Robotic Kneading for Organic Reactions: A Deterministic Platform for Data-Driven Synthesis in Semi-Solid Media

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1. Introduction

Recent advances in materials informatics and the development of self-driving laboratories have accelerated efforts toward automated and data-driven chemical synthesis [1, 2]. Integrated platforms combining robotic reaction execution, real-time analysis, and algorithmic optimization have demonstrated the potential to enhance molecular discovery [3, 4]. As automation technologies mature, increasing attention is being directed toward how reaction modalities themselves can be designed to align with robotic control.

Mechanochemistry has attracted growing interest as a solvent-minimized synthetic strategy [5]. Impact-driven ball milling has enabled diverse transformations and stimulated the development of in situ analytical techniques [6, 7]. Rather than replacing existing approaches, we consider how alternative mechanochemical modes may offer complementary advantages when viewed from the perspective of robotic experimentation.

From a robotic standpoint, effective closed-loop experimentation requires that operational variables be explicitly parameterized and that their relationship to system response be interpretable. In this context, the mechanical interface between actuator and reaction medium becomes a central design element. A reaction modality that enables continuous and structured mechanical interaction may therefore provide particular compatibility with robotic systems.

In this study, we focus on kneading, characterized by continuous shear and compression applied to semi-solid mixtures. Sustained mechanical contact between actuator and reaction medium allows rotation speed, pressing force, and processing time to be defined as explicit numerical variables [8]. This transforms a traditionally manual operation into a reproducible and programmable experimental process.

Furthermore, semi-solid systems introduce an additional design dimension: the physical form of the reaction medium itself. Variations between dispersion, granular, and cohesive paste states influence mechanical energy transmission and interfacial renewal. Treating physical state as an explicit experimental variable enables a structured framework in which mechanical input, material response, and chemical transformation can be systematically linked.

The present work establishes robotic kneading as a mechanochemical platform in which reaction modality is intentionally aligned with robotic controllability, providing a foundation for data-driven optimization in semi-solid media.

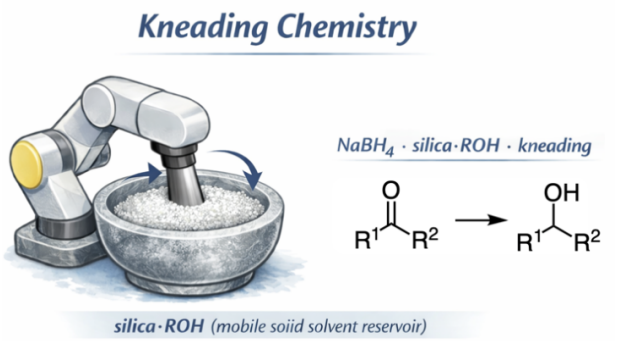

Fig. 1: Conceptual diagram of Kneading Chemistry

2. Methodology

In this study, to convert kneading operations into a quantitative data process, we integrated an automated platform using a single-arm robot with a framework for describing the physical state of the reaction medium.

2.1 Automated Kneading Robot System

We constructed an automated platform based on a robotic system previously developed for dry mechanochemical reactions [8], adapting it for paste-like media. While conventional mechanochemical platforms, such as ball milling, rely on stochastic high-energy collisions, our system utilizes an industrial single-arm robot to apply sustained shear and compression. Continuous shear renews interfacial contact between reagents while maintaining high local concentrations.

Through programmable control of operational parameters—including rotation speed, vertical pressing force (e.g., 5–10 N), and processing time—the kneading process is converted into reproducible numerical variables. This transformation enables systematic recording and optimization of mechanical inputs. An overview of the automated kneading robot system is shown in Fig. 2.

2.2 Stabilization of "Paste State" by Silica Gel

Maintaining an appropriate paste-like state is critical for consistent mechanical transmission. Without a support matrix, reaction mixtures may form oily dispersions where solvent distribution is uneven and shear transfer is inefficient. To address this rheological challenge, we introduced alcohol-impregnated silica gel as a mobile solid solvent reservoir, drawing on principles of liquid-assisted grinding (LAG) [9].

Silica plays a dual role. Mechanically, it immobilizes liquid components to form a cohesive paste un-

der shear. Chemically, it distributes microquantities of protic solvent throughout the matrix, facilitating localized mass transport and in situ hydrolysis of boron species. This approach enables efficient synthesis and robot-compatible workup at the millimole scale with minimal solvent usage (≤ 0.10 mL), supporting reproducible data acquisition for informatics analysis.

Fig. 2: Overview of the automated kneading robot system.

3. Experiments and Results

We evaluated the performance of the robotic kneading platform using the $NaBH_4$ reduction of 4-tert-butylcyclohexanone as a benchmark reaction [10]. The primary objective was to examine how the physical state of the medium, modulated by silica loading, influences reaction efficiency.

3.1 Correlation between Physical State and Yield

As summarized in Table 1, silica loading strongly influenced isolated yields.

- **Dispersion Phase:** At low silica loading (1 g), the mixture formed an oily dispersion with uneven solvent distribution. Under these conditions, effective shear transmission was limited, resulting in reduced yield (49%).
- **Paste Phase:** Increasing silica loading (2–5 g) transformed the mixture into a cohesive paste. This state enabled sustained shear and compression, and yields improved to 88–94%.

3.2 Control of Reaction Outcome via Physical State

These findings suggest that reaction efficiency is strongly coupled to the macroscopic physical state of the medium, rather than being determined solely by intrinsic chemical kinetics. Adjustment of the solid-to-liquid ratio provides a tunable physical parameter that influences reaction outcome. This indicates that the robotic kneading platform offers a controllable mechanical environment compatible with data-driven optimization strategies.

