

C–H Functionalisation

Subjects: [Chemistry](#), [Organic](#)

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C–H bond functionalisation describes the transformation of a C–H bonds into a C–X bonds (X = C, N, O, B, halides, among many others). The term is typically associated with transition metals in processes like C–H activation.

However, other methods such as nitrene/carbene insertion and hydrogen atom transfer (HAT) can also be used to functionalise C–H bonds with varying selectivity and ability to introduce different functional groups depending on the method used.

hydrogen atom transfer

functionalisation

radicals

photoredox

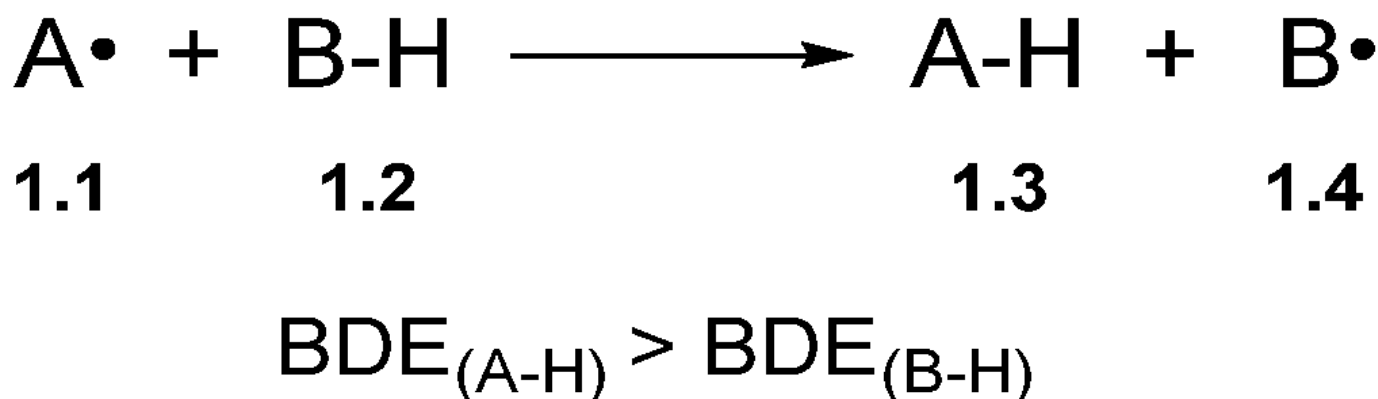
electrochemistry

1. Introduction

The ability to use C–H bonds as de facto functional handles has streamlined the synthesis of complex organic molecules and changed how chemists approach retrosynthesis [\[1\]\[2\]\[3\]\[4\]\[5\]](#). Using C–H bonds as functional handles instead of pre-functionalised substrates, the yields' various benefits include lower step counts in multistep synthesis and an improved atom economy of reactions [\[3\]\[6\]\[7\]\[8\]](#). Furthermore, the diversity of transformations available to C–H bonds potentially enables access to a wide array of functionality to be introduced into a common core [\[7\]\[9\]\[10\]](#). Broadly speaking, C–H functionalisation is achieved by generating reactive intermediates from C–H bonds to subsequently harness their reactivity. This can be achieved through organometallic C–H activation [\[6\]\[11\]\[12\]\[13\]\[14\]](#), carbene/nitrene C–H insertion [\[2\]\[11\]\[15\]\[16\]\[17\]](#), enzymatic C–H functionalisation [\[18\]](#), or hydrogen atom transfer (HAT) [\[11\]\[19\]\[20\]](#). However, site-selective C–H functionalisation is challenging due to the minimal differences between C–H bonds in organic molecules [\[6\]\[21\]\[22\]\[23\]](#). HAT generates alkyl radicals from C–H bonds through the radical abstraction of hydrogen atoms [\[19\]](#). Alkyl radicals are highly reactive intermediates that are relatively insensitive to steric crowding and do not form aggregates [\[24\]](#). Alkyl radicals react chemoselectively with radical traps or couple with other radicals, even with substrates that contain *N*-heterocycles as well as polar and acidic functional groups [\[20\]\[24\]\[25\]\[26\]\[27\]\[28\]](#). Additionally, HAT processes can be fine-tuned towards specific C–H bonds through choice of HAT reagent, change of solvent, or addition of certain additives [\[29\]\[30\]](#).

