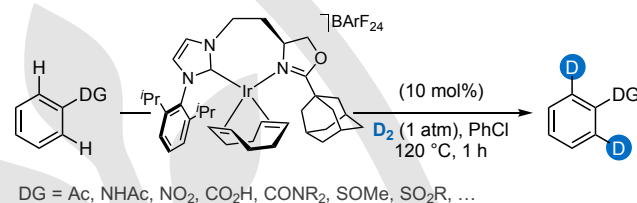
DG = Ac, NHBoc, OMe, CO₂Et, SO₂R₂, P(=O)R₂, CH₂CO₂R, ...

Ready for tritiation



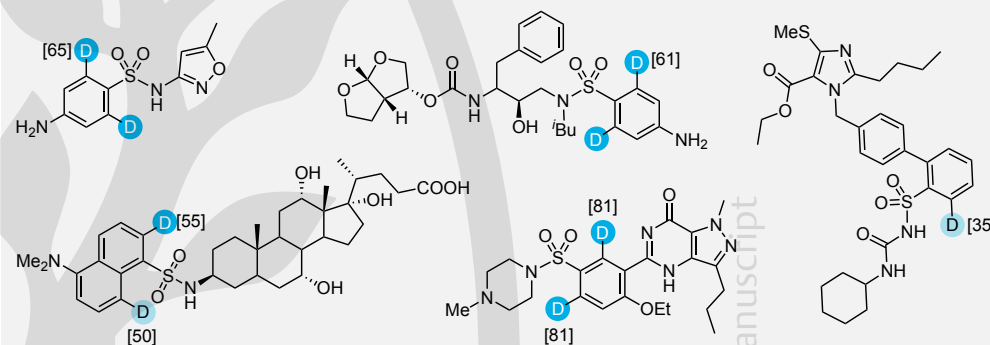
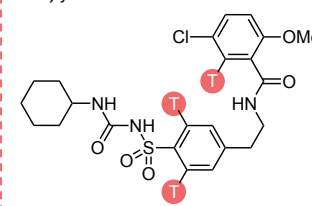
(10b) Tamm, *Adv. Synth. Catal.* **2017**, *359*, 629; (10c) Tamm, Atzrodt and Derdau, *J. Label. Compd. Radiopharm.* **2018**, *61*, 380; (10d) Derdau and Tamm, *Chem. Eur. J.* **2019**, *25*, 6517; (10e) Tamm, *Adv. Synth. Catal.* **2022**, *365*, 367.

NHC-Oxazoline System



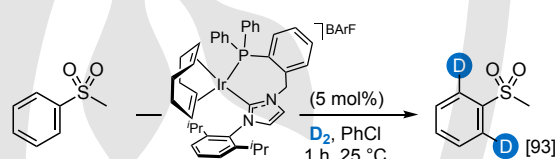
DG = Ac, NHAc, NO₂, CO₂H, CONR₂, SOMe, SO₂R, ...

Ready for tritiation

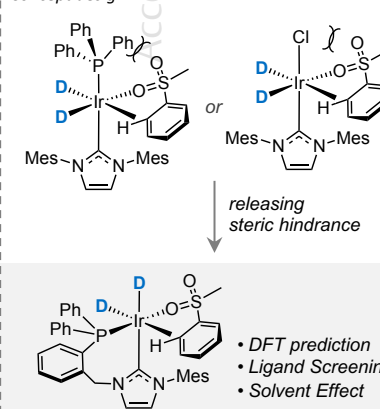


(10f) Atzrodt and Derdau, *Eur. J. Org. Chem.* **2017**, 1418; (10g) Atzrodt and Derdau, *J. Label Compd. Radiopharm.* **2017**, *60*, 343; (10h) Derdau, *ChemistryOpen* **2019**, *8*, 1183.

Phosphine-NHC System



Concept design

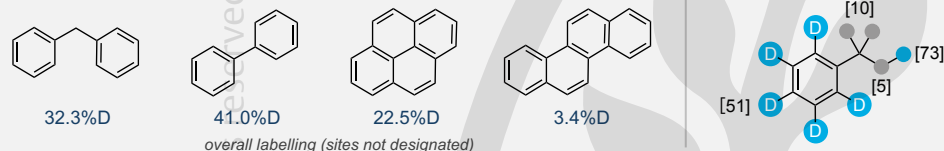
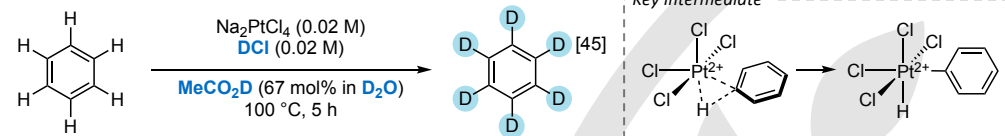


(10i) Kerr, *ACS Catal.* **2020**, *10*, 11120.

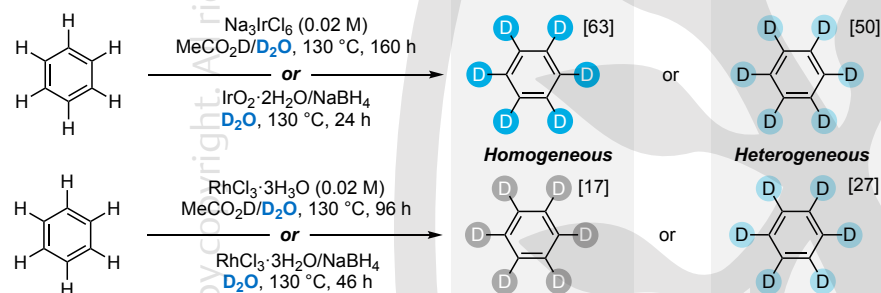
Figure 3 HIE based on oxidative addition with directing group (3): Iridium catalysts with bidentate ligands.^{10a-i}

Seminal Studies

Key Intermediate

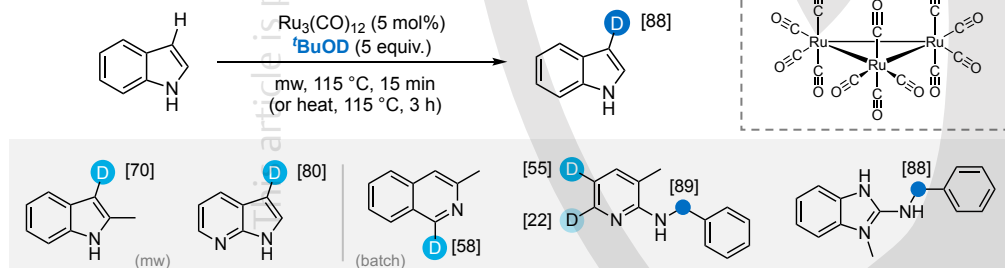


Comparison for heterogeneous and homogeneous catalysis



(11a) Garnett, *Chem. Commun.* **1967**, 23, 1220; (11b) Garnett, *J. Am. Chem. Soc.* **1967**, 89, 4546; (11c) Garnett, *J. Phys. Chem.* **1968**, 72, 1673; (11d) Garnett, *J. Phys. Chem.* **1969**, 73, 1525; (11e) Garnett, *J. Chem. Soc. D* **1970**, 11, 698; (11f) Garnett, *J. Chem. Soc. D* **1971**, 19, 1227; (11g) Garnett, *J. Chem. Soc., Chem. Commun.* **1973**, 19, 749; (11h) Garnett, *J. Chem. Soc., Chem. Commun.* **1975**, 23, 930.

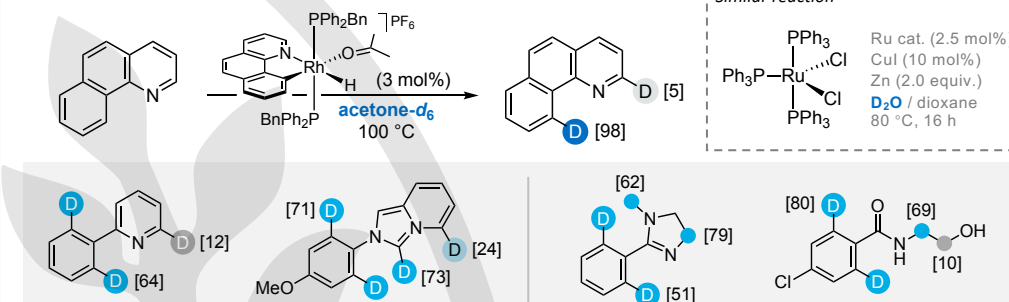
Ligand-free labelling framework



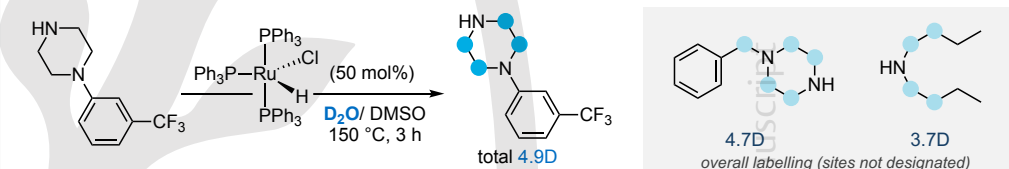
(11i) Schnürch, *J. Org. Chem.* **2012**, 77, 4432.

Phosphine ligands supported homogeneous HIE

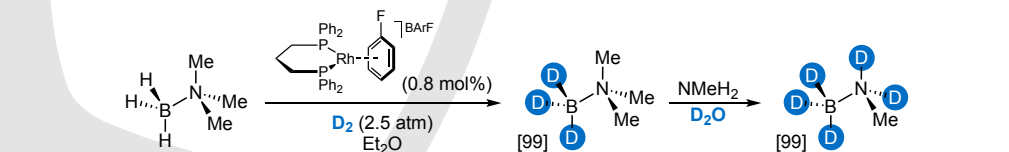
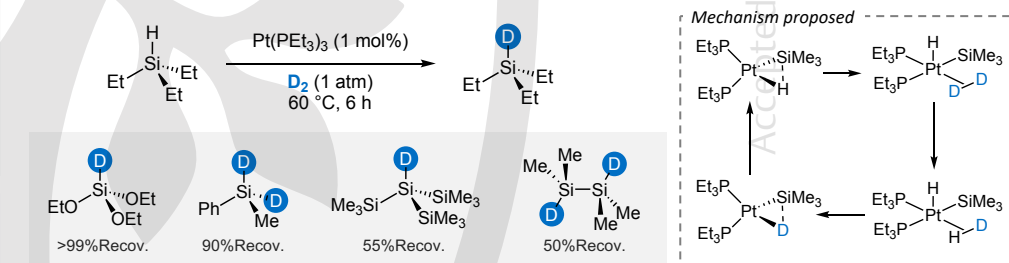
Similar reaction



(11j) Li, *Tetrahedron Lett.* **2008**, 49, 6929; (11k) Plietker, *Chem. Eur. J.* **2019**, 25, 16550.
Further reading for [Os] complex promoted HIE: (11l) Esteruelas, *Organometallics* **2009**, 28, 3700.



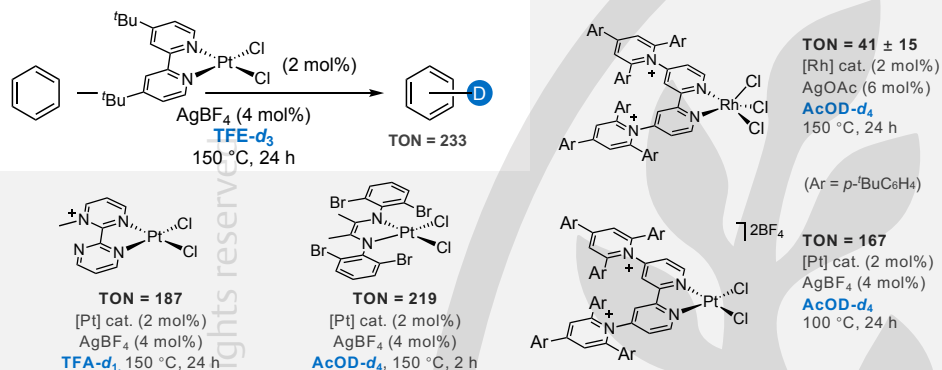
(11m) Lockley, *Tetrahedron Lett.* **2005**, 46, 4291;
Further reading: (11n) Chaudret, *J. Organomet. Chem.* **1984**, 268, c33.



(11o) Bravo-Zhivotovskii and Apeloig, *ACS Omega* **2017**, 2, 372. (11p) Weller, *Chem. Eur. J.* **2018**, 24, 5450.
Further reading: (11q) Peters, *Organometallics* **2016**, 35, 686; (11r) Fryzuk, *Organometallics*, **1991**, 10, 2537; (11s) Grellier and Sabo-Etienne, *Organometallics*, **2005**, 24, 3824. (11t) Sabo-Etienne, *Adv. Synth. Catal.* **2014**, 356, 759.

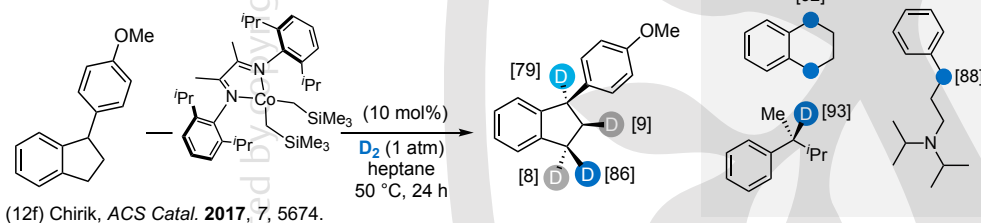
Figure 4 HIE based on oxidative addition without directing group (1): phosphine ligands supported metal catalysts.¹¹

Pt-bipyridine and Pt-diimine systems in benzene HIE

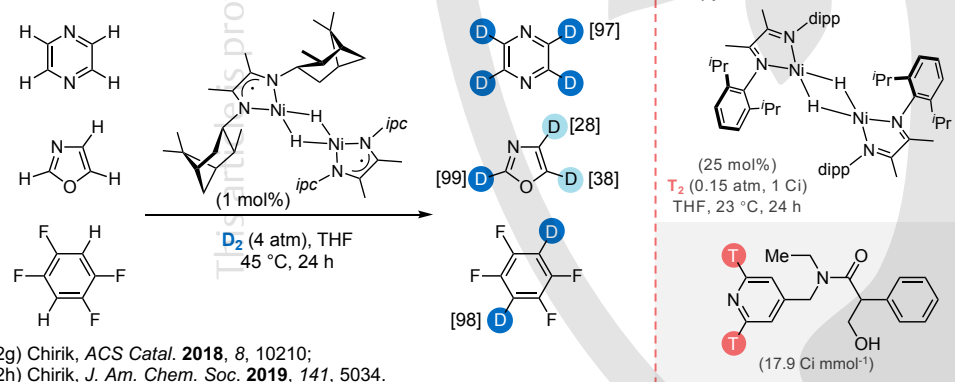


(12a) Sanford, *Organometallics* **2009**, 28, 5316; (12b) Sanford, *Organometallics* **2010**, 29, 257; (12c) Sanford, *Angew. Chem. Int. Ed.* **2010**, 49, 5884; (12d) Sanford, *Top. Catal.* **2012**, 55, 565; (12e) Sanford, *Organometallics* **2012**, 31, 1761.

Co-diimine system



Ni-diimine system



NHC-supported metal catalyzed HIE

Seminal works

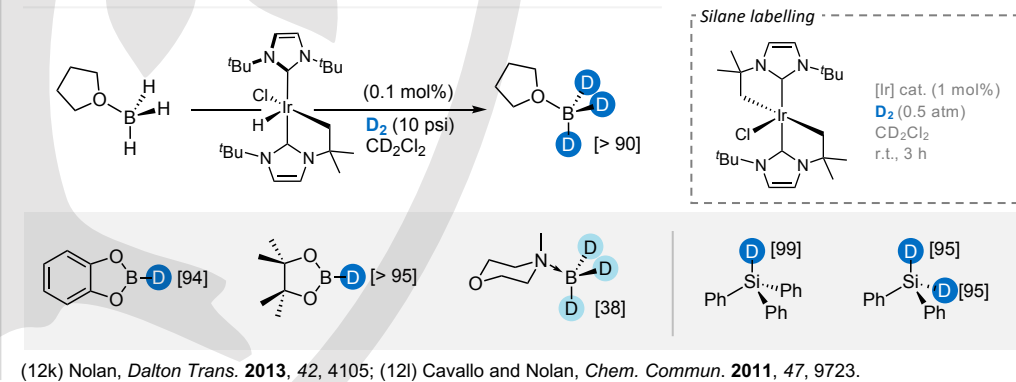
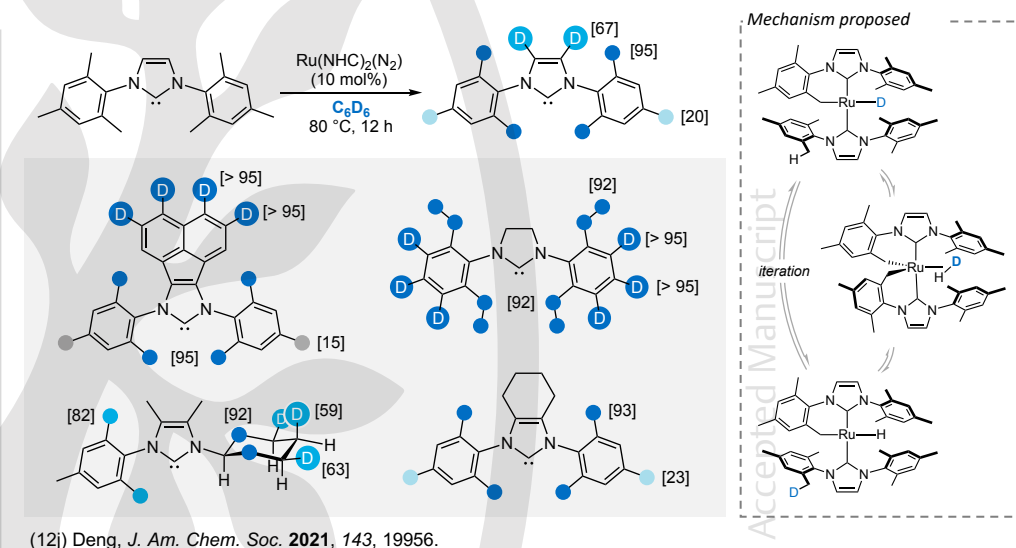
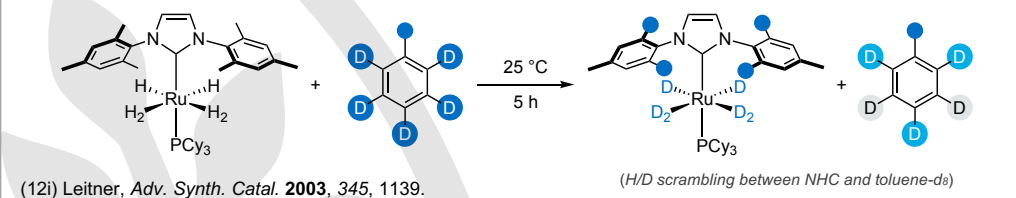
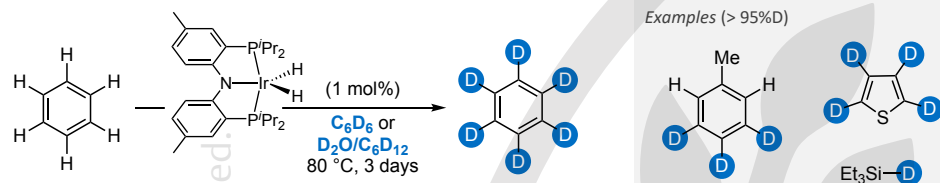
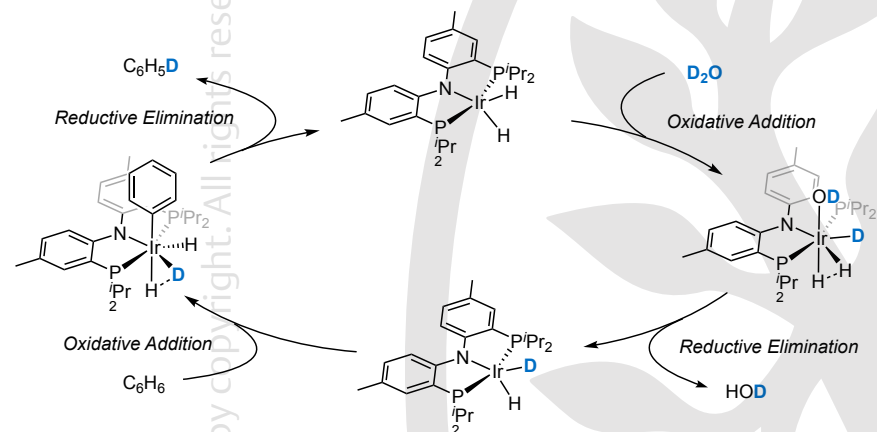


Figure 5 HIE based on oxidative addition without directing group (2): Bipyridine, imine, NHC ligands supported metal catalysts ^{12a-k}

Ir-PNP framework

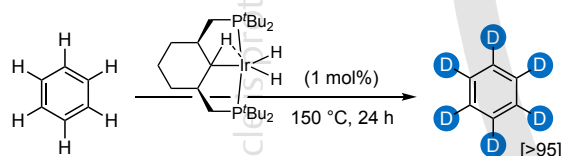


Mechanism proposed (heavy water as deuterium source)

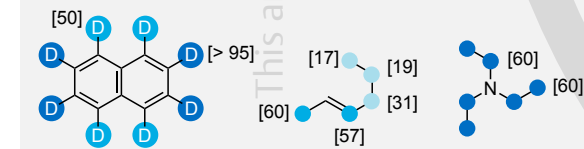
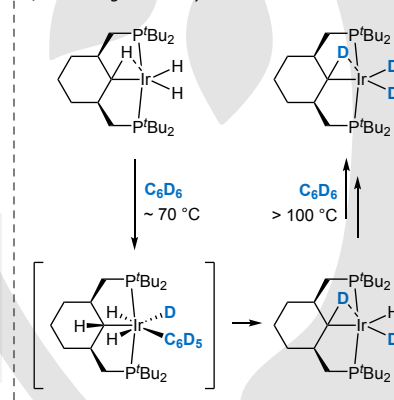


(13a) Grubbs, *Organometallics* **2012**, 31, 39.

