Mechanochemistry

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A Mechanochemical Approach to Deracemization**

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The synthesis and isolation of enantiopure compounds remains an important challenge for many applications in medicinal, materials, and synthetic chemistry.[1–3] In general, chiral molecules of high enantiopurity are prepared by asymmetric synthesis or the resolution of their respective racemates.[4] The latter approach is more common but can be tedious, and the yields of isolated products are inherently restricted to, at best, 50%.[4–11] An ideal solution to this problem is to reconfigure the stereochemistry of the undesired enantiomer during the resolution process. While dynamic kinetic resolution (DKR)[5–11] or attrition-enhanced deracemization[12–15] methods may be used to overcome this fundamental limitation, the substrate scope for these methods is confined to compounds that can be chemically or thermally racemized. Given the recent advances in mechanochemistry,[16,17] where the mechanical force generated under ultrasound may be used to surmount thermally inaccessible isomerization barriers,[18–22] we envisioned a new method for enriching the enantiopurity of optically active species. Herein we report a cooperative method that combines a mechanically facilitated reconfiguration process[21] with stereoselective enzymatic hydrolysis[23] to isolate (*S*)-1,1′-bi-2-naphthol ((*S*)-binol) in 90% yield with an enantiopurity of higher than 98% from a racemic precursor.

Chiral molecules that are devoid of stereogenic centers and the asymmetry of which is derived from hindered rotation around single bonds are known as atropisomers.[4] These compounds have been successfully used as scaffolds for materials with molecular recognition capabilities and serve as the basis for many chiral ligands used to confer enantioselectivity to catalytically active metals.[24,25] (*S*)-binol, in particular, is an essential component used in the preparation of (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (*S*-binap),[2,26] which is critical for the large-scale synthesis of (−)-menthol and other industrially important and biologically active compounds.[27] Enantiopure atropisomers, including (*S*)-binol, are typically isolated by the resolution of a racemic precursor and are therefore subject to the fundamental and practical constraints described above.[26,28]

Recently, we demonstrated that mechanical force may be used to reconfigure atropisomers.[21] By growing poly(methyl acrylate) (PMA) chains from enantiopure (*R*)- or (*S*)-binol and subjecting solutions of these materials to ultrasound, we were able to convert one stereoisomer to the other in an iterative process that ultimately produced racemic mixtures.[21] Because of their high isomerization barriers (>30 kcal mol^{-1}),[24–28] upon heating these same materials to temperatures exceeding 250°C for longer than 72 h no isomerization was observed.[21]

To deracemize *rac*-binol, we envisioned using the aforementioned mechanical isomerization methodology in conjunction with the enzyme cholesterol esterase, which is known to stereoselectively hydrolyze esters of (*S*)-binol.[23] We hypothesized that in a racemic mixture of polymer-embedded binol units, the enzyme would selectively cleave the polymer chains connected to an (*S*)-binol derivative (i.e., $PMA_{(S)\text{-binol}}$, Scheme 1). Subsequent mechanically induced reconfiguration of the residual enantiomer (i.e., $PMA_{(R)\text{-binol}}$)[21] followed by in situ enzymatic hydrolysis should then repeat until (*S*)-binol, which is not of sufficient molecular weight to experience ultrasound-induced isomerization,[16–22] is formed as the exclusive chiral product (Scheme 1). In addition to establishing a new method for enriching the enantiopurity of optically active compounds, we reasoned that the solubility differences between high-molecular-weight polymers and small molecules would allow the isolation of the enantiopure products.

To test our hypothesis, a polymerization initiator amenable to hydrolysis by cholesterol esterase was required.[23] As summarized in Scheme 2, coupling 3-(2-bromo-2-methylpropanoyloxy) propanoic acid with *rac*-binol using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and catalytic amounts of 4-dimethylamino pyridine (DMAP) afforded a racemic initiator, *rac*-I.[29] PMA chains were then grown from this difunctional initiator using a copper(0)-catalyzed controlled radical polymerization (CRP).[29,30] The resulting polymer, $PMA_{rac\text{-binol}}$, was isolated by precipitation into methanol and subsequent filtration. Analysis of the isolated material by gel permeation chromatography (GPC) revealed that it possessed a number average molecular weight (M_n) of 67 kDa and a polydispersity index (PDI) of 1.3 (Figure 1a, blue trace) and therefore was of sufficient size to undergo an ultrasound-induced mechanochemical activation process.[16–22] As expected, the circular dichroism (CD) profile of this racemic material exhibited no significant optical activity (Figure 1b, blue).

