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Recent Advances

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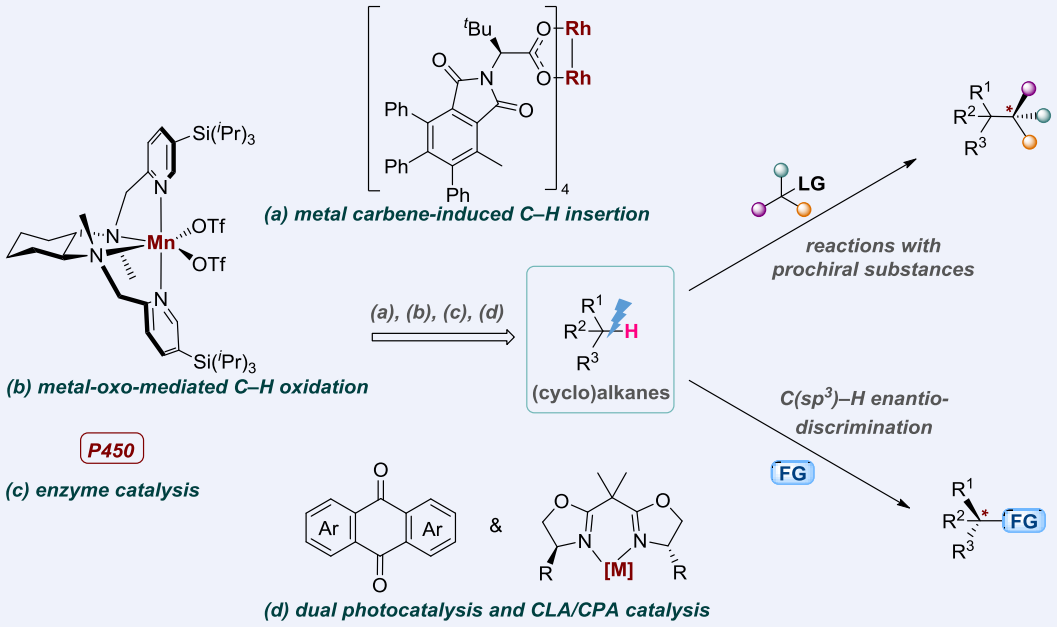
Recent Advances in Asymmetric Transformations of Unactivated Alkanes and Cycloalkanes through Direct C—H Functionalization

Shiyan Cheng,[a] Qianyu Li,[a] Xiuliang Cheng,[a] Yu-Mei Lin[a] and Lei Gong*[,a,b]

[a] *Key Laboratory of Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, China*
[b] *Innovation Laboratory for Sciences and Technologies of Energy Materials of Fujian Province (IKKEM), Xiamen, Fujian 361005, China*

Comprehensive Summary

The direct conversion of unactivated alkanes and cycloalkanes into structurally diverse molecules through aliphatic C—H functionalization is a useful process, which has attracted intense interest from academia and industry. Methods to control chemo- and site-selectivity, combined with asymmetric catalysis, provide appealing access to high value-added enantiomer-enriched compounds but are far less developed. This review focuses on recent progress in (*i*) asymmetric reactions of alkanes or cycloalkanes with prochiral substrates which generate a stereocenter adjacent to the cleaved C(sp^3)–H bond, and (*ii*) C(sp^3)–H enantiodiscriminatory reactions creating a new stereogenic center on the carbon of a cleaved C(sp^3)–H bond. Elegant strategies are discussed, including (*a*) metal carbene-induced C—H insertions by chiral rhodium catalysts, (*b*) metal-*oxo*-mediated C—H oxidation by biomimetic manganese catalysts, (*c*) enzyme catalysis by cytochromes P450 variants, and (*d*) dual catalysis by a photocatalyst and a chiral Lewis acid (CLA) or a chiral phosphoric acid (CPA). These catalytic systems can not only precisely recognize primary, secondary and tertiary C—H bonds at specific positions in alkanes and cycloalkanes, but also support a high level of stereoselectivity in the reactions. It is expected that the advances will stimulate further progress in asymmetric catalysis, synthetic methodology, pharmaceutical development and industrial processes.



Keywords

Asymmetric catalysis | C—H functionalization | Alkane | Site-selectivity | Enantioselectivity

*E-mail: gongl@xmu.edu.cn

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Left to Right: Shiyan Cheng, Qianyu Li, Xiuliang Cheng, Yu-Mei Lin, Lei Gong

Shiyan Cheng received her B.Sc. degree from Guangxi Normal University in 2021. She is a M.Sc. candidate under the guidance of Professor Lei Gong at Xiamen University. Her current research interest is the development of visible light-induced C—H functionalization reactions.

Qianyu Li obtained her B.Sc. degree from Kunming University in 2016 and M.Sc. degree from Guangxi Normal University in 2019. She is currently a Ph.D. candidate under the supervision of Professor Lei Gong at Xiamen University. Her current research interest is the photocatalyzed asymmetric synthesis and C—H functionalization.

Xiuliang Cheng obtained her B.Sc. and M.Sc. degree from Nanning Normal University in 2018 and 2021, respectively. In 2021, she moved to Xiamen University to pursue a doctoral degree under the guidance of Professor Lei Gong. Her research interests focus on development of new methods for visible light-driven asymmetric synthesis.

Yu-Mei Lin received her Ph.D. degree (2010) from Xiamen University under the guidance of Professor Haiping Xia. Thereafter, she worked with Professor Stefanie Dehnen in Philipps-University Marburg, Germany, as a Humboldt Alexander fellow. In 2013, she joined Xiamen University as an Associate Professor. Her current research interests include the synthesis and reactivity of metalla-aromatic compounds, as well as the design of new catalysts based on organometallic scaffolds.

Lei Gong is a professor at Xiamen University, China. He received his B.Sc. (2002) and Ph.D. degree (2008) from Xiamen University under the guidance of Professor Haiping Xia. Thereafter he moved to Philipps-Universität Marburg, Germany, where he worked as a postdoctoral fellow with Professor Eric Meggers. In 2011, he was appointed as an Associate Professor at the College of Chemistry and Chemical Engineering at Xiamen University. Since 2019, he has been a full professor at Xiamen University. He received the Thieme Chemistry Journals Award in 2021. His current research interests include the development of economic and environmentally-friendly photochemical organic synthesis, photocatalyzed C—H functionalization, and asymmetric photocatalysis.

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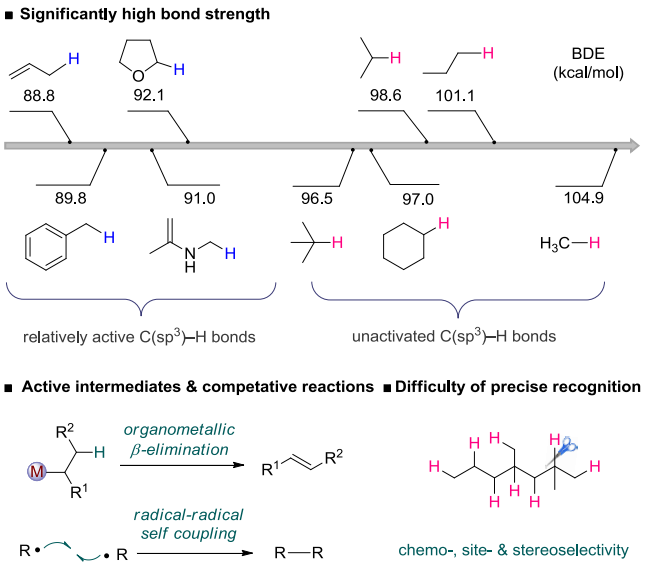
1. Introduction

Alkanes and cycloalkanes are among the most readily available organic molecules, and many such compounds can be isolated from petrochemicals. They are generally used as fuels, sources of energy for propulsion and electricity, and nonpolar solvents for chemical reactions.[1] In synthetic chemistry, the controllable conversion of alkanes and cycloalkanes into functionally diverse products through direct C(sp^3)–H functionalization is an important and valuable topic,[2-13] but is much less developed than similar reactions involving benzylic, allylic, α-oxy and α-amino C—H substances.[14-28] The absence of activation by adjacent π-electron systems, heteroatoms or directing groups leads to the high bond dissociation energies (BDE) of 96—105 kcal/mol, low polarity and very similar inherent properties of C(sp^3)–H bonds in alkanes and cycloalkanes.[29] Consequently, to achieve useful reactivity, chemo-, site- and stereoselectivity in their direct transformations remains a remarkably challenging task, through either an organometallic pathway or a radical-mediated process.[30] As a consequence, maneuverable protocols that can facilitate cleavage and precise recognition of C(sp^3)–H bonds in these compounds are highly desirable (Scheme 1).