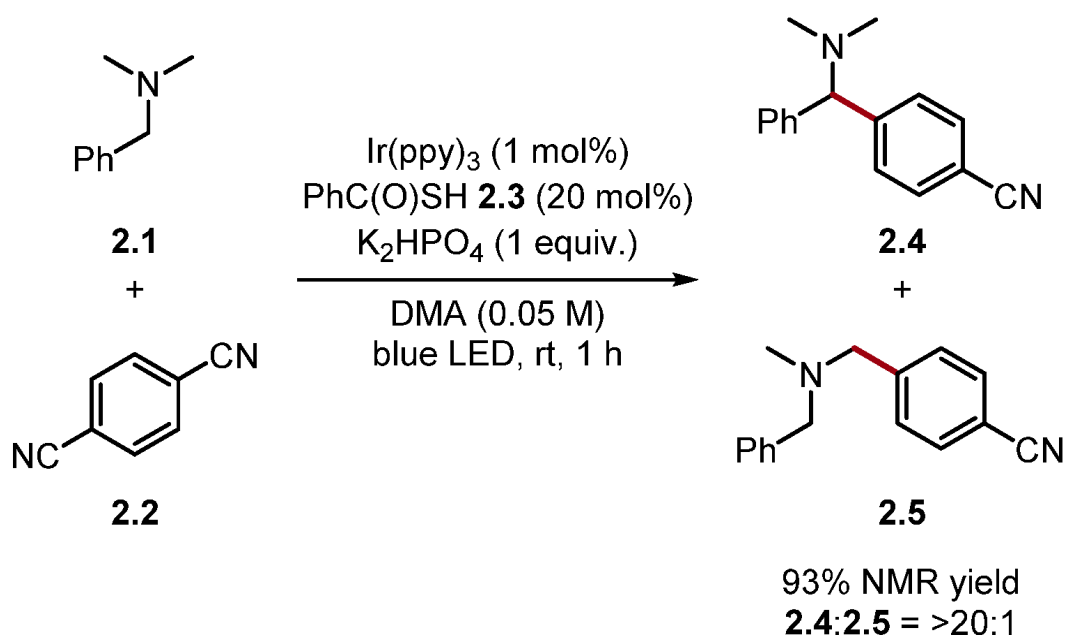
2. HAT Background and Mechanism

Hydrogen atom transfer is a one-step process that transfers a hydrogen atom (proton and electron) from one species to another (Scheme 1) [\[31\]\[32\]](#). However, in the context of synthesis, HAT is used for C–H functionalisation by harnessing the reactivity of the alkyl radical with various radical traps [\[19\]](#).



