ChemComm

ROYAL SOCIETY OF CHEMISTRY

FEATURE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Commun.*, 2021, **57**, 9956

Homogeneous catalytic C(sp^3)–H functionalization of gaseous alkanes

Antonio Pulcinella,† Daniele Mazzarella† and Timothy Noël *

Received 27th July 2021,
Accepted 1st September 2021

DOI: 10.1039/d1cc04073a

rsc.li/chemcomm

The conversion of light alkanes into bulk chemicals is becoming an important challenge as it effectively avoids the use of prefunctionalized alkylating reagents. The implementation of such processes is, however, hampered by their gaseous nature and low solubility, as well as the low reactivity of the C–H bonds. Efforts have been made to enable both polar and radical processes to activate these inert compounds. In addition, these methodologies also benefit significantly from the development of a suitable reactor technology that intensifies gas–liquid mass transfer. In this review, we critically highlight these developments, both from a conceptual and a practical point of view. The recent expansion of these mechanistically-different methods have enabled the use of various gaseous alkanes for the development of different bond-forming reactions, including C–C, C–B, C–N, C–Si and C–S bonds.

Introduction

Gaseous alkanes are among the most abundant and cheapest carbon-based feedstocks, which are generally used as a source of energy for heating, propulsion or electricity generation.[1] In conjunction with these uses, methane, ethane, and heavier analogues could also be employed as building blocks for chemical synthesis.[2] This is an increasingly fascinating area of research as the conversion of greenhouse gases into chemical feedstocks and/or bulk chemicals would be of extreme value for the chemical industry as well as for the environment. Indeed, the direct use of alkanes would also bypass the need for functionalized reagents, *e.g.* haloalkanes and organometallic reagents.[3] However, there are several issues that need to be addressed in order to realize this goal (Fig. 1), such as the general inertness of the C–H bonds and the poor solubility of the gases in common organic solvents. Moreover, the desired products are often easier to activate than the gaseous alkanes, leading to issues related to over-reaction.[4]

Flow Chemistry Group, Van't Hoff Institute for Molecular Sciences (HIMS), University of Amsterdam Science Park 904, 1098 XH, Amsterdam, The Netherlands. E-mail: t.noel@uva.nl; Web: www.NoelResearchGroup.com
† These authors contributed equally.

Antonio Pulcinella

Antonio Pulcinella received his BSc in Chemistry in 2018 at the University of Roma Tor Vergata and carried out his thesis at IRBM Science Park Spa. In 2020, he completed a Master in Chemistry in the context of the Double Degree Programme between the University of Giessen and the University of Padova, working in the group of Prof. Dr Peter Schreiner on the synthesis of 2-deoxy-C-glycoside amino acids. Currently, he is a Marie S. Curie PhD candidate at the University of Amsterdam under the supervision of Prof. Dr Noël, working on the continuous-flow C–H activation of aliphatic scaffolds promoted by photochemistry and/or electrochemistry.

Daniele Mazzarella

Daniele Mazzarella studied chemistry at the universities of Rome and Bologna (Italy). After a brief experience in Japan working for Nippon Kayaku Co. Ltd, in 2016, Daniele joined Prof. Paolo Melchiorre's group at the ICIQ (Tarragona, Spain) to carry on doctoral studies in the fields of organocatalysis and synthetic photochemistry. After having obtained his PhD degree cum laude in 2020, Daniele joined the group of Prof. Timothy Noël at the University of Amsterdam (The Netherlands), where he is currently pursuing the development of novel electrochemical and photochemical transformations in a microfluidic environment.

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

This journal is © The Royal Society of Chemistry 2021

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

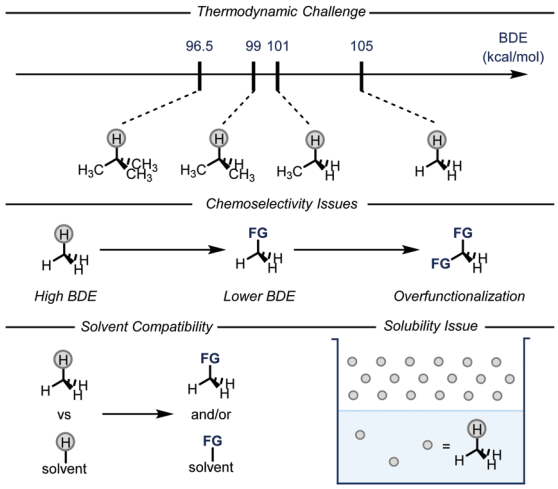

Fig. 1 General representation of the issues related to the C–H functionalization of gaseous alkanes. BDE: bond dissociation energy; FG: functional group.

While huge attention has been directed to the use of methane to produce methanol,[5] less focus has been devoted to its valorization for the production of different methyl-containing derivatives. Additionally, the vast majority of these processes are carried out under heterogeneous conditions,[5a,c] which are well known to pose an additional problem in terms of selectivity. Notably, reports that exploit the use of a homogeneous catalyst, outside of the field of methanol formation,[5b] are rare and remain largely underdeveloped.

The scope of this article is to cover the state-of-the-art in the functionalization of gaseous alkanes under homogeneous catalytic conditions, with the aim of showcasing the main achievements, as well as the different activation mechanisms and the future challenges within the field. We have divided the review based on the nature of the bond formed after the functionalization of the gaseous alkane, namely C–B, C–C, C–N, C–Si and C–S. Specifically for the C–C bond formation, processes able to induce chirality have also been highlighted. Regarding the formation of C–O bonds, possibly the most studied reaction for the functionalization of methane and other gaseous alkanes, this topic has been recently reviewed by Periana and co-workers[5b] and will not be discussed within this article.

Timothy Noël

Timothy Noël currently holds a position as Full Professor at the University of Amsterdam, where he is the chair of Flow Chemistry. His research interest ranges from organic chemistry to chemical engineering and encompass more specifically flow chemistry, organic synthesis and synthetic catalytic methodology development. His work received several awards, including the DECHEMA prize (2017), the Hoogewerff Jongerenprijs (2019), the IUPAC-ThalesNano prize in flow chemistry and microfluidics (2020) and the KNCV Gold Medal (2021). He also serves as editor-in-chief of Journal of Flow Chemistry.

C–B bond formation

Protocols capable of converting feedstock chemicals such as light alkanes in added-value building blocks are highly sought after. In the field of catalytic C–H functionalization, particular interest has been directed towards the borylation of inert aliphatic substrates.[6] This is motivated by the high synthetic versatility of the resulting organoboron compound, which can be easily converted in a wide range of other functional groups such as amines, alkenes and alcohols or can be engaged in C–C bond forming reactions.[7] Earlier works demonstrated that Re, Rh, Ru and Ir are all competent catalysts for the homogeneous borylation of liquid alkanes.[6f,h,j] Specifically, Rh-based catalysts are capable of forming metal bis(boryl) complexes after oxidative addition of a diboron precursor (B_2pin_2, Fig. 2).[6a,b] These species have been reported to react with alkanes under neat conditions, leading to the formation of alkyl-metal boryl complex **I**. This intermediate undergoes reductive elimination to produce one molecule of the borylated product and metal hydride **II**. The latter reacts with the borylating reagent affording intermediate **III** that, upon extrusion of HBpin,[6h] is able to activate C(sp^3)–H bonds to restore active species **I**. Another plausible and concomitantly operating reaction pathway concerns the oxidative addition of the formed HBpin, leading in this case to the formation of the borylated alkyl species along with molecular hydrogen.[6a] However, from a thermodynamic viewpoint, diboron species determine a greater enthalpic driving force due to the weaker B–B bond compared to the B–H bond in boranes.[8]

Despite these literature precedents, translating these thermal catalytic protocols to the activation of C–H bonds within light alkanes faced some major challenges. The first problem to address is the choice of an appropriate solvent that should not outcompete the gaseous alkane during the C–H activation step.

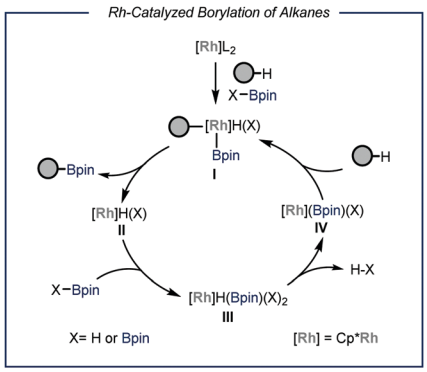

Fig. 2 General representation of the Rhodium-catalyzed borylation of C–H bonds. Pin: pinacolato; Cp*: pentamethylyclopentadienyl.

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Specifically, the higher BDE of methane (bond dissociation energy, BDE = 105 kcal mol^{-1} for methane) compared to other liquid alkanes poses a unique challenge.[5b] In addition, the over-functionalization of the product is another likely scenario given the presence of more labile C–H bonds compared to the ones present in the gaseous alkane.[9–11]

The borylation of gaseous hydrocarbons was pioneered by the groups of Sanford[9] and Mindiola,[10] who simultaneously reported two transition metal-catalyzed methodologies capable of borylating methane and ethane under thermal conditions.

In their report, Sandford and coworkers[9] identified optimal conditions for the borylation of methane using a high-pressure batch reactor employing Rh-based catalyst [Cp*Rh(η^4-C_6Me_6)], 35 bar of methane and B_2pin_2 **1** as the limiting reagent in cyclohexane at 150 °C (Fig. 3). The choice of the catalyst was made based on earlier density functional theory (DFT) studies reported by Hall *et al.*, proving the theoretical feasibility of the process.[12] Crucial for the success of the desired transformation was the choice of the solvent: cyclohexane granted good solubility of the catalyst without compromising the selectivity. Indeed, due to the more strained and hindered nature of the C–H bonds in cyclohexane, only traces of the borylated solvent byproduct **3** were observed.[13] Under the optimized reaction conditions, high selectivity and yield were obtained for the mono-borylated methane **2**. Additionally, by testing other known catalysts previously employed in the borylation of heavy alkanes, the authors demonstrated that the fine-tuning of the catalyst structure had significant impact on the selectivity of the process.[6a] The relationship between steric hindrance and selectivity was further corroborated by a competition experiment using known molar quantities of methane and ethane: all the tested catalysts preferentially functionalized the less sterically-encumbered methane.

