Abstract
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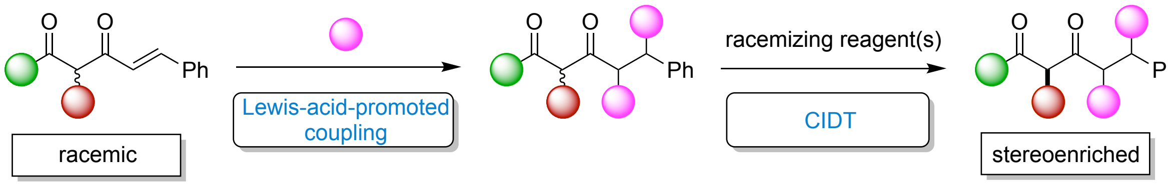
Controlling asymmetric configuration is critical for synthesizing complex organic molecules, particularly in pharmaceutical industry. Various enantioselective synthesis techniques involving the use of chiral catalysts are well studied when the synthesized asymmetric center involves newly constructed C-C bonds. However, to control multiple constructed and labile asymmetric centers on the same molecule in tandem is challenging. To minimize the number of undesirable stereoisomers and simplify the process of product purification, crystallization-induced diastereomer transformation (CIDT) is a promising approach. CIDT provides stereoselectivity via thermodynamic equilibrium, and is more efficient in both timely and cost-effect manners compared to traditional separation methods such as HPLC. We studied asymmetric transformation of racemic starting materials followed by resolution of the α-stereocenter through CIDT to acquire highly stereoenriched products (scheme 1). We attempted to optimize the chiral catalyst, electronic properties of substrates, and other factors affecting the yield as well as diastereomer ratio (dr).



- stereoconvergent
- isolation by single filtration
- access to stereoenriched α-substituted β-dicarbonyls
- compatible with multiple function groups

Scheme 1. Conceived transformations of this project.

Overall, our results highly suggest that not only is CIDT a promising and powerful tool when coupled with previous non-asymmetric transformations to produce stereo-rich products, but its optimal solvent is also likely to be substrate-based and worth further investigation. We confirmed that both Friedel-Crafts reactions and Diels-Alder reactions are compatible with a variety of γ-δ-unsaturated β-ketoamides and electron-rich arene derivatives with metallic Lewis-acid catalysts. For all substrates, we achieved the most promising result in CIDT when using solvent systems based on toluene and TEA as racemizing reagent, while a solvent mixture of ethyl acetate with hexane and MTBE/ether with acetonitrile also led to different extent of stereoenriched product. When Friedel-Crafts reactions or Diels-Alder reactions on γ-δ-unsaturated β-ketoamides are followed with CIDT, products of a dr that is greater than 20:1 can be separated at as high as 44% yield.