Mechanochemistry Unveiled: Non-Covalent Interactions, Cocrystals, and Polymorphism in Cyclorhodation Reactions

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UNIVERSIDAD DE ANTIOQUIA
Facultad de Ciencias Exactas y Naturales

45th International Conference on Coordination Chemistry

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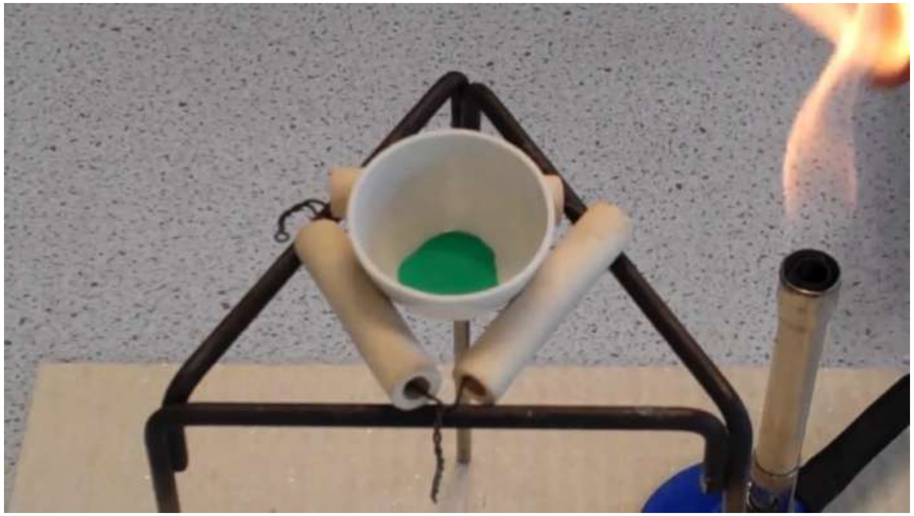
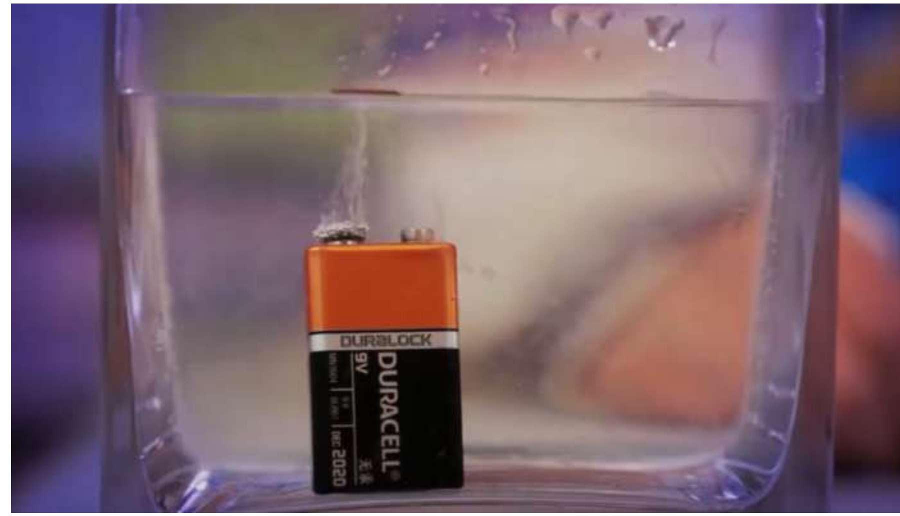
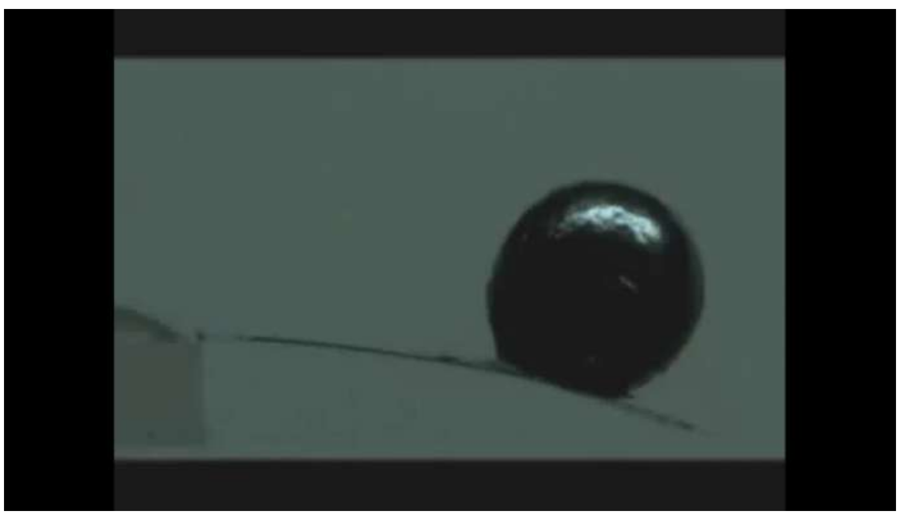
Thermal activation



Electrochemical activation



Photochemical activation



Mechanochemical activation

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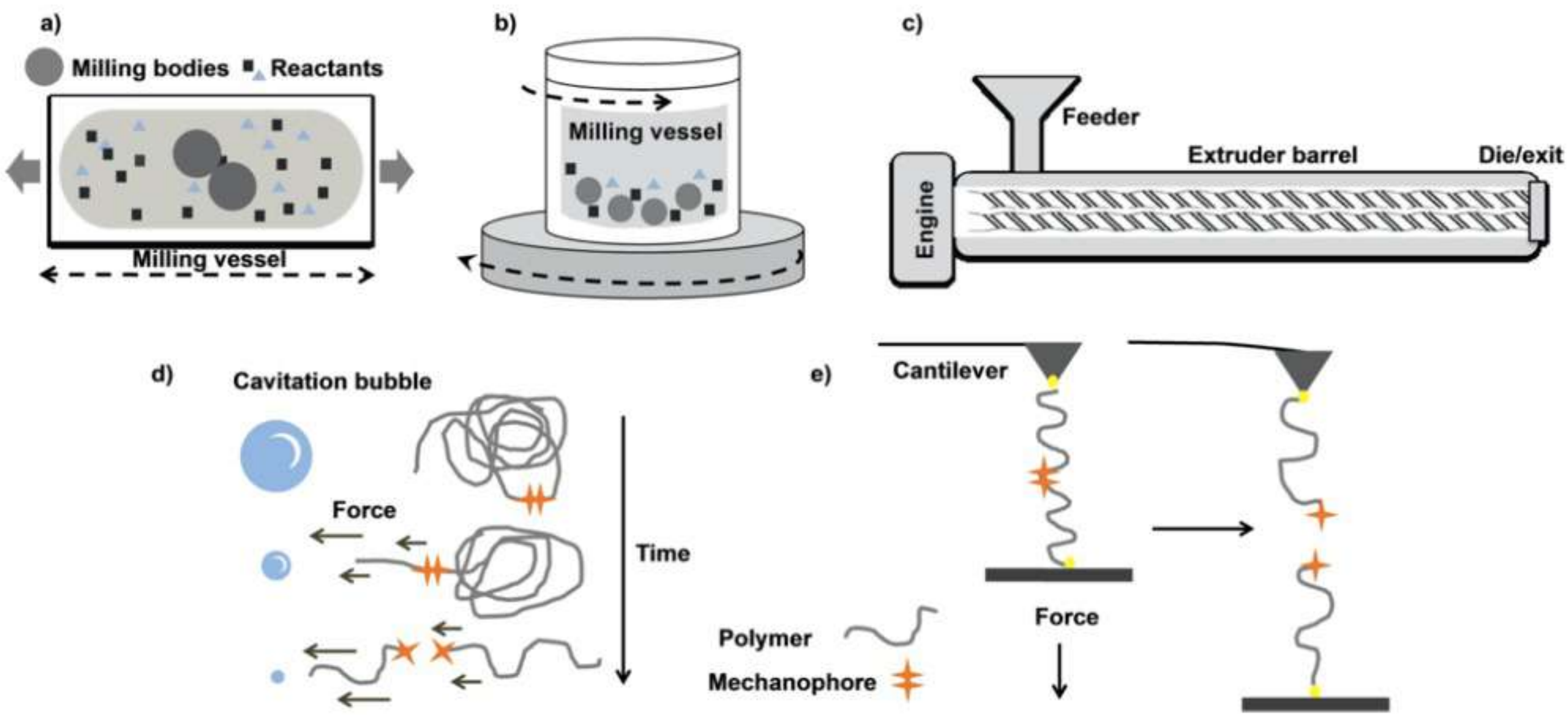
Mechanochemistry encompasses physico-chemical changes facilitated by the use of mechanical energy.



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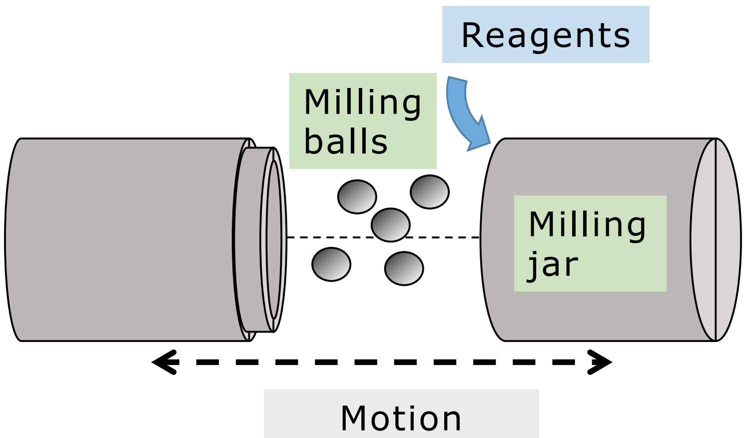
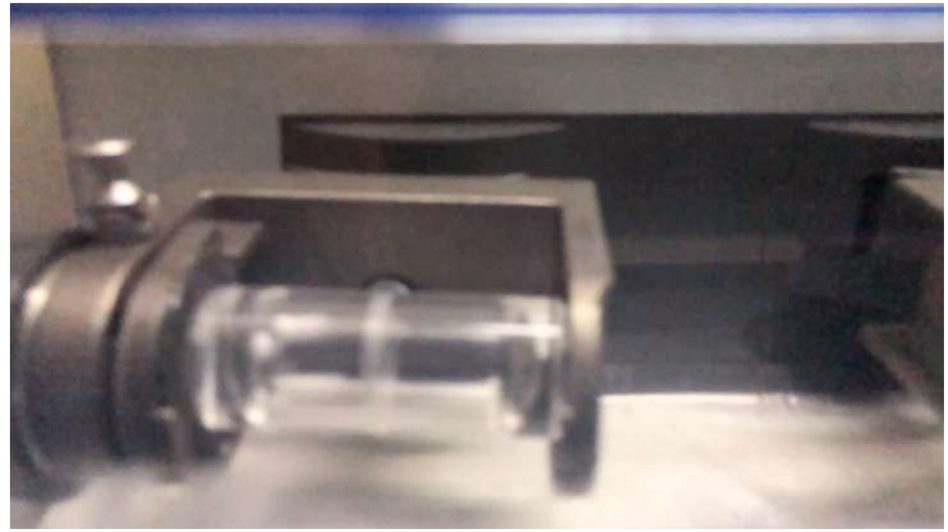
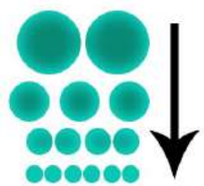
Mixer mill

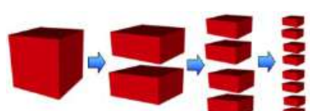


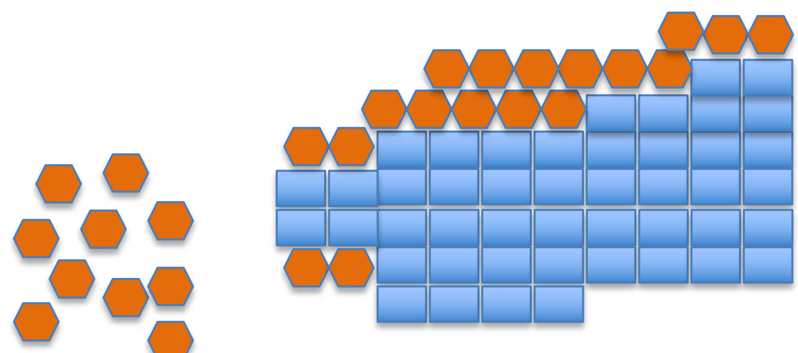


Effects of milling on the reactants

- **-Permanent defects**
- **-Transient defects**
- **-Dislocations**
- **-Amorphization**
- **-Metastable regions**
- **-Polymorphic transformations**







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Mechanochemistry enabled exploring unconventional chemical transformations

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Altering Product Selectivity by Mechanochemistry

José G. Hernández* and Carsten Bolm*

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https://doi.org/10.1021/acs.joc.6b02887

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Mechanochemistry: A Force of Synthesis

Jean-Louis Do and Tomislav Friščić*

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Publication Date: December 29, 2016
https://doi.org/10.1021/acscentsci.6b00277

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Mechanochemistry: New Tools to Navigate the Uncharted Territory of "Impossible" Reactions

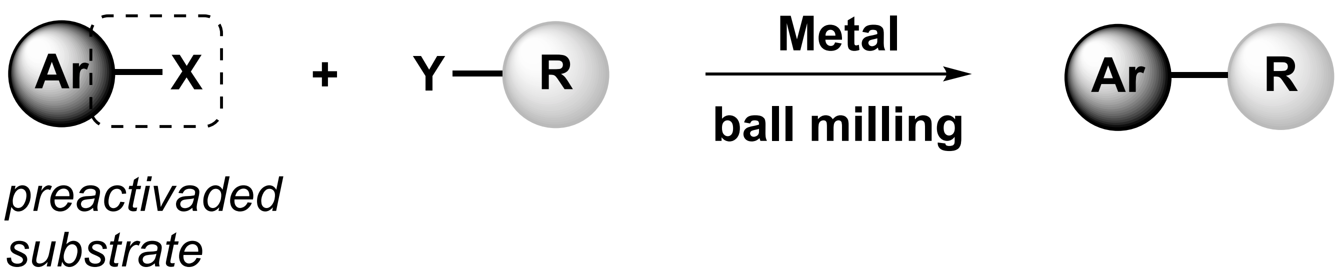
Federico Cuccu, Prof. Dr. Lidia De Luca, Prof. Dr. Francesco Delogu, Prof. Dr. Evelina Colacino, Prof. Dr. Niclas Solin, Dr. Rita Mocci, Prof. Dr. Andrea Porcheddu

First published: 21 July 2022 | https://doi.org/10.1002/cssc.202200362 | Citations: 55

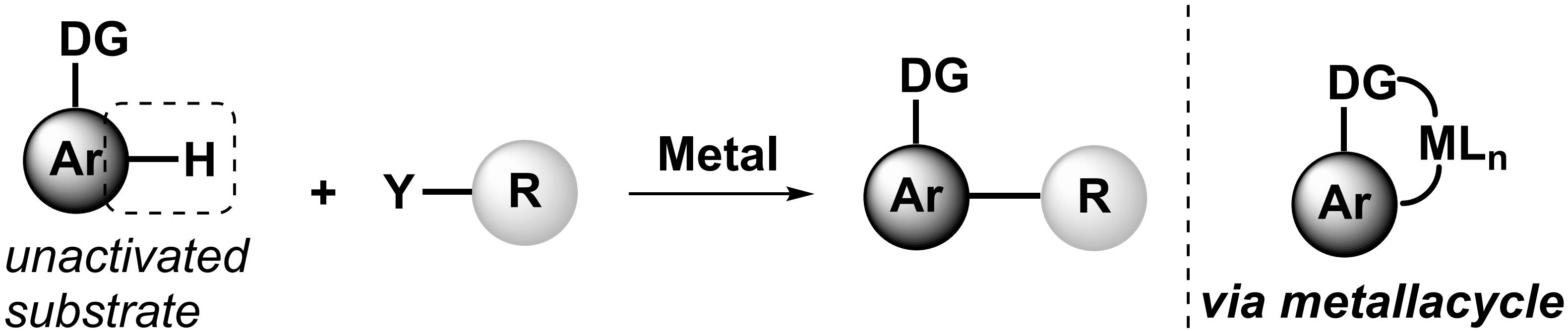
Activation of C–H bonds by mechanochemistry

Metal-catalyzed C–H bond functionalizations

Mechanochemical cross-coupling reactions



Direct C–H bond functionalization



DG = directing group; **M** = metal; **L** = ligand

Chem. Eur. J. **2017**, *23*, 17157.

Dalton Transactions

PERSPECTIVE

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Cite this: DOI: 10.1039/c5dt03866a

Advances in organometallic synthesis with mechanochemical methods

Nicholas R. Rightmire and Timothy P. Hanusa*

Solvent-based syntheses have long been normative in all areas of chemistry, although mechanochemical methods (specifically grinding and milling) have been used to good effect for decades in organic, and to a lesser but growing extent, inorganic coordination chemistry. Organometallic synthesis, in contrast, represents a relatively underdeveloped area for mechanochemical research, and the potential benefits are considerable. From access to new classes of unsolvated complexes, to control over stoichiometries that have not been observed in solution routes, mechanochemical (or 'M-chem') approaches have much to offer the synthetic chemist. It has already become clear that removing the solvent from an organometallic reaction can change reaction pathways considerably, so that prediction of the outcome is not always straightforward. This *Perspective* reviews recent developments in the field, and describes equipment that can be used in organometallic synthesis. Synthetic chemists are encouraged to add mechanochemical methods to their repertoire in the search for new and highly reactive metal complexes and novel types of organometallic transformations.