Simultaneously, the group of Mindiola[10] reported an elegant iridium-catalyzed borylation of methane (Fig. 4). Given the well-known efficacy of iridium-based catalytic systems for the borylation of inert C–H bonds,[6f,14] the authors conducted an extensive screening of commercially available iridium catalysts and nitrogen-based ligands. Preliminary results revealed that the highest conversion and selectivity for the monoborylated product **2** were obtained in the presence of an Ir(I) precatalyst and $\mathbf{L_1}$ (3,4,7,8-tetramethyl-1,10-phenanthroline) as ligand using tetrahydrofuran as a solvent under 35 bar of methane at 120 °C. Under these conditions, the desired product was obtained in 4.1% yield (determined *via* gas-chromatography (GC) analysis). The mechanism, as predicted by DFT calculations, begins with the substitution of the ligand to afford Ir(III) complex **V**, which is the putative resting state of the catalyst. After methane coordination at one of the vacant sites of the complex, the rate-determining oxidative addition occurs *via* transition state **A** yielding intermediate **VII**. Ligand reorganization, followed by reductive elimination, affords the desired product **2** and complex **IX**, which further regenerates the catalyst resting state by reacting with B_2pin_2. Since the C–H bond cleavage implies the oxidation of Ir(III) to Ir(IV) within intermediate **VI** (transition state **A**), the authors postulated that, in light of their reduced Lewis basicity, phosphine ligands might enhance the polarizability of the metal center, thus facilitating oxidative addition. Indeed, employing $\mathbf{L_2}$ as ligand under the optimized conditions, the desired product was

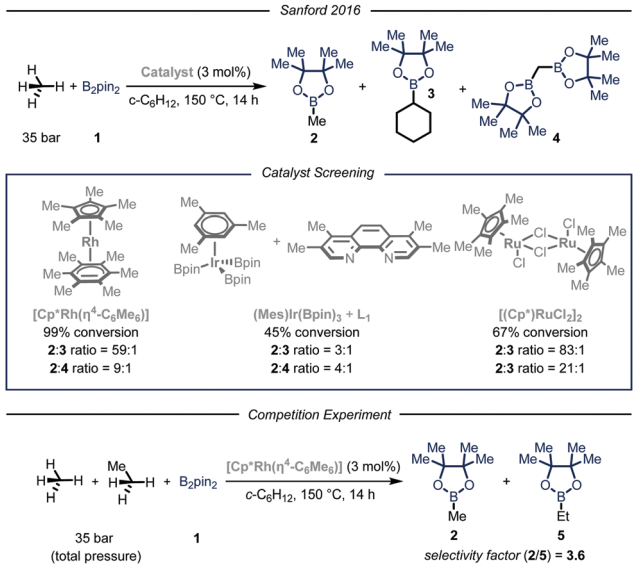

Fig. 3 Borylation of methane developed by Sanford and co-workers. Pin: pinacolato; Cp*: pentamethylyclopentadienyl.

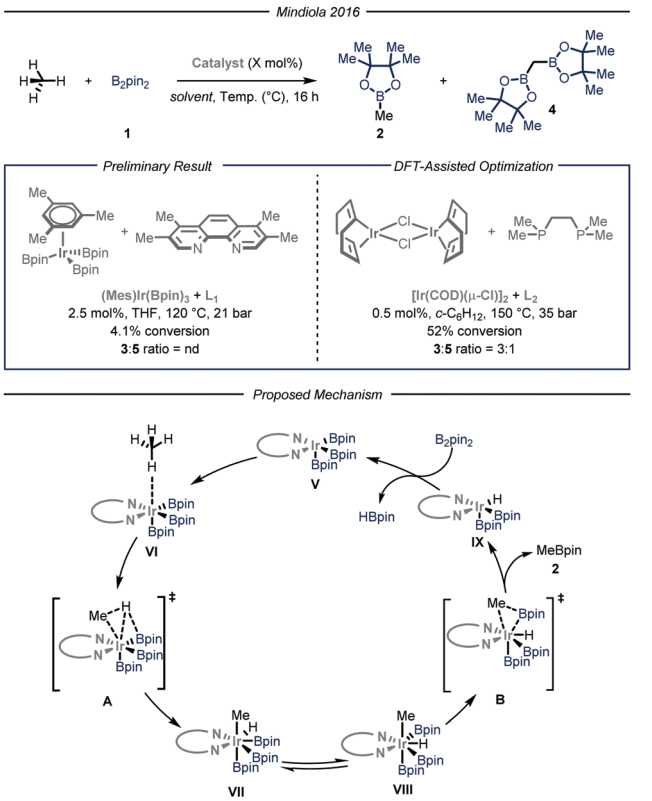

Fig. 4 Iridium-catalyzed borylation of methane developed by Mindiola and co-workers. Pin: pinacolato; THF: tetrahydrofuran.

This journal is © The Royal Society of Chemistry 2021

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

obtained in 52% yield with a 3 : 1 chemoselectivity over the monofunctionalized compound. Isotopic labeling studies using $^{13}CH_4$ confirmed that the light alkane is the methylating reagent under the described reaction conditions.

C–C bond formation

Carbon–carbon bond-forming reactions are essential tools for the synthetic community as these bonds constitute the framework of every organic molecule. Within this field, the installment of light alkyl fragments, especially the methyl one, can strongly alter the binding affinities of the parent molecule, boosting its potency as a drug, and has therefore deep implications in medicinal chemistry.[15] However, these reactions are generally performed using reactive prefunctionalized alkyl derivatives, either halides or organometallic ones. As such, the direct use of gaseous alkanes would avoid unnecessary functionalization steps and would generally provide a more sustainable process.

Several types of C–H functionalization strategies have been exploited to engage volatile alkanes directly in carbon–carbon bond-forming reactions. The first one, reported by Fujiwara and co-workers,[16] is based on a transition–metal-catalyzed C–H activation mechanism.[17] In these seminal contributions, the authors proved how light alkanes could be converted into carboxylic acids **6** through the action of palladium and/or copper catalysis, using CO as the carboxylating reagent and $K_2S_2O_8$ as the oxidant in an autoclave (Fig. 5). Specifically for the palladium catalysis, the authors suggest an electrophilic C–H activation of the gaseous alkane by the catalyst to afford intermediate **XI**. The latter can undergo CO insertion to yield carbonyl-palladium species **XII** that ultimately is converted into the target carboxylic acid **6** while the palladium catalyst **X** is regenerated by the oxidant (1–41% yield). Notably, the same group also expanded this mode of action to the aminomethylation of gaseous alkanes by employing *in situ* generated iminium ions in place of carbon monoxide as electrophilic partners.[18]

Later on, Lin and Sen[19] described a rhodium-based catalytic system able to promote the same carboxylation reaction of methane under much milder conditions, employing water instead of trifluoroacetic acid as solvent and oxygen as the oxidant.

In 2020, Chang and co-workers reported a copper-catalyzed process to promote the cross-dehydrogenative-coupling (CDC)[20] between gaseous alkanes and polyfluorinated arenes **7** (Fig. 6).[21] After an extensive optimization screening, the authors identified β-diketimine $\mathbf{L_3}$ as the optimal ligand for the copper catalyst, *t*-butyl peroxide as the oxidant, *t*-BuONa as the base in benzene at 80 °C. Apart from the efficient functionalization of liquid and solid alkanes, the authors demonstrated how, in a high-pressure reactor, also *n*-butane and propane could be productively converted into the corresponding arylated products **8** (39–51% yield).

The authors performed a thorough mechanistic investigation, encompassing both experimental and computational work. Overall, the process relies on a dual activation mode, where the copper catalyst is activating the C–H bonds of both polyfluorinated arene **7** and the alkane. Specifically, active copper complex **XII** reacts with *t*-butyl peroxide to afford *t*BuO$^\bullet$ and Cu(II) intermediate **XIII**. The latter is responsible for both the activation of the alkane through a radical pathway and of the fluoroarene *via* a polar mechanism. The ensuing Cu(III) species **XVIII** undergoes reductive elimination to afford product **8** and close the catalytic cycle.

Apart from direct C–H activation methods, the groups of Asensio, Etienne and Pérez[22] reported in 2011 a method that takes advantage of the formation of a metal carbenoid species[23] between a silver-based catalyst $\mathbf{L_4Ag}$ and ethyl diazoacetate **9** (Fig. 7). This intermediate is capable of inserting into the C–H

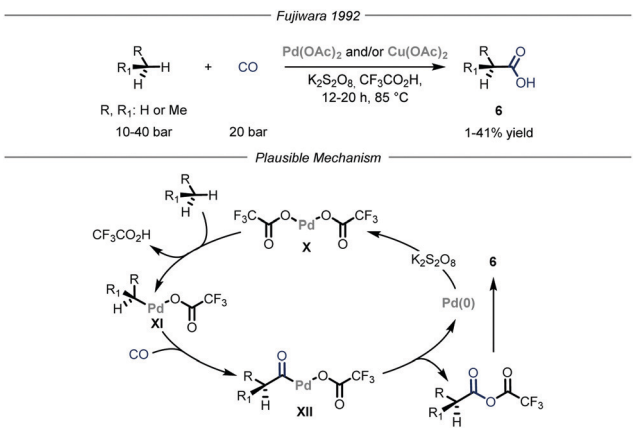

Fig. 5 Palladium-catalyzed carboxylation of methane by Fujiwara and co-workers.