Ir-PCP framework

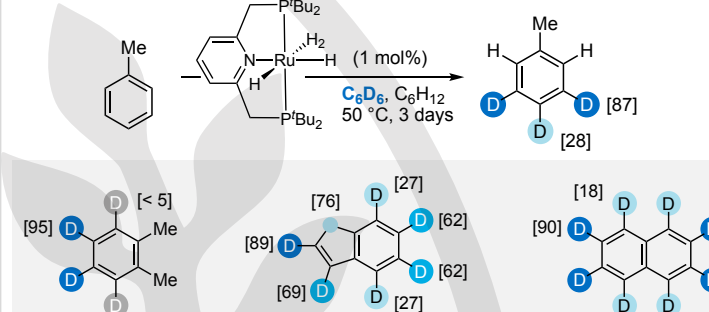


H/D exchange on catalyst



(13b) Wendt, *Organometallics* **2016**, 35, 2600.

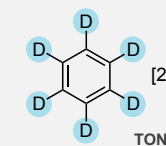
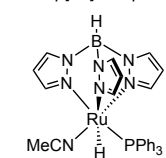
Ru-PNP framework



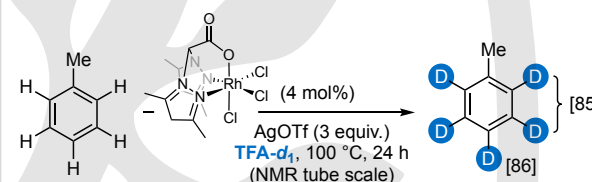
(13c) Leitner, *Angew. Chem. Int. Ed.* **2007**, 46, 2269; (13d) Leitner, *Eur. J. Inorg. Chem.* **2008**, 3493.

Further reading for tridentate Tp[Ru] complex: (13e) Tsang, Jia, Lin and Lau, *Organometallics* **2003**, 22, 641; (13f) Lin and Lau, *Organometallics* **2007**, 26, 1924.

Tridentate Tp[Ru] complex

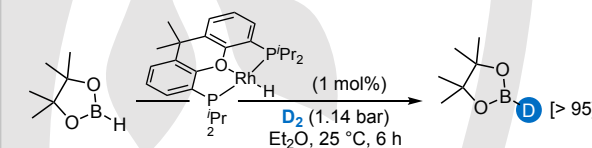
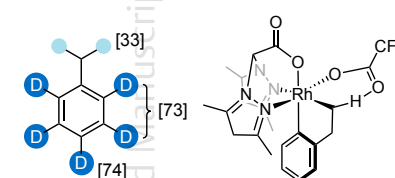


Rh-POP framework

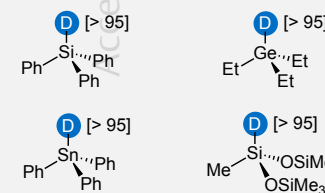


(13g) Jones, *Organometallics* **2012**, 31 (5), 1943.

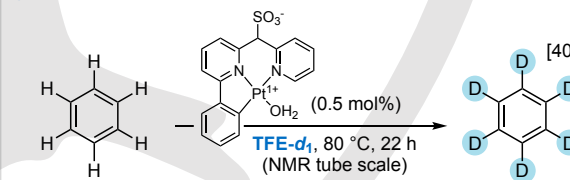
Observed β -deuteration



(13h) Esteruelas, *J. Org. Chem.* **2020**, 85, 15693.



Pt-Pincer framework



(13i) Vedernikov, *Organometallics* **2020**, 39, 4102.

H/D scrambling

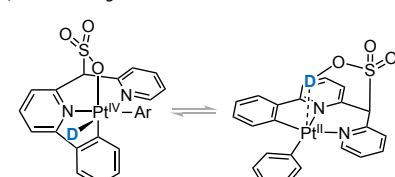
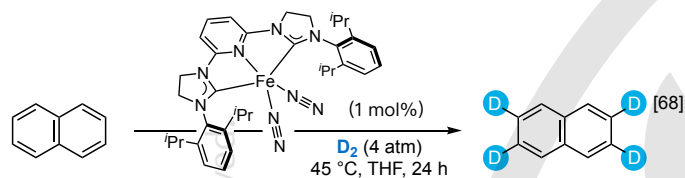
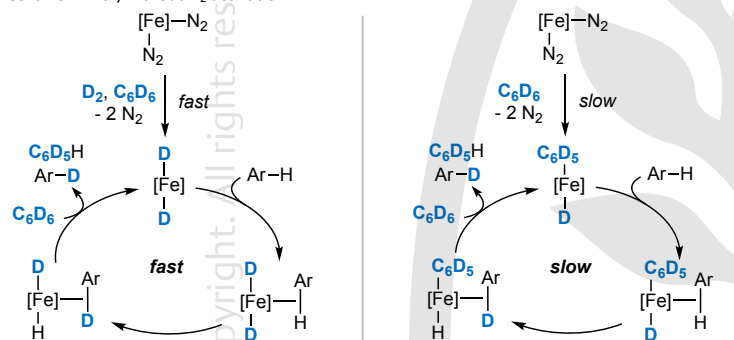


Figure 6 HIE based on oxidative addition without directing group (3): Tridentate ligands supported noble metal catalysts.^{13a-i}

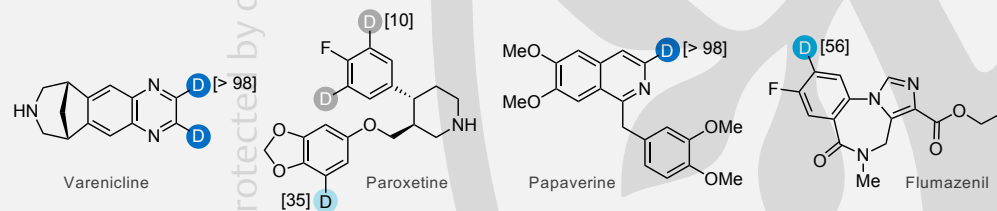
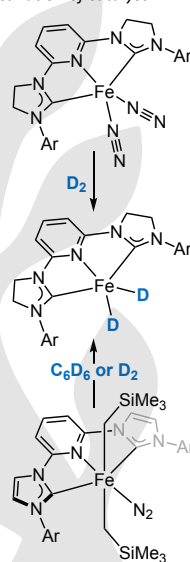
Fe-[CNC] pincer system



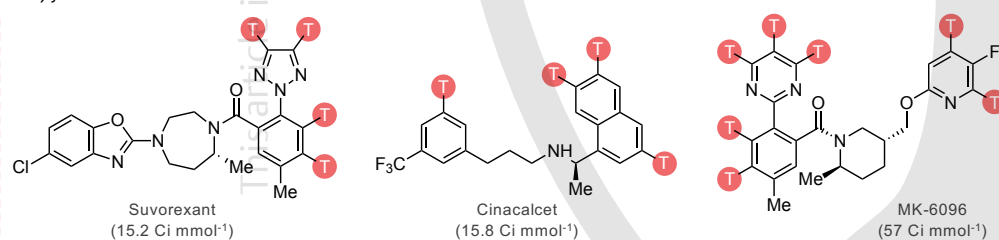
HIE mechanism with/without H₂ activation



Activation of catalyst

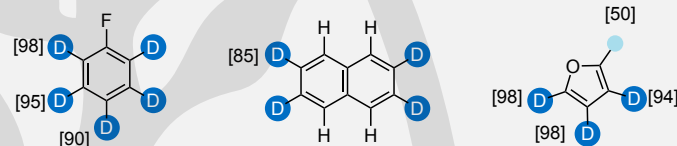
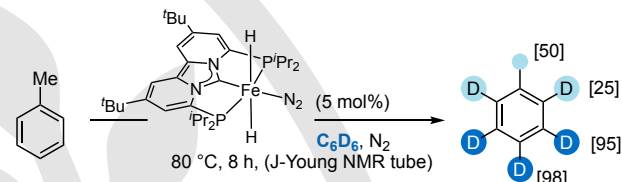


Ready for tritiation



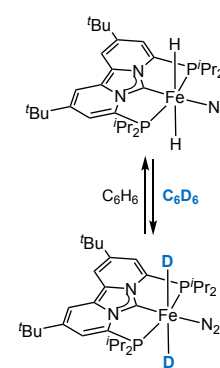
(14a) Chirik, *Nature* **2016**, 529, 195; (14b) Chirik, *ACS Catal.* **2020**, 10, 8640.

Fe-PCP framework

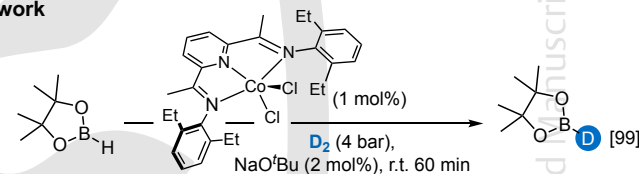


(14c) de Ruiter, *J. Am. Chem. Soc.* **2020**, 142, 17131

HIE on catalyst

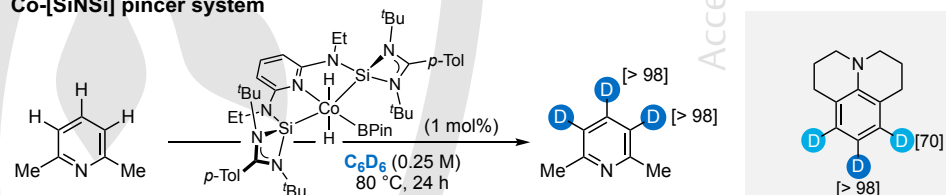


Co-NNN framework

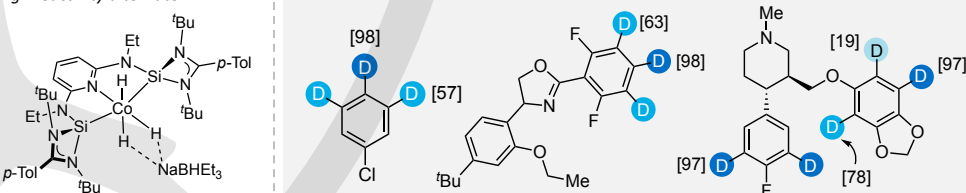


(14d) Docherty and Thomas, *Tetrahedron* **2020**, 76, 131084.

Co-[SiNSi] pincer system



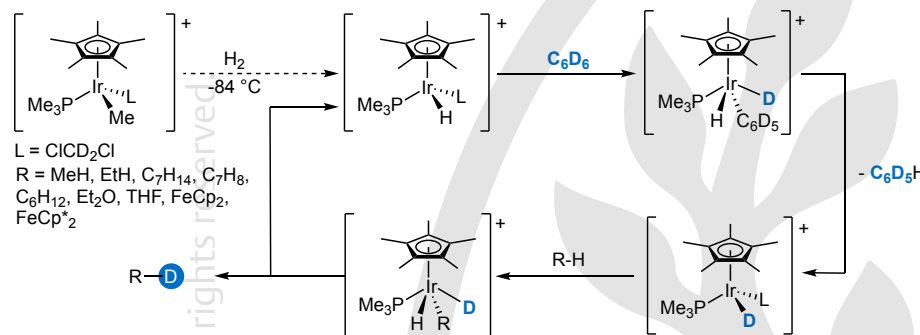
High reactivity alternate



(14e) Chirik, *ACS Catal.* **2022**, 12, 8877.

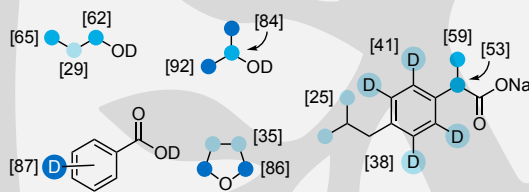
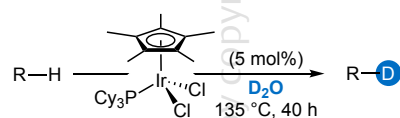
Figure 7 HIE based on oxidative addition without directing group (4): Tridentate ligands supported earth-abundant metal catalysts.^{14a-e}

- Piano-stool complex
- Compatible with D_2O , D_2 , and $acetone-d_6$

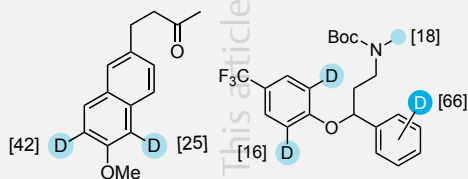
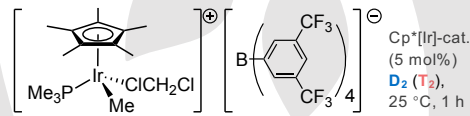
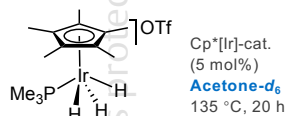


(15a) Andersen and Bergman, *J. Am. Chem. Soc.* **2001**, 123, 5837;
(15b) Skaddan and Bergman, *J. Am. Chem. Soc.* **2004**, 126, 13033.

Cp*Ir(PR₃)X₂



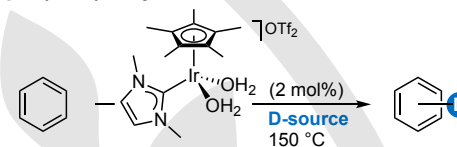
Further development and application in HIE



(15c) Tilley and Bergman, *J. Am. Chem. Soc.* **2002**, 124, 2092; (15d) Skaddan and Bergman, *Org. Lett.* **2004**, 6, 11;
(15e) Skaddan, *J. Label Compd. Radiopharm.* **2006**, 49, 623.

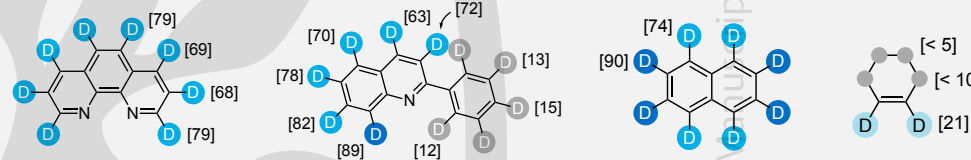
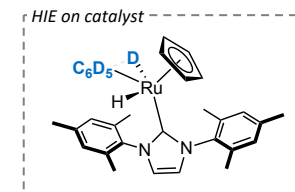
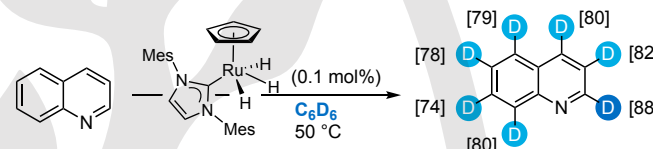
Further reading: (15f) Peris, *J. Am. Chem. Soc.* **2006**, 128, 3974.

Cp*Ir(NHC)X₂ System



(15g) Ison, *Organometallics*, **2010**, 29, 2857; (15h) Ison, *ACS Catal.* **2013**, 3, 2304.

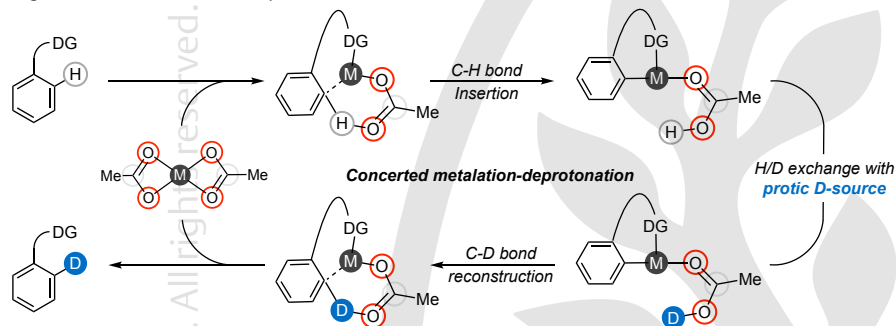
CpRu(NHC) System



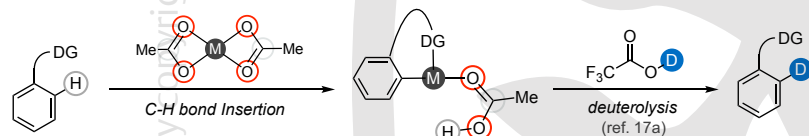
Basic process for CMD based H/D exchange

- C-H bond cleavage under the assistance of additional ligands
- Protic solvent as deuterium source, especially of D₂O
- Various labelling sites selectivity under designed directing group or non-directing system

H/D exchange based on reversible CMD process

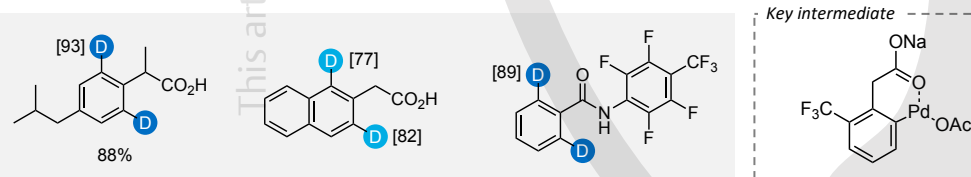
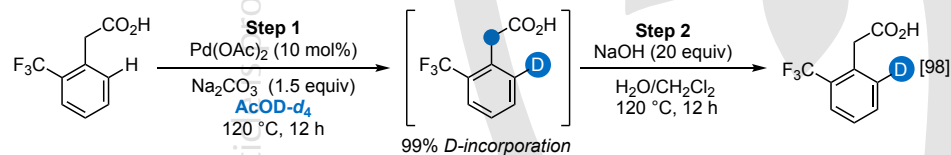


Alternative mechanism proposed for CMD based H/D exchange



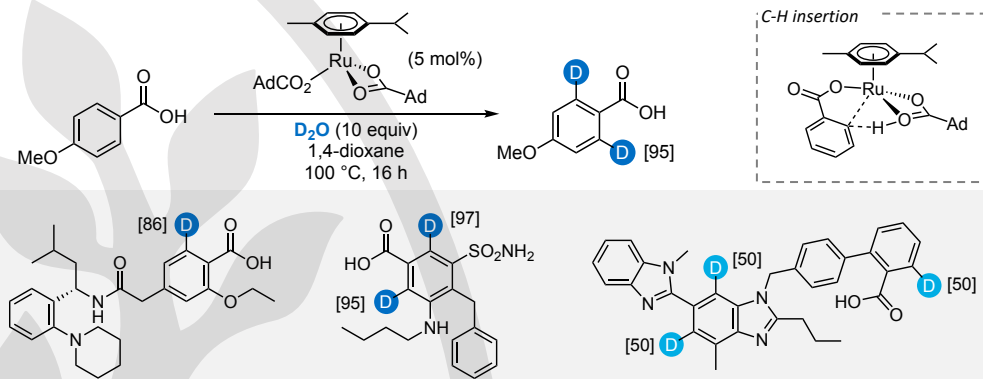
(16a) Gorelsky and Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848; (16b) Ackermann, *Chem. Rev.* **2011**, *111*, 1315; (16c) Yu, *Angew. Chem. Int. Ed.* **2024**, *63*, e202400509.

