Highly Enantioselective Direct Alkylation of Arylacetic Acids with Chiral Lithium Amides as Traceless Auxiliaries

**Synthesis of a γ-Secretase Modulator**

**Significance:** The synthesis of the γ-secretase modulator depicted illustrates an efficient enantioselective alkylation of enediolates derived from aryacetic acids using the chiral lithium amide base H as a stereodirecting agent. The chiral base is required in stoichiometric amounts, but it is recoverable and easily prepared in two steps from styrene oxide (M. J. Frizzle et al. Org. Process Res. Dev. 2007, 11, 215).

**Comment:** The scope of the asymmetric alkylation was established using 24 aryl- and hetero-arylacetic acids and 12 alkylating agents (36 examples in total) with yields typically exceeding 70% (6 exceptions) and ee values typically exceeding 90% (5 exceptions). Under the standard conditions outlined above, simple alkanoic acids did not undergo highly enantioselective alkylation.