# A VR-Assisted Hybrid Teaching Model for Sustainable Mechanochemical Synthesis: Educational Overview and Case Study of a Cu-N-Heterocyclic Carbene Undergraduate Laboratory

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# Lab Manual

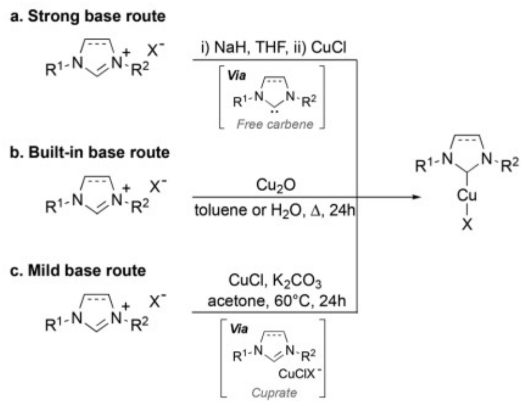
## 1. Main Objective

Integrate virtual reality (VR) with hands-on laboratory work on neat grinding/mechanosynthesis of Cu(Cl)(NHC) complex to enhance student understanding, safety awareness, and procedural competence, using a hybrid learning approach.

## 2. Introduction

Mechanochemical synthetic routes have been successfully applied to the preparation of copper(I)-NHC complexes. Lamaty and co-workers reported the synthesis of [Cu(Cl)(NHC)] complexes via ball milling of metallic copper with imidazolium chloride salts (NHC.HCl) under aerobic conditions, as well as through the mechanochemical transmetallation of preformed NHC-silver complexes to the corresponding copper species[1]. These studies demonstrated that mechanosynthesis enables efficient copper N-heterocyclic carbene (Cu-NHC) formation without the need for inert atmospheres or solution-based protocols[2]. Complementary work by Cazin and co-workers described the synthesis of [Cu(Cl)(NHC)] complexes via ball milling of carbene precursor salts with copper(I) chloride in the presence of potassium carbonate, which serves as a mild base[3]. This weak-base strategy was subsequently extended to a broad range of five-membered saturated and unsaturated NHC ligands, including imidazolin-2-ylidene, imidazolidin-2-ylidene, and triazolylidene systems[4]. Notably, the methodology was shown to be scalable, enabling the preparation of up to 5 g of the [Cu(Cl)(IPr)] in good yields and demonstrating its applicability across multiple metal systems[5]. Building on these advances, Teichert and co-workers further explored mechanochemical approaches to the synthesis of the [Cu(Cl)(IPr)] using $K_3PO_4$ as an alternative base. In contrast, the use of stronger bases such as NaOtBu, NaHMDS, and NaH under mechanochemical conditions proved ineffective: no desired product was observed with NaO*t*Bu or NaHMDS, while NaH led to an intractable mixture containing only trace amounts of the target the [Cu(Cl)(IPr)] complex. These findings highlight the critical role of base selection in mechanochemical NHC metalation and underscore the advantages of mild, carbonate-based systems for efficient and selective Cu-NHC formation[6].

In this new case study experiment, the synthesis of a copper complex can be conducted as a hybrid study that integrates VR with a hands-on laboratory in four parts. Students can first visualize the mechanosynthesis of a copper complex through immersive VR, and practice reagent selection while adhering to safety protocols in an immersive virtual environment. After completing the VR session, students perform the actual copper complex synthesis in laboratory facilities with greater confidence and technical readiness. This hybrid approach develops learning outcomes, accessibility, and safety while preserving essential hands-on laboratory skills.



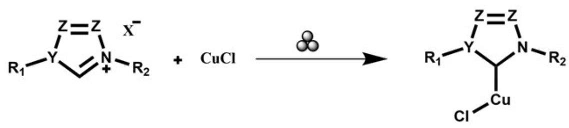




**Figure 1.** Conventional synthesis of a copper complex using a base.

**Figure 2.** Mechanosynthesis of copper complex.

## 3. Learning Objectives:

The hybrid laboratory session was designed to achieve the following learning objectives:

1. Enhance students' understanding of green chemistry principles, catalysis and sustainability within modern laboratory practice.