With the desired material in hand, a biphasic solution of $PMA_{rac\text{-binol}}$ (50 mg mL^{-1}) in methyl isobutyl ketone and phosphate buffer (pH 7.0; 1:1 v/v) containing cholesterol esterase (2 U) and deoxycholic acid (6.3 mM) was prepared.[23,29] The mixture was then subjected to pulsed ultrasound at 9°C (conditions: 1 s on, 1 s off; power density =

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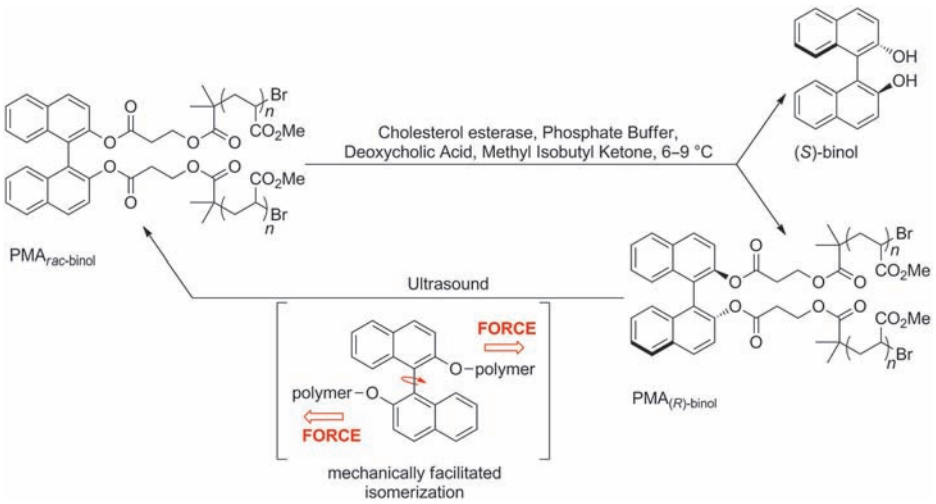
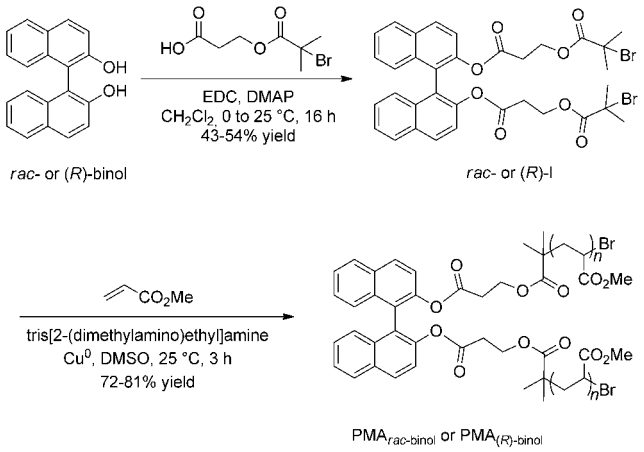


Scheme 1. Subjecting $PMA_{rac\text{-}binol}$ to cholesterol esterase results in the selective hydrolysis of the *S* isomer, yielding (*S*)-binol. The other product of this reaction, $PMA_{(R)\text{-}binol}$, undergoes reconfiguration through an ultrasound-induced mechanical isomerization process. The cycle repeats until the formation of (*S*)-binol is maximized.



Scheme 2. Synthesis of *rac*-I or (*R*)-I and $PMA_{rac\text{-}binol}$ or $PMA_{(R)\text{-}binol}$.