Received 3rd October 2015,
Accepted 5th January 2016

DOI: 10.1039/c5dt03866a

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1. Introduction

All of us involved with chemistry are reminded—perhaps not often enough—to "question our assumptions" about concepts and conventions that seem too well-established or reasonable to doubt.[1] It is prudent advice, as the failure to reconsider long-held beliefs has repeatedly stalled advances in multiple areas of science, including synthetic studies. Entire chemical families, such as molecular complexes containing 'inaccessible' divalent lanthanides (*e.g.*, those with Pr^{II}, Gd^{II}, Ho^{II}, and others[2,3]), or compounds of the 'unreactive' noble gases,[4,5] were at one time thought to be unisolable, for seemingly impeccable scientific reasons. Yet an assumption far older and

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Nicholas R. Rightmire

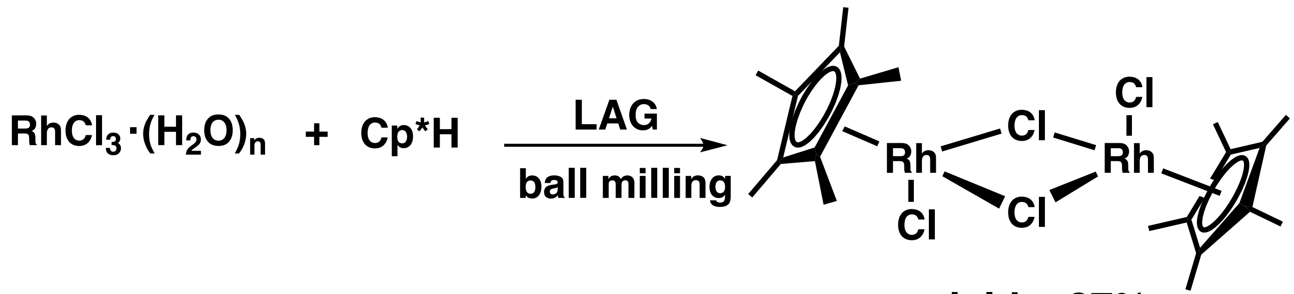
Nicholas R. Rightmire is a native of Cincinnati, Ohio, and received his bachelor's degree in chemistry from Bellarmine University (Louisville, Kentucky) in 2010. He completed his graduate studies in 2015 at Vanderbilt University in Nashville, Tennessee, working in the group of T. P. Hanusa on the chemistry of sterically bulky allyl complexes. He is currently studying f-element chemistry in a postdoctoral appointment with William J. Evans at the University of California, Irvine.

Timothy P. Hanusa

Timothy P. Hanusa received his bachelor's degree in chemistry from Cornell College (Mount Vernon, Iowa). He received his Ph.D. in 1983 from Indiana University, Bloomington, working with heteroboranes under the direction of Lee J. Todd. After postdoctoral research on organolanthanides with William J. Evans at Irvine, California, he joined the chemistry faculty at Vanderbilt University in Nashville, Tennessee in 1985, where he is now Professor of Chemistry. His research has focused on organometallic complexes of the main group elements, and on magnetically variable compounds of the transition metals. More recently, he is investigating mechanochemical approaches to organometallic synthesis across the periodic table.

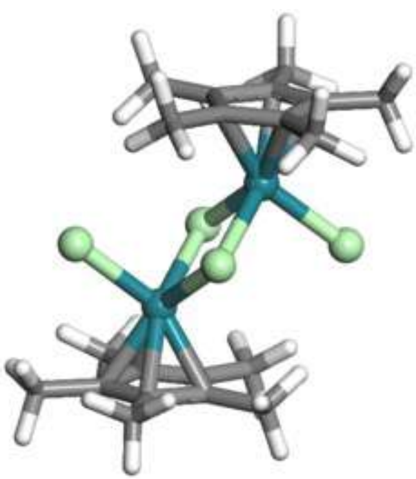
Dalton Trans, **2016**, *45*, 2352.

-Mechanosynthesis of $[Cp^*RhCl_2]_2$



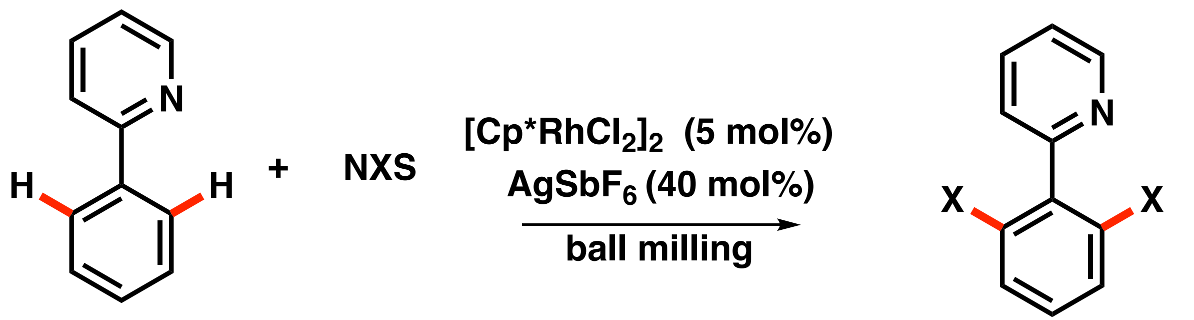
yield = 87%

Hernández, J. G.; Bolm, C. *Chem. Commun*. **2015**, *51*, 12582.



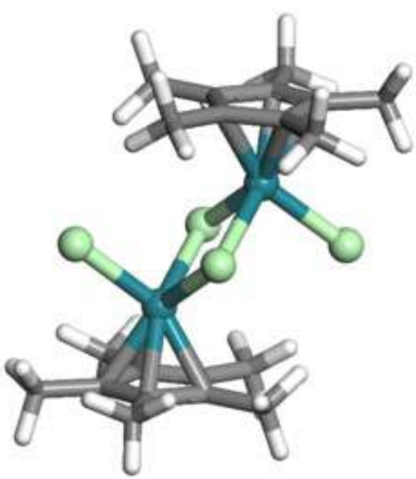
Prof. Carsten Bolm

-Mechanochemical C–H funcionalization



X = Br; yield 74%
X = I; yield 84%

Hernández, J. G.; Bolm, C. *Chem. Commun*. **2015**, *51*, 12582.



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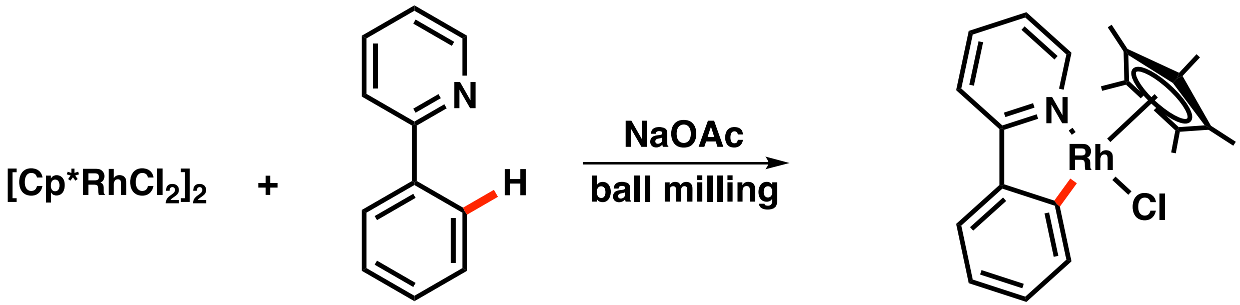
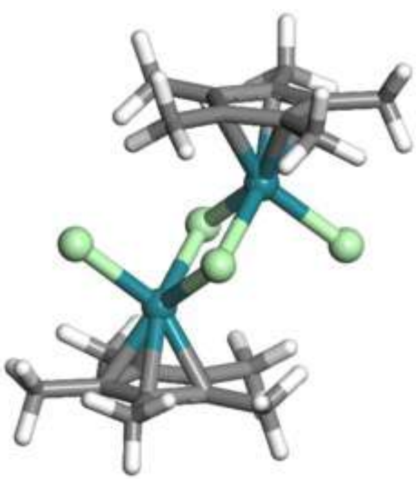
-Synthesis of the rhodacycle [Cp*Rh(PhPy)Cl] by ball milling



yield = 89%

Hernández, J. G.; Bolm, C. *Chem. Commun*. **2015**, *51*, 12582.



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DIAMOND OPEN ACCESS

Palladium-catalyzed *ortho*-halogenations of acetanilides with *N*-halosuccinimides via direct sp^2 C–H bond activation in ball mills

n-Wu Wang[1,2]

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Mechan

Function

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Gary N. He

Organic Letters

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n: C-2

Iridium-Catalyzed Cage B(4)-Amidation Reaction of *o*-Carboranes with Dioxazolones: Selective Synthesis of Amidated *o*-Carboranes and Amidated and Methoxycarbonylated *nido*-Carboranes

Gi Uk Han, Yonghyeon Baek, Kyungsup Lee, Seohyun Shin, Hee Chan Noh, and Phil Ho Lee*

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Synthesis & Catalysis

Publication Date: December 16, 2020

https://doi.org/10.1021/acssuschemeng.0c07465

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Mechanochemical Cobalt-Catalyzed C–H Bo

by Ball Milling

ternationa

Full Paper | Full Access

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

The Journal of Organic Chemistry

Angewandte International Edition Chemie

Mechanochemically Activated Oxidative Coupling of Indoles with Acrylates through C–H Activation: Synthesis of 3-Vinylindoles and β,β-Diindolyl Propionates and Study of the Mechanism

Kan-Yan Jia†, Jing-Bo Yu‡, Zhi-Jiang Jiang‡, and Wei-Ke Su*‡

arević, Dr. Ivica Đilović, Dajana Barišić, ić

01802403 | Citations: 17

: 40

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Mechanochemical Rh

Alkynylations of Indol

Mills

Gary N. Hermann, Marvin T. Unruh, Se-Hyeong Jung, Maik Krings, Prof. Dr. Carsten Bolm

First published: 11 June 2018 | https://doi.org/10.1002/anie.201805778 | Citations: 40

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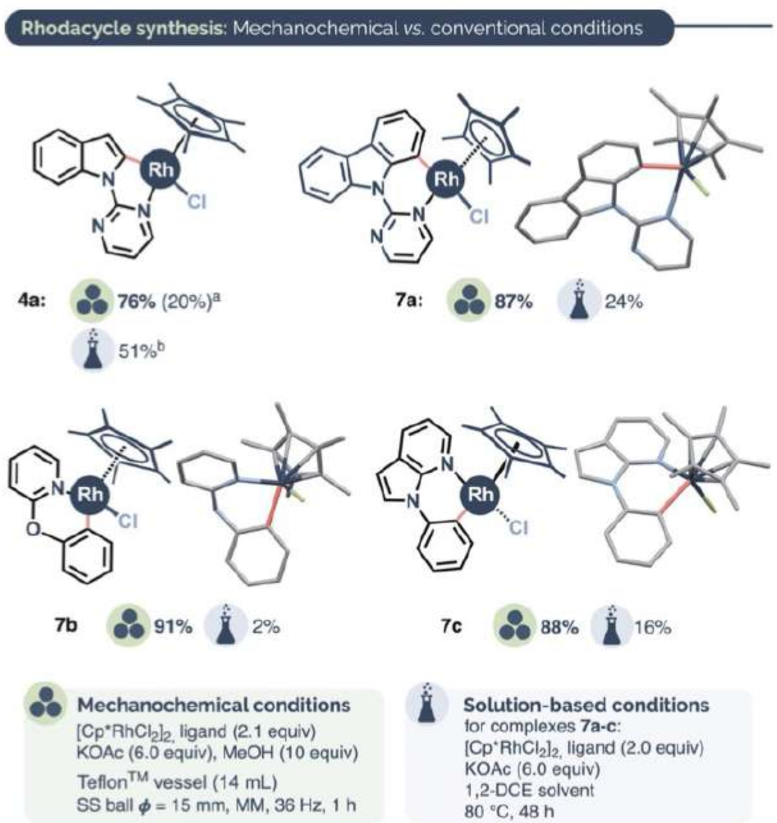
Angewandte Chemie International Edition
GDCh — A Journal of the German Chemical Society

Research Article | Open Access

Mechanochemical Solvent-Free Catalytic C–H Methylation

Dr. Shengjun Ni, Matic Hribersek, Swarna K. Baddigam, Fredric J. L. Ingner, Dr. Andreas Orthaber, Dr. Paul J. Gates, Dr. Lukasz T. Pilarski

First published: 08 October 2020 | https://doi.org/10.1002/anie.202010202 | Citations: 25



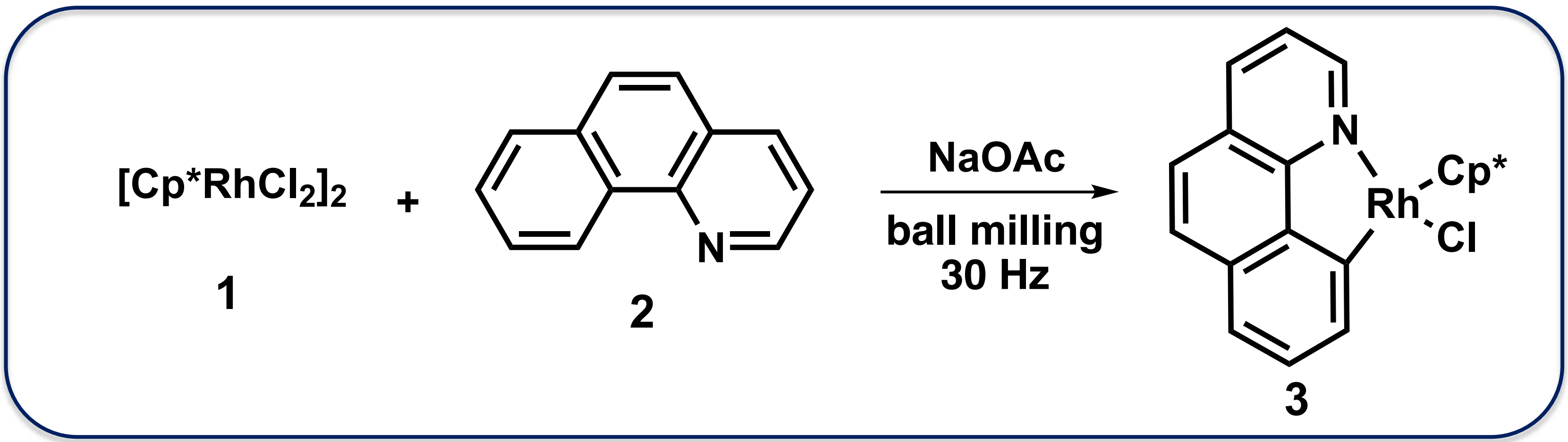
"We […] described **the considerable superiority** of ball milling for the synthesis of five- and especially six-membered rhodacyclic species that are difficult to generate conventionally."

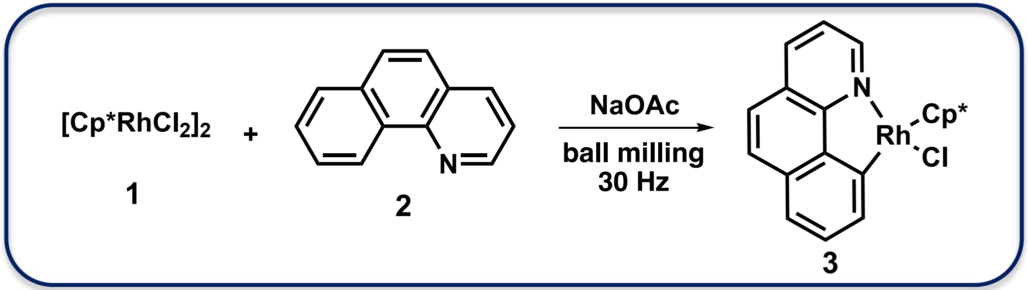
How do mechanochemically acetate-assisted C–H activations with $[Cp^*RhCl_2]_2$ occur?

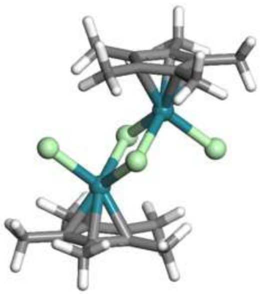
How do mechanochemically acetate-assisted C–H activations with $[Cp^*RhCl_2]_2$ occur?

Why do acetate-assisted C–H activations with $[Cp^*RhCl_2]_2$ proceed more efficiently by mechanochemistry?

