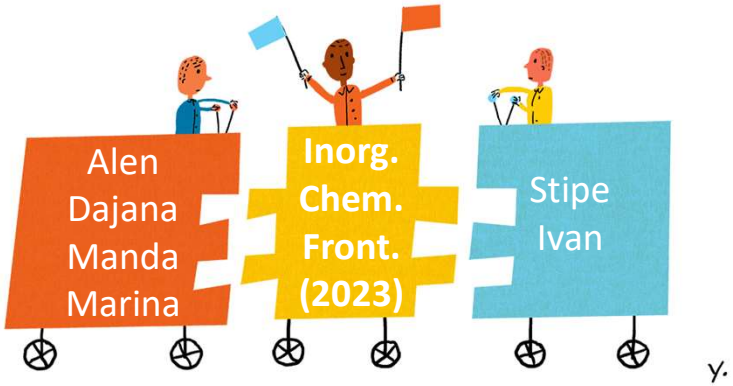
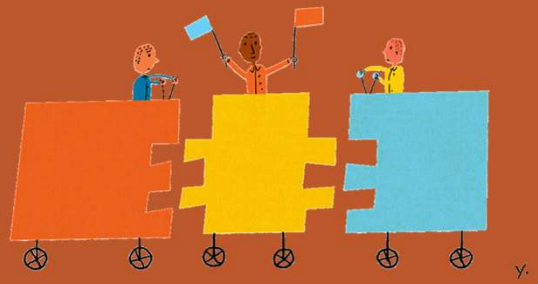



# Computational Study of Deuteration of Palladated Azobenzenes by Cysteine-$d_4$

MARINA JURIBAŠIĆ KULCSÁR,

ALEN BJELOPETROVIĆ, DAJANA BARIŠIĆ, IVAN HALASZ, MANDA ĆURIĆ, STIPE LUKIN

*Computational chemistry day 2023*, Zagreb, 16. 09. 2023.



*Experiments, isolation, characterization, spectroscopy:*
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dr. sc. Dajana Barišić
dr. sc. Manda Ćurić

*Solid-state analysis:*
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dr. sc. Ivan Halasz

*DFT calculations:*
dr. sc. Marina Juribašić Kulcsár

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RESEARCH ARTICLE

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**Cite this:** DOI: 10.1039/d3qi00932g

# Deuteration of Pd-activated C($sp^2$)–H bonds in the solid state†

Alen Bjelopetrović, ‡[a] Dajana Barišić, ‡[a,b] Marina Juribašić Kulcsár, *[a] Ivan Halasz, [a] Manda Ćurić[a] and Stipe Lukin *[a]

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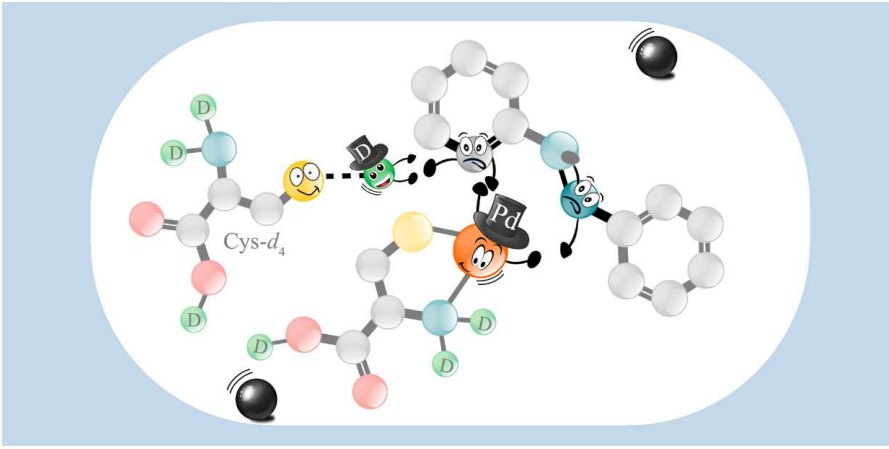
rsc.li/frontiers-inorganic

We report mechanochemically-induced deuteration of Pd-activated aromatic C($sp^2$)–H bonds at ambient temperature under solvent-free conditions. Deuterium was sourced from cysteine-$d_4$ to obtain mono- or dideuterated products from various aromatic palladacycles. Next to good deuteration yields, based on time-resolved *in situ* Raman monitoring and DFT calculations, we present a detailed view of the reaction course in the solid state. The obtained knowledge could lead to the broader application of this methodology for the deuteration of organics.



# Background – D-labeled compounds

**D-labeled compounds** widely used in:

- mass spectrometry and chromatography
- mechanistic and metabolic studies (*e.g.* kinetic isotopic effects)
- drug discovery and fine-tuning of the drug activity

1st deuterated drug, deutetrabenazine, approved for treating chorea associated with Huntington's disease.