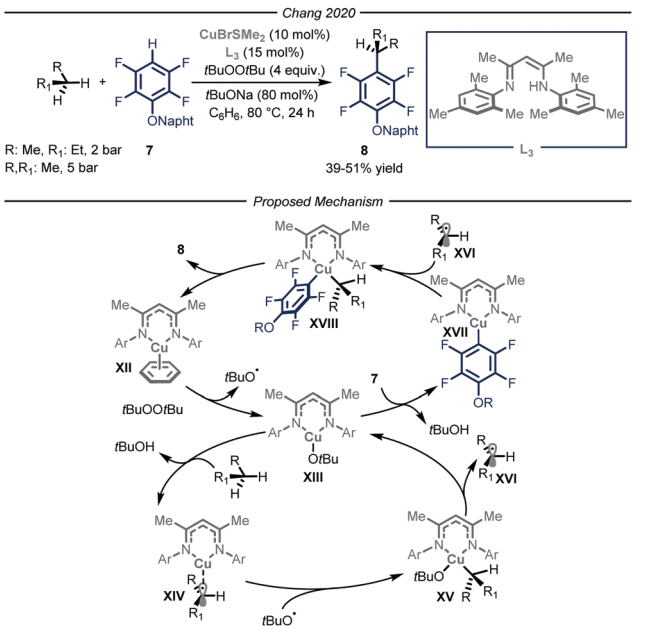

Fig. 6 Copper-catalyzed cross-dehydrogenative coupling of alkanes and polyfluoroarenes.

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

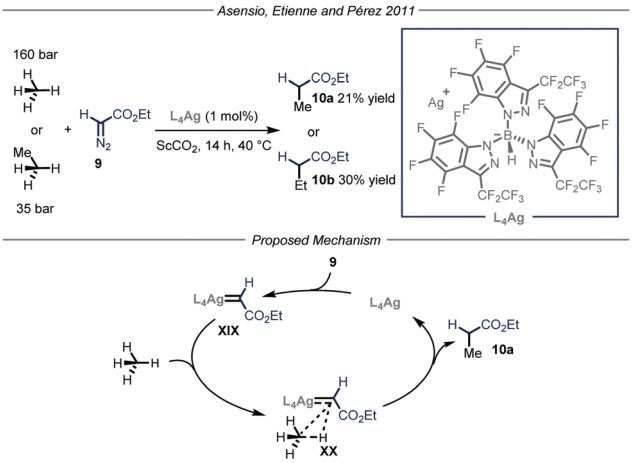

Fig. 7 Use of silver carbenoid for the functionalization of methane and ethane. $ScCO_2$: supercritical CO_2.

bond of methane and ethane, producing ethyl acetate and propionate respectively. Two parameters were crucial for the good outcome of the whole process. First of all, because of the pronounced reactivity of metal carbenoids and of the strength of the C–H bonds within methane and ethane, as well as the low solubility of the gaseous reagents, the choice of the reaction solvent becomes extremely important. Indeed, the use of a solvent possessing weaker C–H bonds with respect to methane would lead to the functionalization of the former. Consequently, the authors used supercritical CO_2 ($ScCO_2$) in a high-pressure reactor thermostated at 40 °C; $ScCO_2$ provides the required inertness and displays complete miscibility with methane. The second crucial parameter is the choice of the ligand to tune the reactivity of the metal catalyst. In order to activate a strong chemical bond such as the C–H bonds in methane and ethane, a highly electrophilic metal carbenoid is required. The authors, based on their experience in the development of coinage metal complexes to catalyze C–H insertion reactions,[24] selected catalyst **L_4Ag** due to the enhanced electrophilic properties granted by the ligand. Under the optimized conditions, methane and ethane were converted into ethyl acetate and propionate respectively with good efficiency (21–30% yield) taking into account the difficulty of the transformation. As for the mechanism, in analogy with other metal carbenoid-promoted C–H functionalizations, the authors proposed a metal-catalyzed N_2 extrusion from compound **9** to form silver carbenoid **XIX** that subsequently undergoes carbene transfer onto methane or ethane to give the corresponding products **10**.

A third strategy used to drive the C–H functionalization of gaseous alkanes relies on the formation of radical intermediates. The advent of photoredox catalysis[25] has enabled the generation of open-shell species under extremely mild conditions, namely light illumination in the presence of substoichiometric quantities of a photocatalyst at room temperature.[26] Upon photoexcitation, the catalyst has enhanced redox properties and can either promote single electron transfer (SET) events or directly cleave C(sp^3)–H bonds through a hydrogen

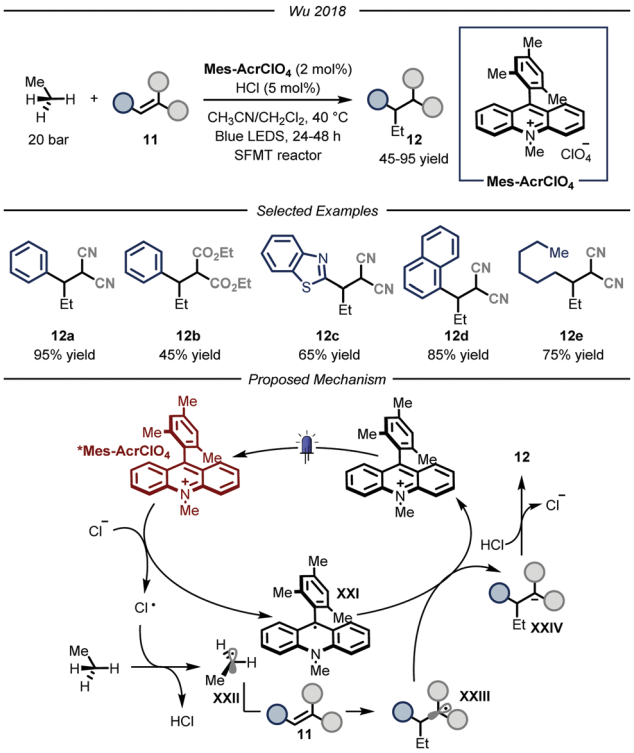

Fig. 8 Use of chlorine radical as HAT catalyst for the activation of ethane. LED: light emitting diode; SFMT: stopped flow microreactor.

atom transfer (HAT) pathway.[27] Notably, both these mechanisms of activation have been used with the aim of functionalizing gaseous alkanes.

In 2018, the group of Wu reported a photocatalytic process that could promote the functionalization of ethane by using hydrochloric acid as an efficient HAT catalyst (Fig. 8).[28] The authors, based on previous findings on the photocatalytic value of chlorine radicals as HAT reagents,[29] envisioned that, upon single electron oxidation, HCl itself could be used to generate $Cl^{\bullet}$ under catalytic conditions. Nonetheless, the development of such a process poses several challenges. First of all, because of the gaseous nature of both ethane and hydrochloric acid, the use of classical batch reactors was not a viable option. Moreover, because of the necessity to establish uniform irradiation to efficiently promote the photochemical steps, the use of high pressure reactors was also discarded. Within the field of photocatalytic transformations, microreactor technologies have provided a platform based on short length scales which ensure homogeneous irradiation of the reaction mixture while simultaneously guaranteeing efficient gas–liquid mass transfer to saturate the gaseous reagents in the reaction mixture.[30] Taking this into consideration, the group of Wu decided to develop the aforementioned process under micro-scale conditions using narrow capillaries. Specifically, the authors employed a so-called ''stop-flow'' microtubing (SFMT) reactor,[31] consisting of a capillary equipped with two shut-off valves at each end of the reactor (PFA (perfluoroalkoxy alkanes), I.D. = 762 μm, V = 3.0 mL). Under the optimized conditions, several electron-poor olefins **11** could be functionalized with ethane, affording

This journal is © The Royal Society of Chemistry 2021

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

adducts **12** in good yields (45–95% yield). Mechanistically, the reaction kicks off with the photoexcitation of the organic photocatalyst Mes-AcrClO$_4$ to afford species *Mes-AcrClO$_4$ that features enhanced oxidizing properties (E_{RED} = 2.05 V *vs.* SCE)[32] and is therefore able to take one electron from the chloride anion (E_{OX} = 2.03 V *vs.* SCE),[33] affording Cl$^{\bullet}$. The latter can perform HAT on ethane to produce hydrochloric acid alongside the nucleophilic ethyl radical **XXII** that is intercepted by electron-poor olefin **11** to afford radical **XXIII**. This intermediate is prone to single electron reduction by the reduced form of the photocatalyst (**XXI**) to yield, after protonation by hydrochloric acid, product **12** while regenerating both the catalysts. As a general limitation, only strongly electron-poor olefins could be employed due to the fleeting nature of the ethyl radical, which requires a fast trapping by the acceptor, and due to the limited oxidizing properties of the radical adducts to turn-over the photocatalytic cycle. Moreover, under these conditions, the functionalization of methane proved to be unsuccessful, presumably due to the too high BDE of its C–H bonds.

The group of Noël developed a direct photocatalytic HAT method, catalyzed by tetrabutylammonium decatungstate (TBADT, Fig. 9).[34] Addressing the same problems faced by the group of Wu, namely the need for a uniform irradiation and an efficient gas–liquid mass transfer, the authors developed a continuous-flow procedure, using the commercially available Vapourtec UV-150 (PFA, for *i*-butane and propane: I.D. = 1300 μm, *V* = 10.0 mL; for ethane and methane: I.D. = 762 μm, *V* = 10.0 mL). Thanks to the good photocatalytic properties of TBADT,[35] as well as the use of back-pressure regulators to enable higher pressures within the microflow reactor that completely solubilizes the gaseous alkane into the liquid phase, these processes enabled the functionalization of several substrates. The scope of the reaction is quite broad for what concerns the gaseous alkanes: *i*-butane, propane, ethane and even methane could all be employed to afford the corresponding products **13** in good to excellent yields (38–93% yield). Mechanistically, the process is initiated by the absorption of a near-UV light irradiation by TBADT to reach an electronically excited state. Upon photoexcitation, the ensuing TBADT* is able to split C(sp^3)–H bonds within the alkane substrate, affording carbon-centered nucleophilic radical **XXV** which is trapped by the electron-poor olefin **11** to generate the second radical intermediate **XXV**. The latter, having now an opposite polarity, is able to take back the hydrogen atom from the reduced form of the photocatalyst, TBADTH, to afford product **13** and turn over the catalyst.