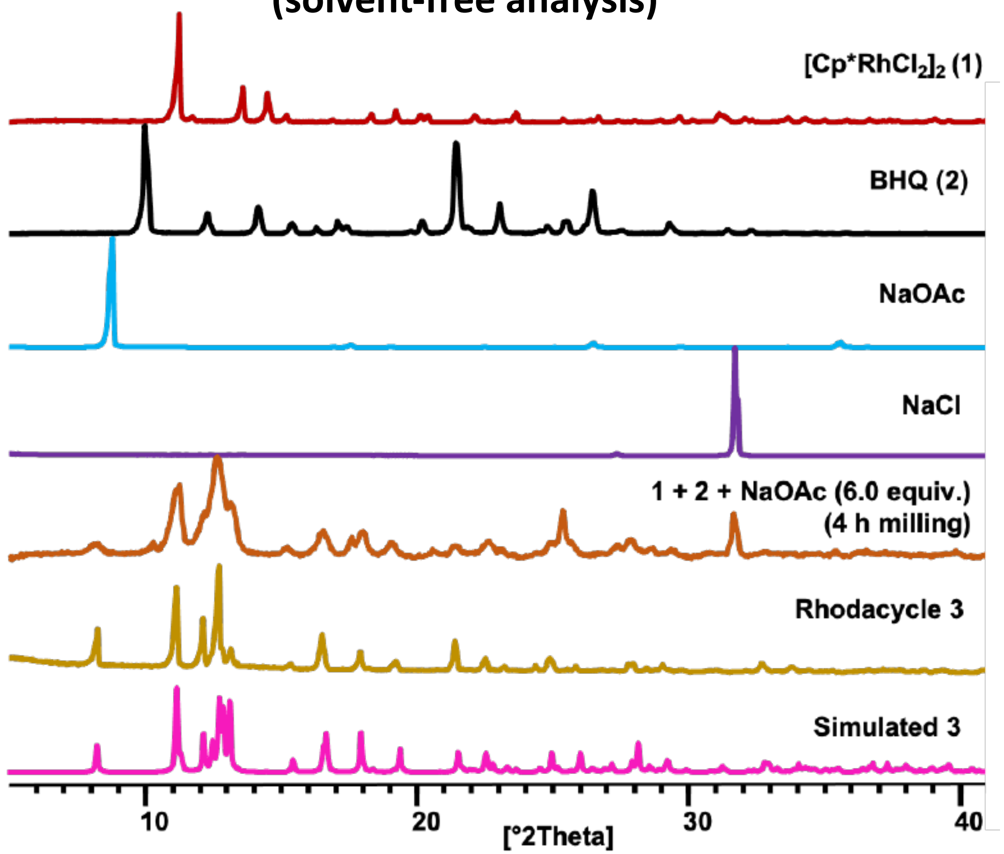
Mechanistic Study of the Mechanochemically Acetate-Assisted C–H Activation with $[Cp^{*}RhCl_2]_2$

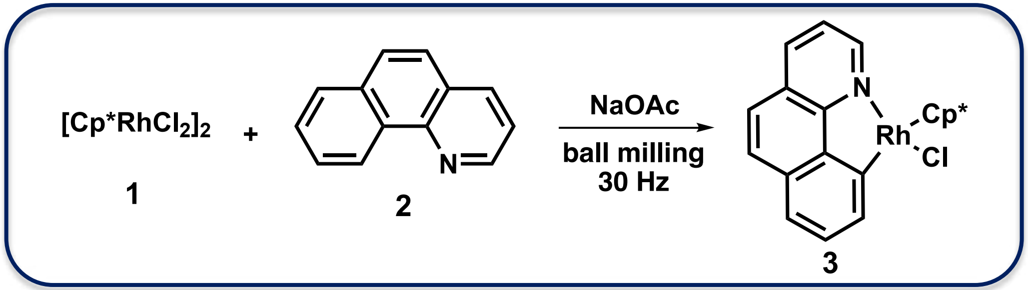




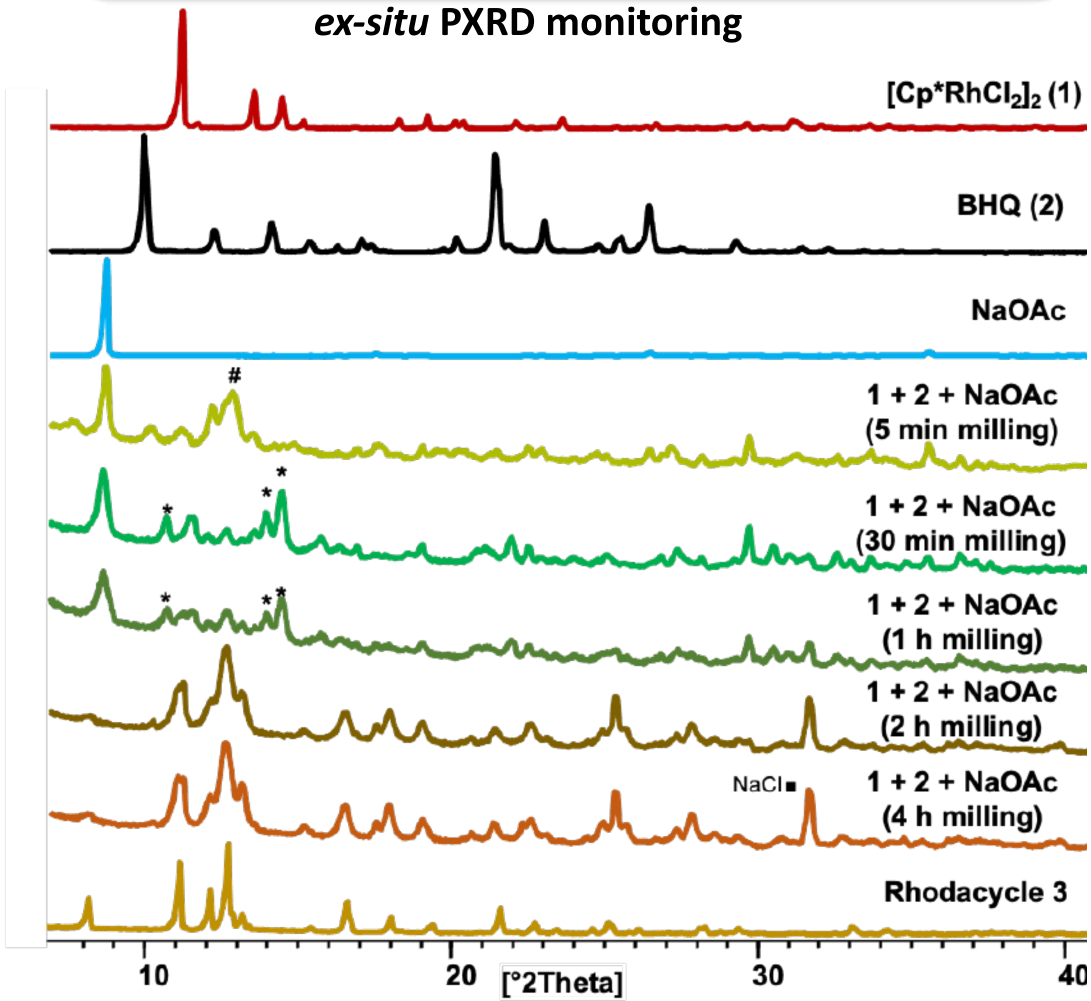


Powder X-Ray Diffraction (PXRD) analysis (solvent-free analysis)

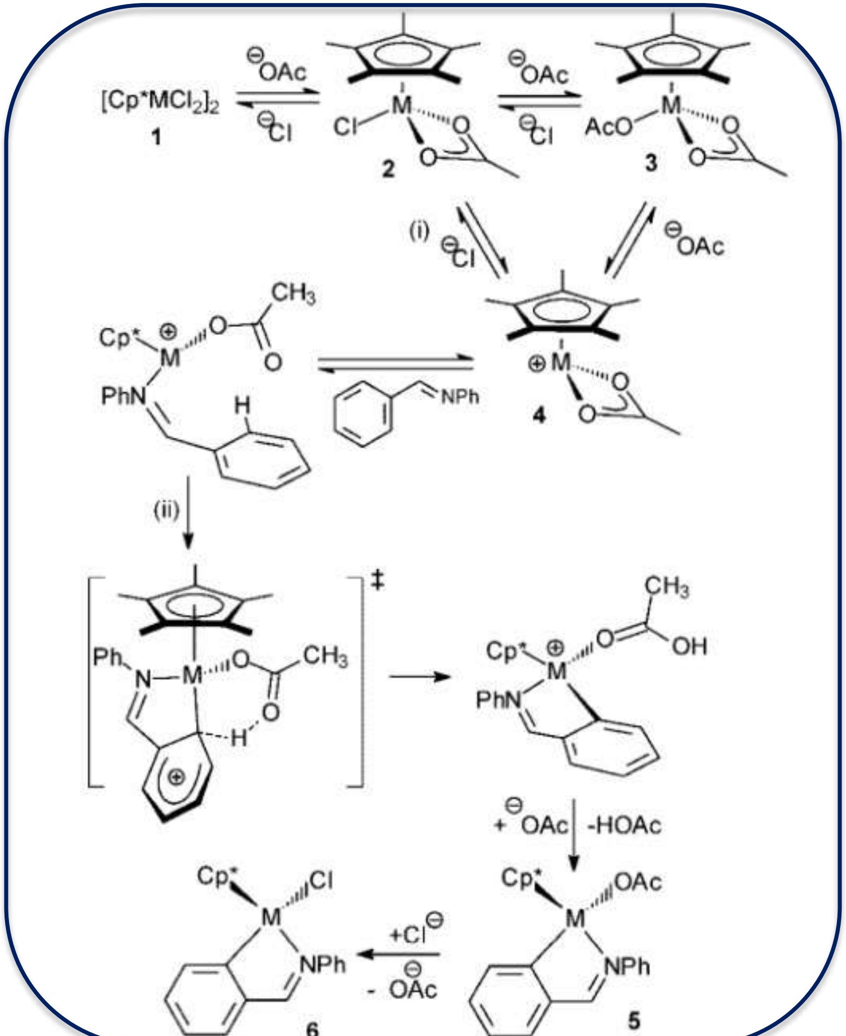


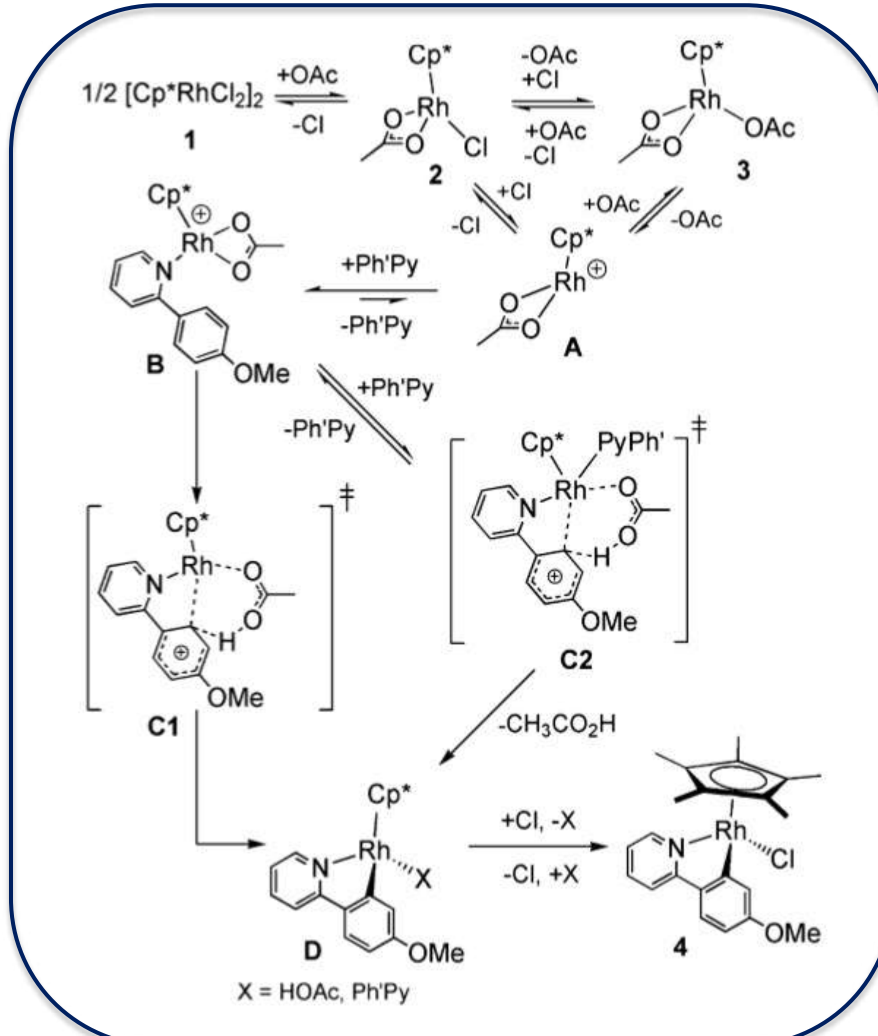


ex-situ **PXRD monitoring**



Concerted Metalation Deprotonation (CMD)

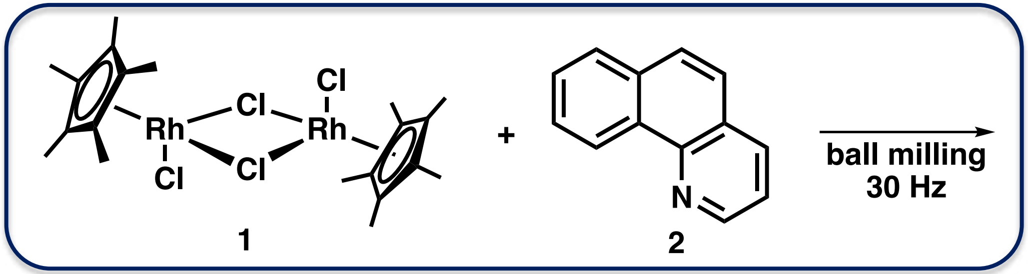


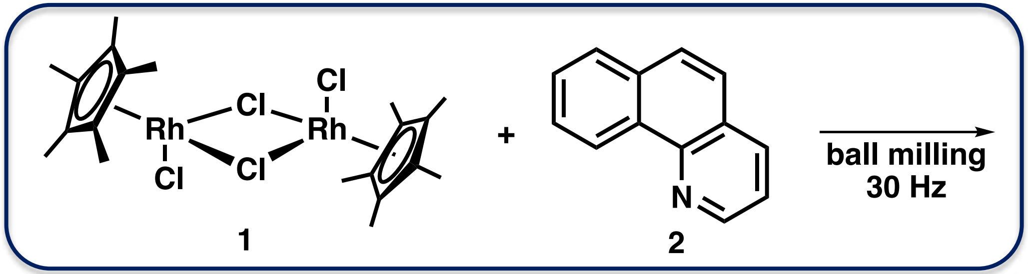


L. Li, W. W. Brennessel, W. D. Jones, *Organometallics* **2009**, *28*, 3492.

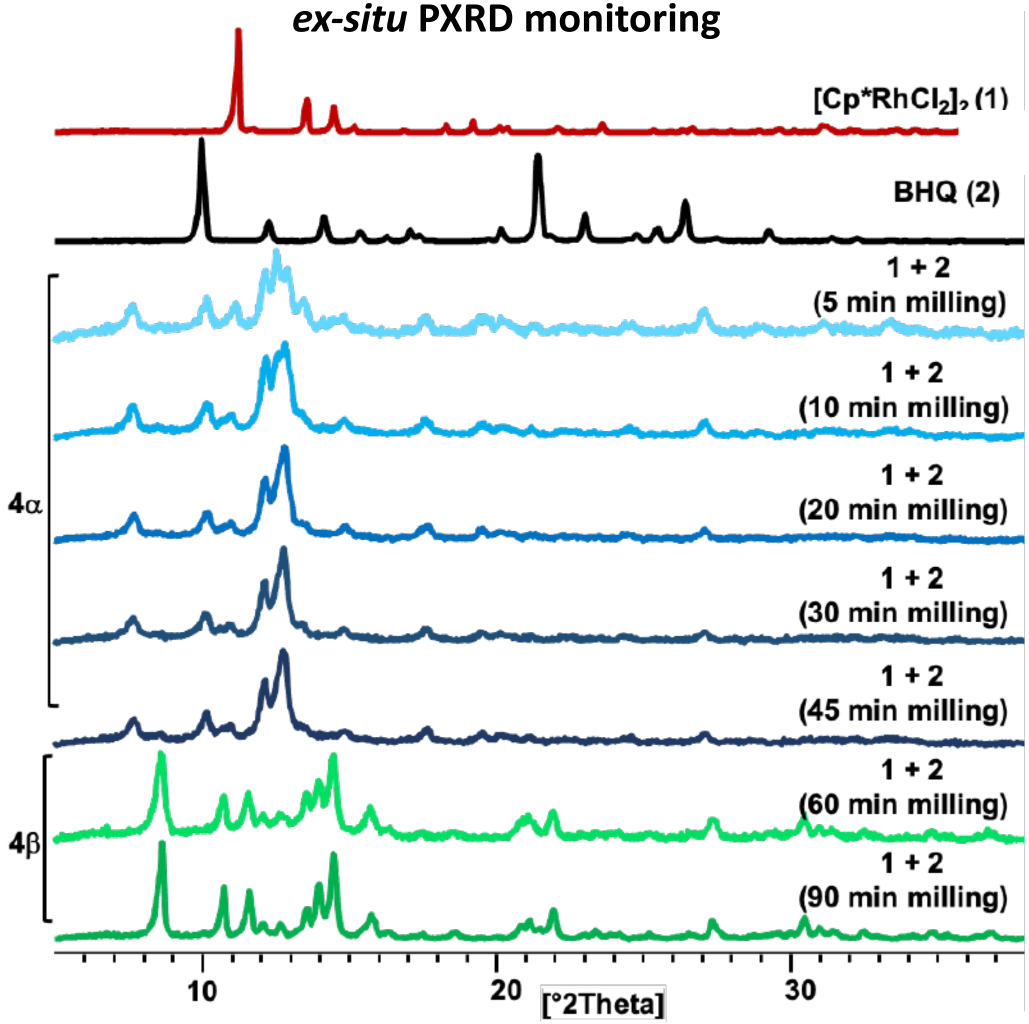
A. P. Walsh, W. D. Jones, *Organometallics* **2015**, *34*, 3400.