9.65 W cm^{-2}) and analyzed by CD spectroscopy over time. The ellipticity signal observed at 230 nm, which was consistent with the λ_{max} value and optical profile of (*S*)-binol, smoothly increased with the sonication period (Figure 1b, pink shades). After 48 h (Figure 1b, red), the intensity of the signal was determined to be greater than 90% of that of enantiopure (*S*)-binol (measured independently at the same concentration; see Figure 1b, black). Subsequent purification of the reaction mixture by aqueous extraction to remove the enzyme followed by precipitation into methanol and filtration to remove the polymer afforded (*S*)-binol in 90% yield.[29] The structure of this product was unambiguously determined using ^{1}H NMR spectroscopy and mass spectrometry, and its enantiomeric excess (*ee*) was measured by CD spectroscopy to be higher than 98%. The precipitated polymer was also collected and analyzed by GPC, which revealed a 50% reduction in molecular weight (M_n = 34 kDa; PDI = 1.4; Figure 1a, red trace) compared to the material before sonication, a result consistent with hydrolysis of the polymer chains from the centrally positioned binol unit.

To confirm that the observed deracemization was due to a mechanically facilitated process, a series of control experiments was performed. First, the aforementioned reaction was carried out in the absence of sonication by vigorously stirring the reaction mixture at 25 °C for 48 h.[29] Subsequent analysis by CD spectroscopy revealed that the crude reaction mixture did not exhibit a significant enhancement in its optical activity (Figure 1b, green). However, GPC analysis of the polymeric material isolated from this experiment revealed

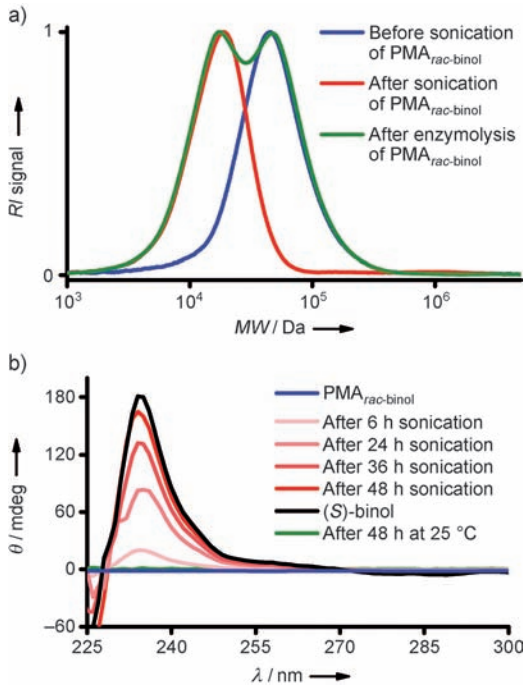


Figure 1. a) Normalized gel-permeation chromatograms of $PMA_{rac\text{-}binol}$ before (blue) and after sonication for 48 h in the presence of cholesterol esterase (red) and $PMA_{rac\text{-}binol}$ that had not been sonicated after treatment with cholesterol esterase at 25 °C for 48 h (green). Molecular weights (*MW*) are reported relative to polystyrene standards in tetrahydrofuran using a refractive index (*RI*) detector. b) CD spectra of acetonitrile solutions of $PMA_{rac\text{-}binol}$ (initial polymer concentration = 12 mg mL^{-1} corresponding to an initial binol concentration of $[binol]_0$ = 0.05 mg mL^{-1}) obtained after exposure to ultrasound and cholesterol esterase for the time period indicated (pink shades). For comparison, an acetonitrile solution of enantiopure (*S*)-binol (0.05 mg mL^{-1}) was also analyzed (black). Spectra of $PMA_{rac\text{-}binol}$ before sonication (blue) and after treatment with cholesterol esterase at 25 °C for 48 h (green) are also shown (initial polymer concentration = 12 mg mL^{-1}; $[binol]_0$ = 0.05 mg mL^{-1}).