Direct functionalization of strong aliphatic C—H bonds represents a more ideal approach to molecular construction.[31-33] Several appealing strategies relying on transition metal catalysis by rhodium, manganese and other metals, enzyme catalysis and radical-mediated processes have been developed, leading to the development of a variety of selective C—H transformations in aliphatic hydrocarbons under mild conditions.[34] Some of these strategies can be combined with asymmetric catalysis for the direct construction of optically active compounds from simple hydrocarbons.[35] The chemo-, site-selectivity and stereochemistry of these reactions can be controlled simultaneously by a single

Scheme 1 Challenges in the direct and selective C(sp^3)–H functionalization of alkanes and cycloalkanes



catalyst or a dual catalyst system, featuring appealing reagent, atom and step economy.[36]

This review aims to provide an overview of the field of asymmetric synthesis through selective C—H functionalization of alkanes and cycloalkanes. The two sets of reactions that will be discussed are: (*i*) asymmetric transformations of (cyclo)alkanes with prochiral substrates, in which a stereogenic center is built up adjacent to the cleaved C(sp^3)–H bond, and (*ii*) C(sp^3)–H enantiodiscrimination of (cyclo)alkanes with a stereocenter generated on the carbon of the cleaved C(sp^3)–H bond. Strategies of transition metal carbene-induced C—H insertion by chiral rhodium catalysts, metal-*oxo*-mediated C—H oxidation, enzyme catalysis by cytochromes P450 variants, and dual catalysis by a photocatalyst (**PC**) and a chiral Lewis acid (CLA) or a chiral phosphoric acid (CPA) are involved, showcasing significant potential in both recognition of C—H bonds at the specific positions and asymmetric induction (Scheme 2).

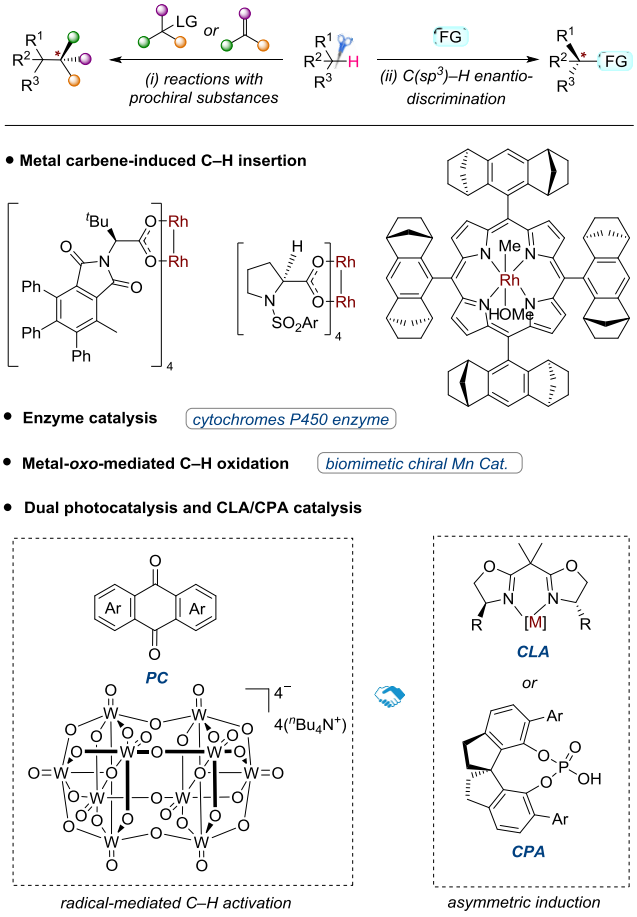
2. Asymmetric Transformations of Alkanes or Cycloalkanes with Prochiral Substrates

A straightforward approach to asymmetric transformation of alkanes and cycloalkanes is to engineer their C(sp^3)–H functionalization with prochiral substances, whose stereochemistry is controlled by sophisticatedly designed chiral catalysts. This strategy however suffers from several inherent drawbacks. It is extremely difficult for example, to control the site-selectivity because these compounds typically contain many quite similar C—H bonds. Additionally, C(sp^3)–H cleavage often gives rise to highly active intermediates, which can cause a number of side reactions and difficulty to govern the selectivity. To find a compatible catalytic system capable of simultaneously activating C—H bonds and governing stereochemistry is also a challenging task.[37-38] To date, only limited success has been achieved, and those methods are discussed separately in this section.

2.1. Reactions enabled by metal carbene-induced C—H insertion

Insertion of reagents, such as carbenes, nitrenes or oxygen, bound to transition metals into the C—H bonds has been recognized as a powerful tool for functionalization of inactive C—H

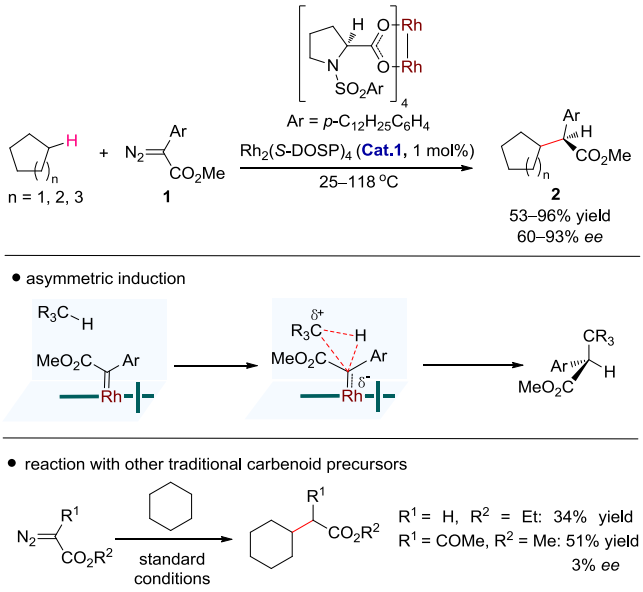
Scheme 2 Asymmetric synthesis through selective C—H functionalization of alkanes and cycloalkanes



bonds. This strategy is especially effective in intramolecular transformations.[39] A typical reaction sequence involves generation *in situ* of a metal carbene or nitrene intermediate and subsequent insertion of the M=C or M=N moiety into an unactivated C—H bond to form a new C—C or C—N bond. During this process, the chemo- and site-selectivity can be induced by the distinctive steric and electronic properties present in the substrates and the ligands, as well as the priority to form 5- or 6-membered rings.[40] In contrast, the transition metal-induced intermolecular C—H insertion reactions, in particular those of alkanes and cycloalkanes, have long been regarded as inefficient and unselective processes.[41]

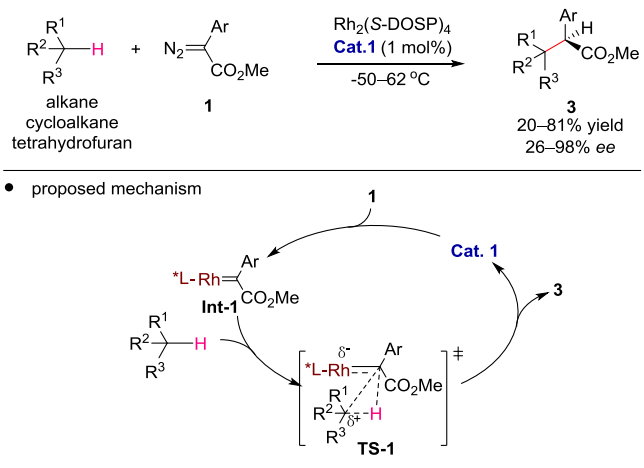
In 1997, Davies *et al.* disclosed that a chiral dirhodium complex, rhodium(II) (*S*)-*N*-(*p*-alkylphenyl)sulfonylprolinate (Rh_2(*S*-DOSP)$_4$, **Cat. 1**), was capable of catalyzing an enantioselective reaction of cycloalkanes with prochiral aryl diazoacetates (**1**) (Scheme 3).[42] The reaction proceeded, even at room temperature, but delivered better yields of 53%—96% at 25—118 °C. A high level of enantioselectivity of 60%—93% enantiomeric excess (*ee*) was obtained, possibly due to the steric requirements of the carbenoid intermediate. The C—H insertion is proposed to occur in a concerted but asynchronous manner in which a positive charge is formed at the carbon of the C—H bond. The more traditional carbenoid precursors, such as ethyl diazoacetate and ethyl 2-diazo-3-oxobutanoate, react similarly but give a reduced yield or much lower enantioselectivity, demonstrating the efficiency of the rhodium-catalyzed aryl diazoacetate system as a more robust source of donor/acceptor carbenes for asymmetric C—H insertions.