● Pd-catalyzed ortho-H/D exchange without additional ligands

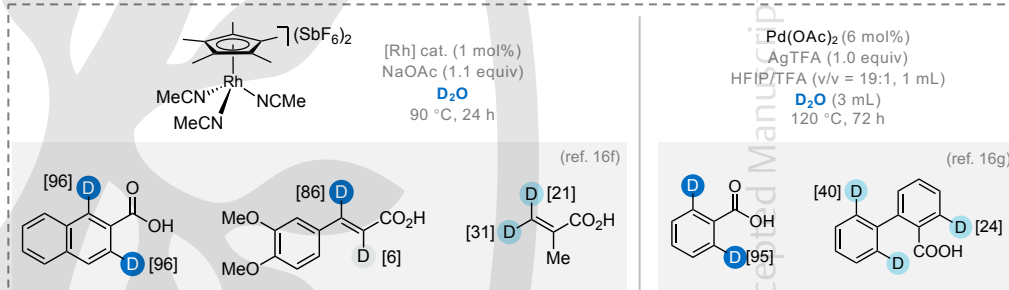


(16d) Yu, *Angew. Chem. Int. Ed.* **2014**, *53*, 734.

- H/D exchange on benzoic acids

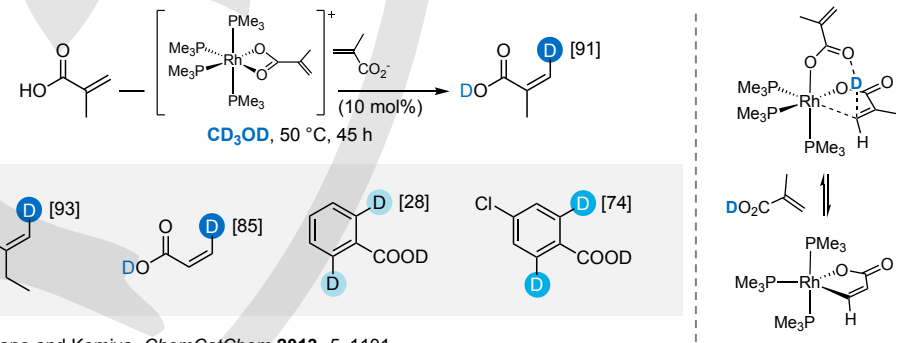


(16e) Ackermann, *ChemCatChem* **2020**, *12*, 100.



(16f) Young, *Org. Lett.* **2019**, *21*, 7044; (16g) Chen and Gao, *Synthesis* **2022**, *54*, 4907.

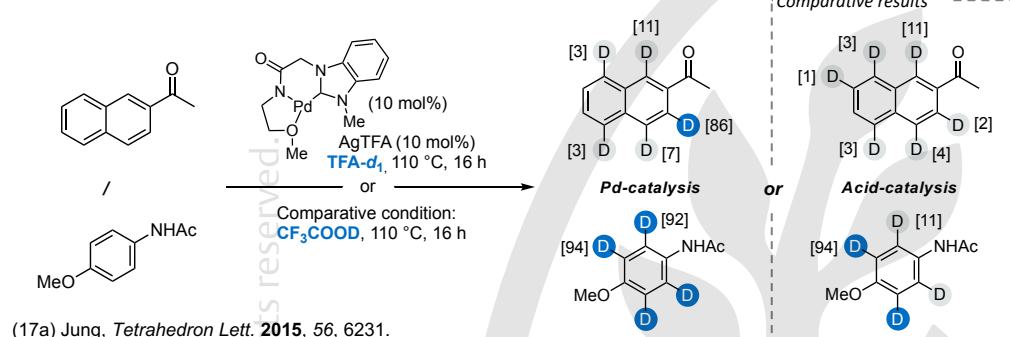
- H/D exchange on acrylic acid



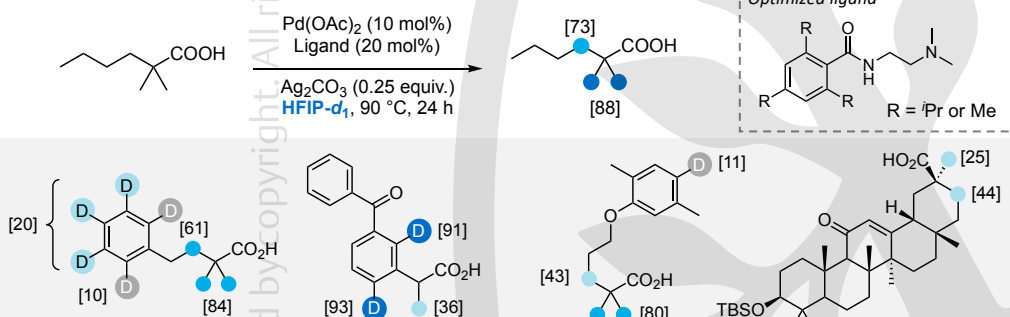
(16h) Hirano and Komiya, *ChemCatChem* **2013**, *5*, 1101.

Figure 9 HIE based on concerted metalation-deprotonation (1): Directing group enabled *ortho*-selective deuteration.^{16a-h}

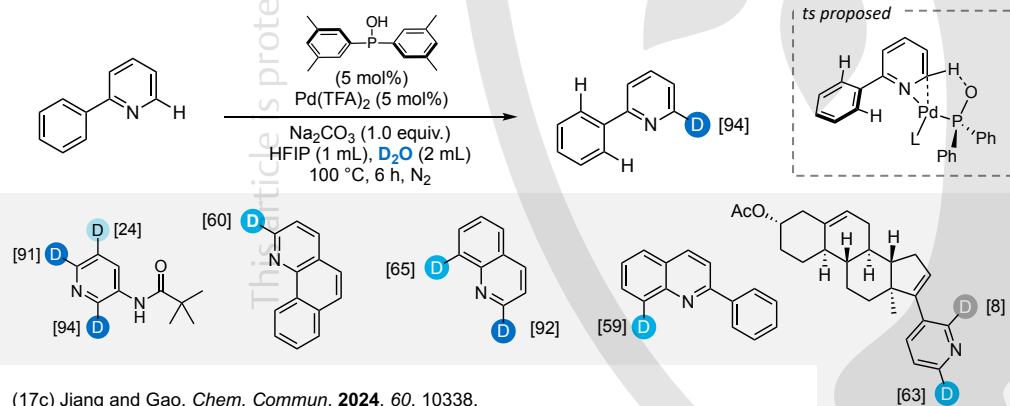
Supporting ligand assisted H/D exchange



(17a) Jung, *Tetrahedron Lett.* **2015**, 56, 6231.

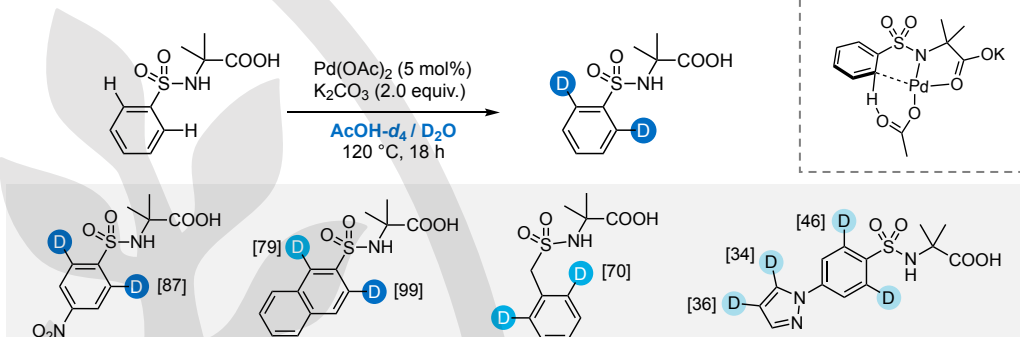


(17b) van Gemmeren, *J. Am. Chem. Soc.* **2021**, 143, 10895.



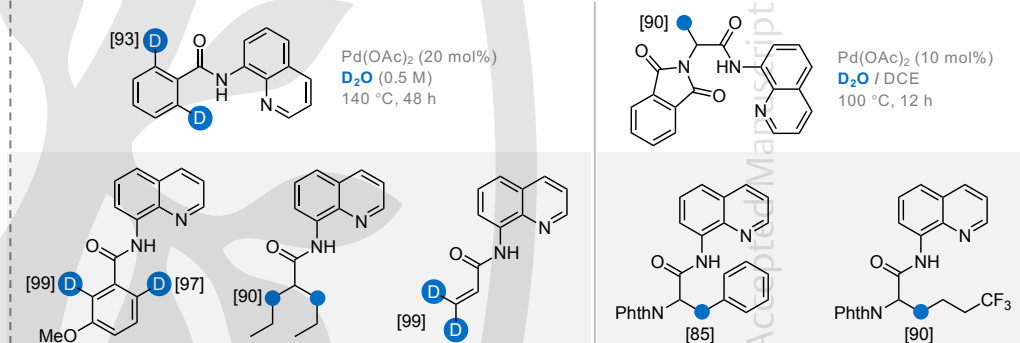
(17c) Jiang and Gao, *Chem. Commun.* **2024**, 60, 10338.

ortho-H/D exchange with additional binding site on substrate



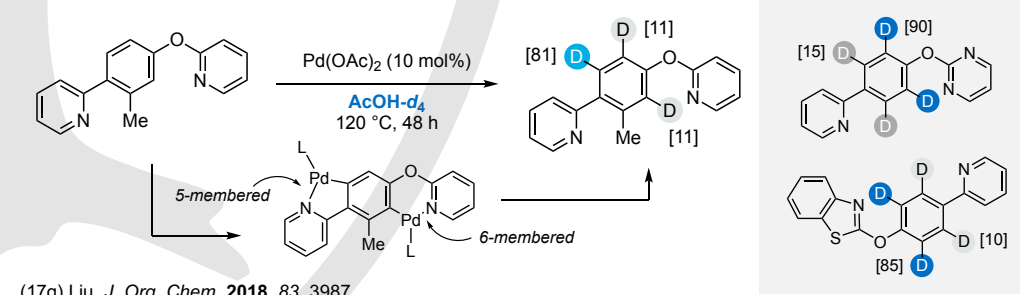
(17d) Yan, *Tetrahedron*, **2018**, 74, 4111.

Similar Strategies



(17e) Zhang and Yu, *J. Org. Chem.* **2018**, 83, 7860; (17f) Zhang, *J. Org. Chem.* **2022**, 87, 16084.

Competing Labelling with dual directing groups

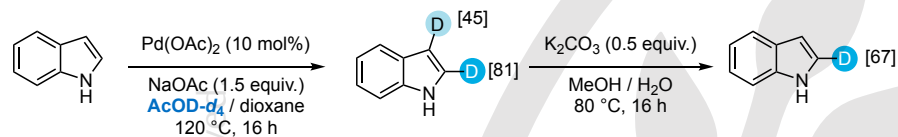


(17g) Liu, *J. Org. Chem.* **2018**, 83, 3987.

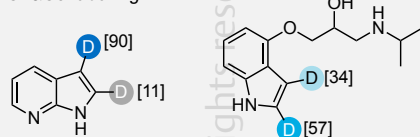
Figure 10 HIE based on concerted metalation-deprotonation (2): Supporting ligands and bidentate substrate enabled regioselective deuteration.^{17a-g}

● Pd-catalyzed selective H/D exchange on indole

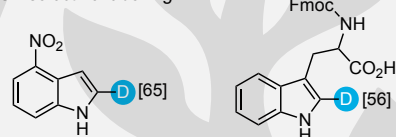
- C2-Deuteration on Indoles



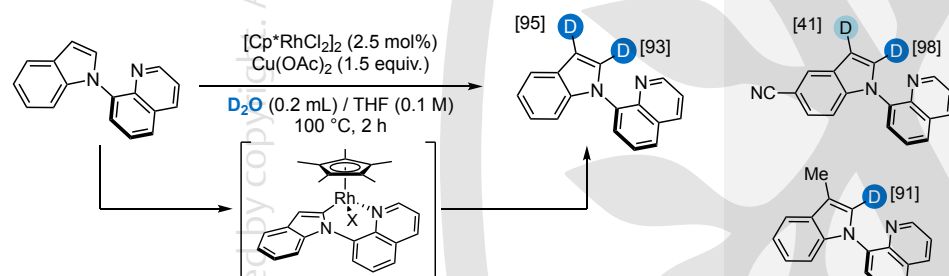
C2&C3-labelling



C2-selective labelling

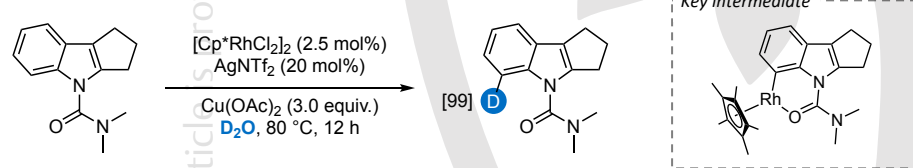


(18a) O'Duill, *J. Org. Chem.* **2023**, 88, 10772.

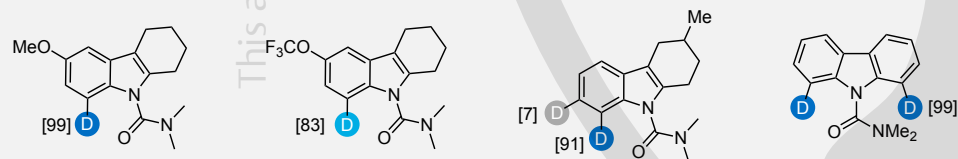
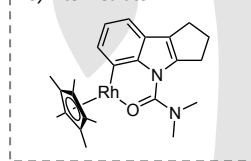


(18b) Wu, Shang and Zhang, *Org. Chem. Front.* **2021**, 8, 3032.

- C7-Deuteration on Indoles

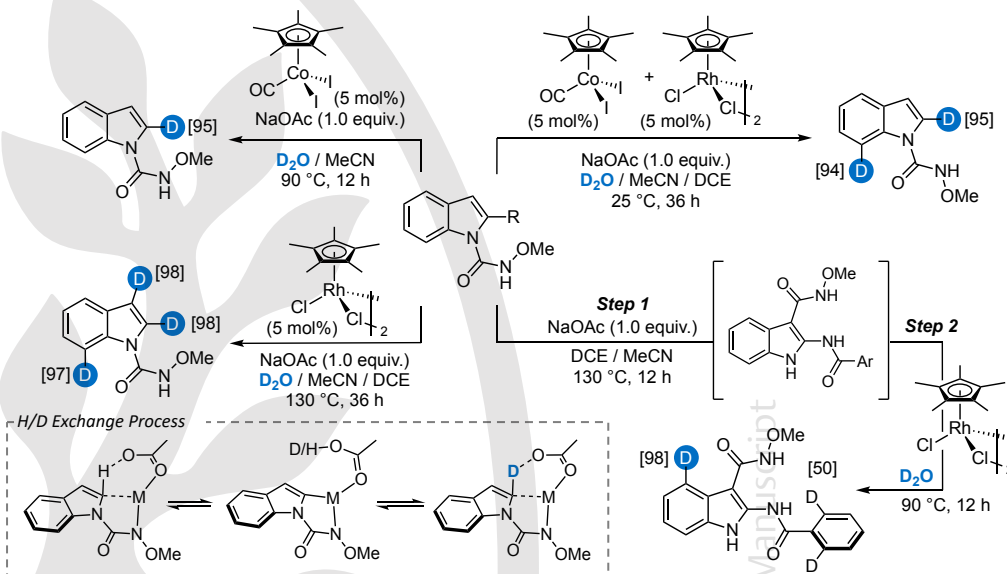


Key intermediate



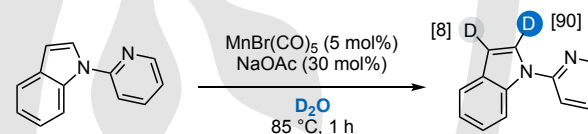
(18c) Kong and Wang, *RSC Adv.* **2021**, 11, 8356.

● Rhodium and Cobalt-catalyzed ortho-H/D exchange on indole



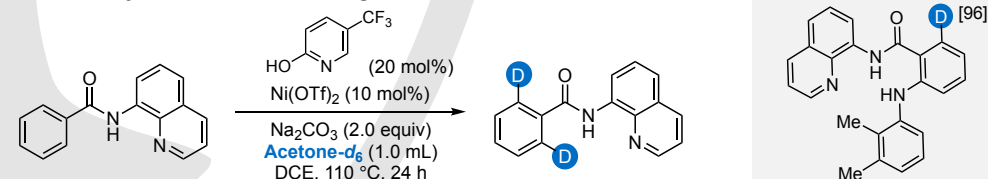
(18d) Zou, *ACS Catal.* **2020**, 10, 7486.

● Manganese-catalyzed ortho-H/D exchange



(18e) McGlacken, *Tetrahedron Green Chem.* **2023**, 2, 100019.

● Nickel-catalyzed ortho-H/D exchange

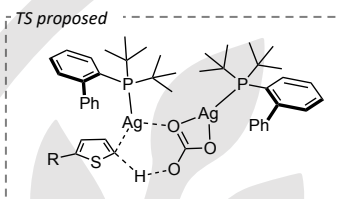
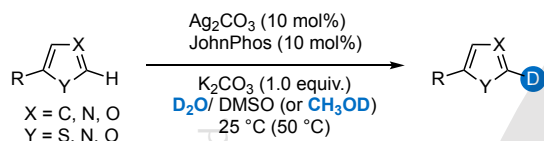


(18f) Jiang and Gao, *Chem. Commun.* **2024**, 60, 384.

Further reading for [Ru] and [Os] promoted HIE based on CMD: (18g) Lokare, Neilsen and Periana, *J. Mol. Catal. A Chem.* **2011**, 339, 17; for [Cu] promoted HIE based on CMD: (18h) Jiang, Chen, and Gao, *Chem. Eur. J.* **2024**, in press, doi: 10.1002/chem.202403121.