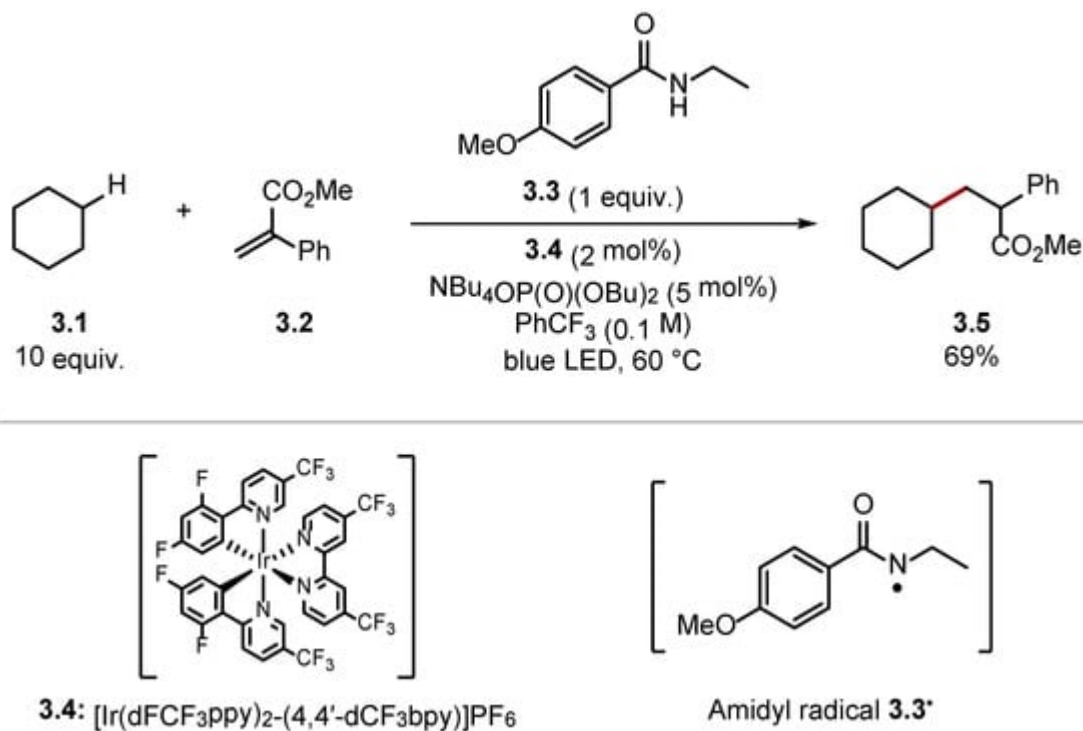
Scheme 1. Generic HAT process.

The bond dissociation energy (BDE) is the key driving force for HAT [33][34][35]. Accordingly, the BDE of A–H in Compound **1.3** (A–H) should be greater than the C–H bond being abstracted (B–H) to favour product formation [32]. Fortunately, BDE values are well-documented in the chemical literature [33][36][37]. BDE values can also be matched to ensure the desired hydrogen atom is abstracted. For example, thiyl radicals undergo HAT with relatively weak C–H bonds to form the corresponding alkyl radical and a thiol [alkyl thiols $BDE_{S-H} \approx 87$ kcal/mol] [38]. Hamashima and co-workers developed an arylation of benzylamine **2.1** C(sp³)–H bonds, which proceeded through regio- and chemo-selective HAT of the benzylic C(sp³)–H using a thiyl radical derived from thiobenzoic acid **2.3** [*N,N*-dimethylbenzylamine **2.1** $BDE_{C-H} = 84.9$ kcal/mol versus thiobenzoic acid **2.3** $BDE_{S-H} = 87.4$ kcal/mol] (Scheme 2) [39].



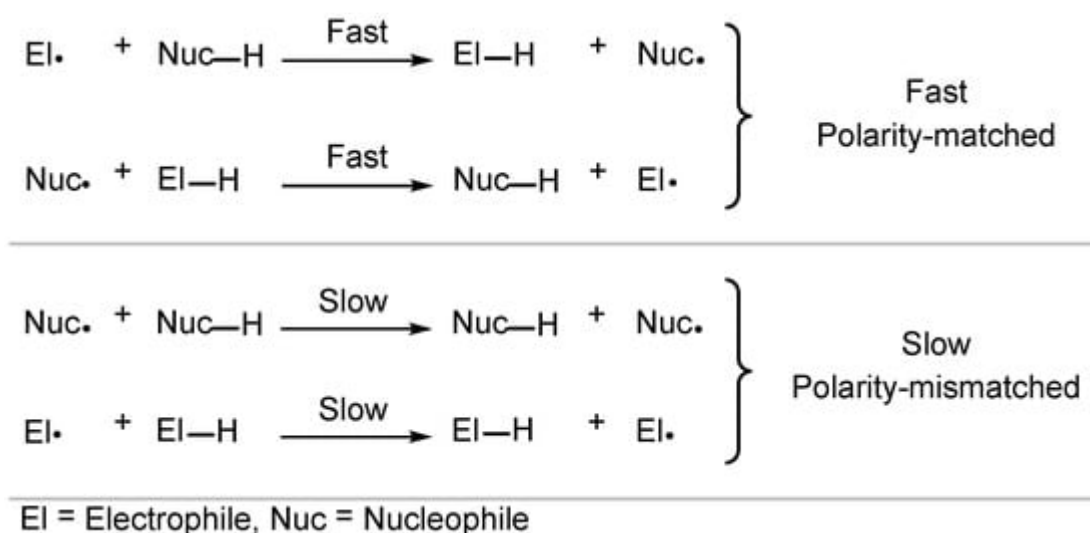
Scheme 2. Benzylamine C–H arylation using a thiyl radical formed from thiobenzoic acid.

