Selective β mono- and di- C–H halogenation of alcohols via radical relay chaperones

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Abstract: A radical-mediated strategy for selective β C–H halogenation of alcohols was achieved via a radical relay chaperone strategy. This approach employed an imidate radical capable of performing a 1,5-hydrogen atom transfer (HAT) and enabled mono- and di-halogenation at the β carbon of alcohols by using simple iodide, bromide, and chloride salts. This imidate chaperone developed by our group was installed in a single step and provided controllable selectivity to functionalize unactivated C-H bonds even in the presence of weaker bonds. Notably, this chaperone design employed a non-nucleophilic nitrogen atom capable of performing multiple HATs instead of the typical nucleophilic substitution observed in N-centered radical oxidations. Our streamlined protocol converted alcohols to mono- and di-haloimidates, followed by hydrolysis revealed β-halogenated alcohol analogs. Further manipulation of the geminal di-iodide allowed access to medicinally relevant di-fluoro and di-deutero derivatives.

Keywords: C–H halogenation; Imidate; Chaperones; Hydrogen atom transfer