Figure 11 HIE based on concerted metalation-deprotonation (3): Regioselective deuteration on indoles, and earth abundant metal catalyzed deuteration. ^{18a-g}

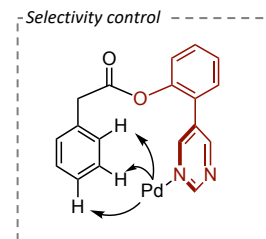
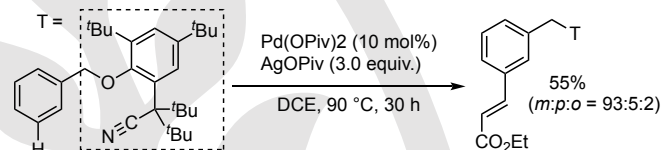
● Silver-catalyzed *ortho*-H/D exchange



● Pd-catalyzed *meta*-selective H/D exchange

meta-selective C-H activation

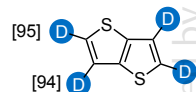
- Template directed *meta*-selectivity
- Distance enabled H/D exchange site discrimination



Further reading for *meta* C-H activation: (20a) Yu, *Nature*, **2012**, 486, 518; (20b) Yu, *Nature* **2014**, 507, 215; (20c) Dey and Maiti, *Angew. Chem. Int. Ed.* **2019**, 58, 10820; (20d) Maiti, *Acc. Chem. Res.* **2022**, 55, 354.

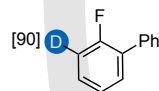
Further Developments

- Deuteration on β -sites

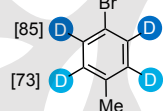


Ag_2CO_3 (0.5 equiv.)
 MePhos (0.5 equiv.)
 D_2O (40 equiv.)
 Toluene, 100°C , in air
 (ref. 19c)

- Deuteration on Aromatic Halides (Ar-X)

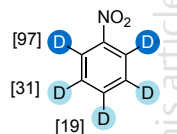


Ag_2CO_3 (0.5 equiv.)
 SPhos (0.5 equiv.)
 K_2CO_3 (1.0 equiv.)
 D_2O (10 equiv.)
 Toluene, 90°C , 12 h
 (ref. 19d)

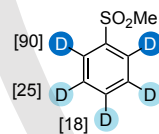


Ag_2CO_3 (20 mol%)
 CyPPH_2 (50 mol%)
 D_2O (20 equiv.)
 Toluene, 120°C , 24 h
 (ref. 19e)

- Multi-position deuteration on electro-deficient aromatic rings

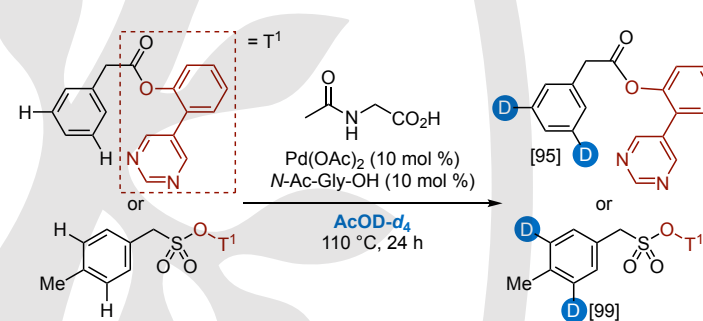


Ag_2CO_3 (20 mol%)
 PPh_3 (60 mol%)
 K_2CO_3 (1.0 equiv.)
 D_2O (1 mL)
 MTBE, 120°C , 24 h
 (ref. 19f)



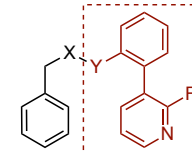
Ag_2CO_3 (10 mol%)
 CyPPH_2 (30 mol%)
 K_2CO_3 (1.0 equiv.)
 D_2O (0.5 mL)
 Toluene, 120°C , 24 h
 (ref. 19g)

(19a) Zhang, Zhang and Huang, *Org. Lett.* **2019**, 21, 6745; (19b) Hartwig, *ACS Catal.* **2021**, 11, 1119; (19c) Zhang, *Org. Biomol. Chem.* **2022**, 20, 1176; (19d) Zhang, *Org. Biomol. Chem.* **2020**, 18, 6627; (19e) Zhang, *Org. Lett.* **2021**, 23, 1554; (19f) Jiang, Gao, and Gao, *J. Org. Chem.* **2023**, 88, 1560; (19g) Jiang, Gao and Gao, *J. Org. Chem.* **2024**, 89, 8468.

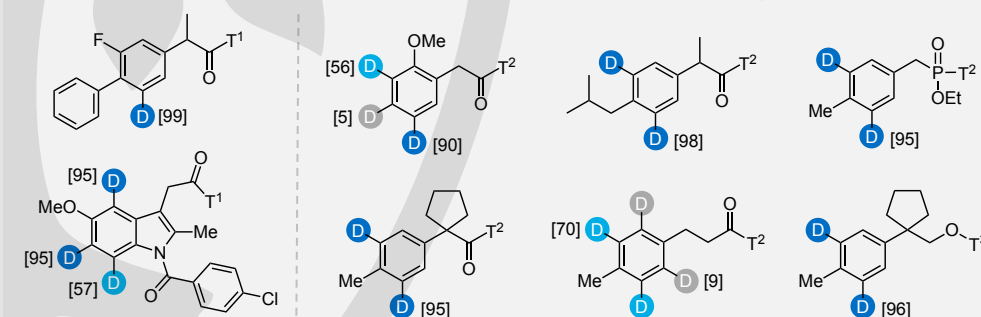


Dai&Yu's condition

Pd(OAc)_2 (10 mol%)
 $\text{AcOD-}d_4$, 80°C , 24 h



$\text{X} = \text{CO, SO}_2, \text{O}$
 $\text{Y} = \text{O (T}^2\text{), CO (T}^3\text{)}$



(20e) Maiti, *Chem. Eur. J.* **2019**, 25, 9433; (20f) Dai and Yu, *Org. Lett.* **2019**, 21, 4887.

Figure 12 HIE based on concerted metalation-deprotonation (4): Silver catalyzed deuteration,^{19a-g} and *meta*-selective deuteration^{20a-e}

- Aldimine as TDG



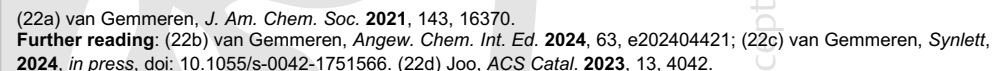
Reaction scheme showing the synthesis of deuterated compounds 83 and 84. The reaction involves acetophenone, a ruthenium catalyst (2.5 mol%), 2-amino-3-(trifluoromethyl)benzidine (20 mol%), AgSbF_6 (20 mol%), $p\text{-Cl-PhCO}_2\text{H}$ (50 mol%), D_2O (20 eq.), and DCE at 120°C for 16 h. The product is a deuterated benzimidazole derivative, shown in two isotopologues: 83 (with D at positions 7, 8, 9, and 10) and 84 (with D at positions 7, 8, 9, and 10, and an additional D at position 11).

(21d) Neumann and Beller, *Chem. Eur. J.* **2021**, 27, 9768.

Condition A
Pd(OAc)₂ (10 mol), LigComb.A
AgF (30 mol%),
HFIP/D₂O = 3:7 (2 mL)
80 °C, 18 h

Condition B
Pd(OAc)₂ (10 mol), LigComb.B
HFIP/D₂O = 3:7 (2 mL)
120 °C, 48 h

ts structure

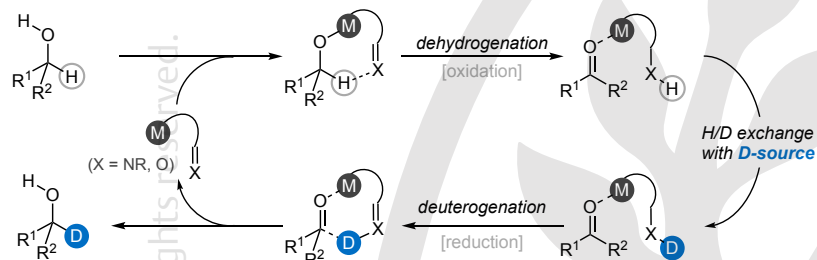
[illegible]

(22e) Lahiri, Pieters, Werz and Maiti, *Angew. Chem. Int. Ed.* **2024**, e202410162.

Figure 13 HIE based on concerted metalation-deprotonation (5): Application of transient-directing strategy,^{21a-d} and non-directing strategy in deuteration.^{22a-e}

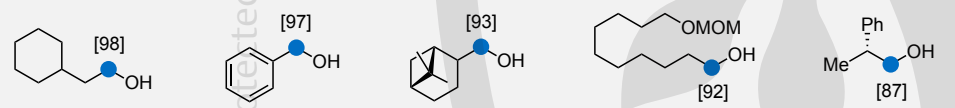
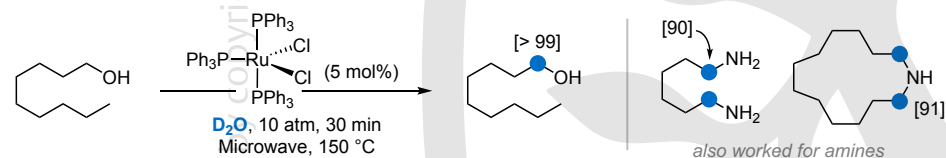
Basic process for hydrogen-borrowing based H/D exchange

- Continuous oxidation and reduction promoted H/D exchange
- Ligand or metal-center act as hydrogen transferring center
- Available for H/D exchange of alcohols and amines

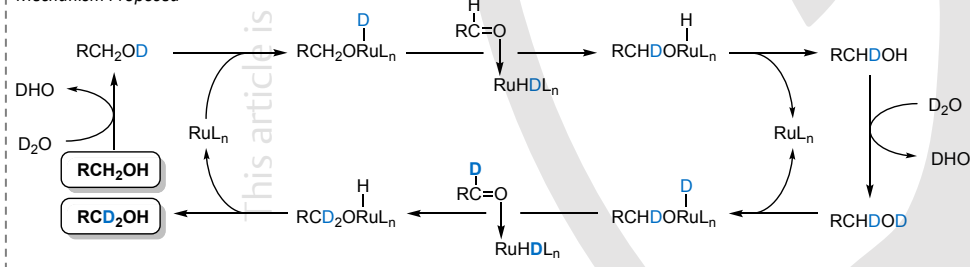


Further reading for hydrogen-borrowing strategy: (23a) Morrill, *ACS Cent. Sci.* **2021**, 7, 570; (23b) Corma and Sabater, *Chem. Rev.* **2018**, 118, 1410; for review of labelling on heteroatom adjacent sites: (23c) Roche, *Synthesis* **2019**, 51, 131.

Seminal studies



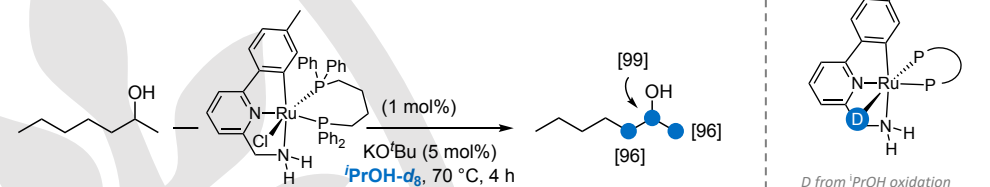
Mechanism Proposed



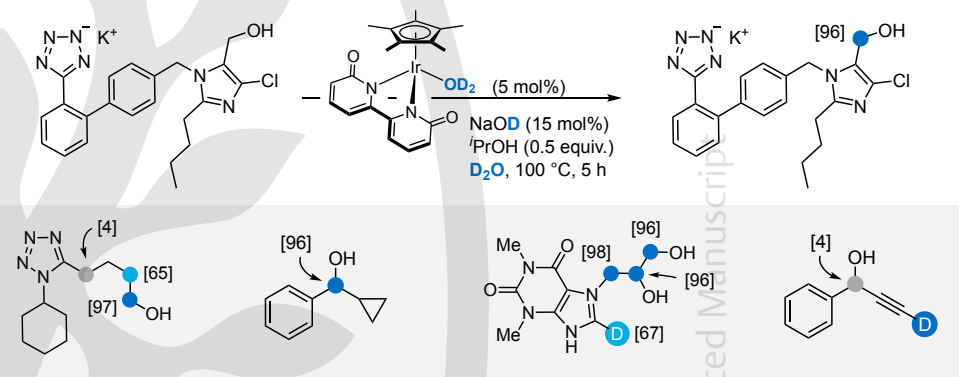
(23d) Matsubara, *Chem. Lett.* **2005**, 34, 192.

H/D exchange on alcohols

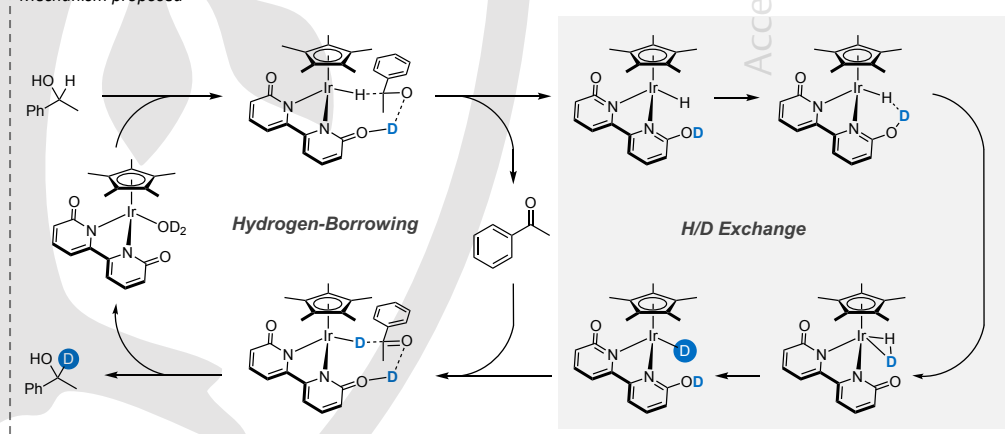
H/D exchange without ligand participation



(23e) Baratta, *Dalton Trans.* **2011**, 40, 8986



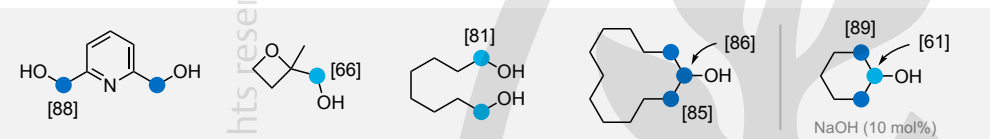
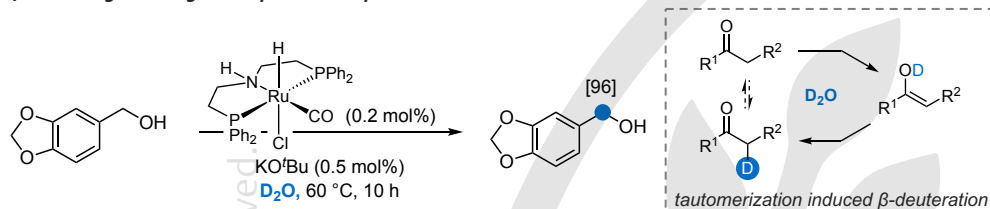
Mechanism proposed



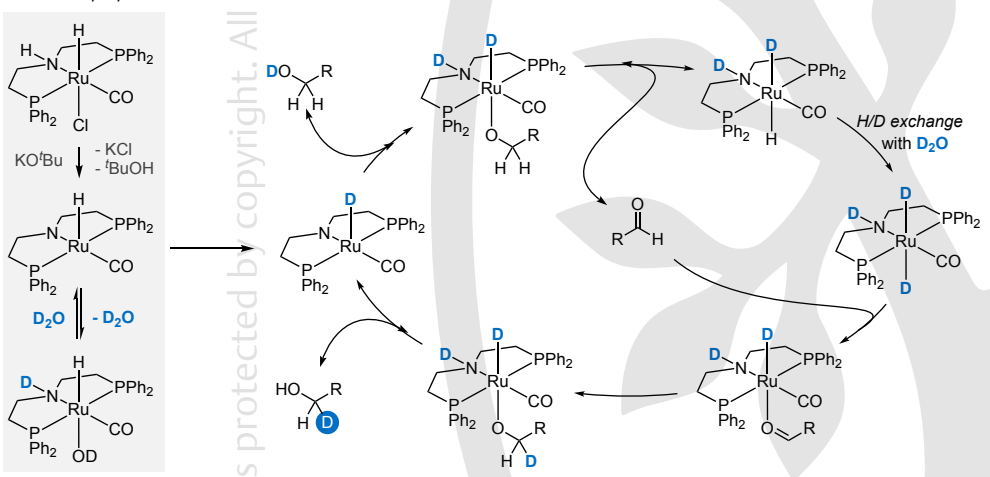
(23f) Naka, *Chem. Sci.* **2022**, 13, 8744.

Figure 14 HIE based on hydrogen-borrowing (1): Principles, seminal work, and α -deuteration on alcohols via metal hydride intermediate.^{23a-f}

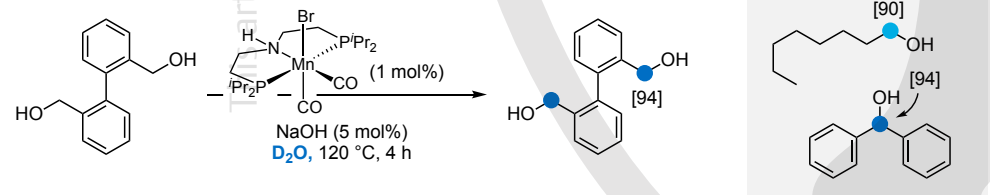
- H/D exchange with ligand as proton acceptor



Mechanism proposed

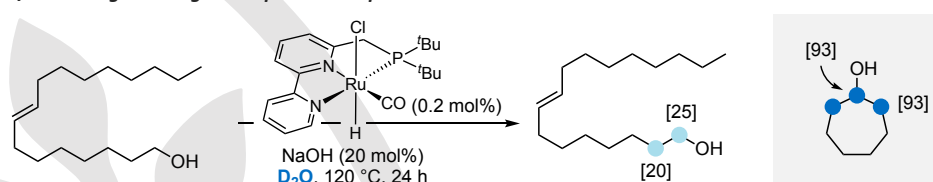


(23g) Gunanathan, *Org. Lett.* **2015**, 17, 4794; (23h) Dumeignil and Gauvin, *Catal. Commun.* **2016**, 84, 67.

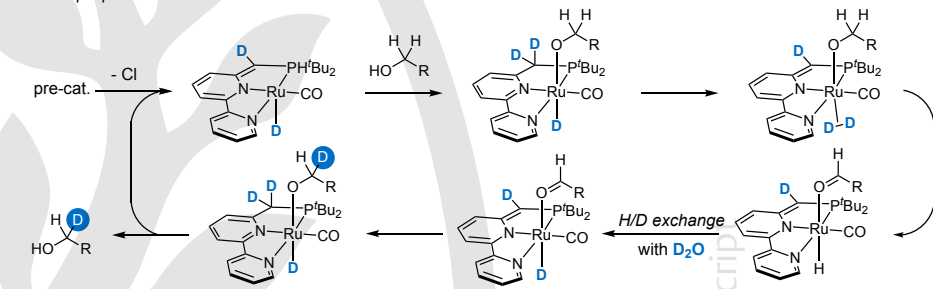


(23i) Prakash, *Green Chem.* **2018**, 20, 2706.