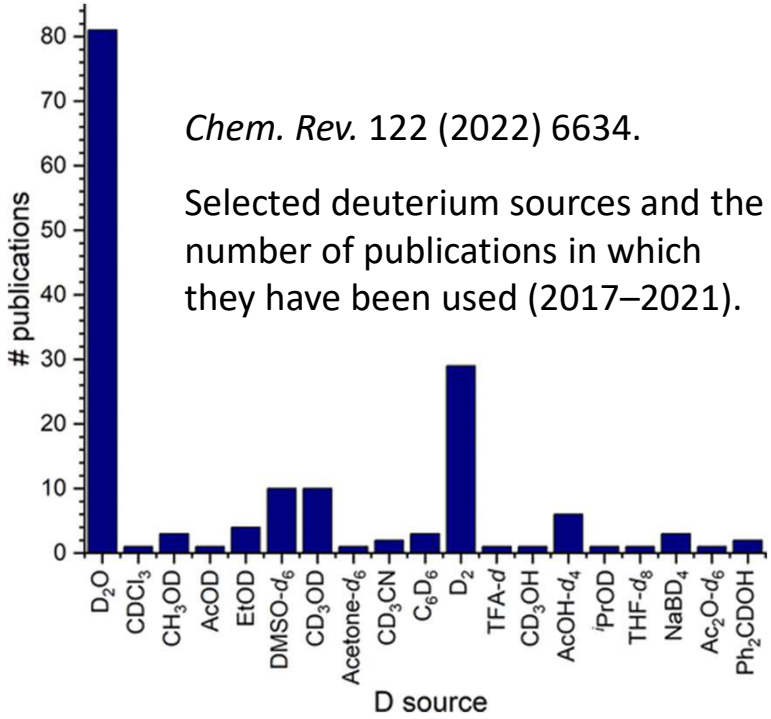
*Nat. Biotechnol*. 35 (2017) 493.


Deuteration commonly achieved by:

**Transition-metal-catalyzed hydrogen isotopic exchange (HIE)**

**Pd, Rh, Ru, Mn, Ir-catalyzed *ortho*-Directed HIE**

**D-source** for deuteration:
Usually used in an excess to achieve high enrichments with deuterium
Price ???
Availability ???




*Chem. Rev.* 122 (2022) 6634.

Selected deuterium sources and the number of publications in which they have been used (2017–2021).

*Chem. Rev*. 111 (**2011**) 4857. *Angew. Chem. Int. Ed*. 57 (**2018**) 1758. *J. Med. Chem*. 62 (**2019**) 5276.

# Background – Mechanochemistry

**Mechanochemistry, grinding, miling** = reactions in the solid state

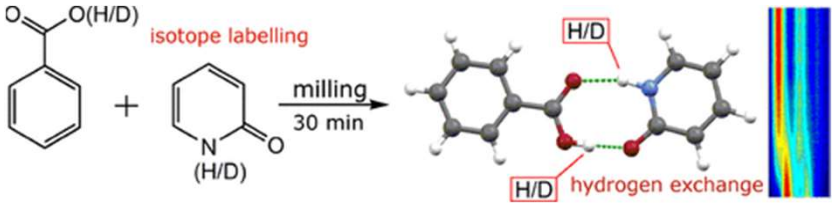
A good alternative to the classical chemistry that can achieve:

- shorter reaction times
- higher yields
- isolation of compounds that are not stable in the solution
- uses solids or liquids as reactants
- no need for a solvent
- **no solubility issues** – synthesis of insoluble compounds or work with insoluble reactants

Possible **high influence of the additives and the auxiliary solid** on the reaction outcome

# Background – experimental methodology

S. Lukin et al. *J. Am. Chem. Soc.* 141 (**2019**) 1212.
**Isotope Labeling Reveals Fast Atomic and Molecular Exchange in Mechanochemical Milling Reactions**




Halasz group

More about **Raman monitoring** of the mechanochemical reactions:

S. Lukin et al. *Nature Protocols* 16 (**2021**) 3492.
**Raman spectroscopy for real-time and *in situ* monitoring of mechanochemical milling reactions**

S. Lukin et al. *Acc. Chem. Res.* 55 (**2022**) 1262.
**Toward Mechanistic Understanding of Mechanochemical Reactions Using Real-Time *In Situ* Monitoring**

# Background – compounds

## 2014
## 1st C–H bond activation in the solid state

ChemComm

COMMUNICATION

Cite this: *Chem. Commun.*, 2014, 50, 10287

Received 10th June 2014,
Accepted 17th July 2014

DOI: 10.1039/c4cc04423a

www.rsc.org/chemcomm

**Mechanochemical C–H bond activation: rapid and regioselective double cyclopalladation monitored by *in situ* Raman spectroscopy†**

Marina Juribašić,‡ Krunoslav Užarević,‡ Davor Gracin and Manda Ćurić*

Ćurić group

**In solution**:

*Inorg. Chem.* 44 (**2005**) 5975.
*Inorg. Chem.* 47 (**2008**) 10446.
*Inorg. Chem.* 52 (**2013**) 12749.
*Inorg. Chem.* 59 (**2020**) 17123.