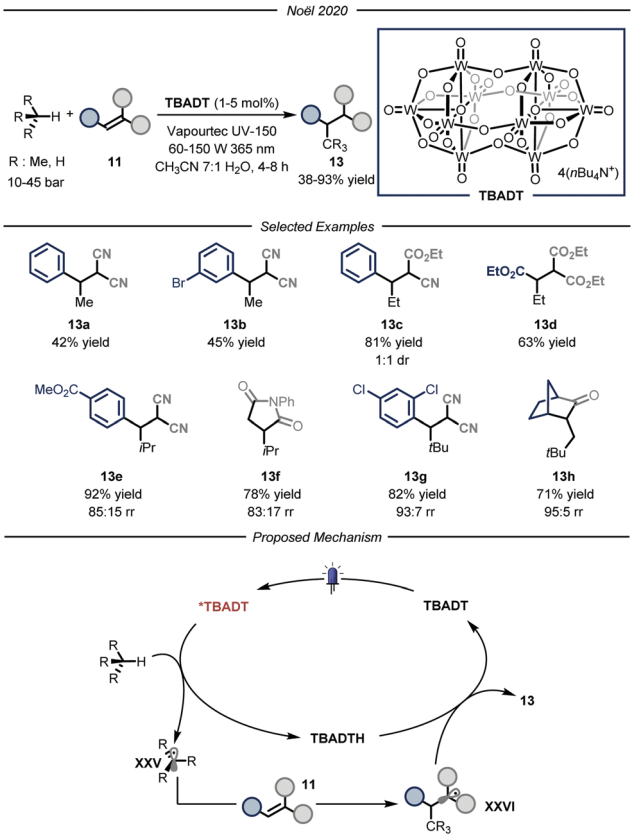

Fig. 9 Use of TBADT as HAT photocatalyst for the activation of *i*-butane, propane, ethane and methane.

Enantioselective C–C bond formation

The previously described catalytic processes have shown the potential of both transition metal and photocatalysis to enable the conversion of feedstock chemicals such as gaseous alkanes into added-value compounds. Despite these undeniable contributions, the development of asymmetric variants would be highly relevant as it could serve as a platform for the asymmetric installment of light alkyl fragments. Enantioselective catalysis is one of the most efficient chemical approaches to target chiral compounds with high optical purity and in an economical and environmental benign way. As such, the possibility to combine the aforementioned processes for the activation of gaseous alkanes and enantioselective catalysis would greatly enrich the chemical toolbox of the synthetic community.

The group of Davies[36] expanded the reactivity of catalytically generated metal carbenoid species[23] towards the asymmetric C(sp^3)–H functionalization of alkane derivatives.[37] Within this seminal contribution, the authors also demonstrated the viability of *i*-butane as starting alkyl substrate (Fig. 10). As the reaction was performed in batch, for this specific compound, the process was performed at −12 °C to condense the gaseous reagent and use it directly as solvent. Moreover, in order to exert stereocontrol over the process, the authors used a chiral dirhodium-based catalyst, Rh$_2$(*S*-DOSP), responsible for the formation of chiral carbenoid intermediate **XXVII** that can insert into the C–H bond of *i*-butane and ultimately yield the enantioenriched product **15** (20% yield, 75% ee).

Similarly to the organometallic approach, also the photocatalytic HAT approach has been combined with enantioselective catalysis. The development of asymmetric photocatalytic methods has been one of the major area of research in the past two decades,[38] however the enantioselective photochemical functionalization of gaseous reagents has remained underdeveloped so far. In 2019, Gong and co-workers[39] reported a procedure that merged photo-HAT activation and chiral Lewis acid catalysis to

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

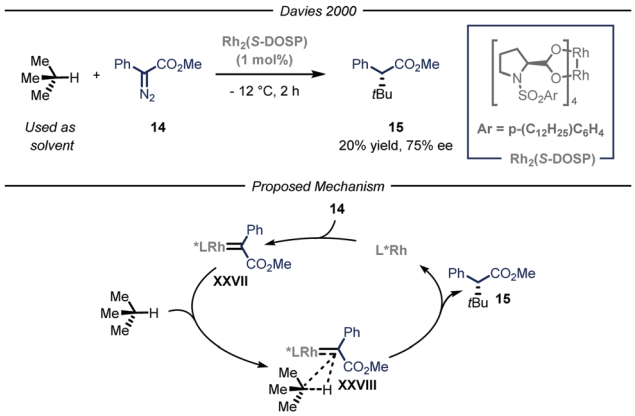

Fig. 10 Use of rhodium carbenoids for the asymmetric functionalization of *i*-butane.

enable the stereocontrolled functionalization of imine derivatives **16** with, amongst others, propane and *i*-butane (Fig. 11). Specifically, this cooperative system is composed by a chiral bisoxazoline ligand chelated to a copper metal center as the Lewis catalyst and pentacenetetrone (PT) as the photocatalyst under blue light irradiation for 48 hours. The mechanism of the reaction relies on the visible-light excitation of the photocatalyst to afford a biradical species that is able to perform HAT on the alkyl derivatives, affording radical intermediates **XXIX** and **XXX**. In parallel, the copper-based Lewis acid is chelated by imine

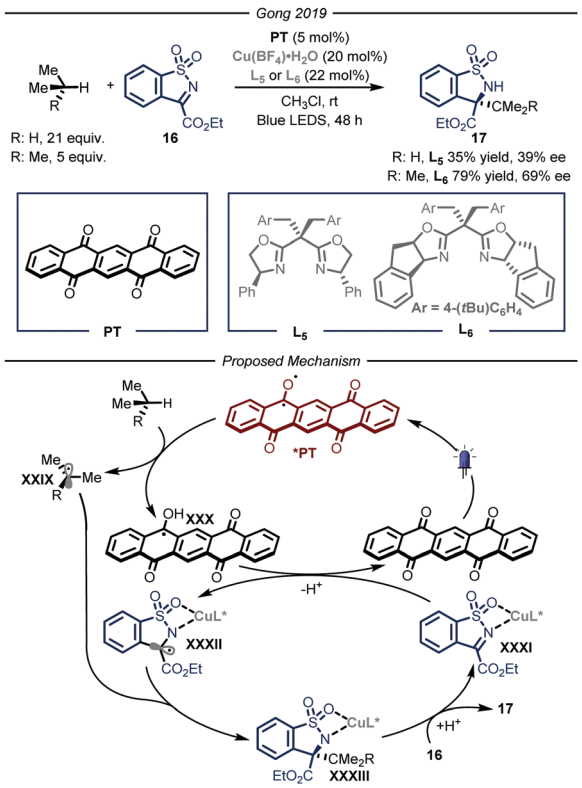

Fig. 11 Merger of photocatalyzed HAT and Lewis acid catalysis for the enantioselective functionalization of *i*-butane and propane. LED: light emitting diode.

substrate **16** affording complex **XXXI** which is reduced by **XXX** to generate the second open-shell intermediate **XXXII** and turnover the photocatalytic cycle. At this point, the authors propose a stereocontrolled intermolecular radical–radical coupling, driven by the chiral ligand of the Lewis acid catalyst, to afford the desired product **17** (35–79% yield, 39–69% ee).

Despite the fact that both these methodologies are affected by either low chemical yields and/or limited enantiomeric excess, they serve as a valuable proof of concept for the development of asymmetric procedures for the functionalization of gaseous alkanes.

C–N bond formation

Given the widespread presence of carbon–nitrogen bonds in biologically active molecules and pharmaceuticals, new methods capable to rapidly establish these bonds are of high interest for the scientific community.[40] Despite remarkable achievements in this field,[41] the development of new catalytic methodologies addressing the direct conversion of earth-abundant inert alkanes into valuable fine chemicals featuring a C–N bond is highly attractive from an industrial perspective. Moreover, installing nitrogen-containing functional groups in gaseous hydrocarbons by C–N bond forming processes has proved to be highly challenging.

The first example of such a transformation was reported by Crabtree and co-workers describing the formation of imines from methane and ammonia employing Hg photosensitization (Fig. 12).[42] The protocol takes advantage of the formation of an exciplex [Hg–NH_3]*, where ammonia is strongly bound to the mercury atom.[43] Indeed, the so-formed three electrons bond ensures proximity and facilitates an energy transfer process from mercury to ammonia, thus promoting N–H bond cleavage.[44] The authors envisioned that an electrophilic N-centered radical (N–H BDE = 107 kcal mol^{-1}) might promote the C–H abstraction of inert gaseous alkanes.[45] In order to prevent further over-functionalization of the product, the authors devised a reactor where a peristaltic pump continuously introduces the gas mixture in a photolysis chamber and a cold trap (−20 °C), which ensures condensation of the products. When an equimolar mixture of alkane/ammonia,

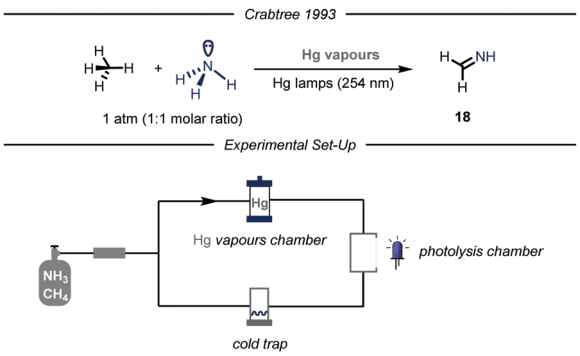

Fig. 12 Functionalization of methane using ammonia and Hg sensitization.

