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Regio- and Enantioselective Synthesis of Azole Hemiaminal Esters by Lewis Base Catalyzed Dynamic Kinetic Resolution

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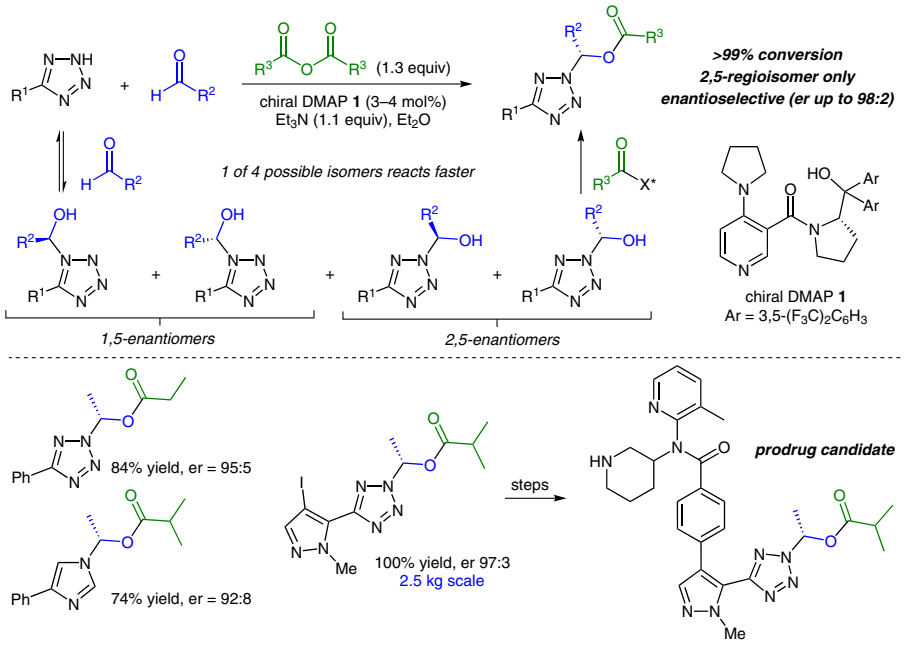
Lewis Base-Catalyzed Dynamic Kinetic Resolution of Azole Esters



Significance: The tetrazole motif is a well-known carboxylic acid isostere and, as such, part of a valuable class of heterocycles in drug-discovery programs. Access to N-substituted tetrazoles is typically plagued by poor regioselectivities (i.e., mixtures of 1,5- and 2,5-regioisomers) or harsh conditions. A mild and completely regioselective method is reported for the synthesis of 2,5-disubstituted tetrazoles with chiral *N*-hemiaminal esters. The products are formed by treating unsubstituted tetrazoles with aldehydes and anhydrides in the presence of triethylamine and a Lewis base (DMAP). The use of a prolinol-based chiral DMAP catalyst permitted dynamic kinetic resolution (DKR) to occur, generating 2,5-substituted tetrazoles in high enantiomeric ratios. This method was extended to other azoles (imidazoles, pyrazoles) and was applied to the large-scale (2.5 kg) synthesis of a prodrug candidate.

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Comment: The method is a unique example of a regio- and enantioselective DKR for an entry into 2,5-substituted hemiaminal esters. The DKR takes advantage of the equilibrium between four transient hemiaminal adducts (see scheme). A kinetic analysis reveals that mixtures of hemiaminal adducts can be observed (NMR) for sterically hindered substrates. However, high regioselectivity and enantioselectivity can be achieved in the rate-determining acylation step. Overall, the yields (71–100%), regioselectivity (100:0), and enantiomeric ratio (≤98:2) are excellent. Several anhydrides, aliphatic aldehydes (linear, α-branched), and benzaldehydes were used successfully, and the scope was also extended to hemiaminal carbonates and sulfonates. This method provides access to a range of enantioenriched azole prodrugs, so that their rates of enzymatic hydrolysis can be tailored to the needs of medicinal chemistry projects.

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Category

Synthesis of Heterocycles

Key words

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