

Mechanochemical Deracemization: A Fast and Solvent-Minimized Approach to Enantiopurity

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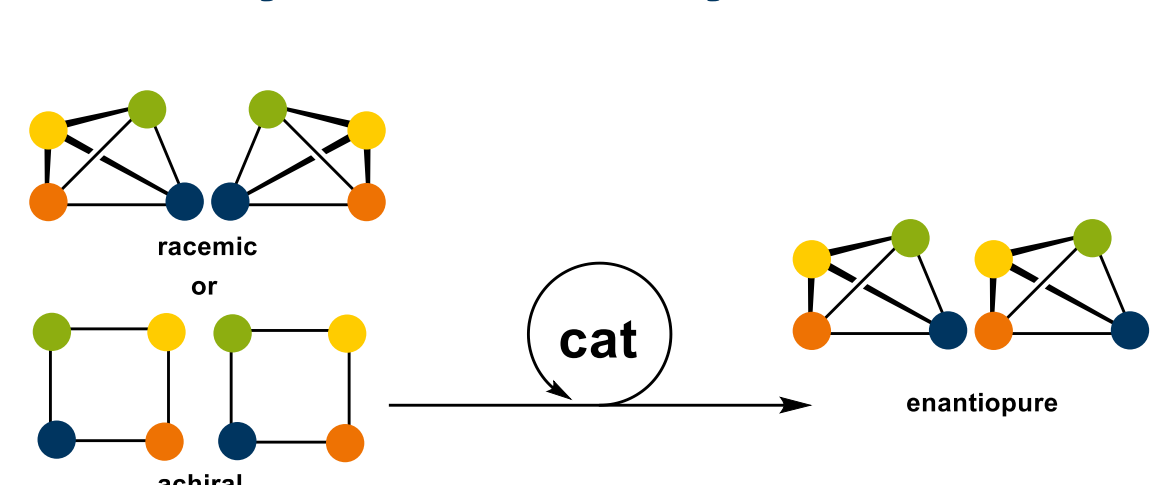


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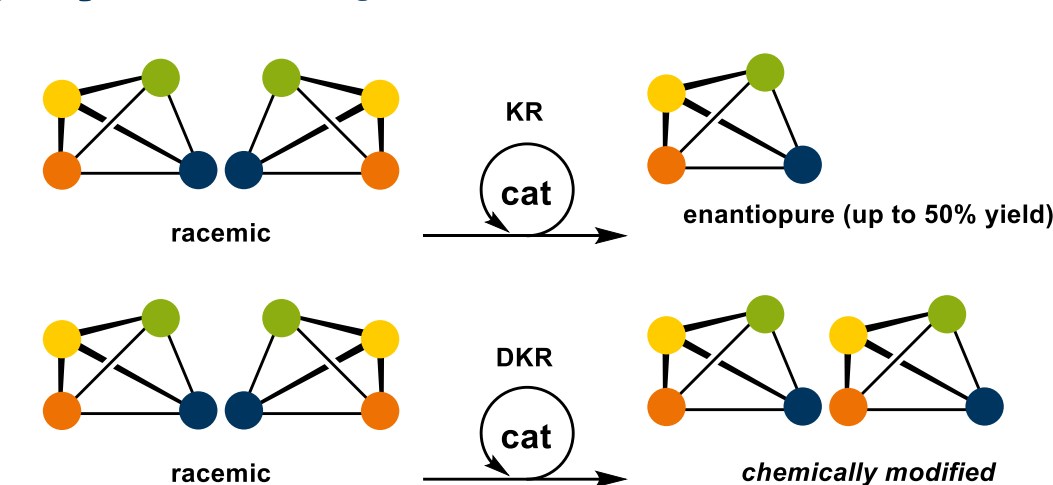
We introduce mechanochemical deracemization (MCDR) as a novel strategy for obtaining enantiopure compounds. This study demonstrates the successful transposition of six archetypical deracemization reactions from a solvent-based to a solvent-minimized ball milling environment. The scope includes a ketone, isoindolinones, imines, an ester, and an inorganic compound, all of which deracemized successfully. Key parameters such as milling material, ball number and size, the use of a bulk material and liquid-assisted grinding (LAG) were systematically investigated, revealing their crucial role. Quantitative enantiomeric excesses (ee) were achieved, while reaction times were reduced by up to 97 % and solvent consumption by as much as 100 %. This work establishes MCDR as a versatile, sustainable pathway to enantiopure compounds. By highlighting the generalizability of this approach and its huge potential for minimizing waste, this study provides the foundation for future advancements in mechanochemical deracemization.