Conversely, stronger HAT reagents can be used to abstract unactivated C(sp³)-H bonds of alkanes [33]. Knowles and co-workers reported the alkylation of cyclohexane **3.1** through HAT with amidyl radical **3.3**• [amide **3.3** BDE_{N-H} = 107 kcal/mol versus cyclohexane **3.1** BDE_{C-H} = 99.5 kcal/mol] (Scheme 3) [40]. The high BDE value of N-H bonds in amides allows for HAT of unactivated C(sp³)-H bonds of alkanes. Hence, BDE values of the HAT reagent and the substrate should be matched carefully to ensure the HAT process is thermodynamically spontaneous and selective [33].



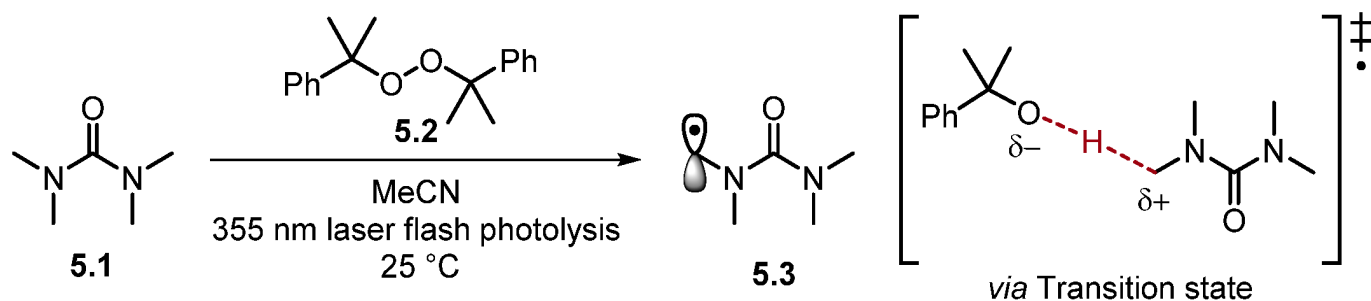
Scheme 3. C(sp³)-H alkylation using amide **3.3** as a HAT reagent.

Despite radicals being electronically neutral species, electronic factors in transition states of radical reactions greatly influence their rate and selectivity [41][42][43][44]. In this context, polar effects describe the effect the charge transfer has on the activation energy, and HAT is strongly influenced by such electronic factors. Usually, polarity-matched HAT describes the tendency of electrophilic HAT reagents to abstract electron-rich (“hydridic”) hydrogen atoms and nucleophilic HAT reagents to abstract electron-poor (“protic”) hydrogen atoms (Scheme 4) [41][45].



Scheme 4. Polarity effects in HAT processes.