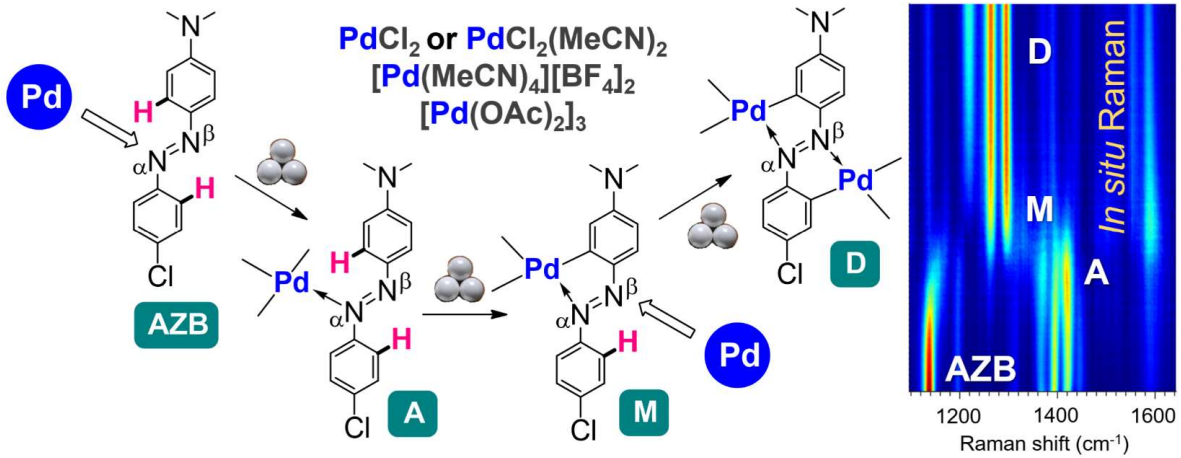
## 2018
## Detailed study of the solid-state C–H bond activation

ChemPubSoc Europe
DOI: 10.1002/chem.201802403
CHEMISTRY A European Journal Full Paper

Bond Activation |*Hot Paper*|

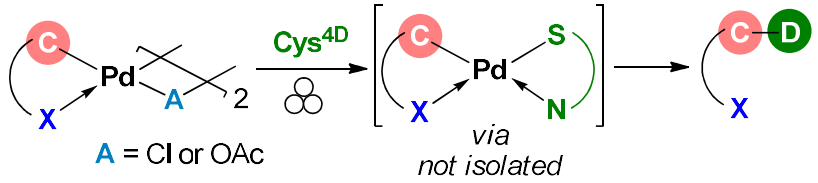
**Mechanism of Mechanochemical C–H Bond Activation in an Azobenzene Substrate by Pd$^{II}$ Catalysts**

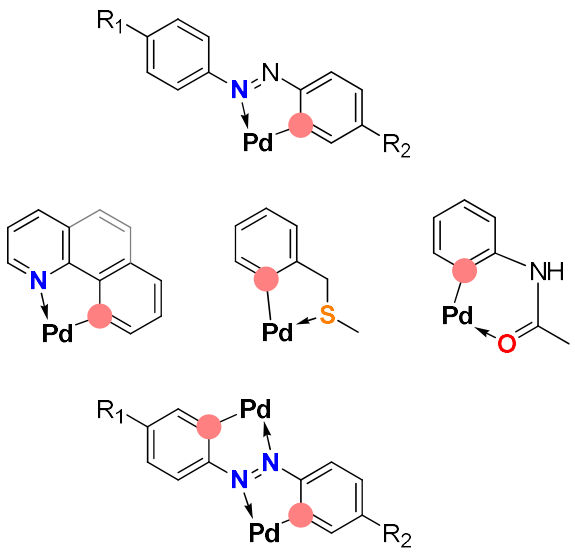
Alen Bjelopetrović,[+,a] Stipe Lukin,[+,a] Ivan Halasz,[a] Krunoslav Užarević,[a] Ivica Đilović,[b] Dajana Barišić,[a] Ana Budimir,[c] Marina Juribašić Kulcsár,*[a] and Manda Ćurić*[a]