- H/D exchange with ligand as proton acceptor

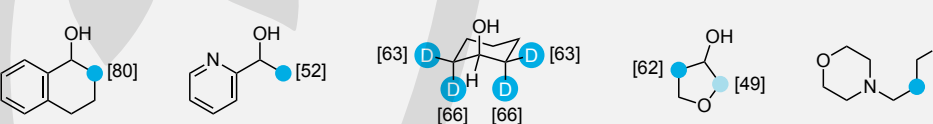
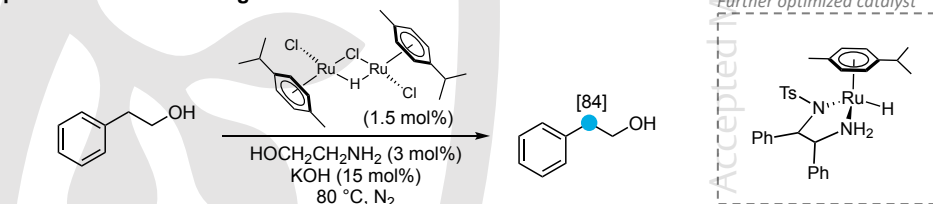


Mechanism proposed

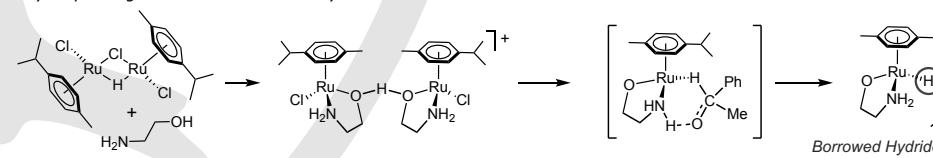


(23j) Milstein, *ACS Catal.* **2013**, 3, 448.

β-selective H/D exchange on alcohols



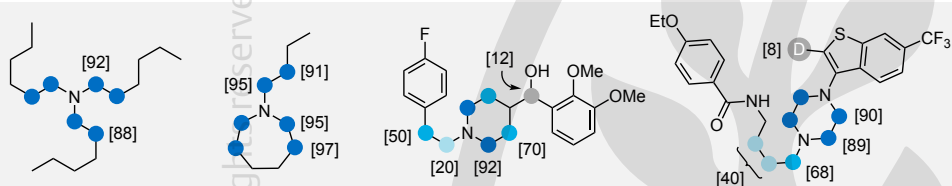
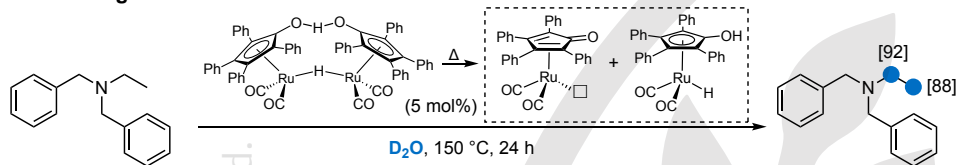
Catalytic species generation and β-selectivity



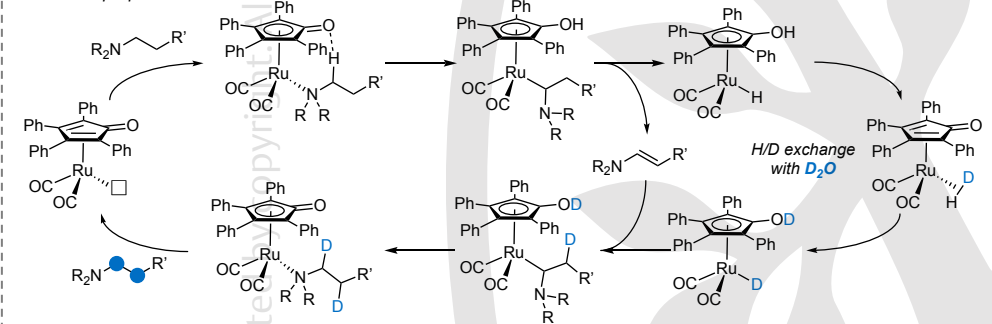
(23k) Jia, *Chem. Eur. J.* **2011**, 17, 13918; (23l) Lin and Jia, *Organometallics* **2015**, 34, 3686.

Figure 15 HIE based on hydrogen-borrowing (2): α- and β-deuteration on alcohols via ligand enabled hydride transfer.^{23g-j}

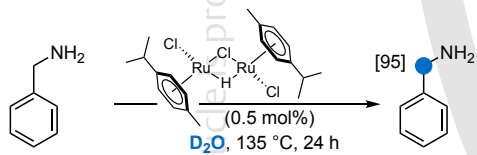
- **H/D exchange on amines**



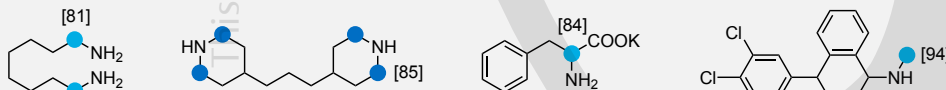
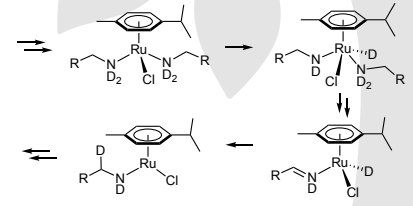
Mechanism proposed



(24a) Beller, *J. Am. Chem. Soc.* **2012**, *134*, 12239.



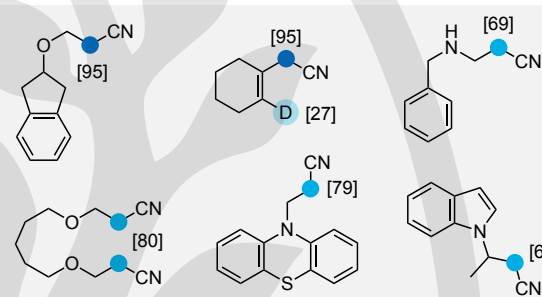
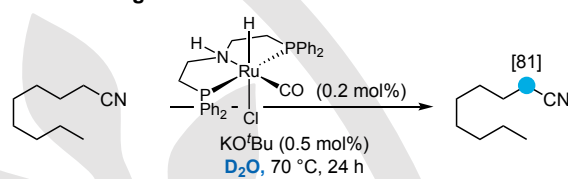
H/D exchange steps



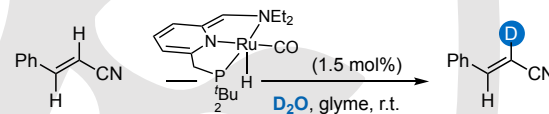
(24b) Gunanathan, *Org. Lett.* **2016**, 18, 5892.

Further reading: (24c) Szymczak, *J. Am. Chem. Soc.* **2016**, 138, 13489.

- **H/D exchange on nitriles**

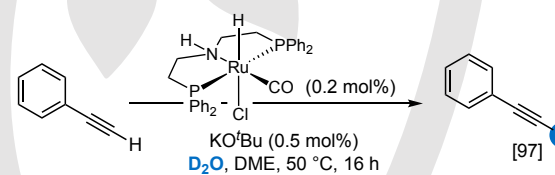


(24d) Gunanathan, *Chem. Commun.* **2018**, 54, 8705.

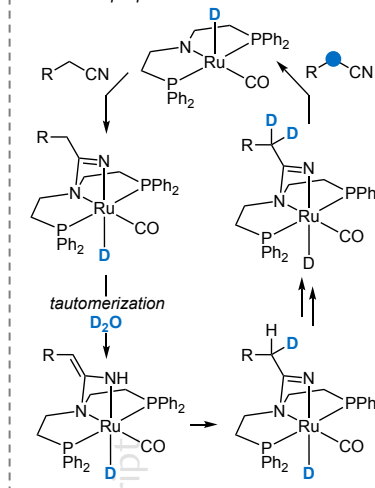


(24e) Vries, Otten, *Adv. Synth. Catal.* **2022**, 364, 179

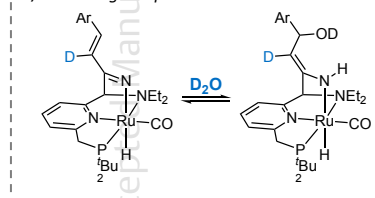
- **H/D exchange on terminal alkynes**



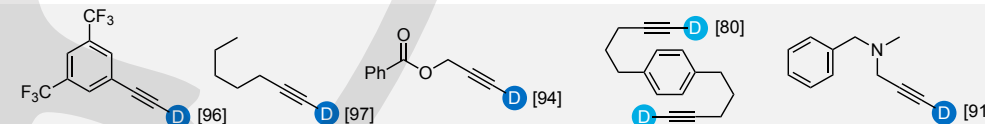
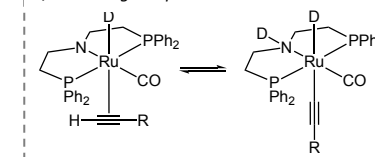
Mechanism proposed



H/D exchange steps



H/D exchange steps

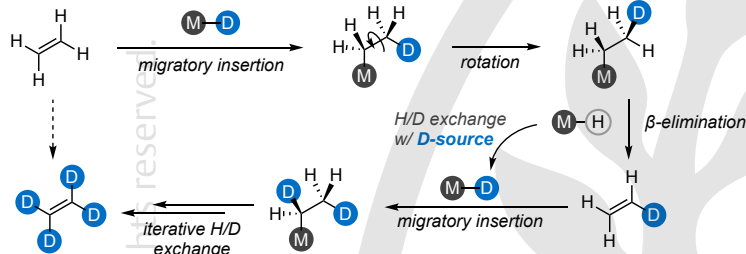


(24f) Gunanathan, *Chem. Commun.* **2016**, 52, 4509

Figure 16 HIE based on hydrogen-borrowing (3): deuteration on amines, nitriles, and alkynes.^{24a-f}

Basic process for migratory insertion / β -elimination based H/D exchange

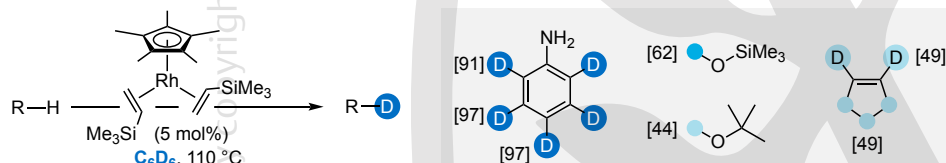
- Reversible migratory insertion / β -elimination under metal catalysis
- Preferred C-H bond cleavage based on kinetic isotope effect
- Iterative process enabled H/D exchange balance.



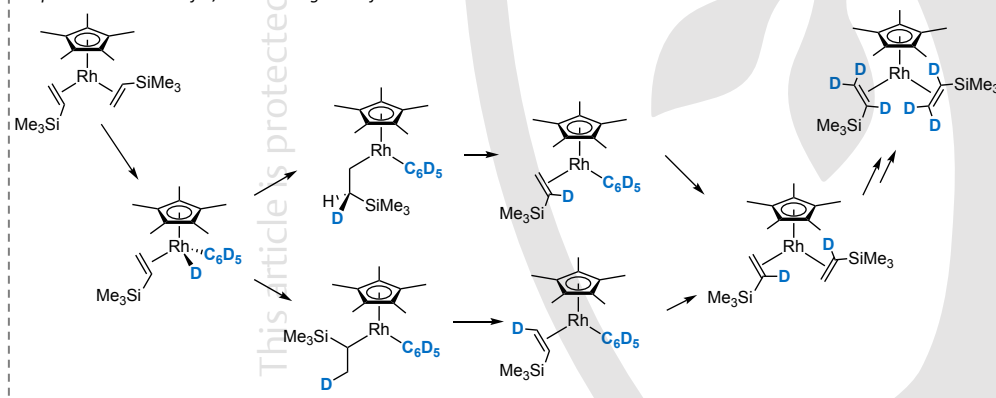
(25a) Faller, *Organometallics* **1989**, 8, 602;

Further reading: (25b) Ender, *Organometallics* **2005**, 24, 4774; (25c) Di Giuseppe, Castarlenas and Oro, *Chem. Eur. J.* **2014**, 20, 8391.

H/D exchange on alkene ligands



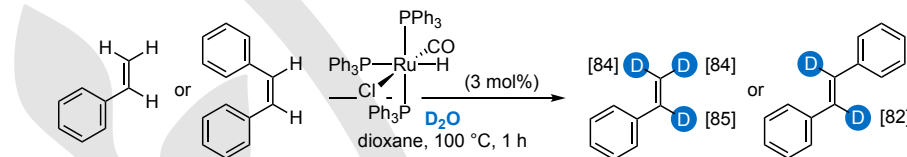
Proposed mechanism of H/D scrambling on olefin



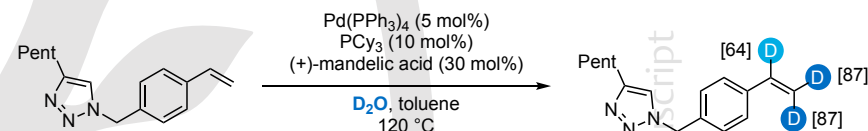
(25d) Brookhart, *J. Am. Chem. Soc.* **1999**, 121, 4385; (25e) Brookhart, *Organometallics* **2000**, 19, 1247.

Further reading: (25f) Brookhart, *J. Am. Chem. Soc.* **1997**, 119, 3165; (25g) Brookhart, *J. Organomet. Chem.* **1997**, 528, 199; (25h) Brookhart, *J. Am. Chem. Soc.* **1998**, 120, 6965;

Catalytic H/D exchange of olefins



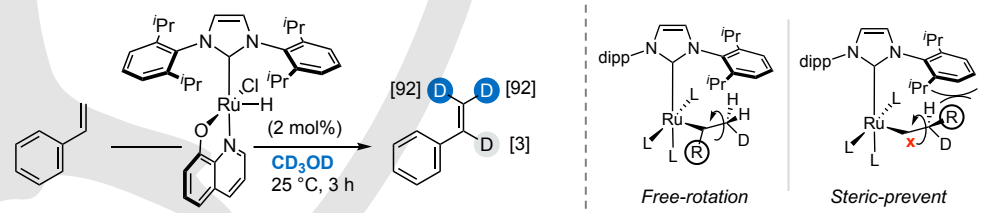
(25i) Lin, Jia, *Adv Synth Catal* **2010**, 352, 1512.



(25j) Maestri, *Synthesis* **2020**, 52, 1762.

Further reading: (25k) Nishimura, *Org. Lett.* **2016**, 18, 3674; (25l) Ackermann, *ChemCatChem* **2019**, 11, 435.

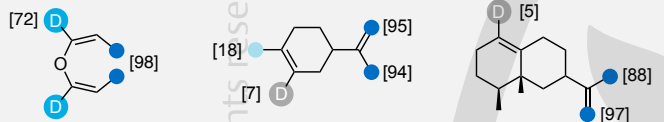
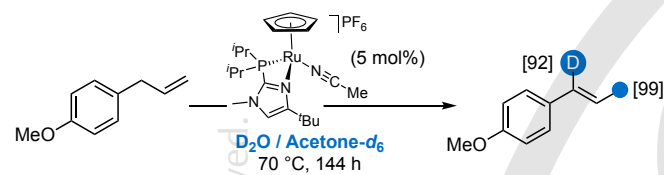
β -selective H/D exchange of olefins



(25m) Di Giuseppe, Castarlenas, and Oro, *Angew. Chem. Int. Ed.* **2011**, 50, 3938.

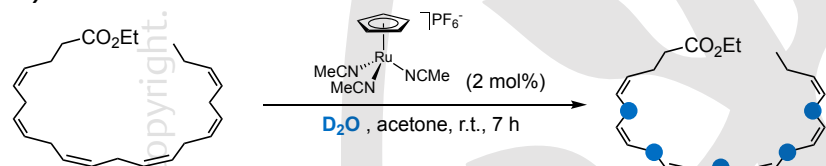
Figure 17 HIE based on iterative migratory insertion/ β -elimination (1): deuteration on olefins.^{25a-1}

● H/D exchange on allylic sites



(25n) Grotjahn, *J. Am. Chem. Soc.* **2009**, 131, 10354;
(25o) Grotjahn, *Top. Catal.* **2010**, 53, 1055.

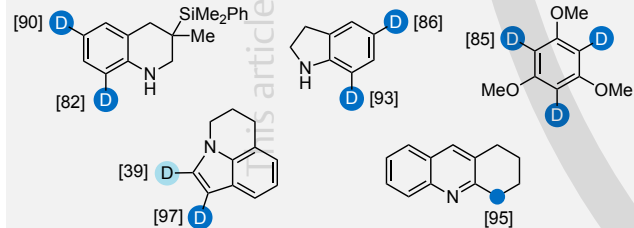
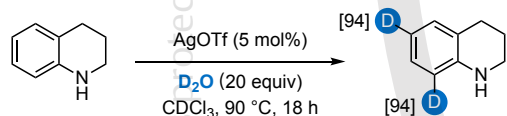
- Multi-site allylic deuteration



(25p) Shchepinov and Vidović, *J. Org. Chem.* **2017**, 82, 13115.

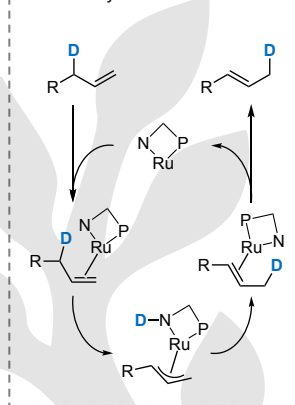
Further reading for Chain-walking deuteration, see: (25q) Cramer, *J. Am. Chem. Soc.* **1966**, 88, 2272; (25r) Matsubara, *Chem. Lett.* **2005**, 34, 664.

● Lewis acid facilitated H/D exchange

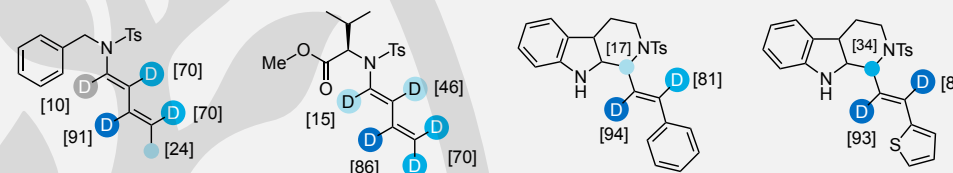
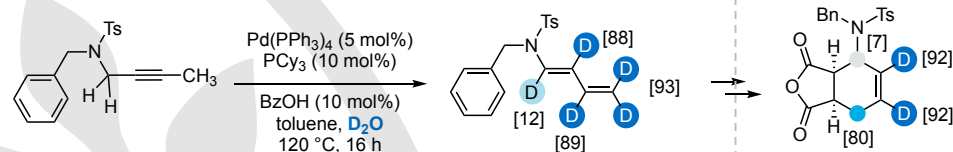


(26a) Cong and Hao, *RSC Adv.* **2020**, 10, 25475.

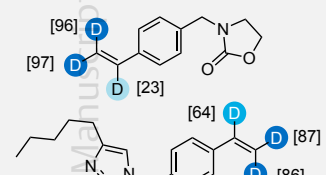
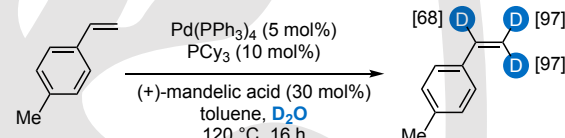
Mechanism for isomerization



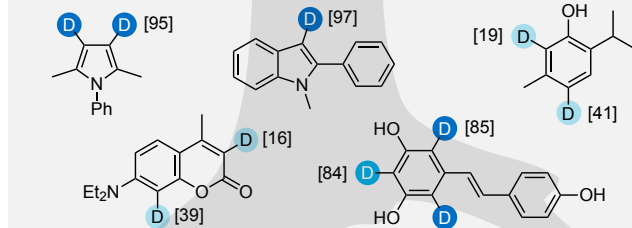
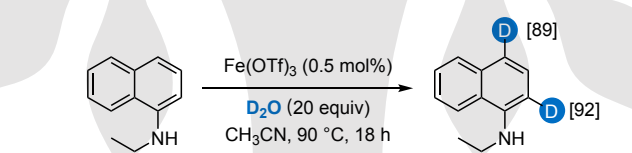
● H/D scrambling during the rearrangement



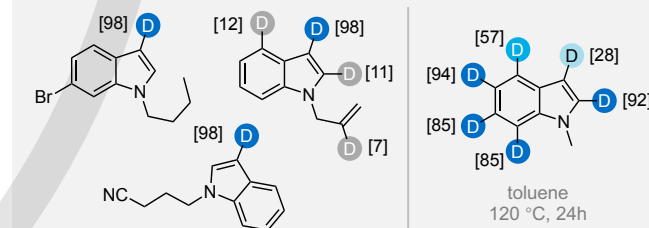
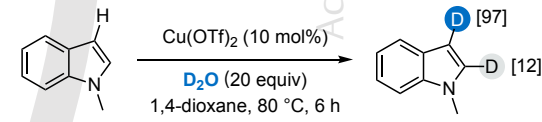
H/D scrambling on olefin



(25s) Maestri, *Chem. Sci.* **2019**, 10, 10297.



