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## Recent advances in metal-free aerobic C–H activation

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Herein we describe recent developments in selective, metal-free, dioxygen-induced C–H activation. This method of activating C–H bonds is an attractive alternative to traditional methodologies as it uses dioxygen, an inherently sustainable and widely accessible oxidant, in place of expensive or toxic metals and/or hazardous peroxides. Reactions developed on the basis of using aerobic C–H activation are also discussed.

### C–H bond activation

Direct C–H bond activation has long been credited as the ‘holy grail’ of organic chemistry.<sup>1</sup> The concept of discriminatively activating what is typically an inert C–H bond is a fundamentally powerful tool in synthesis for a number of reasons: (i) C–H bonds are ubiquitous in organic molecules, (ii) C–H bond functionalisation typically reduces the amount of transformations in multi-step syntheses which can consist of long and laborious protection–deprotection sequences, (iii) it establishes an ideal transformation regarding atom economy and

waste minimisation when compared to classic cross-coupling reactions (e.g. Negishi coupling, Suzuki coupling, *etc.*). Over the past few decades, great strides have been made in the development of elegant C–H bond activation methodologies which has seen the process turn from being an aspirational idea to a commonplace reaction that is now heavily studied<sup>2</sup> and used in both academia and industry.<sup>3,4</sup> Modern C–H functionalisation reactions are carried out through (i) C–H bond homolysis *via* use of radical initiators followed by radical functionalisation, (ii) C–H insertion through use of carbenes or nitrenes, or (iii) metallic C–H activation *via* a C–metal intermediate by way of  $\sigma$ -bond metathesis, concerted metalation deprotonation, and oxidative addition. Unfortunately, each protocol commonly utilises harsh reagents or additives to activate what is otherwise an unreactive C–H bond. Owing to the

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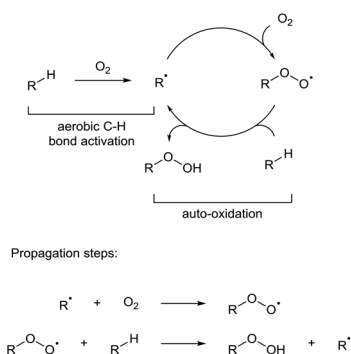
*Dr Vijay Chudasama obtained his MSci degree and PhD from University College London in 2008 and 2011, respectively. Following post-doctoral studies under the supervision of Prof. Stephen Caddick, Vijay obtained a Ramsay Memorial Fellowship. During this time, he was made Technical Director of a biotechnology spin-out (ThioLogics™). In April 2015, he was awarded a lectureship (Reader from October 2017) at UCL for him to focus on the research areas of aerobic C–H activation and various aspects of Chemical Biology. Vijay's research has recently been highlighted by Forbes, Scientific American, CNN News, Nature Chemistry and the Royal Society of Chemistry.*



ever-increasing popularity and widespread usage of C–H activation processes, there is significant pressure to improve the sustainability of C–H reactions from an environmental standpoint: radical initiators are generally toxic or shock sensitive, nitrenes and carbenes are high-energy materials that require intricate and heavily-monitored reaction conditions and organometallic C–H bond activation often requires the use of precious metals and stoichiometric amounts of oxidants (*i.e.*  $\text{MnO}_2$ ). Indeed, it has been highlighted recently by the ACS Green Chemistry Institute® that C–H activation processes utilising green oxidants whilst giving predictable site-selectivities is one of the top three research areas that would benefit from improvements in process ‘greenness’.<sup>5</sup> To achieve this, chemists have created increasingly elegant and boundary-pushing ideas for organometallic C–H bond activation including catalysis by Earth-abundant metals (*e.g.* iron,<sup>6</sup> copper<sup>7</sup>) or forgoing the use of metals altogether.<sup>8</sup> In the goal for effectively using greener and milder oxidants, recent advances have been achieved in using arguably the most sustainable oxidant: dioxygen. Dioxygen is abundant; indeed, molecular dioxygen makes up 20.94% of the Earth’s atmosphere, and one of its most fascinating and under-exploited uses is its ability to initiate auto-oxidation (alternatively referred to as autoxidation) processes. Whilst process chemists have previously utilised an essentially free reagent (air) in the homogenous catalytic oxidation of organic and inorganic compounds, the use of dioxygen has very rarely been used as the focal point for C–H bond activation.