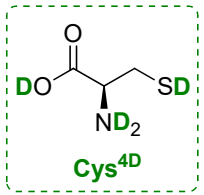


# Concept and experimental setup

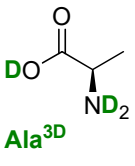
**Solid-state deuteration of the aromatic C($sp^2$)–H bonds**



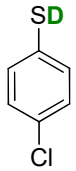



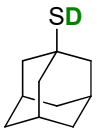

58-93 % isolated yield
Up to 88 % deuteration degree




Gly$^{2D}$
$D_2O$
EtOD
$ND_4Cl$




no reaction




Low isolated yield
Low deuteration degree

Palladated precursor + Cys$^{4D}$

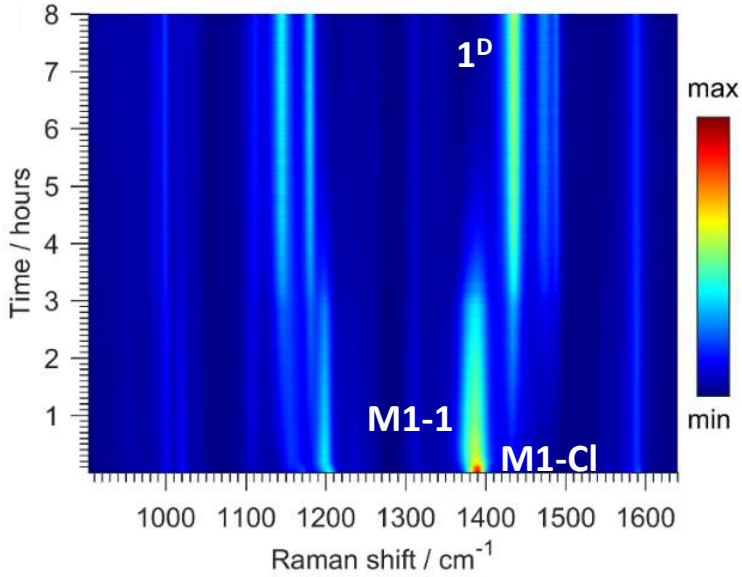
Excess of Cys$^{4D}$ (4 equiv. to **Pd**)

Mixer mill, 30 Hz
PMMA jar
$ZrO_2$ ball (4.5 g)
15-48 h
No grinding auxiliary
No additives

**PALLADATED PRECURSORS** | **D-source** | **REACTION CONDITIONS**

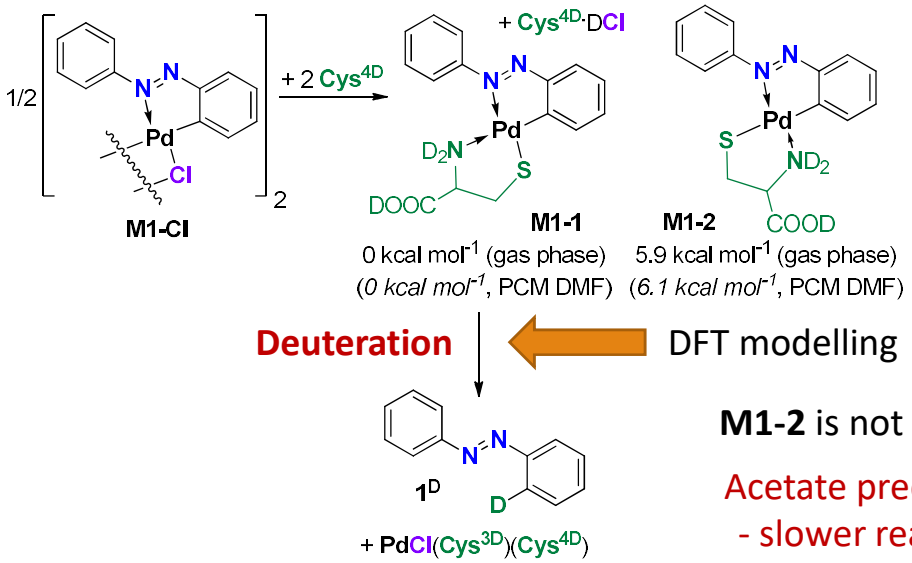
# Monopalladated precursor – experimental data

*Ex situ* NMR data (in solution) +
*In situ* Raman data (in solid state)




2D plot of the time-resolved Raman monitoring of the reaction of **M1-Cl** with **Cys$^{4D}$**.

**Ligand exchange**
(fast and quantitative)




**M1-2** is not formed.

Acetate precursors
- slower reaction!