Ways to Enantiopurity

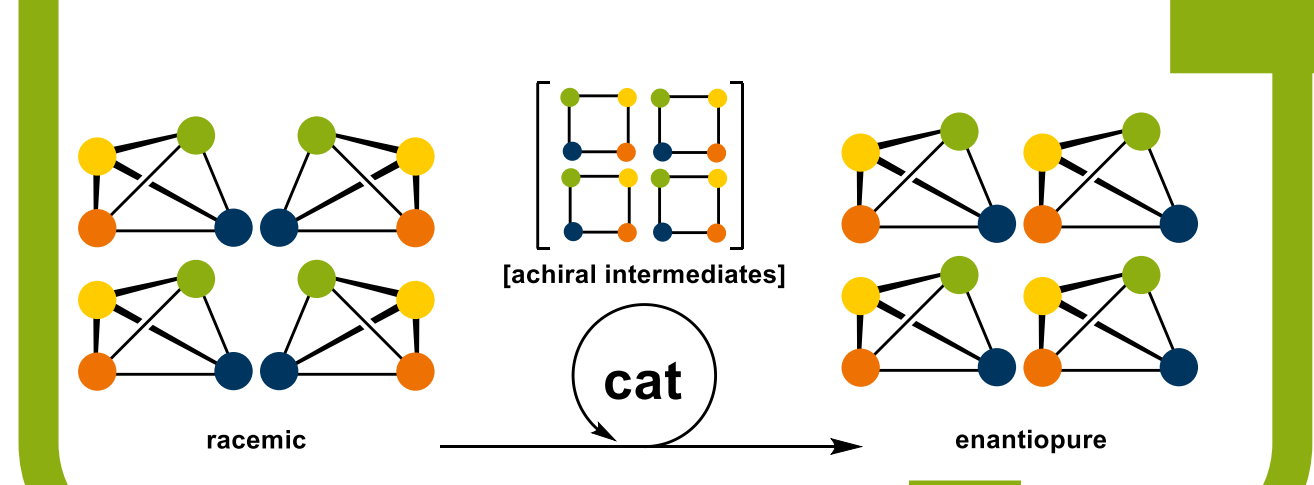
Asymmetric Synthesis



(Dynamic) Kinetic Resolution



Deracemization



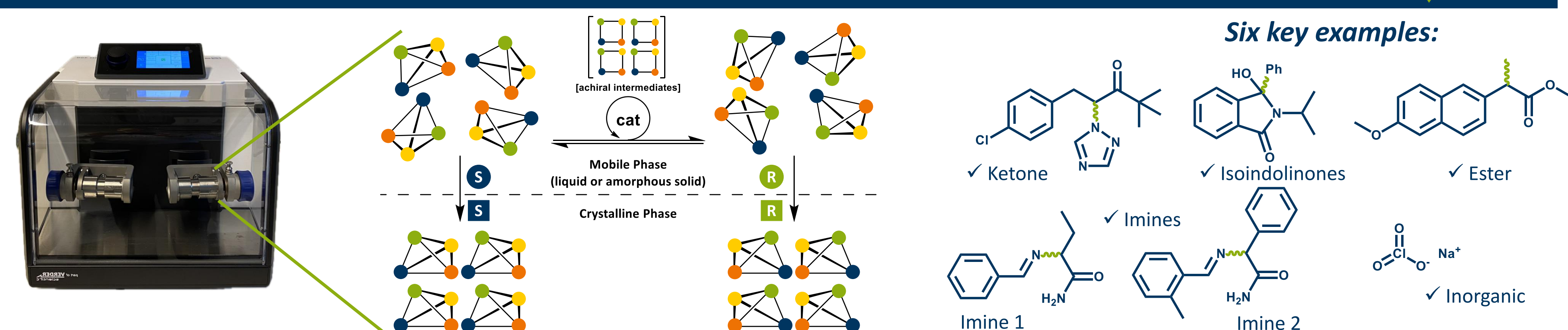
Possible via:

- Chemical (RedOx) Energy
 - Chiral catalyst/reagent
 - Stoichiometric RedOx-agents
 - Large amounts of solvents