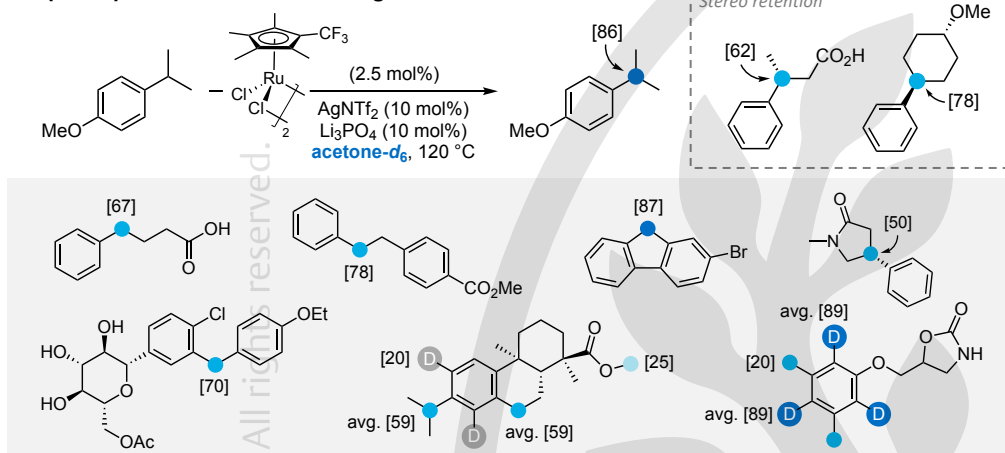
(26b) Junge and Beller, *Synlett* **2023**, 34, 332.



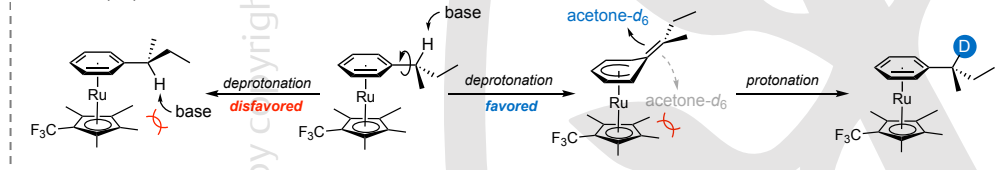
(26c) Zhang, *Tetrahedron Lett.* **2024**, 135, 154884.

Figure 18 HIE based on iterative migratory insertion/ β -elimination (2): deuteration on allyl and chain-walking deuteration.^{25m-r} Miscellaneous case of homogenous HIE (1): Lewis acid catalyzed deuteration.^{26a-c}

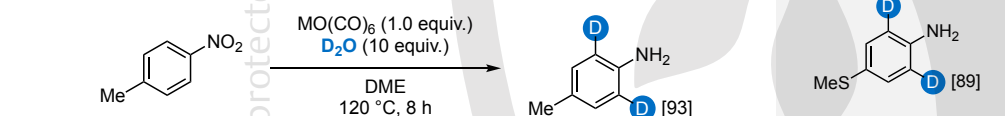
- η^6 -complex facilitate H/D exchange



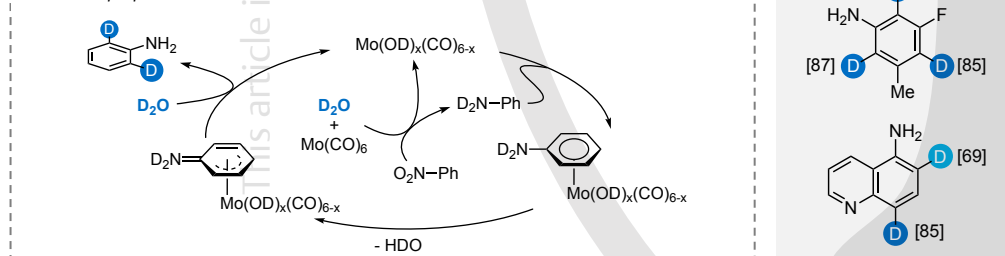
1 Mechanism proposed



(27a) Shi, *Angew. Chem. Int. Ed.* **2022**, 61, e202117381.

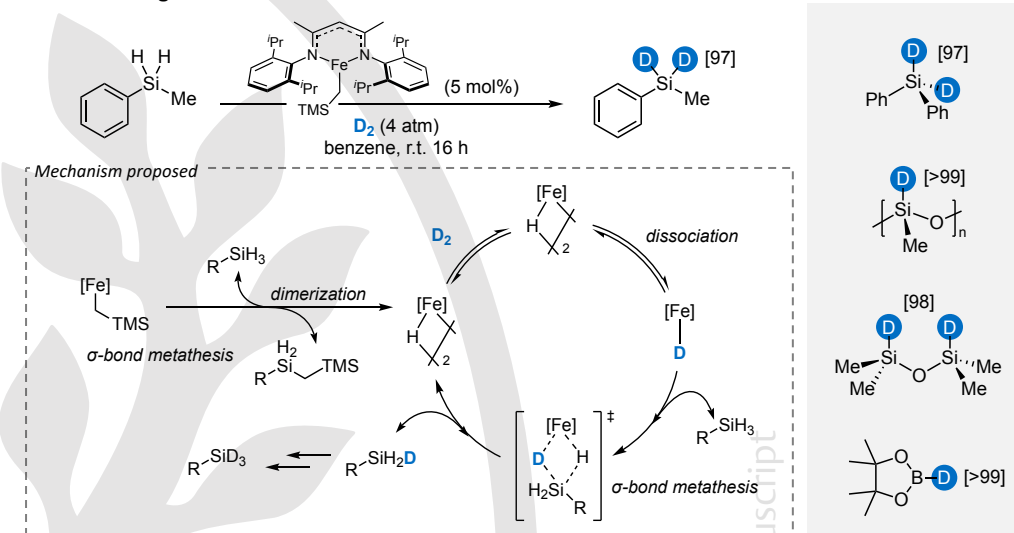


Mechanism proposed



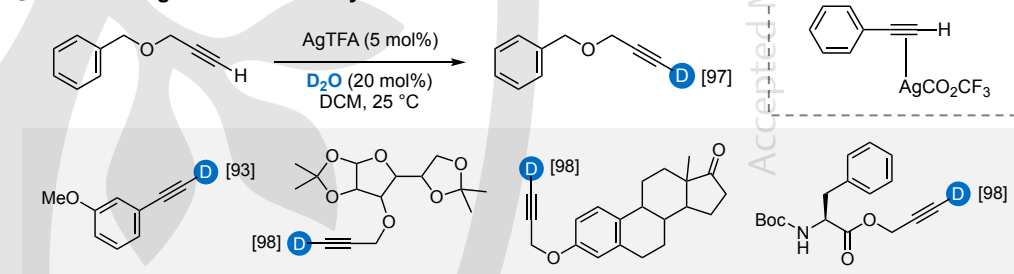
(27b) Lang and Peng, *Org. Chem. Front.* **2024**, 11, 5473.

- **H/D exchange based on σ -bond metathesis**



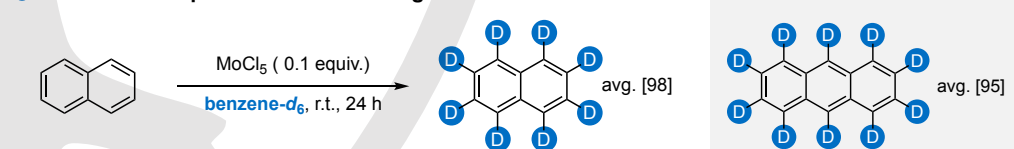
(28) Grayson and Webster, *ACS Catal.* **2022**, 12,, 2979.

- **H/D exchange on Terminal Alkyne**



(29) Zhang, Shen and Liu, *Tetrahedron Lett.* **2021**, 66, 152807.

- **Metal chloride promoted H/D exchange**



(30a) Guo, *Chin. J. Chem.* **2005**, 23, 341.

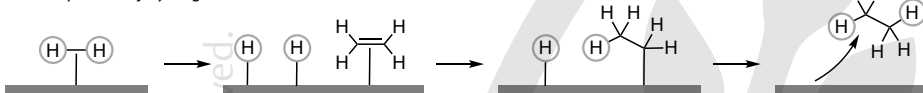
Further reading for early works of EtAlCl₂ promoted HIE: (30b) Garnett, *J. Am. Chem. Soc.* **1972**, *94*, 5913; (30c) Garnett, *J. Am. Chem. Soc.* **1972**, *94*, 8632; (30d) Long, *J. Chem. Soc., Perkin Trans. 2* **1975**, 1298.

Figure 19 Miscellaneous case of homogenous HIE (2): deuteration catalyzed by η^6 complex^{27a-b}, σ -metathesis²⁸, π -acid²⁹, and metal chloride.^{30a-d}

Basic process for H/D scrambling on heterogeneous catalysis

- Reversible C-H bond cleavage on the surface of heterogeneous catalyst
- H₂ (D₂) pressure manipulated H/D exchange process

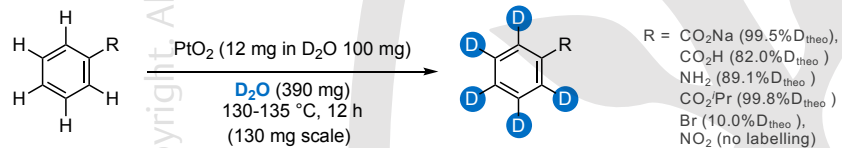
Conventional process of hydrogenation



H/D Exchange under lower pressure

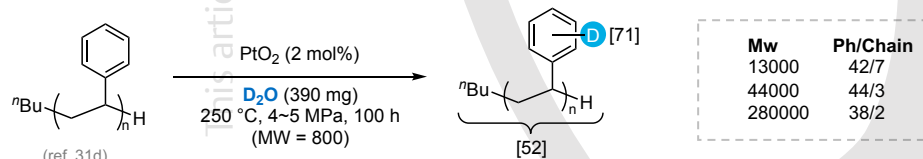
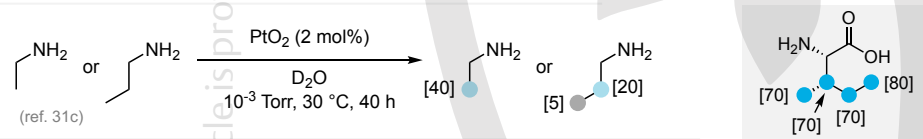
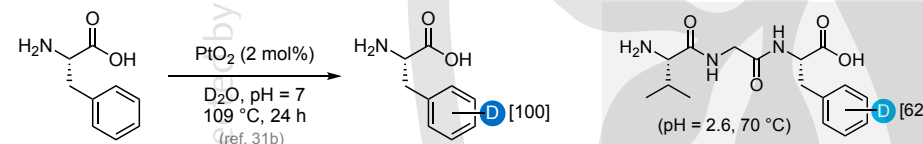


Seminal studies with PtO₂



(31a) Garnett, *J. Am. Chem. Soc.* **1958**, *80*, 5272.

Application in H/D Exchange

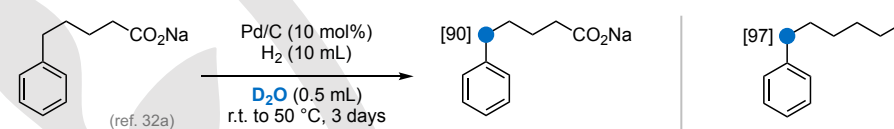


(31b) Norton, *J. Catal.* **1975**, *39*, 53; (31c) Kawazoe, *Chem. Pharm. Bull.* **1977**, *25*, 3329; (31d) Matsubara, *Chem. Commun.* **2004**, *15*, 1714.

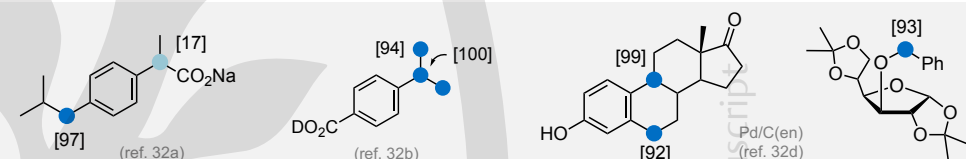
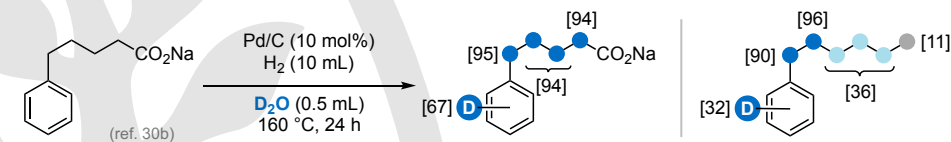
Further reading: (31e) Jones, *Can. J. Chem.* **1998**, *76*, 726.

Pd/C-H₂-D₂O system promoted HIE

- Benzylic selection at room temperature



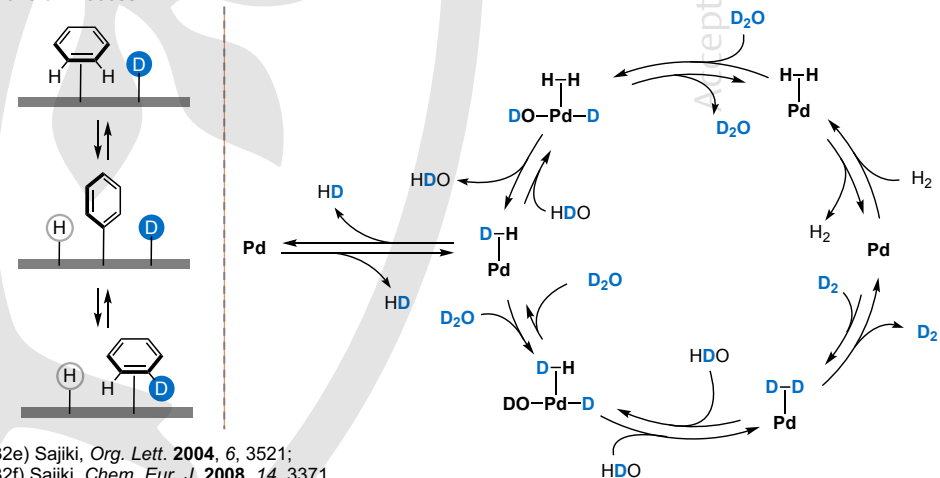
- Perdeuteration at elevated temperature (>110 °C)



(32a) Sajiki and Hirota, *Synlett* **2002**, 1149; (32b) Sajiki and Hirota, *Org. Lett.* **2004**, *6*, 1485; (32c) Sajiki, *Chem. Eur. J.* **2007**, *13*, 4052; For Pd/C(en) system, see: (32d) Sajiki, *Chem. Eur. J.* **2008**, *14*, 664.

in-situ D₂ generation of Pd/C-H₂-D₂O system

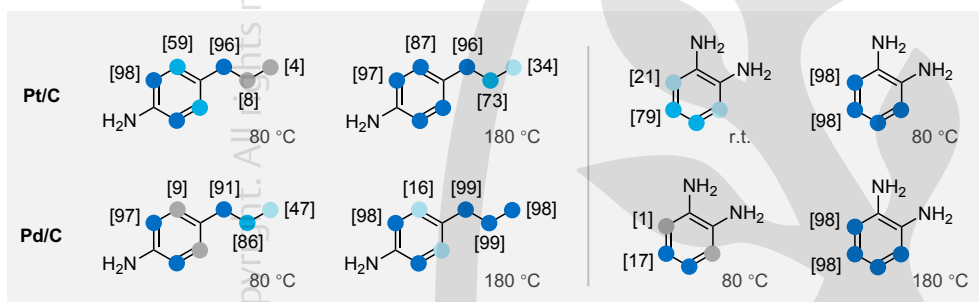
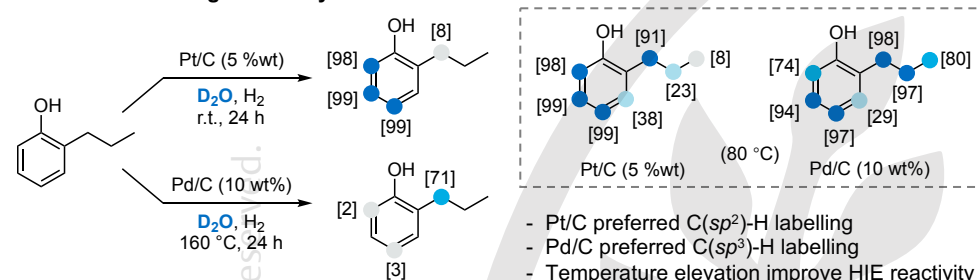
General Process



(32e) Sajiki, *Org. Lett.* **2004**, *6*, 3521;
(32f) Sajiki, *Chem. Eur. J.* **2008**, *14*, 3371.

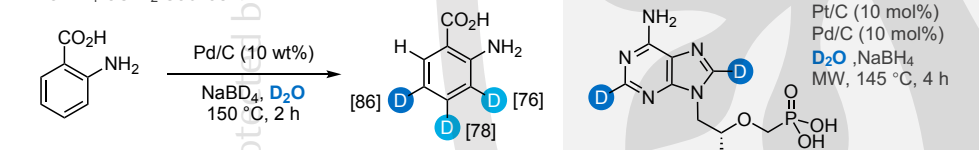
Figure 20 Heterogeneous HIE catalyzed by active carbon supported metal catalyst (1): seminal works of PtO₂,^{31a-e} and Pd/C-H₂-D₂O system (1).^{32a-f}

Deuterium Labelling selectivity of Pt/C and Pd/C



(32g) Sajiki, *Tetrahedron Lett.* **2005**, 46, 6995.

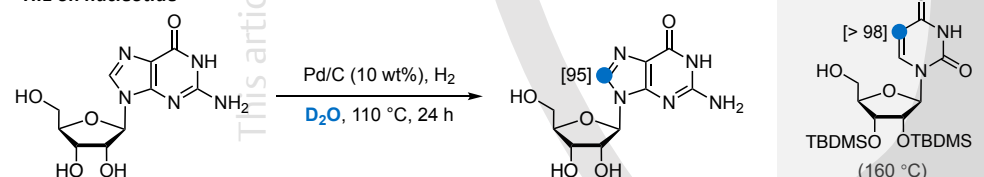
- NaBD₄ as H₂ source



(32h) Derdau, *Chem. Eur. J.* **2009**, 15, 10397; (32i) Zhang, *ChemistrySelect* **2018**, 3, 8724.

