Racemization-Resistant C-N Axially Chiral Enolates: Application to Asymmetric α–Fluorination of α-Amino Acid Derivatives.

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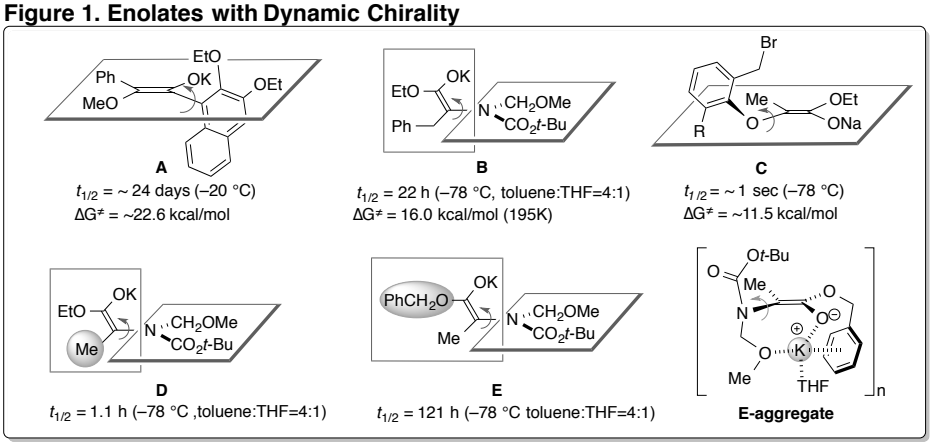
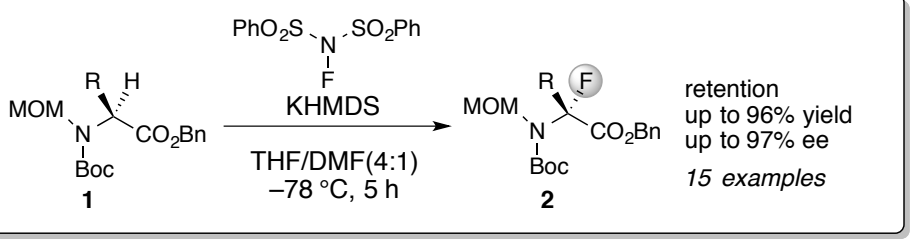
Abstract: We have studied asymmetric reactions that proceed via chiral enolates **A**, **B**, and **C** based on restricted bond rotation around the chiral C-C,[1] C-N,[2,3] and C-O[4] axes, respectively (Figure 1). The typical racemization barriers of these chiral enolates are ~22, ~16, and ~12 kcal/mol, respectively, which corresponds to half-lives of racemization of ~24 days at –20 °C, ~22 h at –78 °C, and ~1 sec at –78 °C, respectively. Although chiral enolate **B** with a chiral C-N axis derived from phenylalanine has relatively long half-life of racemization (22 h) at –78 °C, chiral enolate **D** derived from alanine has short half-life of racemization (1.1 h) even at –78 °C. These circumstances limited the use of chiral enolate **D** for asymmetric intermolecular reactions due to the partial racemization during the relatively long reaction times for intermolecular reactions. Under these backgrounds, we found a simple solution to this problem. The half-life of racemization of chiral enolate **E** derived from an alanine benzyl ester was found to be >100 times longer than that of **D** derived from the corresponding ethyl ester. The tremendous elongation of the lifespan of enolate chirality could be ascribed to its aggregate structure including cation-π interaction as shown in **E-aggregate**. By virtue of this protocol for racemization-resistant chiral enolates, we have successfully developed asymmetric α–fluorination of α–amino acid derivatives, which proceeded in up to 97 % ee (Scheme 1).

Figure 1. Enolates with Dynamic Chirality



Scheme 1. Asymmetric α-Fluorination via Memory of Chirality



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