2. Introduce the principles of mechanochemical synthesis and the evaluation of green chemistry metrics.

3. Integrate inorganic and organic chemistry concepts within an advanced, multistep laboratory workflow.

4. Design, synthesize and characterize Cu-NHC complex using sustainable methodologies.

## 4. Lab Session Components and Flow

| Phase | Description | Time |
|---|---|---|
| **Pre-Lab** | Pre-lab questions | 5 min |
| **Safety & Orientation** | Safety overview, learning objectives, and VR introduction | 10 min |
| **Mechanochemical Background** | Introduction to mechanochemistry and synthesis comparison | 10 min |
| **VR Module 1** | Virtual reaction preparation | 3 min |
| **Hands-On Lab 1** | Students prepare the reaction mixture | 5 min |
| **VR Module 2** | Ball-milling visualization of copper NHC synthesis | 5 min activity |
| **Hands-On Lab 2** | Launch the milling process | 5 min |
| **VR Module 3** | Virtual work-up demonstration | 3–4 min |
| **Hands-On Lab 3** | Work-up, filtration, evaporation, precipitation, and drying of the previous sample by students | 60 min + 5 min activity |
| **VR Module 4** | NMR demonstration, interpretation, and Q&A | 25 min |
| **Wrap-Up Discussion** | Yields, NMR interpretation, green chemistry reflection, and lab report discussion | 20 min |

## 5. Laboratory Risk Assessment

| Reagents, Products, and Instruments | T | A | F | I | O | W | Other |
|---|---|---|---|---|---|---|---|
| 1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium-2-ide chloride (IPR.HCl) | | 2 | | | | | Skin and eye irritation |
| Cuprous chloride (CuCl) | | 2 | | | | | |
| Potassium carbonate ($K_2CO_3$) | | 2 | | | | | Skin and eye irritation |
| Silicon dioxide ($SiO_2$) | | 2 | | | | | It is dangerous to the lungs; it must be used in a fumehood. |
| Acetone | | | 2 | | | | |
| Pentane | | | 2 | | | | |
| Deuterated solvent (Chloroform-d) | | 2 | | | | | Health hazard: Possible-residual injury |

HAZARD AND EXPOSURE POTENTIAL CODES

| Hazard Category | Number Code |
|---|---|
| Not significant | 0 |
| Low | 1 |
| Medium | 2 |
| High | 3 |
| Severe | 4 |
| Extreme | 5 |

| **Exposure potential** | **Code** |
|---|---|
| Low | X |
| Medium | XX |
| High | XXX |

| Hazard Code Classifications | |
|---|---|
| T = Toxic | C = Carcinogenic |
| A = Corrosive/Irritant | F = Flammable |
| R = Radioactive | X = Explosive |
| O = Oxidising agent | W = Violent reaction with water |
| M = Microbiological | N = Harmful to the environment |
| G = Liberates toxic gases on contact with water/acid/base | |
| I = Instrument/glassware/equipment hazard | |

Protection Code

| Stage | Operation | SOP | Hazard category | Exposure potential | P Code | Precautions |
|---|---|---|---|---|---|---|
| 1 | Glassware | | 1 | x | P1 | |

| P-Code Classifications |
|---|
| P1 = Open laboratory work (lab coat and safety glasses) |
| P2 = Restricted open laboratory (no naked flames) |
| P3 = Contact protection (lab coat, safety glasses, and suitable gloves) |
| P4 = Fume cupboard |
| P5 = Fume hood and additional safety (gloves, visor/ respirator, etc.) |
| P6 = Glove box/ remote operation |

## 6. Procedure

**Mechanosynthesis of [Cu(Cl)NHC] under aerobic condition**

**A-VR-Assisted-Prelaboratory Experiment:**

1- Participate in a safety and orientation session, including an introduction to the VR environment and the learning objectives.
2- Use **VR Modules 1 and 2** to visualize the reaction preparation and mechanical grinding setup, reagent loading, and formation of a copper–NHC complex by neat grinding under aerobic conditions.

**B-Preparation of Reaction Mixture (Hands-On):**

- Charge the stainless-steel milling jar with IPr.HCl (200.0 mg, 0.473 mmol, 1.0 equivalent), CuCl (47.00 mg, 0.473 mmol, 1.0 equivalent), and $K_2CO_3$ (196.0 mg, 1.420 mmol, 3.0 equivalents).
- Add five stainless-steel balls to the jar.
- Seal the jar tightly.

