Kinetic Resolution of Thiols

Significance: An efficient direct acylative kinetic resolution of racemic secondary thiols 1 was reported by the authors, using a novel sulfonamide catalyst derived from a cinchona alkaloid. Under optimal conditions (10 mol% catalyst loading, –30 °C in MTBE), with 2 as the electrophile, various secondary aromatic thiols can be resolved with high er at ~50% conversion. The selectivity \( S = k_{\text{fast}}/k_{\text{slow}} \) of the resolution is in the range of 50–275. In addition, during the kinetic resolution of the thiols, a simultaneous desymmetrization of a meso-anhydride electrophile (like 2) also occurred with excellent enantioselectivity.

Comment: Although the kinetic resolution of alcohols is a well-established process, analogous methods for thiols are rare. This organocatalytic transformation involving a kinetic resolution of a racemic thiol and a simultaneous enantioselective desymmetrization of an achiral anhydride, is quite useful and atom-economic. The preparation of the hemiamide 7 [a precursor for \((R)-\text{pregabalin}\)] shown in the Scheme is a nice demonstration. Both enantiomers (5 and 6) of the thiol and the desymmetrization product 7 can be obtained in high yields and high enantiomeric ratios.