Scheme 3 Enantioselective reaction of cycloalkanes with aryldiazoacetates catalyzed by a chiral dirhodium complex



The chiral dirhodium catalyst (**Cat. 1**) and the aryl diazoacetate-type carbene precursors (**1**) were later applied to asymmetric transformations of alkanes, cylcoalkanes and tetrahydrofurans (Scheme 4).[43] At −50–62 °C in the presence of 1 mol% **Cat. 1**, these inactive C(sp^3)–H donors were successfully converted into functionalized products (**3**) in 23%—81% yield and with 26%—98% *ee*. In a proposed reaction mechanism, a meta-carbenoid complex (**Int-1**) is first generated through decomposition of the aryl diazoacetate substrate (**1**) enabled by **Cat. 1**. The formation and release of gaseous nitrogen is considered to be the driving force for this critical step. Intermediate **Int-1** is a particularly reactive species, which then undergoes intermolecular C—H insertion by means of a three-membered transition state (**TS-1**). A chiral product (**3**) is formed, meanwhile regenerating the rhodium catalyst for a subsequent reaction cycle. This reaction shows excellent site-selectivity and preference towards tertiary C—H bonds over secondary and primary bonds, probably due to the electron density which in the order of primary < secondary < tertiary C—H bonds. Tertiary C—H bonds are the most susceptible to attack by electrophilic rhodium–carbene intermediates. The observation of higher

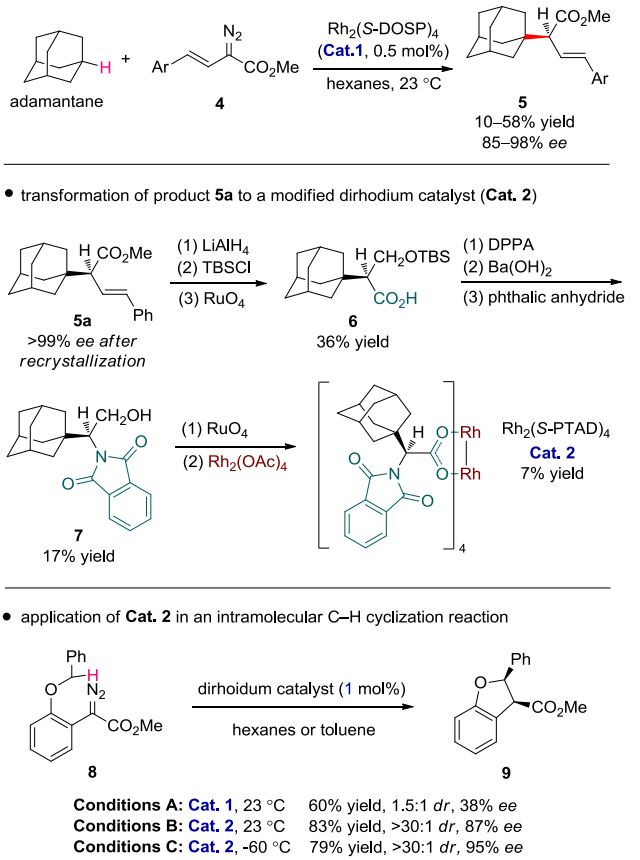
Scheme 4 Catalytic asymmetric transformations of alkanes, cycloalkanes and tetrahydrofurans



enantioselective C—H insertions at secondary sites in comparison to those at tertiary sites can be explained by the less favored close approach of the catalyst to a sterically more demanding tertiary C—H bond. These results further establish that rhodium carbenoids derived from aryl diazoacetates are useful intermediates for asymmetric transformations of inactive C(sp^3)–H precursors *via* intermolecular C—H reactions.

In 2006, Davies *et al*. used a similar protocol in the presence of 0.5 mol% of **Cat. 1** for the reaction of adamantane with vinyldiazoacetates (**4**) (Scheme 5).[44] This reaction, in hexane at 23 °C led to alkylated products (**5**) which were obtained as single regioisomers with 85%—98% *ee*, and in which C—H functionalization similarly occurred at the electronically more favored tertiary C—H bonds. The reaction of adamantane + **4a** → **5a** (Ar = Ph) was the most practical, due to its scalability to a 40—50 g scale, and the possibility of improving the optical purity of the product to >99% *ee* by recrystallization. A synthetic pathway involving Rh_2(*S*-PATD)$_4$ (**Cat. 2**), a modified dirhodium catalyst, was developed starting from **5a**. First, a carboxylic acid (**6**) was obtained in 36% yield through a reaction sequence involving ester reduction, TBS protection (TBS = *tert*-butyldimethylsilyl) and alkene oxidation. Compound **6** was converted into a phthalimide derivative (**7**) in 17% yield by a Curtius rearrangement followed by treatment with phthalic anhydride. The final alcohol oxidation and ligand exchange with $Rh_2(OAc)_4$ afforded **Cat. 2** in 7% yield. Compared to **Cat. 1**, this phthalimide-derived catalyst exhibited higher catalytic activity and selectivity in several cases of asymmetric C—H insertion reactions. For example, with **Cat. 2** as the catalyst, an intramolecular C—H cyclization reaction of the aryl diazoacetate (**8**) at 23 °C gave a benzodihydrofuran product (**9**) in 83% yield and with >30 : 1 diastereomeric ratio (*dr*) and 87% *ee*. In contrast, a reduced yield of 60% and much lower stereoselectivity of 1.5 : 1 *dr*

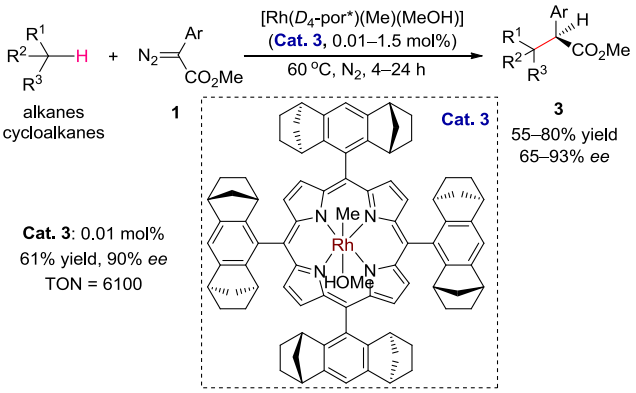
Scheme 5 Catalytic asymmetric reaction of adamantane and its synthetic application



and 38% *ee* were obtained in the presence of **Cat. 1** under similar conditions.

Fine-tuning of ligands on the chiral rhodium catalysts can alter the electronic and steric features, leading to the formation of less-reactive and more-selective rhodium carbene intermediates. For example, Che *et al*. designed a structurally well-defined and sterically encumbered rhodium catalyst bearing a chiral porphyrin ligand, [Rh(D_4-por*)(Me)(MeOH)] (**Cat. 3**), for the C—H functionalization of alkanes and cycloalkanes with aryl diazoacetates (**1**) (Scheme 6).[45] In contrast to the order of primary < secondary < tertiary C—H bonds observed in many rhodium carbene-induced C—H insertions, **Cat. 3** exhibited a primary/secondary selectivity of up to 3.8 : 1 regioisomeric ratio (*rr*) and an enantioselectivity of up to 93% *ee* for secondary C—H bonds. The catalyst loading could be reduced to 0.01 mol%, still giving 61% yield and 90% *ee* within 8 h, thereby leading to an excellent turnover number (TON) of 6100.

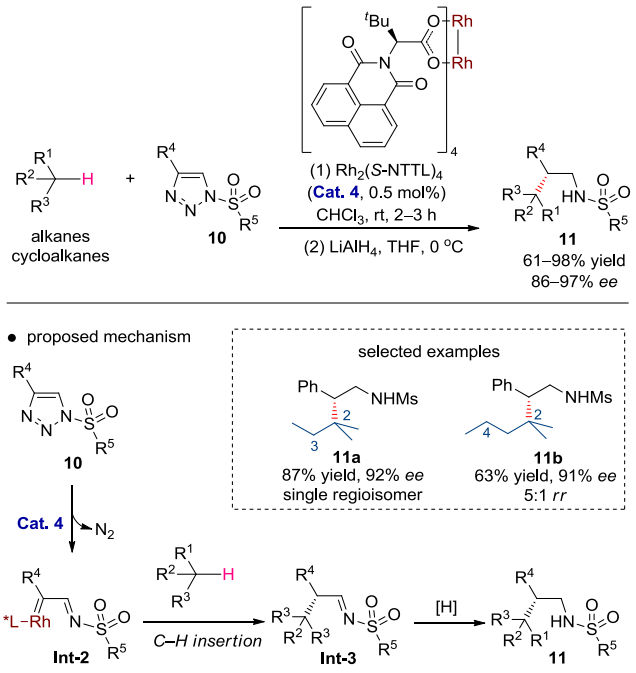
Scheme 6 Development of rhodium-porphyrin catalysts for C—H functionalization of alkanes and cycloalkanes with aryl diazoacetates