## Dioxygen-initiated auto-oxidation

The auto-oxidation process describes the auto-catalytic oxidation of organic or inorganic systems. For organic molecules, it is usually used to describe the propagation reactions in a chain reaction cycle in which carbon radicals couple with dioxygen to form peroxy radical species, which in turn can then abstract H-atoms to form a peroxide product and regenerate further carbon radicals (Scheme 1). However, in these radical chain reactions, use of a radical initiator or UV light is commonly employed to initially activate a C–H bond. A rare



**Scheme 1** General dioxygen-initiated autoxidation pathway.

but intriguing discussion regarding auto-oxidation is the observation that molecular dioxygen can directly interact with certain C–H bonds to generate carbon radicals without the apparent use of any additional initiator species. This allows for the possibility of C–H functionalisation through reaction of the transiently-formed radical species.

This review highlights recent examples of ground-breaking research in which dioxygen is used to activate C–H bonds as a means to achieve green and sustainable C–H bond functionalisation (Scheme 2). Historically, aerobic C–H bond activation has been scarcely used in synthesis outside of simple C–H oxidation reactions,<sup>9</sup> but its true potential in synthesis is starting to be uncovered with an increasing number of research groups utilising dioxygen as a radical initiator. It should be highlighted that different research groups have had differing logistic protocols of introducing dioxygen in their procedures: use of a pressurised environment of  $\text{O}_2$  through use of an autoclave (>1 atm), use of a dioxygen atmosphere *via* balloon (1 atm), bubbling compressed air into a reaction mixture under an inert environment, or by simple exposure of the reaction to the dioxygen in air (referred to as *atmospheric* dioxygen). We believe that, where possible, the strive should be made to use atmospheric dioxygen as the source of dioxygen as it represents the greenest and a freely accessible form of the oxidant to be utilised in synthesis.

Modern dioxygen-induced C–H bond functionalisation reactions have utilised aldehydes, ethers, benzylamines and glycine derivatives as precursors to aerobic activation, and reactions developed on this basis are described within.

## Aldehydes

Aldehydes are amongst the most desirable substrates to achieve C–H functionalisation owing to ubiquity of the acyl group in molecular architecture. Radical C–H functionalisation is particularly useful for this purpose due to the susceptibility to hydrogen abstraction of aldehydic C–H bonds. Aldehydes are one of the most classical and studied examples of a reagent class that undergoes auto-oxidation.<sup>10,11</sup> The mechanism for aldehyde auto-oxidation is identical to that shown above (Scheme 1) except that the peracyl product can undergo further reaction with another molecule of aldehyde to form an intermediate that breaks down into two molecules of carboxylic acid as the final product.<sup>11</sup> The immediate species



**Scheme 2** Model example of aerobic C–H bond activation *via* dioxygen-induced radical initiation through trapping of initial radical adduct species.

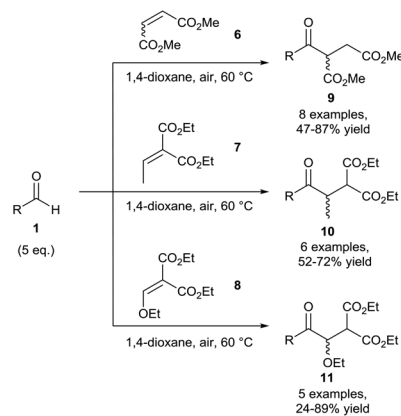


formed through aldehyde auto-oxidation is the acyl radical which is nucleophilic in nature and can efficiently participate in radical addition to electron-deficient unsaturated bonds.