A. I. VanderWeide, W. W. Brennessel, W. D. Jones, *J. Org. Chem.* **2019**, *84*, 12960


Rh
Cl
Cl
Rh
Cl
Cl
1
+
N
2
ball milling
30 Hz



ex-situ PXRD monitoring



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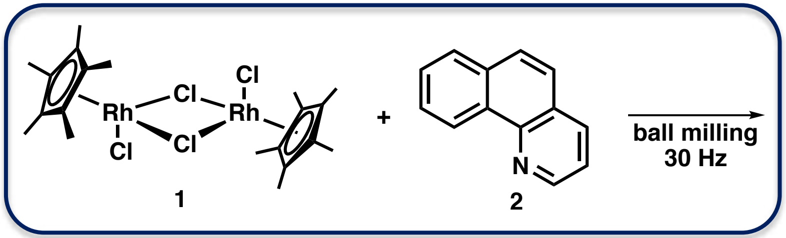
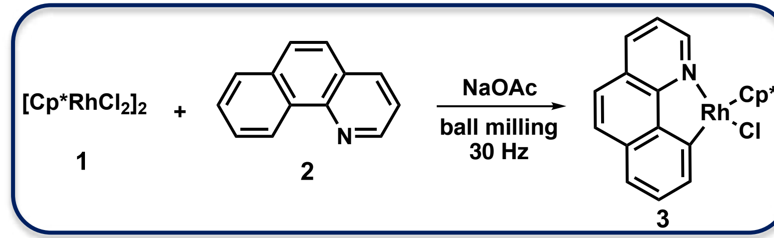
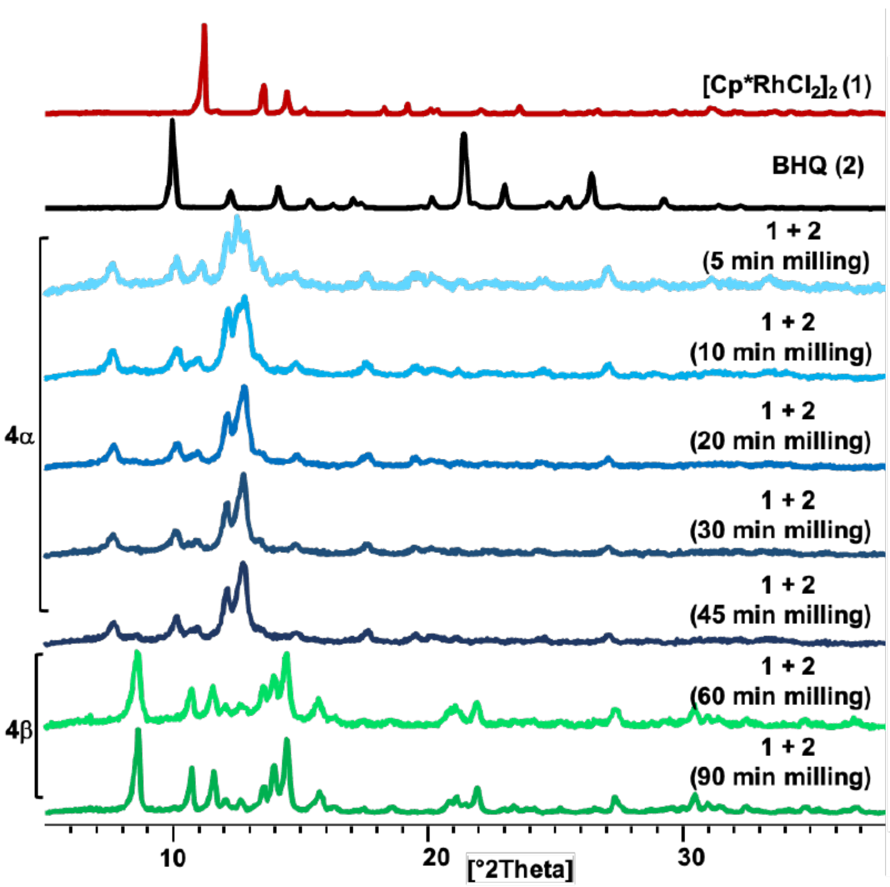
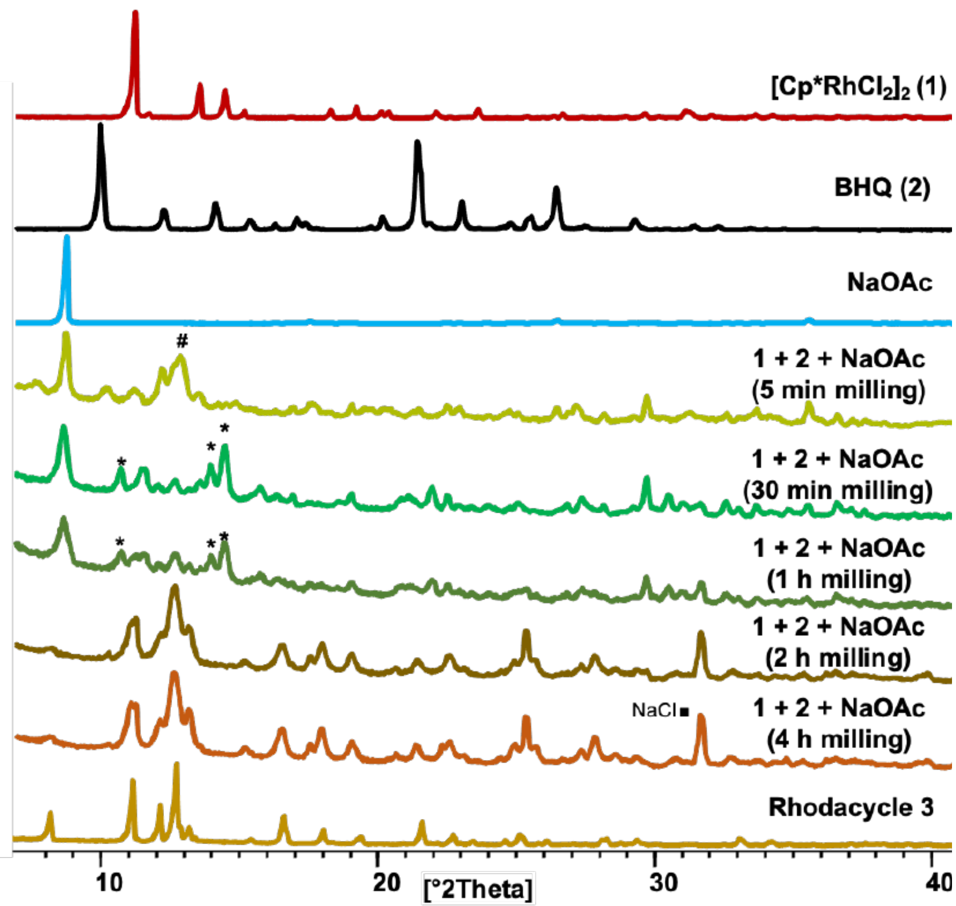




ex-situ PXRD monitoring





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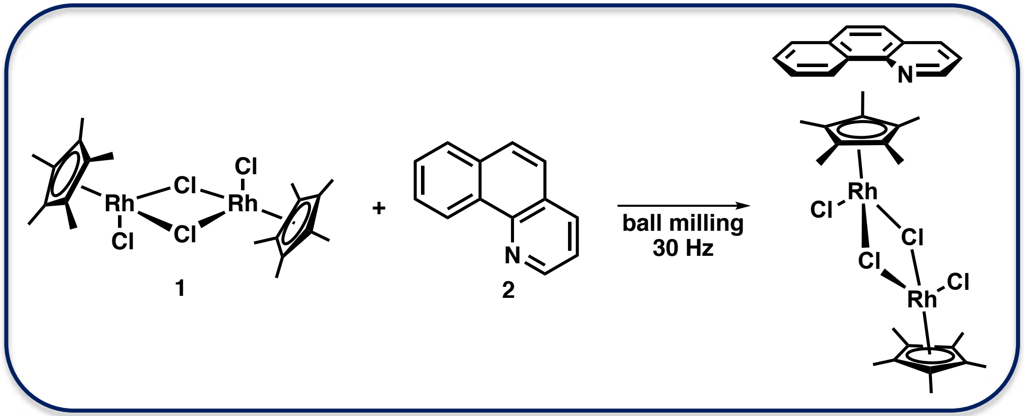
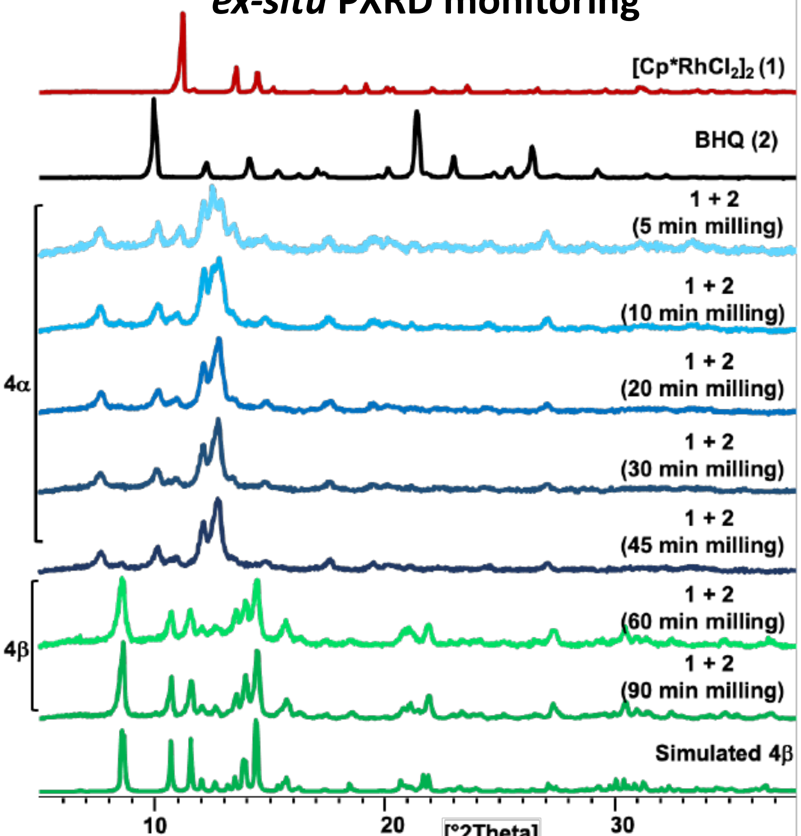
Could 4α and 4β be intermediates of the mechanochemical C–H bond activation of BHQ?

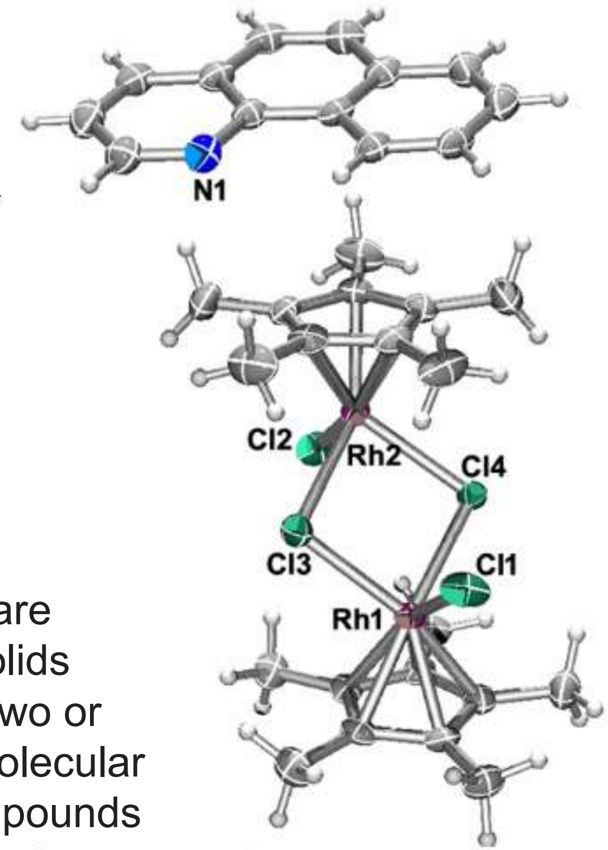
What do 4α and 4β look like?



Molecular structure for 4α

ex-situ PXRD monitoring





Cocrystals are crystalline solids composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio.

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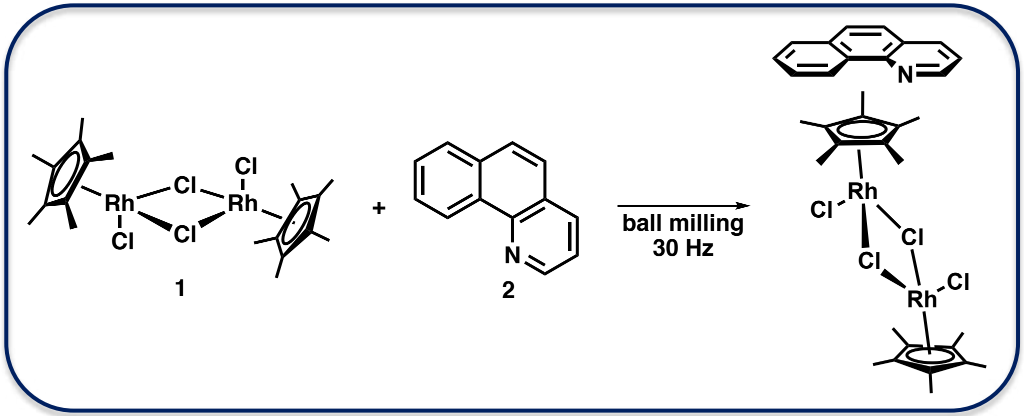
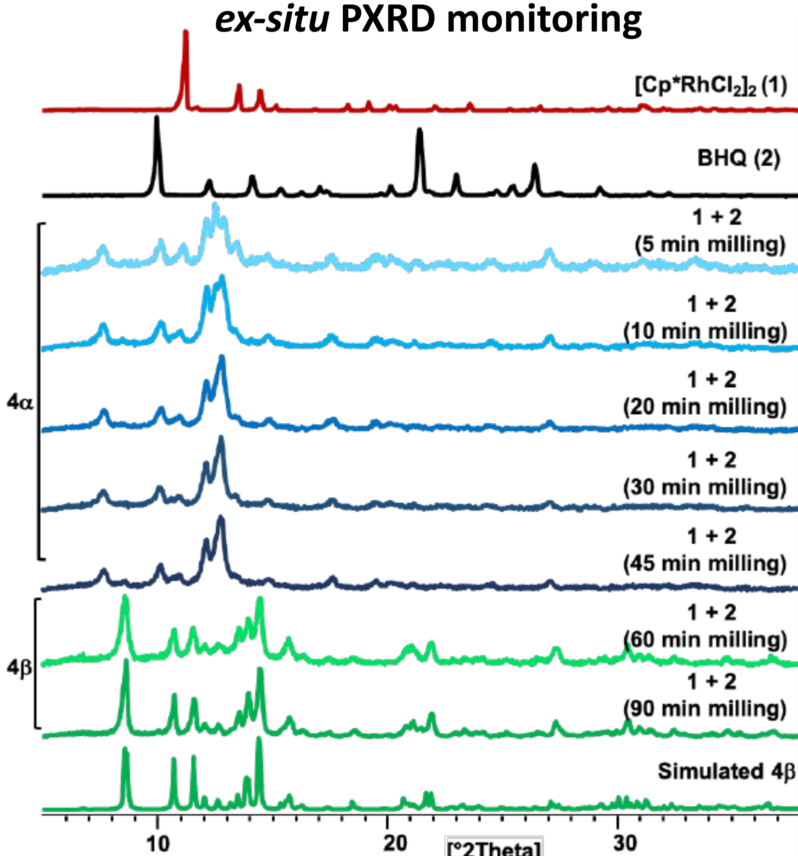
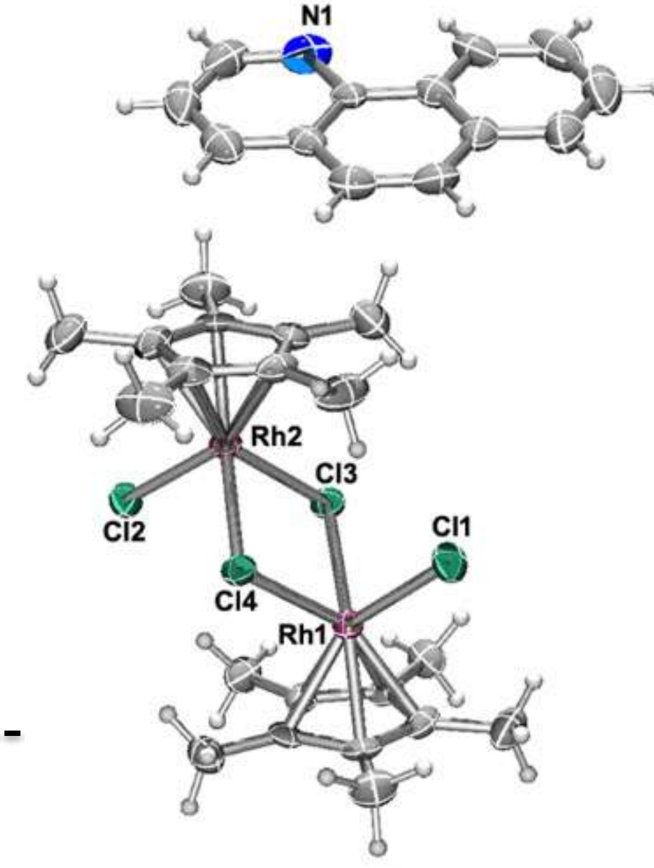