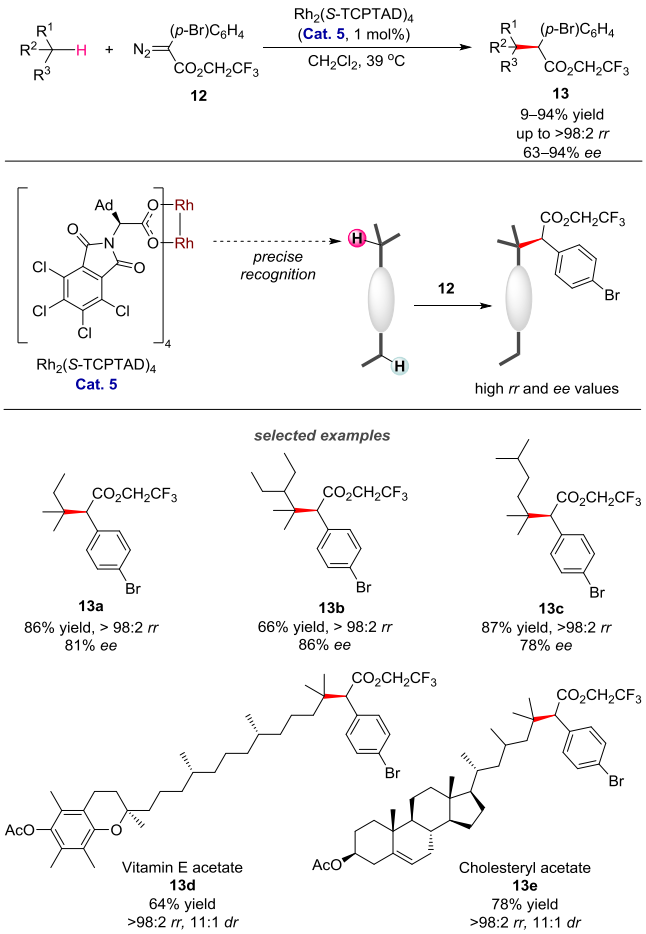
In 2011, *Fokin et al*. found that the reaction of alkanes or cycloalkanes with 1-sulfonyl-1,2,3-triazoles (**10**) could be accelerated by a dirhodium catalyst bearing a (*S*)-2-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-3,3-dimethyl butyrate ligand, (Rh_2(*S*-NTTL)$_4$) (**Cat. 3**) (Scheme 7).[46] A variety of *β*-chiral sulfonamides were obtained in yields of 61%—98% and with high enantioselectivity (86%—97% *ee*). In comparison to the carboxylic ester congeners in aliphatic C—H insertions with diazoacetate substrates, C—H functionalization with 1-sulfonyl-1,2,3-triazoles proceeded *via* a pathway involving the formation of azavinyl carbenes (**Int-2**), and showed much higher site-selectivity toward tertiary over secondary C—H bonds. For example, the reaction of 2-methylbutane occurred only at the C-2 site, affording the product (**11a**) as a single regioisomer in 87% yield and 92% *ee*. The reaction of 2-methylpentane gave a regioisomeric mixture containing **11b** (reaction at the C-2 or C-4 site, respectively) in 63% and with 5 : 1 *rr* and 91% *ee*. This reaction represents the first example of Rh(II)-catalyzed enantioselective intermolecular C—H insertion of azavinyl carbenes.

In 2017, Davies *et al.* developed a highly effective, site- and enantioselective functionalization of non-activated tertiary C—H bonds of alkanes enabled by a tetrachlorphthalimido-derived dirhodium catalyst, Rh_2(TCPTAD)$_4$ (TCPTAD = adamantan-1-yl-(4,5,6,7-tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2yl)-acetic acid, **Cat. 5**) (Scheme 8).[47] The use of a 2,2,2-trichloroethyl aryldiazoacetate (**12**) as a more robust source of donor/acceptor carbenes allowed high catalytic efficiency at room temperature and elaborate site- and stereoselectivity in the transformations of alkanes. For example, the reaction of isopentane gave a chiral product (**13a**) in 86% yield, with > 98 : 2 *rr* towards the tertiary C—H site and 81%

Scheme 7 The first Rh(II)-catalyzed enantioselective intermolecular C—H insertion of azavinyl carbenes



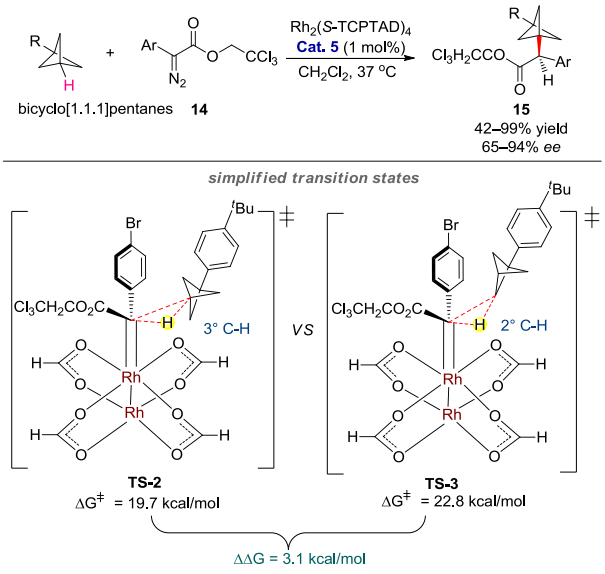
Scheme 8 Rh(II)-catalyzed site- and enantioselective functionalization of tertiary C—H bonds of alkanes



ee. In the case of 3-ethyl-2-methylpentane which contains two different tertiary C—H bonds, the sterically less demanding site was preferred and product **13b** with > 98 : 2 *rr* and 86% *ee* was produced. Structurally more complex biomolecules, such as vitamin E acetate and cholesteryl acetate were also tolerated and gave the modified chiral products (**13d** and **13e**, respectively) as single regioisomers and with high diastereoselectivity. A combination of structural analysis and computational studies revealed that the dirhodium catalyst (**Cat. 5**) basically adopts a C_4 symmetric shape with a shallow pocket. Such structural features enable the most accessible tertiary C—H bonds of alkanes to approach the phthalimido face of the corresponding rhodium-bound carbene in the reaction.

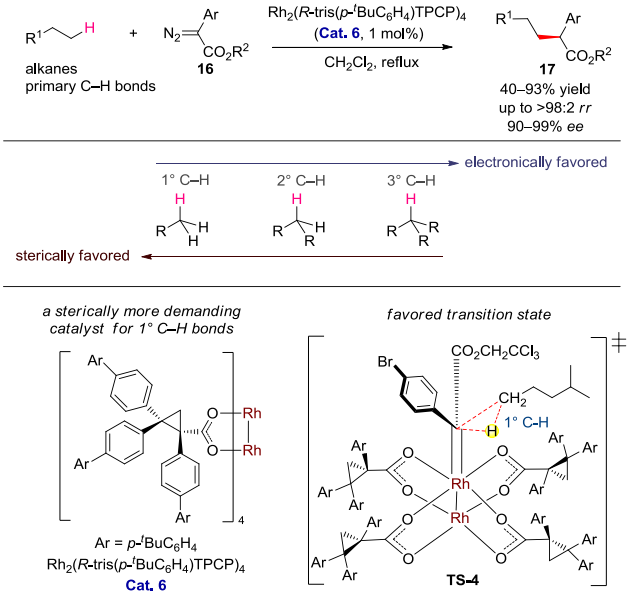
This rhodium catalyst (**Cat. 5**) was subsequently used for the enantio- and site-selective modification of bicyclo[1.1.1]pentanes (BCP) with similar donor/acceptor diazo compounds (**14**) as the reaction partners (Scheme 9).[48] BCPs are a class of unique carbocyclic molecules bearing highly strained aliphatic rings, which are difficult to functionalize without losing the integrity of their carbocyclic framework. The reaction at 37 °C in the presence of 1 mol% **Cat. 5** gave a variety of alkylated BCPs (**15**) as exclusive regioisomers with 65%—94% *ee*. The observation of site-selectivity favoring the tertiary over secondary C—H bonds is consistent with the density functional theory (DFT) calculations which indicated that the energy barrier for tertiary C—H insertion (**TS-2**) is 19.7 kcal/mol, 3.1 kcal/mol lower than that for secondary C—H insertion (**TS-3**, 22.8 kcal/mol).

Scheme 9 Rh-catalyzed site- and enantioselective functionalization of tertiary C—H bonds of bicyclo[1.1.1]pentanes



In contrast to tertiary C—H bonds, primary C—H bonds are electronically less favored in the metal carbene-induced C—H functionalizations because these reactions begin with a hydride transfer and consequently prefer to occur at C—H sites where stabilization of a positive charge is benefited. However, primary C—H bonds are sterically more favored and this allows them to easily approach the rhodium-carbene species. After screening of a library of chiral dirhodium catalysts, Davies *et al*. found that a highly sterically demanding catalyst (Rh_2(*R*-tris(*p*-^{t}BuC_6H_4)TPCP)$_4$, **Cat. 6**) could effectively recognize primary C—H sites of linear or branched alkanes containing all primary, secondary and tertiary C—H bonds (Scheme 10).[49] The corresponding products (**17**) were obtained in 40%—93% yield, with up to > 98 : 2 *rr* and a high level of enantioselectivity (90%—99% *ee*). In terms of the mechanism, the C—H functionalization proceeds through a concerted asynchronous pathway, in which a hydrogen atom of one primary C—H bond in the alkane substrate approaches the rhodium-carbene site to form a sterically preferred and energetically favored transition state (**TS-4**).