This journal is © The Royal Society of Chemistry 2021

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

containing a trace of mercury vapor was irradiated with UV light (254 nm), the corresponding imine **18** was obtained. Mechanistically, after C–H bond cleavage by the HAT reagent, the alkyl radical undergoes radical–radical coupling with the *N*-centered radical. The ensuing amine can undergo two consecutive HAT events to yield the final imine.

More recently, the group of Zuo reported a photocatalytic C–N bond formation protocol capable of converting methane, ethane and higher alkanes into the corresponding protected *N*-alkylated hydrazines **20** by using a homogeneous cerium-based photocatalyst $CeCl_3$ and an alcohol co-catalyst subjected to 400 nm light irradiation (Fig. 13).[46] Under the optimized conditions, using a standard pressure batch reactor, methane, ethane, propane and *n*-butane were all converted to the desired products in good to excellent yields (15–97% yield) using a variety of diazodicarboxylates **19** as radical traps. Additionally, the authors proved the scalability of the methodology by using a continuous-flow reactor.[47] For ethane, an excellent yield of 90% was obtained after 6 minutes of residence time and a high productivity of 2.0 mmol h^{-1} was accomplished at 15 bar pressure and ambient temperature. The same transformation using methane as the alkylating agent led to a maximum of 15% yield due to the low pressure limit of the reactor employed, which hampered adequate solubilization of the gas. Furthermore, the authors demonstrated the possibility to establish new C–C bonds by intercepting the nucleophilic radicals with both electron poor olefins and electron deficient heteroaromatic scaffolds.[48]

Concerning the reaction mechanism, the authors initially postulated that a photoinduced ligand-to-metal charge transfer (LMCT) of a transient Ce(IV)-alkoxide species ($[CeCl_5(OCH_2CCl_3)]^{2-}$) could lead to the formation of an oxygen-centered radical, responsible for the HAT step. However, recent studies by Schelter, Walsh and co-authors convincingly showed that oxygen-centered radicals are not involved in the catalytic cycle.[49] Indeed, titration of cerium pre-catalyst ($[NEt_4]_2[CeCl_6]$) with increasing amounts of CCl_3CH_2OH did not determine any change in its UV-visible absorption spectrum. Preparation of the Ce(IV)-alkoxide complex ($[CeCl_5(OCH_2CCl_3)]^{2-}$) was pursued, and UV-visible spectrum of this species displayed lower absorptivity and a blue shift, thus demonstrating the absence of this intermediate. Additionally, preliminary studies demonstrated that visible light irradiation of ($[NEt_4]_2[CeCl_6]$), formed *in situ* from $CeCl_3$ and [N*n*Bu$_4$]Cl, promotes the formation of Cl$^\bullet$ upon LMCT.[50] Kinetic studies showed that the initial rate of photolysis of ($[NEt_4]_2[CeCl_6]$) has no dependence on the concentration of $HOCH_2CCl_3$. In addition, control experiments confirmed the presence of chlorine-radical trapping products. Based on these observations, an alternative mechanistic scenario was suggested in which a photoinduced LMCT of $[Ce^{IV}Cl_6]^{2-}$ generates a chlorine radical atom which is capable of performing HAT on the alkane substrate, thus generating radical **XXXIV** that is intercepted by the electrophilic nitrogen source **19**. The formed N-centered radical intermediate **XXXV** is then reduced by $[Ce^{III}Cl_5]^{2-}$ through a single electron transfer and protonated by HCl affording the targeted *N*-alkylated protected hydrazine **20**.

Recently, the groups of Hartwig and Pérez, reported a copper-catalyzed C–H amidation protocol using gaseous hydrocarbons as alkylating agents (Fig. 14).[51] Under the optimized conditions, using *t*-butyl peroxide as both the oxidant and HAT reagent and CuI–phenantroline complex as the catalyst, ethane, propane, *n*-butane and *i*-butane were smoothly converted to the corresponding *N*-alkyl amides **22** (6–94% yield). Regarding the

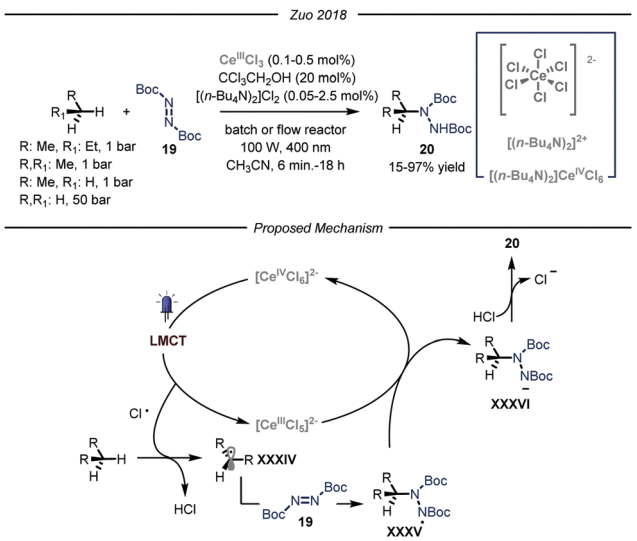

Fig. 13 Photocatalyzed C–N bond formation using light alkanes by Zuo and co-workers. LMCT: ligand to metal charge transfer.

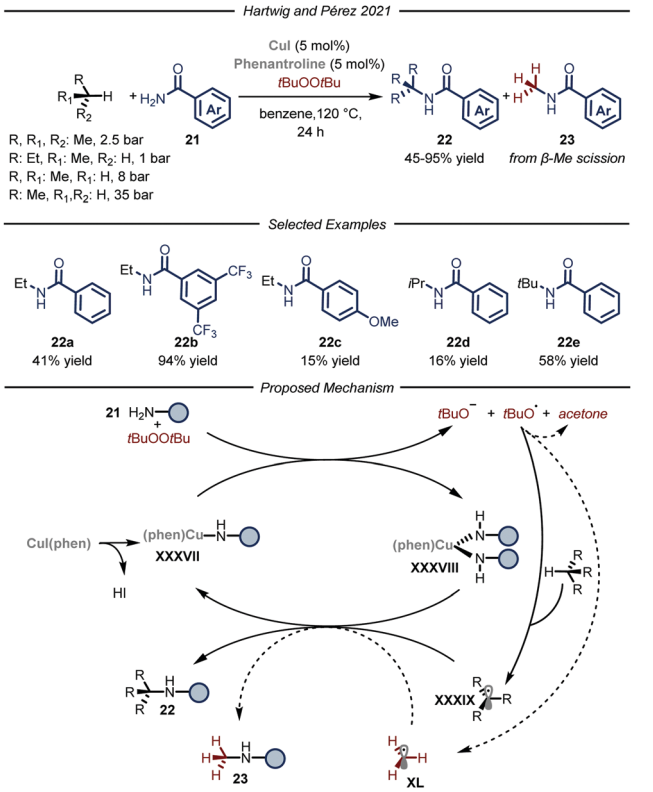

Fig. 14 Copper-catalyzed amidation of light alkanes by Hartwig, Pérez co-workers.

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

selectivity of the process, substrates containing two different C–H bonds were functionalized at both sites yielding mixtures of regioisomers. For all the tested gaseous alkanes, *N*-methylbenzamide **23** was detected as a side-product and accounted for the remaining mass balance. The recurring presence of **23** implies the involvement of a *t*-butoxy radical in the catalytic cycle, which is prone to undergo β-Me scission,[52] thus generating methyl radical **XL** which ultimately leads to the formation of the methylated side-product. Indeed, removal of the alkane substrate led to the selective formation of **23**. In order to distinguish between the two pathways when using methane as a substrate, the amidation of the latter was carried out employing the perdeuterated analogue of *t*-butyl peroxide. Under these conditions, 3% yield of the product derived from methane incorporation was observed along with 50% yield of the side-product bearing a deuterated methyl unit. Mechanistically, in accordance with a previous report,[52a] the Cu(I) complex **XXXVII** promotes the reductive fragmentation of the peroxide, thus leading to Cu(II) species **XXXVIII** and an oxygen centered radical. While the former reacts with one equivalent of amide **21**, the latter can either abstract a hydrogen atom from the gaseous substrate to generate **XXXIX** or undergo fragmentation affording methyl radical **XL**. Radical combination with Cu(II) intermediate **XXXVIII**, followed by reductive elimination, affords the *N*-alkylated product **22** and regenerates the Cu(I) catalyst.