Since 2009, hydroacylation of C=C and N=N bonds utilising acyl radicals formed through the exposure of aldehydes **1** to atmospheric dioxygen has allowed the green and efficient formation of various unsymmetrical ketones and acyl hydrazide moieties in good to excellent yields.<sup>12</sup> Caddick and co-workers reported the reaction of aldehydes with several vinyl sulfonates **2** under atmospheric conditions to afford unsymmetrical ketones **3** in respectable yields (*ca.* 70%) and all was reported at room temperature (Scheme 3).<sup>13</sup> Optimal yield was achieved when utilising 5 equivalents of aldehyde, which is very competitive with regards to existing hydroacylation methodologies. The reaction was completely inhibited when conducted in the presence of radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol), providing evidence of a radical mechanism. Whilst the initial account reported 1,4-dioxane as an optimal solvent, further research from the group found that the use of water as a solvent, the ideal "green" solvent, produced similar if not better yields of the ketones.<sup>14</sup>

The Chudasama and Caddick groups then further utilised aerobically-generated acyl radicals to achieve hydroacylation of various vinyl sulfones **4**. Here, aliphatic aldehydes were found to perform best in the reaction with vinyl sulfones to achieve consistent yields (*ca.* 60%) of the desired ketone product **5** (Scheme 4) at 21 °C using water as the reaction solvent.

Chudasama *et al.* then expanded the scope of this hydroacylation methodology to include various unsaturated esters **6–8** where aliphatic aldehydes were once again found to be the best performers, affording yields of **9–11** of up to 89% (Scheme 5). This work paved the way for expanding the scope of radical acceptors that were applicable for use in this methodology.<sup>15</sup> It should be noted that efficient reaction conversion was achieved through raising the reaction temperature to 60 °C. It was postulated that the increase in temperature resulted in a lowering of dissolved oxygen in the reaction mixture, combating over-oxidation of the acyl radical (auto-oxi-

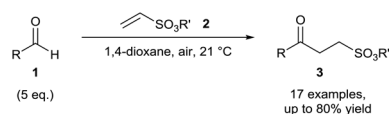


**Scheme 5** Hydroacylation of unsaturated esters **6–8** via aerobic C–H activation.

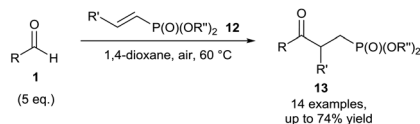
ation) and increasing conversion of alkenes **6–8** to the desired ketone products **9–11**.

Chudasama *et al.* then extended the scope of the developed protocol to include vinyl phosphonates **12**, which were successfully utilised as acyl radical acceptors (Scheme 6). A reaction temperature of 60 °C was again used to achieve efficient conversion of the alkene.<sup>16</sup> The addition of a dioxane radical to a vinyl phosphonate was also observed when this protocol was used, providing supporting evidence of radicals being formed in the reaction mixture.

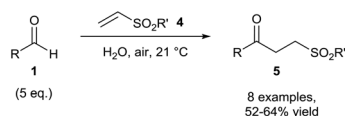
In 2011, using a similar aerobic activation protocol, acyl hydrazides **15** were synthesised in a highly efficient manner when using azodicarboxylates **14** as radical acceptors (Scheme 7). Acyl hydrazides are extremely useful synthetic intermediates which have found use in the formation of many medicinally desirable entities (amides, indazoles, hydroxamic acids, *etc.*).<sup>17–22</sup> Both diethyl azodicarboxylate (DEAD) and diisopropyl azodicarboxylate (DIAD) were shown to be compatible with both aliphatic and aromatic aldehydes towards hydroacylation *via* aerobic C–H bond activation. The efficiency of the reaction was clearly demonstrated with excellent yields being



**Scheme 3** Hydroacylation of vinyl sulfonates **2** via aerobic C–H activation.



**Scheme 6** Hydroacylation of vinyl phosphonates **12** via aerobic C–H activation.



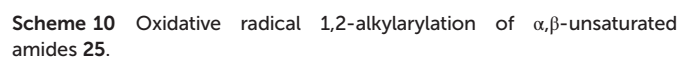
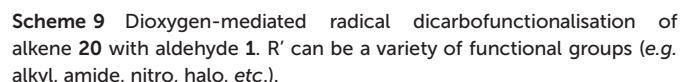
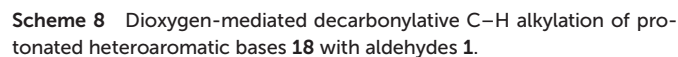
**Scheme 4** Hydroacylation of vinyl sulfones **4** via aerobic C–H activation.



**Scheme 7** Hydroacylation of azodicarboxylates **14** via aerobic C–H activation.



In 2017, Miyamoto and co-workers initially reported the facile auto-oxidation of isobutyraldehyde **1a** under a dioxygen atmosphere (use of balloon) in 1,2-dichloroethane at 40 °C in



† Precise yield not stated.