Scheme 10 Rh-catalyzed site- and enantioselective functionalization of primary C—H bonds of alkanes



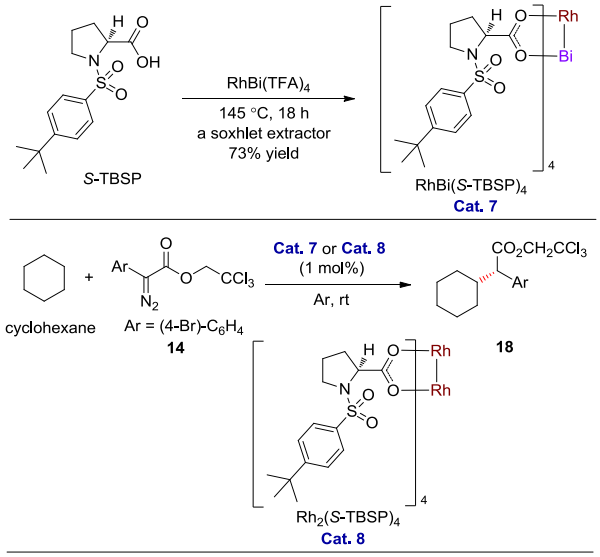
These examples clearly demonstrate that electronic and steric features of chiral ligands in the dirhodium catalysts have significant influence on the site- and stereoselectivity. In particular, fine-tuning of chiral ligands can even alter the site of the reaction from electronically favored tertiary C—H bonds to sterically favored primary C—H bonds.

Another option for catalyst modification is to change the transition metal centers. In 2018, Davies *et al.* developed a unique heteronuclear bimetallic catalyst (**Cat. 7**), which retains a similar bimetallic scaffold but with a rhodium center and a bismuth atom.[50] **Cat. 7** was synthesized *via* ligand exchange by heating a toluene solution of $RhBi(TFA)_4$ with a chiral carboxylic acid, (*S*)-1-((4-(*tert*-butyl)phenyl)sulfonyl)pyrrolidine-2-carboxylic acid (H(*S*-TBSP)) in a Soxhlet extractor with K_2CO_3 in its thimble at 145 °C for 18 h (Scheme 11). The replacement of one rhodium center with a bismuth atom led to a change in the electronic properties of corresponding metal carbene intermediates, giving it much slower reaction rates and asymmetric induction similar to that of the C—H insertion reaction of cyclohexane catalyzed by its dirhodium analog (Rh_2(*S*-TBSP)$_4$, **Cat. 8**). In an asymmetric cyclopropanation reaction with styrene derivatives proceeding through a similar metal-carbene insertion, the Rh-Bi catalyst (**Cat. 7**) exhibited clearly improved enantioselectivity in comparison to the Rh-Rh catalyst (**Cat. 8**).

2.2. C—H oxidation mediated by metal-*oxo* species

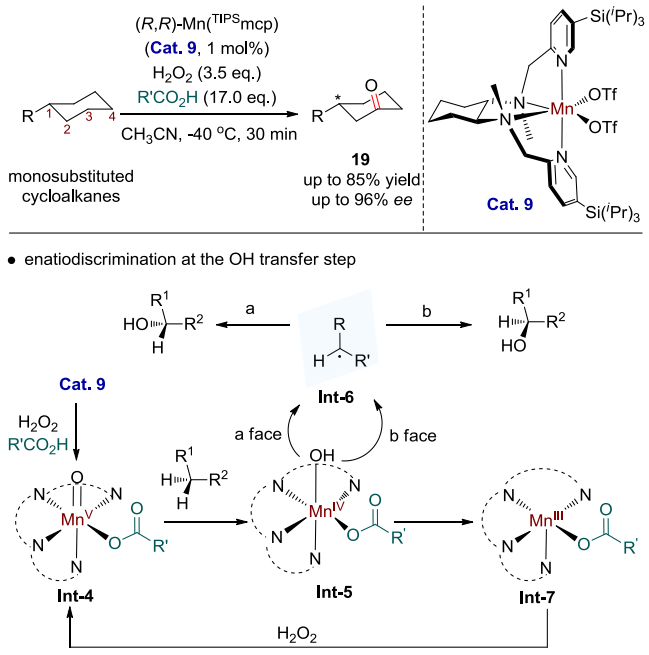
The oxidation of unactivated aliphatic C—H bonds is a valuable process to create C—O bonds in organic synthesis, but remains challenging due to the particular difficulties associated with the oxidative recognition of C(sp^3)–H bonds with similar bond strength and polarity.[51] High valent metal-*oxo* complexes have long been recognized as useful species for C—H oxidation in many biological processes.[52] Bio-inspired transition metal catalysts, that can generate such metal-*oxo* intermediates *in situ*, have been developed for organic oxidation reactions, but only a few examples of enantioselective C(sp^3)–H oxidation have been reported.

Scheme 11 Catalytic activity of a rhodium-bismuth bimetallic catalyst in an asymmetric C—H insertion reaction of cyclohexane



Catalyst	Time	Yield (%)	*ee* (%)
Cat. 7	15 h	78	86
Cat. 8	15 min	97	90

Scheme 12 Desymmetric C—H oxidation of monosubstituted cycloalkanes catalyzed by a biomimetic chiral manganese complex



These are often limited to relatively weak benzylic, allylic C—H bonds, or those adjacent to heteroatoms, and most commonly deliver low yields.[53-57]

In 2017, Costas, Bietti *et al*. developed a site- and enantioselective C—H oxidation reaction of monosubstituted cycloalkanes with hydrogen peroxide catalyzed by a chiral manganese complex (**Cat. 9**) in the presence of a carboxylic acid additive (Scheme 12).[58] X-ray diffraction crystallographic analysis revealed that the metal catalyst features a C_2-symmetric *cis*-α geometry, and its chirality is located at the manganese center (Λ and Δ), and is in turn determined by the chirality of the cyclohexanediamine backbone. Two triflate ions bind with the metal as liable ligands, which can react with oxidants to form a high valent manganese *oxo* species.

The C—H oxidation of a monosubstituted cyclohexane selectively occurs at C-3 and C-4 methylenic sites, furnishing a number of chiral desymmetrized cyclohexanone products (**19**). A modest enantioselectivity of 64% *ee* and site-selectivity of 2 : 1 *rr* were achieved for the reaction of *tert*-butylcyclohexane, while up to 96% *ee* and exclusive site recognition toward C-3 were obtained for the reactions of *N*-cyclohexylalkanamides. A putative mechanism suggests that a pentavalent manganese-*oxo* intermediate (**Int-4**) is generated by oxidation of **Cat. 9** by H_2O_2, and this is followed by ligand exchange with the carboxylic acid additive. **Int-4** undergoes hydrogen atom abstraction from the cyclohexane substrate, delivering a Mn−OH intermediate complex (**Int-5**) and a carbon-centered radical (**Int-6**). The subsequent transfer of a hydroxyl moiety from the metal center to the radical species is believed to be the enantioselectivity-determining step, which might be achieved by embedding the manganese center in a robust chiral cavity defined by bulky TIPS groups of the ligand and the assistance of a carboxylic acid. The resultant enantio-enriched alcohol and trivalent manganese complex (**Int-7**) are further oxidized, affording the corresponding ketone product (**19**) and intermediate **Int-4**, respectively. This study demonstrates the possibility of achieving effective stereoselective C(sp^3)–H oxidation through precise design of chiral metal catalysts that can form reactive metal-*oxo* species during the reactions, and provides a useful platform for the development of other C—H oxidative asymmetric transformations.