In the same year, Chang and co-workers reported a highly selective C–N bond formation methodology capable of converting a wide range of inactivated alkanes into the corresponding *N*-alkyl carbamic acid ester derivatives **25** (Fig. 15).[53] Among the tested compounds, gaseous substrates, such as *n*-butane, propane and ethane, afforded the desired products **25** in moderate to good yields (34–73% yield). The protocol takes advantage of the formation of an electrophilic cobalt-nitrenoid species **XLI** that is responsible for the putative hydrogen atom abstraction. The design of a novel Cp*Co(III)($\mathbf{L}_7$) catalyst, featuring enhanced

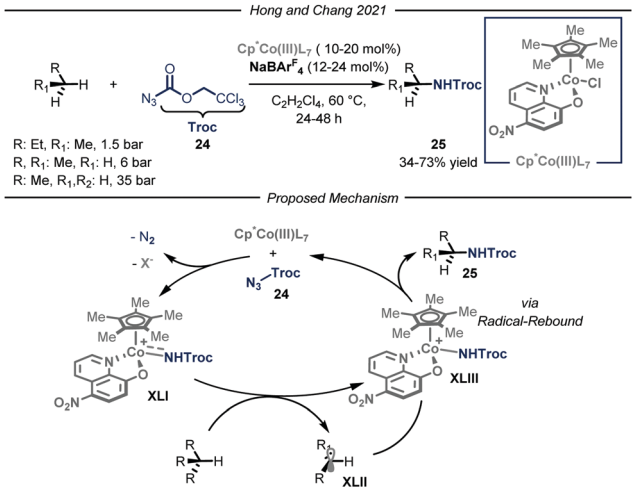

Fig. 15 Cp*Co(III)LX-catalyzed site-selective C–N bond formation of light alkanes. Cp*: pentamethylcyclopentadienyl; Troc: trichloroethyl chloroformate.

electrophilicity and adequate steric hindrance, proved to be of key-importance to obtain the desired reactivity and site-selectivity. Concerning the first aspect, the authors envisioned that installing an electron-withdrawing group within the bidentate ligand scaffold, might boost the overall electrophilicity of the cobalt–nitrenoid intermediate **XLI**, enabling the intermolecular activation of unbiased alkanes. This constitutes a transformation which is still elusive *via* similar catalytic manifolds.[54] Another advantage of the disclosed method is the high site-selectivity: indeed, for *n*-butane and propane, high preference for the functionalization of the methylene unit over the methyl one was observed. Interestingly, neither undesired over-functionalization nor solvent activation occurred. Based on a set of mechanistic studies, including electron paramagnetic resonance (EPR), DFT computations, radical clock experiments and kinetic isotope effect (KIE) studies, the authors proposed a cobalt(III)-nitrene radical activation mode in agreement with previous studies.[55] Coordination of Cp*Co(III)($\mathbf{L}_7$) to substrate **24** followed by a rate-determining nitrogen extrusion affords key metal-nitrenoid intermediate **XLI**. This species is then capable of abstracting a hydrogen atom from the aliphatic substrate, which in turn rapidly undergoes radical rebound affording the desired *N*-alkylated carbamic acid ester **25**.

C–Si bond formation

The synthesis of organosilicon compounds is an increasingly important field because of its ramifications in both medicinal[56] and material chemistry.[57] Moreover, the ensuing compound is a useful synthon due to its feature of acting as a carbon-based nucleophile in cross-coupling reactions.[58] Taking this into account, several methods to perform the direct silylation of C(sp^3)–H bonds have been reported.[59] Within this field, efforts for the installment of the silicon functionality on gaseous alkanes have been made. Specifically, the group of Tilley,[60] based on previous findings on the activation of methane by $Cp^*_2ScR_2$ complexes,[61] used this type of catalysts to install the silicon-based group on both methane and cyclopropane in a Parr high-pressure vessel (Fig. 16). After a thorough mechanistic study under both stoichiometric and catalytic conditions, the reaction has been proposed to initiate with an intra-complex C–H activation of one of the methyl substituents on the cyclopentadienyl ring and subsequent release of molecular hydrogen to afford complex **XLIV**. This intermediate is responsible for the activation of the alkane substrate, thus generating **XLV** which reacts with the silylating reagent **26**, to yield product **27a** and regenerate Cp^*_2ScH. Notwithstanding that the overall reactions are slow, this is an intriguing and significant achievement as it is one of the few processes catalyzed by an early metal that proceed under a non-radical mechanism.[62]

C–S Bond formation

Owing to their involvement in many processes such as protein folding and electron transfer events, sulfur containing

 This journal is © The Royal Society of Chemistry 2021

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

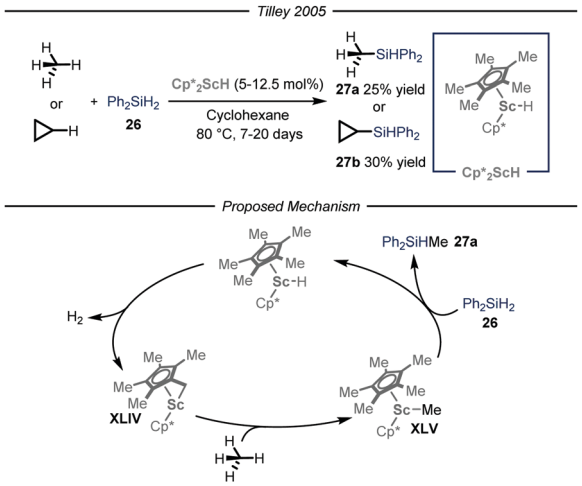

Fig. 16 Scandium-catalyzed silylation of light alkanes through C–H activation. Cp*: pentamethylcyclopentadienyl.

molecules occupy a privileged role in biochemistry.[63] Additionally, this class of compounds is routinely selected as novel candidates in the field of agricultural and pharmaceutical chemistry.[64] In the context of feedstock valorization, particular emphasis has been given on identifying chemoselective synthetic routes capable of converting methane into methane sulfonic acid (MSA). Indeed, MSA has recently emerged as an ideal electrolyte for many electrochemical industrial processes such as the electrodeposition of metals on electronic devices.[65]

Early examples of methane conversion into MSA took advantage of either K_2SO_4 or metal peroxides as radical initiators and SO_3 as the sulfonating agent, with sulfuric acid as solvent medium.[66] In the same period, inspired by an elegant vanadium-catalyzed sulfoxidation of inactivated alkanes,[67] Bell and coworkers published the first synthesis of MSA using methane as the alkylating agent and SO_2 as the sulfur source.[68] The reaction was carried out in triflic acid, with potassium persulfate and calcium salts used as, respectively, the oxidant and the promoter. Shortly after, the same group reported the first homogeneous catalytic sulfonation of methane using SO_2.[69] The highest conversion of sulfur dioxide into MSA was achieved using a dual catalytic system of Pd(II) and Cu(II) salts, with O_2 acting as an effective oxidant in a Parr autoclave reactor under 83 bar of methane (Fig. 17, 20% yield). As for the solvent, only strong acids proved suitable for the desired transformation. Despite the mechanism was not fully elucidated, similarly to Fujiwara and co-workers,[16] the authors postulate that the Pd species might promote an electrophilic activation of methane, followed by sulfur dioxide insertion and oxidation. Cu(II) and oxygen are proposed to be involved in the reoxidation of Pd(0) to Pd(II). Indeed, omission of Cu(II) resulted in formation of Pd-black with consequent inhibition of the reactivity.

Recently, the chemical division of Grillo-Werke AG reported a highly selective thermal process (99% selectivity and yield) for the conversion of methane and sulfur trioxide into MSA (Fig. 18).[70] The protocol employs a highly electrophilic sulfonyl

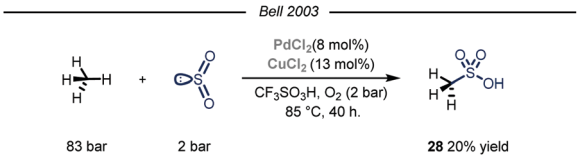

Fig. 17 Pd(II)–Cu(II) dual catalytic manifold for the conversion of methane into methanesulfonic acid.

peroxide initiator, formed *in situ* from MSA, H_2O_2 and Oleum (SO_3 36% weight in H_2SO_4). The initial optimization, carried out in a high pressure Parr autoclave, revealed that the highest conversion was obtained at 50 °C using 100 bar of methane. Concerning the reaction mechanism, the authors carried out a series of experiments aimed at demonstrating the non-radical nature of the presented transformation. Given the known tendency of the sulfonylperoxides to undergo homolytic cleavage of the O–O bond,[71] the authors conducted the same transformation at ambient temperature under exposure to UV-light (190 nm). After eight hours of irradiation no change in the methane pressure was observed, thus excluding the involvement of a radical pathway. Furthermore, inclusion of molecular oxygen in the reaction mixture did not inhibit the desired reactivity.[72] Despite these evidences, the reaction mechanism of the catalytic transformation remains unclear and computational studies demonstrated the unfeasibility of a polar cationic pathway.[73]

In light of the industrial relevance, the authors realized a pilot plant to scale-up the presented transformation with a projected capacity of 20 metric tons year^{-1}. As shown in Fig. 18, the facility features three stainless-steel reactors connected in series. In the first tank, methane and SO_3 are introduced and immediately reacted with the pre-formed electrophilic initiator. When the reaction mixture reaches the last reactor, the excess of SO_3 is quenched while methane is recycled. The crude

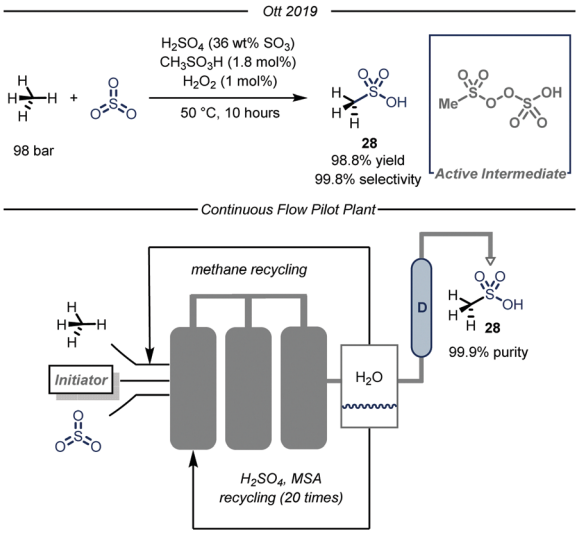

Fig. 18 Highly selective conversion of methane and sulfur trioxide into methanesulfonic acid.

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

mixture obtained after quenching is transferred to a distillation apparatus (D, Fig. 18) which delivers pure MSA. The exhausted solution containing H_2SO_4 and MSA is further recirculated to the first tank in order to form back the initial solution.

Conclusions

Over the past years, several groups have contributed to the homogeneous functionalization of gaseous alkanes. In this review, we have outlined the different catalytic tools used to perform this transformation, including transition metal-catalyzed C–H activation, carbenoid C–H functionalization and photocatalytic HAT, encompassing both polar and radical reactivity modes. Up to now, these methods have enabled the forging of C–B, C–C, C–N, C–O, C–Si and C–S bonds. Specifically for the C–C bond formation, enantioselective variants have been developed. Moreover, we have also detailed the importance of suitable setups, such as high-pressure Parr vessels or continuous-flow reactors.