**Scheme 12** Aerobically-generated hypervalent iodine(III) dicarboxylate species **33**.

was never carried out when utilising air as the dioxygen source, it was reported that the reaction procedure for the oxidative cleavage of 1,2-diols was almost as effective when the reaction mixture was exposed to air (*ca.* 90% compared to quantitative yield when utilising a balloon).

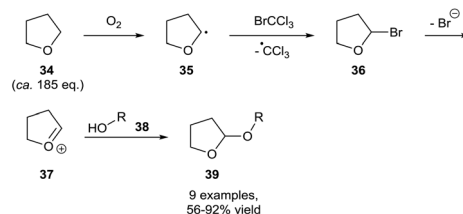
Powers and co-workers carried out a similar experiment for the oxidation of iodobenzene **30** to iodobenzene diacetate **33** (Scheme 12).<sup>28</sup> Their initial results highlighted the auto-oxidation of different aldehydes as a means to oxidise iodobenzene at 23 °C. Benzaldehyde, isobutyraldehyde and butyraldehyde all proved ineffective with minimal amount of product formed (0%, 2% and 6% respectively). However, use of acet-aldehyde gave a somewhat capricious formation of desired product **33** with 42–91% yield observed over 5 repeats. The group speculated that the variability of oxidation efficiency was due to inconsistent initiation of radical auto-oxidation chemistry. Although the work published showed the possibility of the reaction being able to proceed through a dioxygen-mediated C–H activation process, the group eventually settled on using a cobalt-based initiator (1 mol%) and utilised the *in situ* formation of the iodine(III) diacetate species to oxygenate a wide range of substrates (alkenes,  $\beta$ -keto esters, *etc.*).

## Ethers

Owing to their common usage as reaction solvents, ethereal auto-oxidation is the most studied and understood auto-oxidation process,<sup>29,30</sup> however it should be noted that it is uncommonly utilised as a means for aerobic C–H bond activation. This is likely due to final oxidation product of ethers being relatively explosive peroxide species, meaning that historically, measures have been taken to prevent the activation of ethereal C–H bonds through dioxygen interaction (through use of an inert atmosphere or intentional doping with radical inhibitors). Nonetheless, a few research groups have shown the effective utilisation of (cyclic) ethers as precursors for aerobic C–H bond activation. All ethereal C–H bond activations have been carried out whilst utilising the ether substrate as the reaction solvent, which represents a great excess of the ether substrate. Owing to the observed sensitivity of ethers to auto-oxidation, all methods have utilised transient dioxygen in the atmosphere and forgo the need for a dioxygen balloon.

An early example of ethereal aerobic C–H bond activation was achieved in 2000 by Parsons and co-workers who used bromotrichloromethane as a means of brominating the  $\alpha$ -position on THF **34** (Scheme 13).<sup>31</sup> The subsequent entity **36** was found to be unstable with regards to elimination and thereby resulted in oxocarbenium cation **37** formation. The group then used this cation as a means of tetrahydrofuranyl-protecting alcohol groups, a very desirable protecting group that can be selectively cleaved even in the presence of THP-ethers.<sup>32</sup> It should be noted that owing to the use of THF as the reaction solvent, the substrate is used in a great excess (*ca.* 185 equivalents). It does not appear that efforts were made to utilise the ether in a smaller stoichiometry coupled with possibly a greener, non-nucleophilic solvent (*i.e.* esters).

More recently, Troisi *et al.* extended the available reaction partners that can be coupled to THF following aerobic C–H bond activation.<sup>33</sup> It was showed that allyl chloride **40** can be utilised as a chlorinating agent. Doing so formed an allyl radical capable of abstracting an ethereal H-atom, propagating the radical chain reaction. Although not explicitly stated, it was suspected that the resulting  $\alpha$ -chloro product **41** had the same decomposition effect displayed by the  $\alpha$ -bromo species **36** described by Parsons and co-workers in which release of halide resulted in oxocarbenium species **37**, which can then be trapped using alcohols **38**. Utilising this method, Troisi *et al.* showed the tetrahydrofuranylation of simple (phenol, benzylic) and complex (cholesterol) alcohols (Scheme 14). Further studies confirmed the importance of dioxygen in their protocol by observing no product formation when the reaction was conducted under a nitrogen atmosphere and using deaerated THF. Evidence supporting a radical mechanism was then provided by showing complete reaction inhibition when



**Scheme 13** Aerobically-initiated protocol for the protection of alcohols **38** as 2-tetrahydrofuranyl ethers **39** utilising bromotrichloromethane.