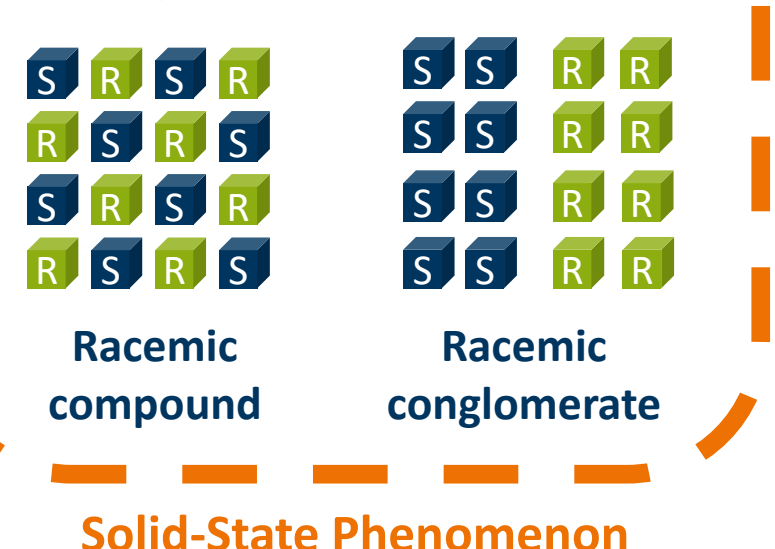
- Photonic Energy
 - Chiral catalyst/reagent
 - Large amounts of solvents

- Mechanical Energy (Viedma-Ripening)
 - No chiral catalyst/reagent
 - Large amounts of solvents
 - Long reaction times (days)

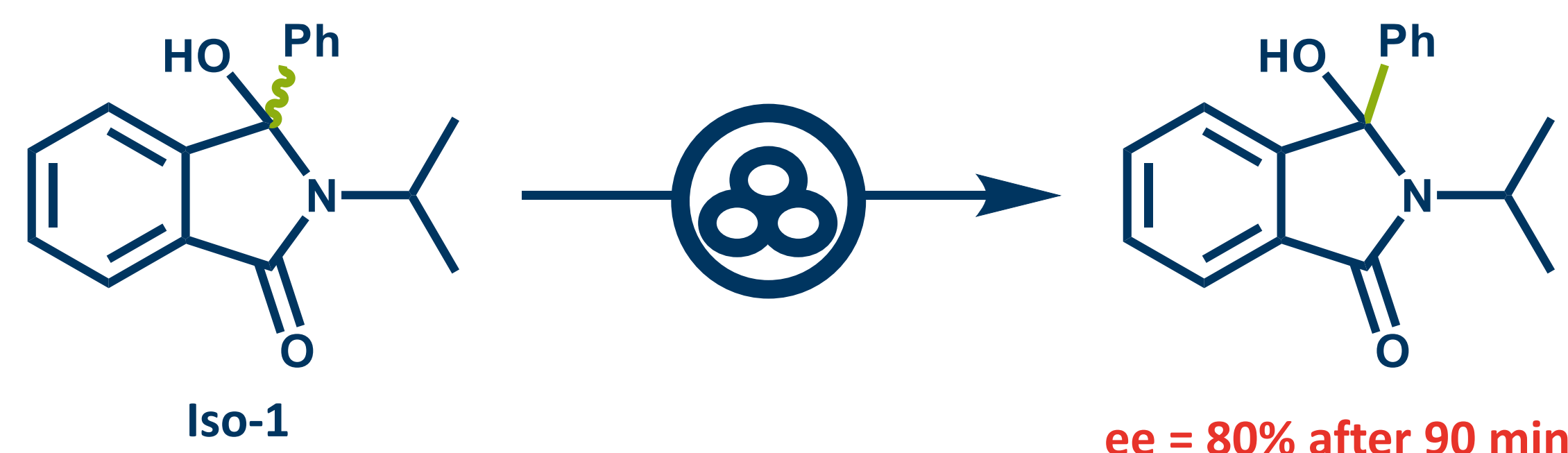
This Work: Mechanochemical Deracemization (MCDR)



- Prerequisites
 - ✓ Conglomerate crystals
 - ✓ Racemization in solution
 - ✓ Deracemization via crystallization