Future efforts should be directed to construct new chemical bonds, such as C–P or C–Se, with these gaseous coupling partners. In addition, the functional group tolerance of these transformations needs to be further increased to enable the use of volatile alkanes as alkylating reagents within the synthetic routes towards more complex molecules. Other catalytic tools and activation modes should be identified and exploited to promote the functionalization of these recalcitrant substrates. At the same time, as technology clearly plays a crucial role to support these transformations, future endeavours should be also directed towards the development of suitable reactors, which can handle these chemicals efficiently and safely, and can ensure the scale up of the developed transformations. Finally, to bridge the gap with asymmetric catalysis, more efforts are required to ensure high enantioselectivities across various bond-forming reactions.

Author contributions

The concept of this article was conceived and agreed upon after discussions with all authors. D. M. and A. P. carried out the literature study and wrote the article (equal contributions). The entire manuscript was corrected and edited by T. N.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

A. P. and T. N. have received funding from the European Union H2020 research and innovation program under the Marie S. Curie Grant Agreement no. 860762 (MSCA ITN: CHAIR).

Notes and references

1 (*a*) R. A. Kerr, *Science*, 2010, **328**, 1624; (*b*) J. Cooper, L. Stamford and A. Azapagic, *Energy Technol.*, 2016, **4**, 772.
2 A. Caballero and P. J. Pérez, *Chem. Soc. Rev.*, 2013, **42**, 8809.
3 For selected reviews on the topic of the C(sp3)–H functionalization of liquid and solid alkanes see: (*a*) W. Ali, G. Prakash and D. Maiti, *Chem. Sci.*, 2021, **12**, 2735; (*b*) J. Das, S. Guin and D. Maiti, *Chem. Sci.*, 2020, **11**, 10887; (*c*) J. C. K. Chu and T. Rovis, *Angew. Chem., Int. Ed.*, 2018, **57**, 62.
4 (*a*) R. H. Crabtree, *Chem. Rev.*, 1995, **95**, 987; (*b*) H. Schwarz, *Angew. Chem., Int. Ed.*, 2011, **50**, 10096.
5 (*a*) M. Ravi, M. Ranocchiari and A. van Bokhoven, *Angew. Chem., Int. Ed.*, 2017, **56**, 16464; (*b*) N. J. Gunsalus, A. Koppaka, S. H. Park, S. M. Bischof, B. G. Hashiguchi and R. A. Periana, *Chem. Rev.*, 2017, **117**, 8521; (*c*) P. Tang, Q. Zhu, Z. Wu and D. Ma, *Energy Environ. Sci.*, 2014, **7**, 2580; (*d*) V. N. Cavaliere, B. F. Wicker and D. J. Mindiola, *Adv. Organomet. Chem.*, 2012, **60**, 1.
6 (*a*) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, *Chem. Rev.*, 2010, **110**, 890; (*b*) J. F. Hartwig, *Acc. Chem. Res.*, 2012, **45**, 864; (*c*) S. Kawamorita, R. Murakami, T. Iwai and M. Sawamura, *J. Am. Chem. Soc.*, 2013, **135**, 2947; (*d*) S. H. Cho and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, **135**, 8157; (*e*) C. Shu, A. Noble and V. K. Aggarwal, *Nature*, 2020, **586**, 714; (*f*) C. W. Liskey and J. F. Hartwig, *J. Am. Chem. Soc.*, 2012, **134**, 12422; (*g*) R. Oeschger, B. Su, I. Yu, C. Ehinger, E. Romero, S. He and J. F. Hartwig, *Science*, 2020, **368**, 736; (*h*) H. Chen, S. Schlecht, T. C. Semple and J. F. Hartwig, *Science*, 2000, **287**, 1995; (*i*) M. R. Jones, C. D. Fast and N. D. Schley, *J. Am. Chem. Soc.*, 2020, **142**, 6488; (*j*) H. Chen and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1999, **38**, 3391.
7 (*a*) *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*, ed. D. G. Hall, Wiley-VCH, Weinheim, 2005; (*b*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*c*) J. W. B. Fyfe and A. J. B. Watson, *Chem*, 2017, **3**, 31; (*d*) D. Leonori and V. K. Aggarwal, *Acc. Chem. Res.*, 2014, **47**, 3174.
8 P. R. Rablen and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 4648.
9 A. K. Cook, S. D. Schimler, A. J. Matzger and M. S. Sanford, *Science*, 2016, **351**, 1421.
10 K. T. Smith, S. Berritt, M. Gonzalez-Moreiras, S. Ahn, M. R. Smith III, M. H. Baik and D. J. Mindiola, *Science*, 2016, **351**, 1424.
11 A. A. Fokin and P. R. Schreiner, *Chem. Rev.*, 2002, **102**, 1551.
12 J. F. Hartwig, K. S. Cook, M. Hapke, C. D. Incarvito, Y. Fan, C. E. Webster and M. B. Hall, *J. Am. Chem. Soc.*, 2005, **127**, 2538.
13 For a pertinent review on the topic: (*a*) J. F. Hartwig, *Chem. Soc. Rev.*, 2011, **40**, 1992for selected examples: (*b*) J. D. Lawrence, M. Takahashi, C. Bae and J. F. Hartwig, *J. Am. Chem. Soc.*, 2004, **126**, 15334; (*c*) C. S. Wei, C. A. Jiménez-Hoyos, M. F. Videa and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 3078.
14 M. A. Larsen, C. V. Wilson and J. F. Hartwig, *J. Am. Chem. Soc.*, 2015, **137**, 8633.
15 (*a*) H. Schönherr and T. Cernak, *Angew. Chem., Int. Ed.*, 2013, **52**, 12256; (*b*) C. S. Leung, S. S. F. Leung, J. Tirado-Rives and W. L. Jorgensen, *J. Med. Chem.*, 2012, **55**, 4489.
16 (*a*) Y. Fujiwara, K. Takaki and Y. Taniguchi, *Synlett*, 1996, 591; (*b*) T. Nishiguchi, K. Nakata, K. Takaki and Y. Fujiwara, *Chem. Lett.*, 1992, 1141; (*c*) K. Nakata, T. Miyata, T. Jintoku, A. Kitani, Y. Taniguchi, K. Takaki and Y. Fujiwara, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 3755; (*d*) K. Nakata, Y. Yamaoka, T. Miyata, Y. Taniguchi, K. Takaki and Y. Fujiwara, *J. Organomet. Chem.*, 1994, **473**, 329.
17 R. H. Crabtree and A. Lei, *Chem. Rev.*, 2017, **117**, 8481 and related thematic issue.
18 Y. Taniguchi, S. Horie, K. Takaki and Y. Fujiwara, *J. Organomet. Chem.*, 1995, **504**, 137.
19 M. Lin and A. Sen, *Nature*, 1994, **368**, 613.
20 For reviews on the topic, see: (*a*) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2013, **53**, 74; (*b*) C. J. Scheuermann, *Chem. – Asian J.*, 2010, **5**, 436.
21 W. Xie, J. Heo, D. Kim and S. Chang, *J. Am. Chem. Soc.*, 2020, **142**, 7487.
22 A. Caballero, E. Despagnet-Ayoub, M. M. Díaz-Requejo, A. Díaz-Rodríguez, M. E. González-Núñez, R. Mello, B. K. Muñoz, W.-S. Ojo, G. Asensio, M. Etienne and P. J. Pérez, *Science*, 2011, **332**, 835.

 This journal is © The Royal Society of Chemistry 2021

Open Access Article. Published on 01 September 2021. Downloaded on 22.01.2026 15:08:39.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