**D-source** options:

- **Cys$^{4D}$**
- **Cys$^{4D}$·DCl**
- **DCl**
- AcO**D**

*Preferred D-source?*
*D-source donor group?*

# Method

**B3LYP-D3/6-311+G**/SDD(Pd)/gas phase**

Other tested methods:

1) a small basis set: B3LYP-D3/6-31G*/SDD(Pd)/gas phase;

2) no empirical dispersion correction: B3LYP/6-311+G**/SDD(Pd)/gas phase;

3) a more modern basis set: B3LYP-D3/def2tzvp/gas phase;

4) a more modern functional: ωB97x-D/6-311+G**/SDD(Pd)/gas phase;

5) including solvation effects by PCM: B3LYP-D3/6-311+G**/SDD(Pd)/PCM


Gaussian16

Recently-published methodology for the medium influence on the solid-state reactions: *ChemSusChem* 14 (**2021**) 2763.
→ PCM modelling using dielectric constant calculated from the dielectric constants of the reaction components

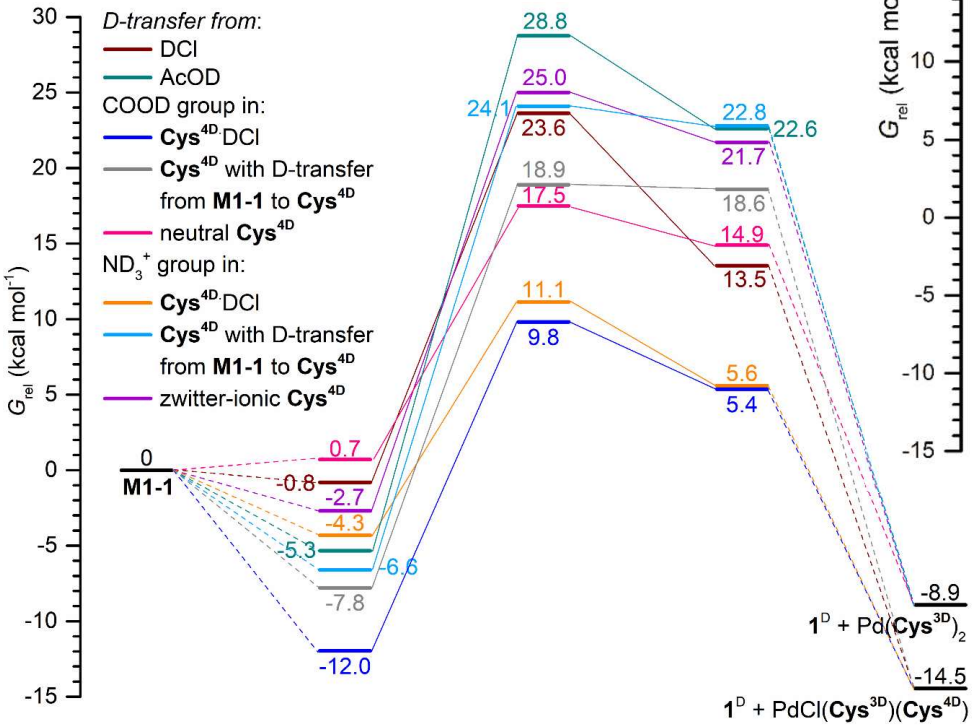
Dielectric constants of all components in our system are **not available**.

PCM modelling used as a rigorous computational check of the medium influence on the computed results. Two solvents, propanoic acid ($\varepsilon$ = 3.44) and DMF ($\varepsilon$ = 37.22), were chosen as examples.

# Monopalladated precursor – DFT data

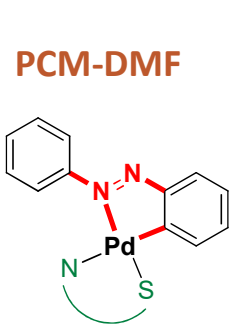
**Gas phase**

**Cys$^{4D}$·DCl < Cys$^{4D}$ << AcOD**




**PCM-DMF**

**Cys$^{4D}$·DCl ≈ Cys$^{4D}$ << AcOD**




**M1-1**




Lowest-lying transition state for D-transfer by the COOD group in **Cys$^{4D}$·DCl**



Excess **Cys$^{4D}$** → no free **DCl**

D-transfer to **M1-1** from various D-sources leading to **1$^{D}$**.

# Dipalladated precursor – experimental data

Fast, quantitative

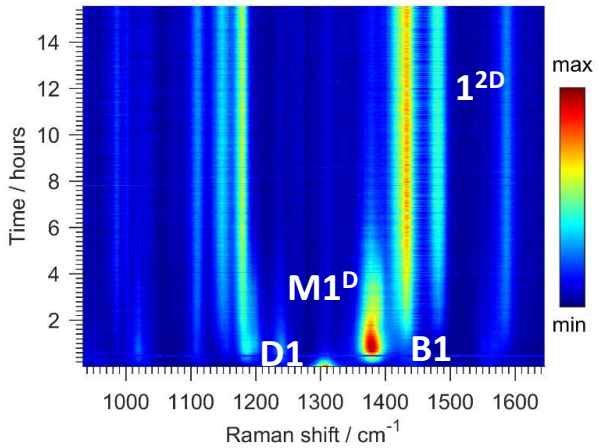
1) Ligand exchange Cl/DMF → ***S*-Cys$^{3D}$**