**Scheme 14** Aerobic protocol for the protection of alcohols **38** as 2-tetrahydrofuranyl ethers **39** utilising allyl chloride.





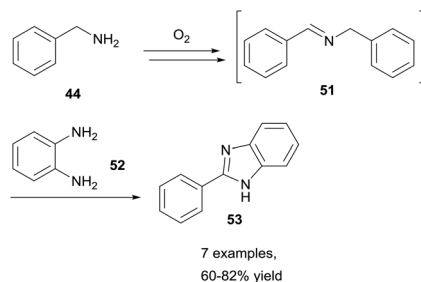
**Scheme 15** Ethereal radical addition to phenylacetylene **42** to afford alkene **43**.

carried out in the presence of TEMPO. Interestingly, Troisi *et al.* then provided further evidence by observing no reaction when utilising commercially stabilised THF, and then rapid subsequent reaction upon addition of CrCl<sub>2</sub> oxidant to the reaction mixture, which consumed the antioxidant stabiliser and allowed uninhibited aerobic C–H bond activation.

Following this, Troisi then briefly showed the possibility of the tetrahydrofuranyl radical **35** participating in radical addition to imines and an alkyne **42** (Scheme 15). Troisi postulated that the reaction was likely to follow a similar mechanism. Although substrate scope was scarcely explored, and THF was again used as the reaction solvent, it was shown that the ethereal radical was able to add to C=N bonds and C≡C bonds, both of which were unexplored with respect to aerobically-induced acyl radical addition.

## Benzylamines

Benzylamines represent a class of molecules that have gathered recent attention due to observed imine formation in reactions that are heated in the presence of air. The Fu and Nguyen groups have both exploited this and have shown that aerobically-induced C–H bond activation of benzylamines **44** resulted in oxidative coupling to form imines **50** (Scheme 16).<sup>34,35</sup> Fu and co-workers showed that by utilising a dioxygen balloon, metal-free aerobic oxidative coupling of amines can be achieved whilst utilising water as the reaction solvent, with good to excellent yields (51–85%) achieved in 12–64 h. Furthermore, there was no product formation observed when the reaction was conducted under a nitrogen atmosphere, highlighting the significance of dioxygen for the reaction. The group also declared an unchanging yield when the reaction was conducted in a Teflon-reactor, excluding the possibility of light- or glass-catalysed processes. Although aliphatic amines have low susceptibility to aerobic C–H bond



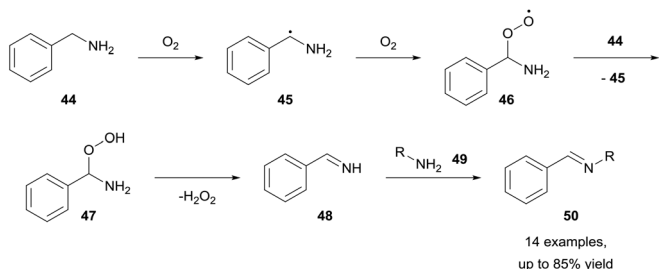
**Scheme 17** Synthesis of benzimidazoles **53** through aerobic C–H bond activation of benzylamines **44**.

activation, they were able to be effectively utilised (45–77% yield) in the cross-coupling with benzylamines when used in excess (1.8 equivalents). Whilst the exact mechanistic pathway was not discerned, it was clear dioxygen played a role in the reaction *via* aerobic C–H bond activation.