Milling Process:

- Place the jar in the vibrational ball mill.
- Set the milling speed to 25 rpm.
- Subject the mixture to milling for 60 minutes.

**Activity Questions 1**

What is the primary impact of each parameter used in the mechanosynthesis to form the Copper N-Heterocyclic Carbene Complex?

1- The number and the size of the milling balls: 5 milling balls (7 mm, 1.36 g), different ball sizes could alter the impact force and energy transferred to the reactants, possibly affecting the reaction rate and yield, and the number of milling balls plays an essential role in collision and friction between reactants.
2- The duration of the reaction is 60 minutes: Milling in intervals can prevent excessive heating, thereby enabling better control and monitoring of the response, consistent with principle 12 of green chemistry (real-time analysis).
3- The size of the milling jar is 30 mL, so the reagents can have enough space to collide with each other.
4- The material of the milling jar: stainless steel, which will not interfere with the reactants.
5- The mole ratio between reactants: 1:1
6- The solvent: not used, as the type of synthesis is neat grinding.

**C-VR-Guided Work-Up Demonstration**

Use **VR Module 3** to view a virtual demonstration of product extraction, filtration, and precipitation before performing the real work-up.

**D-Product Work-Up and Isolation (Hands-On)**

- Extraction and Filtration:

- After milling, remove the jar from the mill.
- Open the jar and transfer the crude product to a suitable container.
- Mix well with acetone (15 mL) with the crude product.
- Pass the mixture through a Hirsch funnel packed with silicon dioxide ($SiO_2$).
- Collect the filtrate.

- Solvent Removal and Precipitation:

- Use a vacuum apparatus to reduce the volume of the solvent.
- Allow the product to precipitate (approximately 7-8 mL in volume).
- Add pentane (10 mL) as a cosolvent to aid precipitation.

-Product Isolation:

- Filter the mixture to isolate the [Cu(Cl)(NHC)] product.
- Wash the product with pentane if necessary.
- Dry the product under vacuum if required.

**Activity Questions 2**

1-Why is acetone used during the extraction of the crude [Cu(Cl)(NHC)]?

Acetone is a polar solvent that can dissolve [Cu(Cl)(NHC)], separating it from the insoluble byproducts and any other unreacted starting materials.

2-What is the role of reducing the solvent volume using a rotary evaporator after the extraction step?

It increases the product concentration, thereby promoting adequate precipitation upon addition of the cosolvent.

3-Explain why pentane is used as a cosolvent to crystallize the [Cu(Cl)(NHC)] complex.

Pentane is much less polar than acetone, so it precipitates the product from the acetone while many impurities remain dissolved in the acetone layer.

**E-Characterization and Data Interpretation**

Use **VR Module 4** to review NMR spectral features, signal assignments, and interpretation after collecting experimental data. The NMR spectra are provided in Section 10.

**Activity questions-3**

Based on the VR observations of the NMR spectrum, answer the following questions:

1- Assign the prominent peaks' signals (chemical shift, multiplicity, integration) to proton types.

ArH: ~7.49 (t, 2H) and ~7.30 (d, 4H), NCH=CHN: ~7.14 (s, 2H), iPr-CH: ~2.59–2.53 (m, 4H), iPr-$CH_3$: ~1.29 (d, 12H) and ~1.23 (d, 12H).

2- Which peak in the NMR spectrum supports the conversion of IPr·HCl → Cu–NHC complex?

The disappearance of the 9–11 ppm peak for IPr·HCl.

**Wrap-Up, Storage, and Disposal:**

- Conduct a guided wrap-up session to discuss reaction yield, NMR results, and sustainability metrics.
- Store the labeled [Cu(Cl)(NHC)] product in the designated storage area.
- Dispose of waste materials in accordance with institutional chemical waste guidelines.

**Safety Precautions:**

- Ensure you have studied the Laboratory Hazard Assessment Sheet for the experiment carefully before coming to the laboratory.
- Students must wear departmentally approved protection while performing this experiment.
- Wash your hands before touching your eyes, before and after completing this experiment.

**Waste Collection:**

After you finish the experiment, dispose of the chemicals in a waste container.

