Routine Characterization of Enantiomerically Selective Reactions by Molecular Rotational Resonance (MRR) Spectroscopy

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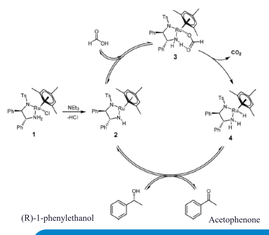
Introduction:

- Enantiomeric composition critically impacts drug efficacy and safety, yet traditional routine chiral purity analysis remains limited by complex method development, usability challenges, and low throughput.
- Using 1-phenylethanol as a model system, MRR provides unambiguous differentiation of enantiomers.
- Advances in automation, software, and spectral libraries streamline method development, improving simplicity, robustness, and throughput compared to conventional chiral chromatography.

Synthetic pathway



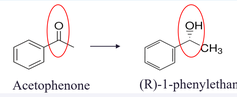


Figure 1. Synthetic pathway of (R)-1-phenylethanol[1]. Asymmetric hydrogenation using Ru-based Noyori-type catalyst with a hydrogen source and an 18-hour heated incubation step[2].

Reaction and Preparation

Reaction Setup

Starting materials:
- Formic acid + Triethylamine
- Acetophenone (10 mM)

Catalyst:
- Ru catalyst- [(R,R)-TETH - TSDPEN RuCl]

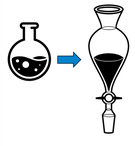
Condition:
- Temperature: 40 °C
- Stirring: 200 – 250 rpm
- Duration: 0 – 14 h

Reaction

- Stir the reaction at 40°C with stirring
- Withdraw samples at 3, 6, 9, 12 and 14 h

Quenching

- Quench the reaction with water



Extraction

- Extractions using ethyl acetate
- Collect the aqueous layer
- Dry over anhydrous sodium sulphate

Concentration

- Concentrate using a rotavap under reduced pressure at ~40 °C
- Remove ethyl acetate and acetonitrile

Final product

- Crude oil type of sample
- Contains (R)-1-phenylethanol
- and traces of Acetophenone

Chiral MRR Analysis of Reaction Mixture

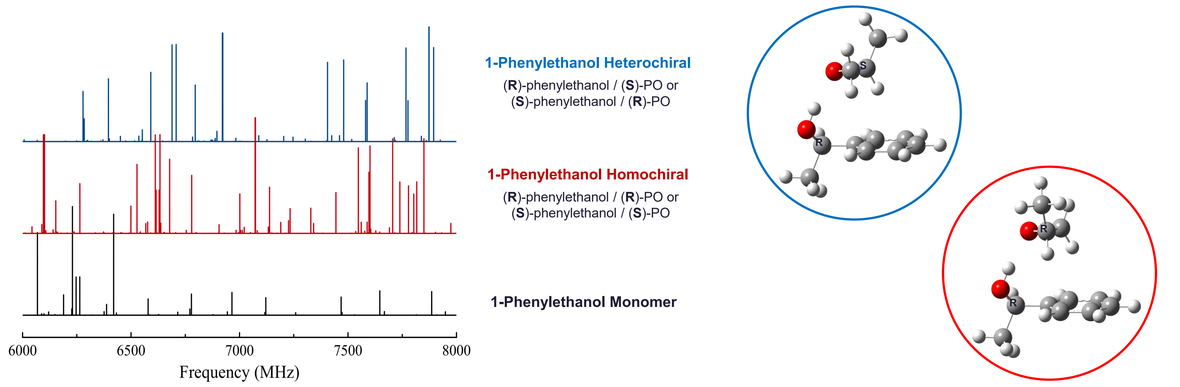


Figure 2. Structural Workflow: Enantiomers of 1-Phenylethanol are first identified through Broadband MRR structural ID of the chiral-tagged complexes.

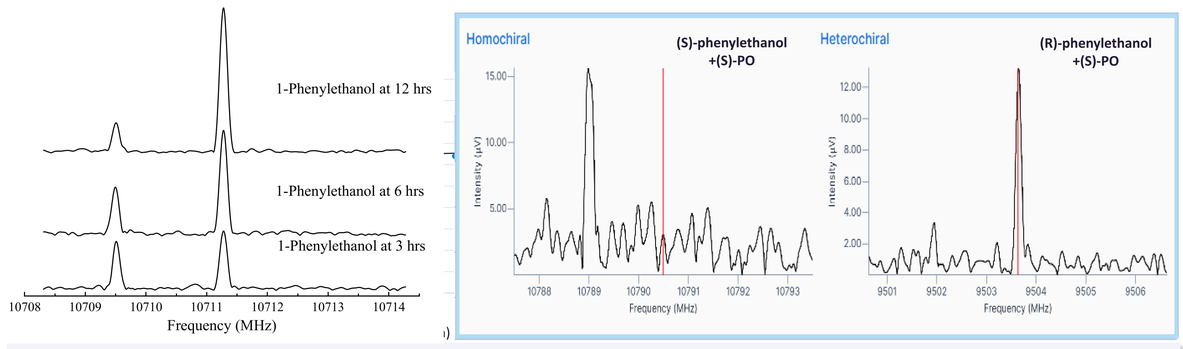
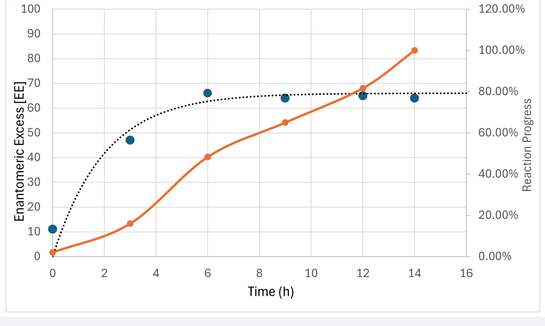


Figure 3. Quantitative Workflow: Targeted MRR provides routine, rapid interrogation of the reaction mixtures, yielding both reaction progress and EE measurements at each time interval.



Time (h)	Intensity (µV)	EE (%)
0	6	11%
3	48	47%
6	145	66%
9	195	64%
12	245	65%
14	300	65%

Figure 4. Results: Time-course studies reveal reaction efficiency through structure-specific automated MRR quantitation.

Key Advantages of MRR

Chiral Resolution with MRR

- Chiral tagging forms diastereomeric complexes with distinct rotational spectra.
- Rotational spectra directly encode molecular structure, enabling clear differentiation of (R) and (S) species.
- Enantiomeric composition can be quantified without enantiomerically pure standards.

Advantages Over Traditional Chiral Methods

- No chiral chromatography required, eliminating column screening and method development.
- Direct spectral differentiation of enantiomers, avoiding peak overlap or co-elution challenges.
- Minimal sample preparation supports rapid reaction screening.

Routine and Scalable Workflow

- Direct injection workflow simplifies analysis and reduces sample handling.
- Compatible with automated analysis pipelines, supporting routine monitoring of enantioselective reactions.
- Structural confirmation and quantitation in a single measurement accelerate reaction optimization.

References

1. Insight into catalyst speciation and hydrogen co evolution during enantioselective formic acid driven transfer hydrogenation with bifunctional ruthenium complexes from multi technique *operando* reaction monitoring. *Faraday Discussions* 2019, 220, 45–57.

2. The application of two-phase catalytic system in enantioselective separation of racemic (R,S)-1-phenylethanol. *Catalysts* 2023, 13(2), 292.

3. Chiral chromatography method screening strategies: Past, present and future. *Journal of Chromatography A* 2021, 1638, 461878.