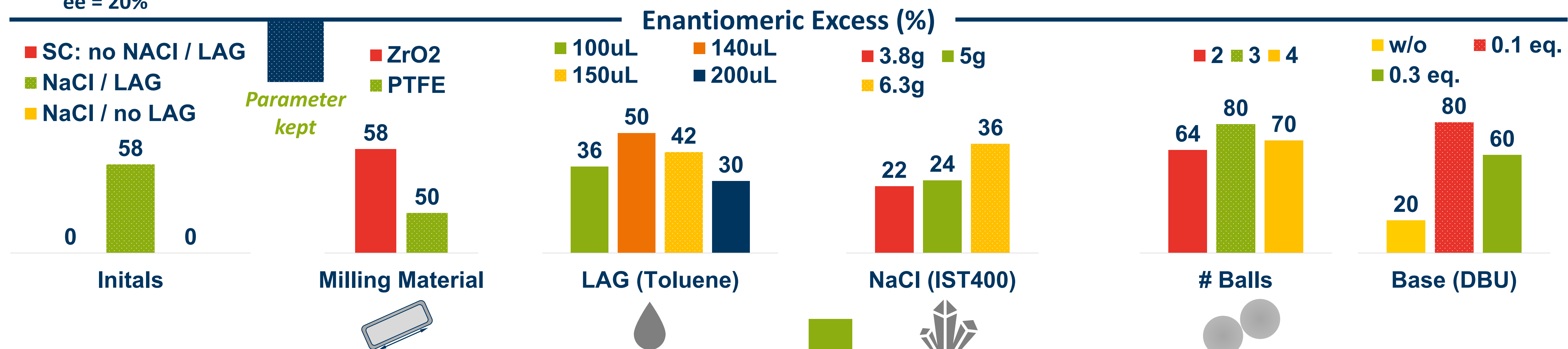


Example Optimization: MCDR of Isoindolinones (20%ee)



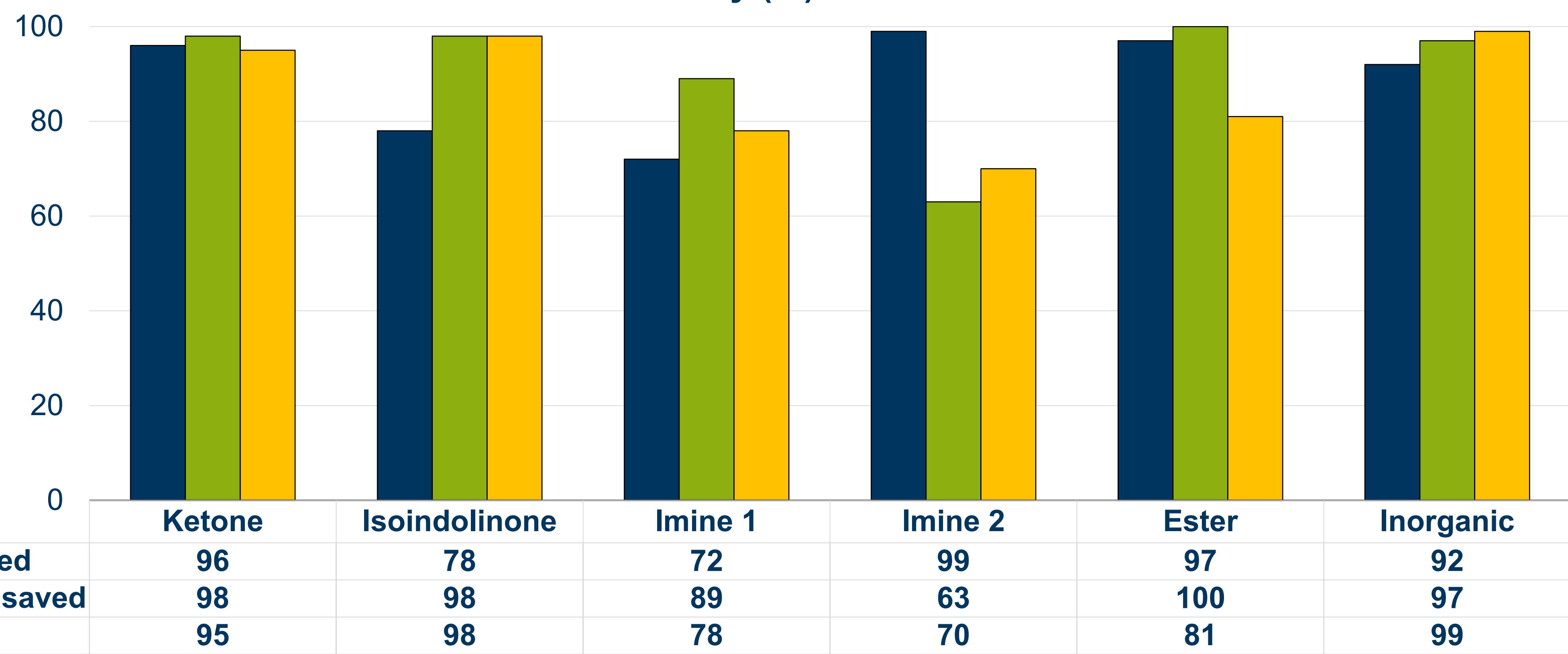
Starting cond.:
200 mg Iso-1, 0.1 eq. DBU, 100 μ L
Toluene, 1 or 2 ZrO₂ Balls, 10mL
ZrO₂ Vessel, 90 min., 30 Hz