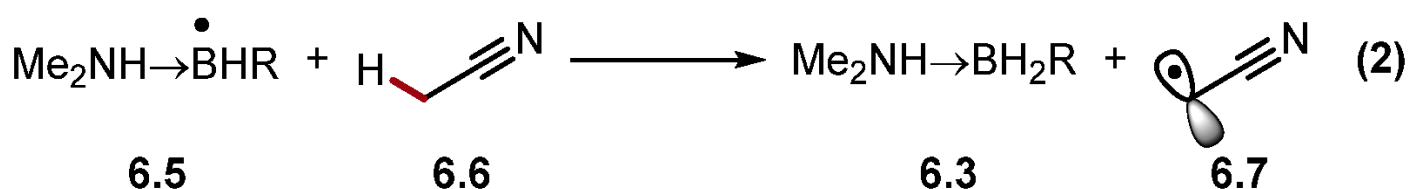
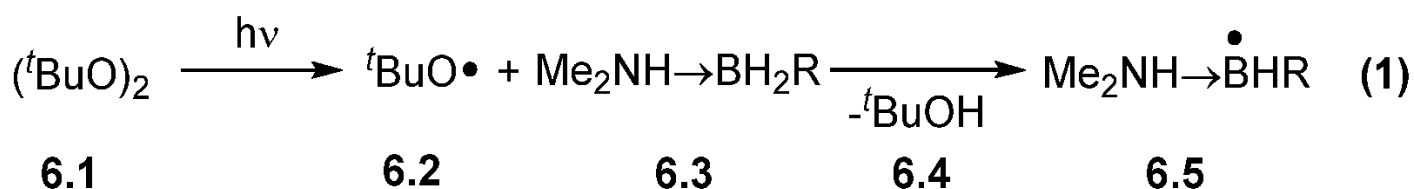
Most HAT reagents are electrophilic and selectively abstract electron-rich hydrogen atoms [30]. As a result, HAT normally occurs adjacent to an electron-donating group (EDG) or another stabilizing functional group [19][46]. Bietti and co-workers have extensively studied the reaction rates of HAT [29][30][37][47][48][49][50][51][52][53][54][55][56][57][58][59][60]. Recently, Bietti studied the rates of HAT for saturated *N*-containing heterocycles and tetramethyl urea **5.1** using dicumyl peroxide **5.2** (Scheme 5) [47].



Scheme 5. Transition state (‡) of HAT with cumyloxyl radical.

The HAT transition state can be described as developing a partial positive charge at the C–atom, along with a partial negative charge on the abstracting radical (cumyloxyl radical in this case) [29][34][35]. Functional groups such as amides stabilise the partial positive charge on the incipient radical atom through an orbital overlap of the σ^* of the α -C–H (developing SOMO) with a heteroatom lone pair or a π -system [47]. This transition state model has been probed through experimental observations, Hammett plot analysis, and computational studies [35][45][48][61]. HAT processes are dictated by an electron density at different C–H bonds meaning a change in solvent, an addition of H-bond donor/acceptors, or Brønsted/Lewis-acid/base additives can alter the rates of HAT [29][30]. For instance, strong H-bonding solvents [such as hexafluoroisopropanol (HFIP)] are used to suppress undesired HAT adjacent to H-bond acceptors (e.g., heteroatoms) [50][62][63][64][65]. However, H-bonding solvents are also known to accelerate HAT at cyclohexane and 1,4-cyclohexadiene through H-bonding to oxyl-radicals [29][66][67][68].

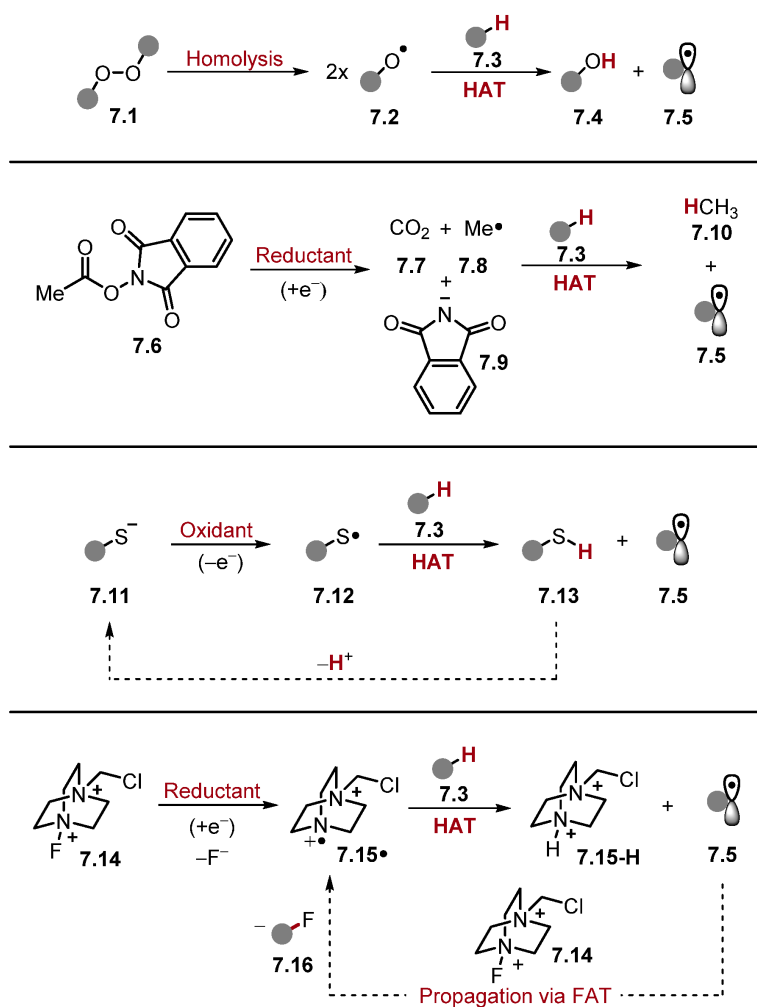
The abstraction of protic hydrogen atoms is difficult as most HAT-capable radicals are inherently electrophilic heteroatom-centred radicals or radical cations [30]. However, the abstraction of protic hydrogens can be accomplished through a polarity reversal catalysis (PRC) [41]. PRC can generate a nucleophilic HAT reagent through an initial polarity-matched HAT step (Scheme 6) [69][70]. For example, electrophilic alkoxy radical **6.2** reacts with amino boranes **6.3** to form a nucleophilic amine boryl radical **6.5**, which abstracts protic hydrogen atoms selectively, such as acetonitrile **6.6** α -C(sp³)-H to generate electrophilic alkyl radical **6.7**.