**Labware & Equipment:**

For each group (group of two students)

| Glassware for each group | Instrument |
|---|---|
| Round-bottom flask ( 50 mL) | 1- Mixer Mill: Retsch-MM-400<br>2- Rotoevaporator-BUCHI-R215<br>3- Stainless steel milling balls (7 mm, 1.36 g)<br>4- Two stainless steel grinding jars (35 mL) |
| Beaker (50 mL) | |
| Beaker (100 mL) | |
| Glass rod | |
| Spatula | |
| Weighing boat | |
| Watch glass | |
| Filter paper | |
| Hirsch funnel | |
| Vacuum pump | |
| Separatory funnel (50 mL) | |
| NMR-tube | |

## 7. Chemicals

| *Solid chemicals* | *Liquid Chemicals* |
|---|---|
| 1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium-2-ide chloride (IPr.HCl) | Acetone |
| Cuprous chloride (CuCl) | Pentane |
| Potassium carbonate ($K_2CO_3$) | Deuterated solvent (Chloroform-d) |
| Silicon dioxide ($SiO_2$) | |

## 8. Pre-Lab Questions

1- State the twelve principles of "Green Chemistry" and which of them can be applied to the mechanosynthesis of [Cu(Cl)(NHC)]?

Answer:

a. **Prevention**: Avoid creating waste rather than treating or cleaning it up afterward.
b. **Atom Economy**: Maximize the incorporation of all materials used in the process into the final product.
c. **Less Hazardous Chemical Syntheses**: Design synthetic methods to use and generate substances with minimal toxicity.
d. **Designing Safer Chemicals**: Create functional chemical materials with minimal toxicity.
e. **Safer Solvents and Auxiliaries**: Use safer solvents and minimize the use of auxiliary substances.

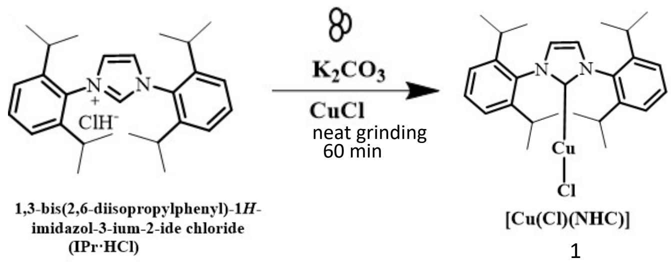
f. **Design for Energy Efficiency**: Reduce energy consumption by conducting reactions at ambient temperature and pressure.
g. **Use of Renewable Feedstocks**: Use renewable raw materials whenever possible.
h. **Reduce Derivatives**: Minimize derivatization and temporary modifications in multistep synthesis, such as blocking or protecting groups.
i. **Catalysis**: Use catalysts to improve reaction efficiency and reduce waste.
j. **Design for Degradation**: Design chemical products that can break down into non-harmful substances after use.
k. **Real-time Analysis for Pollution Prevention**: Monitor and control chemical processes in real time to prevent pollution.
l. **Inherently Safer Chemistry for Accident Prevention**: Choose chemicals and processes that minimize the risk of accidents, such as explosions or releases of toxic substances.

The principles "a, c, e, I, j, and k" can be applied to the mechanosynthesis of the [Cu(Cl)(NHC)].

2- Why is mechanosynthesis eco-friendly, energy efficient, and more sustainable?

Answer: It can provide a shorter reaction time compared to any conventional reaction, and it uses a minimum quantity of solvent by considering the η value.

3- Calculate the theoretical mass of the reaction product (Cu(IPR)Cl) based on the balanced chemical equation of this experiment?




IPr.HCl: 200.0 mg, 0.473 mmol, 1.0 equivalent
CuCl: 47.00 mg, 0.473 mmol, 1.0 equivalent
Molar mass of the copper complex = 487 g/mol

The expected theoretical mass of the copper complex = 230.3 mg.

4- List the main essential applications of the [Cu(Cl)(NHC)] complex.

Answer: catalyst for Sonogashira cross coupling and metal transfer reagent such as synthesis of [Au(IPr)Cl].

5- Why is the preparation of [Cu(Cl)(NHC)] carried out under basic conditions?

Answer: To deprotonate IPr.HCl, activating it as an N-heterocyclic carbene ligand that can bind to the copper (I) ion.