Optimized cond.:
280 mg Iso-1, 0.1 eq. DBU, 150 μ L
Toluene, 6.3 g NaCl, 3 ZrO₂ Balls,
14mL PTFE Vessel, 90 min., 30 Hz

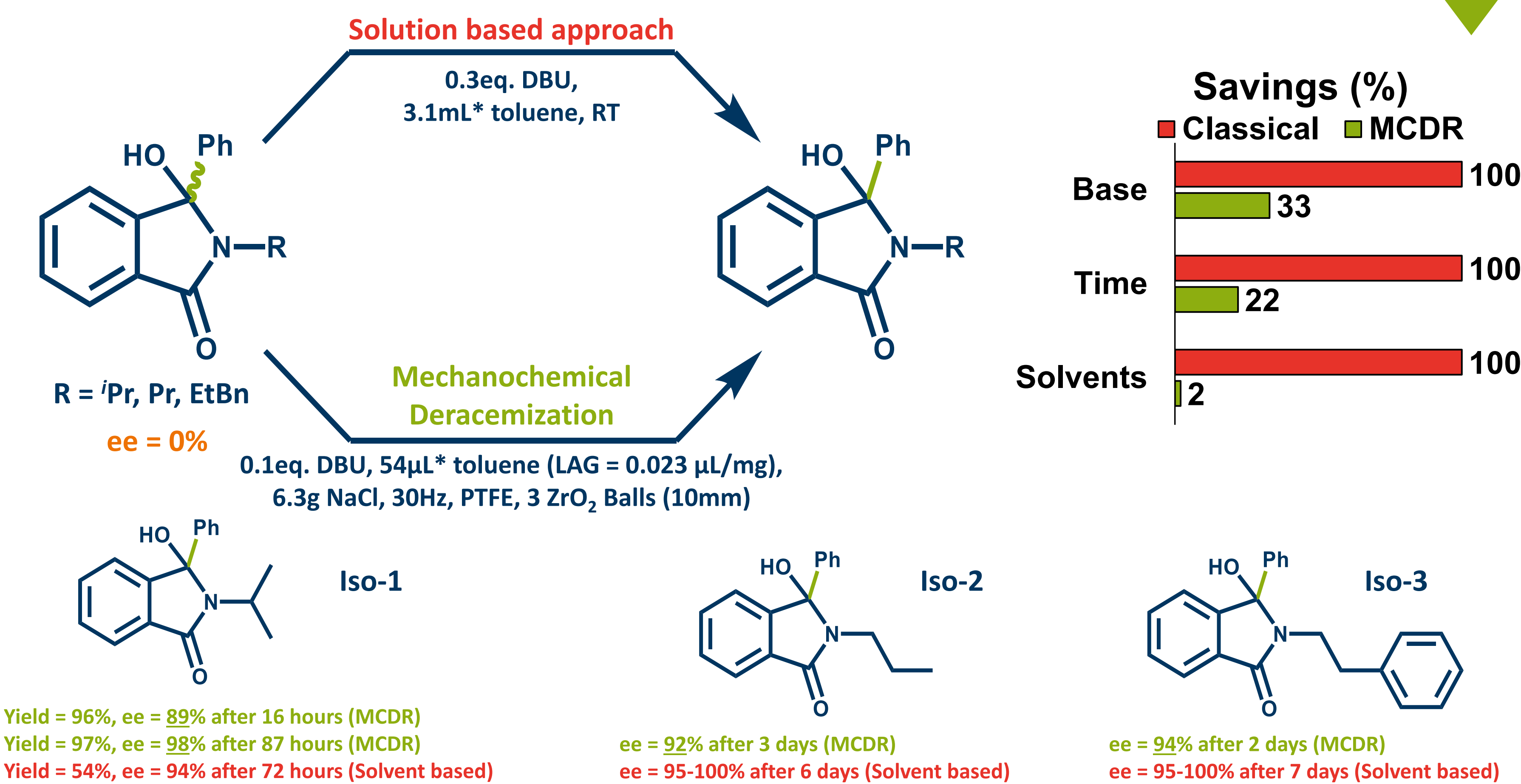


Savings: MCDR vs. Solution

Summary (%)



From 0%ee



Conclusion

- ✓ Developed a generalizable approach to deracemization via mechanochemistry
- ✓ Identified critical parameters (milling material, ball size/number, bulk material)
- ✓ Achieved significant reductions in solvent use (63–100%) and reaction times (72–99%)