Table 1: Effect of silica gel loading and solvent amount on robotic kneading $NaBH_4$ reduction of 4-tert-butylcyclohexanone under solvent-minimized conditions.

Entry	SiO_2 (g)	Solvent	Solvent (mL)	Yield (%)	cis/trans
1	5	No solvent	0	6	15/85
2	5	2-propanol	0.10	88	8/92
3	2	2-propanol	0.10	94	7/93
4	1	2-propanol	0.10	49	8/92
5	2	*t*-BuOH	0.10	66	6/94
7	2	1-propanol	0.10	48	11/89
8	2	1-propanol	0.20	79	12/88

4. Conclusion

We have established kneading chemistry as a quantifiable mechanochemical regime compatible with robotic automation. By utilizing silica gel as a distributed reaction medium (mobile solid solvent reservoir), we achieved efficient solvent-minimized reductions of solid ketones while maintaining mechanical control of the reaction environment.

Importantly, kneading has been transformed from an intuition-dependent manual technique into a reproducible, parameterized process. This work provides a step toward integrating structured mechanical inputs into self-driving laboratory frameworks, enabling AI-assisted exploration of physical–chemical parameter spaces in semi-solid media.

Ongoing studies are extending this framework to additional organic transformations to evaluate its generality across diverse reaction classes.

References

[1] Gary Tom, Stefan P. Schmid, Sterling G. Baird, Yang Cao, Kourosh Darvish, Han Hao, Stanley Lo, Sergio Pablo-García, Ella M. Rajaonson, Marta Skreta, Naruki Yoshikawa, Samantha Corapi, Gun Deniz Akkoc, Felix Strieth-Kalthoff, Martin Seifrid, and Alán Aspuru-Guzik. Self-Driving Laboratories for Chemistry and Materials Science. *Chemical Reviews*, 124(16):9633–9732, 2024.

[2] Naruki Yoshikawa, Yuki Asano, Don N. Futaba, Kanako Harada, Taro Hitosugi, Genki N. Kanda, Shoichi Matsuda, Yuuya Nagata, Keisuke Nagato, Masanobu Naito, Tohru Natsume, Kazunori Nishio, Kanta Ono, Haruka Ozaki, Woosuck Shin, Junichiro Shiomi, Kunihiko Shizume, Koichi Takahashi, Seiji Takeda, Ichiro Takeuchi, Ryo Tamura, Koji Tsuda, and Yoshitaka Ushiku. Self-driving laboratories in Japan. *Digital Discovery*, 4(6):1384–1403, 2025.

[3] Sebastian Steiner, Jakob Wolf, Stefan Glatzel, Anna Andreou, Jarosław M. Granda, Graham Keenan, Trevor Hinkley, Gerardo Aragon-Camarasa, Philip J. Kitson, Davide Angelone, and Leroy Cronin. Organic synthesis in a modular robotic system driven by a chemical programming language. *Science*, 363(6423):eaav2211, 2019.

[4] Daniel Cortés-Borda, Eric Wimmer, Boris Gouilleux, Elvina Barré, Nicolas Oger, Lubna Goulamaly, Louis Peault, Benoît Charrier, Charlotte Truchet, Patrick Giraudeau, et al. An autonomous self-optimizing flow reactor for the synthesis of natural product carpanone. *The Journal of Organic Chemistry*, 83(23):14286–14299, 2018.

[5] Stuart L. James, Christopher J. Adams, Carsten Bolm, Dario Braga, Paul Collier, Tomislav Friscic, Fabrizia Grepioni, Kenneth D. M. Harris, Graeme Hyett, William Jones, Albert Krebs, Jennifer Mack, Lalitha Maini, Guy A. Orpen, Anthony Parkin, William C. Shearouse, Jonathan W. Steed, and David C. Waddell. Mechanochemistry: opportunities for new and cleaner synthesis. *Chemical Society Reviews*, 41:413–447, 2012.

[6] Eva Gil-González, María del Rocío Rodríguez-Laguna, Pedro E. Sánchez-Jiménez, Antonio Perejón, and Luis A. Pérez-Maqueda. Unveiling mechanochemistry: Kinematic-kinetic approach for the prediction of mechanically induced reactions. *Journal of Alloys and Compounds*, 866:158925, 2021.

[7] Tomislav Friščić, Ivan Halasz, Patrick J. Beldon, Ana M. Belenguer, Frank Adams, Simon A. J. Kimber, Veijo Honkimäki, and Robert E. Dinnebier. Real-time and in situ monitoring of mechanochemical milling reactions. *Nature Chemistry*, 5(1):66–73, 2013.

[8] Yusaku Nakajima, Kai Kawasaki, Yasuo Takeichi, Masashi Hamaya, Yoshitaka Ushiku, and Kanta Ono. Force-controlled robotic mechanochemical synthesis. *Digital Discovery*, 3:2130–2136, 2024.

[9] Tomislav Friščić, Andrew V. Trask, William Jones, and W. D. Samuel Motherwell. Screening for inclusion compounds and systematic construction of three-component solids by liquid-assisted grinding. *Angewandte Chemie International Edition*, 45(45):7546–7550, 2006.

[10] Fumio Toda, Koji Kiyoshige, and Minoru Yagi. $NaBH_4$ Reduction of Ketones in the Solid State. *Angewandte Chemie International Edition in English*, 28(3):320–321, 1989.