6- Explain the significance of the carbene ligand (IPr.HCl) in the synthesis of [Cu(Cl)(NHC)]?

Answer: The carbene ligand precursor (IPr·HCl) plays a crucial role in the synthesis of [Cu(Cl)(NHC)] by generating a strongly σ-donating N-heterocyclic carbene (NHC) that stabilizes the copper(I) center. Upon deprotonation, the NHC binds strongly to Cu(I), enhancing complex stability and facilitating efficient complex formation under mild conditions. The cyclic carbene framework also provides steric protection, which helps prevent undesired side reactions and supports the formation of a well-defined Cu–NHC complex.


Free Carbene

## 9. Post Lab Questions

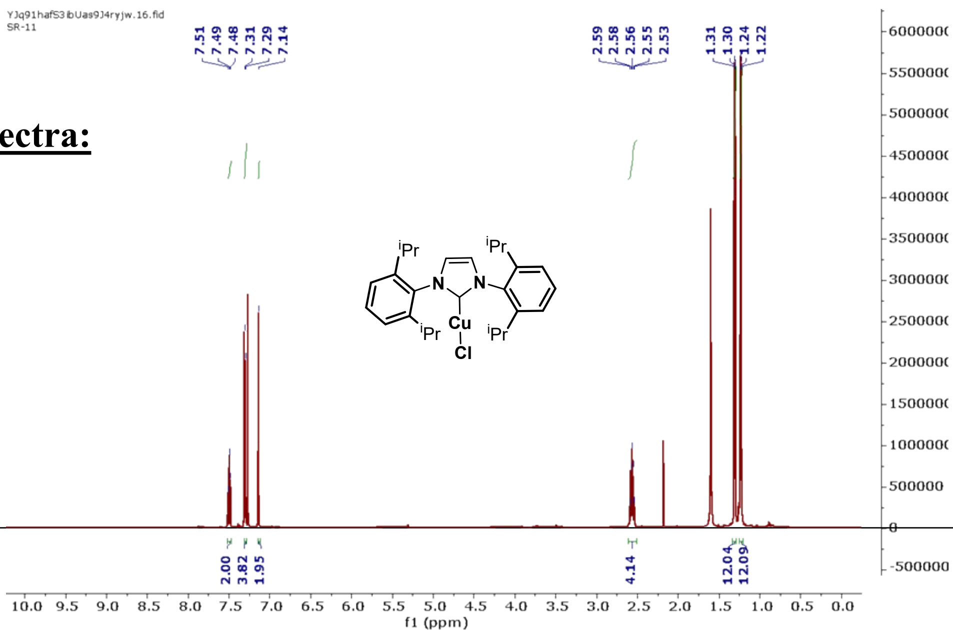
Create a Scientific Poster that visually demonstrates the following:

1- How mechanochemistry improves sustainability (e.g., solvent-free reactions, time, and waste reduction),
2- The Green Metrics calculations (atom economy (AE), reaction mass efficiency (RME), optimum efficiency (OE), mas intensity (MI), environmental factor (E-factor)) based on the reagents used in the chemical reaction.
3- Mechanosynthesis of [Cu(Cl)(NHC)] under aerobic conditions

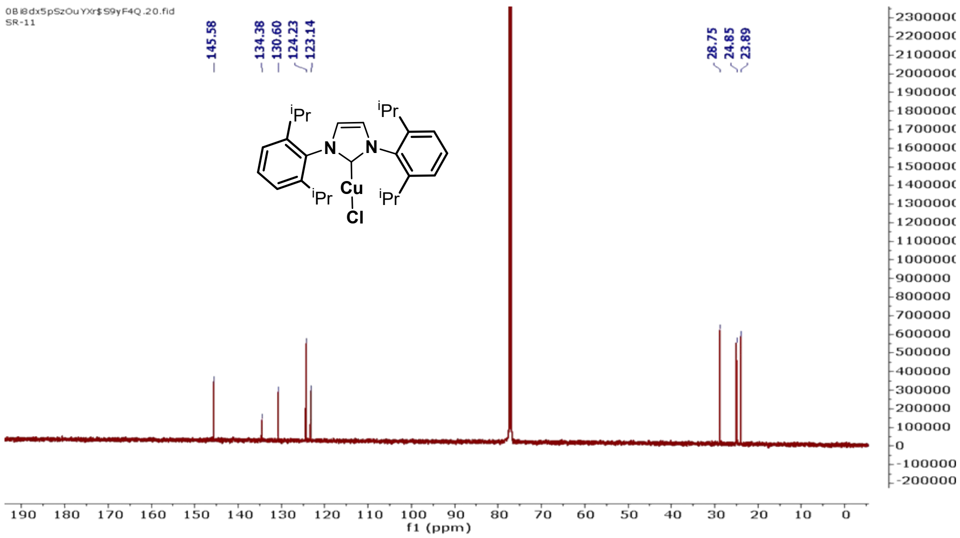
The poster should highlight the hybrid VR-experimental lab design supporting the learning outcomes of the session