ex-situ PXRD monitoring



Molecular structure for 4β



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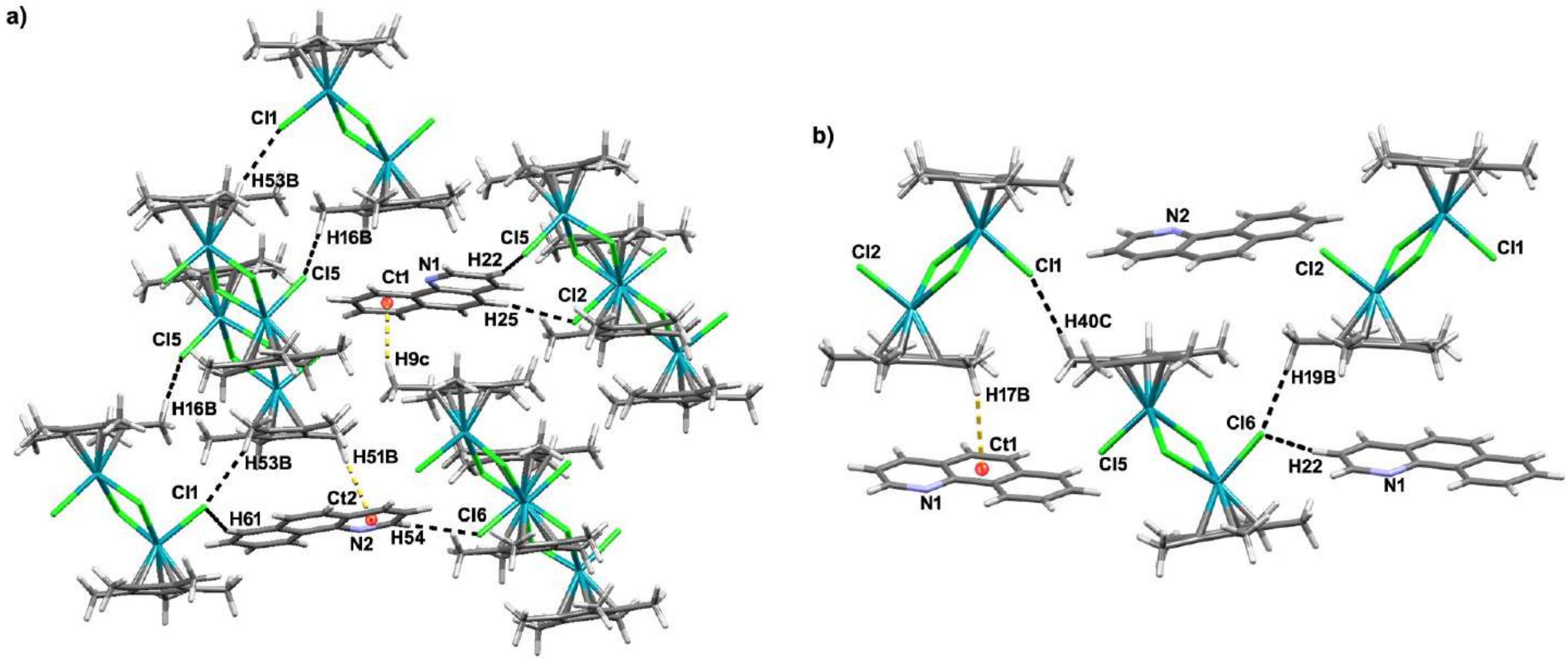
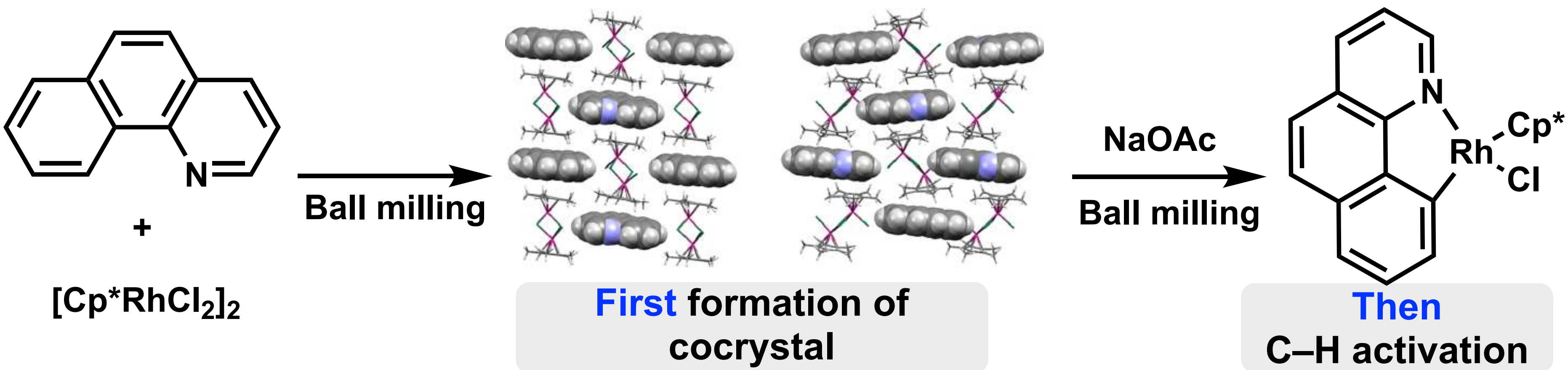
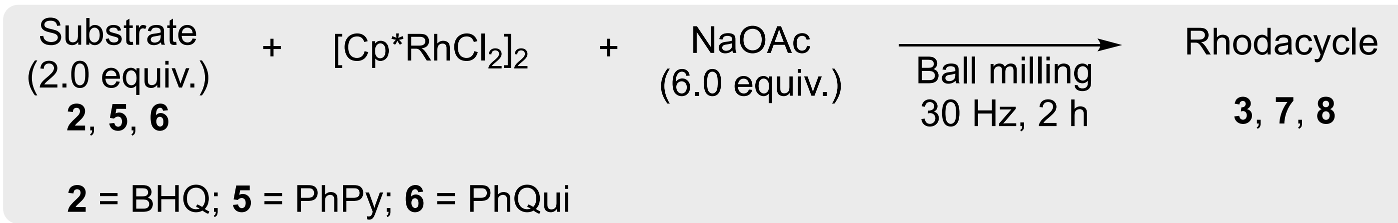


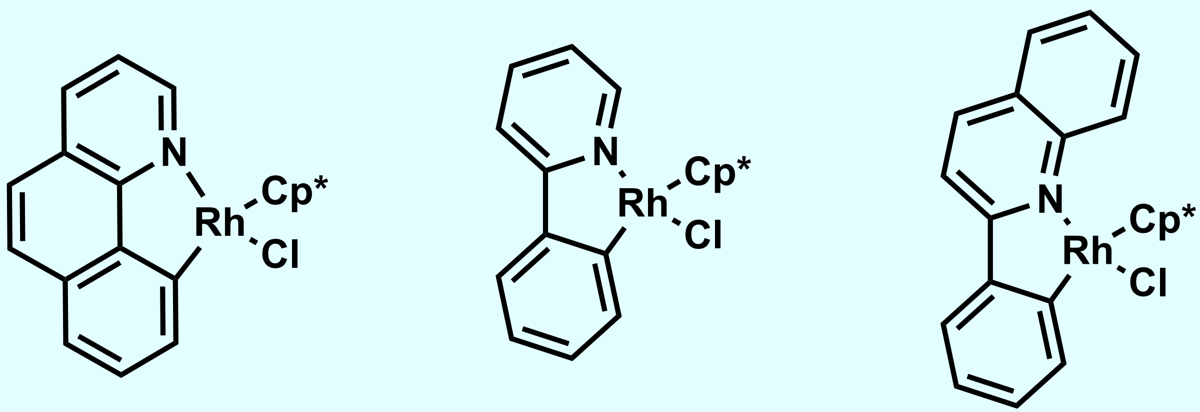
Crystal packing in: a) **4α** and b) **4β**. C–H···Cl interactions are highlighted as black dashed lines, while C–H··· π interactions are highlighted in yellow. In figure a), Ct1 and Ct2 refers to the centroids of the outer aromatic rings of BHQ molecules, while in b) Ct1 refers to the centroid of the inner aromatic ring of BHQ.

Under mechanochemical conditions



But, how general is the formation of cocrystals before the C–H activation step?



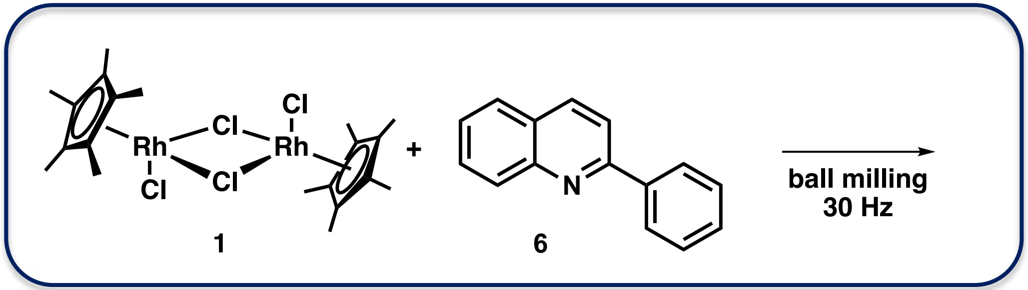


3 yield = 78%

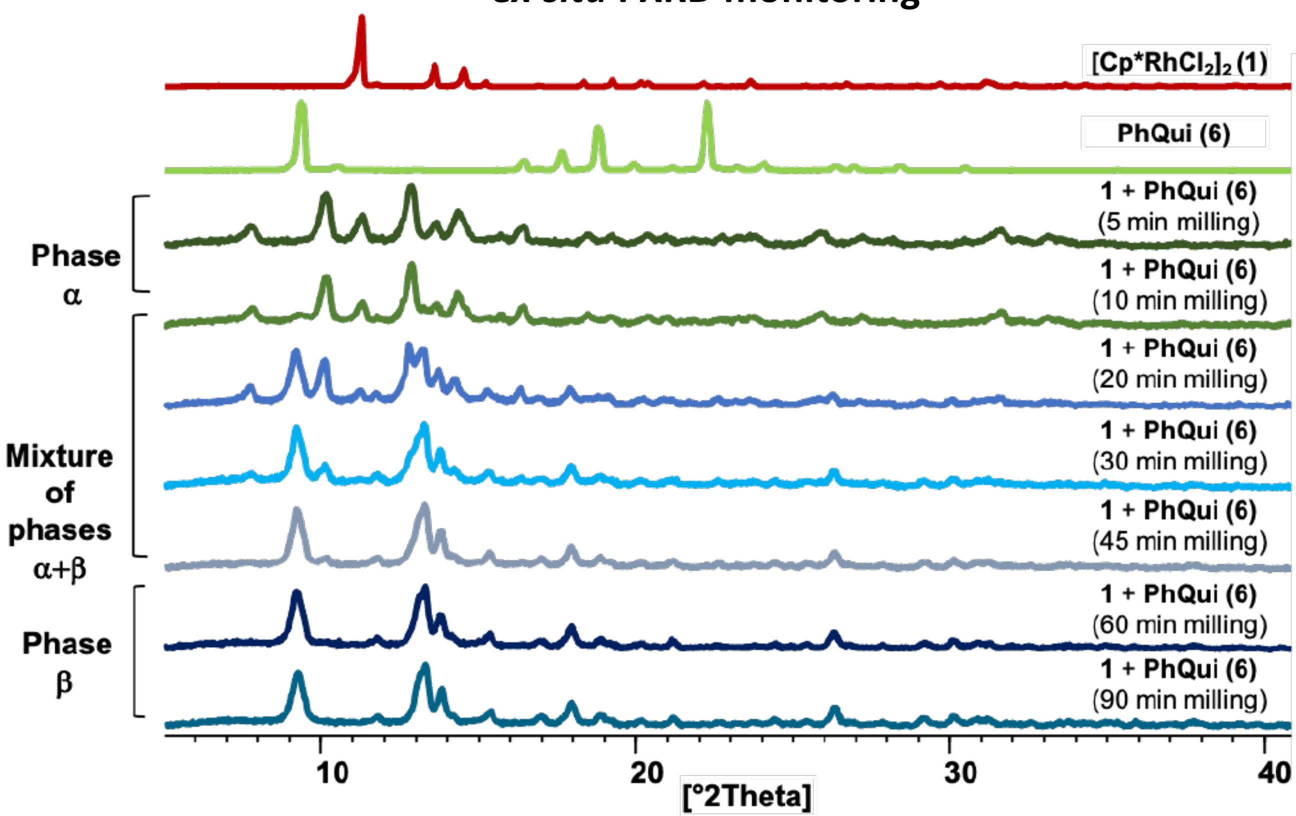
7 yield = 76%

8 yield = 52%

But how general is the formation of cocrystals before the C–H activation step?



ex-situ PXRD monitoring



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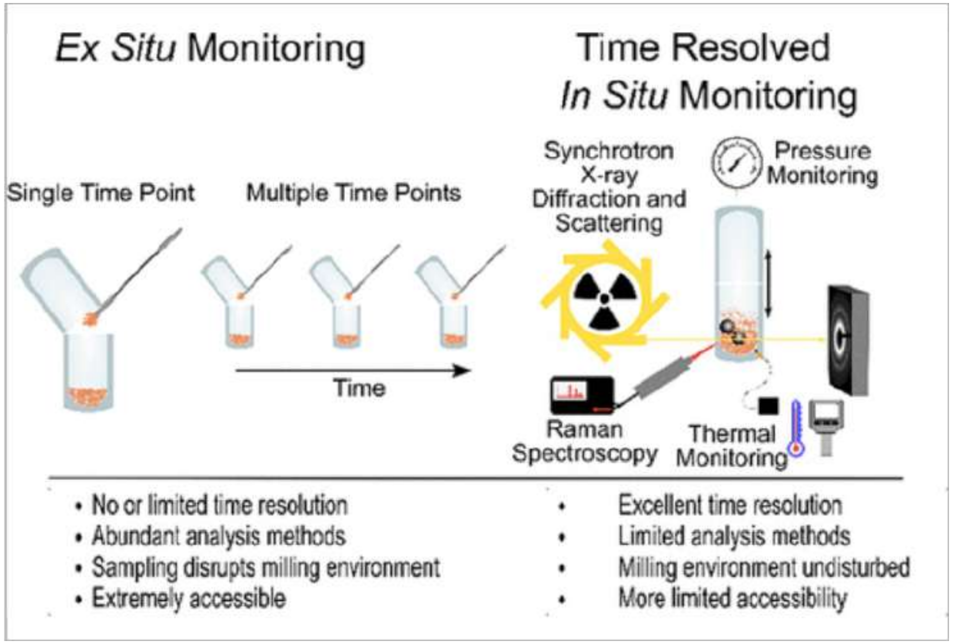
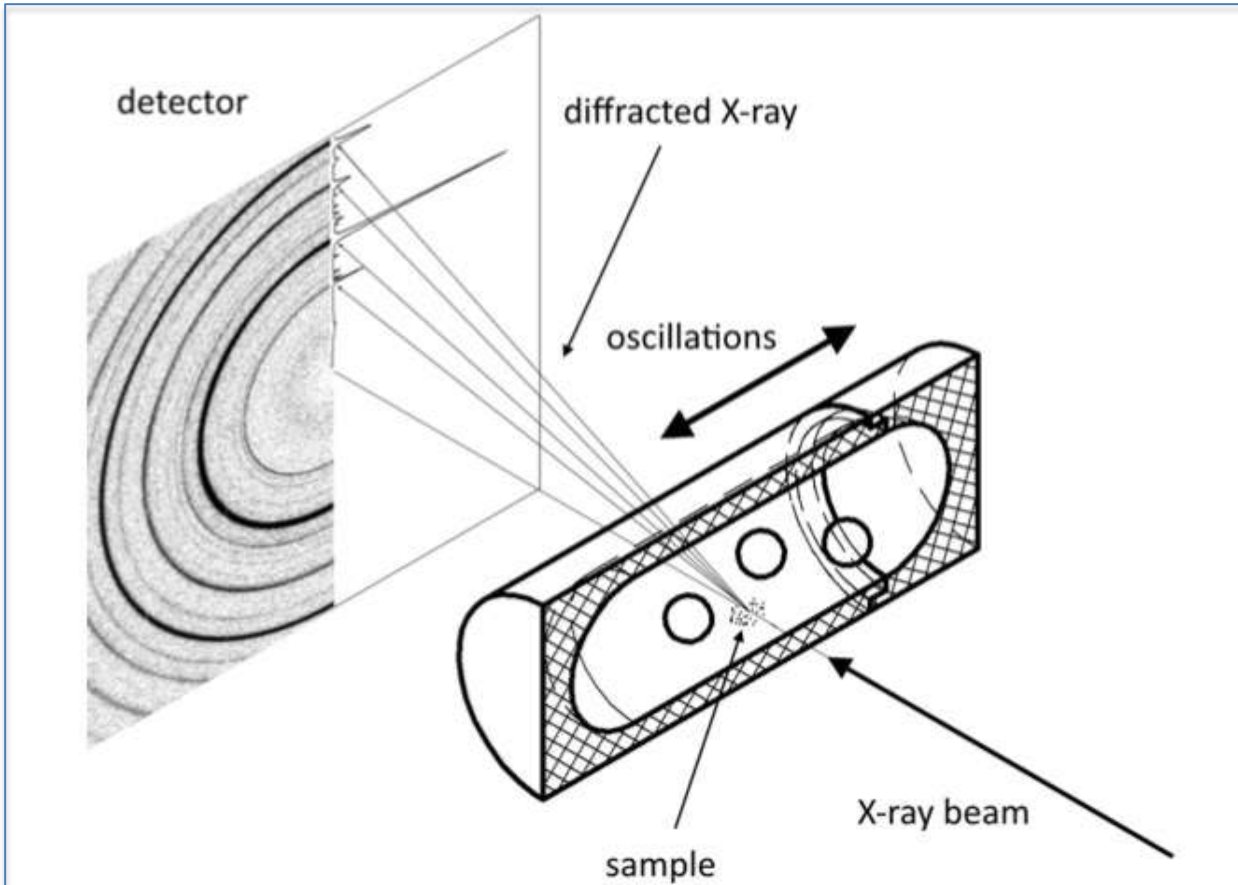
Are the cocrystals really present in the reaction or were they an artifact formed because of the ex situ monitoring?