2) Isomerisation Planar → *S*-bridged

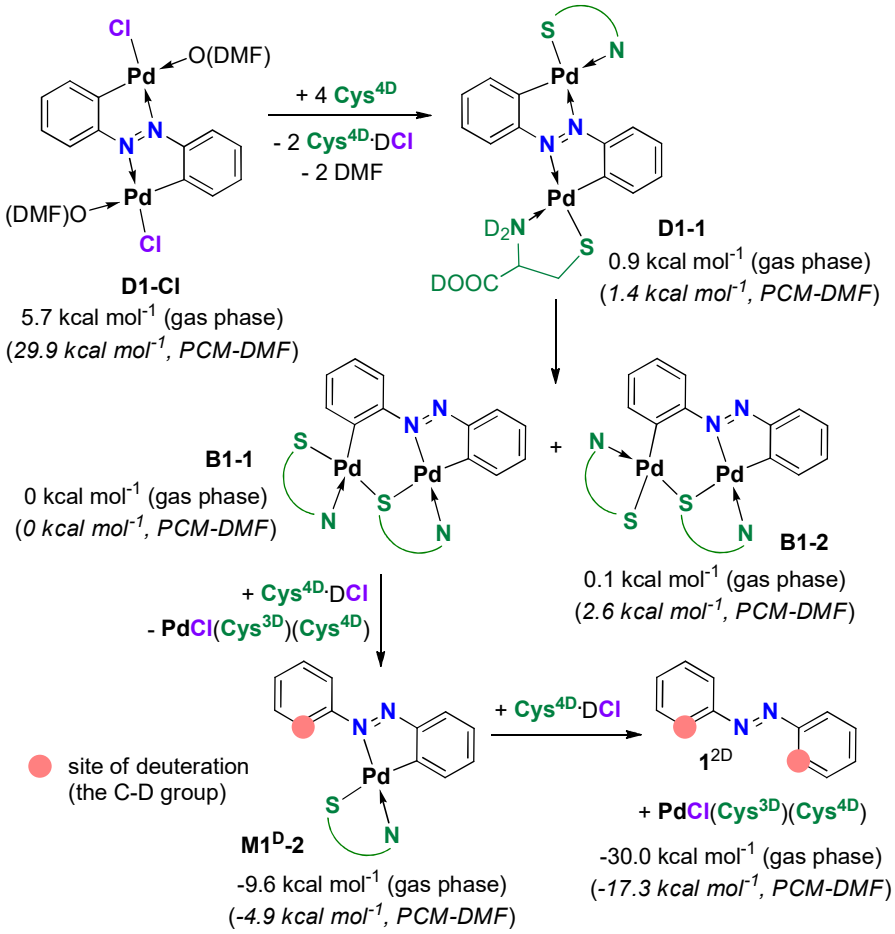
3) Deuteration

DFT modelling

*Ex situ* NMR data (in solution) +
*In situ* Raman data (in solid state)




2D plot of the time-resolved Raman monitoring of the reaction of **D1-Cl** with **Cys$^{4D}$**.




Proposed reaction route from **D1** to **$1^{2D}$**.

More on bridged complexes: *Dalton Trans.* 39 (**2010**) 8769; *Chem. Commun.* 47 (**2011**) 11543; *Inorg. Chem.* 56 (**2017**) 5342.