Answer: An example of a student poster is provided in the manuscript.

## 10. Spectra: $^1$H-NMR and $^{13}$C-NMR



*[1]H-NMR*




*[13]C-NMR*

## 11. Green metrics calculations

Calculations were based on the reagents used in the chemical reactions, and the workup was not included.

1. Mechanosynthesis of [Cu(Cl)(IPr)] for 200 mg batch.

| Yield | AE | RME | OE | MI | E-factor |
|---|---|---|---|---|---|
| 66% | 93.3% | 61.5% | 65.9% | 2.91 | 1.91 |

$$AE = \frac{MW_{product}}{total\ MW_{reactants}} * 100$$

$$AE = \frac{488}{424(IPr.HCl) + 99\ (CuCl)} * 100$$

$$RME = \frac{mass_{isolated\ product}}{total\ mass\ reactants} * 100$$

$$RME = \frac{152}{200\ (IPr.HCl) + 47\ (CuCl)} * 100$$

$$OE = \frac{RME}{AE} * 100$$

$$OE = \frac{61.5}{93.3} * 100$$

$$MI = \frac{total\ mass\ in\ the\ reaction}{mass\ of\ the\ product}$$

$$MI = \frac{200\ (IPr.HCl) + 47\ (CuCl) + 196\ (K2CO3)}{152}$$

$$E - factor = \frac{total\ mass\ of\ the\ reactant - mass\ of\ product}{mass\ of product}$$

$$E - factor = \frac{443 - 152}{152}$$

## 12. References


(1) Beillard, A.; Métro, T. X.; Bantreil, X.; Martinez, J.; Lamaty, F. Cu(0), O2 and Mechanical Forces: A Saving Combination for Efficient Production of Cu-NHC Complexes. *Chem. Sci.* **2017**, *8* (2), 1086–1089. https://doi.org/10.1039/c6sc03182j.

(2) Quintin, F.; Pinaud, J.; Lamaty, F.; Bantreil, X. Mechanosynthesis of Noels-Type NHC-Ruthenium Complexes and Applications in Ring-Opening Metathesis Polymerization. *Organometallics* **2020**, *39* (5), 636–639. https://doi.org/10.1021/acs.organomet.0c00013.

(3) Pisanò, G.; Cazin, C. S. J. Mechanochemical Synthesis of Cu(i)-N-Heterocyclic Carbene Complexes. *Green Chem.* **2020**, *22* (16), 5253–5256. https://doi.org/10.1039/d0gc01923b.

(4) Martynova, E. A.; Tzouras, N. V.; Pisanò, G.; Cazin, C. S. J.; Nolan, S. P. The "Weak Base Route" Leading to Transition Metal-N-Heterocyclic Carbene Complexes. *Chem. Commun.* **2021**, *57* (32), 3836–3856. https://doi.org/10.1039/d0cc08149c.

(5) Furst, M. R. L.; Cazin, C. S. J. Copper N-Heterocyclic Carbene (NHC) Complexes as Carbene Transfer Reagents. *Chem. Commun.* **2010**, *46* (37), 6924–6925. https://doi.org/10.1039/c0cc02308f.

(6) Remy-Speckmann, I.; Zimmermann, B. M.; Gorai, M.; Lerch, M.; Teichert, J. F. Mechanochemical Solid State Synthesis of Copper(I)/NHC Complexes with K3PO4. *Beilstein J. Org. Chem.* **2023**, *19*, 440–447. https://doi.org/10.3762/bjoc.19.34.