Cryst. Growth Des. **2022**, 22, 5726–5754

How are the cocrystals involved in the mechanochemically induced C–H bond activation?

in situ real-time monitoring by powder X-ray diffraction (PXRD)



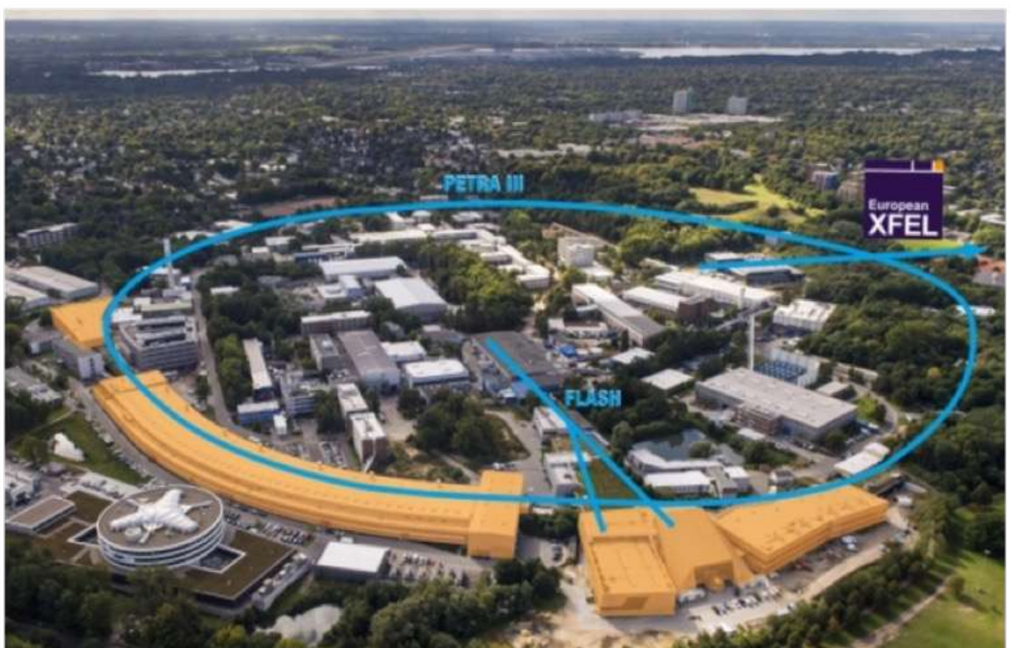
N. Tumanov, et al. *J. Appl. Cryst*. **2017**, *50*, 994.

in situ real-time monitoring by powder X-ray diffraction (PXRD)

DESY.

Deutsches Elektronen-Synchrotron · DESY Group PETRA III

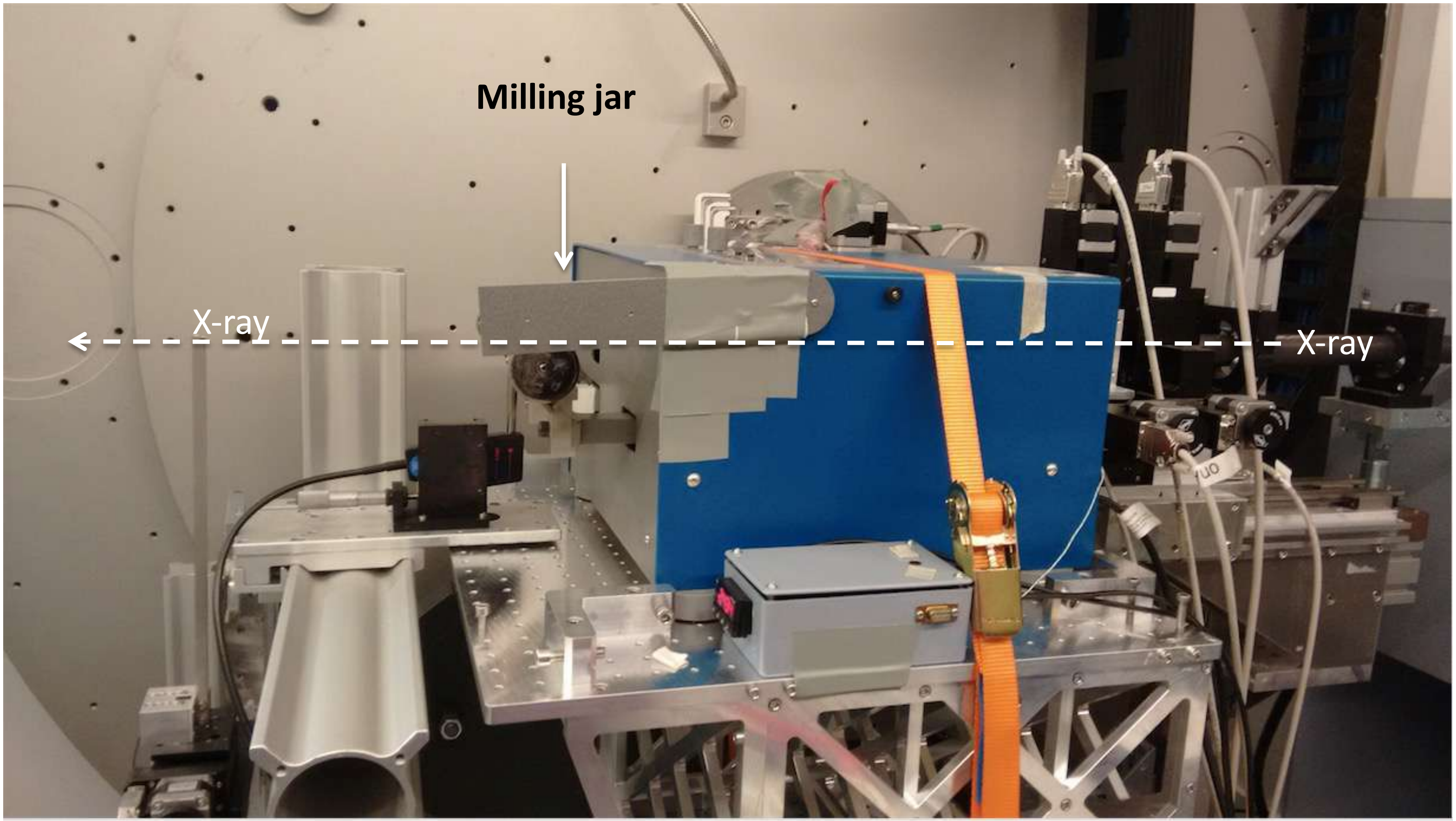
Dr. Martin Etter

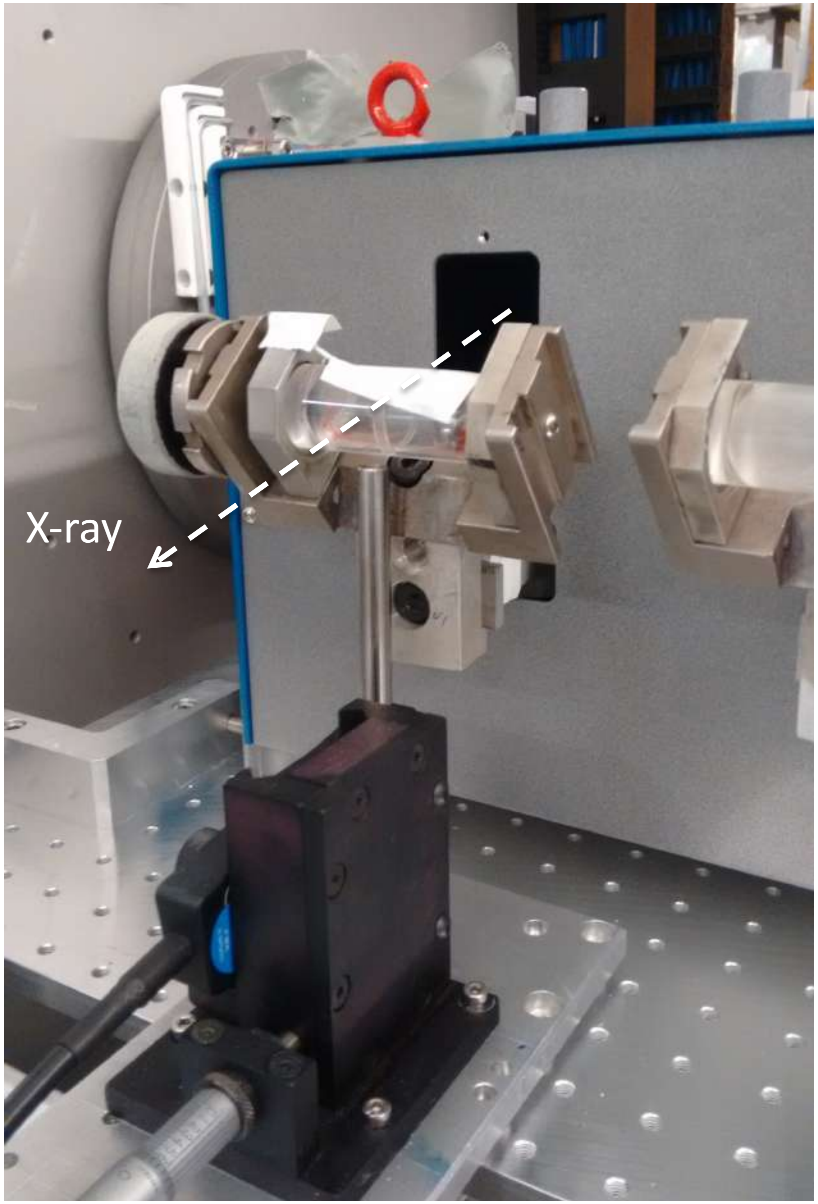


Dr. Tomislav Stolar

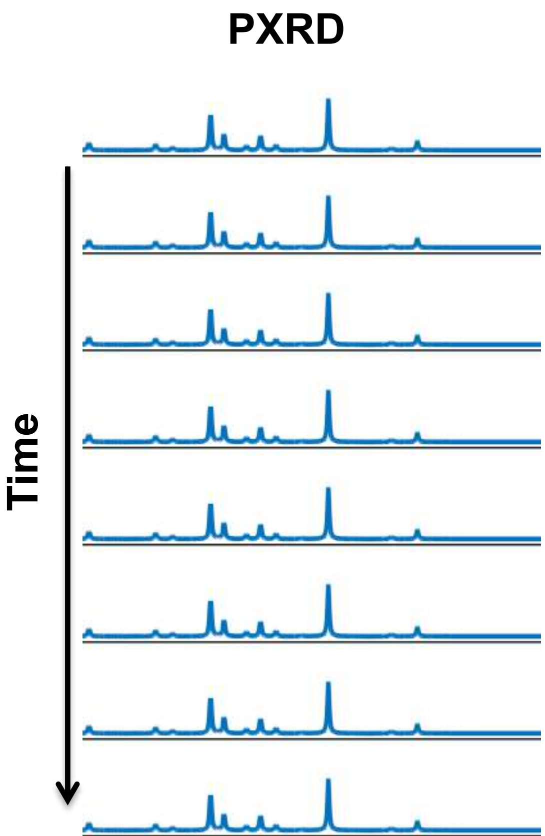
Institut Ruđer Bošković

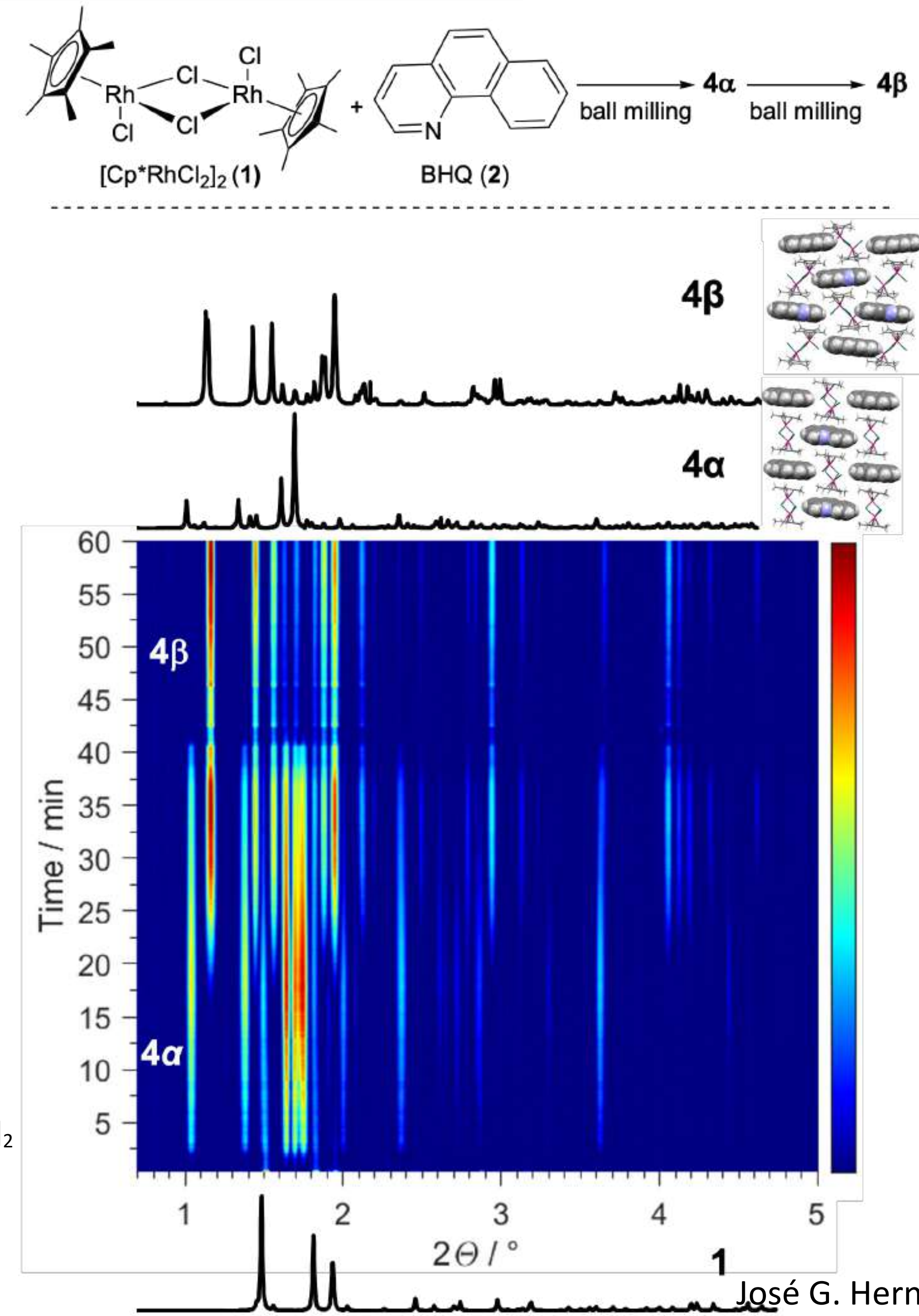
BAM
Bundesanstalt für Materialforschung und -prüfung