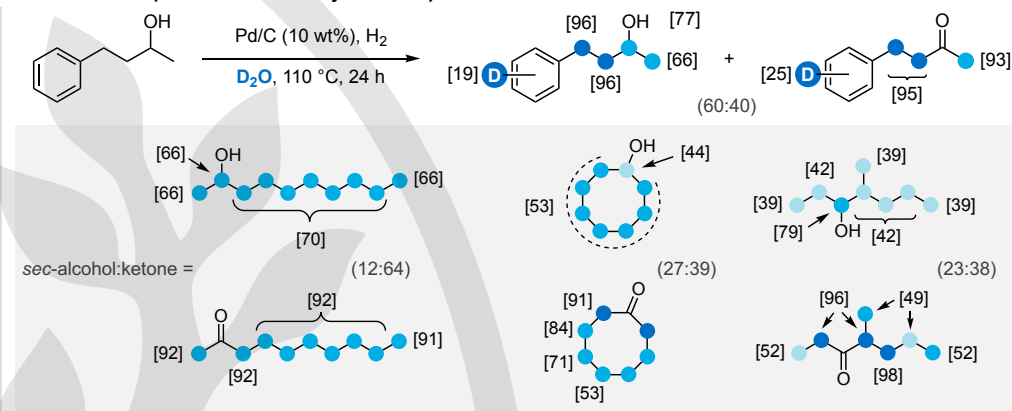
● Pd/C-H₂-D₂O system promoted HIE

- HIE on nucleotide



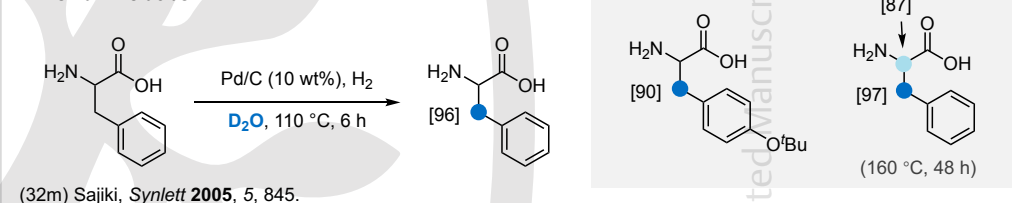
(32j) Sajiki, *Synlett* **2005**, 9, 1385; (32k) Sajiki, *Heterocycles* **2005**, 66, 361.

- HIE on alcohol (with side reaction of oxidation)



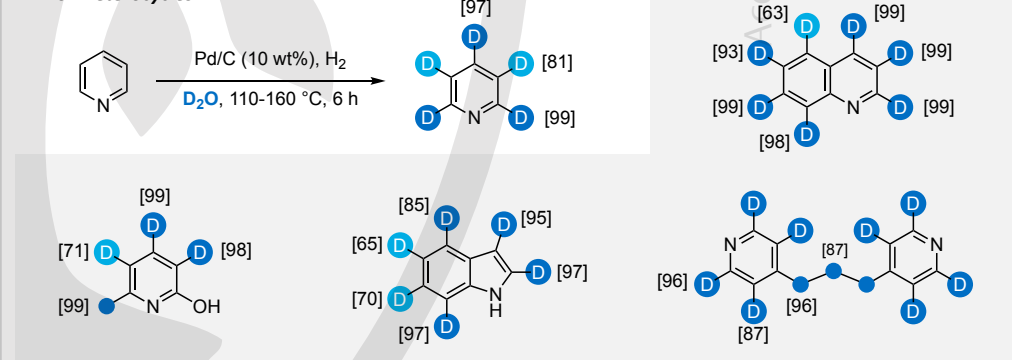
(32l) Sajiki, *J. Org. Chem.* **2007**, 72, 2143.

- HIE on amino acids



(32m) Sajiki, *Synlett* **2005**, 5, 845.

- HIE on heterocycles

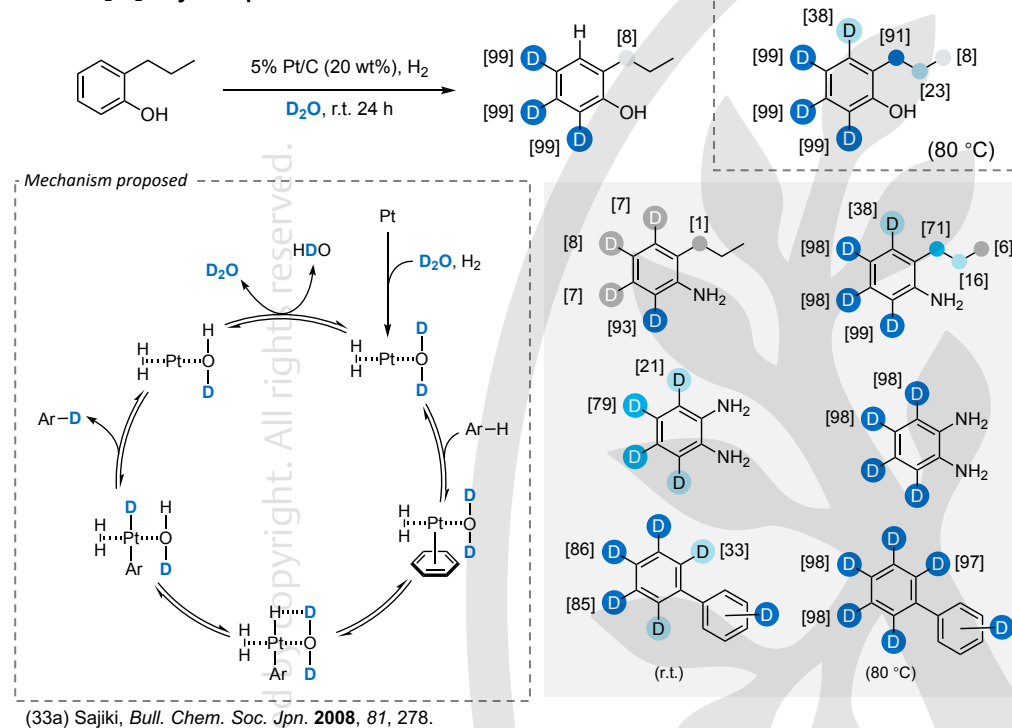


(32n) Sajiki, *Tetrahedron* **2006**, 62, 10954.

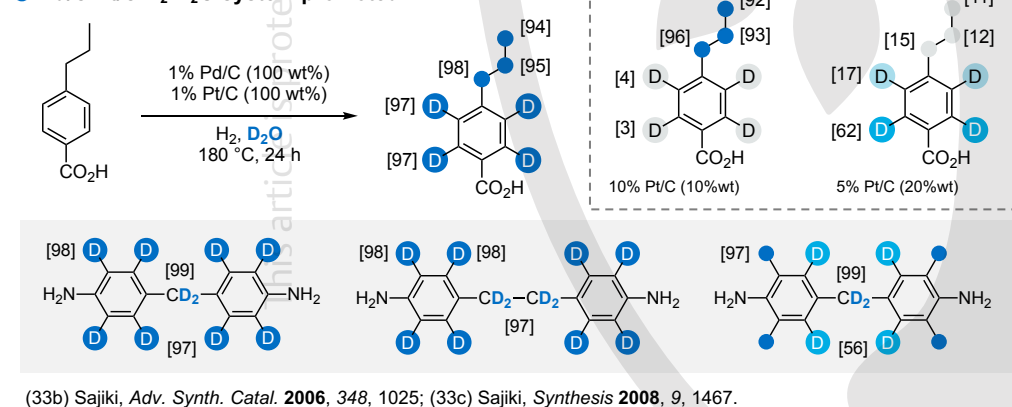
Further reading: (32o) Atzrodt, *J. Label Compd. Radiopharm.* **2010**, 53, 674.

Figure 21 Heterogeneous HIE catalyzed by active carbon supported metal catalyst (2): Pd/C-H₂-D₂O System(2).^{32g-o}

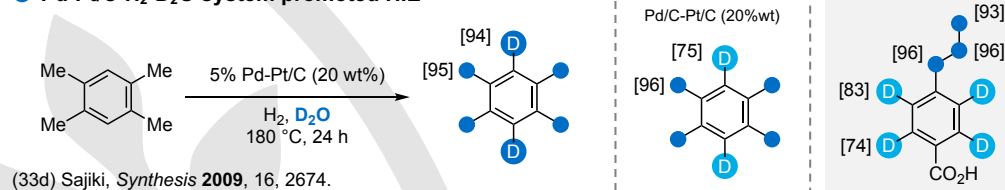
- **Pt/C-H₂-D₂O system promoted HIE**



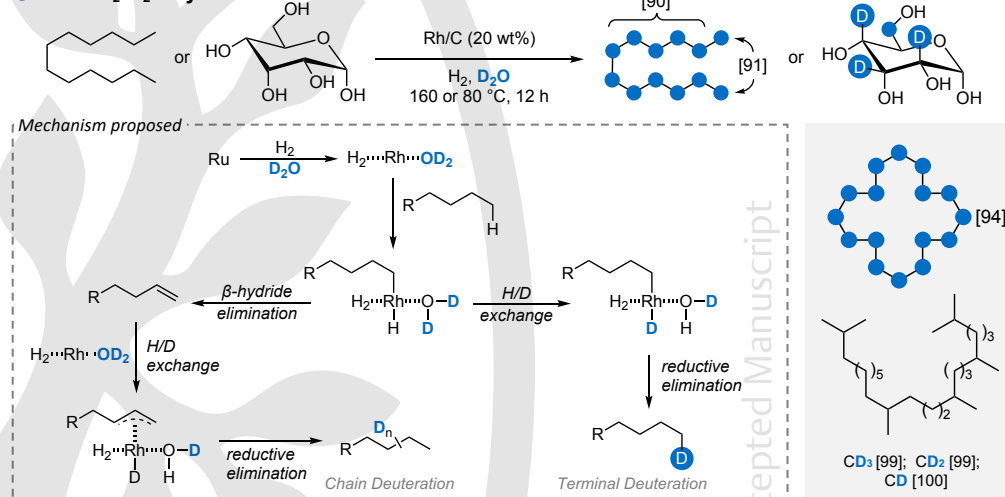
- Pd/C-Pt/C-H₂-D₂O system promoted HIE



- Pd-Pt/C-H₂-D₂O system promoted HIE



- **Rh/C-H₂-D₂O system**



 Ru/C-D₂ system promoted HIE

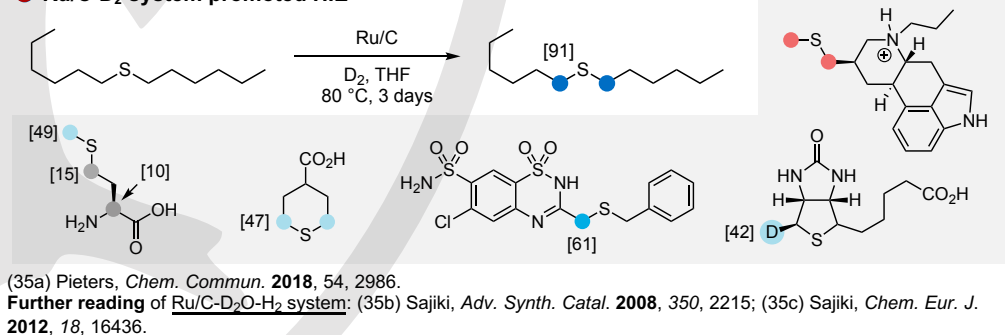
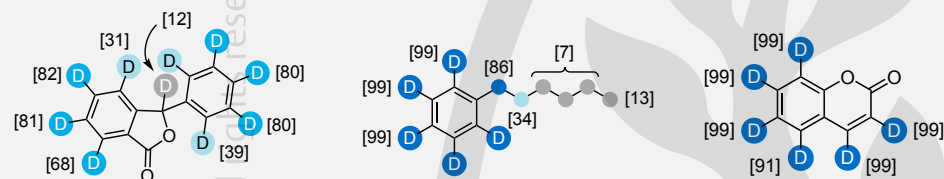
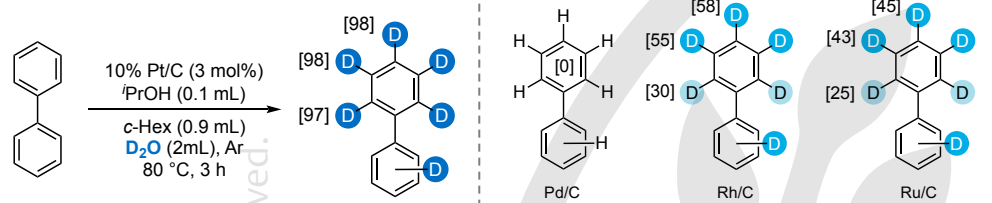
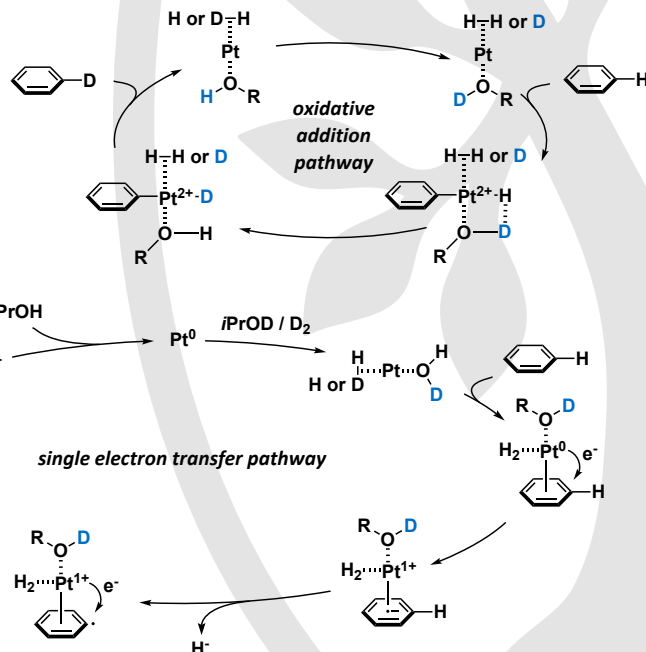
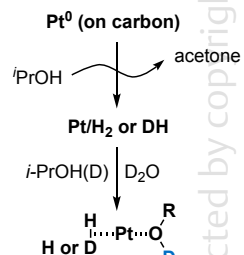


Figure 22 Heterogeneous HIE catalyzed by active carbon supported metal catalyst (3): Further application of M/C-H₂-D₂O systems, Pt/C^{33a-c}, Rh/C^{34a-e}, and Ru/C^{35a-c}

● M/C-*i*-PrOH-D₂O system promoted HIE

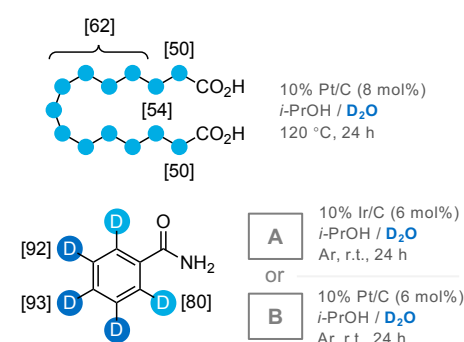
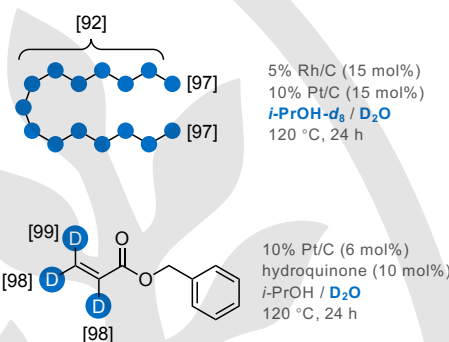


in-situ H₂ generation



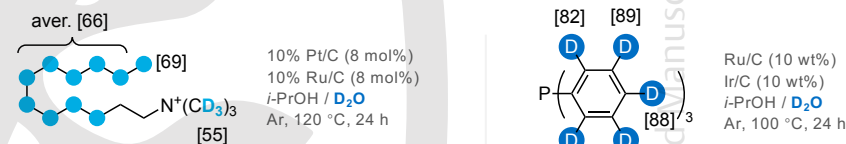
(36a) Sajiki, *Adv. Synth. Catal.* **2013**, 355, 1529.

- Application of *i*-PrOH as hydride source



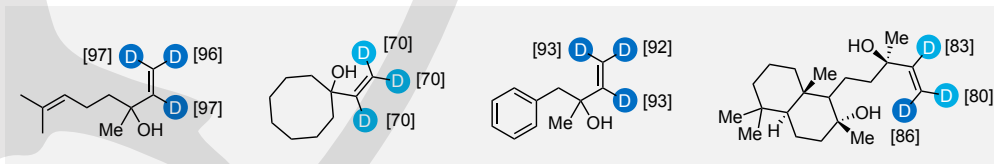
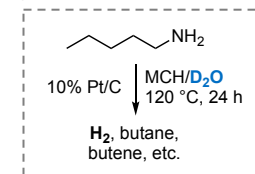
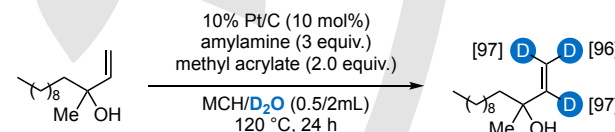
(36b) Sawama and Sajiki, *RSC Adv.* **2015**, 5, 13727; (36c) Sawama and Sajiki, *Adv. Synth. Catal.* **2016**, 358, 3277; (36d) Park and Sajiki, *Adv. Synth. Catal.* **2018**, 360, 2303; (36e) Sawama and Sajiki, *Org. Process Res. Dev.* **2019**, 23, 648.

- Application in Raman-based Live-cell imaging



(36f) Sawama, Sajiki, *Asian J. Org. Chem.* **2023**, 12, e202200710; (36g) Sawama, *Chem. Commun.* **2023**, 59, 12100.

● Pt/C-*n*BuNH₂-D₂O system

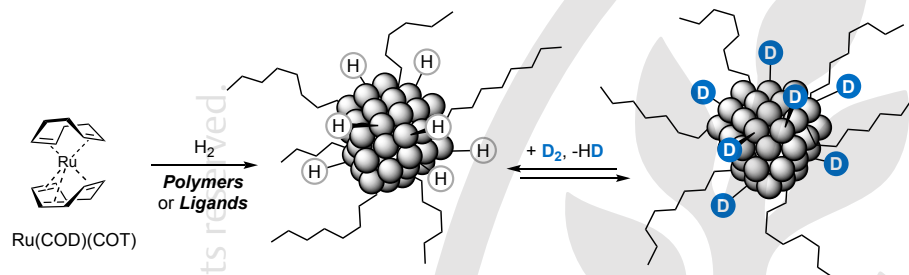


(37) Park, Sajiki, *Org. Chem. Front.* **2022**, 9, 1986.

Figure 23 Heterogeneous HIE catalyzed by active carbon supported metal catalyst (4): M/C-*i*-PrOH-D₂O system^{36a-g}, and Pt/C-*n*BuNH₂-D₂O.³⁷

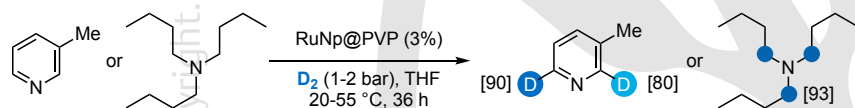
H/D exchange on metal nanoparticles collides

- Ruthenium nanoparticles was stabilized by polymers and ligands
- H/D exchange observed on RuNP@HDA

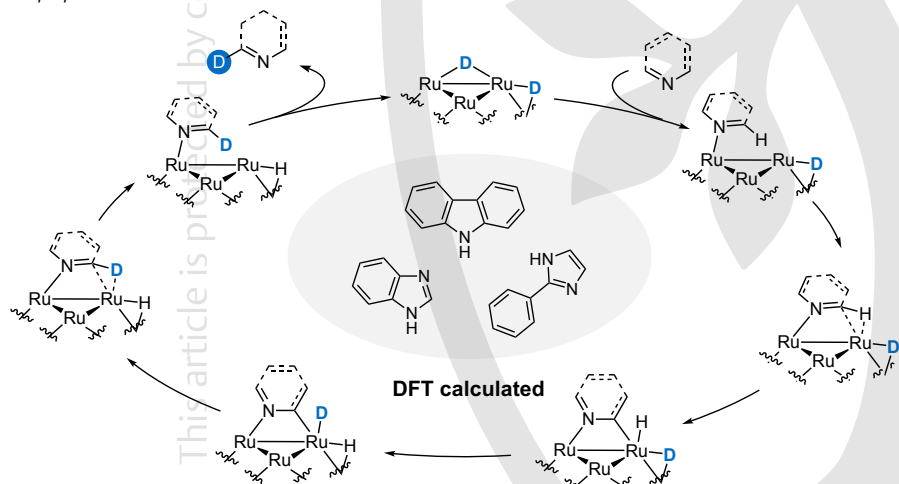


(38a) Chaudret, C. R. *Chimie*, **2003**, 6, 1019; (38b) Buntkowsky, Limbach and Chaudret, *ChemPhysChem* **2005**, 6, 605; (38c) Chaudret, *Angew. Chem. Int. Ed.* **2008**, 47, 2074.