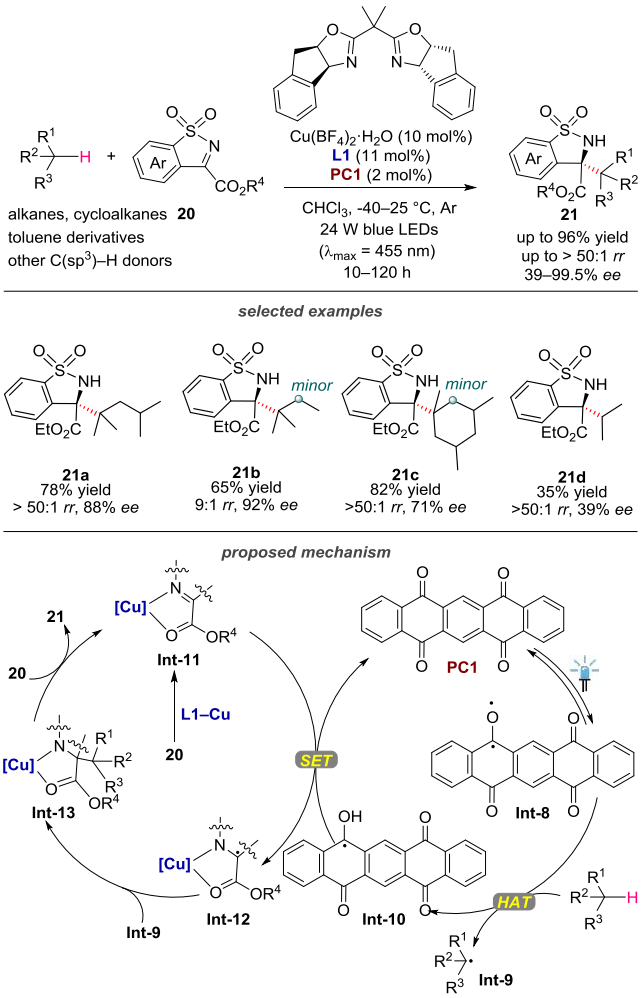
2.3. Reactions enabled by dual photocatalysis and CLA/CPA catalysis

Photocatalyzed hydrogen atom transfer (HAT) has emerged as an attractive strategy for C—H functionalization due to its ability to cleave inert bonds under mild reaction conditions.[59-64] The combination of a photoredox catalyst and a HAT reagent/catalyst, or the use of a bifunctional HAT photocatalyst, allows the development and direct modification of many C(sp^3)–H precursors, including toluene derivatives, ethers, alcohols, amides, amines, esters and alkanes.[65] Nevertheless, application of such methods to asymmetric synthesis has been scarcely explored. The engagement of high-energy alkyl radical intermediates, in combination with difficulty of achieving compatible photocatalytic and asymmetric induction processes, makes the stereocontrolled C—H transformations significantly challenging.[66-69]

To address these problems, our group developed a dual photocatalytic system employing 5,7,12,14-pentacenetetrone (**PC1**) as the HAT photocatalyst and a copper-based chiral Lewis acid (CLA) of a bisoxazoline ligand (**L1**) for stereo-discrimination. The radical-mediated C—H activation and asymmetric catalysis were matched well with each other (Scheme 13).[70] Upon irradiation with a 24 W blue LEDs lamp, a wide variety of alkanes, cycloalkanes and other C(sp^3)–H donors underwent formal asymmetric addition to prochiral cyclic *N*-sulfonylimines (**20**) with high site-selectivity (up to > 50 : 1 *rr*) and enantioselectivity (up to 99.5% *ee*). For example, the reaction with 2,4-dimethylpentane furnished product **21a** in 78% yield and with > 50 : 1 *rr* towards the tertiary C—H sites as well as 88% *ee*. In the reactions of isopentanes bearing all primary, secondary and tertiary C—H bonds, a high site-selectivity (9 : 1 *rr*) was still obtained for product **21b**, with 92% *ee*. A typical site-selectivity toward tertiary C—H bonds over secondary and primary bonds in the reaction can probably be attributed to the different formation rates of primary, secondary and tertiary carbon radicals, and the steric recognition by the HAT photocatalyst and transition-metal catalyst. Propane was also tolerated in the reaction but gave a reduced enantioselectivity (product **21d**, 39% *ee*).

In a proposed reaction mechanism, the HAT photocatalyst (**PC1**) is first excited by visible light, producing a triplet state (**Int-8**)

Scheme 13 Photocatalytic site- and stereoselective C(sp^3)–H functionalization of unactivated hydrocarbons

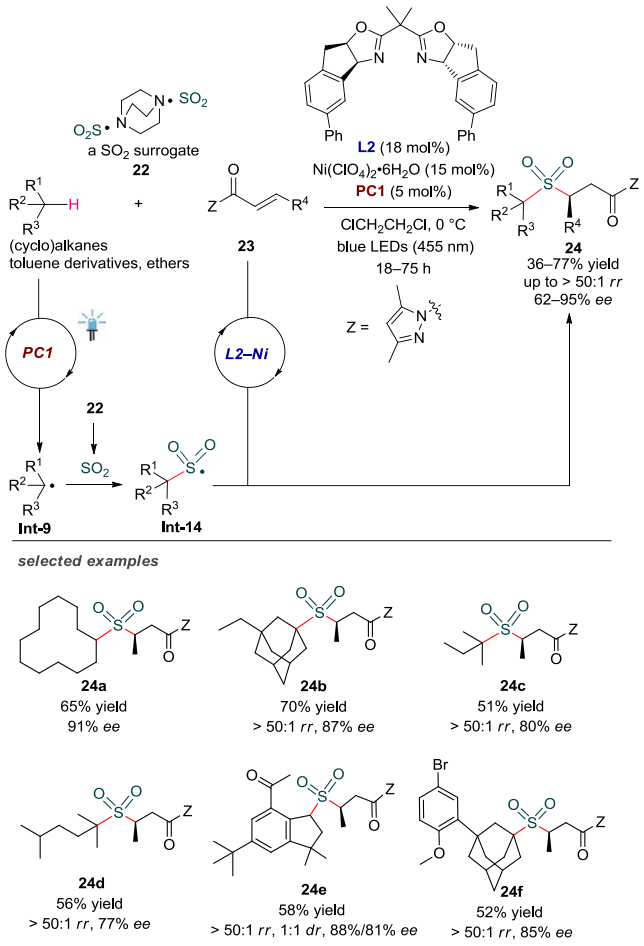


with biradical reactivity. **Int-8** abstracts a hydrogen atom from a C(sp^3)–H bond on the hydrocarbon substrate, which leads to the formation of a carbon-centered radical (**Int-9**) and a radical intermediate (**Int-10**). Meanwhile, the cyclic *N*-sulfonylimine (**20**) reacts with the chiral copper catalyst of **L1** *via* ligand exchange. The resultant coordinated imine complex (**Int-11**) performs a single electron transfer (SET) with **Int-10** to form a reduced complex (**Int-12**) and regenerates **PC1**. As the enantioselectivity-determining step, a radical combination of **Int-9** with **Int-12** provides a copper-coordinated product (**Int-13**). The final protonation and ligand substitution gives the *N*-sulfonylamine product (**21**) and regenerates complex **Int-11** for a next cycle. Lewis acid activation by the chiral copper catalyst is supported by the observation that other chiral Lewis acids of zinc, nickel or cobalt can also catalyze the reaction.

This method represents the first example of photocatalytic site- and stereoselective C(sp^3)–H functionalization of alkanes. The merits of broad substrate scope, mild reaction conditions without the need of any noble metals and structurally complex catalysts, and the high stereo-discrimination, allow it considerable potential in the construction of high value-added chiral molecules from abundant small hydrocarbons. Nevertheless, there are two deficiencies that were not addressed well in this study. These are the requirement of specific cyclic *N*-sulfonylimines as reaction partners to suppress side reactions such as self-coupling, and the diminished efficiency and selectivity of the conversions of cycloalkanes, which is probably due to the lack of an effective and general radical trapping channel.

On the basis of these concerns, a sulfur dioxide insertion approach was introduced in an effort to solve the problems. We found that a three-component reaction of a cycloalkane (or any other inactive C(sp^3)–H precursor), a SO_2 surrogate (**22**) and the reaction of a common *α,β*-unsaturated carbonyl compound (**23**) could be effectively catalyzed by the combination of an HAT photocatalyst (**PC1**) with a chiral nickel catalyst of a bisoxazoline ligand (**L2**), delivering biologically interesting *α*-carbon chiral sulfones with up to > 50 : 1 *rr* and 62%—95% *ee* (Scheme 14).[71] A wide variety of cycloalkanes, alkanes, benzylic or allylic hydrocarbons and ethers were tolerated under the mild reaction conditions. For example, the reaction of cyclododecane gave the desired product (**24a**) in 65% yield and with 91% *ee*, while that of 1-ethyladamantane or isopentane afforded **24b** or **24c** as a single reigoisomers with 87% or 80% *ee*, respectively. This method was successfully applied to late-stage modification of drug-like molecules. For example, the perfume celestolide and a synthetic intermediate of differin, an anti-acne agent were converted into the corresponding sulfone products **24e** and **24f** with exclusive regioselectivity and 81%—88% *ee*.