Milling jar
X-ray
X-ray

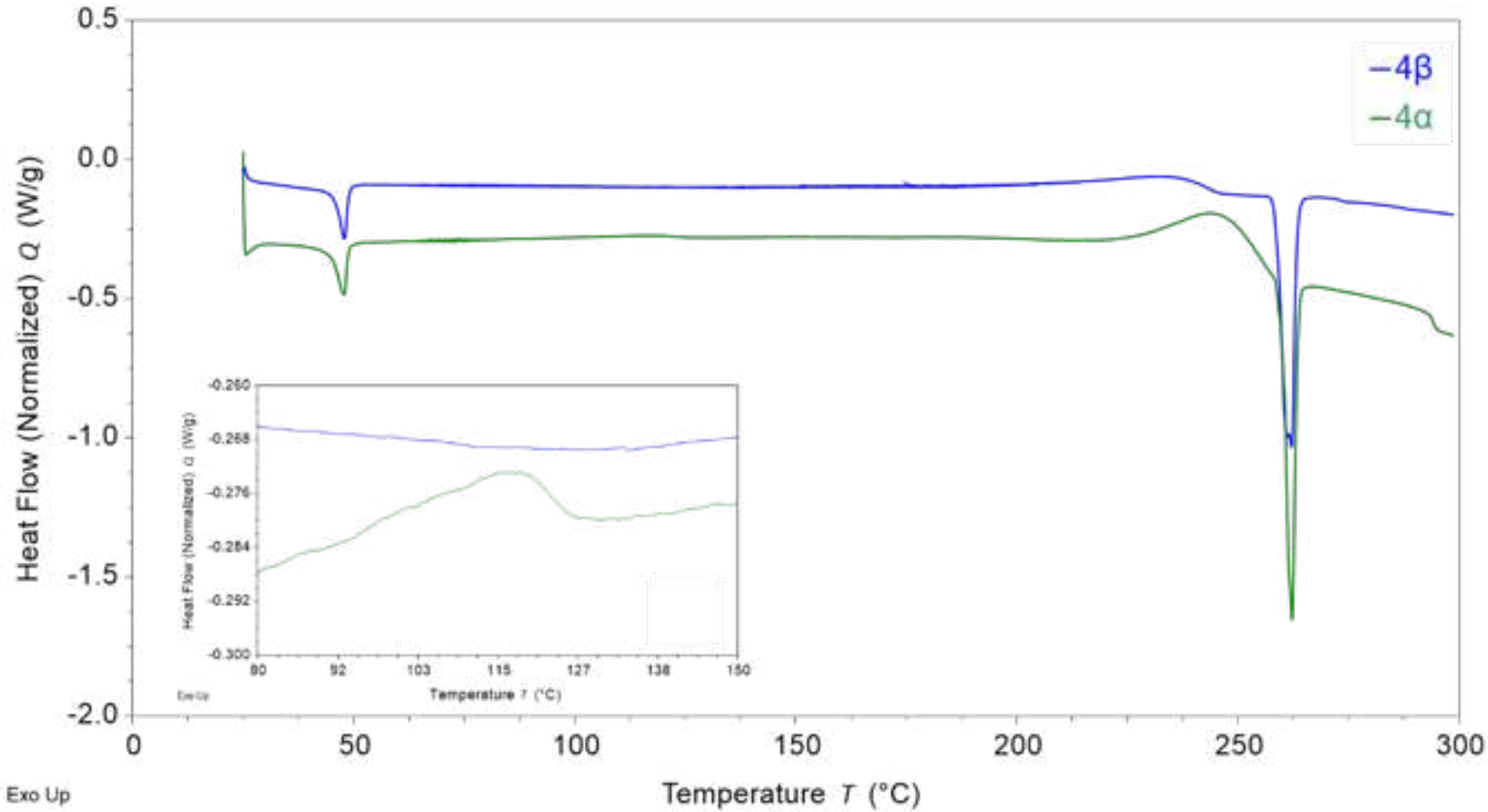

X-ray


X-ray detector
Diffracted X-rays



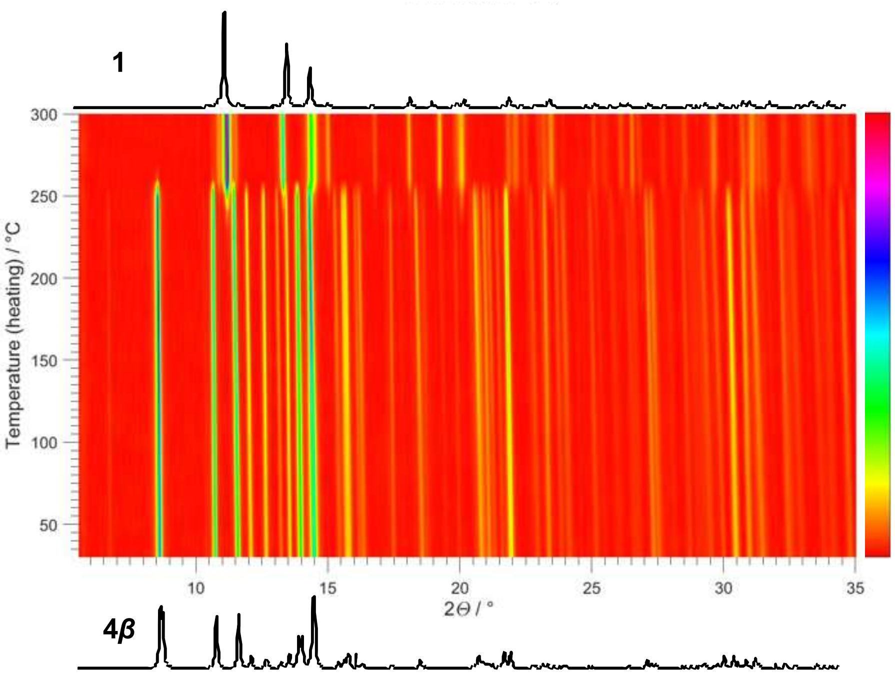


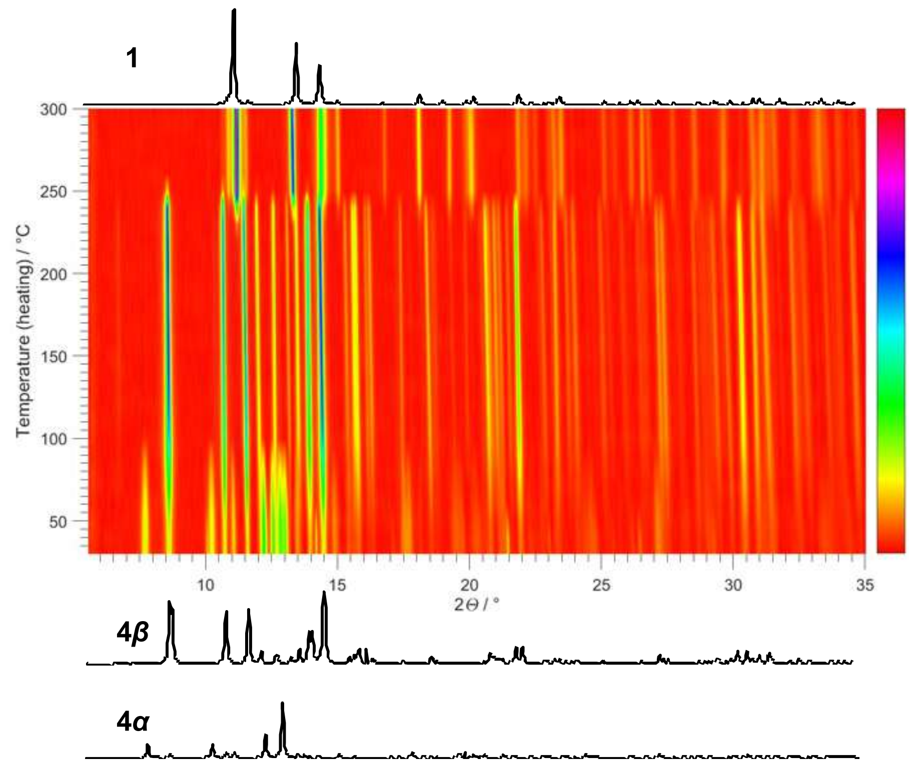
Time-resolved diffractograms for the reaction of $[Cp^*RhCl_2]_2$ (0.24 mmol), **BHQ** (2.0 equiv.) at 30 Hz (λ = 0.20741 Å).



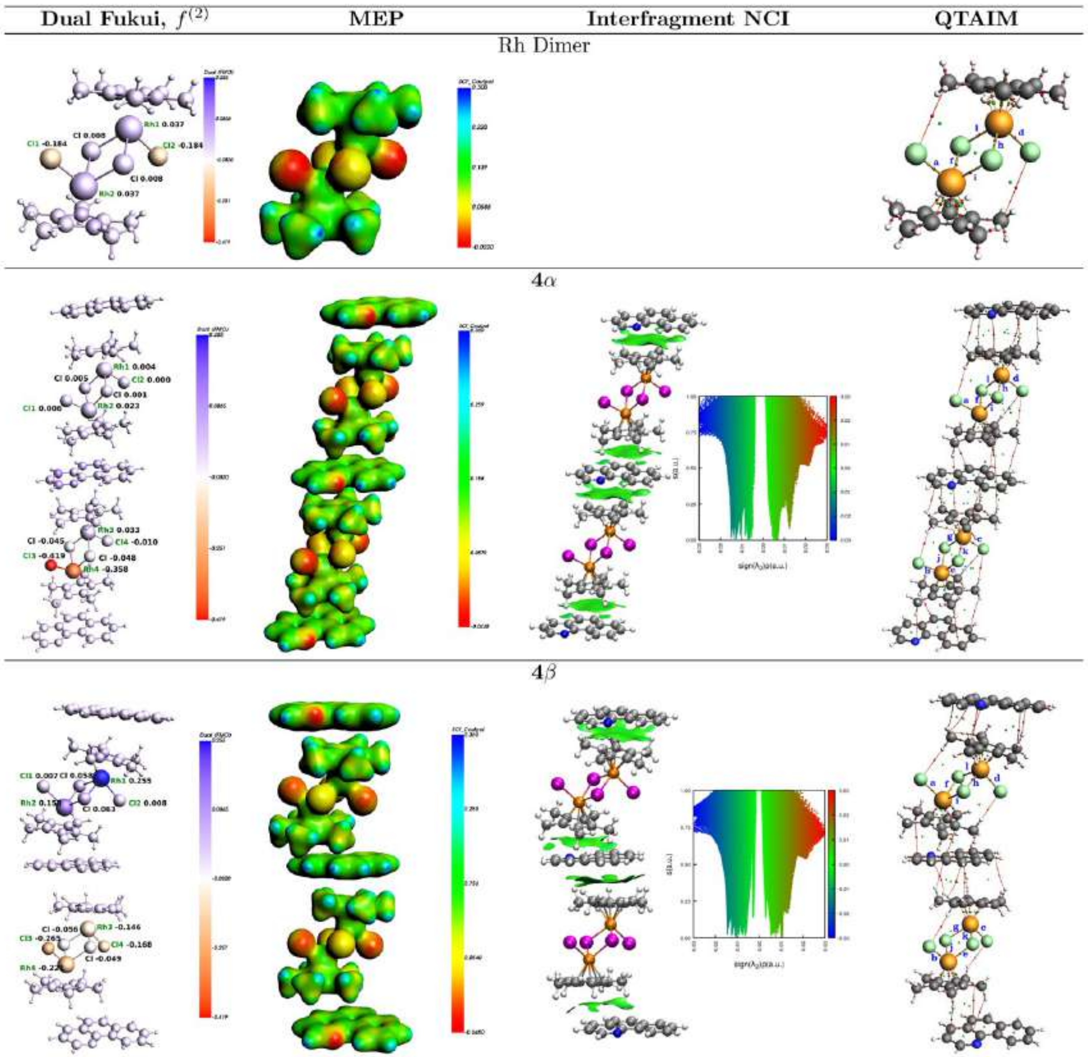
DSC traces of **4α** and **4β**. Inset shows a detail at 120 °C.

in situ variable temperature powder X-ray diffraction (VT-PXRD)





VT-PXRD patterns for cocrystal **4β** (left) and VT-PXRD patterns for a mixture initially containing **4α** and **4β** (λ = 1.54 Å) (right).



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Dr. Sara Gómez

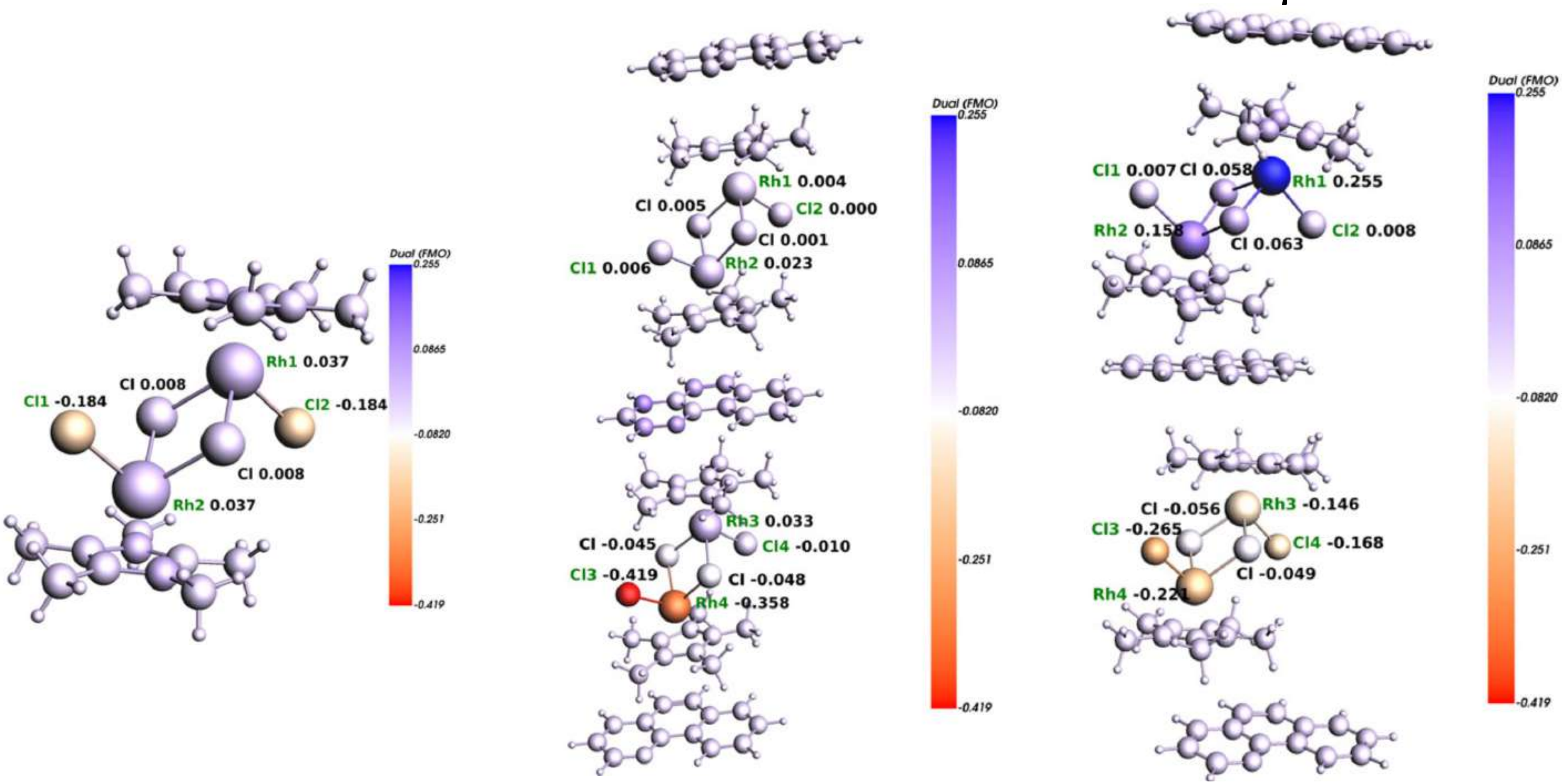
Scuola Normale Superiore di Pisa

Reactivity and structural descriptors on the 3 : 2 (BHQ : Rc) clusters. From left to right: Dual Fukui functions, molecular electrostatic potentials (MEP), 3D and 2D reduced density gradient (RDG) surfaces for intermolecular interactions and QTAIM molecular graphs with Rh–Cl bond labels.