# General reaction course

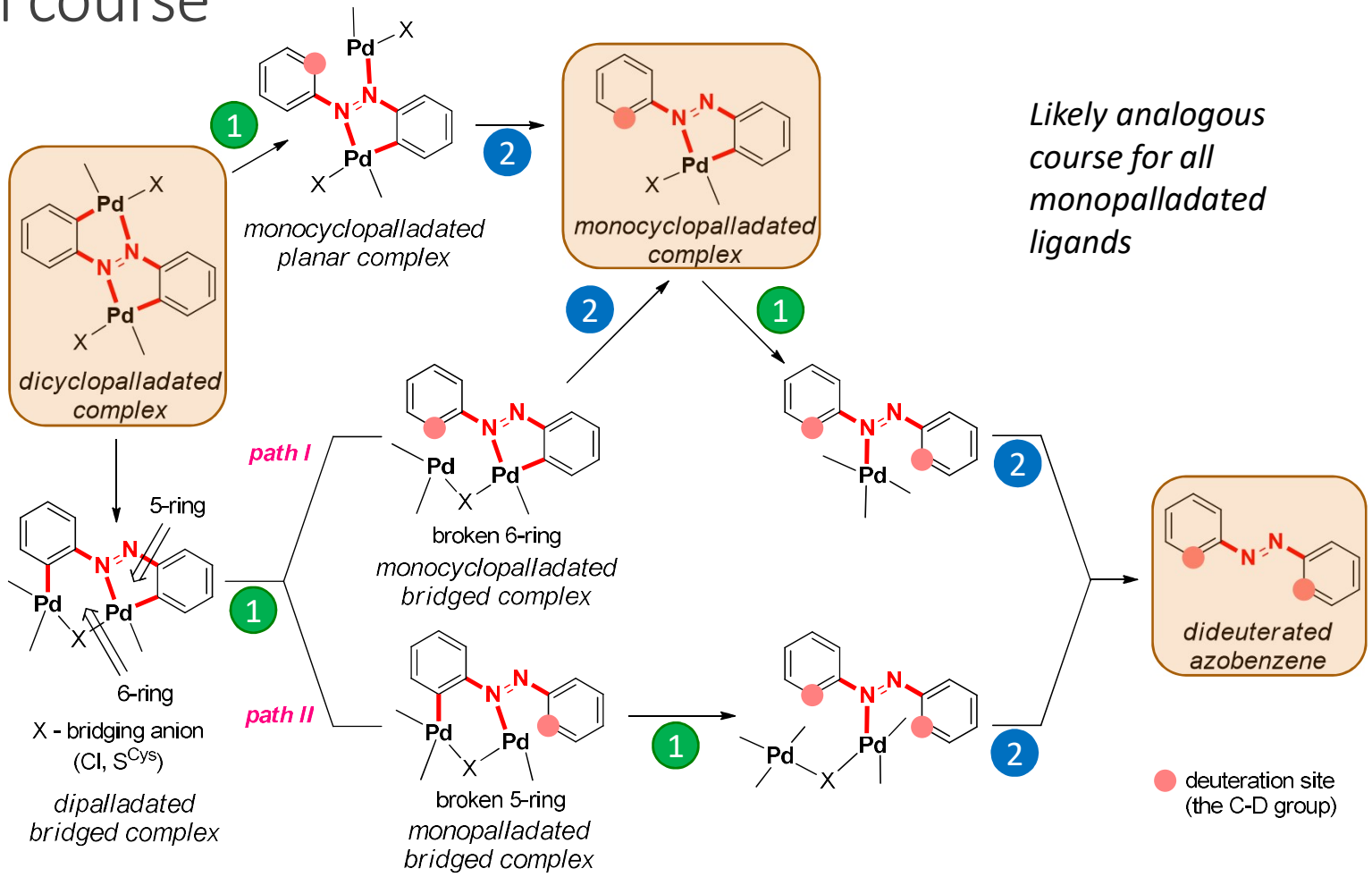
**D-source** options:

- **Cys$^{4D}$**
- **Cys$^{4D}$·DCl**
- **DCl**
- AcO**D**

*Preferred D-source?*
*D-source donor group?*

**Deuteration steps**:

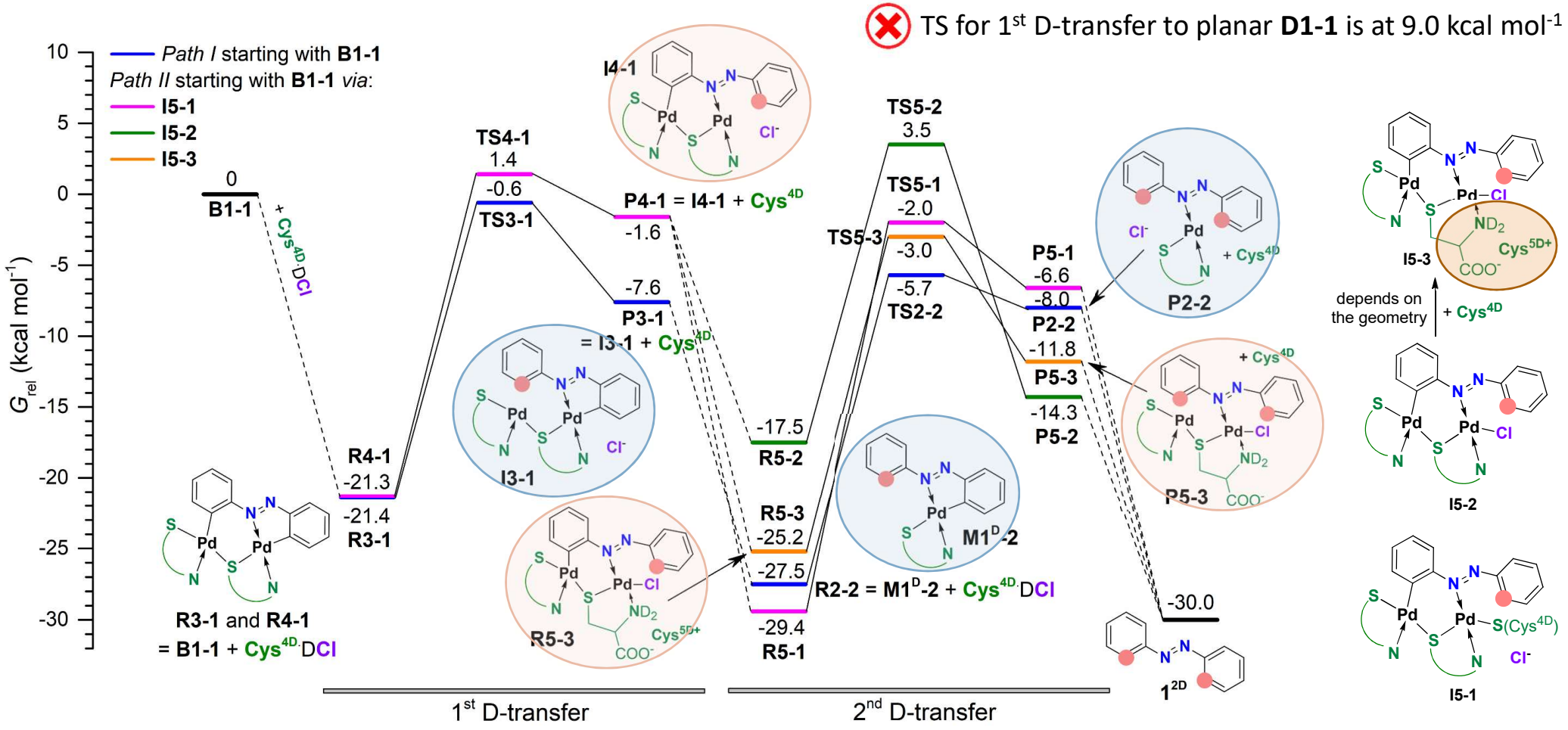
1. Pd–C bond cleavage
2. Pd elimination




*Likely analogous course for all monopalladated ligands*

More on bridged complexes: *Dalton Trans.* 39 (**2010**) 8769; *Chem. Commun.* 47 (**2011**) 11543; *Inorg. Chem.* 56 (**2017**) 5342.

# Dipalladated precursor – DFT data



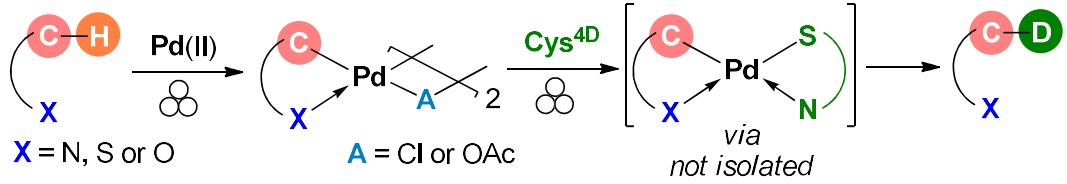
# Takeaways

EXPERIMENTAL

**1st solid-state deuteration of C–H bonds**

*New method for HIE of aromatic C($sp^2$)–H bonds*
*Regioselective HIE*
*High yields (up to 93%)*
*Medium to high deuteration*

**Hydrogen isotopic exchange (HIE)**




***C–H bond activation*** — *ChemComm* **2014**

***deuteration*** — *Inorg. Chem. Front.* **2023**

CALCULATIONS

DFT data agree with the experiment
- *for mono- and dipalladated precursors*:
» cysteine complexes are the first intermediates

- *for dipalladated precursors*:
» bridged intermediate is preferred rather than the planar cysteine complex in the 1st D-transfer
» six-membered ring is broken first and forms the monocyclopalladated complex

**$Cys^{4D}$·DCl** is the preferred D-source for the chloride palladated precursors

*Synergy of the expertise in our Laboratory*

# Acknowledgements


**FUNDING**

HrZZ grants:
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**COMPUTATIONAL RESOURCES**

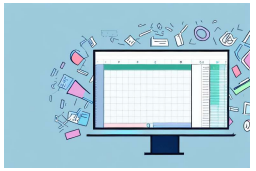
isabella CLUSTER

**PEOPLE**

Laboratory for solid-state synthesis and catalysis


Dr. sc. Alen Bjelopetrović
Dr. sc. Dajana Barišić
Dr. sc. Stipe Lukin
Dr. sc. Ivan Halasz
Dr. sc. Manda Ćurić

Dr. sc. Darko Babić, GTK, ZFK



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NMR center

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**THANK YOU!**