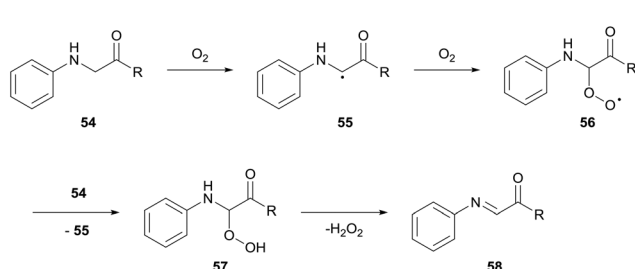
Nguyen *et al.* then reported a similar reaction that forgoes the need for a solvent altogether.<sup>35</sup> Nguyen reported that simply heating benzylamines under an oxygen environment was sufficient for achieving oxidative coupling of amines to imines in good to excellent yields (62–83%) in 24 h. Nguyen reported that whilst effective benzylamine auto-oxidation was observed utilising a flask exposed to air, evaporation of volatile benzylamines rendered the method inconvenient. Nonetheless, the reaction was proven to be effective, and Nguyen *et al.* used this process of generating imines to construct many medicinally relevant nitrogen heterocycles (*i.e.* benzimidazoles, Scheme 17).

## Glycine derivatives

Pioneering research by Huo and co-workers has shown the functionalisation of the α-carbon in glycine derivatives **54**.<sup>36,37</sup> The modification of glycine is particularly attractive for medicinal chemistry owing to the possibility of simple diversification of unnatural amino acids. Since 2014, Huo and co-workers have exploited the auto-oxidation of glycine derivatives **54**. The mechanism for glycine auto-oxidation is similar to that displayed by benzylamines in which an imine intermediate **58** is formed through the release of H<sub>2</sub>O<sub>2</sub> (Scheme 18). The group have developed elegant methodologies for C–C formation *via*



**Scheme 16** Aerobic oxidative coupling of benzylamines **44**.



**Scheme 18** Aerobic C–H bond activation of glycine derivatives **54**.





**Scheme 19** Utilising aerobic generation of **58** to facilitate Povarov/aromatisation tandem reactions with styrenes **59**.

nucleophilic attack on the imine intermediate formed *via* aerobic activation; styrenes, indoles and arenes were used as nucleophilic partners for C–C bond formation.<sup>36</sup>

For the reaction with indoles, a dioxygen balloon was utilised at 40 °C. Reaction times varied (4–60 h) with average to high yields reported (30–83%). Analogous reactions conducted under an argon atmosphere reported a significant drop in yield, thus indicating the significance of dioxygen for the reaction. Furthermore, no desired product was observed upon the addition of TEMPO, thereby providing further evidence of a radical mechanism.

For the coupling of the glycine imine to styrene moieties **59**, an open flask with access to air was utilised (Scheme 19). However, yields were comparatively low (28–53%) owing to an alternative pathway providing formation of self-oxidation side product **61** (7–40% yield). Finally, the use of electron-rich arenes allowed for efficient nucleophilic addition to the protonated imine intermediate at room temperature and utilising atmospheric dioxygen. Moderate to good yields were observed (34–76%) when utilising a stoichiometric amount of arene to glycine ester.

To provide further proof of the mechanism for benzylamine auto-oxidation, the group showed that when 1 mol% of MnO<sub>2</sub> was added at the end of a reaction, gas evolution was observed. This suggested the formation of H<sub>2</sub>O<sub>2</sub> as an auto-oxidation by-product since MnO<sub>2</sub> reacts with H<sub>2</sub>O<sub>2</sub> to form dioxygen and water.

## Conclusions

Aerobic C–H bond activation in which dioxygen interacts and activates a C–H bond is a fundamentally green progress with regards to atom economy and waste minimisation when compared with typical C–H activation reagents. Utilising dioxygen as the activating species ensures the use of an inherently green oxidant species (especially through the use of atmospheric dioxygen) which is of timely interest as scientists strive for more environmentally friendly protocols. In this review we highlight the realisation of new synthetic protocols that utilise aerobic C–H bond activation as a means of initiating radical reactions. Whilst these new reactions use relatively few functional groups as aerobic C–H activation precursors (*e.g.* alde-

hydes, ethers, benzylamines and glycine derivatives) it is hoped that these breakthroughs will lead to further efforts in exploring novel motifs that are amenable to this methodology. For example, by looking more closely at other molecules/functionalities that “degrade” aerobically and/or appraising various parameters (*e.g.* dissolved oxygen concentration of solvent, stirring rate, surface area to volume ratio, *etc.*) that promote the aerobic oxidation of alternative C–H bearing functional groups.

## Conflicts of interest

There are no conflicts to declare.

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