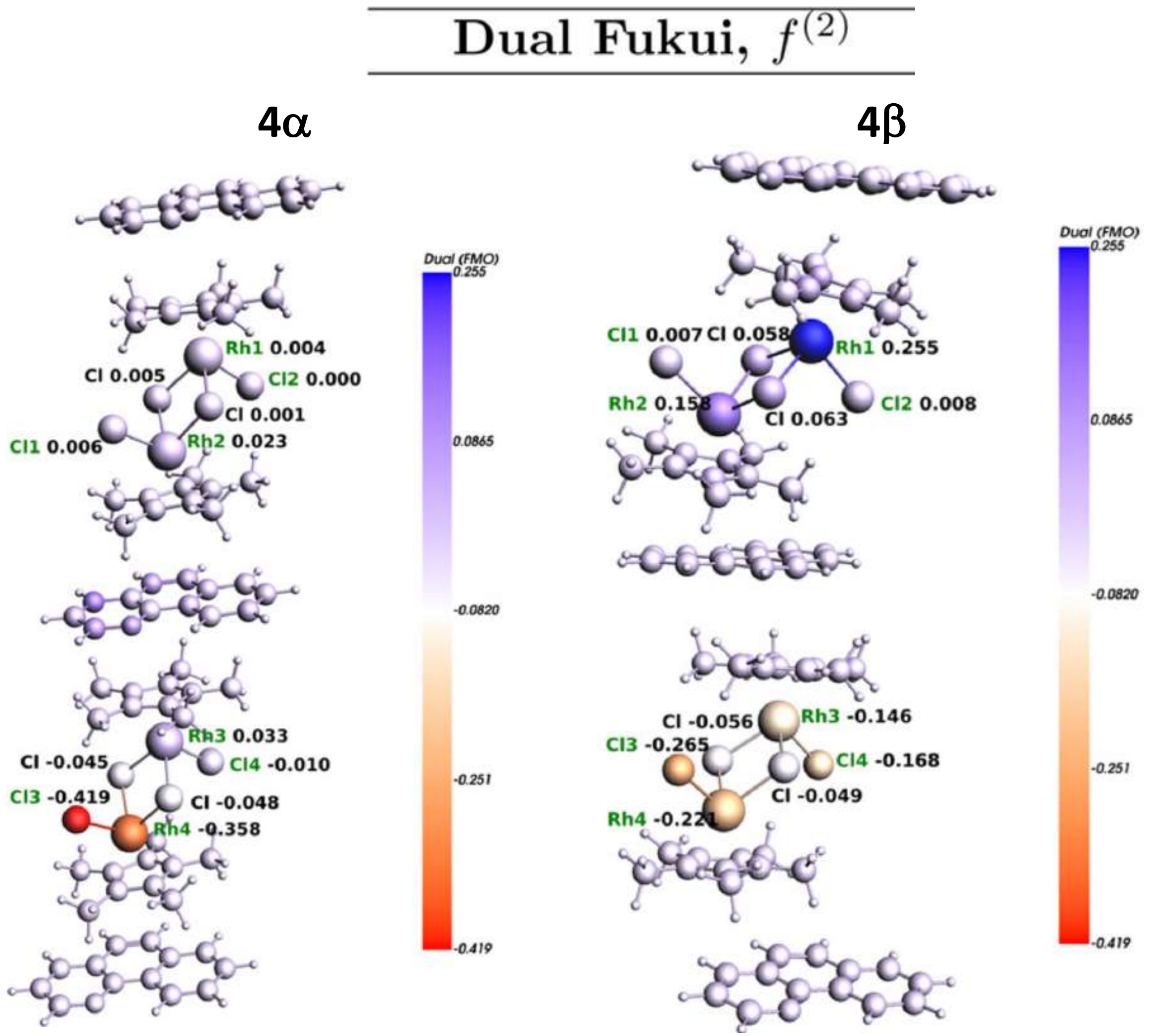
-*Phys. Chem. Chem. Phys*. **2024**, *26*, 2228–2241

Dual Fukui, $f^{(2)}$

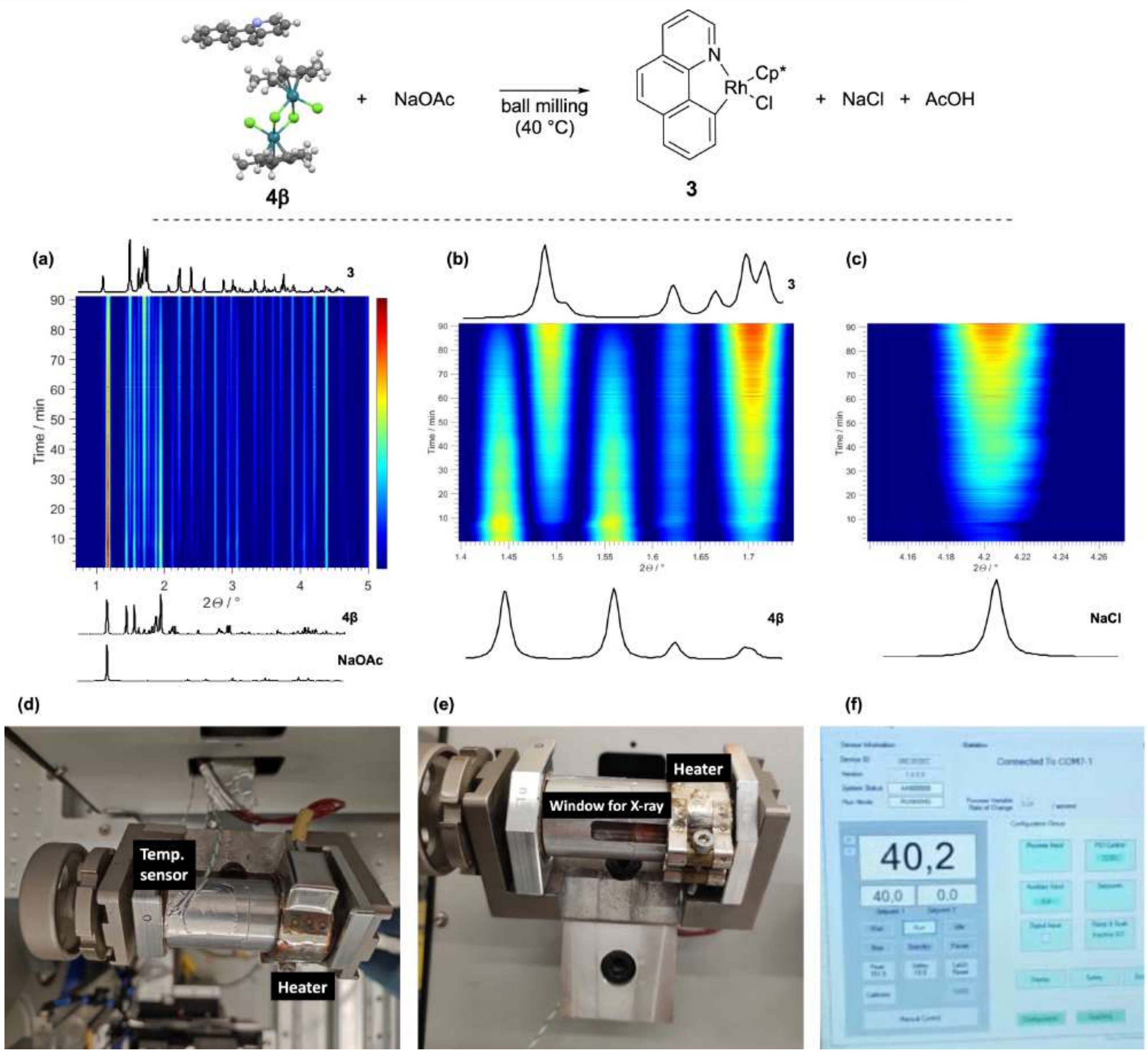
4α **4β**



We observed that the Fukui function of the $[Cp^{*}RhCl_2]_2$ crystal more closely resembles the Fukui function of the **4α** phase.



$$[Cp^*RhCl_2]_2 + NaOAc \longrightarrow 1/2[Cp^*Rh(k^2\text{-}OAc)Cl] + NaCl \quad \text{(Eq. 1)}$$

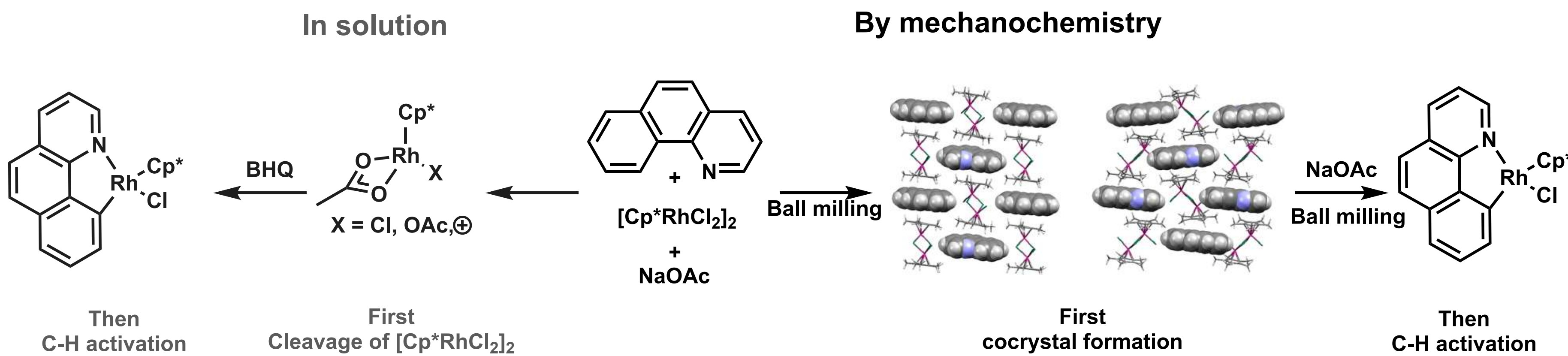


In situ synchrotron X-ray powder diffraction monitoring of the mechanochemical reaction of cocrystal **4β** with.

-*Chem. Eur. J.* **2023**, *29*, e202301290

Conclusions

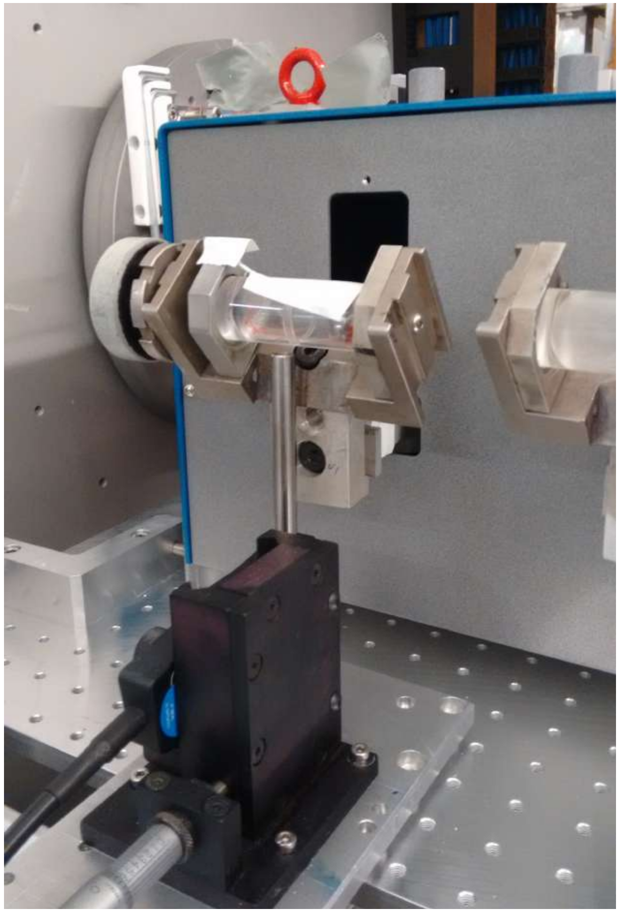
-Our results revealed the formation of unusual crystalline phases between the substrates and the rhodium (and iridium) dimer prior to the C–H activation step.



José G. Hernández

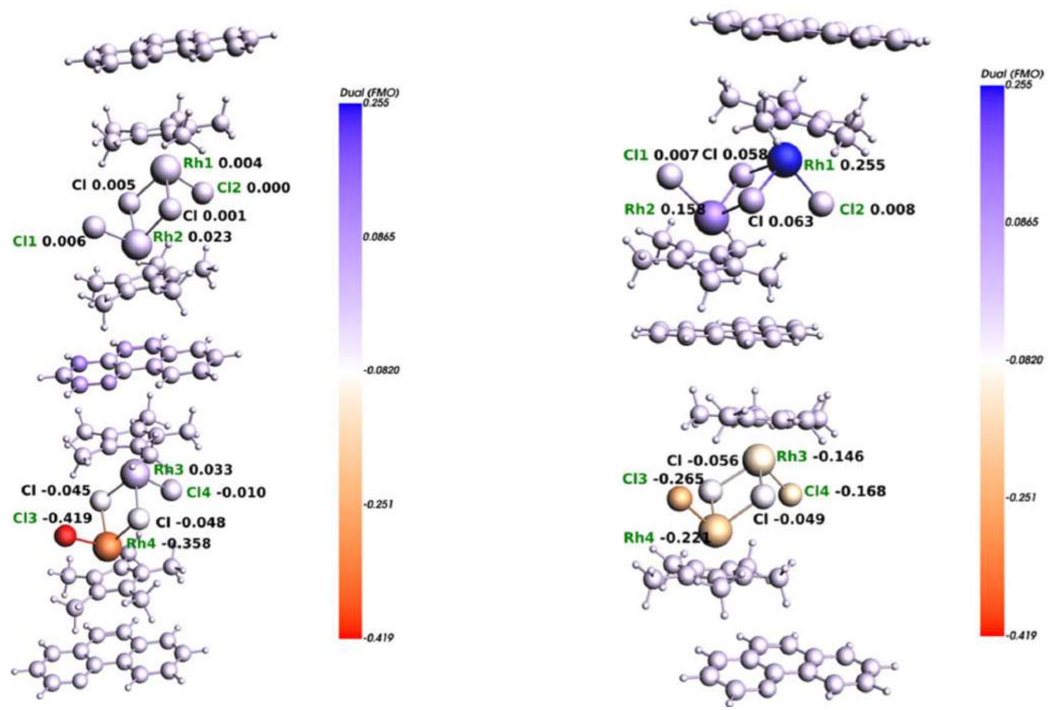
Conclusions

-Real-time and continuous examination of the reaction enabled us to unequivocally demonstrate the formation of two cocrystals, **4α** and **4β**, during the milling process and not as an artifact of the *ex situ* analysis.



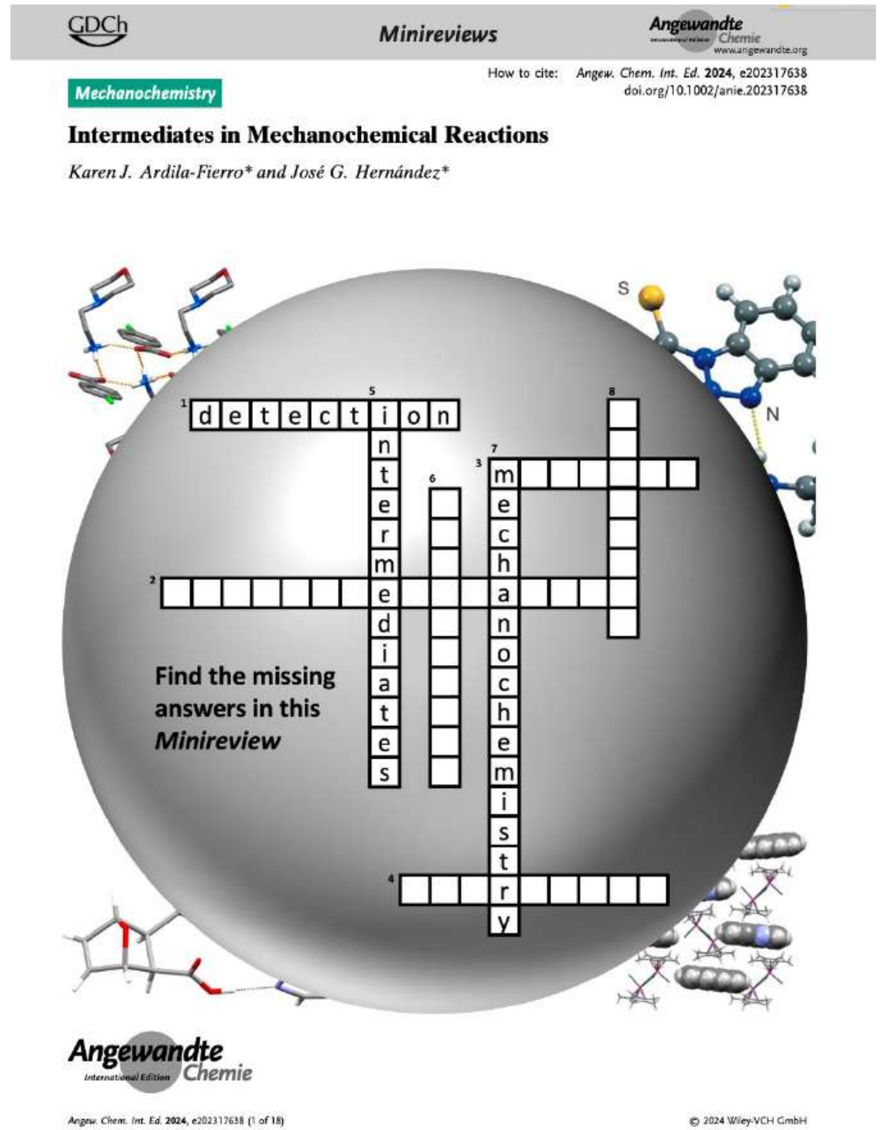
Conclusions

-Computational investigations enabled us to pinpoint the origin of the stability in **4**α and **4**β as well as revealing their structural and electronic differences. Disparities in the crystal packing between both cocrystals and differences in their intermolecular interactions make the $[Cp^{*}RhCl_2]_2$ units in **4**β more activated towards the reaction with NaOAc than in cocrystal **4**α.



Conclusions

-Reactive **intermediates have been detected in mechanochemical reactions** spanning organic, organometallic, inorganic, and materials chemistry. **Many of these intermediates were stabilized by non-covalent interactions**, which played a pivotal role in guiding the chemical transformations and could be responsible for the change in selectivity of many mechanochemical reactions.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Mechanochemistry

Intermediates in Mechanochemical Reactions

Karen J. Ardila-Fierro and José G. Hernández**

Angewandte Chemie International Edition

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2022-48630

Thank you