23 (*a*) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704; (*b*) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (*c*) M. M. Díaz-Requejo and P. J. Pérez, *Chem. Rev.*, 2008, **108**, 3379; (*d*) M. M. Díaz-Requejo, T. R. Belderraín, M. C. Nicasio and P. J. Pérez, *Dalton Trans.*, 2006, 5559.
24 (*a*) J. Urbano, T. R. Belderraín, M. C. Nicasio, S. Trofimenko, M. M. Díaz-Requejo and P. J. Pérez, *Organometallics*, 2005, **24**, 1528; (*b*) E. Despagnet-Ayoub, K. Jacob, L. Vendier, M. Etienne, E. Álvarez, A. Caballero, M. M. Díaz-Requejo and P. J. Pérez, *Organometallics*, 2008, **27**, 4779.
25 R. C. McAtee, E. J. McClain and C. R. J. Stephenson, *Trends Chem.*, 2019, **1**, 111.
26 (*a*) L. Marzo, S. K. Pagire, O. Reiser and B. König, *Angew. Chem., Int. Ed.*, 2018, **57**, 10034; (*b*) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075; (*c*) D. Ravelli, S. Protti and M. Fagnoni, *Chem. Rev.*, 2016, **116**, 9850; (*d*) K. L. Skubi, T. R. Blum and T. P. Yoon, *Chem. Rev.*, 2016, **116**, 10035; (*e*) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (*f*) J. Xuan and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 6828; (*g*) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102.
27 (*a*) L. Capaldo, L. L. Quadri and D. Ravelli, *Green Chem.*, 2020, **22**, 3376; (*b*) L. Guillemard and J. Wencel-Delord, *Beilstein J. Org. Chem.*, 2020, **16**, 1754; (*c*) L. Capaldo and D. Ravelli, *Eur. J. Org. Chem.*, 2017, 2056.
28 H.-P. Deng, Q. Zhou and J. Wu, *Angew. Chem., Int. Ed.*, 2018, **57**, 12661.
29 (*a*) B. J. Shields and A. G. Doyle, *J. Am. Chem. Soc.*, 2016, **138**, 12719; (*b*) M. K. Nielsen, B. J. Shields, J. Liu, M. J. Williams, M. J. Zacuto and A. G. Doyle, *Angew. Chem., Int. Ed.*, 2017, **56**, 7191; (*c*) H. Deng, X. Fan, Z. Chen, Q. Xu and J. Wu, *J. Am. Chem. Soc.*, 2017, **139**, 13579.
30 For reviews on the benefits of flow technology for C–H functionalization chemistry, see (*a*) C. Sambiagio and T. Noël, *Trends Chem.*, 2020, **2**, 92; (*b*) S. Govaerts, A. Nyuchev and T. Noël, *J. Flow Chem.*, 2020, **10**, 13; (*c*) S. Santoro, F. Ferlin, L. Ackermann and L. Vaccaro, *Chem. Soc. Rev.*, 2019, **48**, 2767; (*d*) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel and T. Noël, *Chem. Rev.*, 2016, **116**, 10276.
31 F. Xue, H. Deng, C. Xue, D. K. B. Mohamed, K. Y. Tang and J. Wu, *Chem. Sci.*, 2017, **8**, 3623.
32 D. J. Wilger, J.-M. M. Grandjean, T. R. Lammert and D. A. Nicewicz, *Nat. Chem.*, 2014, **6**, 720.
33 A. A. Isse, C. Lin, M. L. Coote and A. Gennaro, *J. Phys. Chem. B*, 2011, **115**, 678.
34 G. Laudadio, Y. Deng, K. van der Wal, D. Ravelli, M. Nuño, M. Fagnoni, D. Guthrie, Y. Sun and T. Noël, *Science*, 2020, **369**, 92.
35 D. Ravelli, M. Fagnoni, T. Fukuyama, T. Nishikawa and I. Ryu, *ACS Catal.*, 2018, **8**, 701.
36 H. M. L. Davies, T. Hansen and M. R. Churchill, *J. Am. Chem. Soc.*, 2000, **122**, 3063.
37 For a review on the topic, see: H. M. L. Davies and K. Liao, *Nat. Rev. Chem.*, 2019, **3**, 347.
38 For reviews on the topic see: (*a*) A. Lipp, S. O. Badir and G. A. Molander,, *Angew. Chem., Int. Ed.*, 2021, **60**, 1714; (*b*) C. Prentice, J. Morrisson, A. D. Smith and E. Zysman-Colman, *Beilstein J. Org. Chem.*, 2020, **16**, 2363; (*c*) H.-H. Zhang, H. Chen, C. Zhu and S. Yu, *Sci. China: Chem.*, 2020, **63**, 637; (*d*) D. Saha, *Chem. – Asian J.*, 2020, **15**, 2129; (*e*) C. Jiang, W. Chen, W.-H. Zheng and H. Lu, *Org. Biomol. Chem.*, 2019, **17**, 8673; (*f*) M. Silvi and P. Melchiorre, *Nature*, 2018, **554**, 41.
39 Y. Li, M. Lei and L. Gong, *Nat. Catal.*, 2019, **2**, 1016.
40 (*a*) A. Klapars, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 7421; (*b*) S. R. Chemler, *Science*, 2013, **341**, 624; (*c*) R. Hili and A. K. Yudin, *Nat. Chem. Biol.*, 2006, **2**, 284; (*d*) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960.
41 P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**, 12564.
42 D. Michos, C. A. Sassano, P. Krajnik and R. H. Crabtree, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1491.
43 M. C. Duval, B. Soep and W. H. Breckenridge, *J. Phys. Chem.*, 1991, **95**, 7145.
44 M. Z. Hoffmann, M. Goldwasser and P. L. Damour, *J. Chem. Phys.*, 1967, **47**, 2195.
45 (*a*) A. W. Hofmann, *Chem. Ber.*, 1883, **16**, 558; (*b*) G. Kumar, S. Pradhan and I. Chatterdjee, *Chem. – Asian J.*, 2020, **15**, 651.
46 A. Hu, J.-J. Guo, H. Pan and Z. Zuo, *Science*, 2018, **361**, 668.
47 Z. Dong, Z. Wen, F. Zhao, S. Kuhn and T. Noël, *Chem. Eng. Sci.: X*, 2021, **10**, 100097.
48 The group of Duan reported a similar functionalization of light alkanes for forging C–C bonds mediated by an iron catalyst and visible light: Y. Jin, Q. Zhang, L. Wang, X. Wang, C. Meng and C. Duan, *Green Chem.*, 2021, DOI: 10.1039/D1GC01563J.
49 Q. Yang, Y.-H. Wang, Y. Qiao, M. G. P. J. Carroll, P. J. Walsh and E. J. Schelter, *Science*, 2021, **372**, 847.
50 (*a*) H. Yin, J. E. Hertzog, K. C. Mullane, P. J. Carroll, B. C. Manor, J. M. Anna and E. J. Schelter, *J. Am. Chem. Soc.*, 2016, **138**, 16266; (*b*) L. L. Costanzo, S. Pistara and G. Condorelli, *J. Photochem.*, 1983, **21**, 45.
51 M. A. Fuentes, R. Gava, N. I. Saper, E. A. Romero, A. Caballero, J. F. Hartwig and P. J. Pérez, *Angew. Chem., Int. Ed.*, 2021, **60**, 18467.
52 (*a*) B. L. Tran, B. Li, M. Driess and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 2555; (*b*) A. Vasilopoulos, S. W. Krska and S. S. Stahl, *Science*, 2021, **372**, 398.
53 J. Lee, S. Jin, D. Kim, S. H. Hong and S. Chang, *J. Am. Chem. Soc.*, 2021, **143**, 5191.
54 (*a*) J. Lee, J. Lee, H. Jung, D. Kim, J. Park and S. Chang, *J. Am. Chem. Soc.*, 2020, **142**, 12324; (*b*) Y. Baek, A. Das, S. L. Zheng, J. H. Reibenspies, D. C. Powers and T. A. Betley, *J. Am. Chem. Soc.*, 2020, **142**, 11232; (*c*) H. Lu, V. Subbarayan, J. Tao and X. P. Zhang, *Organometallics*, 2010, **29**(2), 389; (*d*) F. Ragaini, A. Penoni, E. Gallo, S. Tollari, C. L. Gotti, M. Lapadula, E. Mangioni and S. Cenini, *Chem. – Eur. J.*, 2003, **9**, 249.
55 V. Lyaskovskyy, A. I. O. Suarez, H. Lu, H. Jiang, X. P. Zhang and B. de Bruin, *J. Am. Chem. Soc.*, 2011, **133**, 12264.
56 (*a*) G. A. Showell and J. S. Mills, *Drug Discovery Today*, 2003, **8**, 551; (*b*) A. K. Franz and S. O. Wilson, *J. Med. Chem.*, 2013, **56**, 388.
57 S. A. Ponomarenko and S. Kirchmeyer, *Adv. Polym. Sci.*, 2011, **235**, 33.
58 T. Komiyama, Y. Minami and T. Hiyama, *ACS Catal.*, 2017, **7**, 631.
59 B. Li and P. H. Dixneuf, *Chem. Soc. Rev.*, 2021, **50**, 5062.
60 (*a*) A. D. Sadow and T. D. Tilley, *J. Am. Chem. Soc.*, 2005, **127**, 643; (*b*) A. D. Sadow and T. D. Tilley, *Angew. Chem., Int. Ed.*, 2003, **42**, 803.
61 M. E. Thompson, S. M. Baxter, A. R. Bulls, B. J. Burger, M. C. Nolan, B. D. Santarsiero, W. P. Schaefer and J. E. Bercaw, *J. Am. Chem. Soc.*, 1987, **109**, 203.
62 The group of Tilley exploited this mode of activation to also drive C–C bond formation: A. D. Sadow and T. D. Tilley, *J. Am. Chem. Soc.*, 2003, **125**, 7971.
63 (*a*) M. Fontecave, S. Ollagnier-de-Choudens and E. Mulliez, *Chem. Rev.*, 2003, **103**, 2149; (*b*) R. Zabel and G. Weber, *Anal. Bioanal. Chem.*, 2016, **408**, 1237; (*c*) M. Kazemi, S. Sajjadifar, A. Aydi and M. M. Heydari, *J. Med. Chem. Sci.*, 2018, **1**, 1.
64 (*a*) P. Devendar and G. F. Yang, *Top. Curr. Chem.*, 2017, **375**, 82; (*b*) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. A. Hor and X. Liu, *Chem. Soc. Rev.*, 2015, **44**, 291.
65 M. D. Gernon, M. Wu, T. Buszta and P. Janney, *Green Chem.*, 1999, **1**, 127.
66 (*a*) L. J. Lobree and A. T. Bell, *Ind. Eng. Chem. Res.*, 2001, **40**, 736; (*b*) S. Mukhopadhyay and A. T. Bell, *Ind. Eng. Chem. Res.*, 2002, **41**, 5901; (*c*) S. Mukhopadhyay and A. T. Bell, *Angew. Chem., Int. Ed.*, 2003, **42**, 1019; (*d*) S. Mukhopadhyay and A. T. Bell, *Org. Proc. Res. Dev.*, 2003, **7**, 161.
67 Y. Ishii, K. Matsunaka and S. Sakaguchi, *J. Am. Chem. Soc.*, 2000, **122**, 7390.
68 S. Mukhopadhyay and A. T. Bell, *J. Am. Chem. Soc.*, 2003, **125**, 4406.
69 S. Mukhopadhyay and A. T. Bell, *Chem. Commun.*, 2003, 1590.
70 C. Díaz-Urrutia and T. Ott, *Science*, 2019, **363**, 1326.
71 F. Minisci, A. Citterio and C. Giordano, *Acc. Chem. Res.*, 1983, **16**, 27.
72 N. Basickes, T. E. Hogan and A. Sen, *J. Am. Chem. Soc.*, 1996, **118**, 13111.
73 V. A. Roytman and D. A. Singleton, *Science*, 2019, **364**, eaax7083.