that the enzyme was active, because a bimodal distribution of polymers was observed (Figure 1a, green trace): one with a molecular weight similar to that of the $PMA_{rac\text{-binol}}$ before sonication and the other similar to that of the material obtained after sonication. These results are consistent with the selective hydrolysis of the polymers containing (*S*)-binol, leaving those containing (*R*)-binol intact. No optical enhancement was observed, when a mixture of the initiator, *rac*-I, which is not of sufficient molecular weight to undergo an ultrasound-induced isomerization,[16–22] and cholesterol esterase were exposed to the sonication conditions described above.[29] Finally, to test whether the above resolution could be achieved thermally, the enantiopure initiator (*R*)-I was heated in acetonitrile at 82 °C for 48 h;[31] subsequent CD spectroscopy analysis of this solution revealed no loss of optical activity when compared to the starting material (Figure S3 in the Supporting Information).[29]

Given these results, we reasoned that our methodology could be extended to reconfigure (*R*)-binol to its mirror image isomer. To test this supposition, an enantiopure initiator was synthesized from (*R*)-binol (i.e., (*R*)-I; see Scheme 2)[29] and PMA chains were grown by a copper(0)-catalyzed CRP[30] to afford $PMA_{(R)\text{-binol}}$, a polymer of sufficient molecular weight ($M_n = 52$ kDa; PDI = 1.2) to undergo mechanochemical activation.[16–22] Similar to its enantiomer, this polymer exhibited a λ_{max} value of 230 nm, although its ellipticity was of the opposite sign (Figure 2, blue). Sonication of $PMA_{(R)\text{-binol}}$ in the presence of cholesterol esterase,[29] as described above for the racemic derivative, revealed a gradual reversal in the ellipticity over time, such that after 72 h the intensity of the signal was greater than 85% of that of enantiopure (*S*)-binol (Figure 2, red). In the absence of sonication, no change in the optical activity of the $PMA_{(R)\text{-binol}}$ was observed (Figure 2, green).[29] We concluded from these results that the aforementioned (*R*)-binol derivative was successfully reconfigured through the combination of a mechanically facilitated isomerization process with enzymatic hydrolysis.

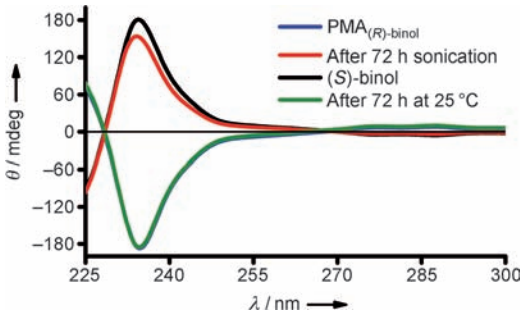


Figure 2. CD spectra of an acetonitrile solution of $PMA_{(R)\text{-binol}}$ (initial polymer concentration = 9 mg mL^{-1}; $[binol]_0 = 0.05$ mg mL^{-1}) obtained after exposure to ultrasound in the presence of cholesterol esterase for 72 h (red). For comparison, an acetonitrile solution of enantiopure (*S*)-binol (0.05 mg mL^{-1}) was also analyzed (black). Spectra of $PMA_{(R)\text{-binol}}$ before sonication (blue; underneath green curve) and after treatment with cholesterol esterase at 25 °C for 72 h (green) are also shown (initial polymer concentration = 9 mg mL^{-1}; $[binol]_0 = 0.05$ mg mL^{-1}).

In summary, we have shown that the combination of ultrasound-induced isomerization and enzymatic resolution may be used to selectively convert either *rac*- or (*R*)-binol to (*S*)-binol in good yield and high enantiopurity, a process that cannot be achieved using DKR, attrition-enhanced, or other thermal deracemization methods. Moreover, to our knowledge, this is the first example of preparing (*S*)-binol in high enantiomeric excess from a racemic precursor in a single reaction vessel. A comprehensive series of control experiments, involving polymeric and small-molecule analogues, indicated that the formation of the observed product was in part facilitated by a mechanically induced isomerization process. Collectively, these results establish a fundamentally new method for deracemizing stereoisomers and for changing molecular configurations using mechanical force. Moreover, we believe the mechanochemical approach described herein complements DKR and other chemical deracemization methods and may be combined with known[32] stereoselective transformations to enrich the enantiopurity of other chiral molecules.

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