Scheme 14 Photocatalytic three-component asymmetric sulfonylation via direct C(sp^3)–H functionalization

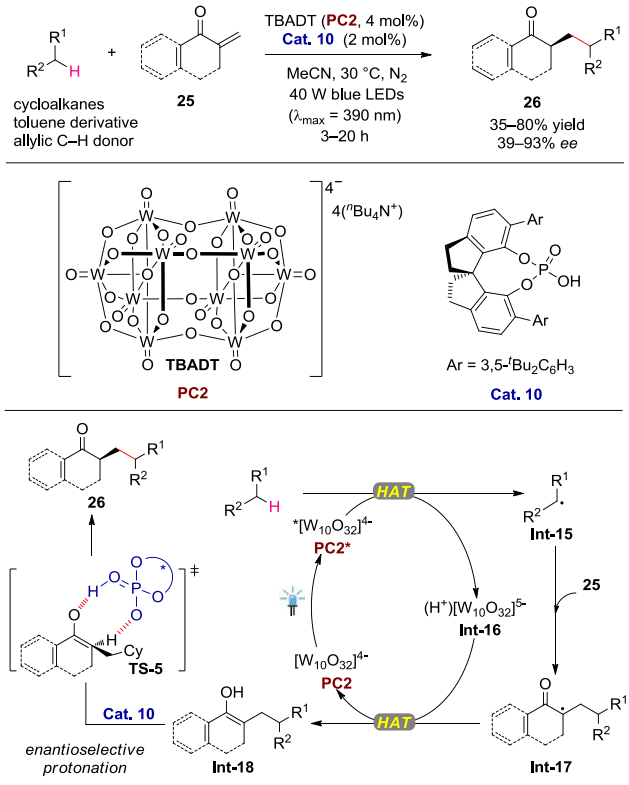


A radical relay sequence is proposed to illuminate the role of the SO_2 precursor (**22**) in the photochemical transformation. Because of its high affinity towards nucleophilic radicals, sulfur dioxide released *in situ* tends to capture the *C*-centered radical intermediate (**Int-9**) derived from a photo-induced HAT process, producing a long-lived sulfonyl radical (**Int-14**). **Int-14** is electronically rich and sterically demanding, and can effectively add to the nick-

el-activated Michael acceptor (**23**) with high enantiodiscrimination.

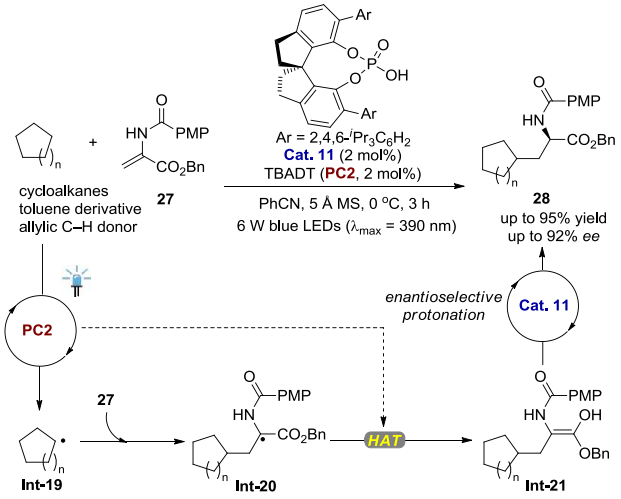
In 2020, Wang *et al*. reported an enantioselective reaction of a hydrocarbon with an exocyclic enone (**25**) enabled by a decatungstate-based HAT photocatalyst (**PC2**) and a chiral phosphoric acid (CPA, **Cat. 10**) (Scheme 15).[72] A wide range of cycloalkanes, benzylic and allylic hydrocarbons are tolerated in this reaction, giving the chiral adducts (**26**) in 35%—80% yield and with 39%—93% *ee*. In the proposed reaction mechanism, the photocatalyst (**PC2**) is excited upon visible light irradiation to give a triplet state intermediate (**PC2***). A subsequent HAT with the hydrocarbon provides a *C*-centered radical (**Int-15**) and a reducing photocatalyst (**Int-16**). The radical species (**Int-15**) undergoes a conjugate radical addition with the exocyclic enone substrate (**25**) to generate an *α*-carbonyl adduct radical (**Int-17**). A second HAT between the reducing photocatalyst (**Int-16**) and **Int-17** leads to closure of the photocatalytic cycle. Finally, the simultaneously formed enol intermediate (**Int-18**) is converted into its chiral ketone derivate (**26**) through an enantioselective protonation governed by the chiral spiro phosphoric catalyst (**Cat. 9**). Considering the very common substrates and the readily available photocatalysts and chiral organocatalysts, this method offers appealing opportunities for the rapid construction of enantioenriched *α*-stereogenic ketones from simple hydrocarbon feedstocks.

Scheme 15 Photocatalytic enantioselective reaction of hydrocarbons and exocyclic enones enabled by decatungstate-based HAT photocatalysis and CLA catalysis



A strategy reliant on a radical relay sequence of photo-induced HAT/radical addition/hydrogen abstraction/enantioselective protonation was later applied to a photocatalytic enantioselective C(sp^3)–H addition to *α*-substituted acrylates (**27**) (Scheme 16).[73] A dual catalytic system consisting of **PC2** and another CPA catalyst (**Cat. 11**) provided high reaction rates (up to 95% yield within 3 h) and enantioselectivity (up to 92% *ee*). As in the former study, the final protonation of *α*-amidoester enolate intermediates (**Int-21**) is the enantioselectivity-determining step, in which

Scheme 16 Photocatalytic enantioselective C(sp^3)–H addition to *α*-substituted acrylates



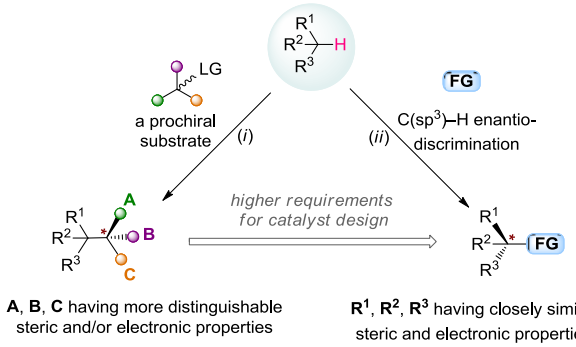
the presence of the N—H bond as a potential hydrogen-bond donor is beneficial to the formation of favored transition states, thus leading to a high level of asymmetric induction.

All of these examples indicate strongly that the synergistic combination of photocatalyzed HAT processes and asymmetric catalysis by chiral Lewis acids or chiral phosphoric acids is an emerging tool for enantioselective C(sp^3)–H additions of unactivated hydrocarbons to prochiral substances. We anticipate that such methods will have considerable potential in the future development of general, convenient synthesis of diverse chiral molecules of high added value from abundant alkanes and other inert aliphatic C—H donors.

3. C(sp^3)–H Enantiodiscrimination of Alkanes or Cycloalkanes

In comparison to the reactions of an alkane or a cycloalkane with a prochiral substrate to fashion a stereogenic center adjacent to a cleaved C—H bond (Scheme 17, reaction type (*i*)), the C(sp^3)–H enantiodiscrimination necessary to build up a stereocenter located precisely on the carbon of a C—H bond is even more challenging (Scheme 17, reaction type (*ii*)). This is probably due to the insurmountable difficulties of finding a chiral catalyst capable of distinguishing alkyl substituents with closely similar steric and electronic properties (R^1, R^2, R^3) around the reacting C—H sites. To date, very few methods, relying either on enzyme catalysis by randomly mutated cytochromes P450 BM-3 enzymes, or involving metal carbene-induced C—H insertions by a sophisticated designed chiral rhodium catalyst, have been developed.

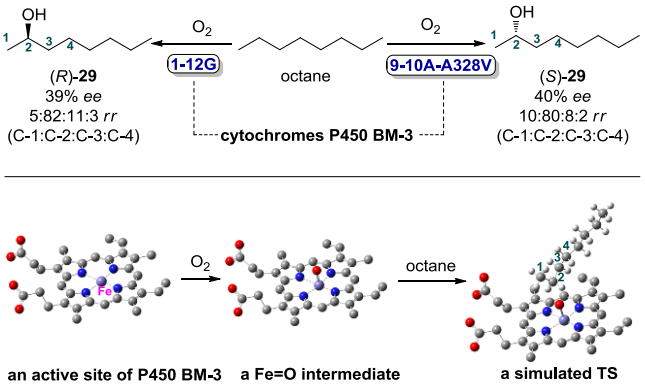
Scheme 17 Significant challenges of the C(sp^3)–H enantiodiscrimination of alkanes and cycloalkanes



3.1. Reactions enabled by enzyme catalysis

Cytochromes P450 are members of a family of iron porphyrin-based enzymes derived from bacteria.[74] They can efficiently catalyze the aerobic hydroxylation of a wide variety of unactivated aliphatic C—H bonds, with high selectivity in many cases.[75] In 2003, Arnold *et al.* reported a site- and enantioselective hydroxylation of linear alkanes with engineered cytochromes P450 BM-3 (Scheme 18).[76] A number of P450-based oxidation catalysts, such as mutant 9-10A-A328V and 1-12G, were obtained through directed evolution starting from wild-type cytochrome P450 BM-3, including 9-10A-A328V. In a representative reaction, octane was converted into its alcohol derivative ((*S*)-**29**) with 10 : 80 : 8 : 2 *rr* (C-1 : C-2 : C-3 : C-4) and 40% *ee* in the presence of 9-10A-A328V. Interestingly, mutant 1-12G showed a similar site-selectivity towards the C-2 position with 5 : 82 : 11 : 3 *rr* (C-1 : C-2 : C-3 : C-4), but gave an inverted enantiomeric excess (39% *ee* of (*R*)-**29**). Mechanistically, the iron porphyrin moiety on the engineered enzyme is first oxidized by oxygen to form an iron-*oxo* complex, which serves as a key intermediate which abstracts a hydrogen atom from an alkane molecule, followed by a subsequent hydroxyl transfer in a site- and enantioselective fashion. The highly unsymmetrical and diverse steric environment of these P450 mutants allows their specific recognition of different C—H bonds of alkanes, and simultaneous generation of a new carbon stereocenter with certain enantiomeric excess during the hydroxylation process.