Scheme 6. HAT of protic hydrogen atom from MeCN using PRC.

3. Indirect HAT

As mentioned before, indirect HAT describes protocols where a radical H-atom abstractor is generated in situ [19][71]. Radicals capable of HAT are typically formed in the following ways (Scheme 7).



Scheme 7. Methods of generating a HAT-capable species in situ.

(1) Homolytic/Heterolytic cleavage of a weak bond. The weak O–O bond in peroxides **7.1** undergoes homolysis to form two oxygen-centred radicals **7.2** capable of HAT [${}^t\text{BuCH}_2\text{O}-\text{OCH}_2{}^t\text{Bu}$ $\text{BDE}_{\text{O}-\text{O}} = 36.4$ kcal/mol] [36][72]. The peroxide **7.1** can also undergo heterolysis with a reducing agent/acid to form one equivalent of O-centred radical **7.2** [72].

(2) Mesolytic cleavage of a radical ion. For instance, a redox active ester (RAE) **7.6** can be reduced to a radical anion [73][74][75][76]. The radical anion undergoes mesolytic cleavage forming CO_2 **7.7**, phthalimide anion **7.9**, and a methyl radical **7.8**, which is a competent HAT reagent [77].

(3) Oxidation of a heteroatom or an anion using photoredox catalysis or (less commonly) electrochemistry [78]. For example, a thiolate **7.11** can be oxidised to a thiyl radical **7.12**, which can abstract a hydrogen atom to form a thiol **7.13** and alkyl radical **7.5** [79]. Deprotonation of the thiol **7.13** allows the turnover of the HAT reagent to make the process catalytic.

(4) Radical propagation steps can continuously regenerate the HAT reagent (otherwise known as chain transfer). In the provided example, a fluorine atom transfer (FAT) between alkyl radical **7.5** and Selectfluor **7.14** affords the

fluorinated product **7.16** and generates an equivalent of TEDA^{2+} **7.15** for further HAT [80]. Notably, chain transfer can also be a contributing pathway in reactions where Methods (1), (2), and (3) are the main pathways with widely varying degrees of chain contribution. In photoredox chemistry, the contribution of the chain transfer to the reaction mechanism can be investigated using quantum-yield measurements or “light/dark experiments” [81]. However, reactions that utilise chain propagation as the major pathway typically use a sub-stoichiometric amount of initiator to initiate the process [82][83][84][85][86].

Each method can form a radical species capable of HAT, therefore facilitating the generation of radicals from corresponding C–H bonds, as well as X–H bonds (where X = heteroatom). Harnessing the high reactivity of radicals allows for a multitude of transformations [28][33][87][88][89][90].

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