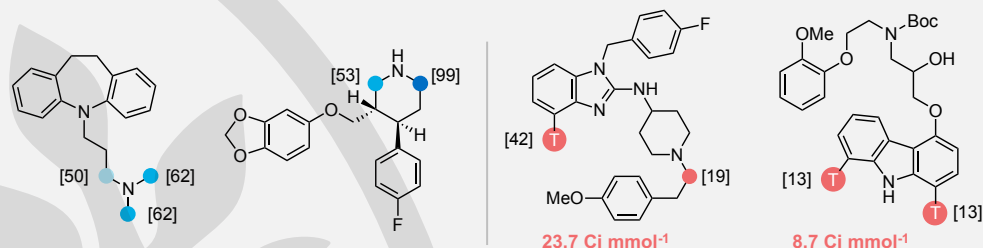
RuNP@PVP Colloid / PVP stabilized Ru Nanoparticles



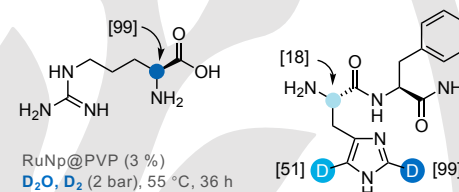
Mechanism proposed



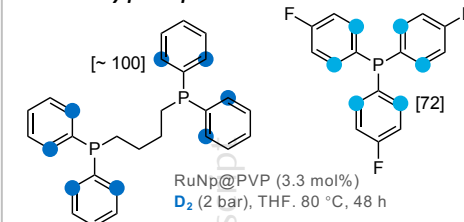
(38d) Chaudret and Rousseau, *Angew. Chem. Int. Ed.* **2014**, 53, 230;
(38e) Poteau and Pieters, *Chem. Eur. J.* **2020**, 26, 4988.



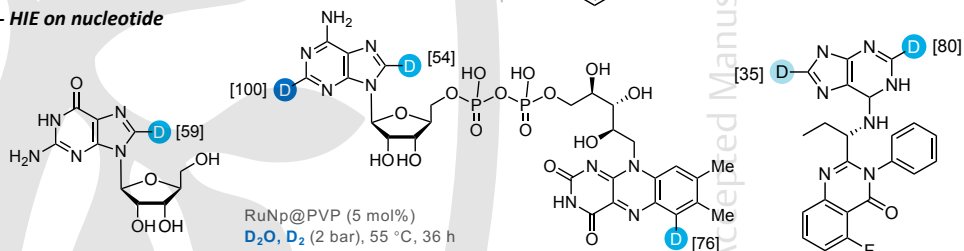
- HIE on amino acids



- HIE on arylphosphines

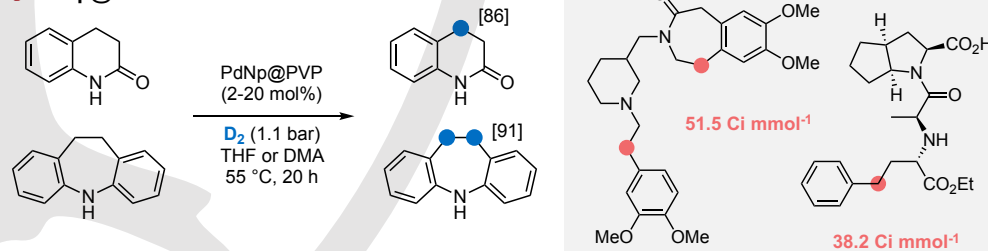


- HIE on nucleotide



(38f) Pieters, *Angew. Chem. Int. Ed.* **2015**, 54, 10474; (38g) Chaudret and Castillón, *Chem. Commun.* **2015**, 51, 16342;
(38h) Feuillastre and Pieters, *Angew. Chem. Int. Ed.* **2019**, 58, 4891.

PdNP@PVP Colloid

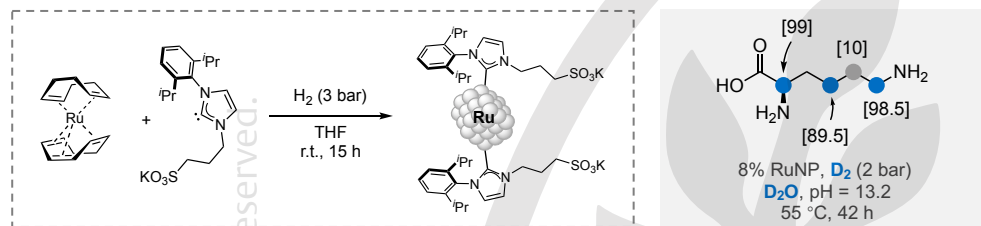


(38i) Pfeifer, *Angew. Chem. Int. Ed.* **2021**, 60, 26671;
Further reading for early study of PdNP@PVP in HIE, see: (38j) Shapley, *Organometallics*. **2009**, 28, 4020.

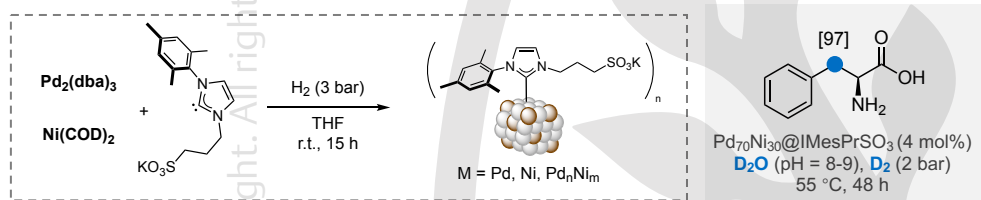
Figure 24 Heterogeneous HIE catalyzed by metal nanoparticles (1): PVP supported metal nanoparticle.^{38a-i}

NHC Stabilized Nanoparticle

- Improve the solubility and stability of nanoparticles

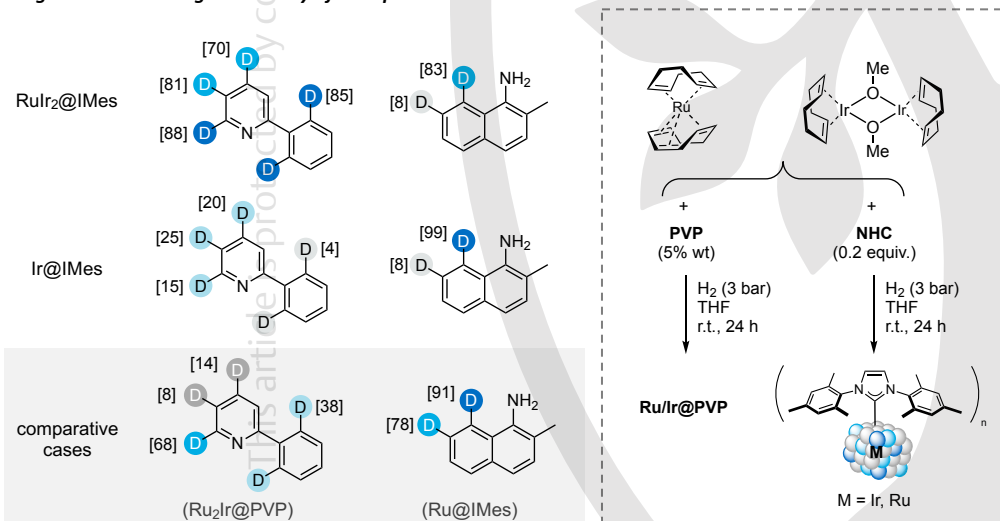


(39a) Martínez-Prieto and Chaudret, *Chem. Commun.* **2017**, 53, 5850.



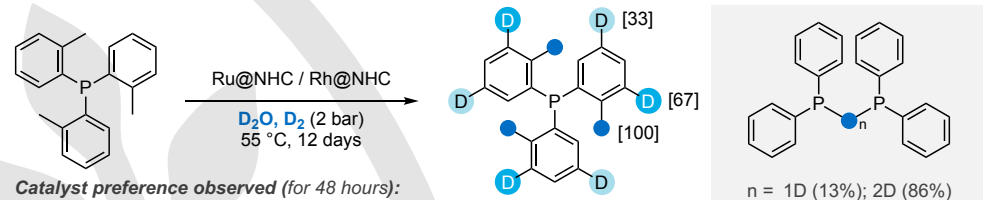
(39b) Baquero, *Chem. Commun.* **2023**, 59, 1062.

- Ligand enhanced regioselectivity of nanoparticles



(39c) Mencia, Baquero and Chaudret, *Organometallics* **2022**, 41, 3313.

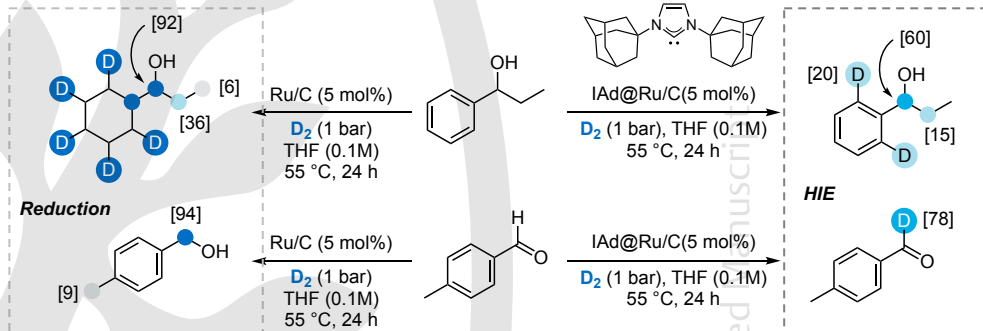
- Ligand shifted regioselectivity of nanoparticles



Catalyst preference observed (for 48 hours):
 Ru@NHC ($D_{Ar}:D_{Me} = 47:53$); Rh@NHC ($D_{Ar}:D_{Me} = 17:83$)

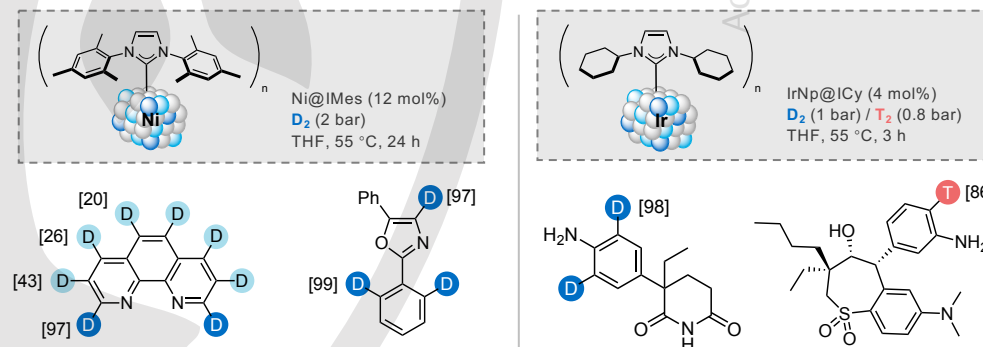
(39d) Carbó, Godard and Catillon, *Inorg. Chem.* **2023**, 62, 4570.

- Reactivity regulation on Ru/C



(39e) Pieters, *Angew. Chem. Int. Ed.* **2020**, 59, 20879.

- Further applications

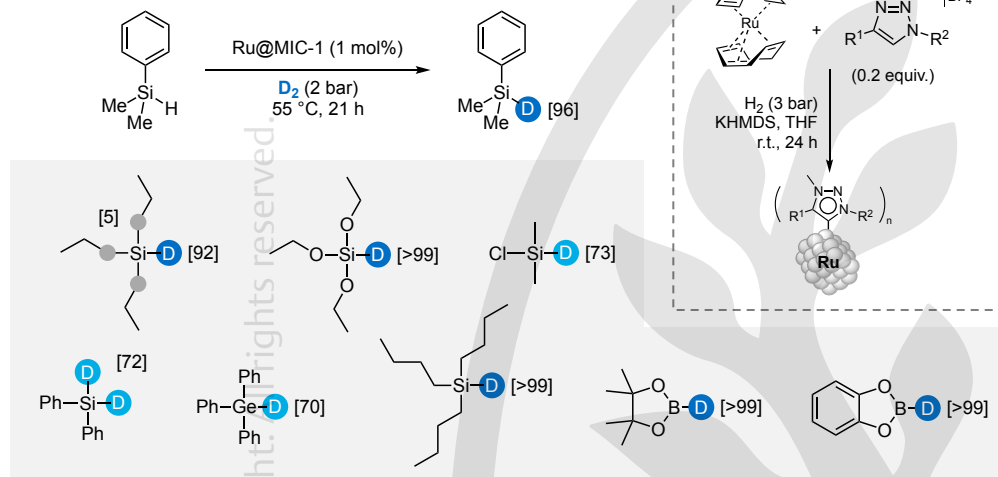


(39f) Asensio, Tricard and Chaudret, *Nanoscale*, **2020**, 12, 15736;

(39g) Pieters, Chaudret and Deraud, *Angew. Chem. Int. Ed.* **2020**, 59, 3517.

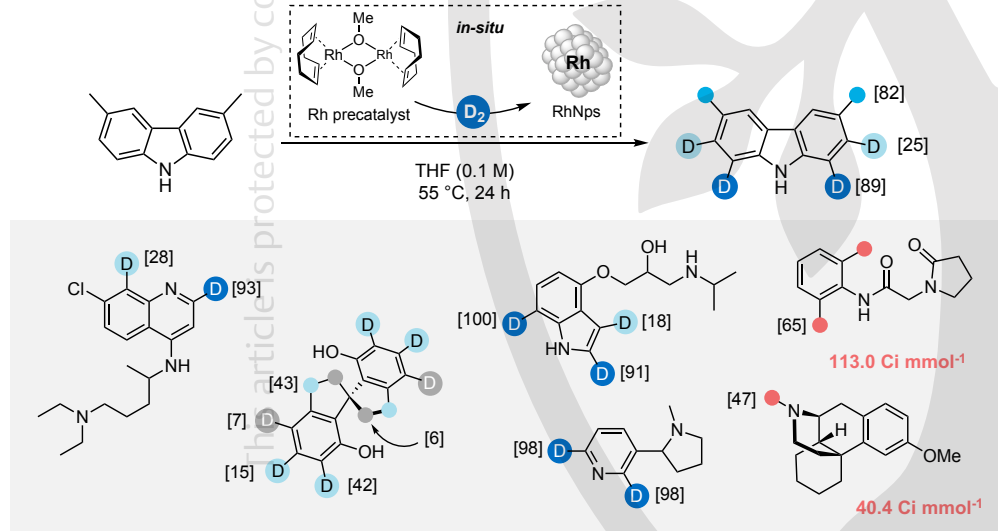
Figure 25 Heterogeneous HIE catalyzed by metal nanoparticles (2): NHC supported metal nanoparticles (1).^{39a-g}

● Ru@MIC promoted HIE on Group XIV elements and borane



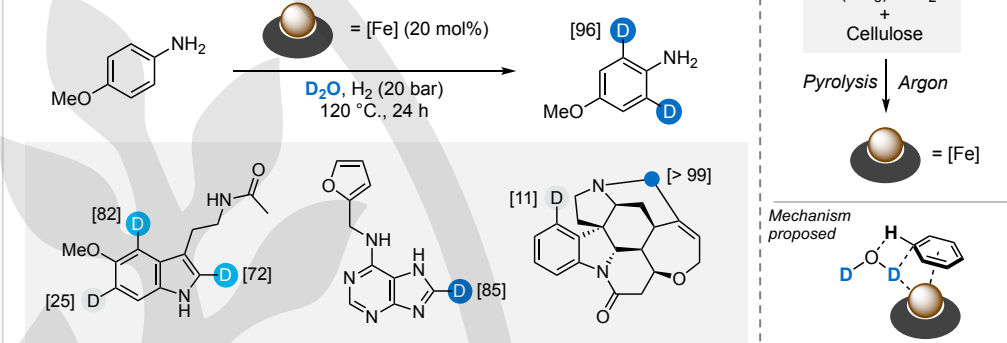
(39h) Rendón, Lara and Suárez, *Nanoscale* **2023**, 15, 14488.

● ***in-situ* generated Ru-nanoparticle catalyzed HIE**

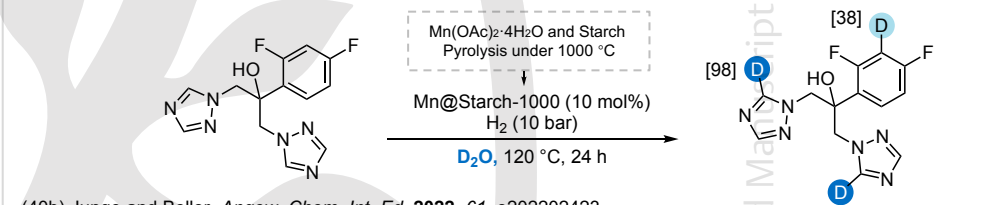


(39i) Feuillastre and Pieters, *JACS Au* **2022**, 2, 801.

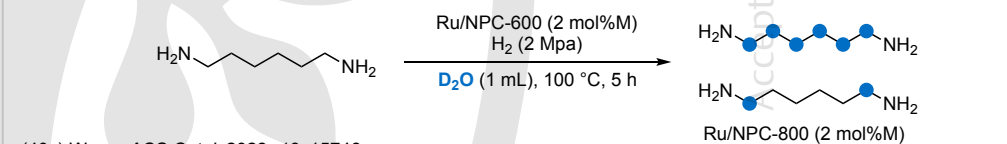
- **Pyrolytic carbon supported nanoparticles**



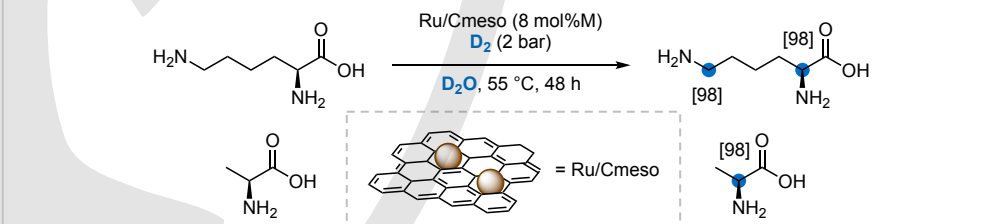
(40a) Brückner, Lei and Beller, *Nat. Chem.* **2022**, 14, 344.



(40b) Junge and Beller, *Angew. Chem. Int. Ed.* **2022**, 61, e202202423



(40c) Wang, *ACS Catal.* **2023**, 13, 15746.



(40d) Chaudret, *Catal. Sci. Technol.* **2024**, 14, 4904.

Further reading: (40e) Wang, *ChemSusChem* **2023**, 16, e202202395; (40f) Shao and Wang, *Asian J. Org. Chem.* **2023**, 12, e202200662.

Figure 26 Heterogeneous HIE catalyzed by metal nanoparticles (3): NHC supported metal nanoparticles (2),^{39h-i} and pyrolytic carbon supported novel metal nanoparticle.^{40a-f}

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Conflict of Interest

The authors declare no conflict of interest.

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