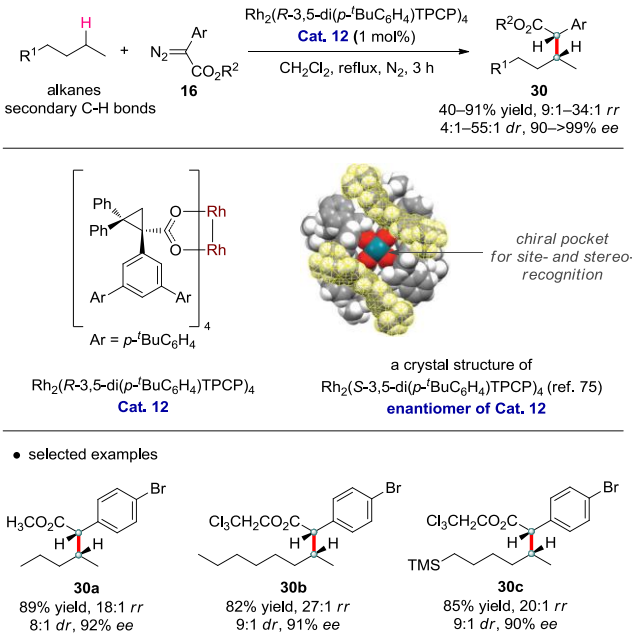
Scheme 18 Site- and enantioselective hydroxylation of octane enabled by cytochromes P450 BM-3



3.2. Reactions enabled by dirhodium catalysis

Rhodium-catalyzed C—H insertion has exhibited significant power to control enantioselectivity of reactions of alkanes or cycloalkanes with a prochiral carbene precursor, thus constructing a stereogenic center adjacent to the cleaved C(sp^3)–H bond. In 2016, Davies *et al*. found that the design of dirhodium catalysts with well-defined chiral pockets would allow simultaneous stereodiscrimination of a new build-up stereocenter located on the carbon of a cleaved secondary C(sp^3)–H bond (Scheme 19).[77] In the presence of **Cat. 12** containing a chiral triarylcyclopropanecarboxylate ligand (*R*-3,5-di(p-^{t}BuC_6H_4)TPCP), a range of *n*-alkanes or C-1 substituted *n*-alkyl compounds were selectively functionalized at the unactivated C-2 position, giving products with vicinal stereocenters (**30**) in 40%—91% yield, with 9 : 1—34 : 1 *rr*, 4 : 1—55 : 1 *dr* and 90%–>99% *ee*. For example, the reaction of *n*-pentane afforded the desired product (**30a**) in 89% yield and with 18 : 1 *rr*, 8 : 1 *dr* and 91% *ee*, and that of *n*-octane or hexyltrimethylsilane also gave excellent yields, site-selectivity and stereoselectivity (products **30b**, **30c**). The authors conducted X-ray crystallographic and computational studies in an effort to explain why **Cat. 12** is such an effective catalyst in the reaction. The outcomes reveal that the

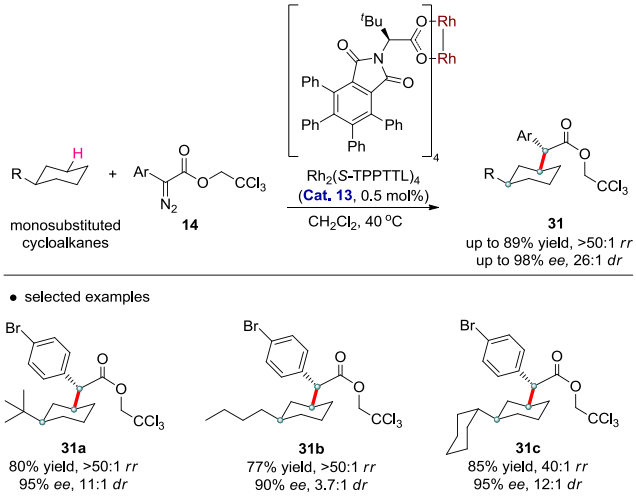
Scheme 19 Rhodium-catalyzed diastereo- and enantioselective functionalization of secondary C—H bonds of alkanes



rhodium catalyst adopts a D2 symmetric *α, β, α, β*-orientation and can limit the number of possible orientations of the corresponding rhodium-carbene intermediates. The bulky steric environment of the modified TPCP catalysts makes it possible to distinguish the size difference between a methyl and an *n*-propyl group in the reaction of *n*-pentane (product **30a**), thus causing a high level of diastereoselectivity. Considering the high reaction efficiency, excellent site-selectivity and the diastereo- and enantioselectivity, this method represents one of the most effective selective C—H functionalization reactions of alkanes.

A phthalimido-derived rhodium catalyst, Rh_2(*S*-TPPTTL)$_4$ (**Cat. 5**), was later designed by the same group for the reaction of monosubstituted cycloalkanes with aryl diazoacetates (**14**), potentially furnishing three stereocenters in one step.[78] The catalyst showed excellent site-selectivity toward the C-3 site of cycloalkanes as well as high diastereo- and enantioselectivity (Scheme 20). All the products (**31**) were obtained with up to > 50 : 1 *rr*, 26 :

Scheme 20 Rhodium-catalyzed diastereo- and enantioselective C(sp^3)–H functionalization of monosubstituted cycloalkanes



1 *dr* and 98% *ee*, and no ring diastereomers were observed. This work further confirms that the subtle and precise design of dirhodium catalysts can be used to address many intractable selectivity issues in C—H functionalization reactions.

4. Conclusions and Perspectives

Over the past decades, the direct and selective C—H functionalization of alkanes and cycloalkanes has emerged as an appealing approach to construction of structurally diverse, high value-added organic compounds from abundant starting materials. Its incorporation with asymmetric catalysis however, remains a remarkably challenging task. This is due to the insurmountable difficulties associated with site-selective cleavage of an unactivated C(sp^3)–H bond at the specific position, and simultaneous control of the stereoselectivity.

In this context, some elegant strategies have shown considerable potential for such reactions, which are based on metal carbene-induced C—H insertions by chiral dirhodium catalysts, metal-*oxo*-mediated C—H oxidation by bio-inspired manganese catalysts, enzyme catalysis by cytochromes P450 variants or dual catalysis by a photocatalyst and a chiral Lewis acid (CLA) or a chiral phosphoric acid (CPA). These reactions go through either an organometallic pathway or a radical-involved process. The site-selectivity and stereochemistry can be governed by fine-tuning the electrical and steric properties of the chiral catalysts and reaction partners. In particular, the sophisticatedly designed rhodium catalysts with well-defined chiral pockets are not only able to recognize all primary, secondary or tertiary C—H bonds of alkanes and cycloalkanes, but can also build up one or more stereogenic centers around the cleavage C(sp^3)–H bonds with high diastereo- and enantioselectivity. Detailed experimental and computational studies have offered mechanistic insight into these reactions, and provide more guidance for the design of new generation of catalysts and other valuable C—H transformations.

Despite of these significant advances, the installation of chirality onto unactivated alkanes and cycloalkanes mainly relies on reactions of (cyclo)alkanes and prochiral substances. Enantiodiscrimination during the cleavage and transformation of C(sp^3)–H bonds remains far less developed. More effective catalyst systems that can facilitate controllable aliphatic C—H functionalization are required. Furthermore, there is pressing need for powerful strategies to govern chemo- and site-selectivity in reaction processes, which can precisely recognize C—H bonds at specific positions of long-chained or high branched alkane alkanes. Innovative methods for diverse, enantioselective functionalization of remote C—H bonds in natural products and pharmaceutical targets, thus providing useful approaches to late-stage modification, is also of great research interest. We expect that the new development will stimulate further practical applications in asymmetric synthesis, pharmaceutical chemistry and industrial processes.

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