



**THE UNIVERSITY OF ADELAIDE**

**Recent Advances in the Design, Understanding and  
Utilisation of Free-Radical Homolytic Substitution  
Chemistry**

A thesis presented for the degree of

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by

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# Abstract

The research described in this thesis represents a comprehensive study into the understanding, design and utilisation of free-radical homolytic substitution chemistry. The work is divided into sections which broadly cover synthetic, mechanistic, and stereochemical aspects of homolytic substitution.

The first section reports efforts to develop new effective methodology based on homolytic substitution chemistry with the principal aim of providing synthetically viable procedures. Radicals generated from alkyl and aryl iodides, pyridine-2-thioneoxycarbonyl (PTOC) esters and imidate esters, as well as through electron transfer, are shown to effectively undergo intramolecular homolytic substitution at selenium and tellurium atom, with the expulsion of appropriate leaving groups to afford a variety of novel higher heterocycles. Specific highlights include the preparation of the anti-inflammatory pharmaceutical, *Ebselen*, selenium-containing carbohydrates, as well as selenium and tellurium containing anti-oxidants.

The second section reports the use of high-level *ab initio* molecular orbital theory as a tool for understanding the mechanistic details surrounding free-radical attack at a variety of main-group higher heteroatoms. We report that reactions involving sulfur, selenium and the halogens are likely to undergo homolytic substitution via transition states in which the attacking and leaving radicals adopt a collinear arrangement resulting in Walden inversion, while those involving group(IV) elements are predicted to proceed via both front-side and back-side attack mechanisms. Interestingly, only reactions involving phosphorus, tellurium, and for one example, selenium are predicted to involve hypervalent intermediates. The synthetic consequences of these findings are discussed.

The third section describes attempts to trouble-shoot problems involving standard radical precursors in reactions involving the benzylseleno moiety. This work resulted in the development of the telluroformate functional group and novel palladium-mediated cross-coupling procedures for its effective preparation.

The last section of this thesis describes recent work aimed at the development of enantioselective free-radical reducing agents. Several chiral non-racemic stannanes have been prepared and their suitability in free-radical reductions scrutinised. By combining chiral stannanes with bulky Lewis acids, enantioselectivities in excess of 96% are reported. These results have the potential of revolutionising chiral free-radical chemistry.